National Clinical Guideline Centre

Final, August 2015

Type 1 diabetes in adults

Type 1 diabetes in adults: diagnosis and management

Clinical guideline NG17

Appendix G

August 2015

2015 update

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The Royal College of Surgeons of England

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Contents

Appendix G: Clinical evidence tables 5
References 640

Appendix G: Clinical evidence tables

G.1 Diagnosis

G.1.1 Distinguishing between different types of diabetes

G.1.1.1 Population: Adults only (n≥50)

Table 1: AMROUCHE 2008 (100)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
Ch Amrouche, H. Jamoussi Kamoun, N. Trabelsi, and S. Blouza Chabchoub. Latent autoimmune diabetes in Tunisian adults (LADA): identification of autoimmune markers. *Tunis Med* 86 (4):316-318, 2008.	Observational: cross-sectional study Tunisian study	Total n=100 T2D **Inclusion criteria:** • T2D • Age at disease onset >30 years • Insulin treatment required >6 months to 1st 6 years after diagnosis • Insulin required after failure of oral therapy • Spontaneous ketosis under maximal doses of a-diabetic oral treatment **Exclusion criteria:** • Age >80 years • Diabetes caused by any	• ADULTS • DIABETES TYPE: o T2D	**T2D** n=107	• **T2D:** o GADA o IA-2 o ICA **Cut-offs for positivity** None given	n/a	**T2D**		**Funding:** None mentioned **Risk of bias:** • n/a
			Age, years (SD)	53 (10.5)			GADA+	18%	
			Age at onset of diabetes, years (SD)	43.4 (10)			IA-2, %	42%	
							ICA, %	49%	
							Presence of GAD65 was SS higher when ICA was absent		

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
REF ID: AMROUCHE 2008		endocrinopathy or pancreatopathy • MODY or mitochondrial diabetes • Diabetes with chromosomal abnormalities • Ketoacidosis within 1st 6 months of diabetes • Insulin requirement after 6 years of diabetes • Any other indication of insulin treatment					

Table 2: ANDERSEN 2014 (318)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
M. K. Andersen, M. Sterner, T. Forsen, A. Karajamaki, O. Rolandsson, C. Forsblom, P.-H. Groop, K. Lahti, P. M. Nilsson, L. Groop, and T. Tuomi. Type 2 diabetes susceptibility gene variants predispose to	Observational: cross-sectional study several Scandanavian registries used, but genotyping done on patients.	n=1317 adults n=911 LADA n=406 type 1 diabetes (study also assessed non-diabetic controls – not included here) Inclusion criteria: LADA or type 1 diabetes Diagnosis at >35 years of age LADA diagnosis: GADA and sufficient B-cell function at time of	ADULTS DIABETES TYPE: type 1 diabetes LADA		Type 1 diabetes: Fasting C-pep Cut-offs for positivity C-pep: detection limit 0.01 nM	Baseline	Type 1 diabetes adults		Funding: A number of non-pharma grants. Risk of bias: n/a
			Type 1 diabetes adults n=406				fC-pep, nmol/litre	0.04	
							LADA adults		
			Age	55 years			fC-pep, nmol/litre	0.73	
			Age of onset	45 years					
			Male	48%					
			HbA1c, %	8.5%					

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
adult-onset autoimmune diabetes. Diabetologia 57 (9):1859-1868, 2014. REF ID: ANDERSEN 2014		diagnosis, indicated by no insulin treatment and/or C-peptide level >0.2 nmol/litre. type 2 diabetes diagnosis: initial diagnosis of type 1 diabetes by treating physician, fasting C-peptide <0.2 nmol/litre at time of investigation, and initiation of permanent insulin treatment within 6 months from diagnosis. Exclusion criteria: None given	(SD)						
			LADA adults n=911						
			Age	61 years					
			Age of onset	56 years					
			Male	53%					
			HbA1c, %	7.5%					

Table 3: ARSLAN 2014 (319)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
D Arslan, A Merdin, D Tural, M Temizel, O Akin, S Gunduz, A Murat Tatli, F Avci, and M Uysal. The effect of	Observational: retrospective case-series Turkey	n=52 type 1 diabetes Inclusion criteria: type 1 diabetes (ADA criteria)	ADULTS DIABETES TYPE: type 1 diabetes		Type 1 diabetes: GAD ICA Cut-offs for positivity	At diagnosis	Type 1 diabetes adults		Funding: None mentioned. Risk of bias: n/a retrospective
							GAD+ and/or ICA+	62%	
				Type 1 diabetes adults					

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
autoimmunity on the development time of microvascular complications in patients with type 1 diabetes mellitus. Med Sci Monit 20:1176-1179, 2014. REF ID: ARSLAN 2014		Developed microvascular complications(retinopathy, neuropathy, nephropathy) Had been tested for markers: GAD, and ICA. Exclusion criteria: None given		n=52	Compared to reference range.				
			Age mean, (SD)	34 years (8)					
			Male	42%					
			Disease duration, range	0-12 months					

Table 4: ARIKAN 2005 (102)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
Ender Arikan, Tevfik Sabuncu, Esref M. Ozer, and Husrev Hatemi. The clinical characteristics of latent autoimmune diabetes in adults and its	Observational Cross-sectional study. Study carried out in Turkey	n=54 adult participants (39 females and 15 males) with type 2 diabetes referred to a hospital due to poor glycaemic control. (n=37 type 2 diabetes and n=17 LADA –	Adult with: type 2 diabetes LADA identified from GADA-positive patients. Classification of diabetes: GADA-positive patients were identified as LADA patients. Comparison of the data	Serum C peptide (nmol/litre) GADA (defined as LADA)	Not stated	Patients who were GADA positive had significantly earlier diabetes onset age than did the GADA-negative patients. GADA positive patients had significantly lower BMI and lower serum C-peptide value than the GADA-negative patients.	Funding: Not given Risk of bias: n/a

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
relation with chronic complications in metabolically poor controlled Turkish patients with Type 2 diabetes mellitus. J.Diabetes Complications 19 (5):254-258, 2005. REF ID: ARIKAN 2005		GAD+) Inclusion criteria: None given Exclusion criteria: None given	between GADA-positive and –negative patients			Cut-offs for positivity Serum C-PEPTIDE: not given GADA-positive: >1.5 U/ml		GAD+: 17/54 (31.5%)		
				GAD+ (LADA) n=17	GAD- (type 2 diabetes) n=37					
			Age (years)	56.6± 6.7	59.8± 6.7					
			Age at onset, (years)	45.1± 5.8	50.8± 8.0					
			Retinopathy (%)	61.5	28.6					
			Nephropathy (%)	84.6	50.0					
			Neuropathy (%)	60.0	40.0					

Table 5: BARKER 2014 (300)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
A. Barker, A. Lauria, N. Schloot, N. Hosszufalusi, J.	Observational: prospective	n=1665 adults subgroup	ADULTS subgroup (age at onset >18 years) DIABETES TYPE:	Type 1 diabetes: Fasting C-pep Stimulated C-pep	Baseline, 1 and 5 years	Type 1 diabetes adults		Funding: Centro Internazionale
						Baseline f-C-pep, nM (SD)	0.30 (0.38) n=1655	

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
Ludvigsson, C. Mathieu, D. Mauricio, M. Nordwall, B. Van Der Schueren, T. Mandrup-Poulsen, W. A. Scherbaum, I. Weets, F. K. Gorus, N. Wareham, R. D. Leslie, and P. Pozzilli. Age-dependent decline of beta-cell function in type 1 diabetes after diagnosis: a multi-centre longitudinal study. Diabetes Obes. Metab. 16 (3):262-267, 2014. REF ID: BARKER 2014	case-series 7 European registries	Total n=3929 type 1 diabetes adults, young people, and children Inclusion criteria: type 1 diabetes (ADA and WHO criteria) Exclusion criteria: None given	type 1 diabetes		(results not given in study due to very small number of stim C-pep mmts made) Cut-offs for positivity C-pep: detection limit 0.01 nM		1-year C-pep, nM (SD)	0.30 (0.36) n=455	Studi Diabete. Risk of bias: n/a lots of missing data at follow-up
				Type 1 diabetes adults n=1665			5-year C-pep, nM (SD)	0.17 (0.33) n=202	
			Age of onset (baseline)	Mean 29.3 years (SD 8.0)					
			Male	n=818					
			HbA1c, % (SD)	11.1 (2.8)					

Table 6: BODALSKA 2006 (52)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes			Comments
J. Bodalska-Lipinska, A. Szadkowska, and L. Markuszewski. Principles of diagnosis of latent autoimmune diabetes in adults (LADA). Diabetol.Dosw.Klin. 6 (2):69-74, 2006. REF ID: BODALSKA 2006	Observational cross-sectional study	n=56 participants with newly diagnosed type 2 diabetes were studied. Inclusion criteria: None given Exclusion criteria: None given	Adult with: type 2 diabetes Immune-mediated type 1 diabetes – Latent Autoimmune Diabetes in Adults (LADA) 13 female aged 19-62 years (46.4±12.9 years) and 43 men aged 23-67 years (46-9±9.9 years).	ICA: units JDF (Juvenile Diabetes Foundation) GADab: arbitrary units (AU) (IA-2ab) FC peptide. Cut-offs for positivity ICA+: ≥ 5 j JDF GADab: sens/spec 75.4% and 98%. Ninety nine percentile (5.2 AU) in control group was the threshold for negative results. IA-2ab: sens/spec 60.5% and 99%. Ninety nine percentile (8.1 AU) in control group was the threshold for negative result. Fasting plasma C-peptide: detection threshold was	Not stated				Funding: Not given Risk of bias: n/a
						Whole population (n=56)			
						ICA+ Titre (JDF U)	n (%) Mean ± SD Range	11/56 (19.6) 36.2±45.7 0-40	
						GAD+ Titre (AU)	n (%) Mean ± SD Range	3/56 (5.3) 89.3±52.9 0-128	
						IA-2+ Titre (AU)	n (%) Mean ± SD Range	3/56 (5.3) 36.2±45.7 0-89	
						C-peptide [pmol/ml]	Mean ± SD Range	1.05±0.94 0.32-2.7	
						The group of 14 patients, which did not meet the diagnostic standards of type 2 diabetes, was classified as immune-mediated type 1 diabetes			

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
				0.025pmol/litre.			

Table 7: BELL 2004 (108)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
David S. H. Bell and Fernando Ovalle. The role of C-peptide levels in screening for latent autoimmune diabetes in adults. Am.J.Ther. 11 (4):308-311, 2004. REF ID: BELL 2004	Observational cross-sectional study.	Total n=78 (n=39 LADA and n=39 type 2 diabetes). Inclusion criteria for participants with LADA: Insidious onset of diabetes after age 30 Initial diagnosis of type 2 diabetes so that insulin was not used in the 12 months after diagnosis Presence of anti-GAD Abs Exclusion criteria: None given Baseline characteristics	Adult with: type 2 diabetes LADA.	Random serum C peptide Anti-GAD antibody titre (GAD-GS) Cut-offs for positivity Random serum C-peptide: normal fasting range, 0.8-4.ong/dL	Not stated	LADA: Mean C-peptide: 1.0±0.2 ng/mL (range, 0-4.3) type 2 diabetes: Mean C-peptide: 5.1 ± 0.4 ng/mL (range, 1.0-11.8 ng/mL). SS difference from LADA All participants with type 2 diabetes had a C-peptide level within or above the normal range.	Funding: Not given Risk of bias: n/a

	LADA (n=39)	type 2 diabetes (n=39)
Age (y)	60.1±1.9	60.1±1.6
Duration	10.0±1.	10.6±1.0

Reference	Study type	Number of patients			Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
		of type 2 diabetes (y)	9							

Table 8: HAMPE 2013 (302)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
CS. Hampe, Murray E. Maitland, Lisa K. Gilliam, Thanh H. T. Phan, Ian R. Sweet, Jared R. Radtke, Vasile Bota, Bruce R. Ransom, and Irl B. Hirsch. High titres of autoantibodies to glutamate decarboxylase in type 1 diabetes patients: epitope analysis and inhibition of enzyme activity. Endocr Pract 19 (4):663-668, 2013.	Observational : cross-sectional study USA	n=100 type 1 diabetes Inclusion criteria: Adults ≥18 years Clinical diagnosis of type 1 diabetes Sc insulin treatment Exclusion criteria: <18 years Serious illness affecting immune system Immunosuppressive medication	Type 1 diabetes adults DIABETES TYPE: type 1 diabetes		Type 1 diabetes: GAD65 Cut-offs for positivity GAD65 (high titre): at least 10x greater than median of entire cohort	n/a	Type 1 diabetes adults		Funding: NIH and ADA. Risk of bias: n/a no missing data
			Type 1 diabetes adults and young people n=187				GAD65+	45%	
			Age median, (range)	16 years (2 - 62)			GAD65+ patients titre, U/ml, median	400 U/mL (range 142-250,000)	
			Male	n=44			High titre (≥2000 U/mL)	n=10	
			Disease duration, median (range)	25 years (2-60)			There was NS correlation between GAD65 titre and age at onset, duration of diabetes, gender, or age at sampling.		
			Age at onset, median (range)	16 years (2-62)					
			Drop-outs/missing data:						

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
REF ID: HAMPE 2013			none					

Table 9: HAWA 2013 (303)

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes (baseline)		Comments
MI. Hawa, Hubert Kolb, Nanette Schloot, Huriya Beyan, Stavroula A. Paschou, Raffaella Buzzetti, Didac Mauricio, et al and Action LADA consortium. Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype: Action LADA 7. Diabetes Care 36 (4):908-913, 2013 REF ID: HAWA	Observational: cross-sectional study 9 European countries	n=114 type 1 diabetes and n=377 LADA (total n=6156 patients met inclusion criteria and were then diagnosed) Inclusion criteria: Adult-onset diabetes Age 30-70 years Primary diabetes Diagnosis in past 5 years ≥2 recorded f-blood glucose mmts ≥7 mmol/litre LADA = age 30-70 years with diabetes-associated auto-Abs, did not require insulin treatment for ≥ 6 months post-diagnosis type 1 diabetes = diabetes and	ADULTS DIABETES TYPE: type 1 diabetes (started insulin at diagnosis, and all Ab+) LADA (free of insulin >6 months post-diagnosis, and Ab+)			Type 1 diabetes: GAD IA-2A ZnT8A LADA: GAD IA-2A ZnT8A Cut-offs for positivity Determined by using standard curve end-point	n/a	Type 1 diabetes		Funding: EU and DeveloGen Risk of bias: n/a no missing data
				Type 1 diabetes n=114	LADA n=377			GAD high titre	79.8%	
								GAD+/IA-2A+, and ZnT8A+	13.2%	
								LADA		
								GAD high titre	78.5%	
			Age, years mean	44.1	51.9			GAD+/IA-2A+, and ZnT8A+	9.0%	
			M/F %	52%	50%					
			Age at onset, mean years	41.8	49.7			Type 1 diabetes patients vs. LADA: type 1 diabetes were younger, lower age of onset. NS difference in number of patients with high GAD titre.		
			BMI, mean	25.6	28.6					
			Duration of disease, mean years	1.93	2.37					
			Drop-outs/missing data: none							

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes (baseline)	Comments
2013		diabetes-associated auto-Abs, and Insulin started at diagnosis or ≤1 month. Exclusion criteria: Insufficient dataset Current pregnancy Renal disease with raised creatinine or proteinuria Acute illness					

Table 10: HOPE 2013 (320)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
S. V. Hope, A. G. Jones, E. Goodchild, M. Shepherd, R. E. J. Besser, B. Shields, T. McDonald, B. A. Knight, and A. Hattersley. Urinary C-peptide creatinine ratio detects absolute insulin deficiency in Type 2 diabetes.	Observational : cross-sectional study UK	n=191 type 2 diabetes Inclusion criteria: Insulin treated type 2 diabetes diagnosis: age ≥45 years, clinical diagnosis of type 2 diabetes, insulin treatment not started within 1 year of diagnosis	ADULTS DIABETES TYPE: type 2 diabetes		type 2 diabetes: UCPCR Cut-offs for positivity UCPCR: ≤0.2 nmol/mmol	n/a	type 2 diabetes adults		Funding: NIHR and other non-pharma sponsors. Risk of bias: n/a a few missing data (small, <10%)
			type 2 diabetes adults n=191				UCPCR, ≤0.2 nmol/mmol	n=24 (13%)	
			Age median, (IQR)	73.5 years (67 - 78)					
			Male	63%					
			Disease duration, median (IQR)	13.5 years (9-19)					

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
Diabet Med 30 (11):1342-1348, 2013. REF ID: HOPE 2013		Exclusion criteria: None reported	Age at onset, median (IQR)	58 years (50 - 65)					
			Missing data:	n=3					
			Drop-outs/missing data: none						

Table 11: HUANG 2013 (304)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
G Huang, Yufei Xiang, Lingling Pan, Xia Li, Shuoming Luo, and Zhiguang Zhou. Zinc transporter 8 autoantibody (ZnT8A) could help differentiate latent autoimmune diabetes in adults (LADA) from phenotypic type 2 diabetes mellitus. Diabetes.Metab .Res.Rev. 29	Observational: cross-sectional study China – 46 centres	n=3062 type 2 diabetes newly diagnosed Inclusion criteria: Adults ≥30 years age at onset Newly diagnosed (≤1 year) type 2 diabetes (WHO criteria) No incidence of ketosis or ketoacidosis within 6 months of disease onset Insulin independence for ≥6 months	type 2 diabetes adults DIABETES TYPE: type 2 diabetes and LADA within the type 2 diabetes group		type 2 diabetes and LADA: GADA IA-2A ZnT8 Cut-offs for positivity Healthy control group values used	n/a	type 2 diabetes adults		Funding: A number of non-pharma sources. Risk of bias: n/a no missing data
			type 2 diabetes adults n=3062				ZnT8	1.99%	
			Age median, (range)	51.3 years (30 - 88)			GADA	6.43%	
			Male	n=1782			IA-2A	1.96%	
							ZnT8+ /GADA+	0.20%	
							ZnT8+/IA-2A+	0.26%	
							GADA+/IA-2A+	0.32%	
							ZnT8+ /GADA+/IA-2A+	0.49%	
							For LADA diagnosis: ZnT8 and/or GADA	7.74%	
							For LADA diagnosis: ZnT8 and/or IA-2A	3.20%	
			Drop-outs/missing data: none				For LADA diagnosis: GADA and or IA-2A	7.58%	
							For LADA diagnosis: GADA and or IA-2A	8.62%	

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
(5):363-368, 2013. REF ID: HUANG 2013		Exclusion criteria: Secondary diabetes mellitus Pregnant Malignant disease					and or ZnT8		
							There was a NS but declining trend in ZnT8 positivity with age.		

Table 12: MAHADEB 2014 (305)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
YP. Mahadeb, D Gruson, Martin Buysschaert, and Michel P. Hermans. What are the characteristics of phenotypic type 2 diabetic patients with low-titre GAD65 antibodies? Acta Diabetol. 51 (1):103-111, 2014. REF ID: MAHADEB 2014	Observational : cross-sectional study USA	n=524 type 2 diabetes Inclusion criteria: type 2 diabetes (criteria of Expert Committee on the Diagnosis and Classification of Diabetes) Exclusion criteria: None given	type 2 diabetes adults DIABETES TYPE: type 2 diabetes		type 2 diabetes: GADA Cut-offs for positivity GADA (high titre): based on healthy individuals. LADA cases were considered as those with GADA titres >59UI/litre (UKPDS cut-off) Low titre GADA+ = 10-59UI/litre (based on UKPDS and healthy	n/a	type 2 diabetes adults		Funding: NIH and ADA. Risk of bias: n/a no missing data consecutive recruitment
			type 2 diabetes adults and young people n=524				GADA+	5.7%	
			Age mean	65 years			GADA+ patients titre, IU/litre, median (IQR)	29.4 IU/litre (15.0 – 42.9)	
			Male	66%					
			Disease duration, mean	14 years (1SD 9 years)			There was NS difference between GADA+ and GADA- for age, and diabetes duration.		
			Drop-outs/missing data:						

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
			none	individuals value in this study).				

Table 13: MARASCHIN 2013 (306)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
JF Maraschin, LS Weinert, N Murussi, V Witter, T da Costa Rodrigues, ER Rossato, and SP Silveiro. Influence of age at diagnosis and duration of diabetes on the positivity of glutamic acid decarboxylase antibody in South-Brazilian type 1 diabetes mellitus. Ann.Clin.Biochem. 50 (patient 3):262-266, 2013. REF ID: MARASCHIN 2013	Observational: cross-sectional study Brazil	n=92 type 1 diabetes group n=298 overall recruited in 3 different population groups (type 1 diabetes, healthy, gestational diabetes) Inclusion criteria: type 1 diabetes group: clinical diagnosis based on history of documented DKA, insulin use up to 3 years after diagnosis,	Type 1 diabetes adults DIABETES TYPE: type 1 diabetes		Type 1 diabetes: GADA C-peptide Cut-offs for positivity GADA (high titre): based on the recruited group of healthy controls.	n/a	Type 1 diabetes adults		Funding: FIPE. Risk of bias: n/a no missing data consecutive recruitment
			Type 1 diabetes adults n=92				GADA+	n=44 (48%)	
			Age mean (SD)	35 (10) years			C-peptide, nmol/litre (SD)	0.17 (0.03)	
			Male	53%					
			Disease duration, years, mean (SD)	16 (9)					
			Age at diagnosis, mean (SD)	20 (9)					
			BMI, kg/m2. Mean (SD)	24 (3)					
			Drop-outs/missing data: none						

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
		fasting baseline C-pep <0.3 nmol/litre. Exclusion criteria: None given						

Table 14: MURAO 2008 (128)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
S Murao, S Kondo, J Ohashi, Y Fujii, I Shimizu, M Fujiyama, K Ohno, et al. Anti-thyroid peroxidase antibody, IA-2 antibody, and fasting C-peptide levels predict beta cell failure in patients with latent	Observational study – prospective case-series	Total n= 57 LADA. n=42/57 completed the 5 year follow-up. Inclusion criteria for LADA patients: Presence of GADAb. Without	ADULT (age>20 years) DIABETES TYPE: LADA		LAD: Fasting C-peptide Postprandial C-peptide GADAb IA-2A Cut-offs for positivity Postprandial C-peptide: criterion for beta cell failure was <0.33 nmol/litre postprandial C-peptide	5 years follow up.	LADA: A – (n=31)		Funding: Supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Science, Sports and Technology.
			Age of LADA patients (n=57) according to the time of registration				FC peptide (nmol/litre)	0.63 (0.42-0.77)	
			Group A				GADAb ≥ 10U/ml	5	
			Age at diabetes onset (years)	56.0 (50.5-59)			IA-2Ab alone	0 (0.0)	
			Group B				LADA: B – (n=6)		
							FC peptide (nmol/litre)	0.82 (0.65-1.28)	
							GADAb ≥ 10U/ml	1	

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
autoimmune diabetes in adults (LADA)--a 5-year follow-up of the Ehime study. Diabetes Res.Clin.Pract. 80 (1):114-121, 2008. REF ID: MURAO 2008		insulin therapy both at the time of registration and 12 months after the diagnosis. Exclusion criteria: None mentioned			GADAb+: >1.5 u/ml IA-2A: Not reported		IA-2Ab alone	0. (0.0)	Risk of bias: n/a
			Age at diabetes onset (years)	58.5 (47-67)			LADA: C – (n=5)		
			Group C				FC peptide (nmol/litre)	0.83 (0.77-0.93)	
			Age at diabetes onset (years)	42 (41-57)			GADAb ≥ 10U/ml	2	
							IA-2Ab alone	1 (20.0)	

Table 15: PASCHKE 2013 (307)

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes (baseline)		Comments
A Paschke, Agata Grzelka, Agnieszka Zawada, and Dorota Zozulinska-Ziolkiewicz. Clinical characteristics and autoantibody pattern in	Observational: cross-sectional study Poland	n=344 LADA Inclusion criteria: Newly diagnosed diabetes diagnosis within ≤3 months before	ADULTS DIABETES TYPE: LADA (split by age at diagnosis)			LADA: GAD IA-2A ICA C-peptide Cut-offs for positivity Determined by using JDF	n/a	LADA		Funding: None mentioned
								C-peptide, fasting, ng/ml (SD)	<35years: 1.15 (0.89) >35 years: 1.06 (0.61)	
								C-peptide, stimulated, ng, ng/ml (SD)	<35years: 2.14 (1.69) >35 years: 1.59 (0.76)	
								1 Ab	n=64 (19%)	
				Age	Age			2 Abs	n=112 (33%)	

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes (baseline)		Comments
newly diagnosed adult-onset autoimmune diabetes. Pol.Arch.Med. Wewn. 123 (7-8):401-408, 2013. REF ID: PASCHKE 2013		hospitalisation Age of onset ≥18 years Positivity for ≥1 anti-islet autoantibodies (ICA, GADA, IA-2A) ≥ 6 months post-diagnosis Exclusion criteria: None mentioned		<35 (but >18 years) n=278	≥35 n=66	reference sample		3 Abs	n=168 (49%)	Risk of bias: n/a no missing data retrospect data collection from patient records
								GADA+	90.7%	
								ICA	79.1%	
			Age at onset, years mean (SD)	25.2 (4.9)	42.6 (7.1)			IA-2A	60.5%	
			Male %	68%	55%			The most common 2-Ab combination was GADA + ICA		
			BMI, mean	22.9	23.4			The presence of multiple auto-Abs was associated with younger age, lower fasting and stimulated C-pep, and shorter duration of symptoms.		
			Duration of disease, mean weeks (SD)	8.2 (11.9)	6.5 (5.2)					
			Drop-outs/missing data: none							

Table 16: ROGOWICZ 2014 (323)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
A Rogowicz-Fontczak, D Zozulilska-Ziolkiewicz, Monika Litwinowicz, Pawel Niedzwiecki, Krystyna Wyka,	Observational: cross-sectional study Poland	n=80 diabetes (n=56 LADA) Inclusion criteria: Diagnosis of diabetes (WHO criteria)	ADULTS DIABETES TYPE: LADA		LADA: GAD ICA IA-2A ZnT8 Fasting C-peptide Stimulated C-peptide	At diagnosis	LADA adults		Funding: Poznan University of Medical Sciences, Poland. Risk of bias: n/a
				LADA adults n=56			Fasting C-pep, ng/ml (SD)	1.1 (0.6)	
							Stim C-pep, ng/ml (SD)	1.7 (1.0)	
							GADA+	83.9%	
							ICA	62.5%	
							IA-2A	42.8%	

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
and Bogna Wierusz-Wysocka. Are zinc transporter type 8 antibodies a marker of autoimmune thyroiditis in non-obese adults with new-onset diabetes? EUR.J.ENDOCRINOL. 170 (4):651-658, 2014. REF ID: ROGOWICZ 2014		Newly diagnosed Non-obese Caucasian race Age 35 – 65 years. Exclusion criteria: BMI ≥30 kg/m2 Cancer Hepatic failure Diagnosed HepB or HepC virus Renal failure Chronic pancreatitis Anaemia Use of drugs affecting glucose metabolism History of alcohol abuse	Age mean	42years	Cut-offs for positivity ICA: >5 JDF units GAD: >10 U/ml IA-2A: >20 U/ml ZnT8: WHO standard curve		ZnT8A	33.0%	
			Male	59%			ZnT8+ /GAD+	84.2%	
			HbA1c, % (SD)	11.4 (2.4)			ZnT8+ /ICA+	89.4%	
							ZnT8+ /IA-2A	47.3%	
							ZnT8-/GAD+	83.8%	
							ZnT8- /ICA+	51.4%	
							ZnT8- /IA-2A	41.6%	
							Titres, median:		
							GADA (U/ml)	522.3 (ZnT8+) 282.8 (ZnT8-)	
							ICA (JDF)	80 (ZnT8+) 20 (ZnT8-)	
							IA-2A (U/ml)	19.1 (ZnT8+) 17.3 (ZnT8-)	

Table 17: ROH 2013 (308)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
MO Roh, Chan Hee Jung, Bo Yeon Kim, Ji Oh	Observational: retrospe	Total n=323 n=37 type 1 diabetes	ADULTS DIABETES TYPE:	LADA: Stim C-peptide	n/a	Type 1 diabetes		Funding: None mentioned
						GADA titre, U/ml, median	0.08 (0.01 – 91.9)	

Reference	Study type	Number of patients	Patient characteristics				Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
Mok, and Chul Hee Kim. The prevalence and characteristics of latent autoimmune diabetes in adults (LADA) and its relation with chronic complications in a clinical department of a university hospital in Korea. Acta Diabetol. 50 (2):129-134, 2013. REF ID: ROH 2013	ctive case-series Korea patients were diagnosed based on the presence of GADA markers and so the useful data for this study is the titres of the markers	n=17 LADA n=268 type 2 diabetes Inclusion criteria: type 1 diabetes (insulin dependent < 6 months after diagnosis) LADA (GADA+ but insulin independent during first 6 months from DX irrespective of age type 2 diabetes (GADA- and insulin independent ≥6 months from diagnosis). Exclusion criteria: None given	LADA type 1 diabetes type 2 diabetes				fC-PEPTIDE GAD Type 1 diabetes: Stim C-peptide fC-PEPTIDE GAD type 2 diabetes: Stim C-peptide fC-PEPTIDE GAD Cut-offs for positivity C-PEPTIDE+ (fasting): ≤0.6ng/ml GADA+: not reported		(range)		
				Type 1 diabetes n=37	LADA n=17	type 2 diabetes n=268			fC-peptide titre, ng/ml, median (range)	0.33 (0.01 – 2.13)	
									StimC-petide titre, ng/ml, median (range)	0.83 (0.01 – 7.22)	
									LADA		Risk of bias: n/a no missing data retrospect data collection from patient records
			Age, years (SD)	29 (10.7)	40.2 (14.0)	48.7 (16.1)			GADA titre, U/ml, median (range)	6.0 (1.5 – 114.85)	
									fC-peptide titre, ng/ml, median (range)	0.39 (0.01 – 9.67)	
			Age at onset, years (SD)	26.1 (11.4)	32.8 (8.1)	44.6 (13.8)			StimC-petide titre, ng/ml, median (range)	0.62 (0.01 – 8.64)	
									type 2 diabetes		
			Disease duration, years, median (range)	1.5 (0-19)	4 (0-17)	1 (0-43)			GADA titre, U/ml, median (range)	0.07 (0.01 – 1.41)	
									fC-peptide titre, ng/ml, median (range)	2.18 (0.01 – 14.3)	
									StimC-petide titre, ng/ml, median (range)	5.33 (0.01 – 28.2)	

Reference	Study type	Number of patients	Patient characteristics				Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments

Table 18: SHISHIKURA 2014 (324)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
K. Shishikura, K. Tanimoto, S. Sakai, Y. Tanimoto, J. Terasaki, and T. Hanafusa. Association between skeletal muscle mass and insulin secretion in patients with type 2 diabetes mellitus. Endocr.J. 61 (3):281-287, 2014. REF ID: SHISHIKURA 2014	Observational: cross-sectional study Japan	n=138 type 2 diabetes Inclusion criteria: type 2 diabetes Attending hospital for treatment Exclusion criteria: Detection of anti-GADA History of gastrectomy Using a cardiac pacemaker or implanted	Adults DIABETES TYPE: type 2 diabetes		type 2 diabetes: Stimulated C-peptide Cut-offs for positivity C-peptide: not mentioned.	n/a	type 2 diabetes adults		Funding: None mentioned Risk of bias: n/a no missing data consecutive recruitment
			type 2 diabetes adults n=138				Stim C-peptide, mg/mL	Male: 4.9 Female: 4.1	
			Age mean	62 years					
			Male	62%					
			BMI	25 kg/m2					
			Medication use	None: 9% Oral hypoglycaemic agent: 42% Insulin: 23% Agent + insulin: 25%					
			Drop-outs/missing data: none						

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
		defibrillator Use of steroid hormones Renal insufficiency cachexia						

Table 19: SORGJERD 2012 (87)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
E. P. Sorgjerd, F. Skorpen, K. Kvaloy, K. Midthjell, and V. Grill. Time dynamics of autoantibodies are coupled to phenotypes and add to the heterogeneity of autoimmune diabetes in adults: the HUNT study, Norway. Diabetologia 55 (5):1310-1318,	Observational: prospective case-series study Nord-Trondelag county in Norway	HUNT 2: n=120 type 1 diabetes and n=120 LADA. HUNT 3: n=147 TID and 85 LADA HUNT2 and HUNT3: n=302 type 2 diabetes. The HUNT study consists of	Adult with: type 1 diabetes LADA type 2 diabetes Classification of diabetes: type 1 diabetes if they started insulin treatment within 12 months of diagnosis and were: (1) antibody-positive, or (2) antibody-negative but with fasting C-peptide levels<150pmol/litre. Type 1 diabetes cases were divided into two subgroups based on the median onset, which was 24 years. Groups were termed	FC-peptide, GADA IA-2A (the latter only in HUNT3). Additional antibody measurements: Serum samples from diabetic cases classified as LADA or type 1 diabetes were analysed for 1A-2A (if not done already in	Prospective data obtained (HUNT2 to HUNT3; 10-13 years follow-up) on 44 LADA, 59 type 1 diabetes and 302 type 2 diabetes cases from HUNT2 and 31 LADA	Pattern of antibody positivity in LADA influences phenotype: 17/161 LADA cases were positive for antibodies other than GADA. 1/17 of these cases was GADA-. LADA cases positive for 2 or 3 Abs (10%, n=16) had a higher GADA titre (p<0.001) and higher non-fasting blood glucose (p=0.011) vs. those positive only for 1 Ab. A majority of diagnosed LADA cases lose antibody positivity: After 10-13 years, in HUNT3, a majority of LADA cases (26 of 44, 59%) were now negative	Funding: The Liaison committee of the Central Norway Regional Health Authority and the ntnu and the liaison committee of St Olav's Hospital Trust and the faculty of

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
2012. REF ID: SORGJERD 2012		three health surveys performed in 1984-1986 (HUNT 1), 1995-1997 (HUNT2) and 2006-2008 (HUNT3). The cases that formed the basis of this analysis were collected from HUNT2 and HUNT3 surveys. Adult population aged >20 years). No age limit was set for LADA. Exclusion criteria: None given	young-onset type 1 diabetes and adult-onset TID. LADA if they were antibody positive and had not been treated with insulin within 12 months of diagnosis. No age limit was set for LADA. type 2 diabetes if GADA-negative and had not been treated with insulin within 12 months of diagnosis. Comparison of clinical characteristics in HUNT2 for LADA patients who participated both in HUNT2 and HUNT3 and who became either antibody-negative or stayed antibody-positive at HUNT3			HUNT3) as well as for ZnT8A. Serum samples from HUNT2 were used to analyse antibodies in cases classified as LADA and type 1 diabetes inn HUNT3 but with no diagnosis of diabetes in HUNT2. Cut-offs for positivity Fasting serum C-PEPTIDE: <150 pmol/litre GADA-negative: Ab- index (ai) relative to a standard serum. Lower limit was 0.01 ai; no upper limit was defined. An	and 24 type 1 diabetes incident cases from HUNT3	for all three antibodies. Twenty eight cases out of 59 type 1 diabetes (47%) were already antibody-negative in HUNT2, whereas 31 cases (53%) were antibody-negative in HUNT3. In contrast to LADA, only three cases (6%) with type 1 diabetes who were positive in HUNT2 had lost positivity in HUNT3. Comparing LADA patients who became antibody-negative with those with type 2 diabetes: LADA patients had less preserved C-peptide levels compared with those with type 2 diabetes (median [min-max]: 492 [30-1,354] vs 700.5 [30-2,059]; p=0.009).		Medicine NTNU Risk of bias: n/a
				Antibody-negative, HUNT3 n=26	Antibody-positive, HUNT3 n=18			Ab- HUNT3		
								C-peptide (pmol/litre)	492 (30-1,384)	
								GADA titre (ai)	0.11 (0.08-0.46)	
			Sex (male), %	46.2 (12)	55.6 (10)			IA-2A titre (ai)	<0.01 (<0.01-0.07)	

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
			(n)			index of ≥ 0.08 antibody index (ai) was considered positive. IA-2A+: A value of ≥ 0.11 ai was considered positive (method range, 0.01-3.00 ai). ZnT8A: A value of >0.08 ai was considered positive (method range >0.01ai)				
			Age at onset, (years)	53.5 (42-75)	44.5 (21-60)			ZnT8A titre (ai)	0.01 (<0.01-0.04)	
			Duration of diabetes (years)	7.5 (1-20)	8.0 (1-43)			Ab+ HUNT3		
								C-peptide (pmol/litre)	118.5 (30-588)	
								GADA titre (ai)	0.51 (0.07-2.43)	
			Clinical characteristics of incident LADA cases from HUNT3 who were either antibody-negative or antibody-positive in HUNT2.					IA-2A titre (ai)	0.01 (<0.01-0.93)	
								ZnT8A titre (ai)	0.01 (<0.01-0.93)	
				Antibody-negative n=10	Antibody-positive n=21			LADA Ab-		
								C-peptide (pmol/litre)	986 (290-2,144)	
			Sex (male), % (n)	50 (5)	52.4 (11)			GADA titre (ai)	0.12 (0.08-1.09)	
								IA-2A titre (ai)	0.018 (<0.01-0.06)	
			Age at onset, (years)	70 (57-80)	55 (31-79)			ZnT8A titre (ai)	<0.01 (<0.01-0.18)	
								LADA Ab+		
								C-peptide (pmol/litre	587 (48-1496)	

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
								)		
								GADA titre (ai)	1.17 (0.1-2.09)	
								IA-2A titre (ai)	0.02 (<0.01 to >3.0)	
								ZnT8A titre (ai)	0.01 (<0.01-0.46)	

Table 20: WILMOT 2013 (309)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
H. Wilmot-Roussel, D. J. Levy, C. Carette, S. Caillat-Zucman, C. Boitard, J. Timsit, and D. Dubois-Laforgue. Factors associated with the presence of glutamic acid decarboxylase and islet antigen-2 autoantibodies in patients with long-standing	Observational : cross-sectional France	n=430 Inclusion criteria: type 1 diabetes At least 10 years duration type 1 diabetes diagnosis: age <20 years, and/or presence of ketosis, and/or presence of autoAbs at onset of diabetes, and strict insulin	Type 1 diabetes adults DIABETES TYPE: type 1 diabetes		Type 1 diabetes: GAD IA-2 Cut-offs for positivity Not mentioned.	n/a	Type 1 diabetes adults		Funding: None mentioned Risk of bias: n/a no missing data retrospect data collection consecutive patients in the centre
			Type 1 diabetes adults n=92				No Ab+	n=189 (44%)	
							1 Ab+ (GAD+ or IA-2+)	n=180 (42%)	
							2 Ab+ (GAD+ and IA-2+)	n=61 (14%)	
							≥1 Ab+	n=241 (56%)	
			Age median (range)	33 (18 - 83) years			Among patients with a single detected AB+, GAD was SS more prevalent than IA-2 (71% vs 29%), p<0.0001		
			Male	n=206					
			Disease	19 (10 -					

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
type 1 diabetes. Diabetes Metab. 39 (3):244-249, 2013. REF ID: WILMOT 2013		dependency from onset. Exclusion criteria: None given	duration, years, median (range)	65)					
			Age at diagnosis, median (range)	12 (1 – 70) years					
			HbA1c %, median (range)	7.9 (4.8 – 15.8)					
			Drop-outs/missing data: none						

Table 21: ZAMPETTI 2012A (310)

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
S Zampetti, M Capizzi, M Spoletini, G Campagna, G Leto, L Cipolloni, C Tiberti, E Bosi, A Falorni, R Buzzetti, and NIRAD Study Group. GADA titre-related risk for organ-specific autoimmunity in LADA subjects	Observational: cross-sectional study Italy (NIRAD cohort) LADA patients	Total n=686 n=236 LADA n=450 type 2 diabetes Inclusion criteria: Exclusion criteria: None given	ADULTS DIABETES TYPE: LADA type 2 diabetes			LADA: GAD IA-2 ZnT8 type 2 diabetes: GAD IA-2 ZnT8 Cut-offs for positivity	n/a	LADA		Funding: NovoNordisk, and ONLUS of Societa Italiana di Diabetologia. Risk of bias: n/a no missing data
				LADA n=236	type 2 diabetes n=450			High GADA titre	n=116	
								Low GADA titre	n=120	
								IA-2	n=98 (42%)	
								ZnT8	n=44 (32%)	
			Age at onset, years (SD)	50.4 (12.9)	51.6 (10.8)			type 2 diabetes		
								IA-2	13 (2.9%)	
			Male	n=123	n=234			ZnT8	7 (1.6%)	

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
subdivided according to gender (NIRAD study 6). J.Clin.Endocrinol. Metab. 97 (10):3759-3765, 2012. REF ID: ZAMPETTI 2012A	were diagnosed based on the presence of GADA markers and so the useful data for this study is the titres of the markers					IA-2+: not reported ZnT8+: not reported GADA+: 99th percentile of control subjects; low titre = ≤32 a.u.; high titre = >32 a.u. (32 a.u. = 300 WHO units)				

Table 22: HILLMAN 2009 (4)

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
M. Hillman, C. Torn, M. Landin-Olsson, and DISS study group. The glutamic acid decarboxylase 65 immunoglob	Observational study (prospective case series). Participants recruited from a study in a defined area in southern Sweden.	Total n=83 TID: n=40 LADA: n=43 Inclusion criteria: LADA: newly diagnosed	Adult with: Adult onset type 1 diabetes LADA Clinical data of the subject at onset and C-peptide level 3 years after clinical onset.			Non-fasting C-peptide. Total GADA GADA IgG subclasses (IgG1, IgG2, IgG3, and IgG4). GADA IgM Cut-offs for positivity	Prospective data obtained (HUNT2 to HUNT3; 10-13 years follow-up) on 44 LADA, 59 type 1	IgM and IgG subclasses in type 1 diabetes SS decrease of mean rank in GADA levels (IgG1, IgG2, IgG3 and IgG4 and IgM levels). The decreasing trend was NS in total GADA, even though the pattern was similar to the IgG1 subclass level.	Funding: The Swedish Medical Research Council and funds from Region Skane
			Median (min-	TIDM (n=40)	LADA (n=43)			IgM and IgG subclasses in LADA: SS decrease in GADA IgM levels 3 years after clinical onset, but no decrease	

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
ulin G subclass profile differs between adult-onset type 1 diabetes and latent autoimmune diabetes in adults (LADA) up to 3 years after clinical onset. Clin.Exp.Immunol. 157 (2):255-260, 2009. REF ID: HILLMAN 2009		diabetes. fulfilling the diagnostic criteria for LADA. Age < 30 years Classified phenotypically as type 2 diabetes Positivity for GADA Without insulin treatment for at least 6 months after clinical onset. TID: Adult onset patients (>18 years). Initiated on insulin treatment at diagnosis Classified clinically as type 1 diabetes Exclusion criteria:	max)			Non-fasting C-PEPTIDE: Reference interval was 0.25-1.0 nmol/litre and detection limit was 0.13 nmol/litre. Total GADA: GADA IgG subclasses (IgG1, IgG2, IgG3, and IgG4). GADA IgM	diabetes and 302 type 2 diabetes cases from HUNT2 and 31 LADA and 24 type 1 diabetes incident cases from HUNT3	in mean rank of any GADA IgG subclasses or total GADA.		Risk of bias: n/a
			Gender (male/female)	26/14	23/20			Comparison of levels between the groups: LADA group SS >IgG3 and IgG4 at clinical onset vs. type 1 diabetes. The diff. between the groups increased further with longer duration for the IgG3 subclass, while the IgG4 subclass maintained approximately the same diff. between the groups. A SS diff. in levels of IgG2 was seen after a year and sustained up to 3 years after diagnosis.		
			Age at clinical onset, (years)	28 (18-65)	36 (30-79)					
			BMI at clinical onset (kg/m2)	20.9 (15.2-25.4)	25.6 (18.7-46.6)			All the GADA IgG subclass levels decreased in the group of type 1 diabetes over time GADA was more sustained in LADA patients over time		
								C-peptide levels in type 1 diabetes and LADA: C-peptide levels were SS lower in type 1 diabetes vs. LADA at clinical onset and after 3 years. Only LADA showed SS decrease over time.		
								Type 1 diabetes		
								C-pep (onset); nmol/litre	0.22 (0.10-0.45)	
								C-pep (3 years);	0.12 (0.10-1.10)	

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
		None given				nmol/litre		
						LADA		
						C-pep (onset); nmol/litre	0.58 (0.38-2.80)	
						C-pep (3 years); nmol/litre	0.44 (0.1-2.90)	

Table 23: MCDONALD 2011 (85)

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
T.McDonald, K. Colclough, R. Brown, B. Shields, M. Shepherd, P. Bingley, A. Williams, A. Hattersley, and Sian Ellard. Islet autoantibodies can discriminate maturity-onset diabetes of the young (MODY) from Type 1 diabetes. Diabet.Med. 28 (9):1028-1033, 2011.	Observational: cross-sectional study UK study	Total n=616 n=98 type 1 diabetes – but adults and adolescents n=508 MODY Inclusion criteria: Clinical history of diabetes HbA1c <6.0% MODY	ADULTS DIABETES TYPE: type 1 diabetes MODY			Type 1 diabetes: GAD IA-2 MODY: GAD IA-2 Cut-offs for positivity GAD+: 64 WHO units/ml (99th percentile)	n/a	Type 1 diabetes		Funding: None mentioned Risk of bias: n/a
				Type 1 diabetes n=98	MODY n=508			GAD+	24/98 (24.5%)	
								IA-2+	19/98 (94.5%)	
								GAD+ and/or IA-2+	80/98 (82%)	
								GAD+ and IA-2+	37/98 (37.8%)	
			Age, years, median (IQR)	15 (12-25)	36 (18-50)			MODY		
								GAD+	5 (1%)	
								IA-2+	0 (0%)	
			Duration of diabetes, years, median (IQR)	< 6 months	9 (4-25)			GAD+ and/or IA-2+	5/508 (1%)	

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
REF ID: MCDONALD 2011		diagnosis by genetic testing type 1 diabetes diagnosis in last 6 months Exclusion criteria: None given				IA-2+: 15 WHO units/ml (99th percentile; lowest calibrator)				

Table 24: SZEPIETOWSKA 2012 (18)

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
B Szepietowska, A Glebocka, U Puch, M Gorska, and M Szelachowska. Latent autoimmune diabetes in adults in a population-based	Observational: cross-sectional study Polish study	Total n=205 n=19 LADA n=186 type 2 diabetes Inclusion criteria: Age 20-65 years Primary care physician and diabetologists	ADULTS DIABETES TYPE: LADA type 2 diabetes			LADA: fC-PEPTIDE GAD type 2 diabetes: fC-PEPTIDE GAD Cut-offs for positivity	n/a	LADA		Funding: Medical University of Bialystok Risk of bias: n/a
				LADA n=19	type 2 diabetes n=186			fasting C-PEPTIDE, pmol/litre (SD)	126.4 (127.9)	
								GAD+	12/19 (63%)	
								type 2 diabetes		
			Age at diagnosis, years (SD)	48.5 (9.4)	54.8 (10.6)			fasting C-PEPTIDE, pmol/litre (SD)	446.3 (592.2)	
								GAD+	2/186 (1%)	

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
cohort of Polish patients with newly diagnosed diabetes mellitus. Arch.Med.Sci. 8 (3):491-495, 2012. REF ID: SZEPIETOWSKA 2012		identified diabetes cases during the study period Exclusion criteria: None given	M/F %	49/51	55/45	C-PEPTIDE+ (fasting): specificity 88%, sensitivity: 0.01 pmol/ml GAD+: >1 U/ml			
			HbA1c, % (SD)	7.9 (3.1)	7.2 (1.7)				

Table 25: DAVIS 2003 (91)

Reference	Study type	Number of patients	Patient characteristics				Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
T. M. E. Davis, Z. Mehta, I. R. Mackay, C. A. Cull, D. G. Bruce, S. Fida, M. J. Rowley, and R. R. Holman.	Observational: cross-sectional study patients from 2 studies (FDS and UKPDS)	Total n=879 FDS study n=119 type 1 diabetes n=427 type 2 diabetes UKPDS study n=333 type 2 diabetes Inclusion criteria: FDS study	ADULTS DIABETES TYPE: type 1 diabetes type 2 diabetes				Type 1 diabetes (FDS): GAD IA-2/ ICA512 type 2 diabetes (FDS):	n/a	Type 1 diabetes (FDS)		
									GAD+	49/119 (41%)	Funding: Bayer Corp., USA
									IA-2 (ICA512)+	21/119 (18%)	
				FDS study		UKPDS			type 2 diabetes (FDS)		Risk of bias: n/a
				Type 1 diabetes	type 2 diabetes	type 2 diabetes			GAD+	17/427 (4%)	

Reference	Study type	Number of patients	Patient characteristics				Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
Autoantibodies to the islet cell antigen SOX-13 are associated with duration but not type of diabetes. Diabet.Med. 20 (3):198-204, 2003. REF ID: DAVIS 2003	Europe (FDS) and UK (UKPDS)	Diabetic patients from one region Taken subset of type 1 diabetes and type 2 diabetes from this. Type 1 diabetes with baseline serum sample available type 2 diabetes random 33% subset UKPDS study 25-65 years type 2 diabetes without significant vascular complications or other illness Subset: random stratified selection to obtain equal no's in the 4 age groups between 25-65, ratio 1:2 for patients GAD+ and/or ICA+ relative to patients Ab negative, and half of all patients requiring insulin treatment within 1st 6 years of diagnosis Exclusion criteria: None given		n=119	n=427	n=333	GAD IA-2/ ICA512 type 2 diabetes (UKPDS): ICA GAD IA-2/ ICA512 Cut-offs for positivity Not given				
			Age, years (SD)	42.2 (15.6)	64.5 (11.1)	47.7 (10.0)			IA-2 (ICA512)+	1/427 (0.2%)	
									type 2 diabetes (UKPDS)		
			M/F %	43/57	57/43	56/44			ICA	88/333 (26%)	
									GAD+	88/333 (26%)	
			HbA1c, % median (IQR)	8.6 (6.8-10.7)	7.7 (6.2-9.6)	7.1 (5.5-9.2)			IA-2 (ICA512)+	26/333 (8%)	
			Disease duration, years, median (IQR)	7.4 (1.8-30.4)	4.3 (1.3-14.7)	0.26 (0.23-0.31)					

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments

Table 26: YANG 2008 (107)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes (baseline)	Comments
L. Yang, Z. G. Zhou, S. Z. Tan, G. Huang, P. Jin, X. Yan, X. Li, H. Peng, and W. Hagopian. Carboxypeptidase-H autoantibodies differentiate a more latent subset of autoimmune diabetes from phenotypic type 2 diabetes among Chinese adults. Ann.N.Y.Acad.Sci. 1150:263-266, 2008. REF ID: YANG 2008	Observational: cross-sectional study and prospective Chinese study	Total n=1710 n=209 type 1 diabetes n=1296 type 2 diabetes n=205 healthy controls Inclusion criteria: patients with phenotypic type 2 diabetes and classic type 1 diabetes and health controls	ADULTS DIABETES TYPE: type 1 diabetes type 2 diabetes Type 1 diabetes n=209 / type 2 diabetes n=1296 Age, years (SD): Adults / Adults M/F %: Not given HbA1c, % (SD): Not given	Type 1 diabetes: GAD type 2 diabetes: fC-PEPTIDE 2hrC-PEPTIDE GAD Cut-offs for positivity C-PEPTIDE+ (fasting): not given GAD+: 0.052 (99.5% upper limit)	3 years but cannot use data (in patients with fC-PEPTIDE >250 pmol/litre)	Type 1 diabetes GAD+: 11/209 (5.3%) type 2 diabetes GAD+: 117/1296 (9%)	Funding: National Natural Science Foundation of China; Eli Lilly Asia, Doctorate Foundation of National Ministry of Education Risk of bias: n/a

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes (baseline)	Comments
		Exclusion criteria: None given					

Table 27: CERNA 2003 (34)

Reference	Study type	Number of patients	Patient characteristics				Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
M. Cerna, P. Novota, K. Kolostova, P. Cejkova, E. Zdarsky, D. Novakova, P. Kucera, J. Novak, and M. Andel. HLA in Czech adult patients with autoimmune diabetes mellitus: comparison with Czech children with type 1 diabetes and patients with type 2 diabetes.	Observational: cross-sectional study Czech republic study patients were diagnosed based on the presence of markers and so the useful data for this study is the titres of the markers	Total n=281 n=80 type 1 diabetes n=70 LADA n=131 type 2 diabetes Inclusion criteria: Diagnosis of diabetes after 35 years of age F-C-	ADULTS DIABETES TYPE: LADA type 1 diabetes type 2 diabetes				LADA: fC-PEPTIDE GAD IA-2 type 1 diabetes: fC-PEPTIDE GAD IA-2 type 2 diabetes: fC-PEPTIDE GAD IA-2 Cut-offs for positivity	n/a	Type 1 diabetes		Funding: Ministry of Education, Youth and Sports of the Czech republic Risk of bias: n/a
									fC-PEPTIDE, % and mean (range), pmol/litre	100% 63 (4-197)	
									GAD, % and mean (range) ng/mL	50% 193 (3-3000)	
									IA-2, %	15%	
									LADA		
			Age, at disease onset, years mean (range)	Type 1 diabetes n=80	LADA n=70	type 2 diabetes n=131			fC-PEPTIDE, % and mean (range), pmol/litre	100% 609 (51-2800)	
									GAD, % and mean (range) ng/mL	100% 379 (210-	

Eur.J.Immunogenet. 30 (6):401-407, 2003. REF ID: CERNA 2003		PEPTIDE, GAD and IA-2 Abs measured at time of investigation Exclusion criteria: None given					C-PEPTIDE+ (fasting): ≥200 pmol/litre GAD+: ≥50 ng/mL IA-2+: ≥0.9 U/mL			1753)	
			M/F %	39/61	43/57	42/58			IA-2, %	11%	
									type 2 diabetes		
			Disease duration, years, mean (range)	16 (4-27)	14 (4-29)	13 (1-22)			fC-PEPTIDE, % and mean (range), pmol/litre	100% 772 (1-50)	
									GAD, % and mean (range) ng/mL	0% 8 (202-3370)	
									IA-2, %	Not given	

Table 28: YDX STUDY: THANABALASINGHAM 2012 (43)

Reference	Study type	Number of patients	Patient characteristics				Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
G Thanabalasingham, A Pal, MP. Selwood, C Dudley, K Fisher, PJ. Bingley, S Ellard, AJ. Farmer, MI. McCarthy, and KR. Owen. Systematic assessment of	Observational: cross-sectional study 12 centres, UK	Total n=569 n= 247 type 1 diabetes n=322 type 2 diabetes (n=14 MODY from the 2 groups above)	ADULTS DIABETES TYPE: MODY (taken from the type 1 diabetes and type 2 diabetes groups) Type 1 diabetes type 2 diabetes				MODY: random C-PEPTIDE GAD Type 1 diabetes: rC-PEPTIDE GAD type 2 diabetes: rC-PEPTIDE	n/a	MODY		Funding: NIHR, Diabetes UK, European Community and Oxford Hospitals charitable fund. Risk of bias: n/a
				MODY n=14/569	Type 1 diabetes n=247	type 2 diabetes n=277 (45 re-			rC-PEPTIDE, % and mean (95% CI), nmol/litre	100% 0.49 (0.17-0.81)	
									GAD+, N (%)	3/14 (21%)	
									Type 1 diabetes		

Reference	Study type	Number of patients	Patient characteristics				Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
etiology in adults with a clinical diagnosis of young-onset type 2 diabetes is a successful strategy for identifying maturity-onset diabetes of the young. Diabetes Care 35 (6):1206-1212, 2012. REF ID: THANABALASINGHAM 2012		Inclusion criteria: Diagnosis of diabetes up to 45 years of age Currently aged ≥18 years Clinical diagnosis of type 1 diabetes or type 2 diabetes MODY diagnosis from the type 1 diabetes and type 2 diabetes groups by genetic testing Exclusion criteria:				classed as LADA)	GAD Cut-offs for positivity C-PEPTIDE+ (random): ≥0.2 nmol/litre GAD+: >14 WHO units/mL				
			Age, at disease onset, years mean (95% CI)	25.5 (20.3-30.7)	23.5 (22.3-24.8)	36.8 (35.9-37.7)			rC-PEPTIDE mean (range), nmol/litre	0.08 (0.05-0.11)	
									GAD, %	58.7%	
			M/F %	36/64	54/46	61/39			type 2 diabetes		
									rC-PEPTIDE, % and mean (range), nmol/litre	100% 0.76 (0.70-0.83)	
			Disease duration, years, mean (95% CI)	18 (9-26.6)	12.5 (11.9-13.1)	14.4 (13.1-15.8)					
									GAD, %	n=277 GAD- and n=45 GAD+ (GAD+ re-classified d as LADA)	

Reference	Study type	Number of patients	Patient characteristics				Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
		None given									

Table 29: HOSSZU 2003 (12)

Reference	Study type	Number of patients	Patient characteristics				Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
N Hosszufalusi, A Vatay, K Rajczy, Z Prohaszka, E Pozsonyi, L Horvath, A Grosz, L Gero, L Madacsy, L Romics, I Karadi, G Fust, and P Panczel. Similar genetic features and different islet cell autoantibody pattern of	Observational: cross-sectional study Hungarian study	Total n=301 n= 54 LADA n= 57 type 1 diabetes n=190 type 2 diabetes Inclusion criteria: LADA, type 1 diabetes or type 2 diabetes Disease onset >25 years of age (adult onset) LADA diagnosis if onset >35	ADULTS DIABETES TYPE: LADA Type 1 diabetes type 2 diabetes				LADA: fC-PEPTIDE GAD IA-2A ICA Type 1 diabetes: fC-PEPTIDE GAD IA-2A ICA type 2 diabetes: fC-PEPTIDE GAD IA-2A ICA	n/a	LADA		Funding: Not mentioned
									fC-PEPTIDE at onset, nmol/litre, median (IQR)	0.53 (0.24-1.40)	
									ICA+, %	33	
									GADA+, %	26	
									IA-2A+, %	0	
									ICA+GADA+, %	22	Risk of bias: n/a
									ICA+IA-2+, %	0	
			Age, years median (IQR)	59.0 (47.5-67.0)	44.5 (34.0-53.0)	63.0 (53.0-72.0)			GADA + IA-2+, %	2	
									ICA+GADA+IA2+, %	17	
									Antibody - , %	0	
			M/F %	46/54	53/47	54/46			Type 1 diabetes (adult onset) – similar values for child onset		
			Disease duration,	4.0 (1.0-	0.1 (0.1-	8.0 (3.0-			fC-PEPTIDE at onset, nmol/litre,	0.46 (0.24-	

Reference	Study type	Number of patients	Patient characteristics				Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
latent autoimmune diabetes in adults (LADA) compared with adult-onset type 1 diabetes with rapid progression. Diabetes Care 26 (2):452-457, 2003. REF ID: HOSSZU 2003		years, any circulating ICA was detected (ICA, GADA or IA-2) and insulin treatment not indicated in 1st 6 months after diagnosis. Exclusion criteria: None given	years, median (IQR)	9.5)	4.5)	15.5)	Cut-offs for positivity C-PEPTIDE+ (fasting): not given ICA+: >10 JDA units/mL GAD+: >1.2 units/mL IA-2+: >1.3 units/mL		median (IQR)	1.05)	
									ICA+, %	14	
									GADA+, %	9	
									IA-2A+, %	0	
									ICA+GADA+, %	19	
									ICA+IA-2+, %	2	
									GADA + IA-2+, %	3	
									ICA+GADA+IA2+, %	32	
									Antibody - , %	21	
									type 2 diabetes		
									fC-PEPTIDE at onset, nmol/litre, median (IQR)	1.23 (0.70-2.55)	
									ICA+, %	3	
									GADA+, %	2	
									IA-2A+, %	0	
									ICA+GADA+, %	0	
									ICA+IA-2+, %	0	
									GADA + IA-2+, %	0	
									ICA+GADA+IA2+, %	0	
									Antibody - , %	95	

Table 30: DAVIES 2008 (88)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
H. Davies, S. Brophy, A. Fielding, P. Bingley, M. Chandler, I. Hilldrup, C. Brooks, and R. Williams. Latent autoimmune diabetes in adults (LADA) in South Wales: incidence and characterization. Diabet.Med. 25 (11):1354-1357, 2008. REF ID: DAVIES 2008	Observational: cross-sectional study 32 centres, UK	Total n=597 (n=387 tested for all markers) n=14 LADA n=373 (387-14) type 2 diabetes Inclusion criteria: Newly diagnosed type 2 diabetes Age >18 years Free of insulin treatment for at least 1 month from diagnosis General practice patient records	ADULTS DIABETES TYPE: LADA type 2 diabetes LADA n=14 /387 tested type 2 diabetes n=646 Age, years (SD): 54.1 (17.4); 60.8 (12.0) M/F %: 50/50; 60/40	LADA: fC-PEPTIDE GADA IA-2 type 2 diabetes: fC-PEPTIDE GADA IA-2 Cut-offs for positivity C-PEPTIDE+ (fasting): not mentioned GADA+: sensitivity 84%, specificity: 92% (≥14 WHO units/mL)?? IA-2+: sensitivity 58%, spec: 98%	n/a	LADA fasting C-PEPTIDE, ng/ml, mean (SD): 3.4 (2.6) GADA+: 100% IA-2, WHO units, mean (SD): 163.9 (441.2) type 2 diabetes fasting C-PEPTIDE, ng/ml, mean (SD): 4.6 (3.0) GADA+: 0% IA-2, WHO units, mean (SD): 2.2 (0.83)	Funding: BUPA foundation Risk of bias: n/a

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
		LADA defined as GADA+ ≥14 WHO units/mL Exclusion criteria: Pregnant Secondary diabetes					

Table 31: HAMAGUCHI 2004 (125)

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
K Hamaguchi, A Kimura, Y Kusuda, T Yamashita, M Yasunami, M Takahasi, N Abe, and H Yoshimatsu. Clinical and genetic characteristics of GAD-antibody positive patients initially diagnosed as	Observational: cross-sectional study Single centre, Japan	Total n=835 type 2 diabetes (screened for GAD+/-) n=55 were GAD+ and n=780 were GAD-. n=137 of the GAD- patients were assigned randomly to be the AGD- controls.	ADULTS DIABETES TYPE: type 2 diabetes			type 2 diabetes: GADA Urinary C-PEPTIDE Cut-offs for positivity GAD+ : >5 Units	n/a	type 2 diabetes GAD+		Funding: Grants-in-Aid for Scientific Research and the Japan Society for the Promotion of Science, Japan. Risk of bias:
				type 2 diabetes				GADA+	55/835 (6.6%)	
				GAD+ n=55	GAD- n=137			GAD titre, U/ml (SD; range)	2,650 (18730; 5.0-139,000)	
								Urinary C-peptide, µg/day (SD)	47.8 (48.9)	
			Age, years (SD)	60.2 (12.3)	62.9 (13.2)			type 2 diabetes GAD-		
			M/F, %	51/49	51/49			Urinary C-peptide,	58.1 (49.9)	
			Age at	47.7	50.0					

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
having type 2 diabetes. Diabetes Res.Clin.Pract. 66 (2):163-171, 2004. REF ID: HAMAGUCHI 2004		Inclusion criteria: type 2 diabetes Admitted to the clinic Age of onset >30 years Not require insulin treatment for at least 6 months after diagnosis Exclusion criteria: None given	onset of diabetes, years (SD)	(11.4)	(12.5)			µg/day (SD)		n/a
			Disease duration, years, (SD)	12.8 (8.6)	13.3 (7.0)					

Table 32: BOTTAZZO 2005 (41)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
G. F. Bottazzo, E. Bosi, C. A. Cull, E. Bonifacio, M. Locatelli, P. Zimmet, I.	Observational: cross-sectional study UK study	Total n=4169 type 2 diabetes (n=2556 measured all 3 Abs) Inclusion criteria:	ADULTS DIABETES TYPE: type 2 diabetes type 2 diabetes (n=4169	type 2 diabetes: GADA IA-2A IA-2β ICA	n/a	type 2 diabetes All patients (n=4169) IA-2A+ IA-2 β+ Only IA-2A+ Only IA-2 β+	 93 (2.2%) 58 (1.4%) 42 (1%) 7 (0.2%)	Funding: UK MRC; British Diabetic Association; British Heart Foundation; UK DH;

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
R. Mackay, and R. R. Holman. IA-2 antibody prevalence and risk assessment of early insulin requirement in subjects presenting with type 2 diabetes (UKPDS 71). Diabetologia 48 (4):703-708, 2005. REF ID: BOTTAZZO 2005	UKPDS patients	type 2 diabetes (new diagnosis) Subset of UKPDS study (4169/5102) Caucasians for whom IA2A and IA-2β were avail Age 25-65 years 2 x fasting plasma glucose values >6.0 mmol/litre Exclusion criteria: Severe vascular disease, renal failure accelerated HT proliferative/pre-proliferative retinopathy Other life-threatening disease Illness requiring systemic steroids Job precludes insulin treatment Ketonuria >3 mmol/litre (that is, suggestive of type 1 diabetes)	IA-2A status	+ n=93	- n=4076	Cut-offs for positivity IA-2A+: 1 Unit IA-2 β+: 1 Unit GADA+: 20 reference units (JDF) ICA+: 5 JDF units		IA-2A+ and IA-2 β+	51 (1.2%)	Italian MoH; National Eye Institute; National Institute of Digestive; Diabetes and Kidney Disease in the NIH (USA); Novo-Nordisk; Bayer; Bristol Myers Squibb; Hoechst; Lilly, Lipha; Farmitalia Carlo Erba. Risk of bias: n/a
			M/F %	58/42	58/42			type 2 diabetes patients measured for all 3 Abs (n=2556)		
			Age, years (SD)	44 (11)	53 (9)			GADA+	257 (10%)	
								ICA+	141 (5.5%)	
								IA-2A+	57 (2.2%)	
								2 or 3 Abs +	96 (3.8%)	
								type 2 diabetes (n=268) Required insulin by 6 years & all 3 Abs measured		
								IA-2A+	42/57 (74%)	
								ICA+	75/141 (53%)	
								GADA+	125/257 (49%)	
								IA-2A+/ICA+/GADA+	35/43 (81%)	
								IA-2A+ and ICA+	2/2 (100%)	
								IA-2A+ and GADA+	3/6 (50%)	
								Only IA-2A+	2/6 (33%)	
								ICA+ and GADA+	34/45 (76%)	
								Only ICA+	4/51 (8%)	
								Only GADA+	53/163 (33%)	
								IA-2A &/or ICA &/or GADA	133/316 (42%)	
								None+	135/2240 (6%)	

Table 33: CASTLEDEN 2006 (92)

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
H. Castleden, B. Shields, P. J. Bingley, A. J. K. Williams, M. Sampson, M. Walker, J. M. Gibson, M. I. McCarthy, G. A. Hitman, J. C. Levy, A. T. Hattersley, B. Vaidya, and E. R. Pearson. GAD antibodies in probands and their relatives in a cohort clinically selected for Type 2 diabetes. Diabet.Med. 23 (8):834-838, 2006. REF ID: CASTLEDEN 2006	Observational: cross-sectional study 7 centres, UK Recruited through primary care or hospital diabetes clinics into the Diabetes UK/MRC familial and case type 2 diabetes genetic resource collection	Total n=2059 type 2 diabetes Inclusion criteria: type 2 diabetes 27-84 years On pharma treatment for diabetes or had biochem confirmation of diabetes. To reduce the recruitment of type 1 diabetes, MODY and other subtypes, all subjects were diagnosed at >25 years of age and did not progress to insulin for at least 1 year after diagnosis and had no first degree relatives with type 1 diabetes. All were UK or Irish or European Caucasian origin Exclusion criteria:	ADULTS DIABETES TYPE: type 2 diabetes			type 2 diabetes: GAD Cut-offs for positivity GAD+ : 30 WHO Units	n/a	type 2 diabetes		Funding: Aspects funded by Diabetes UK and UK MRC. Risk of bias: n/a
				type 2 diabetes				GADA+ %	136/2059 (7%)	
				GAD+ n=136	GAD- n=1876			No difference in GAD+ titre level by age of diagnosis		
			Age, years (SD)	57 (10.2)	58 (9.7)					
			M/F, %	54/46	60/40					
			Age at onset of diabetes, years (SD)	47 (9)	49 (8.6)					

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
		None given					

Table 34: TRABUCCI 2012 (134)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
A Trabucchi, NI. Faccinetti, LL. Guerra, F M. P, Gustavo D. Frechtel, E Poskus, and SN. Valdez. Detection and characterization of ZnT8 autoantibodies could help to screen latent autoimmune diabetes in adult-onset patients with type 2 phenotype. Autoimmunity 45 (2):137-142, 2012. REF ID:	Observational: cross-sectional study and prospective 1 Centre, Argentina	Total n=271 type 2 diabetes Inclusion criteria: type 2 diabetes (Adult onset) Age at diagnosis >30 years Without insulin treatment for the first year of disease Exclusion criteria: None given	ADULTS DIABETES TYPE: type 2 diabetes (adult onset) type 2 diabetes n=271 Age range: 30-84 Age at diagnosis diabetes, years (SD): 53.4 (10.9) M/F %: 62/48	type 2 diabetes: GADA IA-2A ZnT8A Cut-offs for positivity ZnT8A+: SD score >3 GADA+: SD score but cut-off not given IA-2A+: SD score but cut-off not given	6 years but cannot used data n=101 patients followed for 6 years for insulin requirement, but measurement of Abs not given.	type 2 diabetes GADA+: 21 (7.7%) IA-2A+: 3 (1.1%) ZnT8A+: 19 (7.0%) GADA+/IA2A+: 2 (0.7%) GADA+ /ZnT8A+: 4 (1.5%) IA2A+/ZnT8A+: 1 (0.4%) GADA+/ IA2A+/ZnT8A+: 3 (1.1%) None +: 211 (78%)	Funding: Grants from Agency for Science and Technology Promotion, National research Council, and University of Buenos Aires, Argentina. Risk of bias: n/a

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
TRABUCCI 2012							

Table 35: DESAI 2007 (40) from the UKPDS study, follow-up of Davis 2005

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
M. Desai, C. A. Cull, V. A. Horton, M. R. Christie, E. Bonifacio, V. Lampasona, P. J. Bingley, J. C. Levy, I. R. Mackay, P. Zimmet, R. R. Holman, and A. Clark. GAD autoantibodies and epitope reactivities persist after diagnosis in latent autoimmune diabetes in adults but do not predict disease progression: UKPDS 77. Diabetologia 50 (10):2052-2060, 2007.	Observational: prospective case-series UK study	Total n=242 LADA Inclusion criteria: Subset taken from UKPDS study Subset was LADA patients (all GADA+) and all had plasma samples taken at 0.5, 3 and 6 years after diagnosis, with at least 1 being GADA+. Exclusion criteria: None given	ADULTS DIABETES TYPE: LADA LADA n=242 Age, years (SD): 47 (10.8) M/F %: 53/47	LADA: GADA Cut-offs for positivity GADA+: 15 WHO units/ml	6 years Measured at 0.5, 3 and 6 years	LADA GADA+ patients over time, N (%) Baseline: n=242 (100%) 0.5 years: n=237 (98%) 3 years: n=231 (95%) 6 years: n=237 (98%) LADA GADA titre over time, WHO units/ml; median (IQR) Baseline: - 0.5 years: 331 (134-674) 3 years: 199 (96-318) 6 years: 284 (107-518) Although the median titre rose at 6 years, patients who had high titres at 0.5 years remained high and those that had low titres remained low at 3 and 6 years.	Funding: Diabetes UK Risk of bias: n/a

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
REF ID: DESAI 2007							

Table 36: CHOWTA 2010 (2)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
M. N. Chowta, P. M. Adhikari, N. K. Chowta, A. K. Shenoy, and S. D'Souza. Serum C peptide level and renal function in diabetes mellitus. Indian J.Nephrol. 20 (1):25-28, 2010. REF ID: CHOWTA 2010	Observational: cross-sectional India study	Total n=168 type 2 diabetes Inclusion criteria: type 2 diabetes including newly diagnosed cases Data taken from patients screened for participation in clinical trials on type 2 diabetes >18 years of age Exclusion criteria: None given	ADULTS DIABETES TYPE: type 2 diabetes type 2 diabetes n=168 Age, years: 57.6 M/F %: 46/54 Duration of diabetes, years (SD): 4.3 (0.45)	type 2 diabetes: fC-PEPTIDE Cut-offs for positivity C-PEPTIDE (fasting): Not given	Not mentioned	type 2 diabetes C-peptide titre, nmol/litre (SD) Baseline: 0.97 (0.05) There was a negative correlation between fC-PEPTIDE and duration of diabetes (r= -0.171, p>0.05) Duration of disease was higher in patients with below normal fC-PEPTIDE compared to normal and above normal patients. Indicative of progressive beta cell failure.	Funding: None Risk of bias: n/a

Table 37: MONGE 2004 (115)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
L. Monge, G. Bruno, S. Pinach, G. Grassi, G. Maghenzani, F. Dani, and G. Pagano. A clinically orientated approach increases the efficiency of screening for latent autoimmune diabetes in adults (LADA) in a large clinic-based cohort of patients with diabetes onset over 50 years. Diabet.Med. 21 (5):456-459, 2004. REF ID: MONGE 2004	Observational: cross-sectional study Single centre, Italy	Total n=220 type 2 diabetes (met inclusion criteria) n=70 LADA (32%) n=150 (220-70) type 2 diabetes Inclusion criteria: type 2 diabetes Age of onset >50 years At least one of the following features suggestive of insulin deficiency: i) fasting blood glucose ≥15 mmol/litre and/or HbA1c ≥10% despite adequate	ADULTS DIABETES TYPE: LADA type 2 diabetes	LADA: fC-PEPTIDE GADA ICA type 2 diabetes: fC-PEPTIDE GADA ICA Cut-offs for positivity C-PEPTIDE+ (fasting): normal values 0.36-1.17 nmol/litre GADA65+: >0.9 units/mL ICA+: ≥5 JDF units	n/a	LADA fasting C-PEPTIDE, nmol/ml, mean (SD) GADA+/ICA+ Nmol/ml	 0.53 (0.51) 30/70 (43%) fC-pep = 0.34 (0.28)	Funding: Not mentioned Risk of bias: n/a

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
		compliance to diet and treatment; ii) decreasing body wt ≥10% in previous 3 months despite constant diet; iii) BMI <25 mg/kg. Exclusion criteria: None given					

Table 38: KIM 2007 (14)

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
C. S. Kim, M. K. Song, J. S. Park, M. H. Cho, H. J. Kim, J. S. Nam, E. S. Kang, C. W. Ahn, B. S. Cha, E. G. Lee, S. K. Lim, K. R. Kim, H. C.	Observational: cross-sectional study Single centre, Korea	Total n=233 type 1 diabetes; patients with adult onset were analysed further (n=128) n=35/128 LADA (32%) n=93/128 type 1	ADULTS DIABETES TYPE: LADA Type 1 diabetes acute onset			LADA: fC-PEPTIDE Type 1 diabetes adult onset: fC-PEPTIDE Cut-offs for positivity	n/a	All n=233 Type 1 diabetes patients (child-onset, adult-onset) n=105 child onset n=128 adult onset (n=35 LADA + n=93 acute onset) GADA+ in 59.7% of all type 1 diabetes patients GADA+ in 60% of child-onset type 1 diabetes 35/128 (27%) of adult onset type	Funding: Ministry of Health and Welfare, Korea Risk of bias: n/a
				LADA n=35	Type 1 diabetes acute n=93				
			Age, years	46.4 (13.5)	41.1 (13.8)				

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
Lee, and K. B. Huh. The clinical and immunogenetic characteristics of adult-onset type 1 diabetes mellitus in Korea. Acta Diabetol. 44 (2):45-54, 2007. REF ID: KIM 2007		diabetes Acute onset Inclusion criteria: type 1 diabetes Diagnosed as LADA if were GADA+ (>5 U/ml) and age at onset was >35 years, and did not initially (first 6 months) require insulin treatment. Exclusion criteria: None given	(SD)			C-PEPTIDE+ (fasting): not given GADA+: >1.0 micromole/ml IA-2A+: mean+3SD of the control subjects		1 diabetes patients were LADA. 0/105 (0%) of child onset type 1 diabetes patients were LADA. IA-2A+ in 17.6% of all type 1 diabetes IA-2A+ in 19.8% of child onset IA-2A+ in 15.3% of adult onset		
			Age at onset, years, (SD)	41.3 (13.4)	33.5 (11.3)			LADA		
								fasting C-PEPTIDE, micrograms/litre, mean (SD)	0.83 (0.58)	
			Duration of diabetes, years (SD)	5.1 (2.9)	7.7 (6.1)			Type 1 diabetes acute		
								fasting C-PEPTIDE, micrograms /litre, mean (SD)	0.55 (0.32)	
			M/F %	49/51	39/61					

Table 39: AGGARWAL 2010 (60)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
S. Aggarwal, A. Goel, and A. Jain. Role of C-	Observational: cross-section	Total n=100 type 2 diabetes n=34 suspected LADA n=66 classic type 2	ADULTS DIABETES TYPE: Suspected LADA	Suspected LADA: fC-PEPTIDE Classic type 2	6 months	Suspected LADA fasting C-PEPTIDE, ng/ml		Funding: Not mentioned
						Baseline (SD) n=66	0.39 (0.03)	

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
peptide in identification of patients suspected of having latent autoimmune diabetes in adults (LADA) in north indian type 2 diabetes mellitus population. Intl.J.Pharma Bio Sci. 1 (3), 2010. REF ID: AGGARWAL 2010	al study India study	diabetes Inclusion criteria: type 2 diabetes Age of diagnosis >25 years Initial 6 months of insulin independence. C-peptide <0.7 ng/ml was used to identify suspected LADA patients Exclusion criteria: History of ketoacidosis at time of initial diagnosis Intake of diabetogenic drugs Gestational diabetes Other secondary causes of diabetes	type 2 diabetes			diabetes: fC-PEPTIDE Cut-offs for positivity C-PEPTIDE+ (fasting): not given C-peptide <0.7 ng/ml was used to identify suspected LADA patients		6 months (SD) n=44	0.33 (0.04)	Risk of bias: n/a
				LADA n=34	type 2 diabetes n=66					
			Age, years (SD; range)	Not given						
			Age at diagnosis, years, (SD; range)	Not given				Classic type 2 diabetes fasting C-PEPTIDE, ng/ml		
								Baseline (SD) n=34	1.54 (0.09)	
								6 months (SD) n=29	1.43 (0.01)	
			Duration of diabetes, years (SD; range)	Not given						
			M/F %	33/67	49/51					

Table 40: ZHANG 2012A (98)

Reference	Study type	Number of patients	Patient characteristics				Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
S Zhang, Q Sun, K Feng, Y Fu, O Wang, F Ping, and Y Li. Clinical, biochemical, and immunological characteristics of newly diagnosed nonobese diabetic patients aged 18-45 years in China. J.Diabetes Complications 26 (1):40-43, 2012. REF ID: ZHANG 2012A	Observational: cross-sectional study Single centre, China	Total n=102 diabetics n= 11 LADA n= 70 type 1 diabetes n=21 type 2 diabetes Inclusion criteria: Newly diagnosed diabetes (duration < 3 months) Aged 18-45 years old with BMI <23 kg/m2. Through clinical examination and follow-up they were diagnosed as type 1 diabetes,	ADULTS DIABETES TYPE: LADA Type 1 diabetes type 2 diabetes				LADA: fC-PEPTIDE GADA IA-2A ICA Type 1 diabetes: fC-PEPTIDE GADA IA-2A ICA type 2 diabetes: fC-PEPTIDE GADA IA-2A ICA Cut-offs for positivity Not given	n/a	LADA		Funding: Not mentioned Risk of bias: n/a
									fC-PEPTIDE at presentation, mmol/litre (SD)	16.3 (4.9)	
									fC-PEPTIDE, ng/ml (SD)	0.4 (0.2)	
									GADA+, %	100	
									IA-2A+, %	27.3	
									ICA+, %	36.4	
				LADA n=11	Type 1 diabetes n=70	type 2 diabetes n=21			Type 1 diabetes		
			Age, years mean (SD)	42 (5.1)	25 (6.6)	35 (7.5)			fC-PEPTIDE at presentation, mmol/litre (SD)	20.3 (8.8)	
									fC-PEPTIDE, ng/ml (SD)	0.4 (0.3)	
									GADA+, %	64.3	
			M/F %	55/45	46/54	48/52			IA-2A+, %	30	
									ICA+, %	45.7	
			Age range, % - 18-25 - 26-35 - 36-45	 0 9 81	 56 36 9	 19 29 52			GADA+ only	14.3	
									IA-2A+ only	4.3	
									ICA+ only	7.1	
									GADA+/ICA+	20	
									GADA+/IA-2+	8.6	
									ICA+/IA2+	4.3	
									GADA+/ICA+/IA-2A+	4.3	

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
		type 2 diabetes and LADA. LADA diagnosed if: onset age >30 years, presence of circulating islet autoantibodies, lack of requirement for insulin for at least 6 months after diagnosis. Exclusion criteria: None given				GADA+ and/or ICA+: 75.7 GADA+ and/or IA-2A+: 74.3 Antibody - , %: 18.6 Abs by age-group, years % 18-25 / 26-35 / 36-45 GADA+: 64.1 / 60.0 / 66.4 ICA+: 61.5 / 29.2 / 16.7 IA-2A+: 38.5 / 20.8 / 16.7 type 2 diabetes fC-PEPTIDE at presentation, mmol/litre (SD): 11.5 (4.5) fC-PEPTIDE, ng/ml (SD): 1.4 (0.7) GADA+, %: 9.5 IA-2A+, %: - ICA+, %: 4.8	

Table 41: HWANGBO 2012 (11)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
Y Hwangbo, J	Observational:	Total n=462 diabetics	ADULTS	LADA:	n/a	LADA	Funding:

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
T Kim, E K Kim, A R Khang, T J Oh, H C Jang, K S Park, S Y Kim, H K Lee, and Y M Cho. Prevalence and clinical characteristics of recently diagnosed type 2 diabetes patients with positive anti-glutamic Acid decarboxylase antibody. Diabetes Metab. 36 (2):136-143, 2012. REF ID: HWANGO 2012	cross-sectional study Single centre, Korea	n= 20 LADA n= 442 type 2 diabetes Inclusion criteria: >20 years of age Diagnosed with diabetes in past 5 years Exclusion criteria: Type 1 diabetes Other diabetes who started insulin therapy within 1 year after diabetes diagnosis History of DKA Pregnant Chronic liver disease Acute infection History of organ transplantation Current chemotherapy for malignancy Other conditions that could affect glucose metabolism	DIABETES TYPE: LADA type 2 diabetes			fC-PEPTIDE GADA type 2 diabetes: fC-PEPTIDE GADA Cut-offs for positivity GADA+: >1.0 U/mL		fC-PEPTIDE, ng/ml (SD)	1.2 (0.8)	Ministry of health and welfare, Republic of Korea. Risk of bias: n/a
				LADA n=20 GAD+	type 2 diabetes n=442 GAD-			GADA+, %	100	
								type 2 diabetes		
								fC-PEPTIDE, ng/ml (SD)	2.0 (1.2)	
								GADA+, %	0	
			Age at study, years mean (SD)	52.3 (14.1)	55.3 (11.6)					
			Age at onset, years, mean (SD)	50.0 (14.4)	53.6 (11.6)					
			Duration of diabetes, years, mean (SD)	2.3 (1.3)	1.7 (1.6)					
			M/F %	60/40	56/44					

Table 42: MAIOLI 2010 (49)

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
M. Maioli, G. M. Pes, G. Delitala, L. Puddu, A. Falorni, F. Tolu, R. Lampis, V. Orru, G. Secchi, A. M. Cicalo, et al. Number of autoantibodies and HLA genotype, more than high titres of glutamic acid decarboxylase autoantibodies, predict insulin dependence in latent autoimmune diabetes of adults. European journal of endocrinology 163 (4):541-549, 2010. REF ID: MAIOLI 2010	Observational: cross-sectional study Multi-centre, Sardinia	Total n=5568 type 2 diabetes later diagnosed as: n= 251 LADA n= 2510 type 2 diabetes (randomly selected from the total recruited) Inclusion criteria: type 2 diabetes 35-70 years of age Diagnosed with diabetes in past 5 years Exclusion criteria: Severe renal or liver disease	ADULTS DIABETES TYPE: LADA type 2 diabetes			LADA: GADA IA-2 type 2 diabetes: GADA Cut-offs for positivity GADA+: Not given (but based on health controls) IA-2A+: Not given (but based on health controls)	n/a	Total type 2 diabetes recruited (n=5568)		Funding: Italian Ministry for University and Research and Region of Sardinia grant. Risk of bias: n/a
				LADA n=251 GAD+	type 2 diabetes n=2510 GAD-			GADA+	4.9%	
								LADA		
								GADA+, %	100	
								IA-2+, %	21	
			Age at study, years mean (SD)	55.2 (11.6)	58.1 (11.9)			type 2 diabetes		
			Age at diagnosis, years, mean (SD)	54.3 (11.2)	57.7 (10.1)			GADA+, %	0	
			M/F %	47/53	86/14					
			Duration of diabetes <8 months to 5 years No evidence of DKA Not had insulin treatment for at least 8 months from diagnosis							

Table 43: VAZIRI 2010 (131)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
F Vaziri-Sani, S Oak, J Radtke, K Lernmark, K Lynch, CD. Agardh, CM. Cilio, AL. Lethagen, E Ortqvist, M Landin-Olsson, C Torn, and CS. Hampe. ZnT8 autoantibody titres in type 1 diabetes patients decline rapidly after clinical onset. Autoimmunity 43 (8):598-606, 2010. REF ID: VAZIRI 2010	Observational: cross-sectional study Single centre, Sweden	Total n=47 LADA Inclusion criteria: LADA of type 2 diabetes GAD65+ Age 30-70 years Taken from those in a clinical trial of GAD65. diagnosis within previous 5 years Controlled blood glucose with diet, oral hypoglycaemic agents, or both, but not with insulin. Exclusion criteria: Women of child-bearing potential	ADULTS DIABETES TYPE: LADA		LADA: ZnT8 GADA Cut-offs for positivity GADA65: index of 0.04 ZnT8+: 10 and 18 U/ml (for T8R and T8W) IA-2A: not given	n/a	LADA		Funding: NIH; American Diabetes Association; EU framework Programme; Swedish Research Council; Swedish Diabetes Association Risk of bias: n/a
				LADA n=47			GADA+	100%	
			Age at onset, years, median (range)	30-70			ZnT8+ (T8R or T8W)	20/47 (42%)	
			Duration of diabetes, months (SD; range)	3 (1-7)					
			M/F %	83/17					

Table 44: LINDHOLM 2004 (135)

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
E Lindholm, B Hallengren, and C D Agardh. Gender differences in GAD antibody-positive diabetes mellitus in relation to age at onset, C-peptide and other endocrine autoimmune diseases. Diabetes.Metab.Res.Rev. 20 (2):158-164, 2004. REF ID: LINDHOLM 2004	Observational: cross-sectional study Swedish study	Total n=4974 diagnosed as: n= 1078 type 1 diabetes (n=803 adults) n= 3730 type 2 diabetes (n=4956) The rest = other types Inclusion criteria: Diabetics from a local diabetes registry Exclusion criteria: Gestational diabetes Impaired Glucose tolerance	ADULTS DIABETES TYPE: Type 1 diabetes type 2 diabetes			Type 1 diabetes: GADA type 2 diabetes: GADA Cut-offs for positivity GADA+: Not given (but based on health controls)	n/a	Type 1 diabetes		Funding: Skane County Council R+D foundation; Lundbergs Medical Research Council; Malmo University Hospital Research funds; Swedish Diabetes Foundation
				Type 1 diabetes n=1078	type 2 diabetes n=3730			GADA+ All adults	407 (51%)	
								GADA+ Age 20-39 years	270/433 (62%)	
								GADA+ Age 40-59 years	112/152 (74%)	
								GADA+ Age ≥60 years	25/30 (83%)	
								type 2 diabetes		
								GADA+	5.8%	
			Age at study, years mean (SD)	All adult ages						Risk of bias: n/a
			Age at diagnosis, years, mean (SD)	Not given for group as a whole						
			M/F %	Not given for group as a whole						

Table 45: RADTKE 2009 (5)

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
MA. Radtke, K Midthjell, T I. L. Nilsen, and V Grill. Heterogeneity of patients with latent autoimmune diabetes in adults: linkage to autoimmunity is apparent only in those with perceived need for insulin treatment: results from the Nord-Trondelag Health (HUNT) study. Diabetes Care 32 (2):245-250, 2009. REF ID: RADTKE 2009	Observational: cross-sectional study Norwegian study HUNT study	Total n=1049 diagnosed as: n= 943 type 2 diabetes n= 106 LADA Inclusion criteria: Type 1 diabetes and LADA Diabetics from the HUNT2 study Aged ≥20 years Those who filled out questionnaires and had blood sampling and information on insulin treatment. Exclusion criteria: type 1 diabetes Other forms of	ADULTS DIABETES TYPE: type 2 diabetes LADA			Type 1 diabetes: fC-PEPTIDE GADA LADA: fC-PEPTIDE GADA Cut-offs for positivity GADA+: Index ≥0.08 (compared to standard serum)	n/a	type 2 diabetes – with insulin (n=203)		Funding: Norwegian Diabetes Association; GSK Norway. Risk of bias: n/a
								f C-PEPTIDE+ pmol/litre (95% CI)	377 (343-416)	
								GADA+, units (SD)	0.01 (0.01)	
								type 2 diabetes – without insulin (n=740)		
				type 2 diabetes n=943	LADA n=106			f C-PEPTIDE+ pmol/litre (95% CI)	787 (749-827)	
								GADA+, units (SD)	0.01 (0.01)	
								LADA with insulin (n=42)		
			Age at onset years, mean (SD)	68 (0.6)	67 (1.6)			f C-PEPTIDE+ pmol/litre (95% CI)	130 (105-160)	
								GADA+, units (SD)	0.54 (0.03)	
			Diabetes duration, years, mean	10.4 (0.4)	11 (1.0)			LADA without insulin (n=64)		
								f C-PEPTIDE+	682 (577-	

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
		diabetes	(SD)					pmol/litre (95% CI)	806)	
			M/F %	51/49	55/45			GADA+, units (SD)	0.29 (0.02)	

Table 46: LEE 2011A (89)

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
S. A. Lee, W. J. Lee, E. H. Kim, J. H. Yu, C. H. Jung, E. H. Koh, M. S. Kim, J. Y. Park, and K. U. Lee. Progression to insulin deficiency in Korean patients with Type 2 diabetes mellitus positive for anti-GAD antibody. Diabet.Med.	Observational: prospective case-series Single centre, South Korea	Total n=174 type 2 diabetes n= 87 GAD+ n= 87 GAD- (age and sex matched to GADA+) Inclusion criteria: type 2 diabetes outpatients ≥25 years of age at diagnosis No history of DKA fC-PEPTIDE	ADULTS DIABETES TYPE: type 2 diabetes (GAD+ and GAD-) patients were recruited specifically for being GADA- and GADA+			type 2 diabetes: C-PEPTIDE GADA Cut-offs for positivity GADA+: ≥25 WHO units/ml (≥1 IU/ml) GADA+ HIGH titre: ≥250 WHO units/ml (≥10 IU/ml)	6 years	type 2 diabetes GADA+		Funding: None mentioned Risk of bias: n/a
								fC-PEPTIDE, nmol/litre (SD)	0.7 (0.1)	
								type 2 diabetes GADA-		
								f C-PEPTIDE+ pmol/litre (SD)	0.7 (0.1)	
				GADA- n=87	GADA+ n=87			OVER TIME fC-PEPTIDE concentrations in the GADA+ and GADA- groups were similar at baseline. In GADA- group fC-PEPTIDE did not change significantly over time In GADA+ group fC-PEPTIDE declined over time and became significantly lower than in the GADA- group at 1 year and thereafter.		
			Age years, mean (SD)	54 (1.3)	54 (1.3)					
			Age at onset years, mean (SD)	48 (1.2)	48 (1.2)					
			Diabetes duration, years, mean (SD)	5.9 (0.8)	6.3 (0.8)					

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
28 (3):319-324, 2011. REF ID: LEE 2011A		≥0.33 nmol/litre Not using insulin 87 patient of the whole pool were GADA+ Randomly selected 87 age and sex-matched GADA- patients from the same pool of patients. Exclusion criteria: None mentioned	GADA (WHO U/mL)	3.9 (0.4)	470 (121.0)			F-C-PEPTIDE concentrations were similar at baseline in high and low-titre GADA subgroups (0.6 and 0.7 nmol/litre respectively) After 3 years fC-PEPTIDE became significantly lower in the HIGH titre subgroup tan the low titre group.	
			GADA (IU/mL)	0.2 (0.1)	18.7 (4.8)				
			M/F %	57/43	57/43				

Table 47: VLAD 2004 (113)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
A. Vlad, V. Serban, Alexandra Sima, R. Timar, and Mihaela Rosu.	Observational: cross-sectional study	Total n=268 type 2 diabetes	ADULTS DIABETES TYPE: type 2 diabetes	type 2 diabetes: C-PEPTIDE GADA	n/a	fC-PEPTIDE		Funding: None mentioned
						LOW titre <0.58 ng/ml	n=20 (7.5%)	
						NORMAL titre 0.58 - 2.7 ng/ml	n=155 (57.8%)	

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
The value of basal C peptide and its relationship with pancreatic autoantibodies in young adults with type 2 diabetes mellitus. Rom.J.Intern.Med. 42 (2):333-341, 2004. REF ID: VLAD 2004	Romanian study	Inclusion criteria: type 2 diabetes Age of onset between 30 to 50 years Duration of diabetes <5 years Exclusion criteria: None mentioned		type 2 diabetes n=268	Cut-offs for positivity fC-PEPTIDE+: normal range between 0.58 and 2.7 ng/ml ICA+: 0.61 units of optical density GADA+: 2.2 units of optical density		HIGH titre >2.7 ng/ml	n=93 (34.7%)	
			Age at diagnosis, years, mean (SD)	45 (4.5)			Mean fC-PEPTIDE was higher (2.62 ng/ml) in patients who were both GADA-/ICA- vs. those who were positive for at least one Ab (2.32 ng/ml). However the difference was not SS (p=0.07). AUTHORS' NOTE: the n=20 patients in the LOW Titre fC-PEPTIDE group probably represent LADA cases, in act type 1 diabetes. Thus 7.5% of the type 2 diabetes patients may actually have type 1 diabetes.		Risk of bias: n/a
			M/F %	52/48					
				Type 1 diabetes n=655			fC-PEPTIDE+, nmol/litre (range)	1.0 (0.5 – 5.1)	
			Age, years, median (range)	13.3 (11.1 – 15.7)					

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
			M/F %	40/60					

G.1.1.2 Population: Adults and young people (mixed population studies); N≥50

Table 48: BESSER 2011 (311)

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
R. Besser, J. Ludvigsson, A. Jones, T. McDonald, B. Shields, B. Knight, and A. Hattersley. Urine C-peptide creatinine ratio is a noninvasive alternative to the mixed-meal tolerance test in children and adults with	Observational : prospective case-series Adults from diabetes clinic, UK; young people from paediatric clinic, Sweden	Total n=72 type 1 diabetes (mixture of young people and adults) Inclusion criteria: Type 1 diabetes Young people (<19 years) and adults (≥18 years) Age of diagnosis: <30 years on insulin since diagnosis Exclusion criteria: known renal	YOUNG PPLE (n=21) & ADULTS DIABETES TYPE: type 1 diabetes (n=72)			patients underwent a standard mixed-meal tolerance test (MMTT) type 1 diabetes: C-PEPTIDE (serum, sCP) Urine C-peptide creatinine ratio (UCPCR) sCP: collected at 0 and 90 min. Additional samples at 30, 60, and 120min in paediatric patients (n=18), allowing area under the curve (AUC) to be	N/A – immediate testing (up to 120 minutes)	type 1 diabetes (n=75) Association between 90-min sCP (1) and both the MMTT 120-min UCPCR and after the home evening meal In the paediatric cohort, correlations were also determined between AUC sCP and 120-min UCPCR. UCPCR cut-offs equivalent to 90-min sCP ≥0.2 nmol/litre were derived using linear regression equations. UCPCR (120 min)	Funding: Diabetes UK, Peninsula NIHR Clinical Research Facility, EC program Collaborative European Effort to Develop Diabetes Diagnostics; arndiabetesfonden (The Swedish Child Diabetes Foundation)
				Young (n=21)	Adults (n=51)				
			Age, years, median (IQR)	14 (10.9-16.4)	18 (13-24)				
			M/F, %	33/67	51/49				
			Diabetes duration, years, median (IQR)	2.6 (0.6-5.0)	21.4 (2.8-41.0)				
			HbA1c,	7.2	7.8				

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
type 1 diabetes. Diabetes Care 34 (3):607-609, 2011. REF ID: BESSER 2011		impairment (eGFR<60ml/min /1.73m2) severe hypoglycaemic. within last 3 months documented hypoglycaemia unawareness with a blood glucose <3mmol/litre, and HbA1c >10%.	median (IQR), %	(6.6-7.9)	(6.9-9.0)	calculated. Urine was collected as a fasting second morning void immediately before the start of the MMTT (0 min) and after 120 min. Significant endogenous insulin secretion was defined as 90-min sCP ≥0.2 nmol/litre, in accordance with the DCCT Urine: collected in boric acid 120 minutes after evening meal following a pre-meal void. Adult patients took further home urine samples 120 min after a standard 60-g CHO breakfast and following the patients' own lunch. Urine samples brought to the research centre within 24h.		following a home evening meal was compared with that after a MMTT. RESULTS: MMTT 120-min UCPCR was highly correlated to 90-min sCP (r = 0.97; p< 0.0001). UCPCR ≥0.53 nmol/mmol had 94% sensitivity/100% specificity for significant endogenous insulin secretion (90-min sCP ≥0.2 nmol/litre). The 120-min postprandial evening meal UCPCR was highly correlated to 90-min sCP (r = 0.91; p< 0.0001). UCPCR ≥0.37 nmol/mmol had 84% sensitivity/97% specificity for sCP ≥0.2 nmol/litre. AUTHORS' CONCLUSIONS: UCPCR measured during an MMTT or after a home meal is highly correlated	and the Swedish Research Council. Risk of bias: n/a
			To enrich for patients who had endogenous insulin secretion, 43% patients were either within 5 years of diagnosis or known to still secrete C-peptide when previously tested.						

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
						with MMTT sCP. UCPCR testing is a sensitive and specific method for detecting insulin secretion. UCPCR may be a practical alternative to serum C-peptide testing, avoiding the need for inpatient investigation.	

Table 49: BORG 2003 (42)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
H. Borg, H. J. Arnqvist, E. Bjork, J. Bolinder, J. W. Eriksson, L. Nystrom, J. O. Jeppsson, and G. Sundkvist. Evaluation	Observational: prospective case-series Registry, Sweden	Total n= 422 type 1 diabetes & type 2 diabetes – n=285 type 1 diabetes, n=81 type 2 diabetes (mixture of young people and adults)	YOUNG PPLE & ADULTS DIABETES TYPE: type 1 diabetes (n=285) type 2 diabetes (n=81) Unclassified (n=85)		type 1 diabetes & type 2 diabetes: ICA GADA GADA+ index IA-2A IA-2A index Any antibody + 3 Ab 2 Ab ICA & GADA	1 year	type 1 diabetes (n=285)		Funding: Juvenile diabetes foundation-Wallenberg Diabetes research program, Lundstrom foundation, Novo-Nordisk foundation,
				type 1 diabetes & type 2 diabetes			ICA	N (%) = 143 (54)	
							GADA	206 (77)	
							GADA+ index	53 (78)	
							IA-2A	123 (46)	
			Age,	25 (10)			IA-2A index	91 (90)	

Reference	Study type	Number of patients		Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
of the new ADA and WHO criteria for classification of diabetes mellitus in young adult people (15-34 years) in the Diabetes Incidence Study in Sweden (DISS). Diabetologia 46 (2):173-181, 2003. REF ID: BORG 2003		Inclusion criteria: Patients aged 15-34 at diagnosis Exclusion criteria: None stated	years, median (IQR)		ICA & IA-2A 1 Ab ICA GADA IA-2A C-PEPTIDE Cut-offs for positivity C-PEPTIDE+: 0.10 nmol/litre ICA512/IA-2+: Index* of IA-2A: Index* of 1.0 GADA+: Index* of 4.6 ICA+: >4 JDF units *INDEX = sample cpm – negative control cpm /positive control cpm - negative control cpm		Any antibody +	220 (83)	Research funds of Malmo university hospital, faculty of medicine at Lund university, Albert Pahlson Foundation, Swedish Diabetes association
			M/F %	254 (60%)/168 (40%)			3 Ab	89 (40)	
							2 Ab	74 (34)	
							ICA & GADA	47 (21)	
							ICA & IA-2A	6 (3)	
							GADA & IA-2A	21 (10)	Risk of bias: n/a
							1 Ab	57 (26)	
							ICA	1 (0.5)	
							GADA	49 (22)	
							IA-2A	7 (3)	
							type 2 diabetes (n=81)		
							ICA	12 (15)	
							GADA	16 (21)	
							GADA+ index	72 (85)	
							IA-2A	12 (15)	
							IA-2A index	94 (101)	
							Any antibody +	18 (23)	

Reference	Study type	Number of patients		Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
								3 Ab	7 (39)	
								2 Ab	8 (44)	
								ICA & GADA	3 (17)	
								ICA & IA-2A	2 (11)	
								GADA & IA-2A	3 (17)	
								1 Ab	3 (17)	
								ICA	0	
								GADA	3 (17)	
								IA-2A	0	
								P-C-PEPTIDE: Carried out in patients that were tested for C peptide within 1 week after diagnosis At diagnosis: Undetectable (<0.10 nmol/litre): Ab+: 30/123 (24.4%) Ab-: 1/36 (2.8) Low (<0.25 nmol/litre) Ab+: 72/123 (58.5) Ab-:2/36 (5.6) Follow up: Undetectable (<0.10 nmol/litre): Ab+: 13/123 (10.6) Ab-: 3/36 (8.3) Among all Ab- patients, 13/93 had low fasting P-C Peptide (0.25 nmol/litre) and 12/13 had type 1 diabetes		

Table 50: FAN 2013 (301)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
H Fan, QingRong Pan, Pengrui Zhang, Jia Liu, Yuan Xu, and Xinchun Yang. Influence of islet function on typing and prognosis of new-onset diabetes after intensive insulin therapy. Med Sci Monit 19:787-793, 2013. REF ID: FAN 2013	Observational: prospective case-series China	n=187 type 2 diabetes subgroup, n=19 type 1 diabetes subgroup (N<50 thus not using results) Total n=206 type 1 diabetes and type 2 diabetes (n=214 originally recruited who were acceptable) Inclusion criteria: New onset diabetes (WHO criteria) and ketosis type 2 diabetes patients did not require IIT to control blood glucose after initial honeymoon period (blood glucose controlled by diet and exercise for 2-5 weeks and normalised HbA1c levels <7%) Exclusion criteria:	type 2 diabetes adults and young people subgroup DIABETES TYPE: type 2 diabetes		type 2 diabetes: GAD IAA ICA Cut-offs for positivity Not reported	Baseline, and 3 years (follow-up data not given for Abs)	type 2 diabetes adults + young people		Funding: None mentioned. Risk of bias: n/a some missing data at follow-up
				type 2 diabetes adults and young people n=187			Baseline GAD+	4.8%	
							Baseline ICA+	3.2%	
							Baseline IAA+	10.6%	
			Age mean, (SD, range)	43.6 years (5.7, 17-58)			36 month follow-up data not given for Abs		
			Male	n=107					
			Disease duration, range	0-12 months					
			HbA1c, %, range	9.71 – 15.20					
			BMI, kg/m2, range	Mean 26.89; range 19.56 – 31.22					
			Drop-outs/missing data: n=8 due to unauthorised medication, withdrawn consent, and lost-to follow-up						

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
		Stress Severe injured liver or kidney function Diseases affecting the glucose metabolism						

Table 51: LAADHAR 2007 (30)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
L. Laadhar, M. Zitouni, M. Kallel-Sellami, R. Bouguerra, H. Chaabouni, and S. Makni. Spectrum of autoantibodies in Tunisian adult type 1 diabetes mellitus. Ann.N.Y.Acad.Sci. 1107:356-362, 2007.	Observational: cross-sectional study Single centre, Tunisia	Total n=261 type 1 diabetes Inclusion criteria: Clinical diagnosis of type 1 diabetes Exclusion criteria: None mentioned	ADULTS AND YOUNG PEOPLE DIABETES TYPE: type 1 diabetes		type 1 diabetes: fC-PEPTIDE Cut-offs for positivity ICA+: not given	n/a	type 1 diabetes (n=261)		Funding: Not mentioned Risk of bias: n/a
				type 1 diabetes n=261			ICA+	88 (33.7%)	
			Age, years, mean (SD; range)	29.1 (1.9; 16-60)			ICA+ in patients <1yr Diabetes	47.7%	
			Age at diagnosis, years, mean (SD)	20.3 (10.3)					
			M/F %	48/52					

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
REFID: LAADHAR 2007									

Table 52: LU 2014 (321)

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes (baseline)		Comments
H Lu, F Hu, Y Zeng, L Zou, S Luo, Y Sun, H Liu, and L Sun. Ketosis onset type 2 diabetes had better islet beta-cell function and more serious insulin resistance. J Diabetes Res 2014:510643, 2014. REF ID: LU 2014	Observational: cross-sectional study China	n=140 Inclusion criteria: Newly diagnosed type 2 diabetes Without islet-associated autoantibodies Age 16-68 years Diagnosis: WHO criteria If had Plasma glucose >250 mg/ml and positive urine ketone body = diabetic ketosis diagnosis.	ADULTS and YOUNG PPLE DIABETES TYPE: type 2 diabetes			type 2 diabetes: Fasting C-PEPTIDE Cut-offs for positivity AUC	n/a	type 2 diabetes adults and young people		Funding: None mentioned Risk of bias: n/a
				Ketosis onset type 2 diabetes n=62	Non-ketotic onset type 2 diabetes n=78			f-C-PEP, pmol/litre (SD)	Ketosis group: 475.8 (406) Non-ketotic group: 348.2 (283)	

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes (baseline)		Comments
		Exclusion criteria: Evidence of other disease Taking agents known to affect CHO metabolism Obvious precipitating causes for the development of ketosis	Age, years mean	44.8	47.0					
			M/F %	66	72					
			BMI, mean	25.0	24.4			type 1 diabetes patients vs. LADA: people with type 1 diabetes were younger, lower age of onset. NS difference in number of patients with high GAD titre.		
			HbA1c	11.0%	11.8 %					
			Drop-outs/missing data: none							

Table 53: BRUNOVA 2002 (28)

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
J. Brunova, J. Bruna, M. Koning, M. Meyer, G. Joubert, and W. Mollentze. GAD65Ab and primary hypothyroidism in type 1 and 2 diabetic	Observational: cross-sectional study Single centre, South Africa	Total n=192 (n=55 type 1 diabetes and n=137 type 2 diabetes) Inclusion	ADULTS AND YOUNG PEOPLE DIABETES TYPE: type 2 diabetes type 1 diabetes			type 1 diabetes: GAD65 type 2 diabetes: fC-PEPTIDE GAD65 Cut-offs for positivity fC-PEPTIDE+: not	n/a	type 1 diabetes (n=55)		Funding: Not mentioned Risk of bias: n/a
				type 1 diabetes n=55	type 2 diabetes n=137			GAD65+	17/55 (30.9%)	
								type 2 diabetes (n=137)		
								GAD65+	9/137 (6.6%)	
			Age, years, (range)	13 – 85 years				fC-PEPTIDE in GAD- patients, pmol/litre	637.6 (503)	

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
subjects. J.Endocrinol. Metab.Diabetes S.Afr. 7 (1):6-8, 2002. REFID: BRUNOVA 2002		criteria: Clinical diagnosis of type 1 diabetes and type 2 diabetes Exclusion criteria: None mentioned			given GAD65+: not given		(SD)		
							fC-PEPTIDE in GAD- patients, pmol/litre (SD)	1168.1 (732)	
			M/F %	50/50			The presence of GAD65 in type 2 diabetes was associated with lower levels of fC-PEPTIDE		

Table 54: OTA 2005 (126)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
T Ota, T Takamura, Y Nagai, Y Bando, and R Usuda. Significance of IA-2 antibody in	Observational: cross-sectional study	Total n=101 type 1 diabetes Inclusion criteria: type 1 diabetes classified by	ADULTS AND YOUNG PEOPLE DIABETES TYPE: type 1 diabetes		type 1 diabetes: C-PEPTIDE GADA65 IA-2A Cut-offs for	n/a	type 1 diabetes (n=101)		Funding: Not mentioned
				type 1 diabetes			GAD65+	n=60/101 (59%)	
							IA-2+	37/101 (37)	
							IA-2+/ GAD65-	10 (10)	
							GAD65+/ IA-2+	27 (27)	

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
Japanese type 1 diabetes: its association with GAD antibody. Diabetes Res.Clin.Pract. 67 (1):63-69, 2005. REF ID: OTA 2005		American diabetes association Exclusion criteria: None mentioned		n=101	positivity ICA512/IA-2: 0.4 U/mL GAD65+: 1.3 U/mL				
			Age, years, mean (range; SD)	41.3 (14.0-89.0; 15.3)			GAD65+/IA-2-	33 (32)	
			Duration of diabetes, years, mean (SD)	10.4 (9.6)					
							Acute onset type 1 diabetes (n=64)		Risk of bias: n/a
			M/F %	47/54			IA-2 Ab+: GAD Ab concentration (U/mL) Mean (SD)	n=19 67.7 (97.2)	
							IA-2 Ab-: GAD Ab concentration (U/mL)	n=45 31.1 (132.1)	
							GAD+: IA-2 Ab concentration (U/mL)	n=28 1.8 (3.0)	
							GAD-: IA-2 Ab concentration (U/mL)	n=36 1.0 (2.4)	

Table 55: RAJALAKSHMI 2014 (322)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
R Rajalakshmi, A Amutha, Harish Ranjani, Mohammed K. Ali, Ranjit Unnikrishnan, India	Observational: cross-sectional study	n=300 type 1 diabetes and type 2 diabetes (n=150 of each) Inclusion criteria: Diagnosis between ages	ADULTS and YOUNG PPLE DIABETES TYPE: type 1 diabetes type 2 diabetes	type 1 diabetes and type 2 diabetes: Fast C-peptide Stimulated C-	n/a	type 1 diabetes adults and young people		Funding: Global diabetes research centre.
						Fasting C-peptide, pmol/ml	0.29	
						Stimulated C-	0.32	

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
Ranjit Mohan Anjana, K. M. V. Narayan, and Viswanathan Mohan. Prevalence and risk factors for diabetic retinopathy in Asian Indians with young onset type 1 and type 2 diabetes. J.Diabetes Complications 28 (3):291-297, 2014. REF ID: RAJALAKSHMI 2014		10 and 25 years Duration of diabetes >2 years Diagnosis: FPG ≥126 mg/dl, and/or 2hr post-load glucose level ≥200 mg/dl, or self-reported diabetes treated by a physician or on hypoglycaemic. Medications or insulin. type 1 diabetes diagnosis: accompanied by abrupt onset of symptoms like polyuria, polydipsia, or unexplained wt loss, DKA, absent insulin reserve, requirement of insulin from time of diagnosis for control of hyperglycaemia. type 2 diabetes diagnosis: absence of ketosis, good B-cell functional reserve, absence of pancreatic calculi, and good response to oral hypoglycaemic. Agents for >2 years. Exclusion criteria:				peptide Cut-offs for positivity Not mentioned		peptide, pmol/ml		Risk of bias: n/a no missing data
			Adults and young people:					type 2 diabetes adults and young people		
			type 1 diabetes (n=150)		type 2 diabetes (n=150)			Fasting C-peptide, pmol/ml	0.79	
			Age	28	33			Stimulated C-peptide, pmol/ml	1.60	
			Male	54%	62%					
			Diabetes duration, years	12	12					
			Drop-outs/missing data: none							

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
		None mentioned.							

Table 56: SCHOLIN 2011 (93)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
A. Scholin, L. Nystrom, H. Arnqvist, J. Bolinder, E. Bjork, C. Berne, F. A. Karlsson, and Diabetes Incidence Study Group. Proinsulin/C-peptide ratio, glucagon and remission in new-onset Type 1 diabetes mellitus in young adults.	Observational: and prospective case-series Swedish study	Total recruited: n=203 n=78 type 1 diabetes (had complete data at all the time-points and were confirmed type 1 diabetes) Inclusion criteria: type 1 diabetes Age 15-34 years In the nationwide Diabetes Study in Sweden (DISS)	ADULTS AND YOUNG PEOPLE DIABETES TYPE: type 1 diabetes		type 1 diabetes: fC-PEPTIDE Cut-offs for positivity fC-PEPTIDE+: not given	3 years follow-up post diagnosis.	type 1 diabetes (n=78)		Funding: Not mentioned Risk of bias: n/a
				type 1 diabetes n=78			FC-peptide over time: months after diagnosis nmol/litre MEDIAN (min-max)		
							Baseline	0.24 (0.04-1.4)	
							3	0.26 (0.04-1.8)	
							6	0.31 (0.04-1.3)	
			Age, years, mean (SD; range)	26.2 (6.0)			9	0.27 (0-1.9)	
							12	0.27 (0-1.6)	
			M/F %	60/40			15	0.19 (0-1.7)	
							18	0.17 (0-1.1)	
			Islet Ab+, %	86%			24	0.16 (0-1.5)	
							30	0.12 (0.04-1.3)	
							36	0.19 (0.02-1.8)	

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
Diabet.Med. 28 (2):156-161, 2011. REFID: SCHOLIN 2011		type 1 diabetes defined as islet-cell Ab+ and/or need for insulin treatment at diagnosis) Blood samples taken Exclusion criteria: Pregnant type 2 diabetes							

Table 57: SCHOLIN 2004A (112)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
A. Scholin, C. Torn, L. Nystrom, C. Berne, H. Arnqvist, G. Blohme, J. Bolinder, J. W. Eriksson, I. Kockum, M. Landin-Olsson, J. Ostman, F. A.	Observational: prospective case-series	Total n=362 type 1 diabetes Inclusion criteria: People with type 1 diabetes Aged 15-34 years	ADULTS + YOUNG PEOPLE DIABETES TYPE: type 1 diabetes		type 1 diabetes: C-PEPTIDE GADA ICA IA-2 IAA Cut-offs for positivity	n/a	type 1 diabetes - All cases (n=362)		Funding: Juvenile diabetes foundation-Wallenberg Diabetes research program, Swedish Diabetes association,
				type 1 diabetes n=362			P-C-PEPTIDE+ (nmol/litre) Median (range)	0.27 (0.10, 2.13)	
							ICA+	213/346 (62%)	
							IA-2A+	162/345 (47%)	
							GADA+	229/346 (66%)	
			Age, years,	24.7			IAA+	58/248 (23%)	

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
Karlsson, G. Sundkvist, and E. Bjork. Normal weight promotes remission and low number of islet antibodies prolong the duration of remission in Type 1 diabetes. Diabet.Med. 21 (5):447-455, 2004. REF ID: SCHOLIN 2004A		Clinically classified as type 1 diabetes according to WHO criteria Exclusion criteria: None mentioned	mean (range; SD)	(5.6)	C-PEPTIDE+: 0.25 nmol/litre ICA512/IA-2+: Index* of 0.05 GAD65+: Index* of 0.07 ICA+: >5 JDF units IAA: 0.7% *INDEX = sample cpm – negative control cpm /positive control cpm - negative control cpm		type 1 diabetes Ab+ (n=307)		Swedish society of medicine, Agnes & Mac Rudbergs foundation
			Duration of diabetes, years, mean (SD)				P-C-PEPTIDE+ (nmol/litre) Median (range)	0.26 (0.10, 2.13)	
							ICA+	213/295 (72%)	Risk of bias: n/a
							IA-2A+	162/294 (55%)	
			M/F %	242/120			GADA+	229/295 (78%)	
							IAA+	58/215 (27%)	
							type 1 diabetes Ab- (n=53)		
							P-C-PEPTIDE+ (nmol/litre) Median (range)	0.38 (0.10, 1.63)	

Table 58: TRIDGELL 2011 (46)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
DM. Tridgell, C Spiekerman, Richard S. Wang, and	Observational: cross-sectional study	Total n= 5,020 type 1 diabetes Inclusion criteria:	ADULTS AND YOUNG PEOPLE DIABETES TYPE: type 1 diabetes	type 1 diabetes: GADA IA-2A GADA and/or IA-2A	n/a	type 1 diabetes: onset aged 2-7 (n=1,739) -univariate analyses		Funding: type 1 diabetes Genetics consortium,
						GADA+	35.7%	
						IA-2+	43.1%	

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
Carla J. Greenbaum. Interaction of onset and duration of diabetes on the percent of gad and ia-2 antibody-positive subjects in the type 1 diabetes genetics consortium database. Diabetes Care 34 (4):988-993, 2011. REF ID: TRIDGELL 2011		Diagnosed with type 1 diabetes before aged 35 years Treated with insulin within 6 months of diagnosis without subsequent discontinuation of insulin treatment Families with at least 2 non-monozygotic siblings with type 1 diabetes and families where there was a single affected child from a population with a low prevalence of type 1 diabetes Exclusion criteria: None			Cut-offs for positivity GAD65+: NR ICA+: NR		type 1 diabetes: onset aged 8-13 years (n=1,767) -univariate analyses		National institute of diabetes and digestive and kidney diseases, juvenile diabetes research foundation
							GADA+	47.6%	
							IA-2+	53.1%	
							type 1 diabetes: onset aged ≥14 years (n=1,514) -univariate analyses		
							GADA+	58.9%	
							IA-2+	40.6%	
							type 1 diabetes: duration 0-5 year- univariate analyses		
				type 1 diabetes n=5,020			GADA+	58.6%	
			Age, years, median (range)	10 (2-52) DATA FOR ADULTS AND YOUNG PPLE HAS BEEN SEPARATED			IA-2+	60.4%	
							type 1 diabetes: duration 6-13 year- univariate analyses (referent group 0-5 years duration)		
			Duration of diabetes, years, median	8 (0-66)			GADA+	44.8%	
							IA-2+	47.2%	Risk of bias: n/a
							type 1 diabetes: duration ≥14 year-		

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
		mentioned	(range)				univariate analyses (referent group 0-5 years duration)		
			M/F %	50.7%/49.3%			GADA+	35.6%	
							IA-2+	28.3%	
							type 1 diabetes: duration 0-5 year- multivariate analyses		
							GADA+	70.5%	
							IA-2A+	53.4%	
							GADA+ and/orIA-2A+	82.2%	
							type 1 diabetes: duration 6-13 year- multivariate analyses		
							GADA+	65.3%	
							IA-2A+	42.7%	
							GADA+ and/orIA-2A+	73.8%	
							type 1 diabetes: duration ≥14 year- multivariate analyses		
							GADA+	42.5%	
							IA-2A+	26.2%	
							GADA+ and/orIA-2A+	53.4%	

Table 59: SCHOLIN 2004B (69)

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
A. Scholin, L. Bjorklund, H. Borg, H. Arnqvist, E. Bjork, G. Blohme, J. Bolinder, JW. Eriksson, S. Gudbjornsdottir, L. Nystrom et al., and Diabetes Inc. Islet antibodies and remaining beta-cell function 8 years after diagnosis of diabetes in young adults: a prospective follow-up of the nationwide Diabetes Incidence Study in Sweden. J.Intern.Med. 255 (3):384-391, 2004. REF ID: SCHOLIN 2004B	Observational: prospective case series	Total n=312 (patients with blood samples at diagnosis and follow up) - n=254 type 1 diabetes, n=30 type 2 diabetes Inclusion criteria: Aged 15-34 years Diagnosed* with diabetes between 1987-1988 Exclusion criteria: None mentioned *diagnosis based on clinical judgement as	ADULTS AND YOUNG PEOPLE DIABETES TYPE: type 1 diabetes type 2 diabetes		type 1 diabetes: C-PEPTIDE GADA ICA IA-2 ICA & IA-2A ICA & GADA GADA & IA-2A Cut-offs for positivity P-C-PEPTIDE+: <0.1 nmol/litre ICA512/IA-2+: Index* of >1 GAD65+: Index* of >4.6 *INDEX = sample cpm – negative control cpm /positive control cpm - negative control cpm	8 years	type 1 diabetes Baseline (n=312)		Funding: Juvenile diabetes foundation and Wallenberg diabetes research program, Lundstrom foundation, Novo-nordisk foundation, Albert Palson foundation, Swedish diabetes association, children's diabetes fund, Swedish medical research council
				type 1 diabetes			ICA+	n=199/312 (64%)	
							GADA	235/311 (76)	
							IA-2A+	143/311 (46)	
							type 1 diabetes: follow up (n=312)		
			Age, years, mean (range; SD)	24.8 (9.5)			ICA+	73/309 (24%)	
							GADA	200/309 (65%)	
			M/F %	182 (58%)/ 130 (42%)			IA-2A+	106/310 (34%)	
							C-peptide at baseline		
			type 1 diabetes	254 (81)			≥0.1 nmol/litre:	type 1 diabetes: 25/42 (60%) type 2 diabetes: 8/42 (21%)	
			type 2 diabetes	30 (10)			<0.1 nmol/litre:	type 1 diabetes: 204/227 (90%) type 2 diabetes: 10/227 (4%)	
			Unclassifiable	27 (9)			C peptide at follow up		
			Secondary	1 (0)			≥0.1 nmol/litre:	type 1 diabetes: 31/42 (76) type 2 diabetes:	Risk of bias: n/a

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
		reported by diagnosing clinician to DISS registry						8/42 (20)	
							<0.1 nmol/litre:	type 1 diabetes: 208/227 (95) type 2 diabetes: 7/227 (3)	

Table 60: WENZLAU 2010 (55)

Reference	Study type	Number of patients	Patient characteristics				Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
J. M. Wenzlau, M. Walter, T. J. Gardner, L. M. Frisch, L. Yu, G. S. Eisenbarth, A. G. Ziegler, H. W. Davidson, and J. C. Hutton. Kinetics of the post-	Observational: prospective case-series	Total n=506 Inclusion criteria: New onset patients within 6 weeks of diagnosis type 1 diabetes new onset patients (4 years duration) Patients	ADULTS AND YOUNG PEOPLE DIABETES TYPE: type 1 diabetes				type 1 diabetes: C-PEPTIDE ZnT8 GADA IA-2 Cut-offs for positivity C-PEPTIDE+:.3 pmol/mL ZnT8: index* of 0.015-0.020 ICA512/IA-2+: Index* of 0.032	Group 1: 2.5 year Group 2: 7 years Group 3: 3-10.9 years	Group 1: New onset diabetes (n=21) baseline		Funding: Childhood diabetes foundation, Denver; university of Colorado health sciences centre diabetes endocrinology research centre (NIH), juvenile diabetes research foundation
				1 (n=21)	2 (n=61)	3 (n=424)			ZnT8A+	85.7%	
			Age, years, median (SD; range)	20.3 (6.2; 12.2-34.6)	9.8 (5.2; 1.6-36.7)	11.4 (7.6; 0.5-52.7)			GADA+	95.2%	
									IA-2A+	90.5%	
									C Peptide+	100%	
			Duration			26.3			Group 1: New onset diabetes (n=21) 2.5 years follow up		
									ZnT8A+	76.2%	
									GADA+	85.7%	
									IA-2A+	90.5%	

Reference	Study type	Number of patients	Patient characteristics				Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
onset decline in zinc transporter 8 autoantibodies in type 1 diabetic human subjects. J.Clin.Endocrinol.Metab. 95 (10):4712-4719, 2010. REF ID: WENZLAU 2010		with longstanding diabetes (>20 years) Exclusion criteria: None mentioned	of diabetes, years, mean (SD)			(7.6; 12.0-57.1)	GAD65+: Index* of 0.069 *INDEX = sample cpm – negative control cpm /positive control cpm -negative control cpm		C Peptide+	85.7%	autoimmunity prevention centre grant
									Group 1: new onset diabetes at 12 years follow up (prevalence)		
									GAD+	11.5%	
									CWCR	3.3%	Risk of bias: n/a
									IA2+	4.9%	
									GAD/CWCR	4.9%	
									GAD/ IA2	6.6%	
									IA2/CWCR	21.3%	
									GAD/CWCR/IA2	41%	
									Group 2: New onset type 1 diabetes (n=61) Baseline		
									ZnT8A+	80.3%	
									GADA+	63.0%	
									IA-2A+	73.8%	
									C Peptide+	NR	
									Group 2: New onset type 1 diabetes (n=61) 12 years follow up		
									ZnT8A+	42.6%	
									GADA+	32.4%	
									IA-2A+	47.5%	
									C Peptide+ (detected >0.02 pmol/mL)	27.6%	

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
						Group 2: patients with 4 years duration of type 1 diabetes at 12 years follow up (prevalence)		
						GAD+	10.7%	
						CWCR	8.9%	
						IA2+	16.1%	
						GAD/CWCR	3.6%	
						GAD/ IA2	10.7%	
						IA2/CWCR	19.6%	
						GAD/CWCR/IA2	20%	
						Group 3: Patients with longstanding diabetes(>20 years) (n=282) 12 year follow up (prevalence)		
						GAD+	11.0%	
						CWCR	1.4%	
						IA2+	7.8%	
						GAD/CWCR	0.7%	
						GAD/ IA2	7.1%	
						IA2/CWCR	2.1%	
						GAD/CWCR/IA2	2.5%	

Table 61: MCDONALD 2011 (85)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
T. McDonald, K.	Observational:	Total	ADULTS & YOUNG PEOPLE	type 1 diabetes:	n/a	type 1 diabetes	Funding:

Reference	Study type	Number of patients	Patient characteristics			Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
Colclough, R. Brown, B. Shields, M. Shepherd, P. Bingley, A. Williams, A. Hattersley, and Sian Ellard. Islet autoantibodies can discriminate maturity-onset diabetes of the young (MODY) from Type 1 diabetes. Diabet.Med. 28 (9):1028-1033, 2011. REF ID: MCDONALD 2011	cross-sectional study UK study	n=616 n=98 type 1 diabetes – adults and young people n=508 MODY – but adults only Inclusion criteria: Clinical history of diabetes HbA1c <6.0% MODY diagnosis by genetic testing type 1 diabetes diagnosis in last 6 months Exclusion criteria:	DIABETES TYPE: type 1 diabetes MODY			GAD IA-2 MODY: GAD IA-2 Cut-offs for positivity GAD+: 64 WHO units/ml (99th percentile) IA-2+: 15 WHO units/ml (99th percentile; lowest calibrator)		GAD+	24/98 (24.5%)	None mentioned Risk of bias: n/a
				type 1 diabetes n=98	MODY n=508			IA-2+	19/98 (94.5%)	
								GAD+ and/or IA-2)+	80/98 (82%)	
								GAD+ and IA-2+	37/98 (37.8%)	
			Age, years, median (IQR)	15 (12-25)	36 (18-50)			MODY		
								GAD+	5 (1%)	
								IA-2+	0 (0%)	
			Duration of diabetes, years, median (IQR)	< 6 months	9 (4-25)			GAD+ and/or IA-2+	5/508 (1%)	

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes	Comments
		None given					

Table 62: SCHOLIN 2004 (144)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
Anna Scholin, Agneta Siegbahn, Lars Lind, Christian Berne, Goran Sundkvist, Elisabeth Bjork, F. Anders Karlsson, and Diabetes Incidence Study in Sweden group. CRP and IL-6 concentrations are associated with poor	Observational study: prospective case series Diabetic incidence in Sweden study.	Total n= 100 type 1 diabetes . n=3ter excluded as pregnant. Inclusion criteria: Not pregnant. Exclusion criteria: None mentioned	ADULT (15-34 years) DIABETES TYPE: TID Age of type 1 diabetes patients (n=97) at diagnosis	type 1 diabetes: C-peptide ICA+ GADA+ IA-2A+ Cut-offs for positivity C-peptide: reference interval for fasting plasma concentration was 0.25 to 0.75 nmol/litre GADA index: >4.6 u/ml IA-2A index: >1.0 ICA: Not reported	12 months	Assays divided into islet antibody positive (ab+) and negative (ab-) Ab+ (n=78) C peptide (nmol/litre): 0.25 (0.04-1.4) ICA+: 58/78 (74%) GADA+: 69/78 (88%) IA-2A+: 55/78 (70%) Ab- (n=19 : 19.7%) C peptide (nmol/litre): 0.34 (0.08-1.41) Total population (I have added Ab+ and Ab-) ICA+: 58/97 (59.8%) GADA+: 69/97 (71.1%) IA-2A+: 55/97 (56.7%)		Funding: Supported by Grant from the Swedish Research Council, the Swedish Heart Lung Foundation, the Swedish Diabetes Association, the family Ernfors Fund, and the Juvenile Diabetes Foundation International and Knut and Alice Wallenberg Foundation.

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
glycemic control despite preserved beta-cell function during the first year after diagnosis of type 1 diabetes. Diabetes.Metab.Res.Rev. 20 (3):205-210, 2004. REF ID: SCHOLIN 2004				All (n = 97)			C-peptide – mean of Ab+ and Ab- (nmol/litre)	0.25 + 0.34 /2 = 0.295	
			Age (years)	28.1 (15.3-34.8)					

Table 63: VERMEULEN 2011 (250)

Reference	Study type	Number of patients	Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
I. Vermeulen, I. Weets,	Observational : Case-control study	Total n= 665 type 1 diabetes	YOUNG PPLE & ADULTS (data separated for some age-groups and markers)	type 1 diabetes IA-2A IA-2βA	1 year	type 1 diabetes ADULTS aged 20-29 (n=149)		Funding: Juvenile diabetes
						MARKER	N (%)	

Reference	Study type	Number of patients	Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
M. Asanghanwa, J. Ruige, Gaal L. Van, C. Mathieu, B. Keymeulen, V. Lampasona, J. M. Wenzlau, J. C. Hutton, D. G. Pipeleers, and F. K. Gorus. Contribution of antibodies against IA-2beta and zinc transporter 8 to classification of diabetes diagnosed under 40 years of age.	Registry, Belgium	(n=170 aged 0-9 years; n=223 aged 10-19 years; n=149 aged 20-29 years; n=113 aged 30-39 years) Inclusion criteria: Diagnosed with diabetes before age 40 Physician diagnosis of type 1 diabetes on clinical grounds and treated with insulin with 7 days after diagnosis Blood sampled within 7 days after	DIABETES TYPE: type 1 diabetes		ZnT8 IAA GADA Combinations Cut-offs for positivity IAA: ≥0.6% tracer binding IA-2A: ≥0.44% tracer binding IA-2βA: ≥0.39% tracer binding GADA+: ≥2.6% tracer binding ZnT8+: Age 0-14 years = ≥1.28% tracer binding Age15-39 years = ≥1.02% tracer binding		IA-2βA	47 (32)	Research F, EU and Belgian fund for Scientific Research
							ZnT8	76 (51)	
				type 1 diabetes			type 1 diabetes ADULTS aged 30-39 (n=113)		
			Age, years,	n=170: 0-9 years n=223: 10-19 years n=149: 20-29 years n=113 30-39 years Median: 15 (IQR9-26) years			MARKER	N (%)	
							IA-2βA	21 (19)	
							ZnT8	44 (39)	
							type 1 diabetes YOUNG PPLE aged 10-19 (n=223)		
			M/F	383 /272			MARKER	N (%)	
							IA-2βA	105 (47)	
							ZnT8	152 (68)	Risk of bias: n/a
							≥1 Ab+ (GADA, IA-2A or IAA)	207 (93)	
							≥1 Ab+ (GADA, IA-2A or ZnT8)	209 (94)	
							≥2 Ab+ (GADA, IA-2A and/or IAA)	154 (69)	
							≥2 Ab+ (GADA, IA-2A and/or	162 (73)	

Reference	Study type	Number of patients		Patient characteristics	Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
Diabetes Care 34 (8):1760-1765, 2011. REF ID: VERMEULEN 2011		treatment started CONTROLS: sex-matched non-diabetic controls aged 0-39 years. None had relatives with type 1 diabetes. Exclusion criteria: None stated					ZnT8)		
							type 1 diabetes ADULTS aged 20-39 (n=262)		
							≥1 Ab+ (GADA, IA-2A or IAA)	207 (79)	
							≥1 Ab+ (GADA, IA-2A or ZnT8)	206 (79)	
							≥2 Ab+ (GADA, IA-2A and/or IAA)	129 (49)	
							≥2 Ab+ (GADA, IA-2A and/or ZnT8)	139 (53)	
							YOUNG PPLE AND ADULTS: >age 15:		
							≥1 Ab+ (IAA, GADA and IA-2A)	82%	
							≥2 Ab+ (IAA, GADA or IA-2A)	51%	
							≥2 Ab+ (IA-2βA plus one of IAA, GADA or IA-2A)	56%	
							≥2 Ab+ (ZnT8 plus one of IAA, GADA or IA-2A)	63%	
							≥2 Ab+ (ZnT8 and IA-2βA plus one of IAA, GADA or IA-	65%	

Reference	Study type	Number of patients		Patient characteristics		Diagnostic markers assessed	Length of follow-up	Outcome measure and effect sizes		Comments
								2A)		
								The prevalence of IA-2βA and ZnT8 decreased with age at diagnosis (especially after age 20 years).		

G.2 Education programmes and self-care

G.2.1 Structured education programmes

Table 64: HERMANNS (PRIMAS education) [62]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes	Comments
N Hermanns, B Kulzer, D Ehrmann, N Bergis-Jurgan, and T Haak. The effect of a diabetes education programme (PRIMAS) for people with type 1 diabetes: results of a randomized	RCT 23 centres in Germany	n=160 Inclusion criteria: type 1 diabetes ≥18 and ≤75 years Diabetes duration >1 month BMI >20 and <40 kg/m2 HbA1c ≥7 and ≤13		PRIMAS n=81	DTTP n=79	PRIMAS structured education ITT: n=81 ACA/ reported: 75 12 lessons of 90 minutes each over 6 weeks Includes carb counting Based on	DTTP structured education (standard programme in Germany) ITT: n=79 ACA/reported: 74 12 lessons of 90 minutes each over 6 weeks Includes carb	6 weeks intervention; 6 months follow-up (post-intervention).	Final HbA1c, % (SD)	PRI: 7.9 (1.0) DTTP: 8.1 (1.0)	Funding: Grants from Berlin Chemie AG/Menarini Diagnostics, Germany. Risk of bias: Randomisation = good (central, randomisation sequence by computerised system, stratified by centre)
			Severe hypo episodes, per patient/year (SD)	0.33 (1.4)	0.29 (0.9)				Change baseline HbA1c, % (SD)	PRI: -0.4 (1.0) DTTP: 0.0 (0.6)	
			Diabetes, mean years	19.3	19.6				Severe hypoglycaemic. Episodes/patient/year	PRI: 0.06 (0.2); change base: -0.2 (0.9)	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes		Comments
trial. Diabetes Res.Clin.Pract. 102 (3):149-157, 2013. REF ID: HERMANNS 2013		German language Exclusion criteria: Current psychological or psychiatric disorder (under treatment) Dementia or severe cognitive impairment Severe somatic disease (preventing a regular participation in the training course) pregnancy				self-management/empowerment approach	counting		(SD)	DTTP: 0.01 (0.1); change base: -0.3 (1.5)		Allocation concealment = good (Independent research unit were contacted) Blinding = not mentioned and n/a ITT analysis Powered study (HbA1c) Drop-outs = acceptable (<20% and <10% difference between groups)
			Women, %	38	49				Depression – CES-D (SD)	PRI: 13.0 (9.5); change base: -1.2 (7.9) DTTP: 15.9 (9.5); change base: -0.3 (7.1)		
			HbA1c, % (SD)	8.3 (1.1)	8.0 (0.9)				Hypo awareness score (SD) Clarke 0-7 (≥4 = impaired)	PRI: 1.3 (1.2); change base: -0.5 (1.4) DTTP: 1.2 (1.3); change base: -0.4 (1.3)		
			Age, mean	45.9	45.1							
			Depression – CES-D (SD)	14.2 (9.0)	16.1 (8.4)				Diabetes knowledge test, (SD) Score 0-11,	PRI: 7.6 (1.8); change	DTTP: 8.0 (1.8); cha	
			Diabetes knowledge test	7.6 (1.8)	8.0 (1.8)							

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes		Comments
			(SD)						max 11.	base: 0.7 (1.6)	nge base: 0.6 (1.6)	
			Hypo awareness score (SD)	1.8 (1.7)	1.5 (1.6)							
									Adherence (attended <half the lessons)	n=1/81	n=2/79	
			NS differences between groups for any of the baseline characteristics Drop-outs (6 months): n=6 PRIMAS; n=5 DTTP									

Table 65: ROSSI 2013[131]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes	Comments
MC Rossi, A Nicolucci, G Lucisano, F Pellegrini, P Di Bartolo, V Miselli, R Anichini, and G Vespasiani On Behalf Of The Did Study	RCT 12 centres, Italy.	n=127 Inclusion criteria: type 1 diabetes ≥18 years age no previous education on		DID n=63	STD EDU n=64	Standard education ITT: n=64 Standard educational approach used in the centre –	Diabetes Interactive Diary (DID) – telemedicine system ITT: n=63 Up to 2 week	6 months	Final HbA1c, % (SE, SD)	DID: 7.9 (0.1, 0.8) STD: 8.1 (0.1, 0.8)	Funding: Sanofi-Aventis, Italy. Risk of bias: Randomisation =unclear. stratified by centre,
			Age, years (SD)	38.4	34.3				Change baseline HbA1c, % (SE, SD)	DID: -0.49 (0.11, 0.8) STD: -0.48 (0.11, 0.8)	
			Women,	54	33				Severe	DID:49.2	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes	Comments
Group. Impact of the "diabetes interactive diary" telemedicine system on metabolic control, risk of hypoglycemia, and quality of life: a randomized clinical trial in type 1 diabetes. Diabetes Technol.Ther. 15 (8):670-679, 2013. REF ID: ROSSI 2013		CHO counting HbA1c ≥7.5 treatment with basal-bolus regimen with insulin analogues practiced self-monitoring of blood glucose at least 3 times/day adequate familiarity in use of mobile phones Exclusion criteria: treated with NPH insulin OR soluble regular insulin OR CSII OR other regimens than basal-bolus. eating disorder pregnant unable to send or receive short	%			no further details given. Same insulin scheme as DID group	training course given to patients using DID 3 prandial injections of glulisine (15-20 minutes before meal), with basal of glargine. DID was used to estimate the CHO content of the meal, and prandial insulin doses were adjusted based on the DID algorithm. DID=software installed into mobile phone: works as a CHO/insulin bolus calculator. Supports patients in CHO counting through a food atlas and in recording SMBG mmts. All recorded info		hypoglycaemic. Episodes/patient/year INCIDENCE RATE (95% CI, SD)	(46.7 to 51.9, -10.3) STD: 45.6 (43.2 to 48.1, -9.8) Between groups IRR: 1.08 (1.0-1.16)	permuted block randomisation Allocation concealment = adequate. Telephone call to co-ordinating centre Blinding = none. Open label ITT analysis (LOCF) Powered study (HbA1c) Drop-outs = acceptable (<20%) and <10% difference between groups.
			HbA1c, % (SD)	8.4 (0.1)	8.5 (0.1)						
			Diabetes, mean years (SD)	16.2	15.0				DSQoL – fear of hypoglycaemia, change from baseline (SE, SD)	DID:2.03 (2.23, 17.7) STD: -3.91 (2.22, 17.8)	
			Drop-outs (6 months): n=8, 13% (DID) n=7, 11% (STD education)						*NOTE: DSQOL Fear score was 11 itels wath score range of 6 points (Likert scale). Higher scores = better QoL or satisfaction.		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes	Comments
		text messages unable or unwilling to give informed consent any other disease or condition that may interfere with compliance or completion of study.			sent to physician every 1-3 weeks via SMS and reviewed on computer of the diabetes clinic. Any new behavioural and therapeutic prescription can be then sent from the computer to the patient's mobile phone.				

Table 66: DAFNE study[8]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes	Comments
S. Amiel, S. Beveridge, C. Bradley, C. Gianfrancesco, S. Heller, P. James, N. McKeown,	RCT 3 centres in UK	n=169 (n=84 ID group; n=85 DD group) – final included in analysis – 67 and 72		ID n=84	DD n=85	Immediate DAFNE (ID) ITT: n=84 ACA/ reported: 67 and 68 5-day	Delayed DAFNE (DD)/waiting list control ITT: n=85 ACA/reported: 72	6 months after ID group receiving DAFNE (The DD group had not received	HbA1c, % (SD)	ID: 8.4 (1.2) DD: 9.4 (1.3)	Funding: Grants from Diabetes UK. Risk of bias: Randomisation = good (computer generated
			Hypoglycaemic. (severe, 6 months)	15/68 (22%)					Hypoglycaemic. (severe, 6 months)	ID: 12/67 DD: 11/72	
			Diabetes, mean years	16 (9.6)					ADDQoL - average weighted	ID: -1.6 (1.6) DD: -1.9 (1.4)	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes	Comments
D. Newton, L. Newton, L. Oliver, et al, and DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: Dose adjustment for normal eating (DAFNE) randomised controlled trial. Br.Med.J. 325 (7367):746-749, 2002.		respectively. Inclusion criteria: Attendees at hospital diabetes clinics, aged >18 years, clinical feature of type 1 diabetes, moderate or poor glycaemic control (HbA1c 7.5-12%), diabetes duration >2 years without advanced complications Exclusion criteria: Inability to				outpatient group training course (6-8 people/centre) Skills to replace insulin by matching with CHO intake on meal by meal basis Principles of adult education with explicit learning objectives Aim to build confidence and appropriate independence, with goal of patient autonomy. patients goal to adjust insulin to suit lifestyle rather than timing and content of meals to be fixed around	usual care/waiting list for 6 months, then given DAFNE	DAFNE at this point) At 12 months follow-up the DD group had received DAFNE, and this was follow-up 6 months after it.	impact (-9 to +9)	MD change from baseline 0.4 (-0.1, 0.9); p<0.01	random number list for each centre) Allocation concealment = inadequate (sealed opaque envelopes) [RO: needs to also be sequentially numbered] Blinding = not mentioned and n/a Not ITT analysis Powered study (HbA1c) Drop-outs = acceptable (<20%)
			Women, %	56					DTSQ - total satisfaction (0-36)	ID: 31.58 (3.9) DD: 22.82 (6.0) MD 8.75 (7.02, 10.48); p<0.0001	
			HbA1c, % (SD)	9.4 (1.2)	9.3 (1.1)				Symptomatic hypoglycaemia - perceived frequency, 0-6 (SD)	ID: 2.16 (1.3) DD: 2.40 (1.3) MD: -0.23 (-0.68, 0.21), p=0.31	
			Age, mean (SD)	40 (9)							
			Retinopathy, %	15							
			Neuropathy, %	13							
			Nephropathy, %	1.2							
			ADDQoL impact of diabetes on QoL	-2.0 (1.6)	-1.9 (1.4)						
			Hypo unawareness -	2.04 (1.2)	2.12 (1.4)						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes	Comments
REF ID 1500		understand written and spoken English, severe psychiatric illness, pregnancy and complete unawareness of hypoglycaemia.	perceived frequency, 0-6 (SD) NS differences between groups for any of the baseline characteristics Drop-outs (6 months): ID: n=16 (11 did not start, 3 ineligible, 1 dropped out on 1st day, 1 in hospital) DD: n=13 (12 did not start, 1 ineligible) Outcomes: ADDQoL – audit of diabetes-depended QoL questionnaire – impact weighting by importance for 18 domains of life (scores -9 to +9) then averaged. Overall score averages -9 (maximum negative impact of diabetes) to +9 (maximum positive impact of diabetes) DTSQ – diabetes treatment satisfaction questionnaire (8-items; mainly 0-36; higher score = greater satisfaction)	insulin doses. 2- 3 educators taught the course (DSNs and dieticians); educators given previous training, inspections and peer review given during the course					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes	Comments
			W-BQ12 – psychological well-being questionnaire (12-items; 0-36; higher score = greater satisfaction) Hypoglycaemia unawareness (perceived frequency of hypoglycaemia): measured by the DTSQ. Score of 0-6. Higher scores = greater perceived frequency						

Table 67: BGAT III study[136]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
H Schachinger, K Hegar, N Hermanns, M Straumann, U Keller, G Fehm-Wolfsdorf, W Berger, and D Cox. Randomized controlled clinical trial of blood	RCT 6 centres in Switzerland and Germany	n=138 (n=69 BG group; n=69 C group) – included in analysis 56 and 55 respectively Inclusion criteria: type 1 diabetes,		BG n=56	C n=55	BGAT III (BG) ACA/reported: n=56 BGAT III (German version) psycho-educational programme delivered by a physician-psychologist	Control (C) - self-help group: ACA/reported: n=55 self-help control group was guided by 1 physician. Sessions lasted 2	6 months and 12 months	HbA1c, % (SD) – 6 months	BG: 6.93 (1.02) C: 6.95 (0.98)	Funding: Swiss National Diabetes Foundation, Basel Diabetes Foundation, Walter-und Margarethe von Lichtenstein Foundation, Freie Akadamische Gesellschaft Basel, Lilly Inc. Switzerland and
			Age, years (SD)	45 (14.4)	47.9 (13.1)				HbA1c, % (SD) – 12 months	BG: 6.93 (0.96) C: 6.94 (0.94)	
			Women, %	45	38				Hypoglycaemic. -severe,	BG:0.13	
			HbA1c, % (SD)	6.9	6.9						

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
glucose awareness training (BGAT III) in Switzerland and Germany. J.Behav.Med. 28 (6):587-594, 2005. REF ID: SCHACHINGER 2005		verified that people were on a 'state of the art' intensified insulin regimen, performed 3-5 injections and at least 3 blood glucose mmts/day, had a recent adjustment of insulin dose and dosing schedule (if necessary), and routine determination of HbA1c every 3 months. Exclusion criteria: Uncontrolled physical and mental diseases		(0.8)	(0.9)	team groups of 5-12 for 8 x 2 hour sessions (1/week) Focus of initial sessions: internal cues (physical symptoms), disruptions in cognitive and motor performance, mood changes. Taught to use all these signals to more accurately recognise when blood glucose is too high or low Focus of later sessions: how to use exogenous	hours Focus of sessions: current problems related to diabetes, stress and diabetes, anatomy and physiology, physical activity, diabetes in the workplace, relationship conflicts, and previous experiences No homework given.		episodes/6 months at 6 months (SD)	(0.33) C: 1.07 (2.85)	Astra Fonds. Risk of bias: Randomisation = inadequate (matched to controls within each research centre – to reduce known confounders of age and diabetes duration. patients grouped as pairs then a random decision made as to which of the pair was given the main intervention (BGAT III) or control intervention) Allocation concealment = not mentioned Blinding = not mentioned and n/a
			Hypoglycaemic. -severe, episodes/6 months (SD)	1.6 (3.5)	1.8 (3.7)				Hypoglycaemic. -severe, episodes/6 months at 12 months (SD)	BG:0.13 (0.33) C: 1.78 (4.56)	
			Hypoglycaemic. - severe, last 2 years, %	64	47				Hypoglycaemia Fear Survey – worry: 6 months and 12 months	6 months: BG:15.2 (12.1) C: 14.6 (12.2) 12 months BG:13.2 (9.9) C: 14.7 (12.9)	
			Diabetes, mean years (SD)	23.1 (12)	22.7 (12.2)				Hypoglycaemia Fear Survey – behaviour: 6 months and	6 months: BG:	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		(heart or vascular disease, eating disorder, depression or substance abuse). Somatic comorbidity considered uncontrolled when newly diagnosed or new treatment had to be established within the last 3 months prior to entry.				cues to better anticipate when blood glucose is likely to rise or fall: previous insulin injections, food consumption, physical exercise Weekly homework and prep. readings were required			12 months	13.7 (8.2) C: 11.6 (6.4) 12 months: BG: 11.6 (6.9) C: 12.2 (8.5)	Not ITT analysis Powering details not mentioned Drop-outs = not acceptable (>20%; 25%) Selective outcome reporting: results not given for several outcome measures that were recorded: Well-being questionnaire and Diabetes QoL questionnaire – just says 'there was no overall effect of BGAT on either diabetes specific or general QoL measures.
			Hypoglycaemic. unawareness (increased recognition of low blood sugar levels) % detection	52.7 (21.8)	53.5 (28.0)				Hypoglycaemia unawareness (increased recognition of low blood sugar levels), % detection: 6 months and 12 months	6 months: BG: 58.2 (24.8) C: 45.8 (28.7) 12 months: BG: 65.2 (25.2) C: 48.0 (25.5)	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Hypoglycaemia Fear Survey - worry	16.5 (12.2)	15.7 (11.7)						
			Hypoglycaemia Fear Survey - behaviour	14.1 (9)	11.3 (6.6)						
			NS differences between drop-outs and participating people for any of the baseline characteristics except HbA1c (worse in drop-outs, p=0.05) Drop-outs (12 months): Overall: n=27 BG: n=13 (6 attended <50% sessions, 7 non-compliant with follow-up examinations) C: n=14 (8 attended <50% sessions, 6 non-compliant with follow-up examinations) Outcomes: Severe hypoglycaemia – any hypo episode for which the help of others was required (measured in diaries and questionnaire)								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			HbA1c – from diabetes specialists or family physicians QoL – diabetes specific and general QoL questionnaires: Well-being questionnaire and Diabetes QoL questionnaire (results not reported for these in the paper) Hypoglycaemia unawareness (increased recognition of low blood sugar levels): % detection of low blood glucose levels Fear of hypoglycaemia (Hypoglycaemia fear Survey): worry and behaviour domains. Each has multiple items graded on a score of 1-5 (5 indicates very often that is, worse fear-related worry or behaviours). Worry domain has 10 items (total score /50), behaviour domain has 17 items (total score /85). LOW score = better						

Table 68: BITES study[53]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
J. T. George,	RCT	n=114		BI	C	BITES (BI)	Control (C) –	3, 6	HbA1c, mean	0.01 (-	Funding: Not

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
A. P. Valdovinos, I. Russell, P. Dromgoole, S. Lomax, D. J. Torgerson, T. Wells, and J. C. Thow. Clinical effectiveness of a brief educational intervention in type 1 diabetes: Results from the BITES (Brief Intervention in Type 1 diabetes, Education for Self-efficacy) trial. Diabet.Med. 25 (12):1447-1453, 2008.	1 centre in UK	(n=54 BI group; n=60 C group) Inclusion criteria: People with type 1 diabetes attending specialist diabetes service in a hospital setting. type 1 diabetes for >12 months MDI for ≥2 months ≥18 years old ability to read and write.		n=54	n=60	ITT: n=54 ACA: n=50 (at 3, 6 and 12 months) BITES psycho-educational programme Delivered by a specifically trained DSN and SDD (specialist diabetes dietician) Groups of 8-10 as a 2.5 day course over a 6-week period Used written curriculum (pre-approved education material) and sessions were observed by independent researcher.	usual care ITT: n=60 ACA: n=52, n=53 and n=52 (at 3, 6 and 12 months) Controls seen in their usual diabetes clinic in addition to their study patients Had access to DSN and SDD and access to the Clinical Health Psychologist by referral Controls received the full course 12 months later	and 12 months	difference (95% CI) – 3 months	0.23, 0.26); p=0.92	mentioned. Risk of bias: Randomisation = unclear (block randomisation in blocks of 6) Allocation concealment = inadequate (independent evaluator, sealed envelopes in strict ascendant order) Blinding = not mentioned and n/a ITT analysis Powered study (HbA1c) Drop-outs = acceptable (<20%)
			Age, years (SD)	41 (10)	41 (12)				HbA1c, mean difference (95% CI) – 6 months	-0.06 (-0.32, 0.20); p=0.67	
			Women, %	50	60				HbA1c, mean difference (95% CI) – 12 months	0.01 (-0.30, 0.32); p=0.94	
			HbA1c, % (SD)	8.7 (1.51)	8.7 (1.13)				Hypoglycaemic. - severe, episodes/12 months at 12 months, mean difference (95% CI)	BI: 0.41 /patient/year C: 0.48 /patient/year MD: -0.05 (-0.61, 0.50); p=0.85	
			Diabetes, mean years (SD)	19.7 (12.7)	19.4 (11.0)				SF-36 Physical health, 3 months, MD (95% CI)	1.4 (-1.6,4.3): p=0.35	
									SF-36 Physical health, 6 months, MD (95% CI)	2.2 (-0.7, 5.0); p=0.14	
									SF-36 Physical health, 12	1.9 (-0.8, 4.6);	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: GEORGE 2008						Interactive sessions with reflection Group-based problem solving exercises; completed a workbook in-between sessions and received feedback from peers & HC professionals at the next session. Also worked with a fictitious individual with type 1 diabetes throughout the course who they mentored throughout and discussed helping them with change.			months, MD (95% CI)	p=0.17	
			Hypoglycaemia Fear Survey – worry:	Not given	Not given				Hypoglycaemia Fear Survey – worry: 6 months and 12 months	6 months: MD -2.4 (-7.2, 2.4), p=0.33 12 months MD -1.4 (-6.2, 3.4), p=0.57	
			Hypoglycaemia Fear Survey – behaviour:	Not given	Not given				Hypoglycaemia Fear Survey – behaviour: 6 months and 12 months	6 months: MD -0.01 (-2.9, 2.9), p=0.99 12 months MD -1.2 (-4.2, 1.9), p=0.45	
			Groups were comparable at baseline Drop-outs (3, 6 and 12 months): BG: n=2 cumulative total at 12 months (all n=2 dropped out at 3 months) C: n=8 cumulative total at 12 months (all n=8 dropped out at 3 months)								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Outcomes: Severe hypoglycaemia – a hypo episode for which the patient required assistance with treatment and either documented blood glucose <2.7 mmol/litre or detected clinical signs that require oral CHO administered by a third party, SC glucagon or IV glucose. HbA1c SF-36 (QoL) – DKT (Diabetes knowledge test) DES (Diabetes Empowerment Scale) DTS-Q (Diabetes Treatment Satisfaction Questionnaire) DHP (Diabetes health profile) [RO: These outcomes have data reported, just need to decide which we want] Fear of hypoglycaemia (Hypoglycaemia fear Survey): worry and behaviour domains. Each						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			has multiple items graded on a score of 1-5 (5 indicates very often that is, worse fear-related worry or behaviours). Worry domain has 10 items (total score /50), behaviour domain has 17 items (total score /85).						

Table 69: HYPOS study[61]

Reference	Study type	Number of patients	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
N. Hermanns, B. Kulzer, T. Kubiak, M. Krichbaum, and T. Haak. The effect of an education programme (HyPOS) to treat hypoglycaemia problems in patients	RCT 23 outpatient centres in Germany	n=164 (n=84 Hypoglycaemic group; n=80 C group) – included in analysis 74 and 72 respectively Inclusion criteria: type 1	HyPOS (HyP) specific training programme to reduce Hypoglycaemic. ITT: n=84 ACA/reported: n=74 Bio-psychosocial training/education programme Intensively trained diabetologist and diabetes educators (18 lessons) 5 lessons for 90 minutes	Control (C) – standard education: ITT: n=80 ACA/reported: n=72 4 lessons of 90 minutes (1/week) Focus of sessions: standards of insulin	6 months	ADDQoL – impact and importance (-3 to +3)	HyP:1.0 (0.8) C: 1.1 (0.8)	Funding: Berlin-Chemie AG/Menarini Diagnostics. Risk of bias: Randomisation = no details mentioned, just 'randomised' Allocation concealment = not mentioned Blinding = not mentioned and n/a Not ITT analysis Powered study (Hypoglycaemic. awareness,
						HbA1c, % (SD)	HyP:7.2 (0.8) C: 7.1 (0.9)	
						Hypoglycaemic. -severe, episodes/patient year (SD)	HyP:0.9 (1.9) C: 1.2 (2.0)	
						Hypoglycaemic. – very severe, episodes/patient year, %	HyP:0.3 (1.1) C: 0.6 (1.2)	

Reference	Study type	Number of patients	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
with type 1 diabetes. Diabetes.Metab.Res.Rev. 23 (7):528-538, 2007. REF ID: HERMANNS 2007		diabetes and hypoglycaemic. MDI or CSII age 18-70 year At least 1 episode of severe hypoglycaemic. in past 12 months (requiring 3rd party assistance) OR high risk of severe hypoglycaemic. (defined as impaired hypo awareness and tight glycaemic control (HbA1c<6.5 %) and disease duration >10 years).	(1/week) Focus of sessions: inform patients about causes and correct treatment of hypoglycaemic. unawareness. learned that frequent hypoglycaemic. episodes reduce window of opportunity for effective treatment and that avoidance of low blood glucose values improves hypoglycaemic. awareness. Learnt symptoms of hypoglycaemic., used diaries and blood glucose estimation to heighten hypoglycaemic. perception, and developed hypo checks to detect early signs of neuroglycopenia Focussed on detection of hypoglycaemic symptoms AND participants' views on causes and consequences of hypoglycaemic. as well as individual glycaemic targets in order to modify dysfunctional treatment goals or health beliefs.	treatment with regard to Hypoglycaemic avoidance were repeated. Adaptation of insulin dosage and relationships between CHOs and insulin demand.		Hypoglycaemic. unawareness, HAQ	HyP:0.3 (1.1) C: 0.6 (1.2) MD 0.7 (95% CI 0.1, 1.2); p=0.024 (favours Hypoglycaemia)	VAS) Drop-outs = acceptable (<20%)
						Hypoglycaemic. awareness, VAS	HyP:6.1 C: 5.3 MD 0.8 (95% CI 0.2, 1.4); p=0.015 (favours Hypoglycaemia)	
						PAID	Hypoglycaemia: 23.3 (11.7) C: 24.0 (11.4)	
						Depression, CES-D	Hypoglycaemia: 12.6 (7.4) C: 12.1 (7.0)	
						Anxiety, STAI	Hypoglycaemia: 37.6 (6.5) C: 37.1 (6.1)	

Reference	Study type	Number of patients	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		Exclusion criteria: Cancer diagnosis, dementia, pregnancy or diagnosis of current psychiatric disease.	The importance of immediate treatment was stressed, and possible reasons for delayed hypoglycaemic. treatment was analysed. patients analysed their individual insulin treatment with regard to low blood glucose events. Also discussed coping with activities that may pose a risk of hypoglycaemic.; social aspects of hypoglycaemic., and dangers of hypoglycaemic. Outcomes: Hypo unawareness (HAQ): Low score is better Anxiety (STAI): low score is better PAID: low score is better Depression (CES-D): lower score = better					

Table 70: Trento 2011[159]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
M. Trento, A. Trinetta, C. Kucich, G. Grassi, P. Passera, S. Gennari, V. Paganin, S. Tedesco, L. Charrier, F. Cavallo, and M. Porta. Carbohydrate counting improves coping ability and metabolic control in patients with Type 1 diabetes managed by Group Care. J.Endocrinol. Invest. 34 (2):101-105, 2011.	RCT 1 centre in Italy	n=56 (n=27 CCP; n=29 GC) Inclusion criteria: type 1 diabetes Diabetes onset before age 30 years start of insulin treatment within 1 year of diagnosis age <70 years All patients on 4-day insulin injections and practised self-monitoring of blood glucose None were on lipid lowering agents		CCP n=27	GC n=29	Carbohydrate counting programme (CCP) embedded into the usual group care continuing education programme ITT: n=27 As for group care group but with CCP added CCP consisted of 8 sessions including: recognition and how to properly manage hypoglycaemic.; recognising effects of insulin on patients own therapy with daily activities: studying, work, physical activities, eating; define effects of various foods on blood glucose and	Control (GC) – group care continuing education programme ITT: n=29 8 session education (every 3-4 months) Facilitators were a Used principles of adult learning Sessions & group discussions were concerned with motivational aspects, acceptance of diabetes, psychosocial problems, &	30 months	DQoL - change from baseline values (SD)	CCP: -10.7 (1.3) GC: -8.3 (1.47)	Funding: None mentioned. Risk of bias: Randomisation = no details mentioned, just 'randomised' Allocation concealment = not mentioned Blinding = not mentioned and n/a ITT analysis (no drop-outs) Powering not mentioned Drop-outs = acceptable (<20%)
			Age, years (SD)	37.3 (12.6)	36.8 (7.9)				DQoL - final values (SD)	CCP:78.0 (9.9) GC: 80.4 (11.7) MD (final scores): -2.72 (-6.7, 1.2) NS	
			Women, %	33	59				Hypoglycaemic. - severe, episodes during study (SD)	CCP: 5 GC: 6	
			HbA1c, % (SD)	7.6 (1.3)	7.7 (1.24)						
			Diabetes, mean years (SD)	22.0 (10.8)	21.1 (9.5)				HbA1c %, change from baseline values (SD)	CCP:0.21 (0.18) GC: -0.24 (0.22) MD*: -0.63 (-1.2, -0.03); p<0.05	
			DQoL	88.7 (9.2)	88.7 (12.5)				HbA1c %, final	CCP: 7.2 (0.9)	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: TRENTO 2011						identify foods containing CHO; identify which CHO-rich foods are to be preferred and about sweetening agents and dietetic products; All patients did at least 8 group care sessions, whether they were allocated to CCP or not.	coping strategies. patients are helped to identify & share their problems & successes with other members & report their personal experience. Education programme included cognitive and psychomotor abilities Included a patented educational support kit & operating manual Sessions = structured		values (SD)	GC: 7.9 (1.4)	
			Knowledge of diabetes, GISED (SD)	9.3 (1.7)	10.0 (1.1)				Knowledge of diabetes, GISED, final values	CCP:10.6 (0.6) GC: 10.2 (0.9)	
			NS differences between groups for any of the baseline characteristics						Knowledge of diabetes, GISED, change from baseline	CCP: +1.3 (0.24) GC: +0.17 (0.071)	
			Drop-outs (30 months): None mentioned Outcomes: Severe hypoglycaemic: episodes requiring third party help (that is, glucagon injection, iv glucose and/or hospital admission. Diabetes QoL questionnaire (DQoL): 4 scales: satisfaction, impact, diabetes worry & social/ vocational worry. 46 core items, each item scores						*adjusted for gender, age, schooling, duration of diabetes, years of attendance at clinic, and baseline values of the dependent variable.		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			between1 (very satisfied) and 5 (very dissatisfied). Total score thus range: 46 (best QoL) to 230 (worst QoL). CSI (coping) Knowledge of diabetes: 11 item scale questionnaire (GISED) – correct answers = 1 point, incorrect = 0. So total score range 0-11. Higher score = better.						

Table 71: HAATT (Cox 2004)[31]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
D. J. Cox, B. Kovatchev, D. Koev, L. Koeva, S. Dachev, D. Tcharaktchiev, A. Protopopova, L. Gonder-Frederick, and W.	RCT 3 centres in Bulgaria	n=60 (n=30 in each group) Inclusion criteria: type 1 diabetes		HAAT n=30	SMBG n=30	SMBG + HAATT (Hypoglycaemia, Anticipation, Awareness and Treatment Training) programme to reduce Hypoglycaemic.	SMBG (self-monitoring blood glucose) ITT: n=30 SMBG meter and supplies for 4 months (1 month pre	2 months of treatment; follow-up at 6 months post treatment and	HbA1c, % (6 months)	HAAT:8.0 SMBG: 8.1	Funding: Grants from the NIH's Fogarty International and from Roche Diagnostics, Germany.
			Age, years (SD)	37.6 (9.0)	45.9 (13.3)				Hypoglycaemic. - severe/subject (6 months)	HAAT:0.4 SMBG: 1.7 (SS: p=0.03)	
			Women, %	47	46				Hypoglycaemic. -	HAAT:1.76 SMBG:	
			HbA1c, %	8.08	7.98						

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Clarke. Hypoglycemia anticipation, awareness and treatment training (HAATT) reduces occurrence of severe hypoglycemia among adults with type 1 diabetes mellitus. Int.J.Behav. Med. 11 (4):212-218, 2004. REF ID: COX 2004A		Adults History of ≥2 episodes of severe hypoglycaemic. in the past year	(SD)	(0.74)	(0.70)	ITT: n=30 As for SMBG group but with additional HAATT programme. Psycho-educational treatment programme (structured) Group session (10 people) over 7 weeks Daily homework exercises and chapters to go through. Contents included: 1. Anticipation and prevention of hypoglycaemic. (risk and consequences of severe hypoglycaemic. (SH) & personal goals for treatment established; Insulin kinetics & how to anticipate when their insulin action	and post-treatment and 2 months of treatment) Educated by physician during the treatment period on the meaning and use of SMBG data. In both groups, all participants received routine medical care which involved monthly physician visits to make adjustments in insulin, food, and exercise routine based on daily SMBG data.	13-18 months	severe/subject (18 months)	3.65 (SS: p<0.023)	Risk of bias: Randomisation = no details mentioned, just 'randomised' Allocation concealment = not mentioned Blinding = not mentioned and n/a ITT analysis (no drop-outs) No mention of powering Drop-outs = acceptable (<20%)
			Hypoglycaemic. - severe/subject	2.0	1.8				Hypoglycaemic. unawareness (% detection of low blood glucose) – 6 months	HAATT: 70% SMBG: 55% (SS: p=0.005)	
			Diabetes, mean years (SD)	13.93 (9.33)	14.0 (7.64)						
			Hypoglycaemic. unawareness (% detection of low blood glucose)	52%	58%						
			NS differences between groups for any of the baseline characteristics Drop-outs: None mentioned								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Outcomes: Severe hypoglycaemia – inability to treat oneself due to hypoglycaemic stupor or unconsciousness Blood glucose measurements Daily diaries used for recording outcomes	is at its peaks & nadirs; CHO counting & matching intake to insulin action; demands of physical activity & when to optimally perform exercise relative to insulin levels, and how to cover energy expenditure with appropriate CHOs) 2. Recognition & treatment of hypoglycaemic. (recognising, interpreting & using neuroglycopenic & neurogenic cues that signal the presence of hypoglycaemic; using this info to better anticipate, prevent, recognise & treat low blood glucose 3. How to use all					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
				the info once classes finished.					

Table 72: ROSSI 2010[130]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
M. C. Rossi, A. Nicolucci, Bartolo P. Di, D. Bruttomesso, A. Girelli, F. J. Ampudia, D. Kerr, A. Ceriello, Cde L. Mayor, F. Pellegrini, D. Horwitz, and G. Vespasiani. Diabetes Interactive Diary: a new telemedicine system enabling flexible diet and insulin therapy while	RCT Multicentre, Italy, Spain and UK	n=130 (n=67 DID; n=63 CCP) Inclusion criteria: type 1 diabetes ≥18 years age no previous education on CHO counting treatment with MDI of short- and long-acting		DID n=67	CCP n=63	Diabetes Interactive Diary (DID) – telemedicine system ITT: n=67 Software installed into mobile phone: automatic CHO/insulin bolus calculator, records blood glucose and insulin dose injections in real time patient-physician/dietician communication via short text message	Carbohydrate counting programme (CCP) standard education ITT: n=63 Standard educational approach lasting up to 3 months	6 months	HbA1c %, 3 month change from baseline values (SD)	DID: -0.5 (0.8) CCP:-0.4 (0.6)	Funding: Me.Te.Da (developer of DID) and Lifescan, Milpitas USA (medical consultant for Me.Te.Da.) Risk of bias: Randomisation =unclear. stratified by centre, permuted block randomisation Allocation concealment = adequate.
			Age, years (SD)	35.4 (9.5)	36.1 (9.4)				HbA1c %, 6 month change from baseline values (SD)	DID: -0.4 (0.9) CCP: -0.5 (1.0)	
			Women, %	55	59				Hypoglycaemic. - severe, episodes during study (SD)	DID: 0 CCP: 0	
			HbA1c, % (SD)	8.2 (0.8)	8.4 (0.7)						
			Diabetes, mean years (SD)	17.1 (10.8)	15.8 (10.7)				SF-36* physical component,	DID: 1.3 (6.6)	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
improving quality of life: an open-label, international, multicenter, randomized study. Diabetes Care 33 (1):109-115, 2010. REF ID: ROSSI 2010		insulin analogues OR with continuous sc insulin infusion practiced self-monitoring of blood glucose at least 3 times/day adequate familiarity in use of mobile phones possession of personal mobile phone card Inclusion criteria: treated with NPH insulin OR soluble regular				Aim to improve metabolic control, reduce education time and increase QoL Allows patients to manage a flexible diet and calculate the matching insulin bolus at each meal Additional calculation of basal insulin dose based on fasting blood glucose values and presence of hypoglycaemic. episodes System suggests daily CHO intake, summing the amount of CHO consumed progressively. patients can decide what to eat during the meal, choosing between			3 month change from baseline values (SD)	CCP: -1.7 (7.0)	Telephone call to co-ordinating centre Blinding = none. Open label ITT analysis (LOCF) Powered study (HbA1c) Drop-outs = acceptable (<20%)
			SF-36 physical component(SD)	50.3 (8.9)	50.6 (4.9)				SF-36* physical component, 6 month change from baseline values (SD)	DID: 0.6 (7.3) CCP: 1.0 (4.9)	
									SF-36* mental component, 3 month change from baseline values (SD)	DID: 2.2 (8.1) CCP: -0.3 (6.8)	
									SF-36* mental component, 6 month change from baseline values (SD)	DID: 4.2 (12.5) CCP: -0.8 (10.2)	
									Hospital	DID:	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		insulin eating disorder pregnant unable to send or receive short text messages unable or unwilling to give informed consent any other disease or condition that may interfere with compliance or completion of study.	NS differences between groups for any of the baseline characteristics Drop-outs (6 months): n=9 (DID) – n=1 Lost to follow-up, n=8 discontinued intervention n=2 (CCP) Outcomes: Severe hypoglycaemia: episode requiring medical intervention SF-36 scores: Higher score = better QoL	all the foods listed in the software; the quantification of the total calories and CHO consumed is facilitated by a list of pictures showing the specific food and amount ingested. The CHO-to-insulin ratio and the glycaemic correction factor, identified and prescribed by the HC professional, together with other info already filled out in the DID (eg. physical activity, Glycaemic target, insulin dose and specific events), allow it to auto calc. and suggest the most appropriate insulin dose to be injected.			admissions during study	0 CCP: 0	
							*NOTE: SF-36 scores were from questionnaires given to a subgroup of patients (n=30 in each group)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
				DID also provides regular feedback to the patient (periodically sent as text messages and reviewed on the PC of the physician) then any new behavioural prescription can be sent from the computer to the mobile phone, improving the communication between patients and physician. Up to 2 week training course given to patients using DID					

Table 73: BGAT study (Snoek 2008)[149]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		[RO: unclear; as says 2 not avail l for analysis and so 86 were left for analysis,							

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
		Implies 2 more were included at randomisation. This perhaps not ITT either?? UNCLEAR – although abstract says 86 randomised!]										
F. J. Snoek, N. C. W. Van Der Ven, J. W. R. Twisk, M. H. E. Hogenelst, A. M. E. Tromp-Wever, H. M. van der Ploeg, and R. J. Heine. Cognitive behavioural therapy (CBT) compared with blood glucose awareness training (BGAT) in poorly controlled Type 1 diabetic patients: Long-term effects on	RCT Single centre in The Netherlands	n=86 (n=41 in BGAT; n=45 in CBT) Inclusion criteria: type 1 diabetes for at least 1 year Adults HbA1c ≥8.0% on 2 consecutive occasions prior to the study MDIs (≥2) or continuous sc insulin infusion (CSII) Exclusion criteria:		BGAT n=41	CBT n=45	BGAT (blood glucose awareness training) programme ITT: n=?? ACA: n=41 Programme is standard BGAT aims to help type 1 diabetes patients prevent and correct in a timely fashion, extreme blood glucose excursions by means of improving symptom discrimination and	CBT ITT: n=?? ACA: n=45 6 weekly group sessions CBT programme specifically designed for type 1 diabetes patients with prolonged self-care difficulties resulting in elevated Glycated Hb and thus at an increased risk for microvascular complications. patients given info sheets and	6 weeks intervention; 3, 6 and 12 months follow-up (post-intervention)	HbA1c, % Between 6 and 12 months	NS change in either group		Funding: Grant from the Dutch Diabetes Foundation and 3 individuals. Risk of bias: Randomisation = no details mentioned, just 'randomised' Allocation concealment = not mentioned Blinding = not mentioned and n/a ITT analysis Powered study (HbA1c) Drop-outs = NOT acceptable (>20% in one
			Age, years (SD)	37.4 (11.1)	38.1 (9.7)				HbA1c in depressed patients (baseline, 6 months, 12 months)	BGAT: NS decrease in depressed patients (9.5%, 9.5% and 9.4%)	CBT: SS decrease (9.5%, 8.9%, 8.8%)	
			Women, %	66	51				PAID, 6 months	44.4 NS p=0.99	38.7	
			HbA1c, % (SD)	9.1 (1.1)	8.8 (1.3)				PAID, 12 months	45.4 NS p=0.68	38.3	
			Diabetes, mean years (SD)	18.8 (10.9)	17.8 (10.1)				CES-D, 6 months	15.8 NS p=0.74	13.5	
			PAID	49.0	43.4				CES-D, 12 months	15.5 NS	15.4	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
HbA1c moderated by depression. A randomized controlled trial. Diabet.Med. 25 (11):1337-1342, 2008. REF ID: SNOEK 2008		pregnancy severe medical co-morbidity current treatment for cancer visually too impaired to read too functionally impaired to attend classes insufficient Dutch reading skills substance abuse learning difficulties history of psychiatric treatment for schizophrenia organic mental				understanding of the interaction between insulin, food intake and physical activity. BGAT and CBT are comparable in format and intensity In both groups: BGAT and CBT delivered by teams of experienced diabetes nurse educators and clinical psychologist	homework assignments. Topics covered: my barriers and goals; how my thoughts impact on my feelings and self-care; coping with stress; worries about complications; diabetes and relationships; being part of diabetes team. Programme addresses the psychological barriers to improving diabetes self-management helping patients to identify, challenge and reframe their			p=0.19		group and large difference between groups)
			CES-D	16.9	15.7							
			NS differences between groups for any of the baseline characteristics except education level Drop-outs (completed <4/6 sessions): During intervention BGAT: 8%; CBT: 27% After 3 months f-up: 2 excluded from analysis due to cancer or pregnancy Outcomes: HbA1c SMBG QoL scales: CIDS, PAID and CES-D. CIDS = Confidence in Diabetes Self-care; PAID = Problem areas in							

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		disorder or bipolar disorder	Diabetes; measures diabetes emotional stress. 20 items scored from 0-4 (no problem – very serious problem). Transformed total scores to a scale of 0-100, higher scores represent higher levels of distress. CES-D = Centre for Epidemiological studies – depression scale (20-item measure of depressive symptoms in the last week). Total scores 0-60 – higher scores indicate worse depressive symptoms. Scores ≥16 are considered high and indicative of clinical depression)		negative beliefs around diabetes and self-care that often result in feelings of frustration and 'letting it all go' rather than keeping up the effort. In both groups, during the study patients continued to receive usual care				

Table 74: TERENT 1985[151]

Reference	Study type	Number of patients	Patient characteristics					Intervention and Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
A. Terent, O. Hagfall, and U. Cederhol	RCT Single centre	n=37 (n=10 in EDU +		EDU + SMBG (A)	SMBG (B) n=8 vs. REF	EDU (C) n=9	REF (D) n=10	EDU + SMBG (A) ITT: n=10 ACA: n=10	6 months education followed by 6 months	HbA1c, % 6 months	A =12.2 (3.2) B= 12.3 (2.5)	Funding: Not mentioned

Reference	Study type	Number of patients	Patient characteristics					Intervention and Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
m. The effect of education and self-monitoring of blood glucose on glycosylated hemoglobin in type I diabetes. A controlled 18-month trial in a representative population. Acta medica Scandinavica 217 (1):47-53, 1985. REF ID: TERENT 1985	– 1 area of Sweden	SMBG, n=8 in SMBG.=, n=9 in EDU, n=10 in REF) Inclusion criteria: T1aD Duration ≤20 years Adults (≥17 years) Exclusion criteria: kidney transplantation pregnant alcoholic		n=10 [RO Not using these two separately – at 6 months using all EDU (A+C) …	(B+D) and at 6 12 and 18 months using EDU (C) and REF (D)]			SMBG (B) EDU (C) ITT: n=8 ITT: n=9 ACA: n=8 ACA: n=9 REF (D) ITT: n=10 ACA: n=10 First randomisation: patients randomised to 2 groups : n=19 formal education vs. n=18 reference (standard therapy) 6 months duration Second randomisation: After 6 months Each group randomised into 2 further groups: to additional SMBG education or continuing previous	SMBG 6, 12 and 18 months follow-up (18 months = 6 months post-intervention) 6 months results = EDU (group A+C) vs. CONTROL (group B + D) 12 and 18 months results = EDU + SMBG (group A) vs. EDU (group C) vs. SMBG (group B) vs. CONTROL (group D)		C= 10.1 (1.7) D= 10.0 (2.0)	Risk of bias: Randomisation = no details mentioned, just 'randomised' Randomisation was done twice: EDUCATION vs. REFERENCE and then each of those were randomised into two: either additional SMBG or continuing previous education or reference Allocation concealment = not mentioned Blinding = not mentioned ITT analysis
			Age, years (SD)	29 (6)	28 (7)	26 (5)	25 (5)			HbA1c, % 12 months	A =11.0 (2.6) B= 10.8 (1.0) C= 9.9 (2.5) D=9.5 (3.2)	
			Women, %	40	65	56	20			HbA1c, % 18 months	A =10.2 (1.9) B= 9.8 (3.0) C= 10.2 (2.1) D= 10.4 (2.1)	
			HbA1c, %	12.3	11.8	11.2	11.1			Severe hypoglyca	A+B: n=7	

Reference	Study type	Number of patients	Patient characteristics					Intervention and Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			(SD)	(3.2)	(1.4)	(2.0)	(2.3)	education or reference (standard therapy) Thus 4 groups in total after 2nd randomisation: EDU + SMBG vs. EDU vs. SMBG vs. REF Duration 6 months Follow-up: patients followed-up at a further 6 months (18 months total) Education: Individual education 6 x 1hr lessons during 1 month Lessons arranged according to Swedish board of Health and Welfare Special model constructed and used by physicians and dietician to		emic. – episodes treated in hospital	C+D: n=14 [RO can't use as combined data groups]	(no drop-outs) Powering: not mentioned Drop-outs = acceptable (<20%)
			Diabetes, mean years (SD)	12 (6)	13 (4)	5 (4)	13 (5)			Ketoacidosis – number patients treated for	A= 2 B =0 C =3 D =0	
			BMI, kg/m2 (SD)	22 (2)	22 (2)	21 (2)	24 (4)			Knowledge - % correct test answers	6 months A =65 C =55 [RO: wrong groups – can't use data]	
										Adherence/compliance - % attending all sessions	A =100% C =100% [RO wrong groups – can't use data]	
			NS differences between groups for any of the baseline characteristics except duration of type 1 diabetes lower in EDU group.									

Reference	Study type	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Drop-outs: None Outcomes: Compliance/adherence - measured by number of patients attending all sessions Knowledge of diabetes and management – diabetes, insulin, oral hypoglycaemics, testing and physical exercise. Measured by percentage of correct answers to the test.	explain interplay between food consumption, blood glucose levels, insulin and urinary glucose. excretion. Taught also about hypo- and hyper-glycaemia, foot care, injections, and urine testing techniques. Questions also asked of a social nature Materials given to take away Questionnaire at 1 and 6 months after the course Encouraged to test urine for glucose. and ketone bodies. SMBG: Method demonstrated of SMBG Finger-pricking and reagent strips Instructed to				

Reference	Study type	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
				perform test every day but at least 2 days every fortnight (weekly testers). Tests done before breakfast, 1-2 hours after the 2 main meals and at bedtime. Encouraged to change insulin dose to achieve pre-prandial values <7 mmol/litre and post-prandial <10 mmol/litre. Had to record hypoglycaemia. Standard therapy: patients in group B and D continued their pre0-trial checking habits Fasting Blood glucose and 24h urinary glucose. Values were measured every 3rd month at outpatient dept.				

Reference	Study type	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
				Physical examination performed 6-monthly. Patients equipped with devices for monitoring of urinary glucose.				

Table 75: TRENTO 2005[158]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures at 3 years – ACA data	Effect sizes		Comments
M. Trento, P. Passera, E. Borgo, M. Tomalino, M. Bajardi, A. Brescianini, M. Tomelini, S. Giuliano, F. Cavallo, V. Miselli, P. Bondonio, and M. Porta. A 3-year	RCT Single centre in Italy	n=62 (n=31 in EDU; n=31 in Control) Inclusion criteria: type 1 diabetes Adults Onset before age 30 and insulin treatment		EDU n=31	Control (C) n=31	Structured education programme (group) ITT: n=31 ACA: n=30 15 group sessions over 3 years 9 education sessions over 18 – 27 months (one session every 2-3	Usual care (1:1 consultations) - control (C) ITT: n=31 ACA: n=28 Continued to follow habitual 2-3 monthly 1:1 consultations in the diabetes clinic Received individual	18-27 months intervention; 3 year follow-up (includes intervention time)		EDU	C	Funding: Compagnia di San Paolo, Turin, Italy. Risk of bias: Randomisation = random number tables Allocation concealment = not mentioned Blinding = single blind (outcome assessors)
									HbA1c, % (SD) FINAL SCORE	7.88 (0.20)	8.79 (1.38)	
			Age, years median (IQR)	27 (23-33)	31 (25-43)				HbA1c % (95% CI) CHANGE FROM BASELINE	-0.38 (- 0.83 to 0.07) thus SD is 1.21	-0.40 (- 0.85 to 0.04) thus SD is -1.15	
			Women, %	39	42				Knowledge of diabetes – GISED (SD) FINAL SCORE	47.45 (6.03)	43.34 (6.18)	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures at 3 years – ACA data	Effect sizes		Comments
prospective randomized controlled clinical trial of group care in type 1 diabetes. Nutrition, metabolism, and cardiovascular diseases : NMCD 15 (4):293-301, 2005. REF ID: TRENTO 2005		started within 1 year of diagnosis Age <70 and at least 1 year previous attendance in the clinic All patients were on 4-daily insulin injections and practiced SMBG. Exclusion criteria: none given	HbA1c, % (SD)	8.3 (0.15)	9.2 (1.64)	months) 6 more visits delivered over the remainder of the 36 months observation Programme developed further based on two rounds of focus group sessions and feedback Programme topics included: differences between type 1 diabetes and type 2 diabetes; principles of nutrition; classification of nutrients; composition of food and food exchanges (personal habits and day-to-day management; how to embed	education sessions from the same psychopaedagogist involved in the group care Also offered 15 individual visits over the 3-year observation period.		Knowledge of diabetes - GISED (95% CI) CHANGE FROM BASELINE	3.10 (1.56 to 4.65) thus SD is 4.14	0.24 (-0.32 to 0.80) thus SD is 1.44	Not ITT analysis No mention of powering Drop-outs = acceptable (<20%)
			Diabetes, median years (IQR)	16 (13 - 19)	15 (12-19)				DQoL (SD) FINAL SCORE	70.55 (12.2)	84.06 (11.35)	
			GISED (knowledge of diabetes)	44.3 (6.97)	43.10 (6.28)				DQoL (95% CI) CHANGE FROM BASELINE	-8.82 (-12.51 to -5.14) thus SD is 9.87	3.34 (2.38 to 430) thus SD is 551.4	
			QoL (DQoL score)	79.4 (13.9)	80.7 (11.5)							
			NS differences between groups for any of the baseline characteristics except education level									

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures at 3 years – ACA data	Effect sizes	Comments
			(schooling). Concomitant medication: 7 patients in each group were on LisPro insulin, none were on hypolipidaemic agents. Drop-outs: n=1 (EDU) and n=3 (controls) due to lost-to-follow-up or not participating in final visit. Outcomes: HbA1c QoL scales: DQoL DQoL = 4 primary scales: satisfaction, impact, diabetes worry, and social/vocational worry. 46 core items each item score between 1 (very satisfied) and 5 (very dissatisfied. Total score thus ranges between 46 (higher QoL) and 230 (lower QoL). Knowledge of type 1 diabetes (GISED): 57-item questionnaire. Correct	eating patterns into daily life as tastes and habits change over time); physical exercise (adaptation of insulin dosage and daily activity); hypoglycaemia and hyperglycaemia (why they occur, how to recognise and manage them, how to inform relatives and friends); areas of insulin injection and their rotation; retinopathy, neuropathy, microalbinuria and nephropathy (self-care, when and how to screen);					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures at 3 years – ACA data	Effect sizes	Comments
			answers scored 1 point, wrong answers 0. Thus total score of 57.	hypertension and CV aspects. Also discussed HbA1c and day-to-day problems whenever they felt necessary.					

Table 76: KORHONEN 1983[84]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
T. Korhonen, J. K. Huttunen, A. Aro, M. Hentinen, O. Ihalainen, H. Majander, O. Siitonen, M.	RCT 9 centres in Finland	n=77 (n=39 in EDU; n=38 in Control) Inclusion criteria: Insulin-dependent diabetes Treated		EDU n=39	Control (C) n=38	Intensive education programme (group and individual) ITT: n=39 ACA: n=39 5 days in-hospital intensive	Traditional education at the hospital - control (C) ITT: n=38 ACA: n=38 Received in-hospital traditional 'old-fashioned'	5 days intervention 3 month and 1 year follow-up (post-intervention)		EDU	C	Funding: Grants from National Research Council for Medical Sciences, Finland; Nordisk Insulinfond; Finnish Cultural Foundation; Foundation for
			Age, years mean (SD)	31 (11.5)	35 (12.3)				Knowledge of diabetes % correct answers (SD) FINAL SCORE	3mths: 79.5 (1.9) 1 year: 82.3 (1.8)	3mths: 72 (2) 1 year: 73.4 (2)	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Uusitupa, and K. Pyorala. A controlled trial on the effects of patient education in the treatment of insulin-dependent diabetes. Diabetes Care 6 (3):256-261, 1983. REF ID: 150 (in old GL)		with insulin Age 16-57 years Duration of diabetes 1-17 years No symptoms or signs of significant micro- or macro-angiopathy No systematic education before the start of the study. Exclusion criteria: none given	Women, %	46	45	education (2 x 30 min sessions plus pre-pre-printed material) Instruction was both individually and in small groups Given by a team of two physicians, a dietician, and two teaching nurses who specialised in the treatment of diabetes. Met nurse and physician at all follow-up times (1,3,6,9,12,15,18 month post-intervention) Instructed to adjust their insulin dose during sick days and in other special situations and to call the	education that was given before the organisation of diabetes treatment. Met only the physicians during follow-up visits and not advised to change insulin dose without checking with the doctor.					Nutrition Research, Finland. Risk of bias: Randomisation = unclear. Stratified according to age, gender and diabetes duration (method not given) Allocation concealment = not mentioned Blinding = not mentioned ITT analysis (no drop-outs) No mention of powering Drop-outs = acceptable (NONE = <20%) Different extra care and advice given to the intervention
			Diabetes, mean years (SD)	7.8 (3.7)	8 (4)							
			Knowledge of diabetes % correct answers (SD)	69.5 (2.5)	63.2 (2.3)							
			SS differences between groups for baseline knowledge of diabetes but NS for all other characteristics. Concomitant medication: Not mentioned Drop-outs: None reported Outcomes: Compliance Knowledge Diabetic control (glucose measurements) Compliance: was evaluated in terms of diet history, with a 24 hour recall method at									

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			baseline and for every 3 months through to 18 months. Knowledge was assessed at baseline and at 3 and 12 months using a self-administered multiple choice test designed for the study. The questionnaire contained 105 questions covering areas such as diet, insulin administration, urine testing , hypoglycaemia, hyperglycaemia, and foot care Diabetic control: satisfactory metabolic control used abstract criteria with the following 3 criteria having to be met 1) fasting glucose concentration in morning before visit <7.2mmol/litre 2) urinary glucose excretion on the day preceding the visit <20g/24hrs 3) more than 75% of the urine tests since the previous visit free of glucose	nurse whenever problems from diabetes were encountered.					group

Table 77: deWEERDT 1991[35]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures at 6 months	Effect sizes		Comments
I de Weerdt, A. P. Visser, G. J. Kok, O. de Weerdt, and E. A. van der Veen. Randomized controlled multicentre evaluation of an education programme for insulin-treated diabetic patients: effects on metabolic control, quality of life, and costs of therapy. Diabetic Medicine. 8 (4):338-345, 1991. REF ID: 1571	Cluster RCT 15 centres in The Netherlands	n=558 (n=355 in EDU; n=203 in Control) Inclusion criteria: Age 18 to 65 years Insulin treatment over 6 months Able to understand and speak Dutch language Exclusion criteria: Pregnant		EDU n=355	Control (C) n=203	Structured Education programme – professional led or patient led (combined data for the 2 groups) ITT: n=355 ACA: ?? unclear Highly structured programme was on an out-patient basis 4 x weekly group sessions of 3 hours duration A video film, a book, and some practice	Usual care - control (C) ITT: n=203 ACA: ?? unclear Not given any extra education	4 weeks intervention 6 months (ie. 5 months post-intervention)		EDU	C	Funding: Grants from National Research Council for Medical Sciences, Finland; Nordisk Insulinfond Risk of bias: Randomisation = cluster. Unclear. (method not stated) Allocation concealment = not mentioned Blinding = not mentioned No mention of ITT analysis (drop-outs mentioned
			Age, years mean (SD)	44	47				HbA1c %, mean (SE) CHANGE FROM BASELINE	-0.25 (0.15); Calculated SD = 2.8	-0.1 (0.1) Calculated SD = 1.4	
			Women, %	Equal distribution of sexes	Equal distribution of sexes				Hypoglycaemia reactions per month - Grade 2 CHANGE FROM BASELINE (SE)	-0.05 (0.05) Calculated SD = 0.9	-0.1 (0.0) Calculated SD = 0	
			Diabetes, mean years (SE)	12 (0.7)	13.8 (0.7)							
			HbA1c %, mean (SE)	9.0 (1.7)	9.2 (1.6)							
			Hypoglycaemia reactions per month -	0.2 (0.1)	0.2 (0.0)				COST DATA REPORTED in STUDY			

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures at 6 months	Effect sizes	Comments
(in old GL)			Grade 2 NS differences between groups for any baseline characteristics. Concomitant medication: Not mentioned; insulin used similar in both groups (NS difference) Drop-outs: n=45 (7.5%) Outcomes: HbA1c Hypoglycaemia GRADE 2 – requiring assistance of a second person QoL – REPORTED BUT NOT USING DATA (SCALES ARE NOT COMMON: The Bradburn Affect-Balance scale, a general measure of well-being)	materials were used as part of the programme. The lessons also had a motivational function. Led by a trained nurse, a dietician or a patient with diabetes.					but unclear of how analysed or f data imputed or not) No mention of powering Drop-outs = acceptable (<20%)

Table 78: LENNON 1990[95]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures at 1 year	Effect sizes		Comments
G. M. Lennon, K. G. Taylor, L. Debney, and C. J. Bailey. Knowledge, attitudes, technical competence, and blood glucose control of Type 1 diabetic patients during and after an education programme. Diabetic Medicine. 7 (9):825-832, 1990. . REF ID: 1551 (in old GL)	RCT 1 centre in the UK	n=74 (n=42 in EDU; n=32 in Control) Inclusion criteria: Insulin-treated type 1 diabetes from diagnosis Age <60 years Duration of diabetes >1 year Ideal body weight <130% No serious complications Not pregnant Adequate understanding of		EDU n=31	Control (C) n=25	Structured Education programme (motivational and behavioural features) ITT: n=42 ACA: n=31 Education programme 12 x meetings at monthly intervals Different aspects of diabetes treatment and technical skills were considered. Topics were: diet, insulin, hypoglycaemia, diabetic control, exercise and	Usual care - control (C) ITT: n=32 ACA: n=25 received normal clinical care throughout, in which blood glucose control, diet, and insulin were reviewed at intervals of 3-6 months	1 year intervention Additional follow-up at 18 months (but only in intervention group)		EDU	C	Funding: None mentioned. Risk of bias: Randomisation = Unclear. (method not stated) Allocation concealment = not mentioned Blinding = not mentioned Not ITT analysis (completers) No mention of powering Drop-outs = HIGH (>20%)
			Age, years mean (SD)	32 (2.3)	40 (2.5)				HbA1c, % (SD) – 12 months	10.5 (0.3)	11.6 (0.4)	
			Women, %	48	28							
			HbA1c, % (SD)	11.8 (0.4)	11.8 (0.5)							
			Diabetes, mean years (SD)	11.7 (1.2)	15.8 (2.3)				Knowledge of diabetes % correct answers (SD) FINAL SCORE	1 year: 79.1 (3.5)	1 year: 56.3 (5.7)	
			Knowledge of diabetes % correct answers (SD)	62.7 (3.4)	60.1 (4.6)							
			Most baseline variables were similar, but the mean age of the control group was greater than the intervention group (p < 0.02) Concomitant medication: Not mentioned Drop-outs: EDU: n=11 (35%) and C: n=7 (28%)									

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures at 1 year	Effect sizes	Comments
		English language Exclusion criteria: none given	Outcomes: HbA1c Knowledge of diabetes (% questions correct): At baseline was DKQ1 (9 item MCQ questionnaire) on the major areas of diabetes management At 12 and 18 months was DKQ2 (16 item MCQ extended questionnaire to facilitate discrimination amongst patients with improved knowledge.	illness, ketones and hyperglycaemia, the new diet, complications of diabetes, new developments in research, and practical problems in self-management. Teaching was by both individual and group format methods.					

G.2.2 Carb counting

Table 79: BRAZEAU 2013 [19]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
A. S. Brazeau, H. Mircescu, K. Desjardins,	Cross-sectional Accuracy of patient CHO	n=50 Inclusion criteria: Adults aged ≥18 years type 1	Age, years, mean (SD) Women, %	42.7 (11.1) 48	Patient estimate of CHO Masked CGM placed.	Dietician assessment of CHO from food diary Food diaries analysed by	72 hours	HbA1c Major hypoglycaemia, Hypoglycaemia, events	Not reported Not reported Accuracy of patient CHO estimates was not	Funding: Supported by Foundation and research centre of the

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
C. Leroux, I. Strychar, J. M. Ekoe and R. Rabasa-Lhoret. Carbohydrate counting accuracy and blood glucose variability in adults with type 1 diabetes. Diabetes Research and Clinical Practice. 99 (1):19-23, 2013. REF ID: BRAZEAU 2013	estimates	diabetes duration >6 months Patients who had worn a CGM for 72 hours and completed concomitant food record assessing carb counting in ≥75% of meals Exclusion criteria:			Participant taught by a dietician to complete the food diary including their CHO estimates and told to keep food and exercise habits normal.	dietician using Food processor SQL. Mean absolute diff between patient CHO estimate and dietician CHO assessment calc.			significantly associated with the number of hypoglycaemias over the 72 hours	CHUM, an operating grant, Canadian Institutes of Health Research and FRSQ. Other: Main outcome is the accuracy of patient estimates of CHO content and association with BG fluctuations. Risk of bias: Observational study
			Diabetes duration, years, mean (SD)	21.4 (12.7)				Nocturnal Hypoglycaemia,	Not reported	
			BMI, kg/m2, mean (SD)	25.1 (3.6)				Hyperglycaemia, duration over 72 hour period	Low accuracy of CHO content estimates by patients was a predictor of longer time of hyperglycaemia (>10mmol/litre) and shorter time of BG between 4-10mmol/litre	
			HbA1c, %, geometric mean (SD)	7.6 (1.2)						
			Drop-outs: Not reported		IN BOTH GROUPS: • SCII (n=10) • Multiple daily injections with long acting basal analogue injections (n=39) • Intermediate NPH insulin as bedtime insulin (n=1) All patients used a short acting insulin analogue as pre-meal insulin			QOL	Not reported	
								Adverse events	Not reported	

Table 80: BAO 2001 [12]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
J. Bao, H. R. Gilbertson, R. Gray, D. Munns, G. Howard, P. Petocz, S. Colagiuri and J. C. Brand-Miller. Improving the estimation of mealtime insulin dose in adults with type I diabetes. Diabetes Care. 34:2146-2151, 2011. REF ID: BAO 2011	RCT - crossover NIDDA study	n=31 Inclusion criteria: Adults aged ≥ 18 and ≤70 years type 1 diabetes duration ≥1 year Use of insulin pump therapy (including use of bolus dose calculator for ≥2 months) HbA1c ≤9% Reliably performing SMBG at least 4 times daily. Exclusion criteria: Eating disorders Treated with medication known to			CHO counting and the Food Insulin Index (FII) algorithm applied to determine insulin bolus dose Test breakfast using CHO count and FII algorithm (two occasions: meal A had CHO content of 75g CHO; meal B had CHO content of 41g CHO; both had the same energy content). Results reported here only for meal B (75g CHO) with comparison. FII takes into account all dietary factors and not just CHO	CHO counting algorithm applied to determine insulin bolus dose Test breakfast using CHO counting algorithm alone (same CHO content as meal B – 75g)	Monitored for 3 hours after each test meal (3 test breakfasts on consecutive days)	HbA1c	Not reported	Funding: Funding not mentioned. Support provided by the University of Sydney Risk of bias: Order of 3 test meal-bolus algorithms randomly assigned using random digit table Allocation concealment - unclear Blinding = not mentioned Not ITT analysis (used ACA, excluding 3 drop-outs) Powered study (BG
			Age, years, mean (SD)	37.8 (14.4)				Severe hypoglycaemia events during 3-hour post-prandial	FII: 0 episodes CHO alone: 0 episodes	
			Women	17/28				Mild hypoglycaemic events that required treatment	FII: 6 episodes CHO alone: 1 episode	
			Diabetes duration, years, mean (SD)	19.6 (11.4)				Nocturnal Hypoglycaemia	Not reported	
								Time within normal BG (4-10mmol/litre) in 3 hour post-prandial period, min, mean (SD)	FII: 128 (57) CHO alone: 88 (69) Reported as P=0.025	
			HbA1c, %, mean (SD)	7.8 (0.9)						

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		affect blood glucose.	Drop-outs: n=3		IN BOTH GROUPS: Both groups: I:CHO ratio calculated before the study. CGM fitted in all participants Insulin treatment: Rapid acting insulin administered before each test meal and meal eaten within 20 minutes.			Glucose post-prandial 3 hour AUC, mmol x min/litre, mean (SD)	FII: 197 (220) CHO alone: 409 (373) Reported as P=0.015	AUC between CHO count and FII). Drop-outs = acceptable (<20%) ANCOVA analysis for BG level outcomes (best for cross-over studies)
								Peak blood glucose excursion in 3 hour post-prandial period, mmol/litre, mean (SD)	FII: 2.4 (1.9) CHO alone: 4.1 (3.1) Reported as P=0.009	

Table 81: Dias 2010 [38]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
V. M. Dias, J. A. Pandini, A. L. M. Sperandei, E. S. Portella, R. A. Cobas and M. Gomes. Effect of the	Observational before and after study/prospective case-series	n=55 Inclusion criteria: Aged 10-60 years type 1 diabetes (ADA	Age, years, mean (SD)	25.3 (1.55)	Carb counting Diet prescribed based on the carb counting method. Insulin dose adjusted based on carb content of each meal (1	Baseline	3 month	HbA1c, final value %, mean (SD)	9.52 (0.32) P=0.0009 as reported vs. baseline	Funding: Not reported Risk of bias: Before and after study design Not ITT
			Women, %	63				HbA1c direction of change from baseline (proportion of patients)	Reduction: 38/51 Increase: 11/51 Same: 2/51	

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
carbohydrates counting method on glycemic control in patients with type 1 diabetes. Diabetology & Metabolic Syndrome. 2:54, 2010. REF ID: DIAS 2010		criteria) Exclusion criteria: Illiteracy Diabetic nephropathy or retinopathy Pregnancy Mobility impairment	Diabetes duration, years, mean (SD)	11.31 (1.09)	unit SA human insulin for every 15g CHO). No SMBG during study Insulin treatment: All patients used MDI of SA insulin at meals + NPH as basal and at night.			Major hypoglycaemia	Not reported	analysis Drop-outs acceptable (<20%)
			BMI, kg/m2, mean (SD)	22.87 (0.42)				Hypoglycaemia	Not reported	
			HbA1c, %, mean (SD)	10.40 (0.33)				Nocturnal Hypoglycaemia	Not reported	
			Post-prandial glycaemia (mg/dl)	256.78 (12.82)				Post-prandial glycaemia (mg/dl)	3 months: 243.39 (15.92) P=0.46 as reported compared to baseline	
			Drop-outs: n=4 (excluded because did not attend FU)							

Table 82: FRANC 2009 [48]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
S. Franc, D. Dardari, B. Boucherie, J.-P. Riveline, M. Biedzinski, C. Petit, E. Requeda, P. Leurent,	Observational before and after study/prospective case-series	n=35 consecutive patients Inclusion criteria: type 1 diabetes duration >1 year			Personalised prandial algorithms for Flexible intensive insulin therapy (FIT) Patients taught how to use a personal	Baseline (patient been using FIT and personalised algorithms for 6 months but only with paper logbook and	4 months (mean 17 weeks, range 5-25 weeks. Median 18 weeks)	HbA1c, final value at end of study, %, mean (SD)	7.3 (0.6) P=0.003 as reported vs. baseline	Funding: P. Leurent founder, manager, shareholder & CEO of VOLUNTIS (company developed software
			Age, years, mean (SD)	39.1 (10.8)				Major hypoglycaemia, (required assistance)	None reported during study	
			Diabetes duration,	18.8 (11.1)				Minor hypoglycaemia	Baseline: 1.4	

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
M. Varroud-Vial, G. Hochberg, and G. Charpentier. Real-life application and validation of flexible intensive insulin-therapy algorithms in type 1 diabetes patients. Diabetes & Metabolism. 35 (6):463-468, 2009. REF ID: FRANC 2009		Use of the Flexible intensive insulin therapy (FIT) strategy for at least 6 months (CHO counting & algorithms to adjust prandial insulin to achieve post-prandial target of 7.8mmol/litre) and taken 5-day structured inpatient training on FIT at least 6 months before Treated with SCII or MDI Exclusion criteria:	years,		digital assistant phone (instead of paper logbook). Medical team entered personalised algorithms for FIT onto phone Before each meal, patient entered capillary BG and no. of 20g CHO portions intended to eat. Automatic calculation of prandial SA insulin dose (reduced by 30-50% if mod to intensive exercise planned). SMBG recommended 6 times daily (including	not calculated from phone)		(BG<3mmol/litre), events/individual/week	Week 12:0.8 (R2=0.19, P=0.156 as reported)	used). Grant from ALFEDIAM Sanofi-Aventis 2006 and technical support from VOLUNTIS Risk of bias: Before and after study, consecutive patients Drop-outs =acceptable (<20%) Additional: Patients varied CHO content from one day to the next and were shown to enjoy dietary freedom
			Women	12/35				Nocturnal Hypoglycaemia	Not reported	
			BMI, kg/m2, mean (SD)	25.1 (3.5)				Mean of individual BG excursions (2 hour post-prandial and before) mmol/litre	Breakfast: +0.07 Lunch: +0.14 Dinner: +0.06	
			HbA1c, %, mean	7.8 (0.9)						

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
					before and 2 hours after each meal). Data transmitted and feedback could be given by caregivers at all times.					
			Drop-outs: n=6 (due to technical problems with phone)		INSULIN TREATMENT IN BOTH GROUPS: CSII (n=14) MDI (n=21) – glargine and lispro, or aspart					

Table 83: KILBRIDE 2011 [75]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length follow-up	Outcome measures	Effect sizes	Comments
L. Kilbride, J. Charlton, G. Aitken, G. W. Hill, R. C. R. Davison and J. McKnight. Managing blood glucose during and after exercise in type 1 diabetes:	Prospective Cohort study, not randomised	n=14 Inclusion criteria: Adults 20-50years type 1 diabetes duration >2years Stable blood glucose control			Algorithm for CHO & insulin adjustment (week 2) Algorithm considered time of exercise in relation to FA insulin, CHO consumption and BG levels.	Self-management (week 1)	2 weeks (each cross-over period1 week)	HbA1c, final value %,	Not reported	Funding: Supported by an Investigator-initiated Study Program from LifeScan Inc.
			Age, years, mean (SD)	37.5 (9.5)				Severe hypoglycaemia episodes reported in diary (10 patients completed diary)	No events reported during study period	
			Women	6/14				Mild hypoglycaemia	On exercise days:	Risk of bias:

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length follow-up	Outcome measures	Effect sizes	Comments
reproducibility of glucose response and a trial of a structured algorithm adjusting insulin and carbohydrate intake. JCN. 20 3423-3429, 2011. REF ID: KILBRIDE 2011		(HbA1c <10%) Experienced in carb counting and insulin adjustment by education Exclusion criteria: Resting BP >165/90 mmHg Diagnosed peripheral vascular disease Orthopaedic problems preventing brisk walking Diagnosed heart disease Proliferative retinopathy Hypoglycaemia unawareness			Algorithm reduces usual insulin dose when exercising within 2 hours of eating CHO. CHO prescribed as per algorithm if BG <10mmol/litre prior to exercise (30, 20 and 10g for 4, 6 or 8mmol/litre, respectively). Post-exercise 30% reduction in next insulin dose Evening exercise (extra 10-20g CHO consumed before bed if <10mmol/litre)			episodes reported in diary, episodes/week (10 patients completed diary)	Algorithm week: 2 Self-man week: 18 On non-exercise days: Algorithm week: 27 Self-man week: 34	No randomisation Drop-outs = acceptable (<20%) Other: Main outcomes are BG levels during and after exercise (also reports time spent in normal range of 4-9mmol/litre).
			BMI, kg/m2, mean (SD)	25 (4.5)				Hypoglycaemia (mean duration <4mmol/litre during 40min exercise sessions, CGM)	Algorithm week: 0.3 (0.9) minutes Self-man week: 2.8 (4.5) minutes	
			HbA1c, %, mean (SD)	7.5 (0.7)				Hypoglycaemia (mean duration <4mmol/litre during 6-hour post-exercise period, CGM)	Algorithm week: 19.6 (32.4) minutes Self-man week: 24.2 (44.7) minutes	
			Drop-outs: n=1 (only completed week 1)							
					IN BOTH GROUPS:			Nocturnal Hypoglycaemia	Not reported	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length follow-up	Outcome measures	Effect sizes	Comments
				2 exercise sessions during each week to assess BG response to exercise during both management strategies (consisting of 40 min treadmill walk with intensity to elicit 50% VO2max) INSULIN TREATMENT: All used basal bolus insulin regime (long-acting basal insulin once-daily and fast-acting insulin boluses at meal times). All participants used analogue insulin (basal – lantus; bolus – Humalog or novorapid)				

Table 84: KLUPA 2008 [81]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
T. Klupa, T. Benbenek-Klupa, M. Malecki, M. Szalecki and J. Sieradzki. Clinical usefulness of a bolus calculator	Observational retrospective cohort study	n=18 Inclusion criteria: type 1 diabetes Treated with CSII for at least 4 years using SA insulin		BC n=8	Non-users (n=10)	Bolus calculator Treated with paradigm 712 insulin pump with bolus calculator function for at least 9	No bolus calculator (trained in carb counting) Treated with paradigm 712 insulin pump but not using	Patients in interventi on groups using BC for 9 months		BC	Non-users	Funding: T. Benbenek employee of Medtronic Risk of bias: No randomisat ion (observatio
			Age, years, range	19-48	21-51				HbA1c,	6.8%	7%	
			Women	3/8	5/10				2 hour Post-prandial BG over 7 days, mmol/litre, mean (SD)	7.6 (2.2)	8.3 (2.4) *P<0.05	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
in maintaining normoglycaemia in active professional patients with type 1 diabetes treated with CSII. J of Int. Medical Res. 36:1112-1116, 2008. REF ID: KLUPA 2008		analogues Well trained in food counting (including carb, protein and lipid counting and GI estimation) Exclusion criteria: Using sensor augmented insulin pumps with real-time glucose monitoring.	Diabetes duration, years, range	6-16	11-22	months Bolus calculator parameters set by the physician	bolus calculator or treated with MiniMed 508 insulin pump without bolus calculator function.		BG in target range 70-140mg/dl (n=3 in each group CMBG)	78%	69%	nal retrospective cohort study) No ANCOVA
									Hypoglycaemic episodes/day, mean (n=3 in each group CMBG)	1.4	1.6	
									Nocturnal Hypoglycaemia			
			Drop-outs: Not reported			IN BOTH GROUPS: All treated with CSII (Lispro n=15, Aspart n=3) CGMS used by 3 patients in each group SMBG 8 times daily			QOL	Not reported		
									Adverse events	Not reported		

Table 85: LAURENZI 2011 [91]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
A.Laurenzi, A.M. Bolla, G.Panigoni	RCT	n=61 randomised		CHO counting n=28	Control n=28 analyse	Carb counting using Insulin:	Control (n=31	24 weeks-training during first	HbA1c, change score (baseline vs. 24wk) %,	ACA (n=28): P=0.252 as	Funding: Supported by

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
, V.Doria, A. Uccellatore, E. Peretti, A.Saibene, G. Galimberti, E. Bosi and M. Scavini. Effects of carbohydrate counting on glucose control and quality of life over 24 weeks in adult patients with type 1 diabetes on CSII. Diabetes Care. 34:823-827, 2011. REF ID: LAURENZI 2011	GIOCAR trial	Inclusion criteria: Adults aged 18-65 years type 1 diabetes treated with CSII for >3 months Exclusion criteria: Previous training in CHO counting Serum creatinine >124µmol/litre in women and >150µmol/litre in men Celiac disease Pregnancy Severe comorbidities Any disability preventing compliance with study procedures		analysed	d	carbohydrate ratio (I:CHO) and sensitivity factor (n=30 randomised) Patients use I:CHO ratio and sensitivity factor to estimate preprandial insulin dose, taking into account preprandial BG and planned CHO. Trained on carb counting during first 12 weeks (4-5 individual sessions with dietician and diabetologist).	randomised) No training – continued to estimate pre-meal insulin dose in an empirical way	12 weeks. HbA1c measured at 12 and 24 weeks	mean	reported PP analysis: CHO (n=20): -0.4% Control (n=27): -0.05% (P=0.05 as reported)	unrestricted educational grant from GSK. Risk of bias: Randomisation = randomly assigned (computerised random no. generator) Allocation concealment = Yes Blinding = open label. ACA (n=28 per group) performed for QOL (excluded drop-outs but included those not adhering to protocol) – incorrectly reports this as 'ITT' Per-protocol analysis performed for HbA1c
			Age, mean (SD)	41.2 (10.0)	39.8 (9.8)				Major hypoglycaemia requiring assistance	None reported during study	
			Women, %	46.4% (13/28)	67.9% (19/28)				Hypoglycaemia events (BG 2.8mmol/litre)	Freq. reported as similar between 2 groups for both ACA and PP analysis	
			Diabetes duration, years mean (SD)	21.9 (11.0)	19.8 (11.7)	IN BOTH GROUPS: Same glucose meter for SMBG (OneTouch Ultra2; LifeScan Inc.). Patients asked to SMBG 6 times daily. INSULIN TREATMENT: Patients on Glulisine, Lispro or			Nocturnal Hypoglycaemia	Not reported	
			BMI, kg/m2	23.7 (21-	23.8 (20.8-				Adverse events		

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			median (IQR)	25.2)	26.8)	Aspart. All patients attended a session with the dietician about the recommended diet for patients with diabetes before randomisation.					(excluded all drop-outs and those not adhering to protocol) Drop-outs = >20% in intervention group Mixed effects model used for HbA1c levels and hypoglycaemia events
			HbA1c, %, mean (SD)	7.9 (0.9)	8.1 (1.5)						
			Drop-outs: n=14	n=10 (n=6 due to discontinuation of CHO counting (<75% meals); n=2 due to shift from CSII to MDI for >7days; 2 drop-outs)	n=4 (1 due to shift from CSII to MDI for >7days; 3 drop-outs)				DSQOLS, change from baseline at 24weeks (increase = better QOL), median (IQR). Analysed as ACA (n=28)	Social relations: CHO: 2 (-2.5 to 3.5) Control: 0 (-1.5 to 5); Leisure-time: CHO: -0.5 (-2 to 1), Control: 0 (-1.5 to 5); Physical complaints: CHO: 2 (0 to 4.5), Control: 2 (-0.5 to 5); Future worries: CHO: 1 (-1 to 4), Control: 0 (-1.5 to 3); Diet	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
										restrictions: CHO: 5.5 (0.5 to 8.5), Control: 0 (-2 to 3.5); Daily hassles: CHO: 1.5 (-2.5 to 6), Control: 2 (-1.5 to 3.5); Hypoglycaemia fears: CHO: 0.5 (-2 to 7.5), Control: 1 (-5.5 to 5.5) Reported as SS for diet restrictions (P=0.008)	

Table 86: MAURIZI 2011 [101]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
A. R. Maurizi, A. Lauria, D. Maggi, A.	RCT	n=40 Inclusion criteria: Adults aged		Calsulin n=20	Control n=20	Calsulin n=20 Provided with logbook and	Control n=20 Provided with	6 months	HbA1c, final value %, mean (SD) at 3 months	Calsulin: 7.3 (0.5) Control: 7.7 (1.0)	Funding: Educational grant from Thorpe Ltd.

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Palermo, E. Fioriti, S. Manfrini and P. Pozzilli. A novel insulin unit calculator for the management of type 1 diabetes. Diabetes Technology and Therapeutics. 13 (4):425-428, 2011. REF ID: MAURIZI 2011		18-65 years type 1 diabetes defined according to ADA Diabetes duration >1year Exclusion criteria: Learning disabilities Severe diabetic complication Chronic conditions which might influence daily activities (visual or auditory disability, motor impairment for neurological or orthopaedic problems).	Age, years, mean (SD)	34.5 (15)	39.3 (13)	individual target blood glucose, I:CHO ratio and insulin sensitivity factor (ISF) prior to study Trained on use of the insulin units calculator Calsulin (Thorpe Products Ltd.) to administer insulin dose (enter pre-meal BG, I:CHO ratio, CHO content, post-meal exercise).	logbook and individual target blood glucose, I:CHO ratio and insulin sensitivity factor (ISF) prior to study No Calsulin device provided		HbA1c, change score %, at 6 months	Calsulin: -0.85 Control:-0.07 Reported as P<0.05	Thorpe Ltd. Had no role in the study design, management of data or manuscript preparation. Risk of bias: Randomisation = unclear (as details not given) Allocation concealment = not mentioned Blinding = open label Drop-outs and loss to FU not reported Powered study (HbA1c)
			Women, %	35%	35%				Major hypoglycaemia events	Only reported as no significant differences in frequency of hypoglycaemic events between groups	
			Diabetes duration, years, mean (SD)	14.4 (10.8)	13.4 (7.0)				Hypoglycaemia, total events		
			BMI, kg/m2, mean (SD)	23.7 (3.6)	24.7 (6.1)				Nocturnal Hypoglycaemia	Not reported	
			HbA1c, %, mean (SD)	7.9 (1.0)	7.8 (1.6)				QOL	Not reported	
			Drop-outs: Not reported			IN BOTH GROUPS: All subjects provided with a logbook and instructed to SMBG, estimate meal CHO content and perform regular exercise. Target blood glucose, I:CHO ratio and insulin sensitivity factor (ISF) determined for all patients (I:CHO ratio calculated by '500 rule'. ISF			Adverse events	Not reported	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
						calculated by '1800 rule'. INSULIN TREATMENT: Not reported (MDI suggested?) All subjects followed up with visits every 3 months					

Table 87: SCAVONE 2010 [135]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measure	Effect sizes	Comments
G. Scavone, A. Manto, D. Pitocco, L. Gagliardi, S. Caputo, L. Mancini, F. Zaccardi and G. Ghirlanda. Effect of carbohydrate counting and medical nutritional therapy on glycaemic control in type 1 diabetic subjects: a pilot study. Diabetic Medicine.	RCT	n=256 Inclusion criteria: type 1 diabetes duration >5 years Exclusion criteria: BMI>40 kg/m2 Poor glycaemic control (HbA1c>14%) Pregnancy Presence of severe		NEP n= 100	Control n= 156	Nutritional educational programme (NEP) n=100 Phase 1 (4 weeks, 1 session per week): educational training on carb counting & nutrition (including importance of CHO equal to 55-65% of daily calorie intake, and adjustment of insulin to CHO, exercise	Control (no education programme) n=156 No training programme preceded the 9 months	9 months (4 weeks training for intervention group preceded the 9 months).	HbA1c, final value at 9 months, %, mean (SD)	NEP: 7.4 (0.9) Control: 7.5 (1.1) Reported as significant change from baseline (P<0.01, ACA)	Funding: Not reported Risk of bias: Randomisation = unclear (as details not given) Allocation concealment = unclear Blinding = none reported Not ITT. Used ACA and excluded patients lost to FU from
			Age, years, mean (SD)	39 (11)	39 (11)				Hypoglycaemic events, <3.9 mmol/litre	NEP: 4% Control: 7% Reported as P<0.05 (ACA)	
			Women, %	51.0	52.6				Major hypoglycaemia,	Not reported	
			Diabetes duration,	Only reported as not different between groups at baseline					Nocturnal Hypoglycaemia,	Not reported	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measure	Effect sizes	Comments
27:477-479, 2010. REF ID: SCAVONE 2010		diabetic complications No subjects had followed any dietetic/educational programme before the study	Weight, kg,	Only reported as not different between groups at baseline		and pre-meal BG). Based on the guidelines proposed by the EASD. Phase 2: application of NEP (9 months). Patients reassessed every 3 months			QOL	Not reported	analysis Drop-outs = acceptable (<20% in total) but, there was a 27% diff in drop-out between groups with all drop-outs in the intervention group. Not done ANCOVA
			HbA1c, %, mean (SD)	7.8 (1.3)	7.5 (0.8)	IN BOTH GROUPS: Patients measured BG 6-times daily (before and 2 hours after breakfast, lunch and dinner). INSULIN TREATMENT: Basal insulin administered at evening meal or bedtime. Rapid acting insulin administered at each meal Logbook kept of daily BG and hypoglycaemic events.			Adverse events	Not reported	
			Drop-outs: n=27 (loss to FU)	n=27	n=0						

Table 88: SCHMIDT 2012 [138]

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments

Reference	Study type	No. of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes			Comments
Signe Schmidt, Merete Meldgaard, Nermin Serifovski, Camilla Storm, Tomas Moller Christensen, Birthe Gade-Rasmussen, and Kirsten Norgaard. Use of an automated bolus calculator in MDI-treated type 1 diabetes: the BolusCal Study, a randomized controlled	Prospective, randomised, controlled, open label, three-arm parallel, bi-centric study conducted in Denmark	n= 63 (n=8, control; n=21, CarbCount; n=22, CarbCount Automated Bolus Calculator) Inclusion criteria: Age 18-65 years type 1 diabetes duration ≥12 months Use of multiple daily injections (MDI) Exclusion criteria:					CarbCount Automated Bolus Calculator (CarbCountABC): group received FIIT during a 3-h group teaching, were taught carbohydrate counting, estimated individual ICRs and ISFs and were also provided with and instructed in the use of the ABC.	CarbCount (manual bolus calculation) group received FIIT during a 3-h group teaching, were taught carbohydrate counting, estimated individual ICRs and ISFs Control taught principles of healthy diet but not taught carb counting	16 Weeks		ABC	CarbCount	Control	Funding: not reported. Risk of bias: Randomisation: "randomisation with a 1:3:3 ratio in blocks of 14" Allocation concealment: sealed, opaque envelopes containing the group assignments. The envelopes had been prepared by a person not otherwise involved in the study" Blinding: not
				ABC (n=22)	CC (n=21)	Control (n=8)				HbA1c (%), mean (SD)	8.1 (0.4)	8.4 (0.9)	8.9 (1.1)	
			Age (years), mean (SD)	42 (10)	41 (10)	46 (SD 9)				HbA1c (%) within-group difference, (95% CI)	-0.7 (-1.0 to -0.4)	-0.8 (-1.3 to -0.3)	-0.1 (-1 to -0.7)	
			Gender (m/f)	10/12	10/11	6/2				Severe hypoglycaemia, N	2	2	1	
			Diabetes duration (years)	21 (SD 9)	19 (SD 10)	14 (SD 12)				#HFS (0-100 scale) - higher scores indicate more fear, mean (SD)	22.6 (16.7)	22.8 (13.8)	24.5 (18.2)	
			HbA1c (%)	8.8 (SD 0.7)	9.2 (SD 0.6)	9.1 (SD 0.7)				HFS within-group difference, (95% CI)	-3.4 (-7.2 to 0.3)	-5.2 (-9.8 to -0.6)	-1.9 (-10 to 6.2)	
			BMI (kg/m2), mean (SD)	25.8 (SD 3.3)	27.3 (SD 4.4)	26.4 (SD 5.6)				&PAID (0-100 scale) - higher scores indicate	25.6 (15.3)	28.0 (19.2)	27.2 (18.8)	

Reference	Study type	No. of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes			Comments
pilot study. Diabetes Care 35 (5):984-990, 2012. REF ID: SCHMIDT 2012		Pregnancy Nursing Gastroparesis Present or former practice of carbohydrate counting								more problems, mean (SD)				applicable – open label trial ITT analysis: Powered study: study was powered. Drop-outs: 12 patients (19%) dropped out overall. Drop-outs per group not reported. Relatively small sample size
										PAID within-group difference, (95% CI)	-6.9 (-13.5 to -0.4)	-5.8 (-12 to -0.5)	-3.3 (-21 to 14.4)	
										^ADDQoL Total (-9 to 9) - higher scores indicate positive impact, mean (SD)	-1.8 (1.6)	-1.8 (1.6)	-1.4 (0.9)	
										ADDQoL within-group difference, (95% CI)	0.4 (0.0 to 0.7)	0.2 (-0.1 to 0.5)	0.6 (-0.8 to 1.9)	
										DTSQ Total (0 - 36) - higher scores indicate treatment satisfaction, mean	31.5 (3.3)	26.4 (6.0)	28.5 (5.1)	

Reference	Study type	No. of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes			Comments
							(SD)				
							DTSQ within-group difference, (95% CI)	9.1 (6 to 12. 2)	3.0 (0.8 to 5.3)	2.0 (-0.5 to 4.5)	
			Drop-outs: 12 patients (19%) dropped out overall. Drop-outs per group not reported. Baseline characteristics of the randomised patient sample did not differ significantly between the 3 study groups				*Comparison of means between Control, CarbCount, and CarbCountABC. Analysis performed using ANOVA. #HFS – Hypoglycaemia Fear Survey. &PAID – Problem Areas In Diabetes. ^ADDQoL – Audit of Diabetes-Dependent Quality of Life. DTSQ – Diabetes treatment satisfaction questionnaire				

Table 89: ZIEGLER 2013 (ABACUS TRIAL)

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
ABACUS trial R Ziegler, DA. Cavan, I Cranston, K Barnard, J Ryder, C Vogel, CG.	RCT (parallel) Multicentre (UK and Germany)	n= 218 type 1 diabetes and type 2 diabetes (93% type 1 diabetes) n=218	type 1 diabetes and type 2 diabetes patients (92.7% type 1 diabetes)			Advanced usual care + integrated bolus calculator BG meter (Accu-Chek Aviva Expert blood glucose	Standard bolus + enhanced usual care Standard BG meter and manual	26 weeks		BC n= 105	Standard bolus n= 113	Funding: Roche Diagnostics
				Standard Bolus	BC n= 105				HbA1c, % change from baseline	-0.7 (SD 0.7)	-0.5 (SD 0.7)	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Parkin et al. Use of an Insulin Bolus Advisor Improves Glycemic Control in Multiple Daily Insulin Injection (MDI) Therapy Patients With Suboptimal Glycemic Control: First results from the ABACUS trial. Diabetes Care, 2013. REF ID: ZIEGLER 2013		Inclusion criteria: type 1 diabetes and type 2 diabetes ≥18 years Poorly controlled diabetes (>7.5% HbA1c) MDI-treated for ≥6 months Adjustment of meal doses based on CHO content Completion of CHO training within the past 2 years. Exclusion criteria: Treatment with NPH,		n= 113		meter; Roche) patients had to discontinue use of their current BG meter The Aviva Expert includes automated bolus advisor (prandial and correction bolus recommendations based on current BG value, planned CHO intake, and individual therapy parameters programmed into the meter Meter auto calculates insulin bolus for the user and stores BG ad meal info in an electronic diary. Investigators entered each	bolus calculation ---------- In both groups: patients received individualised MDI and CHO counting training to address knowledge deficits (as identified at screening)					Risk of bias: Randomisation: unclear Allocation concealment: not reported Blinding: not applicable ITT analysis: adequate Powered study: HbA1c Drop-outs: acceptable <20%
			Age (years), mean (SD)	42 (15)	43 (14)				Hypoglycaemia (<70mg/dl), number of patients	43	31	
			Diabetes duration mean years, (SD)	17 (12)	18 (11)				Severe hypoglycaemia (<36mg/dl or 3rd party assistance, number of patients	11	7	
			Male, %	53	58				QoL Improvement (Diabetes treatment satisfaction Questionnaire): DTSQ (8 questions each on a 7-point scale)	11.4 (SD 6.0)	9.0 (SD 6.3)	
			HbA1c, % (SD)	8.9 (1.3)	8.9 (1.1)				Nocturnal hypoglycaemia	Not reported		
			Drop-outs: BOLUS: n=20 (18%) and STD: n=5 (5%)						Adverse events	Not reported		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		pre-mixed insulin, noninsulin injectable a-diabetic medication or oral a-diabetic agents (except metformin) Use of fixed dose treatment Use of sliding scale insulin doses determined exclusively by specific BG results.		patients therapy parameters into their meter and conducted 1hr training sessions regarding its use.					

G.2.3 Glycaemic index diet

Table 90: Calle-Pascual 1988[23]

Reference	Study type	Number of participants	Participant characteristics			Intervention	Comparison	Length of follow-up	Outcome measure	Effect sizes	Comments
Calle-Pascual AL, Gomez V,	Non-randomised crossover	n = 34 of which	All participants	HFD n = 12	LFD n = 12	Low GI diet (Diet A)	High GI diet (Diet B)	Each dietintervention lasted	HbA1c, final value at 4 weeks, %,	type 1 diabetes only:	Funding: Not reported

Reference	Study type	Number of participants	Participant characteristics			Intervention	Comparison	Length of follow-up	Outcome measure	Effect sizes	Comments
Leon E, Bordiu E. Foods with a low glycemic index do not improve glycemic control of both type 1 and type 2 diabetic patients after one month of therapy. Diabetes and Metabolisme. 1988; 14(5):629-633	study	type 1 diabetes = 16 type 2 diabetes = 18 Inclusion criteria: Not strictly inclusion criteria but the study states that the participants were chosen from "a group previously educated in self-monitoring of capillary glucose at home" and that they were all "under treatment with 2 daily doses of insulin".	underwent both interventions as this was a crossover study.	(type 1 diabetes only)	(type 1 diabetes only)	This included 5 different foods with GI between 29 and 36: lentils, chickpeas, red kidney beans, haricot beans and peas.	This included 5 different foods with GI between 50 and 92: rice, potatoes, carrots, spaghetti and beetroot.	for 4 weeks (i.e. 8 weeks in total), and HbA1c was measured at the end of each period.	mean (SD)	Low GI = 9.27 (0.45) High GI = 9.02 (0.39)	Risk of bias: Observational study Participant comparability = Unclear Allocation method = High Blinding = High Treatment comparability = Low Follow-up length = Low Outcome availability = Low Outcome definition = High Drop-outs = High Overall = VERY HIGH
			Age, years, mean (SD)	type 1 diabetes only: 25.6 (4.3)					Hypoglycaemic events, <3.0 mmol/litre, per patient per month, mean (SD)	Not reported	
			Sex, M:F	Not reported					Major hypoglycaemia	Not reported	
			Diabetes duration	Not reported					Nocturnal Hypoglycaemia	Not reported	
			BMI, kg/m2,	type 1 diabetes only: 20.96 (2.21)					Post prandial hyperglycaemia	Not reported	
			HbA1c, %, mean (SD)	Not reported		IN BOTH GROUPS: The participants were given a diet with a high carbohydrate (60%) and low fat (20%) content. A quarter (25%) of the carbohydrates was supplied at lunch. Each of the food listed above was			Adherence to treatment (Poor compliance was <45% of total energy +/- fibre consumption >20g/day LFD,	No figures have been given. "Patients had to bring the reagent strips used	

Reference	Study type	Number of participants	Participant characteristics		Intervention	Comparison	Length of follow-up	Outcome measure	Effect sizes	Comments
		Exclusion criteria: No pre-enrolment exclusion criteria have been stated, however, the study intended to and did exclude participants during the study period if they i) went through any changes in weight >1% of their initial body weight, or ii) changed their insulin doses.			eaten 5 or 6 times and had to be eaten at lunch.			<30g day HF diet)	for determining their capillary glucose the following day and their compliance was confirmed. ”	
			Insulin dose (U/day)	type 1 diabetes only: 39.98 (16.58)				QoL	Not reported	
			Drop-outs	type 1 diabetes only: n = 4				Satisfaction with treatment	Not reported	
								Adverse events (gastrointestinal, flatulence, meteorism and diarrhoea)	Not reported	

Table 91: Fontvieille 1992[46,47]

Reference	Study type	Number of participants	Participant characteristics			Intervention	Comparison	Length of follow-up	Outcome measure	Effect sizes	Comments
Fontvieille AM, Rizkalla SW, Penfornis A, Acosta M, Bornet FR, Slama G. The use of low glycaemic index foods improves metabolic control of diabetic patients over five weeks. Diabetic Medicine. 1992; 9(5):444-450	Crossover RCT	n = 18 type 1 diabetes = 12 type 2 diabetes = 6 Inclusion criteria: The study does not list inclusion criteria, however, it provides a description of the participants: "Twelve were classified as having Type I diabetes on the basis of a past clinical history of severe ketosis and	All participants underwent both interventions as this was a crossover study.	HFD n = 18 (9 in one period)	LFD n = 18 (9 in one period)	Low GI Intake of rice, biscuits, pasta, apples, peas/beans and rye bread was recommended	High GI Intake of bread, potato and bananas was recommended	5 weeks of each period (10 weeks in total)	No statistically different results were observed for type 1 diabetes and type 2 diabetes patients, thus, results are considered for the whole group.		Funding: Pierre and Marie Curie University, Paris, France Risk of bias: Randomisation = High Allocation concealment = High Blinding = High Drop-outs = Low Outcome assessment not described fully = High Outcome indirect (type 1 diabetes & type 2 diabetes combined) Overall =
									HbA1c, final value at 5 weeks, %, mean (SD)	Low GI = 8.3 (1.5) High GI = 8.3 (1.4)	
			Age, years, mean (SD)	1D only:1D only: 42.7 (10.3)					Hypoglycaemic events, <3.0 mmol/litre, per patient per month, mean (SD)	Not reported	
			Sex, M:F	type 1 diabetes only: 10:2					Major hypoglycaemia,	Not reported	
			Diabetes duration	type 1 diabetes only: 13.4 (5.1)					Nocturnal Hypoglycaemia,	Not reported	
			BMI, kg/m2,	type 1 diabetes only: 23.7 (2.2)					Post prandial hyperglycaemia	Not reported	

Reference	Study type	Number of participants	Participant characteristics		Intervention	Comparison	Length of follow-up	Outcome measure	Effect sizes	Comments
		weight loss at onset, and low or undetectable plasma C-peptide values at entry. The other six patients were classified as having Type 2 diabetes and were treated with oral antidiabetic drugs. Before entry into the study, the patients had been seen on a regular basis (at least every 6 months) at our department. ”	HbA1c, %, mean (SD)	Not reported	IN BOTH GROUPS: Each participant entered a run-in period of 15 days to have a homogeneous group. During this period they were asked to follow their usual diet more strictly. Participants were recommended to consume 55% of their caloric intake as carbohydrate, 15% as protein and 30% as lipid. However, baseline dietary inquiry showed that they actually consumed 45% carbohydrate, 18% protein and 37% lipid.			Adherence to treatment (Poor compliance was <45% of total energy +/- fibre consumption >20g/day LFD, <30g day HF diet)	“The diet plans were followed as prescribed .”	VERY HIGH
			Insulin dose (U/day)	40.9 (12.8)				QoL	Not reported	
			Drop-outs	n = 0				Satisfaction with treatment	“Both diets were fond acceptable by the participants.”	
								Adverse events (gastrointestinal, flatulence, meteorism and diarrhoea)	Not reported	

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measure	Effect sizes	Comments
		Exclusion criteria: Not reported							

Table 92: Lafrance 1998[89]

Reference	Study type	Number of participants	Participant characteristics			Interventions	Interventions	Length of follow-up	Outcome measure	Effect sizes	Comments
Lafrance L, Rabasa-Lhoret R, Poisson D, Ducros F, Caisson JL. Effects of different glycaemic index foods and dietary fibre intake on glycaemic control in type 1 diabetic patients on intensive	Crossover RCT	n = 9 Inclusion criteria: The study does not list inclusion criteria, however, it provides a description of the participants: "The participants had been on intensive insulin therapy for at least 3 months and	All participants underwent all four interventions as this was a crossover study.	Group A = Low GI = 9	Group B = Intermediate GI = 9	Group A Low GI GI < 60 diet	Group B (Control period) Intermediate GI All patients began with this intermediate GI (60 - 90) and low fibre intake diet and were then randomised consecutively without wash-out to Group A, C or D.	12 days for each intervention (48 days in total)	HbA1c, final value at 12 days, %, mean (SD)	All capillary blood glucose concentrations were comparable between the diets. HbA1c before study for all groups = 5.8% (0.6%) HbA1c after study for all groups = 5.4% (0.6%)	Funding: Pierre and Marie Curie University, Paris, France Risk of bias: Randomisation = High Allocation concealment = High Blinding = High Drop-outs = Low Overall = VERY HIGH
				Group C = High GI = 9	Group D = High fibre = 9						
			Age, years, mean (SD)	Not reported					Hypoglycaemic events, <3.0	Minor hypoglycaemia (< 4.0 mmol/litre :	

Reference	Study type	Number of participants	Participant characteristics		Interventions	Interventions	Length of follow-up	Outcome measure	Effect sizes	Comments
insulin therapy. Diabetic Medicine. 1998; 15(11):972 -978		were accustomed to calculating their pre-meal insulin dose. Gastroparesis was excluded in all patients by gastric emptying analysis.” Exclusion criteria: Not reported						mmol/litre, per patient per month, mean (SD)	Low GI = 4.3 (1.3) Interm GI = 3.2 (0.24) High GI = 4.0 (2.8) High fibre = 2.7 (2.8)	
			Sex, M:F	7:2	Group C High GI GI > 90 diet	Group D High fibre Intermediate GI (60 - 90) + high fibre food choices ensuring a daily intake of at least 40g of fibre		Major hypoglycaemia,	Group A = 0 Group B = 0 Group C = 0 Group D = 0	
			Diabetes duration	15.0 (7.5)				Nocturnal Hypoglycaemia,	Not reported	
			BMI, kg/m2,	type 1 diabetes only: 23.7 (2.2)				Post prandial hyperglycaemia	Not reported	
			HbA1c, %, mean (SD)	5.8 (0.6)	IN ALL GROUPS: For each experimental diet, the subjects were advised to maintain their usual energy intake and distribution: 50 - 55% carbohydrate, 15 - 20% protein and 25 - 30% lipids. They were counselled on keeping dietary records but had no instruction on the GI or fibre content of food.			Adherence to treatment (Poor compliance was <45% of total energy +/- fibre consumption >20g/day	Based on the dietary diaries of the participants, the diets were reported to be identical for energy intake and distribution	

Reference	Study type	Number of participants	Participant characteristics			Interventions	Interventions	Length of follow-up	Outcome measure	Effect sizes	Comments
									LFD, <30g day HF diet)	of carbohydrates, lipids and proteins. The prescribed distribution was closely followed for the 3 daily meals with the exception of a slightly but significantly lower carbohydrate intake for dinner on the high GI diet (45.5%; p=0.01)	
			Insulin dose (U/day)	Not reported					QoL	Not reported	
			Drop-outs	n = 0	n = 0				Satisfaction with treatment	Not reported	
									Adverse events (gastrointestinal, flatulence,	Not reported	

Reference	Study type	Number of participants	Participant characteristics	Interventions	Interventions	Length of follow-up	Outcome measure	Effect sizes	Comments
							meteorism and diarrhoea)		

Table 93: McCulloch 1985[105]

Reference	Study type	Number of participants	Participant characteristics			Intervention	Comparison	Length of follow-up	Outcome measure	Effect sizes	Comments
McCulloch DK, Mitchell RD, Ambler J, Tattersall RB. A prospective comparison of 'conventional' and high carbohydrate/ high fibre/low fat diets in adults with established type 1 (insulin-dependent) diabetes. Diabetologia. 1985; 28(4):208-212	RCT	n = 25 randomised to either of the 2 groups in the 2nd part of this study (this is the part that is relevant to this review) Inclusion criteria: type 1 diabetes Completion of the initial run-in period (3 months) Completion of the first intervention (6 months) of either small group		New diet* (ND) n = 12 (13 initially randomised)	Current diet (CD) n = 10 (12 initially randomised)	*New diet = High carb + high fibre + low fat In addition to being instructed to maintain a consistent daily carbohydrate profile, participants were told to alter the content of the diet in accordance with the British Diabetic Association's "dietary recommendations for diabetics in the	Current diet Continuation of current diet	Assessment for the current diet group took place 6 months after enrolment for the 2nd part of the study. The new diet group followed their new regimen for 4 months, then they were followed up 6 months	N.B. Final assessment time points: ND = 10 months CD = 6 months		Funding: British Diabetic Association development project grant Risk of bias: Comparability of interventions = High Randomisation = High Allocation concealment = High Blinding = High Drop-outs = High Different follow-up time points = Very high
			Age, years, mean (SD)	ND = 39.3 (3.9) CD = 29.8 (2.8)					HbA1c, final value, %, mean (SD)	ND = 10.0 (0.6) CD = 9.5 (0.4)	
			Sex, M:F	ND = 7:5 CD = 5:5					Hypoglycaemic events, <3.0 mmol/litre, per patient per month, mean (SD)	Not reported	
			Diabetes duration	ND = 14.3 (1.8) CD = 11.6 (1.3)					Major hypoglycaemia	Not reported	
			BMI, kg/m2,	ND = 24.3 (0.5) CD = 23.2 (0.8)					Nocturnal Hypoglycaemia	Not reported	
									Post prandial hyperglycaemia	Not reported	

Reference	Study type	Number of participants	Participant characteristics		Intervention	Comparison	Length of follow-up	Outcome measure	Effect sizes	Comments
		teaching using a videotape or practical lunchtime demonstrations Willingness to continue participating in the study for a further 6 to 10 months			1980s": most carbohydrate to be eaten as polysaccharides, particularly fibre-rich unprocessed foods, and liberal consumption of vegetables and fruits at both midday and evening meals.		after the end of the new diet (i.e. 10 months after enrolment for the 2nd part of the study)			Overall = VERY HIGH
		Exclusion criteria: Not reported	HbA1c, %, mean (SD)	ND = 12.9 (0.5) CD = 12.0 (0.6)	IN BOTH GROUPS: During the last 6 months of the study, the participants were neither seen nor given dietary advice unless they had a specific query.			Adherence to treatment Definitions used in this study: Coefficient of variation (SD/mean x 100), based on the participants' self-reported food records Comparability of daily fibre intake	ND = 29.8% (SEM=6.7) CD = 28.1% (SEM=11.7) The daily fibre intake did not differ	

Reference	Study type	Number of participants	Participant characteristics			Intervention	Comparison	Length of follow-up	Outcome measure	Effect sizes	Comments
										significantly between the groups. Daily fibre intake (g): ND = 31.8 (1.7) CD = 28.5 (3.0)	
			Insulin dose (Unit/kg/day)	ND = 0.67 (0.03) CD = 0.88 (0.08)					QoL	Not reported	
			Drop-outs	n = 1	n = 2				Satisfaction with treatment	No comparative data (degree of enjoyableness only assessed for ND group)	
									Adverse events (gastrointestinal, flatulence, meteorism and diarrhoea)	Not reported	

Table 94: Venhaus 1988[162]

Reference	Study type	Number of participants	Participant characteristics			Intervention	Comparison	Length of follow-up	Outcome measure	Effect sizes	Comments
Venhaus A, Chantelau E. Self-selected unrefined and refined carbohydrate diets do not affect metabolic control in pump-treated diabetic patients. Diabetologia. 1988; 31(3):153-157	Crossover RCT	n = 10 Inclusion criteria: It is unclear whether the given description was inclusion criteria or not. It is stated that the participants were "self-selected (i.e. volunteered) non-obese outpatients with well-controlled Type 1 diabetes who are on subcutane	All participants underwent both interventions as this was a crossover study.	Unrefined carbohydrate diet (URD) n = 10	Refined carbohydrate diet (RD) n = 10	URD: Low GI (and rich in fibre) The participants were instructed to avoid refined fibre-depleted carbohydrates, such as sucrose, white bread, white rice, mashed potatoes and other highly-processed foods, including juices, except for treatment of hypoglycaemia. Whole grain products, leguminous seeds, such as peas, lentils, beans, vegetables	RD: High GI (and fibre-depleted) The participants were instructed to avoid whole grain products, and the intake of vegetables and fruits was limited to one serving of processed vegetables per day and less than five servings of fresh fruit per week. Refined sugar was permitted up to	6 weeks for each period (i.e. 12 weeks in total)	HbA1c, final value at 6 weeks, %, mean (SD)	URD = 6.3 (0.8) RD = 5.8 (0.5)	Funding: Peter Klockner Stiftung, Duisburg, Germany (West Germany at the time of publication) and the West German Sugar Bureau Risk of bias: Randomisation = High Allocation concealment = High Blinding = High Drop-outs = Low Outcome definitions not fully described =
			Age, years, mean (SD)	27 (9)					Hypoglycaemic events, <3.0 mmol/litre, per patient per month, mean (SD)	Mild hypoglycaemic episodes (≤ 2.5 mmol/litre per group per month): URD = 9.6 (6.6) RD = 11.4 (8.5)	
			Sex, M:F	8:2					Major hypoglycaemia,	None	
			Diabetes duration	13 (8)					Nocturnal Hypoglycaemia,	Not reported	

Reference	Study type	Number of participants	Participant characteristics		Intervention	Comparison	Length of follow-up	Outcome measure	Effect sizes	Comments
		ous insulin infusion therapy. Exclusion criteria: Not reported	BMI, kg/m2,	22.6 (1.7)	and fruits were recommended to the participants.	50g/day.		Post prandial hyperglycaemia	Overall hyperglycaemia episodes: URD = 18.2 (9.5) RD = 16.7 (7.5)	High Overall = VERY HIGH
			HbA1c, %, mean (SD)	6.4 (0.7)	IN BOTH GROUPS: All participants had a 4-week run-in period on their habitual diet prior to randomisation.			Adherence to treatment (Poor compliance was <45% of total energy +/- fibre consumption >20g/day LFD, <30g day HF diet)	Not reported in the methods section that compliance to diet prescription was attested at two further diet inquiries taken at the end of each 3-week period, however, no figures have	

Reference	Study type	Number of participants	Participant characteristics			Intervention	Comparison	Length of follow-up	Outcome measure	Effect sizes	Comments
										been reported.)	
			Insulin dose (U/day)	41.7 (6.9)					QoL	Not reported	
			Drop-outs	n = 0	n = 0				Satisfaction with treatment	Not reported	
									Adverse events (gastrointestinal, flatulence, meteorism and diarrhoea)	No ketoacidosis occurred during the study. No other adverse events were reported.	

G.3 Blood glucose monitoring

G.3.1 HbA1c

Table 95: Araszkiewicz 2006

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments

Reference	Study type	Number of patients	Patient characteristics		Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
A. Araszkiewicz, D. A. Zozulinska, M. M. Trepinska, and B. Wierusz-Wysocka. Inflammatory markers as risk factors for microangiopathy in type 1 diabetic patients on functional intensive insulin therapy from the onset of the disease. Diabetes Res.Clin.Pract. 74 (2 suppl.):S34	Case series (prospective) Country: Poland	N = 100 recruited N = 88 completed baseline measurements Inclusion criteria: Aged < 30 years Newly diagnosed type 1 diabetes Hospitalised due to DKA at a particular diabetes department in Poland between 1994 and 1999. Attendance at a 5-day structured training program during hospitalisation Exclusion	Age (years) - mean (SD)	24.3 (6.2)	All participants were treated with intensive functional insulin therapy from the onset of disease and there was no comparator.	Mean follow-up = 6.1 ± 1.6 years	After 6 years of follow-up, diabetic retinopathy was found in 18 participants (20%) and positive albuminuria in 17 participants (19%).		Funding: Poznań University of Medical Sciences Risk of bias: Appropriate eligibility criteria Appropriate measurement of exposure and outcome Controlled for confounding factors Adequate follow-up
			Number of M:F	22:33			C-peptide level, ng/ml	W/ retinopathy (n=17) 0.17 ± 0.42	
			type 1 diabetes	100%				W/out retinopathy (n=69) 0.06 ± 0.19	
			Mean age at onset of diabetes (SD)	Not reported				Positive low-level (micro) albuminuria (n=18) 0.06 ± 0.25	
			Mean diabetes duration (SD)	Not reported				Negative low-level (micro) albuminuria (n=70) 0.1 ± 0.30	
			Mean HbA1c (%) ± SD	8.1 ± 1.9			High sensitivity C-reactive protein, mg/litre	W/ retinopathy (n=17) 2.3 ± 0.6	
			Mean BMI (kg/m2) ± SD	23.5 ± 3.2				W/out retinopathy (n=69) 2.0 ± 0.3	
			Missing data:					Positive low-level (micro) albuminuria (n=18) 4.9 ± 1.5	
								Negative low-level (micro) albuminuria (n=70) 1.8 ± 0.2	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
-S40, 2006. Araszkiewicz 2006		criteria: Acute or latent inflammatory focuses Liver dysfunction Connective tissue disease Renal failure and other severe diseases				Relationship between development of retinopathy and HbA1c	HbA1c <7.0% vs. >7.0% OR = 1.35 95% CI 0.21 to 8.52 p = 1.0 Patients with retinopathy had higher values of HbA1c (p = 0.04) than those without	
						Relationship between development of low-level (micro) albuminuria and HbA1c	HbA1c <7.0% vs. >7.0% OR = 4.25 95% CI 0.50 to 35.50 p=0.27 Patients with low-level (micro) albuminuria had higher values of HbA1c (p = 0.04) than those without	
						Number of people reaching target HbA1c, n/N (%)	Not reported	
						Final HbA1c value, %	W/ retinopathy (n=17) 8.8 ± 1.3	
							W/out retinopathy (n=69) 8.1 ± 1.4	
							Positive low-level (micro)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
							albuminuria (n=18) 8.8 ± 1.3	
							Negative low-level (micro) albuminuria (n=70) 8.8 ± 1.3	
						Incidence of hypoglycaemic episodes	Not reported	
						Incidence of severe hypoglycaemic episodes	Not reported	
						Incidence of nocturnal hypoglycaemic episodes	Not reported	
						Number of adverse events/complications/avoidance	Not reported	
						Quality of life	Not reported	

Table 96: Eeg-Olofsson 2010

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
K Eeg-Olofsson,	Case series (retrospectiv	N = 7,454	Mean age	All patients 36.9 [10.0 to	Patients with HbA1c 5.0 –	All patients were	Number of adverse events n (events per 1,000 person years)		Funding: The

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
Jan Cederholm, Peter M. Nilsson, Bjorn Zethelius, Ann Marie Svensson, Soffia Gudbjornsdottir, and Bjorn Eliasson. Glycemic control and cardiovascular disease in 7,454 patients with type 1 diabetes: an observational study from the Swedish National Diabetes Register (NDR). Diabetes Care 33 (7):1640-1646, 2010.	e) Country: Sweden	Inclusion criteria: type 1 diabetes patients on the Swedish National Diabetes Register Age range of 20 to 65 years Diabetes duration of 1 to 35 years Exclusion criteria: Not reported	[95% CI]	0.12] HbA1c 5.0 – 7.9% 36.4 [9.8 – 0.15] HbA1c 8.0 – 11.9% 37.4 [10.2 – 0.18] p = < 0.001	7.9% vs. Patients with HbA1c 8.0 – 11.9%	followed from baseline until a cardiovascular event or death or otherwise until censor date 31 December 2007. Maximum follow-up = 5 years Mean follow-up = 4.95 years			Swedish Association of Local Authorities and Regions funds the Swedish National Diabetes register.
			M:F (overall)	55.8%:44.2%			All CVD	All patients = 154 (4.7) HbA1c 5.0 to 7.9% = 55 (3.0) HbA1c 8.0 to 11.9% = 99 (6.9) p = < 0.001	
			type 1 diabetes	100%			Fatal CVD	All patients = 36 HbA1c 5.0 to 7.9% = 17 HbA1c 8.0 to 11.9% = 19	
			Mean age of diabetes onset ± SD	Not reported			All CHD	All patients = 131 (4.0) HbA1c 5.0 to 7.9% = 45 (2.4) HbA1c 8.0 to 11.9% = 86 (6.0) p = < 0.001	
			Mean diabetes duration (years) ± SD	All patients 19.9 [9.1 to 0.11] HbA1c 5.0 – 7.9% 19.1 [9.3 – 0.14] HbA1c 8.0 – 11.9%			Fatal CHD	All patients = 34 HbA1c 5.0 to 7.9% = 17 HbA1c 8.0 to 11.9% = 17	
							All stroke	All patients = 37 (1.1) HbA1c 5.0 to 7.9% = 14 (0.7)	

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
Eeg-Olofsson 2006				20.9 [8.9 – 0.15]					
				p = < 0.001				HbA1c 8.0 – 11.9% = 23 (1.6)	
								p = < 0.05	
			Mean HbA1c (%) ± SD	All patients 8.0 [1.2 to 0.01]			Fatal stroke	All patients = 4 HbA1c 5.0 to 7.9% = 0 HbA1c 8.0 to 11.9% = 4	
				HbA1c 5.0 – 7.9% 7.2 [0.6 to 0.01]			All mortality	All patients = 94 (2.8)	
								HbA1c 5.0 – 7.9% = 50 (2.7)	
				HbA1c 8.0 – 11.9% 9.0 [0.8 to 0.01]				HbA1c 8.0 – 11.9% = 44 (3.0)	
				p = < 0.001				Non-significant	
			Mean BMI (kg/m2) [95% CI]	All patients 25.3 [3.7 to 0.04]			Non-CVD mortality	All patients = 58 HbA1c 5.0 – 7.9% = 33 HbA1c 8.0 – 11.9% = 25	
				HbA1c 5.0 – 7.9% 25.1 [3.5 to 0.06]			Incidence and hazard ratios of adverse events with baseline or updated mean HbA1c as predictor n/N (%); HR [95% CI] i) Model 1: adjusted for age, sex, diabetes duration, systolic BP, total cholesterol ii) Model 2: Model 1 + adjusted for albuminuria (>20µg/min)		
				HbA1c 8.0 – 11.9% 25.5 [3.8 to 0.07]					
				p = < 0.001					

Reference	Study type	Number of patients	Patient characteristics	Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
			Missing data:			All CVD	154/7454 (2.07%) Baseline HbA1c as predictor: i) 1.26 [1.09 to 1.45] ii) 1.22 [1.06 to 1.40] Updated mean HbA1c as predictor: i) 1.32 [1.14 to 1.54] ii) 1.27 [1.09 to 1.80]	
						All CHD	131/7454 (1.76%) Baseline HbA1c as predictor: i) 1.31 [1.12 to 1.52] ii) 1.28 [1.09 to 1.49] Updated mean HbA1c as predictor: i) 1.34 [1.14 to 1.58] ii) 1.30 [1.10 to 1.53]	
						All stroke	37/7454 (0.50%) Baseline HbA1c as predictor: i) 1.12 [0.83 to 1.51] ii) 1.08 [0.80 to 1.47] Updated mean HbA1c as predictor: i) 1.24 [0.89 to 1.72] ii) 1.19 [0.86 to 1.66]	
						All mortality	94/7454 (1.26%) Baseline HbA1c as predictor: i) 0.97 [0.80 to 1.17] ii) 0.92 [0.76 to 1.11]	

Reference	Study type	Number of patients	Patient characteristics	Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
							Updated mean HbA1c as predictor: i) 1.04 [0.85 to 1.28] ii) 0.98 [0.80 to 1.20]	
						Incidence and hazard ratios for adverse events with baseline HbA1c as predictor, by mean baseline HbA1c categories n/N (%); HR [95% CI] i) Model 1 adjustment (details as above) ii) Model 2 adjustment (details as above)		
						All CVD	HbA1c 5.0 to 7.9%: n/N (%) = 55/4186 (1.31%) i) HR = 1 ii) HR = 1 HbA1c 8.0 to 11.9%: n/N (%) = 99/3268 (3.03%) i) HR = 1.70 [1.21 to 2.38] ii) HR = 1.59 [1.13 to 2.24]	
						All CHD	HbA1c 5.0 to 7.9%: n/N (%) = 45/4186 (1.08%) i) HR = 1 ii) HR = 1 HbA1c 8.0 to 11.9%: n/N (%) = 86/3268 (2.63%) i) HR = 1.80 [1.24 to 2.60] ii) HR = 1.71 [1.18 to 2.48]	
						All stroke	HbA1c 5.0 to 7.9%: n/N (%) = 14/4186 (0.33%)	

Reference	Study type	Number of patients	Patient characteristics	Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
							i) HR = 1 ii) HR = 1 HbA1c 8.0 to 11.9%: n/N (%) = 23/3268 (0.70%) i) HR = 1.51 [0.76 to 2.98] ii) HR = 1.40 [0.70 to 2.79]	
						Incidence of any hypoglycaemic episodes	Not reported	
						Quality of life	Not reported	

Table 97: Forrest 2000

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparisons	Length of follow-up	Outcome measures	Effect sizes	Comments
K. Y. Forrest, D. J. Becker, L. H. Kuller, S. K. Wolfson, and T. J. Orchard. Are predictors of coronary	Case series (prospective) Country: USA	N = 658 met eligibility criteria Inclusion criteria: Diagnosed or seen within a year of diagnosis at a particular hospital	Mean age	28	Not applicable	6 years	Incidence of coronary heart disease (CHD)	No CHD = 566 (86.0%)	Funding: National Institutes of Health, USA
			M:F	332:326				CHD morbidity = 46 (7.0%)	
			type 1 diabetes	100%				CHD mortality = 18 (2.7%)	
			Mean age of diabetes onset ± SD	Not reported				Total CHD = 64* (9.7%)	
			Mean diabetes duration (years) ±	No CHD 18.4 ± 7.2			The subjects who developed either macrovascular outcome were found to be older and to have a longer duration of type 1 diabetes. The prevalence of hypertension and blood pressure levels were higher at baseline for		
				CHD morbidity 25.7 ± 6.6					

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparisons	Length of follow-up	Outcome measures	Effect sizes	Comments
heart disease and lower-extremity arterial disease in type 1 diabetes the same? A prospective study. Atherosclerosis 148 (1):159-169, 2000. Forrest 2000		between 1950 and 1980 Diagnosed at an age of <17 years On insulin therapy at discharge Exclusion criteria: Not reported	SD, by CHD status	CHD mortality 25.9 ± 7.1			those who subsequently developed CHD or LEAD. Diastolic blood pressure showed no relationship to subsequent LEAD. HbA1c levels did not differ significantly between subjects whether or not they subsequently developed CHD or LEAD. Insulin dose was significantly lower in those with subsequent CHD, especially CHD morbidity, but showed no association with LEAD. The independent predictors of CHD mortality were hypertension, type 1 diabetes duration, Beck Depression Inventory scores, and white blood cell counts. The independent predictors of total CHD were hypertension, type 1 diabetes duration, Beck Depression Inventory scores, high density lipoprotein level and overt nephropathy. The independent predictors of LEAD were type 1 diabetes duration, HbA1c, low density lipoprotein level and smoking.		
				Total CHD 25.7 ± 6.6					
			Mean HbA1c (%) ± SD, by CHD status	No CHD 10.4 ± 1.9					
				CHD morbidity 10.2 ± 2.0					
				CHD mortality 10.7 ± 1.8					
				Total CHD 10.2 ± 1.9					
			Mean BMI (kg/m2) ± SD, by CHD status	No CHD 23.5 ± 3.3					
				CHD morbidity 24.3 ± 3.3					
				CHD mortality 23.3 ± 2.8					
				Total CHD 24.1 ± 3.3					
			Missing data: 623/658 (94.7%) provided follow-up data for coronary heart disease (CHD) incidence 567/658 (86.2%) provided follow-up data for lower-				Hypoglycaemic episodes, quality of life and other protocol-specified outcomes were not reported.		

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparisons	Length of follow-up	Outcome measures	Effect sizes	Comments
			extremity arterial disease (LEAD) incidence					

Table 98: Guerci 1999

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
B. Guerci, L. Meyer, S. Sommer, J. L. George, O. Ziegler, P. Drouin, and K. Angioi-Duprez. Severity of diabetic retinopathy is linked to lipoprotein (a) in type 1 diabetic patients. Diabetes & Metabolism 25 (5):412-	Cross-sectional study Country: France	N = 341 Inclusion criteria: type 1 diabetes patients of an outpatient clinic, diagnosed according to WHO criteria C-peptide negative On a weight-maintaining diet Treated by intensive conventional insulin therapy (split and mixed insulin regimens) Exclusion criteria: Recent onset of diabetes	Mean age	NR = 43.9 ± 15.7	Group 1 (NR): No retinopathy Group 2 (N-PDR): Non-proliferative diabetic retinopathy Group 3 (PDR): Proliferative diabetic retinopathy	N/A	Number of people in each group	NR = 123 N-PDR = 188 PDR = 30	Funding: Ministère de la Santé et de la Solidarité Nationale: Projet Hospitalier de Recherche Clinique 1994
				N-PDR = 48.7 ± 13.3			Number of people who had been diabetic for ≥20 years in each group	NR = 30 N-PDR = 108 PDR = 24	
				PDR = 49.9 ± 10.3			Independent variables that significantly predicted retinal status in all subjects	Diabetes duration Prevalence of microproteinuria Hypertension HbA1c	
				p < 0.01			Independent variables that significantly predicted retinal status in those who had had	Prevalence of microproteinuria HbA1c Lipoprotein (a)	

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
418, 1999. Guerci 1999		An episode of DKA, thyroid or liver disease, non-diabetic renal disease, pregnancy, acute/chronic inflammatory syndrome, alcoholism/malnutrition On diuretics, beta blockers, hypolipaemic agents, or any other drug or hormone known to influence lipid or lipoprotein metabolism					diabetes for ≥20 years		
			M:F	199:142			Hypoglycaemic episodes, adverse events, quality of life and other protocol-specified outcomes were not reported.		
			type 1 diabetes	100%					
			Mean age of diabetes onset ± SD	Not reported					
			Mean diabetes duration (years) ± SD	NR = 15.4 ± 8.8					
				N-PDR = 21.1 ± 7.8					
				PDR = 25.8 ± 3.5					
				p < 0.0001					
			Mean HbA1c (%) ± SD	NR = 7.25 ± 0.97					
				N-PDR = 7.44 ± 1.14					
				PDR = 8.01 ±1.32					
				p < 0.01					
			Mean BMI (kg/m2) ± SD	NR = 7.25 ± 0.97					
				N-PDR = 7.44 ± 1.14					
				PDR = 8.01 ± 1.32					
				p < 0.01					

Table 99: Hietala 2013

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
K. Hietala, J. Waden, C. Forsblom, V. Harjutsalo, J. Kyto, P. Summanen, P. H. Groop, and FinnDiane Study Group. HbA1c variability is associated with an increased risk of retinopathy requiring laser treatment in type 1 diabetes. Diabetologia 56 (4):737-745, 2013. Hietala 2013	Case series (Prospective) Country: Finland	N = 2,019 Inclusion criteria: Adult patients with type 1 diabetes C-peptide negative Age of onset <40 years Insulin treatment initiated within 1 year of diagnosis Exclusion criteria: Not reported	Mean age ± SD	35.0 ± 11.4	HbA1c variability quartiles: First quartile = 361 Second quartile = 365 Third quartile = 365 Fourth quartile = 368 In total, 1,459 patients were prospectively followed as a sub-cohort.	First follow-up: Mean ± SD = 5.2 ± 2.2 years	Number of people who had their first laser treatment during the follow-up period	175	Funding: Folkhälsan Research Foundation Wilhelm and Else Stockmann Foundation Finnish Eye Foundation European Commission Medicinska Understödsföreningen Liv och Hälsa Signe and Ane Gyllenberg Foundation Waldemar von Frenckell Foundation An EVO governmental grant
			M:F	995:1024					
			TID	100%					
			Mean age of diabetes onset ± SD	15.3 ± 9.2			Estimated 5-year cumulative incidence of laser treatment (%)	1st Q = 10% 2nd Q = 9% 3rd Q = 12% 4th Q = 19% p < 0.001	
							Mean HbA1c (%) at the first follow-up visit (N = 1,459)	1st Q = 8.1 ± 1.1 2nd Q = 8.3 ± 1.1 3rd Q = 8.4 ±1.1 4th Q = 8.6 ± 1.4 p < 0.001	
							Patients with nephropathy (N = 1,459)	1st Q = 4% 2nd Q = 4% 3rd Q = 6% 4th Q = 10% p = 0.001	
			Mean diabetes duration	22.9 ± 11.9			Mortality (N = 1,459)	1st Q = 1% 2nd Q = 2%	

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes			Comments
			(years) ± SD					3rd Q = 2% 4th Q = 2% p < 0.001			
			Mean HbA1c (%) ± SD	8.4 ± 1.2							
			Mean BMI (kg/m2) ± SD	25.0 ± 3.4			HbA1c variability by retinopathy status				
								No retinopathy (n = 311)	Non-proliferative retinopathy (n = 601)	Proliferative retinopathy (n=434)	
							Mean HbA1c (%) ± SD (p < 0.001)	8.2 ± 1.2	8.5 ± 1.2	8.7 ± 1.3	
							HbA1c variability (p = 0.03)	0.082 ± 0.050	0.081 ± 0.042	0.088 ± 0.042	
							Risk of proliferative retinopathy by HbA1c quartile: HR [95% CI]; p-value	1st Q: HR = 1; p = 0.003 2nd Q: HR = 1.3 [0.97 to 1.8]; p = 0.07 3rd Q: HR = 1.5 [1.1 to 2.0]; p < 0.001 4th Q: HR = 1.7 [1.3 to 2.2] Mean HbA1c: HR = 1.2 [1.1 to 13]; p < 0.001			

Reference	Study type	Number of patients	Patient characteristics	Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
						Hypoglycaemic episodes, quality of life and other protocol-specified outcomes were not reported.		

Table 100: Kullberg 1994

Reference	Study type	Number of patients	Patient characteristics		Interventions Comparisons	Length of follow-up	Outcome measures	Effect sizes	Comments
C. E. Kullberg, K. Finnstrom, and H. J. Arnqvist. Severity of background retinopathy in type 1 diabetes increases with the level of long-term glycated haemoglobin. Acta Ophthalmol (Oxf) 72 (2):181-188, 1994. Kullberg 1994	Case series (Retrospective) Country: Sweden	N = 90 Inclusion criteria: Adult type 1 diabetes patients that regularly attended an outpatient diabetes clinic during 1988 to 1991 Age at diagnosis ≤30 years Duration of diabetes ≤25 years Glycated haemoglobin followed for ≥5 years Having background	Mean age ± SD	35.2 ± 7.7	Not applicable	This was a retrospective data analyses of patients who were attending the clinic between 1988 and 1991. Their glycated haemoglobin had been determined on average for 9.2 years before the examination of retinopathy.	Mean HbA1c for whole measurement period (%) ± SD	7.2 ± 1.0	Funding: The Swedish Medical Research Council, the Swedish Diabetes Association, and the County Council of Östergötland
			M:F	50:40			Relative risks (RR) of background retinopathy for patients with HbA1c > 8% (n=22) vs. HbA1c ≤ 7% (n=41)	Patients with mean HbA1c > 8% had higher RRs for all kinds of background retinopathy compared to patients with HbA1c ≤ 7%	
			TID	100%					
			Mean age of diabetes onset ± SD	Not reported					
			Mean diabetes duration (years) ± SD	19.3 ± 4.2			Multiple regression analyses: Dependent variables were scores for retinopathy: higher score = worse state Independent variables were long and short term HbA1c	Mean HbA1c for the preceding year did not contribute further to any regression model.	
			Mean HbA1c (%) ± SD previous year	7.2 ± 1.3				The impact of long-term HbA1c concentration was significant	

Reference	Study type	Number of patients	Patient characteristics		Interventions Comparisons	Length of follow-up	Outcome measures	Effect sizes	Comments
		retinopathy at the latest regular retinopathy screening during 1988 to 1991 Exclusion criteria: Not reported					diabetes duration, age, sex, BMI, insulin dose per kg of body weight, hypertension, smoking	for all sets of retinopathy scores.	
			Mean BMI (kg/m2) ± SD	24.8 ± 3.2				Short and long term HbA1c measures were correlated (Pearson's r = 0.749, p < 0.001)	
							Hypoglycaemic episodes, quality of life and other protocol-specified outcomes were not reported.		

Table 101: LeCaire 2013

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
TJ. Lecaire, Mari Palta, Ronald Klein, Barbara E. K. Klein, and Karen J. Cruickshanks. Assessing progress in	Case series (prospective) Country: US	N = 888 [Wisconsin Diabetes Registry Study (WDRS) = 305 Wisconsin Epidemiologic Study of Diabetic	Mean age ± SD at exam	WDRS = 30.9 ± 7.0 WESDR = 33.4 ± 7.4	WDRS population was compared with WESDR population	20 years of diabetes duration was applied for data analyses	Presence of any diabetic retinopathy (DR)	WDRS = 281 (92.1%) WESDR = 567 (97.2%)	Funding: WDRS was supported by the National Institute of Diabetes and Digestive and Kidney Diseases.
			M:F	WDRS = 150:155 WESDR = 292:291			Proliferative DR or treated DR (DR grade ≥60 = very severe)	WDRS = 32 (10.5%) WESDR = 208 (35.7%)	

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes			Comments
retinopathy outcomes in type 1 diabetes: comparing findings from the Wisconsin Diabetes Registry Study and the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Diabetes Care 36 (3):631-637, 2013. LeCaire 2013		Retinopathy (WESDR) = 583] Inclusion criteria: WDRS All residents ≤30 years old in 28 counties of central and southern Wisconsin newly diagnosed with type 1 diabetes during May 1987 through to April 1992 WESDR type 1 diabetes patients from 11 counties of	TID	100%			DR category and HbA1c trend				WESDR was supported by the National Eye Institute, National Institutes of Health, Bethesda, MD.
			Mean age of diabetes onset ± SD	WDRS = 11.2 ± 7.0 WESDR = 14.1 ± 7.3			Registry	WDRS			
			Mean diabetes duration (years) ± SD	WDRS = 19.7 ± 1.2 WESDR = 19.2 ± 1.4			DR severity	None to minimal	Mild to moderate	Vision threatening	
							n (%)	n = 104 (34.1%)	n = 146 (47.9%)	n = 55 (18.0%)	
							Mean HbA1c (%)	7.6 ± 1.3	8.0 ± 1.4	8.8 ± 1.7	
							HbA1c < 7%	34.0%	18.5%	18.2%	
			Mean HbA1c (%) ± SD	WDRS = 8.0 ± 1.5 WESDR = 9.3 ± 1.7							
							Registry	WESDR			
			Number of patients with HbA1c <7%	WDRS = 72 (23.7%) WESDR = 40 (7.4%)			DR severity	None to minimal	Mild to moderate	Vision threatening	
							n (%)	n = 94 (16.1%)	n = 239 (40.5%)	n = 253 (43.4%)	
							Mean	8.7 ± 1.7	9.1 ± 1.6	9.7 ±	

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes			Comments
		central and southern Wisconsin during 1979 to 1980 who were diagnosed at <30 years old, all of whom were using insulin Exclusion criteria: Not reported					HbA1c (%)			1.7	
			Mean BMI (kg/m2) ± SD	WDRS = 28.3 ± 5.9 WESDR = 26.1 ± 4.6			HbA1c < 7%	11.1%	9.5%	4.2%	
			Number of patients on intensive insulin management (MDI or CSII)	WDRS = 285 (93.4%) WESDR = 124 (21.3%)			Odds ratios [95% Wald CI] from ordinal logistic regression analysis modelling the odds of DR severity by HbA1c (per 1%)	Adjusted for WESDR study cohort, age, sex, diabetes duration, education, and HbA1c: OR = 1.34 [1.23 to 1.47]			
								Adjusted for BPs in addition to the above adjustments: OR = 1.31 [1.20 to 1.43]			
							Ordinal logistic regression models for the three DR severity categories confirmed higher, unadjusted average odds of more severe retinopathy in the WESDR era than in the WDRS era (OR 3.3 [95% CI 2.5 to 4.3]). With adjustment for age, sex, diabetes duration and education, the OR was reduced to 3.0 [95% CI 2.2 to 4.0]. The inclusion of 20-year HbA1c in the model further reduced the OR for WESDR vs. WDRS to 2.2 [95% CI 1.6 to 3.0].				

Reference	Study type	Number of patients	Patient characteristics	Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
						Hypoglycaemic episodes, quality of life and other protocol-specified outcomes were not reported.		

Table 102: Nordwall 2009

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes			Comments
M Nordwall, Hans J. Arnqvist, Mats Bojestig, and Johnny Ludvigsson. Good glycemic control remains crucial in prevention of late diabetic complications--the Linkoping Diabetes Complications Study. Pediatr.Dia	Case-series with prospective and retrospective elements Country: Sweden	N = 269 Inclusion criteria: type 1 diabetes patients diagnosed <15 years old during 1961 to 1985 in the catchment area of a paediatric clinic in Sweden Exclusion criteria: Not reported	Mean age	Not reported	The study population was divided into 5 groups, according to the period of type 1 diabetes onset: G1) 1961 - 1965 G2) 1966 - 1970 G3) 1971 - 1975 G4) 1976 - 1980 G5) 1981 - 1985	The study patients diagnosed with type 1 diabetes during 1961 to 1985 were followed up until the end of the 1990s. HbA1c was measured regularly at the clinical visits 3 to 4 times per year.	HbA1c as a risk factor for diabetic retinopathy (DR) p < 0.001	No DR (n = 64)	Background DR (n = 131)	Severe laser-treated DR (n = 69)	Funding: The Juvenile Diabetes Research Foundation International (JDRF)-Wallenberg, the Swedish Research Council, and the Swedish Child Diabetes Foundation
			M:F	Not reported			Long-term HbA1c ± SD (%)	7.8 ± 0.8 (n = 62)	8.5 ± 0.8 (n = 130)	9.0 ± 1.0 (n = 52)	
			TID	100%			In a multivariable model, only diabetes duration (OR 1.2 [95% CI 1.1 to 1.3]; p < 0.001) and HbA1c (OR 4.1 [95% CI 1.8 to 9.2]; p = 0.001) showed a significant correlation to any retinopathy.				
			Mean age of diabetes onset ± SD	8.6 ± 3.8			HbA1c as a risk factor for nephropathy (DN) p < 0.001	No DN (n = 210)	Low-level (micro) albuminuria (n = 20)	Overt DN (n = 36)	
			Mean diabetes duration (years) ± SD	25.2 ± 7.6			Long-term HbA1c ± SD (%)	8.3 ± 0.9 (n = 206)	8.7 ± 0.9 (n = 19)	9.7 ± 1.1 (n = 19)	
							As with retinopathy, the significant correlation to				

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
betes 10 (3):168-176, 2009. Nordwall 2009			at last follow-up of retinopathy				nephropathy was shown only by diabetes duration (OR 1.1 [95% CI 1.0 to 1.2]; p = 0.016) and HbA1c (OR 2.6 [95% CI 1.3 to 5.1]; p = 0.007)		
			Mean diabetes duration (years) ± SD at last follow-up of nephropathy	25.5 ± 7.6			The influence of possible risk factors on the occurrence of overt nephropathy and severe retinopathy was analysed with Cox regression models. When the significant variables in the univariate analysis were entered in the model, the only significant variable for occurrence of retinopathy was HbA1c (HR 2.1 [95% CI 1.2 to 3.4]; p = 0.005), and for development of nephropathy, it was also HbA1c (HR 5.3 [95% CI 2.3 to 12.4]; p < 0.001) only. Other models with other combination of variables yielded the same result with HbA1c as the only significant variable.	
			Mean HbA1c (%) ± SD by period of onset	G1: 8.6 ± 0.9 G2: 8.5 ± 0.8 G3: 8.5 ± 0.9 G4: 8.4 ± 1.1 G5: 8.2 ± 0.9 p = 0.19			Hypoglycaemic episodes, quality of life and other protocol-specified outcomes were not reported.		
			Mean BMI (kg/m2) ± SD by period of onset	G1: 25.7 ± 3.5 G2: 25.5 ± 3.4 G3: 26.0 ± 4.2					

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
				G4: 25.6 ± 3.3 G5: 24.9 ± 3.6 p=0.63					
			Number of patients with severe retinopathy	69 (26.1%)					
			Number of patients with low-level (micro) albuminuria	20 (7.5%)					
			Number of patients with overt nephropathy	36 (13.5%)					

Table 103: Rossing 1996

Reference	Study type	Number of patients	Patient characteristics				Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
P. Rossing, P. Hougaard, K. Borch-Johnsen, and H. H. Parving.	Prospective or retrospective cohort study? Country: Denmark	N = 939 Inclusion criteria: Insulin-dependent	Nephropathy status	Normoal buminuria (n = 593)	Low-level (micro) albuminuria (n = 181)	Overt nephropathy (n = 165)	Not applicable	10 years	All-cause mortality, n (%)	Overall = 207/939 (22% of the study population died during the follow-up period)	Funding: None
			Mean	40 ± 12	38 ± 14	40 ± 13					

Reference	Study type	Number of patients	Patient characteristics				Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
Predictors of mortality in insulin dependent diabetes: 10 year observational follow up study. BMJ (Online) 313 (7060):779-784, 1996. Rossing 1996		diabetes ≥18 years old Had diabetes for ≥ 5 years Onset of diabetes at ≤40 years old Exclusion criteria: Patients who had been referred by the study group were excluded.	age ± SD (not significant)							w/ normoalbuminuria = 90/207 (43.5%) w/ low-level (micro) albuminuria = 45/207 (21.7%) w/ overt nephropathy = 72/207 (34.8%)	
			M:F (not significant)	302:291	96:85	95:70			Cardiovascular (CV) mortality, n (%)	Overall = 74/207 (35.7% of the deaths were due to CV causes) w/ normoalbuminuria = 33/74 (44.6%) w/ low-level (micro) albuminuria = 18/74 (24.3%) w/ overt nephropathy = 23/74 (31.1%)	
			Mean diabetes duration (years) [range] (p < 0.001)	17 [5 to 60]	21 [5 to 56]	22 [6 to 54]					
			Mean	8.8 ± 1.7	9.2 ± 2.0	9.5 ± 1.8			Significant	Male sex; age;	

Reference	Study type	Number of patients	Patient characteristics				Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
			HbA1c (%) ± SD ($p < 0.05$)						predictors of all-cause mortality (Cox multiple regression analysis)	eight; smoking; social class; presence of albuminuria; hypertension; log10 serum creatinine concentration; HbA1c (RR 1.11 [95% CI 1.03 to 1.20]; $p < 0.02$)	
			Number of people with retinopathy ($p < 0.001$)	107 (69%)	157 (87%)	162 (98%)					
			Mean age of diabetes onset ± SD	Not reported					Significant predictors of CV mortality (Cox multiple regression analysis)	Age; smoking; presence of low-level (micro) albuminuria; presence of overt nephropathy; hypertension	
			Mean BMI (kg/m2) ± SD	Not reported							
			type 1 diabetes	100%					Hypoglycaemic episodes, quality of life and other protocol-specified outcomes were not reported.		
			Missing data:								

Table 104: Weinstock 2013

Reference	Study type	Number of patients	Patient characteristics	Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes				Comments
R S. Weinstock, Dongyuan Xing, David M. Maahs, Aaron Michels, Michael R. Rickels, Anne L. Peters, Richard M. Bergenstal, Breanne Harris, Stephanie N. DuBose, Kellee M. Miller, Roy W. Beck, and D. Exchange Clinic Network. Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: results from the type 1 diabetes Exchange clinic registry. J.Clin.Endocrinol. Metab. 98 (8):3411-3419, 2013. Weinstock 2013	Cross-sectional study Country: US	N = 7012 Inclusion criteria: Patients on the type 1 diabetes Exchange Clinic Network database (registered by US-based paediatric and adult endocrinology practices) ≥ 26 years old Duration of type 1 diabetes ≥ 2 years Exclusion criteria: Not reported	type 1 diabetes	100%	Not applicable	There was no follow-up period as such as this was a cross-sectional study, however, information on the occurrence of severe hypoglycaemia (SH) and diabetic ketoacidosis (DKA) in the 12 months prior to enrolment was obtained from the participants.	Data available	SH data from 4973 participants DKA data from 6797 participants				Funding: The type 1 diabetes Exchange Clinic Network is funded through a grant provided by the Leona M. an Harry B. Helmsley Charitable Trust. Some of the authors of the study have received funding from industry.
			Age range	26 to 93 years old (mean age not reported)			Incidence of SH	≥ 1 SH events = 587/4973 (11.8%)				
							Incidence of DKA	≥ 1 DKA events = 326/6796 (4.8%)				
			Age categories: taken from those who provided DKA data	26 to 49 years old = 4108/6796 (60.4%)			HbA1c and frequency of SH event					
							Mean HbA1c (%)	n	% with ≥ 1 SH events	Initial multivariate model*, OR [95% CI] (p < 0.001)	Final multivariate model **, OR [95% CI] (p < 0.001)	
				50 to 64 years old = 2010/6796 (29.6%)			< 6.5	582	13.9	1.88 [1.34 to 2.62]	1.95 [1.40 to 2.72]	
							6.5 - 6.9	672	12.5	1.59 [1.15 to 2.21]	1.64 [1.18 to 2.72]	
				65 years old and above = 678/6796 (9.98%)			7.0 - 7.4	1002	8.3	1.0	1.0	
							7.5 - 7.9	907	12.4	1.46 [1.07 to	1.47 [1.09	

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes				Comments
										1.98]	to 2.00]	
			M:F	3078 (45%) : 3717 (55%)			8.0 - 8.9	1058	13.7	1.59 [1.19 to 2.13]	1.62 [1.21 to 2.17]	
			Ethnicity	91% non-Hispanic White			9.0 - 9.9	393	9.4	0.96 [0.63 to 1.46]	1.01 [0.66 to 1.52]	
			Mean diabetes duration (years) [IQR]	24 [15 to 34]			≥ 10.0	264	12.1	1.19 [1.76 to 1.89]	1.25 [0.80 to 1.97]	
							*The initial multivariate model includes variables having p-value of < 0.10. **The final multivariate model was conducted by using backward selection, keeping those variables with p value<0.01 and variables of clinical interest.					
							HbA1c and frequency of DKA event					
							Mean HbA1c (%)	n	% with ≥ 1 SH events	Initial multivariate model*, OR [95% CI] (p < 0.001)	Final multivariate model **, OR [95% CI] (p < 0.001)	
			Mean	Not			< 6.5	854	1.6	0.77	0.80	

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes				Comments
			age of diabetes onset ± SD	reported						[0.40 to 1.45]	[0.42 to 1.51]	
							6.5 - 6.9	983	2.7	1.24 [0.74 to 2.09]	1.26 [0.75 to 2.13]	
							7.0 - 7.4	1413	2.3	1.0	1.0	
			Mean HbA1c (%) ± SD	7.7 ± 1.2			7.5 - 7.9	1218	4.2	1.68 [1.07 to 2.64]	1.67 [1.06 to 2.61]	
							8.0 - 8.9	1363	5.5	1.93 [1.26 to 2.95]	1.98 [1.30 to 3.02]	
							9.0 - 9.9	503	10.3	3.16 [1.98 to 5.04]	3.41 [2.15 to 5.40]	
			BMI categories (mean BMI not reported): taken from those who provided	Underweight or Normal = 1697/4969 (34.2%)			≥ 10.0	334	21.0	5.22 [3.28 to 8.31]	6.26 [3.99 to 9.83]	
				Overweight = 1938/49			Quality of life and other protocol-specified outcomes were not reported.					

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
			DKA data	69 (39.0%)					
				Obese = 1334/4969 (26.8%)					
			Missing data:						

Table 105: Aiello 2014

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
LP Aiello and DCCT/EDIC Research Group. Diabetic retinopathy and other ocular findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care 37 (1):17-23, 2014. AIELLO 2014	Prospective Case-series (DCCT data as well as 10-year follow-up of original DCCT RCT = EDIC) NOTE: data linking HbA1c and retinopathy during the 10-year follow-up is	N = 1441 for the DCCT Inclusion criteria: DCCT patients follow-up 17 years (ie. 10 years EDIC) Original RCT: n=1441 (n=711 randomly assigned to intensive treatment, and n=730 to conventional treatment).	type 1 diabetes	DCCT: n=1441	After original DCCT (RCT) all patients who volunteered entered into a follow-up trial (EDIC) and were put on intensive therapy	DCCT: 6.5 years		At end of DCCT (6.5 years)	Funding: A number of research grants from National Institutes and academic bodies.
			NOT REPORTED				Retinopathy: Higher values of HbA1c were all associated with higher rate of retinopathy progression For each 10% decrease in HbA1c –eg. 9.0-8.1): 44% decreased risk of progression).		

Reference	Study type	Number of patients	Patient characteristics	Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
	not reported in this paper. Country: USA	Exclusion criteria: Not reported						

Table 106: Jacobsen 2013

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
JACOBSEN 2013 AM. Jacobson, BH. Braffett, PA. Cleary, RA. Gubitosi-Klug, ME. Larkin, and DCCT/EDIC Research Group. The long-term effects of type 1 diabetes treatment and complications on health-related quality of life: a 23-year follow-up of the Diabetes Control and Complications/Epidemiology of	Prospective Case-series (23-year follow-up of original DCCT RCT) Country: USA	N = 1177 (91%) completers of the 1287 EDIC patients Inclusion criteria: DCCT patients follow-up 23 years (ie. 17 years EDIC) Original RCT: n=1441 (n=711 randomly assigned to intensive treatment, and n=730 to	type 1 diabetes	DCCT 23 years/EDIC 17years: n=1175	After original DCCT (RCT) all patients who volunteered entered into a follow-up trial (EDIC) and were put on intensive therapy	23 years (DCCT) and 17 years (EDIC)		At 23 years follow-up	Funding: A number of research grants from National Institutes and academic bodies.
			Age mean	51			DQOL: Higher values of HbA1c were all associated with a sustained drop of ≥5 points in DQOL score (multivariate: HR 1.12, 95% CI 1.06 – 1.19; p<0.01). DQOL = 46 items; scale of 0-100. 100 = highest QoL.		
			Duration of diabetes, mean years	29.5					
			HbA1c, mean (SD)	7.9 (1.2)					
			Retinopathy	92%					
			DQOL, total	74.5			Retinopathy: Higher values of HbA1c were all associated with		

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
Diabetes Interventions and Complications cohort. Diabetes Care 36 (10):3131-3138, 2013.		conventional treatment). Completed DQoL survey at end of follow-up Exclusion criteria: Not reported	score, mean				a sustained drop of ≥5 points in DQOL score (multivariate: HR 1.12, 95% CI 1.06 – 1.19; p<0.01).		

Table 107: LIND 2011

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
LIND 2011 M Lind, I Bounias, M Olsson, S Gudbjornsdottir, AM Svensson, and A Rosengren. Glycaemic control and incidence of heart failure in 20,985 patients with type 1 diabetes: an observational study. Lancet 378 (9786):140-146, 2011.	Prospective Case-series Country: Sweden	N = 20,985 (n=635, 3% admitted to hospital for HF). Inclusion criteria: Age ≥18 years type 1 diabetes No known Heart Failure patients from Swedish National Diabetes registry (NDR) treatment with	type 1 diabetes	n=20,985	Followed until hospital admission for heart failure, death, or end of follow-up (Dec 2009)	Median follow-up 9.0 years (IQR 7.3-11.0)		At Follow-up	Funding: AstraZeneca, NovoNordisk, Swedish Heart and Lung Foundation, Swedish Research Council.
			Age mean	38.6			Heart failure: Incidence increased monotonically with HbA1c, with a range of 1.42 - 5.20 per 1000 patient-years in the lowest (<6.5%) and highest (≥10.5%) categories of HbA1c. Risk of HF per 1% increase in HbA1c: HR 1.30 (95% CI 1.21 – 1.40; p<0.0001).		
			Female	45%					
			Duration of diabetes, mean years	23.1					
			HbA1c, mean (SD)	8.8 (1.34)			Risk of HF at intervals of HbA1c (multivariate*):		
			BMI	25.0			<6.5% (reference)	1.0	
							6.5 to <7.5%	HR 1.26 (0.76	

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
		insulin only Age of onset ≤30 years Exclusion criteria: Not reported						– 2.07)	
							7.5 to <8.5%	HR 1.47 (0.91 – 2.38)	
							8.5 to <9.5%	HR 1.75 (1.07 – 2.85)	
							9.5 to <10.5%	HR 2.58 (1.54 – 4.34)	
							≥10.5%	HR 3.98 (2.23 – 7.14)	
							*adjusted for age, sex, duration of diabetes, smoking, BMI, blood pressure, comorbidities.		

Table 108: ZOFFMANN 2014

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
ZOFFMANN 2014 V. Zoffmann, D. Vistisen, and M. Due-Christensen. A cross-sectional study of glycaemic control, complications and psychosocial functioning among 18- to 35-year-old adults with Type 1 diabetes.	Cross-sectional study Country: Norway	N = 710 (completers, n=406, 57.2%) Inclusion criteria: Age 18-35 years type 1 diabetes From a referral centre Exclusion criteria: Not reported	type 1 diabetes	n=406 completers	Patient questionnaire PAID score (max 100): High levels of diabetes distress = PAID ≥30	N/A			Funding: Steno Diabetes Centre.
			Age mean	27.1			PAID score: SS higher prevalence of diabetes distress (PAID ≥30) among patients with HbA1c ≥8% (Score 48.3, 95% CI 41.4-55.3) vs. those with lower HbA1c (score 35.7, 95% CI 29.0 – 42.9), p<0.01. HbA1c was positively correlated with: lack of motivation, and the PAID score (both p<0.001). HbA1c was negatively correlated		
			Duration of diabetes, mean years	13.5					
			HbA1c, mean (SD)	8.2 (1.5)					
			BMI	24.8					
			CSII	13.3%					

Reference	Study type	Number of patients	Patient characteristics		Study groups	Length of follow-up	Outcome measures	Effect sizes	Comments
Diabet.Med. 31 (4):493-499, 2014.			No. of SMBG mmts/week PAID score, max 100 (SD)	28.9 29.1 (21.1)			with: perceived competence, self-esteem, well-being, and autonomy index (all p<0.001).		

Table 109: Agardh 1997[7]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Agardh 1997 [7]	Prospective case series Sweden	n=442 Inclusion criteria: type 1 diabetes, at least one HbA1c measurement per patient per observation year or at least two measurements in case of death (34 patients did not fulfil these criteria and were excluded from further	Age, years (mean±SD)	35±11	Case series; glucose control treatment not reported	5 years	Retinopathy Severe retinopathy (clinically significant macular oedema, severe non-proliferative or proliferative retinopathy) Urinary albumin concentration (UAC) change Death MI	Any retinopathy (n=64); HbA1c; 8.2±1.1% No retinopathy (n=57); HbA1c; 7.5±1.1%, p<0.01 Cumulative frequency retinopathy; 50% patients who still had no signs of retinopathy at 5 years, the mean HbA1c levels were <7.5% during the observation period 50% patients who developed any type of retinopathy, the mean HbA1c levels were >8.3% (P <0.0002 for all comparisons).	Funding: Crafoord Fndn, Lund, the Royal Physiographic Society, Lund, Crown Princess Margareta's Cittee for the Blind, the Medical Faculty, University of Lund, Tore Nilsson Fndn, the Swedish Society of Medicine, the
			Women, %	47	Concomitant therapy: some patients on antihypertensives				

		analysis) Exclusion criteria: none listed	TIDM, %	100			CV disease	In 50% patients who progressed to severe retinopathy mean HbA1c levels were >8.9%, (P <0.001) compared with patients without retinopathy at follow-up or those who developed any type of retinopathy	Novo Nordisk Research Fndn Swedish Diabetes Federation Risk of bias: Appropriate eligibility criteria=yes, although limited inclusion criteria Appropriate measurement of exposure and outcome=yes Controlled for confounding factors =unclear as no details of logistic regression modelling and unclear adjustments Adequate follow-up=yes 5 years
			Age at onset of diabetes, years (mean±SD)	15±8				UAC; logistic regression analysis; increase UAC associated mean HbA1c levels (p<0.01)	
			Diabetes duration, years (mean±SD)	20±12				MI CV disease, death not associated with mean HbA1c levels	
			HbA1c, % (mean±SD)	8.5±1.6				5 year period; the meanHbA1c value for the entire patient group was 8.4±1.3%. HbA1c values were measured 16±5 times. The mean HbA1c values correlated with the levels at entry (r = 0.72, P <0.001) and at follow up (r = 0.73, P <0.001)	
			Weight or BMI	NR					
			Missing data: 34 patients						

Table 110: Brinchmann-Hansen 1992[20]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Brinhmann-Hansen 1992[20]	Prospective case-series of patients originally enrolled in Oslo 1985 RCT[34] Norway	n=45 Inclusion criteria: type 1 diabetes history diabetes for more than seven years Initially randomised to 3 different treatments: continuous subcutaneous insulin infusion, multiple insulin injections, or continued conventional treatment with two daily injections of mixed insulin Exclusion criteria: none listed	Age, years mean (range)	26(18-36)	Cohort at 7 years: 10 patients used insulin pumps 29 used multiple injections (regular insulin before meals and isophane insulin at bedtime) delivered by an insulin pen 6 patients used conventional treatment (regular insulin and isophane insulin twice daily) Glycaemic control estimated every second month by concentration of "stable" HbA1c	7 years	Retinopathy	Mean ±SD number of microaneurysms and haemorrhages according to mean HbA1: <9.0% (n=20) Baseline; 11.8(14.8) 7 years; 25.5(43.1) Change; 13.8(39.5) 9.1 to 10.0% (n=13) Baseline; 24.7(40.8) 7 years; 41.1(58.7) Change; 16.4(56.6) >10.1% (n=12) Baseline; 17.6(16.2) 7 years; 80.5(66.7) Change; 62.8(65.8)* *p= 0.014 compared with patients with HbA1 <10.0% No definitive thresholds were observed giving	Funding Norwegian Council for Science & Humanities, Norwegian Diabetes Association, Norwegian Council on CV Diseases, University of Oslo, Ander Jahres Medial Fndn, Novo-Nordisk Risk of bias: Appropriate eligibility criteria=yes, although limited inclusion criteria Appropriate measurement of exposure and
			Women, %	53	Concomitant therapy: NR				
			TIDM, %	100					
			Age at onset of diabetes, years (mean±SD)	NR					

			Diabetes duration, years mean (range)	28(6-23)				definite increase in progression or below which the subject protected, but in the 15 (34%) patients with a seven year mean HbA1 >8.7% there was no severe progression of retinopathy Multivariate regression analysis (to identify independent variables) severity of retinopathy not correlated to age, BP, or kidney function, patients with retinopathy at baseline were more likely to have more severe retinopathy at 7 years (r = 0.41; p=0.005) independent variables; baseline HbA1, change Hb1A1, duration diabetes, baseline retinopathy regression coefficient(95%CI); baseline HbA1 r=0.36(0.06 to 0.66) p=0.027, change Hb1A r=-0.35(-0.068 to -0.02) p=0.041 duration diabetes r=0.009(0 to 0.018)p=0.44, baseline retinopathy r=0.35(0.02 to 0.68) p=0.046 Initial treatment code did	outcome=yes Controlled for confounding factors(multivariate regression model)=yes Adequate follow-up=yes 7 years
			HbA1, % (mean±SD)	11.2±2.2					
			Weight or BMI	NR					
			Severity of retinopathy: counts of micro-aneurysms, haemorrhages(both eyes), mean(range)	17(0-154)					
			Missing data: none						

							not contribute (p>0.05) outcome of retinopathy at 7 years At 7 years retinopathy not correlated with baseline HbA1 value (r-0.22, p=0.14)	

Table 111: DCCT 1993[152], DCCT 1995[1], DCCT 1996[2], DCCT 1997[3]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
DCCT 1993[152] DCCT 1995[1] DCCT 1996[2] DCCT 1997[3]	RCT Diabetes Control and Complications Trial (DCCT) USA	n=1441 Primary cohort; n=726 Secondary cohort; n=715 Inclusion criteria: DCCT type 1 diabetes insulin dependent, HbA1c <6.5%, age of 13 to 39 years; and the absence of hypertension, hypercholesterolemia, and severe diabetic complications or medical conditions Primary prevention cohort; IDDM for 1-5 years, no retinopathy,	Age, years (range)	Intensive therapy(n=711); 27±7 Conventional therapy (n=730); 27±7	Intensive therapy ≥ 3 insulin injections or external insulin pump use; dose adjustments based on at least four≥ 4 SMGM/day, daily glucose target; 70 to 120 mg/dl (3.9 to 6.7 mmol/litre) before meals Conventional therapy had no	6.5 years	Progression to retinopathy; three steps or more on fundus photography that was sustained over a 6-month period Macular oedema Severe non-proliferative or proliferative retinopathy Nephropathy; UAE (mg/24 hours)	Progression of retinopathy; Primary prevention cohort; intensive vs. conventional RR (95%CI) 0.73 (0.62 to 0.85) Secondary prevention cohort; intensive vs. conventional RR (95%CI) 0.54 (0.39 to 0.66)	Funding: Division of Diabetes, Endocrinology, and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases and by the National Heart, Lung, and Blood Institute, the National Eye Institute, the National Center for

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		UAE of < 40 mg/24 hours Secondary intervention cohort, IDDM for 1-15 years, very-mild-to-moderate non-proliferative retinopathy, UAE < 200 mg/24 hours Exclusion criteria: excluded patients with a history of cardiovascular disease or with hypertension (defined by a blood pressure of 140/90 mm Hg or more) or hypercholesterolemia (defined by a serum cholesterol level obtained after an overnight fast that was at least 3 SD above age- and sex-specific means			glucose target (prevent symptoms of hyperglycaemia and hypoglycaemia only), 1-2 daily insulin injections		≥40 ≥300 Clinical neuropathy at 5 years; abnormal neurologic examination consistent with presence of peripheral sensorimotor neuropathy plus either abnormal nerve conduction in at least 2 peripheral nerves or unequivocally abnormal autonomic-nerve testing Mortality Hypoglycaemia		Research Resources, and various corporate sponsors Risk of bias: Randomisation: adequate Allocation concealment: adequate Blinding: adequate ITT analysis: yes Powered study: yes
			Women, %	Intensive therapy; 49 Conventional therapy; 46	Percentage of patients on intensive therapy at EDIC start (1993); Intensive group; 98% Conventional group; 2% Percentage of patients on intensive therapy at year 11 EDIC follow-up; Intensive group; 97% Conventional group; 94%			Absolute rate reduction per 100 patient-years (95%CI) Progression of retinopathy Primary cohort Conventional; 4.7 Intensive; 1.2 Risk reduction 76 (95%CI 62 to 85) Secondary cohort Conventional; 7.6 Intensive; 3.7 Risk reduction 54 (95%CI 39 to 66)	

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
					Concomitant therapy: NR				
			TIDM, %	100				Macular oedema Secondary cohort Conventional; 3.0 Intensive; 2.0 Risk reduction 54 (95%CI -13 to 48) Severe non-proliferative or proliferative retinopathy Secondary cohort Conventional; 2.4 Intensive; 1.1 Risk reduction 47 (95%CI 14 to 68)	
			Age at onset of diabetes,	NR				UAE ≥40 mg/24 hours Primary cohort	

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			years (mean±SD)					Conventional; 3.4 Intensive; 2.2 Risk reduction 34 (95%CI 2 to 56) Secondary cohort Conventional; 5.7 Intensive; 3.6 Risk reduction 43 (95%CI 21 to 58)	
			Diabetes duration, years (mean±SD) 13.8±1.0	Intensive therapy; 6±4 Conventional therapy; 5±4				UAE ≥300 mg/24 hours Primary cohort Conventional; 0.3 Intensive; 0.2 Risk reduction 44 (95%CI -124 to 86) Secondary cohort Conventional; 1.4 Intensive; 0.6 Risk reduction	

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
								56 (95%CI 18 to 76)	
			HbA1c, % (mean±SD),	Primary cohort Intensive therapy; 8.8±1.6 Conventional therapy; 8.8±1.7 Secondary cohort Intensive therapy; 8.9±3.8 Conventional therapy; 8.6±3.7			Clinical neuropathy at 5 years Primary cohort Conventional; 9.8 Intensive; 3.1 Risk reduction 34 (95%CI 2 to 56) Secondary cohort Conventional; 16.1 Intensive; 7.0 Risk reduction 57 (95%CI 29 to 73) Mortality; conventional 7 patients died vs. intensive 4 patients died Regression model	
			BMI or weight	NR					
			Missing data: 8 patients						

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
							estimates of the effect of 10% higher mean HbA1c on the change in risk of other outcome Retinopathy; ≥3 microaneurysms (primary cohort only) Conventional therapy %change in risk; 56, 95%CI 39 to 74 Intensive therapy %change in risk; 66, 95%CI 39 to 96 Neuropathy at 5 years; confirmed Conventional therapy %change in risk; 41, 95%CI	

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
							19 to 66 Intensive therapy %change in risk; 43, 95%CI 9 to 87 Nephropathy; AER≥300 mg/24 hours Conventional therapy %change in risk; 71, 95%CI 32 to 121 Intensive therapy %change in risk; 57, 95%CI 7 to 133 Hypoglycaemia requiring assistance HbA1c at eligibility screening subgroups; intensive versus	

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
							conventional therapy <7.825%; intensive n=189, conventional n=171 RR(95%CI) 2.098 (1.37 to 3.19) 7.825-8.819%; intensive n=185, conventional n=175 RR(95%CI) 3.12(2.15 to 4.51) 8.820-10.099%; intensive n=166, conventional n=192 RR(95%CI) 4.13(2.79 to 6.13) >10.100%; intensive n=190, conventional	

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
							n=173 RR(95%CI) 4.89 (3.05 to 7.83) Relative risk reductions associated with a 10% lower mean HbA1c among HbA1c values ≤8 vs. values >8% estimated from a segmented (change point) model Sustained retinopathy progression, %risk reduction (95%CI) Intensive ≤8%; 49 (27 to 65) vs. >8%; 37 (17 to 53), p=0.46 Conventional ≤8%; 69 (29 to 87) vs. >8%; 37 (26 to 41), p=0.055 Sustained low-	

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
							level (micro) albuminuria, %risk reduction (95%CI) Intensive ≤8%; 43 (2 to 67) vs. >8%; 44 (17 to 62), p=0.97 Conventional ≤8%; 58 (-50 to 87) vs. >8%; 33 (17 to 45), p=0.47 Confirmed clinical neuropathy, %risk reduction (95%CI) Intensive ≤8%; 30 (-19 to 58) vs. >8%; 35 (-17 to 64), p=0.87 Conventional ≤8%; 32 (-70 to 56) vs. >8% ; 29 (13 to 42), p=0.90	

Table 112: DCCT/EDIC 2005[116,117], DCCT/EDIC 2008[166,167]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
DCCT/EDIC 2005[116,117] DCCT/EDIC 2008[166,167]	Prospective case series study; Epidemiology of Diabetes Interventions and Complications (EDIC) of patients originally enrolled in RCT (Diabetes Control and Complications Trial (DCCT) USA	n=1441 Inclusion criteria: DCCT type 1 diabetes insulin dependent, age of 13 to 39 years; and the absence of hypertension, hypercholesterolemia, and severe diabetic complications or medical conditions Exclusion criteria: excluded patients with a history of cardiovascular disease or with hypertension (defined by a	Age, years (range)	DCCT at Baseline (1983–1989); Intensive therapy(n=711); 27±7 Conventional therapy (n=730); 27±7 End of DCCT (1993); Intensive therapy (n=698); 34±7 Conventional therapy (n=723); 33±7 Year 11 of EDIC (2004); Intensive therapy (n=593); 45±7 Conventional therapy (n=589); 45±7	Intensive therapy ≥ 3 insulin injections or external insulin pump use; dose adjustments based on at least four≥ 4 SMGM/day, daily glucose goals; 70 to 120 mg/dl (3.9 to 6.7 mmol/litre) before meals Conventional therapy had no glucose target (prevent symptoms of hyperglycaemia and hypoglycaemia only), 1-2 daily insulin injections	17 years	CVD events; non-fatal MI, stroke; CVD death; angina Retinopathy	End DCCT; HbA1c; 9.1±1.5% intensive group vs.7.4±1% conventional group, p<0.01 End 11 year EDIC; Absolute difference in the HbA1c between groups; 0.1% CVD event at 17 years; 144 events in 83 patients Intensive therapy; 46 in 31 patients, 0.38 events/100 patient years Conventional therapy; 98 in 52 patients, 0.80 events/100 patient-years (p=0.007 vs. intensive therapy) Progression to retinopathy from DCCT closeout to EDIC at 10 years (n=1211) Risk reduction (95%CI) with intensive vs. conventional therapy; 53% (43% to 61%),	Funding: Not reported Risk of bias: Appropriate eligibility criteria=yes Appropriate measurement of exposure and outcome=yes Controlled for confounding factors =yes proportional hazard model adjustment appropriate Adequate follow-up=yes 17 years

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		blood pressure of 140/90 mm Hg or more) or hypercholesterolemia (defined by a serum cholesterol level obtained after an overnight fast that was at least 3 SD above age- and sex-specific means						p<0.001 HbA1c intensive vs. conventional therapy; 87.07% vs. 7.98% p=ns	
			Women, %	DCCT at Baseline (1983–1989); Intensive therapy; 49 Conventional therapy; 46 End of DCCT (1993); Intensive therapy; 49 Conventional therapy; 46 Year 11 of EDIC (2004); Intensive therapy; 48 Conventional therapy; 46	Percentage of patients on intensive therapy at EDIC start (1993); Intensive group; 98% Conventional group; 2% Percentage of patients on intensive therapy at year 11 EDIC follow-up; Intensive group; 97% Conventional group; 94% Concomitant therapy: NR			Cumulative incidence 1st CVD event Intensive vs. conventional therapy vs. ; RR (95%CI) 0.59 (0.9 to 0.63), p=0.02 Cumulative incidence 1st non-fatal MI, stroke or CVD death Intensive vs. conventional therapy; RR (95%CI) 0.57 (0.12 to 0.79), p=0.02 HbA1c; per 10% increase (adjusted for HbA1c, age, cholesterol, smoking status at baseline); HR (95%CI) 1.25 (1.10 to 1.43) HbA1c; per 10% decrease (adjusted for HbA1c, age, cholesterol, smoking status at baseline); HR (95%CI) 0.8 (0.70 to 0.91)	
			TIDM, %	100				Higher HbA1c levels (9.5% vs. 9.0%), at DCCT	

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
								baseline associated with occurrence of the CV events independent of treatment assignment (p=0.014)	
			Age at onset of diabetes, years (mean±SD)	NR					
			Diabetes duration, years (mean±SD) 13.8±1.0	DCCT at Baseline (1983–1989); Intensive therapy; 6±4 Conventional therapy; 5±4 End of DCCT (1993); Intensive therapy; 12±5 Conventional therapy; 12±5 Year 11 of EDIC (2004); Intensive therapy; 24±5					

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
				Conventional therapy; 23±5					
			HbA1c, % (mean±SD),	DCCT at Baseline (1983–1989); Intensive therapy; 9.1±1.6 Conventional therapy; 9.1±1.6 End of DCCT (1993); Intensive therapy; 7.4±1.1 Conventional therapy; 9.1±1.5 Year 11 of EDIC (2004); Intensive therapy; 7.9±1.3 Conventional therapy; 7.8±1.3				

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			BMI or weight	NR					
			Missing data: None						

Table 113: Diamante 1997[37]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcomes	Effect sizes	Comments
Diamante 1997[37]	Cross-sectional study Spain; 18 centres	n=1822 2 subgroups; type 1 diabetes <5 years type 1 diabetes >30 years Inclusion criteria: type 1 diabetes, all patients visited over 3 month period, > 18 years, insulin dependent, disease detected prior age 30 years and required	Age, years (mean±SD)	30.5±9.7	Insulin treatment (%) 1 dose; 1.1 2 doses; 35.7 3 doses; 46.3 4 doses; 16.4	4 years	Nephropathy Normal; UAE (at least 3) < 20 µg/min (minimum of one determination being within last 6 months) Micro-albuminuria or macro-albuminuria; UAE 20-200 µg/min or >200 µg/min respectively, detected in 2 out of 3 consecutive	Logistic regression analysis HbA1c correlated with ESRF vs. no ESRF (p<0.00005) HbA1c correlated with low-level (micro) albuminuria vs. normoalbuminuria (p<0.00005) Low-level (micro) albuminuria vs. CVD; HbA1c no influence	Funding: Not stated Risk of bias: Appropriate eligibility criteria=yes, although limited inclusion criteria Appropriate measurement of exposure and outcome=yes Controlled for confounding factors
			Women, %	49	Concomitant therapy; NR			HbA1c (all patients) Normoalbuminuria; 7.3±1.6% Low-level (micro) albuminuria; 8.0±1.6% Macroalbuminuria + ESRF; 7.7±1.9%	

		insulin treatment within 6 months Exclusion criteria: none listed	TIDM, %	100			tests (in the absence of urinary infection) ESRF; plasma creatinine > 1.4 mg/dl (2 occasions)	HbA1c (diabetes <5 years evolution) Normoalbuminuria; 7.3±1.6% Low-level (micro) albuminuria; 8.0±1.6% Macroalbuminuria + ESRF; 7.7±1.9%	=unclear description limited Adequate follow-up=NA cross-sectional study
			Age at onset of diabetes, years (mean±SD)	15±8					
			Diabetes duration, years (mean±SD)	NR					
			HbA1c, % (mean±SD)	7.5±1.6					
				±3.2					
			Missing data: None						

Table 114: Eid Fares 2010[44]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Eid Fares 2010[44]	Retrospective case series	n=117 Inclusion criteria:	Age, years (range)	9–33	Glycaemic control; NR	5 years	Fluctuations in HbA1c defined as an; increase in HbA1c > 2%	Nephropathy 18/117 (15.4%) developed nephropathy HbA1c in patients with;	Funding: Not listed

	UK	type 1 diabetes, within 18 months of diagnosis Exclusion criteria: duration of diabetes <5 years, wolfram syndrome, thalassemia or other haemoglobinopathy					between 2 consecutive measurements (3 months interval±2 weeks) or an increase in HbA1c >1% at 2 points in time (from estimated between-individual difference in HbA1c > 2% more than doubles risk of developing microvascular complications Neuropathy; rate of albumin excretion between 20-200 micro-g/min (or between 30-300 mg/24 h)	Neuropathy; 9.4±1.6% No neuropathy; 8.5±1.1% Overall; 8.6± 1.2%	Risk of bias: Appropriate eligibility criteria=some patients <18 years (proportion not given) Appropriate measurement of exposure and outcome=yes Controlled for confounding factors =regression analysis adequately adjustments Adequate follow-up=yes 5 years
			Women, %	55	Concomitant therapy: NR			Fluctuations in HbA1c; Present with nephropathy; 15/18(83%) Present without nephropathy; 54/117(54%) Absent with nephropathy; 3/18(17%) Absent without nephropathy; 45/117(45%)	
			TIDM, %	100				Multivariate analysis; prediction of diabetic nephropathy	
			Age at onset of diabetes, years (mean±SD)	Neuropathy (n=18), 10.94±4.5 No neuropathy(n=99); 10.12±3.9				Average mean of HbA1c; OR(95%CI) 1.66 (1.03 to 2.68) [Model 1], 1.55 (1.01; 2.38) [Model 2], 1.75 (1.18; 2.59) [Model 3] Fluctuations in HbA1c; OR(95%CI) 1.89 (0.42 to 8.41) [Model 1], 2.34 (0.56 to 9.77) [Model 2], 4.17 (1.13 to 15.31) [Model 4] Gender; OR(95%CI) 0.85 (0.27 to 2.63) [Model 1] Family history; OR(95%CI) 1.32 (0.42 to 4.13) [Model	

								1] Age at onset; OR(95%CI) 1.06 (0.88 to 1.26) [Model 1] Time between onset of diabetes till admission to diabetes clinic; OR(95%CI) 0.93 (0.80 to 1.08) [Model 1] Baseline BMI; OR(95%CI) 0.93 (0.75 to 1.14) [Model 1] Model 1; all risk covariates (average mean of HbA1c, Fluctuations in HbA1c, gender, family history, age at onset, time between diabetes onset to clinic admission, baseline BMI) Model 2; mean and fluctuations HbA1c Model 3; mean HbA1c Model 4; fluctuations HbA1c	
			Time period from onset of diabetes to admission to Chronic Care Center for children and young adults, years (mean±SD)	Neuropathy; 3.96±4.2 No neuropathy; 3.72±4.2				Fluctuations on incidence of nephropathy in 77 patients HbA1c≤8%; With nephropathy, fluctuations present; 15(26%) With nephropathy, fluctuations absent; 5(1%) Without nephropathy; fluctuations present;	

								42(74%) Without nephropathy, fluctuations absent 19(95%)	
			HbA1c, % (mean±SD) Result at each visit	Neuropathy; 9.4±1.6 No neuropathy; 8.5±1.1 Overall; 8.6± 1.2					
			BMI, (kg/m2) (mean±SD)	Neuropathy; 19.84±5.2 No neuropathy; 19.04±3.4					
			Missing data: None						

Table 115: Hislop 2008[65]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparisons	Length of follow-up	Outcome measures	Effect sizes	Comments
Hislop 2008[65]	Prospective case series Australia	n=108 Inclusion criteria: type 1 diabetes for at least 12 months Exclusion	Age, years (mean±SD)	21.6±2.8	On continuous subcutaneous insulin fusion; 17 patients	6 months	Quality of life Centre for Epidemiological Studies-Depression Scale (CES-D); 20 items about the individual's	Patients with abnormal CES-D score (≥16) poorer glycaemic higher HbA1c compared with those with normal CES-D (9.4% vs. 8.4%, p=0.01)	Funding: Australian Diabetes Society Servier Research Award, NovoNordisk Australia, Regional
			Women, %	50	Concomitant therapy: NR			No correlation between HbA1c and CES-D in total cohort (r=0.2, p=0.14)	

		criteria: type 2 diabetes	TIDM, %	100			behaviour, higher scores indicate greater distress, scores <16 were classified as 'normal', ≥16 'depressive symptoms', scores > 23 'severe depressive symptoms'	Controlling for CSII use, CES-D and HbA1c correlated (r = 0.3, p=0.02)	Diabetes Support Scheme Risk of bias: Appropriate eligibility criteria=yes Appropriate measurement of exposure and outcome= yes Controlled for confounding factors =unclear Adequate follow-up=yes 10 years
			Age at onset of diabetes, years (mean±SD)	12.2±5.9				Patients on CSII vs. patients not; lower HbA1c (7.9 vs. 8.9%, p=0.03)	
			Diabetes duration, years (mean±SD)	9.3±5.4				No difference in glycaemic control between patients with normal ASR-T scores (≤ 59) and psychologically distressed ASR-T scores (≥ 60)	
			HbA1c, % (mean±SD)	8.7±1.8			Adult-Self-Report Scale (ASR); ASR subdivided into Internalising and Externalising. Anxious/Depressed, Withdrawn, Somatic Complaints, Thought Problems, Attention Problems, Aggressive Behaviour, Rule-Breaking		
			BMI, (kg/m2), (mean±SD)	NR					
			Missing data: None						

						behaviour, and Intrusive. Higher scores indicate higher distress. Total Problem Score (ASR-T), Internalising (ASR-I) and Externalising scores, (ASR-E). For each scale, recommended cut-off scores were used (<60 = normal, 60-63 = borderline, >63 = clinical distress, with those scoring ≥60 being considered 'psychologically distressed'.		

Table 116: Larsen 1990[90]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Larsen 1990[90]	RCT	n=240, consecutive	Age, years (mean	Control group	Monitored group; HbA1c levels	1 year intervention, year 2 post		Visited the clinic ≥ 4 times 1st year;	Funding: Not listed

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
	On the basis of the 1st measurement of HbA1c, age and sex, patients were matched and randomly assigned to one of two comparable groups HbA1c measured every 3 months Denmark	patients Inclusion criteria: type 1 diabetes, symptoms before 30 years, IDDM, propensity to ketosis, > 60 years, Exclusion criteria: None listed	(range))	Men Women Monitored group Men Women	available to staff, used with blood or urine glucose values to adjust treatment, target NFBG <9mmol/(162 mg /dl)	intervention		Monitored group; n=117 Control group; n=107 Mean number of visits during the year was 4.2 (range 4 to 8) in the control group and 4.5 (range 4 to 7) in the monitored group Mean(±)HbA1c in monitored (n=98) vs. control group (n=99) Baseline; monitored group 10.1±1.9% vs. control 9.9±1.8% 3 months; monitored group 9.9±1.9% vs. control; 10.1±1.6% 6 months; monitored group 9.8±1.7% vs. control; 10.2±1.7% 9 months; monitored group 9.9±1.6% vs. control; 10.2±1.7% 12 months; monitored group 9.4±1.4% vs. control; 10.0±1.7%, p<0.02 18 months; monitored group 9.6±1.4% vs. control; 10.1±1.5%	Risk of bias: Risk of bias: Randomisation : unclear Allocation concealment: unclear Blinding: single blind ITT analysis: no Powered study: unclear

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
								24 months; monitored group 9.3±1.2% vs. control; 10.1±1.5%	
			Women, %	43	Control group; HbA1c levels (including the randomisation values) not entered into the patients' records during study period, staff treated patients on blood or urine glucose values, target NFBG <9mmol/(162 mg /dl)			Mean(±)HbA1c in monitored (n=98) vs. control group (n=99) Baseline; monitored group 10.1±1.9% vs. control 9.9±1.8% 3 months; monitored group 9.9±1.9% vs. control; 10.1±1.6% 6 months; monitored group 9.8±1.7% vs. control; 10.2±1.7% 9 months; monitored group 9.9±1.6% vs. control; 10.2±1.7% 12 months; monitored group 9.4±1.4% vs. control; 10.0±1.7%, p<0.02 18 months; monitored group 9.6±1.4% vs. control; 10.1±1.5% 24 months; monitored group 9.3±1.2% vs. control; 10.1±1.5%	
			TIDM, %	100	At 1 year, all HbA1c values				

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Age at onset of diabetes, years (mean±SD)	Neuropathy (n=18), 10.94±4.5 No neuropathy(n=99); 10.12±3.9	controls entered into their records, HbA1c measurement was then routine, both groups followed 2nd year (compared HbA1c in 2 groups after another 6 and 12 months (18 and 24 months after randomisation)				
			Time period from onset of diabetes to admission to Chronic Care Center for children and young adults, years (mean±SD)	Neuropathy ; 3.96±4.2 No neuropathy; 3.72±4.2				Treatment changes during 1 year Group/regimen Control group (n=107) 1 daily injection; at entry 14.0% vs. 11.2% at 12 months 2 daily injections; at entry 80.4% vs. 67.7% at 12 months 3 or 4 daily injections; at entry 5.6% vs. 27.1% at 12 months Monitored group (n=115) 1 daily injection; at entry 10.4% vs4.3% at 12 months 2 daily injections; at entry 80.0% vs. 55.7% at 12 months 3 or 4 daily injections; at entry 9.6% vs. 40.0% at 12 months (p<0.05	

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
								for comparison between groups)	
			HbA1c, % (mean±SD) Result at each visit	Monitored 9.9±1.8 Control; 10.1±1.9					
			BMI, (kg/m2) (mean±SD)	Neuropathy; 19.84±5.2 No neuropathy; 19.04±3.4					
			Missing data: None						

Table 117: Lehto 1999[93]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Lehto 1999[93]	Prospective case series Finland	n=177 Inclusion criteria: type 1 diabetes, age from 45-64 years, diabetes diagnosed at the age of	Age, years (mean±SD)	Men without CHD (n=70) 53.5±0.5 Men with (n=17) CHD 58.6 ±1.4 Women without CHD (n=79) 56.1 ±1.8 Women with	Glycaemic control; NR Concomitant therapy: NR	7 years	CHD death CHD event; death from CHD or non-fatal MI	Univariate Cox regression model; HbA1 associated with risk of CHD death (p<0.001) and all CHD events (p<0.01) poor Glycaemic control (10.4% versus ≤10.4%) was associated with the incidence of CHD death	Funding: Academy of Finland, the Finnish Heart Research Fndn, Aarne and Aili Turunen Fndn Risk of bias: Appropriate

		30 years or later Exclusion criteria: none listed		(n=11) CHD 56.4 ±1.8				(p<0.05) high HbA1 (>10.4) associated with all CHD events	eligibility criteria=yes Appropriate measurement of exposure and outcome=yes Controlled for confounding factors =yes multivariate analysis adjustment appropriate Adequate follow-up=yes 7 years
			Women, %	50				Multivariate analysis (adjustment CV factors; age, sex, area of residence, previous MI, smoking, BMI, hypertension, total cholesterol, total triglycerides, and HDL cholesterol); high HbA1 (>10.4%, HR 5.4 [1.4 to 20.4]) associated with the incidence of CHD death (p=0.013) high HbA1 (>10.4%, HR 2.8 [1.2 to 6.9]) associated with the incidence of all CHD events (p=0.021)	
			TIDM, %	100					
			Age at onset of diabetes, years (mean±SD)	NR					
			Diabetes duration, years (mean±SD) 13.8±1.0	Men without CHD 13.8±1.0Men with CHD 15.7±1.6Women without CHD 13.0 ±0.8					

				Women with CHD 56.4 ±1.8					
			HbA1, % (mean±SD)	Men without CHD 9.5±0.21 Men with CHD 10.5±0.4 Women without CHD 10.1 ±0.2 Women with CHD 11.1±0.4					
			BMI, (kg/m2), (mean±SD)	Men without CHD 25.1±0.Men with CHD 24.4±0.8 Women without CHD 25.5±0.5 Women with CHD 26.1 ±1.4					
			Missing data: None						

Table 118: Lustman 2005 [100]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparisons	Length of follow-up	Outcome	Effect sizes	Comments
Lustman	Cross sectional	n=118	Age, years	40.7±12.	Use of insulin pump;	NA	Quality of life	SDSA;	Funding:

2005 [100]	observational study USA	Inclusion criteria: type 1 diabetes Exclusion criteria: none listed	(mean±SD)	7	55/188(29%) Total daily insulin dose, units mean(±SD); 37.2±20.9		Symptom Checklist-90 (SCL-90) and the Summary of Diabetes Self-Care Activities (SDSCA) SCL-90; Measures psychological symptom patterns both psychiatric and medical patients (validated in both populations). Each item rated on a five-point distress scale (0–4) ranging from "not at all" at one pole to "extremely" at the other. The SCL-90 is scored and interpreted in terms of 9 primary	HbA1c levels positively correlated with depression symptoms on SDSA (t=0.44, p<0.02)	National Institutes of Health Risk of bias: Appropriate eligibility criteria=yes Appropriate measurement of exposure and outcome= yes Controlled for confounding factors =yes Adequate follow-up=NA
			Women, %	50	Concomitant therapy: NR			SDSA; HbA1c levels were higher in the depressed than in the non-depressed patients (covariate-adjusted means±standard error of mean=8.8%± 0.3% vs. 7.6%±0.1%, F=10.1, p<0.0001)	
			TIDM, %	100				SDSCA composite score; Addition of SDSCA composite score to regression analysis, the parameter estimate for depression effect on HbA1c level was attenuated minimally (parameter estimate 0.50, t =3.3, p<0.001), SDSCA score had no effect within the model (p=0 .40)	
			Age at onset of diabetes, years (mean±SD)	21.7±13.2				SCL-90; Scores on SCL-90 depression subscale were 2.3±0.4 in the depressed group compared with 0.6± 0.4 in the non-depressed group	

			Diabetes duration, years (mean±SD)	NR			dimensions or subscales, one of which assesses depression, 20 items that comprise this subscale used to assess the severity of depression symptom	SCL-90; HbA1c levels correlated to severity depression symptoms within depressed group (p<0 .02, across subgroups)	
			HbA1c, % (mean±SD)	7.7±1.3			SDSCA assesses diabetes self-care were assessed; 12-item self-report questionnaire that measures levels of self-care behaviour and degree of adherence with physician-recommended activities including diet amount, exercise, and adherence to glucose monitoring		
			Weight (lbs), (mean±SD)	169.3±34.0					
			Missing data: None						

						Raw scores for each converted to z scores and averaged to form composite z score for the SDSCA, higher score indicates greater attention to self-care		

Table 119: Pirez Mendez 2007[124]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Pirez Mendez 2007[124]	Prospective case series Spain	n=59 Inclusion criteria: type 1 diabetes and bad metabolic control (glycosylate haemoglobin HbA1c values equal to or higher than 9% in the previous year)	Age, years mean (range)	31.9(15-47)	Cohort Patients offered change of insulin regimen from a conventional to Multiple Dose Insulin; 2 or 3 daily injection of NPH insulin with short-acting analogue lispro as a pre-meal bolus (59/73 changed from conventional	7 years	Target HbA1c values of <6.2% Frequency of severe hypo-glycaemia (coma or neuroglycopenia requiring 3rd party, with /without need for intra-muscular	Mean values of HbA1c: 7.5±1.5%, 7.2±1.8%, 7.6±1.6%, 7.1±1.7%, 7±1.4±6.6 1.6% and 6.8±1.4% for first, second, third, fourth, fifth, sixth and seventh year of follow-up	Funding None stated Risk of bias: Appropriate eligibility criteria=yes, although limited inclusion criteria Appropriate measurement

		Exclusion criteria: unwilling to transfer from conventional to Multiple Dose Insulin regime			therapy and were included in study) HbA1c measured every 3 months and frequency of hypoglycaemia episodes The goal of HbA1cvalues was <6.2%		glucagons or intravenous glucose or emergency hospitalisation) Frequency of mild hypo-glycaemia (any self-treated episode without need for assistance from 3rd party)	respectively Percentage of patients reaching target HbA1c < 6.2% for the first, second, third, fourth, fifth, sixth and seventh year of follow-up: 16%, 27.5%, 15.7%, 33.3%, 28.6%, 42% and 33% Severe hypoglycaemic episodes (episodes/patient-year) year before study; 0.32±0.2 during study; 0.28±0.1 (ns compared with before study) Mild/moderate hypoglycaemia episodes (episodes/patient-month) year before study started; 17.7±6	of exposure and outcome=yes Controlled for confounding factors=no Adequate follow-up=yes 7 years
			Women, %	41	Concomitant therapy: NR				
			TIDM, %	100					
			Age at onset of diabetes, years (mean±SD)	NR					
			Diabetes duration, years mean (range)	9.9±8.4					
			HbA1c, % (mean±SD)	NR					
			BMI, (kg/m2), (mean±SD)	23.2±3.1					
			Missing data: 2 patients dropped out						

							during study; 16.5±4 to 21.7±5 (ns compared with before study value) (mean±SD) insulin (IU); 43±23.1, 36.7±22.5, 50.8±21.1, 53.9±16.3, 52±16.4, 54.4±17.2, 52.8±19.8 for first, second, third, fourth, fifth, sixth and seventh years of follow-up respectively	
		Dropout rate: not reported						

Table 120: Pittsburgh EDC 2002[121]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Pittsburgh EDC 2002[121]	Prospective case series	n=586	Age, years (range)	Without LEAD; 26.5±7.6 With LEAD;	Glycaemic control; NR	10 years	Lower extremity arterial	LEAD events in 70/586 patients (11% men, 13% of women)	Funding: National Institutes of

	Analysis of cohort from Pittsburgh Epidemiology of Diabetes Complications (EDC) study (type 1 diabetes children < 17 years, 10 year study, follow-up 1996-1998) USA	Inclusion criteria: type 1 diabetes diagnosed before age of 17 years Exclusion criteria: patients with LEAD in original cohort at baseline were excluded		31.3±7.1			disease(LEAD); claudication (Rose questionnaire), foot ulceration or lower extremity amputation	Total of 40 first events were claudication, 13 amputation, 10 ulcer, and 7 combined, with no gender differences in type of first event	Health Grant Risk of bias: Appropriate eligibility criteria=yes Appropriate measurement of exposure and outcome=yes Controlled for confounding factors =yes multivariate analysis adjustment appropriate Adequate follow-up=yes 10 years
			Women, %	Without LEAD; 48 With LEAD; 53	Concomitant therapy: NR			HR(95%CI) for 10 year incident LEAD (men and women); 1.53(1.22 to 1.92), p<0.001	
			TIDM, %	100				HR(95%CI) for 10 year incident LEAD (men); 1.70(1.27 to 2.29), p<0.001	
			Age at onset of diabetes, years (mean±SD)	NR					
			Diabetes duration, years (mean±SD) 13.8±1.0	Without LEAD; 18.1±7.2 With LEAD 23.4±7.1					
			HbA1, % (mean±SD)	Without LEAD 10.3±1.8 With LEAD 10.9±1.9					
			BMI or weight	NR					
			Missing data: None						

Table 121: Pittsburgh EDC 2003[122]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Pittsburgh EDC 2003[122]	Prospective case series Analysis of cohort from Pittsburgh Epidemiology of Diabetes Complications (EDC) study (type 1 diabetes children < 17 years, 10 year study, follow-up 1996-1998) USA	n=603 Inclusion criteria: type 1 diabetes diagnosed before age of 17 years Exclusion criteria: CAD at baseline	Age, years (range)	Without CAD; 25.9±7.3 With CAD; 33.0±6.8	Case Series Insulin dose/kg BW; Patients without CAD; 0.81±0.25 Patients with CAD; 0.75±0.31	10 years	CAD death, Non-fatal MI, ECG ischaemia Revascularisation Angina	CAD death; 5/606 patients Non-fatal MI; 25/606 ECG ischaemia; 17/606 Angina; 49/606 Revascularisation 12/606	Funding: National Institutes of Health Grant Risk of bias: Appropriate eligibility criteria=yes Appropriate measurement of exposure and outcome=yes Controlled for confounding factors =yes multivariate analysis adjustment appropriate Adequate follow-up=yes 10 years
			Women, %	Without CAD; 50 With CAD; 42	Concomitant therapy: NR			HbA1 no association with subsequent CAD events	
			TIDM, %	100				RR (95% CI) for HbA1 (per 1–percentage point increase) and incident coronary heart disease CAD death, non-fatal MI, ECG ischaemia, revascularisation, angina); 0.97 (0.86 to 1.09)	
			Age at onset of diabetes, years	NR					

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			(mean±SD)						
			Diabetes duration, years (mean±SD) 13.8±1.0	Without CAD; 17.6±6.9 With CAD 24.9±6.9					
			HbA1, % (mean±SD)	Without CAD 10.4±1.8 With CAD 10.3±1.8					
			BMI or weight	NR					
			Missing data: None						

Table 122: SDIS 1995[127-129]

Reference	Study type	Number of patients	Patient characteristics			Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
SDIS 1995[127-129]	RCT/ Prospective cohort study Sweden	n=89 Inclusion criteria: non proliferative retinopathy, normal s-creatinine,		ICT Therapy; n=42	ST n=47	Intensified conventional insulin treatment (ICT); insulin with education to ensure constant	94 months /10 years	Retinopathy; on scale of 0 (no retinopathy) over 1 (only micro-aneurysms) to 6 (proliferative	Cumulative frequency of serious retinopathy; increased with higher HbA1c levels only in patients with mild retinopathy at baseline, no increase in patients with moderate retinopathy	Funding: Swedish Division of NOVO-Nordisk Inc, Boehringer Mannheim Scand Inc

		inadequate blood glucose control Exclusion criteria: albuminuria				monitoring and treatment Standard therapy (ST); 2 to 3 insulin injections/day		changes) Mean retinopathy level of ≥ 2.5 = mild, levels 3-5 = moderate (still non proliferative) Serious retinopathy = sight-threatening retinal changes with immediate need for focal or scatter photocoagulation due to macular oedema or proliferations Relationship between mean HbA1c during the 1st 5 years and serious retinopathy after 94 months analysed separately for patients with	(shown graphically) Patients with mild retinopathy with mean HbA1c below 7% did not develop serious retinopathy	Risk of bias: Appropriate eligibility criteria=yes, although limited inclusion criteria Appropriate measurement of exposure and outcome=yes Controlled for confounding factors =unclear as not controlled for ICT vs. ST Adequate follow-up=yes,94 months
			Age, years (mean± SD)	30±8	32±7	Concomitant therapy: NR			Visual acuity seldom deteriorated in patients with initial mild retinopathy if HbA1c <8%	
			Women, %	50	53				No deterioration in visual acuity in patients with mean HbA1c <7%	
			type 1 diabetes	100	100				Patients with moderate retinopathy at baseline; visual acuity sometimes deteriorated even if the HbA1c <7% for mean HbA1c <8% patients had less visual deterioration compared patients with mild retinopathy (p= 0.01)	
			Age at onset of diabetes, years (mean± SD)	NR	NR				Analysis of variance (nonparametric) showed a significant difference between proportions of patients with serious retinopathy between the various HbA1c levels when initial retinopathy was mild (p<0.01)	

								mild (n=53) and moderate (n=47) retinopathy at study entry Nephropathy; albumin excretion of > 20 µg/min normal, 20-200 µg/min = low-level (micro) albuminuria, and > 200 µg/min = diagnostic of manifest nephropathy Neuropathy; combination of symptoms of peripheral neuropathy in legs and nerve conduction velocity of at least 1 nerve of leg below the lower normal limit (41 m/sec)	Development of serious retinopathy at any time during follow-up; Related to HbA1c at baseline [OR(95%CI) 1.70(1.0 to 2.8)] and during first 6 to 60 months of follow-up [OR(95%CI) 2.4(1.4 to 4.3)], not after 60 months OR for HbA1c during the study Serious retinopathy; 2.70(1.55 to 4.69) Nephropathy; 3.33(1.66 to 7.56) Neuropathy; 3.13 (1.56 to 6.28)	

								Relationship between mean HbA1c during the 1st 5 years and serious retinopathy after 94 months analysed separately for patients with mild (n=53) and moderate (n=47) retinopathy at study entry Renal function Neuropathy		
			Diabetes duration, years (mean± SD)	18±7	16±5			HbA1c analysed at entry, after 6 months, and then every 4 months	Nephropathy; patients with a mean HbA1c > 9% did not develop nephropathy 5/10 patients with a mean HbA1c ≥ 9% developed nephropathy 0/12 patients with mild initial retinopathy and mean HbA1c ≥ 9% during the study had nephropathy	
			HbA1c, % (mean± SD)	9.5±1.3	9.4±1.4					
			BMI,	22.5±	22.8.±					

			(kg/m2), (mean± SD)	1.9	27				Urinary albumin excretion (microgram/min); HbA1c <7%; 87±40 HbA1c 7%-7.99%; 21±5 HbA1c 8%-8.99%; 55±19 HbA1c ≥9% 308±123 HbA1c ; 266±150 Neuropathy Neuropathy (patients without neuropathy at baseline) HbA1c <7% (6.5±0.1%); 2/20 patients HbA1c 7%-7.99% (7.5±0.1%); 8/24 patients HbA1c 8%-8.99% (8.4±0.1%); 7/18 patients HbA1c ≥9% (9.6±0.2%); 3/7 patients OR for HbA1c Serious retinopathy; 2.70 (1.55 to 4.69) Nephropathy; 3.33(1.66 to 7.56) Peripheral neuropathy; 3.13 (1.56 to 6.28)	
			Missing data: None							

Table 123: Shaban 2006[143]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparisons	Length of follow-up	Outcome	Effect sizes	Comments
Shaban	Cross	n=273	Age, years	38.7±11.	Glycaemic	NA	The Hospital	HbA1c positively	Funding:

2006[143]	sectional observational study UK	Inclusion criteria: type 1 diabetes (defined by clinical parameters suggestive of absolute insulin deficiency e.g. low body mass index and ketonuria) aged 16-60 years, duration at least 1 year Exclusion criteria: aged >60 years	(mean±SD)	4	control; NR		Anxiety and Depression Scale (HADS); 2 subscales assess symptoms anxiety and depression separately, each subscale consists 7 questions with maximum score of 21 Scores interpreted to indicate symptomatology that is either mild (between 8 and 10), or moderate to severe (between 11 and 21)	correlated with HADS scores (anxiety r=0.2, p=0.001, depression r=0.14, p=0.02)	British Diabetic Association Grant Risk of bias: Appropriate eligibility criteria=yes Appropriate measurement of exposure and outcome= yes Controlled for confounding factors =unclear Adequate follow-up=NA
			Women, %	45	Concomitant therapy: NR			Patients 'moderate to severe levels' of anxiety demonstrated poorer glycaemic control than those reporting 'none to mild'; Anxiety ≥ 11: HbA1c 9.4%; anxiety < 8, HbA1c 8.5%, p= 0.001)	
			TIDM, %	100				No difference in HbA1c for patients reporting different symptom severity for depression (depression ≥ 11: HbA1c 8.7%; depression < 8, HbA1c 8.9% p=0.5)	
			Age at onset of diabetes, years (mean±SD)	NR					
			Diabetes duration, years (mean±SD)	17.2±12.0					
			HbA1c, % (mean±SD)	8.8±1.5					
			BMI, (kg/m2), (mean±SD)	NR					
			Missing data:						

			1 patient did not return questionnaire (excluded from analysis)					

Table 124: Tabaei 2004[150]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparisons	Length of follow-up	Outcome measures	Effect sizes	Comments
Tabaei 2004[150]	Cross-sectional study USA	n=634 Inclusion criteria: type 1 diabetes(onset before 30 year and IDDM) Exclusion criteria: none listed	Age, years median (min.-max.)	33(18-78)	Glycaemic control; NR	NR	Quality of life Quality of Well-Being Self-Administered (QWB-SA); symptoms (acute and chronic) and functioning (self-care, mobility, physical activity and social activity) to provide a health-utility score as a summary measure of quality of life Subgroups: subjects (younger onset), with diabetes diagnosis < 30 years (IDDM)	Linear regression HbA1c not associated with QWB-SA derived utility score	Funding: Not reported Risk of bias: Appropriate eligibility criteria=yes Appropriate measurement of exposure and outcome=yes validated scale Controlled for confounding factors =yes Adequate follow-up=NA
			Women, %	54	Concomitant therapy: NR			Multivariable regression analysis (adjustments; hypoglycaemia, gender, complications) HbA1c not associated with QWB-SA derived utility score (partial R2 = -0.05, p= 0.25)	
			TIDM, %	100				Suggested lack of association explained in part by the generally good Glycaemic control and narrow range of HbA1c levels observed (fewer than 10% of patients with diabetes had HbA1c levels >11%)	
			Age at onset of	NR					

			diabetes, years (mean±SD)						
			Diabetes duration, median (min.-max.)	19(0-77)					
			HbA1c, % median (min.-max.)	8.3(4.7-14.1)					
			BMI, (kg/m2), median (min.-max.)	25(15-70)					
			Missing data: NR						

Table 125: Van Tilburg 2001[161]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparisons	Length of follow-up	Outcome	Effect sizes	Comments
Van Tilburg 2001[161]	Cross sectional observational study USA	n=30 Inclusion criteria: type 1 diabetes and type 2 diabetes patients	Age, years (mean±SD)	40.7±14.7	Insulin pump; 9/30(30%) Insulin 1–2 injections/day ; 5/30 (17%) Insulin ≥3 injections/day ; 16/30(53%)	NA	Quality of life Beck Depression Inventory (BDI); scores 16 indicate depression in population	Linear regression HbA1c levels positively correlated with BDI scores with (r=0 .44, p<0.02)	Funding: Not reported Risk of bias: Appropriate eligibility criteria=yes

		presenting to routine clinic appointment (type 1 diabetes analyses separately) Exclusion criteria: documented history of psychiatric diagnosis, history of stroke, brain surgery, or closed head injury, mild dementia, pregnancy, or recent infection or illness that could have affected glucose control, inability to independently complete the BDI questionnaire	Women, %	70	Concomitant therapy: NR			Age, duration of illness, BMI, and gender not associated with either BDI or HbA1c	Appropriate measurement of exposure and outcome= yes Controlled for confounding factors =unclear Adequate follow-up=NA
			TIDM, %	100					
			Age at onset of diabetes, years (mean±SD)	NR					
			Diabetes duration, years (mean±SD)	19.3± 12.5					
			HbA1c, % (mean±SD)	8.3±1.2					
			BMI, (kg/m2), (mean±SD)	24.6±4.8					
			Missing data: None						

Table 126: WESDR 1998a [79,80]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
WESDR 1998a [79,80]	Prospective case series	n=634 Inclusion criteria: type 1 diabetes, IDDM, Physician diagnosis; primary care of physician during the study period Exclusion criteria: none listed	Age, years (mean±SD)	26.8±11.2	Glycaemic control; NR	14 years	Retinopathy; macular oedema defined as thickening of the retina with or without partial loss of transparency within one disc diameter from the centre of the macula, estimated from all patients without macular oedema and had not been previously treated with photocoagulation at baseline (n=688 for younger onset patients, 329 for older	Retinopathy After controlling for baseline retinopathy, duration of diabetes and gender, each percentage point of lower glycosylated haemoglobin at baseline was associated with increased odds of improvement of retinopathy (odds ratio 1.41; 95% CI 1.19, 1.67)	Funding: National Institutes of Health Grant, Research to Prevent Blindness Risk of bias: Appropriate eligibility criteria=yes Appropriate measurement of exposure and outcome=yes Controlled for confounding factors =regression analysis adequately adjustments Adequate follow-up=yes 10 years
			Women, %	51	Concomitant therapy: NR			Progression to retinopathy HbA1 5.1-9.4% (n=187); 75.4%, RR 1.00 HbA1 9.5 to 10.5% (n=153); 79.5%, RR (95%CI) 1.37 (1.12 to 1.68) HbA1 10.6 to 12.0%(n=174); 95.2%, RR (95%CI) 1.99 (1.67 to 2.38) HbA1 12.1 to 19.5% (n=168); 95.0%, RR (95%CI) 2.64 (2.18 to 3.20) Incidence of macular oedema HbA1 5.1-9.4% (n=187); 12.7%, RR 1.00 HbA1 9.5 to 10.5%	

							onset patients) Nephropathy proteinuria estimated from patients with < 0.30 g/litre urine protein concentration at baseline (n=666 for younger onset patients, 376 for older onset patients taking insulin) (proteinuria was defined protein concentration ≥ 0.30 g/litre) Neuropathy Loss of tactile sensation or loss of temperature sensitivity was defined as reporting a history of these complications patients who	(n=153); 22.6%, RR (95%CI) 1.90 (1.12 to 3.25) HbA1 10.6 to 12.0% (n=174); 33.9%, RR (95%CI) 3.11 (1.95 to 4.95) HbA1 12.1 to 19.5% (n=168); 36.8%, RR (95%CI) 3.37 (2.12 to 5.34)	
			TIDM, %	100					
			Age at onset of diabetes, years (mean±SD)	14.2±7.4					
			Diabetes duration, years (mean±SD)	12.6±9.0					

							did not have them at the baseline (n=444 for younger onset patients, 148 for older onset patients)		
			HbA1, % (mean±SD)	10.6±2.0					
			BMI, (kg/m2) (mean±SD)	NA					
			Missing data:75(18%) patients from 10 year follow-up; 765 patients participated at 10 year follow-up						

Table 127: WESDR 1994[111,113]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
WESDR 1994[111,113]	Prospective case series	n=2990 Inclusion criteria: type 1 diabetes diagnosed before age of 17 years	Age, years (range)	Younger onset; 19.1±13.3 Older onset; 11.6±8.1	Glycaemic control; NR	10 years	Ischaemic heart disease mortality	Younger onset; HR (95% CI) for ischaemic heart disease mortality for a 1–percentage point increase in GHb; 1.18 (1.00 to 1.40)	Funding: National Institutes of Health Grant Risk of bias: Appropriate eligibility
			Women, %	Younger onset; 49 Older onset; 54	Concomitant therapy: NR			Older onset; HR (95% CI) for ischaemic heart disease mortality for	

		Exclusion criteria: LEAD						a 1–percentage point increase in GHb; 1.18 (1.04 to 1.17)	criteria=yes Appropriate measurement of exposure and outcome=yes Controlled for confounding factors =yes multivariate analysis adjustment appropriate (18 factors for proportional hazards model in addition to age and sex for younger onset, 28 factors proportional hazards model in addition to age and sex for older onset) Adequate follow-up=yes 10 years
			TIDM, %	100					
			Age at onset of diabetes, years (mean±SD)	Younger onset; 14.5±7.5 Older onset; 55.0±12.4					
			Diabetes duration, years (mean±SD) 13.8±1.0	Younger onset; 14.6±10.5 Older onset; 11.6±8.1					
			GHb, % (mean±SD)	Younger onset; 12.6±2.6 Older onset; 11.1±2.4					
			BMI, (kg/m2)	Younger onset; 23.6±4.3 Older onset; 28.8±5.7					
			Missing data: None						

Table 128: WESDR 1999[111,112]

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments

WESDR 1999[111,112]	Prospective case series USA	n=1890 Inclusion criteria: type 1 diabetes, IDDM, Physician diagnosis; primary care of physician during the study period (1 July 1979 to 30 June 1980, and 3) were alive and resided within the 11-county area during the same period Exclusion criteria: none listed	Age, years (mean±SD)	Younger onset (n=906); 14.4±7.5 Older onset (n=984); 53.5±12.3	Glycaemic control; NR Concomitant therapy: NR	14 years	Lower extremity amputations (LEA); (amputations of toes, feet, or legs, traumatic amputations and unrelated to diabetes excluded)	Univariate analysis LEA Younger onset; GHb 5.6-9.4% (n=223); incidence=2.5%, RR 1.00 GHb 9.5-10.5% (n=206); incidence= 6.7%, RR(95%CI)2.93 (1.10 to 7.83) GHb 10.6-12.0% (n=220); incidence=7.6%, RR(95%CI) 3.21 (1.24 to 8.33) GHb 12.1-19.5% (n=216); incidence=13.4%, RR(95%CI) 5.64 (2.43 to 13.10)	Funding: National Institutes of Health Research to Prevent Blindness Risk of bias: Appropriate eligibility criteria=yes Appropriate measurement of exposure and outcome=yes Controlled for confounding factors =unclear no description confounders Adequate follow-up=yes 14 years
			Women, %	Younger onset; 50 Older onset; 56				Univariate analysis LEA Older onset GHb 5.4-8.1% (n=244); incidence= 4.4%, RR 1.00 GHb 8.2-9.4% (n=218); incidence=8.5%, RR (95%CI) 1.98 (0.78 to 4.99) GHb 9.5-10.8% (n=223); incidence=12.6%, RR(95%CI) 2.68 (1.15 to 6.24) GHb 10.9-20.8% (n=225); incidence=14.6%, RR(95%CI) 3.79 (1.72 to 8.35)	

			TIDM, %	Younger onset; 100 Older onset; 100				Multivariable analyses (linear logistic model) Younger onset GHb associated with a higher incidence of amputations; OR 1.39 (1.21-1.59), p<0.0001 Older onset GHb associated with a higher incidence of amputations; OR 1.25 (1.09-1.43), p<0.005	
			Age at onset of diabetes, years (mean±SD)	NR					
			Diabetes duration, years (mean±SD) 13.8±1.0	Younger onset; 13.5±9.6 Older onset; 10.9±7.8					
			GHb, % (mean±SD)	Younger onset; 10.8±2.1 Older onset; 9.6±2.0					
			BMI, (kg/m2)	Younger onset; 23.4±4.2 Older onset; 29.2±5.7					
			Missing data: None						

Table 129: WESDR 1998[76,80]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
WESDR 1998[76,80]	Retrospective cohort study	n=987 Inclusion criteria: type 1 diabetes, IDDM, Physician diagnosis; primary care of physician during the study period (1 July 1979 to 30 June 1980, and 3) were alive and resided within the 11-county area during the same period	Age, years (mean±SD)	Younger onset (n=654); 23.9 ±11.0 Older onset (n=333); 58.4 ±11.2	Glycaemic control; NR Concomitant therapy: NR	14 years	Quality of life measured using SF-36 Scales; general health (GH), physical functioning (PF), physical role (RP) Subgroups: subjects (younger onset), with diabetes diagnosis < 30 years (IDDM) subjects (older onset), with diabetes diagnosis ≥30 years (IDDM)	Multiple linear regression Younger onset subgroup; GHb variable for negatively associated general health coefficient (r= -1.6, p<0.005), no association with physical functioning or physical role Older onset subgroup; GHb variable no association with general health, physical functioning or physical role	Funding: National Institutes of Health Grant Risk of bias: Appropriate eligibility criteria=yes Appropriate measurement of exposure and outcome=yes Controlled for confounding factors =unclear no description of analysis Adequate follow-up=yes 14 years
			Women, %	Younger onset; 49 Older onset; 50					
			TIDM, %	Younger onset; 100 Older onset; 100					
			Age at onset of diabetes, years (mean±SD)	NR					
			Diabetes duration,	Younger onset;					

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		Exclusion criteria: none listed	years (mean±SD) 13.8±1.0	11.6 ±9.0 Older onset; 8.9±6.7					
			GHb, % (mean±SD)	Younger onset; 10.9±2.1 Older onset; 9.6±2.6					
			BMI, (kg/m2), (mean±SD)	Younger onset; 22.8±3.8 Older onset; 29.6±5.5)					
			Missing data: None						

Table 130: WESDR 1995[77,78]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
WESDR 1995[77,78]	Prospective case series USA	n=2990 Inclusion criteria: type 1 diabetes, IDDM, Physician diagnosis;	Age, years (mean±SD)	Younger onset (n=1210); 29.3 Older onset (n=824); 652	Glycaemic control; NR	10 years	Retinopathy; proliferative retinopathy for patients free of this complication at the baseline (n=112 for younger onset	Retinopathy Younger onset patients; OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of progression to proliferative retinopathy; 0.58 (0.48 to 0.72)	Funding: National Institutes of Health Grant, Research to Prevent Blindness Risk of bias:

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		primary care of physician during the study period Exclusion criteria: none listed					patients, 417 for older onset) macular oedema defined as thickening of the retina with or without partial loss of transparency within one disc diameter from the centre of the macula, estimated from all patients without macular oedema and had not been previously treated with photocoagulation at baseline (n=688 for younger onset patients, 329 for older-	Older onset patients OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of progression to proliferative retinopathy; 0.69 (0.47 to 1.04) Younger onset patients; OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of macular oedema; 0.53 (0.43 to 0.66) Older onset patients OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of macular oedema; 1.06 (0.67 to 1.69)	Appropriate eligibility criteria=yes Appropriate measurement of exposure and outcome=yes Controlled for confounding factors =regression analysis adequately adjustments Adequate follow-up=yes 10 years
			Women, %	NA	Concomitant therapy: NR			Nephropathy Younger onset patients; OR of (95%CI) 2% difference in GHb from	

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
							onset patients) Nephropathy proteinuria estimated from patients with < 0.30 g/litre urine protein concentration at baseline (n=666 for younger onset patients, 376 for older onset patients taking insulin) (proteinuria was defined protein concentration ≥ 0.30 g/litre) Neuropathy Loss of tactile sensation or loss of temperature sensitivity was defined as	baseline to 6 year follow-up on the incidence of gross proteinuria; 0.71 (0.59 to 0.86) Older onset patients OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of gross proteinuria; 0.81 (0.61 to 1.09) 2% difference GHb from baseline to 4 years estimated to lead to 29% decrease in 10-year incidence of gross proteinuria in younger-onset patients, and 19% decrease in older onset patients	
			TIDM, %	Younger onset; almost all Older onset; 100				Neuropathy Younger onset patients; OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of self-reported loss of	

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
							reporting a history of these complications patients who did not have them at the baseline (n=444 for younger onset patients, 148 for older onset patients)	tactile sensation; 0.81 (0.67 to 0.98) Older onset patients; OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of self-reported loss of tactile sensation; 0.77 (0.54 to 1.06) Younger onset patients; OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of self-reported loss of self-reported loss of temperature sensitivity; 0.84 (0.67 to 1.04) Older onset patients; OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of self-reported loss of self-reported loss of temperature sensitivity;	

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
								0.84 (0.61 to 1.16) 2% difference GHb from baseline to 4 years estimated to lead to 19% decrease in 10-year incidence of loss of tactile sensation in younger onset patients, and 23% decrease in older onset patients 2% difference GHb from baseline to 4 years estimated to lead to 16% decrease in incidence of self-reported loss of temperature sensitivity in younger and older onset patients	
			Age at onset of diabetes, years (mean±SD)	NA				Younger-onset; any retinopathy GHb 5.6-9.4% (n=52), incidence; 82.1%, RR 1.0 GHb 9.5-10.5% (n=61), incidence 86.4%, RR(95%CI) 1.1 (0.8 to 1.4) GHb 10.6-12.0% (n=71) incidence 93.1%, RR(95%CI) 1.3 (1.0 to 1.7)	

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
								GHb 12.1-19.5% (n=64) incidence 96.9%, RR(95%CI) 1.6 (1.3 to 2.1) Younger-onset; progression to proliferative retinopathy GHb 5.6-9.4% (n=52), incidence; 6.2%, RR 1.0 GHb 9.5-10.5% (n=61), incidence 11.6%, RR(95%CI) 1.9 (0.8 to 4.5) GHb 10.6-12.0% (n=71) incidence 34.4, RR(95%CI) 5.9 (3.0 to 11.6) GHb 12.1-19.5% (n=64) incidence 96.9, RR(95%CI) 9.9 (5.4 to 18.0) older onset; any retinopathy GHb 5.6-9.4% (n=40), incidence; 65.9%, RR 1.0 GHb 9.5-10.5% (n=40), incidence 85.0%, RR(95%CI) 1.1 (0.9 to 2.1) GHb 10.6-12.0% (n=32) incidence 78.8%, RR(95%CI) 1.2 (0.7 to 1.9) GHb 12.1-19.5% (n=23) incidence 100.0%, RR(95%CI) 2.1 (1.4 to 3.2)	

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
								older onset; progression to proliferative retinopathy GHb 5.6-9.4% (n=40), incidence; 10.7 %, RR 1.0 GHb 9.5-10.5% (n=40), incidence 13.1%, RR(95%CI) 1.1 (0.4 to 2.8) GHb 10.6-12.0% (n=32) incidence 27.6%, RR(95%CI) 1.3 (1.2 to 5.5) GHb 12.1-19.5% (n=23) incidence 37.9%, RR(95%CI) 1.6 (1.6 to 7.3)	
			Diabetes duration, years (mean±SD)	Younger onset; 14.7 Older onset; 15.0					
			GHb, % (mean±SD)	Younger onset; 10.8 Older onset; 10.2					
			BMI, (kg/m2)	NA					
			Missing data:						

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			None					

Table 131: Wikblad 1996[168,169]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparisons	Length of follow-up	Outcome measures	Effect sizes	Comments
Wikblad 1996[168,169]	Retrospective case series Sweden	n=108 Inclusion criteria: type 1 diabetes born between 1939 to 1959, duration of diabetes at least 5 years (onset of diabetes in 1975 or earlier), currently treated with ≥ 20 U insulin daily Exclusion criteria: none listed	Age, years (mean±SD)	43±5.7	Glycaemic control; NR	10 years	Quality of life SWEDQUAL, a questionnaire (61 items) measures 7 dimensions of quality of life; physical functioning, role functioning, pain, sleep, emotional well-being, family functioning and general health perceptions) Items are scored (0-100); high score indicates better health/more favourable	Patients grouped according to metabolic control; good acceptable, unsatisfactory, unacceptable	Funding: Not reported Risk of bias: Appropriate eligibility criteria=yes Appropriate measurement of exposure and outcome=yes Controlled for confounding factors =unclear Adequate follow-up=yes 10 years
			Women, %	49	Concomitant therapy: NR			Mean values for HbA1c (during 1 year); Good;HbA1c ≤ 7.0, n=35 Acceptable; HbA1c = 7.1–8.0%, n=23 Unsatisfactory; HbA1c = 8.1 – 9.0%, n=24	
			TIDM, %	100				Physical functioning; Good; 88.1±2.9 Acceptable; 91.0±2.4	

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparisons	Length of follow-up	Outcome measures	Effect sizes	Comments
							health state Hypoglycaemia	Unsatisfactory; 78.2±5.5	
			Age at onset of diabetes, years (mean±SD)	14.1±8.3				Satisfaction with physical health; Good; 71.5±4.8 Acceptable; 72.8±5.8 Unsatisfactory; 61.6±6.1	
			Diabetes duration, years (mean±SD)	28.7±9.5				Role limitation due to emotional health; Good; 92.2±3.0 Acceptable; 89.4±5.8 Unsatisfactory; 85.9±4.6	
								Groups comparable for; Satisfaction with family life Marital functioning Sexual functioning General health	

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparisons	Length of follow-up	Outcome measures	Effect sizes	Comments
								Positive feelings Negative feelings Pain Mobility	
			HbA1c, % (mean±SD)	7.7±1.0				Patients who reported episodes of hypoglycaemia had significantly lower HbA1c mean values when compared with patients without severe hypoglycaemia (6.9%±1.0 vs. 7.9%±1.2; F= 5.7, p=0.01)	
			BMI, (kg/m2), (mean±SD)	NR					
			Missing data: Of original cohort; 36 patients moved out of the area and 18 died, of the remaining 131 patients, 108 answered the quality					Patients with hypoglycaemic episodes rated their general health as being poorer compared with those without hypoglycaemia	

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparisons	Length of follow-up	Outcome measures	Effect sizes	Comments
			of life questionnaire				(57.7±9.2 vs. 74.9±3.2; F= 4.2, p=0.04	

Table 132: Wikblad 1991[169]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparisons	Length of follow-up	Outcome measures	Effect sizes	Comments
Wikblad 1991[169]	Prospective /retrospective case series Sweden	n=185 Inclusion criteria: type 1 diabetes born between 1939 to 1959, duration of diabetes at least 5 years (onset of diabetes in 1975 or earlier), currently treated with ≥ 20 U insulin daily Exclusion criteria: none listed	Age, years range	26-46	Glycaemic control; NR	9 years	Retinopathy Nephropathy (negative proteinuria test)	Patients without retinopathy changes HbA1c ≥7.5%; 53% HbA1c 7.6-8.4%; 28% HbA1c 8.5-9.4%; 30% HbA1c ≥9.5%; 29%	Funding: Not reported Risk of bias: Appropriate eligibility criteria=yes Appropriate measurement of exposure and outcome= unclear description outcomes Controlled for confounding factors =unclear Adequate follow-up=yes 9 years
			Women, %	44	Concomitant therapy: NR			Patients without proteinuria; HbA1c ≥7.5%; 88% HbA1c 7.6-8.4%; 77% HbA1c 8.5-9.4%; 58% HbA1c ≥9.5%; 47%	
			TIDM, %	100					
			Age at onset of diabetes, years (mean±SD)	Men 15.5±7.7 Women 12.3±7.9					
			Diabetes duration, years (mean±SD)	22.1±8.5					

			HbA1c, % (mean±SD)	8.7±1.3					
			BMI, (kg/m2), (mean±SD)	25(15-70)					
			Missing data: NR						

G.3.2 SMBG – frequency and timing

Table 133: ABDELGADIR 2006 [4]

Reference	Study type	Number of patients	Patient characteristics		SMBG	Length of follow-up	Outcome measures	Effect sizes	Comments
M. Abdelgadir, M. Elbagir, M. Eltom, and C. Berne. The influence of glucose self-monitoring on glycaemic control in patients with diabetes mellitus in Sudan. Diabetes Res.Clin.Pract. 74	Cross-sectional study carried out in an out-patient clinic in Sudan	n=193 consecutive type 2 diabetes (n=143 (74%)) and type 1 diabetes (n=50 (26%)) Inclusion criteria: Age ≥20 years Duration of diabetes ≥1 year Exclusion criteria: not reported			Fasting blood glucose using portable glucose meters Accutrend sensor		Frequency distribution of SMBG for type 1 diabetes (26%) and type 2 diabetes (74%)		Funding: Supported by grants from In-develop Uppsala and the Swedish Diabetes Association. Risk of bias: No NICE checklist "The study from an urban population in Sudan shows that the frequency of self-monitoring of glucose was
				Patient characteristics (n=193)			Self-monitoring technique	SMBG Blood glucose (mmol/litre)	
			Age (years), mean (SD)	50.0 (SD 13.4)			Once a day (n=4), mean (SD)	6.2 (SD 1.8)	
			Gender (m/f)	95/98			Once a week (n=48)	9.4 (SD 3.5)	
			Duration of diabetes (years), mean (SD)	10.1 (SD 7.9)			None (n=141), mean (SD)	13.1 (SD 4.5)	

Reference	Study type	Number of patients	Patient characteristics		SMBG	Length of follow-up	Outcome measures	Effect sizes		Comments
(1):90-94, 2006. REF ID: ABDELGADIR 2006			HbA1c (%)	Not reported			Random blood glucose values for type 1 diabetes (n=50)			positively associated to good glycaemic control in type 1 diabetes but not in type 2 diabetes patients. Education level of the participants was neither associated to frequency of self-monitoring nor to level of glycaemic control"
			BMI (kg/m2), mean (SD)	22.9 (SD 4.9)				Never monitored blood glucose	Monitored blood glucose	
							Random blood glucose (mmol/litre), mean (SD)	17.2 (SD 4.5)	7.2 (SD 1.8)	
			Drop-outs: None reported				HbA1c (%), mean (SD)	9.4 (SD 2.1)	5.6 (SD 1.5)	

Table 134: BOTT 1994 [16]

Reference	Study type	Number of patients	Patient characteristics	SMBG	Length of follow-up	Outcome measures	Effect sizes		Comments
U. Bott, V.	Prospective	n=697 type 1	type 1 diabetes taking part	Patients	3 years	No. of blood	Patients, n (%)	A1c	Funding:

Reference	Study type	Number of patients	Patient characteristics		SMBG	Length of follow-up	Outcome measures	Effect sizes		Comments
Jorgens, M. Grusser, R. Bender, I. Muhlhauser, and M. Berger. Predictors of glycaemic control in type 1 diabetic patients after participation in an intensified treatment and teaching programme. Diabet.Med. 11 (4):362-371, 1994. REF ID: BOTT 1994	case series Non-randomised multi-centre study Germany	diabetes patients. Inclusion criteria: type 1 diabetes patients, age 15-40 years Free of advanced diabetic late complications Exclusion criteria: not reported	in an in-patient treatment and teaching programme (TTP) for intensified insulin treatment (IIT)		were advised to measure blood glucose before main meals and at bed time and to inject NPH-insulin in the morning and at bedtime and regular insulin before meals		glucose measurement/day		(3-year follow-up)	Financed through a grant by the Bundesminister fur Forschung und Technologie Risk of bias: No NICE checklist One way analysis of variance revealed a significant linear association between the frequency of daily home blood glucose monitoring and HbA1c
				SMBG (n=697) Baseline			0	73 (10)	10.4 (SD 2.2)	
			Age (years), mean (SD)	26 (SD 7)			0 - 1	40 (6)	9.5 (SD 1.8)	
			Duration of diabetes, mean (SD)	8 (SD 7)			1 - 2	115 (17)	9.3 (SD 1.6)	
			HbA1c (%), mean (SD)	10 (SD 2.2)			> 2	469 (67)	8.9 (SD 1.5b)	
			Incidence of severe hypoglycaemia	0.28					bP<0.001	
								Incidence of severe hypoglycaemia (3-year follow-up)	0.13 b	
								bP<0.005		
			Only patients with diabetes							

Reference	Study type	Number of patients	Patient characteristics	SMBG	Length of follow-up	Outcome measures	Effect sizes	Comments
			duration of more than 1 year at baseline (n=547) Drop-outs: None reported			One way analysis of variance revealed a significant linear association between the frequency of daily home blood glucose monitoring and HbA1c		

Table 135: BRAGD 2003 [17]

Reference	Study type	Number of patients	Patient characteristics			Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: BRAGD2003	Prospective case series survey of a cohort at two different time points	n= 178 Inclusion criteria: type 1 diabetes registered at outpatient clinic in 1984 to be repeated in 1998 Exclusion criteria: none listed		1984 n=178	1998 n=178	ITT: n=178. Same cohort followed up 14 years later	14 years. But cross-sectional data collected	Predictors of hypoglycaemia. Variable: Self-monitoring of blood glucose	Stepwise logistic regression analysis showed SMBG was not a predictor of severe hypoglycaemia 1984 x2=1.9, r2=0.22 p=0.19 1998 x2=0.48 r2=0.09 p=0.49	Funding: None listed. Risk of bias: Appropriate eligibility criteria = yes all type 1 diabetes but little detail on inclusion/exclusion criteria Appropriate measurement of exposure and outcome=yes Controlled for confounding factors = yes,
			Age, years (SD)	35±9.8	49±9.8					
			Women, %	54	54	Concomitant medication: none listed				
			% TID	100	100					
			Diabetes duration, years (SD)	17.9±10.9	32.3±10.9					
			Weight or BMI	NA	NA					
			HbA1c/GHb, %	7.6±1.3	7.4±1.1			Change in SMBG+ severe	No significant	

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			(SD) Difference between groups: yes for age, duration of DM, HbA1c, SMBG daily, severe hypoglycaemia Drop-outs: none			hypoglycaemia	association	used stepwise logistic regression analysis. Adjusts for other variables Adequate follow-up = yes, 14 years

Table 136: COX 2007 [30,32]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: COX2007	Prospective case series	n=90 Inclusion criteria: type 1 diabetes taking insulin. Diagnosed for at least 2 years. Exclusion criteria: age >65 years, mental retardation, psychosis, active substance abuse, or significant depression.		n=90	ITT: n=90 One Touch Ultra meter were used to store the SMBG readings. Severe hypoglycaemia episodes were captured in questionnaires	4 months	Prediction of upcoming SH episodes	Min. number of SHBG readings in the 24 h preceding SH episode + % predicted SH episodes. n=3 = 57% n=4 =60% n=5 =63% There is a trend for a higher number of SMBG levels and the prediction of	Funding: Grant from National Institutes of Health Grants and LifeScan. Risk of bias: Appropriate eligibility criteria = yes, although limited inclusion criteria Appropriate
			Age, years (SD)	40.7±11.2					
			Women,	57					

Reference	Study type	Number of patients	Patient characteristics		Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
			%					severe hypoglycaemia.	measurement of exposure and outcome=yes Controlled for confounding factors = unclear. Used an undefined algorithm to find patterns in SMBG data shown to precede severe hypoglycaemic episodes. Adequate follow-up = short-term. 4 months
			% TID	100					
			Diabetes duration, years (SD)	20±10.7					
			Weight or BMI	25.3±4.4					
			HbA1c/GHb, % (SD)	7.6±1.2					
			Difference between groups: not relevant Drop-outs: Unclear, none stated		Concomitant medication: None listed				

Table 137: EVANS1999 [41]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: EVANS1999	Retrospective case-series	n=807 Inclusion criteria: diagnosed with	n=807 TID		ITT: n=807	2 years	Predictor of haemoglobin A1c concentration	Total number of reagent strips dispensed (+180) r=-0.613, p<0.01. A	Funding: Grant from Wellcome trust training
			Age, years	Range; 0 to >65					

Reference	Study type	Number of patients	Patient characteristics		Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
	Non-RCT Diabetes database	T1 diabetes before Jan1993 to Dec 1995 Exclusion criteria: none listed	(SD)	years of age				decrease in haemoglobin A1c concentration for every 180 test strips dispensed (equivalent to one a day) of 0.7%	fellowship in Health Services Research Risk of bias: Appropriate eligibility criteria = no, included <18 year olds. Also provided very little detail Appropriate measurement of exposure and outcome=yes but only in 258 patients with haemoglobin A1c outcome available. Controlled for confounding factors = no, linear regression analysis only. Adequate
			Women, %	Men and women, unclear ratio	Concomitant medication:				
			% TID	100					
			Diabetes duration, years (SD)	Range 0 to >20 years					
			Weight or BMI	NA					
			HbA1c/GHb, % (SD)	NA					
			Difference between groups: not relevant Drop-outs: Not relevant for registry data						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
								follow-up = yes, 2 years

Table 138: GORDON1991 [57]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: GORDEN1991	RCT. Cross-over study. UK	n=25 Inclusion criteria: Insulin dependent patients were recruited from the hospital outpatient clinic. Either sex and aged 18-50 years; have TID for 12 months or longer; taking at least two insulin injections per day; already be performing SMBG for longer than 6 m.	n=25		ITT: n=25 Patients undertook in random order, one of three different protocols: A 4-point profile on any two non-consecutive days per week. One 4-point on any day of the week Two blood glucose measurements on each day for 7 days per week Four-point profiles measured blood glucose before the three main meals of the day and at 22h. Two-point profiles involved measurements at any two of these times but varying from day to day.	3x12 week periods	There was no significant relationship between frequency at which a patient altered insulin dosage and their metabolic control as estimated by mean glycosylated haemoglobin. Patient preference: n=9 preferred 2dx4 tests/week, n=6 preferred 1dx4 tests/week; n=3 preferred 7dx2 tests/wk.		Funding: Grant from CP Pharmaceuticals. Risk of bias: Appropriate eligibility criteria = yes Appropriate measurement of exposure and outcome=yes measured blood glucose, glycosylated Hb, and fructosamine Controlled for
			Age, years (SD)	31±10					
			Women,	36%	Concomitant medication: none				

Reference	Study type	Number of patients	Patient characteristics		Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
		Exclusion criteria: pregnant or planning pregnancy. Significant intercurrent illness (hepatic, renal or life threatening disease or other systemic illness) or hospitalization for diabetic ketoacidosis in previous 12 months.	%		listed.				confounding factors = no. no discussion on confounders or did they account for them in the analysis. Also cross-over trials have a risk of carry-over effects. Adequate follow-up = yes, 12 weeks for each trial
			% TID/type 2 diabetes	100% TID					
			Diabetes duration, years (SD)	10.9±7.7					
			Weight or BMI	NA					
			HbA1c/GHb, % (SD)	NA					
			Drop-outs: n=4 (no reason)						

Table 139: HILLMAN 2004[64]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: HILLMAN2004	Retrospective case-series SPAIN	n=146 Inclusion criteria: consecutive home blood	n=146		ITT: n=146 Blood glucose values obtained before and 2 h after breakfast, lunch and dinner during a	8 weeks	Stepwise multiple regression to assess predictors of HbA1c: Constant β = 3.487		Funding: None listed. Risk of bias: Appropriate eligibility
			Age, years (SD)	NA			Pre-dinner glycaemia	β=0.0118 R2=0.347	

Reference	Study type	Number of patients	Patient characteristics		Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
		glucose records from 71 C-peptide-negative Type 1 diabetic patients undertaking intensive diabetes therapy. Exclusion criteria: None.			period of 8 weeks. Target dose of 3.9-6.7 mmol/litre before meals or during fasting periods and 5.6-7.8 mmol/12 h after meals.			P<0.0001	criteria = yes Appropriate measurement of exposure and outcome= yes Controlled for confounding factors = yes, performed stepwise multiple linear regression. Results were weighted to account for variation in number of records per patient. However, no other potential confounders were discussed. Adequate follow-up = yes, 8 weeks
			Women, %	NA			Pre-breakfast glycaemia	β=0.0063 R2=0.462 p<0.0001	
			% TID/type 2 diabetes	100% TID					
			Diabetes duration, years (SD)	10.2±7.2					
			Weight or BMI	NA			Post-breakfast glycaemia	β=0.0046 R2=0.478 p=0.020	
			Drop-outs: None.		Concomitant medication: All patients received individualized meal plans to ensure an adequate energy intake and to achieve glycaemic goals, with carbohydrate and monounsaturated fat providing 60-70% of energy intake. None others listed.		Mean pre-breakfast and mean post-breakfast glycaemia correlated significantly and independently with HbA1c. The model accounted for 47.8% of the variance in HbA1c.		

Table 140: KARTER2001 [71]

Reference	Study type	Number of patients	Patient characteristics			Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: KARTER2001	Retrospective case-series Observational – registry cohort USA	n=1159 Inclusion criteria: >19 years of age with continuous membership to database from Jan1, 1996 to Dec 31 1997, full pharmacy benefits and HbA1c level that was measured during follow-up were included. Exclusion criteria: non-listed	n=1159 Adherers = monitored at least 3xday			ITT: n=1159 Monitoring ≥ 3xday, if average utilization was >2.5 strips/day, n=395 1-<3x/day, if utilization was <2.5 to >0.75 strips/day, n=385 <1 daily if <0.75 but >0 strips/day, n=189 No practicing self-monitoring if no record of strip utilization, n=190	1 year	Adherence was associated with significantly greater glycaemic control (lower HbA1c levels), after adjusting for demographic, socioeconomic, behavioural, and clinical variables Adherent = 7.7 (7.6,7.9) Non-A = 8.7 (8.6, 8.9)		Funding: Grant from American Diabetes Association, NIH and Kaiser Research Foundation Institute. Risk of bias: Appropriate eligibility criteria = yes. Appropriate measurement of exposure and outcome= yes, self-monitoring levels were based on average daily strip utilization. Controlled for confounding factors = yes, adjusted for variables in
				Adherent n=395	Non-Adherent, n=764			As monitoring frequency increased, adjusted HbA1c levels declined. No utilization=9.1% < 1 daily = 8.9% Daily = 8.5% ≥ 3xday = 7.7%		
			Age, years (SD)	43.2 12.9	40.4 12.6			In pharmacologically treated patients, the largest improvement in HbA1c levels was in those with monitoring at the recommended frequency (<3 x daily)		
			Women, %	59%	49%	Concomitant medication: use of diet and exercise as therapy, 43% and 48%				
			% TID	100%	100%					
			Diabetes							

Reference	Study type	Number of patients	Patient characteristics			Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			duration, 0-9 years ≥10years	14% 86%	18% 83%	respectively.		whereas lesser frequencies conferred little benefit		analysis. Adequate follow-up = yes 12 months
			Weight or BMI	NA	NA					
			HbA1c/GHb, % (SD)	7.6±1. 4	8.8±1.9					
			Difference between groups: Differences were detected for HbA1c, age, female sex, ethnicity, occupation, years since diagnosis, injections per day, use of diet, smoking. Drop-outs: Missing data n=100 from large study 24,312.							

Table 141: KLEIN 1992 [80]

Reference	Study type	Number of patients	Patient characteristics		SMBG	Length of follow-up	Outcome measures	Effect sizes	Comments
R. Klein, S. E. Moss, and B. E. Klein. Change in glycemia in a four-year interval in younger-	Prospective case-series Non-randomised study conducted in 11 county area	n=1210 eligible patients with IDDM. n=996 participated in the baseline examination	Patients attending out-patient clinic, who had been on IIT for at least a year		33% of the population was practicing self-monitoring of blood glucose at least once a day or more 64% of the population was using two or more insulin injections per day 68% was using a	Participants followed up over 4 years	Frequency of blood glucose self-testing/week	Change in glycosylated haemoglobin (%)a	Funding: study was supported by grant to the primary author from the National Eye Institute. Risk of bias: No
				SMBG (n=996)			Never test (n=254)	-0.6	
							< 6 (n=212)	-0.6	
			Age	Diagnosed at 30 years or			7 – 13 (n=71)	-1.0	

Reference	Study type	Number of patients	Patient characteristics	SMBG	Length of follow-up	Outcome measures	Effect sizes	Comments
onset insulin-dependent diabetes. Ann Epidemiol 2 (3):283-294, 1992. REF ID: KLEIN 1992	in southern Wisconsin	. n=891 participated in the follow-up examination . Inclusion criteria: Having diabetes before 30 years old Patients taking insulin Exclusion criteria: not reported	older Drop-outs: 26% of the participants.	combination of intermediate and short acting insulin		14 – 20 (n=83) ≥ 21 (n=77) a Test of trend P <0.01 Hypoglycaemia	-1.3 -1.1 Not reported	NICE checklist

Table 142: MINDER 2013

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
AE. Minder, D. Albrecht, J. Schafer, and H. Zulewski. Frequency of blood glucose	Cross-sectional study Switzerland	n=150 Inclusion criteria: type 1 diabetes adults (well-	n=150 All patients were treated with principles of flexible intensified insulin therapy, and patients were encouraged to SMBG at least 4 times/day. Age, 46	Monitoring SMBG measurements HbA1c measurements	n/a	Mean HbA1c declined with increasing number of SMBGs per day Decline continued up to at least 4 SMBGs/day before flattening Differences in HbA1c corresponding to an 1 measurement increase in no. of SMBGs/day were as follows (adjusted model):		Funding: Grant from Santesuisse and Gottfried and Julia Bangerter-Rhyner-Foundation.

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
testing in well educated patients with diabetes mellitus type 1: How often is enough? Diabetes Res.Clin.Pract. 101 (1):57-61, 2013. REF ID: MINDER 2013		educated) Availability of at least one HbA1c mmt and concomitant data set of directly preceding SMBG data Exclusion criteria: none listed	years median				No. of SMBGs/day per 1 mmt increase and difference in HbA1c (95% CI) ≤4 SMBGs = -0.19% (-0.42,0.05) >4 SMBGs = -0.02 (-0.10, 0.06) Study concludes to measure SMBG at least 4 times/day		Risk of bias: No NICE checklist for this study type
			Women, %	44					
			Diabetes duration, median	21					
			Median BMI	24					
			SH within past 5 years	31%					
			Median most recent HbA1c (IQR)	7.1 (6.6-7.8)					
			Drop-outs: N/A.						

Table 143: NATHAN1996[117]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Length of follow-up	Outcome measures Effect sizes	Comments
REF ID: NATHAN19	Prospective case-series	n= 183	Group recruited	1984-5 n=94	1992-3 n=89	ITT: n=183 Usual care	12 months	Multiple linear regression models of	Funding: Grant from

Reference	Study type	Number of patients	Patient characteristics			Intervention	Length of follow-up	Outcome measures Effect sizes	Comments
96	data we are using, but main study design is prospective cohort Registry data. Cohort analysis.	Inclusion criteria: Consecutive outpatients who had a haemoglobin A1c assay performed in during March 1985 and 1993. Exclusion criteria: did not carry the diagnosis for at least 1 year. Patients enrolled in diabetes research studies.	Age, years (SD)	27±17	31±18	Concomitant medication: none listed	(unclear)	mean HbA1c in the combined 1985 and 1993 IDDM groups showed that frequency of insulin injections and of self-monitoring of blood glucose were independently and significantly associated with HbA1c, R2 = 0.15, p<0.001 Frequency: Visits β=0.16, p=0.12 Self-monitoring β=-0.30, p=0.010 HbA1c measurement β=-0.29, p=0.065 Insulin injection = β=-0.47, p=0.034	Earle. P Charlton Jr. Charitable Foundation and Mallinckrodt General Clinical Research Centre. Risk of bias: Appropriate eligibility criteria = yes Appropriate measurement of exposure and outcome= yes, good spread of patients representing different no. of injections per day Controlled for confounding factors = yes, multiple linear regression
			Women, %	48	54				
			% TID	100	100				
			Diabetes duration, years (SD)	11±10	13±12				
			Weight or BMI	NA	NA				
			HbA1c/% (SD)	9.47±2.1	8.77±1.7				
			Difference between groups: HbA1c Drop-outs: Registry data, so not relevant						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures Effect sizes	Comments
							analysis was performed. Adequate follow-up = 1 year, unclear what the mean was for patients

Table 144: PICKUP 2006[125]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: PICKUP2006	Prospective case series	n=30 Inclusion criteria: consecutive patients in a hospital based programme of intensification of diabetic control, where subjects were offered a trial of CSII if they failed to achieve good control on MDI. Twenty of the subjects had been included in		On MDI n=30	On CSII n=30	All subjects were receiving multiple daily injections (MDI) as part of their routine therapy at entry into the study, be we made a renewed attempt to achieve optimum control on MDI over 5 months. At the end of the period on MDI	5 months (3-9 months) on MDI and 16mo on CSII	Multivariate correlates of HbA1c	During MDI Within-day blood glucose variability β=0.62 SE=0.22 p=0.01 Blood glucose <3.5mmol/litre β =-0.10, SE=0.02, p=0.001	Funding: Grant from Medtronic Ltd. Risk of bias: Appropriate eligibility criteria = yes Appropriate measurement of exposure and outcome= cross-over trial, risk of carry over
			Age, years (SD)	41.6±11.0	-					
			Women, %	66%	-			Multivariate predictor of HbA1c on CSII	During CSII Only MDI on HbA1c β=0.70 SE=0.18 p=0.001	
			% TID	100	-					

Reference	Study type	Number of patients	Patient characteristics			Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
		a previous study. Exclusion criteria: 5 were excluded because of incomplete blood glucose self-monitoring data and one because she became pregnant	Diabetes duration, years (SD)	23.4±11.3	-	all patients switched to DSII and reviewed at 2, 6, 11, 16 months after the start of therapy. ITT: n=30 CSII – continuous s.c. insulin infusion.		Hypoglycaemia frequency was negatively correlated with HbA1c during MDI. Within day BG variability was correlated with HbA1c on MDI. Hypoglycaemia frequency and within-day blood glucose variability were only significant at the p=0.09 level. Hypoglycaemia (BG <3.5 mmol/litre) was reduced from a median of 9.5% during MDI to 3.8% during pump therapy (p=0.01). Within day and between day blood glucose variability were also significantly reduced on CSII compared with MDI		effect. In fact, correlate of HbA1c on CSII was HbA1c on MDI Controlled for confounding factors = yes, multivariate analysis but unclear which variables included Adequate follow-up = yes, 5 m and 16m
			BMI	25.6±3.6	25.9±4.3					
			HbA1c % (SD)	8.5±1.4	7.3±0.9					
			SMBG test/day	4.2±1 3	4.6±0.7					
			Difference between groups: HbA1c and hypoglycaemia Drop-outs: none			Concomitant medication: none listed				

Table 145: SCHIFFRIN 1992[137] 1982

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: SCHIFFRIN 1992	Cross-over design	n=21 Inclusion criteria:	No patient characteristics provided	CSII= continuous subcutaneous insulin infusion MSI = multiple subcutaneous insulin injections	21 months	Group A	HgbA1% Initiation: 8.1±0.5 Phase I: 7.9±0.4 Phase II: 10.3±0.5	Funding: Grant from Montreal Children's

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
		Insulin dependent diabetes aged 15-36 years participated in the study. All patients had fasting C-peptide levels below 0.08pmol/ml and responded to i.v. glucogen with C-peptide levels below 0.2 pmol/ml. Patients followed a diet which consisted of 30-40% fat, 15-20% protein, and 40-45% carbohydrate given as 3 meals and a bedtime		CBG = capillary self-blood glucose Cross-over trial. Initiation: 0-12m 0-6m n=14 on CSII + MSI, 5-7 x/d CBG. 6-12m n=7 on CSII 6-12m n=7 on MSI 0-12m n=7 on CSIII+MSI Phase 1: 12-18m Group A – CSII 4x/d CBG Group B – CSII 2x/d CBG Group C – MSI 4x/d CBG Group D – MSI 2x/d CBG Phase 2: 18-21m Group A – CSII 2x/day CBG Group B – CSII 4x/day CBG Group C – MSI 2x/day CBG Group D – MSI 4x/day CBG Phase 3: >21 m All 4x/day CBG			Phase III: 8.0±0.1	Hospital Research Institute and Diabetic Children's Foundation, Canada Risk of bias: Appropriate eligibility criteria = unclear. Patients aged 15-36 and no details on their characteristics provided. Appropriate measurement of exposure and outcome= cross-over trial, so risk of carry-over effect from one phase to the next Controlled for confounding factors = no. Adequate
			Difference between groups: None provided Drop-outs: Unclear			Group B	HgbA1% Initiation:7.9±0.4 Phase I: 10.2±0.5 Phase II: 8.2±0.4 Phase III: 8.1±0.2	
						Group C	HgbA1% Initiation:8.3±0.6 Phase I: 8.1±0.4 Phase II: 10.0±0.9 Phase III: 8.0±0.6	
						Group D	HgbA1% Initiation:8.2 Phase I:10 Phase II:8.6 Phase III:8.7	
							Conclusion: Diabetic control was significantly better during periods of frequent self-monitoring Frequent SMBG is critical for the long-term maintenance of glycaemic control.	
				Concomitant medication: controlled diet				

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
		snack. Exclusion criteria: none listed						follow-up = yes, each phase min 6 months.

Table 146: SCHUTT 2006 [139]

Reference	Study type	Number of patients	Patient characteristics		SMBG	Length of follow-up	Outcome measures	Effect sizes		Comments
M. Schutt, W. Kern, U. Krause, P. Busch, A. Dapp, R. Grziwotz, I. Mayer, J. Rosenbauer, C. Wagner, A. Zimmermann, W. Kerner, R. W. Holl, and D. P. V. Initiative. Is the frequency of self-monitoring of blood	Prospective case series Standardised, prospective, multicentre, computer-based documentation of diabetes care and outcome from 191 centres in Germany and Austria	n=24500 participants with 19491(80%) type 1 diabetes (type 1 diabetes). For each patient the most recent complete year of diabetes care was evaluated. Inclusion criteria: Patients on intensive conventional insulin therapy for at least 6 months Performing	Patients with type 1 diabetes		SMBG: Intensified conventional (≥4 daily injections) or continuous subcutaneous insulin infusion therapy (CSIIT) conventional (1-3 daily injections) therapy (CT) On average patients with type 1 diabetes performed 4.4 blood glucose measurements per day. This	At least 6 months		CSIIT	CT	Funding: Financial support for the development of the DPV software was provided by the Bundesministerium fur Gesundheit and NovoNordisk Germany. Risk of bias: No NICE checklist
				SMBG (n=19491)			HbA1c (%) - reduction for one additional measurement /day	0.3% reduction	0.16 % reduction	
			Age (years), mean (SD)							
			Gender (m/f)							
			Duration of diabetes, mean	5.8 years						
			HbA1c (%), mean	8.5%						

Reference	Study type	Number of patients	Patient characteristics		SMBG	Length of follow-up	Outcome measures	Effect sizes		Comments
glucose related to long-term metabolic control? Multicenter analysis including 24,500 patients from 191 centers in Germany and Austria. Exp.Clin.Endocrinol.Diabetes 114 (7):384-388, 2006. REF ID: SCHUTT 2006		SMBG for at least 6 months using the dextrostix-glucometer system Previous instruction on the use of SMBG during a 5-day inpatient educational session Exclusion criteria: not reported			number increased continuously during the last 10 years (1995: 3.1 values/day and 2004: 4.9 values/day; p<0.0001). SMBG frequency was significantly associated with better metabolic control (p<0.0001). One additional daily blood glucose measurement improved the HbA1c level by 0.26%.					
			Data were adjusted for age, diabetes duration,							

Reference	Study type	Number of patients	Patient characteristics	SMBG	Length of follow-up	Outcome measures	Effect sizes	Comments
			gender, BMI, treatment centre and year of therapy. Drop-outs: None reported					

Table 147: SERVICE 2007 [141,142]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
F. John Service and Peter C. O'Brien. Influence of glycemic variables on hemoglobin A1c. Endocr Pract 13 (4):350-354, 2007. REF ID SERVICE 2007	Prospective case series from the Diabetes Control and Complications Trial database (DCCT)	n=565 volunteers. n=296 assigned to conventional therapy; n=269 assigned to intensive therapy Inclusion criteria: Volunteers whose 7-point capillary profiles collected			Intensive therapy – no details	Conventional therapy – no details	>4 years	Correlation between various components of the 7-point capillary glucose profile and haemoglobin AIC*			Funding: Not reported Risk of bias: No NICE checklist Drop-outs = none reported In the multivariate analysis, the primary predictor of A1C was Mean Blood Glucose (MBG). All other glucose variables
								Glucose variable	R2	P value	
								Overall mean	0.443	<0.0001	
								**Mean digestive	0.406	<0.0001	
			Age (years)	Not reported				Mean postprandial	0.399	<0.01	
			Type of diabetes	Not reported				***Mean inter-digestive	0.316	<0.01	
								Mean after supper	0.256	<0.01	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
		pre-prandial and 90 minutes postprandial for each of the major meals and at bedtime were complete in 80% or more of quarterly collections who were in the study for 4 years or longer Exclusion criteria: "women in the conventional treatment group who became pregnant"							Mean after lunch	0.255	<0.01	added nothing further to the models. Conclusion: "within the limitations of correlating 7-point glucose profiles obtained quarterly (over several years) with A1C, the strongest influence is from overall mean glycaemia. Furthermore there seem to be unidentified influences on this relationship not attributable to variability of glycaemia".
									Mean bedtime	0.231	<0.01	
									Mean before supper	0.224	<0.01	
									Mean after breakfast	0.201	<0.01	
									Mean fasting	0.170	<0.01	
									Mean before lunch	0.168	<0.01	
			Drop-outs: None reported						*R2 = multivariate coefficient of determination. **Mean of after breakfast, before and after lunch, and before and after supper. ***mean of bedtime and fasting.			

Table 148: SHIMIZU 2008 [145]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Hiroyuki Shimizu, Yutaka Uehara, Shuichi Okada, and Masatomo Mori. Contribution of fasting and postprandial hyperglycemia to hemoglobin A1c in insulin-treated Japanese diabetic patients. Endocr.J. 55 (4):753-756, 2008. REF ID: SHMIZU 2008	Non-randomised cross-sectional outpatient study conducted in Japan	n=57 type 1 diabetes and type 2 diabetes participants. n=24 (type 1 diabetes; 1, type 2 diabetes; 23) treated with insulin twice a day n=33 ((type 1 diabetes; 14, type 2 diabetes; 19) intensively treated (IIT) Inclusion criteria: Diagnosis of diabetes for at least 12 months Exclusion criteria: not reported				Intensively treated group (IIT)	Twice daily			IIT	Twice daily	Funding: not reported Risk of bias: No NICE checklist
				Twice daily	IIT				HbA1c levels and fasting glucose (FG) correlation	In the intensely treated group, a significant correlation between HbA1c levels and FG levels was found before lunch and at 2hr after breakfast and dinner.		
			Age (years), mean (SD)	60.7 (SD 3.3)	46.4 (SD 2.9)				HbA1c levels and fasting glucose (FG) correlation	In all subjects, only FG levels before lunch correlated significantly with HbA1c levels although post prandial glucose (PPG) levels were significantly correlated		
			M/F	7/17	6/27							

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
										with HbA1c at all points		
			HbA1c (%), mean (SD)	7.71 (SD 0.38)	7.92 (SD 0.26)							
			BMI (kg/m2), mean (SD)	24 (SD 0.8)	25.2 (SD 1)							
			Drop-outs: Dropout rate: not reported									

Table 149: SKEIE 2009 [148] (randomised study)

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Svein Skeie, Gunn B. B. Kristensen, Siri Carlsen,	Parallel RCT. Single	n= 134 adults with type 1 diabetes.	Patients 18-70 years with type 1 diabetes and A1C levels of ≥8%.	Inter	Contr	Focussed, structured 9-month SMBG: Six visits	Regular care: Daily SMBG performance	9 months	A1C (%), at	Intervention group 10% had reached	Funding: research was supported by grants from

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
and Sverre Sandberg. Self-monitoring of blood glucose in type 1 diabetes patients with insufficient metabolic control: focused self-monitoring of blood glucose intervention can lower glycated hemoglobin A1C. J Diabetes Sci Technol 3 (1):83-88, 2009. REF ID: SKEIE 2009	centre trial carried out at the diabetes outpatient clinic at Stavanger University Hospital, Norway	n=65, control group ; n=69, intervention Inclusion criteria: Glycated haemoglobin (A1C) ≥8% Treatment with multiple insulin injections or continuous subcutaneous insulin infusion pump (CSII) 18-70 years and a SMBG user Exclusion criteria: Unstable condition with more than 5KG		vention group (n=59)	ol group (n=64)	scheduled over 9 months Participants introduced to HemoCue Monitor Consultation performed by a diabetes nurse and a biomedical laboratory scientist Enhance focus on BG self-management Participants received and brought a BG diary for BG profiles at every visit, a "fasting BG map", and a hypoglycaemia registration	, weekly eight-point SMBG profiles, and an A1C goal of <7.0-7.5%. All patients performed a number of additional measurements for monitoring hypoglycaemia		study end	A1C<7%, 24% had A1C<7.5%, and 39% had A1C <8%		the Juvenile Diabetes Research Foundation. Risk of bias: Randomisation: "recruited and randomised consecutively" Allocation concealment: not reported Blinding: not reported ITT analysis: "analysis was based on ITT principle" Powered study: pre-study power calculations reported In the control group, 22.5% of patients were insulin
			Age (years) , mean (SD)	39 (SD 12)	38 (SD 9)					Control group		
			Diabetes duration (years), mean (SD)	20 (SD 11)	19 (SD 12)				A1C (%), at study end	No patient obtained A1C<7.5%, and 13% had A1C<8%		
										Intervention group	Control group	
									A1C (%), at study end	Comparing the 2 groups, A1C was approximately 0.6% lower in the intervention group		
			Body mass index (kg/m2)	25 (SD 3)	26 (SD 5)				Hypoglycaemia	No increase in major or minor hypoglycaemia in both groups during the study period		
			Women (%)	57.4	52.4							
			CSII users (%)	20.4	22.5							
			Mean A1C at	8.65 (SD	(SD							

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		weight variation	inclusion (%)	0.1)	0.09)						pump users at study start, 25% at study end.
		More than 1.5% variation in A1C within past 12 months Hypoglycaemia unawareness Mental instability Any condition limiting the patient's ability to follow the study protocol	In the control group, 2 additional patients started pump therapy during the study period. All patients had a long-standing experience in performing Drop-outs: Dropout rate: 23% dropped out of the intervention group and 2% dropped out of the control group								

Table 150: TILDESLEY 2004 [156]

Reference	Study type	Number of patients	Patient characteristics		SMBG	Length of follow-up	Outcome measures	Effect sizes		Comments
H. D. Tildesley and K. W. Johns.	Prospective case series Observational	1447 patients attended the 4-day	n=934 TID using insulin therapy		The number of insulin injections per day increased during the 10-year	10 year observation period with an average of 4.7				Funding: Not reported
				SMBG (n=934)			HbA1c (%), mean (SD)	A1C values were negatively		

Reference	Study type	Number of patients	Patient characteristics		SMBG	Length of follow-up	Outcome measures	Effect sizes	Comments
Long-term treatment of type 1 diabetes in the outpatient setting: Results of 934 patients during up to 10 years' follow-up. Can.J.Diabetes 28 (3):190-195, 2004. REF ID: TILDESLEY 2004	study conducted at a diabetic teaching and training centre in Canada. Retrospective cohort study	diabetes education program, of which 934 (64.5%) returned for at least 1 follow-up visit and 513 (35.5%) were lost to follow-up. n=934 TID using insulin therapy Inclusion criteria: Age at onset of diabetes <30 years History of proven diabetic ketoacidosis Negative C Peptide challenge Exclusion criteria: not reported			observation period. The majority of patients included in the study used 2 injections of insulin per day, with a treatment goal of A1C<8.0% (normal range: 4.0% to 6.0%)	visits		correlated with the frequency of SMBG at baseline (p<0.001) and 5 years (p<0.008). At year 10, this correlation was not significant. A correlation between all quartiles and frequency of SMBG was observed at baseline (p<0.0001) but was not maintained at 5 years (p=0.057).	Risk of bias: No NICE checklist
							Hypoglycaemia	At 5 and 10 years, there was a trend toward a reduction in the number of hypoglycaemic episodes, but was not significant (p<0.055)	
			Age (years), mean	44 (SD 13.2)					

Reference	Study type	Number of patients	Patient characteristics		SMBG	Length of follow-up	Outcome measures	Effect sizes		Comments
			(SD)							
			Male (%)	55.5						
			Duration of diabetes, mean (SD)	21.1 (SD 12.2)						
			HbA1c (%), mean (SD)	6.9 (SD 1.4)						
			Drop-outs: None reported							

Table 151: WEITGASSER 1994 [165]

Reference	Study type	Number of patients	Patient characteristics	SMBG	Length of follow-up	Outcome measures	Effect sizes		Comments
R. Weitgasser, F. Schnoll, I. Pretsch, and U. Gruber.	Prospective case-series Observational study carried out in an out-	n=57; on intensive insulin therapy (IIT) requiring SMBG Inclusion criteria:	Patients attending out-patient clinic, who had been on IIT for at least a year	At baseline (year one) and five years SMBG was done ≤2 per day by 51% versus 12%, >2 but <4/day in 20% versus 21%, and ≥4/day by	5 years		Year 1 (baseline) n=57	Year 5 n=57	Funding: Not reported Risk of bias: No NICE checklist
						HbA1c (%),	7.2	6.4	

Reference	Study type	Number of patients	Patient characteristics		SMBG	Length of follow-up	Outcome measures	Effect sizes		Comments
Evaluation of self-monitoring of blood glucose after five years of intensive insulin therapy following a basal bolus regimen. Diabetol.Croat. 23 (1):13-17, 1994. REF ID: WEITGASSER 1994	patient clinic in Austria	Patients attending out-patient clinic Intensive insulin therapy (IIT) for at least a year Exclusion criteria: not reported			29% versus 67% of the patients. Authors observed an increase in daily SMBG from median of 2.5 in year one to 4.5 in year five when the sum of all blood glucose measurements of all patients (n=57) was analysed.		mean (SD)	(SD 1.2)	(SD 1.1)	
							Severe hypoglycaemia (events per patient years)	0.24	0.26	
				SMBG (n=57)			Retinopathy	19*/ 8+	24*/ 11+	
			Age (years), mean (SD)	34 (SD 9)			Neuropathy	11	15	
			Gender (m/f)	18/39						
			Duration of diabetes, mean (SD)	18 (SD 8)	Type of insulin administered: Short acting insulin Intermediate Long acting insulin External pump treatment		Subgroup of patients who increased frequency of SMBG from <4 to ≥4/day (n=21)			
								HbA1c (%), mean (SD)	7.2 (SD 1.6)	6.2 (SD 1.4)
			Drop-outs: None reported				*Background retinopathy			

Reference	Study type	Number of patients	Patient characteristics	SMBG	Length of follow-up	Outcome measures	Effect sizes	Comments
						+Proliferative retinopathy		

Table 152: WILLEY 1993[170]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
K. A. Willey, S. M. Twigg, M. I. Constantino, D. K. Yue, and J. R. Turtle. Home blood glucose monitoring: How often? Pract.Diabetes 10 (1):22-25, 1993. REF ID: WILLEY 1993	Prospective case-series Observational study	n=12 insulin dependent diabetes mellitus (IDDM) participants treated three to four times daily were asked by their clinicians to perform Home Blood Glucose Monitoring (HBGM) Inclusion criteria: not reported Exclusion criteria: not	Twelve insulin dependent diabetes mellitus (IDDM)		Once daily HBGM at a variable time each day (Var1/day), derived by extracting one blood glucose reading from consecutive time zones.	Four times daily (4/Day) HBGM. Blood glucose readings divided into the following time zones: Pre-breakfast Pre-lunch Pre-dinner Pre-bed Participants tested their blood glucose levels for four weeks using the Ames Glucometer M.	4 weeks		Var1/day	4/day	Funding: one of the authors (Stephen Twigg) is a recipient of a Juvenile Diabetes Foundation International Summer Student Scholarship. Risk of bias: No NICE checklist Risk of bias: Outcome assessors were not informed that there were two profiles from
				SMBG				Mean blood glucose	No significant difference in the mean blood glucose values. Comparison of 4/day with 1/day HBGM taken at a set time of the day did show a significant difference ($p<0.05$) in three of the 12 patients		
			Age (years), mean	32 (SD 12); range =				Hypoglycaemia not			

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
		reported	(SD)	21-69 years				reported			each patient's HBGM data (one from 4/day and one from Var1/day HBGM), nor were they given any details about the frequency of testing used to derive each profile. "this study showed that 1/day HBGM at a variable time gave similar information to 4/day HBGM for glycaemic control (mean blood glucose levels), whereas 1/day HBGM at a set time each day was found to produce different
			Duration of diabetes, mean (SD)	7.4 (SD 3.5); range = 2-13 years							

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
											results on some occasions”
			Drop-outs: Dropout rate: not reported								

Table 153: ZIEGLER 1993 [172,173]

Reference	Study type	Number of patients	Patient characteristics		SMBG	Length of follow-up	Outcome measures	Effect sizes		Comments
O. Ziegler, M. Kolopp, J. Louis, J. P. Musse, A. Patris, G. Debry, and P. Drouin. Self-monitoring of blood glucose and insulin dose alteration in type 1 diabetes mellitus. Diabetes	Cross-sectional study	n=80 insulin dependent diabetic patients chosen at random among diabetic patients treated by intensive insulin therapy (IIT) Inclusion criteria: Patients on intensive	Patients attending out-patient clinic, who had been on IIT for at least a year		Blood glucose measured 4 times a day (1 + 1 + 2 in a 3-injection regimen, 2 + 2 in a 2-injection-split and mixed regimen) before each meal and at bed-time. Fewer than 2 daily blood glucose determination was considered as incompatible with proper use of SMBG	Intensive conventional insulin therapy for at least 6 months		Good compliance n=59	Poor compliance n=21	Funding: Not reported Risk of bias: No NICE checklist “this limited cross-sectional study seems to indicate that SMBG can lead to an improvement in metabolic control but only if it is coupled with a
				SMBG (n=80)			HbA1c (%), mean (SD)	6.7 (SD 1.1)	7.5 (SD 1.9)	
							Hypoglycaemia not reported			
			Age (years), mean (SD)	34 (SD 14)						
			Gender (m/f)	43/37						

Reference	Study type	Number of patients	Patient characteristics		SMBG	Length of follow-up	Outcome measures	Effect sizes		Comments
Res.Clin.Pract. 21 (1):51-59, 1993. REF ID: ZIEGLER 1993		conventional insulin therapy for at least 6 months Performing SMBG for at least 6 months using the dextrostix-glucometer system Previous instruction on the use of SMBG during a 5-day inpatient educational session Exclusion criteria: not reported	Duration of diabetes, mean (SD)	12 (SD 8)						regular alteration of insulin dosage"
			HbA1c (%), mean (SD)	6.9 (SD 1.4)						
			Drop-outs: None reported							

Table 154: Summary table of papers that were not fully extracted.

Reference	Sample size	Duration	Patients	Intervention	Comparison	SMBG	Insulin regimen	Results
ANON 1993[152]	n=1441	6.5 years RCT	IDDM	Intensive ≤4xday	Conventional 1xday	≤4 vs. 1 times a day	Insulin injections Intensive ≤3xday Conventional 1-2xday	NS difference in mortality Intensive n=7 vs. conventional n=4 Hypoglycaemic episodes

Reference	Sample size	Duration	Patients	Intervention	Comparison	SMBG	Insulin regimen	Results
								per 100 patient-years Intensive 62 vs. conventional 19 Diabetic ketoacidosis per 100 patient-years Intensive 2 vs. 1.8 conventional Quality of life no difference (no numbers provided)
ARASZKIEWICZ 2008 [9,10]	n=86	7.1±1.5 years Prospective case series	Type 1 diabetic patients	No intervention. Only logistic regression model was used to estimate RR for diabetic retinopathy and low-level (micro) albuminuria events.		3.6 to 4.1xday	Multiple daily injections with adapting short-acting insulin for before meals After 7 years Retinopathy Yes Self-control n/day=3.9±1.7 Hypoglycaemic episodes/m = 5.8±7.1 No Self-control n/day=3.8±1.4 Hypoglycaemic episodes/m = 6.0±5.7 Low-level (micro) albuminuria Yes	Subjects who developed retinopathy had higher HbA1c. Risk of retinopathy was associated with infrequent monitoring of blood glucose RR=5.5 (2-15.11) Risk of low-level (micro) albuminuria was associated with bad self-monitoring of glucose (RR=2.86 (1.1-7.24)

Reference	Sample size	Duration	Patients	Intervention	Comparison	SMBG	Insulin regimen	Results
							Self-control n/day=3.6±1.6 Hypoglycaemic episodes/m = 5.3±6.0 No Self-control n/day=4.1±1.3 Hypoglycaemic episodes/m = 6.2±6.3	
BELL 1994 [14,15]	n=211	Questionnaire 3 months Prospective case series	Insulin dependent diabetes	No intervention. Only interviewed over 3 months. Comparisons were made between those with and without a history of severe hypoglycaemia.		2.3 to 2.5xday	History of SH N injections/day = 2.72 N glucose tests/day = 2.26 No history of SH N injections/day = 3.06 N glucose tests/day = 2.49	Patients with severe hypoglycaemia took a greater number of insulin injections per day. Also more likely to be using animal insulin and perform home glucose monitoring tests more frequently
BELL [15]1984	n=36	Prospective case series, 3-4 months	Diabetic patients	No intervention.		1xday 24% 2-3xday 36% 4xday 10% <3xweek 23%	n=30 insulin 1xday n=54 insulin 2xday	Frequent testing was not more prevalent in those whose haemoglobin A1 improved.
BRUTTOMESSO 1992 [22]	n=17	Retrospective case-series mean 23.6 months (3-	Type 1 diabetes	No intervention. Correlation analysis.		1.6 times a day	Analysis of blood glucose levels. Mean readings/day/patient =1.6 (0.5-5)	A weak correlation was found between number of blood glucose readings/day and daily

Reference	Sample size	Duration	Patients	Intervention	Comparison	SMBG	Insulin regimen	Results
		83mo)						blood glucose level, r=0.44, and serum HbA1c r=0.45, both p<0.05
CHAN 2009 [24,25]	n=1898	Prospective case-series 5 years, this includes 2 week cross-sectional and a 9-month longitudinal survey.	Type 1 diabetes	No intervention. Logistic univariate regression analysis was used to identify factors for achieving A1C<7%		Regular	73% regularly self-monitors blood glucose. No other details.	SMBG vs. not was associated with two to three fold increased odds of reaching the A1C goal of <7%. Patient self-adjusted insulin was not predictive of reaching the goal of A1C.
BRINCHMANN-HANSEN 1992 [20]	n=45	Prospective case series 7 years	Insulin dependent diabetic patients	Insulin pumps (continuous s.c. insulin infusion)	Multiple injections (4-6 x day) and conventional insulin (2xday)	Unclear	See intervention	Intensified insulin treatment and home blood glucose monitoring improved concentrations of HbA1c from 11.2% to 9.5%
GONDER 1988 [56]	n=30	2 weeks Prospective case series	Adults with insulin dependent diabetes of at least 1 year	Use of memory meters	Record test results in diaries	0.21 to 4.43 x day	Fast and intermediate-acting insulin, except one who used multiple injections of regular insulin	Self-report of SMBG frequency correlated with HbA1 (r=-0.39) Majority of patients were self-reporting as often or more often than they had been instructed.
HARTEMANN2001 [60]	n=122	Cross-sectional	Adults with Type 1 DM	Good glycaemic control. HbA <7.5%	Poor glycaemic control HbA >8.5%	2.7 to 3.6 x day	Daily injections 3.1± 0.9 Number of daily blood glucose tests	Well controlled group carried out more home blood glucose tests and fewer complications (physical complaints,

Reference	Sample size	Duration	Patients	Intervention	Comparison	SMBG	Insulin regimen	Results
							Good = 3.6 ± 1.7 Poor = 2.7 ± 1.7	psychological distress, leisure restrictions, conscious experience and management of hypoglycaemia, diet, difficulties at work)
LLOYD 1993 [98]	n=592	Cross-sectional	Adults with insulin dependent diabetes	No intervention. Multiple regression analysis to assess which factors are independent correlates of glycaemic control (as measured by GHb).		NA	NA	The number of blood and urine tests performed daily were all significant predictors of glycaemic control. Number of daily injections r=-0.15, p=0.0253 Number of tests performed daily r=-0.12 p=0.0146 Injecting at recommended times r=-0.15 p=0.19 STRATA. Correlates of glycaemic control Proliferative retinopathy Number of tests performed, r=-0.25 p=0.0013 Neuropathy Injecting at recommended times, r=-0.32 p=0.0003

Reference	Sample size	Duration	Patients	Intervention	Comparison	SMBG	Insulin regimen	Results
								Number of daily injections r=-0.23 p=0.0041
MERIMEE 1984 [106]	n=15 adults	6 months Prospective case series	Diabetic patients (unclear if T1 or T2 DM) with normal IGF-I and IGF-II values	Glucose monitored initially daily, later 2xweek		1xday then 2xweek	Min 2x/day injections of insulin with supplementary insulin given on the basis of monitoring blood glucose 4x/day	HbA1c Baseline: 14.8±0.95% 3 months: 10.7±0.82% 6 months: 10.3±0.80% HbA1c decreased significantly.
MCCLEAN 2005 [104]	n=290	Cross-sectional	Type 1 and Type 2 diabetes	No intervention. Logistic regression analysis was used to identify characteristics associated with the presence of complications.		Microvascular complications Daily blood monitoring 46.8% daily testing 53.2% no daily testing No microvascular complications Daily blood monitoring 34.4% daily testing 65.6% no daily testing	NA	When controlling for other predictors, patients at risk of developing retinopathy/neuropathy were those who had a HbA1c of 8% or more Blood glucose monitoring was not associated with patients at risk of developing retinopathy/neuropathy
MILLER 2013 [109,110]	n=8914	Cross-sectional	Type 1	No intervention. General		SMBG	NA	A higher number of

Reference	Sample size	Duration	Patients	Intervention	Comparison	SMBG	Insulin regimen	Results
		registry study	diabetes (adult data only)	linear relationship between HbA1c levels and SMBG		Mean±SD Age group 18 to <26 =4.4±2.3 per day 26 to <50=5.2±2.6 per day 50 to <65 =5.5±2.5 per day >65 = 5.6±2.2 per day		SMBG measurements per day was strongly associated with a lower HbA1c in all groups.
NAYAK 2011[118] ABSTRACT	n=127	Cross-sectional study	Type 1 diabetes 61.4%	No Intervention. Regression analysis was used to determine factors that predicted HbA1c.		NA	NA	Blood glucose variability explained 39% of variance of HbA1c. HbA1c is a weak reflection of glycaemic attainment HbA1c is more closely related to variability of blood glucose than the central or median attainment
SJOBERG 1988 [147]	n=44	Cross sectional analysis	Insulin dependent diabetes. Excretors of C-peptide vs. non-excretors	No intervention. Pearson correlation analysis.		4x month (range 0 -120)	n=34 insulin 2xday, n=8 3xday, n=1 4xday. 82% were receiving a combination of intermediate or long-acting insulin and soluble insulin. The	In the group with residual insulin secretion a correlation was found between low HbA1c and frequency of SMBG (r=-0.62, p<0.01)

Reference	Sample size	Duration	Patients	Intervention	Comparison	SMBG	Insulin regimen	Results
							other 8 patients were receiving single injections of intermediate or long-acting insulin.	
VANTILBURG 2001[161]	n=30	Cross sectional analysis	Type 1 diabetes	No intervention. Linear regression analysis.		25.5±09.9x week	53% ≥3 injections/day 30% insulin pump 17% 1-2 injections/day	Self-reported SMBG frequency correlated with HbA1c (r=-0.47, p<0.01)
WOO 2011 [171] ABSTRACT	n=325 type 1 diabetes n=293 type 2 diabetes	Cross sectional study	Type 1 diabetes (and type 2 but results presented separately)	No intervention. Assess relationship between the frequency of home glucose monitoring and HbA1c in people with T1 and T2 diabetes		< 2 to > 3 times a day	NA	HbA1c values for type 1 diabetes <2 checks/day = 8.65% 2-3 checks/day = 8.58% >3 checks/day = 8.22% NS different
ZIEGLER [172]1989	n=14	21 days Prospective case series	Type 1 diabetes mellitus	Memory-reflectance meters	Log book	≥3x day	NA	The number of SMBG measurements recorded in the memory reflectance meter was negatively correlated with HbA1c (r=-0.85, p<0.001). Over-reporting was positively correlated with HbA1c r=0.76, p<0.01.
ZIEGLER 2012 [172,174] ABSTRACT	n=202 TIDM n=17	Cross sectional analysis from RCT	Type 1 and Type 2 diabetes	Data extracted from an RCT. Correlation between clinical outcomes and SMBG frequency.		4.34±1.51 times a day Frequency of		SBMG frequency correlated with HbA1c (r=-0.30) More frequent SMBG is associated with

Reference	Sample size	Duration	Patients	Intervention	Comparison	SMBG	Insulin regimen	Results
	type 2 diabetes					SMBG x/day Type 1 4.34 (1.51) Type 2 3.76 (1.35) NS different.		lower HbA1c independent on the type of diabetes

G.3.3 SMBG – glucose targets

Table 155: COX1994 [29,32]

Reference	Study type	Number of patients	Patient characteristics		SMBG	Length of follow-up	Outcome measures	Effect sizes	Comments
D. J. Cox, B. P. Kovatchev, D. M. Julian, L. A. Gonder-Frederick, W. H. Polonsky, D. G. Schlundt, and W. L. Clarke. Frequency of severe hypoglycemia in insulin-dependent diabetes mellitus can	Prospective case series Non-randomised multicentre study carried out in the USA	n=78 Insulin Dependent Diabetic Mellitus (IDDM) Inclusion criteria: IDDM for at least 2 years Insulin usage since time of diagnosis Routine SMBG of twice daily or more No diagnosable depression of substance abuse Exclusion criteria: not reported		Patient characteristics (n=78)	50 SMBG readings over a 2 to 3 week period with a hand held computer.	Data collected during a 6 month baseline period.	Results Blood glucose (BG) is associated with a greater low BG index, a greater SMBG and a lower glycosylated HbA1c. Participants with a BG index less than 2.75 had an average of 5.2 hypoglycaemic episodes, whereas participants with a low BG index of 2.75 or more had 13.6 episodes. Participants with SMBG below 4.6 had an average of 6.5 hypoglycaemic episodes, whereas subjects with a SMBG of 4.6 or greater had 12.3 such episodes		Funding: Not reported Risk of bias: No NICE checklist The Predictor variables were not linearly related to the number of severe hypoglycaemic episodes. Participants demonstrating a smaller low BG index and less BG variance were

Reference	Study type	Number of patients	Patient characteristics		SMBG	Length of follow-up	Outcome measures	Effect sizes	Comments
be predicted from self-monitoring blood glucose data. J.Clin.Endocrinol.Metab. 79 (6):1659-1662, 1994. REF ID: COX 1994			Age (years), mean (SD)	38.2 (SD 9.05)			Low glycosylated Hb was no significantly associated with the number of severe hypoglycaemic episodes.		more likely to have to have no severe hypoglycaemic episodes.
			Gender (m/f)	28/50					
			Duration of diabetes, mean (SD)	19.3 (SD 10.04)					
			HbA1c (%), mean (SD)	10.25 (SD 2.13)					
			Insulin dose (U/day)+, mean (SD)	38.6 (SD 16.04)					
			Drop-outs: None reported						

Table 156: KOVATCHEV2000 [85]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
B. P.	Prospective	n=608	Patients	SMBG: all participants were		6 months	HbA1c within categories		Funding:

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Kovatchev, D. J. Cox, M. Straume, and L. S. Farhy. Association of self-monitoring blood glucose profiles with glycosylated hemoglobin in patients with insulin-dependent diabetes. Methods Enzymol. 321:410-417, 2000. REF ID KOVATCHEV 2000C	case series Non-randomised study conducted by Amylin Pharmaceuticals	participants with Insulin Dependent Diabetes Mellitus (IDDM) Data for n=608 participants were completed with SMBG and HbA1c records Inclusion criteria: not reported Exclusion criteria: not reported	characteristics not reported			instructed to use blood glucose (BG) memory meters for 4-6 months and to measure their BG two to four times a day. During the same period of time 5 to 8 HbA1c assays were performed for each subject.			identified by average SMBG			Supported by the National Institutes of Health grant, by Amylin Pharmaceuticals, San Diego, CA and by Lifescan Inc., Milpitas, CA. Risk of bias: No NICE checklist "The SMBG records were considered accurate according to an automated rejection criterion" "Only subjects who had SMBG records and HbA1c assays were selected for analysis".
									SMBG categories	Mean HbA1c (%)	SEM	
									Below 8.6 mM (n=118)	8.29	0.06	
									8.6-9.7 mM (n=124)	8.70	0.06	
									9.7-10.6 mM (n=119)	9.14	0.08	
			Age (years),	-	-				10.6-12 mM (n=126)	9.50	0.07	
			Male/female	-	-				Above 12 mM (n=121)	121	0.12	
			Duration diabetes (months)	-	-							
									Average SMBG within categories identified by HbA1c			

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
			HbA1c (%)					HbA1c (%) category	Mean SMBG	SEM		
								Below 8.3 (n=125)		8.58	0.11	
								8.3-8.8 (n=123)		9.54	0.11	
								8.8-9.4 (n=118)		10.28	0.13	
								9.4-10 (n=116)		11.01	0.15	
								Above 10 (n=126)		12.74	0.22	
			Drop-outs: Seven hundred participants recruited for study and data available for 608 (87%) participants.									

Table 157: MUHLHAUSER1998 [114,115]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
I. Muhlhauser, H. Overmann, R. Bender, U. Bott, and M. Berger. Risk factors of severe hypoglycaemia in adult patients with Type I diabetes--a prospective population based study. Diabetologia 41 (11):1274-1282, 1998. REF ID MUHLHAUSER 1998	Prospective case series population based study from a random sample of 630 family physician practices in the district of Northrhine	n=669 with type 1 diabetes Inclusion criteria: Age 18 years or older Initiation of insulin therapy before 31 years of age Exclusion criteria: not reported			A self-administered questionnaire was used in order to assess patients' treatment goals. The instrument consisted of 10 items which were rated on a 6-point Likert scale (1 = very important; 6 = totally unimportant). For this study, five questions possibly relevant for the prediction of severe hypoglycaemia (SH) were used.		19 months follow up				Funding: Not reported Risk of bias: No NICE checklist Blood glucose self-monitoring - score 0: patients who report to measure at least twice daily; score 1: patients who measure less often.
								Number of blood glucose values <3.3 mmol/litre	Baseline: n (%)	SH during 19 months follow-up (events per patients	
				n=669				0	256 (38)	0.22	
								1-2	211 (32)	0.34	
			Age (years), mean (SD)	36 (11); range: 18-77				>2	202 (30)	0.39	
			Male/women	392/277				Trend to show number of BG values <3.3 mmol/litre, the higher the number of episodes of severe hypoglycaemia.			
			Diabetes duration, mean (SD)	18 (SD 11)							
			BMI (kg/m2), mean (SD)	24.6 (SD 3.4)							
			HbA1c (%),	8 (SD							

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
			mean (SD)	1.5)							
			Drop-outs: None reported								

Table 158: SERVICE 2001 [140,141]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
F. John Service and Peter C. O'Brien. Influence of glycemic variables on hemoglobin A1c. Endocr Pract 13 (4):350-354,	Prospective case series from the Diabetes Control and Complications Trial database (DCCT)	n=565 volunteers. n=296 assigned to conventional therapy; n=269 assigned to intensive therapy	Each participant was expected to collect at quarterly intervals, a 7-point set of capillary specimens preprandially and 90min	Intensive therapy: administration of insulin at least 3 times a day by injection pump, with doses adjusted based on	Conventional therapy: one or two daily insulin injections	?1-15 years	Glycaemic parameters for study cohort during DCCT			Funding: Not reported Risk of bias: No NICE checklist Drop-outs = none reported
							Glucose variable	Intensive a	Conventional	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
2007. REF ID SERVICE 2001		Inclusion criteria: Volunteers whose 7-point capillary profiles collected pre-prandial and 90 minutes postprandial for each of the major meals and at bedtime were complete in 80% or more of quarterly collections who were in the study for 4 years or longer Exclusion criteria: "women in the	postprandially for each of the 3 major meals and before bedtime snack	self-blood glucose monitoring and with the goal of normoglycaemia.						Risk of retinopathy: In the multivariate analysis, the primary determinants for risk of a 3-step change in retinopathy were updated mean blood glucose (MBG) p< 0.001 and baseline mean amplitude of glycaemic excursion (MAGE) p< 0.005. The association between updated MBG and risk for retinopathy

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
		conventional treatment group who became pregnant"								was non-linear. No association with updated MBG was observed for values below 8.3 mmol/litre. Beyond 8.3 mmol/litre the risk increased with increasing updated MBG with approximately a 15-fold increase in risk at updated MBG of 16.6 mmol/litre relative to updated MBG at 8.3mmol/litre.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes			Comments
											Results show that an increase in updated MBG from 8.3 mmol/litre to 11.1 mmol/litre increases the risk by approximately fourfold.
				Intensive therapy	Conventional therapy			HbA1c (%), mean (SD)	7 (SD 0.7)	9 (SD 1.3)	
								Mean blood glucose (mmol/litre), mean (SD)	8.4 (SD 1.2)	13 (SD 2.5)	
								Mean postprandial (mmol/litre), mean	9.4 (SD 1.4)	14.4 (SD 2.7)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes			Comments
								(SD)			
			Age (years), mean (SD)	29 (SD 7)	27 (SD 7)			Mean prepran dial (mmol/litre), mean (SD)	7.7 (SD 1.3)	11.7 (SD 2.4)	
			Adolescent (%): 13-18years	22 (8)	47 (16)			Before breakfast blood glucose (mmol/litre), mean (SD)	8.3 (SD 1.6)	11.4 (SD 2.5)	
			Male/female	122/147	138/158						
			Duration of type 1 diabetes (months)	76	69			90min after breakfast blood glucose (mmol/litre), mean (SD)	10.8 (SD 2.1)	15.5 (SD 3.1)	
			HbA1c (%)	8.7	8.7			Before lunch blood glucose (mmol/litre), mean	7 (SD 1.5)	11 (SD 2.9)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes			Comments
								(SD)			
			Mean blood glucose (mmol/litre)	12.1	13			90min after lunch blood glucose (mmol/litre), mean (SD)	8.6 (SD 1.6)	13.8 (SD 2.8)	
								Before supper blood glucose (mmol/litre), mean (SD)	7.7 (SD 1.7)	12.6 (SD 3.1)	
								90min after supper blood glucose (mmol/litre), mean (SD)	8.8 (SD 1.6)	13.9 (SD 3.4)	
								Bedtime blood glucose (mmol/litre), mean (SD)	8 (SD 1.6)	12.6 (SD 3.4)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Drop-outs: None reported				p≤ 0.001 comparing intensive and conventional therapies for each glucose variable. The intensive treatment group had significantly lower values of each glycaemic parameter and HbA1c than the conventional treatment group during the total period of the study.		

Table 159: VERVOORT 1996 [163]

Reference	Study type	Number of patients	Patient characteristics		SMBG	Length of follow-up	Outcome measures	Effect sizes	Comments
G. Vervoort, H. M. Goldschmidt, and L. G. van Doorn. Nocturnal blood glucose profiles in patients with type 1 diabetes mellitus on multiple (> or = 4) daily insulin injection regimens. Diabet.Med	Prospective case-series Non-randomised study conducted in the Netherlands	n=31 type 1 diabetes randomly selected from the population of a diabetes outpatient clinic. Inclusion criteria: Stable patients for more than I year on multiple daily injection therapy		Patient characteristics (n=31)	All treated with short acting insulin at least three times a day and intermediate-acting insulin at night.	Participants observed overnight.	Results Two separate intervals of hypoglycaemia were observed during the night: Early night from 23.00 to 01.00 h Early morning from 04.00 to 07.30 h There were 5 participants with hypoglycaemic episodes in the early night and 6 with episodes in the early morning; 2 experienced an 'early night' as well as an 'early morning' hypoglycaemia. A fasting glucose of ≥5.5mmol/litre was never preceded by 'early morning'		Funding: Novo Nordisk The Netherlands for financial support. Risk of bias: No NICE checklist "The study shows a high frequency (29%) of nocturnal hypoglycaemia, defined as a blood glucose

Reference	Study type	Number of patients	Patient characteristics		SMBG	Length of follow-up	Outcome measures	Effect sizes	Comments
. 13 (9):794-799, 1996. REF ID: VERVOORT 1996		Exclusion criteria: not reported "all patients received intensive education including the use of simple algorithms to correct their blood glucose levels"					hypoglycaemia. A fasting blood glucose level at 07.30 h of <5.5mmol/litre was associated with 'early morning' hypoglycaemia in 6 of 12 patient-nights; in 4 cases a fasting glucose <3mmol/litre at 07.30 h was measured.		level <3.0 mmol/litre, in type 1 diabetes patients on multiple insulin injections regimens".
			Age (years)	40.4 (19-67)			'Early night' hypoglycaemia was already apparent at 23.00 h in 4 of 5 cases.		
			Gender (m/f)	20/11					
			Duration of diabetes (years)	17.6 (2-57)					
			HbA1c (%)	8.6 (6.1-11.6)					
			Total Insulin dose (IU/kg), mean (SD)	0.68 (SD 0.15)					
			Drop-outs: None reported						

Table 160: WHITE1982 [167]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
N. H. White, S. R. Waltman, T. Krupin, and J. V. Santiago. Reversal of abnormalities in ocular fluorophotometry in insulin-dependent diabetes after five to nine months of improved metabolic control. Diabetes 31 (1):80-85, 1982. REF ID WHITE 1982	Prospective case series non-randomised cohort study	n=36 participants with Insulin Dependent Diabetes Mellitus (IDDM). 5.5% (2) of the population <18 years of age. n=25 assigned to conventional therapy; n=11 non-obese assigned to intensive therapy Inclusion criteria: Initial abnormal vitreous fluorophot				Intensive therapy: home blood glucose monitoring and either multiple daily insulin injections or a portable insulin infusion pump. All participants were taught home blood glucose monitoring using Dextrostix and reflectance meter	Conventional therapy: conventional methods employing urine glucose monitoring and one or two injections of mixtures of insulin daily.	4-6 months				Funding: Supported in part by grants from the Diabetic Children's Welfare Association, American Diabetes Association St. Louis Affiliate, and NIH grants Risk of bias: No NICE checklist Participants choosing treatment with multiple injections did so because they thought that the insulin infusion pump would
				Intensive therapy (n=11)	Conventional therapy (n=25)					Intensive group	Conventional group	
			Age (years)	Range 13-33	Mean 25.3 (SD 8.4)				HbA1c (%), mean (SD)	7.5 (0.2)	11.0 (SD 0.4)	
			Male/female	5/6	-				Retinopathy	1	0	
			Duration of diabetes (years)	Range 3-22	Mean 9.8 (SD 4.9)							
			HbA1c (%), mean (SD)	10.4 (SD 0.7)	10.2 (SD 0.5)							

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		ometry measurement Willingness to participate in a research study involving home blood glucose monitoring and either multiple daily insulin injections or a portable insulin infusion pump Exclusion criteria: not reported.	Drop-outs: None reported				All participants in the intensively treated group achieved excellent glycaemic control with preprandial blood glucose values mostly under 200mg/dl and complete absence of glycosuria.		be more cumbersome, complicated, or unnecessary. They were given regular insulin 15-60 min before each meal depending on preprandial blood glucose measurements, and either long-acting insulin in the morning and evening or intermediate-acting insulin at bedtime. Participants were also trained in the operation of insulin pump and taught to adjust the insulin dose

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
									on the basis of measured capillary blood glucose

Table161: WEI 2014

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
N Wei, Hui Zheng, and David M. Nathan. Empirically Establishing Blood Glucose Targets to Achieve HbA1c Goals. Diabetes Care 37 (4):1048-1051, 2014. REF ID WEI 2014	Prospective case-series People from the ADAG study (Nathan 2006)	n=387 (237 type 1 diabetes and 141 type 2 diabetes) Data from type 1 diabetes reported only. Inclusion criteria: Adults with diabetes from the ADAG study participants who had HbA1c values at 3 months between	No further details given	SMBG monitored over an average of 11 days per person during the 12 week study period 8-point SMBG: Fasting blood glucose, pre-meal, post-meal and bedtime SMBG HbA1c was measured monthly	12 weeks	type 1 diabetes subgroup only: mean (95% CI) blood glucose values for specified HbA1c levels	Fasting blood glucose values for: HbA1c of 5.5-6.49 = 122 mg/dL (113-132) HbA1c of 6.5-6.99 = 144 mg/dL (134-154) HbA1c of 7.0-7.49 = 155 mg/dL (143-168) HbA1c of 7.5-7.99 = 170 mg/dL (159-181) HbA1c of 8.0-8.49 = 178 mg/dL (161-194) Preprandial blood glucose values for: HbA1c of 5.5-6.49 = 119 mg/dL (115-124) HbA1c of 6.5-6.99 = 140 mg/dL (134-147) HbA1c of 7.0-7.49 = 156 mg/dL (150-163) HbA1c of 7.5-7.99 = 159 mg/dL (151-166) HbA1c of 8.0-8.49 = 175 mg/dL (162-188) Postprandial blood glucose values for:	Funding: National Institute of Diabetes and Digestive and Kidney Diseases training grant. Risk of bias: No NICE checklist Drop-outs = none reported

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
		5.5 and 8.5% Blood glucose values (SMBG) monitored over 12 weeks ns Exclusion criteria: "women in the conventional treatment group who became pregnant"				HbA1c of 5.5-6.49 = 139 mg/dL (133-145) HbA1c of 6.5-6.99 = 161 mg/dL (155-168 HbA1c of 7.0-7.49 = 175 mg/dL (167-183) HbA1c of 7.5-7.99 = 190 mg/dL (180-199) HbA1c of 8.0-8.49 = 197 mg/dL (188-205) Bedtime blood glucose values for: HbA1c of 5.5-6.49 = 140 mg/dL (132-148) HbA1c of 6.5-6.99 = 154 mg/dL (144-164) HbA1c of 7.0-7.49 = 180 mg/dL (164-195) HbA1c of 7.5-7.99 = 179 mg/dL (166-193) HbA1c of 8.0-8.49 = 214 mg/dL (189-240)		

G.3.4 SMBG technologies

Table 162: GROSS 2003

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Todd M. Gross, David Kayne, Allen King, Carla Rother, and	RCT A two-period cross-over repeater-	n= 49 participants with TID and on Continuous Subcutane	Participants with type 1 diabetes, and on CSII therapy using Medtronic MiniMed insulin pumps.	Bolus calculator software implemented on a PDA platform.	Standard bolus period	7 days then cross-over for 7 days		Bolus calculator	Standard bolus	Funding: not reported Risk of bias: Randomisation: unclear Allocation

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Suzanne Juth. A bolus calculator is an effective means of controlling postprandial glycemia in patients on insulin pump therapy. Diabetes Technol.Ther. 5 (3):365-369, 2003. REF ID: GROSS 2003	measure randomised design from two clinical sites.	ous Insulin Infusion (CSII) Inclusion criteria: type 1 diabetes On CSII therapy for a minimum of 3 months Exclusion criteria: not reported		n=49	Participants were required to enter their pre-meal blood glucose value (obtained from their home blood glucose meter) and the total CHO (g) in the meal into the bolus calculator in order to obtain a pre-meal bolus insulin dose. After 7 days, participants crossed over to the alternate treatment period. The software setup required each participants to			*Hypoglycaemia events/week, mean (SD)	3.1 (SD 2.9)	3.4 (SD 3.1)	concealment: not reported Blinding: not applicable ITT analysis: not reported Powered study: not reported Drop-outs: not reported Wash-out period: not reported "no adverse events were reported in either period" "the target blood glucose, ISF, and CIR were determined for all subjects, individually, by the physician using subjects'
			Age (years), mean (SD)	43 (SD 15)				Adverse events	0	0	
			Diabetes duration (years), mean (SD)	22 (SD 16)							
			Male/female (%)	43/57				HbA1c not reported			

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
				input his or her Target blood glucose Insulin sensitivity factors (ISF) Carbohydrate to insulin ratios (CIR)					logbooks at the start of their BC period in the study"
			Participants were asked to test their blood glucose using their home meters. Drop-outs: Dropout rate: not reported				*Hypoglycaemia was defined as blood glucose >250mg/dL		

Table 163: SCHMIDT 2012

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Signe Schmidt, Merete Meldgaard, Nermin Serifovski, Camilla Storm, Tomas Moller Christensen, Birthe Gade-Rasmussen, and Kirsten Norgaard. Use of an automated bolus calculator in MDI-treated type 1 diabetes: the BolusCal Study, a randomized controlled pilot study.	RCT Prospective, randomised, controlled, open label, three-arm parallel, bi-centric study conducted in Denmark	n= 51 with type 1 diabetes (n=8, control; n=21, CarbCount; n=22, CarbCount Automated Bolus Calculator) Inclusion criteria: Age 18-65 years type 1 diabetes duration ≥12 months Use of multiple daily injections (MDI) Exclusion	Patients' ≥ 18 years with type 1 diabetes			CarbCount Automated Bolus Calculator (CarbCountABC): group received FIIT during a 3-h group teaching, were taught carbohydrate counting, estimated individual ICRs and ISFs and were also provided with and instructed in the use of the ABC.	Control arm: not trained in estimating the carbohydrate content of food but received FIIT during a 3-h group teaching.	16 Weeks		*Carb Count ABC	*Control	Funding: not reported. Risk of bias: Randomisation: "randomisation with a 1:3:3 ratio in blocks of 14" Allocation concealment: sealed, opaque envelopes containing the group assignments. The envelopes had been prepared by a person not otherwise involved in the study" Blinding: not applicable – open label
				CarbCountABC (n=22)	Control (n=8)				HbA1c (%), mean (SD)	8.1 (SD 0.4)	8.9 (SD 1.1)	
			Age (years), mean (SD)	42 (SD 10)	46 (SD 9)				HbA1c (%) within-group difference, (95% CI)	-0.7 (-1.0 to -0.4)	-0.1 (-1.0 to 0.7)	
			Gender (m/f)	10/12	6/2							
			Diabetes duration (years)	21 (SD 9)	14 (SD 12)				#HFS (0-100 scale) - higher scores indicate more fear, mean (SD)	22.6 (SD 16.7)	24.5 (SD 18.2)	
			HbA1c (%)	8.8 (SD 0.7)	9.1 (SD 0.7)				HFS within-group difference, (95% CI)	-3.4 (-7.2 to 0.3)	-1.92 (-10 to 6.2)	
			BMI (kg/m2), mean (SD)	25.8 (SD 3.3)	26.4 (SD 5.6)				&PAID (0-100 scale) - higher scores indicate	25.6 (SD 15.3)	27.2 (SD 18.8)	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Diabetes Care 35 (5):984-990, 2012. REF ID: SCHMIDT 2012		criteria: Pregnancy Nursing Gastroparesis Present or former practice of carbohydrate counting							more problems, mean (SD)			trial ITT analysis: Powered study: study was powered. Drop-outs: 12 patients (19%) dropped out overall. Drop-outs per group not reported. Relatively small sample size
									PAID within-group difference, (95% CI)	-6.9 (-13.5 to -0.4)	-3.3 (-21 to 14.4)	
									^ADDQoL Total (-9 to 9) - higher scores indicate positive impact, mean (SD)	-1.8 (SD 1.6)	-1.4 (SD 0.9)	
									ADDQoL within-group difference, (95% CI)	0.4 (0.0 to 0.7)	0.6 (0.8 to 1.9)	
			Drop-outs: 12 patients (19%) dropped out overall. Drop-outs per group not reported. Baseline characteristics of the randomised patient sample did not differ significantly between the 3 study groups						*Comparison of means between Control, CarbCount, and CarbCountABC. Analysis performed using ANOVA. #HFS – Hypoglycaemia Fear Survey. &PAID – Problem Areas In Diabetes. ^ADDQoL – Audit of Diabetes-Dependent Quality of Life.			

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments

G.3.5 SMBG versus CGM

Table 164: LITTLE 2014

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
S. A. Little, L. Leelarathna, E. Walkinshaw, H. K. Tan, O. Chapple, A. Lubina-Solomon, T. J. Chadwick, S. Barendse, D. D. Stocken, C. Brennand, S. M. Marshall, R. Wood, J. Speight, D. Kerr, D. Flanagan, S. R. Heller, M. L. Evans, and J. A. Shaw.	RCT	N = 96 Inclusion criteria: Age 18 - 74 years C-peptide negative type 1 diabetes Impaired awareness of hypoglycaemia confirmed by Gold score ≥4 Exclusion criteria:		RT-CGM (n = 48)	SMBG (n = 48)	All participants were given an insulin pump enabling benefit from direct transmission of SMBG levels to bolus calculator.		Every 4 weeks for 24 weeks		RT-CGM (n=48)	SMBG (n=48)	Funding: Peer review grant from Diabetes UK, the National Institute for Health Research, and the Cambridge National Institute for Health Research Biomedical Research Centre Risk of bias: Randomisatio
						RT-CGM: Real-time continuous glucose monitoring (Medtronic) The participants were trained on sensor insertion, calibration, and use of monitor including trend analysis and hypo/hyperglycaemia alerts.	SMBG: Self-monitoring of blood glucose As described above for all participants and no access to RT-CGM.		HbA1c (%) at 24 weeks	8.2 (1.1)	8.1 (0.9)	
									HbA1c final value mean difference - calculated (95% CI; SE)	0.10 (-0.30 to 0.50; -0.2) p=0.63		
			Age (years), mean (SD)	50.1 (12.6)	47.1 (11.8)				Severe hypoglycaemia, annualized rate (patient-year), mean (SD)	0.8 (1.8)	0.9 (2.1)	
			Gender, male	15/48 (31.3	20/48 (41.7							

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Recovery of Hypoglycemia Awareness in Long-Standing Type 1 Diabetes: A Multicenter 2 x 2 Factorial Randomized Controlled Trial Comparing Insulin Pump With Multiple Daily Injections and Continuous With Conventional Glucose Self-Monitoring (HypoCOMPass). LID - DC_140030 [pii]. Diabetes Care (1935-5548 (Electronic)), 2014.		Not reported	(%)	%)	%)	Continuous real-time use was encouraged but not mandatory.						n: Low Allocation concealment: Low Blinding: Not possible ITT analysis carried out Drop-out = 12/96 (12.5%) in total - acceptable (<20%). Difference in drop-out rate was 12.5%.
			Diabetes duration (years), mean (SD)	31.0 (12.2)	26.7 (12.1)	All participants recorded severe hypoglycaemia episodes prospectively and were recalled every 4 weeks up to 24 weeks. Each study visit was preceded by a 7-day retrospective CGM profile, with participants and investigators blinded to data until study completion. All participants were telephoned weekly to reinforce insulin titration guidelines and maintain focus on hypoglycaemia avoidance.			Quality of life	Not reported		
			HbA1c (%), mean (SD)	8.2 (1.1)	8.3 (1.3)				Adverse events (No. of DKA episodes) - There were no hospital admissions or insulin delivery/monitoring-related infections.	0	3	
			BMI (kg/m2), mean (SD)	26.9 (4.7)	26.1 (4.3)				Adherence	Not reported		
			Drop-outs	3/48 (6.3%)	9/48 (18.8 %)							

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
LITTLE 2014												

Table 165: SEQUEIRA 2013

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
PA. Sequeira, L Montoya, V Ruelas, D Xing, V Chen, R Beck, and AL. Peters. Continuous glucose monitoring pilot in low-income type 1 diabetes patients. Diabetes Technol.Ther. 15 (10):855-858, 2013. SEQUEIRA	Crossover RCT	N = 39 Inclusion criteria: Diagnosis of diabetes ≥6 months prior to enrolment Subject self-report of SMBG ≥3 times/day On multiple daily insulin injections Age ≥18 years Exclusion criteria: Not	All the participants were economically challenged type 1 diabetes patients, primarily of Latino ethnicity with minimal prior education on intensive diabetes management.		Participants were provided with education on CHO counting and insulin dose adjustments using developed educational materials.		Aspirationally, up to 28 weeks per period, however, the length of participation varied greatly amongst the participants.		Group A (CGM then SMBG)	Group B (SMBG then CGM)	Funding: JDRF Artificial Pancreas grant Risk of bias: Randomisation: Unclear Allocation concealment: Unclear Blinding: Not possible Insufficient and unclear description given for study methods ACA Drop-out rate significantly high Population is
					Group A = RT-CGM first: Before starting CGM use, all had 1 week of a CGM blind period where participants were not able to see the glucose values recorded in the receiver. There	Group B = SMBG first: In the absence of clear description for the comparator group, it is assumed that normal self-monitoring of blood glucose was performed		HbA1c	Baseline = 8.3% End of Period 1 = 8.0% End of Period 2 = 8.5%	Baseline = 8.3% End of Period 1 = 7.8% End of Period 2 = 8.3%	
			Age (years), mean (SD)	patients who completed study only: 40 (13)				Severe hypoglycaemia, annualized rate (patient-	Not reported		
			Gende	patients who							

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
2013		reported	r, male (%)	completed study only: 13/25 (52%)	onwards, it is presumed that the participants were able to see the recorded values. At each routine clinic visit, the participants brought in their meter for downloading in the clinic providing the researcher with access to the patient CGM downloads and CHO counting logs.	by the participants.		year), mean (SD)		very specific
			Diabetes duration (years), median (IQR)	patients who completed study only: 13 (10 - 21)				Quality of life	Not reported	
			HbA1c (%), mean (SD)	patients who completed study only: 8.5 (1.7)				Adverse events	Not reported	
			BMI (kg/m2), mean (SD)	patients who completed study only: Not reported				Adherence	Not reported	
			Drop-outs	Overall = 14/39 (35.9%)						

Table 166: BATTELINO 2012

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
T. Battelino, I. Conget, B. Olsen, I. Schutz-Fuhrmann, E. Hommel, R. Hoogma, U. Schierloh, N. Sulli, and J. Bolinder. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: A randomised controlled trial. Diabetologia 55 (12):3155-3162, 2012. REF ID:	Cross-over RCT. 6 month treatment periods with 4 month wash-out Multicentre- four adult and four paediatric sites in Europe	n=153; 53% adults and 47% children. (n=77 CGM sensor on first; n=76 CGM sensor off first) Inclusion criteria: Age 6-70 years type 1 diabetes for >1 year HbA1c 7.5-9.5% Using CSII for >6 months Naïve to CGM Exclusion criteria: ≥3 incidents of severe hypoglycaemia in the last 12 months History of				CGM sensor on (MiniMed Medtronic) Patients were all fitted with insulin pump system with CGM. During 1 month run-in phase sensors were off and patients advised to use SMBG. Each treatment period was 6 months long, with a 4 month washout phase between two periods.	CGM sensor off Self-monitoring blood glucose (SMBG): Approximately 8 daily SMBG readings.	6 months		CGM sensor on	CGM sensor off	Funding: Medtronic International Risk of bias: Randomisation: electronically generated sequence. Stratified randomisation, paediatric and adult groups. Allocation concealment: randomisation implemented by statistician. Blinding: not possible due to nature of intervention. No blinding to HbA1c results Baseline values not reported ITT analysis carried out Drop-outs = 15 (10%) total n=8 in on/off
				CGM on first (n=77)	CGM off first (n=76)				HbA1c (%) mean difference in adults population at 6 months	Mean difference (-0.41 (95% CI -0.28%, -0.53%; p<0.001))		
			Age (years), mean (SD)	28 (SD 16)	28 (SD 17)				Severe hypoglycaemic events (per 100 patient years)	5.7 per 100 patient years	2.83 per 100 patient years	
			Gender (m/f)	42/34	37/40							
			Diabetes duration (years), mean (SD)	16 (SD 12)	14 (SD 12)							
			HbA1c (%), mean (SD)	8.3 (SD 0.7)	8.5 (SD 0.6)							

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
BATTELINO 2012		hypoglycaemic unawareness Concomitant chronic disease affecting diabetes control Pharmacological treatment that might modify glycaemic values									sequence group n=7 in off/on sequence group
			Drop-outs: 15 (10%) total n=8 in on/off sequence group n=7 in off/on sequence group								

Table 167: BECK 2010 –JUVENILE 2010 study

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
R. W. Beck, J. M. Lawrence, L. Laffel, T. Wysocki, D. Xing, E. S. Huang, B. Ives, C. Kollman, J.	Parallel RCT. Multicentre trial carried out in	n= 451 adults and children (stratified into two groups according to age: ≥ 18 years, and < 18 years)	Patients ≥ 18 years with type 1 diabetes and initial A1C levels of <7%.			CGM: Participants were instructed to use the CGM daily if possible.	Standard glucose monitoring (SMBG): instructed to perform BGM ≥4 times per day.	26 weeks		CGM	SMBG	Funding: research was supported by grants from the Juvenile Diabetes Research Foundation.
				CGM (n=122)	SMBG (n=106)				QoL: SF12 Physical component, scale 0-100 (high is better), mean (SD) at 26	55.5 (SD 4.9)	54.1 (SD 6.9)	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Lee, K. J. Ruedy, and W. V. Tamborlane. Quality-of-life measures in children and adults with type 1 diabetes: Juvenile Diabetes Research Foundation Continuous Glucose Monitoring randomized trial. Diabetes Care 33 (10):2175-2177, 2010. W. V. REF ID: BECK 2010	10 centres in the USA.	with type 1 diabetes. Adult (≥ 18 years) = 228 (> 50% of total population) Sub-group analysis based on baseline A1c (≥7.0% versus <7.0%) carried out for ≥ 18 years population. For the ≥ 18 years population (n=122, continuous glucose monitoring [CGM] ; n=106, self-monitoring blood glucose (SMBG)							weeks			Risk of bias: Randomisation: reported but insufficient information given. Allocation concealment: not reported Blinding: not reported ITT analysis: not reported Powered study: not reported Drop-outs: not reported
			Baseline QoL (SF-12): Physical component , mean (SD)	54.1 (SD 5.9	54.1 (SD 7.2)				SF12 Mental component, scale 0-100 (high is better), mean (SD) at 26 weeks	48.4 (SD 10.1)	48.7 (SD 9.6)	
			Baseline Mental component, mean (SD)	49.5 (SD 8.4)	48.2 (SD 10.0)							
									Hypoglycaemia Fear Survey (HFS), total score (scale 0-100, high = worse); mean (SD)	33.3 (SD 11.5)	36 (SD 13.6)	
									Problem Areas in Diabetes (PAID), (scale 0-100, high = worse) mean (SD)	18.1 (SD 14.1)	18.2 (SD 14.6)	
									HbA1c not reported			

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
		Inclusion criteria: type 1 diabetes at least 1 year. Use of either an insulin pump or at least 3 daily insulin injections. HbA1c level of <7% Exclusion criteria: not reported							Hypoglycaemia not reported			
			*Social Functioning Health Survey (SF-12) version 2. Drop-outs: Dropout rate: not reported									

Table 168: CHICO 2003

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Chico A, Vidal-Rios P, Subira M, Novials A. The continuous glucose	Parallel RCT. Single centre trial carried	n= 105 diabetic patients (75 with type 1 diabetes, 30 with	Patients' ≥ 25 years with type 1 diabetes and initial A1C levels of 7 to 10%.			CGM: CSII; Disetronic, MiniMed. CGM group monitored three days using the	Standard glucose monitoring (SMBG): frequent capillary glucose	3 months		CGM	SMBG	Funding: not reported. Risk of bias: Randomisation : unclear
				CGM (n=40)	SMBG (n=35)				HbA1c (%), mean (SD) at 3 months	7.5 (SD 1.2)	7.5 (SD 0.8)	
			Age	36.5	41				hypoglycaemia			

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
monitoring system is useful for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. Diabetes Care 2003;4:1153–7. REF ID: CHICO 2003	out in Spain.	type 2 diabetes) were included in the study. For the type 1 diabetes population (n=40, continuous glucose monitoring [CGM] ; n=35, self-monitoring blood glucose (SMBG) Inclusion criteria: Inadequate metabolic control Exclusion criteria: n.a.	(years), mean (SD)	(SD 12)	(SD 10)	CGM and the information obtained was used to modify treatment. They were instructed to enter glucose meter values (at least four a day).	measurement: At least 8 measurements per day for 3 days: before each meal, 2h after meals, at bedtime, and at 4:00 A.M		not reported			Allocation concealment: not reported Blinding: not reported ITT analysis: not reported Powered study: study was adequately powered. Drop-outs: None reported.
			Gender (m/f)	18/22	17/18							
			Diabetes duration (years)	17 (SD 12)	21 (SD 10)							
			HbA1c (%)	8.3 (SD 1.6)	8.0 (SD 1.4)							
			Drop-outs: All patients completed follow-up									

Table 169: GARG 2006

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
S. Garg, H. Zisser, S. Schwartz, T. Bailey, R. Kaplan, S. Ellis, and L. Jovanovic. Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. Diabetes Care 29 (1):44-50, 2006. REF ID: GARG2006	Parallel RCT.	n= 91 (n= 47 continuous glucose monitoring [CGM] ; n=44, self-monitoring blood glucose (SMBG) (75 of 91 patients [82%] type 1 diabetes) Inclusion criteria: Age ≥ 18 years old type 1 diabetes or type 2 diabetes requiring insulin therapy				CGM sensor on (STS DexCom System) for three 72 hour periods. Patients were fitted with STS Dexcom System (CGM) and all assigned two SMBG meters, one to calibrate CGM and for comparison/confirmation of alerts. Patients were instructed to use SMBG values to guide major therapeutic decisions in diabetes management	CGM sensor off with self-monitoring blood glucose (SMBG): Patients were fitted with STS Dexcom System (CGM) but continuous glucose data was not displayed. Control group was also asked to calibrate CGM twice daily with SMBG meters and to use SMBG values to guide treatment.	10 days		CGM	SMBG	Funding: Devices provided by DexCom Risk of bias: Randomisation : computer generated stratified randomisation patients with type 1 diabetes and type 2 diabetes. Allocation concealment: not described. Blinding: not blinded due to nature of intervention ITT analysis : not reported Drop-outs: none reported
			Age (years)	44 (SD 13)					Severe hypoglycaemic events (requiring assistance)	0	2	
			Gender (m/f)	53/38					HbA1c not reported			
			Diabetes duration (years), mean (SD)	21 (SD 12)								
				CGM (n=44)	SMBG (n=47)							
			CSII	27	24							
			HbA1c (%), mean (SD)	8.0 (SD 1.5)	7.6 (SD 1.1)							
			Drop-outs: None reported									

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		Exclusion criteria: n/a							

Table 170: NEWMAN 2009

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
S. P. Newman, D. Cooke, A. Casbard, S. Walker, S. Meredith, A. Nunn, L. Steed, A. Manca, M. Sculpher, M. Barnard, D. Kerr, J. Weaver, J. Ahlquist, and S. J. Hurel. A randomised controlled trial to compare minimally	RCT (parallel trial) RCT Multicentre trial with participants recruited from care diabetes clinics in four hospitals in England. Stratified by age, centre and type of diabetes	n= 106 adults with type 1 diabetes (n=53, continuous glucose monitoring [CGM]; n=53, standard treatment (One Touch Ultra meter) reflecting common practice in the UK.	Participants aged over 18 years with insulin-treated DM for at least 6 months receiving two or more injections of insulin daily.			CGMS (MiniMed): Participants were requested to wear it for 72 hrs. In addition to wearing the CGMS participants were asked to continue to perform capillary blood glucose monitoring as desired.	Standard care using an OneTouch Ultra meter. They were asked to monitor capillary blood glucose at their normal frequency.	18 months		CGMS	Attention control	Funding: funded by the National Institute of Health Research, Health Technology Assessment Programme. Risk of bias: Randomisation was site specific and ensured balanced allocation in terms of centre, age and type of
				CGMS (n=53)	Attention control (n=52)				Percentage Change in HbA1c (%), mean at 18 months follow-up, mean (SD)	-5.7 (SD 9.4)	-3.1 (SD 14.8)	
			Age (years), median (IQR)	53 (42-63)	51 (42-59)				Hypoglycaemia not reported			
			Diabetes duration (years),	15 (9-26)	14 (9-24)							

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE). Health Technol.Assess. 13 (28):iii-194, 2009. REF ID: NEWMAN 2009		Inclusion criteria: Individual with insulin-treated DM receiving two or more injections daily Age over 18 years. Duration of diabetes over 6 months. HbA1c results: Two HbA1c levels greater than or equal to 7.5%, one in the last 3 months and another	median (IQR)									diabetes by use of the minimisation method. Allocation concealment =adequate (Central randomisation) Blinding = not reported ITT analysis carried out Study was powered. Drop-outs (overall) = acceptable (<20%)
			Years on insulin, median (IQR)	11 (5-25)	12.5 (5.5-22)							
			Baseline HbA1c (%), mean (SD)	9 (SD 1.1)	9.4 (SD 1.3)							

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		within the previous 15 months. Fluent in English, Bengali, Cantonese or Turkish. Exclusion criteria: Previous inability to use a capillary glucose meter Previous use of the CGMS sensor. Presence of elevated levels of Hbf or HbS (abnormal haemoglobin) Pregnancy or planned								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		pregnancy. Skin conditions, e.g. eczema, psoriasis or other skin irritation, at the sites of monitor use. Receiving dialysis Visual or physical impairment limiting ability to use monitors. Planned major surgery. Participation in any other on-going trial.							

Table 171: PICKUP 2011C

Reference	Study type	Study details	Intervention	Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
John C. Pickup, Suzanne C. Freeman, and Alex J. Sutton. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. *BMJ (Online)* 343:d3805, 2011.	IPD meta-analysis IPD meta-analysis of just HbA1c data, and includes the following studies: DEISS 2006 [164], HIRSCH 2008[310], O'CONNELL 2009[530], RACCAH 2009 [573], JDRF study (2 papers).	6 RCTs n=892 adults with type 1 diabetes n=449 CGM, n=443 SMBG. Inclusion criteria for studies: • Literature search done up to June 2010 • RCTs • MDI or CSII for at least 2 months • Study length at least 2 months • T1D only Risk of bias of included studies: 1. All studies had appropriate randomisation 2. No mention of allocation concealment in any of the trials 3. No trials double blind (either single – patient - blinding, or not mentioned. 4. Drop-outs <20% (range 1.6 – 12.9%) in all trials OVERALL RISK OF BIAS OF TRIALS = HIGH	CGM (real-time)	SMBG	Up to 6 months (studies ranged from 13-26 weeks duration)	Mean overall change in HbA1c, %: MD 0.30% (95% CI -0.42 to -0.17) Random efefts model used	Funding: None mentioned

Reference	Study type	Study details	Intervention	Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments

Table 172: RACCAH 2009

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
D. Raccah, V. Sulmont, Y. Reznik, B. Guerci, E. Renard, H. Hanaire, N. Jeandidier, and M. Nicolino. Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled	Parallel RCT. Multicentre trial carried out in 8 outpatients centres in France.	n= 132 (81 adults and 51 children) with uncontrolled type 1 diabetes. Adult population = 61%. (n=55, continuous glucose monitoring [CGM] ; n=60, self-monitoring blood glucose (SMBG)	Patients with type 1 diabetes. Insulin pump users = 0%.			CGM: Paradigm (Metronic Minimed). All patients continued to perform fingerpick measurements for glucose self-monitoring as they did before the study.	Standard glucose monitoring (SMBG) plus insulin pump.	6 months.		CGM	SMBG	Funding: study was funded by Medtronic France. The study was designed and approved by the sponsor. Risk of bias: Randomisation: not clear Allocation concealment: not clear Blinding: open label study. "physicians and patients were blinded to
				CGM (n=55)	SMBG (n=60)				Change in HbA1c (%), mean (SD) at 6 months – full analysis set population	-0.81 (SD 1.09)	-0.57 (SD 0.94)	
			Age (years), mean (SD)	28.1 (SD 5.1)	28.8 (SD 16.7)				Hypoglycaemia (episodes/day) – full analysis set population	0.1 (SD 0.9)	0.1 (SD 0.7)	
			Gender (m/f)	30/25	34/26							
			Diabetes duration (years), mean (SD)	11.2 (SD 9.0)	12.3 (SD 8.8)				SAEs	3/55	7/60	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
type 1 diabetes: the RealTrend study. Diabetes Care 32 (12):2245-2250, 2009. REF ID: RACCAH 2009.		Inclusion criteria: Age between 2 and 65 years. type 1 diabetes >1 year. Follow up by the respective investigator for at least 3 months HbA1c ≥8%. Treatment with basal/bolus MDI with rapid insulin analogues at mealtimes. Exclusion criteria: not reported.	Baseline HbA1c (%), mean (SD)	9.11 (SD 1.28)	9.28 (SD 1.19)							centralised A1c data from baseline to completion of study" ITT analysis: primary covariance analysis was based on the comparison of HbA1c changes between the groups using last observation carried forward (LOCF) method on the full analysis set (FAS) of patients. Analysis on the FAS population was ITT. Analyses were adjusted for age as patients were randomly assigned within age groups.
			Drop-outs: Dropout rate: 14 (25%) from the CGM group (6 (10%) children and 8 (15%) adults) and 6 (10%) from the SMBG group.									

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
									Powered study: not reported. Drop-outs = 14 (25%) from the CGM group (6 (10%) children and 8 (15%) adults) and 6 (10%) from the SMBG group. Results for adults and children were combined. No subgroup analysis.

Table 173: RADERMECKER 2010

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
R. P. Radermecker, A. Saint Remy, A. J. Scheen, J. Bringer, and E. Renard. Continuous	RCT (cross-over after 12 weeks) 1 centre (clinic) in	n=13 (n=7 started with CGM by Continuous Subcutaneo			Permanent use of a CGM device (Guardian Medtronic) which displays	Self-Monitoring Blood Glucose (SMBG)	24 weeks		CGM	SMBG	Funding: financially supported in part by the Leon Fredericq Foundation at the University
			Diabetes duration, mean (SD) years	25 (SD 15) years				HbA1c (change scores), mean (SD)	-0.53 (SD 0.66)	0.09 (SD 0.50)	
			CSII, mean (SD) years	5.5 (SD 7) years				DQOL total score	-2.3 (SD	0.7 (SD 4.1)	

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
glucose monitoring reduces both hypoglycaemia and HbA1c in hypoglycaemia-prone type 1 diabetic patients treated with a portable pump. Diabetes Metab. 36 (5):409-413, 2010. REF ID: RADERMECKER 2010	Belgium	us Insulin Infusion (CSII) plus SMBG ; n=6 started with SMBG only) Inclusion criteria: type 1 diabetes More than six recorded capillary blood glucose (CBG) values <60mg/dL Exclusion criteria: Not reported			estimated blood glucose levels at 5-min intervals plus SMBG			(change scores), scale 0-100 (high = better), mean (SD)	5.3)		of Liege, Belgium. Risk of bias: Randomisation = unclear (as details not given) Allocation concealment not reported Blinding not reported ITT analysis not reported Powered study: unclear Drop-outs >20% (about 31%) NS significant differences in baseline characteristics between the nine who completed the study and the 13 who were initially
								Number of hypoglycaemic episodes – events per 14 days (change scores), mean (SD)	6.2 (SD 5.2)	0.67 (SD 6.9)	
			NS differences between groups for any of the baseline characteristics Drop-outs: Four patients withdrew from the study within the first 2 weeks. And results reported for the 9 completers								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
									randomised.

Table 174: TAMBORLANE 2008 – JUVENILE 2008 STUDY

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
W. V. Tamborlane, R. W. Beck, B. W. Bode, B. Buckingham, H. P. Chase, R. Clemons, R. Fiallo-Scharer, L. A. Fox, L. K. Gilliam, I. B. Hirsch, E. S. Huang, C. Kollman, A. J. Kowalski, L. Laffel, J. M. Lawrence, J. Lee, N. Mauras, M.	Parallel RCT. Multicentre trial carried out in 10 centres in the USA.	n= 322 adults and children (stratified into three groups according to age: ≥ 25 years, 15 to 24 years, and 8 to 14 years) with type 1 diabetes. ≥ 25 years = 98 (30% of total population); 15-24 years = 110 (34% of	Patients' ≥ 25 years with type 1 diabetes and initial A1C levels of 7 to 10%., either used an insulin pump or received at least 3 daily insulin.			CGM: patients were instructed to use the device on a daily basis and to verify the accuracy of the glucose measurement with a home blood glucose meter (provided by the study) Dexcom Seven, Paradigm Real-Time Insulin Pump CGMS	Standard glucose monitoring (SMBG): home monitoring with a blood glucose meter. Patients were given blood glucose meters and test strips and asked to perform home blood glucose monitoring at least 4	26 weeks		CGM	SMBG	Funding: research was supported by grants from the Juvenile Diabetes Research Foundation. Risk of bias: Randomisation: "patients meeting these criteria were randomly assigned with the use of a permuted block design". Allocation concealment:
				CGM (n=52)	SMBG (n=46)				Change in HbA1c (%) ≥25 years, mean (SD) at 26 weeks	-0.50 (SD 0.56)	-0.02 (SD 0.45)	
									Change in HbA1c (%) 15-24 years, mean (SD) at 26 weeks	-0.18 (SD 0.65)	-0.21 (SD 0.61)	
			Age: ≥25 years, mean (SD)	41.2 (SD 1.2)	44.6 (SD 12.3)				Severe hypoglycaemia ≥25 years: no. of patients (%)	5/52 (10)	4/46 (9)	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
O'Grady, K. J. Ruedy, M. Tansey, E. Tsalikian, S. Weinzimer, D. M. Wilson, H. Wolpert, T. Wysocki, and D. Xing. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N.Engl.J.Med. 359 (14):1464-1476, 2008. REF ID: TAMBORLANE 2008		total population) Sub-group analysis carried out for ≥25 years population and 15-24 years For the ≥ 25 years population (n=52, continuous glucose monitoring [CGM] ; n=46, self-monitoring blood glucose (SMBG) For the 15-24 years population (n=57, continuous	Age: 15-24 years, mean (SD)	18.8 (SD 3)	18.2 (SD 2.7)	(Medtronic) FreeStyle Navigator (Abbot Diabetes Care).	times daily.					not reported Blinding: control group had blinded CGM at 13 and 26 weeks ITT analysis: not sufficient information. Powered study: study was adequately powered. Drop-outs = acceptable (<20%).
			Gender (m/f): ≥25 years	21/31	20/26							
			Gender (m/f): 15-24	22/29	15/38				Severe hypoglycaemia 15-24 years: no. of patients (%)	3/57	5/53	
			Diabetes duration ≥25 years, mean (SD)	23.6 (SD 10.6)	21.8 (SD 10.4)				Adverse events: no. of patients	0	0	
			Diabetes duration 15-24 years, mean (SD)	9.5 (SD 4.8)	8.8 (SD 4)							
			HbA1c	7.6 (SD	7.6							

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
		glucose monitoring [CGM] ; n=53, self-monitoring blood glucose (SMBG) Inclusion criteria: type 1 diabetes at least 1 year before randomisation. Use an insulin pump or received at least 3 daily insulin injections. HbA1c level of 7 to 10% Exclusion criteria: Use of CGM at home in the 6	(%): ≥25 years, mean (SD)	0.5)	(SD 0.5)							
			HbA1c (%): 15-24 years, mean (SD)	8 (SD 0.7)	7.9 (SD 0.8)							
			Drop-outs: Dropout rate: < 5%									

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		months leading up to the trial.							

Table 175: TANENBERG 2004

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
R. Tanenberg, B. Bode, W. Lane, C. Levetan, J. Mestman, A. P. Harmel, J. Tobian, T. Gross, and J. Mastrototaro. Use of the Continuous Glucose Monitoring System to guide therapy in	Parallel RCT. Multicentre trial carried out in 7 centres in the USA.	n= 128 participants between 19 and 76 years with insulin treated diabetes (76% (97) being type 1 diabetes) (n=62, continuous glucose monitoring [CGM] ; n=66, self-monitoring	Patients with insulin treated diabetes ≥ 19years. insulin pump users: 46%			CGM (Medtronic MiniMed) for 2 periods of 3 days (week 1 and week 3). The CGM glucose values are reported retrospectively in the range of 40 to 400 mg/dl.	Self-monitoring blood glucose (SMBG): At least 4 times each day (before meals and at bed time) and in response to symptoms of hypoglycaemia for the duration of the study.	3 months		CGM	SMBG	Funding: study was sponsored by Medtronic Minimed. Risk of bias: Randomisation by random number list, computer generated by Medtronic Minimed with SAS statistical software was used. Allocation concealment: random
				CGM (n=51)	SMBG (n=58)				Change from baseline HbA1c (%), mean at 3 months	-0.74 (SD 0.95)	-0.73 (SD 1.17)	
			Age (years), mean (SD)	44 (SD 10.2)	44.5 (SD 12.6)				Severe hypoglycaemia events at 3 months.	1/51	1/58	
			Gender (m/f)	19/32	25/33							
			Diabetes duration	20.4 (SD 10.7)	19.5 (SD 11.9)							

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
patients with insulin-treated diabetes: a randomized controlled trial. Mayo Clin Proc 79 (12):1521-1526, 2004. REF ID: TANENBERG 2004		blood glucose (SMBG) Inclusion criteria: Insulin treated diabetes Age 17-76 years HbA1c levels ≥ 7.9% Exclusion criteria: n.a.	(years), mean (SD)									assignments to the treatment or control group were provided to the study centres in sealed envelopes. Blinding = not reported ITT analysis not reported Powered study: study was powered according to the result of a 5-week pilot study. Drop-outs = 18% (11/62) in CGM versus 12% (8/66) in control group
			HbA1c (%), mean (SD)	9.1 (SD 1.1)	9 (SD 1)							
			Drop-outs: Dropout rate 18% (11/62) in CGM versus 12% (8/66) in control group									

G.4 Insulin therapy

G.4.1 Rapid-acting insulin

G.4.1.1 Lispro (+NPH) versus human insulin (+NPH)

Table 176: Pfutzner 1996 (ID 1053)

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Pfutzner A, Kustner E, Forst T, Schulze-Schleppinghoff, Trautmann ME, Haslbeck, Schatz H, Beyer J 1996 Intensive insulin therapy with insulin lispro in patients with type 1 diabetes reduces the frequency of hypoglycemic episodes. Experimenta	RCT - crossover Multicentre, Germany	n=107 Inclusion criteria: type 1 diabetes (WHO) Insulin treatment at least 2 months Exclusion criteria: Known allergy to insulin CV or CeV symptoms of atherosclerosis Cancer Renal or hepatic failure Signs of drug abuse Life threatening		All patients n=107	Lispro + NPH Lispro NPH basal Timing and regimen not stated in paper	Regular human + NPH Regular human NPH basal Timing and regimen not stated in paper	3 months treatment (each cross-over period)	HbA1c, final value, % (SD)	LI: 7.42 (0.12) HI: 7.47 (0.12) NS diff	Funding: Drugs from Eli Lilly Risk of bias: Randomisation = unclear (as details not given) Allocation concealment = not mentioned No wash-out period Blinding = open label to allow optimal time administration. Not ITT
			Age, years (SD)	32 ± 9.7 range 18-65 years						
			Women, %	50.5%				Hypoglycaemia, episodes/month (SEM)	LI: 8.57 (0.70) HI: 9.61 (0.72) P=0.008	
			Diabetes, mean years (SD)	9.55 ± 7.74				Treatment satisfaction	Significant improvement in LISPRO vs. Human group	
			HbA1c, % (SD)							
			Drop-outs:		BOTH GROUPS: ---					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
l & Clinical Endocrinology & Diabetes 104:25-30 REF ID: PFUTZNER 1996 (ID 1053)		disease Pregnant or lactating women or those planning pregnancy	n=10						analysis No mention of powering Drop-outs = acceptable (<20%) Unclear if done ANCOVA analysis (best for cross-over studies).

Table 177: Annuzzi 2001

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
G. Annuzzi, Prato S. Del, R. Arcari, Damato A. Bellomo, L. Benzi, D. Bruttomesso, M. C. Calderini, C. Coscelli, D. Fedele, A.	RCT - crossover 8 centres, Italy	n=85 Inclusion criteria: type 1 diabetes (WHO) diagnosis before age 35 and interval between treatment and		All patients n=85	Lispro + NPH + ISOCALORIC DIET Lispro NPH once/day (added before breakfast or lunch	Regular human + NPH + ISOCALORIC DIET Regular human NPH c once/day	3 months treatment (each cross-over period)	HbA1c, final value, % (SD)	LI: 8.12 (0.85) HI: 8.27 (0.79) P<0.05	Funding: Drugs from Eli Lilly Risk of bias: Randomisation = unclear (as details not given) Allocation
			Age, years (SD)	31.4 ± 7.6 range 18-65 years						
			Women, %	56%				Hypoglycaemia, episodes/month/patient	LI: 256 HI: 204 NS	
			Weight, kg (SD)	65.9 (9.9)						

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Galluzzo, M. Giordano, R. Giorgino, A. Lapolla, P. Orsini, G. Pagano, D. Santoro, and G. Riccardi. Preprandial combination of lispro and NPH insulin improves overall blood glucose control in type 1 diabetic patients: a multicenter randomized crossover trial. Nutrition, metabolism, and cardiovascular diseases: NMCD 11 (3):168-175, 2001.		diagnosis of <1 year Age 18-50 Diabetes duration >2 years At least 3 daily Insulin injections for >2 months Insulin dose >0.3 U/Kg HbA1c 7.5-10.0%. Exclusion criteria: History of cancer CeV or symptomatic peripheral vascular disease Heart failure Liver or renal disease Visual impairment Pregnant or lactating women Clinically significant hypoglycaemia. unawareness	Diabetes, mean years (SD)	12.1 ± 7.6	according to needs) Lispro taken 0-5 minutes before meals	(added before breakfast or lunch according to needs) Human insulin taken 30-45 minutes before meals		Severe hypoglycaemia, episodes/month/patient	LI: 0.7 HI: 1.0 NS	concealment = not mentioned No wash-out period Blinding = open label Not mention ITT analysis No mention of powering Drop-outs = acceptable (<20%) Unclear if done ANCOVA analysis (best for cross-over studies).
			HbA1c, % (SD)	8.67 (0.72)				Weight, kg (SD)	LI: 66.7 (10.3) HI: 66.4 (10.5)	
			Drop-outs: n=5							
					BOTH GROUPS: NPH could be given 3 times/day before each meal			DTSQ	Preference for Lispro (p<0.001)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: ANNUZZI 2001									

Table 178: VIGNATI 1997 (275)

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
L. Vignati, J. H. Anderson, Jr., and P. W. Iversen. Efficacy of insulin lispro in combination with NPH human insulin twice per day in patients with insulin-dependent or non-insulin-dependent diabetes mellitus. Multicenter Insulin Lispro	RCT - crossover 16 countries, 75 centres	n=379 type 1 diabetes (707 total of type 1 diabetes and type 2 diabetes); type 1 diabetes subgroup analysis done so results are for type 1 diabetes only. Inclusion criteria: IDDM or NIDDM (WHO) Regular human + NPH insulin twice/day for at least 2 months 18-70 years		All patients n=379	Lispro + NPH Lispro = Humalog NPH = Humulin N Twice/day (morning and eve meals) Lispro taken immediately before meals	Regular human + NPH Regular human = Humulin R NPH = Humulin N Twice/day (morning and eve meals) Human insulin taken as had done before enrolment	2 months treatment (each cross-over period)	HbA1c, final value, % (SD)	LI: 7.8 (1.4) HI: 7.9 (1.5) P=0.660	Funding: Drugs and main authors from Eli Lilly Risk of bias: Randomisation = Adequate (computer generated) Allocation concealment = adequate (sequence assignment from central location) No wash-out period
			Age, years (range)	39.1 (18-70)						
			Women, %	44%				Hypoglycaemia, episodes/month (SD)	LI: 4.6 (5.5) n=365 HI: 4.5 (5.0) P=0.677 n=363	
			BMI, kg/m2 (range)	24.8 (17.7-50.5)						
			Diabetes, mean years (range)	13.1 (0.2-48.2)						
			HbA1c, % (SD)	7.9 (1.5)						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Study Group. Clin.Ther. 19:1408-1421, 1997. REF ID: VIGNATI 1997 (275)		Exclusion criteria: Severe concomitant disease Use of oral hypoglycaemia. agents or other factor that would preclude patients participation or completion of the study.	Drop-outs: Overall 4.1%	BOTH GROUPS: patients were allowed to use premix or self-mixed insulin during treatment with regular human insulin Allowed only self-mixed insulin during insulin Lispro treatment Dose adjustment could be done monthly					Blinding = open label ITT analysis Powered study (Blood glucose.) Drop-outs = acceptable (<20%) Unclear if done ANCOVA analysis (best for cross-over studies).

Table 179: GALE 2000 (1060)

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
E. A. Gale. A randomized, controlled trial comparing insulin lispro with human soluble insulin in patients with Type 1	RCT - crossover 10 sites in UK	n=93 Inclusion criteria: type 1 diabetes before age 40 years Diabetes >1 year No evidence of major		All patients n=93	Lispro + NPH Lispro (before meals) NPH = Humulin I (bedtime)	Regular human + NPH Regular human = Humulin S (before meals) NPH = Humulin I (bedtime)	12 weeks (each cross-over period)	HbA1c, final value, % (SD)	LI: 7.5 (1.1) HI: 7.4 (1.1) P=0.807	Funding: Eli Lilly Risk of bias: Randomisation = unclear (no details given) Allocation concealment = not mentioned
			Age, years median (range)	35 (18-63)						
			Women, %	47%				Hypoglycaemia, episodes/month (SD)	LI: 2.6 (3.0) HI: 3.1	
			BMI, kg/m2, median	25.2 (20-33.7)						

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
diabetes on intensified insulin therapy. The UK Trial Group. Diabet.Med. 17:209-214, 2000. REF ID: GALE 2000 (1060)		complications Good to moderate control (HbA1c <1.5x upper limit of non-diabetic range) 4 daily insulin injections Injections within 15 minutes of meals on >50% of occasions Exclusion criteria: None given	(range)						(4.4) P=0.96	No wash-out period Blinding = double blind ITT analysis Powered study (HbA1c) Drop-outs = acceptable (<20%) Unclear if done ANCOVA analysis (best for cross-over studies).
			Diabetes, median years (range)	13.1 (1-51)				Nocturnal hypoglycaemia, episodes/month (SD)	LI: 0.7 (1.6) HI: 1.8 (3.1) P<0.001	
			HbA1c, % (SD)	Not given						
			Drop-outs: Overall n=6					Severe hypoglycaemia, no. of patients	LI: 2/92 HI: 6/89	
					BOTH GROUPS: Insulin supplied double blind as pens Doses adjusted according to target Blood glucose values			Severe hypoglycaemia, episodes (SD)	LI: 3 HI: 10 P=0.135	

Table 180: FERGUSON 2001

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
S. C. Ferguson, M. W. Strachan, J. M.	RCT - crossover	n=40 Inclusion		All patients n=40	Lispro + NPH	Regular human + NPH	12 weeks (each	HbA1c, final value, % (SD)	LI: 9.1 (0.83) HI: 9.3 (1.0)	Funding: Eli Lilly Risk of bias:

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Janes, and B. M. Frier. Severe hypoglycaemia in patients with type 1 diabetes and impaired awareness of hypoglycaemia: a comparative study of insulin lispro and regular human insulin. Diabetes.Metab.Res.Rev. 17 (4):285-291, 2001. REF ID: FERGUSON 2001	1 centre in UK	criteria: type 1 diabetes 19-65 years Reduction in their warning symptoms of hypoglycaemia in last 2 years Experienced 2 or more episodes of hypoglycaemia in past 2 years (ie. impaired awareness of hypoglycaemia) HbA1c (5.0-6.5%) Exclusion criteria: Systemic, renal or hepatic disease Pregnancy	Age, years mean (SD; range)	46 (11; 19-65)	BOTH GROUPS: The regimen could be either: a) twice/day (ie. SA insulin and NPH mixed and given before breakfast and main evening meal), or b) MDI (ie. SA insulin before meals and NPH before bed) Doses adjusted according to target Blood glucose values		cross-over period)	Hypoglycaemia, episodes	LI: 1156 HI: 1115 P=NS	Randomisation = unclear (no details given) Allocation concealment = not mentioned No wash-out period Blinding = open label ITT analysis (no drop-outs) No mention of powering Drop-outs = none mentioned Unclear if done ANCOVA analysis (best for cross-over studies).
			Women, %	46%				Nocturnal hypoglycaemia, episodes	LI: 25 HI: 47 p=0.01	
			BMI, kg/m2, mean (SD)	25.4 (2.6)				Severe hypoglycaemia, no. of patients	LI: 18/33 HI: 18/33	
			Diabetes, mean years (SD)	25.8 (9.8)				Severe hypoglycaemia, episodes	LI: 55 HI: 84 P=0.087	
			HbA1c, % (SD)	9.0 (1.1)				DTSQ – QoL questionnaire	NS difference between groups	
			Drop-outs: Overall: none mentioned					HFS (Hypo Fear survey) – QoL questionnaire	NS difference between groups	

Table 181: HOLLEMAN 1997 (1051)

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
F. Holleman, H. Schmitt, R. Rottiers, A. Rees, S. Symanowski, J. H. Anderson, P. Van Crombrugge, F. Fery, L. F. Van Gaal, R. Rottiers, G. Somers et al. Reduced frequency of severe hypoglycemia and coma well-controlled IDDM patients treated with insulin lispro. Diabetes Care 20 (12):1827-1832, 1997. REF ID: HOLLEMAN 1997 (1051)	RCT - crossover 19 centres in UK, Belgium and Netherlands	n=199 Inclusion criteria: IDDM (WHO criteria) Age 16-65 years Insulin treatment for at least 1 year MIT using regular insulin for past 3 months HbA1c <1.5x upper limit of normal range of local lab). Exclusion criteria: History of hypoglycaemia unawareness More than 2		All patients n=199	Lispro + NPH Lispro = Humalog (before meals) NPH = Humulin (once/day)	Regular human + NPH Regular human = Actrapid (before meals) NPH = Insulatard or Protaphane (once/day)	12 weeks (each cross-over period)	HbA1c, final value, % (SD)	LI: 7.6 (1.3) HI: 7.5 (1.2) p=0.697	Funding: Eli Lilly Risk of bias: Randomisation = unclear (no details given) Allocation concealment = not mentioned No wash-out period Blinding = open label ITT analysis No mention of powering Drop-outs = acceptable (<20%) Unclear if done ANCOVA analysis (best for cross-over studies).
			Age, years mean (SD)	35.4 (9.6)				Hypoglycaemia, episodes	LI: 2249 HI: 2344 p=NS	
			Women, %	37%						
			BMI, kg/m2, mean (SD)	25.0 (3.1)				Nocturnal hypoglycaemia, episodes	LI: 176 HI: 312 p<0.001	
			Diabetes, mean years (SD)	13.1 (9.1)						
			HbA1c, % (SD)	7.3 (1.1)				Severe hypoglycaemia, episodes	LI: 36 HI: 58 p=0.037	
			Body weight, kg (SD)	75.0 (12.7)						
			Drop-outs: Overall n=10		BOTH GROUPS: Regular insulin to be taken 30 minutes before meals, and Lispro immediately before meals Doses adjusted according to target Blood glucose values			Body weight, kg (SD)	LI: 75.3 (13.1) HI: 75.8 (13.0) p=0.03	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		hospitalisations for hypoglycaemia in the past year.							

Table 182: CHAN 2004

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
WB Chan, CC Chow, VTF Yeung, JCN Chan, WY So, and CS Cockram. Effect of insulin lispro on glycaemic control in Chinese diabetic patients receiving twice-daily regimens	RCT - crossover Chinese study	n=12 type 1 diabetes (30 total of type 1 diabetes and type 2 diabetes); type 1 diabetes subgroup analysis done so results are for type 1 diabetes only. Inclusion criteria: type 1 diabetes or type 2 diabetes 18-70 years Receiving twice/day insulin injections Exclusion criteria:		All patients n=30	Lispro + NPH Lispro NPH = Humulin (twice/day) Lispro taken immediately before meals	Regular human + NPH Regular human = Humulin R NPH = Humulin N (twice/day) Human insulin taken as had done before enrolment	12 weeks treatment (each cross-over period)	HbA1c, final value, %	LI: 6.8) HI: 6.6	Funding: Not mentioned Risk of bias: Randomisation = Unclear (details not given) Allocation concealment Unclear (details not given) No wash-out period Blinding = open label ITT analysis (no
			Age, years (range)	42.2 (20-67)						
			Women, %	47%				-	-	
			BMI, kg/m2 (range)	25.0 (4.3)						
			Diabetes, mean years (range)	7.8 (2.7)				-	-	
			HbA1c, % (SD)	9.0 (2.2)						
								-	-	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
of insulin. Chin.Med.J .(Engl). 117 (9):1404-1407, 2004. REF ID: CHAN 2004		Weakened liver function Impaired renal function CV events in previous 6 months History of peripheral vascular disease Pregnant, lactating or planning pregnancy. Unlikely to complete study due to non-compliance, inability to self-inject History of allergies to insulin	Drop-outs: None mentioned	BOTH GROUPS: Dose adjustment based on HMBG values					drop-outs) Not mention powering Drop-outs = none Not done ANCOVA analysis (ANC best for cross-over studies).

Table 183: HELLER 1999

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures PERIOD 1	Effect sizes	Comments
S. R. Heller, S. A. Amiel, and P. Mansell. Effect of the fast-acting insulin analog lispro on the	RCT - crossover 11 centres in UK	n=165 Inclusion criteria: type 1 diabetes for at least 2 years Using basal-bolus		Lispro n=68	RHI n=67	Lispro + NPH Lispro = Humalog (before meals)	Regular human + NPH Regular human = Actrapid	12 weeks (each cross-over period)	HbA1c, final value, % (SD)	LI: 6.0 (0.9) HI: 6.2 (0.8)	Funding: Eli Lilly Risk of bias: Randomisation = unclear (no details
			Age, years mean (SD)	37 (11)	39 (11)						
			Women,	49%	46%				Hypoglycaemi	LI: 775	

risk of nocturnal hypoglycemia during intensified insulin therapy. U.K. Lispro Study Group. Diabetes Care 22 (10):1607-1611, 1999. REF ID: HELLER 1999		regimen for at least 3 months HbA1c <8% Desire to achieve tight glucose control Exclusion criteria: Active proliferative retinopathy Symptomatic peripheral neuropathy Serum creatinine >250 micromole/litre Hospitalisation >3 times with severe hypoglycaemia. in past 12mths.	%			NPH = Humulin (once/day)	(before meals) NPH = Insulatard or Protaphane (once/day)		a, episodes	HI: 1156 p=0.04	given) Allocation concealment = not mentioned No wash-out period Blinding = open label ITT analysis No mention of powering Drop-outs = acceptable (<20%) Unclear if done ANCOVA analysis (best for cross-over studies).
			BMI, kg/m2, mean (SD)	25.2 (2.6)	25.4 (2.9)				Nocturnal hypoglycaemia, episodes	LI: 52 HI: 181 P=0.001	
			Diabetes, mean years (SD)	16.4 (9.6)	16.7 (8.8)				Severe hypoglycaemia, no. of patients	LI: 2 HI: 6	
			HbA1c, % (SD)	6.2 (1.1)	6.4 (0.9)	BOTH GROUPS: Regular insulin to be taken 30 minutes before meals, and Lispro immediately before meals Doses adjusted according to target Blood glucose values			Severe hypoglycaemia, episodes	LI: 8 HI: 12 p=NS	
			Body weight, kg (SD)	74.8 (11.4)	73.5 (10.1)						
			Drop-outs: Overall n=10						Body weight, kg (SD)	LI: 74.7 (11.7) HI: 75.7 (10.2)	

Table 184: ANDERSON 1997 (1062)

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
J. H. Anderson, Jr., R. L. Brunelle, V. A. Koivisto, A.	RCT - crossover 102	n=11,008 Mainly adults as high mean and small SD		All patients n=11008	Lispro + NPH or Ultralente	Regular human + NPH Regular	3 months (each cross-	HbA1c, final value, % (SE)	LI: 8.2 (0.1) HI: 8.2	Funding: Eli Lilly
			Age, years	33.2 (0.4)						

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Pfutzner, M. E. Trautmann, L. Vignati, and R. DiMarchi. Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. Multicenter Insulin Lispro Study Group. Diabetes 46:265-270, 1997. REF ID: ANDERSON 1997 (1062)	centres in 17 countries	Inclusion criteria: IDDM (WHO criteria) Age 12-70 years Insulin treatment for at least 2 months. Exclusion criteria: Presence of other severe disease Pregnancy BMI >35 kg/m2 Daily insulin dose >2.0 U/kg History of clinically significant hypoglycaemia. unawareness.	mean (SD)		Lispro = Humalog (before meals) NPH = Humulin N Ultralente = Humulin U Basal insulin once or twice/day – 54% once/day	human = Humulin R (before meals) NPH = Humulin N Ultralente = Humulin U Basal insulin once or twice/day – 56% once/day	over period)		(0.1)	Risk of bias: Randomisation = not mentioned Allocation concealment = not mentioned No wash-out period Blinding = open label ITT analysis (LOCF) Not mention powering but huge study Drop-outs = no details ANCOVA analysis for hypoglycaemia. rate (best for cross-over studies).
			Women, %	42%				Hypoglycaemia, episodes	LI: 11906 HI: 21522	
			BMI, kg/m2, mean (SD)	24.2 (0.1)						
			Diabetes, mean years (SD)	12.0 (0.3)				Hypoglycaemia, episodes/ 30 days (SE)	LI: 6.4 (0.2) HI: 7.2 (0.3) p<0.001	
			HbA1c, % (SD)	8.5 (0.1)						
			Body weight, kg (SD)	71.2 (0.4)	BOTH GROUPS: Regular insulin to be taken 30-45 minutes before meals, and Lispro immediately before meals patients allowed to mix pre-meal and basal insulin in the syringe at time of injection Doses adjusted according to target Blood glucose values			Severe hypoglycaemia, no. of patients	LI: 24 HI: 36	
			Drop-outs: Overall not mentioned					Severe hypoglycaemia, episodes	LI: 30 HI: 42	

Table 185: LALLI 1999 (1066)

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
C. Lalli, M. Ciofetta, P. Del Sindaco, E. Torlone, S. Pampanelli, P. Compagnucci, M. G. Cartechini, L. Bartocci, P. Brunetti, and G. B. Bolli. Long-term intensive treatment of type 1 diabetes with the short-acting insulin analog lispro in variable combination with NPH insulin at mealtime. Diabetes Care 22 (3):468-477, 1999. REF ID: LALLI 1999 (1066)	RCT 1 centre in Italy	n=56 Inclusion criteria: type 1 diabetes In long-term near-normoglycaemia (HbA1c6.0-7.5%) during intensive treatment Treated with intensive insulin therapy C-peptide negative Free of any detectable microangiopathic complications Negative for autonomic neuropathy Exclusion criteria: None given		Lispro n=28	RHI n=28	Lispro + NPH Lispro (at meals) NPH (bedtime + with meals if needed – most patients did 3 or 4 times/day) 64% mixed Lispro with NPH in syringes– rest used separate insulin pens	Regular human + NPH Regular human = Hum-R (at meal) NPH (bedtime – most patients did twice/day) 71% mixed RHI with NPH in syringes – rest used separate insulin pens	1 year	HbA1c, final value, % (SD)	LI: 6.34 (0.1) HI: 6.71 (0.11)	Funding: None mentioned Risk of bias: Randomisation = unclear (no details given) Allocation concealment = not mentioned Blinding = open label ITT analysis (no drop-outs) No mention of powering Drop-outs = none
			Age, years mean (SD)	35 (2.2)	33 (3)				Hypoglycaemia, episodes (SD)	LI: 7.4 (0.5) HI: 11.5 (1.2)	
			Women, %	46%	43%				Severe hypoglycaemia, no. of patients	LI: 0 HI: 0	
			BMI, kg/m2, mean (SD)	22.6 (1)	22.5 (0.9)						
			Diabetes, mean years (SD)	13.6 (2.8)	16 (2.6)						
			HbA1c, % (SD)	6.6 (0.23)	6.7 (0.2)						
			Drop-outs: None mentioned			BOTH GROUPS: Regular insulin to be taken 10-40 minutes before meals, and Lispro 0-5 minutes before meals Doses adjusted according to target Blood glucose values					

Table 186: CIOFETTA 1999

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
M. Ciofetta, C. Lalli, P. Del Sindaco, E. Torlone, S. Pampanelli, L. Mauro, D. L. Chiara, P. Brunetti, and G. B. Bolli. Contribution of postprandial versus interprandial blood glucose to HbA1c in type 1 diabetes on physiologic intensive therapy with lispro insulin at mealtime. Diabetes Care 22 (5):795-800, 1999. REF ID: CIOFETTA 1999	RCT - Parallel 10 centres in Europe and South Africa	n=24 Inclusion criteria: type 1 diabetes Exclusion criteria: None given patients were free of detectable microangiographic complication patients having treatment with intensive insulin therapy (regular insulin at each meal, NPH at bedtime)		HI + NPH once n=8	Lisp + NPH once n=8	MIX Lisp + NPH bed n=8	Hum R (+ NPH bedtime) Pre-meal human regular insulin. NPH at bedtime. ---------- Lispro + NPH Pre-meal insulin lispro. NPH at bedtime. Lispro given 0-5mins, and Hum R at 10-40 minutes before meals	SELF-MIX: Lispro + NPH (+ NPH bedtime) Pre-meal Mixed insulin (Lispro + NPH). NPH at bedtime. Pre-meal Lispro given in separate injection to pre-meal NPH	3 months treatment	HbA1c, final value, % (SEM)	HI: 6.84 (0.2) Lisp: 6.96 (0.2) MIX: 6.41 (0.12)	Funding: BB and sons Risk of bias: Randomisation = unclear (details not given) Allocation concealment = not mentioned Blinding = not mentioned. ITT analysis (no drop-outs) Powering not mentioned. Drop-outs = None
			Age, years (SEM)	33 (4) thus likely to be all adults - small SE								
			Women, %	29						Severe hypoglycaemia., no. of patients	HI: 0 Lisp: 0 MIX: 0	
			Diabetes, mean years (SEM)	13 (2.1)								
			HbA1c, % (SEM)	Overall 6.84 (0.20)						Mild hypoglycaemia, episodes/ patient/month (SEM)	HI: 4.0 (0.5) Lisp: 8.1 (0.8) MIX: 5.2 (1.2)	
			HbA1c, % (SEM)	6.79 (0.17)	6.89 (0.16)	6.83 (0.18)						
			Drop-outs (6 months): None mentioned				BOTH GROUPS: Injections by pen HumaPen, Eli Lilly). Doses adjusted to specific treatment goals of blood			Unclear if done ANCOVA analysis (best for cross-over studies).		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
				glucose.					

Table 187: LILLY 1994

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Eli Lilly and Company. Clinical study summary: study F3Z-MC-IOAA(b). LY275585 vs. Humulin R: pre-meal therapy in type 1 diabetes. Anonymous. Anonymous. 1994. REF ID: LILLY 1994 Eli Lilly	RCT 14 centres in 6 countries	n=167 – most are adults as mean age is 31.5 years Inclusion criteria: type 1 diabetes (WHO) Ages 12-70 On human insulin for at least 2 months prior to study Exclusion		Lispro n=81	RHI n=86	Lispro + NPH Lispro (before meals) NPH = Humulin U (once or twice/day)	Regular human + NPH Regular human =Humulin R (before meals) NPH = Humulin U (once or twice/day)	1 year	HbA1c, final value, % (SD)	LI: 8.14 (1.3) HI: 8.38 (1.37)	Funding: Eli Lilly: registered trial data (not published in a journal) Risk of bias: Randomisation = unclear (no details given) Allocation concealment = not mentioned Blinding = open label ITT analysis No mention of powering Drop-outs = acceptable (<20%)
			Age, years mean (SD)	29.1	32						
			Women, %	49%	54%				Hypoglycaemia, no. of patients	LI: 69/75 HI: 70/80	
			BMI, kg/m2, mean (SD)	24.2	24.5				Hypoglycaemia, episodes/patient/30 days (SD)	LI: 5.41 (6.74) n=81 HI: 5.4 (6.36) n=86	
			Diabetes, mean years (SD)	12.3	13.3				Body weight, kg (SD) – change from baseline	LI: 1.43 (3.56) n=81	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
registered trial data (not published in a journal.		criteria: None given	HbA1c, % (SD)	8.17 (1.41)	8.32 (1.67)	BOTH GROUPS: Regular insulin to be taken 30-45 minutes before meals, and Lispro immediately before meals Doses adjusted according to target Blood glucose values				HI: 1.04 (2.62) n=86	Unclear if done ANCOVA analysis (best for cross-over studies).
			Body weight, kg (SD)	71.97 (12.73)	70.56 (11.28)				Body weight, kg (SD) – final value	LI: 73.4 (13.27) n=81 HI: 71.6 (11.13) n=86	
			Drop-outs: LI: n=7 HI: n=7								

Table 188: LILLY 1995A

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Eli Lilly and Company. Clinical study summary: study F3Z-MC-IOAC(b). LY275585 vs. Humulin R: pre-meal therapy in type 1 diabetes. Anonymous.	RCT 17 centres in 8 countries	n=169 – most are adults as mean age is 33.5 years Inclusion criteria: type 1 diabetes (WHO) Ages 12-70 On human insulin for at		Lispro n=81	RHI n=88	Lispro + NPH Lispro (before meals) NPH = Humulin N (frequency not mentioned)	Regular human + NPH Regular human =Humulin R (before meals) NPH = Humulin N (frequency	12 months treatment	HbA1c, final value, % (SD)	LI: 8.08 (1.43) HI: 8.22 (1.44)	Funding: Eli Lilly: registered trial data Risk of bias: Randomisation = unclear (no details given) Allocation concealment
			Age, years mean	35.2	32.0						
			Women, %	49.4%	47.7%				Hypoglycaemia, no. of patients	LI:62 n=76 HI: 64 n=84	
			BMI, kg/m2,	24.0	24.3				Hypoglycaemia,	LI: 3.48 (4.91)	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Anonymous. 1995. REF ID: LILLY 1995A Eli Lilly registered trial data (not published in a journal.		least 2 months prior to study Exclusion criteria: None given	mean				not mentioned)		episodes/patient/30 days (SD)	n=76 HI: 3.69 (4.19) n=84	= none Blinding = open label ITT analysis No mention of powering Drop-outs = acceptable (<20%) Unclear if done ANCOVA analysis (best for cross-over studies).
			Diabetes, mean years	13.0	10.9				Body weight, kg (SD) – change from baseline	LI: 0.92 (3.61) n=76 HI: 2.41 (8.32) n=84	
			HbA1c, % (SD)	8.28 (1.58)	8.14 (1.62)	BOTH GROUPS: Regular insulin to be taken 30-45 minutes before meals, and Lispro immediately before meals Doses adjusted according to target Blood glucose values					
									Body weight, kg (SD) – final value	LI: 72.16 (11.57) n=76 HI: 74.51 (13.05) n=84	
			Drop-outs: LI: n=6 RHI: n=5								

Table 189: LILLY 1995B

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Eli Lilly and Company. Clinical study summary:	RCT 19 centres	n=98 – most are adults as mean age is 25 years		Lispro n=50	RHI n=48	Lispro + NPH	Regular human + NPH	12 months treatm	HbA1c, final value, % (SD)	LI: 7.77 (2.24) HI: 7.84	Funding: Eli Lilly: registered trial data
			Age, years	24.1	24.6						

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
study F3Z-MC-IOAE. LY275585 vs. Humulin R: premeal therapy in new patients with type 1 diabetes. Anonymous. Anonymous. 1995. REF ID: LILLY 1995B Eli Lilly registered trial data (not published in a journal.	in 6 countries	Inclusion criteria: type 1 diabetes (WHO) Ages 12-70 On human insulin for at least 2 months prior to study (NEW PTS WITH type 1 diabetes) Exclusion criteria: None given	mean			Lispro (before meals) NPH = Humulin N or U (once/day – before evening meal or bedtime)	Regular human =Humulin R (before meals) NPH = Humulin N or U (once/day – before evening meal or bedtime)	ent		(2.35)	Risk of bias: Randomisation = unclear (no details given) Allocation concealment = none Blinding = open label ITT analysis No mention of powering Drop-outs = acceptable (<20%) Unclear if done ANCOVA analysis (best for cross-over studies).
			Women, %	44%	33.3%				Hypoglycaemia, no. of patients	LI: 30 n=45 HI: 35 n=43	
			BMI, kg/m2, mean	23.3	23.1				Hypoglycaemia, episodes/patient/30 days (SD)	LI: 3.28 (4.36) n=45 HI: 3.74 (5.13) n=43	
			Diabetes, mean years	0.17	0.19				Body weight, kg (SD) – change from baseline	LI: 4.02 (8.73) n=45 HI: 4.61 (4.75) n=43	
			HbA1c, % (SD)	Not given	Not given	BOTH GROUPS: Regular insulin to be taken 30-45 minutes before meals, and Lispro immediately before meals Doses adjusted according to target Blood glucose values					
									Body weight, kg (SD) – final value	LI: 72.88 (15.52) n=45 HI:71.02 (16.08) n=43	
			Drop-outs: LI: n=5 RHI: n=5								

Table 190: LILLY 1995C

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Eli Lilly and Company. Clinical study summary: study F3Z-MC-IOAG. LY275585 vs. Humulin R: premeal therapy in type 1 diabetes. Anonymous. Anonymous. 1995. REF ID: LILLY 1995C Eli Lilly registered trial data (not published in a journal.	RCT - cross-over 101 centres in 17 countries	n=1008 – most are adults as mean age is 33 years Inclusion criteria: type 1 diabetes (WHO) Ages 12-70 On human insulin for at least 2 months prior to study Exclusion criteria: None given		Lispro n=508	RHI n=500	Lispro + NPH Lispro (before meals) NPH = Humulin U or N (once or twice/day)	Regular human + NPH Regular human =Humulin R (before meals) NPH = Humulin U or N (once or twice/day)	3 months treatment (each cross-over period)	HbA1c, final value, % (SD)	LI: 8.24 (1.49) HI: 8.17 (1.46)	Funding: Eli Lilly: registered trial data Risk of bias: Randomisation = unclear (no details given) Allocation concealment = not mentioned Blinding = open label No wash-out period ITT analysis No mention of powering Drop-outs = acceptable (<20%) Unclear if done ANCOVA analysis (best for cross-over studies).
			Age, years mean (SD)	33.3	33.16				-	-	
			Women, %	42%	42%				Hypoglycaemia, episodes/patient /30 days (SD)	LI: 6.44 (7.63) HI: 7.19 (8.08)	
			BMI, kg/m2, mean (SD)	24.2	24.3				Body weight, kg (SD) – change from baseline	LI: 0.3 (2.5) HI: 0.6 (3.5)	
			Diabetes, mean years (SD)	12.18	11.77				Body weight, kg (SD) – final value	LI: 71.5 (12.3) HI: 71.8 (12.5)	
			HbA1c, % (SD)	8.45 (1.71)	8.45 (1.71)	BOTH GROUPS: Regular insulin to be taken 30-45 minutes before meals, and Lispro immediately before meals Doses adjusted according to target Blood glucose values					
			Drop-outs: Overall: 48								

G.4.1.2 Lispro (+glargine) versus human insulin (plus glargine)

Table 191: BRUNETTI 2010

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
P. Brunetti, M. Muggeo, L. Cattin, A. Arcangeli, P. Pozzilli, V. Provenzano, A. Francesconi, P. Calatola, and F. Santeusanio. Incidence of severe nocturnal hypoglycemia in patients with type 1 diabetes treated with insulin lispro or regular human insulin in addition to basal insulin glargine. Nutr Metab Cardiovasc	RCT 47 centres in Italy	n=395 Inclusion criteria: type 1 diabetes for at least 3 years Age 18-60 years Using MDI basal-bolus regimen (with NPH or glargine as basal) HbA1c ≤9% fC-peptide ≤0.1 nmol/litre with fBG >6.9 mmol/litre BMI <30 kg/m2 Ability and willingness to perform		Lispro n=202	RHI n=193	Lispro + Glargine Lispro (at meals) Glargine (dinner time)	Regular human + Glargine Regular human (at meals) Glargine (dinner time)	16 weeks treatment, 2 weeks follow-up	HbA1c, final value, % (SD)	LI: 6.95 (0.78) HI: 7.1 (0.83)	Funding: Sanofi-Aventis Risk of bias: Randomisation = adequate??? sequence generated by biometrician but no other details given Allocation concealment = not concealed Blinding = open label Not true ITT analysis Underpowered Drop-outs = acceptable (<20%) Unclear if done ANCOVA analysis (best for cross-over studies).

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Dis 20 (7):519-526, 2010. REF ID: BRUNETTI 2010		SMBG Adequate contraception Exclusion criteria: Diabetes other than type 1 diabetes Total insulin dose ≥1U/kg/day Serum creatinine >1.5 mg/dl History of renal transplantation Current renal dialysis Congestive heart failure Hypoglycaemia unawareness Concomitant									

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		used of β-blockers, thiazides or systemic corticosteroids >1 episode of severe hypoglycaemia. with seizure or coma during past year.									

G.4.1.3 Lispro (plus glargine) versus glulisine (plus glargine)

Table 192: DREYER 2005A

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
M. Dreyer, R. Prager, A. Robinson, K. Busch, G. Ellis, E. Souhami, and R. Leendert. Efficacy and safety of	RCT 62 centres in 14 countries	n=683 Inclusion criteria: type 1 diabetes Requiring continuous insulin treatment since		Lispro n=341	Glucose n=342	Lispro + GLARGINE	Glulisine + GLARGINE	26 weeks treatment	HbA1c, final value, % (SD)	LI: 7.45 (0.92) GL: 7.46 (0.91)	Funding: Aventis Pharma Risk of bias: Randomisation = unclear (no details given)
			Age, years mean (SD)	37.9 (12.4)	39.1 (12.1)	Lispro (before meals)	Glulisine (before meals)				
			Women, %	43%	42%	GLARGINE (once/day)	GLARGINE (once/day)		Hypoglycaemia, episodes/patien	LI: 3.48 (4.38)	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
insulin glulisine in patients with type 1 diabetes. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et métabolisme 37 (11):702-707, 2005. REF ID: DREYER 2005A		diagnosis and >1 year before study Ages ≥18 years Age of onset <40 years BMI <35 kg/m2 HbA1c 6-11% Exclusion criteria: Active proliferative/unstable retinopathy in 6 months before study Impaired hepatic or renal function History of seizures or hypersensitivity to insulin or excipients in glulisine formulation.							t-months (SD)	GL: 3.64 (4.49)	Allocation concealment = none Blinding = open label ITT analysis No mention of powering Drop-outs = acceptable (<20%)
			BMI, kg/m2, mean	25.1	24.9				Severe hypoglycaemia, episodes/patient-months (SD)	LI: 0.02 (0.11) GL: 0.03 (0.12)	
			Diabetes, mean years	15.6 (10.3)	17.4 (10.9)				Nocturnal hypoglycaemia, episodes/patient-months (SD)	LI: 0.53 (0.84) GL: 0.55 (0.94)	
			HbA1c, % (SD)	7.58 (0.89)	7.60 (0.96)	BOTH GROUPS: SA insulin to be taken 0-15 minutes before meals Dose adjustment not mentioned			Injection site reactions, no. of patients	LI: 14 GL: 11	
			Drop-outs: LI: n=21 (6%); GL: n=13 (4%)								

Table 193: KAWAMORI 2009

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures – 6 months	Effect sizes	Comments
R. Kawamori, T. Kadowaki, H. Ishii, M. Iwasaki, and Y. Iwamoto. Efficacy and safety of insulin glulisine in Japanese patients with type 1 diabetes mellitus. Diabetes Obes.Metab. 11 (9):891-899, 2009. REF ID: KAWAMORI 2009	RCT 24 centres in Japan	n=267 Inclusion criteria: ≥18 years type 1 diabetes At least 1 year continuous insulin treatment treatment with bolus every meal and basal once or twice/day for at least 12 weeks before study BMI <35 kg/m2 HbA1c ≥6.0-11.0% Exclusion criteria: Receiving		Glucose n=132	Lispro n=135	Glulisine + GLARGINE (+ intensive diet and exercise) Glulis (0-15 minutes before meals) GLARGINE = (once/day - bedtime)	LISPRO + GLARGINE GLARGINE (+ intensive diet and exercise) Lispro (0-15 minutes before meals) GLARGINE = (once/day - bedtime)	28 weeks	HbA1c, final value, % (SD)	GL: 7.54 (0.97) LI: 7.54 (0.98)	Funding: Sanofi-Aventis. Risk of bias: Randomisation = unclear (only says minimisation method) Allocation concealment = unclear (no details given) Blinding = open label ITT analysis No mention of powering Drop-outs = acceptable (<20%) ANCOVA analysis done
			Age, years mean (SD)	38.9 (14.3)	38.8 (12.9)				Symptomatic hypoglycaemia, events/patient-month	GL: 3.93 LI: 3.86 p=0.164	
			Women, %	62%	62%				Severe hypoglycaemia, events/patient-month	GL: 0.02 LI: 0.02 p=0.658	
			BMI, kg/m2, mean	23.11	22.8				DTSQ, change from baseline, median (range)	GL: 0.0 (-15 to 13) LI: 0.0 (-16 to 11)	
			Diabetes, mean years (SD)	12.8 (9.5)	11.1 (7.1)						
			HbA1c, % (SE)	7.44 (0.93)	7.50 (0.96)	BOTH GROUPS: Dose adjustment to meet targets for blood glucose control			treatment satisfaction	NS difference, p=0.313	
			Drop-outs:						Body weight, kg	NS change	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures – 6 months	Effect sizes	Comments
		treatment or have diseases considered to interfere with the conduct of the study	Glucose: n=3; HI: n=9	To perform intensive diet and exercise therapies (details not given)				in either group	

G.4.1.4 Aspart (plus NPH) versus human insulin (plus NPH)

Table 194: HOME 1998 (ID 1021)

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
P. D. Home, A. Lindholm, B. Hylleberg, and P. Round. Improved glycemic control with insulin aspart: a multicenter randomized double-blind crossover trial in type 1 diabetic patients. UK Insulin Aspart	RCT - crossover 11 centres in the UK.	n=104 type 1 diabetes Inclusion criteria: type 1 diabetes Men only (as pending reproductive drug toxicology for aspart). 18-60 years BMI <29.0 kg/m2 HbA1c <9.0% Using unmodified pre-meal insulin + NPH at bedtime for at least 1 month before		All patients n=104	Aspart + NPH Aspart at meals NPH = Insulatard (once/day bedtime) Lispro taken immediatel	Regular human + NPH Regular human = Actrapid at meals NPH = Insulatard (once/day bedtime) Human insulin taken immediately	4 weeks (each cross-over period)	Hypoglycaemia, no. of patients	AS: 16 HI: 24	Funding: NovoNordisk Risk of bias: Randomisation = Unclear (details not given) Allocation concealment Unclear (details not given) No wash-out period Double blind ITT analysis
			Age, years (SD)	34.3 (8.6)						
			Women, %	0%				Hypoglycaemia, episodes	AS: 20 HI: 44	
			BMI, kg/m2 (SD)	25.3 (2.3)						
			Diabetes, mean years (SD)	14.8 (8.7)				-	-	
			HbA1c,	7.1 (1.0)						

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Study Group. Diabetes Care 21 (11):1904-1909, 1998. REF ID: HOME 1998 (ID 1021)		study Exclusion criteria: Active proliferative retinopathy or nephropathy Recurrent severe hypoglycaemia Insulin resistance Other systemic diseases Drug abuse	% (SD) Drop-outs: n=14		y before meals BOTH GROUPS: Doses adjusted according to target Blood glucose values	before meals		- 	- 	Powered study (fructosamine) Drop-outs = acceptable (<20%) Not done ANCOVA analysis (ANC best for cross-over studies).

Table 195: TAMAS 2001

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Gy Tamas, M. Marre, R. Astorga, I. Dedov, J. Jacobsen, and A. Lindholm. Glycaemic control in type 1	RCT 48 centres in 11 countries across Europe and Israel	n=423 Inclusion criteria: 18-70 years type 1 diabetes (WHO criteria) for at least 2 years treatment by intensified meal-		Aspart n=213	HI=213	Aspart + NPH Aspart = Novorapid (before meals) NPH = Insulatard	Human Insulin + NPH Human insulin = Actrapid (before meals) NPH =	12 weeks data collected (but 64 weeks of treatment – final 64 week results	HbA1c, final value, % (SE)	AS: 8.02 (0.05) HI: 8.18 (0.05)	Funding: Not mentioned Risk of bias: Randomisation = unclear (no details given) Allocation concealment = adequate (
			Age, years mean (SD)	35.6 (11.4)	36.1 (11.7)						
			Women, %	42%	45%				Major hypoglycaemia, episodes	AS: 32 HI: 31	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
diabetic patients using optimised insulin aspart or human insulin in a randomised multinational study. Diabetes Res.Clin.Pract. 54 (2):105-114, 2001. REF ID: TAMAS 2001		time + Basal insulin regimen BMI ≤35 kg/m2 HbA1c 7-10% Exclusion criteria: Requirement of >1.4 U/kg/day insulin Active proliferative retinopathy or nephropathy Recurrent severe hypoglycaemia or hypo unawareness Significant CV or hepatic disease Systemic corticosteroid treatment Pregnant Abusing drugs	BMI, kg/m2, mean	24.2	24.0	(twice or 3 times/day) Aspart to be injected within 0-5 minutes before meals	Insulatard (twice or 3 times/day) HI to be injected within 30 minutes before meals	nor given)	Major hypoglycaemia, no. of patients	AS: 15 HI: 17	central telephone voice response system) Blinding = open label ITT analysis (LOCF) No mention of powering Drop-outs = acceptable (<20%)
			Body weight, kg (SD)	71.2 (12.3)	69.9 (11.3)				DTSQ (score 0-6)	MD: -0.33 (95% CI -0.56 to -0.10; p=0.005 Aspart SS lower – ie. Asp perceived high blood glucose levels to be less marked than people on HI.	
			Diabetes, mean years (SD)	14.0 (9.1)	14.2 (9.2)						
			HbA1c, % (SE)	8.36 (0.05)	8.29 (0.05)						
			Drop-outs: AS: n=5; HI: n=11			BOTH GROUPS: Dose adjustment algorithm; targets for blood glucose control			Treatment satisfaction	NS difference between groups	

Table 196: NIELSEN 1995 (ID 1034)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
F. S. Nielsen, L. N. Jorgensen, M. Ipsen, A. I. Voldsgaard, and H. H. Parving. Long-term comparison of human insulin analogue B10Asp and soluble human insulin in IDDM patients on a basal/bolus insulin regimen. Diabetologia 38 (5):592-598, 1995. NIELSEN 1995 (ID 1034)	RCT - crossover Single centre, Denmark	n=21 type 1 diabetes Inclusion criteria: IDDM Men only 18-40 years Duration >1 year Treated with MDI >6 months BMI <27.0 kg/m2 HbA1c <10.0% Stable metabolic control (HbA1c varying <1% for previous 6 months) Exclusion criteria: History of hypo. Unawareness Local lipodystrophy Urinary albumin excretion >400mg/24h Proliferative retinopathy Other medication Concurrent disease		All patients n=21	Aspart + NPH Aspart at meals NPH = Protaphane (once/day bedtime) Aspart taken <5 minutes before meals	Regular human + NPH Regular human = Actrapid at meals NPH = Protaphane (once/day bedtime) Human insulin taken <5 minutes before meals	8 weeks treatment (each cross-over period)	HbA1c, final value (SD)	AS: 7.7 (0.9) HI: 7.8 (0.6)	Funding: NovoNordisk Risk of bias: Randomisation = Unclear (details not given) Allocation concealment Unclear (details not given) No wash-out period Double blind ITT analysis Powered study (HbA1c) Drop-outs = none Not done ANCOVA analysis (ANC best for cross-over studies).
			Age, years median (range)	28 (23-33)				Severe hypoglycaemia, episodes	AS: 0 HI: 3 p=NS	
			Women, %	0%				-	-	
			BMI, kg/m2 (SD)	23.6 (1.8)				-	-	
			Diabetes, median years (range)	111 (2-28)						
			HbA1c, % (SD)	8.0 (1.2)						
			Drop-outs: None		BOTH GROUPS: Doses adjusted according to target Blood glucose values					

Table 197: BROCK 2011 ()

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Jacobsen Brock, I, B. F. Vind, L. Korsholm, A. Flyvbjerg, J. Frystyk, J. J. Holst, H. Beck-Nielsen, and J. E. Henriksen. Counter-regulatory hormone responses to spontaneous hypoglycaemia during treatment with insulin aspart or human soluble insulin: a double-blinded randomized cross-over study. Acta Physiol. 202 (3):337-347, 2011. REF ID: BROCK 2011	RCT - crossover Single centre in Denmark.	n=16 type 1 diabetes Inclusion criteria: type 1 diabetes 18-60 years Duration >1 year Treated with MDI >6 months BMI 18-27.5 kg/m2 Use of soluble human insulin before all meals and NPH at bedtime for at least 3 months prior to study Exclusion criteria: Pregnancy Impaired vision Impaired renal or hepatic function Cardiac diseases Uncontrolled hypertension Hypoglycaemia unawareness		All patients n=16	Aspart + NPH Aspart = NovoRapidat meals NPH = twice/day (split dose between morning and eve)	Regular human + NPH Regular human = Actrapid at meals NPH = twice/day (split dose between morning and eve)	8 weeks treatment (each cross-over period)	HbA1c, final value (SD)	AS: 7.0 (1.2) HI: 7.0 (1.2)	Funding: NovoNordisk Risk of bias: Randomisation = Unclear (details not given) Allocation concealment Unclear (details not given) No wash-out period Double blind No mention of ITT analysis No mention of powering Drop-outs = acceptable (<20%) Not done ANCOVA analysis (ANC best for cross-over studies).
			Age, years mean (SD)	44.4 (8.2)						
			Women, %	18.8%				Hypoglycaemia, events	AS: 214 HI: 297	
			BMI, kg/m2 (SD)	24.6 (1.3)						
			Diabetes, mean years (SD)	19 (10)				Hypoglycaemia, events/patient/week	AS: 0.9 (0.1) HI: 1.1 (0.2)	
			HbA1c, % (SD)	7.8 (1.1)						
			Drop-outs: n=2					Nocturnal Hypoglycaemia, events	AS: 3 HI: 5	
					BOTH GROUPS: Doses adjusted according to algorithm target Blood glucose values			treatment satisfaction, VAS 0-6 (6=very satisfied)	NS difference	

Table 198: RASKIN 2000A

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures – 6 months	Effect sizes	Comments
P. Raskin, R. A. Guthrie, L. Leiter, A. Riis, and L. Jovanovic. Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. Diabetes Care 23 (5):583-588, 2000. REF ID: RASKIN 2000A	RCT 59 centres in USA and Canada	n=882 Inclusion criteria: 18-75 years type 1 diabetes for at least 18 months BMI ≤35 kg/m2 HbA1c ≤11% Exclusion criteria: Impaired hepatic, renal or cardiac function Recurrent major hypoglycaemia Active proliferative retinopathy Total daily insulin dose ≥1.4 IU/kg		Aspart n=596	HI=286	Aspart + NPH Aspart = (before meals) NPH = Novolin N (once/day - bedtime) Aspart to be injected immediately before meals	Human Insulin + NPH Human insulin = Novolin R (before meals) NPH = Novolin N (once/day - bedtime) HI to be injected within 30 minutes before meals	6 months (extra 6 months extension in n=714 patients)	HbA1c, final value, % (SE)	AS: 7.78 (0.03) HI: 7.93 (0.05)	Funding: Authors supported by NovoNordisk. Risk of bias: Randomisation = unclear (only says random in 2:1 ratio) Allocation concealment = unclear (no details given) Blinding = open label ITT analysis (LOCF) No mention of powering Drop-outs = acceptable (<20%) ANCOVA analysis done
			Age, years mean (SD)	38.9 (10.5)	39.9 (12.2)						
			Women, %	49%	47%				Major hypoglycaemia, episodes/patient year	AS: 0.91 HI: 1.13	
			BMI, kg/m2, mean	25.6	25.7				Major nocturnal hypoglycaemia, % of patients	AS: 4% HI: 8%	
			Diabetes, mean years (SD)	15.7 (9.7)	15.8 (9.3)						
			HbA1c, % (SE)	7.90 (1.13)	7.95 (1.25)	BOTH GROUPS: Dose adjustment to meet targets for blood glucose control <4% patients were treated with twice/day NPH					
			Drop-outs: AS: n=44 (7%); HI: n=23 (8%)								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures – 6 months	Effect sizes	Comments
		Pregnant, breastfeeding or not practicing contraception							

Table 199: HELLER 2004

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
S. R. Heller, S. Colagiuri, S. Vaaler, B. H. Wolffenbuttel, K. Koelendorf, H. H. Friberg, K. Windfeld, and A. Lindholm. Hypoglycaemia with insulin aspart: a double-blind, randomised, crossover trial in subjects with Type 1 diabetes. Diabet.Med. 21 (7):769-775, 2004.	RCT - crossover 19 centres in Europe and Australia	n=155 type 1 diabetes Inclusion criteria: type 1 diabetes 18-65 years Duration >2 years BMI ≤35 kg/m2 HbA1c ≤9.0% On human insulin (at meals) and NPH once/day or twice/day for 3 months before trial. Exclusion criteria: Impaired renal or		All patients n=155	Aspart + NPH Aspart = NovoRapidat meals NPH = Insulatard (once or twice/day) Aspart injected 0-5 minutes before meals	Regular human + NPH Regular human = Actrapid at meals NPH = Insulatard (once or twice/day) Aspart injected 0-5 minutes before meals	16 weeks treatment (each cross-over period)	HbA1c, final value (SD)	AS: 7.7 (0.8) HI: 7.7 (0.9)	Funding: NovoNordisk Risk of bias: Randomisation = good (computer generated) Allocation concealment = good (central telephone) No wash-out period Double blind Not ITT analysis Powered study (hypoglycaemia)
			Age, years mean (SD)	35.7 (9.4)						
			Women, %	-				Major hypoglycaemia, episodes	AS: 38 HI: 51	
			BMI, kg/m2 (SD)	24.0 (2.6)						
			Diabetes, mean years (SD)	-				Major hypoglycaemia, events/patient/ year	AS: 0.85 HI: 1.11	
			HbA1c, % (SD)	8.6 (1.1)						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: HELLER 2004		hepatic function Cardiac problems Uncontrolled hypertension Presence of progressed late-diabetic complications Drug or alcohol abuse Concurrent treatment with systemic corticosteroids	Drop-outs: n=16	BOTH GROUPS: Doses adjusted according to algorithm target Blood glucose values			Major nocturnal Hypoglycaemia, events	AS: 9 HI: 31	Drop-outs = acceptable (<20%) Not done ANCOVA analysis (ANC best for cross-over studies).

Table 200: HOME 2000 and BOTT 2003 x

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures – 6 months	Effect sizes	Comments
P. D. Home, A. Lindholm, and A. Riis. Insulin aspart vs. human insulin in the management of long-term	RCT 88 centres in Europe	n=1070 Inclusion criteria: Adults type 1 diabetes (WHO)		Aspart n=707	HI n=358	Aspart + NPH Aspart = NovoRapid (immediately before meals) NPH =	Soluble human insulin + NPH Human = Actrapid (30 minutes	6 months treatment	HbA1c, final value, % (SE)	ASP: 7.88 (0.03) HI: 8.0 (0.04)	Funding: NovoNordisk. Risk of bias: Randomisation = unclear (only says randomised)
			Age, years mean (SD)	38 (11)	38 (12)						
			Women,	45%	44%				Minor	ASP:	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures – 6 months	Effect sizes	Comments
blood glucose control in Type 1 diabetes mellitus: A randomized controlled trial. Diabet.Med. 17 (11):762-770, 2000. REF ID: HOME 2000 U. Bott, S. Ebrahim, S. Hirschberger, and S. E. Skovlund. Effect of the rapid-acting insulin analogue insulin aspart on quality of life and treatment satisfaction in		Diabetes duration ≥2 years Insulin treatment 1 year BMI <35 kg/m2 HbA1c ≤11.0% Exclusion criteria: Active proliferative retinopathy Nephropathy Recurrent severe hypoglycaemia. Significant CV disease Systemic corticosteroid treatment Requiring >1.4 U/kg/day	%			Insulatard (once or twice/day)	before meals) NPH = Insulatard (once or twice/day)		hypoglycaemia, no. of patients	563/707 HI: 270/358	Allocation concealment = unclear (no details given) Blinding = open label ITT analysis Sample size calculation met (HbA1c) Drop-outs = acceptable (<20%)
			BMI, kg/m2, mean (SD)	25.1 (3.1)	24.9 (3.9)				Minor hypoglycaemia, episodes	ASP: 10113 HI: 4322	
			Diabetes, mean years (SD)	15 (10)	15 (10)	BOTH GROUPS: Dose adjustment to meet targets for blood glucose control % of patients on once or twice/day NPH at end of trial was not reported in the paper. At baseline 40% were on >1/day. NOTE: QoL was only measured in a subset of patients. ASP: n=271, HI: n=148. DSQoL and DTSQ: HIGHER SCORE = better QoL for both			Minor hypoglycaemia, episodes/patient-year	ASP: 7.64 HI: 7.542	
			HbA1c, % (SD)	7.96 (1.16)	7.98 (1.17)				Major hypoglycaemia, no. of patients	ASP: 111/707 HI: 65/358	
			Drop-outs: Aspart: 4%; HI: 6%						Major hypoglycaemia, episodes	ASP: 314 HI: 152	
									Major hypoglycaemia, episodes/patient-year	ASP: 0.81 HI: 0.97	
									DTSQ total, points (SE) Max score=36	ASP: 32 (0.3), n=271 HI: 29.7	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures – 6 months	Effect sizes	Comments
patients with type 1 diabetes. Diabet.Med. 20 (8):626-634, 2003. REF ID: BOTT 2003		insulin Pregnant Drug abuse						(0.4), n=148	
							DSQoL total, change from baseline, between group differences	ASP: SS greater improvement compared to HI (p<0.0001)	

Table 201: HOME 2006 (TRIAL EXTENSION OF HOME 2000)

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures – 6 months	Effect sizes	Comments
PD. Home, P. Hallgren, KH. Usadel, T. Sane, J. Faber, V. Grill, and HH. Friberg. Pre-meal	RCT extension (OF Home 2000 study) Completers from Germany, Switzerland,	n=753 Inclusion criteria: Adults type 1 diabetes (WHO) Diabetes duration ≥2		Asp n=567	HI n=186	Aspart + NPH Aspart = NovoRapid (immediately before meals) NPH =	Soluble human insulin + NPH Human = Actrapid (30 minutes before	30 months treatment extension (ie. 36 months total treatment); however data used was for 30 months	HbA1c, final value, % (SE)	ASP: 8.09 (0.04) HI: 8.25 (0.07)	Funding: NovoNordisk. Risk of bias: Randomisation = unclear (no details) Allocation concealment = unclear (no
			Age, year mean (SD)	38 (11)	40 (12)						
			Women, %	73%	69%				Minor hypoglycaemia, no. of patients	ASP: 488/567 HI:	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures – 6 months	Effect sizes	Comments
insulin aspart compared with pre-meal soluble human insulin in type 1 diabetes. Diabetes Res.Clin.Pract. 71 (2):131-139, 2006. REF ID: HOME 2006	Austria and the UK	years Insulin treatment 1 year BMI <35 kg/m2 HbA1c ≤11.0% Exclusion criteria: Active proliferative retinopathy Nephropathy Recurrent severe hypoglycaemia. Significant CV disease Systemic corticosteroid treatment Requiring >1.4 U/kg/day insulin Pregnant Drug abuse				Insulatard (once or twice/day)	meals) NPH = Insulatard (once or twice/day)	total treatment because Aspart became commercially available in the respective countries at various times between 30 and 36 months.		153/186	details given) Blinding = open label ITT analysis Sample size calculation met (HbA1c) Drop-outs = unacceptable (fine for longer trial duration, but differential between two arms is >10%; due to ineffective treatment in HI arm).
			BMI, kg/m2, mean (SD)	25.1 (3.1)	24.8 (2.9)				Minor hypoglycaemia, episodes	ASP: 25253 HI: 6543	
			Diabetes, mean years (SD)	14.8 (10.2)	15.6 (11.0)	BOTH GROUPS: Dose adjustment to meet targets for blood glucose control % of patients on once or twice/day NPH at end of trial was not reported in the paper. At baseline 40% were on >1/day.			Minor hypoglycaemia, episodes/month	ASP: 2.46 HI: 2.03	
			HbA1c, % (SD)	Values from end of the previous trial (6 months)					Major hypoglycaemia, no. of patients	ASP: 162/567 HI: 58/186	
			Drop-outs: Aspart: 17%; HI: 32%; main reason for difference was due to ineffective therapy in the HI group.						Major hypoglycaemia, episodes	ASP: 820 HI: 261	
									Major hypoglycaemia., episodes/month	ASP: 0.08 HI: 0.08	

G.4.1.5 Glulisine (plus glargine) versus human insulin (plus glargine)

Table 202: GARG 2005

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures – 6 months	Effect sizes	Comments
S. K. Garg, J. Rosenstock, and K. Ways. Optimized Basal-bolus insulin regimens in type 1 diabetes: insulin glulisine versus regular human insulin in combination with Basal insulin glargine. Endocr Pract 11 (1):11-17, 2005. REF ID: GARG 2005	RCT Multicentres in USA, Canada and Australia	n=860 Inclusion criteria: ≥18 years type 1 diabetes Required continuous insulin treatment from diagnosis BMI ≤35 kg/m2 HbA1c 6.0-11% Exclusion criteria: Active proliferative retinopathy History of		GLU (pre) n=286	GLU (post) n=296	HI n= 278	Glulisine (pre-meal) + GLARGINE Glulis = (0-15 minutes before meals) GLARGINE = Lantus (once/day - bedtime)	Human Insulin + GLARGINE Regular human insulin (30-45 minutes before meals) GLARGINE = Lantus (once/day - bedtime)	12 weeks treatment	HbA1c, change from baseline (98.8% CI)	GPre: -0.26 (-0.02 to -0.29) GPost: -0.11 (-0.11 to -0.16) HI: -0.13 (-0.26 to -0.01)	Funding: Sanofi-Aventis. Risk of bias: Randomisation = unclear (only says random in 1:1:1 ratio) Allocation concealment = unclear (no details given) Blinding = open label ITT analysis Sample size calculation Drop-outs = acceptable (<20%)
			Age, years mean (SD)	40.8 (11.9)	39.8 (11.8)	40.2 (11.4)						
			Women	44%	47%	50%						
			BMI, kg/m2, mean	27.0	27.3	27.0						
			Diabetes, mean years (SD)	20.0 (11.4)	20.2 (11.5)	19.4 (11.2)	Glulisine (post-meal) + GLARGINE Glulis = (20 minutes after starting or immediately after meals; whichever came first)			Body weight, kg change	GPre: +0.3 GPost: -0.3 HI: +0.3	
			HbA1c, % (SE)	7.7 (0.056)	7.7 (0.055)	7.6 (0.057)				Symptomatic hypoglycaemia, no. of patients	GPre: 234 GPost: 248 HI: 228	
			Drop-outs:							Symptom	GPre:	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures – 6 months	Effect sizes	Comments
		seizure disorders Hypersensitivity to insulin or analogues Impaired renal or hepatic function Pancreatectomy or islet cell transplant History of alcohol or drug abuse Any other clinically relevant physical or psychological medical condition	Overall: n=69	GLARGINE = Lantus (once/day - bedtime)			atic hypoglycaemia, rate/patient/month (SD)	3.46 (4.11) GPost: 3.71 (4.97) HI: 3.49 (4.16)	
							Severe hypoglycaemia, no. of patients	GPre: 24 GPost: 25 HI: 28	
							Severe hypoglycaemia, rate/patient/month (SD)	GPre:0.05 (0.24) GPost: 0.05 (0.23) HI: 0.13 (0.96)	
							Nocturnal hypoglycaemia., no. of patients	GPre: 161 GPost: 156 HI: 151	
							Nocturnal hypoglycaemia., rate/patie	GPre: 0.64 (0.99) GPost:	
				BOTH GROUPS: Dose adjustment to meet targets for blood glucose					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures – 6 months	Effect sizes	Comments
							nt/month (SD)	0.71 (1.19) HI: 0.71 (1.086)	

G.4.2 Long-acting insulin

G.4.2.1 Glargine versus NPH

Table 203: Rosenstock 2000

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: ROSENSTOCK 2000	RCT USA study	n=256 Inclusion criteria: type 1 diabetes 18-70 years old BMI 18-28 HbA1c <10% Post-prandial		Glarg 30 n=82	Glarg 80 n=86	NPH n=88	Glargine 30 (ZnCl 30 micrograms/ml) ITT: n=81 ACA: n=81 Contained the recombinant human insulin analogue equimolar to	NPH ITT: n=88 ACA: n=87 SD abdominal injection once/day at bedtime OR twice/day (before breakfast and	4 weeks treatment	Hypoglycaemic episodes	Glarg30 : 97.6% Glarg80 : 100% NPH: 93.2%	Funding: None mentioned but authors have grants from Pharma Risk of bias: Randomisation = unclear (as details
			Age, years (SD)	37.5 (11.7)	37 (11.5)	37.9 (12.5)						
			Women, %	49	49	47				HbA1c, change from baseline, % (SD)	Glarg30 : -0.4 (0.48)	
			Diabetes,	16.7 (11.3)	15.8 (10)	16.3 (10.8)						

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		serum C-peptide <0.2 pmol/ml Been on basal bolus MDI for at least 2 months Exclusion criteria: None given	mean years (SD)				100 U/ml human insulin SD abdominal injection once/day at bedtime Initial dose was to be equal to the total daily dose of NPH insulin the patient was using at the time of randomisation to treatment. ---------- Glargine 80 (ZnCl 80 micrograms/ml) ITT: n=86 ACA: n=85 As for glargine 30	at bedtime) – based on the patient's pre-study regimen. NPH contained 100 U/ml recombinant human insulin.			Glarg80: -0.4 (0.49) NPH: -0.4 (0.48)	not given) Allocation concealment = not mentioned Blinding = n/a for NPH vs. Glarg but double for glargine vs. glargine. NPH was not possible to blind as drug is cloudy. ITT analysis (patients with pre-treatment and during treatment value) Sample size calculation based on FPG Drop-outs = acceptable (<20%)
			HbA1c, % (SD)	7.8 (1.1)	7.9 (1.2)	8.0 (1.2)						
			NS differences between groups for any of the baseline characteristics Drop-outs (6 months): n=2 (n=1 in each group)									
							BOTH GROUPS: Injections of regular insulin were					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
				administered before meals according to patient's usual practice. Basal insulin doses were adjusted during titration phase to maintain FBG between 4-7 mmol/litre (72-126 mg/dl) Dose was increased (or reduced) if higher (or lower) FPG values were obtained over a 2-4 day period in the absence (or presence) of nocturnal hypoglycaemia. Dose of regular insulin was adjusted every 2–4 days if needed to achieve target ranges (basis of 1–4 U per meal). Premeal and bedtime target blood glucose were 4–7 mmol/litre (72–126 mg/dl) and 6–8 mmol/litre (100–144 mg/dl).					

Table 204: PIEBER 2000

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
	RCT	n=333		Glargine (30	NPH	4	Severe	G30: 7/110	Funding:

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: PIEBER 2000	Austria /France study	(n=110 Glarg 30, n=113 Glarg 80 and n=110 NPH) Inclusion criteria: type 1 diabetes Been receiving insulin therapy for 1 year A basal-bolus regimen of NPH insulin once daily at bedtime (n = 177) or twice daily in the morning and at bedtime (n = 156) plus regular human insulin before meals was used for at least 2 months Exclusion criteria: presence of		Glarg 30 n=110	Glarg 80 n=113	NPH n=110	micrograms of zinc) Once daily (bedtime) ITT: n=110	Once daily (bedtime) or twice daily (morning and bedtime) ITT: n=110 (47.3% on twice/day – thus counted as once/day as most started on once/day)	weeks treatment	hypoglycaemia., N At 4 weeks treatment	G80: 5/113 NPH: 5/110	None mentioned but authors have grants from Pharma Risk of bias: Randomisation = unclear (as details not given) Allocation concealment = not mentioned Blinding = not possible for NPH vs. glargine as NPH cloudy. Double blind for glargine vs. glargine Unclear if ITT analysis (seems like some missing data but not mentioned)
			Age, years (SD)	35.6	37.5	35.7	Glargine (80 micrograms of zinc) Once daily (bedtime) ITT: n=113					
			Women, %	44	34	38				HbA1c, % (SE)	G30: 7.85 ± 0.10 (n=110) G80: 7.80 ± 0.10 (n=112) NPH: 7.79 ± 0.09 (n=109)	
			Diabetes, median years (range)	11.0 (1.0–36.0)	8.0 (1.0–48.0)	11.0 (2.0–48.0)	IN ALL 3 GROUPS: Bedtime insulin was injected into the abdomen between 2100 and 2300, and injection time was kept as stable as possible throughout the study. The first 3 weeks of the treatment phase were used to adjust the daily basal insulin dose according a titration scheme (FBG from 4 to 7 mmol/litre without					
			HbA1c, % (SE)	8.09 ± 0.11	7.96 ± 0.11	7.85 ± 0.11				HbA1c, % (SE) Change from baseline	G30: 0.25 ± 0.05 (n=110) G80: 0.15 ± 0.05 (n=112) NPH: 0.03 ±	
			Drop-outs (6 months): None mentioned									

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		known proliferative diabetic retinopathy impaired hepatic or renal function history of hypoglycaemia unawareness		nocturnal hypoglycaemia); basal insulin then was maintained during the final week of treatment. The dose of regular insulin was adjusted according the patients' habits, the premeal blood glucose concentration, and the carbohydrate content of the meal.				0.05 (n=109)	Powering not mentioned Drop-outs = acceptable (<20%)
							AEs, N during 4 weeks treatment (injection site reactions)	G30: 3 G80: 10 NPH: 3	
				Concomitant medication: In all groups patients received regular human insulin before meals					

Table 205: RATNER 2000

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: RATNER 2000	RCT Multicentre, USA.	n=534 Inclusion criteria: type 1 diabetes		Glarg n=264	NPH n=270	Glargine (once/day before bedtime) ITT: n=264	NPH (once or twice daily ITT: n=270	28 weeks treatment (6 months)	Severe hypo, at least 1 episode, %	Glarg: 1.9% NPH: 5.6% p=0.0117	Funding: Grant from Hoechst Marion Roussel
			Age,	38.2	38.9				HbA1c/GH	Glarg:	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		18–80 years old Postprandial C-peptide levels of ≤0.5 nmol/litre Duration at least 1 year GHb ≤12.0%. Exclusion criteria: treatment with antidiabetic drugs other than insulin within 1month of study entry pregnancy impaired hepatic or renal function	years (SD)	(12.2)	(11.9)				b, % (SEM) change from baseline	-0.16 (0.05)/n= 256 NPH: -0.21 (0.05)/n= 262	Risk of bias: Randomisation = unclear (just says randomised) Allocation concealment = not mentioned Blinding = not possible as NPH cloudy) ITT analysis Powered study (GHb) Drop-outs = acceptable (<20%)
			Women, %	47	52	In both groups: dose titration of both basal insulins was based on capillary fasting blood glucose (FBG) levels. Goal was premeal blood glucose conc. 4.4–6.7 mmol/litre (80–120 mg/dl). Dose increases were made if morning capillary FBG levels consistently >6.7 mmol/litre with no symptomatic nocturnal hypoglycaemia. Dose decreases were made if morning capillary FBG levels were <4.4 mmol/litre or if symptomatic nocturnal hypoglycaemia. was evident			Injection site reactions, %	Glarg: 15.2% NPH: 10.4%	
			Diabetes duration, years (SD)	17.9 (11.7)	16.9 (10)						
			HbA1c/GHb, % (SD)	7.6 (1.19)	7.7 (1.2)				Injection site pain, N	Glarg: 10/264 NPH: 3/270 All pain was rated as mild	
			There was NS difference between groups for all of the baseline characteristics Drop-outs: Discontinued drug - Glarg: 11.7%, NPH: 8.1%								
						Concomitant medication: Both gps used regular insulin approx. 30 min before meals to meet prandial insulin requirements.			Withdrawals due to AEs, %	Glarg: 8/264 NPH: 3/270	

Table 206: RASKIN 2000

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: RASKIN 2000	RCT 60 centres, USA.	n=619 Inclusion criteria: type 1 diabetes 18–80 years old Been receiving NPH at least 1 year and premeal insulin lispro at least 3 months Serum C-peptide levels of ≤0.5 nmol/litre in presence of glucose ≥99.0 mg/dl (5.5 mmol/litre) GHb ≤12.0%. Exclusion criteria: Treatment with antidiabetic drugs other than insulin within 1mth of study pregnancy impaired hepatic or renal function		Glarg n=310	NPH n=309	Glargine (once/day before bedtime) ITT: n=310	NPH (once or twice daily ITT: n=309	16 weeks treatment (4 months)	Severe hypo, n	Glarg: 20/310 NPH: 60/309	Funding: Grant from Hoechst Marion Roussel Risk of bias: Randomisation = unclear, telephone Allocation concealment = unclear, telephone Blinding = not possible as NPH cloudy) ITT analysis = yes. Not mentioned but all numbers included in calculation Powering not mentioned Drop-outs = acceptable (<20%)
			HbA1c/GHb, % (SD)	7.7 (1.2)	7.7 (1.1)				HbA1c/GHb, % (SD) final value	Glarg: 7.5 (1.19) NPH: 7.60 (1.14)	
			Age, years (SD)	38.9 (12.2)	39.5 (12.2)	In both groups: Starting dosages of glargine and NPH were based on prior NPH insulin dosage on a unit-for-unit basis but were left to the discretion of the investigator. Investigators were informed of results of phase II comparative studies, which suggested a 10% decrease in the insulin glargine dose compared with total dosage in patients receiving NPH insulin twice a day. Thereafter, glargine and NPH doses were to be individually titrated to obtain a target fasting blood glucose <120.6 mg/dl (6.7 mmol/litre).			AEs – Cancer (but not study drug related)	Glarg: 1/310 NPH: 0/309	
			Diabetes duration, years (SD)	18.7 (11.5)	18.4 (11.8)						
			Women, %	49.4	47.6				Injection site pain, %	Glarg: 6.1% NPH: 0.3%	
			BMI, kg/m2	25.5 (3.4)	25.7 (3.9)						
			There was NS difference between groups for all of the baseline characteristics except once daily insulin use before study was SS higher in glargine group Drop-outs:						Body weight, change from baseline, kg	Glarg: +0.12 NPH: +0.54; p=0.034	
						Concomitant medication:			Withdraw	Glarg:	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Glarg: n=15 (4.8%) NPH: n=16 (5.2%)	Both gps continued to administer individually titrated insulin lispro before meals.			als due to AEs, N	0/310 NPH: 2/309	

Table 207: HOME 2005

Reference	Study type	Number of patients	Patient			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: HOME 2005	RCT 63 centres, across Europe.	n=602 randomised; n=585 treated. Inclusion criteria: type 1 diabetes 17-77 years old Treated with insulin for at least 1 year Serum post-prandial C-peptide levels of <0.5 nmol/litre in presence of blood glucose ≥100 mg/dl (5.5		Glarg n=292	NPH n=293	Glargine (once/day before bedtime) ITT: 301 ACA: n=292 Dose determined on 1st treatment day by the total basal dose the day before. Protocol of dose titration by ≥1% according to SMBG (FBG) levels. Nominal target of 80-120	NPH (once or twice daily ITT: 301 ACA: n=293 Once or twice daily injection according to person's previous treatment regimen. Starting evening doses were same as those on the previous day,	28 weeks treatment (6 months)	HbA1c, % (SD) change from baseline	Glarg: 0.21 (0.05) NPH: 0.10 (0.05)	Funding: Aventis Pharma Risk of bias: Randomisation = unclear; just says randomised. Allocation concealment = telephone central randomisation, independent agency Blinding = not possible as NPH cloudy) Not mention ITT
			Age, years (SD)	39 (12)	39 (12)				AEs – Severe hypoglycaemia: at least 1 episode, N (%)	Glarg: 31 (10.6) NPH: 44 (15)	
			Diabetes duration, years (SD)	16 (12)	15 (9)						
			Women, %	45	43				Injection site reaction, n (%)	Glarg: 3 (1) NPH: 6 (2)	
			Weight, kg (SD)	73.2 (11.8)	74.8 (12.5)						
			HbA1c,	7.9	8.0						

Reference	Study type	Number of patients	Patient			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		mmol/litre) Exclusion criteria: None given	% (SD)	(1.2)	(1.2)	mg/dL averaged over at least 2-4 days and absence of nocturnal hypoglycaemia. All adjustments at investigator and diabetic's discretion.	with subsequent adjustment as described for insulin glargine group. Morning insulin was adjusted as required.				analysis. Powering not mentioned Drop-outs = acceptable (<20%)
			The groups were similar for all of the baseline characteristics. Drop-outs: Glarg: n=16 (5%) NPH: n=21 (7%) Main reason was they did not wish to continue.						Withdrawals due to AEs, n/N	Glarg: 2/292 NPH: 2/293	
						Concomitant medication: Both gps used unmodified human insulin before meals, according to their individual habit.					

Table 208: BOLLI 2009

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: BOLLI 2009	RCT 21 centres, Italy	n=175 Inclusion criteria: type 1 diabetes 18–60 years old >3 years duration Been receiving intensive insulin treatment: NPH twice or more		Glarg n=85	NPH n=90	Glargine (once/day before bedtime) using pen ITT: n=85 ACA: n=78	NPH (twice or more daily) using pen ITT: n=90 ACA: n=74	24 weeks treatment (5 months)	HbA1c, final value, % (SD)	Glarg: 7.26 (0.74) NPH: 7.26 (0.98)	Funding: Sanofi-Aventis Risk of bias: Randomisation = unclear. Just says randomised. Allocation
			Age, years (SD)	35.5 (10.6)	37.0 (9.4)	In both groups: Dinnertime glargine and bedtime NPH were titrated to achieve			Serious (not severe) hypoglycae	Glarg: 1.01 (1.07)	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		daily, and lispro or regular human insulin at mealtimes. Fasting plasma C-peptide levels of <0.1 nmol/litre HbA1c 7-9%. BMI 18-26 kg/m2. Exclusion criteria: Micro or macro-angiographic complications				FBG target value of 90-120 mg/dL, but avoiding nocturnal hypoglycaemia. Lunchtime dose of NPH was adjusted to a target pre-dinner BG 90-120 mg/dl.			mia. Episodes/patient/month, mean (SD) final value	NPH: 0.88 (1.04)	concealment = not mentioned. Blinding = not possible as NPH cloudy) Not ITT analysis = not true ITT (had to have at least one baseline visit and one dose of study drug). Under powered (for FBG) Drop-outs = acceptable (<20%)
			Diabetes duration, years (SD)	12.9 (8.3)	14.8 (9.6)						
			Women, %	44	46				QoL: WED, median (IQR) : Impact, Satisfaction, general worries, Diabetes-related worries	NS difference between groups for any of the scores except diabetes worries was SS better in the glargine group.	
			Weight, kg (SD)	67.5 (9.4)	68.4 (10.4)	Concomitant medication: Both groups took insulin lispro. Dose of lispro was adjusted to a target post-prandial BG of <140 mg/dL. Additional doses of lispro (1 or 2 U) were also used to correct unexpected hyperglycaemia.					
			HbA1c, % (SD)	7.8 (0.7)	7.8 (0.6)						
			There was NS difference between groups for any of the baseline characteristics Drop-outs: Glarg: n=7 (8%) NPH: n=12 (13%) plus additional n=4 withdrew consent and did not participate (thus n=16 did not complete = 18%) Outcomes: WED questionnaire – quality of life Well-Being Enquiry for Diabetics. 50 item questionnaire on symptoms, discomfort, serenity and impact. Low score = better						Withdrawals due to AEs, N	Glarg: 0/85 NPH: 0/90	

Table 209: FULCHER 2006

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: FULCHER 2006	RCT 9 centres, Australia	n=125 Inclusion criteria: type 1 diabetes 18–80 years old At least 1 year of insulin treatment Inadequate glycaemic control (HbA1c ≥8%). Exclusion criteria: Nightshift workers Impaired hepatic function Sensitivity to study drugs or related drugs Clinically relevant physiological or psychological medical conditions. Use of systemic corticosteroids and BG lowering drugs was not permitted.		Glarg n=65	NPH n=63	Glargine (once/day before bedtime) using pen ITT: n=65 ACA: ?	NPH (once/day before bedtime) using pen ITT: n=63 ACA: ?	30 weeks treatment (7 months)	HbA1c, change from baseline, %	Glarg: -0.89 NPH: -0.67	Funding: Aventis Risk of bias: Randomisation = unclear. Just says randomised. Allocation concealment = not mentioned. Blinding = Single. Double blinding not possible as NPH cloudy. Not ITT analysis = not true ITT (had to have at least one dose of study medication). But unclear if ITT as some outcomes it is out of the
									HbA1c, final value, %	Glarg: 8.3 NPH: 9.1	
			Age, years (SD)	41.6 (12.9)	39.3 (13.9)	In both groups: targets were FBG 5.5 mmol/litre, pre-prandial BG 3.9-6.7 mmol/litre, 2h post-prandial BG <8 mmol/litre and 3am BG >3.6 mmol/litre. Basal insulin dose adjustments were made twice/week during titration phase, and fortnightly in the treatment follow-up phase, based on FBG measurements.			Severe hypoglycaemia. Events/100 patient days	Glarg: 0.87 NPH: 0.99	
			Diabetes duration, years (SD)	17.9 (10.5)	17.1 (9.7)						
			Women, %	61	60				At least 1 symptomatic hypoglycaemia episode, n/N	Glarg: 65/65 NPH: 59/63	
			BMI, kg/m2 (SD)	27.0 (3.6)	26.0 (3.9)	Concomitant medication: Both groups took preprandial insulin lispro three times/day.					
			HbA1c, % (SD)	9.2 (1.1)	9.7 (1.3)				Injection site reactions, n/N	Glarg: 5 NPH: 7/	
			There was NS difference between groups for any of						Body weight,	Glarg: +1.97	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			the baseline characteristics except HbA1c was SS higher in the NPH group. Drop-outs: Glarg: n=4 (6.4%) NPH: n=14 (22%) None were due to AEs				change from baseline, kg Withdrawals due to AEs, N	NPH: +2.34 Glarg: 0/65 NPH: 0/63	total. Powering not mentioned Drop-outs = not acceptable (>20% in NPH and large differential between groups)

Table 210: CHATTERJEE 2007

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
CHATTERJEE 2007	RCT UK study	n=58 randomised, n=60 recruited. Initially n=25 glargine, and n=33 NPH then crossed over. Inclusion criteria: type 1 diabetes 18–75 years old At least 6 months		n=60	Glargine (once/day, bedtime) using pen	NPH (twice/day, 30 minutes before breakfast and evening meal) using pen	16 weeks treatment (4 months)	HbA1c, final value, %	Glarg: 8.07 NPH: 8.26 MD: -0.19, 95% CI -0.36 to -0.01. p=0.04	Funding: Novo Nordisk and Aventis Risk of bias: Randomisation = unclear. Just says randomised. Allocation concealment = poor -
			Age, years (SD)	42.9 (12.5)						
			Women, %	42	In both groups: when switching from glargine to NPH dose was increased by 20% to compensate for switching from a once/day to			Severe hypoglycaemia. N	Glarg: 1/58 NPH: 1/58	
			Diabetes duration,	18.2 (11.8)				DTSQ	NS difference between	

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		diabetes Previously using twice/day or MDI inulin. BMI <45 Baseline HbA1c 6-11% Ability and willingness to perform SMBG. Exclusion criteria: None given.	years (SD)		twice/day regimen. When switching from NPF to glargine, dose was decreased by 20% to compensate for switching from a twice/day to once/day regimen. Dose was adjusted according to local algorithm. Targets were pre-prandial 4-6.7 mmol/litre, and 2h post-prandial and bedtime <8 mmol/litre.				groups for perception of hyper or hypo - glycaemia. Greater satisfaction with glargine (4 points difference) vs. NPH.	consecutively numbered sealed envelopes. Open. Double blinding not possible as NPH cloudy. 4-week run-in period but no mention of washout between crossing over Not ITT analysis. Powered study (HbA1c) Drop-outs = acceptable (<20%)
			Weight, kg (SD)	81.0 (14.0)						
			HbA1c, % (SD)	8.5 (1.2)	Concomitant medication: Both groups took insulin aspart as the rapid-acting insulin.					
								ADDQoL	NS difference between groups. P=0.08	
			Drop-outs: Glarg: n=4 (16%) NPH: n=2 (6%) None were due to AEs					Body weight, kg	Glarg: 81.86 NPH: 81.92. MD -0.24, 95% CI -0.87 to 0.39. p=0.45	

Table 211: PORCELATTI 2004

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: PORCELLATTI 2004	RCT 1 centre in Italy	n=121 Inclusion criteria: type 1 diabetes Fasting plasma C-peptide <0.15nmol/litre On 4 times daily NPH insulin plus mealtime insulin lispro for at least 2 years Exclusion criteria: Detectable microangiopathic complication Autonomic neuropathy		Glarg n=61	NPH n=60	Glargine (once/day: dinner time) Titrated to blood glucose 6.4-7.2mmol/litre (fasting, before meals and at bedtime) and 8.0-9.2 after meals.	Continue NPH (4/day) Titrated to same as Glargine group	1 year	HbA1c, final %	Glargine: 6.7 (0.1) at 4 months vs. NPH: 7.1 (0.1) at 12 months	Funding: National Ministry of Scientific Research and University of Perugia (no pharmaceutical sponsorship) Risk of bias: Randomisation = adequate (computer generated) Allocation concealment = adequate (independent person; locked unreadable computer file) Blinding = no (open study) ITT analysis = yes Sample size: powered for HbA1c Drop-outs =
			Age, years (SD)	36 (1.0)	34 (1.0)						
			Women, %	44.3	45.0						
			Diabetes duration, years (SD)	13 (0.3)	15 (0.3)	Concomitant medication: Both groups took insulin lispro as the rapid-acting insulin.			Severe hypoglycaemia	None	
			Weight, BMI (SD)	22.9 (0.14)	23.2 (0.15)				Mild hypoglycaemia, episodes/patient-month	Glargine: 7.2 (0.5) NPH: 13.2 (0.6)	
			HbA1c, % (SD)	7.1 (0.1)	7.1 (0.2)				Body weight	No change with either treatment	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
									acceptable (none)

G.4.2.2 Degludec versus glargine

Table 212 MATHIEU 2013

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
C Mathieu, P Hollander, B Miranda-Palma, J Cooper, E Franek, D Russell-Jones, J Larsen, SC Tamer, SC. Bain, and Flex T. BEGIN. Efficacy and safety of insulin degludec in a	RCT Multinational	n=493 randomised (3 arm trial but only using the 2 relevant arms) Inclusion criteria: type 1 diabetes Adults ≥18 years On basal-bolus therapy HbA1c ≤ 10% BMI		Degludec n=165 44.5 (13.1) 43% 20.0 (12.5) 7.7 (0.9)	Glargine n=164 44.1 (12.6) 48% 18.2 (11.9) 7.7	Degludec Once/day, titrated to fasting blood glucose targets. Degludec – Forced-flex regimen Given Mon, Wed, Fri mornings, and Tues, Thurs, Sat and Sun evenings.	Glargine Once/day, titrated to fasting blood glucose targets.	26 weeks + extension (extension data not using here as mixed randomised groups)		Deg	Glarg	Funding: NovoNordisk Risk of bias: Randomisation = unclear (no details given) Allocation concealment = adequate (central activated voice response) Blinding = no (open study) ITT analysis =
			Mean (SD) age (year)						HbA1c, % (SD) change from baseline	-0.41 (0.71)	-0.58 (0.72)	
			Female (%)						Weight, kg (SD) change from baseline	0.8 (2.5)	1.6 (3.7)	
			Duration of diabetes (year)						Severe hypo, no. of patients	21/165	16/161	
									Hypo, no. of patients	164/165	156/161	
									Nocturnal hypo, no. of	121/165	117/161	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
flexible dosing regimen vs. insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. J.Clin.Endocrinol.Metab. 98 (3):1154-1162, 2013. REF ID: MATTHIEU 2013		≤35kg/m2 Basal insulin allowed at screening: Glargine, detemir, or NPH (as 1 or 2 daily injections) Bolus insulin allowed at screening: 3 or more daily injections of (aspart, lispro, glulisine, or human) Exclusion criteria: Any other antidiabetes glucose lowering drug within past 3 months Initiation or change in any systemic treatment	HbA1c (%)		(0.9)	ALL GROUPS: mealtime insulin bolus Aspart.			patients.			yes Powered study for HbA1c. Drop-outs = acceptable (<20% in each arm, and <10% differential between groups)
									AEs, events per 100-pt years of exposure	550	527	
									SAEs, % of patients	4.2% (n= approx. 7/165)	5.0% (n= approx. 8/161)	
									Injection site reactions, no. of patients	3/165	4/161	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
		which could interfere with glucose metabolism CVD within past 6 months Uncontrolled severe Hypertension Impaired liver or renal function Recurrent SH or hypo unawareness Proliferative retinopathy or maculopathy requiring treatment Pregnancy, breastfeeding or planning pregnant Cancer and history of cancer										

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
		Clinically significant disease or disorder which could interfere with trial results.										

Table 213: BIRKELAND 2011 and HOME 2012 (same study)

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes	Comments
K. I Birkeland, P. D. Home, U Wendisch, et al. Insulin degludec in type 1 diabetes. Diabetes Care 34:661-665, 2011. REF ID: BIRKELAND 2011 and	RCT 28 centre in 5 countries: Australia, Germany, Norway, Sweden and the US	n=178 (n=59 IDeg(A) group; n=60 IDeg (B) group; n=59 IGlar group) Inclusion criteria: Age 18-75 years type 1 diabetes for at least		IDeg(A) n=59	IDeg (B) n=60	IGlar n=59	IDeg(A) (600µmol/litre; 1 unit = 6nmol; once daily in the evening) ITT: n=59 IDeg(B) (900µmol/litre; 1 unit = 9nmol; once daily in the evening) ITT: n=60 Basal insulin	IGlar (100 units/mL once daily in the evening) ITT: n=59 Basal insulin doses adjusted once a week aiming for fasting plasma glucose 4-6mmol/litre	16 weeks treatment	Decrease in HbA1c, mean (SD) %	0.57 (0.76) IDeg(A); 0.54 (0.78) IDeg (B); 0.62 (0.68) IGlar	Funding: Novo Nordisk A/s Risk of bias: Randomisation = unclear (not stated) Allocation concealment = adequate (remote voice response system) Blinding = no (open
			Age, years (SD)	44.5 (12.7); 45.6 (12.5); 47.2 (13.5)						Final mean (SD) HbA1c	7.8 (0.8) IDeg(A); 8.0 (1.0) IDeg (B); 7.6 (0.8) IGlar	
			Women, %	37%; 38%; 46%						Decrease in fasting plasma glucose mean (SD)	1.60 (4.66) IDeg(A); 2.06 (5.17) IDeg (B); 0.54 (4.36) IGlar	
			Diabetes, mean years (SD)	22.7 (14.6); 20.8 (10.6); 19.1 (10.8)						Final fasting plasma glucose	8.3 (4.0) IDeg(A); 8.3 (2.8) IDeg (B); 8.9 (3.5) IGlar	
			White Black/African	98%; 98%; 97% 2%; 0%; 0%								

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes	Comments
Home PD, Meneghini L, Wendisch U, et al. Improved health status with insulin degludec compared with insulin glargine in people with Type 1 diabetes. Diabet Med 29: 716-720, 2012 REF ID: HOME 2012		12 months Treated continuously with insulin HbA1c 7.0 to 11.0% Exclusion criteria: Clinically significant concomitant illness Impaired renal and hepatic function history of recurrent major hypoglycaemia or hypoglycaemia unawareness pregnant or breastfeed	Asian Other	0%; 2%; 2% 0%; 0%; 2%	doses adjusted once a week aiming for fasting plasma glucose 4-6mmol/litre Concomitant medication: In both groups, patients received IAsp at mealtimes (100 units/mL) titrated weekly to 2-hour post-prandial target of 4-8mmol/litre			mean (SD)		label) ITT analysis (LOCF) Powered for treatment difference not superiority/ non-inferiority (HbA1c) Drop-outs = acceptable (<20%)
			Baseline HbA1c	8.4 (0.9)%; 8.5 (1.0)%; 8.3 (0.8)%				Confirmed hypoglycaemia (events/ patient-year)	47.9 IDeg(A) (RR 0.72 vs. IGlar, 95% CI 0.52 to 1.00); 59.5 IDeg (B) (RR 0.90 vs. IGlar, 95% CI 0.65 to 1.24); 66.2 IGlar	
			Pre-trial insulin: basal (once daily) + mealtime basal (twice daily) + mealtime Other	51%; 50%; 56% 42%; 43%; 42% 7%; 7%; 2%				Confirmed nocturnal hypoglycaemia (events/ patient-year)	5.1 IDeg(A) (RR 0.42 vs. IGlar, 95% CI 0.25 to 0.69); 8.8 IDeg (B) (RR 0.71, 95% CI 0.44 to 1.16); 12.3 IGlar	
			Basal insulin dose at baseline	29 (12) units; 28 (13) units; 23 (11) units (described as "small difference" between degludec and glargine groups				AE	8.7 IDeg(A); 6.5 IDeg (B); 9.1 IGlar events/ patient-year; most mild or	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes	Comments
		ing						moderate; unlikely relation to study insulins	
			No major differences between groups for any other baseline characteristics; minor differences adjusted in analysis Drop-outs (16 weeks): 7 (12%; 2 AE, 2 non-compliance; 1 ineffective; 2 other reasons) IDeg (A) group; 5 (8%; 0 AE; 1 non-compliance; 2 ineffective; 2 other reasons) IDeg (B) group; 7 (12%; 1 AE, 1 non-compliance; 0 ineffective; 5 other reasons) IGlar group				Serious AE	Abdominal distension IDeg(A); hypoglycaemic unconsciousness IDeg(A); hypoglycaemia IDeg (B); diabetic ketoacidosis IGlar	
							Body weight change mean (SD)	+0.1 (2.7) kg IDeg(A); +1.0 (2.5) kg IDeg (B); +0.7 (1.6) kg IGlar	
							SF36 Change in physical component score (Mean (SE))	0.26 (1.08) IDeg vs. -0.41 (1.07) IGlar	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes	Comments
							Change in mental component score (Mean (SE))	1.88 (0.98) IDeg vs. -1.13 (0.97) IGlar	

Table 214: HELLER 2012 and BODE 2013 – BEGIN trial

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Heller S, Buse J, Fisher M, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in	RCT 79 centres in 6 countries.	n=629 (52 weeks); n=469 (extension) Degludec group: n=472 Glargine group: n=157 Inclusion criteria:	1 year (n=629) patients baseline data	Degludec: n=472	Glargine: n=157	Degludec: 100U/mL, titrated to before-breakfast glucose of 3.9mmol/litre to less than 5mmol/litre n=472 Concomitant medication: Insulin aspart at mealtimes,	Glargine: 100U/mL, titrated to before-breakfast glucose of 3.9mmol/litre to less than 5mmol/litre n=157	52 weeks and 104 weeks (extension trial of additional 52 weeks)	52 weeks data (Heller 2012)		Funding: Novo Nordisk Risk of bias: Randomisation adequate (computer generated using blocks) Allocation concealment = adequate (interactive voice
			Age, mean (SD) years	42.8 (13.7)	43.7 (13.3)				Decrease in HbA1c, Mean (SE) %	0.40 (0.03) % IDeg vs. 0.39 (0.07) IGlar	
			Women, %	41	43				Final HbA1c <7%	188/472 (40%) IDeg vs. 67/157 (43%) IGlar	
									Confirmed hypo. (no. patients)	451 (96%) IDeg vs. 147 (95%) IGlar	
			HbA1c ≥10%, %	7.7 (0.9)	7.7 (1.0)				Confirmed nocturnal hypo. (no. patients)	341 (72%) IDeg vs. 114 (74%) IGlar	
			BMI	26.3	26.4				Severe hypo. (no. patients)	58 (12%) IDeg vs. 16 (10%) IGlar	
									AE, no. of	397 (84%) IDeg vs.	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 379: 1489-97, 2012. REF ID: HELLER 2012		Age ≥18 years type 1 diabetes for at least 12 months Treated with basal bolus insulin injections ≥12 months HbA1c ≤10.0% BMI 35kg/m2 Exclusion criteria: not stated (but in appendix)	kg/m2 (SD)	(3.7)	(4.2)	titrated to 3.9mmol/litre to less than 5mmol/litre before next meal			patients at	128 (83%) IGlar	response system) Blinding = open label ITT analysis (LOCF) Powered study (to detect non-inferiority) Drop-outs = 1 year acceptable (<20% and <10% differential between groups) Drop-outs = 2 years acceptable (30% and <10% differential between groups)
			Diabetes duration, years	19.1 (12.2)	18.2 (11.4)				SAE, no. of patients	49 IDeg 17 IGlar	
			Comparable between groups for all of the baseline characteristics Drop-outs at 1 year: IDeg 14% (3% AE; 2% non-compliance; <1% ineffective; 3% withdrawal criteria for lack of effect; 6% other); IGlar 11% (<1% professional reason; 1% AE; 2% non-compliance; 2% withdrawal criteria for lack of effect; 6% other) Drop-outs at 2 years (extension): IDeg 6% of those entering extension (330/351) and 30% from baseline. IGlar 4% of those entering extension (113/118) and 28% from baseline.						Body weight change mean (SE)	+1.8 (0.2)kg IDeg +1.6 (0.3)kg IGlar	
									104 week data (extension; Bode 2013)		
									HbA1c (final values)	Deg: 7.3% Glarg: 7.5%	
									HbA1c (change)	Deg: -0.31% Glarg: -0.24%; MD -0.04% (95% CI -0.17 to 0.09)	
									Confirmed Hypoglycaemia. (episodes/patient-year)	MD: 0.98 (95% CI 0.80 to 1.20); NS	
									Confirmed Nocturnal hypoglycaemia. (episodes/patient-year)	MD: 0.75 [95% CI 0.59–0.95); p=0.02 Favours degludec	
									Severe hypoglycaemia (episodes/patient-year)	Deg: 0.17 Glarg: 0.15 (NS between	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
								groups)	
							AEs, no. of patients	Deg: 413/472 Glarg: 137/154	
							SAEs, no. of patients	Deg: 71/472 Glarg: 29/154	
							Body weight increase, kg	Deg: 2.1, Glarg: 2.0 (NS between groups)	
							Injection site reactions, no. of patients	Deg: 14/475 Glarg: 9/154	

G.4.2.3 Degludec versus detemir

Table 215: IWAMOTO 2013

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Y. Iwamoto, P. Clauson, T. Nishida, and K. Kaku. Insulin degludec in Japanese patients with type 1 diabetes	RCT 8 centres, Japan	n=65 Degludec: n=33 Detemir: n=32 Inclusion criteria: Age ≥20 years type 1 diabetes for at least 12 months		Deg: n=33	Det: n=32	Degludec: once daily (bedtime) titrated aiming for fasting blood glucose values.	Detemir: once daily (bedtime) titrated aiming for fasting blood glucose values.	6 weeks treatment	HbA1c	Not reported	Funding: Novo Nordisk Risk of bias: Randomisation = unclear (just says randomised
									Severe hypo, no of patients:	Deg: 0 Det: 0	
									AEs and SAEs	Deg: 0 Det: 0	
			Age, mean	45.5	43.2						

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
mellitus: A randomized controlled trial. J.Diabetes Invest. 4 (1):62-68, 2013. REF ID: IWAMOTO 2013		HbA1c <10.4% BMI <30 kg/m2 Treated for at least 12 weeks with basal-bolus insulin of glargine or NPH, and aspart. Exclusion criteria: Clinically significant concomitant disease Impaired renal or hepatic function Non-stabilised proliferative retinopathy or maculopathy History of Recurrent severe hypoglycaemia or hypo unawareness. pregnant or breastfeeding	years			Concomitant medication: Mealtime insulin aspart	Concomitant medication: Mealtime insulin aspart				1:1) Allocation concealment = adequate (external registration centre) Blinding = no (open label) ITT analysis Not calculated powering/sample size Drop-outs = acceptable (<20%)
			Women, %	27	40						
			Diabetes duration, mean years	13.2	11.8				Nocturnal hypo, no of patients:	Deg: 12 Det: 17	
			HbA1c mean % (SD)	7.79 (0.86)	7.72 (0.86)						
			BMI (SD) kg/m2	22.9 (2.49)	22.9 (2.5)						
			Drop-outs: n=0 in each group								

G.4.2.4 Detemir versus glargine

Table 216: HELLER 2009

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Heller S, Koenen C, Bode B. Comparison of insulin detemir and insulin glargine in a basal-bolus regimen, with insulin aspart as the mealtime insulin, in patients with type 1 diabetes: a 52-week, multinational, randomized, open-label, parallel-group, treat-to-target noninferiorit	RCT Multinational	n=443 Detemir group: n=300 Glargine group: n=147 Inclusion criteria: Age ≥18 years type 1 diabetes for at least 12 months Treated with basal bolus insulin injections ≥3 months HbA1c ≤11.0%		Detemir: n=300	Glargine: n=147	Detemir: once daily (evening), or twice daily (if achieving target at breakfast but not dinner, a second dose - initially 4U administered in the morning was added) 66% ended up on twice/day detemir. Concomitant medication: Insulin aspart at mealtimes, adjusted to 90-minute post-prandial	Glargine: once daily (evening) no second dose added. In both groups the dose was titrated to specific target blood glucose values.	52 weeks	OVERALL: Final HbA1c (SE) HbA1c ≤7% HbA1c ≤7% without hypoglycaemia	Det: 7.57 (0.05); n=283 Glarg: 7.56 (0.06); n=134 87/263 det. 37/122 glarg 84/263 det 35/122 glarg	Funding: Novo Nordisk Risk of bias: Randomisation = unclear (just says randomised) Allocation concealment = adequate (telephone system) Blinding = open label ITT analysis (LOCF) Power = adequate (435 patients enough to give 95% power to demonstrate
			Age, mean (SD) years	42 (13)	41 (12)						
			Diabetes duration	17.2 (11.7)	17.3 (10.7)				HbA1c, change from baseline (SE)	Det: -0.53 (0.05); n=283 Glarg:-0.54 (0.06); n=134	
									HbA1c: detemir once/day	90 patients -0.49% change; final 7.59%	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
y trial. Clinical Therapeutics 31(10): 2086-2097, 2009. REF ID: HELLER 2009		Exclusion criteria: Proliferative retinopathy or maculopathy requiring acute treatment within 6 months before study history of recurrent major hypoglycaemia anticipated change in any medication affecting glucose metabolism impaired renal or hepatic function cardiac problems or uncontrolled	BMI kg/m2	26.5 (4.0)	26.3 (3.9)	target ≤9mmol/litre			HbA1c: detemir twice/day	173 patients -0.58% change; final 7.60%	non-inferiority based on a 1-sided p=0.025; SD 1.0% and dropout rate of 15%; margin 0.4% Drop-outs = acceptable (<20%)
			Women, %	44.1	43.8				Hypoglycaemic episodes/patient-year	53.6 det vs. 57.3 glar	
			HbA1c %	8.1 (1.1)	8.1 (1.2)				Final fasting plasma glucose	8.58 det vs. 8.81 glarg	
			Comparable between groups for all of the baseline characteristics Drop-outs: Detemir: 37/300 (6 AE; 6 ineffective therapy; 15 non-compliance; 10 other); Glargine: 25/147 (4 AE; 5 ineffective therapy; 4 non-compliance; 12 other)						Body weight change	+0.36kg det vs. +0.42kg glarg	
									Major hypoglycaemic episodes/patient-year	0.5 detemir vs. 0.4 glargine	
									Nocturnal hypoglycaemic episodes/pt-year	9.9 detemir vs. 8.9 glargine	
									Hypoglycaemic episodes classified as	<0.1 detemir vs. <0.1	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		hypertension believed to affect study participation					SAE/ pt-year	glargine	
							AE (no. patients)	277/299 det vs. 129/144 glarg	
							Serious AE (no. patients)	35 (11.7%) vs. 7 (4.9%)	
							Injection site reactions	24 (8%) det vs. 2 (1.4%) glarg	

Table 217: RENARD 2011

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Renard E, Dubois-Laforgue D, Guerci B, et al. Non-inferiority of insulin glargine versus insulin detemir on blood glucose variability	RCT 25 centres in France.	n=88 Detemir first group: n=38 Glargine first group: n=50 Inclusion criteria:		Detemir first: n=34 (PP population)	Glargine first: n=44 (PP population)	Detemir: once daily evening injection, titrated on fasting blood glucose (5mmol/litre to ≤7.2mmol/litre), but second dose could be added if	Glargine: once daily evening injection, titrated on fasting blood glucose (5mmol/litre to ≤7.2mmol/litre)	16 weeks each treatment period; no washout	Coefficient of variation of fasting blood glucose (%)	39.9 (10.9) detemir vs. 41.1 (12.0) glargine	Funding: Sanofi-Aventis Risk of bias: Randomisation = unclear (just says randomised) Allocation concealment = unclear (just says randomised)
			Age, mean (SD) years	46.4 (14.1)	48.3 (13.6)				Decrease in HbA1c, mean (SD) %	0.20 (0.55) first detemir period; 0.14 (0.38) second detemir	
			Women, %	44.1	34.1						

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
in type 1 diabetes patients: a multicenter, randomized, crossover study. Diabetes Technology and Therapeutics 13 (12): 1213-1218, 2011 REF ID: RENARD 2011		type 1 diabetes for at least 3 years Intensive insulin therapy at least 6 months using basal bolus regimen with glargine as evening basal insulin HbA1c ≤8.5% >50% of pre-dinner blood glucose ≤8.3 mmol/litre in last 3 weeks of run-in period using glulisine as prandial insulin Exclusion				patients failed to reach pre-dinner target Concomitant medication: Glulisine as the mealtime insulin, titrated using 1-2 hour post-meal blood glucose <9.9mmol/litre				period; 0.19 (0.34) first glargine period; 0.10 (0.52) second glargine period;	Blinding = no ITT analysis = no (per protocol) Power = adequate (86 patients required for power of 95% at p=0.025 for a true difference of 1.05 SD 0.2, margin 1.25, drop out 15% Drop-outs = acceptable (<20%)
			Diabetes duration (years)	18.5 (10.1)	17.1 (8.4)				Body weight change	Decreased 0.2kg on detemir and unchanged on glargine	
			HbA1c %	7.16 (0.71)	7.06 (0.69)				AE (n, % of patients)	32/88 (36.0%) on detemir vs. 29/88 (32.9%) on glargine	
			BMI kg/m2	25.3 (3.5)	24.6 (3.5)						
									Serious AE (no. patients)	4 detemir vs. 4 glargine	
			Comparable between groups for all of the baseline characteristics Drop-outs: Ten patients excluded from analysis due to protocol						Severe hypoglycaemia reported as serious AE	1 in glargine group	
									Median monthly rate symptomatic hypoglycaemia	2.16 detemir vs. 2.32 glargine	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		criteria: not stated	violations (crossover period duration <3 months (8) or number of fasting blood glucose measurements <42 per period (2)				Severe symptomatic hypoglycaemia	4/88 on detemir vs. 10/88 on glargine	

G.4.2.5 Detemir versus NPH

Table 218: GOLEN 2013

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures – all n=28 patients	Effect sizes	Comments
L. W. Golen, R. G. Ijzerman, M. C. Huisman, J. F. Hensbergen, ET AL. Cerebral blood flow and glucose metabolism in appetite-related brain regions in type 1 diabetic patients after	RCT (cross-over) Multicentre, The Netherlands.	n=28 Detemir: n=28 (started as 13) NPH: n=28 (started as 15) Inclusion criteria: Age 18-65 years type 1 diabetes BMI 18-35 kg/m2		All patients: n=28	Detemir: once daily (evening); dose titrated where needed for fasting glucose of <7. Concomitant medication: Mealtime insulin aspart	NPH: 100U/mL once daily (evening) titrated as for detemir group Concomitant medication: Mealtime insulin aspart	12 weeks treatment (each cross-over period) Had 4-week run-in period to optimise current insulin therapy, before randomisation.	Final HbA1c Mean (SD) %	Det: 7.4 (0.6) NPH: 7.4 (0.6)	Funding: Novo Nordisk Risk of bias: Randomisation = adequate (randomised block design by the trial pharmacy) Allocation concealment = inadequate (the author enrolled and
								Final weight Mean (SD) kg	Det: 82.4 (12.4) NPH: 83.4 (13.0)	
			Age, mean years	36.9				DTSQ – perceived hypo and hyper-glycaemia	NS diff between groups (details not reported)	
			Diabetes duration, mean years	12.8						
			HbA1c mean % (SD)	7.5 (0.6) Det: 7.4 (0.6); NPH: 7.3 (0.6)				Patient satisfaction	SS greater for detemir vs. NPH (p=0.003)	
			BMI kg/m2	24.9 (SD 2.7)						

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures – all n=28 patients	Effect sizes	Comments
treatment with insulin detemir and NPH insulin: A randomized controlled crossover trial. Diabetes Care 36 (12):4050-4056, 2013. REF ID: GOLEN 2013		Exclusion criteria: Duration <1 year HbA1c >8.5% Proliferative retinopathy History of recurrent SH History of hypo unawareness History of CV, renal, liver or severe head trauma, neurological or psychiatric disorder. Endocrine diseases not well controlled in last 3 months Substance abuse Use of anticoagulants, oral	Body weight, kg (SD)	Det: 83.1 (12.6) NPH:82.7 (12.6)						assigned them, by envelopes) Blinding = no (open label) ITT analysis Powered study (for glucose mmts) Drop-outs = acceptable (<20%)
			Drop-outs: Up to 18 patients (<20% drop-outs) were included for some outcomes, but ITT analysis done on all n=28. Unclear numbers of drop-outs for each outcome.							

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures – all n=28 patients	Effect sizes	Comments
		steroids or any centrally acting agent							

Table 219: BARTLEY 2008

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Bartley PC, Bogoev M, Larsen J, et al. Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with type 1 diabetes using a treat-to-target	RCT 33 centres in 10 countries.	n=497 Detemir group: n=331 NPH group: n=166 Inclusion criteria: Age ≥18 years type 1 diabetes for at least 12 months		Detemir: n=331	NPH: n=164 (2 withdrew before treatment)	Detemir: once daily (evening) or twice/day (add at breakfast) if not achieve targets MOST PTS (63% FINISHED THE TRIAL ON TWICE/DAY BASAL) Concomitant	NPH: once daily (evening) or twice/day (add at breakfast) if not achieve targets MOST PTS (55% FINISHED THE TRIAL ON TWICE/DAY BASAL) In both groups,	24 months	Reduction in HbA1c	0.94% detemir vs. 0.72% NPH	Funding: Novo Nordisk Risk of bias: Randomisation = unclear (just says randomised) Allocation concealment = adequate (telephone randomisation system) Blinding = no (open label) ITT analysis Powered study (HbA1c) Drop-outs =

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. Diabet Med 25: 442-449, 2008. REF ID: BARTLEY 2008		Treated with basal-bolus insulin regimen ≥3 months HbA1c ≤11.0% BMI ≤35kg/m2 Able and willing to self-measure plasma glucose Exclusion criteria: Proliferative retinopathy or maculopathy Other significant medical disorders Recurrent				medication: Mealtime insulin aspart	insulin doses were titrated to achieve specific target blood glucose values				acceptable (<20%)
									Final HbA1c Mean (SE) %	7.36 (0.06) n=320 detemir vs. 7.58 (0.08) n=159 NPH	
									HbA1c ≤7.0% without confirmed hypoglycaemia in last month of treatment	73/331 (22%) detemir vs. 21/164 (13%) NPH	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		major hypoglycaemia Allergy to insulin pregnant or breastfeeding									
			Age, mean (range) years	35 (18-75)	35 (18-70)				Reduction in fasting plasma glucose mmol/litre	3.01 detemir vs. 1.93 NPH	
			Women, %	44.4	47.0						
			Diabetes duration, mean (range) years	12.7 (1.0-50.4)	13.5 (1.1-49.4)				Final fasting plasma glucose Mean (SE) mmol/litre	8.35 (0.27) n=318 detemir vs. 9.43 (0.38) n=158 NPH	
			HbA1c mean (range) %	8.3 (5.0-11.6)	8.4 (5.3-11.4)						
			BMI kg/m2	24.7 (15.4 - 34.6)	24.7 (16.9 - 34.7)				Weight gain kg	1.7 detemir vs. 2.7 NPH	
									Final weight Mean (SE) kg	72.92 (0.26) n=320 detemir vs. 73.91 (0.37) n=159 NPH	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
							Major hypoglycaemia (no. patients)	49/331 (14.8%) detemir vs. 42/164 (25.6%) NPH	
			Comparable between groups for all of the baseline characteristics Drop-outs: 52 (15.7%) discontinued detemir (13 AE, 2 ineffective therapy, 8 non-compliance, 31 other reasons); 22 (13.3%) discontinued NPH (1 AE, 2 ineffective therapy, 6 non-compliance, 13 other reasons)				Nocturnal hypoglycaemia	237/331 detemir vs. 124/164 NPH	
							Hypoglycaemia reported as serious AE (no. patients)	14 detemir vs. 12 NPH	
							AE possibly/ probably related to trial drug	36/331 (10.9%) detemir vs. 28/164 (17.1%) NPH	
							Serious AE possibly/ probably related to trial drug	14/331 (4.2%) detemir vs. 11/164 (6.7%) NPH	

Table 220: HERMANSEN 2001

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
K. Hermansen, S. Madsbad, H. Perrild, A. Kristensen, and M. Axelsen. Comparison of the soluble basal insulin analog insulin detemir with NPH insulin: A randomized open crossover trial in type 1 diabetic subjects on basal-bolus therapy. Diabetes Care 24 (2):296-301, 2001. REF ID:	RCT (cross-over) 7 centres in Denmark	n=59 Inclusion criteria: Age 18-55 years type 1 diabetes for at least 2 years Had received once/day (evening) NPH plus meal-time human soluble insulin for at least 6 months HbA1c ≤8.7% Glucagon-stimulated C-peptide ≤0.1 nmol/litre or fC-pep ≤0.04 nmol/litre NPH dose <40 IU/day BMI <27.5 kg/m2 Exclusion criteria: Proliferative retinopathy Impaired renal or hepatic function Decompensated heart failure Unstable angina pectoris MI within the past year Hypertension		All: n=56	Detemir + Human insulin Det: Once/day (evening) HI: = Actrapid (30 minutes before meals) Dose of detemir was titrated to reach target blood glucose. levels	NPH + Human insulin NPH: Once/day (evening) HI: = Actrapid (30 minutes before meals) Dose of NPH was titrated to reach target blood glucose. levels	6 weeks (each cross-over period)	HbA1c	NO DATA	Funding: Novo Nordisk Risk of bias: Randomisation = adequate?? (symmetrically in blocks of 4 to a treatment sequence) Allocation concealment = unclear (just says randomised) Blinding = no (open label) Not ITT analysis Powered study (serum glucose). Drop-outs = acceptable (<20%)
			Age, mean (range) years	34.5 (19-52)				Hypoglycaemia, no. of patients	Det: 54/57 NPH: 51/56	
			Women, %	17.9				Hypoglycaemia, episodes	Det: 432 NPH: 577	
			Diabetes, mean (range) duration years	14.8 (2.6-47.8)				Major hypoglycaemia, no. of patients	Det: 4/57 NPH: 7/56	
			HbA1c % (range)	7.9 (5.7-8.7)				Major hypoglycaemia, episodes	Det: 4 NPH: 11	
			Weight (SD) kg/m2	23.8 (2.0)				AEs Numbers have been reported in the paper if we need to get data for HEc		
			Drop-outs: n=3 at beginning of trial					Nocturnal hypo (episodes): Det: 23 NPH: 38		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
HERMANSEN 2001/ID 1045		Hypoglycaemia unawareness Recurrent major hypoglycaemia Allergy to insulin or any component Drug or alcohol abuse Use of systemic corticosteroids, BBs or hormones within past month Pregnant, breast-feeding or inadequate contraception							

Table 221: HERMANSEN 2004

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Hermansen K, Fontaine P, Kukolja KK, et al. Insulin analogues (insulin detemir and insulin	RCT 64 centres in Europe.	n=595 Detemir group: n=298 NPH group: n=297		Detemir: n=298	NPH: n=297	Detemir: 100U/mL morning and bedtime titrated to pre-breakfast and pre-dinner 5.7-7.3 mmol/litre	NPH: 100U/mL morning and bedtime titrated to pre-breakfast and pre-dinner 5.7-7.3 mmol/litre	18 weeks (6 week titration and 12 week maintenance)	Change in HbA1c	-0.50% detemir vs. -0.28% NPH	Funding: Novo Nordisk Risk of bias: Randomisation = unclear (just says randomised
			Age, mean (SD) years	38.8 (13.5)	39.3 (12.9)				Final HbA1c mean (SE) %	7.88 (0.05) n=298 detemir vs. 8.11 (0.05) NPH n=297	
									Final fasting	7.58 (0.19)	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. Diabetologia 47: 622-629, 2004 REF ID: HERMANSEN 2004		Inclusion criteria: Age ≥18 years type 1 diabetes for at least 12 months Current treatment any basal-bolus insulin regimen or biphasic insulin treatment at least 6 months Total daily insulin <1.4 U/kg HbA1c ≤12.0% BMI ≤35kg/m2 Exclusion criteria: Proliferative retinopathy requiring acute treatment Impaired renal or hepatic function Severe cardiac problems				Concomitant medication: Mealtime insulin aspart 100U/mL immediately before meals, titrated to 8.5-10.1mmol/litre 90 minutes after a meal	Concomitant medication: Mealtime regular human insulin 100U/mL 30 minutes before meals titrated to 8.5-10.1mmol/litre 90 minutes after a meal		plasma glucose mean (SE) mmol/litre	n=298 detemir vs. 8.10 (0.20) NPH n=297	) Allocation concealment = unclear (just says randomised) Blinding = no (open label) ITT analysis Power education study (HbA1c). Drop-outs = acceptable (<20%)
			Women, %	38.6	35.0				Change in weight mean (SE) kg	-0.95 (0.14) n=298 detemir vs. +0.07 (0.14) NPH n=297	
			Diabetes, mean (SD) duration years	15.4 (10.1)	15.1 (10.4)				Final weight mean (SE) kg	73.0 (0.14) detemir vs. 74.1 (0.14) NPH	
			HbA1c % (SD)	8.48 (1.12)	8.29 (1.19)				Coefficient of variation within person in overall plasma glucose (%)	36.9% detemir vs. 39.6% NPH	
			BMI mean (SD) kg/m2	24.8 (3.0)	24.9 (3.2)				Major hypoglycaemia (no. patients)	19/298 (6.5%) detemir vs. 18/297 (6.3%) NPH	
			Comparable between groups for all of the baseline characteristics except slightly higher HbA1c and slightly lower fasting plasma glucose level in detemir group						nocturnal hypoglycaemia (no. patients)	113/298 detemir vs. 173/297	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		Uncontrolled hypertension Recurrent major hypoglycaemia Allergy to insulin History of drug or alcohol dependence pregnant or breast-feeding	Drop-outs: 9 withdrew from detemir group (5 AE, 2 non-compliance, 2 other reasons); 14 from NPH group (1 AE, 4 ineffective therapy, 3 non-compliance, 6 other reasons)				AE	141/298 (47.3%) detemir vs. 139/297 (46.8%) NPH	
							Serious AE	12/298 detemir vs. 7/297 NPH	
							Withdrawal due to serious AE considered to be related to trial product	3/298 detemir vs. 0/297 NPH	

Table 222: HOME 2004

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Home P, Bartley P, Russell-Jones D,	RCT 52	n=408 Detemir 12		Detemir 12h: n= 137	Detemir Morn + bed: n= 139	NPH: n= 132	Detemir: 100U/mL	NPH: (twice/day)	16 weeks	Decrease in HbA1c mean (SE)	Detemir 12h: 0.85 (0.07)%;	Funding: Novo Nordisk

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
et al. Insulin detemir offers improved glycaemic control compared with NPH insulin in people with type 1 diabetes. Diabetes Care 27: 1081-1087, 2004 REF ID: HOME 2004	centres in Australasia and Europe.	hour group: n=137 Detemir Morn + bed group: n=139 NPH group: n=132 Inclusion criteria: Age >18 years type 1 diabetes for at least 12 months Using mealtime + basal regimen >2 months Daily basal insulin <100 U/day HbA1c ≤12.0% BMI					either before breakfast and at bedtime (morn + bed) or at 12 hour intervals (12-hour), titrated to pre-breakfast/night 4.0-7.0mmol/litre and post-prandial ≤10mmol/litre Concomitant medication: Insulin aspart at mealtimes	before breakfast and at bedtime titrated to pre-breakfast/ night 4.0-7.0mmol/litre and post-prandial ≤10mmol/litre			Detemir Morn + bed: 0.82 (0.07)%; NPH: 0.65 (0.07)%	Risk of bias: Randomisation = unclear (just says randomised) Allocation concealment = adequate (remote telephone randomisation) Blinding = no (open label) ITT analysis (missing data interpolated) Powered study Drop-outs = acceptable (<20%)
			Age, mean (SD) years,	40.9 (13.0)	41.3 (11.4)	38.3 (12.4)				Final HbA1c mean (SE)	Detemir 12h: 7.75 (0.07); Detemir Morn + bed: 7.78 (0.07); NPH: 7.94 (0.07)	
			Women, %	48	43 %	47				Final fasting plasma glucose (mean (SE) mmol/litre)	Detemir 12h: 9.75 (0.37); Detemir Morn + bed: 8.94 (0.37); NPH: 11.24 (0.38)	
			BMI kg/m2	25.1 (3.3)	25.2 (3.6)	25.2 (3.7)						
			Diabetes, years	17.1 (10.6)	17.6 (10.7)	15.1 (10.6)				Mean (SE) change in body weight (kg)	Detemir 12h: 0.02 (0.22); Detemir Morn + bed: 0.24 (0.22); NPH: 0.86 (0.23)	
			HbA1c %	8.55 (1.20)	8.74 (1.20)	8.52 (1.19)						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		≤35.5kg/m2 Exclusion criteria: Significant medical problems (including proliferative retinopathy, recurrent major hypoglycaemia, impaired hepatic or renal function, uncontrolled cardiovascular problems using medication know to interfere with glucose metabolism pregnant or breastfeeding	Comparable between groups for all of the baseline characteristics Drop-outs: 17 withdrew (5 IDet 12 h; 4 IDet morn + bed; 8 NPH): 2AE, 3 ineffective therapy, 9 non-compliance, 3 other (fear of hypoglycaemic event, withdrawal of consent, pregnancy)				Major hypoglycaemia (no. patients)	Detemir 12h: 6/137 (4%); Detemir Morn + bed: 11/139 (8%); NPH: 10/132 (8%)	
							All nocturnal hypoglycaemia (no. patients) – major + minor events	Detemir 12h: 62/137 ; Detemir Morn + bed: 52/139; NPH: 58/132	
							SAE	Combined detemir group: 14/276 (5%) vs. NPH group: 4/132 (3%)	

Table 223: KOLENDORF 2006

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Kølendorf K, Ross GP, Pavlik-Renart I, et al. Insulin detemir lowers the risk of hypoglycaemia and provides more consistent plasma glucose levels compared with NPH insulin in type 1 diabetes. Diabet Med 23: 729-735, 2006. REF ID: KØLENDORF 2006	RCT (crossover) 11 centres in Australia, Europe and South Africa.	n=130 (crossover; periods pooled apart from weight) Detemir first: n=66 NPH first: n=64 Inclusion criteria: Age ≥18 years type 1 diabetes for at least 12 months Treated with basal bolus insulin injections ≥4 months Able and willing to perform SMPG		Detemir first: n=66	NPH first: n=64	Detemir: 100 U/mL twice daily, (before breakfast and at bedtime); bedtime dose titrated by pre-breakfast glucose (increase dose if >7mmol/litre), pre-breakfast dose titrated by pre-evening meal glucose (increase dose if >7mmol/litre) Concomitant medication: Pre-meal insulin aspart immediately before each main meal, titrated to	NPH: 100IU/mL twice daily (before breakfast and at bedtime); bedtime dose titrated by pre-breakfast glucose (increase dose if >7mmol/litre), pre-breakfast dose titrated by pre-evening meal glucose (increase dose if >7mmol/litre)	16 weeks each treatment	Decrease in HbA1c	Detemir: 0.3%; NPH 0.3%	Funding: Novo Nordisk Risk of bias: Randomisation = unclear (just says randomised) Allocation concealment = unclear (just says randomised) Blinding = no (open label) ITT analysis Power education study (hypoglycaemia) Drop-outs = acceptable (<20%)
			Age, mean (SD) years	38.5 (12.3)	39.9 (12.4)				Final HbA1c mean (SE)	7.6 (0.06)% detemir; 7.6 (0.06)% NPH	
			White (%)	92.4	95.3				Pre-breakfast plasma glucose ≤6.0%	30/125 (24%) detemir; 19/127 (15%) NPH	
			Women, %	48.5	43.8				Pre-evening meal plasma glucose ≤6.0%	16/125 (13%) detemir; 27/127 (21%) NPH	
			Diabetes duration mean (SD) years	16.5 (10.0)	16.6 (10.6)				Coefficient of variation of SMPG	38.4% detemir vs. 41.1% NPH	
			BMI mean (SD) kg/m2	25.1 (3.4)	25.6 (3.5)				Change in body weight	Period 1: detemir -0.3kg vs. NPH -1.0kg Period 2: -0.2kg detemir vs. +1.3kg NPH	
			HbA1c mean	7.9 (0.7)	7.9 (0.8)				Hypoglycaemia (PG	97/125 (77.6%)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		HbA1c ≤9.0% BMI ≤35kg/m2 C-peptide negative Total daily insulin dose ≤1.4 IU/kg/day Basal insulin requirement ≥30% of total daily dose Exclusion criteria: Significant medical disorders recurrent major hypoglycaemia or hypoglycaemia unawareness allergy to insulin pregnant or	(SD) %	≤8.0mmol/litre 90 minutes post-prandially			<3.1mmol/litre with symptoms)	detemir vs. 104/128 (81.3%) NPH	
							Nocturnal hypoglycaemia	58/125 detemir vs. 81/128 NPH	
			Comparable between groups for all of the baseline characteristics Drop-outs: 7 withdrawn (3 AE, 2 personal reasons, 1 ineffective therapy (2nd period on NPH) and 1 non-compliance)				Severe hypoglycaemia (episodes not patients)	19 episodes detemir vs. 33 episodes NPH	
							Hypoglycaemic coma reported as SAE	0 detemir vs. 2 NPH	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		breastfeeding							

Table 224: LEEUW 2005

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Leeuw ID, Vague P, Selam JL, et al. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. Diabetes, Obesity and Metabolism	RCT 42 centres in Europe.	n=428 initially randomised; 316 of 425 eligible at 6 months accepting extension phase; NS difference between accepters and decliners Detemir group: n=216 NPH group: n=99 Inclusion criteria: Caucasian Age ≥18 years type 1 diabetes for at least 12 months Treated with basal bolus insulin injections ≥2 months		Detemir: n=216	NPH: n=99	Detemir: 1200nmol/mL; twice daily before breakfast and at bedtime, titrated to 4-7mmol/litre for fasting blood glucose Concomitant medication: Mealtime insulin aspart, titrated to 90 minute post-prandial target <10.0mmol/litre	NPH: 100IU/mL twice daily before breakfast and at bedtime	12 months (initial 6 months trial then 6 month extension phase)	Decrease in HbA1c	0.64% detemir vs. 0.56% NPH	Funding: Novo Nordisk Risk of bias: Randomisation = unclear (just says randomised) Allocation concealment = unclear (just says randomised) Blinding = no (open label) ITT analysis Powered study (non-inferiority) Drop-outs = acceptable
			Age, mean (SD) years	40.1 (12.8)	40.8 (13.2)				Final mean (SE) HbA1c	7.53 (0.10)% detemir vs. 7.59 (0.13)% NPH	
			Women, %	46.3	47.5				Decrease in fasting plasma glucose (mmol/litre)	0.58 detemir vs. 0.42 NPH	
			Diabetes duration mean (SD) years	17.8 (9.7)	16.6 (10.2)				Final fasting plasma glucose (mmol/litre)	10.7 detemir vs. 10.8 NPH	
			HbA1c % (SD)	8.18 (1.14)	8.03 (1.11)						
			BMI mean (SD) kg/m2	24.4 (2.9)	24.6 (3.5)				Major hypoglycaemia	30/216 (14%) detemir vs. 21/99	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
7: 73-82, 2005 REF ID: LEEUW 2005		Total daily basal insulin requirement ≤100IU/day HbA1c ≤12.0% BMI ≤35kg/m2 Exclusion criteria: Proliferative retinopathy Impaired hepatic or renal function severe cardiac problems uncontrolled hypertension recurrent major hypoglycaemia allergy to insulin pregnant or breastfeeding								(21%) NPH	(<20%)
									Weight change (kg)	-0.1 detemir vs. +1.2kg NPH	
			Comparable between groups for all of the baseline characteristics Drop-outs: 1 detemir patient lost to follow up before treatment; 5 withdrew (1 non-compliance, 2 AE, 2 other); 3 withdrew from NPH group (ineffective therapy, non-compliance and other)						Final weight mean (SD) kg	71.2 (11.4) detemir vs. 72.7 (13.1) NPH	
									Severe AE possibly/ probably related to study drug	2/216 detemir vs. 2/99 NPH	
									Serious AE (no. patients)	12/216 detemir vs. 7/99 NPH	
									Injection site reactions	4/216 (1.9%) detemir vs. 1/99 (1.0%) NPH	

Table 225: RUSSELL-JONES 2004

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Russell-Jones D,	RCT	n=747		Detemir	NPH:	Detemir: 100U/mL at bedtime,	NPH: 100U/mL at	6 month	AE possibly/	1/491 detemir	Funding: Novo

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Simpson R, Hylleberg B, et al. Effects of QD insulin detemir or Neutral Protein Hagedorn on blood glucose control in patients with type 1 diabetes mellitus using a basal-bolus regimen. Clinical Therapeutics 26: 724-736, 2004 Ref ID: RUSSELL-JONES 2004	92 centres in Europe and Australia	Detemir group: n=491 NPH group: n=256 Inclusion criteria: Age ≥18 years type 1 diabetes for at least 12 months Treated with basal bolus insulin injections ≥2 months Total daily basal insulin requirement ≤100IU/day HbA1c ≤12.0% Exclusion criteria:		n=491	n=256	titrated to pre-breakfast/ night 4.0-7.0mmol/litre and 90 minutes post-prandial ≤10.0mmol/litre Concomitant medication: Regular human insulin 100IU/mL with main meals	bedtime	s	probably related to treatment	vs. 1/256 NPH	Nordisk Risk of bias: Randomisation = adequate (computer randomisation) Allocation concealment = unclear (just says randomised) Blinding = no (open label) ITT analysis Powered study (HbA1c). Drop-outs = acceptable (<20%)
									Change in HbA1c mean (SD) %	-0.06 (0.92) detemir vs. +0.06 (1.05) NPH	
									Final HbA1c	8.30 (1.08) detemir vs. 8.41	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		Proliferative retinopathy Impaired hepatic or renal function severe cardiac problems uncontrolled hypertension recurrent major hypoglycaemia concomitant medications known to interfere with glucose metabolism pregnant or breastfeeding								(1.32) NPH	
									Change in fasting plasma glucose mean (SD) mmol/litre	-1.61 (5.98) detemir vs. -0.15 (6.24) NPH	
			Women (%) Mean (SD)	34.4	38.7				Final fasting plasma glucose mean (SD) mmol/litre	10.27 (3.95) detemir vs. 11.40 (5.13) NPH	
			Age (year) Mean (SD)	40.9 (12.4)	39.8 (12.3)				Coefficient of variability SMPG (%)	37.4 detemir vs. 43.0 NPH	
			BMI kg/m2	25.1 (3.4)	25.4 (3.4)				Change in body weight mean (SD) kg	-0.23 (2.83) detemir vs. +0.31 (2.93)	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
										NPH	
			Mean (SD) duration diabetes (year)	17.1 (11.3)	16.4 (9.5)				Final body weight mean (SD) kg	76.3 (12.4) detemir vs. 76.5 (12.3) NPH	
			HbA1c	8.35 (1.20)	8.35 (1.21)				Major hypo-glycaemia	31/491 detemir vs. 22/256 NPH	
			Drop-outs: AE Ineffective therapy Non-compliance Other Completed	 26 5 3 2 17 465	 21 2 0 5 15 235				Nocturnal hypo-glycaemia	339/491 detemir vs. 180/256 NPH	
									Serious AE possibly/ probably related to study drug	<2% both detemir and NPH	
			Comparable between groups for all of the baseline characteristics								

Table 226: STANDL 2004

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Standl E, Lang H, Roberts A. The 12-month efficacy and safety of insulin detemir and NPH insulin in basal-bolus therapy for the treatment of type 1 diabetes. Diabetes Technology and Therapeutics 6(5): 579-588, 2004 Ref ID: STANDL 2004	RCT 47 centres in Europe, Australia and New Zealand	n=461 initially enrolled, 421 completed initial 6 month period; 289 entered extension Detemir group: n=154 NPH group: n=135 Inclusion criteria: Age 18-74 years type 1 diabetes for at least 12 months Treated with twice daily basal insulin plus mealtime bolus injections ≥2 months Total daily basal insulin requirement ≤100IU/day HbA1c ≤12.0% BMI ≤35kg/m2		Detemir n=154	NPH: n=135	Detemir: 100U/mL twice daily , titrated to fasting 4.0-7.0mmol/litre and 90 minutes post-prandial ≤10.0mmol/litre	NPH: 100U/mL twice daily, titrated to fasting 4.0-7.0mmol/litre and 90 minutes post-prandial ≤10.0mmol/litre	Initial 6 months, then 6 months extension = 12 month results	Final mean (SE) HbA1c	7.88 (0.082) detemir vs. 7.78 (0.088) NPH	Funding: Novo Nordisk Risk of bias: Randomisation = unclear (just says randomised) Allocation concealment = unclear (just says randomised) Blinding = no (open label) ITT analysis Power not stated Drop-outs = acceptable (<20%)
			Women (%)	34.4	38.7				Final fasting plasma glucose mean (SE) mmol/litre	10.1 (0.45) detemir vs. 9.84 (0.48) NPH	
			Age (year), mean (SD)	40.7 (13.4)	42.5 (12.3)				Major hypo-glycaemia (no. patients	18/154 detemir vs. 14/135 NPH	
			BMI kg/m2 Mean (SD)	25.2 (3.0)	25.6 (3.3)						
			Duration diabetes (year), Mean (SD)	16.1 (9.1)	16.0 (10.6)				Nocturnal hypo-glycaemia	102/154 detemir vs.	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		Exclusion criteria: Proliferative retinopathy Impaired hepatic or renal function severe cardiac problems uncontrolled hypertension recurrent major hypoglycaemia insulin allergy pregnant or breastfeeding	HbA1c % (SD)	7.72 (1.26)	7.66 (1.19)					94/135 NPH	
			Drop-outs: Protocol violation AE Ineffective therapy Non-compliance Other Completed	20 1 2 6 6 6 134	17 1 0 8 2 7 118	Concomitant medication: Human soluble insulin with main meals			Mean weight change	-0.3kg detemir vs. +1.4kg NPH	
									AE possibly/ probably related to study drug	17/154 (11%) detemir vs. 8/135 (6%) NPH	
			Comparable between groups for all of the baseline characteristics						Serious hypo-glycaemia recorded as AE (episodes)	4 detemir vs. 3 NPH	
									Injection site reaction	1 detemir vs. 0 NPH	

Table 227: VAGUE 2003

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
P. Vague, J. L. Selam, S. Skeie, I. Leeuw, J. W. Elte, H. Haahr, A. Kristensen, and E. Draeger. Insulin detemir is associated with more predictable glycaemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin	RCT 46 centres in 5 countries in Europe.	n=448 Detemir group: n=301 NPH group: n=146 Inclusion criteria: type 1 diabetes for at least 1 year Treated with basal-bolus insulin regimen ≥2 months HbA1c ≤12.0% BMI ≤35kg/m2 Exclusion criteria: Proliferative retinopathy Impaired hepatic or renal function		Detemir: n=301	NPH: n=146	Detemir: 1200nmol/mL twice/day (morning and evening) titrated aiming for fasting/pre-prandial 4-& mmol/litre; post-prandial <10 mmol/litre; from 0200 to 0400, 4-7 mmol/litre Concomitant medication: Mealtime insulin aspart	NPH: 600nmol/mL twice/day (morning and evening) titrated aiming for same targets as Detemir group	26 weeks treatment			Funding: Novo Nordisk Risk of bias: Randomisation = unclear. 2:1 ratio telephone randomisation system (Interactive voice response system). Allocation concealment = adequate (telephone randomisation system) Blinding = not mentioned Not true ITT analysis (patients exposed) Powering
			Age, mean (SD) years	8.9 (13.3)	41.8 (14.2)				Final HbA1c Mean (SE) %	7.60 (0.09) n=280 detemir vs. 7.64 (0.10) n=139 NPH	
			Women, %	46.2	49.3				Final weight Mean (SE) kg	70.9 (0.28) n=282 detemir vs. 71.8 (0.33) n=138 NPH	
			Diabetes duration, mean (SD) years	17.1 (9.9)	17.4 (11.0)				Major hypoglycaemia (no. patients)	24 detemir vs. 21 NPH	
			HbA1c mean (SD) %	8.18 (1.14)	8.11 (1.12)				No AEs thought to be related to study drug		
			Weight, kg (SD)	71.5 (11.9)	71.2 (11.5)				Nocturnal hypoglycaemia (no.	198/301 detemir vs. 110/146 NPH	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
aspart. Diabetes Care 26 (3):590-596, 2003. REF ID: VAGUE 2003		Severe cardiac problems Uncontrolled HT Recurrent major hypoglycaemia Allergy to insulin Pregnant or breast-feeding women	Comparable between groups for all of the baseline characteristics Drop-outs: 5.6% (Detemir) 3.4% (NPH)				patients)		not mentioned Drop-outs = acceptable (<20%)

Table 228: ZACHARIAH 2011

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Zachariah S, Sheldon B, Shojaee-Moradie F, et al. Insulin detemir reduces weight gain as a result of reduced food intake in patients with type 1 diabetes.	RCT (crossover) 1 centre in the UK	n=23 Inclusion criteria: Age >18 years type 1 diabetes for at least 12 months Treated with basal insulin plus mealtime bolus injections >3 months HbA1c 7.0-11.0% BMI <40kg/m2	Women: 39.1% Mean (SE) age: 38.8 (2.17) year Mean (SE) BMI: 28 (3.6) kg/m2 Mean (SE) duration diabetes: 19.95	Detemir: once or twice daily, titrated to pre-breakfast and pre-dinner <6.0mmol/litre without hypoglycaemia Concomitant medication:	NPH: once or twice daily, titrated to pre-breakfast and pre-dinner <6.0mmol/litre without hypoglycaemia	16 weeks each treatment	Weight change mean (SE) kg Final mean (SE) HbA1c Major hypo-glycaemia	-0.69 (0.39) detemir vs. +1.7 (0.52) NPH 7.8 (0.23) detemir vs. 7.5 (0.26) NPH none in either group	Funding: Novo Nordisk Risk of bias: Randomisation = unclear (just says randomised) Allocation concealment = unclear (just says

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Diabetes Care 34: 1487-1491, 2011 Ref ID: ZACHARIAH 2011		Exclusion criteria: Anticipated change in medication known to affect glucose metabolism Proliferative retinopathy Impaired hepatic or renal function uncontrolled hypertension recurrent major hypoglycaemia or hypoglycaemia unawareness pregnant	(2.09) year HbA1c mean (SE) 8.2 (0.22)% Drop-outs: 1 dropped out for personal reasons	Insulin aspart with main meals			(no. patients)		randomised) Blinding = no (open label) ITT analysis = not stated Power not stated Drop-outs = acceptable (<20%)

G.4.3 Mixed insulin

G.4.3.1 Basal-bolus (mixed insulin) versus basal (NPH)-bolus (HI)

Table 229: CIOFETTA 1999

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
M. Ciofetta, C. Lalli, P. Del Sindaco, E. Torlone, S. Pampanelli, L.	RCT - Parallel 10	n=24 Inclusion criteria:		HI + NPH once n=8	Lisp + NPH once n=8	MIX Lisp + NPH bed n=8	Hum R (+ NPH bedtime) Pre-meal human regular insulin.	SELF-MIX: Lispro + NPH (+ NPH bedtime)	3 months treatment	HbA1c, final value, % (SEM)	HI: 6.84 (0.2) Lisp: 6.96 (0.2)	Funding: BB and sons Risk of bias:

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Mauro, D. L. Chiara, P. Brunetti, and G. B. Bolli. Contribution of postprandial versus interprandial blood glucose to HbA1c in type 1 diabetes on physiologic intensive therapy with lispro insulin at mealtime. Diabetes Care 22 (5):795-800, 1999. REF ID: CIOFETTA 1999	centres in Europe and South Africa	type 1 diabetes Exclusion criteria: None given patients were free of detectable microangiographic complication patients having treatment with intensive insulin therapy (regular insulin at each meal, NPH at bedtime)	Age, years (SEM)	33 (4) thus likely to be all adults - small SE			NPH at bedtime. ---------- Lispro + NPH Pre-meal insulin lispro. NPH at bedtime. Lispro given 0-5mins, and Hum R at 10-40 minutes before meals	Pre-meal Mixed insulin (Lispro + NPH). NPH at bedtime. Pre-meal Lispro given in separate injection to pre-meal NPH			MIX: 6.41 (0.12)	Randomisation = unclear (details not given) Allocation concealment = not mentioned Blinding = not mentioned. ITT analysis (no drop-outs) Powering not mentioned. Drop-outs = None
			Women, %	29						Severe hypoglycaemia., no. of patients	HI: 0 Lisp: 0 MIX: 0	
			Diabetes, mean years (SEM)	13 (2.1)								
			HbA1c, % (SEM)	Overall 6.84 (0.20)						Mild hypoglycaemia, episodes/patient/month (SEM)	HI: 4.0 (0.5) Lisp: 8.1 (0.8) MIX: 5.2 (1.2)	
			HbA1c, % (SEM)	6.79 (0.17)	6.89 (0.16)	6.83 (0.18)						
			Drop-outs (6 months): None mentioned				BOTH GROUPS: Injections by pen HumaPen, Eli Lilly). Doses adjusted to specific treatment goals of blood glucose.			Unclear if done ANCOVA analysis (best for cross-over studies).		

Table 230: Herz 2002

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
M. Herz, V. Arora, B. Sun, S. C. Ferguson, G. B. Bolli, and B. M. Frier. Basal-bolus insulin therapy in Type 1 diabetes: Comparative study of pre-meal administration of a fixed mixture of insulin lispro (50%) and neutral protamine lispro (50%) with human soluble insulin. Diabet.Me	RCT - crossover 10 centres in Europe and South Africa	n=109 Inclusion criteria: type 1 diabetes 22-43 years old type 1 diabetes > 2 years duration In good health HbA1c <1.75 x upper limit of non-diabetic range SMBG Using basal-bolus regimen with pre-meal human soluble insulin or Lispro, supplemented by NPH at bedtime, for at least 3 months. Regular meals at least 3/day		Mix50/ HI n=53	HI/Mix 50 n=56	Humalog Mix50 + NPH Pre-meal insulin lispro mixture (Humalog Mix50). NPH at bedtime. Lispro given 0-5mins before meals	Human soluble Insulin + NPH Pre-meal Human Soluble Insulin. NPH at bedtime. Human insulin given 30mins before meals	12 weeks treatment (each cross-over period)	HbA1c, final value, % (SD)	Mix: 8.1 (1.3) HI: 8.2 (1.2) NS diff	Funding: Eli Lilly Risk of bias: Randomisation = unclear (as details not given) Allocation concealment = not mentioned No wash-out period Blinding = open label as different appearances of drugs. ITT analysis (LOCF) Powered study (Blood glucose.). Drop-outs = acceptable (<20%) Not done ANCOVA
			Age, years (SD)	34.4 (9.8)	31.4 (8.9)				Hypoglycaemia, episode/patient (SD)	Mix: 4.8 (5.1) HI: 5.1 (5.3) NS diff	
			Women, %	56	46				Nocturnal hypoglycaemia, No. patients	Mix: 69 HI: 71 NS diff	
			Diabetes, mean years (SD)	11.2 (7.2)	11.0 (7.3)				Severe hypoglycaemia, No. patients	Mix: 6 HI: 10 NS diff	
			HbA1c, % (SD)	8.1 (1.2)	7.9 (1.5)				Weight, change from baseline, kg (SD)	Mix: 0.3 (2.2) HI: 1.0	
			Both groups similar for all baseline characteristics								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
d. 19 (11):917-923, 2002. REF ID: HERZ 2002		Exclusion criteria: 2 or more episodes of severe hypoglycaemia. (requiring external assistance within the previous 3 months)	Drop-outs (6 months): n=9 (Mixed) and n=10 (HI)	BOTH GROUPS: Injections given using a pen device (HumaPen, Eli Lilly). Doses adjusted to specific treatment goals of blood glucose.				(2.2)	analysis (best for cross-over studies).

G.4.3.2 Basal (some patients)-bolus (mixed insulin) versus basal (NPH)-bolus (HI)

Table 231: CHEN 2006

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
J. W. Chen, T. Lauritzen, A. Bojesen, and J. S. Christiansen. Multiple mealtime	RCT - crossover Denmark study	n=27 Inclusion criteria: Adults aged ≥18 years		All completers (n=23)	Biphasic Insulin Aspart (BIAsp 30) + NPH (in n=48% patients) Pre-meal	Human short-acting (SA) soluble Insulin + NPH Pre-meal	12 weeks treatment (each cross-over	HbA1c, final value %, geometric mean (range)	MIX: 8.3 (6.7-9.8) HI: 8.6 (7.4-11.4)	Funding: Novo Nodisk Risk of bias: Randomisation = unclear (as details not
			Age, years, median	44.8 (20.6 –				patient preference for	n=19 (83%)	

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
administration of biphasic insulin aspart 30 versus traditional basal-bolus human insulin treatment in patients with type 1 diabetes. Diabetes Obes.Metab. 8 (6):682-689, 2006. REF ID: CHEN 2006		Insulin-treated type 1 diabetes (ADA criteria) Diabetes duration >12 months Treated with soluble human insulin (Actrapid) 3x/day plus bedtime NPH (Insulatard) during last 6 months – total daily insulin dose <1.8 IU/kg BMI <35 kg. Mean HbA1c ≥8% in last 6 months Exclusion criteria: Diabetic complications requiring acute treatment Uncontrolled hypertension History of drug and alcohol abuse	(range)	62.5)	BIAsp30 (NovoMix30 FlexPen). NPH at bedtime (in some patients). BIAsp30 given immediately before meals	Human SA soluble insulin (ActRapid Pen). NPH (Insulatard FlexPen) at bedtime. Human insulin given between 0-10 minutes before meals.	period)	MDI MIX vs. Basal-bolus HI		given) Allocation concealment = not mentioned No wash-out period Blinding = open label. Not ITT analysis (for blood glucose, unclear otherwise) Powered study (HbA1c). Drop-outs = acceptable (<20%) Not done ANCOVA analysis (best for cross-over studies).
			Women, %	35				Major hypoglycaemia, no patients	MIX: 2 HI: 1	
			Diabetes duration, years, median (range)	19.35 (1.6 – 44.6)				Hypoglycaemia, total events/patient /week, median (range)	MIX: 1.2 (0.1-3.1) HI: 0.7 (0 0-3.3)	
			Weight, kg, mean (SD)	77.6 (10.9)				Nocturnal Hypoglycaemia, total events/patient /week, median (range)	MIX: 0.2 (0.1-0.7) HI: 0.2 (0.1-0.7)	
			HbA1c, %, geometric mean (range)	9.2 (8.1-12.3)						
			Drop-outs: n=4		IN BOTH GROUPS: Dose adjustments made by patients according to Blood glucose. Targets and results of SMBG and advice of diabetes nurse.			IN PTS WHO TOOK MIX + NPH: Hypoglycaemia, total events/patient /week, median (range)	MIX + NPH: 1.2 (0.1-3.1)	
								IN PTS WHO TOOK MIX ONLY:	MIX ONLY: 1.1 (0.3-1.9)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		Treated with other drugs known to affect blood glucose.					Hypoglycaemia, total events/patient/week, median (range)		

G.4.3.3 Basal-bolus (mixed insulin) versus basal (HI)- (bolus optional)

Table 232: KHACHADURIAN 1989

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
A. K. Khachadurian, J. A. Davidson, S. Braunstein, G. Redmond, M. Greenfield, A. A. Lauritano, and P. Haycock. Comparison of fixed-	RCT 5 centres, USA	n=78 (n=72 analysed) type 1 diabetes + type 2 diabetes but >70% type 1 diabetes Inclusion criteria: Adults Diabetes (type 1 diabetes and type 2 diabetes) Treated with MDI of animal NPH insulin with or		MIX (n=29)	HI (n=43)	MIXED fixed dose: 30% regular human/70% NPH 30% Semisynthetic regular human insulin (Novolin R) and 70% NPH semisynthetic human	Human (LA) semi-synthetic insulin + optional bolus Human semi-synthetic insulin NPH (Novolin N) Varying dose	12 weeks treatment	HbA1c, final value %, mean	MIX: 8.4 HI: 8.6	Funding: Not mentioned Risk of bias: Randomisation = unclear (as details not given) Allocation concealment = not mentioned Blinding = not mentioned.
			Age, years, mean (SE)	44.0 (2.9)	42.9 (2.3)				Ketoacidosis, no. of patients	MIX: 1 HI: 0	
			Women, %	52	58				Hypoglycaemia, events/week, mean	MIX: 0.8 HI: 1.4 NS diff between groups or change from baseline	
			Diabetes duration, years, mean (SE)	15.1 (1.5)	15.0 (1.4)						

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
ratio versus variable-ratio regular and NPH semisynthetic human insulin in insulin-requiring diabetic patients. Clin.Ther. 11 (4):485-494, 1989. REF ID: KHACHADURIAN 1989		without supplemental regular insulin. Exclusion criteria: Significant hypertension or CV, renal, hepatic or neurological disease Life expectancy <3 years Cancer Alcoholism Pregnancy or risk of conception Hypersensitivity or allergy or resistance to insulin Significant abnormalities in laboratory values Use within preceding 3 months of any insulin formulations other than animal NPH insulin.	Weight, kg, mean (SE)	76.8 (2.7)	72.9 (2.3)	insulin isophane suspension (Novolin N) Given BID (ie. twice/day) patients mixed the insulins in the syringe (as no pre-mix available at the time). Insulin injection administered immediately after mixing.	supplements of regular semisynthetic human insulin (Novolin R) could be added to the NPH (Novolin N) if necessary.		Injection site reactions, no of patients	MIX: 2 HI: 3	Not ITT analysis for efficacy but ITT for safety Powering not mentioned. Drop-outs = acceptable (<20%)
			HbA1c, %, mean	8.3	8.2						
			Type of diabetes: type 1 diabetes type 2 diabetes	20 (69%) 9 (31%)	32 (74%) 11 (26%)						
			NS for all baseline characteristics except for Mean FSG SS higher in the mixed vs. control group. Drop-outs: n=6 Additionally n=5 patients were mis-randomised from fixed ratio group into the control group.								

G.4.3.4 Basal (mixed)-bolus (aspart) versus basal (detemir)-bolus (aspart)

Table 233: HIRSCH 2012B

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
I B. Hirsch, B Bode, JP Courreges, P Dykiel, E Franek, K Hermansen, A King, H Mersebach, and M Davies. Insulin degludec/insulin aspart administered once daily at any meal, with insulin aspart at other meals versus a standard basal-bolus regimen in patients	RCT 79 sites in 9 countries around the world	n=548 Inclusion criteria: Adults aged ≥18 years type 1 diabetes Diabetes duration ≥12 months Currently treated with insulin (basal-bolus, pre-mixed or self-mixed regimens for at least 12 months. BMI ≤35 kg. Mean HbA1c 7-10% Exclusion criteria: Insulin regimen other than above, within 3 months of trial Basal-bolus regimen with basal insulin		IDeg/Asp (n=366)	IDet (n=182)	IDegAspart + IAsp (n=366) Once/day with main meal IDegAsp (70% LA degludec/30% SA aspart; 3ml Flexpen). 100U/ml Aspart given at the remaining meals (100U/ml, 3ml FlexPen). IDegAsp could be moved to another main meal, at physician's discretion	IDet + IAsp (n=182) IDet (detemir; 3ml Flexpen) once/day at evening meal or bedtime. 100U/ml Aspart given at all meals (100U/ml, 3ml FlexPen). A second dose of detemir could be added in the morning, if inadequate Glycaemic	26 weeks treatment	HbA1c, final value %,	MIX: 7.6 DET: 7.6	Funding: Novo Nodisk Risk of bias: Randomisation = unclear (2:1, stratified based on previous insulin treatment regimen but other details not given) Allocation concealment = not mentioned Blinding = open label, as the drugs required different number and timing of
			Age, years, mean (SD)	40.7 (12.8)	42.6 (13.8)				HbA1c, change from baseline and MD, % NS difference, thus non-inferior	MIX: -0.75% DET: -0.70% Overall MD: -0.05% (95% CI -0.18 to 0.08)	
			Women, %	48	55						
			Diabetes duration, years, mean (SD)	17.2 (11.3)	17.9 (12.3)				% patients reaching target <7.0%	MIX: 24.6 DET: 20.3 NS diff	
			Weight, kg, mean (SD)	76.7 (14.6)	76.0 (14.0)				Severe hypoglycaemia, n	MIX: 35/362 DET: 22/180	
			HbA1c, %, mean (SD)	8.3 (0.8)	8.36 (0.7)				Confirmed hypoglycaemia, n	MIX: 341/362 DET: 168/180	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
with type 1 diabetes: a 26-week, phase 3, randomized, open-label, treat-to-target trial. Diabetes Care 35 (11):2174-2181, 2012. HIRSCH 2012B		injected twice/day (BID). Anticipated change in concomitant medications known to interfere with glucose metabolism Recurrent severe hypoglycaemia or hypoglycaemia unawareness Proliferative retinopathy or maculopathy requiring treatment Pregnancy or breast-feeding Renal or hepatic dysfunction Significant CV disease Cancer Other conditions likely to interfere with trial results.	Previous treatment, % on basal-bolus	91.3	88.5		control (investigator's discretion)		Nocturnal hypoglycaemia, n	MIX: 192/362 DET: 125/180	injection. ITT analysis (LOCF) Non-inferiority study (HbA1c). Drop-outs = acceptable (<20%)
			patients well matched for all baseline characteristics. Drop-outs: MIX: n=46 (12.6%) DET: n=27 (14.3%)			IN BOTH GROUPS: Aspart given immediately before the meals Dose adjustments once/week according to protocol-specified titration guidelines (details are given in paper). Treat to target approach (details are given in paper). Adjustments based on mean SMBG from preceding 3 days.			SF-36 physical, change from baseline: MIX – DET	0.3 (95%CI -0.6 to 1.3) NS diff	
									SF-36 mental, change from baseline: MIX – DET	-0.1 (95%CI -1.6 to 1.3) NS diff	
									AEs, n	MIX: 239/362 DET: 114/180	
									SAEs, probably related to trial treatment, n	MIX: 15/362 DET: 5/180	

G.4.3.5 Basal/bolus (self-mixed insulin) versus basal (NPH) plus bolus (human regular)

Table 234: JANSSEN 2000

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
M. M. Janssen, F. J. Snoek, N. Masurel, R. P. Hoogma, W. L. Deville, C. Popp-Snijders, and R. J. Heine. Optimized basal-bolus therapy using a fixed mixture of 75% lispro and 25% NPL insulin in type 1 diabetes patients: no favorable effects on glycemic control,	RCT Netherlands study	n=35 (mainly adults) Inclusion criteria: Diabetes (type 1 diabetes) Reasonable glycaemic control (HbA1c <8.3%) Using MIT (multiple injection therapy) with human regular insulin before meals and NPH at bedtime. Exclusion criteria: None given.		MIX (n=17)	HI (n=18)	MIXED fixed dose: Lispro high mixture (HM) and NPL 75% Lispro/25% NPL Given BID (ie. twice/day) patients self-mixed the insulins in the syringe (as no pre-mix available at the time). Insulin HM taken immediately before meals	Human (SA) regular insulin + NPH (LA) Human semi-synthetic insulin NPH (Novolin N) Varying dose supplements of regular semisynthetic human insulin Regular Insulin to be taken 30 minutes before meals	12-14 weeks treatment	HbA1c, final value %, mean (SD)	MIX: 7.2 (0.7) HI: 6.7 (0.6)	Funding: Eli Lilly Risk of bias: Randomisation = unclear (as details not given) Allocation concealment = not mentioned Blinding = open label. ITT analysis (no drop-outs mentioned) Powering not mentioned. Drop-outs = not mentioned
			Age, years, mean (SD)	33.0 (8.5)	29.4 (8.7)				Severe hypoglycaemia. n/N	MIX: 1/17 HI: 1/18	
			Women, %	35	39				DTSQ Treatment satisfaction – 6 item Likert scale 0-6	No different between groups (data not given)	
			Diabetes duration, years, mean (SD)	15.7 (7.7)	11.9 (8.5)				WBQ (well-being questionnaire) – 3 item Likert scale 0-3	No difference between groups (data not given)	
			BMI, kg/m2, (SD)	24.9 (3.1)	23.0 (2.3)						
			HbA1c, %, mean , SD	7.5 (0.5)	7.0 (0.7)						
			All baseline characteristics were similar for both groups, except for mean HbA1c levels in the Mixed vs. Regular group. Drop-outs:			IN BOTH GROUPS: dose of insulin if necessary were					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
hysiological responses to hypoglycemia, well-being, or treatment satisfaction. Diabetes Care 23 (5):629-633, 2000. REF ID: JANSSEN 2000			Not mentioned	adjust by increments of 2U every 3 days to attain glucose targets. patients kept SMBG diaries.					

G.4.3.6 Basal/bolus (mixed insulin: aspart) versus basal/bolus (mixed insulin: human)

Table 235: BOEHM 2002

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
B. O. Boehm, P. D. Home, C. Behrend, N.	RCT	n=294 type 1 diabetes and type 2 diabetes	type 1 diabetes subgroup	BIAsp (n=55)	BHI (n=49)	MIXED: BIAsp 30	MIXED: BHI 30	12 weeks treatm	Major hypoglycaemia, no. of	BIAsp: 14	Funding: Part of Novo Nordisk

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
M. Kamp, and A. Lindholm. Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in Type 1 and Type 2 diabetic patients. Diabet.Med. 19 (5):393-399, 2002. REF ID: BOEHM 2002	36 centres in Europe	(only n=104/36% type 1 diabetes) – but type 1 diabetes subgroup analysis was presented for outcome of major hypoglycaemia Inclusion criteria: Adults Diabetes (type 1 diabetes and type 2 diabetes) BMI <35.0 HbA1c ≤11.0% Already using twice/day insulin regimens. Exclusion criteria: None given.	Age, years, mean (SD)	43.2 (13.4)	46.3 (12.8)	BIPHASIC ASPART 30 /70 (pre-mix of30% free IAsp and 70% protamine-bound IAsp) Given twice/day, before breakfast and dinner) BiAsp30 to be injected within 10 minutes before meals	BIPHASIC HUMAN INSULIN 30/70 (Pre-mix equivalent of BiAsp) Given twice/day, before breakfast and dinner) BHI to be injected approx. 30 minutes before meals	ent	episodes in type 1 diabetes patients	BHI: 30	programme Risk of bias: Randomisation = unclear. Blocks of 8, stratified within each centre; but details of generation method not given Allocation concealment = good. Electronic drug request/voice response system Blinding = open label. Not true ITT analysis Powered study (HbA1c) Drop-outs = <20%
			Women, %	36	31						
			Diabetes duration, years, mean (SD)	14.9 (11.0)	17.0 (13.0)						
			Weight, kg (SD)	76.1 (14.2)	79.7 (14.5)						
			HbA1c, %, mean , SD	8.37 (1.24)	8.38 (1.14)						
			All baseline characteristics were similar for both groups. Drop-outs: Unclear for type 1 diabetes subgroup. However overall trial population was only 10% drop-outs in BIAsp group and 4% in the BHI group. In the BIAsp group some drop-outs were due to personal reasons, and so the two groups have almost exactly the same % drop-outs for all other /study-related reasons.			IN BOTH GROUPS: Dose of both biphasic insulins were initially 100U/litre and contained in a 1.5ml Penfill cartridges (Novo Nordisk), administered using NovoPen 1.5 device.					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
				Doses adjusted according to SMBG measurements.					overall, type 1 diabetes not mentioned.

G.4.3.7 Basal/bolus (mixed insulin: Humalog25 or Novolog30) versus basal-bolus (glargine plus glulisine)

Table 236: TESTA 2012A

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
MA. Testa, J Gill, M Su, RR. Turner, L Blonde, and DC. Simonson. Comparative Effectiveness of Basal-Bolus Versus Premix Analog Insulin on Glycemic Variability and Patient-Centered Outcomes during Insulin Intensification in Type 1 and	RCT – crossover 52 centres in USA	n=388 type 1 diabetes and type 2 diabetes (only n=82 /21% type 1 diabetes) – but type 1 diabetes subgroup analysis was presented for outcome of QoL Inclusion criteria: Adults age 21-70 years Diabetes (type 1 diabetes and type 2 diabetes) for at	type 1 diabetes + type 2 diabetes	GLARG (n=192)	MIX (n=196)	GLARGINE + GLULISINE Glargine once/day Glulisine before meals	MIXED BIPHASIC ANALOGUE: HUMALOG25 or NOVOLOG 30 Pre-mixed insulins Humalog 25 = 25% Lispro/75% Lispro-protamine Novolog 30 = 30% aspart/70%	12 weeks treatment	treatment satisfaction, type 1 diabetes patients mean (SE) Data from both periods combined	GLARG: 56.2 (2.6) MIX: 28.5 (2.6)	Funding: Part of Novo Nordisk programme Risk of bias: Randomisation = unclear (no details provided). Allocation concealment = unclear (not mentioned) Blinding = not
			Age, years, mean (SD); range	53.7 (10.7); 22-76	53.4 (11.5); 23-76						
			Women, %	20.3	21.9						
			Diabetes duration, years, mean (SD)	15.5 (9.3)	16.6 (9.7)				Regimen acceptance, type 1 diabetes patients mean (SE)	GLARG: 64.6 (1.3) MIX: 60.6	
			BMI, kg/m2 (SD)	34.7 (7.9)	33.9 (7.74)						

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Type 2 Diabetes: A Randomized, Controlled, Crossover Trial. J.Clin.Endocrinol.Metab. 97 (10):3504-3514, 2012. REF ID: TESTA 2012A		least 6 months Stable on premix 75/25 or 70/30 insulin, NPH or insulin glargine with SA insulin consisting of 2 injections/day, with or without concomitant oral medications (metformin, thiazolidione, and/or α-glucosidase inhibitor) for 3 months before screening. HbA1c between 7.0% and 9.0% Employed, unpaid work or active lifestyle. Exclusion criteria: Significant cardiac disease Cancer Laboratory abnormalities	HbA1c, %, mean , SD	7.8 (0.7)	7.8 (0.7)		aspart-protamine Mix taken twice/day		Data from both periods combined	(1.3)	mentioned. No wash-out period ITT analysis No details of powering, Drop-outs = approx.. 20% overall, type 1 diabetes not mentioned. Not done ANCOVA analysis (best for cross-over studies).
			treatment satisfaction (type 1 diabetes patients), mean	44.8		IN BOTH GROUPS: Doses adjusted according to pre-specified algorithm to achieve target blood glucose. Values. Clinic staff phone patients each week to provide insulin-dosing recommendations. patients adjusted dose according to diet and exercise requirements (but not given a specific CHO counting algorithm). OUTCOME MEASURES: QoL 1. Treatment satisfaction: 71-item Treatment Satisfaction module – actual score range not given. 2. Regimen acceptance: 12-item Comparative Treatment Preference module – actual score range not given. HIGHER SCORES= more				
			Regimen acceptance (type 1 diabetes patients), mean	63.5							
			No difference between groups for any of the baseline characteristics. Drop-outs: Unclear for type 1 diabetes subgroup. However overall trial population was only 10% drop-outs in each group after period 1; and after period 2 was 3.5% and 13.9% (Glarg vs. MIX groups respectively). In the MIX group some drop-outs were due to personal reasons, and so the								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		Insulin pump or concomitant oral diabetes medications not listed above Inability to complete a 72 hour CGM session after 3 attempts during the lead-in period before randomisation.	two groups have almost exactly the same % drop-outs for all other /study-related reasons.	favourable response					

G.4.3.8 Basal/bolus (mixed insulin: Lispro25 and 50) versus basal/bolus (mixed human 50 and 30)

Table 237: ROACH 1999 (ID 1029)

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
P. Roach, M. Trautmann, V. Arora, B. Sun, and J. H. Anderson, Jr. Improved postprandial blood glucose control and	RCT – crossover 20 centres in Europe	n=100 type 1 diabetes and type 2 diabetes (only n=37 /37% type 1 diabetes) – but type 1 diabetes subgroup analysis was presented for	type 1 diabetes	LISPRO MIX (n=19)	HI MIX (n=18)	LISPRO MIX25 and MIX50 AM Before breakfast: Pre-mix lispro Mix50	HUMAN INSULIN MIX 50/50 and MIX 30/70 AM Before breakfast: Pre-mix human	3 months each treatment period	HbA1c, final value, % (for type 1 diabetes subgroup)	LISP: 7.69 HI: 7.40 P=0.44	Funding: Not mentioned specifically, but main authors work for Eli Lilly and drugs provided by
			Age, years, mean	42.2	36.5						
			Women, %	37	28						

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
reduced nocturnal hypoglycemia during treatment with two novel insulin lispro-protamine formulations, insulin lispro mix25 and insulin lispro mix50. Mix50 Study Group. Clin.Ther. 21 (3):523-534, 1999. REF ID: ROACH 1999 (ID 1029)		HbA1c and all hypoglycaemia. Outcomes. Inclusion criteria: Adults age 18-70 years Diabetes (type 1 diabetes and type 2 diabetes) (WHO criteria) Treated with commercially avail human insulin twice/day for at least 120 days prior to study Exclusion criteria: HbA1c >9.2% Significant renal, hepatic or cardiac disease Cancer History of drug or alcohol abuse Insulin allergy Recurrent severe	Diabetes duration, years, mean	14.3	11.4	(50% lispro/50% NPL) PM Before dinner: Mix25 Lispro mixes given immediately before the meals	insulin 50/50 (50% regular/50% NPH) PM Before dinner: mix 30/70 Human mixes given 30-40 minutes before the meals.		Severe hypoglycaemia., number of episodes (for type 1 diabetes subgroup)	LISP: 2 HI: 4 P=NS	Eli Lilly. Risk of bias: Randomisation = unclear (no details provided). Allocation concealment = unclear (not mentioned) Blinding = open label. No wash-out period ITT analysis – LOCF; all dropouts had 1 month data No details of powering, Drop-outs = <20%. Unclear if done ANCOVA analysis (best for
			BMI, kg/m2	25.1	24.5				Hypoglycaemia, % patients (for type 1 diabetes subgroup)	LISP: 71% HI: 68% p=NS	
			HbA1c, %, mean ,	Not given							
			Both groups similar for all baseline characteristics. Drop-outs: n=3 (8.1%) for type 1 diabetes subgroup; between the two treatment groups.			IN BOTH GROUPS: Doses adjusted by investigators to reach specific treatment goals of blood glucose.			Nocturnal hypoglycaemia, mean (SD) episodes/patient (for type 1 diabetes subgroup)	LISP: 1.5 (2.3) HI: 2.9 (5.1) P=0.13	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		hypoglycaemia Anaemia or haemoglobinopathy Treated with oral antidiabetic agents, systemic glucocorticoids Insulin doses >2.0U/kg/day.							cross-over studies).

G.4.3.9 Basal/bolus (mixed insulin: Lispro) versus basal/bolus (mixed Human)

Table 238: ROACH 2001 (ID 1043)

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
P. Roach, T. Strack, V. Arora, and Z. Zhao. Improved glycaemic control with the use of self-prepared mixtures of insulin lispro and insulin	RCT 5 centres world wide	n=166 type 1 diabetes and type 2 diabetes (n=100 /60% type 1 diabetes) – but type 1 diabetes subgroup analysis was presented for hypoglycaemia outcomes.	type 1 diabetes and type 2 diabetes	LP/NPL MIX (n=86)	HR/NPH MIX (n=80)	LP/NPL MIX LP = Lispro NPL = Lispro-protamine Self-mixed Twice/day (morning and evening, 0-15	HR/NPH MIX HR = human regular insulin (humulin R) NPH = Human NPH (Humulin N) Self-mixed Twice/day	12 months treatment	Hypoglycaemia, median rate (episodes/patient/30 days) (for type 1 diabetes subgroup)	LP/NPL: 1.61 HR/NPH: 1.65	Funding: Not mentioned specifically, but main authors work for Eli Lilly and drugs provided by Eli Lilly.
			Age, years, mean	47.0	47.0						
			Women, %	31.4	33.8						
			Diabetes	14.0	14.9						

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
lispro protamine suspension in patients with types 1 and 2 diabetes. Int.J.Clin.Pract . 55 (3):177-182, 2001. REF ID: ROACH 2001 (ID 1043)		Inclusion criteria: Adults age 18-75 years Diabetes (type 1 diabetes and type 2 diabetes) (WHO criteria) Treated with mixed insulin SA or RA (regular human or Lispro) and IA or LA insulin twice/day (self-mixed or pre-mixed) for at least 120 days before study Exclusion criteria: HbA1c >9.2% Significant renal, hepatic or cardiac disease Cancer History of drug or alcohol abuse Insulin allergy Recurrent severe hypoglycaemia Anaemia or haemoglobinopath	duration, years, mean			minutes before the two meals)	(morning and evening, 30-45 minutes before the two meals)					Risk of bias: Randomisation = unclear (no details provided). Allocation concealment = unclear (not mentioned) Blinding = open label. ITT analysis – LOCF No details of powering, Drop-outs =not mentioned.
			BMI, kg/m2	25.6	26.1						
			HbA1c, %, mean ,	Not given							
			NS differences between groups for all baseline characteristics except SS lower post-prandial blood glucose. In the LP/NPL group. Drop-outs: Not mentioned.			IN BOTH GROUPS: Doses adjusted to meet blood glucose. Targets After 3 month visit, investigators and patients allowed to alter treatment regimen based on SMBG.					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		y Proliferative retinopathy BMI >35 kg/m2 Lactating, pregnant or intending to become pregnant Treated with oral antidiabetic agents, systemic glucocorticoids Insulin doses >2.0U/kg/day.							

G.4.3.10 Basal/bolus (mixed insulin: Penmix) versus basal/bolus (usual human mix)

Table 239: DUNBAR 1999 (ID 1054)

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
J. M. Dunbar, P. M. Madden, D. T. Gleeson, T. M. Fiad, and T. J. McKenna. Premixed insulin	RCT – cross-over Single centre, Ireland	n=32 Outpatients Inclusion criteria: Adults aged >18 years type 1 diabetes at least 1 year		All completers (n=27)	PEN MIX patients transferred to a SA/LA preparation closest to their previous	PT MIX Continue usual/previous treatment (Human Actrapid and	2 months treatment	HbA1c, % (SD) After both cross-over periods, data combined for all patients	PEN MIX: 11.3 (2.0) PT MIX: 11.2 (2.0)	Funding: Not mentioned specifically, but insulins were Novo Nordisk. Risk of bias:
			Age, years, mean (SD)	34.77 (12.9): range 18-63						
			Women,	Not given						

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
preparations in pen syringes maintain glycemic control and are preferred by patients. Diabetes Care 17 (8):874-878, 1994. REF ID: DUNBAR 1999 (ID 1054)		before study Receiving Human Actrapid & Human Monotard (IA-insulin) as appropriate to clinical requirements. Been on stable insulin regimens for ≥ 2 months Exclusion criteria: None given	%		treatment ratios: Penmix (Novo Nordisk) 10/90%, 20/80%, 30/70%, 40/60% and 50/50% Delivered by Novopen II patients may use different mixtures in morn & eve	Human Monotard (IA-insulin) IN BOTH GROUPS: Doses adjusted by patients or physicians to meet blood glucose. Targets				Randomisation = unclear (no details provided). Allocation concealment = unclear (not mentioned) Blinding = open label. No mention of wash-out period Not ITT analysis No details of powering, Drop-outs <20%. Unclear if done ANCOVA analysis, mentions that used analysis of variance suitable for cross-overs (ANCOVA best for cross-over studies).
			Diabetes duration, years, mean (SD)	10.61 (8.1) – range 9 months – 29 years				Hypoglycaemia grade 3* or 4**, no of patients	PEN MIX: 5 PT MIX: 4	
			BMI, kg/m2	Not given				Hypoglycaemia grade 3* or 4**, no. of episodes	PEN MIX: 8 PT MIX: 22	
			HbA1c, %, mean,	PEN MIX: 11.3 (2.2) PT MIX: 11.8 (1.8) ALL: 11.6 (1.9)				patient preference: 83% Pre-mix Pre-mix easier to use: 86% Continue using pre-mix: 83%		
			Drop-outs: n=5 (16%) other details not mentioned.					*GRADE 3: assistance required (but not parenteral treatment) **GRADE 4: Parenteral treatment or treatment by physician required.		

G.4.3.11 Basal-bolus (bolus normal but mixed basal in evening) versus basal-bolus

Table 240: FANELLI 2002

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
C. G. Fanelli, S. Pampanelli, F. Porcellati, P. Rossetti, P. Brunetti, and G. B. Bolli. Administration of neutral protamine Hagedorn insulin at bedtime versus with dinner in type 1 diabetes mellitus to avoid nocturnal hypoglycemia and improve control. A randomized, controlled trial. Ann.Intern.Med. 136 (137):504-514, 2002.	RCT - crossover 1 centre, Italy	n=22 Inclusion criteria: type 1 diabetes patients receiving long-term intensive insulin treatment (Multiple injections with regular HI before meals and NPH at bedtime) Exclusion criteria: Hypoglycaemia unawareness History of severe hypoglycaemia patients had no detectable microangiographic complications, autonomic neuropathy, peripheral		All patients	BASAL-BOLUS using MIXED evening treatment Regular insulin (RI) at breakfast and lunch, with MIXED INSULIN (regular + NPH) at dinner (evening mixed treatment)	BASAL-BOLUS/split treatment (BB) 4/day INSULIN: (RI) before all 3 meals and NPH bedtime)	4 months treatment	HbA1c, final value %, mean (SE)	MIX: 7.5 (0.15) BB: 7.0 (0.11)	Funding: JDRF International Risk of bias: Randomisation = unclear (as details not given) Allocation concealment = not mentioned Blinding = not mentioned. No mention of wash-out period ITT analysis (no drop-outs) Powered study. Drop-outs = none
			Age, years, mean (SD)	29 (3)				Frequency of self-treatment nocturnal hypoglycaemia. n/patient-day (SE)	MIX: 0.28 (0.04) BB: 0.1 (0.02)	
			Women, %	45				Symptomatic nocturnal hypoglycaemia, episodes/patient-day (SE)	MIX: 0.045 (0.005) BB: 0.027 (0.003)	
			Diabetes duration, years, mean (SD)	14 (2)						
			BMI, kg/m2, (SD)	23 (1)	IN BOTH GROUPS: Doses of meal-time (SA) insulins and NPH insulin were titrated to attain glucose targets. To prevent nocturnal hypoglycaemia, patients were suggested to consume a snack containing 20g CHO when blood			Severe hypoglycaemia	MIX: 0 BB: 0	
			HbA1c, %, mean , SD	6.7 (0.4)				40% and 50% of hypoglycaemia. episodes (MIX and BB respectively), were corrected by consuming 20g CHO; 60%/43% corrected by 40g CHO.		
			Drop-outs: None							

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: FANELLI 2002 (ID 1019)		neuropathy, or microalbinuria patients had no history or clinical evidence of HT and were taking no other medications other than insulin.		glucose. Reached particular levels at bedtime or at night. If hypoglycaemia. Symptoms were not relieved after 10 minutes, then they were to try another similar snack					Unclear if have done ANCOVA analysis – mentions used 2-period cross-over analysis of variance (ANCOVA best for cross-over studies).

G.4.3.12 Basal/bolus (mixed 3/7) versus basal/bolus (mixed 2/8 – 4/6)

Table 241: CUCINOTTA 1991

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
D. Cucinotta, D. Mannino, A. Lasco, E. Di Cesare, C. Musolino, and R. Alessi. Premixed insulin at ratio	RCT - crossover Single centre, Italy	n=20 Inclusion criteria: type 1 diabetes (IDDM) Insulin treated for at least 1 year		All patients	HUMAN PRE-MIX 3/7 (Actraphane HM) Actraphane = Human + NPH	REGULAR MIX (Human + NPH 2/8 to 4/6) 2/day before	4 months treatment	Hypoglycaemia, episodes/week/patient	MIX 3/7: 0.03 R + NPH: 0.03	Funding: Not mentioned Risk of bias: Randomisation = unclear (as details not given)
			Age, years, mean (range)	41.5 (19-72)				Hypoglycaemia, no. of patients	MIX 3/7: 2 R + NPH: 2	

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
3/7 and regular + isophane insulins at mixing ratios from 2/8 to 4/6 achieve the same metabolic control. Diabetes Metab 17 (1):49-54, 1991. REF ID: CUCINOTTA 1991		Stable insulin dose at last 3 months Constant fasting glucose <200mg/dl during the last 2 months BMI between 20-30 kg/m2 Exclusion criteria: None mentioned patients had treatment with regular + NPH human insulin at mixing ratios ranging from 2/8 to 4/6 injected before breakfast and dinner.	Women, %	45	Timing not mentioned – but assuming same as for comparison group	breakfast and dinner				Allocation concealment = not mentioned Blinding = not mentioned. No mention of wash-out period ITT analysis (no drop-outs) Powering not mentioned. Drop-outs = none Unclear if done ANCOVA analysis (best for cross-over studies).
			Diabetes duration, years, mean (range)	21.4 (4-31)						
			Drop-outs: None					*GRADE3: requires assistance of another person		

G.4.4 Adjuncts

Table 242: PITOCCO 2013

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
D. Pitocco,	RCT	n=42		Metf	Plac	Metformin (+	Placebo (+	6		Metfor	Placebo	Funding:

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
F. Zaccardi, P. Tarzia, M. Milo, G. Scavone, P. Rizzo, et al. Metformin improves endothelial function in type 1 diabetic subjects: a pilot, placebo-controlled randomized study. Diabetes Obes.Metab. 15 (5):427-431, 2013. REF ID: PITOCCO 2013	Single centre, Italy	Inclusion criteria: type 1 diabetes Age >18 years Diabetes duration ≥5 years Exclusion criteria: Baseline HbA1c ≥10% Plasma creatinine >1.6 mg/dl Plasma AST elevated > 2x above normal upper limit Co-morbidities Pregnancy Current or former smoking or alcohol abuse treatment other than insulin at baseline and during study.		(n=21)	(n=21)	insulin as already on insulin) titrated up to 850mg TDS (after 2 weeks)	insulin as already on insulin)	months	HbA1c (95% CI), SE	Between group difference: 0.17 (-0.36, 0.72), -0.27		None mentioned Risk of bias: Randomisation: unclear – no details given just says 'randomised' Allocation concealment: unclear – no details given Blinding: double ITT analysis: yes as no drop-outs Drop-outs: none
			Age Mean (SD)	46 (8)	41 (10)				Total daily insulin (95% CI), SE	Between group difference: -0.027 (-0.10, 0.51), -0.22		
			Disease duration, years	9.2	8.8				Weight, kg (95% CI), SE	Between group difference: -2.27 (-3.99, -0.54), -0.85		
			M/F	9/12	9/12				Severe hypo episodes	0	0	
			HbA1c % (SD)	7.24 (0.90)	7.73 (0.42)				Adverse events: Gastrointestinal side-effects	Not reported		
			BMI	28.7	27.3							
			Weight (SD)	83 (12)	77 (11)							
			Drop outs: none									

Table 243: BURCHARDT 2013

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
P Burchardt, A Zawada, P Tabaczewski, D Naskret, et al. Metformin added to intensive insulin therapy reduces plasma levels of glycated but not oxidized low-density lipoprotein in young patients with type 1 diabetes and obesity in comparison with insulin alone: a pilot study. Pol.Arch.Med .Wewn. 123 (10):526-532, 2013.	RCT Poland	n=68 randomised, n=52 completers Inclusion criteria: type 1 diabetes Age 18-60 years Duration >5 years Lack of metabolic control (HbA1c >7.5% despite education and intensive insulin treatment) Obese patients Exclusion criteria: Metabolically decompensate diabetes with acetonuria Suspected lack of compliance as well as glucose and ketone self-monitoring Hypo unawareness or recurrent SH in past 3 months Recurret DKA Pregnancy or lack of		Metf + insulin (n=33)	Insulin (n=19)	Metformin (+ insulin as already on insulin) Doses adjusted to body fat content of individuals. Overweight followed regime of 500-1500 mg/d; Obese took 1000-2550 mg/d according to drug tolerance Metformin taken with meals to minimise GI side-effects	Remained on usual insulin treatment BOTH GROUPS: before randomised treatment started, both groups wre hospitalised for 1 week to o[ptimise insulin treatment.	6 months		Met	Insulin	Funding: Grant from Ponzan University of Medical Sciences Risk of bias: Randomisation: unclear – no details given just says ‘randomised and 1:1’ Allocation concealment: no details given Blinding: open label ITT analysis: no Drop-outs: >20% overall and >10% diff btwn arms
			Age Mean	35.3	30.5				HbA1c, final (SDI)	7.7 (1.2)	8.1 (1.4)	
			Disease duration, years	15.9	15.9							
			M/F	27 women (total 52 patients)					NOTE: patients in metformin group had a SS higher BMI to start with			
			HbA1c % (SD)	9.0 (1.9)	8.3 (1.0)							
			BMI (SD)	29.5 (3.2)	27.1 (2.4)							
			Drop outs: n=2 (metformin) – 6% n=14 (control) – 41%									

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
REF ID: BURCHARDT 2013		contraception Renal impairment Liver disease								

Table 244: SARKAR 2014

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
G. Sarkar, M. Alattar, R. J. Brown, M. J. Quon, D. M. Harlan, and K. I. Rother. Exenatide treatment for 6 months improves insulin sensitivity in adults with type 1 diabetes. Diabetes Care 37 (3):666-670, 2014. REF ID: SARKAR 2014	RCT (cross-over) USA	n=16 randomised, n=13 completers Inclusion criteria: Long-standing type 1 diabetes (duration mean 21 years) Exclusion criteria: None reported		Baseline (end of run-in period) n=13	Exenatide (+ insulin as already on insulin) +/- daclizumab NOTE: analysis done about effects of daclizumab and shown to make no difference to results if patients had dac or not. Exenatide dose: administered sc at starting dose of 2.5ug 2x/day and increased gradually to 10	Remained on usual insulin treatment BOTH GROUPS: before randomised treatment started, both groups had a 2-4 month optimisation period (insulin doses and carb counting adjusted and improved). This was followed by a run-in period in which no	6 months treatment (each cross-over period)		Exen	Insulin	Funding: Grant from NIDDK and NIH Clinical Centre, USA. Risk of bias: Randomisation: unclear – no details given just says 'randomised' Allocation concealment: unclear – no details given Blinding: open label
			Age Mean	37.3 (10.7)				HbA1c - final (SDI)	6.6 (0.5)	6.7 (0.6)	
			Disease duration, years (SD)	21.3 (10.7)				Weight, kg (SD)	72.7 (11.8)	76.9 (11.3)	
			M/F	n=9 male							
			HbA1c % (SD)	6.4 (0.7)				Insulin, units/kg/day	0.47 (0.1)	0.54 (0.13)	
			BMI (SD)	-							
			Weight, kg (SD)	77.7 (11.0)							
			Drop outs: n=2 (no exenatide)								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
			n=1 (exenatide)	micrograms 4 times a day. Prandial insulin doses were reduced by 50% at initiation of exenatide treatment then gradually increased to reach blood glucose targets.	further insulin dose changes were made.					No wash-out period ITT analysis: no Drop-outs: <20%; approx. 10% difference between arms

Table 245: Edelman 2006[39]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Edelman S, Garg S, Frias J, Maggs D, Wang Y, Zhang B et al. A double-blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin	Parallel RCT	n=296 n=148 Pramlintide n=147 Placebo Inclusion criteria: Age ≥18 years, insulin use >1 year, HbA1c 7.5-9.0%, no severe hypo-glycaemia	Adults with type 1 diabetes treated with multiple daily injections (MDI) OR continuous subcutaneous insulin infusion (CSII)			Pramlintide 15-60 µg/meal	Placebo	29 weeks		Pram	Placebo	Funding: Unclear. Authors affiliated with Amylin pharmaceuticals Risk of bias: Randomisation method unclear Allocation concealment: not reported Blinding: said to be "double blind"
				Pram	Placebo				HbA1c (SD)	-0.5% ±0.87	-0.5% ±0.87	
									Hypo-glycaemia (symptoms of)	136/ 148	134/ 147	
									Dose of insulin (SD not reported)	-12IU	+1IU	
									Weight Change	-1.3 ±3.65	+1.2 ±2.9	
									Quality of	3.74	2.74	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
therapy in type 1 diabetes. Diabetes Care. 2006; 29(10):2189-2195 REF ID: EDELMAN2006		for 6 months before screening. Exclusion criteria: Clinically significant comorbid condition including gastroparesis, using medications affecting gastrointestinal motility, using oral anti-diabetic or antiobesity agents	Age Mean (SD)	41 ±14	41 ±12				Life (Likert Scale 1-6)			ITT analysis: last value carried forward Drop-outs: acceptable <20%
			M/F	60/87	72/76				Adverse events: Nausea	93/148	53/147	
			Hb A1c	8.1 ±0.8	8.1 ±0.8				Vomiting	20/148	9/147	
									Reduced appetite	13/148	3/147	
			Drop outs: Pramlintide 12.2%; Placebo 7.5%									

Table 246: Khan 2006

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Khan AS, McLoughney CR, Ahmed AB. The effect of	Cross-over RCT	n=15 Inclusion criteria: C-	Overweight patients (BMI >27) with type 1 diabetes > 1 year. C-peptide negative	Metformin 850mg TDS	Placebo	16 weeks (4 week washout)		Metfor	Placebo	Funding: Equipment/drugs provided by industry Risk of bias:
							HbA1c ±SD baseline final	8.5±1.4 7.8±1.1	8.7±1.1 8.5±1.4	

metformin on blood glucose control in overweight patients with Type 1 diabetes. Diabetic Medicine. 2006; 23(10):1079-1084 [72,73] REF ID: KHAN 2006		peptide <0.18 nmol/litre at a time when blood glucose level as >5.0,type 1 diabetes for >1 year, BMI>27 stable on insulin therapy, baseline HbA1c >6.1%, no late diabetic complications Exclusion criteria: Not reported		Crossover				Insulin baseline final	60 ±14 50 ±13	60 ±13 58 ±12	Randomisation: computer generated Allocation concealment: adequate Blinding: patients and investigators blinded ITT analysis: true ITT Drop-outs: none
			Age Mean (SD)	48 ± 12				Weight baseline final	91 ±12 89 ±11	91 ±12 90 ±12	
			M/F	8/7				Hypos (per pt. per month)	12 ±7	11 ±6	
			Hb A1c	8.6% ±1.4				Adverse events: Gastrointestinal side-effects	3	1	
			BMI	31.3 ± 2.6							
			Insulin Regimen	Basal bolus: 12 Twice daily: 3							
			Drop outs: none								

Table 247: Levetan 2003

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Levetan C, Want LL, Weyer C, Strobel SA, Crean J, Wang Y et al. Impact of pramlintide	Parallel RCT	n=24 Pramlintide= 18; Placebo n=6 Inclusion criteria: type 1 diabetes	Patients with type 1 diabetes >1 year CSII basal-bolus regimen for at least 6 months		Pramlintide 30 µg/ meal TDS	Placebo	4 weeks		Pramlin	Placebo	Funding: Authors employed by Amylin pharmaceuticals Risk of bias: Randomisation:3
				Baseline characteristic given for Pramlintide				Change in Insulin dose IU (mean mealtime)	-1.2 IU		

on glucose fluctuations and postprandial glucose, glucagon, and triglyceride excursions among patients with type 1 diabetes intensively treated with insulin pumps. Diabetes Care. 2003; 26(1):1-8 REF ID: LEVETAN 2003 [96]		>1 year, not changed total daily insulin dosage by more than ±10% for 2 months before study, no severe hyper/hypo-glycaemia for >4 weeks Exclusion criteria: significant history of cardiac disease, poorly controlled HTN, GI hepatic renal or CNS disorders, acute illness, history of drug or alcohol abuse, treatment with drugs known to affect GI motility or		group only						:1 block randomisation Allocation concealment: unclear Blinding: subjects blinded, other blinding unclear ITT analysis: ACA Drop-outs: acceptable (2/24 8%)

Age Mean (SD)	44 ± 11
M/F	8/10
HbA1c	8.2% ± 1.3
BMI	25 ± 10
Insulin Regimen	Lispro 16 Regular 2
Drop outs:	2

		glucose metabolism								

Table 248: Ratner 2004

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Ratner RE, Dickey R, Fineman M, Maggs DG, Shen L, Strobel SA et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in Type 1 diabetes mellitus: a 1-year, randomized controlled	Parallel RCT	n=304 Safety Data n=651 Inclusion criteria: type 1 diabetes >1 year (C-peptide <1ng/ml/DKA/islet cell Abs), HbA1c >8% at screening, stable weight ±2.5kg and stable daily insulin ±10% for >2 months, no severe hypo/hyper-glycaemia for>2 weeks, females post-	Patients aged 16-76 with type 1 diabetes >1year Placebo / Pramlintide 60 µg TDS / 60 µg QD / 90 µg TDS M/F 53/47 / 52/48 / 52/48 / 47/53 HbA 9.0 ±1. / 8.9 ±1. / 8.9 ±1. / 8.9 ±0.	Pramlintide 60 µg - 90 µg TDS and QDS	Placebo	1 year	HbA1c no SD (p<0.05) Insulin dose (no SDs) Safety data: 90 µg group included Pramlintide / Plac 60 TDS / 60 QD / 90TDS Severe Hypos (per 100	Pramlintide / Placebo -0.316 / -0.04 TDS -3% QDS -6% / ±0%	Funding: Authors employed by Amylin pharmaceuticals Risk of bias: Randomisation : method unclear Allocation concealment: unclear Blinding: double blinded ITT analysis: ITT stated but missing data (not true ITT) Drop-outs: High (pramlintide 42% placebo

Reference	Study type	Number of patients	Patient characteristics					Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes				Comments
trial. Diabetic Medicine. 2004; 21(11):1204-1212 REF ID: RATNER 2004		menopausal, sterilized or using adequate contraception Exclusion criteria: Clinically significant cardiovascular, respiratory, CNS, GI, renal or haematological disorders, drug or alcohol abuse, acute febrile illness, drugs that affect GI motility or glucose metabolism	1c	1	1	0	9				patient years)					33%)
			BMI	26.5 ±4.9	26.4 ±4.5	26.8 ±4.4	26.3 ±4.1				Incidence (%) Nausea Vomiting Anorexia	47 9.8 18	47 11 11	59 12 16	12 6.5 2.6	
			Age ±SD	41.3 ±13.6	39.2 ±13.1	41.9 ±13.1	41.0 ±12.8									
			Drop outs: Placebo = 51/154 (33%) Pramlintide = 210/497 (42%)													

Table 249: Meyer 2002

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Meyer L, Bohme	Parallel	n=62	Outpatients with type	Metformin	Placebo	6 months		Metfor	Placeb	Funding:

<table>
<tr>
<td>P, Delbachian I, Lehert P, Cugnardey N, Drouin P et al. The benefits of metformin therapy during continuous subcutaneous insulin infusion treatment of type 1 diabetic patients. Diabetes Care. 2002; 25(12):2153-2158
REF ID: Meyer 2002 [107,108]</td>
<td>RCT</td>
<td>n= 31 Metformin
n=31 Placebo
Inclusion criteria: type 1 diabetes>1 year, C-peptide <0.3 after IV 1g glucagon, Treated with CSII > 1 year, HbA1c<9%, hypo-glycaemic un awareness
Exclusion criteria: any endocrine/ infectious/ inflammatory disease that modifies blood glucose, cardiac/renal/hepatic dysfunction, unstable retinopathy</td>
<td colspan="3">1 diabetes >1 year. Treated with CSII >1 year (HbA1c<9%)
Drop outs: None reported</td>
<td>850mg BD</td>
<td></td>
<td></td>
<td colspan="3">o
HbA1c ±SD: 7.45% ±0.78 | 7.46 ±0.6
Insulin Dose: -4.3 ±9.9 | -1.7 ±8.3
Weight: Full data not reported
Severe Hypo-glycaemia: 3 | 5
Hypo-glycaemia (events/patient/month): 7.8 ±4.5 | 7.5 ±3.9
Adverse events: Gastrointestinal side-effects: 8 | 2</td>
<td>Unclear. Supported by LIPHA pharmaceuticals
Risk of bias:
Randomisation method unclear
Allocation concealment: unclear
Blinding: double blinded
ITT analysis: true ITT
Drop-outs: None reported</td>
</tr>
<tr><td></td><td>Plac</td><td>Met</td></tr>
<tr><td>Age Mean (SD)</td><td>41.1 ±9.8</td><td>39.9 ±12.9</td></tr>
<tr><td>M/F</td><td>20/ 11</td><td>17/ 14</td></tr>
<tr><td>Hb A1c</td><td>7.57 % ±0.76</td><td>7.58 % ±0.84</td></tr>
<tr><td>BMI</td><td>25.8 ±3.6</td><td>26.4 ±4.6</td></tr>
<tr><td></td><td></td><td></td></tr>
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</table>

Table 250: Whitehouse 2002

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Whitehouse F, Kruger DF, Fineman M, Shen L, Ruggles JA, Maggs DG et al. A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. Diabetes Care. 2002; 25(4):724-730 REF ID: Whitehouse 2002	Multi-centre Parallel RCT	n=480 Inclusion criteria: Aged 16 to 70 years, type 1 diabetes >1 year, C-peptide<1ng /ml, baseline HbA1c 7-13%, no hyper/hypo-glycaemia >2 weeks, not adjusted insulin dose >±10% 1 week Exclusion criteria: Clinically significant IHD, HTN, GI disease, renal disease, unstable diabetic retinopathy, treatment	Patients with type 1 diabetes>1 year			Pramlintide 30-60 µg QDS	Placebo	1 year		Pram	Placebo	Funding: Unclear. Authors affiliated with amylin pharmaceuticals Risk of bias: Randomisation method unclear Allocation concealment: initial randomisation – unclear. Re-randomisation – third party randomisation Blinding: double blinded ITT analysis: ITT stated but missing data (not true ITT) Drop-outs: Pramlintide 28.4% Placebo 29.1%
				Plac	Pram				HbA1c ±SD	-0.39 ±0.824	-0.12 ±0.824	
			Age Mean (SD)	40.4 ±12.1	40.3 ±11.6				Insulin	+2.3% ±27.7	+10.3% ±27.7	
			M/F	55%/ 45%	55%/ 45%				Weight			
			Hb A1c	8.9% ±1.5	8.7% ±1.3							
			BMI	25.8 ±3.5	25.2 ±3.3				Adverse events: (Incidence) Nausea Anorexia Vomiting	 46.5% 17.7% 11.5%	 21.9% 2.1% 8%	
			Drop outs: Pramlintide 28.4%. Placebo 29.1%									

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
		with drugs known to affect GI motility or glucose metabolism								

Table 251: Jacobsen 2009[69]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Jacobsen IB, Henriksen JE, Beck-Nielsen H. The effect of metformin in overweight patients with type 1 diabetes and poor metabolic control. Basic and Clinical Pharmacology and Toxicology. 2009; 105(3):145-149	Parallel RCT Setting: Odense University Hospital Denmark	N =24 n=12 Metformin n=12 Placebo Inclusion criteria: Aged 18-60 years, diagnosed with type 1 diabetes for at least 1 year (plasma C-peptide <5), BMI ≥ 25 kg/m², Exclusion criteria: Pregnancy, impaired	Adults with type 1 diabetes and BMI ≥ 25 kg/m² Met: Age 43.5 ±13.1; BMI 29.5 ±2.7 Placebo: Age 37.3 ±9.6; BMI 29.2 ±2.8 Male:Female 14:10 Drop outs: None reported	Metformin 1g BD	Placebo	24 weeks	Hb A1c Dose of insulin Weight Change Adverse Events: Vomiting Gastro discomfort	Met -0.48% ±0.9 -5.9 IU ±7.6 -3.0 ±3.5 1/12 2/12	Placebo -0.17% ±0.6 -2.9 IU ±5.6 +0.8 ±1.1 0/11 0/11	Funding: Grant from Sehested Masden Foundation. Equipment/drugs provided by industry Risk of bias: Randomisation: method unclear. Number of patients entering run-in period not reported Allocation concealment: not reported Blinding: "double blind" no description

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
REF ID: JACOBSEN2009		vision, impaired renal or hepatic function, cardiac diseases, uncontrolled hypertension, hypo-glycaemic unawareness.								ITT analysis: Unclear Drop-outs: None reported

Table 252: Kielgast 2011[74]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Kielgast U, Krarup T, Holst JJ, Madsbad S. Four weeks of treatment with liraglutide reduces insulin dose without loss of glycemic control in type 1	Parallel RCT	n=19 n=9 Liraglutide n=10 Placebo Inclusion criteria: Aged 18-50 years, BMI 18-27 kg/m², diagnosed between ages of 5 and 40	Adults with type 1 diabetes C-peptide negative			Liraglutide 0.6-1.2 mg/day	Usual Care	4 weeks		Liraglut	Placebo	Funding: Academic grant Risk of bias: Randomisation: adequate, computer generated Allocation concealment: adequate Blinding: no blinding ITT analysis:
									HbA1c	-0.47% ±0.45	-0.2% ±0.32	
									Dose of insulin	-0.13 IU/kg ±0.12	+0.017 IU/kg ±0.06	
									Weight Change	-1.8 ±1.8	+0.2 ±0.95	
				Liraglutide	Placebo							
			Age	35.7	32.9							

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
diabetic patients with and without residual beta-cell function. Diabetes Care. 2011; 34(7):1463-1468 REF ID: KIELGAST2011		years, remission period assumed to be ended, no known late diabetes complications (except low-level (micro) albuminuria), no symptoms of autonomic neuropathy, no use of medication known to affect glucose metabolism Exclusion criteria: Late diabetes complications, autonomic neuropathy, anaemia, HbA1c >8.5%.		±2.2	±1.7							unclear Drop-outs: Not reported
			M/F	9/0	9/1							
			Drop outs: Not reported									

Table 253: Kolterman 1996[82,83]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Kolterman OG, Schwartz S, Corder C, Levy B, Klaff L, Peterson J et al. Effect of 14 days' subcutaneous administration of the human amylin analogue, pramlintide (AC137), on an intravenous insulin challenge and response to a standard liquid meal in patients with IDDM. Diabetologia. 1996; 39(4):492-	Multi-centre Parallel RCT	n=63 n=41Pramlintide (30µg n=18 100µg n=23) n=22 Placebo Inclusion criteria: Aged between 18 and 51 years, IDDM for at least 2 years with fasting plasma C-peptide <1 ng/ml, BMI <27, not needed to vary insulin dose by more than ±10% during the prior week, no severe hypo/ hyper -glycaemia	Adults with type 1 diabetes> 2 years C-peptide negative Pram 30 µg / Pram 100 µg / Placebo Age: 36± 8.5 / 34± 9.6 / 37 ±9.4 Hb A1c: 8.3± 1.87 / 8.8± 1.4 / 8.9 ±1.87 M/F: 11/ 7 / 19/ 4 / 14/8 Drop outs: Pramlintide 30µg – 1/18 Pramlintide 100µg – 1/23 Placebo – 1/22 Total: 3/63	Pramlintide 30µg/meal 100µg/meal (300µg/meal not included for this review) three times daily	Placebo	4 weeks	Adverse Events: Gastro-intestinal Symptoms (including nausea, vomiting and anorexia)	Pram 21/41	Placebo 4/22	Funding: Unclear. Authors affiliated with Amylin pharmaceuticals Risk of bias: Randomisation unclear Allocation concealment: not reported Blinding: "double blinded" ITT analysis: adverse event data, per-protocol analysis Drop-outs: majority drop-outs due to adverse events (outcome) therefore not a significant source of risk of bias

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
499 REF ID: KOLTERMAN 1996		during the 2 weeks prior to the study Exclusion criteria: Not reported								

Table 254: Lund 2008[99]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Lund SS, Tarnow L, Astrup AS, Hovind P, Jacobsen PK, Alibegovic AC et al. Effect of adjunct metformin treatment in patients with type-1 diabetes and persistent inadequate glycaemic control. A randomized	Parallel RCT	n=100 n=49 Metformin n=51 Placebo Inclusion criteria: type 1 diabetes ≥ 5 years, age ≥ 18 years, mean HbA1c ≥ 8.5% at enrolment and in all available measurements during one year before enrolment.	Adults with type 1 diabetes ≥5 years Caucasian.			Metformin 1g BD	Placebo	1 year		Metformin	Placebo	Funding: Equipment/drugs provided by industry Risk of bias: Randomisation adequate, computer generated Allocation concealment: adequate Blinding: double blinded ITT analysis: last value carried forward
									HbA1c	-0.1% ±0.78	-0.23% ±0.79	
									Hypo-glycaemia: Minor Severe	 48/49 15/49	 49/50 10/50	
									Dose of insulin	-3.5 ±7.07	+2.5 ±7.03	
									Weight change	-1.21 ±3.87	0.53 ±4.07	
				Metformin	Placebo				Gastro-intestinal Symptoms	43/49	39/50	
			Age	46.1	44.9							

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
study. PloS One. 2008; 3(10):e3363 REF ID: LUND2008		Exclusion criteria: HbA1c <8.0% at baseline, hypo-glycaemic unawareness, clinical signs of heart failure, plasma creatinine above normal upper limit, plasma AST >3 times above the normal upper limit, factors II, VII and X decreased <0.7, serious co-morbidities, pregnancy, history of drug or alcohol abuse		±11.6	±10.8							Drop-outs: Low rate, similar missing in both groups
			M/F	33/16	31/20							
			Drop outs: Metformin 1/49 (2%) Placebo 1/51 (2%)									

Table 255: Nyholm 1999[119,120]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Nyholm B,	Cross-	n=14	Adults with type 1	Pramlintide	Placebo	4 weeks		Pram	Placebo	Funding:

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Orskov L, Hove KY, Gravholt CH, Møller N, Alberti KG et al. The amylin analog pramlintide improves glycemic control and reduces postprandial glucagon concentrations in patients with type 1 diabetes mellitus. Metabolism: Clinical and Experimental. 1999; 48(7):935-941 REF ID: NYHOLM1999	over RCT	Inclusion criteria: Not reported Exclusion criteria: Not reported	diabetes		30 µg QDS		per intervention with 3-5 week washout period	HbA1c	7.9% ±1.12	8.2% ±1.12	Not reported Risk of bias: Randomisation: unclear Allocation concealment: not reported Blinding: "double blinded" ITT analysis: Unclear. No drop-outs. Switching not reported Drop-outs: None
								Hypo-glycaemia	11/14	7/14	
								Weight change	-2.3 ±1.12	-1.3 ±1.45	
				Crossover							
			Age (range)	36.6 (24-53)							
			M/F	14/0							
			HbA1c (range)	8.6% (7.3-9.9)							
			Drop outs: None								

Table 256: Thompson 1997[154]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Thompson RG, Pearson L, Kolterman OG. Effects of 4 weeks' administration of pramlintide, a human amylin analogue, on glycaemia control in patients with IDDM: effects on plasma glucose profiles and serum fructosamine concentrations. Diabetologia. 1997; 40(11):1278-1285 THOMPSON 1997	Parallel RCT Setting: Outpatient clinic in USA	n=215 n=173 Pramlintide n=42 Placebo Inclusion criteria: Aged 18 to 66 years, IDDM, a basal C-peptide concentration less than 1.0ng/ml and/or a history of diabetic ketoacidosis, and negative results for serum hepatitis B surface antigen Exclusion criteria: Not reported	Adults with type 1 diabetes Pram / Placebo Age 35.3 / 35.6 HbA 1c 8.9% / 9.3% BMI 25.0 / 25.2 Drop outs: Pramlintide 6/173 (3.5%) Due to adverse events Placebo 0/42	Pramlintide 30-60 µg in four different dosing regimens:	Placebo	4 weeks	Hypo-glycaemia: Severe Adverse Events	Pram: 3/173 Placebo: 1/42		Funding: Not reported. Authors employed by Amylin pharmaceuticals Risk of bias: Randomisation method unclear Allocation concealment: not reported Blinding: double blinded ITT analysis: safety data used per-protocol analysis Drop-outs: differential rate acceptable (<10%)

Table 257: Thompson 1997[154,155]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Thompson RG, Peterson J, Gottlieb A, Mullane J. Effects of pramlintide, an analog of human amylin, on plasma glucose profiles in patients with IDDM: results of a multicenter trial. Diabetes. 1997; 46(4):632-636 REF ID: THOMPSON 1997A	Parallel Multicentre RCT	n=168 n=126 Pramlintide n=42 Placebo Inclusion criteria: Aged 18-60 years, IDDM, HbA1c level <13%, negative for hepatitis B surface antigen (HBsAg) and stable body weight prior to admission to trial Exclusion criteria: Not reported	Adults with type 1 diabetes Pram / Placebo Age: 36.8 / 35.3 M/F: 92/34 / 35/7 Drop outs: 3/168	Pramlintide 10µg QDS 30µg QDS 100µg QDS	Placebo	2 weeks		Pram	Placebo	Funding: Authors employed by Amylin Pharmaceuticals Risk of bias: Randomisation: unclear Allocation concealment: not reported Blinding: "double blind" ITT analysis: Not reported Drop-outs: Acceptable (<10%)
							Hypo-glycaemia: Mild	103/126	34/42	
							Adverse Events:			
							Nausea	27/126	1/42	
							Anorexia	5/126	0/42	

G.4.5 Needle length, site and rotation

Table 258: HIRSCH 2012

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
L. J. Hirsch, M. A. Gibney, J. Albanese, S. Qu, K. Kassler-Taub, L. J. Klaff, and T. S. Bailey. Comparative glycemic control, safety and patient ratings for a new 4 mm x 32G insulin pen needle in adults with diabetes. Curr.Med.Res.Opin. 26 (6):1531-1541, 2010. REF ID:	Cross-over RCT. Multicentre trial (four clinical centres) in the United states	n= 173 participants (37% type 1 diabetes) (n= 85: 4mm x 32G vs. 5mm x 31G pen needles (PN); n= 83: 4mm x 32G vs. 8mm x 31G PN) Inclusion criteria: Using insulin pen at least once per day for two months or more BMI 18-50 kg/m2 HbA1c 5.5-9.5% Able to monitor blood glucose at least 4 times per day Exclusion criteria: Physical conditions which would make them unable to perform study procedures	Patients with type 1 diabetes and type 2 diabetes. Participants were either 'low dose' or 'regular dose' users (highest single insulin dose ≤20 units and 21 – 40 units, respectively).			4 mm x 32G pen needles	5 mm x 31G pen needles and 8 mm x 31G pen needles	3 weeks		4mm vs. 5mm (n=68)	4mm vs. 8mm (n=69)	Funding: BD (Beckton, Dickinson and company) provided funding for this study and manufactures all pen needles tested. Risk of bias: Randomisation "using an investor site and dose-group specific computer-generated list of sequential numbers developed by BD biostatistics. Allocation concealment:
				4mm/5mm (n=83)	4mm/8mm (n=81)				VAS scores for pain; mean diff (SD) (SE)	-11.9 (SD 46.3) (5.6)	-23.3 (SD 35.3) (4.2)	
			Age (years), mean (SD)	54.4 (SD 14)	50.8 (SD 16.8)				HbA1c (not reported) Pre- and post-prandial blood glucose (not reported)			
			Male; number (%)	46 (55%)	46 (57%)							
			BMI (kg/m2); mean (SD)	31 (SD 6)	30.1 (SD 6.3)					4mm (n= 173)	5mm (n= 89)	
			HbA1c (%);	7.6 (SD 1)	7.4 (SD 1)				Hypoglycaemia;	36 (20.	21 (23.6)	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
HIRSH 2010		Recent history of unstable diabetes including ketoacidosis or hypoglycaemic unawareness, bleeding disorders, or hypoglycaemic unawareness Bleeding disorders Pregnancy	mean (SD)						number (%)	8)		unclear Blinding: not reported ITT analysis: unclear - not enough info Powered study. Drop-outs: acceptable (<20%) and acceptable differential between groups Both type 1 diabetes (37%) and type 2 diabetes were included in the trial with no sub-group analysis or data reported separately for the type 1 diabetes group.
			Drop-outs: Dropout rate: four (4) participants in the (4/5 mm) group and 1 participant in the 4/8 mm group. Nine participants in total (5%)						Injection site pain; number (%)	27 (15.6)	11 (12.4)	
										4mm (n=173)	8mm (n=84)	
									Hypoglycaemia; number (%)	36 (20.8)	22 (26.2)	
									Injection site pain; number (%)	27 (15.6)	11 (13.1)	

Table 259: IGNAUT 2012

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
D. A. Ignaut and H. Fu. Comparison of insulin diluent leakage post injection using two different needle lengths and injection volumes in obese patients with type 1 or type 2 diabetes mellitus. J Diabetes Sci Technol 6 (2):389-393, 2012. REF ID: IGNAUT 2012	RCT (crossover) Conducted at two outpatient centres in the USA.	n= 56 (n=13 /23% type 1 diabetes and n=43/77% type 2 diabetes). Inclusion criteria: ≥18 years of age with type 1 diabetes or type 2 diabetes. BMI ≥30.0 kg/m2 injecting insulin at least once/day for 6 months before screening Exclusion criteria: >2 abdominal surgical scars >2 inches within the provided injection grid area Self-perceived dullness or loss of sensation on either side of abdomen Known hypersensitivity or allergy to preserved sterile	type 1 diabetes and type 2 diabetes		5mm needles using the HumanPen Memoir insulin pen injector to deliver both 20 U and 60 U equivalent volume injections of preserved sterile insulin diluent.	8mm needles using the HumanPen Memoir insulin pen injector to deliver both 20 U and 60 U equivalent volume injections of preserved sterile insulin diluent.	Not reported		20 U equivalent volume	60 U equivalent volume	Funding: Eli Lilly and Company. Risk of bias: Randomisation: "randomly assigned to 1 of 8 sequence groups in order to reduce bias during study execution" Allocation concealment: unclear Blinding: Single (patients). ITT analysis: not reported Powered study: not reported Wash out period: not reported. Drop-outs:
				Total (N = 56)				*VAS Pain scores, mean (SD) difference (5mm minus 8mm)	0.14 (SD 2.56)	0.74 (SD 2.49)	
			Age (years), mean (SD)	55.75 (SD 9.77)							
			M/Fe	30/26							
			BMI (kg/m2), mean (SD)	35.6 (SD 5.5)				*VAS Pain scores, mean (SD) – reported narratively.			
			type 1 diabetes / type 2 diabetes	13/43				Adverse events	No SAEs reported (NS difference)		
			Drop-outs: No drop-outs - "All patients completed the study"					HbA1c (not reported) Hypoglycaemia (not reported) Pre- and post-prandial blood glucose (not reported)			

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		insulin diluent or insulin Taking anticoagulant or antiplatelet medications other than aspirin diagnosis or past history of significant bleeding disorder Significant wt change (±10% body wt) within 6 weeks of screening.							None.

Table 260: KREUGEL 2011

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
G. Kreugel, J. C. Keers, M. N. Kerstens, and B. H. Wolffenbuttel. Randomized trial on	RCT (crossover) 5 centres in The Netherlands	n= 130 (n=4 /5% type 1 diabetes) Inclusion criteria: ≥18 years of age with type	Adults type 1 diabetes and type 2 diabetes Obese			5mm x 31G pen needles. (Used at 90° angle, no skin fold)	8mm x 31G pen needles (Injected into a lifted skin fold)	3 months each needle	HbA1c, % (SD) FINAL VALUE	5mm: 7.47 (0.9) 8mm: 7.59 (1.0) SS difference (p=0.02)	Funding: Beckton Dickinson. Risk of bias: Randomisation : method not reported.
				Group A	Group B	Both groups			VAS Pain perception	5mm: 7 (0-22)	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
the influence of the length of two insulin pen needles on glycemic control and patient preference in obese patients with diabetes. Diabetes Technol.Ther. 13 (7):737-741, 2011. REF ID: KREUGEL 2011		1 diabetes or type 2 diabetes. BMI ≥30.0 kg/m2 injecting insulin with pen device at least 1 year Exclusion criteria: Self-adjustments of insulin dose incompletely recorded HbA1c >15% variation in past year Hypo unawareness Pregnancy or intention to become pregnant Haemoglobin-opathies Presence of lipodystrophy		(n=64)	(n=62)	used BD microfine Mini and short insulin pen needles Thigh and abdomen recommended sites of injection for LA and SA insulin respectively injections rotated within specific body area. Insulin volume 50 IU per injection (if >50, patients advised to split the dose and give 2 injections into same specific body area).			scores, median (IQR)	8mm: 9 (0-23) NS difference	Allocation concealment: not reported Blinding: none (open label). ITT analysis: no – ACA used. Powered study: to HbA1c and patient preference Wash out period: not reported and N/A. Drop-outs: acceptable (<20%).
			Age, years, mean (SD)	60 (11)	61 (11)						
			M/Fe	34/30	36/26						
			BMI (kg/m2), mean (SD)	36.7 (5.5)	36.1 (5.8)				Hypoglycaemia (self-reported)	NS difference, p=0.337	
			type 1 diabetes/ type 2 diabetes	3/61	2/60				Bleeding	SS less for 5mm vs. 8 mm (p=0.04)	
			HbA1c, % (SD)	7.7 (1.1)	7.6 (0.9)				Insulin backflow	SS less for 5mm vs. 8 mm (p=0.01)	
			Drop-outs: n=4 did not complete study						Bruising	NS difference	
									patient preference	NS difference (46% 5mm vs. 41% 8 mm; p-value not given)	
									Pre- and post-prandial blood glucose (not reported)		

Table 261: MCKAY 2009

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
M. Mckay, G. Compion, and L. Lytzen. A comparison of insulin injection needles on patients' perceptions of pain, handling, and acceptability: a randomized, open-label, crossover study in subjects with diabetes. Diabetes Technol.Ther. 11 (3):195-201, 2009. REF ID: MCKAY 2009	RCT (crossover) 10 centres, UK	n= 119 (n=26 /22% type 1 diabetes) Inclusion criteria: Adults with type 1 diabetes or type 2 diabetes. No further details given Exclusion criteria: Not reported	Adults type 1 diabetes and type 2 diabetes		6mm x 32G pen needles. (no further details given)	8mm x 30G pen needles (no further details given)	1-2 weeks each needle	VAS Pain perception scores	SS less pain with 6mm/32-Gauge vs. 8mm 30G (p<0.001)	Funding: NovoNordisk . Risk of bias: Randomisation : block design (blocks of 4). Allocation concealment: not reported Blinding: none (open label). ITT analysis: yes. Powered study: patient preference Wash out period: not reported and N/A. Drop-outs: acceptable - none.
				Group A (n=119)	Both groups used NovoNordisk Novofine needles with the Flexpen Usual insulin of patients was used using usual regimen.			AEs: Bleeding or bruising, number of events	less for 6mm/32-Gauge vs. 8mm 30G (n=1 vs. n=3)	
			Age, years, mean (SD)	58 (12)						
			M/Fe	62/57				patient preference	SS favouring 6mm/32-Gauge vs. 8mm 30G (58% vs. 27% - p<0.001)	
			BMI (kg/m2), mean (SD)	31 (5.7) range: 20-48.7						
			type 1 diabetes/ type 2 diabetes	26 (22%)/93 (78%)				Pre- and post-prandial blood glucose (not reported)		
			HbA1c, % (SD)	Not reported						
			Drop-outs: None							

Table 262: MIWA 2012

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
T. Miwa, R. Itoh, T. Kobayashi, T. Tanabe, J. Shikuma, T. Takahashi, and M. Odawara. Comparison of the effects of a new 32-Gaugex4-mm pen needle and a 32-Gaugex6-mm pen needle on glycemic control, safety, and patient ratings in Japanese adults with diabetes. Diabetes Technol.Ther. 14 (12):1084-1090, 2012. REF ID: MIWA 2012	RCT (cross over). Conducted at two outpatient centre in Japan.	n= 41 type 1 diabetes (n=5 (12%)) or type 2 diabetes (n =36 (88%)). Inclusion criteria: Age ≥20 years with type 1 diabetes or type 2 diabetes BMI <35 kg/m2 Using insulin pen device ≥1 year, and current users of NovoFine 32G X 6mm tapered needles injecting insulin 2+ times/ day HbA1c level in range 5.9-8.9%. Exclusion criteria: Any physical condition that may hinder adherence to study procedures Any neurological	Participants with type 1 (n = 5) or type 2 (n =36) diabetes.		Group 1: 32G x 4mm needle during the first month of the study then cross-over.	Group 2: 32G X 6mm needle during the first month of the study then cross-over.	2 months (1 month each needle)		Group 1	Group 2	Funding: "the materials used in this study were provided by Nippon Becton Dickinson Company Ltd." Risk of bias: Randomisation: not clear. Allocation concealment: not reported Blinding: Open label ITT analysis: not reported Powered study: reported Wash out period: not reported. Drop-outs: n=2 (10%) Group 1 and n=1 (5%) Group 2.
				Total (N = 41)				Average VAS score for comparative pain – validated 150-mm VAS	-16.6 mm (-26.0 mm, -7.3 mm)		
			Age (years), mean (SD)	64.3 (SD 11.1)							
			Male/female	28/13				Adverse events	None		
			BMI (kg/m2), mean (SD)	23.2 (SD 3.2)				HbA1c (not reported) Hypoglycaemia (not reported) Pre- and post-prandial blood glucose (not reported)			
			Drop-outs: n=3 (7%) excluded from end-point analyses due to protocol deviations. n=2 (10%) from Group 1, n=1 (5%) Group 2).								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		diseases Nephrotic syndrome Pregnancy or lactation.							

G.5 Pancreas transplant and islet cell transplantation

None

G.6 Hypoglycaemia

G.6.1 Identification and quantification of impaired awareness of hypoglycaemia

Table 263: HENDRIECKX 2014

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
C. Hendrieckx, J. A. Halliday, J. P. Bowden, P. G. Colman, N. Cohen, A. Jenkins, and J. Speight. Severe hypoglycaemia and its	Retrospective case-series Country: Australia (3 centres)	n=502 (n=422 completers) Inclusion: Age >18 years Type 1 diabetes for >6 months Able to complete survey in	Adults with type 1 diabetes Invited participants Age: mean 37.5 years Female: 54% Diabetes duration: mean 18.4 years HbA1c: mean 7.8%	Questionnaire given – covered: 1. Hypoglycaemia (recall of events, impaired awareness, and fear of hypo) 2. Psychological well-being and clinical questions.	-	IAH (Gold ≥4): = 20.5% Intact awareness (Gold = 1): 27% Most patients (52.4%) had Gold score 2 or 3. SH: 18.5% at least one event in past 6 months (mean 0.5; ie. 1 event/year) 46% of patients who reported SH episode in past 6 months also reported IAH; only 7% had intact	Not reported

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
association with psychological well-being in Australian adults with type 1 diabetes attending specialist tertiary clinics. Diabetes Res.Clin.Pract. 103 (3):430-436, 2014. HENDRIECKX 2014		English without assistance. Exclusion: None stated	SH recollection in past 6 months: mean 0.5 (range 0-20) IAH (Gold score ≥4): n=86 (21%) SMBG ≥4 times/day: n=285 (67.9%) Most patients on MDI therapy (26% on CSII)	SCORE TO RATE IAH: GOLD score (cut-off ≥4) HypoCOMPASS questionnaire (HypoA-Q) about severe hypo events.		awareness. Patients with SH were more likely to have IAH, experienced fewer symptoms of hypo, and relied more often on others to recognise a hypo event. Multivariate analyses: Greater IAH was SS associated with occurrence of SH IAH was SS associated with more frequent SH.	

Table 264: HOPKINS 2012

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
D. Hopkins, I. Lawrence, P. Mansell, G. Thompson, S. Amiel, M. Campbell,	Retrospective case-series (data from DAFNE audit) Country: UK	n=639 available data (501 for frequency of SH; 539 for IAH)	Baseline (pre-DAFNE) HbA1c: mean 8.5% IAH: 40%	Data collected in audit: subjects were asked to rate their perceived awareness	1 year (mean 380 +/- 62 days)	Baseline data (before DAFNE so not showing intervention effect) IAH: 40% Hypo aware: 60% SH: 25% at least one event in past 1 year; 16% more than one episode in past year.	NIHR (UK)

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
and S. Heller. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. Diabetes Care 35 (8):1638-1642, 2012. HOPKINS 2012		Inclusion: all participants who attended DAFNE courses in one 12-month period DAFNE used adults with type 1 diabetes. Exclusion: None stated	Hypo aware: 60% SH at least 1 event in past year: 25%	of hypoglycaemia by stating whether they usually recognized that they were hypoglycaemic at a blood glucose concentration ≥3 mmol/litre, <3 mmol/litre, or not at all. And self-reported frequency of SH. SCORE TO RATE IAH: IAH = those reporting symptom onset <3 mmol/litre or not at all Hypo aware = those recognizing hypo symptoms at a glucose of ≥3mmol/litre		Baseline data (after DAFNE so showing intervention effect) 62% of those who had experienced SH remained free of further episodes at follow-up 10% of those who had been free of SH in the preceding year experienced one or more episodes. The overall mean SH rate for the cohort fell from 1.93 (range 0–99) to 0.61 (0–70) episodes/person/year after DAFNE (difference 1.15 [95% CI 0.73–1.57]; P < 0.001) At follow-up, 43% of those with IAH at enrolment reported restoration of the ability to detect hypoglycaemia at a blood glucose >3 mmol/litre. The rate of SH fell significantly in both groups. Shows in subgroup of patients who had IAH, 43% reported restored awareness (ability to detect hypo when blood glucose was >3 mmol/litre, 1 year after DAFNE. Rate of SH also fell significantly.	

Table 265: CHOUDHARY 2010A

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
P. Choudhary, J. Geddes, J. V. Freeman, C. J. Emery ET AL. Frequency of biochemical hypoglycaemia in adults with Type 1 diabetes with and without impaired awareness of hypoglycaemia: no identifiable differences using continuous glucose monitoring. Diabet.Med. 27 (6):666-672, 2010. CHOUDHARY 2010A	Prospective case-series Country: UK Data from the UK Hypoglycaemia Group study	n=95 Adults with type 1 diabetes n=74 normal awareness, n=21 impaired hypo awareness (IAH) Inclusion: Type 1 diabetes (WHO criteria) Exclusion: HbA1c >9% Pregnancy Advanced complications of diabetes Severe systemic disease or malignancy History of seizures unrelated to hypo Inability to give informed consent		Weekly 4-point capillary home blood glucose monitoring (HBGM), 5 days of CGM and prospective reporting of severe hypoglycaemia SCORE TO RATE IAH: GOLD score Cut-off ≥4	9-12 months	Patients with IAH vs. normal awareness: 3 x higher incidence of severe hypoglycaemia 1.6 x higher incidence of hypoglycaemia on weekly HBGM NS differences observed with CGM	Funding: Part of another larger study funded by the Department of Transport, UK, not reported

Table 266: CLARKE 1995

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
W. L. Clarke, D. J. Cox, L. A. Gonder-Frederick, D. Julian, D. Schlundt, and W. Polonsky. Reduced awareness of hypoglycaemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care 18 (4):517-522, 1995. CLARKE 1995	Prospective case-series Country: UK	n=78 Adults with type 1 diabetes n=39 IAH Inclusion: IDDM for at least 2 years Between 21 and 55 years old Were routinely performing SMBG Particular efforts were made to recruit and include subjects with extreme degrees of hypoglycaemic awareness. Exclusion: None mentioned.	Mean age 38.3 ± 9.2 years; Duration of diabetes 19.3 ± 10.4 years.	2 assessments separated by 6 months. Each assessment included a battery of questionnaires and a BG symptom rating/ estimation trial. During the intervening 6 months, subjects completed diaries of hypo events. HbA1c was determined before the initial assessment and after 2nd assessment. SCORE TO RATE IAH: CLARKE score (8 questions) Cut-off ≥4 answers as 'R' = reduced awareness, ≤2 = aware. Compared scores with answers to question: "to what extent can you tell by your symptoms that your sugar is low? (never, sometimes, often, always)."	6 months	n=39 with IAH Patients with IAH vs. normal awareness had/were: NS difference for age, disease duration, insulin dose, or HbA1c SS less accurate in detecting BG <3.9 mmol/1 (33.2 ± 47 vs. 47.6 ± 50% detection, P = 0.001) SS fewer autonomic (0.41 ± 0.82 vs.1.08 ± 1.22, P = 0.006) and neuroglycopenic (0.44 ± 0.85 vs. 1.18 ± 1.32, P = 0.004) symptoms per subject. Prospective diary records revealed that reduced-awareness subjects experienced more moderate (351 vs. 238, P = 0.026) and severe (50 vs. 17, P = 0.0062) hypoglycaemic events. The second assessment results were similar to the first and verified the reliability of the data. Authors' conclusions: IDDM subjects who believe they have reduced awareness of hypoglycaemia are generally correct. They have a history of more moderate and severe hypo, are less accurate at detecting BG <3.9 mmol/1, and prospectively experience more moderate and severe	Funding: Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
						hypo than do aware subjects. Neither disease duration nor level of glucose control explains their reduced awareness of hypo. Reduced-awareness individuals may benefit from interventions designed to teach them to recognize all of their potential early warning symptoms	

Table 267: GEDDES 2007

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
J Geddes, RJ. Wright, NN. Zammitt, IJ. Deary, and BM. Frier. An evaluation of methods of assessing impaired awareness of hypoglycaemia in type 1 diabetes. Diabetes Care 30 (7):1868-1870, 2007.	Prospective case-series Country: UK	n=140 (n=80 completers) Inclusion: None stated Exclusion: None stated	Adults with type 1 diabetes Randomly selected cohort	4 times a day HBGM for 4 weeks. Recorded when any value was <3 mmol/litre Also filled out Edinburgh Hypoglycaemia Score (rates the nature and intensity of hypo symptoms experienced). SCORE TO RATE IAH: GOLD score (cut-off ≥4) CLARKE score (cut-	4 weeks	IAH: GOLD = 24%, CLARKE = 26%, PEDERSEN = 63% Strong association between Gold and Clarke methods for IAH (p=0.001) If Pederson used 'occasionally and never' as IAH, the % fell to 15.4% - still a poor correlation between this method and Gold or Clarke methods (rs = 0.5 for both) Patients with IAH vs. normal awareness had/were: SS older (using Gold and Clarke scores). NS difference for Pedersen score. SS longer duration of diabetes (using all 3 methods) NS difference in HbA1c (using all 3 methods) SS more episodes of biochemical	Not reported

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
GEDDES 2007				off ≥4) PEDERSEN-BJERGAARD score (cut-off: always)		hypo over the 4 weeks (using Gold and Clarke scores). NS difference for Pedersen score. Lower autonomic symptoms reported during biochemical hypo (using Gold and Clarke scores). NS difference for Pedersen score. NS difference in self-reported neuroglycopenic symptoms (using all 3 methods). SS incidence of severe hypos in previous year (using all 3 methods).	

Table 268: GEDDES 2008

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
J. Geddes, J. E. Schopman, N. N. Zammitt, and B. M. Frier. Prevalence of impaired awareness of hypoglycaemia in adults	Cross-sectional study Country: UK	n=518 Inclusion: Type 1 diabetes >2 years duration Aged >16 years Exclusion: Pregnancy, advanced renal	Adults with type 1 diabetes Randomly selected cohort n=242 male HbA1c: mean 8.4% (SD 1.4%) Age: median 39 years Duration of diabetes: median 16 years 74% on insulin analogues	Retrospective recall of severe hypo over previous year also assessed. SCORE TO RATE IAH: GOLD score (cut-off ≥4)	4 weeks	IAH: 101 (19.5%) Patients with IAH vs. normal awareness had/were: SS older (p<0.001) SS longer duration of diabetes (p<0.001) 6 x higher number of episodes of severe hypo (per person) in preceding year p<0.001) SS lower intensity of autonomic symptoms during episodes of self-treated hypo (p=0.004).	Not reported

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
with Type 1 diabetes. Diabet.Med. 25 (4):501-504, 2008. GEDDES 2008		failure Inability to understand or complete the questionnaire	18% on mix of analogue and human 8% human alone Basal-bolus: 82% and 18% on twice/day mixed insulin.			NS difference in intensity of neuroglycopaenic symptoms NS difference for HbA1c Moderate and SS association between IAH and duration of diabetes (rs = 0.21, p<0.001) and rate of SH (rs = 0.34, p<0.001).	

Table 269: GIMENEZ 2009

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
M Gimenez, M Lara, A Jimenez, and I Conget. Glycaemic profile characteristics and frequency of impaired awareness of hypoglycaemia in subjects with type 1 diabetes and repeated	Prospective case-series Country: Spain	n=20 Inclusion: Type 1 diabetes >5 years duration Aged >18 years Conventional insulin MDI NS hypo >4/week (for 8 weeks) SH hypo >2 (for 3 years) Exclusion: None mentioned	Adults with type 1 diabetes n=11 male HbA1c: mean 6.9% (SD 1.0%) Age: mean 35 years Duration of diabetes: mean 16 years 100% on MDI.	Compares 2 methods of IAH detection during an acute induction of hypoglycaemia with regular insulin. Hypo symptoms score questionnaire answered after 30 minutes of euglycaemia, and after 30 minutes of hypoglycaemia. Also measured CGM for 72hrs	72 hours	IAH: GOLD = 100%, CLARKE = 95%. Clarke test score was SS negatively correlated with HbA1c values (ie. lower HbA1c = higher Clarke score, thus IAH). Percentage of increase in symptoms during induction of hypo: Clarke's: sensitivity 100%, specificity 25%, Kappa index 0.35 CGM from the whole group revealed 18% of measurements <70 mg/dl; this was correlated with Clarke's test score and with increase in % of signs/symptoms during induced hypo. In patients with abnormal response	Ministerio de Sanidad y Consumo of Spain; and Medtronic Iberica.

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
hypoglycaemic events. Acta Diabetol. 46 (4):291-293, 2009. GIMINEZ 2009				SCORE TO RATE IAH: GOLD score (cut-off ≥4) CLARKE score (cut-off ≥4)		of symptoms during hypo, CGM % of values <70 mg/dl was higher (23% vs. 8%) than in those with a normal response (10%; p<0.028).	

Table 270: GOLD 1994

Reference	Study type	Number of patients	Patient characteristics			Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
A. E. Gold, K. M. MacLeod, and B. M. Frier. Frequency of severe hypoglycaemia in patients with type I diabetes with impaired awareness of hypoglycaemia.	Prospective case-control study Country: UK	n=60 Adults with type 1 diabetes n=31 normal awareness n=29 impaired hypo awareness (IAH) Inclusion: Type 1 diabetes 2 groups recruited simultaneously based on their self-reported		Normal (n=31)	IAH (n=29)	Monitored blood glucose Hypo episodes documented Assessed every 3 months and insulin adjusted accordingly Fear of Hypo questionnaire given. SCORE TO RATE	12 months	IAH vs. normal awareness: • SS more patients had 1 or more episodes of SH (66% vs. 26%) • SS higher incidence of SH episodes/patients/year (2.8 vs. 0.5) • SS more patients had greater worry/fear of hypoglycaemia, but did not modify their behaviour accordingly.	Funding: Not stated.
			Age	44 (11)	48 (12)				
			HbA1c %	10 (1.2)	10 (1.5)				
			Duration of diabetes, years	19	21				
			Insulin: >70% in both groups taking twice/day regimen.						

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
Diabetes Care 17 (7):697-703, 1994. GOLD 1994		awareness of hypoglycaemia (normal vs. impaired awareness). 'Matched for age, duration of diabetes, age at onset and glycaemic control at start of the survey. Exclusion: Taking any medication that may have impaired awareness of hypo (eg. BBs)		IAH: GOLD score Cut-off ≥4			

Table 271: HOIHANSEN 2010

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
T. Hoi-Hansen, U. Pedersen-Bjergaard, and B. Thorsteinsson. Reproducibil	Cross-sectional study Country: Denmark	n=372 responders (n=470 recruited) Inclusion: None mentioned.	Adults with type 1 diabetes 57% male HbA1c: mean 8.2% (SD 1.0%) Age: mean 51 years	Compares 3 methods of IAH Also answered questions on severe hypo in the past and symptoms	n/a	Normal awareness: 75%, 51% and41% Impaired awareness/unawareness (C): 25%, 28% and 13% 46% belonged to intermediate group of impaired awareness (C) and 21% not classifiable (B)	None stated.

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
ity and reliability of hypoglycaemic episodes recorded with Continuous Glucose Monitoring System (CGMS) in daily life. Diabet.Med. 22 (7):858-862, 2005. HOIHANSEN 2010		Exclusion: None mentioned	Duration of diabetes: mean 24 years 81% on MDI (≥4/day).	of hypo. SCORE TO RATE IAH: GOLD score (cut-off ≥4) CLARKE score (cut-off ≥4) PEDERSEN score (cut-off: always)		Higher rates of severe hypo in patients with impaired awareness (A,B)/unawareness (C) vs. aware patients Patients with impaired awareness (C) had more severe hypo than aware patients, and less severe than unaware patients. Lower rate of hypo in method C vs. method A Fractions of patients with normal awareness without an event of severe hypo were 0.81, 0.86, 0.91 All 3 methods of hypo unawareness are feasible in clinical practice since degree of awareness is associated with risk of severe hypo. Method C (trisected method) identifies and intermediate group with impaired awareness and with a risk of severe hypo that is SS different from those of aware and unaware patients.	

Table 272: JANSSEN 2000A

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
M. M.	Prospective	n=19	Adults with type 1	Hand held	2-4 weeks	The composite self-report score	None

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
Janssen, F. J. Snoek, and R. J. Heine. Assessing impaired awareness of hypoglycaemia in type 1 diabetes: agreement of self-report but not of field study data with the autonomic symptom threshold during experimental hypoglycaemia. Diabetes Care 23 (4):529-532, 2000. JANSSEN 2000A	case-series (taken during 10-week lead in to a clinical trial) Country: The Netherlands	Inclusion: Type 1 diabetes Reasonable glycaemic control (HbA1c ≤8.3%) Basal-bolus treatment regular insulin before meals and NPH bedtime. Exclusion: None mentioned.	diabetes n=15 male HbA1c: mean 7.2% (SD 0.6%) Age: mean 30 years Duration of diabetes: mean 13 years 100% basal-bolus with regular and NPH insulin.	computer to assess their recognition of hypo episodes occurring during 2-4 weeks Underwent stepped hypoglycaemic clamp, so could study response to standardised hypo. diagnosis of IAH was based on the self-report questions, a composite self-report score and 3 different cut-off levels for the % of accurately recognised hypo episodes during the field study. Agreement with the hypo clamp measure was tested by kappa, sensitivity and spec. SCORE TO RATE IAH: CLARKE score (cut-off ≥4)		agreed reasonably well with the hypo clamp measure (kappa 0.49, sensitivity 66.7, spec 85.7%) and showed a better agreement than the separate self-report questions. The HHC criterion of IAH did not agree with the hypo clamp criterion at any of the cut-off levels tested.	stated.

Table 273: PEDERSEN 2003

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
U Pedersen-Bjergaard, S Pramming, and B Thorsteinsson. Recall of severe hypoglycaemia and self-estimated state of awareness in type 1 diabetes. Diabetes.Metab.Res.Rev. 19 (3):232-240, 2003. PEDERSEN 2003	Prospective case-series Country: Denmark	n=230 Inclusion: type 1 diabetes Insulin treatment from time of diagnosis Unstimulated C-peptide <300pmol/litre or stimulated C-peptide <600pmol/litre. Exclusion: Haemodialysis Concomitant malignant disease Pregnancy	Adults with type 1 diabetes 60% male HbA1c: mean 8.5% (SD 1.0%) Age: mean 46 years Duration of diabetes: mean 21 years 84% on ≥4 injections/day	Questionnaire based on Pramming and Deary studies for occurrence of hypo, aspects of hypo unawareness and sections on demographic issues and lifestyle. Hypo/SH in previous year was also recorded, and mild hypos in previous week. SCORE TO RATE IAH: PEDERSEN-BJERGAARD score (questionnaire based on Pramming and Deary studies) cut-off: usually = IAH, occasionally or never = severe IAH (unawareness).	1 year	Almost 90% patients correctly recalled whether they had had SH over the previous year. Those with high recorded numbers of episodes had incomplete recall, resulting in 15% underestimation of overall rate. Qu: do you recognise symptoms when you have a hypo? 40% normal awareness, 47% impaired awareness and 13% unawareness. Groups with IAH had 5.1 and 9.6 x higher rates of SH vs. normal awareness groups (p<0.001).	Several Foundations in Denmark.

Table 274: RYAN 2004

Reference	Study type	Number of patients	Patient characteristics			Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
Ryan,E.A.; Shandro,T.; Green,K.; Paty,B.W.; Senior,P.A.; Bigam,D.; Shapiro,A.M.; Vantyghem, M.C. Assessment of the severity of hypoglycaemia and glycemic lability in type 1 diabetic subjects undergoing islet transplantation. Diabetes 53 (4): 955-962. RYAN 2004	Prospective case-series Country: USA	n=151 n=100 type 1 diabetes (random selection; completers of the questionnaire – 877 were originally recruited – data used for these n=100 only) n=51 islet transplantation patients) Inclusion: Adults with type 1 diabetes had attended our diabetes educational program at least once and were cared for by either community physicians or our diabetes clinic staff Exclusion: None stated.		Type 1 diabetes (n=100)	Islet transplant (n=51)	Prospective monitoring of blood glucose ≥2x/day for 4 weeks. Frequency of SH over preceding year also estimated. Composite score comprising: glucose readings collected from patients over a 4 week period; details of each hypoglycaemic event (glucose <3.0 mmol/litre); no. of occurrences of hypoglycaemia; questionnaire about the frequency and severity of hypoglycaemia episodes over the previous year SCORE TO RATE	4 weeks	In the n=100 type 1 diabetes patients IAH patients vs. normal awareness: median 8.0 vs. 2.0 episodes of hypoglycaemia per patient in previous 4 weeks (p<0.001), 0.4 vs. 0.0 SH episodes per patient in previous 4 weeks (p-value not reported).	Juvenile Diabetes Foundation International.

Reference	Study type	Number of patients	Patient characteristics			Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
						IAH: HYPO score Cut-off: Score of ≥433* is representative of problematic hypoglycaemia, ≥1,047* is indicative of very serious problems with hypoglycaemia. Patients with IAH had a median score of ≥850 (IQR 485 – 1228), and those with intact awareness had a score of 91 (IQR 23-203). *NOTE: These cut-off points were based on calculating the median and various percentiles of the distribution of patients in the study itself.			

Table 275: SCHOPMAN 2011

Reference	Study type	Number of patients	Patient characteristics			Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
J. E. Schopman, J. Geddes, and B. M. Frier. Frequency of symptomatic and asymptomatic hypoglycaemia in Type 1 diabetes: effect of impaired awareness of hypoglycaemia. Diabet.Med. 28 (3):352-355, 2011. SCHOPMAN 2011	Prospective case-control study Country: UK	n=38 Adults with type 1 diabetes n=19 normal awareness n=19 impaired hypo awareness (IAH) Inclusion: Type 1 diabetes 2 groups recruited based on their self-reported awareness of hypoglycaemia (normal vs. impaired awareness by GOLD score). Matched for age, sex, duration of diabetes, and glycaemic control (HbA1c). Basal-bolus insulin regimen (rapid before meals, and once/day long		Normal (n=19)	IAH (n=19)	Prospective monitoring of blood glucose 4x/day for 4 weeks. Frequency of SH over preceding year also estimated. SCORE TO RATE IAH: GOLD score Cut-off ≥4	4 weeks	IAH patients vs. normal awareness: 2 x frequency of all episode of hypo over 4-week monitoring period (SS; p=0.003) NS difference in total no of symptomatic hypo episodes. 7 x higher incidence of symptomatic hypo (SS, p=0.001) – comprised 47% of all glucose values <3.0 mmol/litre vs. 14% in normal group. Higher annual prevalence of SH: 53% vs. 5% SS higher incidence of severe events (p=0.001).	Funding: Not stated.
			Age , median	50	54				
			HbA1c %	8.3	7.8				
			Duration of diabetes, years	23	25				
			Insulin: 100% on Basal-bolus (rapid before meals, and once/day long acting)						

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
		acting) Exclusion: None stated.					

Table 276: STREJA 2005

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
D Streja. Can continuous glucose monitoring provide objective documentation of hypoglycaemia unawareness? Endocr Pract 11 (2):83-90, 2005. STREJA 2005	Prospective case-series Country: USA	n=60 Inclusion: Type 1 diabetes Age >18 years Diabetes duration >5 years fC-peptide <0.6 ng/ml HbA1c <9.0% Use of CSII or MDI and preprandial and post-prandial SMPG at least 4x/day. Exclusion: Pregnant or breast feeding Serum creatinine >2.0 mg/dl Unstable CVD	Adults with type 1 diabetes n=27 male HbA1c: mean 7.5% (SD 0.11%) Age: mean 50 years Duration of diabetes: mean 24 years n=17 CSII, rest = MDI.	SMBG and clinical data collected 72hr CGMS IAH Questionnaire SCORE TO RATE IAH: Adapted Janssen questionnaire (cut-off: 3/5 questions answered yes = HUN)	2-4 weeks	HUN by Questionnaire: 42% Best predictor of HUN was maximal duration of hypo, as determined by CGMS (p=0.001) Detection of hypo episodes with duration >90 minutes identified patients with HUN (sensitivity 75%, spec 885) HUN was SS associated with used of ACEs or ARBs (p=0.003), and longer duration of diabetes (p=0.008)	None stated.

Reference	Study type	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures and Effect sizes	Comments
		History of recent substance abuse Poor cognitive function at time of consent Diagnosis of a major comorbid condition other than long-term diabetes complications.					

Table 277: Summary of additional studies – including conference abstracts USED FOR ADDITIONAL GDG INFORMATION ONLY (not fully included in the review)

Study	Intervention/comparison	Population	Outcomes
ACAMPO 2012	Conference abstract Cross-sectional study Dutch translation of the Clarke questionnaire: score ≥3 out of 5 was assumed to indicate HU. SH was assessed on the basis of the same questionnaire.	n=486 Type 1 diabetes adults??	HUN: n=158 patients (33%) and n=103 patients (21%) recalled SH in the year prior to the Clarke questionnaire. HUN was associated with male sex, lower HbA1c, duration of diabetes, autonomic neuropathy and estimated GFR < 60ml/min/1.73 m^2 (all P < 0.05). After adjustments, duration of diabetes, estimated GFR < 60ml/min/1.73 m^2 and lower HbA1c were still SS associated with HUN. SH was independently associated with the presence of autonomic neuropathy (3.62; 1.65-7.94) and the use of benzodiazepines (4.59; 1.80-11.73), but not with HbA1c or diabetes duration. No association with SH or HUN: use of insulin analogues, insulin pump therapy, ACE inhibitors or beta-blockers Conclusion: HUN is still highly prevalent in type 1 diabetes patients despite advances in insulin therapy. Diabetes duration, lower HbA1c level and kidney dysfunction were independent risk factors for HU. Autonomic neuropathy and use of benzodiazepines were risk factors for SH. Clinicians treating patients with type 1 diabetes should be aware of the still high prevalence of HUN and its risk factors. (Table presented).

Study	Intervention/comparison	Population	Outcomes
CZYEWSKA 2012	Conference abstract	n=238 Type 1 diabetes adults and young people	HUN was assessed by Clarke and Gold. HUN: CLARKE = 58 patients (24.4%), GOLD = 68 patients (28.5%). Patient split into 3 groups: Group I- patients with Hypo awareness confirmed by both tests (n = 142) Group II- patients with HUN confirmed by one test (n = 66) Group III- patients with HUN confirmed by both tests (n = 30). Patients with HUN vs. awareness patients: were older (P = 0.040) had longer diabetes duration (P = 0.014) NS difference in lipid level, waist circumference, creatinine level, BMI, arterial pressure and HbA1c. had more glycaemia level below 55 mg/dl (P = 0.016). Performed measurements of glycaemia more frequently (P = 0.049). Conclusion: Hypoglycaemia unawareness was observed in 40% type 1 diabetic patients. The severity of hypoglycaemia unawareness was associated with longer diabetes duration. The patients with hypoglycaemia unawareness had more frequent low glycaemia level
GANDHI 2013	Conference abstract	n=100 Type 1 diabetes (age not given)	HUN assessed by Clarke, Gold and Pederson and the Edinburgh Hypoglycaemic Score, questions on causes and worry for hypoglycaemia scored on a seven-point Likert scale. Clarke score was used to assess HUN. HUN: Clarke = 18%, Gold = 19% and Pederson = 7%. HUN: were SS older (p = 0.0018) Had SS longer duration of diabetes (p = 0.0015) Had SS increased prior severe hypoglycaemic episodes (p = 0.024) Giving the insulin dose twice was increased (p = 0.011) Were SS more worried about night-time hypoglycaemia (p = 0.041) Felt significantly less empowered to avoid future hypoglycaemic episodes (p = 0.047). There was very poor correlation between the Pederson questionnaire and the other two methods

Study	Intervention/comparison	Population	Outcomes
			used to assess HU. There was moderate agreement between the Clarke and Gold scores (kappa = 0.503). Conclusion: This report demonstrates lower prevalence of HU compared with the literature and may reflect recent improvements in Type 1 diabetes management, most notably education. It highlights opportunities to improve education to avoid hypoglycaemia. The findings of this study are in keeping with a previous report suggesting that Clark and Gold questionnaires are better discriminators for HU than Pederson
KANC 2010	Conference abstract	n=114 Type 1 diabetes (n=53) and type 2 diabetes insulin treated	Hypoglycaemia awareness status by Clarke's questionnaire Confirmed high internal consistency reliability of the translated questionnaires (Cronbach's alphas were 0.93, 0.94, and 0.49 for HFS, PAID, and Clarke's questionnaire, respectively). SS correlation found between HFS score and Clarke's score in general (r = 0.20, p = 0.030), type 2 diabetes (r = 0.27, p = 0.036), type 1 diabetes (r = 0.17, p = 0.217), meaning that patients with type 2 diabetes experience an increase in FoH as their awareness decreases (but NS for type 1 diabetes). SS association of HbA1c with HFS score (r = 0.23, p = 0.015) and PAID score (r = 0.47, p < 0.001), indicating worse glucose control with increasing FoH and diabetes problems. On the contrary, four patients had very high PAID and HFS score and low HbA1c. Conclusion: In particular MDI-treated women with type 1 diabetes, bad glycaemic regulation and lower awareness of hypoglycaemia need clinical attention, focused on hypoglycaemia. Patients with excellent glycaemic control, combined with great FoH and pronounced diabetes-related problems however, should not be overlooked
MOHEET 2012 Additional info	Conference abstract	n=18 Type 1 diabetes adults with IAH (Clarke score)	History of severe HG and high total score on CQ (Clarke questionnaire/ Clarke score) is significantly related to reduced CR response to HG in patients with type 1 diabetes. Therefore, such responses on the CQ may indicate those patients with the most profound IAH, which can be of value in both the research and the clinical setting
SPEIGHT 2011	Conference abstract Patient, physician and psychologist discussions drafting new items to the	n=14 type 1 diabetes adults tested the new items of score Score = The	Patient input identified the need for separate questions about: • hypoglycaemia when awake and asleep • ways to improve specificity/acceptability. • 18 items assess recall of hypoglycaemic events, blood glucose thresholds at which symptoms occur, awareness of symptoms, altered awareness, and frequency of checking blood glucose when

Study	Intervention/comparison	Population	Outcomes
	Clarke Score.	Hypo Awareness Questionnaire	'feeling low'. Completion time: average 7 min (range 5-15), shorter following each revision. Authors' Conclusion: A comprehensive, collaborative and iterative design process has generated a detailed measure of IAH with good face and content validity. The Hypo Awareness Questionnaire is likely to be useful in clinical trials and enable improved recognition of IAH together with more accurate evaluation of medical fitness for activities including driving
TAN 2012A	Conference abstract	n=30 type 1 diabetes	Clarke and Gold scores for IAH IAH: GOLD = 8patients (27%) IAH vs. aware patients NS difference in HbA1c SS longer mean duration diabetes Discussed IAH during their consultation with a specialist (88% vs. 64%). Conclusion: The prevalence of IAH was higher in this study than in previous work suggesting that the problem may still be underestimated. It was appropriately recognised, and treatment strategies documented for the majority, on attendance at specialist clinics

G.6.2 Recovering hypoglycaemia awareness

Table 278: BROOKS 2013[21]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
Brooks et al., 2013. Attainment of Metabolic Goals in the Integrated UK Islet Transplant Program With	Retrospective observational case series UK Recipient	n=20 Inclusion: • C-peptide-negative type 1 diabetes • recurrent severe hypoglycaemia ≥1 event over the preceding 12 months requiring assistance to	Male, % 25% Age, median (IQR) 49 (44-54) Duration of diabetes	Islet transplant	12 months and 24 months (13.5-36 months)	Severe Hypoglycaemia, number of patients	Baseline 12 months: 20/20 (100%) During 24 month follow-up: 8/20 (40%)	Funding: UK islet transplant program funded by the NHS National Commissioning group. UK Islet Transplant Consortium

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
Locally Isolated and Transported Preparations. American Journal of Transplantation 2013; 13: 3236–3243 REF ID: BROOKS2013	s of a first islet transplant between April 2008 and March 2011 at all NHS-funded centres	actively administer carbohydrate, glucagon or other resuscitative actions despite optimized conventional management. Exclusion: Insulin resistance Contraindications to immunosuppression therapy Body weight >80kg	median (IQR) 30 (17-39) n=16 islet transplant alone, n=4 islet after kidney					supported by Diabetes UK, Diabetes Research and Wellness Foundation, Diabetes Foundation and Juvenile Diabetes Research Foundation. Current study funded by a Diabetes UK Grant.

Table 279: CHOUDHARY 2013[26]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Choudhary et al. 2013. Real-time continuous glucose monitoring significantly reduces severe hypoglycaemia in	Prospective observational case series UK	n=35 Adults Inclusion: • Type 1 diabetes • Ongoing problematic hypoglycaemia leasing to limitation of daily activities	Age, mean (SD) 43.2 (12.4) Type 1 diabetes duration 29.6 (13.6) Male:Female	CGM 12months CGM in addition to either MDIs or CSII 23 patients used the Medtonic Paradigm Veo system; 7 patients used the Medtonic Paradigm RT system; 3	none	1 year	Severe hypoglycaemia rate, episodes/year, mean (SD) HbA1c, %, mean (SD)	Before intervention: 8.1 (13) After intervention: 0.6 (1.2) Reported as P=0.005 Before intervention: 8.1 (1.2)	Funding: authors received fees or honoraria from Madtronic, Animas, Roche, Abbott. Authors

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
hypoglycaemia-unaware patients with type 1 diabetes. Diabetes Care: 36: 4160-4162 REF ID: CHOUDHARY2013		and Gold score >4 despite structured education with or without CSII • Use of CGM in addition to CSII or MDIs for at least 12 months	11:24 33 used CSII; 1 converted to CSII; 1 used MDI	patients used Dexcom G4 sensors in combination with an Anamas Vibe pump; 1 patient used MDI; 1 patient used a CGM system.				After intervention: 7.8 (1.0) Reported as P=0.007	received funding for clinical trials from Medtronic
							IAH, Gold score (n=19), range 1-7, mean (SD)	Before intervention: 5.0 (1.5) After intervention: 5.0 (1.9) Reported as P=0.67	

Table 280: COX 2004[31,32]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Cox et al., 2004. Hypoglycaemia anticipation, awareness and treatment training (HAATT) reduces occurrence of severe	RCT Country: Bulgaria (HAATT developed in US). Standard care in Bulgari	n=60 Inclusion: • Type 1 diabetes • History of ≥2 episodes of SH (inability to treat oneself due to hypoglyca		HAATT (n=30)	Control (n=30)	SMBG + HAATT (also received SMBG supplies along with a 7 week structured group psycho-educational treatment programme designed to reduce occurrences of low BG, and	SMBG (provided with SMBG Accucheck Easy Meter 1 month pre-treatment and 1 month post-treatment). 2 month treatment phase – educated by their physician on SMBG data	1-18 months post-treatment 2 months treatment	Severe hypoglycaemia/subject	HAATT: before 2.0; after 0.4 SMBG: before 1.8; after 1.7 (F value 5.0; p value 0.03)	Patients matched on baseline hypo occurrence and randomised. Physician change routine based on SMBG

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
hypoglycaemia among adults with type 1 diabetes mellitus. International Journal of Behavioral Medicine: 11: 212-218 REF ID: COX2004	a at the time did not routinely employ SMBG)	emic stupor or unconsciousness) in the past year. • Exclusion:				increase awareness and improve treatment of low BG)					data? As an incentive to participate, participants were given an Accucheck Easy Meter (Roche Diagnostics), 4 months worth of supplies and $20.
			Age	37.6 (9.0)	38.6 (9.8)	Both groups: 6 months before treatment participants recorded moderate and SH 1 month before treatment participants provided with SMBG equipment and diaries 4-times daily participants estimated whether their BG was hypoglycaemic, euglycaemic or hyperglycaemia; whether they were having hypo symptoms; and record their actual BG. Monthly physician visits to make adjustments to insulin, food and exercise routine based on SMBG data			Nocturnal hypoglycaemia/subject	HAATT: before 1.1; after 0.8 SMBG: before 0.6; after 1.6 (F value 3.9; p value 0.055)	
			HbA1c	8.1 (0.7)	8.0 (0.7)				HbA1c	Only reported as estimated HbA1c	
			Male %	53	54						
			Duration of diabetes	13.9 (9.3)	14.0 (7.6)				% low BG accompanied by symptoms	HAATT: before 60%; after 70% SMBG: before 56%; after 58% (F value 0.4; p value NS)	
									% detection of low BG	HAATT: before 52%; after	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
										70% SMBG: before 58%; after 55% (F value 8.4; p value 0.005)	

Table 281: CRANSTON 1994[33]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
Cranston et al., 1994. Restoration of hypoglycaemia awareness in patients with long-duration insulin-dependent diabetes. Lancet: 344: 283-	Prospective observational case series UK	n=12 Inclusion: • IDDM (duration >10years) • History of hypoglycaemia without warning • At least three BG <3mmol/litre per 2 weeks in the month prior to the study	Male: 12/12 IDDM duration range: 11-32 years Two groups: Group A (n=6): Good control HbA1c <7% (mean 6.5±0.2) Group B (n=6): Poor control – swung from one extreme of glycaemia to the	Hypoglycaemia avoidance (treatment programme designed to achieve 3 weeks without BG<3.5 mmol/litre – achieved by diet review, advice about exercise, redistribution of insulin)	Mean period to achieve 3 weeks absence of hypo was 4.1 (1.1) months	HbA1c	Group A: before 6.5 (0.2); after 6.9 (0.3) (p=0.32) Group B: before 8.2 (0.2); after 8.7 (0.3) (p=0.26)	Funding: British Diabetic Association Grant
						Hypoglycaemia (<3mmol/litre). Frequency/month for 3 week period	Group A: before 21; after 0 Group B: before 14; after 0	
				• Symptom scores recorded to		Total autonomic	Both groups had higher scores after	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
287 REF ID: CRANSTON 1994		• Exclusion:	other (mean HbA1c 8.2±0.3) 2 patients on thyroxine and 2 patients on ACEi. 1 patient in group A had peripheral neuropathy	controlled hypoglycaemia during clamp study • 1 month before treatment – continued usual treatment but recorded 4-daily SMBG (3-pre meal and 1 pre-bed) • 3 patients in group B converted from twice daily mixed insulin to pre-meal soluble and overnight intermediate acting insulin.		symptom scores during clamp	the intervention (displayed graphically only)	
						Hospital admissions	1 (group B)	

Table 282: DE ZOYSA 2014[36]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
De Zoysa et al., 2014. A Psychoeducational Program to Restore Hypoglycaemia Awareness: The DAFNE-HART Pilot Study. Diabetes Care. 2014	Prospective case series	n=24 Inclusion: • Type 1 diabetes • Using DAFNE principles for insulin self-adjustment • Persistent impaired awareness	Male, % 50% Age, mean (SD) 54.4 (7.9) Duration of diabetes, mean (SD) 30.7 (11.9) n=15 using twice daily background and pre-meal	DAFNE-Hypoglycaemia Restoration Awareness Training (DAFNE-HART). Relevant sections from DAFNE and interventions targeting problematic hypoglycaemia. 6 week intervention using motivational interviewing and cognitive behavioural techniques	12 months	Self-reported severe hypoglycaemia (<3.5mmol/litre requiring assistance), events/patient-year, median (range)	Before: 3.0 (0-104) After: 0 (0-3)	Funding: NIHR Programme Grants for Applied Research Theme 1 drop out to follow-up
						HbA1c, %	Before: 7.8 (1.2) After: 7.8 (1.1)	
						Gold score, range 1-7, ≥4 = impaired awareness	Before: 5.6 (1.4) After: 4.5 (1.9)	
						Clarke score, ≥4 = impaired awareness	Before: 5.4 (1.2) After: 3.8 (1.8)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
Mar;37(3): 863-6. doi: 10.2337/dc13-1245. Epub 2013 Dec 6. REF ID: DEZOYSA2014		of hypoglycaemia assessed clinically and Gold score ≥4. Exclusion:	insulin, n=8 using pumps			Ryan score, hypoglycaemia burden (<423 considered to indicate hypoglycaemia not a major clinical concern)	Before: 948 (831) After: 372 (466)	
						Anxiety, hospital anxiety and depression score, (score >8 indicates clinically relevant psychological distress)	Before: 5.9 (5.0) After: 6.0 (5.7)	
						Depression, hospital anxiety and depression score, (score >8 indicates clinically relevant psychological distress)	Before: 5.2 (4.6) After: 5.1 (4.7)	
						PAID, score ≥40 indicates clinically relevant psychological distress	Before: 30.7 (22.6) After: 24.7 (20.5)	

Table 283: Fanelli 1993[43]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Fanelli et al., 1993. Meticulous prevention of hypoglycaemia normalizes the glycemic thresholds and	Prospective case series observational before and after study Italy	n=8 (plus n=12 controls) Inclusion: • IDDM (duration ≤7years) • Treatment with intensive insulin therapy • Consistent	Male:Female 4:4 Age, years mean (SE) 26 (2) Duration of diabetes, years mean	Hypoglycaemia avoidance by change in regime and counselling. To prevent hypoglycaemia, insulin doses aimed at fasting, preprandial and bedtime BG of ~7.2-8.3mM.	None	2 weeks and 3 months	Severe hypoglycaemia (coma, seizure or 3rd party assistance), number of patients	Year before study: 2/8 During 3 months: 0/8	Funding: Juvenile Diabetes foundation Grant and Aging Grant.
							HbA1c, %, mean (SE)	Before: 5.8 (0.3) After: 6.9 (0.2) Reported as P<0.05	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycaemia in intensively treated patients with short-term IDDM. Diabetes: 42: 1683-1689 REF ID: FANELLI1993		history of frequent hypoglycaemia (BG<3mM) in the absence of autonomic warning symptoms for at least 6 months before the study • Absence of clinically overt autonomic neuropathy Exclusion: • Diabetic complications, other diseases or other drugs apart from insulin	(SE) 5.0 (0.6) HbA1c, % mean (SE) 5.8 (0.3) Estimated duration of unawareness, years, mean (SE) 1.2 (0.3) All were on 3-4 daily injections	Regular insulin at meal times and intermediate acting NPH at 2300-2330. Diet changed to 3 meals with no snacks. Daily telephone counselling. SMBG 4 times daily.			Autonomic symptom score during hypoglycaemia clamp, mean (SE), scored zero-5 (none-severe) for six autonomic symptoms	Before: 2.2 (0.9) 2 week: 4.7 (1.7)* 3 month: 5.8 (0.6)* *Reported as P<0.05 from baseline	
							Neuroglycopenic symptom score during hypoglycaemia clamp, mean (SE), scored zero-5 (none-severe) for five neuroglycopenic symptoms	Before: 5.4 (1.5) 2 week: 7.4 (1.7)* 3 month: 9.4 (1.1)* *Reported as P<0.05 from baseline	

Table 284: Fanelli 1994[42]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Fanelli et	Prospe	n=21 (plus		Int	Comp	Hypoglycaemia	Continued	2 weeks,	Severe	Not reported	Funding:

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
al., 1994. Long-term recovery from unawareness, deficient counter regulation and lack of cognitive dysfunction during hypoglycaemia, following institution of rational, intensive insulin therapy in IDDM. Diabetologia: 37: 1265-1276 REF ID: FANELLI1994	ctive observational cohort study Italy	n=20 healthy participants) Inclusion: • IDDM • Consistent history of frequent hypoglycaemia (BG<3mmol/litre) in the absence of autonomic warning symptoms for at least 6 months before the study • Absence of clinically overt autonomic neuropathy Exclusion: • Other diseases or other drugs apart from insulin		n=16	n=5	avoidance by change in regime and counselling. To prevent hypoglycaemia, insulin doses aimed at fasting, preprandial and bedtime BG of ~7.2-8.3mM. Insulin changed to 4-daily injections, regular insulin at meal times and intermediate acting NPH at supper. In n=9 patients who had late dinner, NPH was added to regular insulin at lunchtime. Diet changed to 3 meals with no snacks. Daily telephone counselling.	therapeutic regime they followed at entry	3 months and 1 year	hypoglycaemia	for each group separately	Juvenile Diabetes foundation Grant and Aging Grant. All patients reported to be different to those recruited in FANELLI 1993 Control group changed to same insulin regime as intervention group at 3 months due to ethical reasons
			M:F	8:8	3:2						
			Age, years mean (SE)	32 (2.7)	33 (2.7)				HbA1c, %, mean (SE), only reported before and after for intervention group, no group comparison.	Before: 5.8 (0.2) After: 6.9 (0.1)	
			HbA1c, % mean (SE)	5.8 (0.2)	5.8 (0.2)				Autonomic symptom score during hypoglycaemia clamp, final score, mean (SE), scored zero-5 (none-severe) for six autonomic symptoms	2 week Intervention: 6.9 (1.0) Control: 1.9 (0.2) Reported to have normalised at 3 months and 1 year in intervention group	
			Duration of diabetes,	12 (2)	9.2 (3.4)				Neuroglycopenic symptom score during	2 week Intervention: 9.7 (1.1)	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			years mean (SE)						hypoglycaemia clamp, final values, mean (SE), scored zero-5 (none-severe) for five neuroglycopenic symptoms	Control: 6.1 (0.6) Reported to have normalised at 3 months and 1 year in intervention group	
			13 on 2-daily injections of mixed regular and NPH insulin, 8 on 3-daily injections at meal times and NPH at supper.								

Table 285: Ferguson 2001[45]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Ferguson et al., 2001. Severe hypoglycaemia in patients with type 1 diabetes and impaired	Open label randomised crossover study Outpatient clinic	n=40 Adults Inclusion: • Type 1 diabetes > 5years • Aged 19-65 years • Reported a reduction in	Age, mean (SD): not reported Type 1 diabetes duration: not reported Male:Female	Insulin Lispro and human NPH insulin for 6 months 4 week run-in period: all treated with regular	Regular human insulin and human NPH insulin for 6 months	1 year	Severe hypoglycaemia during treatment, no. of patients	Lispro: 18/33 Regular: 18/33 Reported as NS	Funding: Research grant from Eli Lilly Drop-outs 7 ACA n=33
							BG level at which hypoglycaemia initiated the perception of symptoms, mmol/litre	Lispro: 2.5 Regular: 2.6 Reported as NS	
							HbA1c %, end of each	Lispro: 9.1	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
awareness of hypoglycaemia: a comparative study of insulin lispro and regular human insulin. Diabetes/ Metabolism Research and Reviews: 17: 285-291 REF ID: FERGUSON 2001	UK	their warning symptoms for hypoglycaemia for at least 2 years; had ≥2 episodes of SH in the 2 years preceding and self-scored on Likert scale • HbA1c less than double the non-diabetic reference range of 5-6.5% Exclusion: • Systematic, renal or hepatic disease • Pregnancy	19:21	human insulin in combination with NPH SMBG as per normal routine			treatment period, mean (SD)	(0.8) Regular: 9.3 (1.0) Reported as P=0.14	Powered for incidence of SH Open-label, randomised, crossover Not ANCOVA Questionnaire data using ANCOVA
							QOL (DTSQ and HFS)	Reported as NS difference for both DTSQ and HFS	

Table 286: Fritsche 2001[51]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Fritsche et al., 2001. Avoidance of	Prospective observational before and after	n=10 (plus 10 controls and 10 aware type	Male:Female 10:0	Avoidance of hypoglycaemia	None	4 months	HbA1c, %, mean (SD)	Before: 6.8 (0.9) After 7.7 (0.9) Reported as P<0.05	Funding: Grants from the National Institute of

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
hypoglycaemia restores hypoglycaemia awareness by increasing beta-adrenergic sensitivity in type 1 diabetes. Annals of Internal Medicine: 134: 729-736 REF ID: FRITSCHE2001	study (prospective case-series) Germany	1 diabetes) Adults Inclusion: • Type 1 diabetes receiving an intensive insulin regime • Self-reported IAH and a history of SH as defined by DCCT (SH resulting in coma or seizure, requiring assistance from another person and treatment with glucagon or IV glucose	Age, mean (SD) 46 (16) Duration of diabetes, mean (SD) 20 (10) HbA1c, %, mean (SD) 6.8 (0.9) All were receiving intensive insulin regimes (LA insulin in the morning and at bedtime and RA insulin before meals – usually 3 times daily)	Target pre-prandial BG levels increased from 5.6 mmol/litre to 8.3 mmol/litre and at bedtime from 5.6 mmol/litre to 10 mmol/litre. to achieve this, long-acting insulin dose reduced. Daily RA insulin reduced and adjusted for carbs and BG level. SMBG 5 times daily. Participants contacted twice weekly for adjustments of insulin dose to avoid BG levels below 3.9mmol/litre.			Autonomic symptom score during hypoglycaemia clamp, mean (SE), scored zero-7 (none-severe) for nine autonomic symptoms	Before: 1.8 (0.6) After 3.3 (0.7) Reported as P=0.004	Health, Division of Research Resources, General Clinical Research Centre and Deutsche Forschungsgemeinschaft.
							Neuroglycopenic symptom score during hypoglycaemia clamp, mean (SE), scored zero-7 (none-severe) for ten neuroglycopenic symptoms	Before: 2.2 (0.7) After 3.7 (0.7) Reported as P=0.01	
							Severe hypoglycaemia (requiring 3rd party assistance and glucagon or IV glucose), episodes per patient, mean (SE)	4 months before: 2.0 (0.5) During study: 0.0 (0.0)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		Exclusion: • Autonomic neuropathy							

Table 287: GIMENEZ 2010[55]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Gimenez et al., 2010. Sustained efficacy of continuous subcutaneous insulin infusion in type 1 diabetes subjects with recurrent non-severe and severe hypoglycaemia and hypoglycaemia unawareness: a pilot study.	Prospective observational before and after study (prospective case-series) Spain	n=20 (plus 20 aware type 1 diabetes) Inclusion: • Type 1 diabetes duration >5 years • >18 years old • Conventional insulin treatment using MDI of RA (lispro or aspart) and glargine	Male:Female 8:12 Age, years, mean (SD) 34 (7.5) Duration of diabetes, years, mean (SD) 16.2 (6.6) HbA1c %, mean (SD) 6.7 (1.1) Conventional insulin treatment	CSII All received education programme for patients beginning CSII. Patients also seen every 2-3months after the education programme up to 24 months. Patients were encouraged to avoid BG values below 70mg/dl	None	6 months, 12 months and 24 months	SH (require 3rd party assistance), episodes per subject year, mean (SD)	Before: 1.3 (0.4) 24 months: 0.1 (0.2) Reported as P<0.001	Funding: Part sponsored by Medtronic Iberica. Grant from the Ministerio de Sanidad y Consumo of Spain
							Clarke score, number of patients with HU (score≥4) Clarke score, mean (SD)	Before: 19/20 24 months: 3/20 Before: 5.5 (1.2) 6 months: 3.7 (1.7) 12 months: 2.7 (1.1) 24 months: 1.6 (2.0) Reported as P<0.001 for baseline vs. 24 months)	
							Hypoglycaemia symptom score	Before: 31.6 (16.4)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Diabetes technology and therapeutics: 12: 517-521 REF ID: GIMENEZ2010		as basal insulin • Presenting more than 4 mild hypoglycaemia events per week (in the last 8 weeks) and more than 2 SH events (in the last 2 years) Exclusion: • Micro or macro-vascular complications • Low-level (micro) albuminuria • Contradi	using MDI of RA (lispro or aspart) and glargine as basal insulin				questionnaire during hypoglycaemia clamp study, mean (SD)	24 month: 62.3 (23.6) Reported as P<0.001	
							HbA1c %, mean (SD)	Before: 6.6 (1.1) 6 months: 6.7 (0.9) 12 months: 6.7 (0.8) 24 months: 6.3 (0.9) Reported as NS	
							DQoL, 46-item instrument with a 5-point Likert scale and 4 subscales (1-5, lower scores indicate better QOL)	Satisfaction Before: 36.0 (6.4) 24 month: 28.8 (5.5) Reported as P<0.001 Impact of treatment Before: 33.6 (7.5) 24 month: 27.4 (6.0) Reported as P<0.002 Social worry Before: 13.3 (4.1) 24 month: 11.5	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		ctions for CSII						(3.8) Reported as P<0.05 Diabetes related issues Before: 10.1 (2.6) 24 month: 8.0 (1.9) Reported as P<0.01	
							SF-12 health survey questionnaire, mean (SD)	Before: 34.1 (3.9) 24 month: 37.0 (2.9) Reported as P<0.01	

Table 288: HERMANNS 2007[61]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Hermanns et al., 2007. The effect of an education programme (HyPOS) to treat hypoglycae	RCT 23 outpatient centres Germany	n=164 Adults Inclusion: • Type 1 diabetes >10years • MDI or CSII • Aged 18-	Age, mean (SD) HyPOS: 46.0 (11.7) Control: 45.9 (13.3) Male, % HyPOS: 50	Avoidance of hypoglycaemia (n=84): HyPOS training programme focusing on avoiding low BG values, causes of HU,	Control (n=80) Education programme aimed at optimising intensive insulin therapy	6 months	Hypoglycaemia awareness questionnaire (HAQ; Clarke score), 8 items about freq. of SH and MH, detection of these episodes and glycaemic thresholds for detection of low BG. Each item scored 0	Mean difference: 0.7 (95% CI 0.1-1.2) Treatment effect reported as P=0.024 Improvement greater in HyPOS group	Funding: Berlin-Chemie AG funded the developmen t of HyPOS and supported the evaluation

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
mia problems in patients with type 1 diabetes. Diabetes/ metabolism research and reviews: 23: 528-538. REF ID: HERMANNS2007		70 years • At least one episode of SH in the past 12 months (requiring 3rd party assistance) or impaired awareness of hypoglycaemia and tight glycaemic control (HbA1c <6.5%) Exclusion: • Cancer diagnosis, dementia, pregnancy or diagnosis of psychiatric disease	Control: 50 Disease duration: HyPOS: 20.2 (10.8) Control: 22.1 (10.9) % patients with reduced awareness (HAQ Clarke score) HyPOS: 87.8 Control: 83.3 HbA1c, %: HyPOS: 7.2 (0.9) Control: 7.4 (1.1)	improving detection and recognition of warning symptoms and need for treatment of low BG values. 5-weekly lessons (each 90mins)	without regard to hypoglycaemia problems. 4-weekly lessons (each 90mins)		or 1 (total range 0-7, maximal awareness – maximal unawareness)		study. Power analysis done on awareness measured using a VAS Cont. outcomes using ANCOVA 18 drop-outs (11%) (control 13%, Hypos 9%) ACA
							Gold score, modified VAS, range 0-10 (minimal awareness – maximal awareness)	Mean difference: 0.8 (95% CI 0.2-1.4) Treatment effect reported as P=0.015 Improvement greater in HyPOS group	
							Severe hypoglycaemia (requiring 3rd party assistance) , no. of episodes/patient-year	Mean difference: 0.3 (95% CI -0.4-1.0) Treatment effect reported as P=0.4	
							BG level for detection of low BG, mmol/litre	Mean difference: -0.2 (95% CI -0.03-0.4) Treatment effect reported as P=0.02 Improvement greater in HyPOS group	
							HbA1c, %, final values	HyPOS: 7.2 (0.8)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
								Control: 7.1 (0.9)	
							QOL, Problem Areas in Diabetes scale (PAID), 5-point Likert scale 0-4 (no problem-serious problem). PAID scores transformed onto a 0-100 scale (higher scores = more serious problems)	Mean difference: -0.7 (95% CI -4.6-3.2) Treatment effect reported as P=0.7	
							QOL, Audit of Diabetes Dependent QOL (ADDQoL), 7-point scale (-3 to +3)	Mean difference: 0.1 (95% CI -0.1-0.4) Treatment effect reported as P=0.4	

Table 289: HERNANDEZ 2008[63]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Hernandez et al., 2008. Evaluation of a self-awareness interve	Prospective observational case-series Canada	n=23 Inclusion: • Type 1 diabetes for >5 years • >21years old	Male:Female 12:11 Age, median (range) 54 (29-75) Duration of diabetes,	Self-awareness educational intervention Eight 3-hour sessions held biweekly. Aimed at	None	18 months	Number of symptoms of hypoglycaemia, mean (SD)	Baseline: 3.4 (1.9) 6 months: 3.4 (2.0) 12 months: 2.7 (2.3) 18 months: 3.3 (2.6) RM_ANOVA reported as F[3,19]=4.4 P<0.05.	Funding: Canadian Diabetes Association 6 drop-outs
							Severe hypoglycaemia	Baseline: 13.3 (17.4)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
ntion for adults with type 1 diabetes and hypoglycaemia unawareness. Canadian journal of nursing research: 40: 38-56 REF ID: HERNANDEZ2008		• Currently SMBG • Previously diagnosed with HU by an endocrinologist and verified with the Clarke score Exclusion: • Cancer diagnosis, dementia, pregnancy or diagnosis of psychiatric disease	mean (range) 26.5 (10-47)	promoting increased awareness of body cues associated with differing levels of glycaemia and enhancing the well-being of patients with HU			requiring treatment, number of events	6 months: 9.4 (14.8) 12 months: 6.9 (11.0) 18 months: 7.1 (11.6) RM_ANOVA reported as F=0.86 P=0.5	
							HbA1c (units not reported), mean (SD)	Baseline: 0.088 (0.015) 6 months: 0.085 (0.014) 12 months: 0.084 (0.017) 18 months: 0.080 (0.015) RM_ANOVA reported as F=7.54 P=0.002	
							The Diabetes Questionnaire (TDQ), 15 item instrument with 6-point Lekert scale (1-6, strongly disagree-strongly agree)	Baseline: 75.3 (7.8) 6 months: 76.5 (8.7) 12 months: 79.3 (7.7) 18 months: 79.7 (7.0) RM_ANOVA reported as F=4.35 P=0.016	
							DQoL, 46-item instrument with a 5-point Likert scale and 4 subscales (1-5, lower scores indicate better QOL)	Baseline: 93.3 (18.7) 6 months: 126.2 (26.8) 12 months: 88.1 (17.4) 18 months: 120.9 (22.3) RM_ANOVA reported as F=18.5 P=0.000	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
							Hospitalisation, number of events	Baseline: 0.8 (2.2) 6 months: 0.1 (0.4) 12 months: 0.1 (0.5) 18 months: 0.2 (0.4) RM_ANOVA reported as F=1.11 P=0.37	
							Driving incidents, number of events	Baseline: 0.3 (0.7) 6 months: 0.1 (0.3) 12 months: 0.3 (0.8) 18 months: 0.1 (0.5) RM_ANOVA reported as F=1.00 P=0.41	

Table 290: HOPKINS 2012[66]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Hopkins et al., 2012. Improved biomedical and psychological outcomes 1 year after structured education	Retrospective observational case-series DAFNE courses UK	n=539 (subgroup of n=215 with impaired awareness) Inclusion: • Attending DAFNE course • Subgroup with	Age, mean (SD) Not reported for subgroup Male, % Not reported for subgroup Disease duration:	DAFNE course (Dose adjustment for normal eating) – 5 day course focusing on adjustment of insulin for carbohydrate intake and reflective use	none	1 year (300-420 days)	% patients with impaired awareness (n=215), those reporting symptom onset at BG <3mmol/litre or not at all	97/215 (45%)	Funding: broader program funded by the UK NIHR. G.T. employed as the national director of the DAFNE program and funded by the UK DAFNE
							Severe hypoglycaemia, self-reported episodes requiring assistance to treat hypoglycaemia due to incapacity, mean (SD) number of episodes per patient-year	Year preceding: 3.6 (13.6) Year post-DAFNE: 1.3 (5.9)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. Diabetes Care: 35: 1638-1642. REF ID: HOPKINS2012		impaired awareness: those reporting symptom onset at BG <3mmol/litre or not at all were considered to have impaired awareness of hypoglycaemia. Exclusion:	Not reported for subgroup % patients with impaired awareness: 100% (215/215) HbA1c, %: Not reported for subgroup	of home BG monitoring data.			QOL	Not reported for subgroup with impaired awareness of hypoglycaemia	collaborative. No data available for impaired awareness outcome at follow-up for 26/215 (12%)

Table 291: LEELARATHINA 2013[92]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Leelarathina et al., 2013A. Restoration of Self-Awareness of	Prospective case series HypoCOMPaSS trial (this paper reports the	n=18 Inclusion: • 18-74 years • Type 1	Age, mean (SD) 50 (9.0) Type 1 diabetes duration 35.0 (10.0)	Hypoglycaemia avoidance (6 months) HypoCOMPaSS education	This study reports the before and after clamp study data from the	6 months	Edinburgh Hypo Score (at end of clamp study): 11 items rating 4 autonomic symptoms & 5 neuroglycopenic	Total symptoms AUC Before intervention: 500 (365-685) After intervention: 650 (365-1285) Reported as P=0.02	Funding: Diabetes UK grant and Cambridge NIHR BRC. No pharmaceutic

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Hypoglycaemia in Adults With Long-Standing Type 1 Diabetes: Hyperinsulinemic-hypoglycemic clamp substudy results from the HypoCOMPaSS trial. Diabetes Care: 36: 4063-4070 REF ID: LEELARATHINIA2013A	case-series study data for all treatment arms) July 2010-June 2011, 96 adults recruiter to main HypoCOMPaSS trial across 5 UK tertiary centres	diabetes according to WHO criteria • IAH (Gold score ≥4 with or without history of SH in preceding 12 months defined by ADA) • Serum C-peptide <50pmol/litre with simultaneous exclusion of biochemical hypoglycaemia	HbA1c 8.1 (1.0)	tool (at start of 24-week RCT period: individualised education session aimed at avoidance and early detection of BG <4mmol/litre). Followed by 24-week using: 1) MDI + SMBG 2) MDI + SMBG and RT-CGM 3) CSII + SMBG 4) CSII + SMBG and RT-CGM PRIMARY GOAL OF INSULIN DOSE TITRATION THROUGHOUT THE 24-WEEK RCT PERIOD WAS	trial		symptoms (omitted non-specific symptoms nausea and headache from analysis). Each item scored 1-7 (absent-maximal) – converted to scale 0-6 with min-max possible range 0-54)		al company or device manufacturer funded the trial. Authors have received sponsorship, consultancy fees and sit on advisory boards for various companies. 30 consented to baseline clamp and 27 to post-RCT clamp. 25 completed at baseline and 22 post-RCT. Termination of clamp mainly due to cannula issues. Results presented for 18 participant for whom paired clamp
							Self-awareness of hypoglycaemia (clamp study), plasma glucose at which first felt hypoglycaemic, mmol/litre, mean (SD)	Before intervention: 2.6 (0.1) After intervention: 3.1 (0.2) Reported as P=0.017	
							Severe hypoglycaemia, annualised rate (not clamp study), median (IQR)	6 months preceding intervention: 4 (0-7) RCT-period: 0(0-0) Reported as P=0.001	
							IAH, Gold score, range 1-7, mean (SD)	Baseline: 5.2 (0.2) Post-RCT:	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		Exclusion: • Unwilling to undertake intensive insulin therapy and study devices • History of intolerance to glargine • Additional exclusion for clamp study (>60 years); history of epilepsy or ischemic heart disease		ABSOLUTE AVOIDANCE OF ALL BG LEVELS <4mmol/litre Of 18 participants in clamp study: CSII n=9 & MDI n=9 SMBG n=11 & CGM n=7				4.3 (0.4) Reported as P=0.009	data available. Area Under the Curve calculated using trapezoid rule after linear interpolation of any missing data

Table 292: LEITAO 2008[94]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Leitao et al., 2008. Restoration of hypoglycaemia awareness after islet transplantation. Diabetes Care: 31: 2113-2115. REF ID: LEITAO 2008	Retrospective observational case-series US	n=31 Inclusion: • Islet transplantation alone (n=25) or islet transplantation after kidney (n=6) Exclusion:	Age, mean 43.8 (8.7) Type 1 diabetes duration 29.3 (11.8) Male %: 42% Mean Clarke score 5.29 (1.51) Number of patients with HU (Clarke score ≥4): 27/31 (87%)	Islet transplantation (n=25) or islet transplantation after kidney (n=6)	none	47.2 (21.3) months after first intervention	Clarke score (minimum =0; maximum =7), mean (SD) Number of patients with HU (Clarke score ≥4)	Before: 5.29 (1.51) After: 1.35 (1.92) Before: 27/31 (87%) After: 4/31 (13%)	Funding: Supported by NIH/NCRR; Juvenile Diabetes Research Foundation International; NIH/NIDDK; the State of Florida and the Diabetes Research Institute Foundation. Author scholarship from Conselho Nacional de Desenvolvimento Cientifico e Tecnologico.

Table 293: LIU 1996[97]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Liu et al., 1996. Improved counter-regulatory	Prospective case series observational before	n=7 (plus 12 healthy controls) Inclusion:	Male:Female 3:4 Age, mean	3 months less strict glycaemic control aimed at	None	3 months	HbA1c %, mean (SE)	Baseline: 6.9 (0.3) 3 months: 8.0 (0.3) Reported as	Funding: Grant from the Juvenile Diabetes Foundation

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
hormonal and symptomatic responses to hypoglycaemia in patients with insulin-dependent diabetes mellitus after 3 months of less strict glycemic control. Clinical and investigative medicine: 19: 71-82 REF ID: LIU1996	and after study	• IDDM • Intensive insulin therapy and achieved strict glycaemic control • Recurrent hypoglycaemia (BG<3mmol/litre more than twice a week for 5 months and at least one SH requiring assistance during the last 2 years. Exclusion: • Autonomic neuropathy • Other chronic diabetic complications, other diseases influence glucose metabolism or medications influencing HU.	(SE) 36 (3.0) Duration of diabetes, mean (SE) 18 (4.0) HbA1c %, mean (SE) 6.9 (0.3)	increasing daily mean BG to 8-10mmol/litre based on 4-times daily SMBG. Telephone consultation once a week				P<0.05)	International
							Autonomic/neuroglycopenic symptom scores, scores from 0-10 on a VAS, mean (SE)	Sweating Baseline: 1.1 (0.4) 3 months: 5.2 (1.9) Reported as P<0.05) Lack of concentration Baseline: 0.2 (0.2) 3 months: 4.0 (1.1) Reported as P<0.05) Hunger; Palpitation; Tremor; Fatigue all reported as NS difference	

Table 294: MEYER 1998[107]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Meyer et al.,	Prospective	n=3 (plus 10	Male:Female	Islet transplant	None		HbA1c %, mean	Before: 8.0	Funding: not

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
1998. Improved glucose counter regulation and autonomic symptoms after intraportal islet transplants alone in patients with long-standing type I diabetes mellitus. Transplantation: 66: 233-240 REF ID: MEYER1998A	case series observational before and after study Germany	healthy controls) Inclusion: • Type 1 diabetes • Multiple episodes of protracted SH requiring hospitalisation and glucagon or IV glucose Exclusion: • Autonomic and peripheral neuropathy	2:1 Age, years, mean (SD) 35.3 (4.0) Duration of diabetes, years, mean (SD) 25.7 (7.4) HbA1c %, mean (SD) 8.0 (0.5)	One developed insulin-independence over 14 days after transplant, the other two patients required insulin for ~3 weeks. At FU, graft function had slightly declined and all required insulin. Islet transplants were rejected approx. 2 months after withdrawal of immunosuppressant therapy in all patients (approx. 1 month after re-examination)			(SD)	(0.5) After: 8.2 (0.3) Reported as NS	reported

Table 295: RYAN 2005[132]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Ryan et al., 2005. Five-	Retrospective	n=65	Male %	Islet transplantation	None	5 year	HYPO score	Reported to improve	Funding:

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
year follow-up after clinical islet transplantation. Diabetes: 54: 2060-2069. REF ID: 2027	observational case-series Canada	Inclusion: • Received islet transplantation Exclusion:	43% Age years, mean (SE) 42.9 (1.2) Duration of diabetes, mean (SE) 27.1 (1.3) % with problematic hypoglycaemia (frequent recurrent episodes of hypoglycaemia, usually associated with HU and more recently notified with HYPO score ≥1047): 52/65 80%	(52 had two transplants and 11 had three transplants)		Median (range) months, 35.5 (4.1-67.8)		significantly post-transplant	Juvenile Diabetes Foundation International

Table 296: RYAN 2009[133]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Ryan et al., 2009. Use of	Prospective observati	n=16	Male:Female 10:6	CGMS	None (SMBG)	2 month	Modified HYPO score: current 4 week BG (higher	1 month baseline: 857 (184)	Funding: Part

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
continuous glucose monitoring system in the management of severe hypoglycaemia. Diabetes Technology and Therapeutics: 11: 635-639 REF ID: RYAN2009	onal case-series Canada	Inclusion: • Type 1 diabetes treated with MDI • Elevated baseline HYPO-score >75th percentile for type 1 diabetes population (>423) and had at least one SH within the last year Exclusion:	Age years, mean (SE) 52.0 (2.3) Duration of diabetes, mean (SE) 29.4 (2.8) HbA1c %, mean (SE) 8.4 (0.3)	1 month run-in period with CGMS (Medtronic) with built in alarm. Following by 1 month study period with CGMS.			scores for more values <3mmol/litre and more points for lack of symptoms), mean (SE)	Study month: 444 (92)	financed by Medtronic Canada 2 drop-outs
							HbA1c %, mean (SE)	Before: 8.4 (0.3) After: 8.2 (0.3)	

Table 297: THOMAS 2007[153]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Thomas et al., 2007. A randomized pilot study in	RCT UK	n=21 Adults Inclusion: • Type 1 diabetes	Male:Female 11:10 Age years, mean 43 (10)	Education alone (n=7) – maintenance of current insulin	1) Analogue (n=7) – preprandial insulin lispro and evening	24 weeks	HbA1c %, mean (SD)	Education: 8.3 (1.0) Analogue: 7.6 (0.7) CSII: 7.4 (1.0)	Funding: supported by unrestricted donations
							Altered	Education: 2/7	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Type 1 diabetes complicated by severe hypoglycaemia, comparing rigorous hypoglycaemia avoidance with insulin analogue therapy, CSII or education alone. Diabetic Medicine: 24: 778-783 REF ID: THOMAS2007		• At least one episode of SH according to ADA criteria in the preceding 6 months • Naïve to MDI insulin analogue therapy • Recurrent severe hypoglycaemia confirmed in all participant • Questionnaire confirmed altered hypoglycaemia awareness Exclusion:	Duration of diabetes, mean 25 (10) HbA1c % baseline, mean (SD) Education: 8.5 (1.1) Analogue: 8.6 (1.1) CSII: 8.5 (1.9) Altered hypoglycaemia awareness (score ≥4 out of 7 in validated questionnaire), number of patients: Education: 7/7 Analogue: 7/7 CSII: 7/7	regimes and relaxation of SMBG targets (fasting and preprandial BG 7-8.5mmol/litre; post-prandial and pre-bed BG >7mmol/litre) ALL: Uniform structured re-education aimed at rigorous avoidance of biochemical hypoglycaemia while maintaining overall glycaemic control	insulin glargine with conventional BG targets (fasting 4.5-7; preprandial 5-7.5; postprandial 6-8; pre-bed 6.5-8.5) 2) CSII insulin lispro (n=7) delivered by Medtronic 508 pump with conventional BG targets		hypoglycaemia awareness (score ≥4 in validated questionnaire), no. of patients: DQOL, mean (SD) lower scores=better QOL HFS, mean (SD) lower scores=better QOL	Analogue: 4/7 CSII: 3/7 Education: 58 (16) Analogue: 70 (11) CSII: 74 (20) Education: 81 (14) Analogue: 83 (26) CSII: 64 (16)	from Sanofi-Aventis and Medtronic 2 drop-outs from education arm

G.7 Ketone monitoring

G.7.1 Ketone self-monitoring and in-hospital monitoring

Table 298: KURU 2014[86]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
B. Kuru, M. Sever, E. Aksay, T. Dogan, N. Yalcin, Eren E. Seker, and F. Ustuner. Comparing finger-stick beta-hydroxybutyrate with dipstick urine tests in the detection of ketone bodies. Turk.Acil Tip Derg. 14 (2):47-52, 2014. REF ID: KURU 2014	Prospective case series 1 centre in Turkey	n=256 Inclusion criteria: • Patients admitted to ED • Age >14 years • Serum glucose ≥150 mg/dl Exclusion criteria: • Patients whose tests could not be performed	Baseline: Mean age (SD): 62 (14.9); range 15-96 years. 44% male Drop-outs: n/a	**Point of care testing – frequency of monitoring is not mentioned – appears to be once only)** • Capillary blood ketones: Optimum-meter, Optimum TM exceed, TM/Abbott. Measured at bedside using β-ketone test strips. No ketonaemia = 0-0.5 mmol/litre; mild ketonaemia = 0.6-1.5 mmol/litre); moderate = 1.6 – 3.1 mmol/litre; severe = ≥3.2 mmol/litre. Positive blood ketones (ie. ketonaemia) = >0.5 mmol/litre. • Urine ketone bodies: urine ketone dipstick tests (DIRUI H800 analyser). DKA diagnosis: ADA criteria.		n/a	BLOOD vs. URINE KETONES n=221 (83.4%) - no ketones found in urine n=29 (13.1%) of these patients had positive blood ketones. 3 of these patients were severely ketonaemic, 6 moderately ketonaemic, and 20 mildly ketonaemic. 79.6% - no ketones found in blood 53.7% of these patients had no ketones in urine. 8 of these patients were severely ketonaemia, 12 moderately ketonaemic, and 34 mildly ketonaemic.		Funding: Not mentioned Risk of bias: Consecutive recruitment Prospective study

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
AUTHORS' CONCLUSIONS: Performing a capillary blood ketone measurement instead of a urine ketone measurement, was a better predictor of ketonaemia									

Table 299: LAFFEL 2006[88]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes	Comments
L. M. B. Laffel, K. Wentzell, C. Loughlin, A. Tovar, K. Moltz, and S. Brink. Sick day management using blood 3-hydroxybutyrate (3-OHB) compared with urine ketone monitoring reduces hospital visits in young people with type 1 diabetes: A	RCT 2 centres in the USA	n=123 (n=62 Blood group; n=61 urine group) Inclusion criteria: • Children, adolescents and young adults: age range 3-22 years • Type 1 diabetes attained age ≤22 years • Duration of diabetes ≥12 months • insulin dose of≥0.5		Bld n=62	Uri n=61	Capillary blood ketone monitoring (β-OHB) ITT: n=62 Precision Xtra System (Abbott), which measures blood 3-OHB and glucose levels with their respective test strips Patients in both groups were	Urine ketone monitoring (β-OHB) ITT: n=61 Precision QID system with blood glucose strips and urine ketone strips (Ketostix, Bayer)	6 months follow-up	ER use, no episodes	Bld: 8 Urine: 14	Funding: Abbott Laboratories Risk of bias: Randomisation = unclear (done at each site, by patient, but details not given) To ensure equal representation of insulin pump and non-pump users and to avoid confounding by glycaemic control, patients were randomized according to pump status and glycated
			Age, years (SD)	14.3 (4.6)	13.2 (5.0)				Hospitalisation, no. of episodes	Bld: 3 Urine: 8	
			Women, %	61	53				HbA1c, % (SD)	Bld: 8.3 (1.5) Urine: 7.7 (1.2)	
			Diabetes, mean years (SD)	7.5 (4.6)	7.3 (4.7)				HbA1c: after controlling for baseline HbA1c values, there was NS difference in HbA1c at end of the study and NS change from baseline in either group. Patient preference: overall more people preferred to check blood than urine ketones, as easier to perform		
			HbA1c, %	8.3 (1.5)	7.9 (1.3)				Authors conclusions:		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes	Comments
randomized clinical trial. Diabet.Med . 23 (3):278-284, 2006. REF ID: LAFFEL 2006		U/kg/day if age > 5 years or≥0.3 U/kg/day if age ≤5 • Routine glucose monitoring ≥3 times daily Exclusion criteria: • Recurrent DKA • Known emotional problems	NS differences between groups for any of the baseline characteristics Drop-outs (6 months): None mentioned	encouraged to check glucose levels ≥ 3 times daily and to check ketones during acute illness or stress, when glucose levels were consistently elevated (≥13.9 mmol/litre on two consecutive readings), or when symptoms of DKA were present. Participants continued routine diabetes care throughout the study, including 24-h access to an on-call			Blood ketone monitoring during sick days appears acceptable to and preferred by young people with Type 1 diabetes. Routine implementation of blood 3-OHB monitoring for the management of sick days and impending DKA can potentially reduce hospitalization /emergency assessment compared with urine ketone testing and offers potential cost savings.		haemoglobin (HbA1c) Allocation concealment = not mentioned Blinding = not mentioned ITT analysis (no drop-outs) No mention of powering Drop-outs = acceptable (<20%)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes	Comments
				physician					

Table 300: BEKTAS 2004[13]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
F. Bektas, O. Eray, R. Sari, and H. Akbas. Point of care blood ketone testing of diabetic patients in the emergency department . Endocr.Res. 30 (3):395-402, 2004. REF ID: BEKTAS 2004	Observational (prospective case series) 1 centre in Turkey	n=139 included as met criteria and had full records (11,383 screened) Inclusion criteria: • Newly diagnosed or known diabetic patients • Patients presenting to the ED with any medical (non-trauma) complaint	Baseline: Mean age (SD): 57 (14) 42% female Drop-outs: n/a Outcomes: Diabetic ketosis/ketonaemia: venous blood β-HBA ≥0.42 mmol/litre DKA: as above but also pH <7.3 Sensitivity/specificity of DK and DKA detection: lab tests of serum glucose (>200 mg/dL) and β-	**Point of care testing – frequency of monitoring was done weekly (according to the statistical analysis section of the paper)** • Capillary blood ketones: Medisense Optimum Sensor fingertip probe for measuring β-HBA (range between 0.1 to 9.0 mmol/litre) . • Urine ketone bodies: urine ketone dipstick tests were used (positive values ranging from 0-4).		Approximately 6 months	Sensitivity and specificity of ketone measurements: n=30 DK; n=18 DKA Detecting DK Capillary β-HBA: sensitivity 91/specificity 56 Urine β-HBA: sensitivity 82/specificity 54 Detecting DKA Capillary β-HBA: sensitivity 72/ specificity 82 Urine β-HBA: sensitivity 66/ specificity 78 Hyperketonaemic vs. Normoketonaemic patients SS difference between the 2 groups for capillary, venous and urine β-HBA measurements. Hyperketonaemic = ≥0.42 mmol/litre venous blood β-HBA		Funding: Not mentioned

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		• patients with blood glucose ≥200 mg/dL by finger stick testing and blood capillary β-HBA ≥0.1mmol/litre were included. Exclusion criteria: • Chief complaint of trauma • Using L-dopa or its metabolites	HBA ≥0.42 mmol/litre were used as the gold /reference standards.				≥0.42 n=48 hyperketonaemic hyperglycaemia. n=91 normoketonaemic hyperglycaemia. Capillary β-HBA Hyper = 1.48 (1.89) Hypo = 0.23 (0.19); p<0.001 Venous β-HBA Hyper = 1.56 (1.62) Hypo = 0.18 (0.13); p<0.001 Urine β-HBA Hyper vs. hypo: p=0.007 DKA vs. DK patients SS difference between the 2 groups for capillary and venous β-HBA mmts but NS difference for urine β-HBA mmts. DK venous blood β-HBA ≥0.42 DKA venous blood β-HBA ≥0.42 + pH<7.3 n=30 DK; n=18 DKA Capillary β-HBA DK = 0.88 (1.27) DKA = 2.87 (2.26); p=0.002 Venous β-HBA		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
							DK = 1.15 (0.57) DKA = 2.16 (2.40); p<0.001 Urine β-HBA DK vs. DKA: p=0.07 (NS)		
AUTHORS' CONCLUSIONS: A rapid, bedside capillary blood ketone test for β-HBA can accurately measure blood concentrations of β-HBA in an ED setting, and can be used as an accurate diagnostic test to detect emergency metabolic problems in patients such as DK or DKA.									

Table 301: ARORA 2011C[11]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
S Arora, SO. Henderson, T Long, and M Menchine. Diagnostic accuracy of point-of-care testing for diabetic ketoacidosis at emergency-department triage: [49]-hydroxybutyrate versus the urine dipstick.	Observational (prospective case series) 1 centre in USA	n=516 included as met criteria and had full records (859 screened) Inclusion criteria: • Convenience sample of patients presenting to the ED • Patients with capillary blood glucose	Baseline:			**Point of care testing – frequency of monitoring not mentioned** • Capillary blood ketones: Medisense/Abbot precision Xtra meter for measuring β-OHB. • Urine ketone bodies: urine ketone dipstick tests were used (positive or negative). Diagnostic accuracy: Blood capillary using cut-off of >1.5 mmol/litre (considered positive test). Difference in specificity for blood and		Approx. 2 years	Sensitivity and specificity of ketone measurements: n=462 No DKA; n=54 DKA Detecting DKA Capil β-HBA: sensitivity 98.1/specificity 78.6 Urine β-HBA: sensitivity 98.1/ specificity 35.1 Difference for specificity is SS (p<0.01) Capillary β-HBA were stable across a wide range of potential cut-offs. The ROC suggested that optimal β-HBA cut-off is >2 mmol/litre (sensitivity remains 98.1% but spec improves to 82.3%)		Funding: Donation of test strips by Abbot Laboratories. Risk of bias: Sample size calculation of n=54 (study sample stopped after
				DKA n=54	No DKA n=462						
			Median (IQR)								
			Age, years	41	48						
			Female, %	27.8	35.3						
			+ urine dipstick ketones	98.1%	64.9%						
			β-OHB, mmol/litre	0.3 (0.2-1.2)	4.9 (3.7-5.6)						
			Drop-outs:								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Diabetes Care 34 (4):852-854, 2011. REF ID: ARORA 2011C		≥250 mg/dL. Exclusion criteria: • Critically ill • acute psychosis • unable to give informed consent	None mentioned Outcomes: DKA (ADA criteria): serum glucose. ≥250 mg/dL; anion gap >10 mmol/litre; Co2 ≤18 mmol/litre; and pH≤7.3.	urine ketones was assessed.			AUTHORS' CONCLUSIONS: Point of care blood β-OHB and the urine dipstick are equally sensitive for detecting DKA (98.1%). However, blood β-OHB is more specific (78.6% vs. 35.1%), offering the potential to significantly reduce unnecessary DKA work-ups among hyperglycaemic patients in the ED.		enrolling this number of patients)

Table 302: HARRIS 2005[59]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
S. Harris, R. Ng, H. Syed, and R. Hillson. Near patient blood ketone measurements and their utility in predicting diabetic ketoacidosi	Observational (retrospective case series, review of records 1 centre in UK	n=50 (records of first 50 people to have β-OHB measured) Inclusion criteria: Hyperglycaemic or unwell Patients presenting to the ED patients with	Baseline: DKA (n=9) / DK (n=8) / Others (n=33) Age, years: median 23 / 35 / 61 Female, % 11 / 50 / 39 Diabetes new diagnosis, % 11 / 38 / 21 Blood β-OHB, mmol/litre ≥6.0 / 3.4 / 0.3	**Point of care /near patient testing – frequency of monitoring was not reported** • Capillary blood ketones: Medisense /Abbot Optimum for measuring β-OHB from finger-prick (range between 0.0 to 6.0 mmol/litre) . • Urine ketone bodies: urine ketone dipstick tests		Retrospective thus n/a However patients were followed for 48hrs in their records or telephone to see if developed DKA.	Sensitivity and specificity of ketone measurements: n=9 DKA; n=8 DK; n=33 other Detecting DKA Capil β-OHB >1 mmol/litre: sensitivity 100/ spec 76 Capil β-OHB >3 mmol/litre: sensitivity 100/ spec 88 Urine β-OHB: sensitivity 100/spec 52 Detecting patients requiring		Funding: Not mentioned Risk of bias: Gold standard includes blood β-OHB test. Therefore have used another classification system on whether the patients was treated with IV

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
s. Diabet.Med . 22 (2):221-224, 2005. REF ID: HARRIS 2005		blood glucose >11 mmol/litre by finger stick testing	Urine dipstick >1.5 mmol/litre 100% (7/7) 86% (6/7) 33% (5/15) Drop-outs: None mentioned Outcomes: Ketonaemia: urine dipstick (acetoacetate >1.5 mmol/litre or β-OHB >1.0 mmol/litre Diabetic ketosis: ketonaemia (as above) plus metabolic acidosis (pH >7.3 and HCO3 15-24 mmol/litre) DKA: metabolic acidosis (as above) secondary to ketonaemia (as above) but also pH <7.3 Hypoglycaemia alone = all other patients Diagnostic accuracy: for detecting DKA the gold standard would include the β-OHB blood test and thus calculation will overestimate the power of the test. Therefore have				treatment with IV insulin: Capil β-OHB >1 mmol/litre: sensitivity 100/ spec 86 Capil β-OHB >3 mmol/litre: sensitivity 100/ spec 100 Urine β-OHB: sensitivity 100/spec 65 AUTHORS' CONCLUSIONS: Measuring β-OHB when a hyperglycaemic patients is identified, could offer a simple method of identifying at an early stage those patients at highest risk of DKA (β-OHB >3.0 mmol/litre) and redirecting the search for a diagnosis in others (β-OHB >1.0 mmol/litre)		insulin for anything other than procedural reasons.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			used another classification system for detecting whether the patients was treated with IV insulin for anything other than procedural reasons.						

Table 303: TABOULET 2007

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
P. Taboulet, N. Deconinck, A. Thurel, L. Haas, J. Manamani, R. Porcher, C. Schmit, J. P. Fontaine, and J. F. Gautier. Correlation between urine ketones (acetoacetate) and capillary blood ketones (3-beta-hydroxybutyrate) in hyperglycaemic patients. Diabetes Metab. 33	Observational (retrospective case series, review of records 1 centre in France	n=529 Inclusion criteria: • Hyperglycaemic patients • Patients measured for blood ketones, urine ketones and blood glucose Patients presenting to the ED • patients with blood glucose ≥250	Baseline:	Point of care /near patient testing – tested on all patients with blood glucose >13.75 mmol/litre • Capillary blood ketones: Medisense /Abbot Optimum for measuring β-OHB from finger-prick (maximum 6.0 mmol/litre). • Urine ketone bodies: urine ketone dipstick tests (acetoacetate)		Retrospective thus n/a However patients data was from a period of 32 months	Relationship between presence of ketone bodies and ketoacidosis: Incidence of ketoacidosis was 7.7% Ketoacidosis rate increased with elevation of blood ketones and to a lesser degree with elevation of urine ketones Area under ROC curve for capacity to predict ketoacidosis was SS higher for blood ketones (0.984) than for urine ketones (0.941); p<0.0001. The % of patients with ketoacidosis ranged from 0% (at 0.1 mmol/litre blood ketones) to 78% (at ≥3 mmol/litre blood ketones) and		Funding: Not mentioned Risk of bias:

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
(2):135-139, 2007. REF ID: TABOULET 2007		mmol/litre • Determined NCGCNews@rcplondon.ac.uk on patients with malaise, polydyspepsia-poluria, disorders of consciousness, life-threatening situations and in all known diabetic patients.					6% (+ urine ketones) to 49% (+++ urine ketones). Relationship between presence of ketone bodies and hospitalisation: Incidence of hospitalisation was 49.7% Hospitalisation rate increased with elevation of blood ketones and to a lesser degree with elevation of urine ketones Area under ROC curve for capacity to predict hospitalisation was SS greater for blood ketones (0.704) than for urine ketones (0.620); p<0.0001. The % of patients who were hospitalised with ketoacidosis ranged from 42% (at 0.1 mmol/litre blood ketones) to 94% (at ≥3 mmol/litre blood ketones)and 51% (+ urine ketones) to 84% (+++ urine ketones). AUTHORS' CONCLUSIONS: In hyperglycaemic patients in the ED, a good correlation was observed between urine		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
							ketones and blood ketones for low values, but a poor correlation for high values. Either test can therefore be used to exclude ketosis, but the capillary ketones test is more accurate to confirm ketoacidosis.		

G.8 Arterial risk control

G.8.1 Aspirin

LARGE TRIALS ACCORD and ACCEPT-D are in progress - ACCEPT-D not complete for several years as recruitment slow

Table 304: Hansen 2000[58]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes	Comments
HANSEN 2000[58]	RCT (cross-over after 4 weeks) 1 centre in Denmark	n=17 (n=8 Aspirin group; n=9 placebo group) Inclusion criteria: • Type 1 diabetes with persistent low-level (micro)		Aspirin n=8	Placebo n=9	Low dose aspirin (150 mg) ITT: n=8 Aspirin given as one 150 mg tablet/day 4 weeks of treatment and	Placebo ITT: n=9 Placebo tablet 4 weeks of placebo and then 2 week	4 weeks treatment	AEs	NS difference (data not given)	Funding: Danish Diabetes Association; drugs supplied by Leo Pharmaceutical products, Denmark. Risk of bias:
			Age, years (SD)	43 (9)					Dyspepsia	Aspirin: 3 Placebo:3 (NS diff)	
			Women, %	71%					HbA1c, % (95% CI)	Aspirin: 8.4 (8.0, 9.0) Placebo:8.5 (8.1, 9.0)	
			Diabetes, mean	28 (8)							

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes	Comments
		albuminuria (urinary AER between 30 and 300 mg/24h in at least 2 of 3 sterile urine samples) • Insulin dependent from time of diagnosis • Receiving at least 2 daily injections of insulin Exclusion criteria: • SBP >200 mmHg • User of COX-inhibitors • acute gastritis or peptic ulcer disease • pregnant	years (SD)		then 2 week wash-out then crossed over to 4 weeks of placebo Concomitant medication: In both groups, n=15 patients received their usual a-HT treatment (n=14 ACEi, n=11 and/or non-ACEi)	wash-out then crossed over to 4 weeks of aspirin			MD: -0.1 (-0.4, 0.2);p=0.41	• Wash-out period = adequate (2 weeks; mean 19.4 days) • Randomisation = unclear (as details not given) • Allocation concealment = yes it was done, but unclear (as details not given) Blinding = double (but details not given) ITT analysis (no drop-outs) Powered study (urinary AER) Drop-outs = acceptable (<20%)
			Anti-HT treatment, %: ACE/ non-ACE/ none	82/6/12				SD calculated for HbA1c	Aspirin: 0.60 Placebo: 0.59	
			Retinopathy, %: non/simplex, proliferative	18/41/41				UER and GFR	Also NS difference	
			Smokers, %	53						
			NS differences between groups for any of the baseline characteristics Drop-outs (6 months): None mentioned							

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures (6 months)	Effect sizes	Comments

Table 305: ETDRS 1992[40]

Reference	Study type	Number of patients	Patient characteristics (type 1 diabetes subgroup)			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
ETDRS 1992[40]	RCT 22 centres in the USA.	n=3711 Type 1 diabetes and type 2 diabetes (n=1130 Type 1 diabetes; 30%) Aspirin group: n=1856 (all patients) n=559 (Type 1 diabetes) Placebo group: n=1855 (all patients) n=571 (Type 1 diabetes)		Aspirin n=559	Placebo n=571	High dose aspirin (650 mg/day) Type 1 diabetes - ITT: n=559 Aspirin given as two 325 mg tablets once/day During the trial lower doses were considered due to possibility of less AEs, but decided to continue on	Placebo Type 1 diabetes - ITT: n=571 Placebo tablet	5 years (average); range 4-9 years.	Mortality (all cause): end of follow-up	Aspirin: 29/559 Placebo: 39/571	Funding: National Eye Institute, USA. Risk of bias: Randomisation = unclear (just says randomised) Allocation concealment = good (drug assignment not known to patient or personnel) Blinding = double (patient or personnel unaware of
			Age, years, % <30 30-49 ≥50	51 46 3	46 50 4				Mortality (all cause): 5 years life table*	Aspirin: 17/559 Placebo: 27/571 RR given: NS difference	
			Women, %	40	36				Mortality (CV): end of follow-up	Aspirin: 17/559 Placebo: 26/571	
			Diabetes, % <10	3 62.1	4 58				Mortality (CV): 5 years life table*	Aspirin: 10/559 Placebo: 18/571 RR given: NS difference	

Reference	Study type	Number of patients	Patient characteristics (type 1 diabetes subgroup)			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			years 10-19 ≥20 years	34.9	38	650 mg/day. Concomitant medication: Not mentioned					drug assignment) ITT analysis Powered study (compliance and mortality) Drop-outs = acceptable (<30% for long-term study)
		Inclusion criteria: • Diabetes mellitus and 1 of following categories of diabetic retinopathy: mild non-proliferative with macular oedema, moderate to severe non-proliferative or early proliferative (less severe than the high risk proliferative stage) with or without macular oedema • Visual acuity required to	HbA1c ≥10%, %	45.1	51.9				MI (fatal and non-fatal): end of follow-up	Aspirin: 25/559 Placebo: 31/571	
			50% of patients had CV disease history§ 25% of patients had proliferative retinopathy in one or both eyes. §NOTE: History of CV disease was defined a history of any of the following: coronary artery disease, congestive heart failure, MI or intermittent claudication. Patients reporting any of the following drug use were also considered to have CV disease history: long-term anti-anginal agents, BBs, vasodilators, digitalis, antiarrhythmic agents, diuretics or other a-HT						MI (fatal and non-fatal): 5 years life table* RR given: NS difference	Aspirin: 13/559 Placebo: 21/571	
									Stroke (fatal and non-fatal): end of follow-up	Aspirin: 7/559 Placebo: 12/571	

Reference	Study type	Number of patients	Patient characteristics (type 1 diabetes subgroup)	Intervention	Comparison	Length of follow-up	Outcomes	Effect sizes	Comments
		be better than 20/40 in each eye (or 20/400 if acuity was reduced as a result of diabetic macular oedema. • Adults age 18-70 years Exclusion criteria: • SBP >210 mmHg and/or DBP >110 mmHG despite use of a-HT medication • History of GI haemorrhage or diagnosis of active G ulcer in past 2 years • inability or unwillingnes	agents. Patients with SBP ≥160 mmHg were also considered to have CV disease history.						

Reference	Study type	Number of patients	Patient characteristics (type 1 diabetes subgroup)	Intervention	Comparison	Length of follow-up	Outcomes	Effect sizes		Comments
		s to stop taking a-coagulants or a-platelet drugs • allergy to aspirin • pregnancy or lactation • poor prognosis for 5 years of follow-up because of a prior major CV event, cancer, or another chronic disease								
			Comparable between groups for all of the baseline characteristics Drop-outs: Not given for type 1 diabetes subgroup Overall study drop-outs: 3144/3711 survivors 2807 (24%) completed final					Stroke (fatal and non-fatal): 5 years life table*	Aspirin: 4/559 Placebo: 10/571 RR: 0.60 (0.18-2.04) RR given: NS difference Data for	

Reference	Study type	Number of patients	Patient characteristics (type 1 diabetes subgroup)	Intervention	Comparison	Length of follow-up	Outcomes	Effect sizes		Comments
			visit (164 alive, 706 died, 34 unable to contact).						these outcomes should be presented as HRs (Hazard ratios), however data reported in paper is insufficient to calculate these. They have not provided the log-rank or Cox-regression p-values, but have calculated the RRs	

Table 306: ETDRS unpublished data (provided with permission, from personal communication with the authors) (February 2013) - CV events in type 1 diabetes ETDRS participants that had no previous CVD

	Total	Aspirin	
		No	Yes

	N	Col%	N	Row%	N	Row%
Total	1393	100.0	710	51.0	683	49.0
CV event[a]	119	8.5	64	53.8	55	46.2
Yes						
No	1274	91.5	646	50.7	628	49.3
CV death	72	5.2	40	55.6	32	44.4
Yes						
No	1321	94.8	670	50.7	651	49.3
MI	85	6.1	48	56.5	37	43.5
Yes						
No	1308	93.9	662	50.6	646	49.4
Stroke	30	2.2	13	43.3	17	56.7
Yes						
No	1363	97.8	697	51.1	666	48.9

(a) CV events = CV death, MI or stroke, CVD = MI, CAD, CHF, stroke, TIA

G.9 Inpatient management

G.9.1 IV insulin

Table 307: Christiansen 1988 [27]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Christiansen CL et al. Insulin treatment of the insulin-dependent	RCT	n=20 Inclusion criteria: • Adults • Insulin-		IV infusion of glucose, insulin & potassium (GIK) for 24 hours Glucose 55g/litre, potassium chloride	Pre-op SC insulin 0.5 x usual daily dose if BG ≤8 mmol/litre 0.66 x usual daily dose if BG >8 and	3 days (day of operation and 2 days post-op)	Achieving target blood glucose levels (5-10mmol/litre), reported as % of values	During all 3 days: IV GIK: 48% SC: 26% (reported as P<0.01)	Funding: Danish Diabetic Association and Nordic Insulin

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
diabetic patient undergoing minor surgery. Anaesthesia. 1988; 43:533-537 REF ID: 1909		dependent diabetic admitted for minor surgery Exclusion criteria: • Steroid or β-blocker treatment • BG > 15 mmol/litre at 07:00 on the day of op				20mmol/litre and insulin Insulin 8units/litre if BG ≤4 mmol/litre; 16 units/litre if BG 4.1-6.9 mmol/litre; 24units/litre if BG 7-11.9 mmol/litre; 32 units/litre if BG 12-15 mmol/litre; Insulin = Velosulin (Nordisk insulin)	≤15 mmol/litre Concomitant glucose infusion 55g/litre at 100ml/h for 24 hours Insulin = Insulatard (Nordisk Insulin)		within the target range not no. of patients	During infusion period: IV GIK: 67% SC: 28% (reported as P<0.0001) Hyperglycaemia, no. of patients with ≥1 BG level >15mmol/litre IV GIK: 6/10 SC: 10/10	Foundation Risk of bias: Randomisation = unclear Allocation concealment = unclear Blinding = none reported
				IV GIK	SC						
			N	10	10						
			Age, median (range)	52 (25-74)	52 (29-76)						
			% male	40	40						
			HbA1c %, median (rang	8 (7.5-9)	8.8 (7.7-9.2)						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			e)						
			Drop outs: None reported	BOTH GROUPS: Allowed to eat post-op Aim to maintain BG between 5-10mmol/litre If BG >15mmol/litre, 12 units of Velosulin insulin given SC					
							Hypoglycaemia, no. of patients with ≥1 BG level <5mmol/litre	IV GIK: 6/10 SC: 4/10	
							Time spent out of target glucose	Not reported	
							Duration of IV treatment	Not reported	
							inpatient stay, days, median (range)	IV GIK: 5 (1-10) SC: 5 (2-7)	
							Inpatient mortality	Not reported	
							Infection rate/wound healing	Not reported	
							QoL (SF-36, DQoL, DSQoL)	Not reported	

Table 308: Corney 2012 [28]

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Corney SM et al.	Retro-spective	n=99 cases (75 unique		IV	CSII	CSII suspe	IV insulin	CSII: Continue	Inpatient	Achieving target blood	% of cases with ≥1 intra-op	Funding:

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Comparison of Insulin Pump Therapy (CSII) to Alternate Methods for Perioperative Glycemic Management in Patients with Planned Postoperative Admissions. J of Diabetes Science and Technology. 2012; 6(5):1003-1015 REF ID: CORNEY 2012	cohort study	individuals Inclusion criteria: ≥18 years type 1 diabetes/type 2 diabetes Elective surgery Exclusion criteria: Pregnancy CSII discontinued prior to admission Immediate or long-acting basal insulin administered.				nsion.	infusion: Convert from SCII to IV insulin infusion pre-operatively	CSII with supplemental SC or IV insulin if required. Suspend CSII: suspend SCII with or without SC or IV insulin boluses	stay	glucose levels % with intra-op target BG, hypo, moderate and severe hyper only reported graphically (no data). Comparison reported as P=0.034.	hyperglycaemia (BG >179mg/dl) IV: 40% CSII.: 45.3% CSII suspension.: 84.2% Mean BG mg/dl (all intra-op measurements and 1st post-op) IV: 152.3 (28.9) CSII.: 163.5 (58.5) CSII suspension.: 188.3 (44.9) P=0.128 as reported.	Investigator grant from sanofi-aventis Risk of bias: Study design – case-series Consecutive patients included ACA SS baseline diffs in pre-op BG
			N	20	53	19						
			Age	51.6 (11.9)	51.5 (10.4)	55.3 (10.5)						
			% M	35	28.3	21						
			% Type 1 diabetes	90	86.8	84.2						
			HbA1c %	7.49 (1.0)	7.63 (1.2)	8.29 (1.1)						
			BG mg/dl	196.8 (79.9)	146.1 (62.8)	160 (86.3)						
			Drop outs: 7 (5 excluded as CSII status unavailable, 2 dropped from analysis as CSII had been suspended)				ALL GROUPS: Intravenous dextrose treatment given as judged appropriate for all groups.			Hypoglycaemia (severe intra-op; BG <40mg/dl)	IV: 0/20 CSII.: 0/53 CSII suspension.: 0/19	
										Time spent out of target glucose (hypo/hyper)	Not reported	
										Duration of IV treatment	Not reported	
										Duration	Not reported	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
							inpatient stay		
							Inpatient Mortality	Not reported	
							Infection rate/wound healing	Not reported	
							QoL (SF-36, DQoL, DSQoL)	Not reported	

Table 309: Husband 1986 [68]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Husband DJ et al.. Management of Diabetes during Surgery with Glucose-Insulin-Potassium Infusion. Diabetic Medicine. 1986; 3:69-74	Prospective case series	n=128 (n=41 IDDM) Inclusion criteria: • Mainly adults • Type 1 diabetes or type 2 diabetes • Elective ops involving general or			IV infusion of glucose, insulin & potassium (GIK) SC insulin omitted on the morning of op and GIK infused at 100ml/h (at least 1 hour before op; 16U Actrapid insulin, 10mmol potassium chloride and 500ml 10% glucose) Before infusion, if BG < 5mmol/litre insulin decreased to 12U/500ml and	None	3 days (day of operation and 2 days post-op)	Achieving target blood glucose levels Pre-op: 5-10 mmol/litre Op day: 5-12 mmol/litre (with no hypoglycaemia <3 mmol/litre)	Pre-op: 26/41 Operation day: 31/41 (reason for unacceptable below, hypo/hyper) BG values, mmol/litre, mean (SD) Pre-op: 8.2 (3.0) Post-op: 9.6 (3.4) Mean op day: 8.9 (2.3)	Funding: DJH supports by grant from Newcastle-upon-Tyne Health Authority and ACT. British Diabetic Association. Risk of bias: • Study design case-series
			N	41 (IDDM)						
			Age, median (range)	No type 1 diabetes subgroup data						
			Pre-op BG (fasting), mean SD	8.2 (3.0)						

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: HUSBAND 1986		epidural anaesthesia Exclusion criteria: • Cardiopulmonary bypass op			if > 13mmol/litre increased to 20U/500ml GIK infusion adjusted in steps of 4U/500ml to maintain BG 5-10 mmol/litre GIK continued until first post-op meal (SC regime reinstituted)				Mean post-op day 1 (n=14): 9.4 (1.9) Mean post-op day 2 (n=9): 10.2 (2.8)	
			% male	Not reported						
			Drop outs: None reported							
								Hypoglycaemia	On operation day, no. of patients with BG level <5mmol/litre 4/41 Hyperglycaemia: On operation day, no. of patients with BG level >12mmol/litre 6/41	
								Time spent out of target	Not reported	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
							glucose		
							Duration of IV treatment	Not reported	
							inpatient stay	Not reported	
							Inpatient mortality	Not reported	
							Infection rate	Not reported	
							QoL (SF-36, DQoL, DSQoL)	Not reported	

Table 310: McCavert 2010 [103]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
McCavert et al.. Peri-operative blood glucose management in general surgery – A potential element for improved diabetic patient outcomes. Int. J of Surgery.	Prospective case series	n=69 (n=35 type 1 diabetes) Inclusion criteria: • Diabetic patients having elective or emergency surgery Exclusion criteria:	n=35 (Type 1 diabetes) Elective n=21 Emergency n=14	IV infusion of glucose, insulin & potassium (GIK; based on Alberti Regimen) Type 1 diabetes commenced on GIK before, during and after surgery BG measured pre-op (6am), post-op (6pm), post-op day 1 (6am) and post-op day 2 (6am)	None	3 days (day of operation and 2 days post-op)	Achieving target blood glucose levels, mean % for all 4 time points (6.1-10 mmol/litre)	Elective patients (n=21): <6.1mmol/litre: 7.4% 6.1-10mmo/litre: 25.9% >10mmol/litre: 55.6% Not checked: 11% Emergency patients (n=14): <6.1mmol/litre: 4.5% 6.1-10mmo/litre: 22.7% >10mmol/litre:	Funding: None reported Risk of bias: • Study design case-series Adherence to GIK 20/35 Type 1 diabetes received the GIK infusion (elective 14, emergency 6) 5/21 elective

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
2010; 8(6):494-498 REF ID: McCAVERT 2010									65.9% Not checked: 6.8%	patient not treated according to protocol 11/14 emergency patient not treated according to protocol
			Age, median (range)	No Type 1 diabetes subgroup data				hypoglycaemia	'No hypoglycaemic episodes were reported'	
			% male					Time spent out of target glucose	Not reported	
			Drop outs: None reported					Duration of IV treatment	Not reported	
								inpatient stay	Not reported for Type 1 diabetes subgroup	
								Inpatient mortality	Not reported	
								Infection rate	Wound infection: Elective patients:	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
								2/21 Emergency patients: 1/14 Peritonitis: Elective patients: 1/21 Emergency patients: 0/14 Septicaemia: Elective patients: 0/21 Emergency patients: 2/14	
							QoL (SF-36, DQoL, DSQoL)	Not reported	

Table 311: Poppe 2004 [126]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Poppe AY, Vautour L, Yale J-F, Wing SS. Evaluation of a Protocol for the Perioperative Administra	Retrospective case series (consecutive chart review	n=50 Inclusion criteria: • Treated with SC insulin or oral agents • Surgical procedure as inpatient	Type 1 diabetes (n=12, 24%) or type 2 diabetes (n=38, 76%) NOTE: this does not meet the protocol inclusion criteria except	Perioperative IV insulin protocol SC insulin discontinued morning of surgery IV insulin (0.5 patient's daily dose ÷ 24, per hour) with	None	Inpatient stay (first 24 hours of infusion for these outcomes)	Achieving target blood glucose levels	% of levels in the hyperglycaemic range (>12mmol/litre; first 24 hours; type 1 diabetes): 49.7% Mean BG level (first 24 hours; type 1 diabetes only): 12.1 (1.1) mmol/litre	Funding: not reported Risk of bias: Study design – case-series Consecutive patients included 26/50 patients remained on

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
tion of Intravenous Insulin in Patients with Diabetes. Canadian Journal of Diabetes. 2004; 28(2):00-00. REF ID: POPPE2004		(treated with IV insulin during surgery) • Survived for at least 1 day after surgery Exclusion criteria: • Caesarean section • Remained in ICU for >48hours	for subgroup analysis of (a) % BG levels in hyperglycaemic range, (b) mean BG level first 24 hours Age, mean (SE): 62.0 (1.8) not reported for type 1 diabetes subgroup M/F: 30/20 not reported for type 1 diabetes subgroup Drop outs: 26 patients remained on the IV insulin protocol at 24 hours not reported for type 1 diabetes subgroup	glucose (5g/hour). Initial rate decreased by 50% in patients with BG <6mmol/litre. Insulin adjustments made if outside target BG range 8.1-12mmol/litre (increased 25-50% if 12.1-16mmol/litre and by 50-100% if >16mmol/litre)			Hypoglycaemia	No type 1 diabetes subgroup data	the IV protocol at 24 hours (not reported if analysis done on ACA or ITT) Subgroup: Type 1 diabetes n=12 (24% of patients). But, type 1 diabetes subgroup analysis performed (not in all outcomes)
							Time spent out of target glucose (hypo/hyper)	Not reported	
							Duration of IV treatment	Not reported	
							Duration inpatient stay	Not reported	
							Inpatient Mortality	Not reported	
							Infection rate/wound healing	Not reported	
							QoL (SF-36, DQoL, DSQoL)	Not reported	

Table 312: Wagner 1999 [164]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Wagner A, Risse A, Brill H-L, Wienhausen-Wilke V, Rottmann M, Sondern K, Angelkort B. Therapy of Severe Diabetic Ketoacidosis. Diabetes Care. 1999; 22(5):674-677 REF ID: WANGER 1999	Prospective case series Paper also reports retrospective chart review of DKA admissions (Total n=114)	n=114 (15 repeat patients) Prospective insulin intervention study (n=65) Inclusion criteria: • Adults and young people with type 1 diabetes • Severe ketoacidosis, admitted to ICU Exclusion criteria:	Age, mean (SD): 34 (16) Range 11-74 years not reported for intervention study separately M/F: 60% male not reported for intervention study separately Diabetes duration: 12.2 (10.8). Range 0-41 years not reported for intervention study separately Drop outs	'Very low-dose insulin application'. IV insulin infusion 1U/h (0.4-4.0U/h). Initially small insulin boli of 2.0-15.0U given. Target – reduction in BG level of 50mg/dL/h. If BG drop more than 100mg/dL/h, 5% glucose given. Ringer lactate fluid substitution, potassium replacement and heparin.	None	Inpatient stay	Achieving target blood glucose levels (reported as mean (range) BG mg/dl at each time point)	Admission: 606(86-1191) After 1hr: 468(96-1075 After 4hr: 376(66-1003 After 8hr: 283(107-738) After 12hr: 251(89-614)	Also reports results from retrospective case-series review of DKA admissions (not relevant). Funding: not reported Risk of bias: Study design – case-series Consecutive patients included
							hypoglycaemia	Not reported	
							Time spent out of target glucose (hypo/hyper)	Not reported	
							Duration of IV treatment	Not reported	
							Duration inpatient stay	Not reported (duration of ICU stay only)	
							Inpatient Mortality	Not reported	
							Infection rate/wound healing	Not reported	
							QoL (SF-36, DQoL, DSQoL)	Not reported	

G.10 Complications

G.10.1 Gastroparesis

G.10.1.1 The 2 relevant STUDIES FROM THE ORIGINAL 2004 GUIDELINE

Table 313: JANSSENS 1990[70]

Q59 What is the optimum method of managing autonomic neuropathy in adults with Type 1 diabetes?	
Author/Title/Reference/Yr	Janssens, J., Peeters, T. L., Vantrappen, G., Tack, J., Urbain, J. L., De Roo, M., Muls, E., & Bouillon, R. 1990, "Improvement of gastric emptying in diabetic gastroparesis by erythromycin. Preliminary studies", *N Engl J Med*, vol. 322, no. 15, pp. 1028-1031.
n=	n=10 in cross over design Belgium
Research Design	Randomised controlled trial
Aim	To examine the effect of erythromycin on the impaired gastric emptying of people with severe diabetic gastroparesis
Population	Type 1 diabetes
Intervention	200 mg of erythromycin was infused intravenously over a 15-minute period after the meal.
Comparison	A control was infused placebo
Outcome	The outcomes measured were percentages of both solids and of liquid remaining in the stomach after the standard meal, at 1 hour and 2 hours after digestion of the meal The simultaneous gastric emptying of liquids and solids was determined scintigraphically with a double-isotope technique. The technique used a standardized meal consisting of one scrambled egg , two slices of bread, and 150 ml of water. The weight of the solids was 110 g, and they contained 0.966 MJ (231 kcal), consisting of 35 percent fat, 47 percent carbohydrate, and 18 percent protein. The meals were eaten in a mean (±SE) period of 8±2 minutes. Images were obtained every 10 minutes for one hour and then every 15 minutes for another hour. The results were expressed as the percentages of solids and liquids remaining in the stomach over time after the completion of the meal.
Characteristics	Age =51years, Male =30%, Duration of Diabetes =24years, HbA1c =8.0%, Type 1 diabetes =100%
Results	Erythromycin markedly accelerated the extremely slow gastric emptying of solids in those with diabetic gastroparesis. With 85 ±7% of solids remaining in the stomach with placebo at 1 hour compared to 21 ±5% with erythromycin (pless than0.005),

	this effect was also seen at 2 hours Erythromycin accelerated the severely impaired emptying of liquids in the people with diabetes, with only 22 ±5% of liquid remaining in the stomach at 1 hour with IV erythromycin compared to 54 ±5% with placebo There were no outcomes recorded regarding adverse events during the cross-over study period
Hierarchy of Evidence Grading	Ib
Comments	Study is too short to allow valid conclusions about the effect of the drug on long-term control of diabetes. The participants' blood glucose concentrations were maintained between 5.5 and 8.3 mmol per litre by combined infusions of insulin and glucose during the fast and the subsequent study period. No other concomitant therapy was given to either group The effect of erythromycin on gastric emptying in people with severe diabetic gastroparesis seems to confirm the drug's strong gastro-kinetic effect All people in study had chronic gastroparesis that was refractory to other treatments. Small sample size makes extrapolation to a wider population difficult
Reference/Citation	266
ADDITIONAL DATA REQUIRED FOR 2015 GUIDELINE	**RCT: 1 day of erythromycin vs. 1 day placebo (cross-over); 1 day wash-out inbetween.** **Follow-up: All patients were then treatment with erythromycin for 4 weeks NOTE: We are not using this RCT data as it was only treatment for 1 day!** **HbA1c (at end of 4 weeks): 7.6% (range 5.1 – 10.0)** **Baseline was: 8.0% (range 5.3 – 11.6) NOTE: This data has been used as observational**

Table 314: SAMSOM 1997[134]

Q59 What is the optimum method of managing autonomic neuropathy in adults with Type 1 diabetes?	
Author/Title/Reference/Yr	Samsom, M., Jebbink, R. J., Akkermans, L. M., Bravenboer, B., van Berge-Henegouwen, G. P., & Smout, A. J. 1997, "Effects of oral erythromycin on fasting and postprandial antroduodenal motility in patients with type I diabetes, measured with an ambulatory manometric technique.", *Diabetes Care*, vol. 20, no. 2, pp. 129-134.
n=	n=12 in crossover design
Research Design	Randomised controlled trial

Aim	To evaluate the effects of oral erythromycin on inter-digestive and postprandial gastrointestinal motility and dyspeptic symptoms in people with type 1 diabetes
Population	Type 1 diabetes The people with diabetes were selected on the presence of dyspeptic symptoms, such as nausea, vomiting, early satiety, fullness, bloating, and abdominal pain. Mechanical obstruction or other diseases responsible for these symptoms were ruled out by means of endoscopy of the upper intestinal tract and ultrasound examination
Intervention	Erythromycin stearate 250g (orally) three times daily, 30 min before the meal for 14 weeks
Comparison	This was compared to a placebo tablet for the same period
Outcome	The inter-digestive phases were defined as follows: 2) phase I: motor quiescence starting after the end of phase III, 2) phase II: pressure waves greater than2 kPa occurring at a rate higher than two per 10 min and less than the maximum frequency of the antrum (three contractions/min) or the duodenum (10-12 contractions/min), and 3) phase III rhythmic contractile activity at the maximum frequency (three contractions/min) in poi] the antrum for at least 1 min and in the duodenum (10-12 contractions/min) for at least 2 min. Phase III had to be propagated over at lea over at least two recording sites and followed by motor quiescence. The manometric data were analysed visually to determine the position of the pressure transducers and to examine pathological motility patterns, using commercially available software, this was carried out over a 20hour period. Symptom scores for the severity of dyspeptic symptoms were also recorded daily for 14 days Antro-duodenal motility was studied during a 20-h period, using a commercially available meal (stew, mixed vegetables, and potatoes; 1,805 kj; 27 g protein, 29 g carbohydrate, 23 g fat; together with 200 ml water or tea was taken at 6:00 P.M. At 8:00 A.M., they took a standardized breakfast consisting of two slices of bread with margarine and jam (1,140 kj; 1 g protein, 48 g carbohydrate, 10 g fat) and 200 ml water or tea. At 12:0 Antro-duodenal motility was recorded using a six-channel solid-state manometric catheter connected to a portable data logger The symptoms of nausea, vomiting, early satiety, bloating, fullness, and abdominal pain were each scored at10:00 P.M. daily, according to a 3 point grading system, validity not specified, A surveillance for adverse events included weekly visits to the hospital with biochemical analysis of blood samples
Characteristics	Age =43years, Male =25%, Duration of diabetes =26years, HbA1c =9%, Type 1 diabetes =100%
Results	No clinical or bio- chemical side effects were observed during erythromycin treatment. The blood glucose concentrations during 2 weeks of erythromycin or placebo treatment showed no statistically significant difference During fasting The total number of phase III during erythromycin treatment was 62, compared with 48 during placebo which was not significant There was a decrease in the length of the migrating motor complex (MMC) during erythromycin treatment, compared with placebo 86.2 ± 25.3 Vs. 118.9 ± 46.0 min (P = 0.03). The postprandial pattern showed erythromycin significantly decreased the duration of the post- prandial motor Pattem, from 417.0 ± 137.9 to 348.8 ± 93.8 min (P = 0.04).

	After dinner the number of distal antral contractions (P less than 0.01) and motility index (P less than 0.03) were significantly increased by erythromycin. After breakfast, there were no such increases In the total group, the mean symptom score did not improve during erythromycin treatment compared to placebo No correlation between antroduodenal motility parameters and the individual symptoms, except for phase III, which was invariably associated with nausea.
Hierarchy of Evidence Grading	Ib
Comments	It is unlikely that blood glucose concentrations have influenced the results of erythromycin treatment presented in this study. There is no validation of symptom scoring and therefore results may not be reproducible, with unknown effects on outcomes There was a one week washout period but no test to see if this was adequate, with potential contamination of intervention and therefore decreased treatment effect.
Reference/Citation	265
ADDITIONAL DATA REQUIRED FOR 2015 GUIDELINE	• STUDY LIMITATIONS: randomised, double blind, washout period (1 week), not mention allocation concealment , no dropouts • 2 weeks treatment with erythromycin vs. 2 weeks treatment with placebo (and crossed-over) • HbA1c (at baseline was: 9.39% (SD 2.34) – post-treatment data not given! • Mean symptom severity score - out of total of 3: 3= worse severity - (SD): placebo period 1.81 (0.86); erythromycin period 1.53 (0.67); NS difference • NS improvement in any of the individual symptoms either.

G.11 The new studies from the new guideline search

Table 315: OLAUSSEN 2014

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
EA. Olausson, S Storsrud, H Grundin, M Isaksson, S Attvall, and M Simren. A small particle size diet reduces upper gastrointestinal symptoms in patients with diabetic gastroparesis: a randomized controlled trial. Am J Gastroenterol 109 (3):375-	RCT Sweden	n=56 diabetes with gastroparesis (64% Type 1 diabetes) Inclusion criteria: • Insulin-treated diabetes mellitus • Age 18-70 years • Clinical suspicion of gastroparesis • Delayed gastric emptying (scintigraphy) • No evidence of mechanical obstruction • Able to	ALL PTS BASELINE			Small particle diet Eat foods with small particle size or food items that could easily be processed into small particle size. BOTH GROUPS: received instruction from dietician how to fill out questionnaires and dietary food record, and advice on having the	Normal diabetes diet Food usually recommender for people with diabetes. Large particle size acceptable and food should be low GI.	20 weeks	20 weeks treatment	Diet	Control	Funding: None specific for this study. Risk of bias: Randomisation = unclear (details not given) Allocation concealment = not mentioned Blinding = not mentioned ITT analysis: yes – LOCF Drop-outs: unacceptable (>10%
				Intervention diet n=28	Usual diabetes diet n=28				Weight, kg, mean (SD)	77.9 (16)	78.5 (15.8)	
			Age, years; mean	51.5	55.0				Weight change, mean difference, kg	-0.012 (-1.6 to 1.6), p=0.99 no difference		
			Female	64%					HbA1c, % (SD)	7.4 (0.8)	7.8 (1.1)	
			HbA1c, % (SD)	7.4 (0.8)	7.9 (1.2)				SF-36 PCS, out of 100 (SD)	40.2 (10.9)	35.5 (12.8)	
			Mean duration of diabetes, years	28.2	23.6				SF-36 MCS, out of 100 (SD)	43.8 (15.2)	41.5 (14.8)	
			Weight, kg, mean (SD)	78.4 (16.3)	79.0 (15.6)				Severity of nausea/vomiting, mean	-0.56 (-1.01 to -0.11), p=0.01 favours diet		

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
385, 2014. REF ID: OLAUSSEN 2014		understand verbal and written information and complete questionnaires in Swedish. • Exclusion criteria: • Previous GI surgery except appendectomy • Severe psychiatric disease • Sequelae after cerebrovascular disease • Serum creatinine >150 micromole/litre • Untreated disease with a potential impact on gastric				same meal scheme: breakfast, snack, lunch. Snack, dinner, and evening snack. Also received dietary advice from the same dietician at 7 out-patient visits during the 20 weeks.			change difference		differential between groups)
			SF-36 PCS, out of 100 (SD)	39.0 (11.4)	37.6 (12.0)				Severity of fullness/early satiety, mean change difference	-0.61 (-1.14 to -0.08), p=0.02 favours diet	
			SF-36 MCS, out of 100 (SD)	41.5 (15.9)	42.1 (13.3)				Severity of bloating, mean change difference	-0.86 (-1.48 to -0.25), p=0.006 favours diet	
									Severity of upper abdominal pain, mean change difference	-0.36 (-1.01 to -0.28), p=0.27 NS difference	
			Drop-outs : n=1 (3.6%) intervention n=5 (18%) control						Severity of lower abdominal pain, mean change difference	-0.50 (-1.15 to -0.14), p=0.12 NS difference	
									SEVERITY SCORES (PAGI-SYM): 20 items, 6 subscales (nausea/vomiting; fullness/early satiety;		

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		emptying or GI symptoms						bloating; upper abdominal pain; lower abdominal pain; heartburn/regurgitation). Score of 0-6 (6-point Likert scale). 0 = no symptoms, 5 = very severe symptoms.		

Table 316: SNAPE 1982

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
W. J. Snape, Jr., W. M. Battle, S. S. Schwartz, S. N. Braunstein, H. A. Goldstein, and A. Alavi. Metoclopramide to treat gastroparesis due to diabetes mellitus: a double-blind, controlled trial.	RCT (cross-over) USA	n=10 Type 1 diabetes and gastroparesis Inclusion criteria: • IDDM adults • Symptoms of gastric retention, vomiting, bloating, and early satiety Exclusion criteria: None	ALL PTS BASELINE		Metoclopramide (10 mg tablets) four times daily 30 minutes before breakfast, lunch, and dinner, and before sleep.	Placebo	3 weeks (each cross-over period)	3 weeks treatment on each	Met	Placebo	Funding: none mentioned. Risk of bias: No wash-out period. Randomisation = unclear (details not given) Allocation concealment = not mentioned Blinding = double
			Age, years; mean	31.4				Weight loss, no. of patients	3	6	
			Mean duration of diabetes)	16.2 years				Symptoms 'felt better', no. of patients	7	0	
			Mean insulin dose – LA insulin (NPH or Lente)	40.5 (6.6 U)				No vomiting, no of patients	6	0	
								AEs (abdominal pain), no.	0	3	

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Ann.Intern. Med. 96 (4):444-446, 1982. REF ID: SNAPE 1982		mentioned.						of patients			ITT analysis: yes – no drop-outs Drop-outs: acceptable (none)
								Questionnaire given to patients - symptoms were classified as present, not present, mild, moderate, or severe.			
			Drop-outs : None mentioned								

Table 317: RICCI 1985

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
D. A. Ricci, M. B. Saltzman, C. Meyer, C. Callachan, and R. W. Mccallum. Effect of metoclopramide in diabetic gastroparesis. J.Clin.Gastroenterol. 7 (1):25-32,	RCT (cross-over) USA	n=13 Type 1 diabetes and gastroparesis Inclusion criteria: • IDDM adults • Symptoms of gastric stasis • Objective documentation of delayed gastric emptying (radionuclide	ALL PTS BASELINE		Metoclopramide (10 mg tablets) four times daily 30 minutes before breakfast, lunch, and dinner, and before sleep.	Placebo	3 weeks (each cross-over period)	3 weeks treatment on each	Met	Placebo	Funding: Grant from AH Robins Company, and from NIHR. Risk of bias: 1-week wash-out period. Randomisation = unclear (details not given)
			Age, years; mean	44.1				Overall mean symptom score – frequency (SD); max score = 100	26.5 (21.6)	45.3 (45.5)	
			Female	54%				Mean symptom score (total of 100): 5 symptoms (epigastric fullness, pressure and bloating; nausea; vomiting; anorexia; early satiety. Each rated grades			
			Mean duration of diabetes,	12.6 (range 3-28)							

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
1985. REF ID: RICCI 1985		solid meal) • Symptoms of nausea, vomiting, epigastric fullness, bloating and distension, early satiety, and anorexia. Exclusion criteria: • Organic causes of delayed gastric emptying (such as ulceration, obstruction). • Other causes of delayed gastric emptying • Contraindication to metoclopramide • Taking other dopamine antagonists • Other drugs with known	years					0-20 (0= symptom not experienced, 10= daily frequency; 15= 2-3 times/day; 20= 4 or more times/day)		Allocation concealment = not mentioned Blinding = double ITT analysis: yes – no drop-outs Drop-outs: acceptable (none)
			Mean duration of gastric stasis symptoms, years	2.5 (3 months to 7 years)						
			Mean symptom scores, mean (SD)	Met = 50.0 (19.5) Placebo = 52.7 (21.6)						
			Drop-outs : None mentioned							

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		delaying effects on gastric emptying.							

Table 318: MCCALLUM 1983

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
R. W. Mccallum, D. A. Ricci, H. Rakatansky, J. Behar, J. B. Rhodes, G. Salen, J. Deren, A. Ippoliti, H. W. Olsen, K. Falchuk, and . A multicenter placebo-controlled clinical trial of oral metoclopramide in diabetic	RCT USA	n=44 diabetes and gastroparesis (95% type 1 diabetes) Inclusion criteria: • Diabetes • Delayed gastric emptying (test meal study or roentgenologic study) Exclusion criteria: • Ulceration, obstruction, and other organic aetiologies of gastric retention • Other causes of	ALL PTS BASELINE			Metoclopramide (10 mg tablets) four times daily 30 minutes before breakfast, lunch, and dinner, and before bedtime.	Placebo	3 weeks		Met	Placebo	Funding: partly by Medtonic. Risk of bias: Randomisation = unclear (details not given) Allocation concealment = not mentioned Blinding = double ITT analysis: no Drop-outs: 2 in each group
				Metoclop) n=20	Placebo n=24							
			Age, years; mean	40	42				No. of patients getting Improvement of ≥2 on severity scale (for patients with initial rating of moderate or more)			
			Male	45%	29%				Vomiting, no of patients	6/10	4/8	
			Nausea	15 (75%)	18 (75%)							
			Vomiting, n	11 (55%)	10 (43%)				AEs, no. of patients	11/18	20/22	
			Duration of diabetes, years	12.6 (range 3-28)					Patient diaries used to record frequency and severity of symptoms.			

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
gastroparesis. Diabetes Care 6 (5):463-467, 1983. REF ID: MCCALLUM 1983		delayed gastric emptying • Contraindication to metoclopramide • Taking other dopamine antagonists • Other drugs with known delaying effects on gastric emptying. • All disorders other than diabetes	Duration of gastroparesis symptoms, years	2.5 (range 3 months -7 years)				5-point Scale: 0=absent, 1 = slight, 2=moderate, 3 = marked, 4 = extreme		(<20% and no differential between groups)
			Drop-outs : n=2 in each group (10% and 8% respectively)							

Table 319: TIMRATANA 2013[157] – subgroup analysis done in the diabetic patients

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
P. Timratana, K. El-Hayek, H. Shimizu, M. Kroh, and B. Chand. Laparoscopic Gastric Electrical	Case-series (prospective) USA	n=110 gastroparesis (n=55 diabetes; the rest = idiopathic) Inclusion criteria: • Age >18 years • Typical symptoms	DIABETIC SUBGROUP (n=55)		IMPLANTED GES system - Laparoscopic Neurostimulator (Enterra Therapy	No comparison group	Mean 27 months 1-113)	Results DIABETIC SUBGROUP	Pre-op (baseline)	Follow-up	Funding: None Risk of bias: No checklist for before-after studies/case-series
			Age, years; mean	41.3				HbA1c (SD)	Pre-op n=37 7.6 (1.3)	Post-op n=17 8.7 (1.8)	
			Male/fe	17/38				Nausea	SS change, p<0.01		

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Stimulation for Medically Refractory Diabetic and Idiopathic Gastroparesis. J.Gastrointest.Surg. 17 (3):461-470, 2013. REF ID: TIMRATANA 2013		of gastroparesis • Have failed medical management or unable to tolerate medications • Diabetic or idiopathic causes of gastroparesis • Off all narcotics and pro-motility agents for 2 weeks prior to the study Exclusion criteria: • Prior gastric surgery.	male,		System, Medtronic) Programmed to standardised parameters (3V; cycle ON for 0.1 seconds).					
			Duration diabetes, years	18 (1-40)				Vomiting Pain Bloating	SS change, p<0.01 SS change, p=0.009 NS change, p=0.165	
			Duration gastroparesis, years	6.4 (1-20)				AEs (post-surgical complications)	n=5	
			Insulin Pancreas transplant	n=48 n=2				Death	n=4 at mean 14.5 months (1-26)	
								TSS, severity, mean (SD)	6 months: 10.7 (1.7); p<0.05. 12 months: 9.2 (1.5); p<0.05	
			SF-36 mental, mean (SE)	37.3 (3.5)						
			GET (gastric emptying), % retention, median (IQR)	2hrs: 80 (69-88); 4hrs: 46 (28-68)				SF-36, physical, mean (SE)	6 months: 32.0 (2.0); p<0.025. 12 months: 35.2 (2.9); p<0.025	
								SF-36, mental, mean (SE)	6 months: 42.0 (3.5). 12 months: 47.3 (2.2).	
								2hrs GET, median	6 months: 67 (50-79).	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Drop-outs : None in first 2 months 6 months cumulative n=5 diabetics 12 months cumulative n=6				(IQR)	12 months: 46 (29-61)	
							4hrs GET, median (IQR)	6 months: 44 (21-67). 12 months: 16 (1-30), p<0.05.	
							TSS = sum of severity of ratings for 6 symptoms: 5-point symptom questionnaire: 0=absent, 1= mild, 2=moderate, 3=severe, 4= extremely severe. Symptoms measured were upper GI tract symptoms: vomiting, nausea, early satiety, bloating, postprandial fullness, epigastric pain).		

Table 320: ABELL 2003[5] – subgroup analysis done in the diabetic patients

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
T. Abell, R. W. Mccallum, M. Hocking, K. Koch, H. Abrahamsson, I. Leblanc, 11	RCT (cross-over)	n=33 gastroparesis (n=17 diabetes; n=16 idiopathic) Inclusion criteria:	Diabetic subgroup (n=17)	Implanted GES system ON (then off) Neurostimulator (Medtronic	Implanted GES system OFF (then on)	1 month of treatment on or off, then switched.	RCT results (1 month treatment) DIABETIC SUBGROUP	GES ON	GES OFF	Funding: partly by Medtonic. Risk of bias: Wash-out period = none

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
G. Lindberg, J. Konturek, T. Nowak, E. M. M. Quigley, G. Tougas, and W. Starkebaum. Gastric electrical stimulation for medically refractory gastroparesis. Gastroenterology 125 (2):421-428, 2003. REF ID: ABELL 2003	centres in USA, Canada, and Europe.	• >1 episode of vomiting/week • Delayed gastric emptying (>60% retention at 2 hours and >10% at 4 hours (scintigraphic method for solid meals) • Symptoms consistent with gastroparesis for >12 months • Refractories or intolerance to 2 of 3 classes of prokinetic drugs (cholinergics, motilin receptor agonists, dopamine receptor agonists) and 2 of 3 classes of antiemetics (a-histamines, serotonin receptor antagonists, and dopamine receptor antagonists)	Age, years; mean	38.1	model 4300) with 2 implanted leads In the muscularis propria of the greater curvature Programmed to standardised parameters (14Hz, 5mA, 330µs; cycle ON for 0.1 seconds, cycle OFF for 5 seconds). Mean surgery duration: 1.6 hours	BOTH GROUPS - Concomitant medication: Patients continued their current antiemetic or prokinetic treatment during the study	Then 10 months open-label with stimulator ON	WVF, episodes/ week; median (IQR)	6.0 (3.0-14.8)	12.8 (5.5-24.2)	mentioned. Randomisation = unclear (as details not given) Allocation concealment = not reported Blinding = double ITT analysis: not reported Not powered study; enrolment stopped early due to difficulty in recruiting patients. Drop-outs =none for phase 1 RCT (thus ITT analysis)
			Male/female,	9/8				TSS; severity, mean (SD)	11.3 (1.5)	13.2 (1.7)	
			BMI, Kg/m^2; mean (SD)	24.7 (4.7)							
			WVF Weekly vomiting frequency	13.4 (8.8-55.6)				6 and 12 month data (below) is given for DIABETIC SUBGROUP. All had machine ON. (NOTE: this has been added into the observational data section of results)			
			Total symptom score (TSS); mean (SE)	16.87 (1.2)				WVF	6 months: 2.6 (0.9-12.5); p<0.05. 12 months: 4.9 (0.1-7.4); p<0.05		
			SF-36 physical, mean (SE)	26.1 (2.3)				TSS, severity, mean (SD)	6 months: 10.7 (1.7); p<0.05. 12 months: 9.2 (1.5); p<0.05		
			SF-36 mental, mean (SE)	37.3 (3.5)							
			GET (gastric	2hrs: 80				SF-36, physical,	6 months: 32.0 (2.0);		

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		Exclusion criteria: • Documented intestinal pseudo-obstruction, prior gastric surgery, vagotomy, organ transplantation, seizures, primary swallowing disorders, chemical dependency, pregnancy, or psychogenic vomiting • Medically unstable or at high surgical risk.	emptying), % retention, median (IQR)	(69-88); 4hrs: 46 (28-68)				mean (SE)	p<0.025. 12 months: 35.2 (2.9); p<0.025	
								SF-36, mental, mean (SE)	6 months: 42.0 (3.5). 12 months: 47.3 (2.2).	
			Drop-outs : None in first 2 months 6 months cumulative n=5 diabetics 12 months cumulative n=6					2hrs GET, median (IQR)	6 months: 67 (50-79). 12 months: 46 (29-61)	
								4hrs GET, median (IQR)	6 months: 44 (21-67). 12 months: 16 (1-30), p<0.05.	
								TSS = sum of severity of ratings for 6 symptoms: 5-point symptom questionnaire: 0=absent, 1= mild, 2=moderate, 3=severe, 4= extremely severe. Symptoms measured were upper GI tract symptoms: vomiting, nausea, early satiety, bloating, postprandial fullness, epigastric pain).		

Table 321: ABELL 2011[6] – subgroup analysis done in the diabetic patients

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
T. L. Abell, W. D. Johnson, A. Kedar, J. M. Runnels, J. Thompson, E. S. Weeks, A. Minocha, and M. E. Griswold. A double-masked, randomized, placebo-controlled trial of temporary endoscopic mucosal gastric electrical stimulation for gastroparesis. Gastrointest.Endosc. 74 (3):496, 2011.	RCT (cross-over) 1 centres in USA	n=58 gastroparesis (n=13 diabetes; n=38 idiopathic; n=7 postsurgical) Inclusion criteria: • 18-70 years old • Gastroparesis symptoms >1 year (diabetic, postsurgical or idiopathic etiology) • 7 or more episodes of chronic vomiting and/or nausea per week, irrespective of gastric emptying time • Refractory or intolerant to antiemetic drug classes (antihistamines	ALL patients BASELINE			Implanted GES system ON (then off) Neurostimulator (Medtronic Enterrra stimulator),. Programmed to standardised parameters (14Hz, 5-10mA, 330µs; cycle ON for 0.1 – 1.0secs, cycle OFF for 5-4 seconds).	Implanted GES system OFF (then on)	72 hours of treatment on or off, then switched.	RCT results (3 days treatment) DIABETIC SUBGROUP: n=13	GES ON	GES OFF	Funding: partly by Medtonic. Risk of bias: Wash-out period = 24 hrs. Randomisation = unclear (details not given) Allocation concealment = none (unmasked) Blinding = double ITT analysis: no Powered study. Drop-outs = <20% and <10% differential between arms.
				Group A (on/off) n=28	Group B (off/on) n=30							
			Age, years; mean	47	45				Vomiting score	-0.31 units/day (-0.64, 0.02) with stimulation (p=0.069)		
			Male	28%	13%							
			BMI, Kg/m^2; mean (SD)	29.4 (7.4)	27.5 (7.7)							
			Vomiting score (likert 1-5)	1.82 (1.55)	2.68 (1.61)							
			Total symptom score (TSS); mean (SD)	12.8 (4.95)	14.6 (3.8)							
			Nausea score	3.27 (0.92)	3.33 (1.03)							

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: ABELL 2011		and phenothiazines, serotonin receptor antagonists, dopamine receptor antagonists) Exclusion criteria: • Active infection of any kind • Enrolled in another medical device or drug study • Pregnant • Unsuitable for endoscopy • Unwilling or unable to return for follow-up visits.	(likert 1-5)								
			GET (gastric emptying), % retention, mean (SD)	2 hours : 45.5 (24.1) 4hr: 24.5 (26.5)	2 hours : 38.7 (26.2) 4hr: 19.4 (25.4)						
			Drop-outs : n=6 in group A and n=7 in group B. All due to dislodged electrode they discontinued treatment.								

Table 322: BRAUN 1989[18]

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
A. P Braun. Domperidone in the treatment of symptoms of delayed gastric emptying in diabetic patients. Adv.Ther. (6):51-62, 1989. REF ID: BRAUN 1989	RCT – cross-over (with run-in and extension phase all patients on domperidone) USA	n=13 Type 1 diabetes and type 2 diabetes with gastroparesis (95% Type 1 diabetes) – in the RCT phase Inclusion criteria: Diabetes • At least 1 symptom of delayed gastric emptying at moderate to severe intensity Exclusion criteria: • Total gastrectomy • Pregnant or likely to become p0regnant • Conditions or illnesses that could interfere	All patients baseline		Domperidone 10 or 20 mg/day vs. Placebo Domperidone 9/10 patients 10mg/day 4/13 = 20 mg/day at 15-30 minutes before meals and at bedtime. IN BOTH GROUPS: There was a 12 week run-in (open Domperidone treatment phase. Patients received 10mg tablet before each meal and bedtime. If insufficient improvement seen, dose could increase to 20mg. All patients who showed improvement at this phase were entered for 2 year maintenance programme (2 further months of treatment on Dom, then RCT, then extension) The RCT phase followed (1 month cross-over of Dom vs.	12 week run-in (open Domperidone treatment phase); then 1 month RCT phase (1 month each treatment); then long-term open domperidone treatment phase (up to 2 years – mean 467 days).	RCT results (1 monthly treatment) n=13		Funding: None reported. Risk of bias: Wash-out period = 24 hrs. Randomisation = unclear (details not given) Allocation concealment = unclear (details not given) Blinding = double ITT analysis: no No mention of powering. Drop-outs in RCT = <20% and <10% differential between arms.
			Final population of n=18 for efficacy phase	Male: 33% Mean age: 51 Weight: 68kg			Change from baseline: there was SS deterioration in TSS frequency in placebo group, but NS for TSS intensity.		
			NO OTHER BASELINE DETAILS GIVEN				Domperidone was SS better than placebo for: frequency and intensity of early satiety (p<0.05) TSS frequency (p<0.05) TSS intensity (p=0.05). There was NS difference between Domperidone and Placebo for: Nausea Vomiting Anorexia Distention/bloating		
							After the RCT: most physicians rated domperidone as excellent/good (Phys global assessment)		

Reference	Study type	Number of patients	Patient characteristics		Intervention Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		with evaluation of the study drug. • No concurrent medications that could mask GI symptoms or compromise efficacy assessment were allowed during study or 1 week before.			placebo) Last extension phase followed – all patients received open therapy with Dom (up to 2 years).		Open phase 1 (12 weeks treatment on Domperidone, before RCT): n=18 12/18 patients had dose increased to 20mg. SS decrease in intensity and severity of all individual symptoms, and TSS severity and frequency (p<0.05)		
			Drop-outs : • n=20 patients started open phase; n=2 not included in analysis • n=13 started RCT phase.				Open phase 2 (up to 2 years on Domperidone, after RCT): n=13 SS decrease in TSS frequency, intensity and severity (p<0.05).		
							NOTE: TSS (both frequency and intensity) is on a scale of 0-3; with 3 being worse. There were 5 symptoms. 5 symptoms assessed were: anorexia, nausea, vomiting, distention/bloating, early satiety.		

NOTE: only patients who improved on domperidone in run-in phase, entered the subsequent RCT phase of the study.

Table 323: FRIEDENBERG 2008[50] – subgroup analysis done in the diabetic patients

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
F. K. Friedenberg, A. Palit, H. P. Parkman, A. Hanlon, and D. B. Nelson. Botulinum toxin A for the treatment of delayed gastric emptying. Am.J.Gastroenterol. 103 (2):416-423, 2008. REF ID: FRIEDENBERG 2008	RCT 1 centres in USA.	n=32 gastroparesis (n=18 diabetes; n=13 idiopathic; n=1 post-surgical) Inclusion criteria: • 18-75 years • Symptoms consistent with delayed gastric emptying (GCSI score >27) • Delayed gastric emptying (scintigraphy; within past 3 months) • Diabetics required to be under good metabolic control fBG <140 mg/dL) for 1 month before study • Patients on prokinetics with partial effectiveness had	ALL PTS (n=32); n=16 in each group			BOTOX (BoNT/A) 200U BoNT/A (5 mL volume) injected into the pylorus. Clear and odourless reconstitution from powder. Injection administered after an overnight fast and standard upper endoscopy)	PLACEBO Sterile saline injection – 5 mL (administered after an overnight fast and standard upper endoscopy) BOTH GROUPS - Concomitant medication: PTS ON PROKINETICS (if partially effective) DISCONTINUED the treatment	1 month post-treatment (single injection)	1 month post-treatment: DIABETIC SUBGROUP	BoTOX	Placebo	Funding: none mentioned. Risk of bias: Randomisation = ok (although just says randomisation table) Allocation concealment = yes – independent study coordinator accessed. Blinding = double Powered study. Drop-outs =none (thus ITT analysis)
			Age, years; mean	41.6	40.4				GCSI score reduction, mean (SD) p=0.79	11.4 (9.8)	13.7 (16.3)	
			Male	19%	19%				2hr GES, % 4hr GES, % NS	15 8	11 9	
			Gastric retention % (SD) 2hrs	67 (11.3)	64 (13.7)							
			Gastric retention %, (SD) 4hrs	29 (17.8)	28 (22.8)							
			GCSI, (SD)	34.4 (4.2)	36.4 (4.8)							
			GVAS (SD)	603 (139)	584 (131)							
			Previous treatmen						SYMPTOM SEVERITY SCORES:			

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		to have stable dose at least 4 weeks before study. Exclusion criteria: • Pregnant • Unfit to undergo upper endoscopy • Prior abdominal surgery except for hernia repair or appendectomy • Received prior BoNT/A or known allergy to the protein • Unable to stop medications known to exacerbate delayed gastric emptying (eg. Narcotic analgesics)	t: Metoclop Domperid Erythrom y Tegasero d PPI	14 3 2 2 8	11 2 3 2 9		48hrs before GES. Patients on ineffective prokinetics were discontinued the treatment 4 weeks before study.		1. GCSI score (Gastroparesis Cardinal Symptoms Index): 9 symptoms, scale 0 (none) – 5 (very severe). Total score = 45. Score ≥27 = moderate to severe symptoms.		
									GVAS score (Gastroparesis VAS): 8 symptoms, all post-prandial assessed for severity. 100mm VAS; max score 800. QoL (impact of symptoms on QoL and ability to attend and function in work or school. 5-point Likert scale used.		
			Drop-outs : None						GES: normal emptying with test meal = ≤50% retention at 2hrs and ≤10% at 4 hrs.		

Table 324: FROKJAER 2008[52]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
J. B. Frokjaer, N. Ejskjaer, P. Rask, Andersen S. Due, H. Gregersen, A. M. Drewes, and P. Funch-Jensen. Central neuronal mechanisms of gastric electrical stimulation in diabetic gastroparesis. Scand.J.Gastroenterol. 43 (9):1066-1075, 2008.	RCT (cross-over) 1 centres in Denmark.	n=7 Diabetes with gastroparesis (n=6 Type 1 diabetes) Inclusion criteria: • Symptomatic diabetic autonomic neuropathy (minimum of 2 symptoms from different organ systems) • Classic symptoms suggestive of gastroparesis (nausea, vomiting, early satiety and bloating) which were refractory to antiemetics and prokinetics. • Verified delayed gastric emptying of a solid meal and liquids (assessed by	All patients (n=7)		IMPLANTED GES system ON (then off) Neurostimulator (Medtronic 3116). 2 electrodes. Greater curvature of the pylorus. Programmed to standardised parameters (14Hz, 5mA, 330µs; cycle ON for 0.1sec, cycle OFF for 5 seconds).	IMPLANTED GES system OFF (then on) BOTH GROUPS - Concomitant medication: At start of study 2 patients were taking medication affecting GI function; rest were not treatment because of previous insufficient response to various drugs. All	1 month treatment, then crossed-over		ON period	OFF period	Funding: Danish Research Council, Aarhus County, Danish Diabetes Association, Research Council of North Jutland, Aarhus University Hospital, Toyota Foundation, and SparNord Foundation. Risk of bias: No washout period between cross-over Randomisation = ok (although
			Age, years; mean	39 years (25-55)				Vomiting episodes/ day, mean (SEM)	1.13 (0.50) SD calculated: 1.32	0.33 (0.13) SD calculated: 0.34	
			Male/Female	4/3							
			Diabetes type	n=6 Type 1 diabetes; man 25 years duration							
			Vomiting episodes/ day, mean (SEM)	0.61 (0.26)							
			Nausea duration, hours/day, mean (SEM)	4.1 (0.7)							
			Drop-outs : n=1								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
REF ID: FROKJAER 2008		either scintigraphy, or paracetamol absorption method). Thus patients had severe emptying disorder. Exclusion criteria: • Pregnant • Psychogenic vomiting • Prior abdominal surgery • Pseudo-obstruction • Uraemia • Primary eating and swallowing disorders			medication affecting GI function was paused 2 days before all investigation periods.				just says randomisation table) Allocation concealment = not mentioned. Blinding = double No mention of powering. Not ITT analysis Drop-outs: N<20%

Table 325: HOROWITZ 1985[67] Data presented for cases (diabetics) only

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
M. Horowitz,	Prospective	n=12	All type 1 diabetes patients (n=12)	DOMPERIDONE	N/A	35 - 51 days	Anorexia/nausea, mean (SD)	0.42 (.67)	Funding: Janssen

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
P. E. Harding, B. E. Chatterton, P. J. Collins, and D. J. Shearman. Acute and chronic effects of domperidone on gastric emptying in diabetic autonomic neuropathy. Dig.Dis.Sci. 30 (1):1-9, 1985. REF ID: HOROWITZ 1985	case-series Australia	Type 1 diabetes with autonomic neuropathy n=22 normal volunteers also recruited (but not designed as case-control study) Inclusion criteria: Type 1 diabetes for at least 10 years Autonomic neuropathy Other complications of diabetes Non-smokers Not taking medication known to affect GI motility Also normal healthy controls recruited Exclusion criteria: None reported	Age, years; mean	43 (21-61)	20mg 3x/day, 30-60 minutes before meals Patients were tested immediately after given 40mg domeperidone vs. placebo Then later part of trial (results for this are reported here as matched protocol) patients received longer term treatment with domperidone.		treatment (median 38 days)	Early satiety, mean (SD)	0.75 (0.97)	Pharmaceutic Patienty. Ltd. Risk of bias: No NICE checklist for case-series
			Male/Female	6/6				Epigastric fullness/upper abdominal discomfort, mean (SD)	0.58 (0.79)	
			Diabetes type	All type 1 diabetes Duration >10 years						
			Anorexia/ nausea, mean (SD)	1.17 (1.03)				Post-prandial vomiting, mean (SD)	0.08 (0.29)	
			Early satiety, mean (SD)	1.75 (0.97)				TSS severity, mean (SD) – total score of 4 symptoms/max. 12	1.83 (1.99)	
			Epigastric fullness/upper abdominal discomfort, mean (SD)	1.75 (1.23)				Episodes of Hypo	5 patients observed more episodes while taking domperidone (no details given) and reduced their insulin dose	
								HbA1c, % MEDIAN	7.5 (5.6 – 12.1); NS	

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
								(range)	change from baseline	
			Post-prandial vomiting, mean (SD)	0.42 (0.79)				Symptoms severity of GP were SS reduced by domperidone treatment (p<0.001): baseline median 4.5, range 1-10 End of treatment median 1.5, range 0-6		
			TSS severity, mean (SD) – total score of 4 symptoms /max. 12	5.08 (3.09)				Each Symptom score on scale of 0-3 (higher = more severe)		
			HbA1c, % MEDIAN (range)	8.5 (6.8-10.9)						

Table 326: LACY 2004 (case-control)[87]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
B. E. Lacy, M. D. Crowell, A. Schettler-Duncan, C. Mathis, and P. J. Pasricha. The treatment of diabetic Gastroparesis with botulinum toxin injection of the pylorus. Diabetes Care 27 (10):2341-2347, 2004. REF ID: LACY 2004	Prospective case control Open label trial with age and sex-matched control subjects from a tertiary care referral centre for patient with Gastroparesis	n=8 with type 1 diabetes Control group consisted of age and sex-matched control subjects without diabetes and without any complaints. Inclusion criteria: • Details not given Exclusion criteria: • Pregnancy • Known allergy to eggs, botulinum toxin, or lidocane • Previous surgery to the stomach,	Eight type 1 diabetes who had failed standard therapy were enrolled		Injection of the pylorus with 200 units of botulinum toxin A during upper endoscopy. Patient was observed for 1-2 h in the recovery area and then discharged home. Patients underwent esophagogastroduodenoscopy (before intervention) to rule out mechanical obstruction.	N/A	12 weeks		Before	After	Funding: study funded donations to the Marvin M. Shuster Centre for Digestive and Motility Disorders and by unrestricted educational grants Risk of bias: NO NICE CHECK LIST
			Age, years; mean (range)	41 (36-46)				*Mean symptom score	27.0 (n=8)	12.2 (n=8) at week 8	
								Symptom scores of the seven patients who completed all 12 weeks follow up after only one injection of botulinum toxin were not significantly different			
			Male/ female,	2/6				SF-36 questionnaire scores	In the six patients who completely filled out both pre- and post-injection SF-36 questionnaires, total scores did not change significantly.		
			Insulin use, years; mean (range)	24.4 (10-40)				Physical function domain of SF-36	Improvement noted (p<0.05)		
			Diabetes duration, mean	25.3 (10-40)				HbA1c (%)	HbA1c obtained at 8 weeks follow up visit was not significantly different from		

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		pylorus, or small bowel • Previous Nissen fundoplication or other antireflux surgery • Known pyloric stricture • Previous stroke, TIA, or chronic diseases involving the CNS • Concurrent use of opiates or anticholinergics	years (range)						baseline.	
			HbA1c (%)	Baseline value not given				Hospital admission	Not reported	
								Severe hypoglycaemia	Not reported	
			Drop-outs :					*mean symptom score: each patient filled out a symptom questionnaire. Each question asked the patient to rate symptoms from none (0 points) to severe (3 points); the maximum score was 36.		

Table 327: MCCALLUM 2010B[102]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
R. W. Mccallum,	RCT (cross-	n=45	All patients (n=45)	IMPLANTED GES system ON	IMPLANTED GES system	1.5 months	During randomis	ON period	OFF period	Funding: Medtronic,

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
W. Snape, F. Brody, J. Wo, H. P. Parkman, and T. Nowak. Gastric electrical stimulation with Enterra therapy improves symptoms from diabetic gastroparesis in a prospective study. Clin.Gastroenterol.Hepatol. 8 (11):947-954, 2010. REF ID:	over) 8 centres in USA	Diabetes with gastroparesis (94% insulin dependent) Inclusion criteria: ≥18 years old Symptomatic requiring treatment for ≥1 year Unresponsive or intolerant to prokinetic or antiemetic drugs for >1 month At least 7 episodes of vomiting during 7 consecutive days in the 28-day diary Gastric retention: >10% at 4hrs (or >60% at 2hrs if patients unable to complete 4hr test) On a stable does of prokinetic agents at least 30 days before baseline and willing			(then off) Neurostimulator (Enterra system, Medtronic 7425G or 3116). 2 electrodes. Greater curvature of the stomach. Programmed to standardised parameters (14Hz, 5mA, 330µs; cycle ON for 0.1sec, cycle OFF for 5 seconds). BOTH GROUPS – Prior to randomisation, all patients had device turned on for 1.5 months to	OFF (then on) BOTH GROUPS - Concomitant medication: Not mentioned.	all patients on treatment; 3 months treatment randomisation (each period of cross-over) Then follow-up at 12 months (4.5 months all patients on treatment).	ed phase			Inc. Risk of bias: No washout period between cross-over Randomisation = not enough details given just says randomised, 1:1 ratio stratified by centre in block size of 4. Allocation concealment = not sufficient (unblinded person in sealed envelopes). Blinding = double Powered study.
			Age, years; mean	38.3 years				WVF: Vomiting episodes/ week, median (IQR)	3.81 (0.75-14.03)	4.25 (0.38-15.13)	
			Female	65%				Frequency symptom scores, mean (SD) *=SS difference between gps			
			BMI, kg/m^2	26.4 (range 17-42)				Vomiting	2.31 (1.43)	2.03 (1.48)	
			WVF – weekly vomiting frequency : episodes/ week, median	16.8				Nausea	2.81 (1.31)	2.42 (1.56)	
								Early satiety	1.89 (1.47)	1.47 (1.44)	
								Bloating	1.83 (1.58)	2.03 (1.58)	
								Post-prandial fullness	1.44 (1.38)*	1.64 (1.46)*	
								Epigastric pain	1.31 (1.37)	1.28 (1.41)	
			Gastric retention	75.5% at 2hrs 46.5% at 4hrs				Epigastric burning	0.92 (1.18)	1.03 (1.34)	
			Mean	7.95%				TSS	12.5	11.89	

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
MCCALLUM 2010B		to continue through the study. Exclusion criteria: Diagnosis of any underlying illness that affects GI motility Current primary disorders such as psychogenic vomiting, eating disorder or swallowing disorder Previous gastric surgery for total or partial gastric resection, fundoplication, and vagotomy Daily narcotic analgesia for abdominal pain Drug or alcohol dependency within past 12 months Life expectancy <1 year Patients with other	HbA1c	(range 4.6 – 12.4)	allow for recovery from the surgery.				(7.10)	(7.48)	Not ITT analysis Drop-outs: N<20%
			All patients had delayed gastric emptying					Frequency symptom score: 0 = absent, 4 = extremely frequent (≥7 per week). Total symptom frequency score (TSS) = sum of all individual symptoms			
			Drop-outs : n=6 (13%)					Severity symptom scores, mean (SD) *=SS difference between gps			
								Vomiting	2.06 (1.26)	1.64 (1.27)	
								Nausea	2.44 (1.30)	2.03 (1.30)	
								Early satiety	1.39 (1.20)	1.11 (1.06)	
								Bloating	1.39 (1.29)	1.53 (1.25)	
								Post-prandial fullness	1.36 (1.29)	1.33 (1.20)	
								Epigastric pain	1.25 (1.38)	1.25 (1.36)	
								Epigastric burning	1.00 (1.29)	0.92 (1.25)	
								TSS	10.89 (6.73)	9.81 (6.47)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		implantable neurostimulators, pacemakers or defibrillators Pregnant Planning to receive diathermy treatment Undergone radiation treatment of upper abdomen Planning on having MRI					Severity symptom score: 0 = absent, 4 = extremely severe (requiring bed rest) Total symptom severity score (TSS) = sum of all individual symptoms		
					Data has also been reported for 12 month follow-up (ie. All on treatment for 4.5 months) *NOTE: this has been added into the observational data section of the results* 12 months data shows: • SS improvement from baseline for: in-hospital days, Frequency symptom score, severity symptom score, SF-36, % gastric retention at 2hrs and 4hrs. • NS difference for: BMI, HbA1c, weekly hypoglycaemic attack				

Table 328: PATTERSON 1999 (RCT)[123]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
D.	RCT	n=95 with type		Domperidon	Metaclopramid	4 weeks		DOM	METO	Funding:

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Patterson, T. Abell, R. Rothstein, K. Koch, and J. Barnett. A double-blind multicenter comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. Am.J.Gastroenterol. 94 (5):1230-1234, 1999. REF ID: PATTERSON	5 Centres, USA	1 diabetes with Gastroparesis Inclusion criteria: • Age ≥18 years • Type 1 diabetes and at least 3 months of 2 gastroparesis symptoms • TSS severity of 4 symptoms (nausea, vomiting, bloating/distention, early satiety) had to be at least 5/12. Exclusion criteria: • GI tract cancer or major illnesses • Receiving	Age, years; median (range)	39 (19-69)	e n=48 20 mg (4 times a day) BOTH GROUPS: Insulin treatment details not given	e n=45 10 mg (4 x/day) Placebo tablet also taken as there were less tablets required for metocopramide than there were for domperidone. BOTH GROUPS: Tablets taken 15-30 minutes before meals and at bedtime. Medications that could mask the effect of study drugs were not permitted during study. Other drugs affecting GI system were discouraged.					Janssen Research Foundation. Risk of bias: Randomisation = details not given – just says randomised. Allocation concealment = not mentioned. Blinding = double No mention of powering. Not ITT analysis Drop-outs: N<20% (19%)
			HbA1c %, mean (range)	Not reported				4 symptoms: nausea, vomiting, bloating/distention, early satiety			
			Male/ female	33/62							
			Symptom severity	Comparable in both groups				Individual symptoms	NS difference between the treatment groups.		
			Weight, kg; median (range)	68.2 (41-122)				TSS severity score: 4 symptoms (out of 12)	DOM: 4.71 (0.46); 41% reduction	METO: 5.09 (0.5); 38.9% reduction	
			TSS severity score – 4 symptoms (out of 12)	DOM: 8.0 (0.32) MET: 8.33 (0.29)							
			Drop-outs/missing data: n=18 (Of these, 6 dom and 10 meto discontinued treatment prematurely). n=9 patients discontinued								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
1999		dialysis • Undergone prior gastric surgery • Receiving illicit drugs • Received either study drug in past 30 days • Pregnant or likely to become pregnant.	due to AEs (most patients was due to adverse CNS effects).; n=3 dom, and n=6 meto.							

Table 329: SHARMA 2011 (before-after study)[144]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
D. Sharma, G. Morrison, F. Joseph, T. S. Purewal, and P. J. Weston. The role of continuous subcutaneous insulin	Prospective, case-series 2 Centres, UK	n=26 with type 1 diabetes with Gastroparesis • Inclusion criteria: • Type 1 diabetes with gastroparesis • Managed			CSII pump therapy Initiated using flat basal rate to provide 24hr insulin delivery; then tailored to individual. Boluses delivered to cover each meal.	N/A Pre-CSII, patients were on MDI.	12 months after starting CSII		Baseline	12 months	Funding: None reported. Risk of bias: NO NICE CHECK LIST
			Age, years; mean (range)	38.4 (24-53)				Weight gain, mean kg	2.9 kg at 6 months		
			HbA1c %, mean (range)	9.9 (6 - 15.3)				BMI reduction, mean kg/m^2	-1.0 kg/m^2 at 6 months		
			Male/	2/24							

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
infusion therapy in patients with diabetic gastroparesis. Diabetologia 54 (11):2768-2770, 2011. REF ID: SHARMA 2011		previously with MDI then CSII • Gastroparesis Diagnosis based on symptoms (delayed gastric emptying by scintigraphy Exclusion criteria: Structural abnormalities that may cause similar symptoms (as observed by ultrasound and oesophagogastroduodenoscopy).	female		Boluses given in extended form with extension times determined by composition of food, severity of symptoms and the results of the gastric emptying studies. As symptoms improved, bolus doses for carbs were modified by shortening the extension times or by adopting a multi-wave delivery whereby 10% of the total insulin dose was infused as 1st-phase insulin.						
			Diabetes duration	21 (8-34)				HbA1c, % median (range)	SS improvement: 8.0% (5.6-14.3%) vs. 9.8% (6-15.3%); p<0.05		
			BMI, kg/m^2, mean (range)	23.9 (16-33)				Hospital admission related to gastroparesis – inpatient bed days; median days/patients/year (range)	8.5 (0-144)	0 (0-15) days P<0.05	
			Weight, kg, mean (range)	65.4 (42-99)							

Table 330: SILVERS 1998[146]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
D. Silvers, M. Kipnes,	Multicentre	Double masked RCT		Domperidone	Placebo n=103	Double masked 4-	Double masked 4-	4 weeks	Double masked	Domperidon	Placebo	Funding: support

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
V. Broadstone, D. Patterson, E. M. M. Quigley, R. Mccallum, N. K. Leidy, C. Farup, Y. Liu, and A. Joslyn. Domperidone in the management of symptoms of diabetic Gastroparesis: Efficacy, tolerability, and quality-of-life outcomes in a multicenter controlled trial. Clin.Ther. 20 (3):438-453, 1998.	two-phase (single-masked phase and double masked phase) withdrawal study. Single masked phase not randomised. Double masked phase randomised.	n=208 (n=105 Domperidone; n=103 placebo) Inclusion criteria: • Type 1 diabetes, be between 18 and 70 years • Able to take oral medication and have experienced symptoms suggestive of Gastroparesis for at least 6 months Exclusion criteria:		n=105		week phase: Domperidone (two 10-mg tablets) four times daily Only patients (from the single non-randomised phase) whose total symptom score had improved were eligible for entry into the second phase (double masked phase) of the study. Patients receiving cisapride or metoclopramide were required to undergo a washout period of 1 week before	week phase: Placebo (two identical dummy tablets) four times daily		phase	e		provided by Janssen Research Foundation, Titusville, New Jersey Risk of bias: Wash-out period = 1 week Randomisation = unclear (as details not given) Allocation concealment = not reported Blinding = double (but details not given) ITT analysis: details not given Powered study. 93 per treatment group to detect a difference of
			Age, years; mean (SD)	45 (SD 12.6)	45.3 (SD 11.9)				Quality of Life (QoL) – *SF36: physical component scale (PCS); mean (SD)	0.65 (SD 0.75) n=104	-1.77 (SD 0.75) n=99	
			Male/ female, (%)	34/71	31.1/68.9				Quality of Life (QoL) – *SF36: mental component scale (MCS)	-1.08 (SD 1.13) n=104	-0.96 (SD 0.89) n=99	
			History of gastroparetic symptoms, years; mean (SD)	3.5 (SD 3.6)	4.3 (SD 5.4)							
			Smokers, %	32.4%	17.5%				Mean change in **total symptom scores	0.1	0.94	
			Diabetes, mean						Mean change in nausea	0.03	0.32	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
REF ID: SILVERS 1998		• Gastric surgery (including vagotomy) before study entry • History of cancer of the gastrointestinal tract or abdominal radiotherapy • Previous (within the past 30 days) or planned concurrent use of an investigational drug • Previous participation in a study involving domperidone or a compassio	years (SD)			enrolment.						30% at the end of double masked treatment phase at an α level of 0.05 and 80% power Drop-outs = none mentioned All patients underwent scintigraphy to evaluate to evaluate their gastric-emptying status within 4 weeks of enrolment
									Mean change in early satiety	-0.04	0.19	
									Adverse events	63 n=105	65 n=103	
									Vomiting (%)	0 n=105	5 (4.9) n=103	
			Patients were required to have a minimum symptom severity score of 2 (moderate) on a scale of 0-3 for each of nausea, abdominal distension/bloating, early satiety, vomiting, and abdominal pain. Their combined total symptom severity score (sum of the 5 individual symptom scores) had to be ≥8 (out of a possible 15) for entry into the first phase of the study. For entry into the second phase, patients were required to have a total symptom score of ≤6 at the						*SF36 consists of 36 items across 8 domains that can be reduced to 2 indexes –the physical and mental component summaries (PCS and MCS respectively). **Total symptom score calculated by totalling the severity scores of the five individual symptoms of Gastroparesis. Responses were rated on a scale of 0 to 3, in which 0 = none; 1 = mild (awareness of a sign or symptom, symptoms easily tolerated); 2 = moderate (enough discomfort to interfere with usual activities); or 3 = severe (incapacitating symptoms, inability to work or		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
		nate clearance program, and dialysis for renal failure • Pregnancy or child bearing potential • Severe cardiac disease	end of the first phase and a decrease (improvement) in their total severity score of ≥5 units from the baseline visit. NS differences were found between the domperidone and placebo groups at the selection visit, except in smoking behaviour: more patients randomised to domperidone (32.4%) were smokers compared with those randomised to placebo (17.5%) Drop-outs : None mentioned				engage in usual activities).		

Table 331: VANDERVOORT 2005 (before-after study)[160]

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
I. R. van der Voort, J. C. Becker, K. H. Dietl, J. W. Konturek, W.	A prospective case series single centre study	n=17 with type 1 diabetes with Gastroparesis refractory to conventional medical therapy. Prior to entry,	Eight type 1 diabetes who had failed standard therapy were enrolled		All included patients received an electrical stimulation system consisting of a	N/A	12 months		Baseline	12 months	Funding: supported by Medtronic Europe, Tolochenaz, Switzerland
			Age, years;	25-73 years				Weekly vomiting frequency;	26 (19-41)	4 (0-13)*	

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes		Comments
Domschke, and T. Pohle. Gastric electrical stimulation results in improved metabolic control in diabetic patients suffering from Gastroparesis. Exp.Clin.Endocrinol.Diabetes 113 (1):38-42, 2005. REF ID: VANDERVOORT 2005		upper GI ENDOSCOPY was performed to exclude mechanical causes of gastric outlet obstruction. Inclusion criteria: • Details not given Exclusion criteria: • Patients with intestinal pseudo-obstruction • Primary swallowing disorders • Seizures • Psychogenic vomiting • Pregnancy • Previous surgery to the stomach, pylorus, or small bowel • Vagotomy • Organ transplantation	range		stimulator (Itrel 3, Model 7425, Medtronic Kerkrade, the Netherlands)and two unipolar intramuscular electrodes			mean (range)			Risk of bias: NO NICE CHECK LIST
								Weekly nausea frequency; mean (range)	34 (21-49)	12 (2-20)	
			Male/ female,	5/12				HbA1c (%)	Significantly reduced at 6 months and 12 months compared to baseline values. Compared to baseline, the mean value improved by 28% at 6 months and 24% at 12 months. Prior to implantation of the device, no patient had presented with HbA1c values of less than 7.5%		
			Diabetes duration	At least 10 years				Hospital admission	Not reported		
			HbA1c (%)	not given				Severe hypoglycaemia	Not reported		

G.11.1 Acute painful neuropathy

Table 332: Gibbons 2010[54]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
Gibbons C. H., Freeman R. Treatment induced diabetic neuropathy – a reversible painful autonomic neuropathy. Ann Neurol: 67(4): 534-541. 2010	Prospective case-series Setting: US	n=16 (Type 1 diabetes n=9) Inclusion criteria: • Acute painful neuropathy after rapid and sustained glycaemic control	For type 1 diabetes only n=9: HbA1c = 15.5 (1.3)% HbA1c after intensive BG control, baseline before treatment = 6.4(0.6)% Age = 24.9 (3.3) Female% = 78% Duration of type 1 diabetes = 9.6 (2.3) years Initial pain score (following	Medications to reduce neuropathic pain, all patients on different treatments (alone or in combination): Anti-epileptics (gabapentic, pregabalin, lamotrigine or topiramate) TCAs (amitriptyline, nortriptyline or desipramine) Tramadol Methadone Anti-epileptics + TCA + Tramadol n=2 Anti-epileptics + TCA n=1 Anti-epileptics	18 months or more	Duration of treatment for a 50% reduction in pain[a]	15 months (range 12-28)	Funding: Juvenile Diabetes Research Foundation Risk of bias: Study design – case series IENFDL outcome data only available for 6/9 type 1 diabetes patients and FU only available in 3/6 patients 7/9 patients had a remote history of diabetic anorexia and other 2 subjects had historically poor BG control due to treatment non-compliance All patients experienced life event causing them to radically improve BG control
						Pain, 0-10 Likert scale, 0=no pain; 10=worst pain imaginable) [a]	Baseline, mean (SD) = 10 (0) Follow-up: 7-9	
						Retinopathy, no. of patients[a]	Baseline: 7/16 6 months of sustained BG control: 16/16	
						Microalbinuria, number of patients[a]	Baseline: 8/16 1 year: 13/16	
						Neuropathy impairment score in lower limb (NIS-LL; muscle strength graded as normal, zero, to max score of 64 if paraplegic, reflexes graded zero to 8 and sensation graded 0 to 16)[b]	Baseline: 5.1(1.4) 1 year: 5.3 (1.3) reported NS	
						Autonomic symptoms (11 point Likert scale; (0=no symptoms; 10=severe symptoms), baseline vs. 18 months[b]	SS improvement reported in the following scores: orthostatic lightheadedness, orthostatic dizziness, pre-syncope, syncope, orthostatic symptoms	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
			intensive BG control), 0-10 likert scale = 10 (0)	+ SNRI n=1 Anti-epileptics + SNRI + tramadol n=2 Anti-epileptics + tramadol n=1 Anti-epileptics + SNRI + methadone n=1 SNRI + tramadol n=1			worse with standing, nausea, vomiting, diarrhoea, early satiety NS difference reported in the following scores: Orthostatic symptoms after meals, loss of appetite, urinary frequency, nocturia, hyperhidrosis, anhidrosis, erectile dysfunction.	
						Autonomic dysfunction*	Abnormal HR response deep breathing Baseline: 69% 18 months: 48% Abnormal inspiratory-expiratory ratio Baseline: 62% 18 months: 19% Valsalva ratio Baseline: 56% 18 months: 43% Orthostatic hypotension Baseline: 69% 18 months: 31%	
						Intra-epidermal nerve fibre density distal leg (IENFDL), number of patients with normative values	Baseline: 0 One year: 1	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Effect sizes	Comments
						(reported in 6 type 1 diabetes patients, outcome data NA at 1 year for 3 patients)**		

(a) Data from mixed population of type 1 diabetes and type 2 diabetes
(b) Data from type 1 diabetes subgroup analysis

G.11.2 Thyroid disease – frequency of monitoring

G.11.2.1 Prevalence of thyroid disease in type 1 diabetes patients

Table 333: Allen 2008

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Allen S, Huber J, Devendra D. Prevalence of organ-specific autoantibodies in childhood and adult onset type 1 diabetes. Immunology of Diabetes. 2008; 1150:260-262. Ref ID: ALLEN 2008	Cross-sectional prevalence study conducted over 5 years from 2001 to 2006 Records from 5 NHS trust diabetic clinics in the UK	Number of patients Total number of patients who attended diabetic clinics from 2001 to 2006 was 599, of which 271 were excluded as part of exclusion in inclusion criteria Inclusion criteria: • Adults 16 years and above • Exclusion criteria: • If multiple organ-specific antibodies tested for on separate occasions • If organ specific			Thyroid peroxidase autoantibodies (TPO) Thyroid receptor autoantibodies (TRABs) Information on test type or threshold for positive/negative result not reported	Thyroid disease Prevalence of type 1 diabetes patients with positive antibodies to: TPO=11.5% (13/113) and TRAB=9.1% (5/55) in adult onset Prevalence of type 1 diabetes patients with positive antibodies to TPO=11.8% (11/93) and TRAB=1.9% (1/54) in childhood onset
			Number of patients	n=180/328 type 1 diabetes adults		
			Age (years), mean (SD)	Median age at onset diabetes:18 years		
			Gender (m/f)	Not reported		
			Duration of diabetes (years), mean (SD)	Reported as median of 21 (75%CI12-27)		
			HbA1c (%)	Not measured		
			BMI (kg/m^2), mean (SD)	Not measured		
			Treatment			

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
		antibodies were measured after the diagnosis of an autoimmune condition was confirmed	subgroups			
			Diabetes control			

Table 334: Bianchi 1995

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Bianchi G, Montanari P, Fabbri A, Gamberini A, Zoli M, Marchesini. Thyroid volume in type 1 diabetes patients without overt thyroid disease. Acta Diabetologica. 1995; 32:49-52. Ref ID: BIANCHI 1995	Cross-sectional prevalence study Patients admitted to hospital In Italy, but setting not reported	Inclusion criteria: 45 patients with type 1 diabetes with no history of previous thyroid disorders/and or use of drugs known to affect thyroid homeostasis Exclusion criteria: • Not reported			fT3 (pmol/litre) fT4 (pmol/litre) TSH (mU/litre) Normal values for TSH: 0.4-3.5 mU/litre Normal values for fT3: 4.0-8.9pmol/litre Normal values for fT4:9.0-23.0pmol/litre Positive titres for anti-microsome antibodies:>50U/ml Positive titres for anti-thyroglobulin:>100U/ml	Thyroid disease Prevalence of anti-microsomal antibodies: 33% Prevalence of anti-thyroglobulin antibodies: 16%
			Number of patients	n=45 type 1 diabetes adults		
			Age (years), mean (SD)	16-68 (median 40 years)		
			Gender (m/f)	20m/25f		
			Duration of diabetes (years), mean (SD)	All type 1 diabetes patients, but duration of diabetes not reported		
			HbA1c (%)	8.9% (SD 1.8%, range 5.1% to 12%)		
			BMI (kg/m^2), mean (SD)	Not reported		
			Diabetes control	Diabetic ketosis or for evaluation and treatment of complications of diabetic disease		

Table 335: CARDOSO 1995

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Cardosa C, Ohwovoriole AE, KuKu SF. A study of thyroid function and prevalence of thyroid autoantibodies in an African diabetic population	Cross-sectional prevalence study Lagos university teaching hospital, NIgeria and Eko hospital, Lagos, Nigeria	40 consecutive insulin-treated diabetic patients (attending clinics at hospital?) Exclusion criteria: • Not reported			T3 (0.8ng/ml) T4 (50-138ng/ml) TSH(0.6-6.0ng/ml) Serum thyroid autoantibodies: Significantly positive thyroid microsomal antibodies:≥50IU/ml Significantly positive thyroglobulin antibodies:≥100IU/ml	Thyroid disease/function Subclinical hypothyroidism Prevalence of thyroid autoantibody positivity in type 1 diabetes patients was 46.6% (13/28)
			Number of patients	n=28 adults with type 1 diabetes		
			Age (years), mean (SD)	36.46 years (SEM 2.10)		
			Gender (m/f)	12m:16f		
			Duration of diabetes (years), mean (SD)	12.69 years (SEM 1.90)		
			HbA1c (%)	Not reported		
			BMI (kg/m^2), mean (SD)	Not reported		
			Treatment subgroups	Subclinical hypothyroidism		
			Diabetes control	29/40 patients had fairly good control, 11/40 had poor control, but authors do not specify whether type 1 diabetes patients		

Table 336: DAGDELEN 2009

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Dagdelen S, Hascelik G, Bayraktar M. Simultaneous triple organ specific autoantibody profiling in adult patients with type 1 diabetes mellitus and their first-degree relatives. International Journal of Clinical Practice. 2009;63(3):449-456. Ref ID:DAGDELEN 2009	Cross-sectional matched case-control/prevalence study Patients visiting adult outpatient endocrinology and metabolism department at a tertiary university hospital between 2002 and 2004	Inclusion criteria: Patients with type 1 diabetes with onset below 35 years and an interval of <3 years between diabetes onset and insulin requirement, and body mass index, patients with past or present seropositivity for GAD antibodies, IA2, anti-islet or anti-insulin autoantibodies without acanthosis nigricans Exclusion criteria: Age <18 years, duration of diabetes <2 years,			T3 T4 TSH Serum thyroid autoantibodies: Significantly positive thyroid microsomal antibodies:≥50IU/ml Significantly positive thyroglobulin antibodies:≥100IU/ml	Thyroid disease/function Subclinical hypothyroidism Prevalence of thyroid autoantibody positivity in type 1 diabetes patients was 46.6% (13/28)
			Number of patients	n=65 adults with type 1 diabetes		
			Age (years), mean (SD)	29.2 (+/-9.4)		
			Gender (m/f)	52% male:48% female		
			Duration of diabetes (years), mean (SD)	9.8 years (+/-8.3)		
			HbA1c (%)	7.4 (+/-1.4)		
			BMI (kg/m^2), mean (SD)	<25kg/m^2		
			Treatment subgroups	N/A		
			Diabetes control			

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
		secondary diabetes or pancreatic insufficiency and presence of selective immunoglobuli n A deficiency				

Table 337: DUFAITRE 2006

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Dufaitre-Patouraux L, Riveline JP, Renard E, Melki V, Belicar-Schaepelynck P, Selam JL et al. Continuous intraperitoneal insulin infusion does not increase the risk of organ-specific autoimmune disease in type 1 diabetic	Cross-sectional prevalence study, 14 EVADIAC centres, comparative study in France to determine whether implanted pumps enhance the frequency of autoimmune diseases.	Inclusion criteria: 275 Male or female patients between ages 18-70 years already treated by CIPII or CSII for C-peptide negative type 1 diabetes Exclusion criteria: Patients presenting clinical thyroid autoimmune disease at the time of			LT4 treatment and presence of anti-TPO antibodies to determine hypothyroidism Grave's disease was determined by history of treatment for hyperthyroidism and presence of anti-TSH binding inhibitor or anti-TPOab Subclinical diseases were defined by the presence of antiTPOab with normal T3 and T4 for thyroiditis	At time of inclusion (T0): • prevalence of Hashimoto's disease in CIPII patients=8.4% (13/154) vs. 7.4% (9/121) CSII treated patients • prevalence of Grave's disease in CIPII patients=1.3% (2/154) vs. 2.4% (3/121) CSII patients Prevalence of subclinical autoimmune disease by measurement of anti-TPOab: 25.9% (36/139) CIPII patients vs. 30.6% (33/108) CSII patients Total study group prevalence of thyroid autoimmune disease =9.8% for clinical disease and 28% for subclinical disease No new case of autoimmune disease recorded at T1 (1 year after inclusion)
			Number of patients	n= patients with type 1 diabetes, 139 patients in the CIPII group and 108 patients in the CSII group		
			Age (years), mean (SD)	CIPII group=47±10.2 years CSII group=46.3±11.2 years		
			Gender (m/f)	79m:75f		
			Duration of diabetes (years), mean (SD)	CIPII group=24.8±10.2 years CSII group=24.8±10.2 years		
			HbA1c (%)	Not reported		
			BMI (kg/m^2),	Not reported		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
patients: results of a multicentric, comparative study. Diabetes and Metabolism. 2006; 32(5 Patient 1):427-432. Ref ID:DUFAITRE 2006		inclusion to study	mean (SD)		For TSH measurement: Normal thyroid function=0.4-4mU/litre Hyperthyroidism=4-20mU/litre Hypothyroidism=>20 mU/litre Threshold for positive anti-TPOab=60U/litre	
			Treatment subgroups			
			Diabetes control			

Table 338: FIALKOW 1975

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Fialkow PJ, Zavala C, Nielsen R. Thyroid autoimmunity: increased frequency in	Cross-sectional prevalence Patients were assessed from	Inclusion criteria: Type 1 diabetes patients (male and female) between ages			Antibodies to thyroid globulin (TGab) and thyroid microsomal antibodies (TPO) were determined by tanned red cell agglutination and	Prevalence of thyroid antibodies in type 1 diabetes patients=35% (18/52) Prevalence of type 1 diabetes patients with Graves' disease= 1.9% (1/52)
			Number of patients	52 adults with type 1 diabetes		
			Age (years),	37.6		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
relatives of insulin-dependent diabetes patients. Annals of Internal Medicine. 1975; 83(2):170-176. Ref ID FIALKOW 1975	the diabetes instruction classes of the metabolic section at Mason clinic (private practice) in Seattle, USA	30 and 45 years and followed up for two years after the study was initiated for insulin status Exclusion criteria: Patients below 20 years age	mean (SD)		indirect immunofluorescence	Prevalence of type 1 diabetes patients with surgery/goitre=1.9% (1/52) In the age group 20-30, 18/30 patients tested positive for thyroid antibodies. 7/30= TPO+ (low titre), 4/30= TPO+ (high titre), 5/30=TGab+ (low titre), 2/30=TGab+ (high titre) In the age group 40-59, 22 patients tested positive for thyroid antibodies. 2/22= Frequencies of antibodies to thyroglobulin and to thyroid cytoplasm were equally elevated in type 1 diabetes patients Presence of antibodies was not correlated significantly with duration of disease or of insulin therapy (P>0.1)
			Gender (m/f)	26m:26f		
			Duration of diabetes (years), mean (SD)	Not reported		
			HbA1c (%)	Not reported		
			BMI (kg/m^2), mean (SD)	Not reported		
			Treatment subgroups	Age 20-39 Age 40-59		
			Diabetes control	Not reported		

Table 339: GOMEZ 2003

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Gomez JM, Maravall FJ,	Cross-sectional	Inclusion criteria:			TSH normal=<40 IU/ml	Basal TSH levels in males =1.6%±1.14 compared to control group=1.5%±0.78 (95%CI -0.56 to
			Number	n=36 patients with type 1		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Guma A, Abos R, Soler J, Fernandez-Castaner M. Thyroid volume as measured by ultrasonography in patients With type 1 diabetes mellitus without thyroid dysfunction. Hormone and Metabolic Research. 2003; 35(8):486-491. Ref ID GOMEZ2003	study in patients with type 1 diabetes attending an endocrine unit in Spain, younger than 40 years	36 patients with type 1 diabetes Exclusion criteria: Patients who had previous autoimmune thyroid dysfunction, or positive serum anti-thyroid peroxidase antibodies	of patients	diabetes		0.41; P=0.76) Basal TSH levels in females=1.69%±1.08 compared to control group=1.59%±0.96 (P=0.48)
			Age (years), mean (SD)	26.8±5.1		
			Gender (m/f)	Not reported		
			Duration of diabetes (years), mean (SD)	Newly diagnosed diabetes		
			HbA1c (%)	6.6±1.4 (baseline)		
			BMI (kg/m^2), mean (SD)	M:24.6±2.8 F:24.9±3.48		
			Treatment subgroups	N/A		
			Diabetes control	Insulin requirement =0.65±0.25U/kg		

Table 340: Hanukoglu 2003

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Hanakoglu A, Mirachi A, Dalal L, Admoni O, Rakover Y,	Cross-sectional study of young patients with	Inclusion criteria: Type 1 diabetic patients who were diagnosed			Thyroid antibodies directed to thyroglobulin (TG) and to microsomal antigens	The prevalence of autoimmune thyroid disease as determined by positive TPO and/or TG antibody rates among type 1 diabetes probands was 27%, with 6% of those being hypothyroid
			Number of patients	Probands=109 Relatives screened=100 Relatives interviewed=312 Control subjects=78		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Bistritzer Z, Levine A, Somekh E, Lehmann D, Tuval M, Boaz M, Golander A. Extrapancreatic autoimmune manifestations in type 1 diabetes patients and their first-degree relatives. Diabetes care. 2003; 26(4):1235-1240 REF ID: HANUKOGLU 2003	type 1 diabetes and their first degree relatives in a multicentre study in Israel	before the age of 18 years and first degree relatives and a group of healthy subjects with no history of autoimmune disease served as a control group	Age (years), mean (SD)	Probands=9.4+/-4.2)(at diagnosis) Relatives screened=29+/-15.5 Relatives interviewed=29=/-16.4 Control subjects=14.9+/-10.4	(TG and TPO) were determined by enzyme linked immunosorbent assay. TG and TPO titres 1/180 and 1/80, respectively, were considered diagnostic for autoimmune thyroid disease. In all patients screened for thyroid antibodies, free T4 and thyrotropin concentrations were also determined.	The corresponding rates among screened first-degree relatives (positive TPO and/or TG 25%, hypothyroid Hashimoto disease 8%) did not significantly differ from the rates found in probands, but were significantly higher than rates in control subjects The frequencies of positive TPO and TG antibodies alone and together were 18, 19, and 11%, respectively, in probands. The corresponding rates among first-degree relatives were quite similar (19, 17, and 10%, respectively) The TPO titres in three control subjects were only slightly elevated (1/84, 1/118, and 1/98), whereas they were markedly elevated in most probands and family members (5-fold in 13 probands and 12 relatives and 2.5-fold in 3 probands and 6 relatives) In first degree relatives who were screened, medical history revealed pre-existing Hashimoto thyroiditis in five and Graves
			Gender (m/f)	Probands=62/47 Relatives screened=42/58 Relatives interviewed=159/153 Control subjects=41/37		
			Duration of diabetes (years), mean (SD)			
			HbA1c (%)			
			BMI (kg/m^2), mean (SD)			

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
						disease in one The frequency of pre-existing autoimmune thyroiditis detected by interview only, was low (1%) Probands with Hashimoto thyroiditis did not have more relatives with positive antibodies than probands with normal antibody titres. Among 50 probands whose relatives were screened, 12 probands with thyroiditis had 8 relatives with positive antibodies and 13 relatives with normal antibody titres. Among 13 probands without thyroiditis, the corresponding numbers were 16 (positive) and 17 (normal) relatives
			Treatment subgroups			
			Diabetes control			

Table 341: JIN 2011

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Jin P, Huang G, Lin J, Yang	Cross-sectional	Patients with type 1 diabetes			Anti-TPOab positivity=3.6	• TGAb prevalence in type 1 diabetes=23.7% vs. 16.3% LADA
			Number	n=190 type 1 diabetes		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
L, Xiang B, Zhou W et al. High titre of antiglutamic acid decarboxylase autoantibody is a strong predictor of the development of thyroid autoimmunity in patients with type 1 diabetes and latent autoimmune diabetes in adults. Clinical Endocrinology. 2011; 74(5):587-592. Ref ID: JIN2011	study Prevalence Study setting: Second Xiangya Hospital of Central South University from January 2001 and December 2003 in China	and patients with LADA Inclusion criteria: LADA patients age of onset ≥30 years, persistently positive for GAD65Ab at least 1 year after diagnosis, no ketosis within the first 6 months of diagnosis, no insulin treatment within the first 6 months of the initial diagnosis After 4 years follow-up, 184 patients with type 1 diabetes and 130 patients with LADA were included.	of patients	patients n=135 LADA patients	Anti-TGab positivity=3.0 Normal TSH range=0.35-5.5mU/litre Normal T3 range=0.6-1.81nmol/litre Normal T4 range=45-109 pmol/litre Hypothyroidism=elevated TSH level (≥5.5mU/litre) with or without decreased serum thyroid hormone level Hyperthyroidism=decreased serum thyroid hormone level with or without elevated thyroid hormone levels	• TPOab prevalence in type 1 diabetes=24.7% vs. 18.5% LADA • Overall prevalence of thyroid autoantibody= 27.4% in type 1 diabetes vs. 21.5% in LADA patients • Prevalence of sub/clinical, hypo/hyperthyroidism= 9.5% in type 1 diabetes vs. 11.1% in LADA, with most having subclinical hypothyroidism After 4 years follow-up: • Prevalence of TGab=24.5% (45/184) in type 1 diabetes vs. 17.7% (23/130) in patients with LADA • Prevalence of TPOab= 25.5% (47/184) in type 1 diabetes vs. 20.0% (26/130) in patients with LADA • Prevalence of thyroid dysfunction=14.1% in type 1 diabetes vs. 15.3% in patients with LADA • The prevalence of antibodies and thyroid dysfunction increased insignificantly during the 4 year follow-up • Patients (95%) with positive thyroid antibodies tested positive at beginning of study and also during follow-up
			Age (years), mean (SD)	24.9±14.1 years (type 1 diabetes) 49.6±12 years (LADA)		
			Gender (m/f)	110m:80f (type 1 diabetes) 79m:56f (LADA)		
			Duration of diabetes (years), mean (SD)	1.9±1.7 years (type 1 diabetes) 2.3±2.1 years (LADA)		
			HbA1c (%)	Type 1 diabetes+Tab+=8.4±2.3 Type 1 diabetes+Tab-=8.2±2.1 LADA+Tab+=8.2±2.1 LADA+Tab-=8.1±2.4		
			BMI (kg/m^2), mean (SD)	Type 1 diabetes+Tab+=18.8±3.2 Type 1 diabetes+Tab-=19.7±3.4 LADA+Tab+=23.4±3.4 LADA+Tab-=22.8±3.1		
			Treatment subgroups			
			Diabetes	Not reported		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
			control			

Table 342: JUNIK 2006

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Junik R, Kozinski M, Debska-Kozinska K. Thyroid ultrasound in diabetic patients without overt thyroid disease. Acta Radiologica. 2006; 47(7):687-691. Ref ID JUNIK2006	Cross-sectional study/prevalence Patients were referred to the department of endocrinology and diabetology at Nicolaus Copernicus university, Poland	98 patients with diabetes mellitus			TSH (thyrotropin) normal range=0.35mIU/litre -4.94mIU/litre FT3 normal range=1.71-3.71pg/ml FT4 normal range =0.7-1.48ng/dl	Subclinical hyperthyroidism=7% (2/30) Subclinical hypothyroidism=3% (1/30) TSH levels in patients was within normal range (0.97 (0.61-1.58) mIU/litre)
			Number of patients	n=30 patients with type 1 diabetes		
			Age (years), (median)	Median 43 (range 28-50)		
			Gender (m/f)	12m:18f		
			Duration of diabetes (years), mean (SD)	Not reported		
			HbA1c (%)	Not reported		
			BMI (kg/m^2), mean (SD)	Not reported		
			Treatment subgroups	Subclinical hyperthyroidism Subclinical hypothyroidism		
			Diabetes control	Poorly controlled diabetes		

Table 343: KUCERA 2003

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Kucera P, Novakova D, Behanova M, Novak J, Tlaskalova-Hogenova H, Andel M. Gliadin, endomysial and thyroid antibodies in patients with latent autoimmune diabetes of adults (LADA). Clinical and Experimental Immunology. 2003; 133(1):139-143. Ref ID: KUCERA 2003	Cross-sectional/prevalence study Patients selected from the epidemiological study of the diabetes centre at the 3rd medical faculty, Charles university, and also from several out-patient diabetes clinics in Prague and Melnik	Consecutive sera from 158 diabetic LADA (type 1 diabetes) or type 2 diabetes patients			TPOab TGab Normal or positive thresholds not reported	• Positive TPOab=22.1%(15/68) • Positive TGab=8.82%(6/68)
			Number of patients	Group A=68 LADA (type 1 diabetes) patients		
			Age (years), mean (SD)	64.4±10.0		
			Gender (m/f)	29m:39f		
			Duration of diabetes (years), mean (SD)	10.6±7.6		
			HbA1c (%)	Not reported		
			BMI (kg/m^2), mean (SD)	Not reported		
			Treatment subgroups	Not reported		
			Diabetes control	Not reported		

Table 344: LUPI 2013

Reference	Study details	Number of patients	Patient characteristics	Tests	Results
Lupi I,	Cross-	111 patients		FT4 (normal=7-	• 40.5% (45/111) type 1 diabetes patients

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Raffaelli V, Di CG, Caturegli P, Manetti L, Ciccarone AM et al. Pituitary autoimmunity in patients with diabetes mellitus and other endocrine disorders. Journal of Endocrinological Investigation. 2013; 36(2):127-131.	sectional study/prevalence Patients were evaluated from 2009 to 2011 in the department of endocrinology and metabolism at the university of Pisa, Italy	with type 1 diabetes	Number of patients	n=111 patients with type 1 diabetes previously on multiple dose insulin therapy	17 pg/ml) FT3 (normal=2.7-5.7 pg/ml) TSH (normal=0.4-3.4 µU/ml) TPOab (normal=<10U/ml) TGab (normal=<30U/ml) TSHreceptor(normal=<2 U/litre)	found to have one or more autoimmune diseases • Prevalence of Hashimoto's disease =31.5% (35/111) • Prevalence of Grave's disease=6.3% (7/111)
			Age (years), mean (SD)	38.7±1.3		
			Gender (m/f)	44m:67f		
			Duration of diabetes (years), mean (SD)	28.3±1.19		
			HbA1c (%)	Not reported		
			BMI (kg/m^2), mean (SD)	25kg/m^2		
			Treatment subgroups			
			Diabetes control	Not reported		

Table 345: PALMA 2013

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Palma CCSS, Pavesi M,	Cross-sectional	386 patients (type 1			Anti-TPOab=<34IU/ml,	14.6% (12/82) type 1 diabetes positive anti-TPOab autoimmunity
			Number	n=82 patients with type 1		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Nogueira VG, Clemente ELS, Vasconcellos MDFB, Pereira LC et al. Prevalence of thyroid dysfunction in patients with diabetes mellitus. Diabetology and Metabolic Syndrome. 2013; 5(1). Ref ID:PALMA 2013	study/prevalence Patients were recruited from the out-patient clinic of the unit of diabetes at hospital universitario Pedro Ernesto, Rio de Jeneiro, Brazil	diabetes and type 2 diabetes) regularly attending the out-patient clinic Inclusion criteria: Duration of diabetes mellitus longer than one year for those with type 1 diabetes Diagnosis was based on clinical presentation: variable degree of weight loss, polyuria, polydipsia, polyphagia and the need to use insulin continuously since the diagnosis without discontinuation, medical follow-up was	of patients	diabetes	3.4-7.6 FT4=0.93-1.7 ng/dl, 1.8-3.0 TSH=0.27-4.20µg/Ul/ml Thyroid dysfunction was classified as clinical hypothyroidism if TSH levels were >4.20µUl/ml and FT4 lower than 0.93ng/dl Subclinical hypothyroidism= TSH levels >4.20µUl/ml and FT4 ranging from 0.93-1.7ng/dl Subclinical hyperthyroidism= TSH levels lower than 0.27µUl/ml and FT4 higher than 1.7ng/dl Autoimmunity=anti-TPOab levels >34IU/litre	Prevalence of subclinical hypothyroidism without previous thyroid dysfunction was 13% in type 1 diabetes patients New cases of subclinical hypothyroidism in patients with type 1 diabetes was (9/82 (13%) Type 1 diabetes patients with previous thyroid dysfunction had TSH and FT4 levels in the normal range
			Age (years), mean (SD)	33.5±15.8		
			Gender (m/f)	39m:43f		
			Duration of diabetes (years), mean (SD)	14.6±11.7		
			HbA1c (%)	12.3±3.1		
			BMI (kg/m^2), mean (SD)	24.4±5.2 kg/m^2		
			Treatmen	Clinical hypothyroidism		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
		at least one year	t subgroups	Subclinical hypothyroidism Clinical hyperthyroidism Subclinical hyperthyroidism		
			Diabetes control			

Table 346: PERROS 1995

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Perros P, McCrimmon RJ, Shaw G, Frier BM. Frequency of thyroid dysfunction in diabetic patients: value of annual screening. Diabetic Medicine. 1995; 12(7):622-627. Ref ID:PERROS 1995	Cross-sectional study/prevalence Patients were randomly selected from the diabetic outpatient clinic in the royal infirmary, Edinburgh for more than one year and were screened for thyroid dysfunction one year prior	A random sample of 1310 adult diabetic patients were predominantly urban and Caucasian			Thyroid function tests: FT4 TSH Normal range of FT4=9-23nmol/litre Normal range for TSH=0.15-3.5mU/litre Normal thyroid function=FT4 and TSH in normal range Hypothyroidism=FT4 <9nmol/litre and TSH greater than 3.5mUl/litre	Prevalence of hypothyroidism=5.9% in males vs. 14.5% in females Prevalence of hyperthyroidism=1.1% in males vs. 6.4% in females Prevalence of subclinical hypothyroidism=5.4% in males vs. 9.5% in females Prevalence of subclinical hyperthyroidism=0% in males vs. 0.9% in females New cases of thyroid disease: Prevalence of hypothyroidism=1.6% in males vs. 1.8% in females Hyperthyroidism=0% in males vs. 1.4% in females Subclinical hypothyroidism=4.8% in males vs. 8.6% in females
			Number of patients	n=406 type 1 diabetes patients		
			Age (years), mean (SD)	Reported as mean sample age of all diabetic patients =53.8±16.3		
			Gender (m/f)	186m:220f		
			Duration of diabetes (years), mean (SD)	One year previous to recruitment		
			HbA1c (%)	Not reported		
			BMI (kg/m^2), mean (SD)	Not reported		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
	to recruitment				Hyperthyroidism=FT4 >23nmol/litre and TSH <0.15 mUl/litre Subclinical hypothyroidism=FT4 within normal range and TSH >3.5mU/litre Subclinical hyperthyroidism=FT4 within normal range and TSH <0.15mUl/litre	Subclinical hyperthyroidism=0% in males vs. 0.5% in females Action taken as a result of screening: Clinical management was influenced in 49 patients 23 patients received thyroxine replacement treatment for primary hypothyroidism, subclinical hypothyroidism One patient received radioiodine therapy for hyperthyroidism secondary to Graves' disease 7 patients with hyperthyroidism were treated with antithyroid drugs or radioiodine Doses of thyroxine for hypothyroidism and carbimazole for hyperthyroidism were adjusted
			Treatment subgroups	Hypothyroidism Subclinical hypothyroidism Hyperthyroidism Subclinical hyperthyroidism		
			Diabetes control	Not reported		

Table 347: PRAZNY 1999

Reference	Study details	Number of patients	Patient characteristics	Tests	Results

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Prazny M, Skrha J, Limanova Z, Hilgertova J. The evaluation of thyroid and islet autoantibodies in type 1 diabetes mellitus. Sbornik Lekarsky. 1999; 100(3):205-211. Ref ID:PRAZNY 1999	Cross-sectional study/prevalence study Patients were randomly selected from a Czech Republic population Blood samples were taken from patients with type 1 diabetes after overnight fasting , and serum was used for thyroid function testing	Type 1 diabetes patients			Anti-TPOab Anti-TGab TSH T4 Thyroid disease= anti-TPOab >50U/ml and >100U/ml anti-TG	Prevalence of positive antiTPO and antiTG antibodies higher in women than men Prevalence of antiTPO=14% (3/21) in men vs. 21% (5/34) in women 11% (6/55) patients were positive for both antiTPO and antiTG antibodies
			Number of patients	n=55		
			Age (years), mean (SD)	39±13		
			Gender (m/f)	21m:34f		
			Duration of diabetes (years), mean (SD)	18±13		
			HbA1c (%)	Not reported		
			BMI (kg/m^2), mean (SD)	24.1±2.6		
			Treatment subgroups	IA-2 ab GAD ab		
			Diabetes control	Not reported		

Table 348: RATTARASARAN 2000

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Rattarasarn C, Diosdado	Cross-sectional	50 patients with type 1			Anti-TPOab positivity=titres of	Prevalence of positive TGab=18% (9/50)
			Number	n=50 patients with type 1		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
MA, Ortego J, Leelawattana R, Soonthornpun S, Setasuban W et al. Thyroid autoantibodies in Thai type 1 diabetic patients: clinical significance and their relationship with glutamic acid decarboxylase antibodies. Diabetes Research and Clinical Practice. 2000; 49(2-3):107-111. Ref ID: RATTARASARAN 2000	study /prevalence Patients with type 1 diabetes were selected from a Thai population attending a diabetic clinic at prince of Songkla university hospital, Thailand	diabetes and previous history of ketonuria or ketoacidosis at onset or a history of primary or secondary failure to oral hypoglycaemic agents within three years	of patients	diabetes n=47/50 adults	≥1:10 Anti-TGab=titres of ≥1:100 TSH normal range=0.25-4.0mU/litre Follow-up in patients without obvious thyroid dysfunction=19months (SD±8)	Prevalence of positive anti-TPOab=30% (15/50) Prevalence of combined anti-TGab and anti-TPOab positivity 13% (2/16) patients with anti-TPO and anti-TG positivity had previous hyperthyroidism prior to diabetes onset at time of study Of the remaining group of thyroid antibody positive group, two patients had newly diagnosed hyperthyroidism, one patient had clinical hypothyroidism 16% patients were anti-TG or anti-TPO positive (8/50) at time of study. At 19 months follow-up, 25% (2/8) patients developed hypothyroidism 13% (1/8) had elevated TSH levels after 20 months follow-up One patient had elevated TSH levels after 35 months follow-up Patients with thyroid antibodies but without history of thyroid disease had a higher frequency of thyroid dysfunction at the time of study 25% (2/8) patients were at a higher risk of developing thyroid dysfunction at 3 years follow-up
			Age (years), mean (SD)	36.5±17.5		
			Gender (m/f)	31m:19f		
			Duration of diabetes (years), mean (SD)	5.2±4.1		
			HbA1c (%)	Not reported		
			BMI (kg/m^2), mean (SD)	Not reported		
			Treatment subgroups	NA		
			Diabetes control	All patients were treated with insulin at the start of study		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
						68% (34/50) were thyroid antibody negative

Table 349: UMPIERREZ 2003

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Umpierrez GE, Latif KA, Murphy MB, Lambeth HC, Stentz F, Bush A et al. Thyroid dysfunction in patients with type 1 diabetes: a longitudinal study. Diabetes Care. 2003; 26(4):1181-1185. Ref ID:UMPIERREZ 2003	Cross-sectional study /prevalence Patients enrolled in the diabetes control and complication trial at the university of Tennessee health science centre in 1993 and prospectively followed up for 18 years	58 patients with type 1 diabetes Exclusion criteria: hypothyroidism prior to diabetes onset			TSH, T4, T3 measured yearly Anti-TPOab measured at 4 year intervals Anti-TPOab normal range=<32IU/ml TSH normal range=0.4-4.0 mU/ml	Prevalence of thyroid dysfunction=33% (19/58) Prevalence of primary hypothyroidism=31% (18/58) Hypothyroidism was more common in females (44%) vs. males (19%) Patients who are anti-TPO positive were 17.91 times as likely to develop hypothyroidism compared with anti-TPO negative patients
			Number of patients	58 patients with type 1 diabetes with or without hypothyroidism		
			Age (years), mean (SD)	Hypothyroidism+=18±2 Hypothyroidism-=16±1		
			Gender (m/f)	26m:32f		
			Duration of diabetes (years), mean (SD)	8±4		
			HbA1c (%)	No difference between groups		
			BMI (kg/m^2), mean (SD)	Hypothyroidism+=24±1 Hypothyroidism-=22±0.3		
			Treatment subgroups	Hypothyroidism+ Hypothyroidism-		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
			Diabetes control	Monitoring of glycaemic control and diabetes complications		

Table 350: VONDRA 2004

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Vondra K, Vrbikova J, Sterzl I, Bilek R, Vondrova M, Zamrazil V. Thyroid autoantibodies and their clinical relevance in young adults with type 1 diabetes during the first 12 year after diabetes onset. Journal of Endocrinological Investigation. 2004; 27(8):728-732. Ref ID	Cross-sectional study Young adults aged 18-35 years at the time of diagnosis, with newly diagnosed type 1 diabetes were followed up for 12 years after initial diagnosis since 1990s in the institute of endocrinology, Prague	109 patients with type 1 diabetes			AntiTPO at least twice yearly. Cut-off value=1U/ml (>1U/ml=positive) AntiTgab at least twice yearly. Cut-off value=3.8 U/ml (>5.0 U/ml=positive) TSH level greater than 4.5mlU/litre with normal thyroid hormone levels was considered as subclinical hypothyroidism, and was measured twice yearly. Normal range of TSH=0.17-4.05mlU/litre	Prevalence of type 1 diabetes patients with positive antiTPO+antiTG antibodies= 25% (27/109) Prevalence of type 1 diabetes patients with positive antiTPO antibody only=26% (28/109) Prevalence of type 1 diabetes patients with negative thyroid antibodies=49% (54/109)
			Number of patients	n=109		
			Age (years), mean (SD)	18-35 (at time of diagnosis)		
			Gender (m/f)	58m:51f		
			Duration of diabetes (years), mean (SD)	Newly diagnosed diabetes		
			HbA1c (%)	Not reported		
			BMI (kg/m^2), mean (SD)	Group I=22.5 Group II=21.7 Group III=22.7		
			Treatment subgroups	AntiTPO+AntiTgl AntiTPO only T-ab negative		
			Diabetes	Not reported		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
VONDRA2004			control			

Table 351: WALTER 2007

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Walter M, McDonald CG, Paty BW, Shapiro AMJ, Ryan EA, Senior PA. Prevalence of autoimmune diseases in islet transplant candidates with severe hypoglycaemia and glycaemic lability: previously undiagnosed coeliac and autoimmune thyroid disease is identified by screening. Diabetic Medicine. 2007;	Cross-sectional/prevalence study based in Canada	124 type 1 diabetes patients with severe hypoglycaemia and/or glycaemic lability undergoing assessment for islet transplantation and known cases of autoimmune disease , including previous radioiodine therapy or anti-thyroid drug therapy, and individuals receiving L-thyroxine			Serum TSH (threshold 4.5 mU/litre) Anti-TPO antibodies (range/threshold not reported) Patients with elevated TSH and anti-TPOab positivity remaining high were identified as new cases	Autoimmune thyroid disease=31% (38/124) New cases of thyroid disease=11% (4/38) Known cases=87% (33/38) Detection rate for new cases=5.8% (4/86) True prevalence=35% Thyroid disease was more common in women (43% 33/77) than men (21% 10/47)
			Number of patients	n=124 consecutive patients with type 1 diabetes		
			Age (years), mean (SD)	44 (range 23-65)		
			Gender (m/f)	47m:77f		
			Duration of diabetes (years), mean (SD)	28.4 (range 5-52)		
			HbA1c (%)	8.0±1.3		
			BMI (kg/m^2), mean (SD)	24.9±3.5		
			Treatment subgroups	Autoimmune disease No autoimmune disease		
			Diabetes control	Severe hypoglycaemia and/or glycaemic lability, hypoglycaemia unawareness despite		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
24(2):161-165. Ref ID:WALTER 2007				optimised insulin therapy		

Table 352: WHITEHEAD 2010

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Whitehead C, Lunt H, Pearson JF, Cawood TJ. Is screening for hypothyroidism in the diabetes clinic effective? Practical Diabetes International. 2010; 27(3):113-117. Ref ID WHITEHEAD2010	Cross-sectional study /prevalence and laboratory results of patients attending the diabetes centre in Christchurch hospital, New Zealand Missing data: none	800 patients included in study Inclusion criteria: Attendance of patients between January 2007 and January 2009 hypothyroidism to include only patients with autoimmune hypothyroidism Exclusion criteria: Patients residing outside the Canterbury district health board			Normal TSH not reported Normal FT4 not reported	Prevalence of hypothyroidism (including subclinical hypothyroidism) in type 1 diabetes patients=10.8% (43/400) Prevalence of subclinical hypothyroidism=4% (16/400) Prevalence of autoimmune hypothyroidism requiring thyroxine treatment=7% (27/400) Prevalence of hypothyroidism due to surgery or radioiodine treatment or hyperthyroidism=2% (6/400) Prevalence of hyperthyroidism or subclinical hyperthyroidism=1% (2/400) Average dose of thyroxine replacement in patients with hypothyroidism requiring thyroxine treatment and type 1
			Number of patients	n=400 patients with type 1 diabetes		
			Age (years), mean (SD)	>20		
			Gender (m/f)	53%m:47%f		
			Duration of diabetes (years), mean (SD)	Development of diabetes before the age of 40 years and requirement for insulin treatment within 1 year of diagnosis		
			HbA1c (%)	NA		
			BMI (kg/m^2), mean (SD)	NA		
			Treatment subgroups	Hypothyroidism Subclinical hypothyroidism Hypothyroidism+thyroxine		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
		catchment area of under 500,000 people, and not having type 1 diabetes Patients who are post-radioiodine or post-thyroidectomy treatment, or who are on 'block and replace' treatment with an antithyroid drug plus thyroxine. Hypothyroidism was defined as patients with a diagnostic label of hypothyroidism, or who are on thyroxine treatment in the absence of non-autoimmune aetiology of hypothyroidism	Diabetes control	Not reported		diabetes=104µg Annual thyroid hormone testing to detect hypothyroidism requiring thyroxine treatment=1.8% patients with type 1 diabetes Median time of patients to attend a diabetic clinic=9.5 years Prevalence of hypothyroidism requiring thyroxine treatment increased with age, particularly after 50 years

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
		or patients with TSH above the reference range with a normal FT4, who were not on thyroxine treatment Autoimmune hypothyroidism requiring treatment was defined as those with hypothyroidism and who were also on thyroxine treatment				

Table 353: YAMAGUCHI 1991

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Yamaguchi Y, Chikuba N, Ueda Y, Yamamoto H, Yamasaki H, Nakanishi T et al. Islet cell	Cross-sectional study /prevalence study Patients with	Total=316 patients with autoimmune disease Exclusion criteria:			T4 normal range=4.5-11.5µg/dl FT4 normal range=0.6-2.3ng/dl T3 normal range=91-	87.5% (18/21) type 1 diabetes patients were positive for anti-thyroidal autoantibodies
			Number of patients	n=21 type 1 diabetes patients with autoimmune thyroid disease		
			Age (years), mean (SD)	Not reported		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
antibodies in patients with autoimmune thyroid disease. Diabetes. 1991; 40(3):319-322. Ref ID YAMAGUCHI1991	type 1 diabetes and autoimmune thyroid disease were seen in the outpatient endocrinology and metabolism clinic of Nagasaki university hospital, Japan, during 1982-1988	juvenile onset of type 1 diabetes group without autoimmune disease	Gender (m/f)	Not reported	143ng/dl FT3 normal range=2.2-6.7pg/ml TSH normal range=0.5-5.0µl/ml Anti-thyroid microsomal antibodies and anti-thyroglobulin antibodies were considered positive with a dilution > 1x102	
			Duration of diabetes (years), mean (SD)	Not reported		
			HbA1c (%)	Not reported		
			BMI (kg/m^2), mean (SD)	Not reported		
			Treatment subgroups	Not reported		
			Diabetes control	Not reported		

Table 354: YASMIN 2006

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Yasmin T, Ghafoor F, Malik T, Ruhy N, Khan AU. Pattern of thyroid autoimmunity in type 1 and type 2 diabetics.	Cross-sectional study Patients were seen at the diabetic clinic of Shaikh Zayed	163 patients			Hypothyroidism= FT4 values <60nmol/litre and TSH >5mlU/litre) Hyperthyroidism=TSH<0.3mlU/litre Thyroid disease=anti-TPO>100IU/ml	61% (31/51) of type 1 diabetes patients had high levels of anti-TPOab and 84 % (43/51) of these patients had high FT4 levels Anti-TPOab positivity was higher in females than males
			Number of patients	n=51 type 1 diabetes patients		
			Age (years), mean (SD)	36.8±4.7		
			Gender (m/f)	Not reported		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Journal of the College of Physicians and Surgeons--Pakistan. 2006; 16(12):751-754. Ref ID YASMIN2006	hospital, Lahore, Pakistan from August 2004 and April 2005 (8 months)		Duration of diabetes (years), mean (SD)	Not reported		
			HbA1c (%)	Not reported		
			BMI (kg/m^2), mean (SD)	25.6±4.2		
			Treatment subgroups	Not reported		
			Diabetes control	Not reported		

G.11.3 Monitoring of thyroid disease in type 1 diabetes patients

Table 355: BIANCHI 1995

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Bianchi G, Montanari P, Fabbri A, Gamberini A, Zoli M, Marchesini G. Thyroid volume in type 1 diabetes patients	Case control study Patients were admitted to hospital for diabetic ketosis or for evaluation and	45 patients with type 1 diabetes and with no history of previous thyroid disorders and/or use of drugs known to affect the thyroid			Immunometric methods: FT3 normal range=4.0-8.9pmol/litre FT4 normal range=9.0-23.0pmol/litre	All patients had FT4 levels higher than the normal range and FT3/FT4 ratio was reduced 4/45 patients had high levels of FT4 and FT3 and TSH at levels below the detection limit 2/4 patients had anti-TPOab positivity and an ultrasound result showing dis-homogeneous thyroid parenchyma and were confirmed with Hashimoto's thyroiditis (hypothyroidism)
			Number of patients	n=45 patients with type 1 diabetes		
			Age (years), (median)	16-68 (median 40 years)		
			Gender (m/f)	20m:25f		
			Duration	Not reported		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
without overt thyroid disease. Acta Diabetologica. 1995; 32(1):49-52. Ref ID BIANCHI1995	treatment of complication of their diabetic disease Duration of study not reported Country: Italy No missing data	homeostasis	of diabetes (years), mean (SD)		TSH normal range=0.4-3.5mU/litre Anti-TPOab positivity= titres>50U/ml Anti-TGab positivity= titres>100 U/ml Ultrasound=evaluation of thyroid morphology	1/4 patient was confirmed to have asymptomatic Graves' disease and 1/4 patient was confirmed to have hyperthyroidism
			HbA1c (%)	8.9% (range 5.1% to 12.0%)		
			BMI (kg/m^2), mean (SD)	Not reported		
			Treatment subgroups	Not reported		
			Thyroidism at baseline	Not reported		
			Diabetes control	Poor control		

Table 356: VONDRA 2004

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Vondra K, Vrbikova J, Sterzl I, Bilek R, Vondrova M, Zamrazil V. Thyroid autoantibodies and their clinical	Cross-sectional study Young adults aged 18-35 years at the time of diagnosis,	109 patients with type 1 diabetes			AntiTPO at least twice yearly. Cut-off value=1U/ml (>1U/ml=positive) AntiTgab at least twice yearly. Cut-off value=3.8 U/ml (>5.0 U/ml=positive) TSH level greater	Annual and cumulative incidence of patients with newly detected concurrent positivity of both antiTPO and antiTgI during follow-up All new concomitant detection of both thyroid antibodies were made in the first four years from onset of diabetes (96% of all cases), with one patient who was positive for both antibodies in year 8 from onset of diabetes
			Number of patients	n=109		
			Age (years), mean (SD)	18-35 (at time of diagnosis)		
			Gender	58m:51f		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
relevance in young adults with type 1 diabetes during the first 12 year after diabetes onset. Journal of Endocrinological Investigation. 2004; 27(8):728-732. Ref ID VONDRA2004	with newly diagnosed type 1 diabetes were followed up for 12 years after initial diagnosis since 1990s in the institute of endocrinology, Prague No missing data		(m/f)		than 4.5mlU/litre with normal thyroid hormone levels was considered as subclinical hypothyroidism, and was measured twice yearly. Normal range of TSH=0.17-4.05mlU/litre	The cumulative incidence of concomitant positivity of both antibodies in 109 patients reached 25% and remained at this level throughout the follow-up period Annual and cumulative incidence of patients with newly detected anti-TPO positivity varied between 2-8% and reached a cumulative value of 26% in year 9 of the follow-up period. During years 10, 11 and 12 there were no new detected cases
			Duration of diabetes (years), mean (SD)	Newly diagnosed diabetes		
			HbA1c (%)	Not reported		
			BMI (kg/m^2), mean (SD)	Group I=22.5 Group II=21.7 Group III=22.7		
			Treatment subgroups	AntiTPO+AntiTgl AntiTPO only T-ab negative		
			Diabetes control	Not reported		

Table 357: UMPIERREZ 2003

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
Umpierrez GE, Latif KA, Murphy MB, Lambeth HC, Stentz F, Bush A et al. Thyroid dysfunction in patients with type 1	Cross-sectional study Patients with type 1 diabetes were previously enrolled in	58 patients with type 1 diabetes			AntiTPOab normal=<30 IU/ml TSH normal=0.4-4.0mU/ml T3 and T4 assays were performed as recommended by the	Presence of TPO antibodies was associated with an increased risk of hypothyroidism Most patients with TPO positive antibodies tested positive at beginning of the study remained positive throughout the study Patients who were TPO positive were 17.91 times as likely to develop hypothyroidism as
			Number of patients	58 patients with type 1 diabetes		
			Age (years), mean (SD)	19±2		
			Gender (m/f)	26m:32f		
			Duration	Type 1		

Reference	Study details	Number of patients	Patient characteristics		Tests	Results
diabetes: a longitudinal study. Diabetes Care. 2003; 26(4):1181-1185. Ref ID UMPIERREZ2003	the DCCT RCT and were followed prospectively for 18 years in Tennessee, USA		of diabetes (years), mean (SD)	diabetes+hypothyroidism =18±2 Type 1 diabetes only=16±1	manufacturers	patients who were TPO negative (95%CI 3.89-82.54) (controlled for age at onset of diabetes Cox proportional hazard analysis for prediction of development of hypothyroidism from age of onset, sex and TPO status (likelihood ratio X2=15.88, df=3, P=0.001) Adjusted hazard ratio for TPO status=8.99 (95%CI 2.35-34.36) showing that patients positive for antiTPO were much more likely to develop hypothyroidism than those patients who were TPO negative Patients who are TPO negative remain TPO negative throughout 12-28 duration of diabetes. The percentage of patients who tested positive at onset rapidly developed hypothyroidism as the duration of diabetes increased (years), and most of these patients developed subclinical hypothyroidism
			HbA1c (%)	No difference between subgroups		
			BMI (kg/m^2), mean (SD)	Type 1 diabetes+hypothyroidism =24±1 Type 1 diabetes only=22±0.3		
			Treatment subgroups	Normal Hypothyroidism Subclinical hypothyroidism Hyperthyroidism		
			Diabetes control	Not reported		

G.12 Methodological limitations of observational studies in the guideline

G.12.1 Review question: Diagnosis

Study ID	Study design: prospective or cross-sectional	Representative population sample	Outcomes adequately measured	Appropriate statistical analysis (adjusted for confounders where applicable)
Amrouche 2008	✓	✓	✓	n/a
Arikan 2005	✓	✓	✓	n/a
Andersen 2014	✓	✓	✓	n/a
Arslan 2014	X	✓	✓	n/a
Bodalska 2006	✓	✓	✓	n/a
Barker 2014	✓	✓	✓	n/a
Bell 2004	✓	✓	✓	n/a
Cerna 2003	✓	✓	✓	n/a
Davies 2008	✓	✓	✓	n/a
Davis 2003	✓	✓	✓	n/a
Hamaguchi 2004	✓	✓	✓	n/a
Hampe 2013	✓	✓	✓	n/a
Hawa 2013	✓	✓	✓	n/a
Hillman 2009	✓	✓	✓	n/a
Hope 2013	✓	✓	✓	n/a
Hosszu 2003	✓	✓	✓	n/a
Huang 2013	✓	✓	✓	n/a
Lu 2014	✓	Partially - mixed adults + young-people	✓	n/a
Mahadeb 2014	✓	✓	✓	n/a
Maraschin 2013	✓	✓	✓	n/a
McDonald 2011	✓	✓	✓	n/a
Murao 2008	✓	✓	✓	n/a
Paschke 2013	✓	✓	✓	n/a
Rajalakshmi 2014	✓	Partially - mixed adults + young people	✓	n/a
Rogowicz 2014	✓	✓	✓	n/a
Roh 2013	X	✓	✓	n/a
Shishikura 2014	✓	✓	✓	n/a
Sorgjerd 2012	✓	✓	✓	n/a
Szepietowska 2012	✓	✓	✓	n/a
Thanabalasingham 2012	✓	✓	✓	n/a
Wilmot 2013	✓	✓	✓	n/a
Yang 2008	✓	✓	✓	n/a
Zampetti 2012A	✓	✓	✓	n/a

Bottazzo 2005	✓	✓	✓	n/a
Castleden 2006	✓	✓	✓	n/a
Trabucci 2012	✓	✓	✓	n/a
Desai 2007	✓	✓	✓	n/a
Chowta 2010	✓	✓	✓	n/a
Monge 2004	✓	✓	✓	n/a
Kim 2007	✓	✓	✓	n/a
Aggarwal 2010	✓	✓	✓	n/a
Zhang 2012A	✓	✓	✓	n/a
Hwangbo 2012	✓	✓	✓	n/a
Maioli 2010	✓	✓	✓	n/a
Vaziri 2010	✓	✓	✓	n/a
Lindholm 2004	✓	✓	✓	n/a
Radtke 2009	✓	✓	✓	n/a
Lee 2011A	✓	✓	✓	n/a
Vlad 2004	✓	✓	✓	n/a
Besser 2011	✓	Partially - mixed adults + young people	✓	n/a
Borg 2003	✓	Partially - mixed adults + young people	✓	n/a
Brunova 2002	✓	Partially - mixed adults + young people	✓	n/a
Fan 2013	✓	Partially - mixed adults + young people	✓	n/a
Laadhar 2007	✓	Partially - mixed adults + young people	✓	n/a
McDonald 2011	✓	Partially - mixed adults + young people	✓	n/a
Ota 2005	✓	Partially – mixed all ages	✓	n/a
Scholin 2004	✓	✓	✓	n/a
Scholin 2004A	✓	Partially - mixed adults + young people	✓	n/a
Scholin 2004B	✓	Partially - mixed adults + young people	✓	n/a
Scholin 2011	✓	Partially - mixed adults + young people	✓	n/a
Tridgell 2011	✓	Partially - mixed all ages	✓	n/a
Vermeulen 2011	✓	✓	✓	n/a

Wenzlau 2010	✓	Partially - mixed adults + young people	✓	n/a

G.12.2 Review question: Education

No non-comparative observational studies were included for this review

G.12.3 Review question: Carbohydrate counting

Study ID	Study design: prospective or cross-sectional	Representative population sample	Outcomes adequately measured	Appropriate statistical analysis (adjusted for confounders where applicable)
Brazeau 2013	✓	✓	✓	X
Dias 2010	✓	✓	✓	n/a
Franc 2009	✓	✓	✓	n/a

G.12.4 Review question: GI diet

No non-comparative observational studies were included for this review

G.12.5 Review question: HbA1c

Study ID	Study design: prospective or cross-sectional	Representative population sample	Outcomes adequately measured	Appropriate statistical analysis (adjusted for confounders where applicable)
Araszkiewicz 2006	✓	✓	✓	✓
Eeg-Olofsson 2010	X	✓	✓	✓
Forrest 2000	✓	✓	✓	✓
Guerci 1999	✓	✓	✓	✓
Hietala 2013	✓	✓	✓	✓
Kullberg 1994	X	✓	✓	✓
LeCaire 2013	✓	Partially - mixed adults + young people	✓	✓
Nordwall 2009	X both retro and pros	Partially - mixed adults + children	✓	✓
Rossing 1996	✓	✓	✓	✓
Weinstock 2013	✓	✓	✓	✓
Aiello 2014	✓	✓	✓	✓
Jacobson 2013	✓	✓	✓	✓
Lind 2011	✓	✓	✓	✓
Zoffmann 2014	✓	✓	✓	✓
Agardh 1997	✓	✓	✓	✓
Brinchmann-Hansen 1992	✓	✓	✓	✓
DCCT/EDIC 2005; DCCT/EDIC 2008	✓	✓	✓	✓
Nathan 2005; White 2008	✓	✓	✓	✓
Diamante 1997	✓	✓	✓	✓
Eid Fares 2010	X	Partially - mixed adults + young people	✓	✓
Hislop 2008	✓	Partially - mixed adults + young people	✓	✓
Lehto 1999	✓	Partially - only men	✓	✓
Lustman 2005	✓	✓	✓	✓
Perez Mendez 2007	✓	Partially - mixed adults + young people	✓	n/a
Pittsburgh EDC 2002 (Olson 2002A)	✓	Partially – mixed all ages	✓	✓
Pittsburgh EDC 2003 (Orchard	✓	Partially – mixed all ages	✓	✓

2003)				
Shaban 2006	✓	Partially - mixed adults + young people	✓	n/a
Tabaei 2004	✓	✓	✓	✓
Van Tillburg 2001	✓	Partially - Mixed ages	✓	✓
WESDR 1998A (Klein 1998A)	✓	Partially - mixed adults + young people	✓	✓
WESDR 1994 (Moss 1994A)	✓	✓	✓	✓
WESDR 1999 (Moss 1999)	✓	✓	✓	✓
WESDR 1998 (Klein 1998)	X	✓	✓	✓
WESDR 1995 (Klein 1995; 1996)	✓	✓	✓	✓
Wikblad 1996	X	✓	✓	n/a
Wikblad 1991	X	✓	✓	n/a

G.12.6 Review question: SMBG - frequency and timing

Study ID	Study design: prospective or cross-sectional	Representative population sample	Outcomes adequately measured	Appropriate statistical analysis (adjusted for confounders where applicable)
Abdelgadir 2006	✓	✓	✓	n/a
Bott 1994	✓	Partially – mixed adults + children	✓	✓
Bragd 2003	✓	✓	✓	✓
Cox 2007	✓	✓	✓	n/a
Evans 1999	X	Partially – mixed adults + children	✓	✓
Hillman 2004	X	Partially - unclear age	✓	✓
Karter 2001	X	✓	✓	✓
Klein 1992	✓	✓	✓	n/a
Minder 2013	✓	✓	✓	✓
Nathan 1996	✓	Partially – mixed all ages	✓	✓
Pickup 2006	✓	✓	✓	✓
Schiffrin 1992	✓	Partially - mixed adults + young people	✓	n/a
Schutt 2006	✓	✓	✓	✓
Service 2007	✓	Partially - mixed adults + young people	✓	✓

Shimizu 2008	✓	✓	✓	X
Tildesley 2004	✓	Partially - mixed adults + young people	✓	X
Weitgasser 1994	✓	Partially - mixed adults + young people	✓	n/a
Willey 1993	✓	✓	✓	n/a
Ziegler 1993	✓	Partially - mixed adults + young people	✓	n/a
Araszkiewicz 2008	✓	✓	✓	X
Bell 1994	✓ possibly retro	Partially - Mixed all ages	✓	
Bell 1984	✓	Partially - Mixed all ages	✓	n/a
Bruttomesso 1992	X	✓	✓	X
Chan 2009	✓	✓	✓	✓
Brinchmann-Hansen 1992	✓	✓	✓	✓
Gonder 1988	✓	✓	✓	X
Hartemann 2001	✓	✓	✓	n/a
Lloyd 1993	✓	✓	✓	✓
Merimee 1984	✓	Partially - % type 1 diabetes unclear	✓	n/a
McClean 2005	✓	✓	✓	✓
Miller 2013	✓	✓	✓	✓
Nayak 2011	✓	Partially - Mixed diabetes and ages	✓	✓
Sjoberg 1988	✓	✓	✓	X
Van Tilburg 2001	✓	Partially – Mixed all ages	✓	✓
Woo 2011	✓	Partially - unclear ages	✓	n/a
Ziegler 1989	✓	Partially - Mixed all ages	✓	unclear
Ziegler 2012	✓	Partially - Mixed all ages	✓	unclear

G.12.7 Review question: SMBG – glucose targets

Study ID	Study design: prospective or cross-sectional	Representative population sample	Outcomes adequately measured	Appropriate statistical analysis (adjusted for confounders where applicable)
Cox 1994	✓	✓	✓	X

Kovatchev 2000	✓	Partially - unclear age	✓	n/a
Mulhauser 1998	✓	✓	✓	✓
Service 2001	✓	Partially - mixed adults + young people	✓	✓
Vervoort 1996	✓	✓	✓	n/a
Wei 2014	✓	Partially - age unclear	✓	n/a

G.12.8 Review question: SMBG – technologies

No non-comparative observational studies were included for this review

G.12.9 Review question: SMBG versus CGM

No non-comparative observational studies were included for this review

G.12.10 Review question: Insulin therapy –rapid-acting

No non-comparative observational studies were included for this review

G.12.11 Review question: Insulin therapy - long-acting

No non-comparative observational studies were included for this review

G.12.12 Review question: Insulin therapy - mixed

No non-comparative observational studies were included for this review

G.12.13 Review question: Insulin therapy - adjuncts

No non-comparative observational studies were included for this review

G.12.14 Review question: Insulin therapy - needle length, site and rotation

No non-comparative observational studies were included for this review

G.12.15 Review question: Pancreas transplant and islet cell transplantation

No non-comparative observational studies were included for this review

G.12.16 Review question: Hypoglycaemia - identification & quantification of impaired awareness of hypoglycaemia

Study ID	Study design: prospective or cross-sectional	Representative population sample	Outcomes adequately measured	Appropriate statistical analysis (adjusted for confounders where applicable)
Hendrieckx 2014	X	✓	✓	✓
Hopkins 2012	X	✓	✓	n/a

Choudhary 2010A	✓	✓	✓	n/a
Clarke 1995	✓	✓	✓	n/a
Geddes 2007	✓	✓	✓	n/a
Geddes 2008	✓	✓	✓	X
Gimenez 2009	✓	✓	✓	n/a
Gold 1994	✓	✓	✓	n/a
Hoihansen 2010	✓	✓	✓	n/a
Janssen 2000A	✓	✓	✓	n/a
Pedersen 2003	✓	✓	✓	n/a
Ryan 2004	✓	Partially - mainly type 1 diabetes	✓	n/a
Schopman 2011	✓	✓	✓	n/a
Streja 2005	✓	✓	✓	✓

G.12.17 Review question: Hypoglycaemia - recovering hypoglycaemia awareness

Study ID	Study design: prospective or cross-sectional	Representative population sample	Outcomes adequately measured	Appropriate statistical analysis (adjusted for confounders where applicable)
Brooks 2013	X	✓	✓	n/a
Choudhary 2013	X	✓	✓	n/a
Cranston 1994	✓	✓	✓	n/a
De Zoysa 2014	✓	✓	✓	n/a
Fanelli 1993	✓	✓	✓	n/a
Fritsche 2001	✓	✓	✓	n/a
Gimenez 2010	✓	✓	✓	n/a
Hernandez 2008	✓	✓	✓	n/a
Hopkins 2012	X	✓	✓	n/a
Leitao 2008	X	✓	✓	n/a
Liu 1996	✓	✓	✓	n/a
Meyer 1998	✓	✓	✓	n/a
Ryan 2005	X	✓	✓	n/a
Ryan 2009	✓	✓	✓	n/a
Leelarantha 2013A	✓	✓	6 months	n/a

G.12.18 Review question: Ketone monitoring - self-monitoring & in-hospital monitoring

Study ID	Study design: prospective or cross-sectional	Representative population sample	Outcomes adequately measured	Appropriate statistical analysis (adjusted for confounders where applicable)
Bektas 2004	✓	Partially - %	✓	n/a

		type 1 diabetes not given		
Arora 2011C	✓	Partially - % type 1 diabetes not given	✓	n/a
Kuru 2014	✓	Not very - mixed ages + % type 1 diabetes not given	✓	n/a
Harris 2005	X	Partially - % type 1 diabetes not given	✓	n/a
Taboulet 2007	X	Not very - mixed adults + young people, and % type 1 diabetes not given	✓	n/a

G.12.19 Review question: Arterial risk control

No non-comparative observational studies were included for this review

G.12.20 Review question: Inpatient management – IV insulin

Study ID	Study design: prospective or cross-sectional	Representative population sample	Outcomes adequately measured	Appropriate statistical analysis (adjusted for confounders where applicable)
Corney 2012	X	Partially - >70% type 1 diabetes	✓	n/a
Husband 1986	✓	Partially - ages unclear	✓	n/a
McCavert 2010	✓	✓	✓	n/a
Poppe 2004	✓	✓	✓	n/a
Wagner 1999	✓	Partially - mixed adults + young people	✓	n/a

G.12.21 Review question: Complications – gastroparesis

Study ID	Study design: prospective or cross-sectional	Representative population sample	Outcomes adequately measured	Appropriate statistical analysis (adjusted for confounders where applicable)
Timratana 2013	✓	Partially - % type 1 diabetes unclear	✓	n/a
Horowitz 1985	✓	✓	✓	n/a

Sharma 2011	✓	✓	✓	n/a
Vandervoot 2005	✓	✓	✓	n/a

G.12.22 Review question: Complications – acute painful neuropathy

Study ID	Study design: prospective or cross-sectional	Representative population sample	Outcomes adequately measured	Appropriate statistical analysis (adjusted for confounders where applicable)
Gibbons 2010	✓	Partially - 55% type 1 diabetes	✓	n/a

G.12.23 Review question: Complications – thyroid disease

Study ID	Study design: prospective or cross-sectional	Representative population sample	Outcomes adequately measured	Appropriate statistical analysis (adjusted for confounders where applicable)
Allen 2008	✓	✓	✓	n/a
Bianchi 1995	✓	Partially - mixed adults + young people	✓	n/a
Cardoso 1995	✓	✓	✓	n/a
Dagdelen 2009	✓	Partially - mixed adults + young people + children	✓	n/a
Dufaitre 2006	✓	✓	✓	n/a
Fialzok 1997C??? /fialkow 1975?	✓	✓	✓	n/a
Gomez 2003	✓	Partially - mixed adults + young people	✓	n/a
Hanukoglu 2003	✓	Partially - children	✓	n/a
Jin 2011	✓	✓	✓	n/a
Junik 2006	✓	✓	✓	n/a
Kucera 2003	✓	✓	✓	n/a
Lupi 2013	✓	✓	✓	n/a
Palma 2013	✓	Partially - mixed adults + young people	✓	n/a
Perros 1995	✓	✓	✓	n/a
Prazny 1999	✓	Partially - mixed adults + young people	✓	n/a
Rattarassaran 2000	✓	Partially - mixed	✓	n/a

		adults + young people		
Umpierrez 2003	✓	Partially - mixed adults + young people	✓	✓
Vondra 2004	✓	✓	✓	n/a
Walter 2007	✓	✓	✓	n/a
Whitehead 2010	✓	✓	✓	n/a
Yamaguchi 1991	✓	✓	✓	n/a
Yasmin 2006	✓	Partially - mixed adults + young people	✓	n/a

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