Appendix J: Network meta-analyses results and input data for clinical evidence review of blood glucose lowering treatments

Review question 1: Which pharmacological blood glucose lowering therapies should be used to control blood glucose levels in people with type 2 diabetes?

J.1 MODEL FIT STATISTICS FOR ALL TREATMENT PHASES

Table 1: Model fit statistics used to select fixed or random effect models for all treatment phases

Treatment phase	Outcome	Model	Total model DIC	Total model DIC (FE – RE)	Total residual deviance	Number of datapoints	Between-study SD (95% CrI)	Preferred model i.e. FE or RE
Initial therapy	HbA1c at 3 months	FE	1093.9	1276.3	1518.0	173	-	RE preferred
		RE	-182.4		172.1		0.26 (0.22, 0.32)	
	HbA1c at 6 months	FE	61.4	148.2	347.7	152	-	RE preferred
		RE	-86.8		150.1		0.25 (0.19, 0.32)	
	HbA1c at 12 months	FE	-5.8	3.2	54.6	46	-	RE preferred
		RE	-9.0		44.8		0.16 (0.02, 0.33)	
	HbA1c at 24 months	FE	-12.8	0	14.0	13	-	FE preferred
		RE	-12.8		13.0		0.52 (0.03, 1.87)	
	Weight at 12 months	FE	82.3	5.8	34.0	25	-	RE preferred
		RE	76.5		24.6		1.63 (0.46, 4.60)	
	Weight at 24 months	FE	27.3	-1.3	11.0	12	-	FE preferred
		RE	28.6		11.7		1.58 (0.05, 9.10)	
	Dropouts due to AE	FE	845.5	1.3	201.2	186	-	FE preferred
		RE	844.2		186.7		0.25 (0.02, 0.50)	
	Total dropouts	FE	1011.7	4.0	204.4	177	-	RE preferred
		RE	1007.7		183.1		0.16 (0.02, 0.29)	

Treatment phase	Outcome	Model	Total model DIC	Total model DIC (FE – RE)	Total residual deviance	Number of datapoints	Between-study SD (95% CrI)	Preferred model i.e. FE or RE
	Nausea	FE	333.5	-1.4	72.3	71	-	FE preferred
		RE	334.9		68.9		0.21 (0.01, 0.61)	
	Hypoglycaemia	FE	517.6	4.8	116.6	112	-	RE preferred
		RE	512.8		102.4		0.31 (0.07, 0.58)	
First intensification	HbA1c at 3 months	FE	-29.4	45.5	104.9	45	-	RE preferred
		RE	-74.9		47.4		0.22 (0.13, 0.38)	
	HbA1c at 6 months	FE	-60.7	10.3	66.5	47	-	RE preferred
		RE	-71.0		47.4		0.14 (0.06, 0.27)	
	HbA1c at 12 months	FE	-21.9	32.0	75.2	35	-	RE preferred
		RE	-53.9		35.4		0.28 (0.15, 0.55)	
	HbA1c at 24 months	FE	-27.0	-1.0	14.7	14	-	FE preferred
		RE	-26.0		14.0		0.23 (0.01, 1.55)	
	Weight at 12 months	FE	45.5	0.5	23.4	21	-	FE preferred
		RE	45.0		20.4		0.78 (0.06, 2.91)	
	Weight at 24 months	FE	21.4	1.1	20.9	18	-	FE preferred
		RE	20.3		18.1		1.08 (0.08, 7.36)	
	Dropouts due to AE	FE	386.5	19.5	92.9	63	-	RE preferred
		RE	367.0		62.5		0.53 (0.28, 0.91)	
	Total dropouts	FE	475.7	24.7	103.2	67	-	RE preferred
		RE	451.0		66.1		0.31 (0.17, 0.51)	
	Nausea	FE	152.0	2.2	32.2	25	-	FE preferred
		RE	149.8		26.4		0.36 (0.04, 1.21)	
	Hypoglycaemia	FE	350.2	38.6	94.5	47	-	RE preferred
		RE	311.6		47.8		0.64 (0.33, 1.27)	
Second intensification	HbA1c up to 12 months	FE	11.2	24.8	123.3	85	-	RE preferred
		RE	-13.6		87.0		0.31 (0.17, 0.55)	

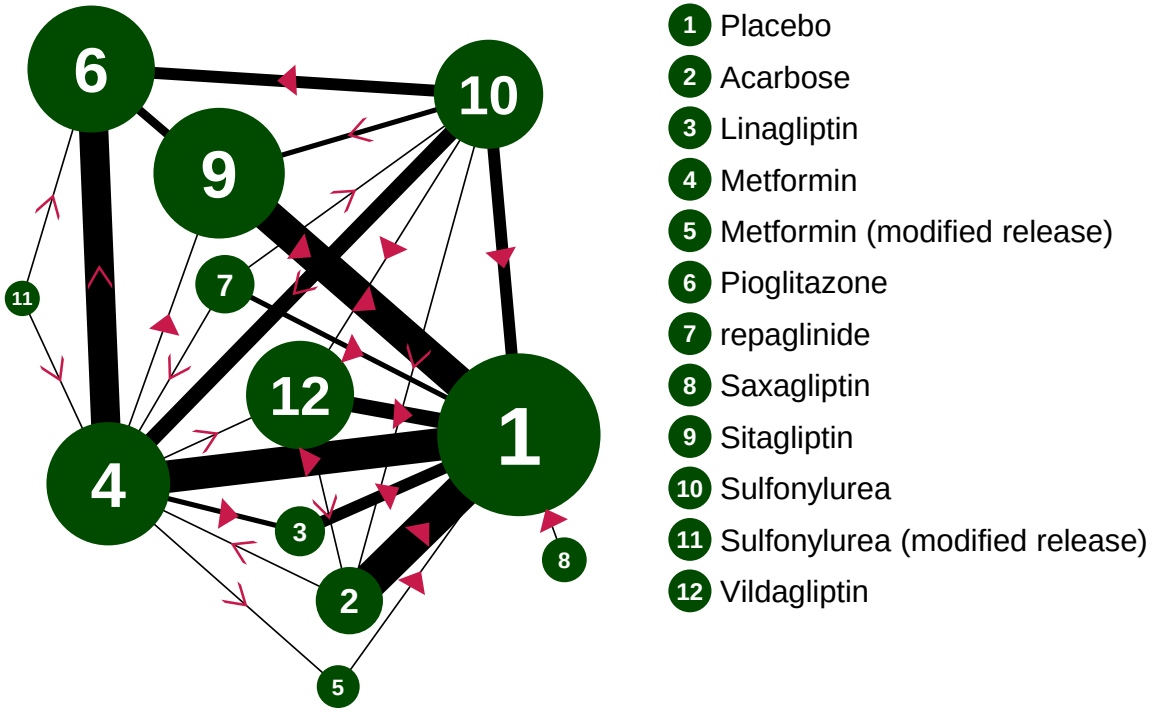
Treatment phase	Outcome	Model	Total model DIC	Total model DIC (FE – RE)	Total residual deviance	Number of datapoints	Between-study SD (95% CrI)	Preferred model i.e. FE or RE
	Weight up to 12 months	FE	114.8	-0.2	64.5	62	-	FE preferred
		RE	115.0		61.2		0.35 (0.02, 1.02)	
	Dropouts due to AE	FE	266.1	-1.4	63.3	61	-	FE preferred
		RE	267.5		62.6		0.57 (0.04, 1.75)	
	Total dropouts	FE	333.3	-0.2	65.3	60	-	FE preferred
		RE	333.5		62.8		0.39 (0.02, 1.34)	
	Nausea	FE	75.5	17.2	27.2	9	-	RE preferred
		RE	58.3		9.2		1.52 (0.69, 1.98)	
	Hypoglycaemia	FE	639.4	32.8	124.1	77	-	RE preferred
		RE	606.6		79.9		0.34 (0.18, 0.59)	

J.2 FULL DATASET

J.2.1 RESULTS FOR INITIAL THERAPY

J.2.1.1 Change in HbA1c at 3, 6, 12 and 24 months

Change in HbA1c at 3 months



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 1: INITIAL THERAPY: HbA1c AT 3 MONTHS – evidence network

Table 2: INITIAL THERAPY: HbA1c AT 3 MONTHS – input data

	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	repaglinide	Saxagliptin	Sitagliptin	Sulfonylurea	Sulfonylurea (modified release)	Vildagliptin
Foley & (2009)										-1.48 (0.85)		-1.13 (0.68)
Kato et al. (2009)				-0.80 (0.91)		-1.10 (1.16)						
Derosa et al. (2009)				-0.50 (0.76)		-0.40 (0.83)						
Bosi et al. (2009)				-1.29 (0.87)								-1.18 (0.86)
Erdem et al. (2008)				-0.59 (0.95)		-0.74 (0.80)						
Gao et al. (2008)				-0.30 (0.58)	-0.30 (0.70)							
Pan et al. (2008)		-1.29 (0.66)										-1.35 (0.65)
Formoso et al. (2008)				-2.20 (0.04)						-1.40 (0.03)		
Goldstein et al. (2007)	0.25 (0.64)			-0.84 (0.61)					-0.70 (0.65)			
Scott et al. (2007)	0.23 (0.73)								-0.38 (0.77)	-0.76 (0.78)		
Jain et al. (2006)						-2.04 (1.19)				-2.45 (1.19)		
Yoon et al. (2011)				-0.80 (0.55)						-1.05 (0.48)		
Haak et al. (2012)	-0.15 (0.62)		-0.65 (0.70)	-1.16 (0.58)								
Haak et al. (2012)	0.45 (0.57)		-0.20 (0.60)	-0.42 (0.55)								
Pan et al. (2012)	-0.32 (0.66)							-0.89 (0.67)				
Shihara et al. (2011)						-0.50 (0.65)				-0.90 (0.57)		
Aschner et al. (2006)	0.20 (0.70)								-0.57 (0.58)			
Bautista et al. (2003)	-0.70 (0.30)									-2.30 (0.30)		
Uehara et al. (2001)	-0.80 (1.93)			-0.70 (0.99)								
Delgado et al. (2002)	0.00 (2.10)	-0.10 (0.99)										
Barzilai et al. (2011)	0.26 (0.50)								-0.33 (0.52)			
Nonaka et al. (2008)	0.41 (0.66)								-0.65 (0.66)			
Hanefeld et al. (2007)	0.12 (0.75)								-0.40 (0.74)			
Kawamori et al. (2012)	0.63 (0.72)		-0.24 (0.76)									
Iwamoto et al. (2010)	0.28 (0.52)								-0.60 (0.51)			
Kikuchi et al. (2009)	0.28 (0.85)											-0.71 (0.77)
Mohan et al. (2009)	0.24 (0.70)								-0.70 (0.75)			
Pi-Sunyer et al. (2007)	-0.42 (0.72)											-0.88 (0.64)
Pratley et al. (2006)	0.00 (1.06)											-0.60 (0.84)

	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	repaglinide	Saxagliptin	Sitagliptin	Sulfonylurea	Sulfonylurea (modified release)	Vildagliptin
Ristic et al. (2005)	-0.13 (0.74)											-0.42 (0.76)
Scherbaum et al. (2008)	0.02 (0.46)											-0.25 (0.30)
Herz et al. (2003)	-0.20 (0.41)					-0.85 (0.54)						
Abbatecola et al. (2006)							-0.48 (0.57)			-0.26 (0.91)		
Jovanovic et al. (2000)	1.25 (2.15)						-0.70 (1.78)					
Schernthaner et al. (2004)				-1.25 (0.68)		-1.00 (0.69)						
Fujioka et al. (2005)	0.19 (0.62)				-0.60 (0.72)							
Campbell et al. (1994)				-2.31 (1.32)						-2.90 (1.49)		
Aronoff et al. (2000)	0.70 (0.89)					-0.15 (1.00)						
Yamanouchi et al. (2005)				-1.80 (0.57)		-1.40 (0.57)				-2.10 (0.46)		
Raz et al. (2006)	0.17 (0.80)								-0.42 (0.64)			
Tessier et al. (1999)				-0.80 (1.10)						-1.00 (1.15)		
Damsbo et al. (1998)	-3.30 (2.90)			-2.80 (1.24)								
DeFronzo & (1995)	0.15 (0.24)			-1.30 (0.60)								
Mather et al. (2001)	-0.30 (1.28)			-0.30 (0.73)								
Braun D,Schonherr (1996)	-0.90 (1.27)	-2.00 (1.27)										
Buchanan et al. (1988)	1.60 (2.56)	1.10 (2.29)										
Chiassonet al. (1994)	0.10 (1.24)	-0.45 (1.40)										
Coniff et al. (1995)	0.31 (1.02)	-0.44 (1.04)										
Fischer et al. (1998)	0.38 (0.77)	-0.46 (0.77)										
Hoffmann & (1994)	-0.06 (0.25)	-0.74 (0.28)								-0.75 (0.24)		
Hoffmann & (1997)	0.10 (0.60)	-0.90 (0.61)		-0.75 (0.57)								
Hotta et al. (1993)	0.20 (1.70)	-1.00 (1.29)										
Santeusanio et al. (1993)	0.30 (0.70)	-0.68 (0.68)										
Scott et al. (1999)	0.25 (1.20)	-0.14 (0.90)										
Birkeland et al. (1994)	0.05 (0.68)									-0.95 (0.79)		
Charbonnel et al. (2005)						-1.08 (0.73)				-1.45 (0.75)		
Moses et al. (2001)	-0.21 (1.50)						-1.21 (1.17)					
Kikuchi et al. (2012)	0.21 (1.10)					-0.91 (1.01)						

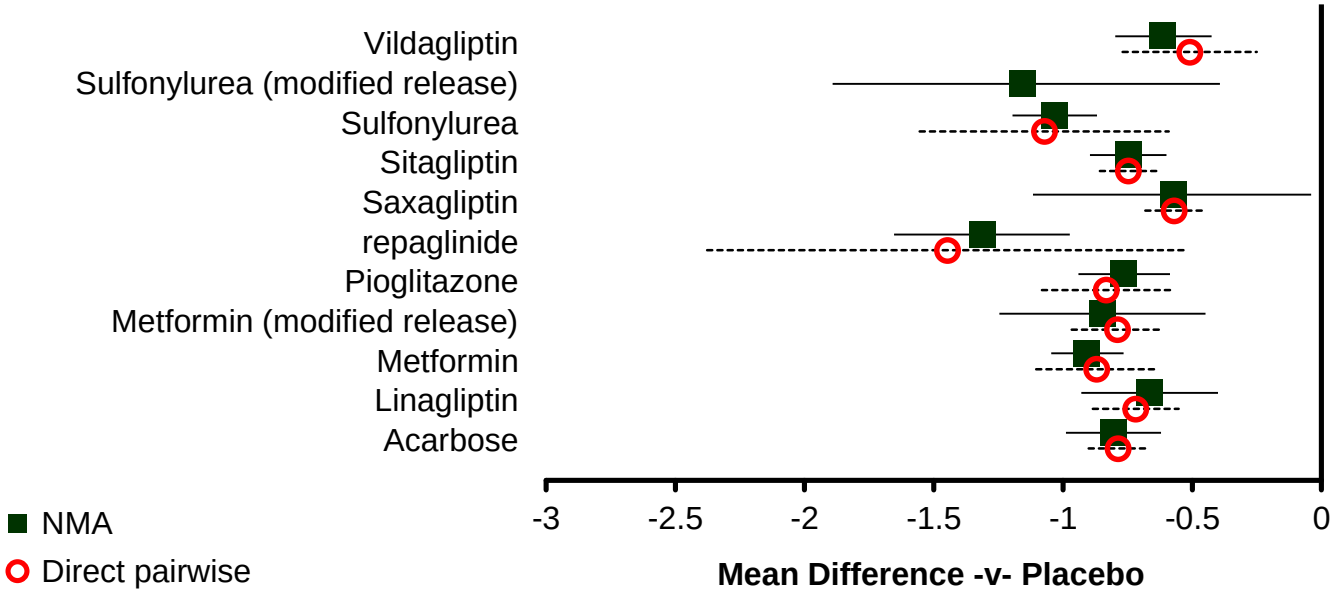
	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	repaglinide	Saxagliptin	Sitagliptin	Sulfonylurea	Sulfonylurea (modified release)	Vildagliptin
Ferrannini et al. (2013)	0.10 (0.92)			-0.70 (1.00)								
Fonseca et al. (2013)	0.26 (0.80)			-0.42 (0.83)								
Arjona et al. (2013)									-0.56 (0.81)	-0.56 (0.83)		
Barnett et al. (2012)	0.24 (1.07)		-0.57 (0.76)									
Genovese et al. (2013)				-0.20 (0.47)		-0.40 (0.58)						
Taslimi et al. (2013)				-1.40 (0.98)		-0.90 (1.16)						
Roden et al. (2013)	-0.02 (0.50)								-0.63 (0.50)			
Erem et al. (2014)				-0.95 (0.77)		-1.13 (1.10)					-1.33 (1.11)	
Fang et al. (2014)				-1.60 (1.50)			-1.80 (1.50)					
Esteghamati et al. (2014)				-0.83 (1.02)		-0.72 (1.30)						

Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 3: INITIAL THERAPY: HbA1c AT 3 MONTHS – relative effectiveness of all pairwise combinations

	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	repaglinide	Saxagliptin	Sitagliptin	Sulfonylurea	Sulfonylurea (modified release)	Vildagliptin
Placebo		-0.79 (-0.90, -0.67)	-0.72 (-0.88, -0.55)	-0.87 (-1.10, -0.64)	-0.79 (-0.97, -0.61)	-0.83 (-1.08, -0.58)	-1.45 (-2.38, -0.52)	-0.57 (-0.68, -0.46)	-0.75 (-0.86, -0.64)	-1.07 (-1.55, -0.59)	-	-0.51 (-0.77, -0.25)
Acarbose	-0.80 (-0.99, -0.62)		-	0.15 (-0.14, 0.44)	-	-	-	-	-	-0.01 (-0.15, 0.13)	-	-0.06 (-0.17, 0.05)
Linagliptin	-0.67 (-0.93, -0.40)	0.14 (-0.18, 0.46)		-0.36 (-0.65, -0.08)	-	-	-	-	-	-	-	-
Metformin	-0.91 (-1.05, -0.77)	-0.10 (-0.32, 0.11)	-0.24 (-0.51, 0.03)		0.00 (-0.21, 0.21)	0.11 (-0.06, 0.27)	-0.20 (-1.01, 0.61)	-	0.14 (0.03, 0.25)	-0.08 (-0.77, 0.61)	-0.38 (-0.99, 0.23)	0.11 (-0.03, 0.25)
Metformin (modified release)	-0.85 (-1.25, -0.45)	-0.04 (-0.48, 0.39)	-0.18 (-0.65, 0.28)	0.06 (-0.34, 0.46)		-	-	-	-	-	-	-
Pioglitazone	-0.76 (-0.94, -0.59)	0.04 (-0.20, 0.29)	-0.10 (-0.40, 0.20)	0.14 (-0.02, 0.31)	0.09 (-0.34, 0.51)		-	-	-	-0.45 (-0.57, -0.32)	-0.20 (-0.90, 0.50)	-
repaglinide	-1.31 (-1.65, -0.97)	-0.51 (-0.89, -0.13)	-0.65 (-1.07, -0.23)	-0.40 (-0.76, -0.05)	-0.46 (-0.99, 0.06)	-0.55 (-0.91, -0.18)		-	-	0.22 (-0.02, 0.45)	-	-
Saxagliptin	-0.57 (-1.12, -0.04)	0.23 (-0.34, 0.80)	0.09 (-0.51, 0.68)	0.34 (-0.22, 0.88)	0.28 (-0.40, 0.95)	0.19 (-0.38, 0.75)	0.74 (0.10, 1.37)		-	-	-	-
Sitagliptin	-0.75 (-0.90, -0.60)	0.06 (-0.18, 0.29)	-0.08 (-0.38, 0.21)	0.16 (-0.03, 0.35)	0.10 (-0.32, 0.52)	0.02 (-0.20, 0.23)	0.56 (0.20, 0.93)	-0.18 (-0.73, 0.39)		-0.19 (-0.56, 0.18)	-	-
Sulfonylurea	-1.03 (-1.20, -0.87)	-0.23 (-0.46, 0.01)	-0.37 (-0.66, -0.07)	-0.12 (-0.30, 0.05)	-0.18 (-0.61, 0.24)	-0.27 (-0.45, -0.08)	0.28 (-0.07, 0.63)	-0.46 (-1.02, 0.11)	-0.28 (-0.48, -0.09)		-	0.35 (0.24, 0.46)
Sulfonylurea (modified release)	-1.16 (-1.89, -0.39)	-0.35 (-1.11, 0.43)	-0.49 (-1.27, 0.30)	-0.25 (-0.98, 0.51)	-0.31 (-1.14, 0.55)	-0.39 (-1.13, 0.37)	0.16 (-0.65, 0.98)	-0.58 (-1.50, 0.35)	-0.41 (-1.16, 0.37)	-0.12 (-0.86, 0.64)		-
Vildagliptin	-0.61 (-0.80, -0.42)	0.19 (-0.05, 0.44)	0.05 (-0.26, 0.37)	0.30 (0.08, 0.51)	0.23 (-0.20, 0.67)	0.15 (-0.09, 0.40)	0.70 (0.32, 1.09)	-0.04 (-0.61, 0.53)	0.14 (-0.10, 0.37)	0.42 (0.19, 0.65)	0.54 (-0.25, 1.30)	

Values given are mean differences in HbA1c in percentage-points.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 2: INITIAL THERAPY: HbA1c AT 3 MONTHS – relative effect of all options versus reference treatment

Table 4: INITIAL THERAPY: HbA1c AT 3 MONTHS – rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.000	12 (12, 12)
Acarbose	0.000	6 (3, 10)
Linagliptin	0.000	9 (4, 11)
Metformin	0.000	4 (3, 7)
Metformin (modified release)	0.020	5 (2, 11)
Pioglitazone	0.000	7 (4, 10)
repaglinide	0.611	1 (1, 3)
Saxagliptin	0.005	10 (2, 11)
Sitagliptin	0.000	7 (4, 10)
Sulfonylurea	0.020	3 (2, 5)
Sulfonylurea (modified release)	0.344	2 (1, 11)
Vildagliptin	0.000	10 (6, 11)

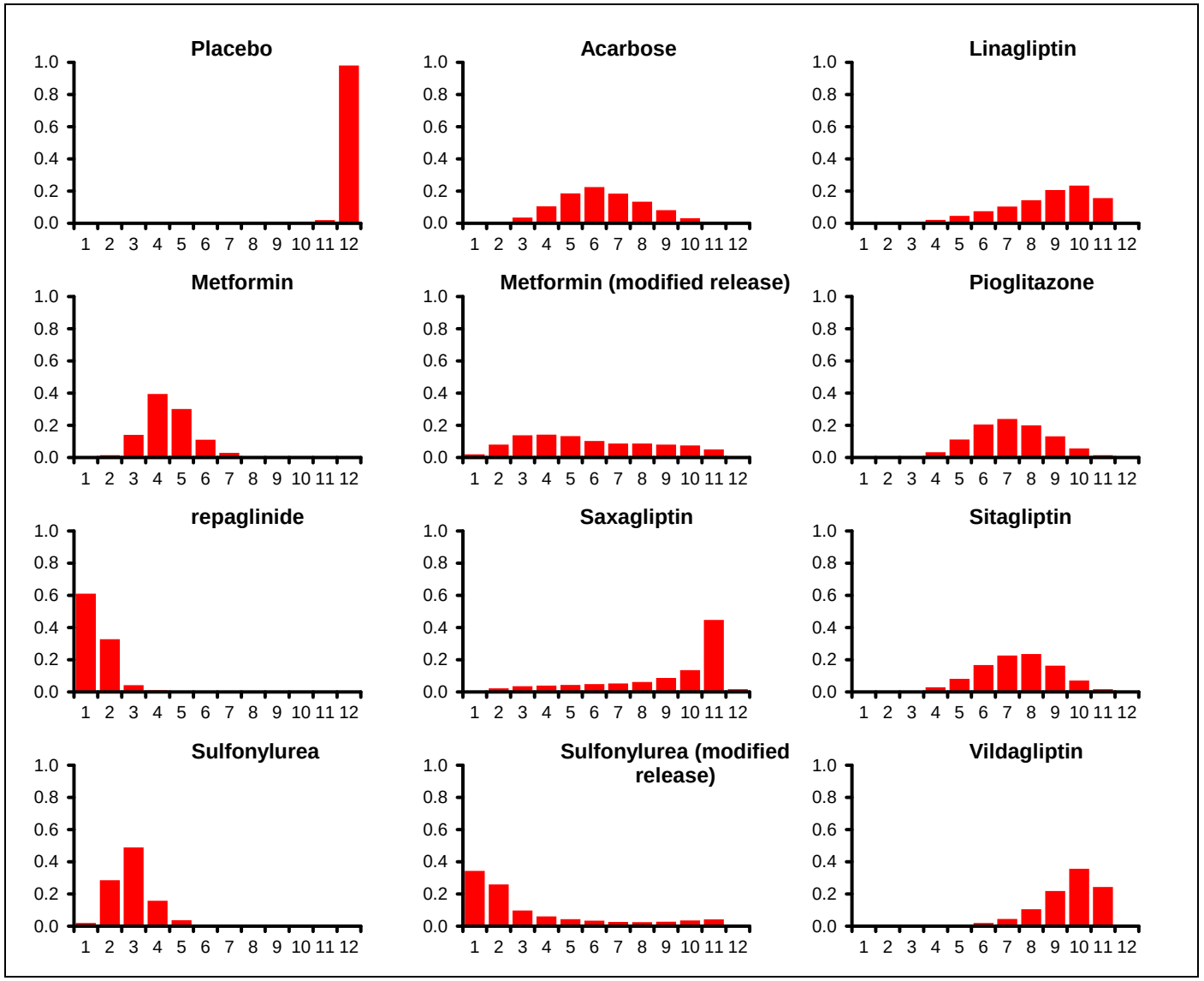


Figure 3: INITIAL THERAPY: HbA1c AT 3 MONTHS – rank probability histograms

Table 5: INITIAL THERAPY: HbA1c AT 3 MONTHS – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
172.1 (compared to 173 datapoints)	-331.422	-480.472	149.05	-182.373	0.262 (95%CI: 0.219, 0.316)

Table 6: INITIAL THERAPY: HbA1c AT 3 MONTHS – notes

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

Change in HbA1c at 6 months

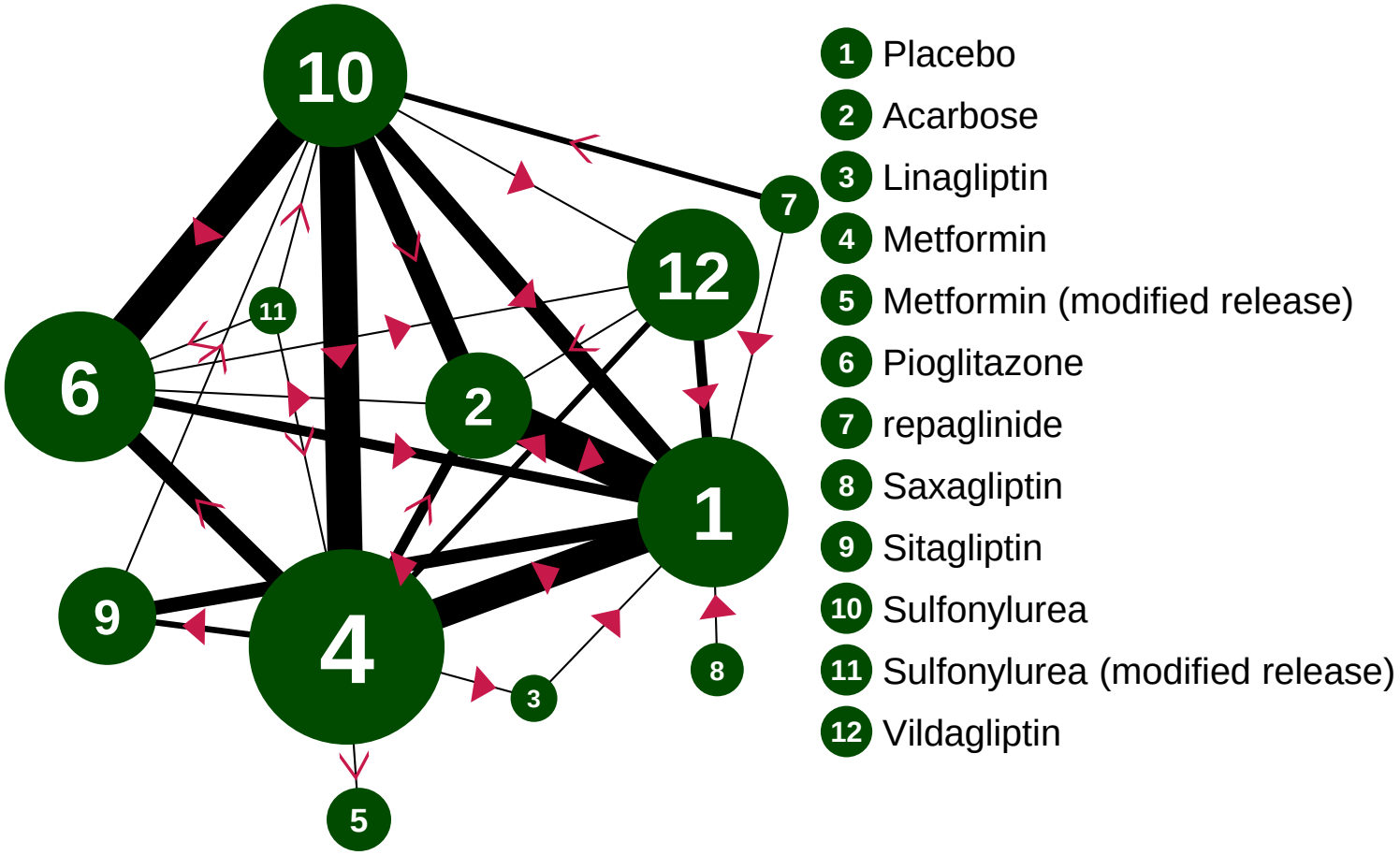


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Figure 4: INITIAL THERAPY: HbA1c AT 6 MONTHS – evidence network

Table 7: INITIAL THERAPY: HbA1c AT 6 MONTHS – input data

	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	repaglinide	Saxagliptin	Sitagliptin	Sulfonylurea	Sulfonylurea (modified release)	Vildagliptin
Esposito et al. (2011)				-0.90 (0.50)		-0.90 (0.50)						
Foley & (2009)										-1.63 (1.12)		-1.18 (1.13)
Schweizer et al. (2009)				-0.75 (0.90)								-0.64 (0.91)
Bosi et al. (2009)				-1.40 (1.01)								-1.10 (1.02)
Pan et al. (2008)		-1.30 (1.37)										-1.40 (1.97)
Goldstein et al. (2007)	0.17 (1.15)			-0.97 (1.10)					-0.66 (1.16)			
Teramoto et al. (2007)						-0.80 (1.14)				-1.43 (1.09)		
Jain et al. (2006)						-2.22 (1.19)				-2.34 (1.19)		
Yoon et al. (2011)				-0.95 (0.69)						-1.07 (0.60)		
Haak et al. (2012)	0.10 (0.81)		-0.50 (1.16)	-0.85 (1.18)								
Pan et al. (2012)	-0.42 (1.02)							-0.95 (1.04)				
Shihara et al. (2011)						-0.86 (0.98)				-0.98 (0.72)		
Derosa et al. (2011)	-0.30 (0.41)	-1.10 (0.55)										
Aschner et al. (2010)				-0.57 (0.53)					-0.43 (0.54)			
Aschner et al. (2006)	0.18 (0.96)								-0.61 (1.00)			
Schwartz et al. (2006)				-1.05 (2.72)	-0.82 (2.67)							
Barzilai et al. (2011)	0.20 (0.97)								-0.50 (1.03)			
Dejager et al. (2007)	-0.30 (0.97)											-0.83 (0.98)
Pi-Sunyer et al. (2007)	0.00 (0.96)											-0.67 (0.94)
Rosenstock et al. (2007)						-1.40 (1.25)						-1.10 (1.22)
Scherbaum et al. (2008)	-0.05 (0.47)											-0.33 (0.41)
Abbatecola et al. (2006)							-0.55 (0.78)			-0.30 (1.49)		
Horton et al. (2000)	0.50 (0.99)			-0.80 (0.99)								
Jovanovic et al. (2000)	1.30 (3.01)						-0.68 (1.78)					
Schernthaner et al. (2004)				-1.70 (0.88)		-1.55 (0.97)						
Schernthaner et al. (2004)										-1.20 (1.00)	-1.30 (1.10)	
Goke (2002)		-0.48 (1.62)				-1.16 (1.60)						

	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	repaglinide	Saxagliptin	Sitagliptin	Sulfonylurea	Sulfonylurea (modified release)	Vildagliptin
Campbell et al. (1994)				-2.61 (1.58)						-2.85 (1.75)		
Aronoff et al. (2000)	0.70 (1.51)					-0.32 (1.54)						
Scherbaum et al. (2002)	-0.34 (0.98)					-0.98 (1.39)						
Watanabe et al. (2005)						-0.80 (0.27)				-0.90 (0.42)		
Ebeling et al. (2001)	-0.20 (0.78)					-1.10 (1.23)				-1.20 (0.75)		
Lawrence et al. (2004)				-1.12 (0.84)		-0.81 (0.63)				-1.21 (0.82)		
Yamanouchi et al. (2005)				-1.90 (0.61)		-2.20 (0.70)				-2.00 (0.66)		
Collier et al. (1989)				-4.70 (2.05)						-4.70 (1.23)		
Tessier et al. (1999)				-1.00 (1.42)						-1.00 (1.58)		
Hermann et al. (1994)				-0.90 (0.87)						-1.30 (0.87)		
DeFronzo & (1995)	0.40 (1.20)			-1.40 (1.19)								
H+¤llsten et al. (2002)	-0.20 (0.34)			-0.70 (0.66)								
Lee & (1998)	0.20 (0.90)			-0.90 (0.90)								
Del et al. (2003)	0.48 (1.58)			-1.02 (1.38)								
Braun D,Schonherr (1996)	-1.00 (2.13)	-2.50 (1.74)										
Chan et al. (1998)	-0.27 (1.10)	-0.70 (1.21)										
Chiasson et al. (1994)	-0.15 (0.93)	-0.90 (1.40)										
Coniff et al. (1995)	0.04 (1.02)	-0.54 (1.05)								-0.99 (1.04)		
Fischer et al. (1998)	0.57 (1.07)	-0.42 (1.05)										
Hoffmann & (1994)	0.16 (0.39)	-0.98 (0.45)								-0.76 (0.39)		
Hoffmann & (1997)	0.30 (0.83)	-1.10 (0.83)		-0.90 (0.81)								
Hotta et al. (1993)	-0.42 (1.30)	-1.38 (1.75)										
Kovacevic et al. (1997)	0.20 (1.40)	-0.70 (0.76)								-1.60 (1.03)		
Rosenthal & (2002)		0.00 (1.29)								0.00 (1.57)		
Salman et al. (2001)		-1.80 (1.33)								-2.20 (0.74)		
Birkeland et al. (1994)	0.05 (0.92)									-0.68 (1.07)		
Charbonnel et al. (2005)						-1.58 (0.99)				-1.83 (1.03)		
Nakamura et al. (2004)						-1.10 (1.16)				-1.10 (1.25)		
Tosi et al. (2003)				-0.50 (1.10)						-0.50 (1.30)		
Saleem et al. (2011)							-0.60 (1.48)			-0.40 (1.48)		

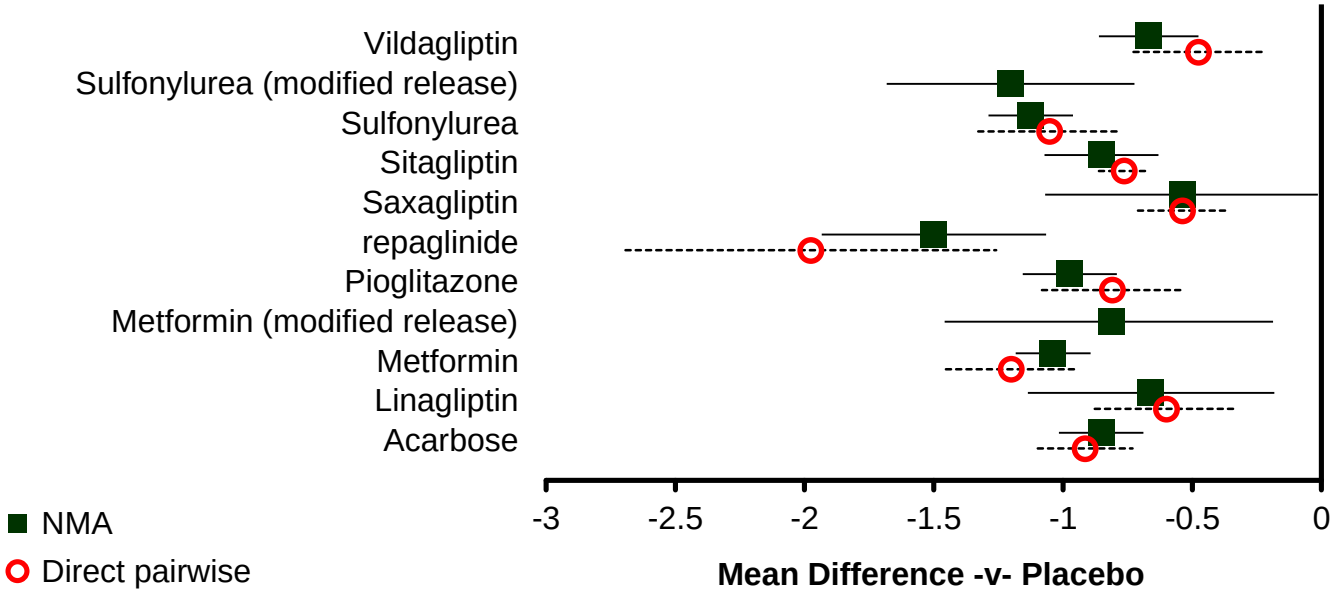
	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	repaglinide	Saxagliptin	Sitagliptin	Sulfonylurea	Sulfonylurea (modified release)	Vildagliptin
Arjona et al. (2013)									-0.67 (0.81)	-0.55 (0.83)		
Wang et al. (2013)		-1.62 (0.68)		-1.70 (0.63)						-1.94 (0.76)		
Roden et al. (2013)	0.08 (0.85)								-0.66 (0.76)			
Yang et al. (2014)		-1.17 (0.68)		-1.19 (0.76)								
Erem et al. (2014)				-1.20 (0.87)		-1.18 (1.40)					-1.34 (1.39)	

Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 8: INITIAL THERAPY: HbA1c AT 6 MONTHS – relative effectiveness of all pairwise combinations

	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	repaglinide	Saxagliptin	Sitagliptin	Sulfonylurea	Sulfonylurea (modified release)	Vildagliptin
Placebo		-0.91 (-1.10, -0.73)	-0.60 (-0.88, -0.32)	-1.20 (-1.45, -0.95)	-	-0.81 (-1.08, -0.54)	-1.98 (-2.69, -1.26)	-0.54 (-0.71, -0.37)	-0.76 (-0.86, -0.67)	-1.05 (-1.33, -0.78)	-	-0.48 (-0.73, -0.23)
Acarbose	-0.85 (-1.02, -0.69)		-	-0.01 (-0.11, 0.09)	-	-0.68 (-1.07, -0.29)	-	-	-	-0.30 (-0.68, 0.07)	-	-0.10 (-0.36, 0.16)
Linagliptin	-0.66 (-1.14, -0.18)	0.19 (-0.30, 0.69)		-0.35 (-0.59, -0.11)	-	-	-	-	-	-	-	-
Metformin	-1.04 (-1.18, -0.89)	-0.19 (-0.37, 0.00)	-0.38 (-0.85, 0.09)		0.23 (-0.24, 0.69)	0.03 (-0.15, 0.21)	-	-	0.20 (0.04, 0.36)	-0.14 (-0.26, -0.02)	-0.14 (-0.88, 0.60)	0.21 (0.03, 0.40)
Metformin (modified release)	-0.81 (-1.46, -0.19)	0.04 (-0.61, 0.68)	-0.15 (-0.94, 0.62)	0.22 (-0.40, 0.84)		-	-	-	-	-	-	-
Pioglitazone	-0.97 (-1.16, -0.79)	-0.12 (-0.33, 0.09)	-0.32 (-0.81, 0.18)	0.06 (-0.11, 0.24)	-0.16 (-0.79, 0.49)		-	-	-	-0.16 (-0.29, -0.04)	-0.16 (-1.05, 0.73)	0.30 (0.02, 0.58)
repaglinide	-1.50 (-1.93, -1.07)	-0.65 (-1.09, -0.21)	-0.84 (-1.47, -0.21)	-0.46 (-0.90, -0.03)	-0.69 (-1.44, 0.07)	-0.52 (-0.97, -0.09)		-	-	0.23 (-0.08, 0.54)	-	-
Saxagliptin	-0.54 (-1.07, -0.01)	0.31 (-0.24, 0.87)	0.12 (-0.60, 0.83)	0.50 (-0.05, 1.04)	0.27 (-0.53, 1.10)	0.44 (-0.12, 0.99)	0.96 (0.29, 1.63)		-	-	-	-
Sitagliptin	-0.85 (-1.07, -0.63)	0.00 (-0.26, 0.26)	-0.19 (-0.71, 0.32)	0.19 (-0.04, 0.42)	-0.04 (-0.69, 0.63)	0.12 (-0.14, 0.39)	0.65 (0.18, 1.12)	-0.31 (-0.88, 0.26)		0.12 (-0.07, 0.31)	-	-
Sulfonylurea	-1.12 (-1.29, -0.96)	-0.27 (-0.46, -0.09)	-0.46 (-0.95, 0.02)	-0.09 (-0.25, 0.07)	-0.31 (-0.94, 0.33)	-0.15 (-0.31, 0.02)	0.38 (-0.04, 0.79)	-0.58 (-1.14, -0.04)	-0.27 (-0.51, -0.03)		-0.10 (-0.35, 0.15)	0.45 (0.29, 0.61)
Sulfonylurea (modified release)	-1.20 (-1.68, -0.72)	-0.35 (-0.84, 0.13)	-0.54 (-1.21, 0.12)	-0.16 (-0.64, 0.31)	-0.39 (-1.16, 0.39)	-0.23 (-0.71, 0.25)	0.30 (-0.33, 0.91)	-0.66 (-1.38, 0.05)	-0.35 (-0.87, 0.16)	-0.08 (-0.54, 0.38)		-
Vildagliptin	-0.67 (-0.86, -0.48)	0.19 (-0.04, 0.41)	-0.01 (-0.51, 0.49)	0.37 (0.17, 0.57)	0.14 (-0.49, 0.80)	0.31 (0.08, 0.54)	0.83 (0.38, 1.29)	-0.13 (-0.69, 0.44)	0.18 (-0.09, 0.46)	0.46 (0.24, 0.67)	0.54 (0.04, 1.04)	

Values given are mean differences in HbA1c in percentage-points.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 5: INITIAL THERAPY: HbA1c AT 6 MONTHS – relative effect of all options versus reference treatment

Table 9: INITIAL THERAPY: HbA1c AT 6 MONTHS – rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.000	12 (11, 12)
Acarbose	0.000	7 (5, 9)
Linagliptin	0.002	9 (3, 11)
Metformin	0.002	4 (2, 6)
Metformin (modified release)	0.027	8 (1, 11)
Pioglitazone	0.000	5 (3, 8)
repaglinide	0.797	1 (1, 3)
Saxagliptin	0.002	10 (4, 11)
Sitagliptin	0.000	7 (4, 10)
Sulfonylurea	0.010	3 (2, 5)
Sulfonylurea (modified release)	0.160	2 (1, 8)
Vildagliptin	0.000	9 (7, 11)

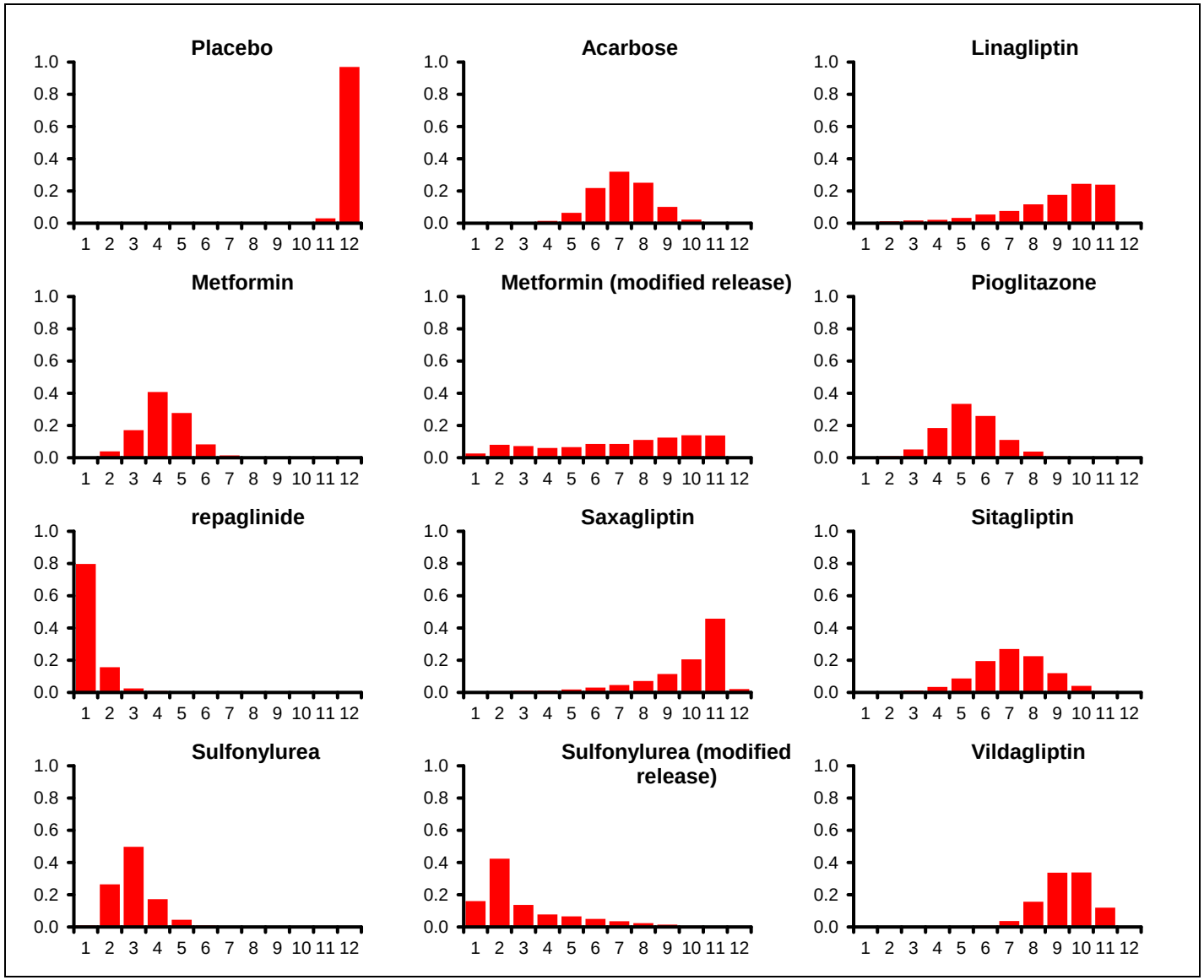


Figure 6: INITIAL THERAPY: HbA1c AT 6 MONTHS – rank probability histograms

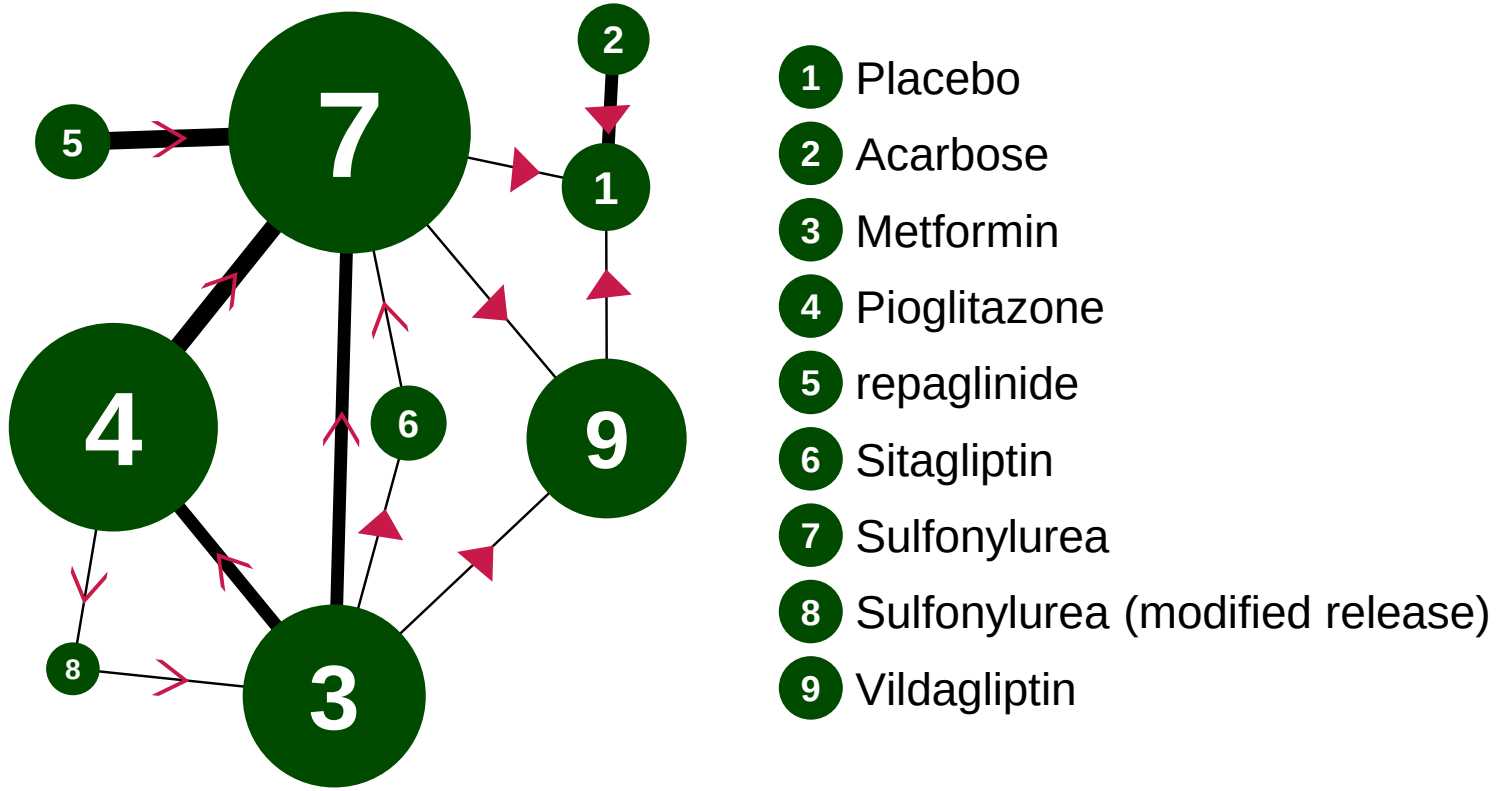
Table 10: INITIAL THERAPY: HbA1c AT 6 MONTHS – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
150.1 (compared to 152 datapoints)	-209.086	-331.383	122.297	-86.788	0.248 (95%CI: 0.193, 0.315)

Table 11: INITIAL THERAPY: HbA1c AT 6 MONTHS – notes

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

Change in HbA1c at 12 months



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 7: INITIAL THERAPY: HbA1c AT 12 MONTHS – evidence network

Table 12: INITIAL THERAPY: HbA1c AT 12 MONTHS – input data

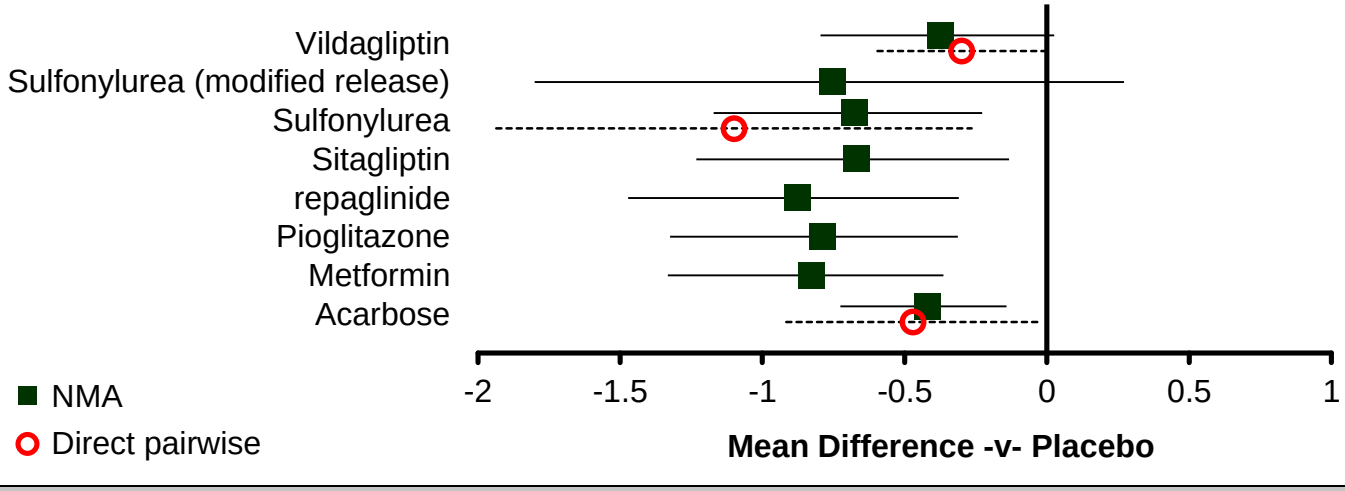
	Placebo	Acarbose	Metformin	Pioglitazone	repaglinide	Sitagliptin	Sulfonylurea	Sulfonylurea (modified release)	Vildagliptin
Foley & (2009)							-1.49 (2.14)		-1.20 (1.86)
Goldstein et al. (2007)			-1.16 (1.15)			-0.80 (1.05)			
Schweizer et al. (2007)			-1.40 (1.58)						-1.00 (2.26)
Jain et al. (2006)				-2.07 (1.19)			-2.02 (1.58)		
Kirkman et al. (2006)	-0.10 (0.81)	-0.19 (0.92)							
Yoon et al. (2011)			-0.92 (0.96)				-0.89 (0.76)		
Derosa et al. (2003)					-1.20 (1.28)		-1.10 (1.42)		
Scherbaum et al. (2008)	0.10 (1.22)								-0.20 (1.25)
Abbatecola et al. (2006)					-0.75 (1.12)		-0.50 (1.84)		
Marbury et al. (1999)					-1.30 (1.41)		-1.10 (1.47)		
Schernthaner et al. (2004)			-1.50 (0.97)	-1.41 (0.97)					
Campbell et al. (1994)			-2.82 (2.15)				-2.03 (2.68)		
Yamanouchi et al. (2005)			-2.10 (1.15)	-2.30 (1.21)			-2.10 (1.08)		
Chiasson et al. (1994)	0.40 (1.09)	-0.50 (1.54)							
Birkeland et al. (1994)	0.45 (1.30)						-0.65 (1.51)		
Charbonnel et al. (2005)				-1.50 (1.42)			-1.40 (1.48)		
Nakamura et al. (2004)				-1.70 (1.55)			-1.50 (1.68)		
Josse et al. (2003)	0.30 (0.99)	-0.30 (0.96)							
Saleem et al. (2011)					-1.10 (2.20)		-0.80 (2.07)		
Arjona et al. (2013)						-0.80 (0.59)	-0.60 (1.22)		
Erem et al. (2014)			-1.22 (1.20)	-1.57 (1.73)				-1.28 (1.67)	

Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 13: INITIAL THERAPY: HbA1c AT 12 MONTHS – relative effectiveness of all pairwise combinations

	Placebo	Acarbose	Metformin	Pioglitazone	repaglinide	Sitagliptin	Sulfonylurea	Sulfonylurea (modified release)	Vildagliptin
Placebo		-0.47 (-0.92, -0.03)	-	-	-	-	-1.10 (-1.94, -0.26)	-	-0.30 (-0.60, 0.00)
Acarbose	-0.42 (-0.73, -0.14)		-	-	-	-	-	-	-
Metformin	-0.83 (-1.33, -0.36)	-0.41 (-0.98, 0.16)		0.07 (-0.04, 0.18)	-	0.36 (0.12, 0.61)	0.04 (-0.16, 0.24)	-0.06 (-0.98, 0.86)	0.40 (0.12, 0.68)
Pioglitazone	-0.79 (-1.33, -0.31)	-0.37 (-0.97, 0.20)	0.04 (-0.22, 0.27)		-	-	0.09 (-0.04, 0.22)	0.29 (-0.79, 1.37)	-
repaglinide	-0.87 (-1.47, -0.31)	-0.45 (-1.11, 0.20)	-0.05 (-0.46, 0.36)	-0.08 (-0.49, 0.34)		-	0.19 (-0.09, 0.48)	-	-
Sitagliptin	-0.67 (-1.23, -0.13)	-0.25 (-0.87, 0.37)	0.16 (-0.15, 0.47)	0.12 (-0.21, 0.49)	0.20 (-0.26, 0.69)		0.20 (-0.02, 0.42)	-	-
Sulfonylurea	-0.68 (-1.17, -0.23)	-0.26 (-0.82, 0.29)	0.15 (-0.08, 0.38)	0.11 (-0.10, 0.35)	0.20 (-0.15, 0.54)	0.00 (-0.33, 0.30)		-	0.29 (0.01, 0.57)
Sulfonylurea (modified release)	-0.75 (-1.80, 0.27)	-0.33 (-1.42, 0.74)	0.08 (-0.85, 1.00)	0.04 (-0.91, 0.98)	0.13 (-0.88, 1.13)	-0.08 (-1.07, 0.89)	-0.07 (-1.02, 0.86)		-
Vildagliptin	-0.37 (-0.80, 0.03)	0.05 (-0.45, 0.56)	0.46 (0.13, 0.79)	0.41 (0.07, 0.81)	0.50 (0.04, 0.98)	0.30 (-0.13, 0.71)	0.30 (-0.01, 0.63)	0.37 (-0.59, 1.37)	

Values given are mean differences in HbA1c in percentage-points.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 8: INITIAL THERAPY: HbA1c AT 12 MONTHS – relative effect of all options versus reference treatment

Table 14: INITIAL THERAPY: HbA1c AT 12 MONTHS – rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.000	9 (8, 9)
Acarbose	0.023	7 (2, 8)
Metformin	0.159	3 (1, 5)
Pioglitazone	0.086	3 (1, 6)
repaglinide	0.364	2 (1, 6)
Sitagliptin	0.030	5 (1, 8)
Sulfonylurea	0.002	5 (3, 7)
Sulfonylurea (modified release)	0.335	4 (1, 9)
Vildagliptin	0.001	7 (5, 8)

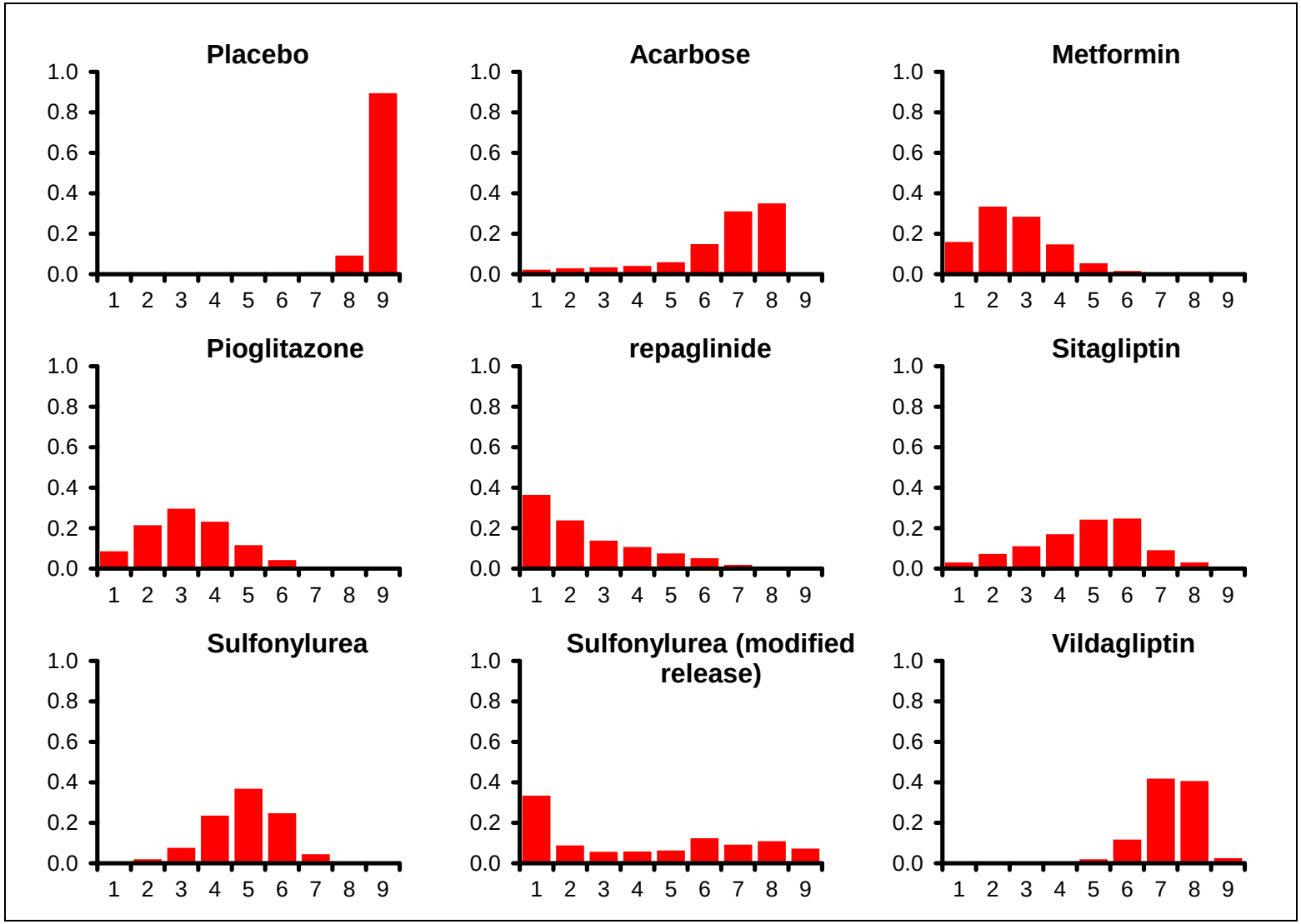


Figure 9: INITIAL THERAPY: HbA1c AT 12 MONTHS – rank probability histograms

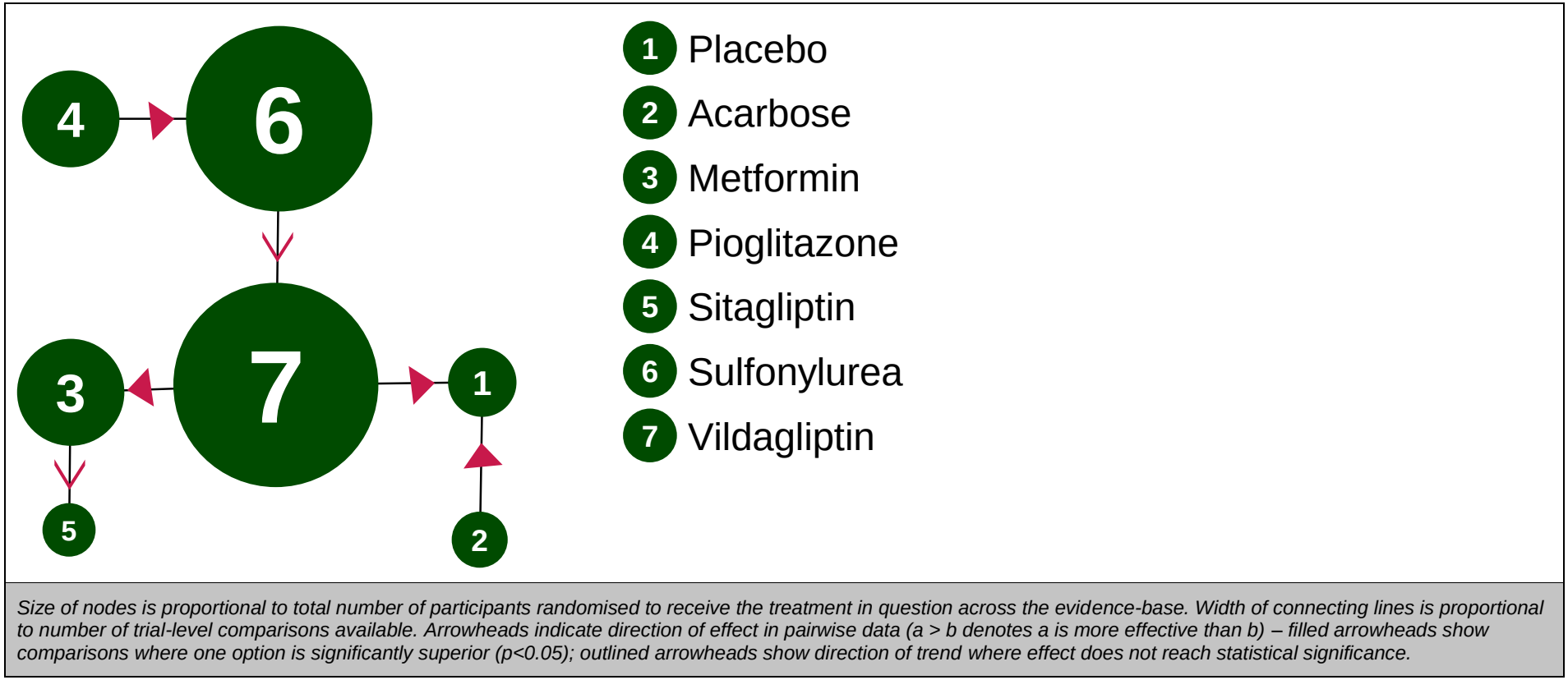
Table 15: INITIAL THERAPY: HbA1c AT 12 MONTHS – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
44.75 (compared to 46 datapoints)	-44.572	-80.181	35.608	-8.964	0.155 (95%CI: 0.021, 0.328)

Table 16: INITIAL THERAPY: HbA1c AT 12 MONTHS – notes

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 200000)

Change in HbA1c at 24 months



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 10: INITIAL THERAPY: HbA1c AT 24 MONTHS – evidence network

Table 17: INITIAL THERAPY: HbA1c AT 24 MONTHS – input data

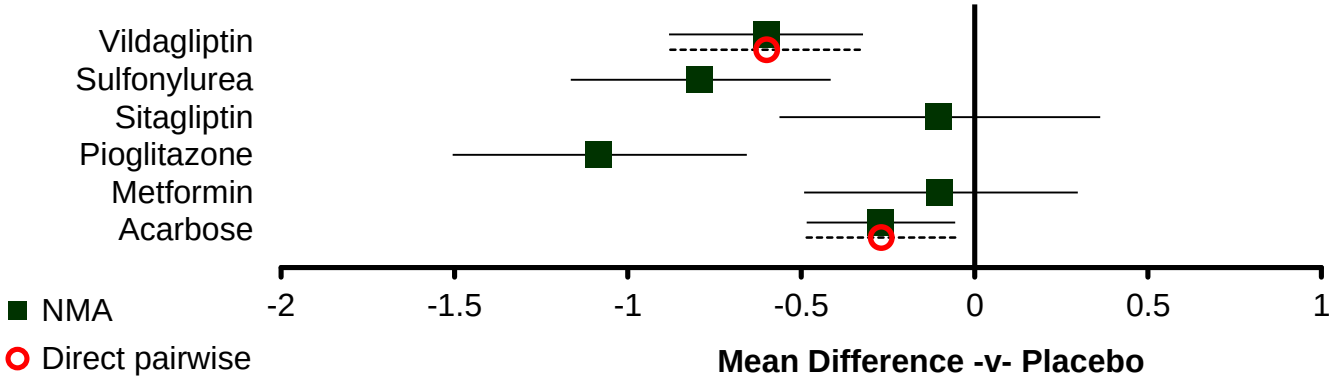
	Placebo	Acarbose	Metformin	Pioglitazone	Sitagliptin	Sulfonylurea	Vildagliptin
Foley & (2009)						-0.89 (1.76)	-0.70 (1.78)
Goldstein et al. (2007)			-1.22 (0.90)		-1.20 (0.72)		
Schweizer et al. (2007)			-1.00 (1.26)				-1.50 (1.75)
Kirkman et al. (2006)	-0.06 (0.63)	-0.33 (0.59)					
Scherbaum et al. (2008)	0.50 (0.78)						-0.10 (0.82)
Charbonnel et al. (2005)				-1.25 (1.15)		-0.96 (1.22)	

Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 18: INITIAL THERAPY: HbA1c AT 24 MONTHS – relative effectiveness of all pairwise combinations

	Placebo	Acarbose	Metformin	Pioglitazone	Sitagliptin	Sulfonylurea	Vildagliptin
Placebo		-0.27 (-0.48, -0.06)	-	-	-	-	-0.60 (-0.88, -0.32)
Acarbose	-0.27 (-0.48, -0.06)		-	-	-	-	-
Metformin	-0.10 (-0.49, 0.30)	0.17 (-0.28, 0.62)		-	0.02 (-0.23, 0.26)	-	-0.50 (-0.78, -0.22)
Pioglitazone	-1.08 (-1.51, -0.66)	-0.81 (-1.28, -0.33)	-0.98 (-1.40, -0.56)		-	0.29 (0.09, 0.49)	-
Sitagliptin	-0.10 (-0.56, 0.36)	0.17 (-0.34, 0.68)	0.00 (-0.25, 0.25)	0.98 (0.49, 1.47)		-	-
Sulfonylurea	-0.79 (-1.17, -0.42)	-0.52 (-0.95, -0.09)	-0.69 (-1.06, -0.32)	0.29 (0.09, 0.49)	-0.69 (-1.13, -0.25)		0.19 (-0.05, 0.43)
Vildagliptin	-0.60 (-0.88, -0.32)	-0.33 (-0.68, 0.02)	-0.50 (-0.78, -0.22)	0.48 (0.16, 0.80)	-0.50 (-0.87, -0.13)	0.19 (-0.05, 0.44)	

Values given are mean differences in HbA1c in percentage-points.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist FE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 11: INITIAL THERAPY: HbA1c AT 24 MONTHS – relative effect of all options versus reference treatment

Table 19: INITIAL THERAPY: HbA1c AT 24 MONTHS – rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.000	7 (5, 7)
Acarbose	0.000	4 (3, 6)
Metformin	0.000	6 (4, 7)
Pioglitazone	0.996	1 (1, 1)
Sitagliptin	0.000	6 (4, 7)
Sulfonylurea	0.002	2 (2, 3)
Vildagliptin	0.001	3 (2, 4)

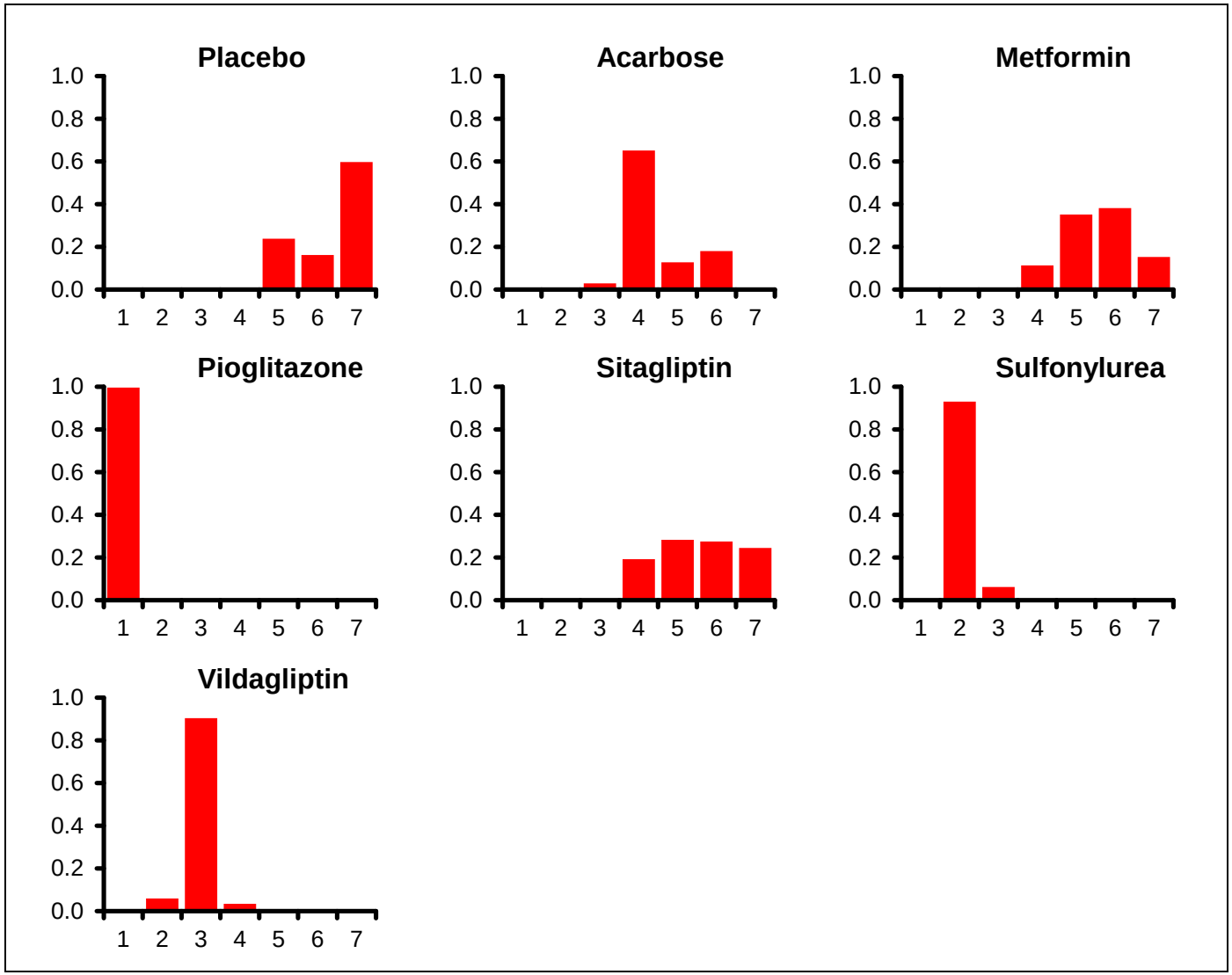


Figure 12: INITIAL THERAPY: HbA1c AT 24 MONTHS – rank probability histograms

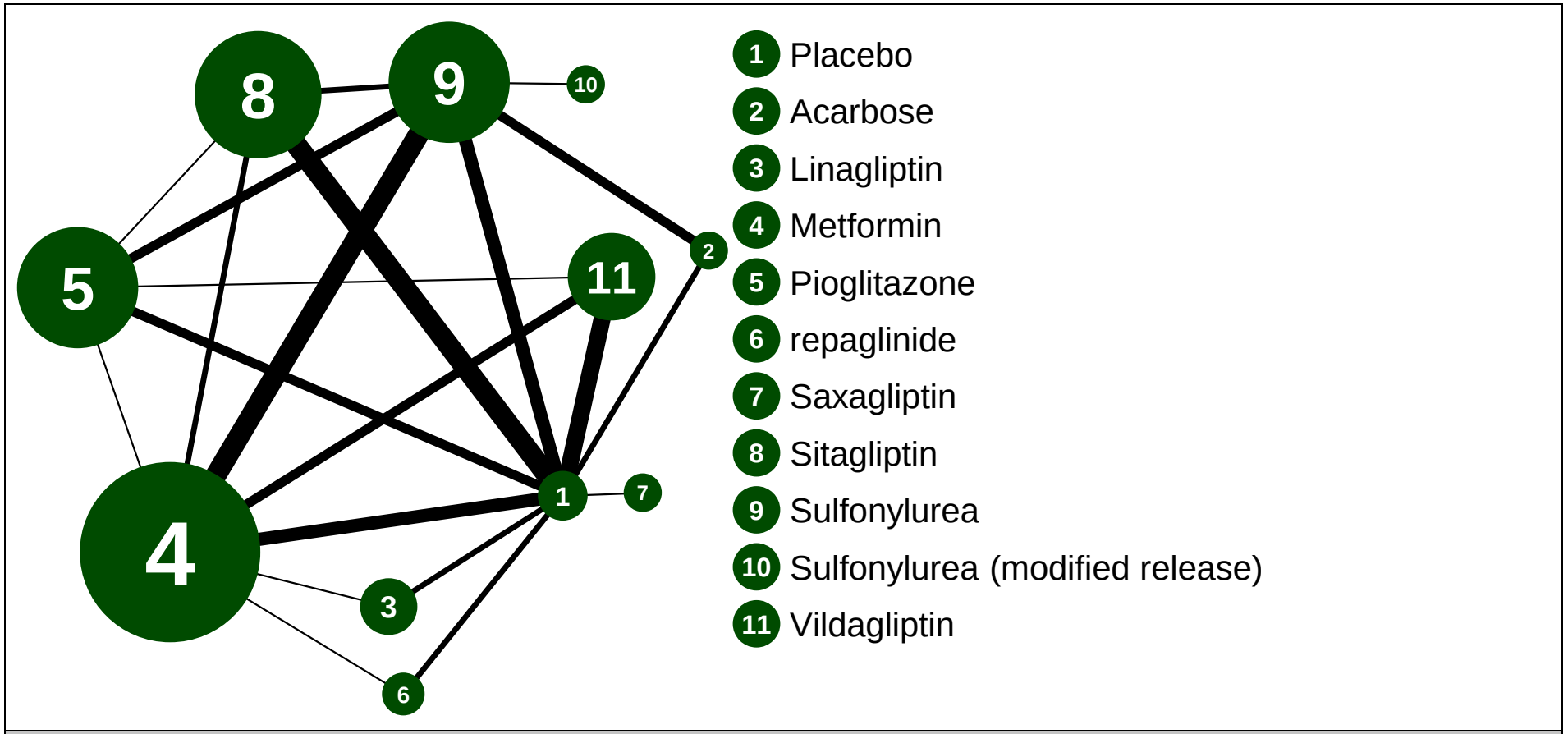
Table 20: INITIAL THERAPY: HbA1c AT 24 MONTHS – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	
13.95 (compared to 13 datapoints)	-24.809	-36.833	12.024	-12.784	

Table 21: INITIAL THERAPY: HbA1c AT 24 MONTHS – notes

- Continuous (normal; identity link); fixed effects
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

J.2.1.2 Hypoglycaemia at study endpoint



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 13: INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – evidence network

Table 22: INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – input data

	Placebo	Acarbose	Linagliptin	Metformin	Pioglitazone	repaglinide	Saxagliptin	Sitagliptin	Sulfonylurea	Sulfonylurea (modified release)	Vildagliptin
Dichotomous proportion data											
Schweizer et al. (2009) - 0.46yr				2/165							0/167
Goldstein et al. (2007) - 1.99yr				7/364				2/179			
Schweizer et al. (2007) - 1.99yr				0/158							1/304
Scott et al. (2007) - 0.23yr	3/125							12/495	21/123		
Yoon et al. (2011) - 0.92yr				4/114					23/118		
Haak et al. (2012) - 0.46yr	1/72		0/142	7/291							
Pan et al. (2012) - 0.46yr	2/284						5/284				
Shihara et al. (2011) - 0.50yr					5/96				7/95		
Aschner et al. (2006) - 0.46yr	2/253							2/238			
Hanefeld et al. (2007) - 0.23yr	0/111							5/441			
Dejager et al. (2007) - 0.46yr	0/157										3/468
Iwamoto et al. (2010) - 0.23yr	2/73							7/222			
Kikuchi et al. (2009) - 0.23yr	1/72										5/219
Rosenstock et al. (2007) - 0.46yr					1/161						1/153
Pratley et al. (2006) - 0.23yr	0/28										1/70
Ristic et al. (2005) - 0.23yr	3/56										14/220
Scherbaum et al. (2008) - 2.07yr	2/150										0/156
Herz et al. (2003) - 0.31yr	11/96				21/191						
Horton et al. (2000) - 0.46yr	3/104			11/104							
Jovanovic et al. (2000) - 0.46yr	8/75					89/286					
Schernthaner et al. (2004) - 0.52yr									15/156	7/133	
Aronoff et al. (2000) - 0.50yr	0/79				4/329						
Raz et al. (2006) - 0.34yr	0/110							3/205			
Collier et al. (1989) - 0.46yr				0/12					2/12		

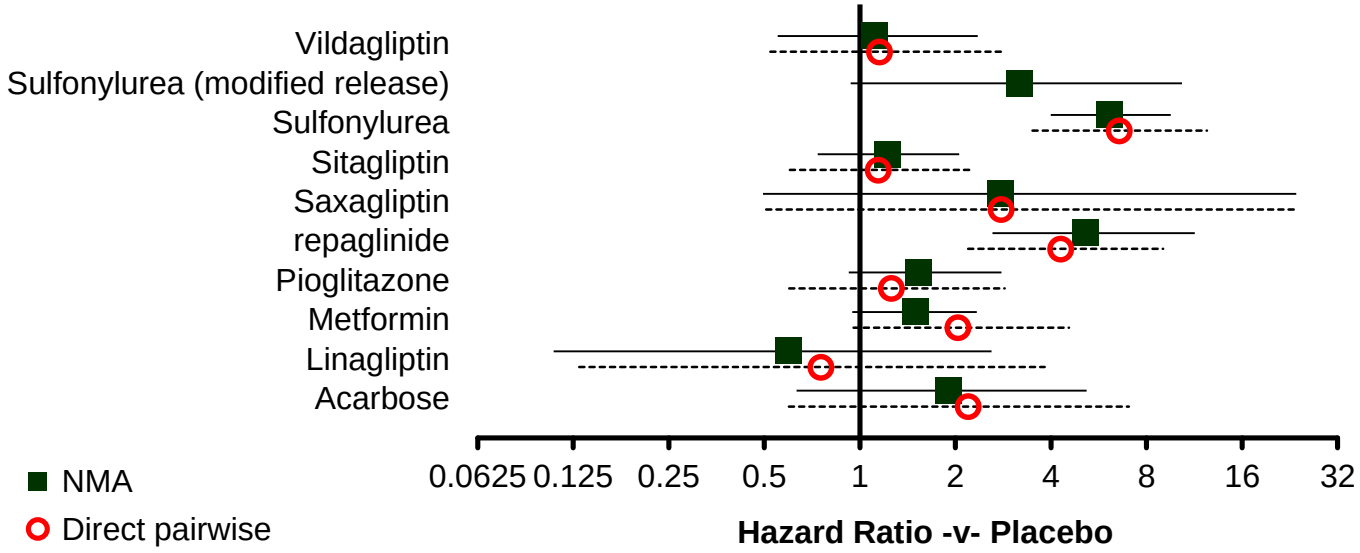
	Placebo	Acarbose	Linagliptin	Metformin	Pioglitazone	repaglinide	Saxagliptin	Sitagliptin	Sulfonylurea	Sulfonylurea (modified release)	Vildagliptin
Tessier et al. (1999) - 0.46yr				3/18					8/18		
Hermann et al. (1994) - 0.46yr				8/38					12/34		
Chiasson & (2001) - 0.69yr	7/83			8/83							
Coniff et al. (1995) - 0.46yr	4/72	6/74							11/71		
Hoffmann & (1994) - 0.46yr	0/30	0/28							2/27		
Johnston et al. (1998) - 1.07yr	8/101								48/104		
Salman et al. (2001) - 0.46yr		0/27							3/30		
Viberti et al. (2002) - 3.99yr				168/1454					557/1441		
Charbonnel et al. (2005) - 1.00yr					22/624				63/626		
Moses et al. (2001) - 0.31yr	4/134					44/260					
Ferrannini et al. (2013) - 0.23yr	1/82			1/80							
Arjona et al. (2013) - 1.03yr								13/210	36/212		
Alba et al. (2013) - 0.23yr	0/53				2/54			0/52			
Count data											
Bosi et al. (2009) - 0.46yr				2/45276							2/45780
Jain et al. (2006) - 1.07yr					24/75460				176/74284		
Bruce et al. (2006) - 0.38yr				0/2030					13/2240		
Aschner et al. (2010) - 0.46yr				23/81396				17/83580			
Barnett et al. (2012) - 0.34yr	0/8820		2/18144								
Genovese et al. (2013) - 0.31yr				0/3080	4/2968						
Fang et al. (2014) - 0.29yr				0/2100		10/4147.5					

Values given are number of events / number of participants (for dichotomous proportion data) and number of events / total patient-days (for count data). Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 23: INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations

	Placebo	Acarbose	Linagliptin	Metformin	Pioglitazone	repaglinide	Saxagliptin	Sitagliptin	Sulfonylurea	Sulfonylurea (modified release)	Vildagliptin
Placebo		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Acarbose	1.91 (0.63, 5.18)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Linagliptin	0.60 (0.11, 2.60)	0.31 (0.04, 1.89)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Metformin	1.50 (0.95, 2.33)	0.78 (0.29, 2.32)	2.50 (0.59, 13.91)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Pioglitazone	1.54 (0.92, 2.79)	0.81 (0.29, 2.62)	2.60 (0.58, 15.21)	1.02 (0.62, 1.93)		N/A	N/A	N/A	N/A	N/A	N/A
repaglinide	5.16 (2.62, 11.36)	2.72 (0.82, 10.42)	8.75 (1.71, 55.99)	3.45 (1.58, 8.33)	3.36 (1.38, 8.31)		N/A	N/A	N/A	N/A	N/A
Saxagliptin	2.78 (0.50, 23.69)	1.48 (0.20, 16.13)	4.84 (0.45, 73.85)	1.86 (0.31, 16.44)	1.81 (0.29, 16.34)	0.54 (0.08, 5.13)		N/A	N/A	N/A	N/A
Sitagliptin	1.23 (0.74, 2.06)	0.65 (0.23, 1.98)	2.05 (0.46, 11.93)	0.82 (0.50, 1.35)	0.80 (0.41, 1.43)	0.24 (0.09, 0.55)	0.44 (0.05, 2.71)		N/A	N/A	N/A
Sulfonylurea	6.13 (3.99, 9.55)	3.21 (1.26, 9.16)	10.28 (2.37, 57.94)	4.08 (2.86, 6.10)	4.00 (2.38, 6.08)	1.19 (0.49, 2.60)	2.20 (0.25, 13.25)	4.98 (3.15, 8.02)		N/A	N/A
Sulfonylurea (modified release)	3.19 (0.94, 10.35)	1.68 (0.38, 7.60)	5.31 (0.80, 41.45)	2.11 (0.64, 6.93)	2.07 (0.57, 6.59)	0.61 (0.14, 2.33)	1.11 (0.10, 9.55)	2.58 (0.75, 8.67)	0.52 (0.16, 1.56)		N/A
Vildagliptin	1.12 (0.55, 2.35)	0.59 (0.18, 2.10)	1.88 (0.38, 11.61)	0.75 (0.35, 1.65)	0.72 (0.30, 1.72)	0.22 (0.07, 0.59)	0.40 (0.04, 2.74)	0.91 (0.40, 2.16)	0.18 (0.08, 0.41)	0.36 (0.09, 1.44)	

Values given are hazard ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.



Values greater than 1 favour placebo; values less than 1 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 14: INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effect of all options versus reference treatment

Table 24: INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.100	3 (1, 5)
Acarbose	0.032	7 (1, 10)
Linagliptin	0.663	1 (1, 8)
Metformin	0.002	6 (3, 8)
Pioglitazone	0.005	6 (2, 8)
repaglinide	0.000	10 (8, 11)
Saxagliptin	0.052	8 (1, 11)
Sitagliptin	0.033	4 (1, 7)
Sulfonylurea	0.000	10 (9, 11)
Sulfonylurea (modified release)	0.008	8 (3, 11)
Vildagliptin	0.106	3 (1, 8)

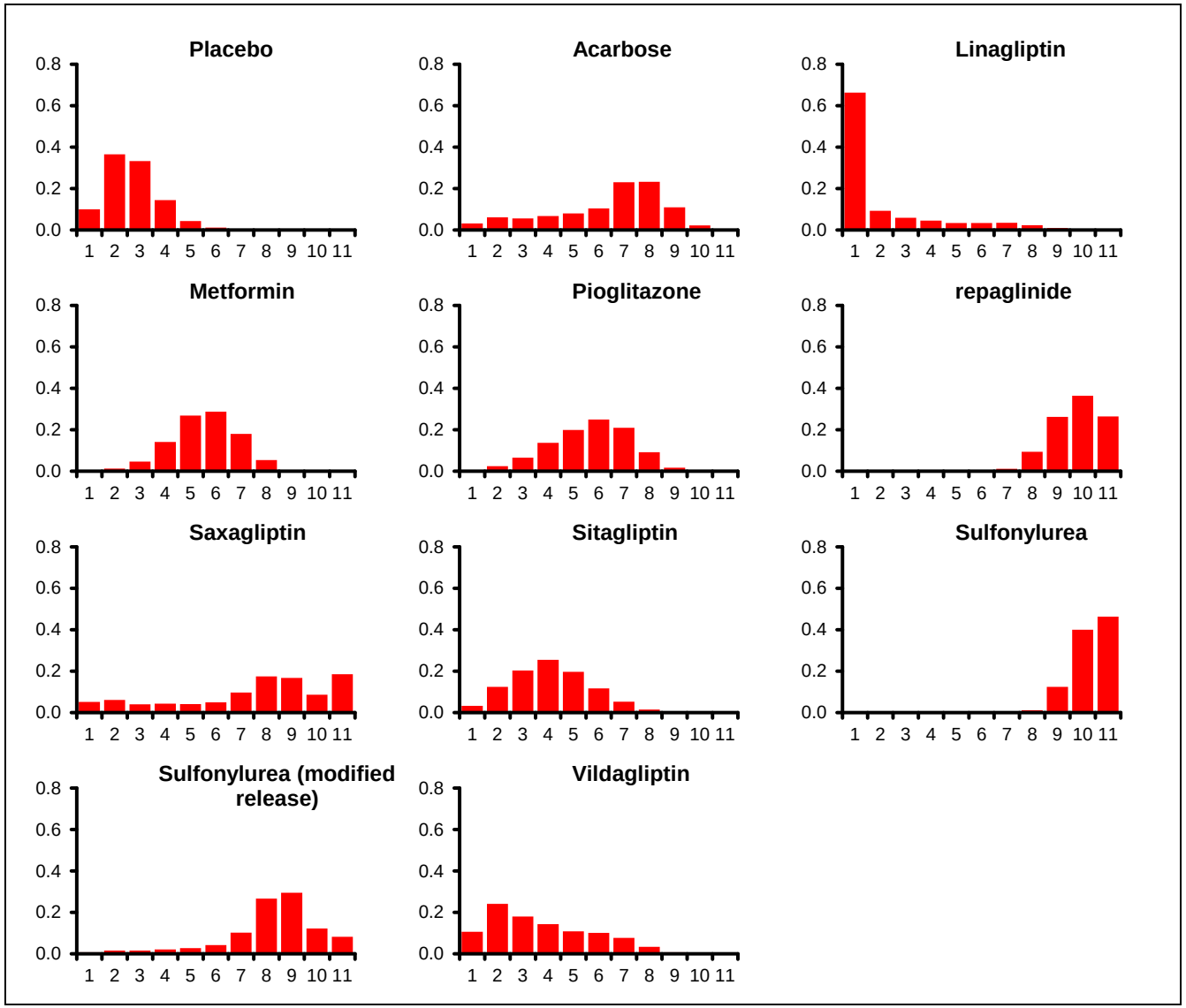


Figure 15: INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – rank probability histograms

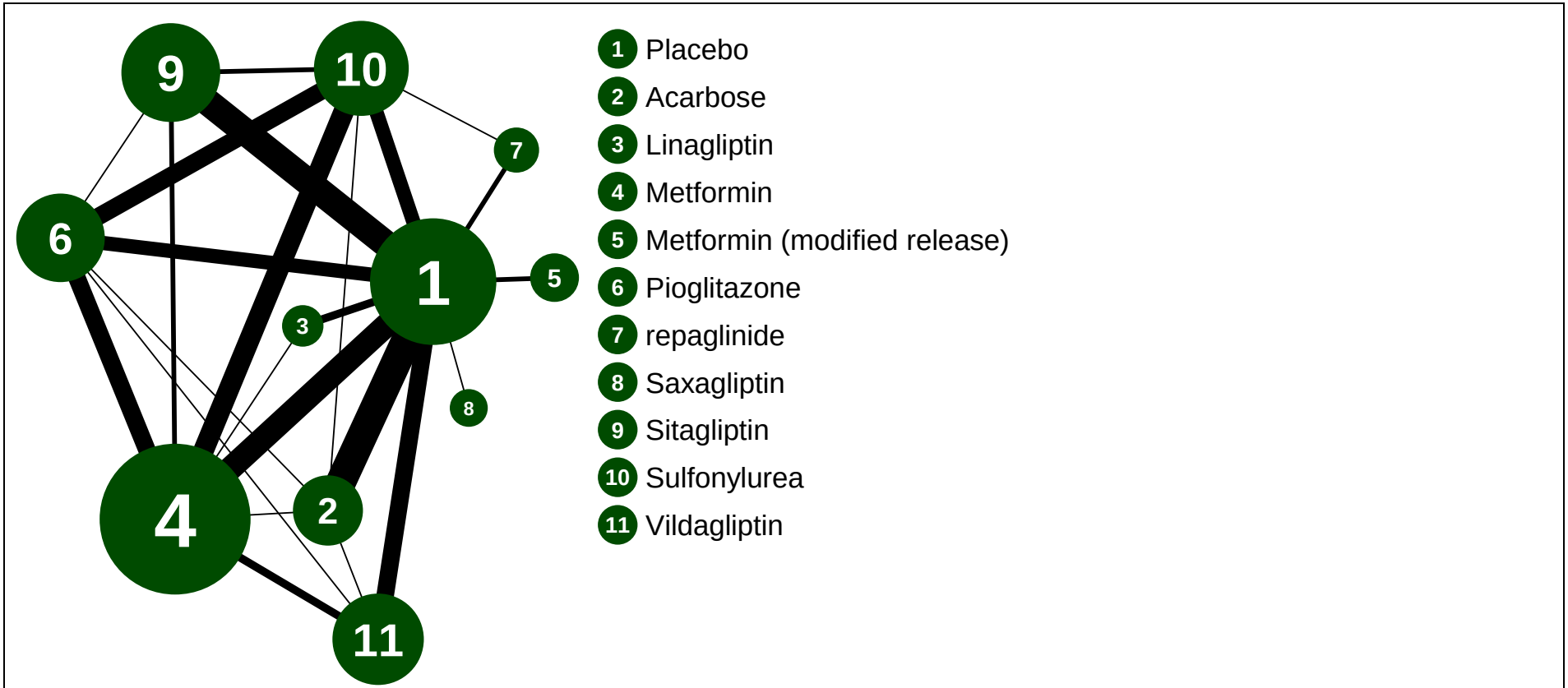
Table 25: INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
102.4 (compared to 112 datapoints)	382.848	329.618	53.23	512.811	0.305 (95%CI: 0.072, 0.582)

Table 26: INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – notes

- Hybrid cloglog--Poisson model for count/dichotomous data; random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

J.2.1.3 Dropouts due to adverse events at study endpoint



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 16: INITIAL THERAPY: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – evidence network

Table 27: INITIAL THERAPY: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – input data

	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	repaglinide	Saxagliptin	Sitagliptin	Sulfonylurea	Vildagliptin
Santilli et al. (2010) - 0.38yr	2/27	2/27									
Derosa et al. (2009) - 1.25yr				5/67		3/69					
Schweizer et al. (2009) - 0.46yr				13/166							6/169
Bosi et al. (2009) - 0.46yr				13/294							7/300
Pan et al. (2008) - 0.46yr		7/220									11/441
Goldstein et al. (2007) - 1.99yr				25/364					14/179		
Schweizer et al. (2007) - 1.99yr				3/158							5/304
Teramoto et al. (2007) - 0.46yr						1/46				3/46	
Scott et al. (2007) - 0.23yr	1/125								9/495	7/123	
Jain et al. (2006) - 1.07yr						14/251				25/251	
Kirkman et al. (2006) - 5.00yr	5/119	13/120									
Bruce et al. (2006) - 0.38yr				0/15						1/17	
Yoon et al. (2011) - 0.92yr				9/114						10/118	
Haak et al. (2012) - 0.46yr	3/72		6/142	10/291							
Pan et al. (2012) - 0.46yr	3/284							3/284			
Derosa et al. (2011) - 0.54yr	1/87	8/88									
Aschner et al. (2010) - 0.46yr				19/522					9/528		
Aschner et al. (2006) - 0.46yr	5/253								5/238		
Derosa et al. (2003) - 1.15yr							0/66			2/66	
Barzilai et al. (2011) - 0.46yr	3/104								5/102		
Nonaka et al. (2008) - 0.23yr	3/76								0/76		
Hanefeld et al. (2007) - 0.23yr	4/111								9/444		
Dejager et al. (2007) - 0.46yr	6/160										11/472
Kawamori et al. (2012) - 0.23yr	6/80		3/159								
Iwamoto et al. (2010) - 0.23yr	0/73								2/222		

	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	repaglinide	Saxagliptin	Sitagliptin	Sulfonylurea	Vildagliptin
Kikuchi et al. (2009) - 0.23yr	1/72										3/219
Mohan et al. (2009) - 0.34yr	4/178								6/352		
Pi-Sunyer et al. (2007) - 0.46yr	3/92										2/262
Rosenstock et al. (2007) - 0.46yr						9/161					4/154
Pratley et al. (2006) - 0.23yr	0/28										2/72
Ristic et al. (2005) - 0.23yr	3/56										11/220
Scherbaum et al. (2008) - 2.07yr	10/150										18/156
Herz et al. (2003) - 0.31yr	1/99					4/198					
Horton et al. (2000) - 0.46yr	9/172			12/178							
Jovanovic et al. (2000) - 0.46yr	12/75						21/286				
Schernthaner et al. (2004) - 1.00yr				39/597		42/597					
Fujioka et al. (2005) - 0.46yr	2/79				8/161						
Fujioka et al. (2005) - 0.31yr	1/117				17/625						
Goke (2002) - 0.50yr		5/136				1/129					
Aronoff et al. (2000) - 0.50yr	2/79					13/329					
Scherbaum et al. (2002) - 0.50yr	2/84					2/167					
Watanabe et al. (2005) - 0.50yr						2/15				1/15	
Lawrence et al. (2004) - 0.46yr				1/21		1/21				2/22	
Pavo et al. (2003) - 0.61yr				0/100		2/105					
Yamanouchi et al. (2005) - 1.00yr				0/39		2/38				0/37	
Raz et al. (2006) - 0.34yr	4/110								1/205		
Tessier et al. (1999) - 0.46yr				1/20						1/19	
Hermann et al. (1994) - 0.54yr				3/34						9/38	
DeFronzo & (1995) - 0.56yr	2/146			14/143							
H+¤llsten et al. (2002) - 0.50yr	0/14			1/16							

	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	repaglinide	Saxagliptin	Sitagliptin	Sulfonylurea	Vildagliptin
Del et al. (2003) - 0.56yr	6/144			16/284							
Chiasson & (2001) - 0.69yr	2/83			5/83							
Coniff et al. (1995) - 0.31yr	3/73	27/145									
Fischer et al. (1998) - 0.46yr	0/97	11/398									
Hotta et al. (1993) - 0.46yr	0/18	1/19									
Johnston et al. (1998) - 1.07yr	6/101									6/104	
Kovacevic et al. (1997) - 0.46yr	3/34	0/34								0/34	
Santeusanio et al. (1993) - 0.31yr	1/29	6/55									
Scott et al. (1999) - 0.31yr	4/52	4/53									
Segal et al. (1997) - 0.46yr	1/65									2/69	
Viberti et al. (2002) - 3.99yr				178/1454						215/1441	
Birkeland et al. (1994) - 5.33yr	4/16									2/30	
Charbonnel et al. (2005) - 1.99yr						33/270				25/297	
Moses et al. (2001) - 0.31yr	2/138						9/270				
Josse et al. (2003) - 1.00yr	3/99	10/93									
Kikuchi et al. (2012) - 0.54yr	1/54					14/159					
Ferrannini et al. (2013) - 0.23yr	0/82			3/80							
Fonseca et al. (2013) - 0.23yr	1/69			1/69							
Arjona et al. (2013) - 1.03yr									16/211	18/212	
Barnett et al. (2012) - 0.34yr	0/76		1/151								
Genovese et al. (2013) - 0.31yr				2/29		4/29					
Alba et al. (2013) - 0.23yr	2/53					0/54			3/52		
Yang et al. (2014) - 0.46yr		9/393		11/395							

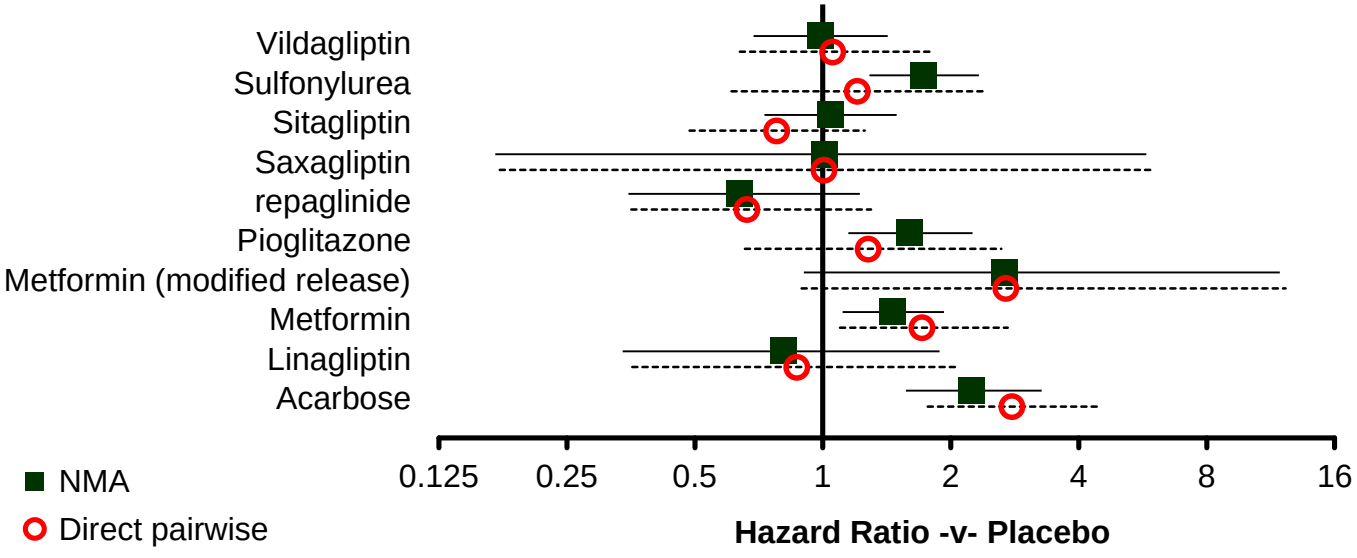
Values given are number of events / number of participants. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 28: INITIAL THERAPY: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations

	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	repaglinide	Saxagliptin	Sitagliptin	Sulfonylurea	Vildagliptin
Placebo		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Acarbose	2.24 (1.57, 3.27)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Linagliptin	0.81 (0.34, 1.88)	0.36 (0.14, 0.90)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Metformin	1.46 (1.11, 1.93)	0.65 (0.43, 0.97)	1.80 (0.77, 4.35)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Metformin (modified release)	2.67 (0.90, 11.88)	1.20 (0.38, 5.60)	3.34 (0.81, 18.41)	1.84 (0.60, 8.32)		N/A	N/A	N/A	N/A	N/A	N/A
Pioglitazone	1.61 (1.15, 2.25)	0.72 (0.45, 1.12)	1.98 (0.83, 4.93)	1.10 (0.85, 1.44)	0.60 (0.13, 1.88)		N/A	N/A	N/A	N/A	N/A
repaglinide	0.64 (0.35, 1.22)	0.28 (0.14, 0.60)	0.79 (0.28, 2.34)	0.44 (0.23, 0.88)	0.24 (0.05, 0.86)	0.40 (0.20, 0.81)		N/A	N/A	N/A	N/A
Saxagliptin	1.01 (0.17, 5.77)	0.45 (0.07, 2.66)	1.25 (0.17, 8.91)	0.70 (0.11, 4.04)	0.37 (0.04, 2.97)	0.63 (0.10, 3.71)	1.58 (0.24, 9.89)		N/A	N/A	N/A
Sitagliptin	1.04 (0.73, 1.49)	0.46 (0.29, 0.75)	1.28 (0.53, 3.24)	0.72 (0.51, 0.99)	0.39 (0.09, 1.23)	0.65 (0.44, 0.97)	1.63 (0.79, 3.27)	1.03 (0.18, 6.42)		N/A	N/A
Sulfonylurea	1.73 (1.29, 2.33)	0.77 (0.50, 1.18)	2.13 (0.90, 5.23)	1.18 (1.00, 1.40)	0.64 (0.14, 2.00)	1.07 (0.82, 1.40)	2.70 (1.35, 5.27)	1.71 (0.29,	1.65 (1.18, 2.34)		N/A

	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	repaglinide	Saxagliptin	Sitagliptin	Sulfonylurea	Vildagliptin
								10.45)			
Vildagliptin	0.99 (0.69, 1.42)	0.44 (0.28, 0.69)	1.21 (0.49, 3.12)	0.68 (0.47, 0.98)	0.37 (0.08, 1.16)	0.61 (0.41, 0.94)	1.54 (0.74, 3.14)	0.98 (0.17, 6.05)	0.95 (0.59, 1.51)	0.57 (0.38, 0.85)	

Values given are hazard ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.



Values greater than 1 favour placebo; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 17: INITIAL THERAPY: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – relative effect of all options versus reference treatment

Table 29: INITIAL THERAPY: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.004	4 (2, 6)
Acarbose	0.000	10 (8, 11)
Linagliptin	0.231	3 (1, 9)
Metformin	0.000	7 (5, 9)
Metformin (modified release)	0.003	11 (3, 11)
Pioglitazone	0.000	8 (6, 10)
repaglinide	0.462	2 (1, 6)
Saxagliptin	0.261	4 (1, 11)
Sitagliptin	0.013	5 (2, 7)
Sulfonylurea	0.000	9 (7, 10)
Vildagliptin	0.026	4 (1, 7)

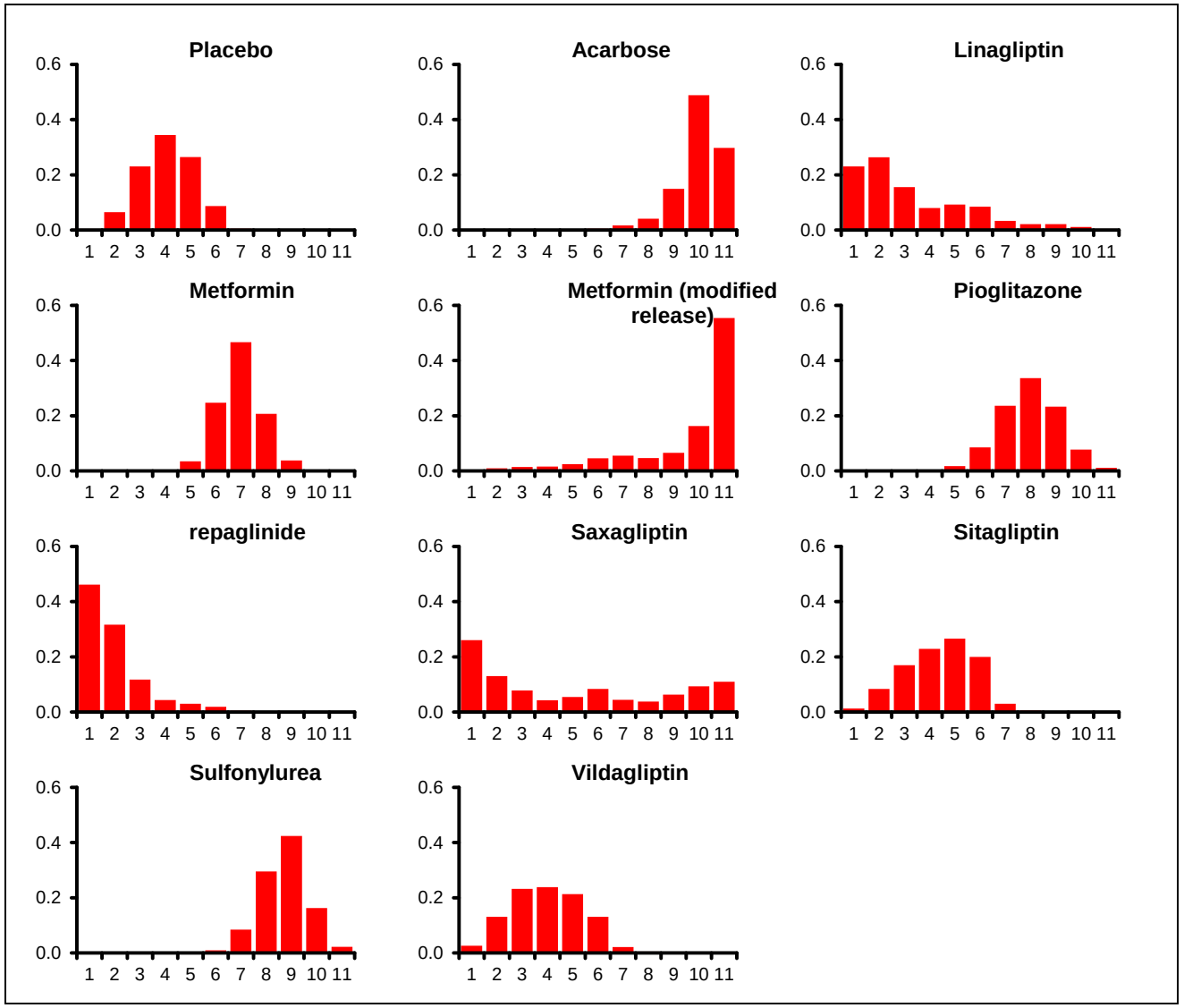


Figure 18: INITIAL THERAPY: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – rank probability histograms

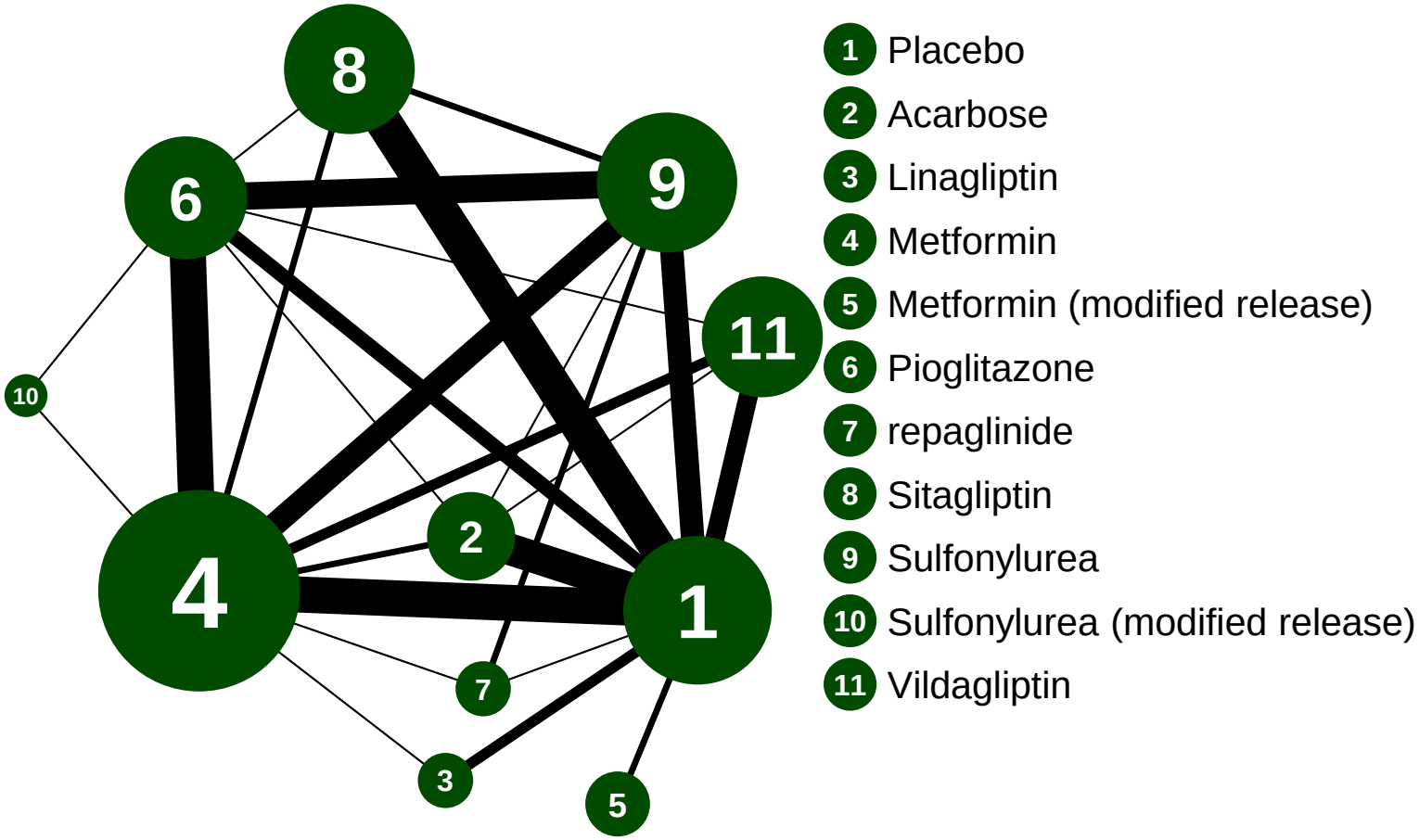
Table 30: INITIAL THERAPY: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	
201.2 (compared to 186 datapoints)	764.01	682.494	81.517	845.527	

Table 31: INITIAL THERAPY: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – notes

- Dichotomous diachronic (binomial; cloglog link); fixed effects
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

J.2.1.4 Total dropouts at study endpoint



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 19: INITIAL THERAPY: TOTAL DROPOUTS AT STUDY ENDPOINT – evidence network

Table 32: INITIAL THERAPY: TOTAL DROPOUTS AT STUDY ENDPOINT – input data

	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	repaglinide	Sitagliptin	Sulfonylurea	Sulfonylurea (modified	Vildagliptin
Esposito et al. (2011) - 0.46yr				4/55		4/55					
Santilli et al. (2010) - 0.38yr	4/27	2/27									
Schweizer et al. (2009) - 0.46yr				26/166							27/169
Bosi et al. (2009) - 0.46yr				49/294							55/300
Erdem et al. (2008) - 0.23yr				4/27		5/26					
Pan et al. (2008) - 0.46yr		28/220									42/441
Goldstein et al. (2007) - 1.03yr				102/364				57/179			
Schweizer et al. (2007) - 1.99yr				112/254							266/526
Teramoto et al. (2007) - 0.46yr						7/46			5/46		
Scott et al. (2007) - 0.23yr	17/125							52/495	23/123		
Jain et al. (2006) - 1.07yr						117/251			123/251		
Kirkman et al. (2006) - 5.00yr	51/119	64/120									
Bruce et al. (2006) - 0.38yr				1/15					2/17		
Yoon et al. (2011) - 0.92yr				43/114					36/118		
Haak et al. (2012) - 0.46yr	18/72		21/142	38/291							
Shihara et al. (2011) - 0.50yr						5/96			9/95		
Derosa et al. (2011) - 0.54yr	5/92	8/96									
Aschner et al. (2010) - 0.46yr				75/522				61/528			
Aschner et al. (2006) - 0.46yr	37/253							29/238			
Derosa et al. (2003) - 1.15yr							4/66		4/66		
Bautista et al. (2003) - 0.31yr	7/22								7/48		
Uehara et al. (2001) - 0.23yr	2/13			2/13							
Barzilai et al. (2011) - 0.46yr	47/104							32/102			

	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	repaglinide	Sitagliptin	Sulfonylurea	Sulfonylurea (modified	Vildagliptin
Nonaka et al. (2008) - 0.23yr	9/76							3/76			
Hanefeld et al. (2007) - 0.23yr	30/111							50/444			
Dejager et al. (2007) - 0.46yr	41/160										80/472
Kawamori et al. (2012) - 0.23yr	6/80		3/159								
Iwamoto et al. (2010) - 0.23yr	5/73							6/222			
Kikuchi et al. (2009) - 0.23yr	6/72										6/219
Mohan et al. (2009) - 0.34yr	45/178							46/352			
Pi-Sunyer et al. (2007) - 0.46yr	29/92										52/262
Rosenstock et al. (2007) - 0.46yr						28/161					18/154
Pratley et al. (2006) - 0.23yr	2/28										7/72
Madsbad et al. (2004) - 0.23yr	5/29								1/27		
Scherbaum et al. (2008) - 2.07yr	100/150										98/156
Herz et al. (2003) - 0.31yr	11/99					14/198					
Abbatecola et al. (2006) - 1.00yr							12/77		16/79		
Horton et al. (2000) - 0.46yr	66/172			45/178							
Schernthaner et al. (2004) - 1.00yr				96/597		98/597					
Fujioka et al. (2005) - 0.46yr	41/79				54/161						
Fujioka et al. (2005) - 0.46yr	28/117				91/625						
Goke (2002) - 0.50yr		39/136				19/129					
Scherbaum et al. (2002) - 0.50yr	19/78					30/155					
Watanabe et al. (2005) - 0.50yr						2/15			1/15		
Lawrence et al. (2004) - 0.46yr				1/21		1/21			2/22		
Pavo et al. (2003) - 0.61yr				9/100		5/105					
Yamanouchi et al. (2005) - 1.00yr				2/39		3/38			3/37		
Raz et al. (2006) - 0.34yr	19/110							17/205			

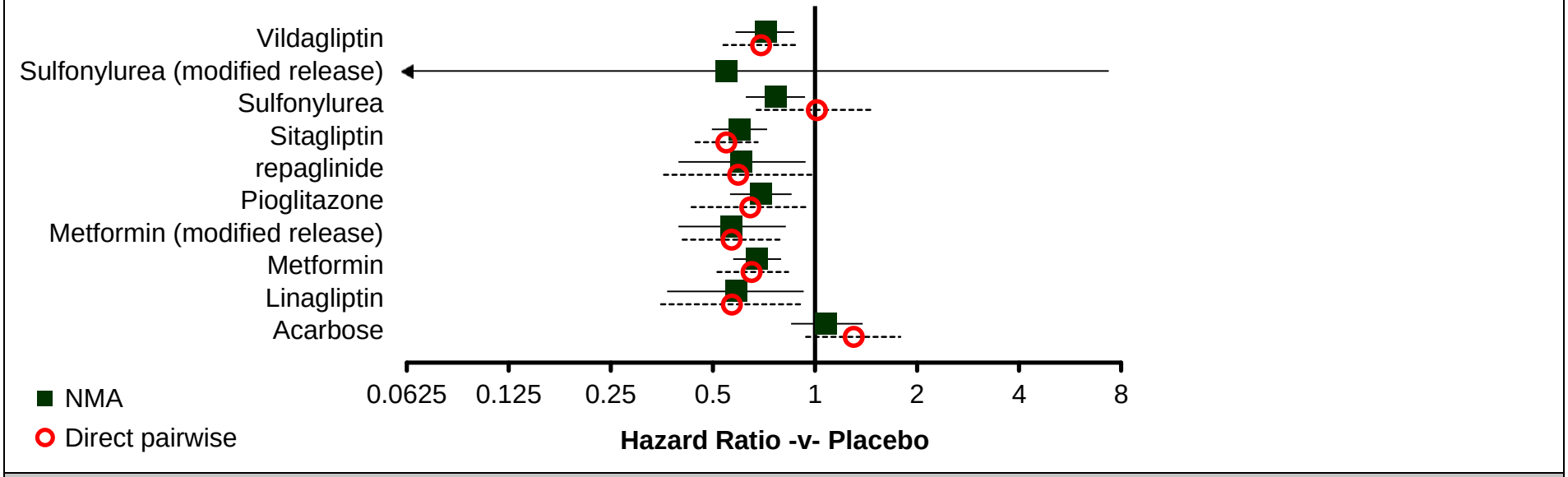
	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	repaglinide	Sitagliptin	Sulfonylurea	Sulfonylurea (modified	Vildagliptin
Tessier et al. (1999) - 0.46yr				2/20					1/19		
DeFronzo & (1995) - 0.56yr	41/146			31/143							
H+¤llsten et al. (2002) - 0.50yr	0/14			3/16							
Lee & (1998) - 0.46yr	8/24			8/24							
Del et al. (2003) - 0.56yr	36/144			45/284							
Chan et al. (1998) - 0.46yr	6/63	11/63									
Fischer et al. (1998) - 0.46yr	11/97	32/398									
Hoffmann & (1997) - 0.46yr	1/32	3/31		1/31							
Johnston et al. (1998) - 1.07yr	9/101								12/104		
Kovacevic I,Profozic V,Skrabalo Z,Cabrijan T,Zjacic-Rotkvic V,Goldoni (1997) - 0.46yr	3/34	1/34							1/34		
Segal et al. (1997) - 0.46yr	6/64								11/61		
Viberti et al. (2002) - 3.99yr				551/1454					634/1441		
Charbonnel et al. (2005) - 1.99yr						477/624			499/626		
Moses et al. (2001) - 0.31yr	41/138						51/270				
Josse et al. (2003) - 1.00yr	5/99	13/93									
Kikuchi et al. (2012) - 0.54yr	11/54					22/159					
Ferrannini et al. (2013) - 0.23yr	6/82			6/80							
Arjona et al. (2013) - 1.03yr								47/211	42/212		
Barnett et al. (2012) - 0.34yr	12/76		14/151								
Genovese et al. (2013) - 0.31yr				3/29		5/29					
Alba et al. (2013) - 0.23yr	5/53					2/54		6/52			
Yang et al. (2014) - 0.46yr		42/393		48/395							
Erem et al. (2014) - 1.00yr				1/20		1/20				1/20	
Fang et al. (2014) - 0.29yr				0/20			1/40				
Esteghamati et al. (2014) - 0.23yr				2/43		5/55					

	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	repaglinide	Sitagliptin	Sulfonylurea	Sulfonylurea (modified	Vildagliptin
Values given are number of events / number of participants. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.											

Table 33: INITIAL THERAPY: TOTAL DROPOUTS AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations

	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	repaglinide	Sitagliptin	Sulfonylurea	Sulfonylurea (modified release)	Vildagliptin
Placebo		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Acarbose	1.08 (0.85, 1.38)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Linagliptin	0.59 (0.37, 0.93)	0.54 (0.32, 0.90)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Metformin	0.67 (0.57, 0.79)	0.62 (0.48, 0.81)	1.15 (0.73, 1.86)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Metformin (modified release)	0.57 (0.40, 0.82)	0.53 (0.34, 0.81)	0.97 (0.54, 1.75)	0.84 (0.57, 1.26)		N/A	N/A	N/A	N/A	N/A	N/A
Pioglitazone	0.69 (0.56, 0.85)	0.64 (0.48, 0.85)	1.19 (0.72, 1.96)	1.03 (0.84, 1.25)	1.22 (0.80, 1.86)		N/A	N/A	N/A	N/A	N/A
repaglinide	0.61 (0.40, 0.94)	0.56 (0.34, 0.92)	1.04 (0.55, 1.94)	0.90 (0.58, 1.41)	1.06 (0.61, 1.87)	0.87 (0.55, 1.39)		N/A	N/A	N/A	N/A
Sitagliptin	0.60 (0.50, 0.72)	0.55 (0.41, 0.74)	1.03 (0.63, 1.68)	0.89 (0.72, 1.09)	1.06 (0.70, 1.58)	0.87 (0.67, 1.10)	0.99 (0.62, 1.57)		N/A	N/A	N/A
Sulfonylurea	0.77 (0.62, 0.93)	0.71 (0.53, 0.94)	1.31 (0.80, 2.16)	1.14 (0.93, 1.37)	1.34 (0.88, 2.04)	1.10 (0.91, 1.34)	1.26 (0.81, 1.96)	1.27 (1.02, 1.61)		N/A	N/A
Sulfonylurea (modified release)	0.55 (0.01, 7.35)	0.51 (0.01, 6.74)	0.93 (0.02, 12.93)	0.81 (0.02, 10.86)	0.97 (0.02, 13.39)	0.79 (0.02, 10.54)	0.90 (0.02, 12.57)	0.91 (0.02, 12.32)	0.72 (0.02, 9.68)		N/A
Vildagliptin	0.72 (0.58, 0.87)	0.66 (0.49, 0.87)	1.22 (0.75, 2.01)	1.07 (0.86, 1.29)	1.26 (0.83, 1.89)	1.04 (0.79, 1.32)	1.18 (0.74, 1.87)	1.19 (0.93, 1.53)	0.94 (0.72, 1.19)	1.30 (0.10, 49.34)	

Values given are hazard ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.



Values greater than 1 favour placebo; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 20: INITIAL THERAPY: TOTAL DROPOUTS AT STUDY ENDPOINT – relative effect of all options versus reference treatment

Table 34: INITIAL THERAPY: TOTAL DROPOUTS AT STUDY ENDPOINT – rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.000	10 (9, 11)
Acarbose	0.000	11 (9, 11)
Linagliptin	0.167	3 (1, 9)
Metformin	0.003	5 (3, 8)
Metformin (modified release)	0.173	3 (1, 9)
Pioglitazone	0.004	6 (2, 9)
repaglinide	0.125	4 (1, 9)
Sitagliptin	0.061	3 (1, 7)
Sulfonylurea	0.000	8 (5, 9)
Sulfonylurea (modified release)	0.465	2 (1, 11)
Vildagliptin	0.003	7 (3, 9)

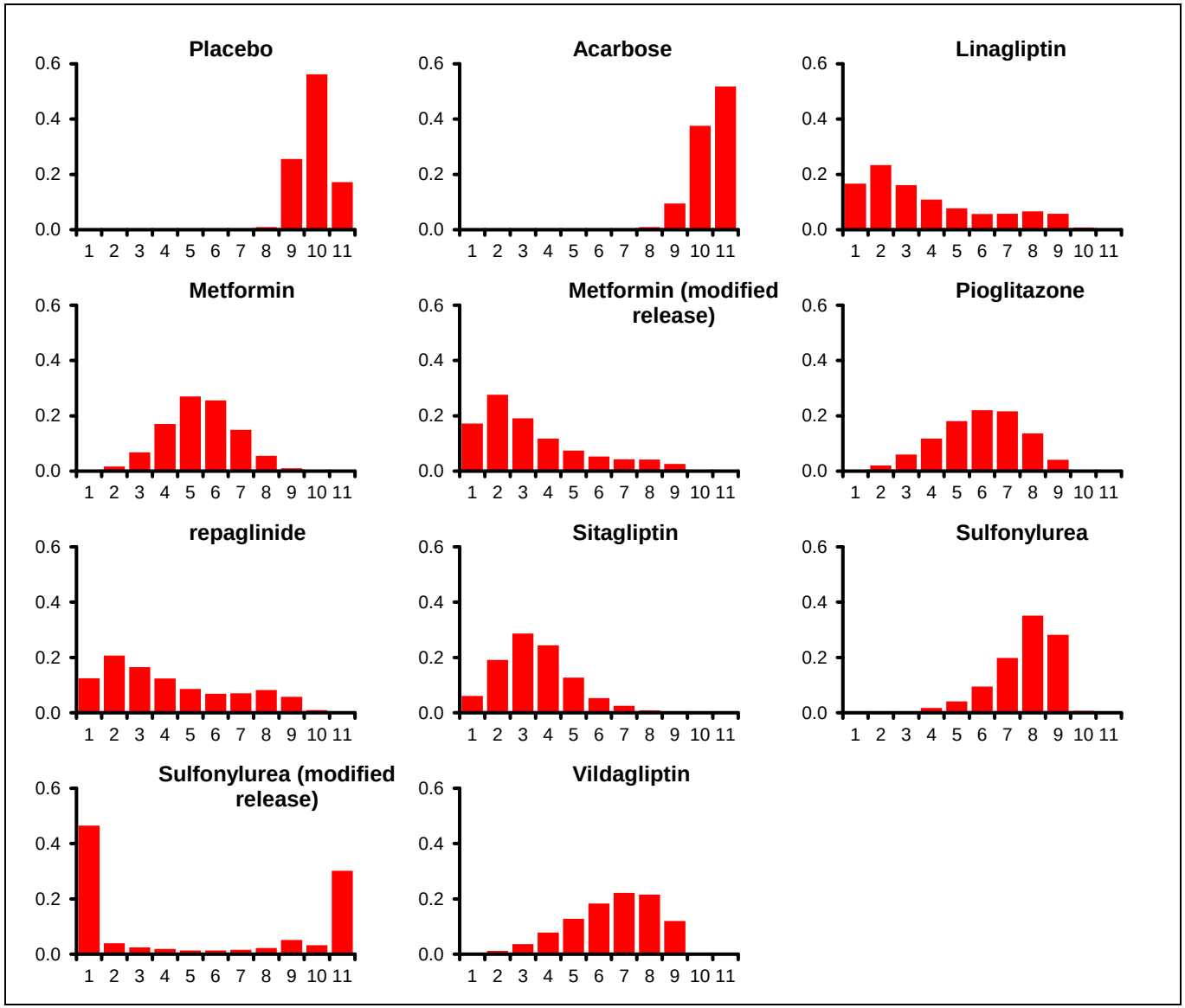


Figure 21: INITIAL THERAPY: TOTAL DROPOUTS AT STUDY ENDPOINT – rank probability histograms

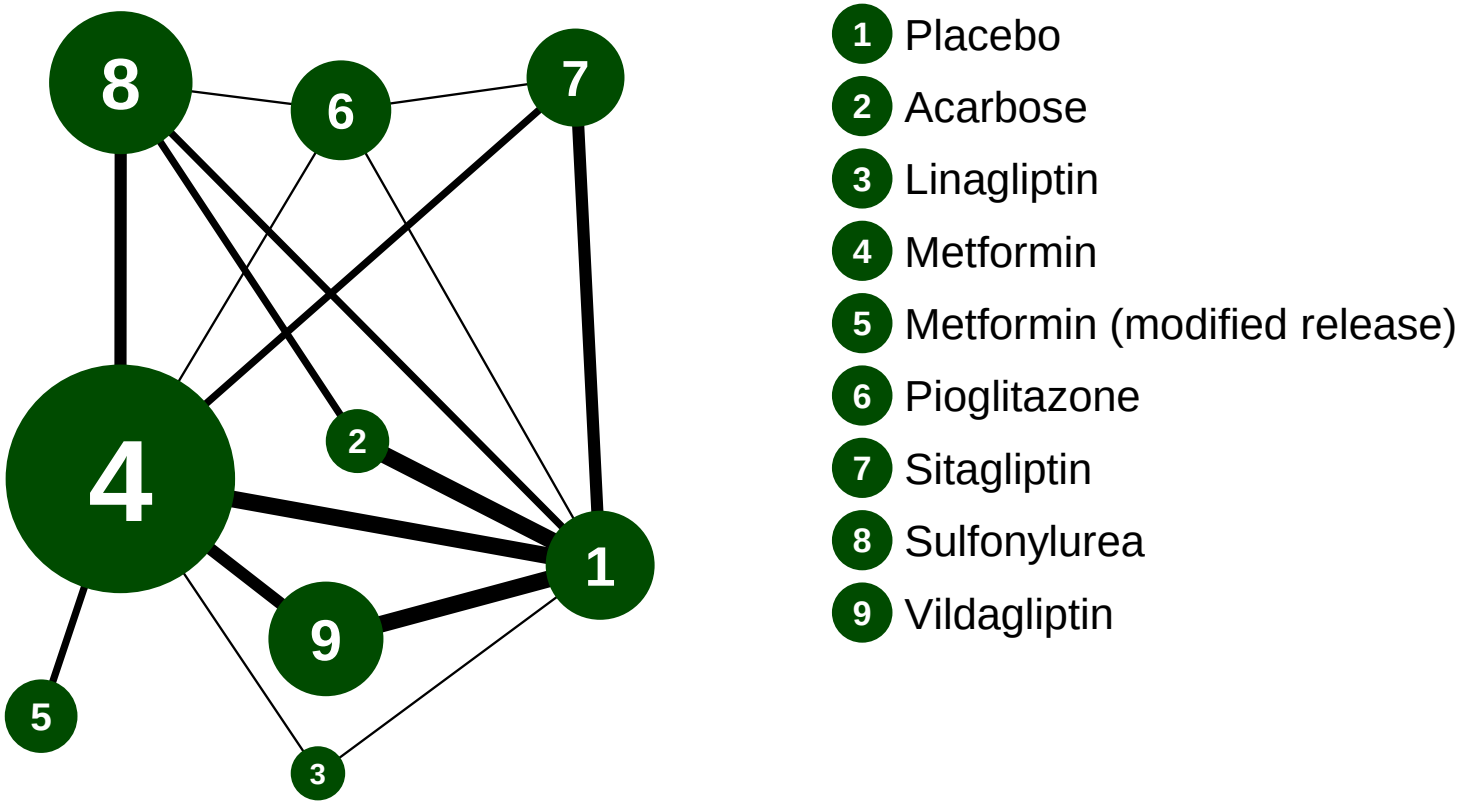
Table 35: INITIAL THERAPY: TOTAL DROPOUTS AT STUDY ENDPOINT – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
183.1 (compared to 177 datapoints)	908.143	808.597	99.546	1007.69	0.158 (95%CI: 0.023, 0.286)

Table 36: INITIAL THERAPY: TOTAL DROPOUTS AT STUDY ENDPOINT – notes

- Dichotomous diachronic (binomial; cloglog link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

J.2.1.5 Nausea at study endpoint



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 22: INITIAL THERAPY: NAUSEA AT STUDY ENDPOINT – evidence network

Table 37: INITIAL THERAPY: NAUSEA AT STUDY ENDPOINT – input data

	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	Sitagliptin	Sulfonylurea	Vildagliptin
Schweizer et al. (2009) - 0.46yr				9/165					5/167
Bosi et al. (2009) - 0.46yr				17/292					7/297
Gao et al. (2008) - 0.23yr				1/71	0/69				
Goldstein et al. (2007) - 1.99yr				25/364			2/179		
Schweizer et al. (2007) - 1.99yr				15/158					9/304
Haak et al. (2012) - 0.46yr	0/72		1/142	5/291					
Aschner et al. (2010) - 0.46yr				16/522			6/528		
Aschner et al. (2006) - 0.46yr	3/253						5/238		
Schwartz et al. (2006) - 0.46yr				19/174	45/532				
Dejager et al. (2007) - 0.46yr	6/157								9/468
Pi-Sunyer et al. (2007) - 0.46yr	0/92								1/91
Pratley et al. (2006) - 0.23yr	1/28								1/70
Ristic et al. (2005) - 0.23yr	3/56								5/220
Horton et al. (2000) - 0.46yr	4/104			10/104					
Schernthaner et al. (2004) - 1.00yr				25/597		14/597			
Raz et al. (2006) - 0.34yr	0/110						2/205		
Collier A,Watson HH,Patrick AW,Ludlam (1989) - 0.46yr				3/12				0/12	
Hermann et al. (1994) - 0.46yr				9/38				3/34	
Chiasson & (2001) - 0.69yr	2/83			14/83					
Braun D,Schonherr (1996) - 0.46yr	1/44	0/42							
Coniff et al. (1995) - 0.46yr	2/72	6/74						7/71	
Coniff et al. (1995) - 0.31yr	0/73	10/145							
Johnston et al. (1998) - 1.07yr	5/101							6/104	
Salman S,Salman F,Satman I,Yilmaz Y,Ozer E,Sengul (2001) - 0.46yr		1/27						0/30	
Viberti et al. (2002) - 3.99yr				170/1454				99/1441	

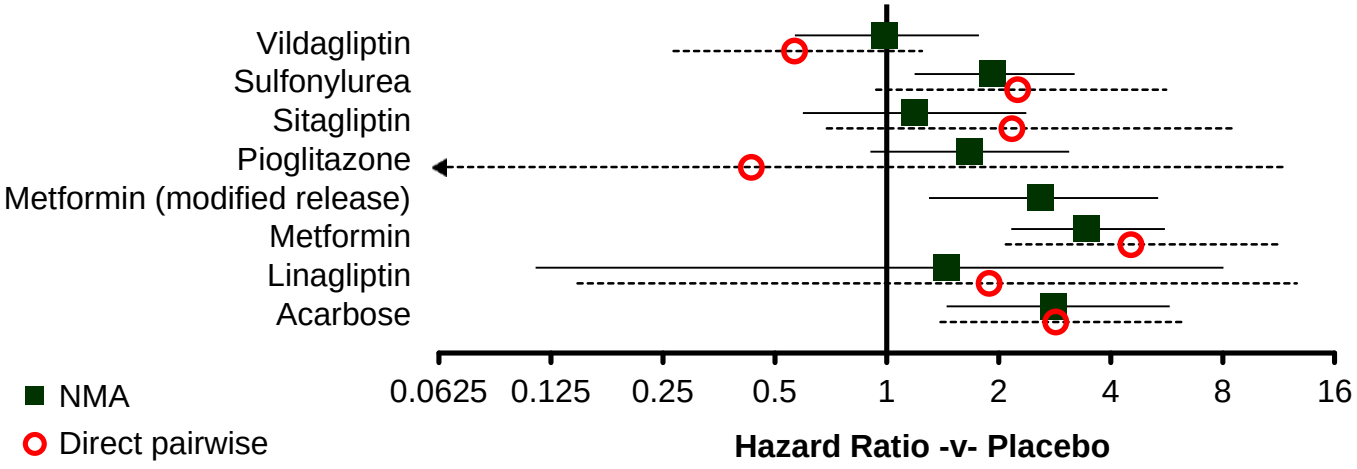
	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	Sitagliptin	Sulfonylurea	Vildagliptin
Charbonnel et al. (2005) - 1.00yr						27/620		32/618	
Josse et al. (2003) - 1.00yr	3/99	10/93							
Ferrannini et al. (2013) - 0.23yr	0/82			3/80					
Alba et al. (2013) - 0.23yr	0/53					0/54	1/52		

Values given are number of events / number of participants. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 38: INITIAL THERAPY: NAUSEA AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations

	Placebo	Acarbose	Linagliptin	Metformin	Metformin (modified release)	Pioglitazone	Sitagliptin	Sulfonylurea	Vildagliptin
Placebo		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Acarbose	2.82 (1.45, 5.76)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Linagliptin	1.45 (0.11, 8.04)	0.51 (0.04, 3.09)		N/A	N/A	N/A	N/A	N/A	N/A
Metformin	3.44 (2.16, 5.59)	1.21 (0.57, 2.56)	2.36 (0.46, 30.19)		N/A	N/A	N/A	N/A	N/A
Metformin (modified release)	2.59 (1.30, 5.37)	0.92 (0.37, 2.30)	1.80 (0.32, 23.48)	0.75 (0.45, 1.30)		N/A	N/A	N/A	N/A
Pioglitazone	1.67 (0.90, 3.09)	0.59 (0.25, 1.36)	1.14 (0.21, 15.01)	0.48 (0.32, 0.74)	0.64 (0.32, 1.24)		N/A	N/A	N/A
Sitagliptin	1.19 (0.59, 2.37)	0.42 (0.16, 1.04)	0.83 (0.14, 10.96)	0.35 (0.18, 0.63)	0.46 (0.20, 1.01)	0.71 (0.34, 1.48)		N/A	N/A
Sulfonylurea	1.93 (1.19, 3.20)	0.68 (0.32, 1.43)	1.33 (0.25, 16.90)	0.56 (0.44, 0.70)	0.74 (0.41, 1.30)	1.16 (0.77, 1.75)	1.61 (0.86, 3.12)		N/A
Vildagliptin	0.99 (0.57, 1.77)	0.35 (0.15, 0.80)	0.69 (0.12, 8.88)	0.29 (0.17, 0.47)	0.38 (0.18, 0.78)	0.59 (0.31, 1.13)	0.83 (0.39, 1.80)	0.51 (0.30, 0.88)	

Values given are hazard ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.



Values greater than 1 favour placebo; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 23: INITIAL THERAPY: NAUSEA AT STUDY ENDPOINT – relative effect of all options versus reference treatment

Table 39: INITIAL THERAPY: NAUSEA AT STUDY ENDPOINT – rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.256	2 (1, 4)
Acarbose	0.000	8 (4, 9)
Linagliptin	0.306	4 (1, 9)
Metformin	0.000	8 (7, 9)
Metformin (modified release)	0.000	7 (4, 9)
Pioglitazone	0.006	5 (2, 7)
Sitagliptin	0.139	3 (1, 6)
Sulfonylurea	0.000	6 (4, 7)
Vildagliptin	0.292	2 (1, 4)

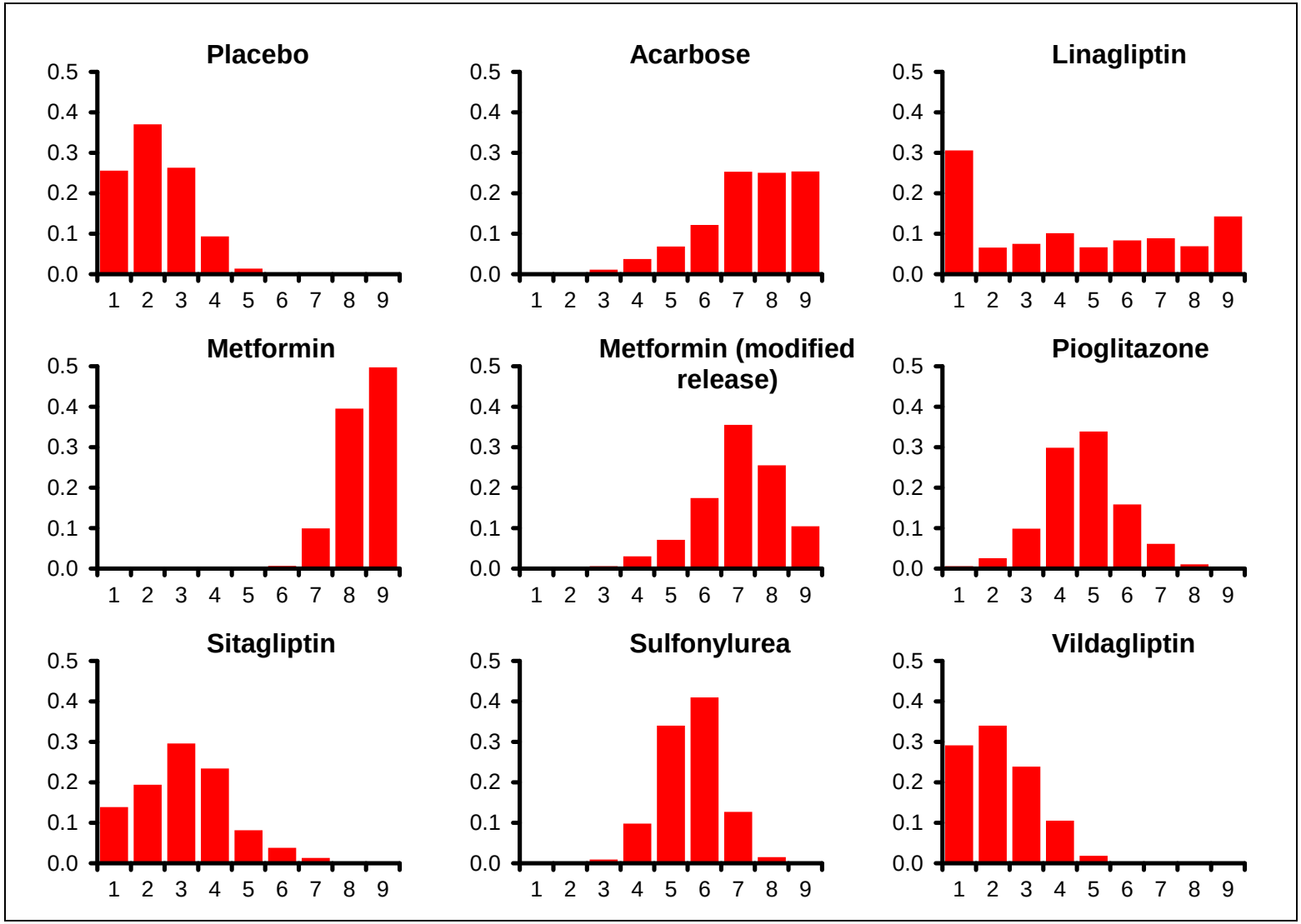


Figure 24: INITIAL THERAPY: NAUSEA AT STUDY ENDPOINT – rank probability histograms

Table 40: INITIAL THERAPY: NAUSEA AT STUDY ENDPOINT – model fit statistics

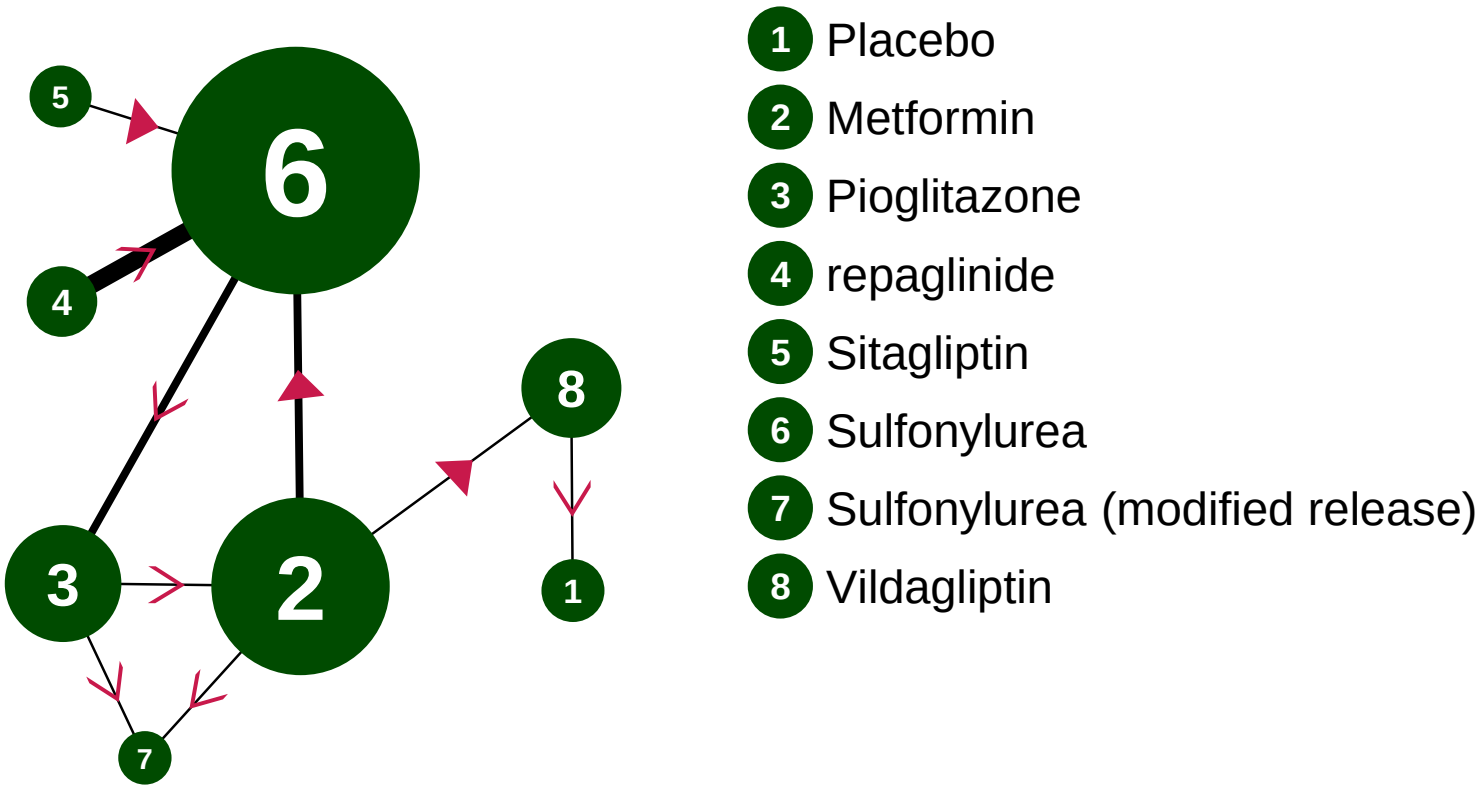
Residual deviance	Dbar	Dhat	pD	DIC	
72.25 (compared to 71 datapoints)	297.292	261.094	36.198	333.49	

Table 41: INITIAL THERAPY: NAUSEA AT STUDY ENDPOINT – notes

- Dichotomous diachronic (binomial; cloglog link); fixed effects
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

J.2.1.6 Change in body weight at 12 and 24 months

Change in body weight at 12 months



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 25: INITIAL THERAPY: BODY WEIGHT AT 12 MONTHS – evidence network

Table 42: INITIAL THERAPY: BODY WEIGHT AT 12 MONTHS – input data

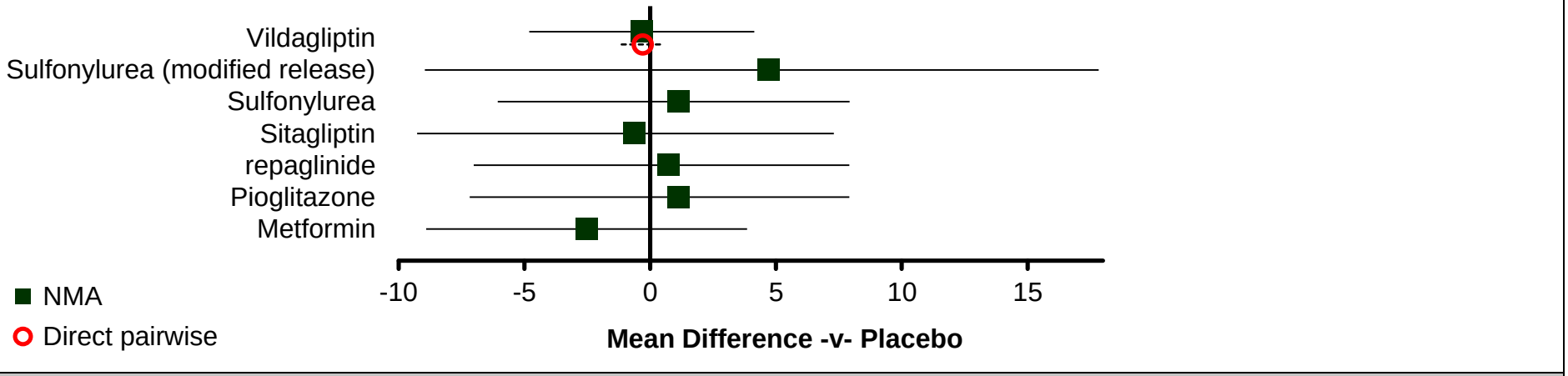
	Placebo	Metformin	Pioglitazone	repaglinide	Sitagliptin	Sulfonylurea	Sulfonylurea (modified release)	Vildagliptin
Schweizer et al. (2007)		-1.90 (4.78)						0.30 (4.59)
Jain et al. (2006)			3.66 (6.14)			1.95 (5.35)		
Derosa et al. (2003)				0.10 (5.25)		-0.50 (5.62)		
Scherbaum et al. (2008)	-0.20 (3.67)							-0.50 (3.75)
Marbury et al. (1999)				2.45 (4.02)		3.64 (4.81)		
Campbell et al. (1994)		-1.97 (3.43)				2.62 (4.41)		
Viberti et al. (2002)		-2.27 (16.47)				1.30 (17.71)		
Charbonnel et al. (2005)			1.70 (16.67)			3.30 (15.04)		
Shah et al. (2011)				-1.80 (9.13)		0.20 (16.39)		
Saleem et al. (2011)				0.20 (9.11)		-1.00 (16.41)		
Arjona et al. (2013)					-0.60 (3.49)	1.15 (3.57)		
Erem et al. (2014)		-4.10 (13.10)	-5.13 (14.10)				0.94 (23.23)	

Values given are mean change in body-weight(SD), in kilograms. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 43: INITIAL THERAPY: BODY WEIGHT AT 12 MONTHS – relative effectiveness of all pairwise combinations

	Placebo	Metformin	Pioglitazone	repaglinide	Sitagliptin	Sulfonylurea	Sulfonylurea (modified release)	Vildagliptin
Placebo		-	-	-	-	-	-	-0.30 (-1.14, 0.54)
Metformin	-2.52 (-8.90, 3.85)		-1.03 (-9.68, 7.62)	-	-	3.81 (2.72, 4.90)	5.04 (-6.95, 17.03)	2.20 (1.49, 2.91)
Pioglitazone	1.14 (-7.17, 7.92)	3.64 (-1.22, 7.14)		-	-	-0.14 (-3.38, 3.10)	6.07 (-6.15, 18.29)	-
repaglinide	0.74 (-7.01, 7.91)	3.26 (-1.07, 7.10)	-0.36 (-4.07, 4.13)		-	0.27 (-1.06, 1.60)	-	-
Sitagliptin	-0.63 (-9.26, 7.30)	1.89 (-3.83, 7.10)	-1.76 (-6.68, 4.09)	-1.39 (-6.49, 3.82)		1.75 (0.92, 2.58)	-	-
Sulfonylurea	1.13 (-6.06, 7.92)	3.64 (0.32, 6.55)	0.02 (-2.65, 3.54)	0.38 (-2.22, 3.07)	1.75 (-2.68, 6.17)		-	-
Sulfonylurea (modified release)	4.72 (-8.96, 17.83)	7.18 (-5.01, 18.96)	3.68 (-8.44, 15.60)	3.95 (-8.53, 16.18)	5.32 (-7.62, 17.97)	3.56 (-8.64, 15.48)		-
Vildagliptin	-0.32 (-4.80, 4.13)	2.21 (-2.18, 6.59)	-1.46 (-6.76, 5.29)	-1.06 (-6.73, 5.18)	0.31 (-6.45, 7.50)	-1.44 (-6.56, 4.12)	-5.02 (-17.48, 7.97)	

Values given are mean differences in body-weight in kilograms.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 26: INITIAL THERAPY: BODY WEIGHT AT 12 MONTHS – relative effect of all options versus reference treatment

Table 44: INITIAL THERAPY: BODY WEIGHT AT 12 MONTHS – rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.103	4 (1, 8)
Metformin	0.576	1 (1, 4)
Pioglitazone	0.018	6 (2, 8)
repaglinide	0.018	5 (2, 8)
Sitagliptin	0.141	3 (1, 8)
Sulfonylurea	0.001	6 (3, 8)
Sulfonylurea (modified release)	0.101	8 (1, 8)
Vildagliptin	0.043	4 (1, 8)

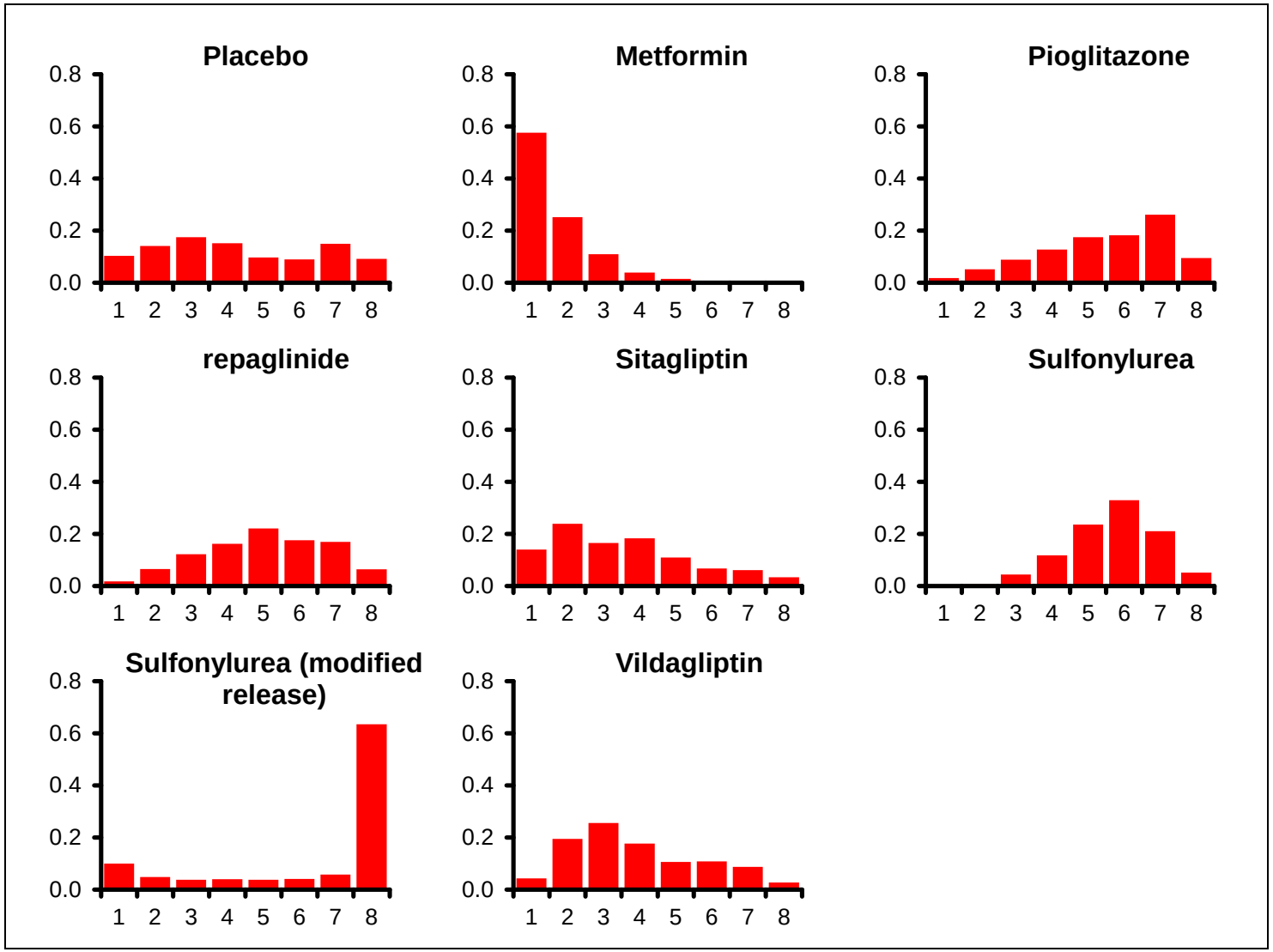


Figure 27: INITIAL THERAPY: BODY WEIGHT AT 12 MONTHS – rank probability histograms

Table 45: INITIAL THERAPY: BODY WEIGHT AT 12 MONTHS – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
24.56 (compared to 25 datapoints)	53.79	31.083	22.707	76.497	1.630 (95%CI: 0.463, 4.596)

Table 46: INITIAL THERAPY: BODY WEIGHT AT 12 MONTHS – notes

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=10)
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

Change in body weight at 24 months

Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 28: INITIAL THERAPY: BODY WEIGHT AT 24 MONTHS – evidence network

Table 47: INITIAL THERAPY: BODY WEIGHT AT 24 MONTHS – input data

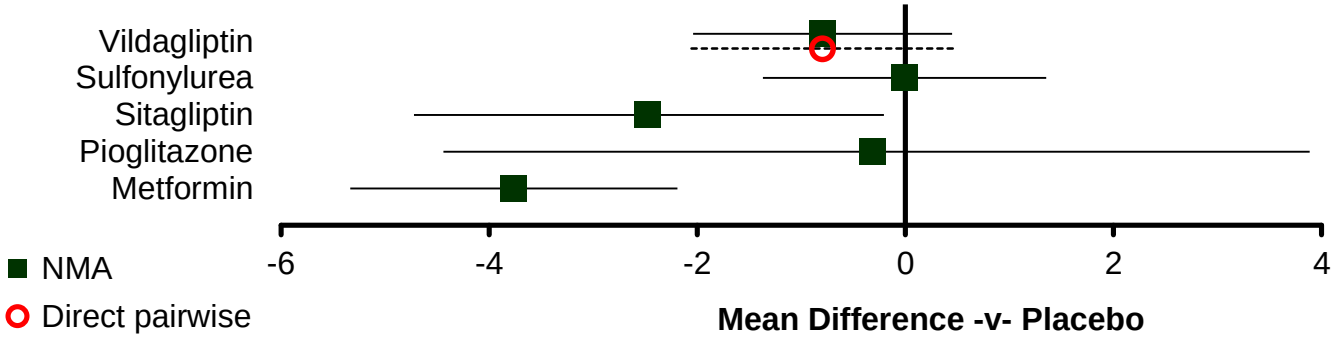
	Placebo	Metformin	Pioglitazone	Sitagliptin	Sulfonylurea	Vildagliptin
Foley & (2009)					1.60 (4.01)	0.80 (4.04)
Goldstein et al. (2007)		-0.80 (4.31)		0.50 (4.33)		
Schweizer et al. (2007)		-2.50 (6.28)				0.50 (6.99)
Scherbaum et al. (2008)	-0.30 (3.17)					-1.10 (4.12)
Viberti et al. (2002)		-2.43 (16.47)			1.30 (17.70)	
Charbonnel et al. (2005)			3.90 (17.52)		4.20 (15.88)	

Values given are mean change in body-weight(SD), in kilograms. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 48: INITIAL THERAPY: BODY WEIGHT AT 24 MONTHS – relative effectiveness of all pairwise combinations

	Placebo	Metformin	Pioglitazone	Sitagliptin	Sulfonylurea	Vildagliptin
Placebo		-	-	-	-	-0.80 (-2.05, 0.45)
Metformin	-3.76 (-5.34, -2.19)		-	1.30 (-0.33, 2.93)	3.73 (2.49, 4.98)	3.00 (1.75, 4.25)
Pioglitazone	-0.31 (-4.44, 3.89)	3.44 (-0.59, 7.54)		-	0.30 (-3.66, 4.26)	-
Sitagliptin	-2.47 (-4.72, -0.21)	1.30 (-0.34, 2.92)	-2.16 (-6.57, 2.22)		-	-
Sulfonylurea	0.00 (-1.37, 1.36)	3.76 (2.85, 4.68)	0.31 (-3.67, 4.23)	2.47 (0.59, 4.32)		-0.80 (-1.35, -0.25)
Vildagliptin	-0.79 (-2.04, 0.45)	2.97 (2.06, 3.90)	-0.48 (-4.50, 3.47)	1.68 (-0.19, 3.55)	-0.79 (-1.32, -0.26)	

Values given are mean differences in body-weight in kilograms.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist FE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 29: INITIAL THERAPY: BODY WEIGHT AT 24 MONTHS – relative effect of all options versus reference treatment

Table 49: INITIAL THERAPY: BODY WEIGHT AT 24 MONTHS – rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.000	5 (3, 6)
Metformin	0.893	1 (1, 2)
Pioglitazone	0.047	4 (1, 6)
Sitagliptin	0.060	2 (1, 4)
Sulfonylurea	0.000	5 (4, 6)
Vildagliptin	0.000	3 (3, 5)

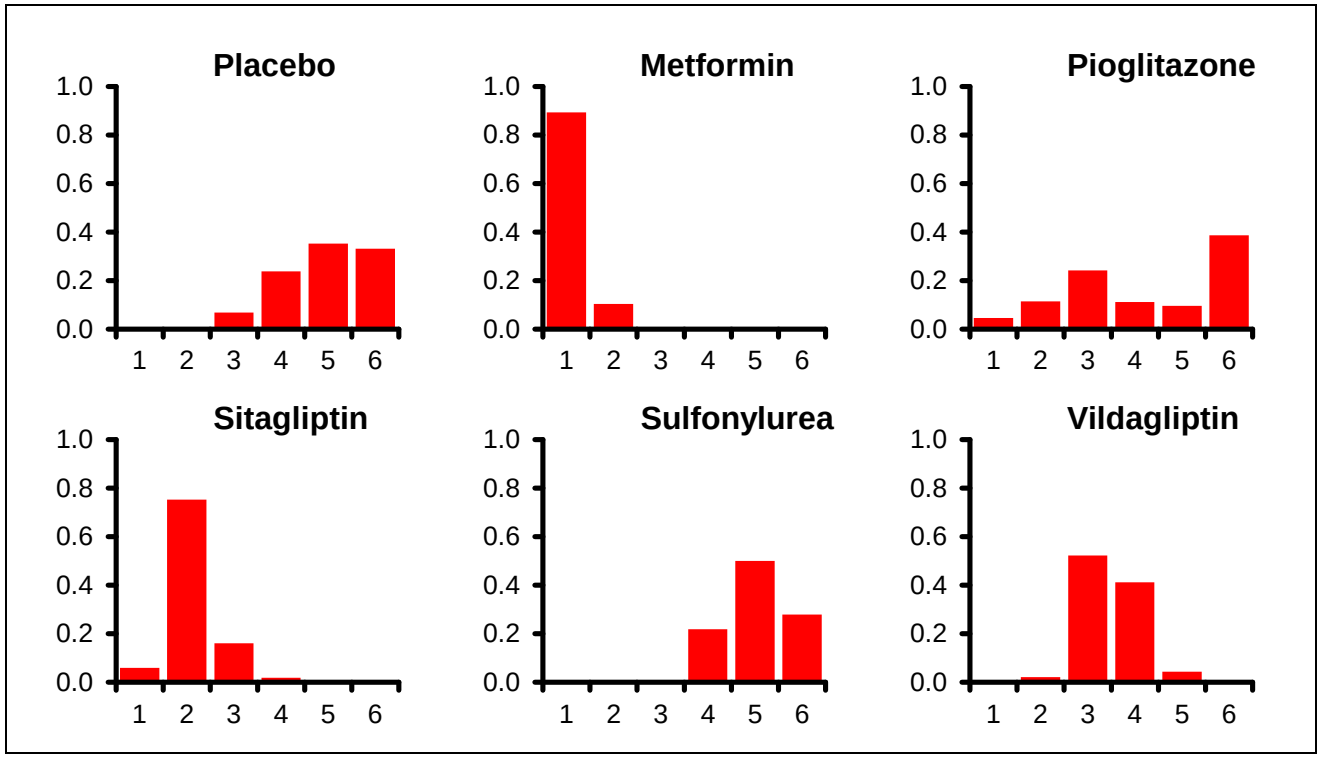


Figure 30: INITIAL THERAPY: BODY WEIGHT AT 24 MONTHS – rank probability histograms

Table 50: INITIAL THERAPY: BODY WEIGHT AT 24 MONTHS – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC
11 (compared to 12 datapoints)	16.272	5.273	10.999	27.27

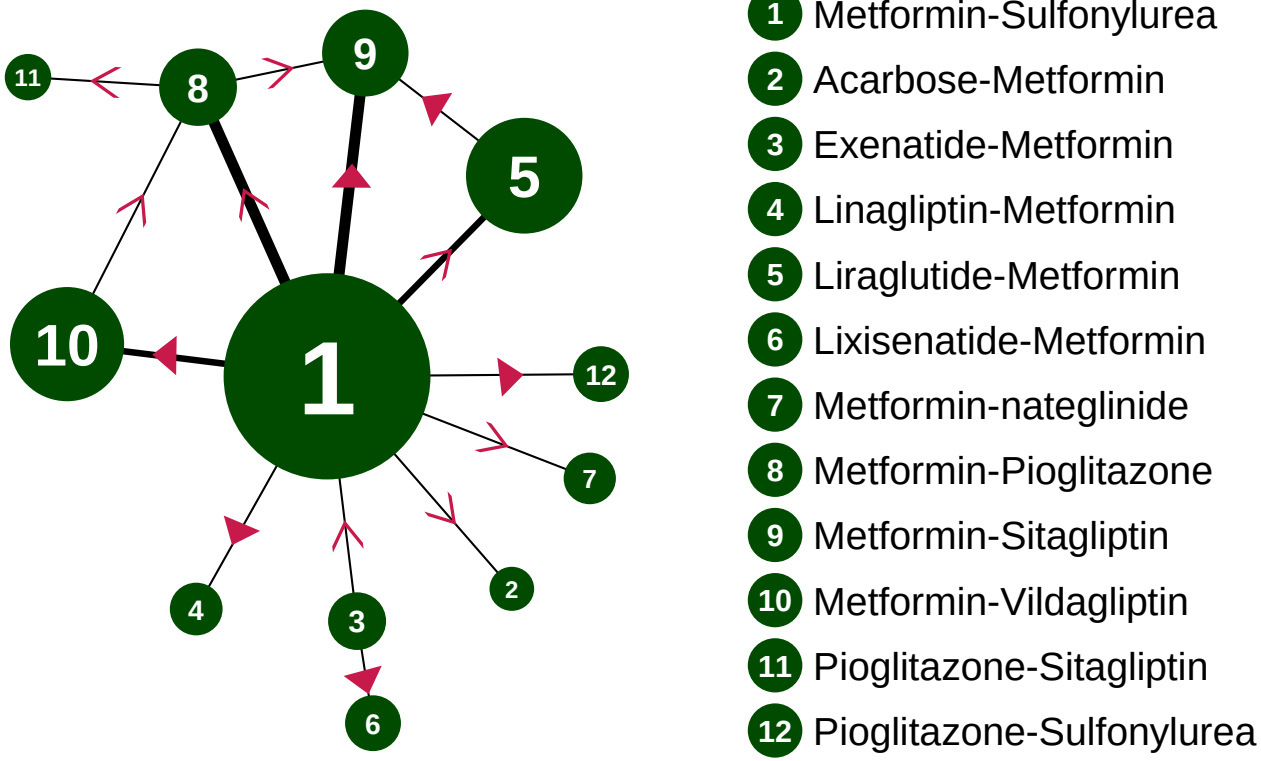
Table 51: INITIAL THERAPY: BODY WEIGHT AT 24 MONTHS – notes

- Continuous (normal; identity link); fixed effects
- 50000 burn-ins; 10000 recorded iterations

J.2.2 RESULTS FOR FIRST INTENSIFICATION OF TREATMENT

J.2.2.1 Change in HbA1c at 3, 6, 12 and 24 months

Change in HbA1c at 3 months



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 31: FIRST INTENSIFICATION: HbA1c AT 3 MONTHS – evidence network

Table 52: FIRST INTENSIFICATION: HbA1c AT 3 MONTHS – input data

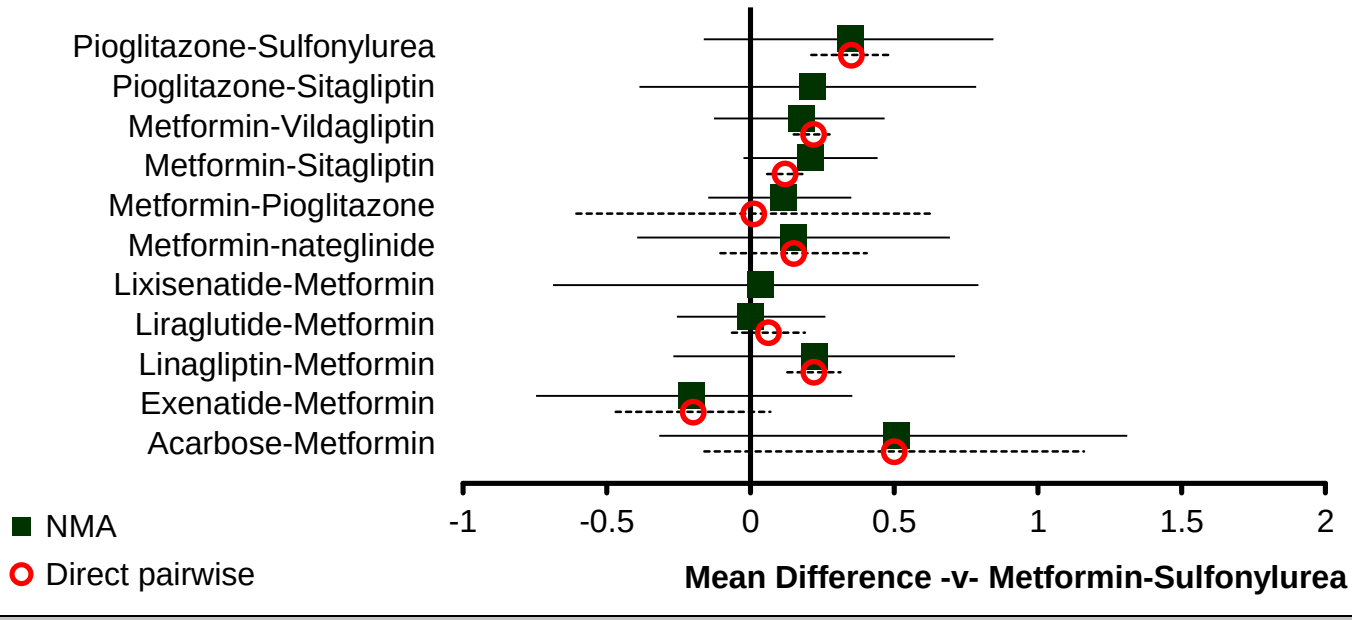
	Metformin-Sulfonylurea	Acarbose-Metformin	Exenatide-Metformin	Linagliptin-Metformin	Liraglutide-Metformin	Lixisenatide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Sitagliptin	Metformin-Vildagliptin	Pioglitazone-Sitagliptin	Pioglitazone-Sulfonylurea
Wang et al. (2011)	-1.20 (1.44)	-0.70 (0.80)										
Derosa et al. (2011)	-0.40 (0.75)		-0.60 (0.66)									
Derosa et al. (2011)	-0.40 (1.08)							-0.20 (1.05)				
Yang et al. (2011)	-1.39 (1.16)				-1.32 (1.14)							
Filozof & (2010)	-1.15 (0.91)									-0.98 (0.90)		
Derosa et al. (2010)								-0.40 (0.72)			-0.30 (0.82)	
Derosa et al. (2009)	-0.50 (0.98)							-1.20 (1.22)				
Ferrannini et al. (2009)	-0.77 (1.08)									-0.53 (0.85)		
Bolli et al. (2008)								-0.91 (0.84)		-0.91 (0.86)		
Nauck et al. (2007)	-0.68 (0.62)								-0.57 (0.53)			
Arechavaleta et al. (2010)	-0.54 (0.94)								-0.43 (0.59)			
Nauck et al. (2009)	-1.00 (1.37)				-0.95 (1.07)							
Matthews et al. (2005)	-1.45 (0.53)							-0.98 (0.71)				
Srivastava et al. (2012)	-0.77 (0.51)								-0.50 (0.42)			
Pratley et al. (2010)					-1.33 (1.04)				-1.00 (1.03)			
Gerich et al. (2005)	-1.90 (1.28)						-1.75 (1.34)					
Hanefeld et al. (2004)	-1.60 (0.89)											-1.25 (0.89)
Gallwitz et al. (2012)	-0.80 (0.54)			-0.58 (0.52)								
Chawla et al. (2013)								-0.75 (0.35)	-0.66 (0.21)			
Rosenstock et al. (2013)			-1.02 (0.85)			-0.78 (0.85)						

Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 53: FIRST INTENSIFICATION: HbA1c AT 3 MONTHS – relative effectiveness of all pairwise combinations

	Metformin-Sulfonylurea	Acarbose-Metformin	Exenatide-Metformin	Linagliptin-Metformin	Liraglutide-Metformin	Lixisenatide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Sitagliptin	Metformin-Vildagliptin	Pioglitazone-Sitagliptin	Pioglitazone-Sulfonylurea
Metformin-Sulfonylurea		0.50 (-0.16, 1.16)	-0.20 (-0.47, 0.07)	0.22 (0.13, 0.31)	0.06 (-0.06, 0.19)	-	0.15 (-0.10, 0.40)	0.01 (-0.61, 0.63)	0.12 (0.06, 0.18)	0.22 (0.15, 0.29)	-	0.35 (0.21, 0.49)
Acarbose-Metformin	0.51 (-0.32, 1.31)		-	-	-	-	-	-	-	-	-	-
Exenatide-Metformin	-0.20 (-0.75, 0.35)	-0.71 (-1.69, 0.27)		-	-	0.24 (0.11, 0.37)	-	-	-	-	-	-
Linagliptin-Metformin	0.22 (-0.27, 0.71)	-0.29 (-1.23, 0.68)	0.43 (-0.32, 1.16)		-	-	-	-	-	-	-	-
Liraglutide-Metformin	0.00 (-0.26, 0.26)	-0.51 (-1.34, 0.36)	0.21 (-0.41, 0.80)	-0.22 (-0.77, 0.33)		-	-	-	0.33 (0.17, 0.50)	-	-	-
Lixisenatide-Metformin	0.04 (-0.69, 0.79)	-0.47 (-1.56, 0.63)	0.24 (-0.25, 0.74)	-0.19 (-1.06, 0.71)	0.03 (-0.74, 0.84)		-	-	-	-	-	-
Metformin-nateglinide	0.15 (-0.39, 0.69)	-0.36 (-1.32, 0.63)	0.36 (-0.42, 1.13)	-0.07 (-0.81, 0.66)	0.15 (-0.46, 0.75)	0.11 (-0.82, 1.02)		-	-	-	-	-
Metformin-Pioglitazone	0.12 (-0.15, 0.35)	-0.39 (-1.23, 0.46)	0.32 (-0.31, 0.90)	-0.10 (-0.67, 0.43)	0.12 (-0.25, 0.44)	0.08 (-0.74, 0.83)	-0.03 (-0.64, 0.55)		0.09 (-0.07, 0.25)	0.00 (-0.14, 0.14)	0.10 (-0.15, 0.35)	-
Metformin-Sitagliptin	0.21 (-0.02, 0.44)	-0.30 (-1.13, 0.55)	0.42 (-0.20, 1.00)	-0.01 (-0.56, 0.53)	0.21 (-0.09, 0.50)	0.17 (-0.61, 0.94)	0.06 (-0.52, 0.65)	0.09 (-0.20, 0.41)		-	-	-
Metformin-Vildagliptin	0.18 (-0.13, 0.47)	-0.33 (-1.19, 0.54)	0.38 (-0.26, 0.99)	-0.04 (-0.62, 0.52)	0.18 (-0.22, 0.56)	0.14 (-0.68, 0.92)	0.03 (-0.59, 0.64)	0.06 (-0.26, 0.41)	-0.03 (-0.40, 0.33)		-	-
Pioglitazone-Sitagliptin	0.22 (-0.39, 0.78)	-0.30 (-1.29, 0.71)	0.42 (-0.41, 1.21)	0.00 (-0.78, 0.73)	0.21 (-0.44, 0.83)	0.18 (-0.79, 1.10)	0.07 (-0.75, 0.84)	0.10 (-0.44, 0.63)	0.01 (-0.63, 0.60)	0.04 (-0.59, 0.65)		-
Pioglitazone-Sulfonylurea	0.35 (-0.16, 0.85)	-0.16 (-1.10, 0.79)	0.55 (-0.20, 1.28)	0.13 (-0.57, 0.83)	0.35 (-0.21, 0.90)	0.31 (-0.59, 1.19)	0.20 (-0.54, 0.94)	0.23 (-0.31, 0.80)	0.14 (-0.42, 0.69)	0.17 (-0.41, 0.75)	0.13 (-0.61, 0.91)	

Values given are mean differences in HbA1c in percentage-points.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 32: FIRST INTENSIFICATION: HbA1c AT 3 MONTHS – relative effect of all options versus reference treatment

Table 54: FIRST INTENSIFICATION: HbA1c AT 3 MONTHS – rankings for each comparator

	Probability best	Median rank (95%CI)
Metformin-Sulfonylurea	0.030	4 (1, 7)
Acarbose-Metformin	0.036	11 (1, 12)
Exenatide-Metformin	0.512	1 (1, 9)
Linagliptin-Metformin	0.038	8 (1, 12)
Liraglutide-Metformin	0.094	4 (1, 9)
Lixisenatide-Metformin	0.103	5 (1, 12)

	Probability best	Median rank (95%CI)
Metformin-nateglinide	0.082	7 (1, 12)
Metformin-Pioglitazone	0.014	6 (2, 10)
Metformin-Sitagliptin	0.001	8 (4, 11)
Metformin-Vildagliptin	0.012	7 (2, 11)
Pioglitazone-Sitagliptin	0.064	8 (1, 12)
Pioglitazone-Sulfonylurea	0.014	10 (2, 12)

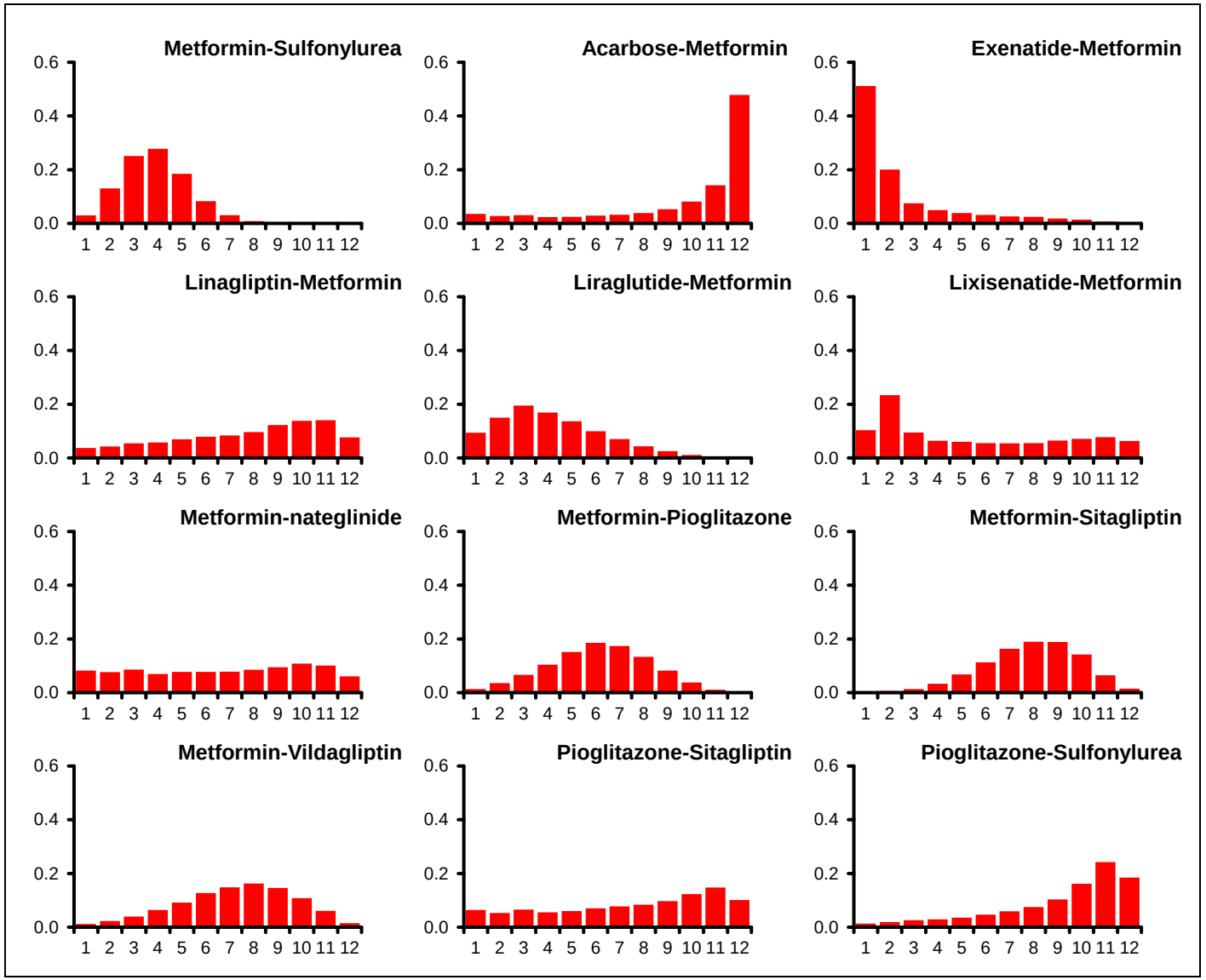


Figure 33: FIRST INTENSIFICATION: HbA1c AT 3 MONTHS – rank probability histograms

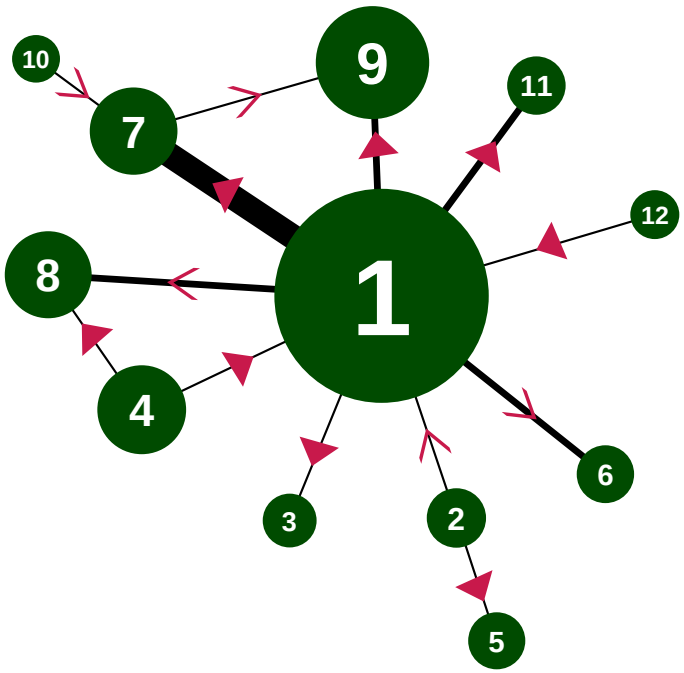
Table 55: FIRST INTENSIFICATION: HbA1c AT 3 MONTHS – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
47.4 (compared to 45 datapoints)	-117.793	-160.698	42.905	-74.888	0.219 (95%CI: 0.127, 0.383)

Table 56: FIRST INTENSIFICATION: HbA1c AT 3 MONTHS – notes

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

Change in HbA1c at 6 months



1 Metformin-Sulfonylurea
2 Exenatide-Metformin
3 Linagliptin-Metformin
4 Liraglutide-Metformin
5 Lixisenatide-Metformin
6 Metformin-nateglinide
7 Metformin-Pioglitazone
8 Metformin-Sitagliptin
9 Metformin-Vildagliptin
10 Pioglitazone-Sitagliptin
11 Pioglitazone-Sulfonylurea
12 Sitagliptin-Sulfonylurea

Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 34: FIRST INTENSIFICATION: HbA1c AT 6 MONTHS – evidence network

Table 57: FIRST INTENSIFICATION: HbA1c AT 6 MONTHS – input data

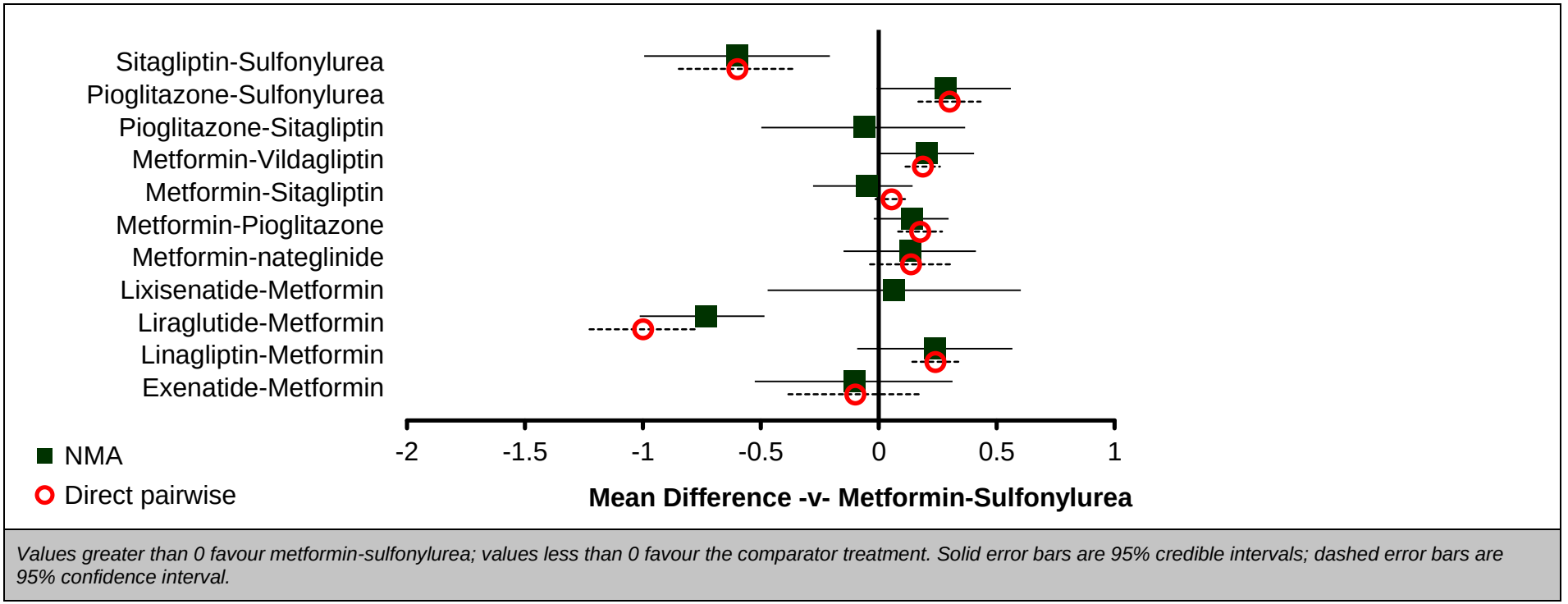
	Metformin-Sulfonylurea	Exenatide-Metformin	Linagliptin-Metformin	Liraglutide-Metformin	Lixisenatide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Sitagliptin	Metformin-Vildagliptin	Pioglitazone-Sitagliptin	Pioglitazone-Sulfonylurea	Sitagliptin-Sulfonylurea
Derosa et al. (2011)	-0.70 (0.78)	-0.80 (0.68)										
Derosa et al. (2011)	-0.50 (1.15)						-0.40 (1.07)					
Pfutzner et al. (2011)	-1.00 (0.90)						-0.80 (0.90)					
Filozof & (2010)	-1.19 (0.93)								-1.01 (0.98)			
Derosa et al. (2010)							-0.60 (0.75)			-0.80 (0.84)		
Papathanassiou et al. (2009)	-0.56 (0.57)						-0.60 (0.85)					
Ferrannini et al. (2009)	-0.74 (1.15)								-0.55 (0.92)			
Bolli et al. (2008)							-1.01 (0.92)		-0.91 (1.04)			
Hermansen et al. (2007)	0.30 (0.87)											-0.30 (0.95)
Nauck et al. (2007)	-0.75 (0.65)							-0.70 (0.55)				
Ristic et al. (2006)	-0.57 (0.87)					-0.41 (0.91)						
Arechavaleta et al. (2010)	-0.52 (0.92)							-0.46 (0.92)				
Nauck et al. (2009)	0.10 (1.56)			-0.90 (1.55)								
Matthews et al. (2005)	-1.39 (0.88)						-1.15 (0.89)					
Pratley et al. (2010)				-1.37 (0.99)				-0.90 (0.98)				
Umpierrez et al. (2006)	-1.30 (0.75)						-1.23 (0.76)					
van der et al. (2009)	-0.80 (0.68)										-0.60 (1.15)	
Gerich et al. (2005)	-2.00 (1.40)					-1.90 (1.46)						
Hanefeld et al. (2004)	-1.70 (0.89)										-1.39 (0.89)	
Gallwitz et al. (2012)	-0.82 (0.55)		-0.58 (0.55)									
Rosenstock et al. (2013)		-0.96 (0.89)			-0.79 (0.89)							
Maffioli et al. (2013)	-0.80 (1.77)						-0.60 (1.48)					

Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 58: FIRST INTENSIFICATION: HbA1c AT 6 MONTHS – relative effectiveness of all pairwise combinations

	Metformin-Sulfonylurea	Exenatide-Metformin	Linagliptin-Metformin	Liraglutide-Metformin	Lixisenatide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Sitagliptin	Metformin-Vildagliptin	Pioglitazone-Sitagliptin	Pioglitazone-Sulfonylurea	Sitagliptin-Sulfonylurea
Metformin-Sulfonylurea		-0.10 (-0.38, 0.18)	0.24 (0.14, 0.34)	-1.00 (-1.23, -0.77)	-	0.14 (-0.04, 0.31)	0.18 (0.08, 0.27)	0.05 (-0.01, 0.12)	0.19 (0.11, 0.26)	-	0.30 (0.17, 0.43)	-0.60 (-0.85, -0.35)
Exenatide-Metformin	-0.10 (-0.53, 0.31)		-	-	0.17 (0.03, 0.31)	-	-	-	-	-	-	-
Linagliptin-Metformin	0.24 (-0.09, 0.57)	0.34 (-0.19, 0.88)		-	-	-	-	-	-	-	-	-
Liraglutide-Metformin	-0.73 (-1.01, -0.48)	-0.63 (-1.14, -0.15)	-0.97 (-1.42, -0.58)		-	-	-	0.47 (0.31, 0.63)	-	-	-	-
Lixisenatide-Metformin	0.07 (-0.47, 0.60)	0.17 (-0.18, 0.51)	-0.17 (-0.81, 0.46)	0.80 (0.22, 1.41)		-	-	-	-	-	-	-
Metformin-nateglinide	0.13 (-0.15, 0.41)	0.24 (-0.27, 0.75)	-0.11 (-0.54, 0.32)	0.86 (0.50, 1.27)	0.07 (-0.53, 0.67)		-	-	-	-	-	-
Metformin-Pioglitazone	0.14 (-0.02, 0.30)	0.25 (-0.20, 0.69)	-0.10 (-0.47, 0.26)	0.87 (0.59, 1.19)	0.08 (-0.48, 0.63)	0.01 (-0.32, 0.33)		-	0.10 (-0.06, 0.26)	-0.20 (-0.45, 0.05)	-	-
Metformin-Sitagliptin	-0.05 (-0.28, 0.14)	0.05 (-0.43, 0.51)	-0.29 (-0.70, 0.08)	0.68 (0.44, 0.93)	-0.12 (-0.71, 0.45)	-0.18 (-0.55, 0.16)	-0.19 (-0.46, 0.06)		-	-	-	-
Metformin-Vildagliptin	0.20 (0.00, 0.40)	0.31 (-0.16, 0.77)	-0.04 (-0.42, 0.35)	0.93 (0.63, 1.28)	0.14 (-0.44, 0.71)	0.07 (-0.28, 0.42)	0.06 (-0.16, 0.29)	0.25 (-0.02, 0.56)		-	-	-
Pioglitazone-Sitagliptin	-0.06 (-0.50, 0.37)	0.04 (-0.57, 0.65)	-0.30 (-0.86, 0.24)	0.67 (0.18, 1.19)	-0.13 (-0.82, 0.57)	-0.20 (-0.71, 0.32)	-0.20 (-0.60, 0.20)	-0.01 (-0.48, 0.48)	-0.26 (-0.73, 0.19)		-	-
Pioglitazone-Sulfonylurea	0.28 (-0.01, 0.56)	0.39 (-0.12, 0.90)	0.04 (-0.40, 0.48)	1.01 (0.64, 1.41)	0.22 (-0.39, 0.82)	0.15 (-0.26, 0.54)	0.14 (-0.18, 0.47)	0.33 (-0.01, 0.69)	0.08 (-0.27, 0.42)	0.34 (-0.17, 0.86)		-
Sitagliptin-Sulfonylurea	-0.60 (-0.99, -0.21)	-0.50 (-1.08, 0.08)	-0.84 (-1.36, -0.32)	0.13 (-0.32, 0.62)	-0.67 (-1.34, 0.01)	-0.73 (-1.21, -0.25)	-0.74 (-1.16, -0.31)	-0.55 (-0.98, -0.09)	-0.80 (-1.24, -0.36)	-0.54 (-1.12, 0.05)	-0.88 (-1.36, -0.39)	

Values given are mean differences in HbA1c in percentage-points.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 35: FIRST INTENSIFICATION: HbA1c AT 6 MONTHS – relative effect of all options versus reference treatment

Table 59: FIRST INTENSIFICATION: HbA1c AT 6 MONTHS – rankings for each comparator

	Probability best	Median rank (95%CI)
Metformin-Sulfonylurea	0.000	6 (4, 8)
Exenatide-Metformin	0.003	4 (2, 10)
Linagliptin-Metformin	0.000	10 (4, 12)
Liraglutide-Metformin	0.712	1 (1, 2)
Lixisenatide-Metformin	0.003	7 (3, 12)
Metformin-nateglinide	0.000	8 (3, 12)

	Probability best	Median rank (95%CI)
Metformin-Pioglitazone	0.000	9 (5, 11)
Metformin-Sitagliptin	0.000	5 (3, 9)
Metformin-Vildagliptin	0.000	10 (6, 12)
Pioglitazone-Sitagliptin	0.003	5 (2, 12)
Pioglitazone-Sulfonylurea	0.000	11 (6, 12)
Sitagliptin-Sulfonylurea	0.278	2 (1, 4)

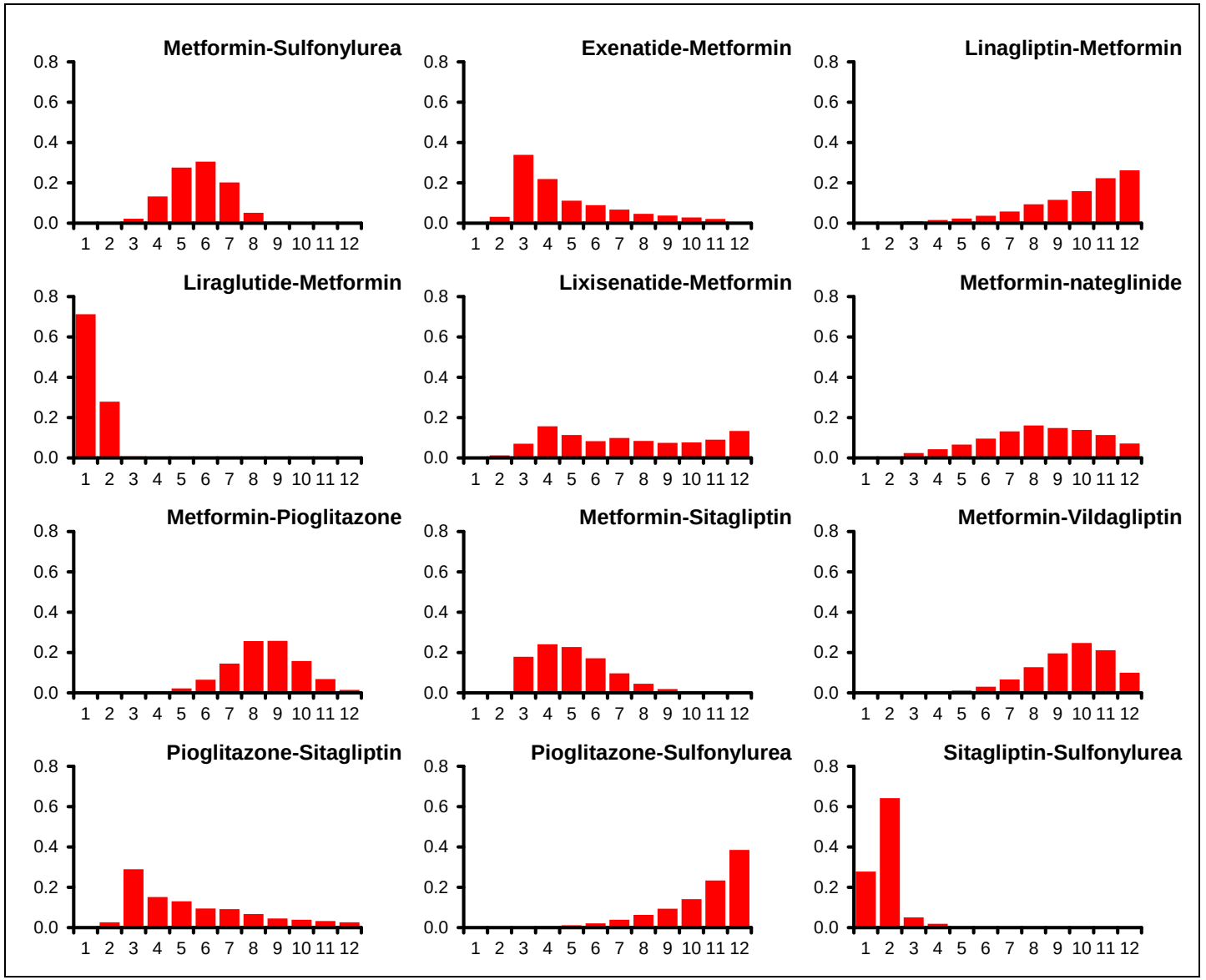


Figure 36: FIRST INTENSIFICATION: HbA1c AT 6 MONTHS – rank probability histograms

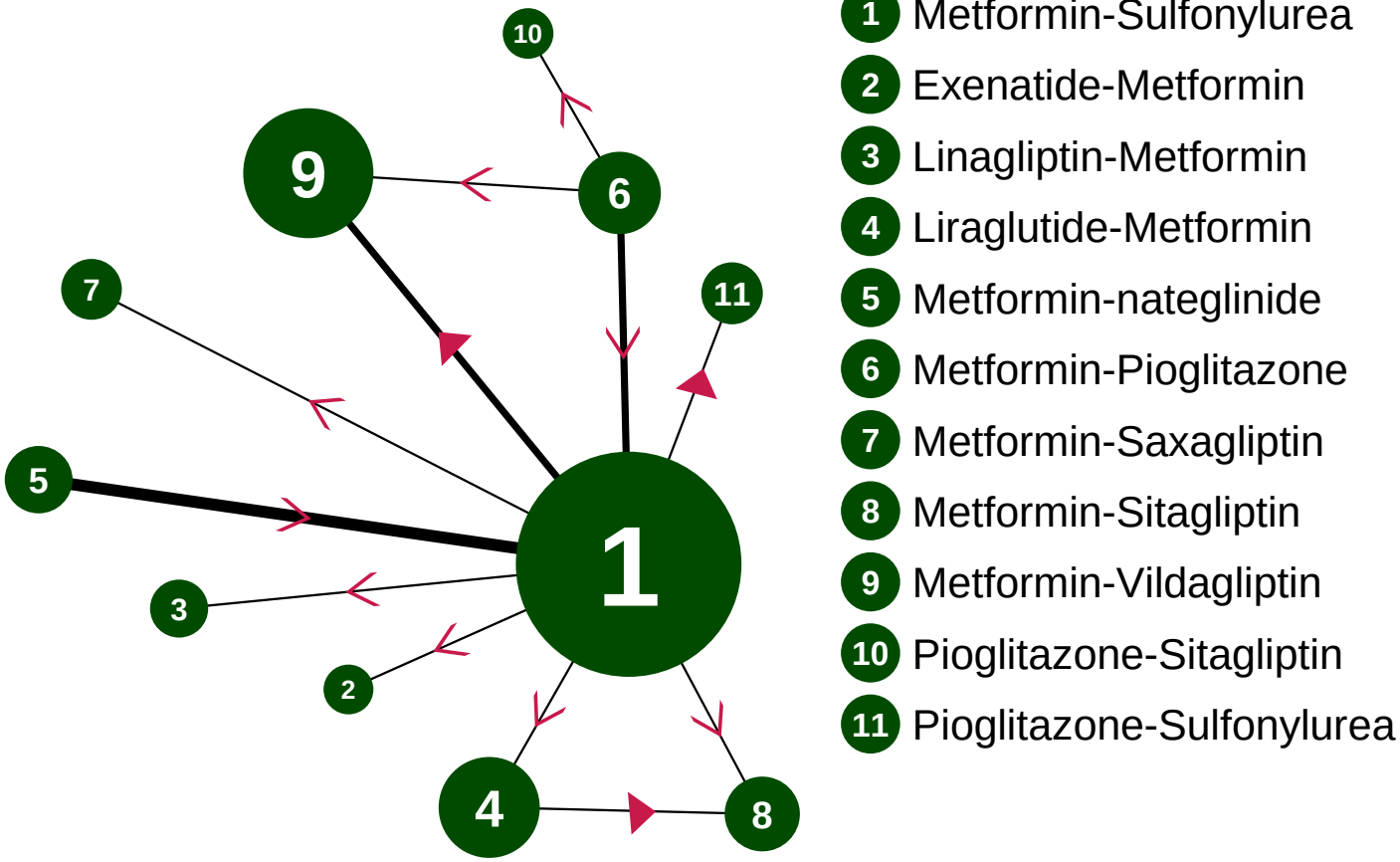
Table 60: FIRST INTENSIFICATION: HbA1c AT 6 MONTHS – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
47.35 (compared to 47 datapoints)	-112.895	-154.753	41.858	-71.037	0.140 (95%CI: 0.056, 0.265)

Table 61: FIRST INTENSIFICATION: HbA1c AT 6 MONTHS – notes

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

Change in HbA1c at 12 months



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 37: FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – evidence network

Table 62: FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – input data

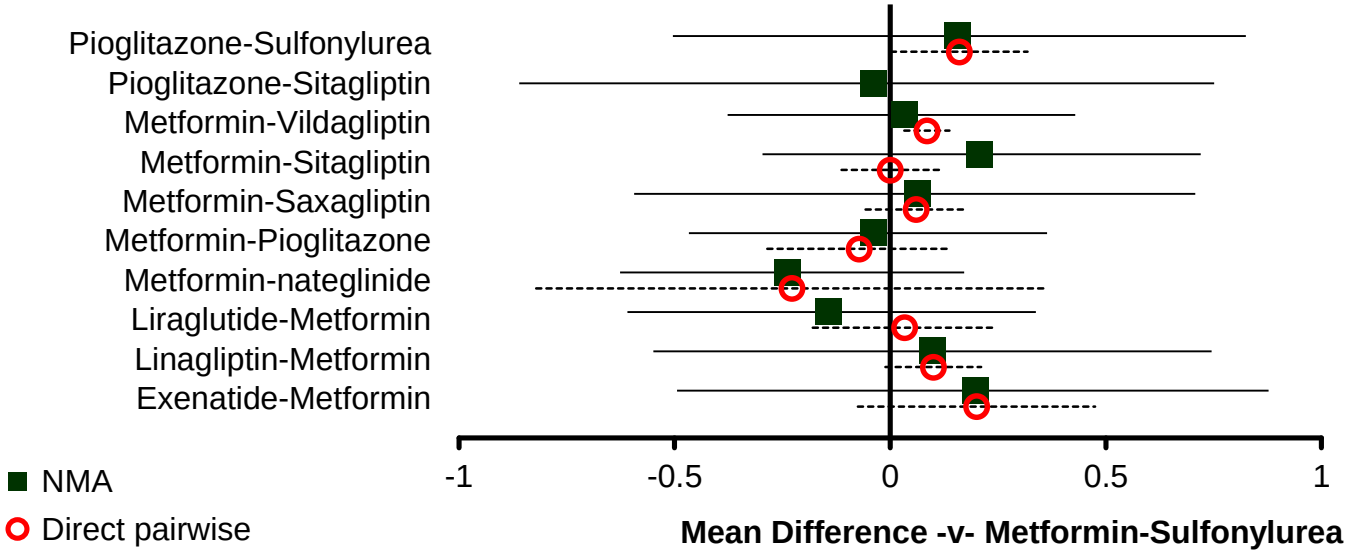
	Metformin-Sulfonylurea	Exenatide-Metformin	Linagliptin-Metformin	Liraglutide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Sitagliptin	Metformin-Vildagliptin	Pioglitazone-Sitagliptin	Pioglitazone-Sulfonylurea
Goke et al. (2010)	-0.80 (0.86)						-0.74 (0.57)				
Derosa et al. (2011)	-1.40 (0.75)	-1.20 (0.65)									
Derosa et al. (2011)	-0.80 (1.12)					-1.00 (1.03)					
Filozof & (2010)	-0.85 (1.19)								-0.81 (1.18)		
Derosa et al. (2010)						-1.40 (0.75)				-1.40 (0.84)	
Ferrannini et al. (2009)	-0.53 (0.65)								-0.44 (0.67)		
Bolli et al. (2008)						-0.60 (1.45)			-0.60 (0.96)		
Derosa et al. (2007)	-0.90 (1.04)				-1.70 (0.93)						
Nauck et al. (2007)	-0.67 (0.83)							-0.67 (0.80)			
Ristic et al. (2006)	-0.20 (1.22)				-0.12 (1.07)						
Nauck et al. (2009)	-0.70 (1.52)			-0.67 (1.32)							
Matthews et al. (2005)	-1.01 (1.59)					-0.99 (1.60)					
Pratley et al. (2010)				-1.40 (1.06)				-0.88 (1.06)			
Gerich et al. (2005)	-1.80 (1.44)				-1.75 (1.50)						
Hanefeld et al. (2004)	-1.36 (1.02)										-1.20 (1.02)
Gallwitz et al. (2012)	-0.77 (0.62)		-0.67 (0.64)								

Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 63: FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – relative effectiveness of all pairwise combinations

	Metformin-Sulfonylurea	Exenatide-Metformin	Linagliptin-Metformin	Liraglutide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Sitagliptin	Metformin-Vildagliptin	Pioglitazone-Sitagliptin	Pioglitazone-Sulfonylurea
Metformin-Sulfonylurea		0.20 (-0.08, 0.48)	0.10 (-0.01, 0.21)	0.03 (-0.18, 0.25)	-0.23 (-0.82, 0.36)	-0.07 (-0.29, 0.14)	0.06 (-0.06, 0.18)	0.00 (-0.11, 0.11)	0.09 (0.03, 0.14)	-	0.16 (0.00, 0.32)
Exenatide-Metformin	0.20 (-0.49, 0.88)		-	-	-	-	-	-	-	-	-
Linagliptin-Metformin	0.10 (-0.55, 0.74)	-0.10 (-1.03, 0.85)		-	-	-	-	-	-	-	-
Liraglutide-Metformin	-0.14 (-0.61, 0.34)	-0.34 (-1.17, 0.52)	-0.25 (-1.04, 0.56)		-	-	-	0.52 (0.35, 0.69)	-	-	-
Metformin-nateglinide	-0.24 (-0.63, 0.17)	-0.43 (-1.23, 0.38)	-0.34 (-1.08, 0.44)	-0.09 (-0.71, 0.53)		-	-	-	-	-	-
Metformin-Pioglitazone	-0.04 (-0.47, 0.36)	-0.24 (-1.05, 0.56)	-0.14 (-0.91, 0.61)	0.10 (-0.54, 0.72)	0.19 (-0.40, 0.76)		-	-	0.00 (-0.20, 0.20)	0.00 (-0.27, 0.27)	-
Metformin-Saxagliptin	0.06 (-0.59, 0.71)	-0.14 (-1.08, 0.81)	-0.04 (-0.95, 0.88)	0.21 (-0.60, 0.99)	0.30 (-0.48, 1.06)	0.10 (-0.67, 0.89)		-	-	-	-
Metformin-Sitagliptin	0.21 (-0.30, 0.72)	0.01 (-0.85, 0.88)	0.11 (-0.71, 0.94)	0.35 (-0.13, 0.83)	0.44 (-0.21, 1.09)	0.25 (-0.39, 0.93)	0.14 (-0.66, 0.97)		-	-	-
Metformin-Vildagliptin	0.03 (-0.38, 0.43)	-0.16 (-0.96, 0.63)	-0.07 (-0.82, 0.69)	0.18 (-0.46, 0.79)	0.27 (-0.31, 0.83)	0.08 (-0.40, 0.56)	-0.03 (-0.80, 0.73)	-0.17 (-0.83, 0.46)		-	-
Pioglitazone-Sitagliptin	-0.04 (-0.86, 0.75)	-0.24 (-1.31, 0.81)	-0.14 (-1.17, 0.87)	0.10 (-0.85, 1.02)	0.20 (-0.72, 1.07)	0.00 (-0.69, 0.68)	-0.10 (-1.16, 0.92)	-0.25 (-1.22, 0.67)	-0.08 (-0.93, 0.75)		-
Pioglitazone-Sulfonylurea	0.16 (-0.50, 0.82)	-0.04 (-1.00, 0.91)	0.06 (-0.87, 0.98)	0.30 (-0.51, 1.12)	0.40 (-0.40, 1.15)	0.20 (-0.57, 0.99)	0.10 (-0.84, 1.02)	-0.05 (-0.88, 0.78)	0.12 (-0.64, 0.90)	0.20 (-0.81, 1.25)	

Values given are mean differences in HbA1c in percentage-points.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 38: FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – relative effect of all options versus reference treatment

Table 64: FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – rankings for each comparator

	Probability best	Median rank (95%CI)
Metformin-Sulfonylurea	0.001	6 (3, 9)
Exenatide-Metformin	0.044	9 (1, 11)
Linagliptin-Metformin	0.061	7 (1, 11)
Liraglutide-Metformin	0.179	3 (1, 9)
Metformin-nateglinide	0.327	2 (1, 8)
Metformin-Pioglitazone	0.039	5 (1, 10)
Metformin-Saxagliptin	0.081	7 (1, 11)
Metformin-Sitagliptin	0.007	9 (2, 11)
Metformin-Vildagliptin	0.025	6 (2, 11)
Pioglitazone-Sitagliptin	0.191	5 (1, 11)
Pioglitazone-Sulfonylurea	0.047	8 (1, 11)

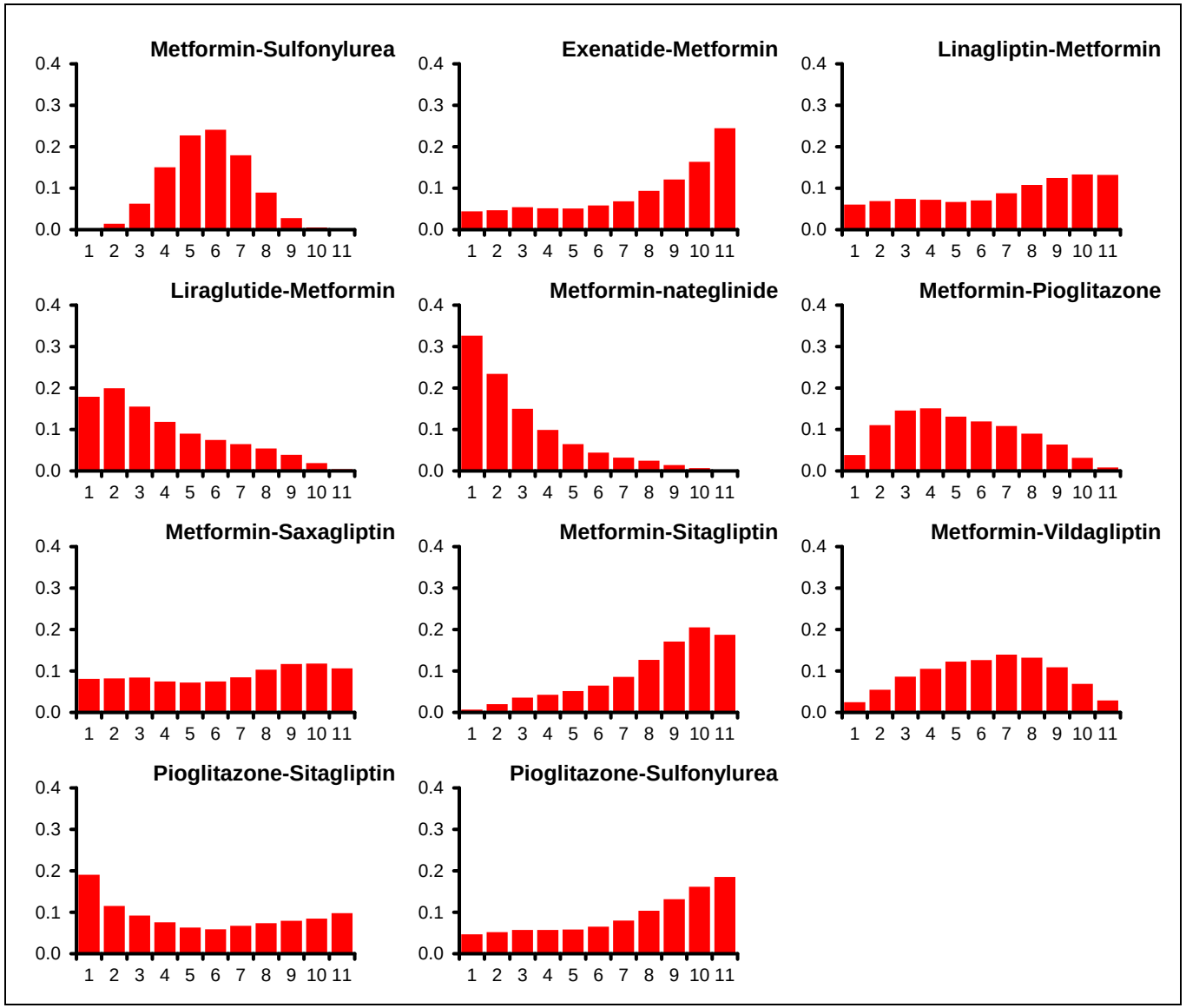


Figure 39: FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – rank probability histograms

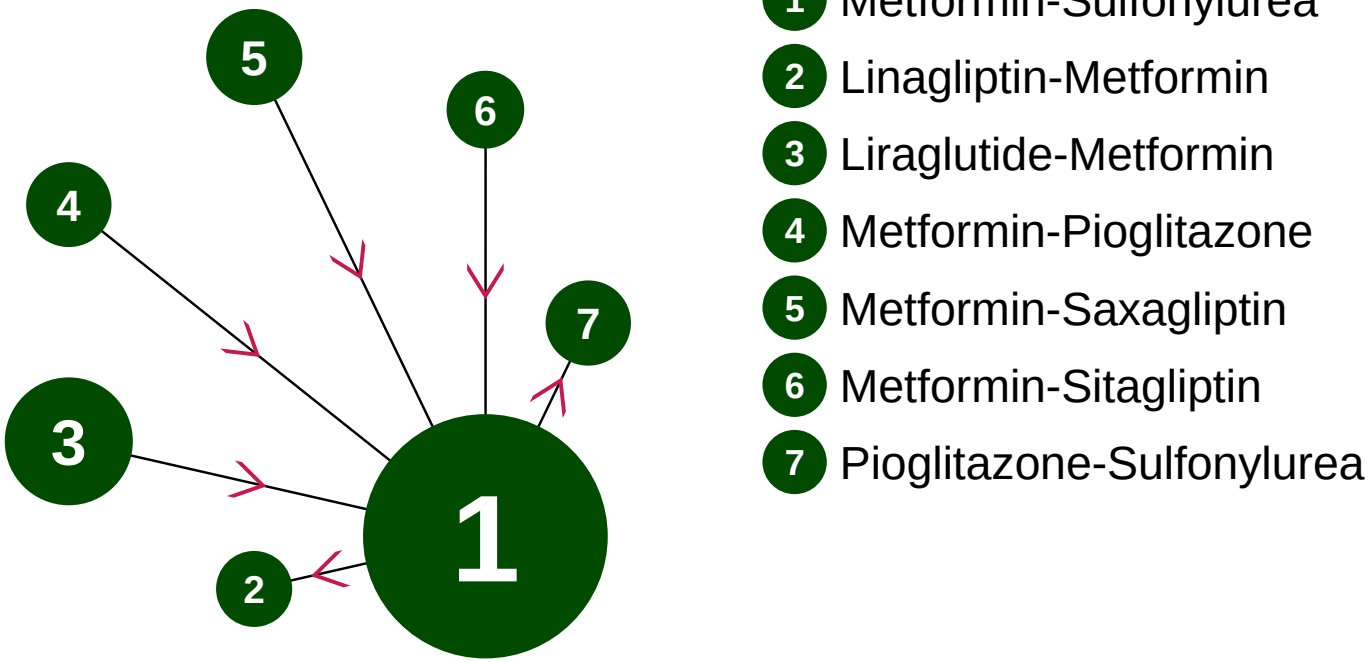
Table 65: FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	Tau
35.37 (compared to 35 datapoints)	-87.735	-121.564	33.829	-53.906	0.283 (95%CI: 0.154, 0.548)

Table 66: FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – notes

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

Change in HbA1c at 24 months



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 40: FIRST INTENSIFICATION: HbA1c AT 24 MONTHS – evidence network

Table 67: FIRST INTENSIFICATION: HbA1c AT 24 MONTHS – input data

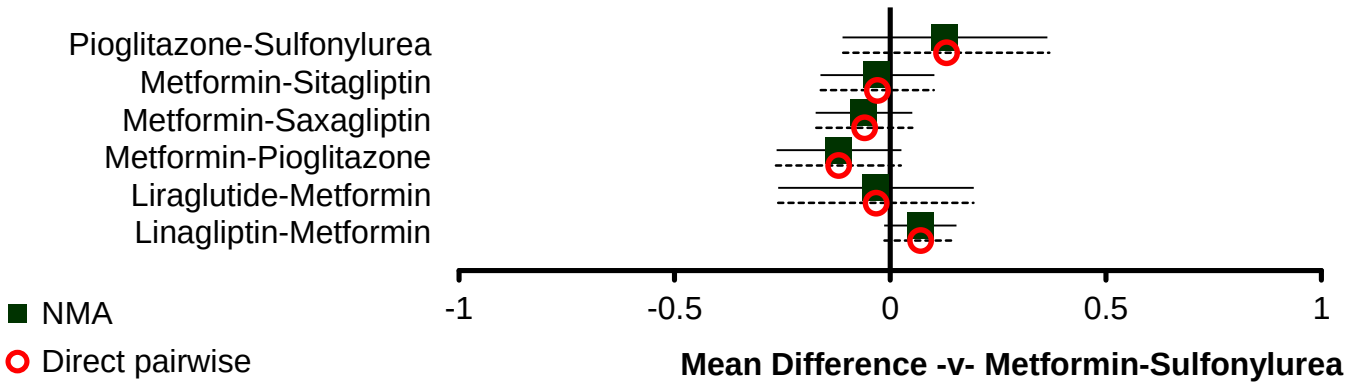
	Metformin-Sulfonylurea	Linagliptin-Metformin	Liraglutide-Metformin	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Sitagliptin	Pioglitazone-Sulfonylurea
Goke et al. (2010)	-0.35 (0.83)				-0.41 (0.83)		
Nauck et al. (2007)	-0.51 (0.73)					-0.54 (0.76)	
Nauck et al. (2009)	-0.50 (1.56)		-0.53 (1.55)				
Matthews et al. (2005)	-0.77 (0.76)			-0.89 (1.07)			
Hanefeld et al. (2004)	-1.16 (1.79)						-1.03 (1.25)
Gallwitz et al. (2012)	-0.63 (0.49)	-0.56 (0.46)					

Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 68: FIRST INTENSIFICATION: HbA1c AT 24 MONTHS – relative effectiveness of all pairwise combinations

	Metformin-Sulfonylurea	Linagliptin-Metformin	Liraglutide-Metformin	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Sitagliptin	Pioglitazone-Sulfonylurea
Metformin-Sulfonylurea		0.07 (-0.01, 0.15)	-0.03 (-0.26, 0.19)	-0.12 (-0.26, 0.02)	-0.06 (-0.17, 0.05)	-0.03 (-0.16, 0.10)	0.13 (-0.11, 0.37)
Linagliptin-Metformin	0.07 (-0.01, 0.15)		-	-	-	-	-
Liraglutide-Metformin	-0.03 (-0.26, 0.19)	-0.10 (-0.34, 0.14)		-	-	-	-
Metformin-Pioglitazone	-0.12 (-0.26, 0.03)	-0.19 (-0.36, -0.02)	-0.09 (-0.35, 0.18)		-	-	-
Metformin-Saxagliptin	-0.06 (-0.17, 0.05)	-0.13 (-0.27, 0.01)	-0.03 (-0.28, 0.22)	0.06 (-0.12, 0.24)		-	-
Metformin-Sitagliptin	-0.03 (-0.16, 0.10)	-0.10 (-0.25, 0.06)	0.00 (-0.26, 0.27)	0.09 (-0.10, 0.28)	0.03 (-0.14, 0.20)		-
Pioglitazone-Sulfonylurea	0.13 (-0.11, 0.36)	0.06 (-0.20, 0.31)	0.16 (-0.17, 0.49)	0.25 (-0.03, 0.53)	0.19 (-0.07, 0.45)	0.16 (-0.11, 0.43)	

Values given are mean differences in HbA1c in percentage-points.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist FE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 41: FIRST INTENSIFICATION: HbA1c AT 24 MONTHS – relative effect of all options versus reference treatment

Table 69: FIRST INTENSIFICATION: HbA1c AT 24 MONTHS – rankings for each comparator

	Probability best	Median rank (95%CI)
Metformin-Sulfonylurea	0.001	4 (3, 6)
Linagliptin-Metformin	0.000	6 (4, 7)
Liraglutide-Metformin	0.201	3 (1, 7)
Metformin-Pioglitazone	0.538	1 (1, 5)
Metformin-Saxagliptin	0.155	3 (1, 6)
Metformin-Sitagliptin	0.088	3 (1, 7)
Pioglitazone-Sulfonylurea	0.018	7 (2, 7)

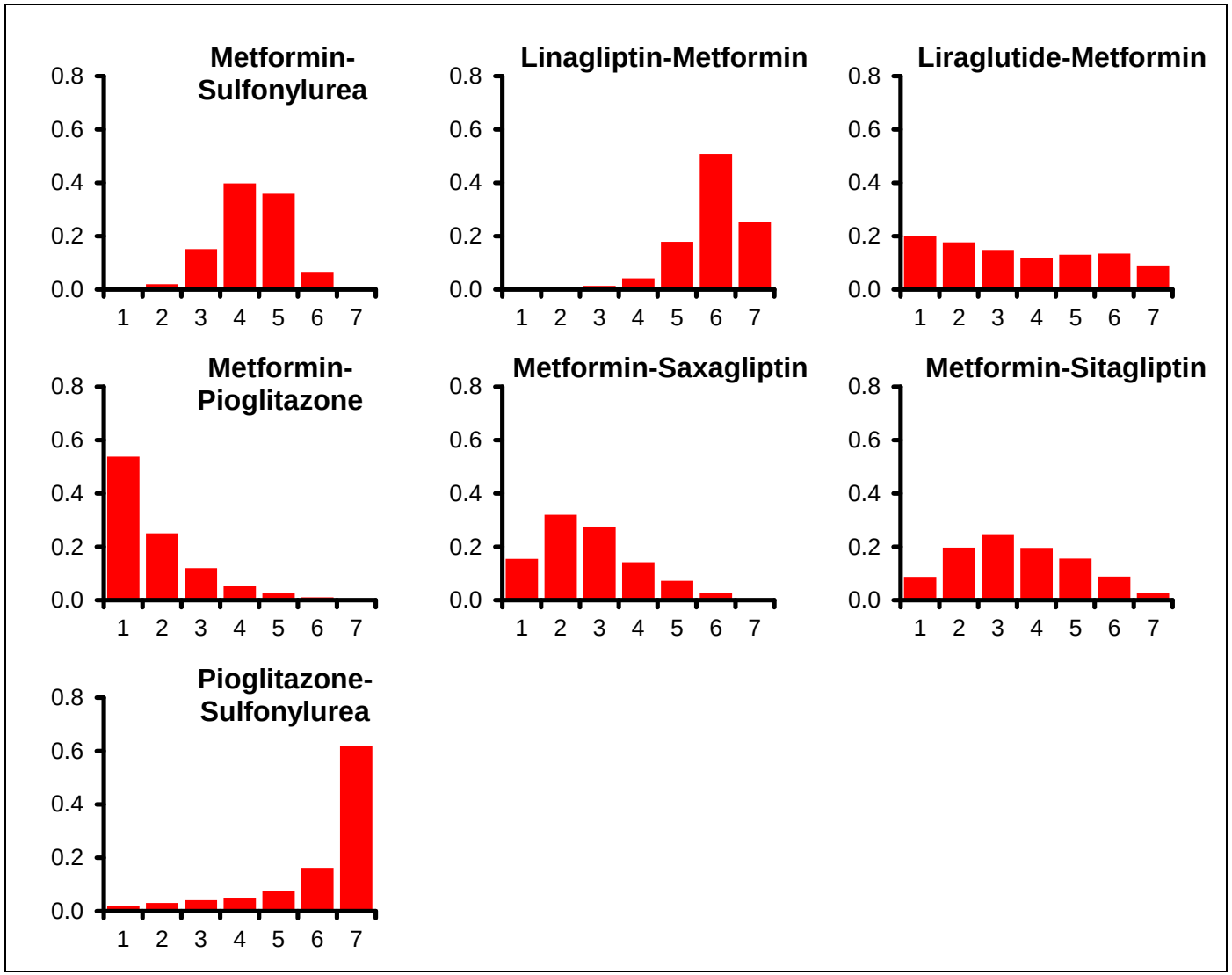


Figure 42: FIRST INTENSIFICATION: HbA1c AT 24 MONTHS – rank probability histograms

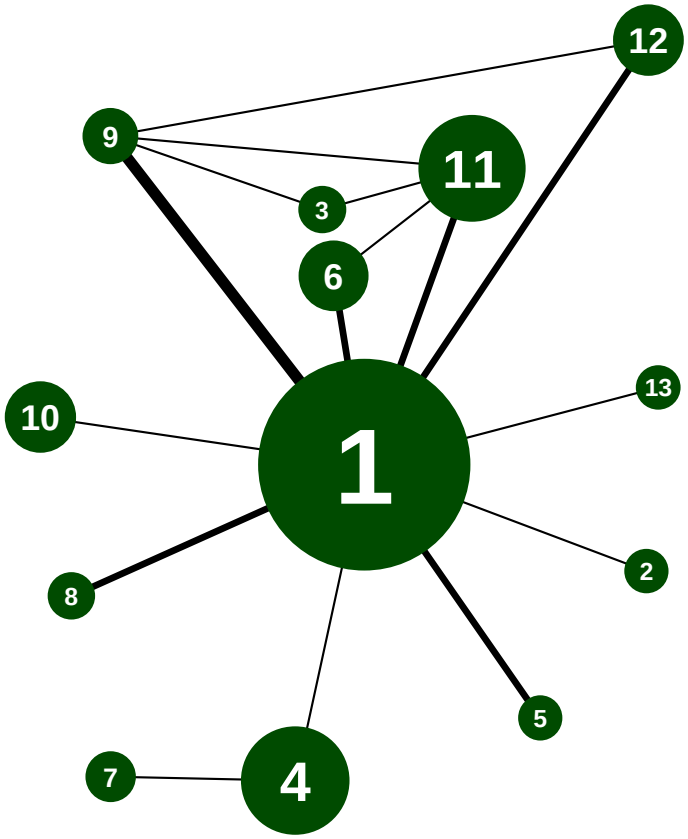
Table 70: FIRST INTENSIFICATION: HbA1c AT 24 MONTHS – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	
14.66 (compared to 14 datapoints)	-38.976	-50.966	11.99	-26.986	

Table 71: FIRST INTENSIFICATION: HbA1c AT 24 MONTHS – notes

- Continuous (normal; identity link); fixed effects
- 10000 burn-ins; 10000 recorded iterations

J.2.2.2 Hypoglycaemia at study endpoint



1 Metformin-Sulfonylurea
2 Acarbose-Metformin
3 Exenatide (once weekly)-Metformin
4 Exenatide-Metformin
5 Linagliptin-Metformin
6 Liraglutide-Metformin
7 Lixisenatide-Metformin
8 Metformin-nateglinide
9 Metformin-Pioglitazone
10 Metformin-Saxagliptin
11 Metformin-Sitagliptin
12 Metformin-Vildagliptin
13 Pioglitazone-Sulfonylurea

Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 43: FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – evidence network

Table 72: FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – input data

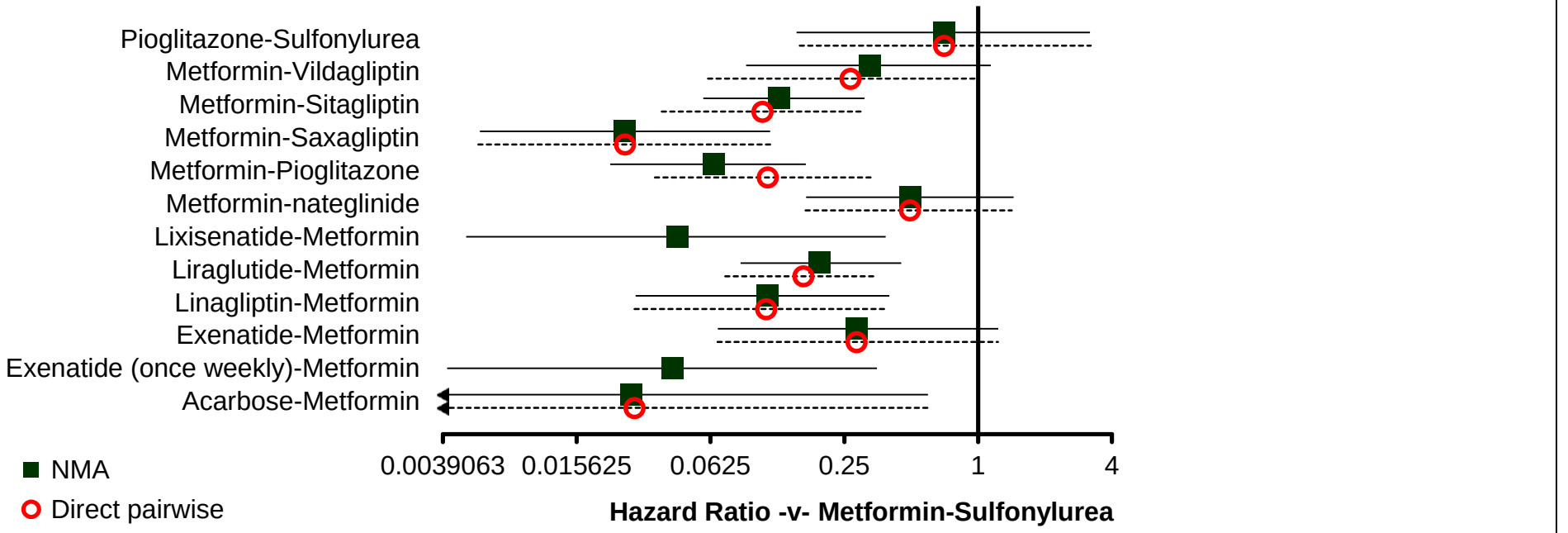
	Metformin-Sulfonylurea	Acarbose-Metformin	Exenatide (once weekly)-Metformin	Exenatide-Metformin	Linagliptin-Metformin	Liraglutide-Metformin	Lixisenatide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Sitagliptin	Metformin-Vildagliptin	Pioglitazone-Sulfonylurea
Dichotomous proportion data													
Wang et al. (2011) - 0.31yr	6/26	0/29											
Forst et al. (2010) - 0.23yr	3/65				0/131								
Jeon & (2011) - 0.61yr	10/51											1/51	
Matthews et al. (2005) - 1.99yr	36/313								7/317				
Umpierrez et al. (2006) - 0.50yr	32/96								1/107				
Gerich et al. (2005) - 1.99yr	35/198							17/208					
Hanefeld et al. (2004) - 1.99yr	50/320												36/319
Gallwitz et al. (2012) - 1.99yr	114/271				14/233								
Count data													
Gallwitz et al. (2012) - 2.99yr	7162/491400			1946/467376									
Goke et al. (2010) - 1.99yr	896/210028									24/215852			
Pfutzner et al. (2011) - 0.46yr	5/22764								2/23352				
Yang et al. (2011) - 0.31yr	84/24976					32/70728							
Bergenstal et al. (2010) - 0.50yr			2/26117						1/26936		9/28210		
Filozof & (2010) - 1.00yr	11/164892											6/167440	
Bolli et al. (2008) - 0.46yr									0/44100			3/46788	
Nauck et al. (2007) - 1.99yr	805/312676										57/306852		
Ristic et al. (2006) - 0.46yr	188/19992							110/21252					
Arechavaleta et al. (2010) - 0.57yr	460/103441										73/103441		
Pratley et al. (2010) - 1.00yr						94/133042					25/67340		
Rosenstock et al. (2013) - 0.46yr				48/49308			8/49980						
Brady et al. (2014) - 0.27yr	127/4410					32/3871							

Values given are number of events / number of participants (for dichotomous proportion data) and number of events / total patient-days (for count data). Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 73: FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations

	Metformin-Sulfonylurea	Acarbose-Metformin	Exenatide (once weekly)-Metformin	Exenatide-Metformin	Linagliptin-Metformin	Liraglutide-Metformin	Lixisenatide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Sitagliptin	Metformin-Vildagliptin
Acarbose-Metformin	0.03 (0.00, 0.59)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Exenatide (once weekly)-Metformin	0.04 (0.00, 0.34)	1.63 (0.03, 1082.00)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Exenatide-Metformin	0.29 (0.07, 1.22)	10.54 (0.35, 6309.00)	6.79 (0.51, 103.90)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Linagliptin-Metformin	0.11 (0.03, 0.40)	4.08 (0.14, 2354.00)	2.65 (0.22, 37.79)	0.39 (0.05, 2.76)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Liraglutide-Metformin	0.19 (0.09, 0.45)	7.06 (0.29, 3790.00)	4.57 (0.53, 51.80)	0.68 (0.13, 3.74)	1.75 (0.38, 8.75)		N/A	N/A	N/A	N/A	N/A	N/A
Lixisenatide-Metformin	0.04 (0.01, 0.39)	1.71 (0.04, 1220.00)	1.08 (0.05, 25.64)	0.16 (0.03, 0.80)	0.40 (0.03, 5.13)	0.23 (0.02, 2.24)		N/A	N/A	N/A	N/A	N/A
Metformin-nateglinide	0.49 (0.17, 1.45)	18.09 (0.71, 9590.00)	11.68 (1.09, 148.90)	1.71 (0.28, 10.51)	4.42 (0.83, 25.26)	2.55 (0.65, 9.66)	11.04 (0.96, 124.20)		N/A	N/A	N/A	N/A
Metformin-Pioglitazone	0.06 (0.02, 0.17)	2.35 (0.09, 1305.00)	1.52 (0.17, 15.52)	0.23 (0.04, 1.28)	0.58 (0.11, 2.94)	0.33 (0.09, 1.11)	1.45 (0.13, 15.27)	0.13 (0.03, 0.54)		N/A	N/A	N/A
Metformin-Saxagliptin	0.03 (0.01, 0.11)	0.96 (0.03, 549.70)	0.61 (0.05, 9.44)	0.09 (0.01, 0.70)	0.23 (0.03, 1.79)	0.13 (0.02, 0.72)	0.58 (0.04, 8.20)	0.05 (0.01, 0.33)	0.40 (0.07, 2.64)		N/A	N/A
Metformin-Sitagliptin	0.13 (0.06, 0.31)	4.67 (0.20, 2622.00)	3.01 (0.42, 30.54)	0.44 (0.09, 2.54)	1.14 (0.26, 5.96)	0.66 (0.27, 1.75)	2.85 (0.29, 30.98)	0.26 (0.07, 1.06)	1.96 (0.66, 7.44)	4.94 (0.93, 28.98)		N/A
Metformin-Vildagliptin	0.33 (0.09, 1.16)	12.01 (0.43, 6413.00)	7.74 (0.68, 108.20)	1.14 (0.17, 7.83)	2.94 (0.46, 18.69)	1.68 (0.36, 7.49)	7.30 (0.59, 88.79)	0.66 (0.13, 3.46)	5.04 (1.15, 24.72)	12.66 (1.79, 89.45)	2.55 (0.54, 10.82)	
Pioglitazone-Sulfonylurea	0.70 (0.15, 3.14)	26.13 (0.82, 15940.00)	16.88 (1.22, 260.10)	2.45 (0.29, 20.50)	6.29 (0.85, 48.11)	3.64 (0.62, 19.71)	15.65 (1.09, 229.10)	1.43 (0.22, 9.35)	10.89 (1.88, 68.21)	27.58 (3.22, 230.50)	5.55 (0.92, 29.34)	2.16 (0.30, 15.60)

Values given are hazard ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.



Values greater than 1 favour metformin-sulfonylurea; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 44: FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effect of all options versus reference treatment

Table 74: FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – rankings for each comparator

	Probability best	Median rank (95%CI)
Metformin-Sulfonylurea	0.000	13 (11, 13)
Acarbose-Metformin	0.401	2 (1, 11)
Exenatide (once weekly)-Metformin	0.167	3 (1, 10)
Exenatide-Metformin	0.000	9 (5, 13)
Linagliptin-Metformin	0.009	6 (2, 10)
Liraglutide-Metformin	0.000	8 (5, 11)
Lixisenatide-Metformin	0.140	3 (1, 9)
Metformin-nateglinide	0.000	11 (7, 13)
Metformin-Pioglitazone	0.016	4 (2, 7)
Metformin-Saxagliptin	0.267	2 (1, 6)
Metformin-Sitagliptin	0.000	6 (4, 9)
Metformin-Vildagliptin	0.000	10 (5, 13)
Pioglitazone-Sulfonylurea	0.000	12 (7, 13)

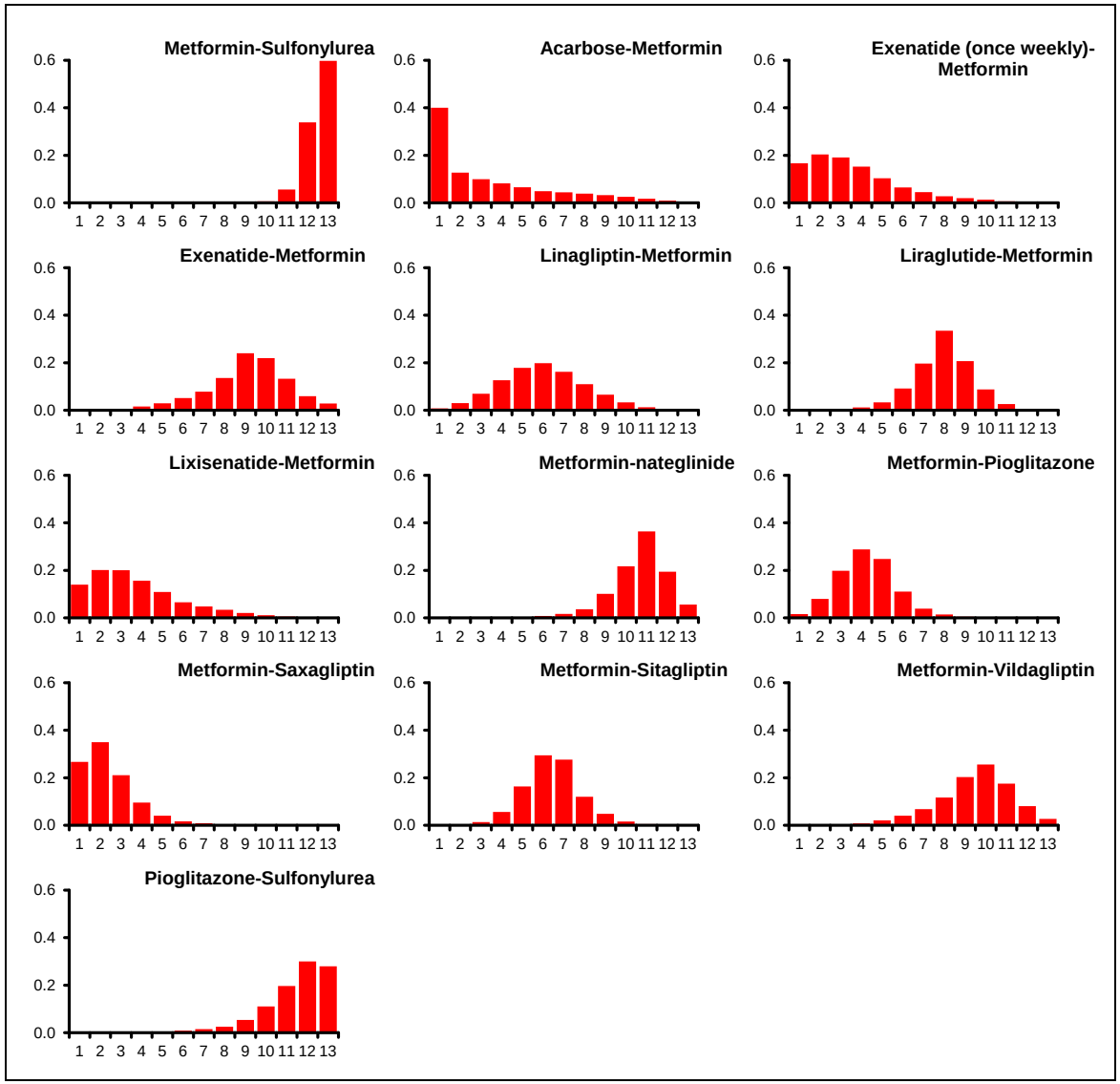


Figure 45: FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – rank probability histograms

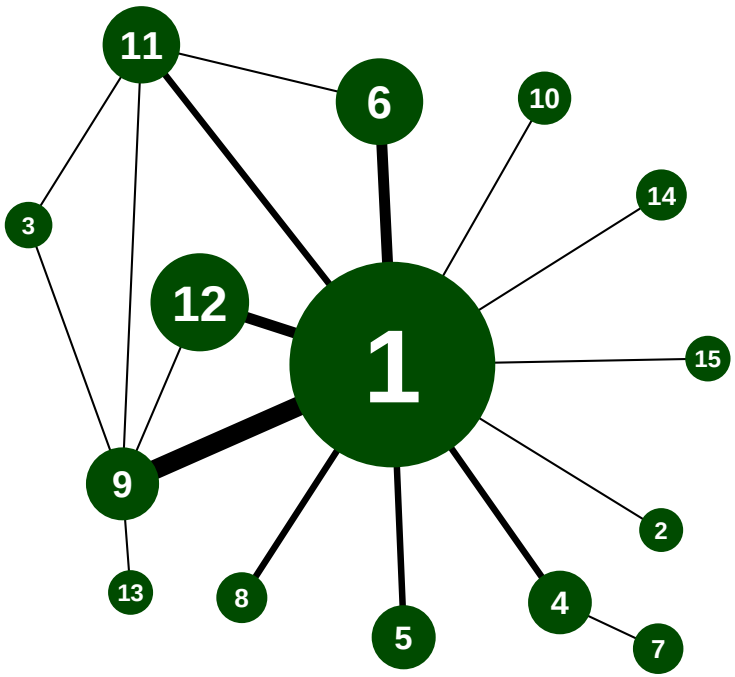
Table 75: FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
47.75 (compared to 47 datapoints)	80.655	66.7	13.955	311.559	0.636 (95%CI: 0.327, 1.272)

Table 76: FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – notes

- Hybrid cloglog--Poisson model for count/dichotomous data; random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

J.2.2.3 Dropouts due to adverse events at study endpoint



1 Metformin-Sulfonylurea
2 Acarbose-Metformin
3 Exenatide (once weekly)-Metformin
4 Exenatide-Metformin
5 Linagliptin-Metformin
6 Liraglutide-Metformin
7 Lixisenatide-Metformin
8 Metformin-nateglinide
9 Metformin-Pioglitazone
10 Metformin-Saxagliptin
11 Metformin-Sitagliptin
12 Metformin-Vildagliptin
13 Pioglitazone-Sitagliptin
14 Pioglitazone-Sulfonylurea
15 Sitagliptin-Sulfonylurea

Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 46: FIRST INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – evidence network

Table 77: FIRST INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – input data

	Metformin-Sulfonylurea	Acarbose-Metformin	Exenatide (once weekly)-Metformin	Exenatide-Metformin	Linagliptin-Metformin	Liraglutide-Metformin	Lixisenatide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Sitagliptin	Metformin-Vildagliptin	Pioglitazone-Sitagliptin	Pioglitazone-Sulfonylurea	Sitagliptin-Sulfonylurea
Gallwitz et al. (2012) - 2.99yr	17/514			49/515											
Wang et al. (2011) - 0.31yr	1/26	0/29													
Goke et al. (2010) - 1.99yr	36/430									32/428					
Derosa et al. (2011) - 1.00yr	4/54			4/57											
Derosa et al. (2011) - 1.00yr	3/99								2/102						
Pfutzner et al. (2011) - 0.46yr	7/150								13/155						
Yang et al. (2011) - 0.31yr	3/231					61/698									
Forst et al. (2010) - 0.23yr	3/65				8/131										
Bergenstal et al. (2010) - 0.50yr			11/160						6/165		5/166				
Filozof & (2010) - 1.00yr	22/494											33/513			
Derosa et al. (2010) - 1.00yr									7/76				4/75		
Ferrannini et al. (2009) - 1.99yr	160/1556											123/1562			
Bolli et al. (2008) - 0.46yr									9/281			8/295			
Hermansen et al. (2007) - 0.46yr	2/113														4/106
Nauck et al. (2007) - 1.99yr	38/584										32/588				
Ristic et al. (2006) - 1.00yr	2/101							1/112							
Jeon & (2011) - 0.61yr	1/51											3/51			
Arechavaleta et al. (2010) - 0.57yr	4/518										18/516				
Nauck et al. (2009) - 0.50yr	8/244					63/725									
Matthews et al. (2005) - 1.99yr	19/313								22/317						
Pratley et al. (2010) - 1.00yr						44/446					7/219				
Umpierrez et al. (2006) - 0.50yr	1/101								4/109						
Gerich et al. (2005) - 1.99yr	28/209							27/219							

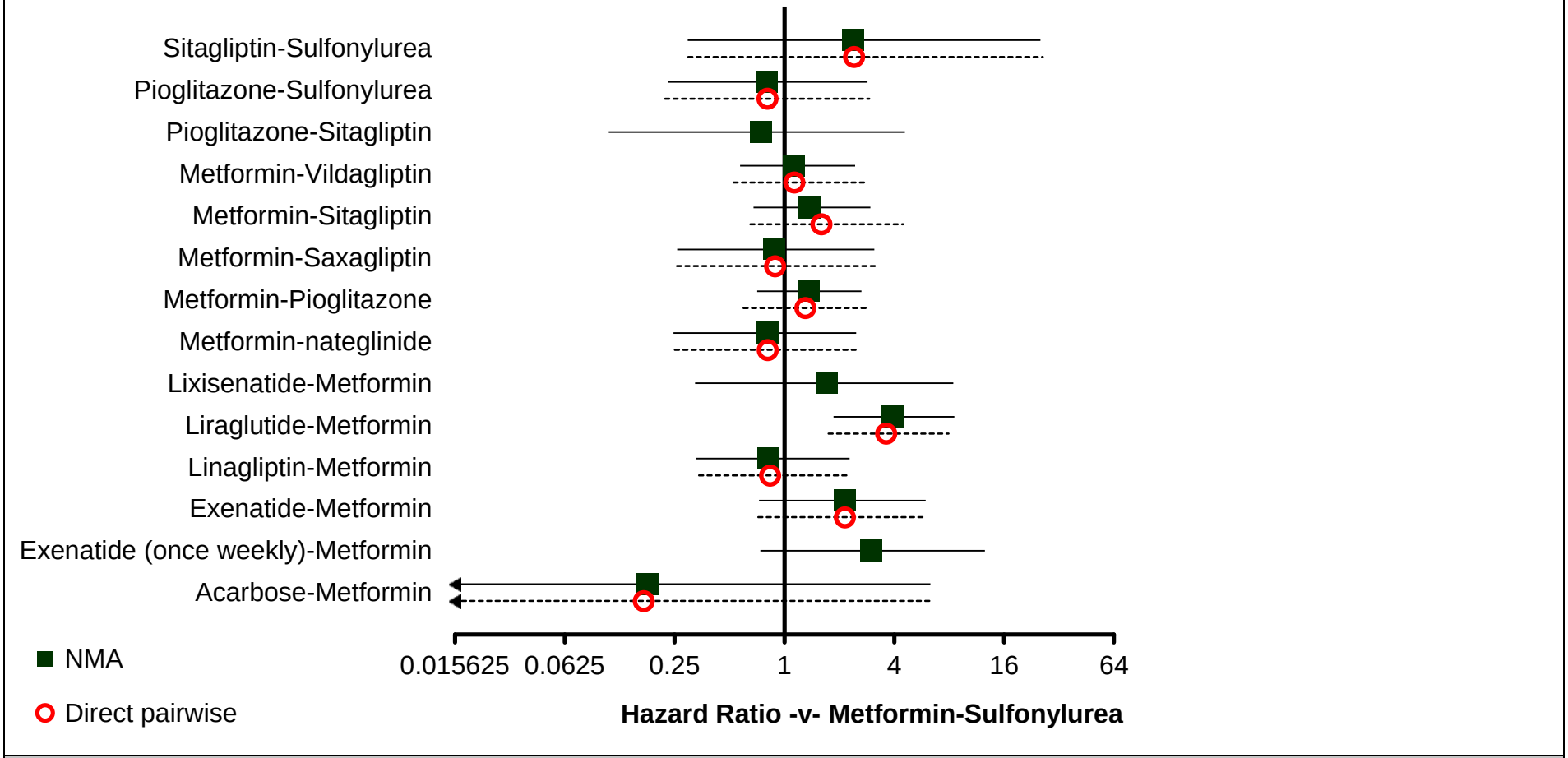
	Metformin-Sulfonylurea	Acarbose-Metformin	Exenatide (once weekly)-Metformin	Exenatide-Metformin	Linagliptin-Metformin	Liraglutide-Metformin	Lixisenatide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Sitagliptin	Metformin-Vildagliptin	Pioglitazone-Sitagliptin	Pioglitazone-Sulfonylurea	Sitagliptin-Sulfonylurea
Hanefeld et al. (2004) - 1.99yr	32/320													26/319	
Gallwitz et al. (2012) - 1.99yr	90/775				61/776										
Rosenstock et al. (2013) - 0.46yr				41/316			33/318								
Maffioli et al. (2013) - 0.50yr	2/84								1/86						
Brady et al. (2014) - 0.27yr	1/52					1/47									

Values given are number of events / number of participants. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 78: FIRST INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations

	Metformin-Sulfonylurea	Acarbose-Metformin	Exenatide (once weekly)-Metformin	Exenatide-Metformin	Linagliptin-Metformin	Liraglutide-Metformin	Lixisenatide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Sitagliptin	Metformin-Vildagliptin	Pioglitazone-Sitagliptin	Pioglitazone-Sulfonylurea
Acarbose-Metformin	0.18 (0.00, 6.32)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Exenatide (once weekly)-Metformin	2.98 (0.74, 12.56)	17.71 (0.35, 7799)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Exenatide-Metformin	2.16 (0.72, 5.94)	12.17 (0.29, 5470)	0.72 (0.12, 4.03)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Linagliptin-Metformin	0.82 (0.33, 2.27)	4.79 (0.11, 1946)	0.28 (0.05, 1.54)	0.38 (0.10, 1.72)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Liraglutide-Metformin	3.93 (1.86, 8.53)	22.59 (0.57, 9350)	1.32 (0.28, 6.10)	1.83 (0.52, 7.01)	4.79 (1.36, 15.97)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lixisenatide-Metformin	1.70 (0.32, 8.43)	9.83 (0.19, 4753)	0.57 (0.06, 4.80)	0.79 (0.23, 2.74)	2.07 (0.29, 12.80)	0.43 (0.07, 2.47)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Metformin-nateglinide	0.81 (0.25, 2.47)	4.71 (0.10, 1962)	0.27 (0.04, 1.59)	0.38 (0.08, 1.76)	0.98 (0.21, 4.09)	0.21 (0.05, 0.77)	0.47 (0.06, 3.53)		N/A	N/A	N/A	N/A	N/A	N/A
Metformin-Pioglitazone	1.36 (0.71, 2.64)	7.76 (0.21, 3243)	0.46 (0.11, 1.80)	0.63 (0.19, 2.31)	1.66 (0.50, 5.11)	0.35 (0.13, 0.93)	0.80 (0.14, 4.79)	1.69 (0.46, 6.63)		N/A	N/A	N/A	N/A	N/A
Metformin-Saxagliptin	0.88 (0.26, 3.11)	5.13 (0.11, 2229)	0.30 (0.04, 1.89)	0.41 (0.09, 2.24)	1.08 (0.21, 5.08)	0.22 (0.05, 0.96)	0.52 (0.07, 4.22)	1.10 (0.20, 6.27)	0.65 (0.16, 2.68)		N/A	N/A	N/A	N/A
Metformin-Sitagliptin	1.38 (0.68, 2.96)	7.87 (0.21, 3237)	0.46 (0.12, 1.87)	0.64 (0.19, 2.47)	1.68 (0.50, 5.53)	0.35 (0.15, 0.85)	0.81 (0.14, 5.14)	1.71 (0.47, 7.00)	1.02 (0.42, 2.52)	1.56 (0.37, 6.74)		N/A	N/A	N/A
Metformin-Vildagliptin	1.13 (0.57, 2.44)	6.53 (0.17, 2634)	0.38 (0.08, 1.82)	0.53 (0.16, 2.02)	1.38 (0.42, 4.57)	0.29 (0.11, 0.85)	0.66 (0.12, 4.30)	1.40 (0.38, 5.86)	0.83 (0.36, 2.03)	1.28 (0.31, 5.63)	0.82 (0.30, 2.32)		N/A	N/A
Pioglitazone-Sitagliptin	0.74 (0.11, 4.57)	4.42 (0.07, 2148)	0.25 (0.03, 2.21)	0.34 (0.04, 2.92)	0.90 (0.11, 6.81)	0.19 (0.02, 1.36)	0.44 (0.04, 5.12)	0.92 (0.10, 8.35)	0.55 (0.09, 2.93)	0.84 (0.09, 7.57)	0.53 (0.07, 3.66)	0.66 (0.09, 4.23)		N/A
Pioglitazone-Sulfonylurea	0.80 (0.23, 2.85)	4.63 (0.10, 1982)	0.27 (0.04, 1.77)	0.37 (0.08, 2.03)	0.98 (0.19, 4.75)	0.20 (0.05, 0.89)	0.48 (0.06, 3.87)	1.00 (0.19, 5.67)	0.60 (0.14, 2.42)	0.91 (0.16, 5.34)	0.58 (0.13, 2.45)	0.71 (0.16, 2.95)	1.09 (0.12, 10.74)	
Sitagliptin-Sulfonylurea	2.39 (0.30, 25.28)	14.73 (0.21, 8124)	0.81 (0.06, 12.44)	1.12 (0.11, 15.10)	2.88 (0.29, 36.84)	0.61 (0.07, 7.27)	1.43 (0.10, 25.49)	2.98 (0.28, 42.18)	1.77 (0.20, 20.25)	2.72 (0.24, 38.38)	1.73 (0.19, 20.38)	2.10 (0.23, 24.98)	3.27 (0.21, 65.77)	2.98 (0.26, 42.47)

Values given are hazard ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.



Values greater than 1 favour metformin-sulfonylurea; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 47: FIRST INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – relative effect of all options versus reference treatment

Table 79: FIRST INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – rankings for each comparator

	Probability best	Median rank (95%CI)
Metformin-Sulfonylurea	0.000	6 (3, 9)
Acarbose-Metformin	0.638	1 (1, 15)
Exenatide (once weekly)-Metformin	0.001	13 (4, 15)
Exenatide-Metformin	0.001	12 (4, 15)
Linagliptin-Metformin	0.036	5 (1, 12)
Liraglutide-Metformin	0.000	14 (11, 15)
Lixisenatide-Metformin	0.017	11 (2, 15)
Metformin-nateglinide	0.054	5 (1, 13)
Metformin-Pioglitazone	0.000	9 (4, 13)
Metformin-Saxagliptin	0.043	5 (1, 13)
Metformin-Sitagliptin	0.001	9 (3, 13)
Metformin-Vildagliptin	0.003	7 (3, 13)
Pioglitazone-Sitagliptin	0.124	4 (1, 14)
Pioglitazone-Sulfonylurea	0.060	5 (1, 13)
Sitagliptin-Sulfonylurea	0.020	12 (2, 15)

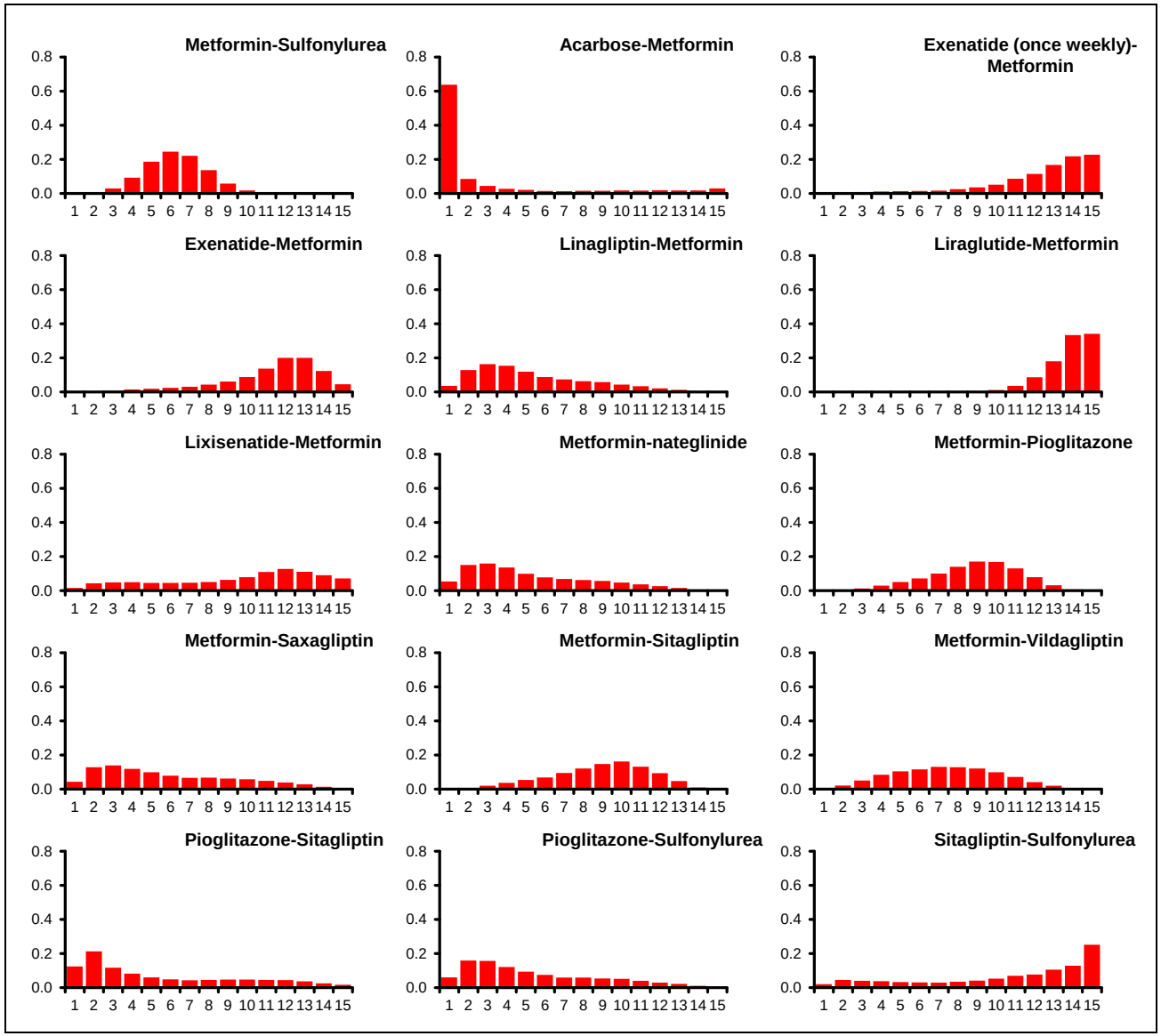


Figure 48: FIRST INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – rank probability histograms

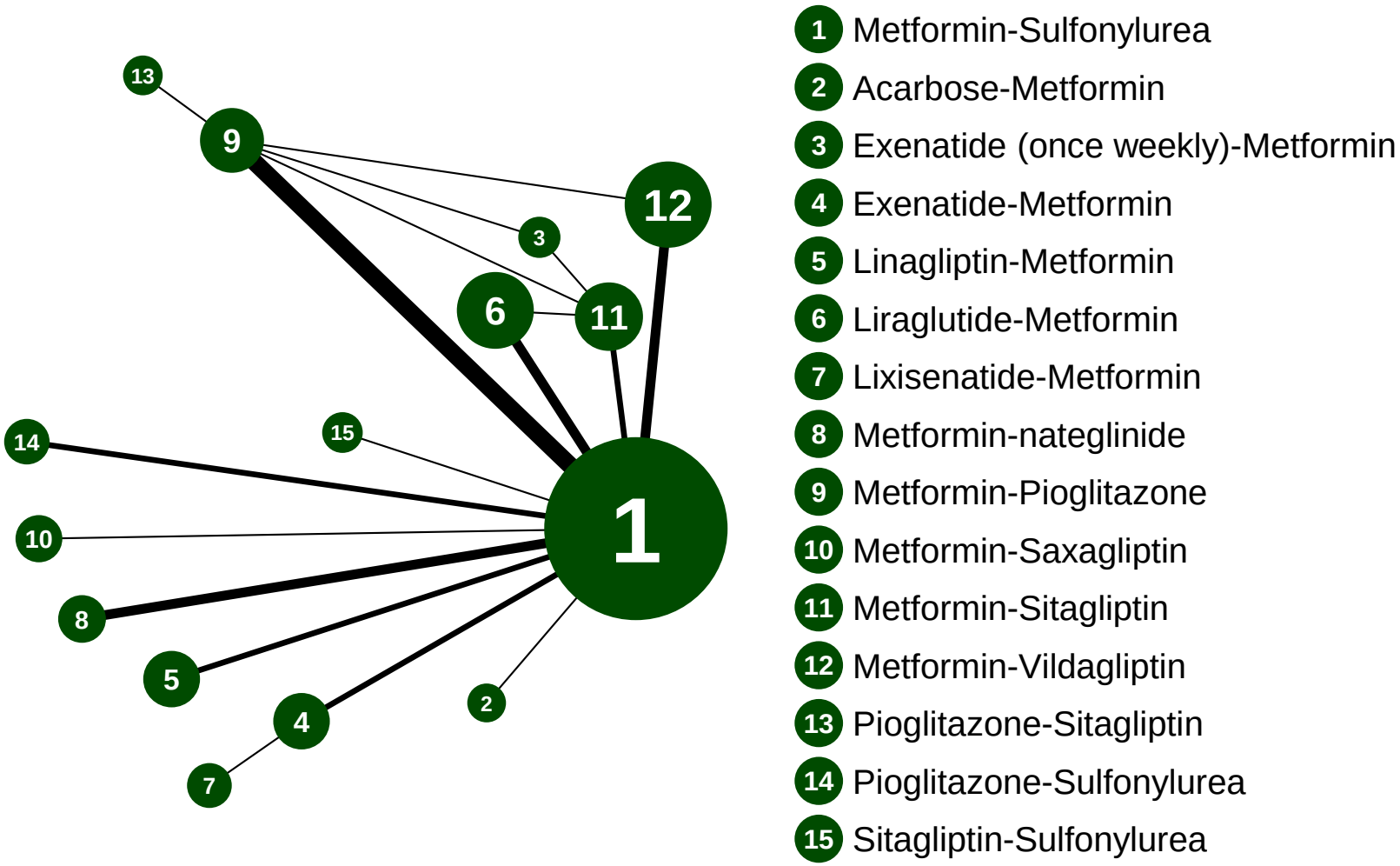
Table 80: FIRST INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
62.51 (compared to 63 datapoints)	314.769	262.537	52.232	367.001	0.534 (95%CI: 0.283, 0.913)

Table 81: FIRST INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – notes

- Dichotomous diachronic (binomial; cloglog link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

J.2.2.4 Total dropouts at study endpoint



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 49: FIRST INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – evidence network

Table 82: FIRST INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – input data

	Metformin-Sulfonylurea	Acarbose-Metformin	Exenatide (once weekly)-Metformin	Exenatide-Metformin	Linagliptin-Metformin	Liraglutide-Metformin	Lixisenatide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Sitagliptin	Metformin-Vildagliptin	Pioglitazone-Sitagliptin	Pioglitazone-Sulfonylurea	Sitagliptin-Sulfonylurea
Gallwitz et al. (2012) - 2.99yr	128/514			174/515											
Wang et al. (2011) - 0.31yr	3/26	1/29													
Goke et al. (2010) - 1.99yr	283/430									263/428					
Derosa et al. (2011) - 1.00yr	5/54			5/57											
Derosa et al. (2011) - 1.00yr	4/99								3/102						
Pfutzner et al. (2011) - 0.46yr	29/150								32/155						
Yang et al. (2011) - 0.31yr	16/231					133/698									
Forst et al. (2010) - 0.23yr	4/65				23/131										
Bergenstal et al. (2010) - 0.50yr			33/160						34/165		22/166				
Filozof & (2010) - 1.00yr	82/494											106/513			
Derosa et al. (2010) - 1.00yr									8/76				6/75		
Ferrannini et al. (2009) - 1.99yr	604/1556											569/1562			
Bolli et al. (2008) - 0.46yr									37/281			33/295			
Derosa et al. (2007) - 1.00yr	10/124							5/124							
Hermansen et al. (2007) - 0.46yr	21/113														23/106
Nauck et al. (2007) - 1.99yr	320/584										333/588				
Ristic et al. (2006) - 1.00yr	3/101							4/112							
Jeon & (2011) - 0.61yr	1/51											3/51			
Arechavaleta et al. (2010) - 0.57yr	51/519										48/516				
Nauck et al. (2009) - 1.99yr	131/244					339/725									
Matthews et al. (2005) - 1.99yr	75/313								84/317						
Pratley et al. (2010) - 1.00yr						161/446					68/219				
Umpierrez et al. (2006) - 0.50yr	13/101								16/109						

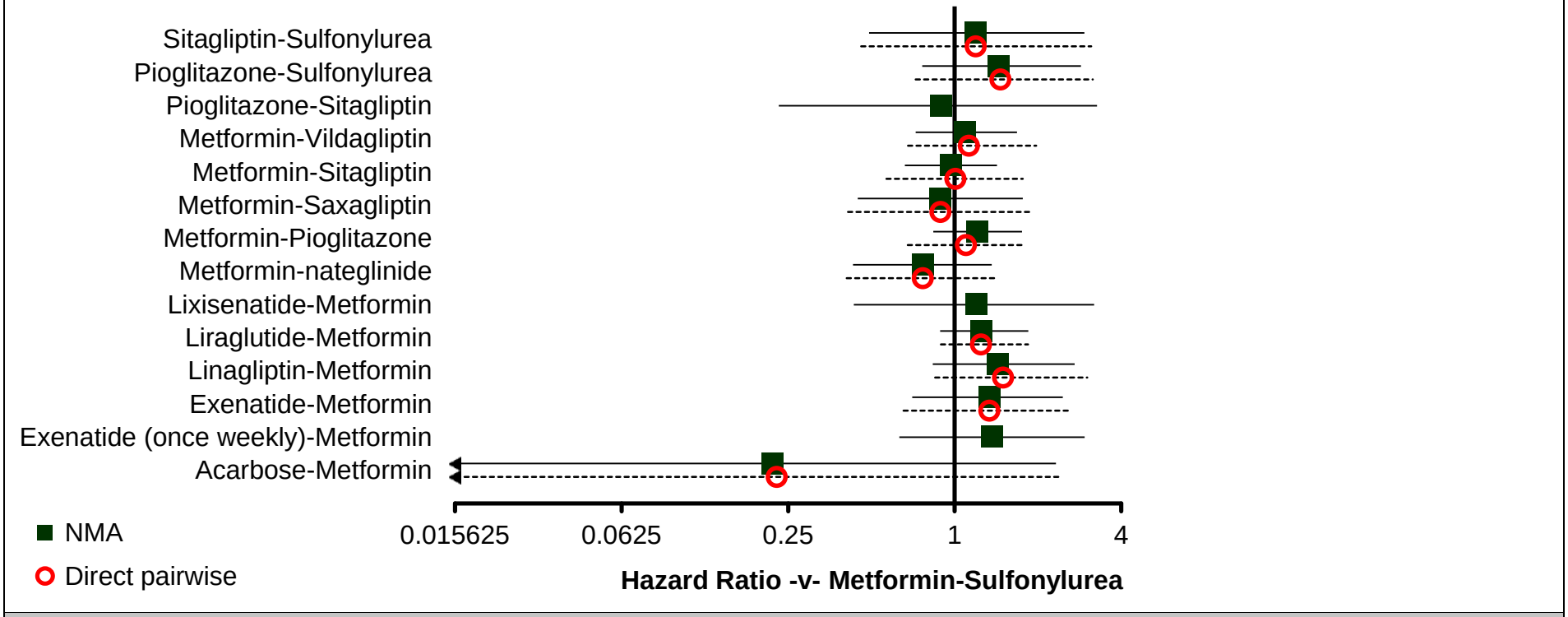
	Metformin-Sulfonylurea	Acarbose-Metformin	Exenatide (once weekly)-Metformin	Exenatide-Metformin	Linagliptin-Metformin	Liraglutide-Metformin	Lixisenatide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Sitagliptin	Metformin-Vildagliptin	Pioglitazone-Sitagliptin	Pioglitazone-Sulfonylurea	Sitagliptin-Sulfonylurea
van der et al. (2009) - 0.46yr	2/39													5/39	
Gerich et al. (2005) - 1.99yr	87/209							78/219							
Hanefeld et al. (2004) - 1.99yr	70/320													88/319	
Gallwitz et al. (2012) - 1.99yr	171/775				189/776										
Rosenstock et al. (2013) - 0.46yr				45/316			41/318								
Maffioli et al. (2013) - 0.50yr	2/84								3/86						
Brady et al. (2014) - 0.27yr	14/52					15/47									

Values given are number of events / number of participants. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 83: FIRST INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations

	Metformin-Sulfonylurea	Acarbose-Metformin	Exenatide (once weekly)-Metformin	Exenatide-Metformin	Linagliptin-Metformin	Liraglutide-Metformin	Lixisenatide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Sitagliptin	Metformin-Vildagliptin	Pioglitazone-Sitagliptin	Pioglitazone-Sulfonylurea
Acarbose-Metformin	0.22 (0.01, 2.32)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Exenatide (once weekly)-Metformin	1.37 (0.63, 2.95)	6.23 (0.52, 197.60)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Exenatide-Metformin	1.34 (0.70, 2.46)	6.08 (0.53, 194.50)	0.98 (0.36, 2.60)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Linagliptin-Metformin	1.43 (0.83, 2.71)	6.59 (0.59, 201.30)	1.06 (0.42, 2.89)	1.07 (0.48, 2.69)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Liraglutide-Metformin	1.25 (0.88, 1.85)	5.74 (0.53, 174.80)	0.92 (0.41, 2.13)	0.94 (0.47, 2.02)	0.88 (0.43, 1.69)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lixisenatide-Metformin	1.20 (0.43, 3.19)	5.48 (0.42, 184.60)	0.88 (0.24, 3.09)	0.90 (0.41, 1.92)	0.84 (0.25, 2.50)	0.96 (0.32, 2.64)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Metformin-nateglinide	0.77 (0.43, 1.36)	3.49 (0.31, 106.20)	0.56 (0.22, 1.46)	0.57 (0.25, 1.37)	0.54 (0.23, 1.16)	0.61 (0.30, 1.19)	0.64 (0.21, 2.06)		N/A	N/A	N/A	N/A	N/A	N/A
Metformin-Pioglitazone	1.20 (0.84, 1.75)	5.47 (0.50, 167.00)	0.88 (0.42, 1.87)	0.90 (0.44, 1.88)	0.84 (0.40, 1.63)	0.96 (0.57, 1.57)	1.00 (0.36, 2.99)	1.57 (0.80, 3.13)		N/A	N/A	N/A	N/A	N/A
Metformin-Saxagliptin	0.89 (0.45, 1.76)	4.07 (0.35, 128.70)	0.65 (0.23, 1.82)	0.66 (0.27, 1.72)	0.62 (0.24, 1.45)	0.71 (0.32, 1.52)	0.74 (0.23, 2.53)	1.16 (0.47, 2.87)	0.74 (0.34, 1.60)		N/A	N/A	N/A	N/A
Metformin-Sitagliptin	0.97 (0.66, 1.42)	4.41 (0.40, 132.50)	0.71 (0.33, 1.51)	0.72 (0.35, 1.54)	0.68 (0.32, 1.31)	0.77 (0.49, 1.18)	0.80 (0.29, 2.42)	1.26 (0.63, 2.52)	0.80 (0.50, 1.30)	1.09 (0.50, 2.39)		N/A	N/A	N/A
Metformin-Vildagliptin	1.09 (0.72, 1.68)	5.01 (0.46, 150.60)	0.80 (0.35, 1.90)	0.81 (0.39, 1.77)	0.76 (0.36, 1.51)	0.87 (0.50, 1.49)	0.90 (0.32, 2.81)	1.42 (0.71, 2.95)	0.90 (0.56, 1.51)	1.22 (0.56, 2.79)	1.13 (0.65, 2.00)		N/A	N/A
Pioglitazone-Sitagliptin	0.90 (0.23, 3.27)	4.12 (0.27, 149.10)	0.65 (0.14, 2.76)	0.67 (0.15, 2.85)	0.62 (0.14, 2.54)	0.71 (0.17, 2.70)	0.75 (0.14, 3.87)	1.16 (0.26, 4.86)	0.74 (0.20, 2.58)	1.01 (0.22, 4.35)	0.92 (0.23, 3.49)	0.82 (0.20, 3.11)		N/A
Pioglitazone-Sulfonylurea	1.44 (0.76, 2.86)	6.64 (0.56, 208.90)	1.06 (0.39, 2.96)	1.08 (0.45, 2.78)	1.01 (0.41, 2.38)	1.15 (0.54, 2.46)	1.21 (0.38, 4.16)	1.88 (0.79, 4.64)	1.20 (0.56, 2.59)	1.62 (0.65, 4.29)	1.49 (0.71, 3.25)	1.33 (0.61, 2.91)	1.62 (0.38, 7.53)	
Sitagliptin-Sulfonylurea	1.19 (0.49, 2.94)	5.49 (0.42, 180.60)	0.87 (0.27, 2.87)	0.89 (0.31, 2.69)	0.83 (0.27, 2.35)	0.95 (0.36, 2.47)	1.00 (0.26, 3.89)	1.55 (0.53, 4.51)	0.99 (0.38, 2.63)	1.34 (0.45, 4.15)	1.23 (0.47, 3.29)	1.10 (0.41, 2.88)	1.34 (0.28, 6.89)	0.83 (0.27, 2.46)

Values given are hazard ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.



Values greater than 1 favour metformin-sulfonylurea; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 50: FIRST INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – relative effect of all options versus reference treatment

Table 84: FIRST INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – rankings for each comparator

	Probability best	Median rank (95%CI)
Metformin-Sulfonylurea	0.000	6 (3, 10)
Acarbose-Metformin	0.754	1 (1, 15)
Exenatide (once weekly)-Metformin	0.006	11 (2, 15)
Exenatide-Metformin	0.001	11 (3, 15)
Linagliptin-Metformin	0.001	12 (4, 15)
Liraglutide-Metformin	0.000	10 (5, 14)
Lixisenatide-Metformin	0.022	10 (2, 15)
Metformin-nateglinide	0.059	3 (1, 12)
Metformin-Pioglitazone	0.000	10 (4, 14)
Metformin-Saxagliptin	0.034	5 (1, 14)
Metformin-Sitagliptin	0.006	6 (2, 12)
Metformin-Vildagliptin	0.002	8 (3, 14)
Pioglitazone-Sitagliptin	0.096	5 (1, 15)
Pioglitazone-Sulfonylurea	0.001	12 (3, 15)
Sitagliptin-Sulfonylurea	0.018	9 (2, 15)

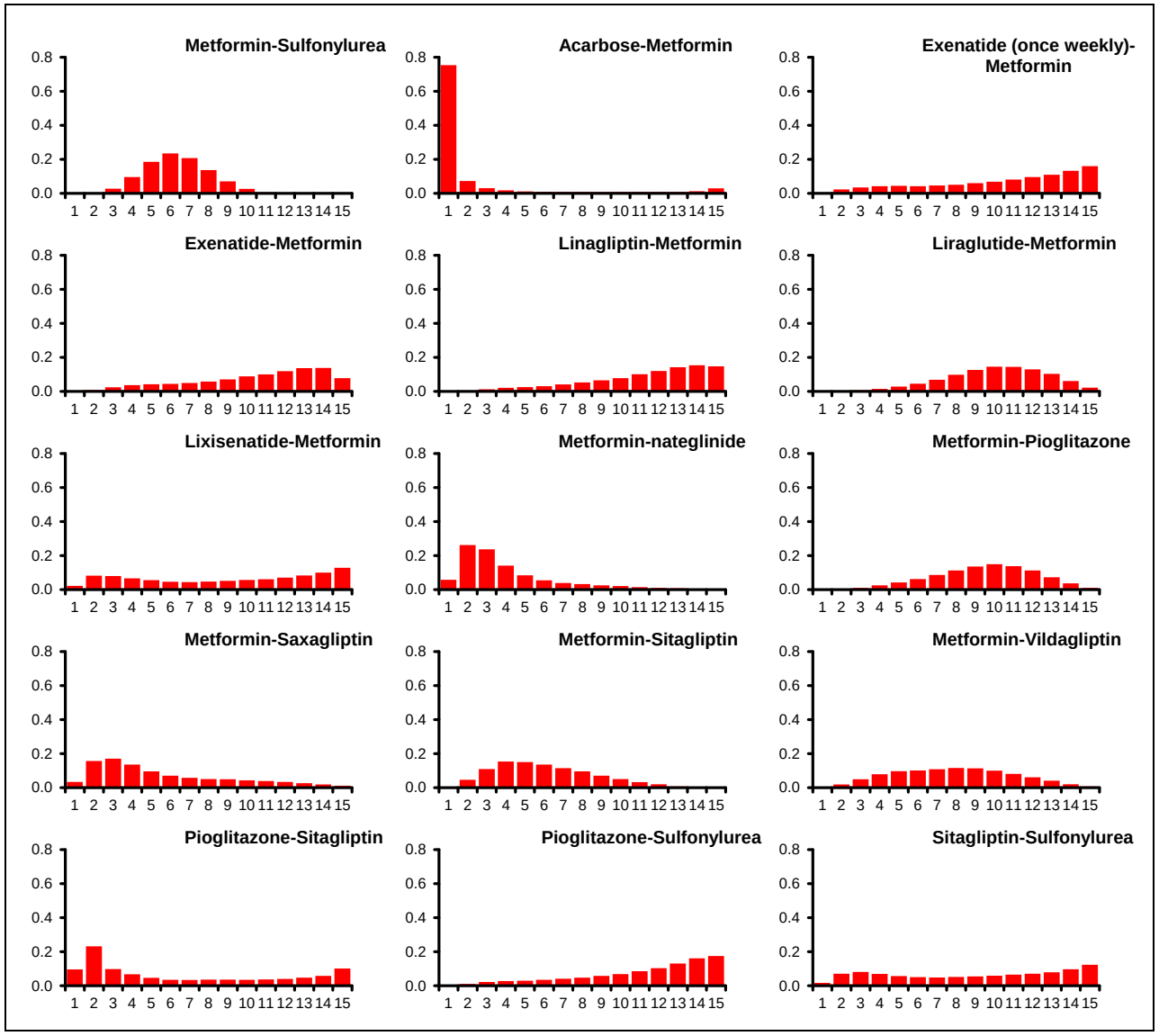


Figure 51: FIRST INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – rank probability histograms

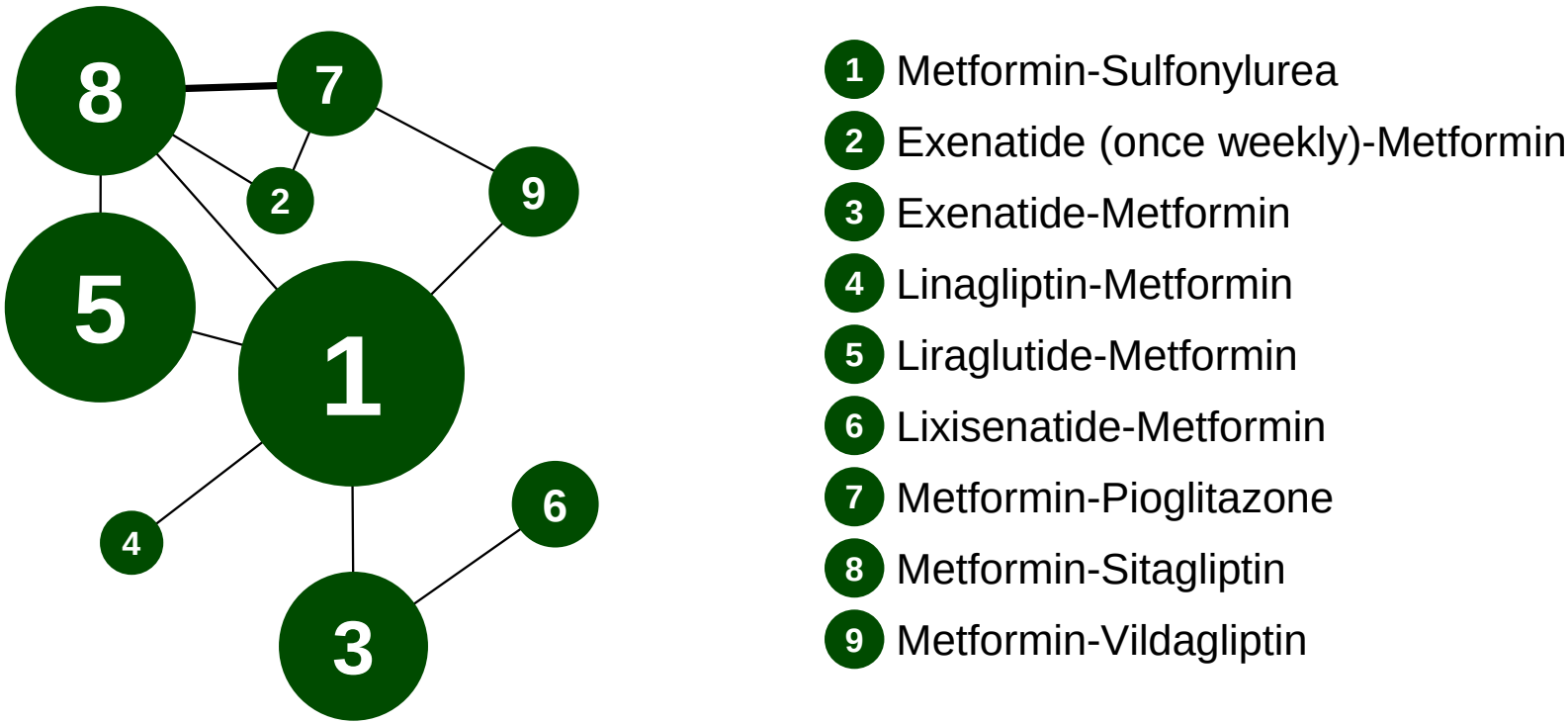
Table 85: FIRST INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
66.1 (compared to 67 datapoints)	394.825	338.662	56.163	450.988	0.309 (95%CI: 0.170, 0.514)

Table 86: FIRST INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – notes

- Dichotomous diachronic (binomial; cloglog link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 100000 burn-ins; 10000 recorded iterations (thinned from 100000)

J.2.2.5 Nausea at study endpoint



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 52: FIRST INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – evidence network

Table 87: FIRST INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – input data

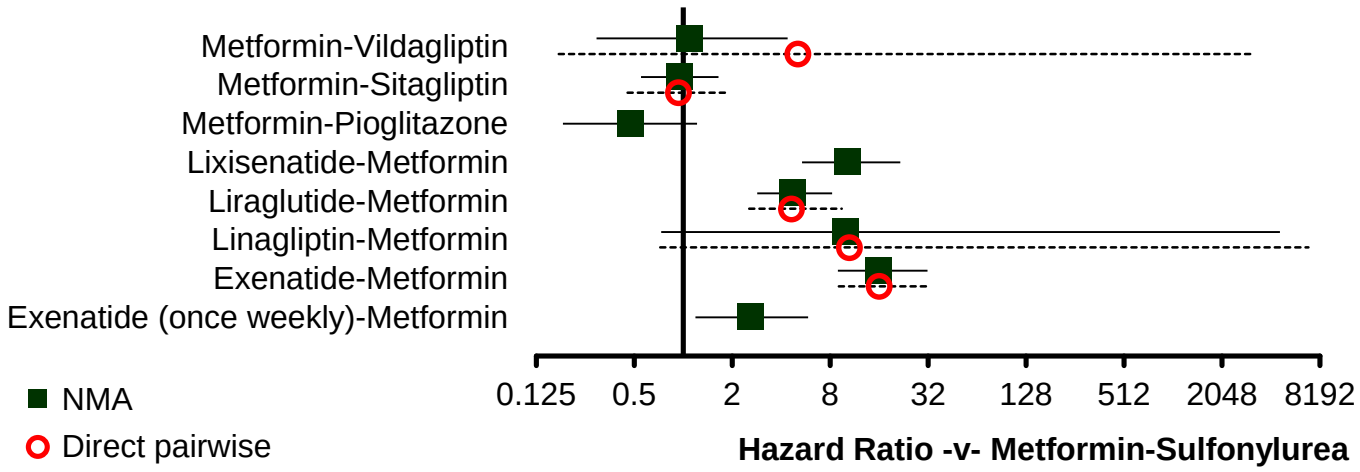
	Metformin-Sulfonylurea	Exenatide (once weekly)-Metformin	Exenatide-Metformin	Linagliptin-Metformin	Liraglutide-Metformin	Lixisenatide-Metformin	Metformin-Pioglitazone	Metformin-Sitagliptin	Metformin-Vildagliptin
Gallwitz et al. (2012) - 2.99yr	11/508		147/511						
Forst et al. (2010) - 0.23yr	0/65			4/131					
Bergenstal et al. (2010) - 0.50yr		38/160					8/165	16/166	
Bolli et al. (2008) - 1.00yr							5/280		10/295
Nauck et al. (2007) - 1.00yr	16/584							15/588	
Jeon & (2011) - 0.61yr	0/51								1/51
Nauck et al. (2009) - 1.99yr	10/244				124/725				
Pratley et al. (2010) - 1.00yr					108/439			12/219	
Chawla et al. (2013) - 0.31yr							0/25	1/25	
Rosenstock et al. (2013) - 0.46yr			111/316			78/318			

Values given are number of events / number of participants. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 88: FIRST INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations

	Metformin-Sulfonylurea	Exenatide (once weekly)-Metformin	Exenatide-Metformin	Linagliptin-Metformin	Liraglutide-Metformin	Lixisenatide-Metformin	Metformin-Pioglitazone	Metformin-Sitagliptin	Metformin-Vildagliptin
Metformin-Sulfonylurea		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Exenatide (once weekly)-Metformin	2.62 (1.19, 5.85)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Exenatide-Metformin	15.89 (8.94, 31.69)	6.12 (2.24, 17.41)		N/A	N/A	N/A	N/A	N/A	N/A
Linagliptin-Metformin	9.91 (0.73, 4659.00)	3.84 (0.24, 1885.00)	0.62 (0.04, 308.60)		N/A	N/A	N/A	N/A	N/A
Liraglutide-Metformin	4.73 (2.85, 8.21)	1.81 (0.84, 3.92)	0.30 (0.13, 0.66)	0.47 (0.00, 6.95)		N/A	N/A	N/A	N/A
Lixisenatide-Metformin	10.34 (5.37, 21.63)	3.98 (1.38, 11.62)	0.65 (0.49, 0.87)	1.05 (0.00, 16.01)	2.19 (0.93, 5.42)		N/A	N/A	N/A
Metformin-Pioglitazone	0.48 (0.18, 1.22)	0.18 (0.08, 0.37)	0.03 (0.01, 0.09)	0.05 (0.00, 0.81)	0.10 (0.04, 0.25)	0.05 (0.01, 0.14)		N/A	N/A
Metformin-Sitagliptin	0.95 (0.55, 1.65)	0.36 (0.20, 0.64)	0.06 (0.03, 0.13)	0.10 (0.00, 1.41)	0.20 (0.12, 0.32)	0.09 (0.04, 0.22)	1.97 (0.92, 4.54)		N/A
Metformin-Vildagliptin	1.10 (0.29, 4.39)	0.42 (0.12, 1.55)	0.07 (0.02, 0.30)	0.11 (0.00, 2.28)	0.23 (0.06, 0.93)	0.11 (0.02, 0.48)	2.30 (0.84, 7.21)	1.16 (0.33, 4.32)	

Values given are hazard ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.



Values greater than 1 favour metformin-sulfonylurea; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 53: FIRST INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – relative effect of all options versus reference treatment

Table 89: FIRST INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – rankings for each comparator

	Probability best	Median rank (95%CI)
Metformin-Sulfonylurea	0.048	3 (1, 4)
Exenatide (once weekly)-Metformin	0.000	5 (4, 6)
Exenatide-Metformin	0.000	9 (8, 9)
Linagliptin-Metformin	0.014	7 (2, 9)
Liraglutide-Metformin	0.000	6 (5, 7)
Lixisenatide-Metformin	0.000	7 (6, 8)
Metformin-Pioglitazone	0.863	1 (1, 3)
Metformin-Sitagliptin	0.023	3 (2, 4)
Metformin-Vildagliptin	0.053	4 (1, 6)

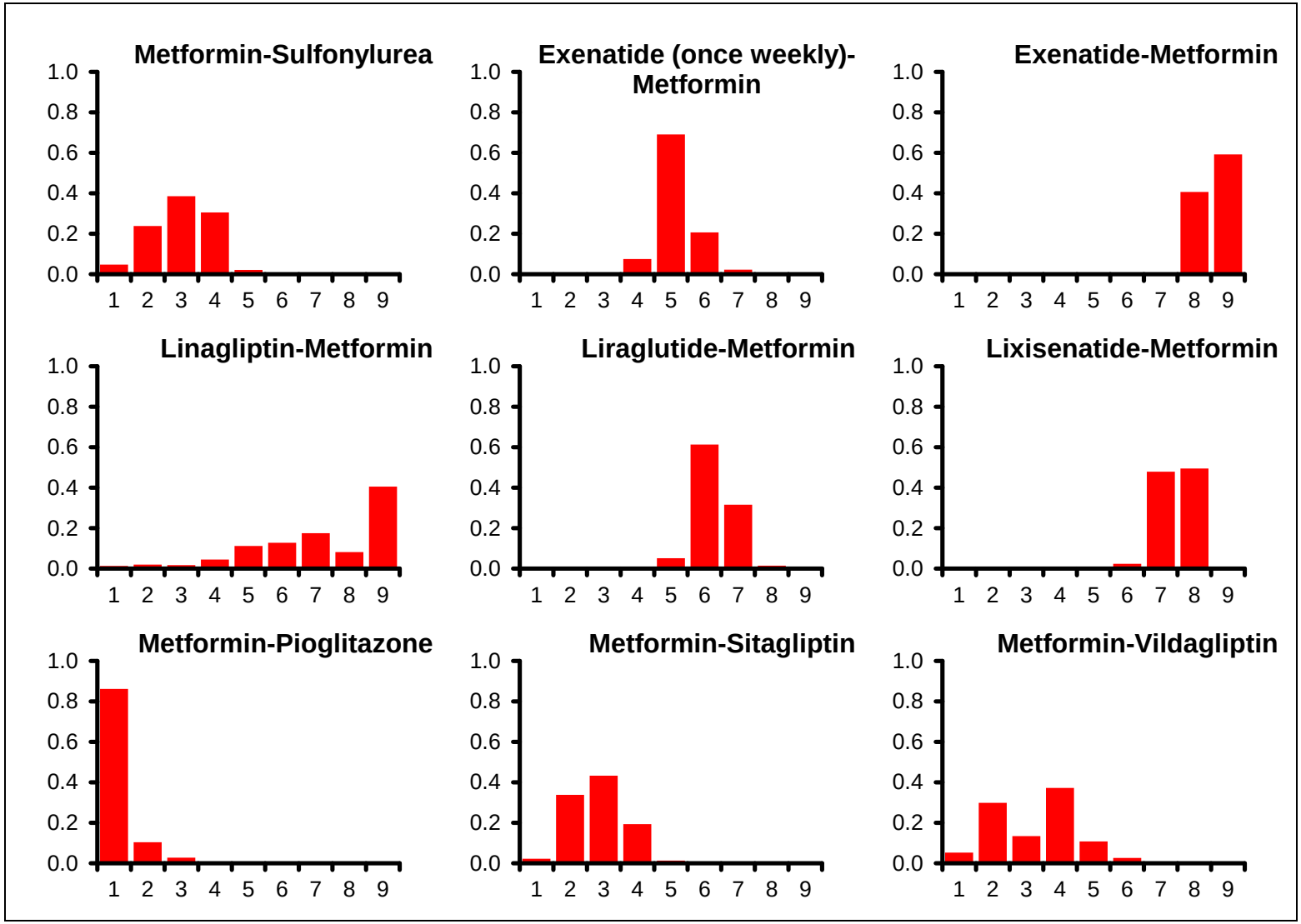


Figure 54: FIRST INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – rank probability histograms

Table 90: FIRST INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – model fit statistics

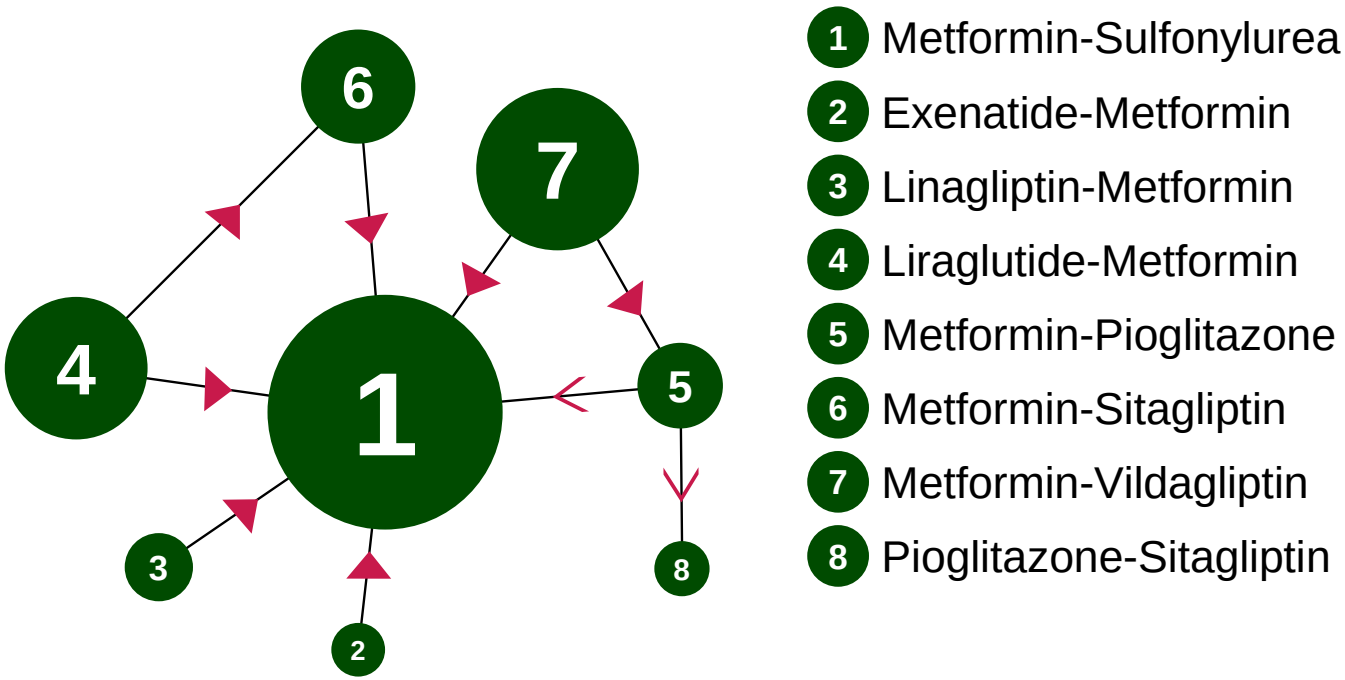
Residual deviance	Dbar	Dhat	pD	DIC
32.22 (compared to 25 datapoints)	134.512	116.986	17.526	152.038

Table 91: FIRST INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – notes

- Dichotomous diachronic (binomial; cloglog link); fixed effects
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

J.2.2.6 Change in body weight at 12 and 24 months

Change in body weight at 12 months



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 55: FIRST INTENSIFICATION: BODY WEIGHT AT 12 MONTHS – evidence network

Table 92: FIRST INTENSIFICATION: BODY WEIGHT AT 12 MONTHS – input data

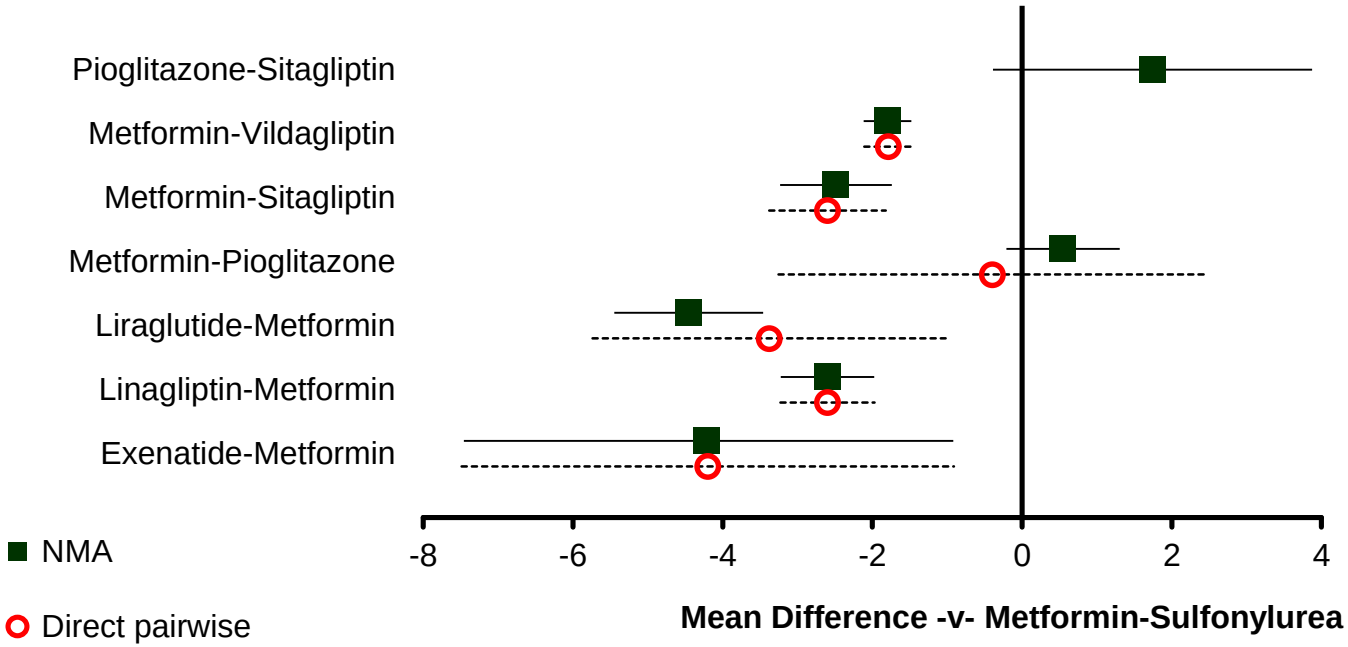
	Metformin-Sulfonylurea	Exenatide-Metformin	Linagliptin-Metformin	Liraglutide-Metformin	Metformin-Pioglitazone	Metformin-Sitagliptin	Metformin-Vildagliptin	Pioglitazone-Sitagliptin
Derosa et al. (2011)	-0.90 (8.89)	-5.10 (7.91)						
Derosa et al. (2011)	1.20 (9.93)				0.80 (10.36)			
Derosa et al. (2010)					-2.80 (5.45)			-1.60 (6.46)
Ferrannini et al. (2009)	1.56 (3.93)						-0.23 (3.68)	
Bolli et al. (2008)					2.60 (5.02)		0.20 (3.44)	
Nauck et al. (2007)	1.10 (6.78)					-1.50 (6.80)		
Nauck et al. (2009)	1.94 (16.23)			-1.44 (16.35)				
Pratley et al. (2010)				-3.23 (4.61)		-1.16 (4.61)		
Gallwitz et al. (2012)	0.95 (3.29)		-1.65 (3.82)					

Values given are mean change in body-weight(SD), in kilograms. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 93: FIRST INTENSIFICATION: BODY WEIGHT AT 12 MONTHS – relative effectiveness of all pairwise combinations

	Metformin-Sulfonylurea	Exenatide-Metformin	Linagliptin-Metformin	Liraglutide-Metformin	Metformin-Pioglitazone	Metformin-Sitagliptin	Metformin-Vildagliptin	Pioglitazone-Sitagliptin
Metformin-Sulfonylurea		-4.20 (-7.49, -0.91)	-2.60 (-3.23, -1.97)	-3.38 (-5.74, -1.02)	-0.40 (-3.25, 2.45)	-2.60 (-3.38, -1.82)	-1.79 (-2.11, -1.47)	-
Exenatide-Metformin	-4.22 (-7.46, -0.92)		-	-	-	-	-	-
Linagliptin-Metformin	-2.60 (-3.22, -1.98)	1.61 (-1.74, 4.90)		-	-	-	-	-
Liraglutide-Metformin	-4.45 (-5.45, -3.46)	-0.24 (-3.69, 3.18)	-1.85 (-3.02, -0.68)		-	2.07 (1.32, 2.81)	-	-
Metformin-Pioglitazone	0.55 (-0.21, 1.31)	4.77 (1.39, 8.10)	3.15 (2.18, 4.14)	5.00 (3.76, 6.25)		-	-2.40 (-3.11, -1.69)	1.20 (-0.80, 3.20)
Metformin-Sitagliptin	-2.49 (-3.24, -1.74)	1.73 (-1.66, 5.08)	0.11 (-0.87, 1.09)	1.97 (1.25, 2.68)	-3.04 (-4.11, -1.96)		-	-
Metformin-Vildagliptin	-1.80 (-2.12, -1.48)	2.42 (-0.88, 5.67)	0.80 (0.11, 1.51)	2.65 (1.61, 3.70)	-2.35 (-3.04, -1.65)	0.69 (-0.13, 1.51)		-
Pioglitazone-Sitagliptin	1.75 (-0.39, 3.87)	5.98 (2.07, 9.85)	4.36 (2.13, 6.55)	6.21 (3.85, 8.56)	1.20 (-0.77, 3.18)	4.25 (1.98, 6.48)	3.55 (1.44, 5.65)	

Values given are mean differences in body-weight in kilograms.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist FE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 56: FIRST INTENSIFICATION: BODY WEIGHT AT 12 MONTHS – relative effect of all options versus reference treatment

Table 94: FIRST INTENSIFICATION: BODY WEIGHT AT 12 MONTHS – rankings for each comparator

	Probability best	Median rank (95%CI)
Metformin-Sulfonylurea	0.000	6 (6, 7)
Exenatide-Metformin	0.445	2 (1, 5)
Linagliptin-Metformin	0.000	3 (2, 4)
Liraglutide-Metformin	0.555	1 (1, 2)
Metformin-Pioglitazone	0.000	7 (6, 8)
Metformin-Sitagliptin	0.000	4 (2, 5)
Metformin-Vildagliptin	0.000	5 (4, 5)
Pioglitazone-Sitagliptin	0.000	8 (6, 8)

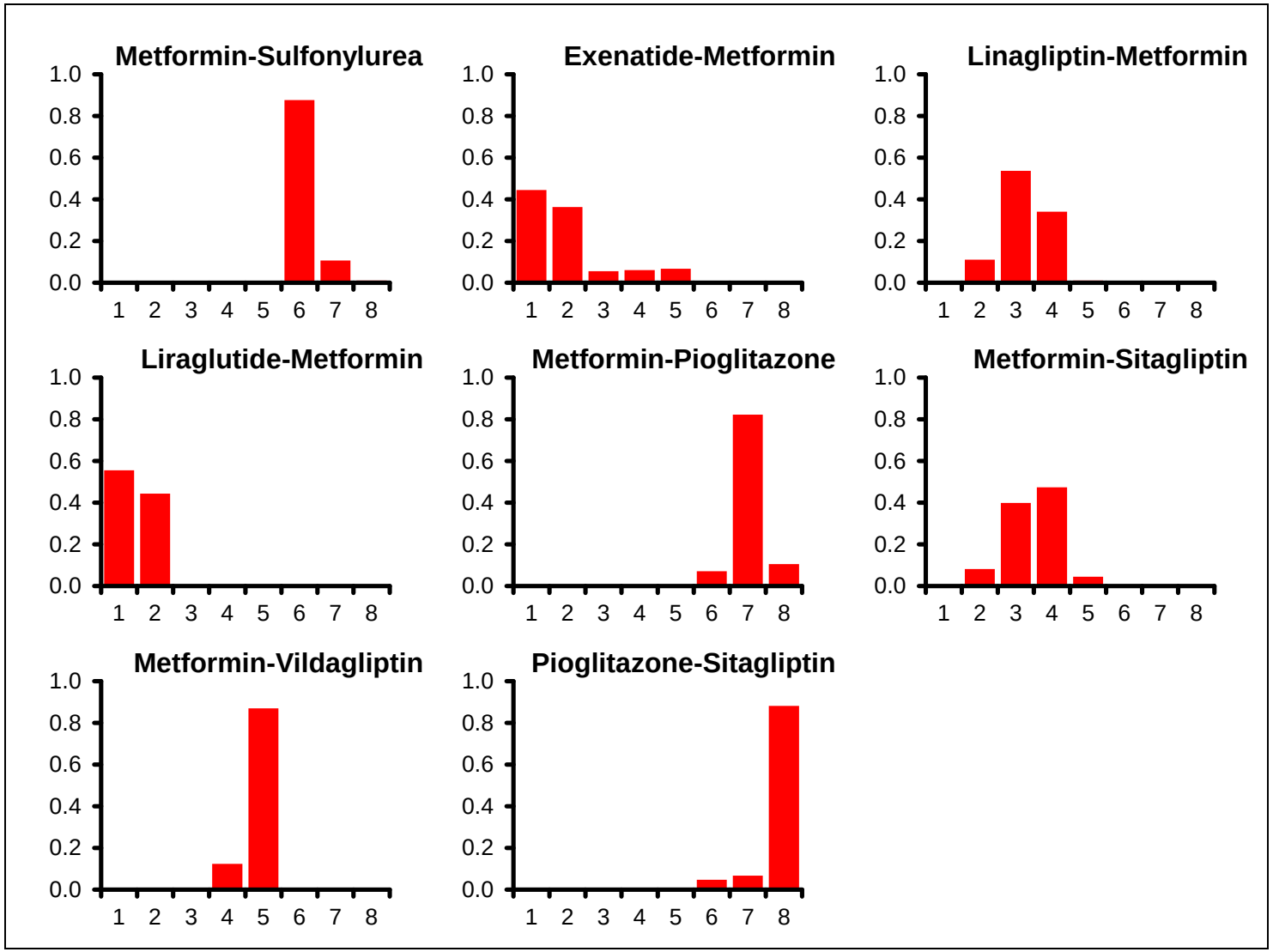


Figure 57: FIRST INTENSIFICATION: BODY WEIGHT AT 12 MONTHS – rank probability histograms

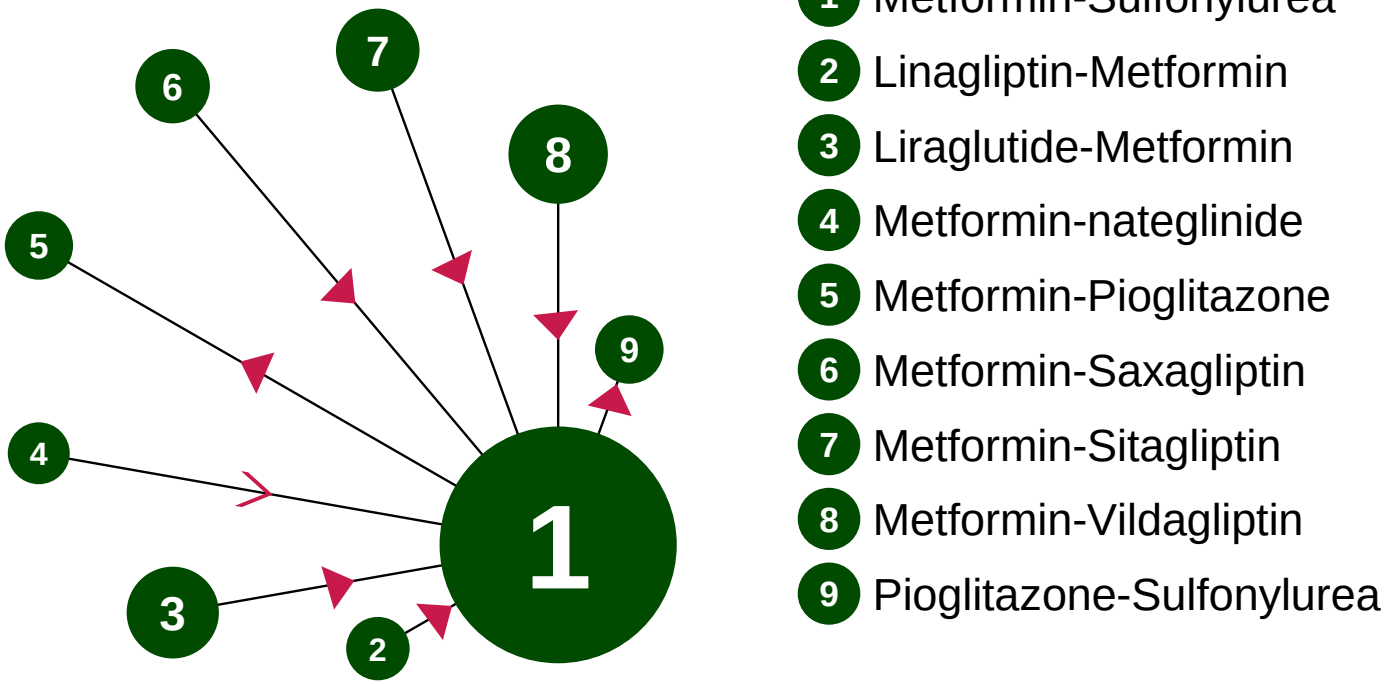
Table 95: FIRST INTENSIFICATION: BODY WEIGHT AT 12 MONTHS – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	
23.36 (compared to 21 datapoints)	29.421	13.38	16.041	45.463	

Table 96: FIRST INTENSIFICATION: BODY WEIGHT AT 12 MONTHS – notes

- Continuous (normal; identity link); fixed effects
- 50000 burn-ins; 10000 recorded iterations

Change in body weight at 24 months



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 58: FIRST INTENSIFICATION: BODY WEIGHT AT 24 MONTHS – evidence network

Table 97: FIRST INTENSIFICATION: BODY WEIGHT AT 24 MONTHS – input data

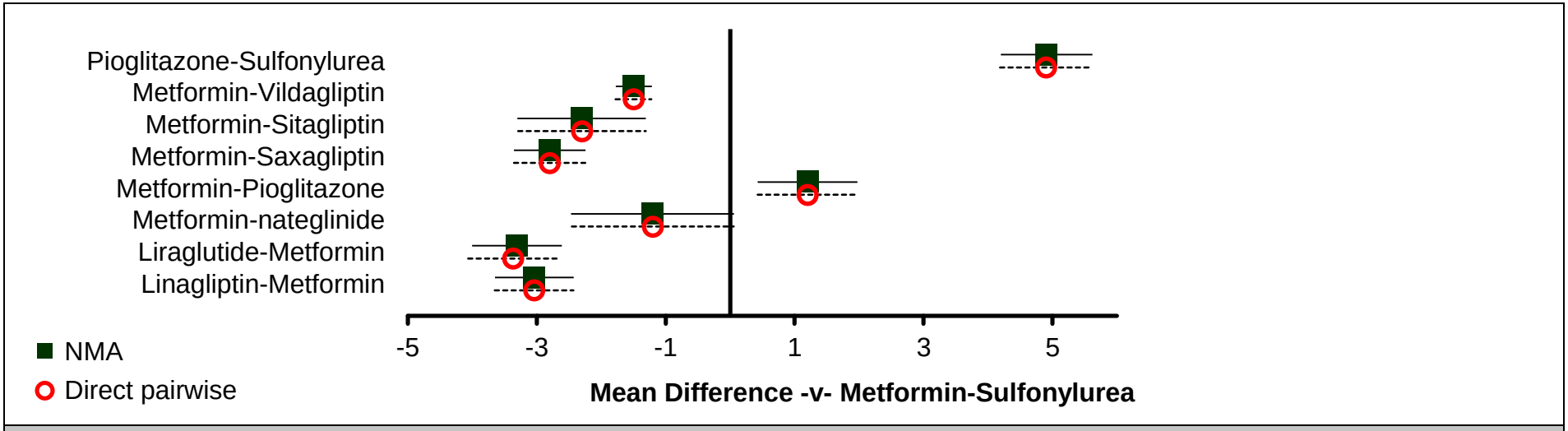
	Metformin-Sulfonylurea	Linagliptin-Metformin	Liraglutide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Sitagliptin	Metformin-Vildagliptin	Pioglitazone-Sulfonylurea
Goke et al. (2010)	1.30 (4.13)					-1.50 (4.12)			
Ferrannini et al. (2009)	1.20 (2.97)							-0.30 (2.92)	
Nauck et al. (2007)	0.70 (8.44)						-1.60 (8.57)		
Nauck et al. (2009)	0.70 (4.68)		-2.67 (5.19)						
Matthews et al. (2005)	1.10 (4.60)				2.30 (5.30)				
Gerich et al. (2005)	0.80 (7.04)			-0.40 (5.77)					
Hanefeld et al. (2004)	-1.70 (4.50)								3.20 (4.70)
Gallwitz et al. (2012)	0.98 (3.79)	-2.06 (3.21)							

Values given are mean change in body-weight(SD), in kilograms. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 98: FIRST INTENSIFICATION: BODY WEIGHT AT 24 MONTHS – relative effectiveness of all pairwise combinations

	Metformin-Sulfonylurea	Linagliptin-Metformin	Liraglutide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Sitagliptin	Metformin-Vildagliptin	Pioglitazone-Sulfonylurea
Metformin-Sulfonylurea		-3.04 (-3.65, -2.43)	-3.37 (-4.06, -2.67)	-1.20 (-2.45, 0.05)	1.20 (0.43, 1.97)	-2.80 (-3.35, -2.25)	-2.30 (-3.29, -1.31)	-1.50 (-1.78, -1.22)	4.90 (4.19, 5.61)
Linagliptin-Metformin	-3.04 (-3.65, -2.43)		-	-	-	-	-	-	-
Liraglutide-Metformin	-3.31 (-4.00, -2.61)	-0.26 (-1.18, 0.66)		-	-	-	-	-	-
Metformin-nateglinide	-1.20 (-2.47, 0.06)	1.84 (0.42, 3.25)	2.11 (0.66, 3.56)		-	-	-	-	-
Metformin-Pioglitazone	1.20 (0.43, 1.98)	4.24 (3.26, 5.23)	4.51 (3.48, 5.55)	2.41 (0.93, 3.89)		-	-	-	-
Metformin-Saxagliptin	-2.80 (-3.35, -2.25)	0.24 (-0.59, 1.07)	0.51 (-0.38, 1.40)	-1.60 (-2.98, -0.22)	-4.00 (-4.96, -3.05)		-	-	-
Metformin-Sitagliptin	-2.30 (-3.30, -1.31)	0.74 (-0.44, 1.89)	1.00 (-0.22, 2.22)	-1.10 (-2.71, 0.50)	-3.51 (-4.77, -2.24)	0.50 (-0.66, 1.63)		-	-
Metformin-Vildagliptin	-1.50 (-1.77, -1.22)	1.55 (0.87, 2.21)	1.81 (1.06, 2.57)	-0.30 (-1.58, 1.01)	-2.70 (-3.52, -1.87)	1.30 (0.68, 1.92)	0.81 (-0.23, 1.85)		-
Pioglitazone-Sulfonylurea	4.91 (4.20, 5.62)	7.95 (7.02, 8.88)	8.21 (7.23, 9.20)	6.11 (4.64, 7.57)	3.70 (2.66, 4.75)	7.70 (6.82, 8.60)	7.21 (5.98, 8.44)	6.40 (5.65, 7.16)	

Values given are mean differences in body-weight in kilograms.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist FE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 59: FIRST INTENSIFICATION: BODY WEIGHT AT 24 MONTHS – relative effect of all options versus reference treatment

Table 99: FIRST INTENSIFICATION: BODY WEIGHT AT 24 MONTHS – rankings for each comparator

	Probability best	Median rank (95%CI)
Metformin-Sulfonylurea	0.000	7 (6, 7)
Linagliptin-Metformin	0.249	2 (1, 4)
Liraglutide-Metformin	0.652	1 (1, 3)
Metformin-nateglinide	0.001	6 (4, 7)
Metformin-Pioglitazone	0.000	8 (8, 8)
Metformin-Saxagliptin	0.068	3 (1, 4)
Metformin-Sitagliptin	0.030	4 (1, 5)
Metformin-Vildagliptin	0.000	5 (4, 6)
Pioglitazone-Sulfonylurea	0.000	9 (9, 9)

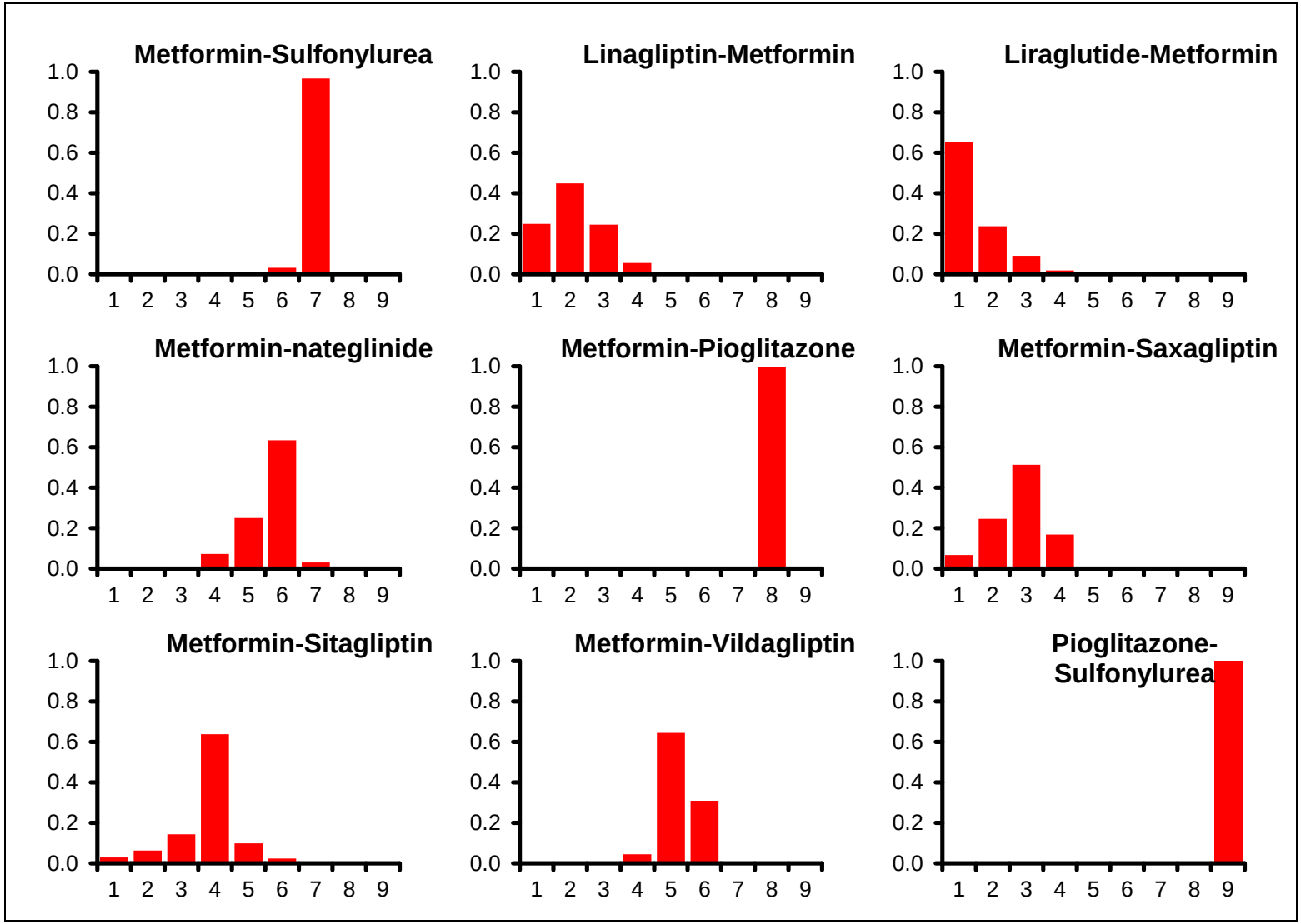


Figure 60: FIRST INTENSIFICATION: BODY WEIGHT AT 24 MONTHS – rank probability histograms

Table 100: FIRST INTENSIFICATION: BODY WEIGHT AT 24 MONTHS – model fit statistics

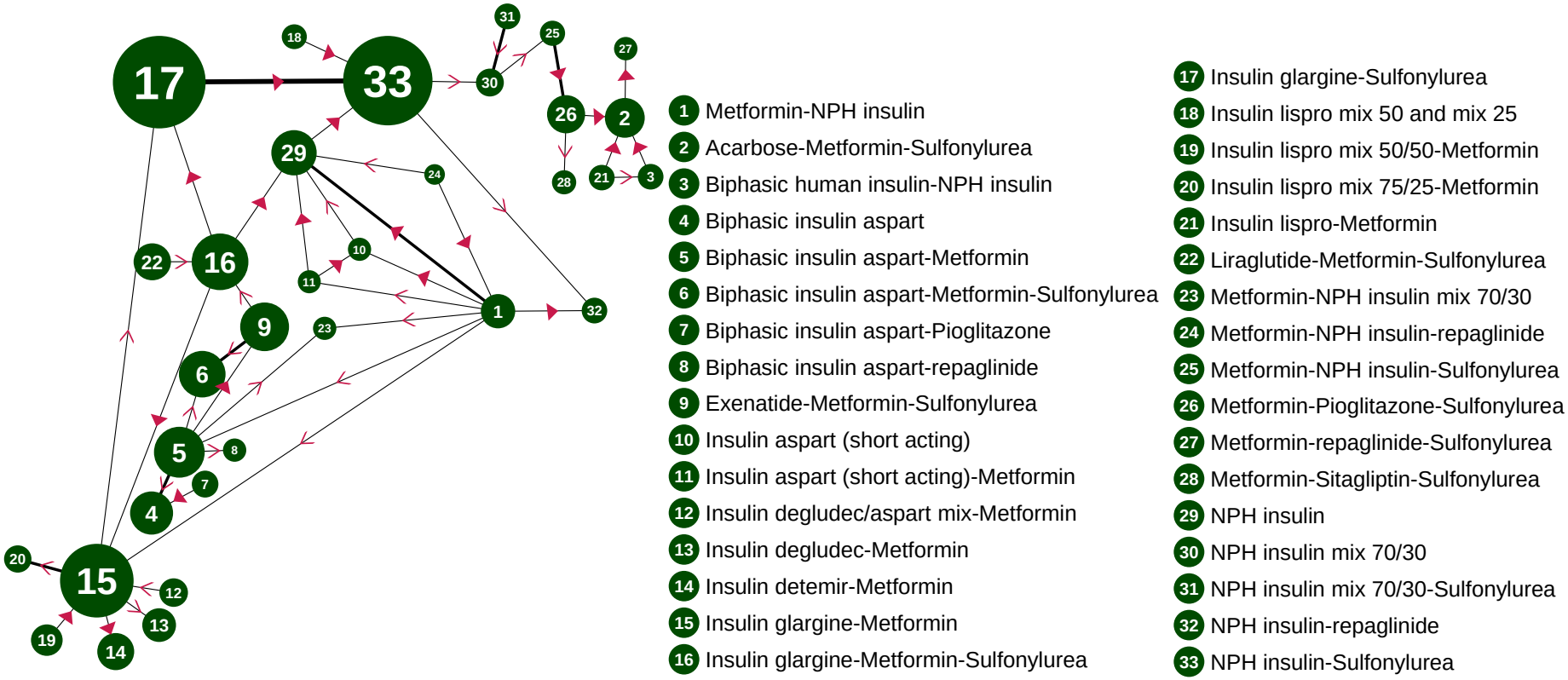
Residual deviance	Dbar	Dhat	pD	DIC	
20.88 (compared to 18 datapoints)	5.351	-10.713	16.064	21.415	

Table 101: FIRST INTENSIFICATION: BODY WEIGHT AT 24 MONTHS – notes

- Continuous (normal; identity link); fixed effects
- 50000 burn-ins; 10000 recorded iterations

J.2.3 RESULTS FOR SECOND INTENSIFICATION OF TREATMENT

J.2.3.1 Change in HbA1c up to 12 months



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 61: SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – evidence network

Table 102: SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – input data

	Metformin-NPH insulin	Acarbose-Metformin-Sulfonylurea	Biphasic human insulin-NPH insulin	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Insulin lispro mix 75/25-Metformin	Insulin lispro-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin mix 70/30	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-repaglinide-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin	NPH insulin mix 70/30	NPH insulin mix 70/30-Sulfonylurea	NPH insulin-repaglinide	NPH insulin-Sulfonylurea
Zinman et al. (2011)													-1.37 (1.10)		-1.50 (1.10)																		
Heise et al. (2011)												-1.40 (1.22)			-1.30 (1.10)																		
Gram et al. (2011)	-1.40 (1.04)									-0.70 (1.04)	-1.30 (1.04)																		-0.50 (1.29)				
Derosa et al. (2010)		-0.90 (0.52)																								-1.40 (0.43)							
Lund et al. (2009)					-1.42 (0.65)			-1.23 (0.70)																									
Hartemann-Heurtier et al. (2009)																									-1.60 (0.50)	-1.20 (0.70)							
Russell-Jones et al. (2009)																-1.09 (1.37)						-1.33 (1.36)											
Milicevic et al. (2009)																		-1.30 (2.00)															-0.50 (1.60)
Derosa et al. (2009)		-1.40 (0.79)																									-1.10 (0.69)						
Bergenstal et al. (2009)					-2.76 (1.79)	-2.34 (1.51)			-1.75 (1.57)																								
Civera et al. (2008)	-0.70 (1.20)																							-2.40 (1.10)					-1.40 (1.60)				
Ushakova et al. (2007)				-2.90 (1.50)	-3.00 (1.60)																												

	Metformin-NPH insulin	Acarbose-Metformin-Sulfonylurea	Biphasic human insulin-NPH insulin	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Insulin lispro mix 75/25-Metformin	Insulin lispro-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin mix 70/30	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-repaglinide-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin	NPH insulin mix 70/30	NPH insulin mix 70/30-Sulfonylurea	NPH insulin-repaglinide	NPH insulin-Sulfonylurea
Robbins et al. (2007)															-0.30 (0.95)				-0.70 (0.90)														
Pan et al. (2007)																	-1.12 (1.04)																-0.92 (1.05)
Nauck et al. (2007)						-0.89 (0.94)			-1.04 (1.11)																								
Eliaschewitz et al. (2006)																	-1.38 (1.32)																-1.44 (1.33)
Yki-Jarvinen et al. (2006)	-2.10 (0.87)														-1.99 (0.87)																		
Raz et al. (2005)				-0.50 (1.29)			-1.20 (1.25)																										
Malone et al. (2005)															-0.89 (0.93)					-0.45 (0.93)												
Janka et al. (2005)																-1.64 (0.92)													-1.31 (0.94)			
Malone et al. (2004)															-0.77 (1.45)					-1.40 (1.13)												
Olsson & (2002)																														-1.30 (0.74)			-1.50 (1.23)
Kokic et al. (2010)		-1.30 (1.64)	-2.20 (1.82)																		-2.60 (1.75)												
Heine et al. (2005)									-0.72 (0.76)							-0.64 (0.76)																	
Aljabri et al. (2004)																										-2.30 (1.50)	-1.90 (1.50)						
Stehouwer et al. (2003)																													-1.10 (1.24)				-0.50 (1.30)

	Metformin-NPH insulin	Acarbose-Metformin-Sulfonylurea	Biphasic human insulin-NPH insulin	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Insulin lispro mix 75/25-Metformin	Insulin lispro-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin mix 70/30	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-repaglinide-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin	NPH insulin mix 70/30	NPH insulin mix 70/30-Sulfonylurea	NPH insulin-repaglinide	NPH insulin-Sulfonylurea
Kilo et al. (2003)	-1.25 (1.40)				-1.20 (1.62)																		-1.10 (1.21)										
Goudswaard et al. (2004)																									-0.80 (1.30)					-1.20 (1.20)			
Furlong et al. (2002)	-0.30 (1.31)																															0.50 (1.27)	
Furlong et al. (2003)																																-0.90 (1.77)	-1.00 (1.66)
Kvapil et al. (2006)				-1.55 (2.00)	-1.80 (1.81)																												
Fritsche et al. (2003)																	-1.10 (1.09)																-0.84 (1.09)
Riddle et al. (1992)																														-0.80 (0.63)	-1.30 (0.33)		
Riddle & (1998)																														-2.10 (1.17)	-2.10 (1.13)		
Liu et al. (2013)																										-0.94 (0.92)		-0.71 (0.93)					
Meneghini et al. (2013)														-0.48 (0.80)	-0.73 (0.66)																		
Park et al. (2014)															-0.80 (0.85)	-1.40 (0.79)	-0.70 (1.17)																

Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 103: SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – relative effectiveness of all pairwise combinations – part A

	Metformin-NPH insulin	Acarbose-Metformin-Sulfonylurea	Biphasic human insulin-NPH insulin	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea
Metformin-NPH insulin		-	-	-	0.05 (-0.56, 0.66)	-	-	-	-	0.70 (0.28, 1.12)	0.10 (-0.33, 0.53)	-	-	-	0.11 (-0.22, 0.44)	-	-
Acarbose-Metformin-Sulfonylurea	2.37 (1.12, 3.68)		-0.90 (-1.44, -0.36)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Biphasic human insulin-NPH insulin	1.47 (0.10, 2.89)	-0.90 (-1.44, -0.36)		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Biphasic insulin aspart	-0.20 (-0.75, 0.34)	-2.57 (-3.99, -1.23)	-1.68 (-3.19, -0.22)		-0.16 (-0.49, 0.17)	-	-0.70 (-1.06, -0.34)	-	-	-	-	-	-	-	-	-	-
Biphasic insulin aspart-Metformin	-0.37 (-0.80, 0.08)	-2.73 (-4.10, -1.44)	-1.84 (-3.31, -0.42)	-0.16 (-0.49, 0.17)		0.42 (-0.04, 0.88)	-	0.19 (-0.07, 0.45)	1.01 (0.53, 1.49)	-	-	-	-	-	-	-	-
Biphasic insulin aspart-Metformin-Sulfonylurea	0.15 (-0.27, 0.57)	-2.22 (-3.57, -0.94)	-1.33 (-2.77, 0.08)	0.35 (-0.14, 0.86)	0.51 (0.14, 0.89)		-	-	-0.04 (-0.21, 0.12)	-	-	-	-	-	-	-	-
Biphasic insulin aspart-Pioglitazone	-0.90 (-1.56, -0.25)	-3.27 (-4.72, -1.89)	-2.38 (-3.92, -0.88)	-0.70 (-1.06, -0.33)	-0.54 (-1.03, -0.05)	-1.05 (-1.68, -0.43)		-	-	-	-	-	-	-	-	-	-
Biphasic insulin aspart-repaglinide	-0.18 (-0.69, 0.34)	-2.55 (-3.93, -1.22)	-1.66 (-3.15, -0.21)	0.03 (-0.39, 0.45)	0.19 (-0.07, 0.45)	-0.33 (-0.78, 0.14)	0.73 (0.18, 1.29)		-	-	-	-	-	-	-	-	-
Exenatide-Metformin-Sulfonylurea	0.09 (-0.31, 0.49)	-2.28 (-3.61, -1.01)	-1.39 (-2.82, 0.01)	0.29 (-0.21, 0.79)	0.45 (0.08, 0.82)	-0.06 (-0.23, 0.10)	0.99 (0.38, 1.62)	0.27 (-0.19, 0.72)		-	-	-	-	-	-	0.08 (-0.25, 0.41)	-
Insulin aspart (short acting)	0.50 (0.10, 0.89)	-1.87 (-3.22, -0.59)	-0.98 (-2.43, 0.43)	0.70 (0.05, 1.35)	0.87 (0.30, 1.42)	0.35 (-0.19, 0.89)	1.40 (0.66, 2.14)	0.68 (0.05, 1.30)	0.41 (-0.11, 0.93)		-0.60 (-1.02, -0.18)	-	-	-	-	-	-
Insulin aspart (short acting)-Metformin	-0.10 (-0.51, 0.30)	-2.48 (-3.82, -1.18)	-1.58 (-3.02, -0.16)	0.10 (-0.56, 0.76)	0.27 (-0.31, 0.83)	-0.25 (-0.79, 0.28)	0.80 (0.05, 1.55)	0.08 (-0.55, 0.70)	-0.19 (-0.71, 0.33)	-0.60 (-1.02, -0.18)		-	-	-	-	-	-
Insulin degludec/aspart mix-Metformin	0.28 (-0.18, 0.72)	-2.10 (-3.47, -0.80)	-1.20 (-2.67, 0.21)	0.48 (-0.19, 1.16)	0.64 (0.05, 1.22)	0.13 (-0.44, 0.68)	1.18 (0.42, 1.95)	0.45 (-0.20, 1.10)	0.19 (-0.36, 0.73)	-0.22 (-0.80, 0.34)	0.38 (-0.20, 0.95)		-	-	0.10 (-0.25, 0.45)	-	-

	Metformin-NPH insulin	Acarbose-Metformin-Sulfonylurea	Biphasic human insulin-NPH insulin	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea
Insulin degludec-Metformin	0.47 (0.05, 0.89)	-1.90 (-3.26, -0.61)	-1.00 (-2.47, 0.42)	0.68 (0.02, 1.33)	0.84 (0.26, 1.40)	0.32 (-0.22, 0.87)	1.38 (0.63, 2.13)	0.65 (0.01, 1.28)	0.38 (-0.14, 0.91)	-0.03 (-0.57, 0.53)	0.57 (0.02, 1.13)	0.20 (-0.27, 0.67)		-	-0.13 (-0.45, 0.18)	-	-
Insulin detemir-Metformin	0.59 (0.28, 0.89)	-1.78 (-3.11, -0.53)	-0.89 (-2.32, 0.50)	0.79 (0.20, 1.38)	0.96 (0.46, 1.44)	0.44 (-0.02, 0.90)	1.49 (0.80, 2.19)	0.77 (0.20, 1.33)	0.50 (0.07, 0.94)	0.09 (-0.39, 0.57)	0.69 (0.21, 1.17)	0.32 (-0.05, 0.69)	0.12 (-0.23, 0.47)		-0.25 (-0.39, -0.11)	-	-
Insulin glargine-Metformin	0.34 (0.06, 0.61)	-2.03 (-3.35, -0.78)	-1.13 (-2.56, 0.24)	0.55 (-0.03, 1.12)	0.71 (0.22, 1.18)	0.19 (-0.25, 0.63)	1.25 (0.57, 1.93)	0.52 (-0.03, 1.07)	0.25 (-0.16, 0.66)	-0.16 (-0.61, 0.30)	0.44 (-0.01, 0.90)	0.07 (-0.28, 0.41)	-0.13 (-0.45, 0.19)	-0.25 (-0.39, -0.11)		-0.60 (-1.00, -0.20)	0.10 (-0.39, 0.59)
Insulin glargine-Metformin-Sulfonylurea	0.05 (-0.27, 0.36)	-2.33 (-3.62, -1.08)	-1.43 (-2.83, -0.06)	0.25 (-0.28, 0.78)	0.41 (-0.01, 0.84)	-0.10 (-0.44, 0.24)	0.95 (0.29, 1.59)	0.22 (-0.28, 0.72)	-0.04 (-0.35, 0.27)	-0.45 (-0.89, -0.01)	0.15 (-0.29, 0.59)	-0.23 (-0.69, 0.24)	-0.43 (-0.88, 0.02)	-0.54 (-0.88, -0.20)	-0.29 (-0.60, 0.02)		0.70 (0.22, 1.18)
Insulin glargine-Sulfonylurea	0.71 (0.34, 1.08)	-1.66 (-2.92, -0.45)	-0.76 (-2.13, 0.58)	0.91 (0.31, 1.52)	1.08 (0.57, 1.58)	0.56 (0.10, 1.01)	1.62 (0.91, 2.32)	0.89 (0.31, 1.46)	0.62 (0.19, 1.05)	0.21 (-0.28, 0.70)	0.81 (0.32, 1.31)	0.44 (-0.07, 0.94)	0.24 (-0.25, 0.72)	0.12 (-0.27, 0.51)	0.37 (0.00, 0.74)	0.66 (0.35, 0.98)	
Insulin lispro mix 50 and mix 25	0.08 (-0.63, 0.80)	-2.29 (-3.68, -0.95)	-1.39 (-2.89, 0.07)	0.29 (-0.57, 1.15)	0.45 (-0.33, 1.25)	-0.06 (-0.83, 0.69)	0.99 (0.06, 1.92)	0.26 (-0.57, 1.10)	0.00 (-0.75, 0.73)	-0.41 (-1.19, 0.37)	0.19 (-0.60, 0.97)	-0.19 (-0.98, 0.60)	-0.39 (-1.17, 0.39)	-0.51 (-1.22, 0.22)	-0.26 (-0.97, 0.46)	0.04 (-0.65, 0.72)	-0.62 (-1.25, -0.01)
Insulin lispro mix 50/50-Metformin	-0.06 (-0.40, 0.28)	-2.43 (-3.76, -1.16)	-1.53 (-2.98, -0.15)	0.15 (-0.47, 0.75)	0.31 (-0.21, 0.82)	-0.21 (-0.69, 0.27)	0.85 (0.14, 1.56)	0.12 (-0.47, 0.70)	-0.15 (-0.61, 0.31)	-0.56 (-1.05, -0.06)	0.04 (-0.46, 0.54)	-0.33 (-0.73, 0.07)	-0.53 (-0.91, -0.15)	-0.65 (-0.89, -0.40)	-0.40 (-0.60, -0.20)	-0.10 (-0.48, 0.26)	-0.77 (-1.19, -0.35)
Insulin lispro mix 75/25-Metformin	0.40 (-0.01, 0.80)	-1.97 (-3.31, -0.69)	-1.07 (-2.52, 0.33)	0.60 (-0.05, 1.25)	0.76 (0.20, 1.32)	0.25 (-0.28, 0.78)	1.31 (0.56, 2.05)	0.58 (-0.04, 1.19)	0.31 (-0.19, 0.82)	-0.10 (-0.63, 0.44)	0.50 (-0.05, 1.05)	0.12 (-0.33, 0.59)	-0.07 (-0.51, 0.36)	-0.19 (-0.52, 0.13)	0.06 (-0.24, 0.36)	0.35 (-0.08, 0.78)	-0.31 (-0.78, 0.16)
Insulin lispro-Metformin	1.07 (-0.29, 2.48)	-1.30 (-1.83, -0.78)	-0.40 (-0.96, 0.16)	1.27 (-0.18, 2.77)	1.44 (0.03, 2.90)	0.92 (-0.47, 2.36)	1.97 (0.48, 3.51)	1.25 (-0.18, 2.73)	0.99 (-0.40, 2.40)	0.57 (-0.82, 2.01)	1.18 (-0.23, 2.61)	0.80 (-0.60, 2.27)	0.60 (-0.80, 2.06)	0.48 (-0.88, 1.90)	0.73 (-0.64, 2.14)	1.03 (-0.32, 2.41)	0.36 (-0.96, 1.71)
Liraglutide-Metformin-Sulfonylurea	-0.19 (-0.59, 0.20)	-2.57 (-3.89, -1.30)	-1.67 (-3.11, -0.28)	0.01 (-0.58, 0.60)	0.17 (-0.32, 0.66)	-0.34 (-0.77, 0.08)	0.71 (0.01, 1.40)	-0.01 (-0.58, 0.54)	-0.28 (-0.68, 0.12)	-0.69 (-1.19, -0.19)	-0.09 (-0.60, 0.41)	-0.47 (-0.99, 0.06)	-0.67 (-1.17, -0.16)	-0.78 (-1.20, -0.36)	-0.53 (-0.93, -0.14)	-0.24 (-0.49, 0.01)	-0.90 (-1.31, -0.51)
Metformin-NPH insulin mix 70/30	-0.02 (-0.52, 0.48)	-2.40 (-3.81, -1.05)	-1.50 (-3.01, -0.04)	0.18 (-0.44, 0.80)	0.34 (-0.18, 0.87)	-0.17 (-0.74, 0.40)	0.88 (0.17, 1.59)	0.15 (-0.43, 0.73)	-0.11 (-0.67, 0.45)	-0.52 (-1.15, 0.10)	0.08 (-0.55, 0.71)	-0.30 (-0.95, 0.35)	-0.49 (-1.14, 0.15)	-0.61 (-1.18, -0.05)	-0.36 (-0.92, 0.19)	-0.07 (-0.62, 0.48)	-0.73 (-1.33, -0.14)
Metformin-NPH insulin-repaglinide	-1.28 (-2.12, -0.45)	-3.65 (-5.19, -2.16)	-2.75 (-4.39, -1.17)	-1.08 (-2.05, -0.10)	-0.92 (-1.83, 0.00)	-1.43 (-2.33, -0.52)	-0.38 (-1.42, 0.67)	-1.10 (-2.06, -0.15)	-1.37 (-2.26, -0.47)	-1.78 (-2.69, -0.89)	-1.18 (-2.09, -0.28)	-1.56 (-2.49, -0.63)	-1.76 (-2.67, -0.85)	-1.87 (-2.74, -1.00)	-1.62 (-2.48, -0.76)	-1.33 (-2.17, -0.47)	-1.99 (-2.87, -1.12)
Metformin-NPH	1.47	-0.90	0.00	1.67	1.83	1.32	2.38	1.65	1.38	0.97	1.57	1.19	1.00	0.88	1.13	1.42	0.76

	Metformin-NPH insulin	Acarbose-Metformin-Sulfonylurea	Biphasic human insulin-NPH insulin	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea
insulin-Sulfonylurea	(0.28, 2.73)	(-1.31, -0.49)	(-0.68, 0.67)	(0.38, 3.02)	(0.59, 3.13)	(0.10, 2.61)	(1.04, 3.76)	(0.37, 2.97)	(0.16, 2.65)	(-0.26, 2.25)	(0.33, 2.85)	(-0.04, 2.50)	(-0.24, 2.29)	(-0.31, 2.14)	(-0.06, 2.38)	(0.24, 2.65)	(-0.38, 1.95)
Metformin-Pioglitazone-Sulfonylurea	1.87 (0.62, 3.18)	-0.50 (-0.61, -0.39)	0.40 (-0.15, 0.94)	2.07 (0.73, 3.49)	2.23 (0.94, 3.60)	1.72 (0.44, 3.07)	2.77 (1.40, 4.21)	2.05 (0.72, 3.43)	1.78 (0.52, 3.11)	1.37 (0.10, 2.72)	1.98 (0.68, 3.31)	1.60 (0.30, 2.96)	1.40 (0.12, 2.76)	1.28 (0.03, 2.60)	1.53 (0.28, 2.84)	1.83 (0.59, 3.12)	1.16 (-0.05, 2.41)
Metformin-repaglinide-Sulfonylurea	2.67 (1.39, 4.02)	0.30 (0.00, 0.60)	1.20 (0.58, 1.81)	2.87 (1.49, 4.32)	3.03 (1.70, 4.44)	2.52 (1.21, 3.90)	3.57 (2.16, 5.05)	2.85 (1.48, 4.26)	2.58 (1.27, 3.95)	2.17 (0.86, 3.55)	2.77 (1.45, 4.15)	2.40 (1.07, 3.80)	2.20 (0.88, 3.59)	2.08 (0.79, 3.44)	2.33 (1.04, 3.67)	2.62 (1.36, 3.95)	1.96 (0.71, 3.25)
Metformin-Sitagliptin-Sulfonylurea	2.10 (0.80, 3.45)	-0.27 (-0.62, 0.08)	0.63 (-0.02, 1.27)	2.30 (0.91, 3.74)	2.47 (1.12, 3.86)	1.95 (0.63, 3.33)	3.00 (1.58, 4.48)	2.28 (0.91, 3.70)	2.01 (0.69, 3.37)	1.60 (0.27, 2.98)	2.21 (0.86, 3.58)	1.83 (0.49, 3.22)	1.63 (0.29, 3.02)	1.51 (0.21, 2.86)	1.76 (0.46, 3.11)	2.06 (0.77, 3.39)	1.39 (0.13, 2.69)
NPH insulin	0.39 (0.09, 0.71)	-1.98 (-3.27, -0.74)	-1.08 (-2.48, 0.28)	0.60 (0.05, 1.15)	0.76 (0.32, 1.20)	0.25 (-0.13, 0.62)	1.30 (0.64, 1.96)	0.57 (0.05, 1.09)	0.31 (-0.04, 0.66)	-0.10 (-0.52, 0.32)	0.50 (0.08, 0.92)	0.12 (-0.35, 0.60)	-0.07 (-0.53, 0.37)	-0.19 (-0.54, 0.15)	0.06 (-0.27, 0.37)	0.35 (0.17, 0.53)	-0.31 (-0.62, -0.01)
NPH insulin mix 70/30	1.08 (0.04, 2.14)	-1.30 (-2.04, -0.55)	-0.40 (-1.31, 0.52)	1.28 (0.13, 2.46)	1.44 (0.33, 2.56)	0.93 (-0.15, 2.03)	1.98 (0.78, 3.22)	1.26 (0.12, 2.40)	0.99 (-0.08, 2.08)	0.58 (-0.50, 1.68)	1.18 (0.09, 2.29)	0.81 (-0.29, 1.92)	0.60 (-0.49, 1.72)	0.49 (-0.56, 1.57)	0.74 (-0.31, 1.80)	1.03 (0.00, 2.08)	0.37 (-0.62, 1.36)
NPH insulin mix 70/30-Sulfonylurea	0.85 (-0.23, 1.95)	-1.52 (-2.33, -0.72)	-0.62 (-1.59, 0.34)	1.06 (-0.14, 2.27)	1.22 (0.08, 2.37)	0.70 (-0.41, 1.85)	1.76 (0.51, 3.02)	1.03 (-0.15, 2.21)	0.77 (-0.34, 1.90)	0.35 (-0.76, 1.50)	0.95 (-0.18, 2.09)	0.58 (-0.56, 1.74)	0.38 (-0.75, 1.53)	0.26 (-0.83, 1.37)	0.51 (-0.57, 1.62)	0.81 (-0.27, 1.89)	0.14 (-0.88, 1.18)
NPH insulin-repaglinide	0.87 (0.40, 1.33)	-1.51 (-2.87, -0.21)	-0.61 (-2.06, 0.82)	1.07 (0.37, 1.78)	1.23 (0.61, 1.85)	0.72 (0.11, 1.32)	1.77 (0.98, 2.57)	1.04 (0.37, 1.71)	0.78 (0.19, 1.36)	0.37 (-0.22, 0.96)	0.97 (0.37, 1.57)	0.59 (-0.03, 1.22)	0.39 (-0.20, 1.01)	0.28 (-0.25, 0.81)	0.53 (0.01, 1.05)	0.82 (0.30, 1.34)	0.16 (-0.35, 0.67)
NPH insulin-Sulfonylurea	0.88 (0.51, 1.25)	-1.49 (-2.74, -0.28)	-0.59 (-1.95, 0.74)	1.09 (0.49, 1.69)	1.25 (0.74, 1.75)	0.74 (0.28, 1.18)	1.79 (1.08, 2.49)	1.06 (0.48, 1.63)	0.80 (0.37, 1.22)	0.39 (-0.10, 0.87)	0.99 (0.50, 1.48)	0.61 (0.11, 1.12)	0.41 (-0.07, 0.90)	0.29 (-0.09, 0.69)	0.54 (0.18, 0.92)	0.84 (0.53, 1.15)	0.17 (0.06, 0.29)

Values given are mean differences in HbA1c in percentage-points.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist FE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.

Continued

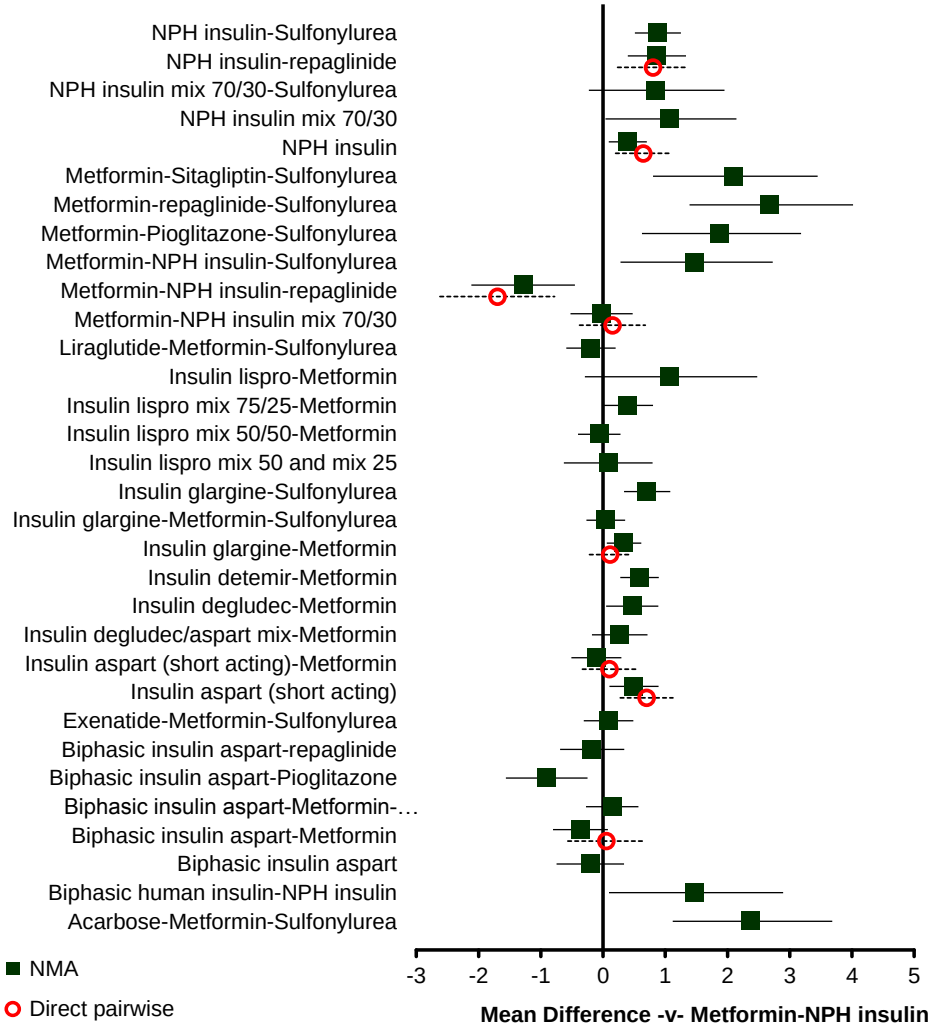
Table 104: SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – relative effectiveness of all pairwise combinations – Part B

	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Insulin lispro mix 75/25-Metformin	Insulin lispro-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin mix 70/30	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-repaglinide-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin	NPH insulin mix 70/30	NPH insulin mix 70/30-Sulfonylurea	NPH insulin-repaglinide	NPH insulin-Sulfonylurea
Metformin-NPH insulin	-	-	-	-	-	0.15 (-0.38, 0.68)	-1.70 (-2.62, -0.78)	-	-	-	-	0.64 (0.20, 1.09)	-	-	0.80 (0.23, 1.37)	-
Acarbose-Metformin-Sulfonylurea	-	-	-	-1.30 (-1.83, -0.77)	-	-	-	-	-0.50 (-0.61, -0.39)	0.30 (0.01, 0.59)	-	-	-	-	-	-
Biphasic human insulin-NPH insulin	-	-	-	-0.40 (-0.96, 0.16)	-	-	-	-	-	-	-	-	-	-	-	-
Biphasic insulin aspart	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Biphasic insulin aspart-Metformin	-	-	-	-	-	0.10 (-0.48, 0.68)	-	-	-	-	-	-	-	-	-	-
Biphasic insulin aspart-Metformin-Sulfonylurea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Biphasic insulin aspart-Pioglitazone	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Biphasic insulin aspart-repaglinide	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Exenatide-Metformin-Sulfonylurea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Insulin aspart (short acting)	-	-	-	-	-	-	-	-	-	-	-	0.20 (-0.27, 0.67)	-	-	-	-
Insulin aspart (short acting)-Metformin	-	-	-	-	-	-	-	-	-	-	-	0.80 (0.32, 1.28)	-	-	-	-
Insulin degludec/aspart mix-Metformin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Insulin degludec-Metformin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Insulin detemir-Metformin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Insulin glargine-Metformin	-	-0.40 (-0.60, -0.20)	0.06 (-0.24, 0.35)	-	-	-	-	-	-	-	-	-	-	-	-	-

	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Insulin lispro mix 75/25-Metformin	Insulin lispro-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin mix 70/30	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-repaglinide-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin	NPH insulin mix 70/30	NPH insulin mix 70/30-Sulfonylurea	NPH insulin-repaglinide	NPH insulin-Sulfonylurea
Insulin glargine-Metformin-Sulfonylurea	-	-	-	-	-0.24 (-0.49, 0.01)	-	-	-	-	-	-	0.33 (0.14, 0.52)	-	-	-	-
Insulin glargine-Sulfonylurea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.17 (0.05, 0.28)
Insulin lispro mix 50 and mix 25		-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.80 (0.19, 1.41)
Insulin lispro mix 50/50-Metformin	-0.14 (-0.88, 0.60)		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Insulin lispro mix 75/25-Metformin	0.31 (-0.45, 1.09)	0.46 (0.10, 0.82)		-	-	-	-	-	-	-	-	-	-	-	-	-
Insulin lispro-Metformin	0.99 (-0.44, 2.48)	1.13 (-0.24, 2.55)	0.67 (-0.72, 2.11)		-	-	-	-	-	-	-	-	-	-	-	-
Liraglutide-Metformin-Sulfonylurea	-0.28 (-1.01, 0.45)	-0.13 (-0.58, 0.31)	-0.59 (-1.08, -0.10)	-1.27 (-2.69, 0.11)		-	-	-	-	-	-	-	-	-	-	-
Metformin-NPH insulin mix 70/30	-0.11 (-0.95, 0.74)	0.04 (-0.56, 0.63)	-0.42 (-1.05, 0.21)	-1.10 (-2.59, 0.36)	0.17 (-0.43, 0.77)		-	-	-	-	-	-	-	-	-	-
Metformin-NPH insulin-repaglinide	-1.37 (-2.43, -0.30)	-1.22 (-2.11, -0.34)	-1.68 (-2.59, -0.77)	-2.35 (-3.97, -0.77)	-1.09 (-1.97, -0.20)	-1.26 (-2.22, -0.29)		-	-	-	-	1.00 (-0.07, 2.07)	-	-	-	-
Metformin-NPH insulin-Sulfonylurea	1.39 (0.10, 2.71)	1.53 (0.32, 2.80)	1.07 (-0.14, 2.35)	0.39 (-0.27, 1.06)	1.66 (0.46, 2.93)	1.49 (0.21, 2.83)	2.75 (1.30, 4.23)		0.40 (0.01, 0.79)	-	-	-	-0.40 (-1.01, 0.21)	-	-	-
Metformin-Pioglitazone-Sulfonylurea	1.79 (0.45, 3.18)	1.93 (0.67, 3.26)	1.47 (0.19, 2.81)	0.80 (0.26, 1.34)	2.06 (0.81, 3.39)	1.90 (0.55, 3.31)	3.15 (1.67, 4.69)	0.40 (0.01, 0.79)		-	0.23 (-0.10, 0.56)	-	-	-	-	-

	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Insulin lispro mix 75/25-Metformin	Insulin lispro-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin mix 70/30	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-repaglinide-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin	NPH insulin mix 70/30	NPH insulin mix 70/30-Sulfonylurea	NPH insulin-repaglinide	NPH insulin-Sulfonylurea
Metformin-repaglinide-Sulfonylurea	2.59 (1.22, 4.02)	2.73 (1.44, 4.10)	2.27 (0.95, 3.65)	1.60 (1.00, 2.20)	2.86 (1.56, 4.23)	2.70 (1.32, 4.15)	3.95 (2.44, 5.53)	1.20 (0.70, 1.70)	0.80 (0.49, 1.12)		-	-	-	-	-	-
Metformin-Sitagliptin-Sulfonylurea	2.02 (0.64, 3.44)	2.16 (0.84, 3.52)	1.70 (0.38, 3.07)	1.03 (0.39, 1.67)	2.29 (0.99, 3.66)	2.13 (0.74, 3.57)	3.38 (1.86, 4.95)	0.63 (0.12, 1.14)	0.23 (-0.10, 0.56)	-0.57 (-1.03, -0.12)		-	-	-	-	-
NPH insulin	0.31 (-0.36, 0.99)	0.45 (0.08, 0.84)	0.00 (-0.44, 0.43)	-0.68 (-2.07, 0.67)	0.59 (0.29, 0.89)	0.42 (-0.13, 0.97)	1.68 (0.84, 2.52)	-1.08 (-2.30, 0.10)	-1.48 (-2.77, -0.24)	-2.27 (-3.59, -1.00)	-1.71 (-3.04, -0.42)		-	-	-	0.60 (0.22, 0.98)
NPH insulin mix 70/30	0.99 (-0.16, 2.16)	1.14 (0.07, 2.22)	0.68 (-0.41, 1.79)	0.00 (-0.90, 0.92)	1.27 (0.22, 2.35)	1.10 (-0.04, 2.26)	2.36 (1.04, 3.69)	-0.39 (-1.00, 0.22)	-0.80 (-1.53, -0.06)	-1.60 (-2.40, -0.80)	-1.03 (-1.84, -0.22)	0.68 (-0.34, 1.72)		-0.22 (-0.52, 0.07)	-	-0.20 (-1.19, 0.79)
NPH insulin mix 70/30-Sulfonylurea	0.77 (-0.42, 1.97)	0.91 (-0.19, 2.03)	0.46 (-0.66, 1.60)	-0.23 (-1.18, 0.74)	1.05 (-0.05, 2.17)	0.88 (-0.30, 2.08)	2.14 (0.79, 3.50)	-0.62 (-1.30, 0.06)	-1.02 (-1.82, -0.23)	-1.82 (-2.68, -0.98)	-1.25 (-2.12, -0.39)	0.46 (-0.60, 1.54)	-0.22 (-0.52, 0.07)		-	-
NPH insulin-repaglinide	0.78 (-0.02, 1.57)	0.93 (0.37, 1.49)	0.47 (-0.12, 1.06)	-0.21 (-1.65, 1.20)	1.06 (0.49, 1.64)	0.89 (0.22, 1.57)	2.15 (1.22, 3.10)	-0.61 (-1.91, 0.63)	-1.01 (-2.37, 0.29)	-1.81 (-3.20, -0.47)	-1.24 (-2.63, 0.11)	0.47 (-0.04, 0.98)	-0.21 (-1.32, 0.88)	0.01 (-1.13, 1.15)		-0.10 (-0.85, 0.65)
NPH insulin-Sulfonylurea	0.80 (0.19, 1.41)	0.94 (0.53, 1.37)	0.49 (0.01, 0.96)	-0.19 (-1.53, 1.14)	1.08 (0.69, 1.47)	0.91 (0.31, 1.50)	2.17 (1.30, 3.04)	-0.59 (-1.78, 0.56)	-0.99 (-2.24, 0.22)	-1.79 (-3.07, -0.54)	-1.22 (-2.51, 0.04)	0.49 (0.19, 0.78)	-0.20 (-1.18, 0.78)	0.03 (-1.01, 1.05)	0.02 (-0.49, 0.52)	

Values given are mean differences in HbA1c in percentage-points.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist FE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



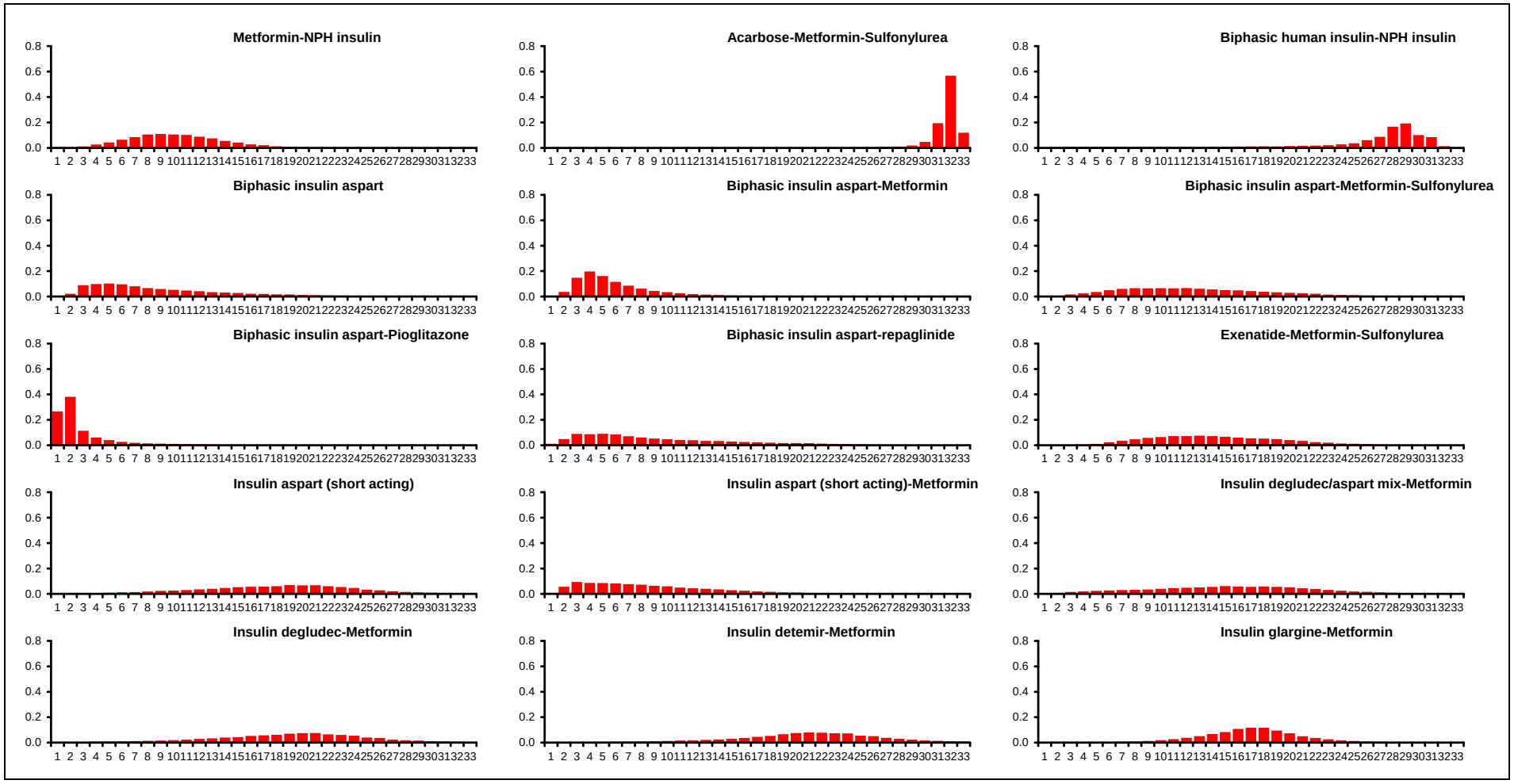
Values greater than 0 favour metformin-NPH insulin; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 62: SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – relative effect of all options versus reference treatment

Table 105: SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – rankings for each comparator

	Probability best	Median rank (95%CI)
Metformin-NPH insulin	0.000	10 (5, 15)
Acarbose-Metformin-Sulfonylurea	0.000	32 (31, 32)
Biphasic human insulin-NPH insulin	0.000	28 (14, 30)
Biphasic insulin aspart	0.000	6 (3, 16)
Biphasic insulin aspart-Metformin	0.000	4 (3, 9)
Biphasic insulin aspart-Metformin-Sulfonylurea	0.000	13 (7, 21)
Biphasic insulin aspart-Pioglitazone	0.236	2 (1, 3)
Biphasic insulin aspart-repaglinide	0.000	6 (3, 16)
Exenatide-Metformin-Sulfonylurea	0.000	12 (6, 18)
Insulin aspart (short acting)	0.000	20 (12, 27)
Insulin aspart (short acting)-Metformin	0.000	8 (3, 16)
Insulin degludec/aspart mix-Metformin	0.000	15 (7, 23)
Insulin degludec-Metformin	0.000	19 (12, 26)
Insulin detemir-Metformin	0.000	21 (17, 27)
Insulin glargine-Metformin	0.000	17 (12, 21)
Insulin glargine-Metformin-Sulfonylurea	0.000	11 (6, 16)
Insulin glargine-Sulfonylurea	0.000	22 (18, 28)
Insulin lispro mix 50 and mix 25	0.001	12 (3, 23)
Insulin lispro mix 50/50-Metformin	0.000	8 (3, 15)
Insulin lispro mix 75/25-Metformin	0.000	18 (10, 25)
Insulin lispro-Metformin	0.001	26 (5, 28)
Liraglutide-Metformin-Sulfonylurea	0.000	6 (3, 12)
Metformin-NPH insulin mix 70/30	0.000	9 (3, 20)
Metformin-NPH insulin-repaglinide	0.761	1 (1, 3)
Metformin-NPH insulin-Sulfonylurea	0.000	28 (19, 29)
Metformin-Pioglitazone-Sulfonylurea	0.000	30 (26, 31)
Metformin-repaglinide-Sulfonylurea	0.000	33 (32, 33)

	Probability best	Median rank (95%CI)
Metformin-Sitagliptin-Sulfonylurea	0.000	31 (29, 32)
NPH insulin	0.000	18 (13, 23)
NPH insulin mix 70/30	0.000	26 (13, 29)
NPH insulin mix 70/30-Sulfonylurea	0.000	24 (6, 27)
NPH insulin-repaglinide	0.000	24 (18, 31)
NPH insulin-Sulfonylurea	0.000	24 (22, 30)


Metformin-NPH insulin
Acarbose-Metformin-Sulfonylurea
Biphasic human insulin-NPH insulin
Biphasic insulin aspart
Biphasic insulin aspart-Metformin
Biphasic insulin aspart-Metformin-Sulfonylurea
Biphasic insulin aspart-Pioglitazone
Biphasic insulin aspart-repaglinide
Exenatide-Metformin-Sulfonylurea
Insulin aspart (short acting)
Insulin aspart (short acting)-Metformin
Insulin degludec/aspart mix-Metformin
Insulin degludec-Metformin
Insulin detemir-Metformin
Insulin glargine-Metformin

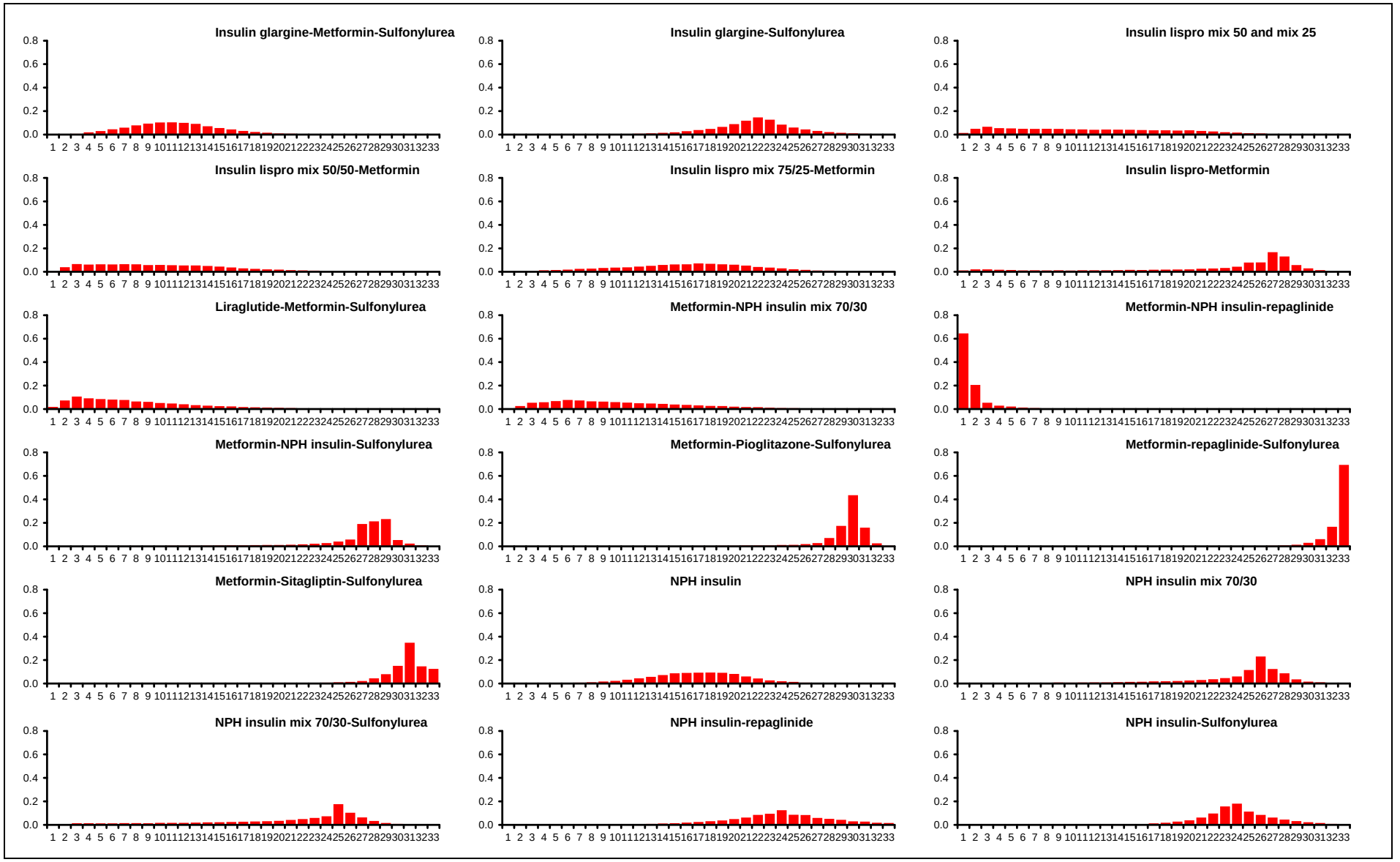


Figure 63: SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – rank probability histograms

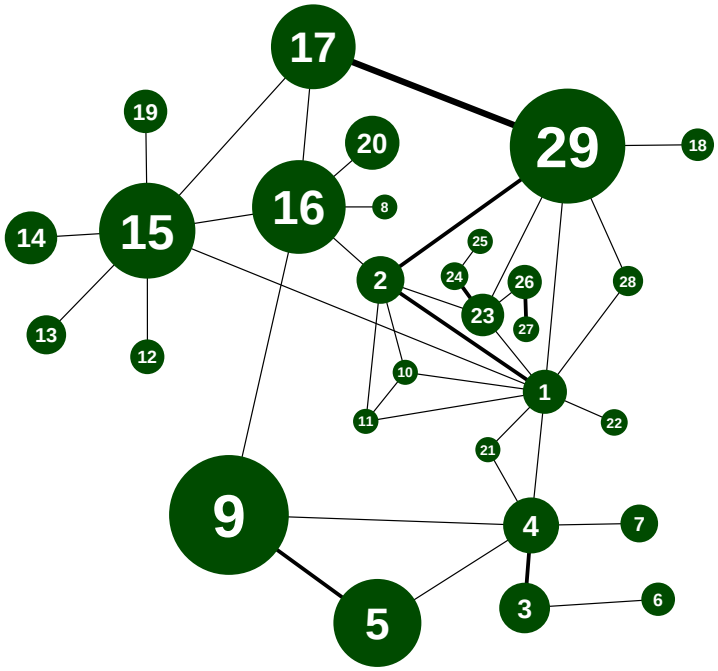
Table 106: SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	
123.3 (compared to 85 datapoints)	-57.69	-126.5	68.86	11.17	

Table 107: SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – notes

- Continuous (normal; identity link); fixed effects
- 50000 burn-ins; 10000 recorded iterations

J.2.3.2 Hypoglycaemia at study endpoint



1 Metformin-NPH insulin
2 _NPH insulin
3 Biphasic insulin aspart
4 Biphasic insulin aspart-Metformin
5 Biphasic insulin aspart-Metformin-Sulfonylurea
6 Biphasic insulin aspart-Pioglitazone
7 Biphasic insulin aspart-repaglinide
8 Exenatide (once weekly)-Metformin-Sulfonylurea
9 Exenatide-Metformin-Sulfonylurea
10 Insulin aspart (short acting)
11 Insulin aspart (short acting)-Metformin
12 Insulin degludec/aspart mix-Metformin
13 Insulin degludec-Metformin
14 Insulin detemir-Metformin
15 Insulin glargine-Metformin
16 Insulin glargine-Metformin-Sulfonylurea
17 Insulin glargine-Sulfonylurea
18 Insulin lispro mix 50 and mix 25
19 Insulin lispro mix 50/50-Metformin
20 Liraglutide-Metformin-Sulfonylurea
21 Metformin-NPH insulin mix 70/30
22 Metformin-NPH insulin-repaglinide
23 Metformin-NPH insulin-Sulfonylurea
24 Metformin-Pioglitazone-Sulfonylurea
25 Metformin-Sitagliptin-Sulfonylurea
26 NPH insulin mix 70/30
27 NPH insulin mix 70/30-Sulfonylurea
28 NPH insulin-repaglinide
29 NPH insulin-Sulfonylurea

Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 64: SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – evidence network

Table 108: SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – input data

	Metformin-NPH insulin	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide (once weekly)-Metformin-Sulfonylurea	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/ aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/ 50-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin mix 70/ 30	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin	NPH insulin mix 70/ 30	NPH insulin mix 70/ 30-Sulfonylurea	NPH insulin-repaglinide	NPH insulin-Sulfonylurea
Dichotomous proportion data																													
Gram et al. (2011) - 1.99yr	33/ 45								43/ 48	36/ 45															35/ 46				
Diamant et al. (2010) - 1.61yr							25/ 69								37/ 66														
Hartemann-Heurtier et al. (2009) - 0.46yr																						10/ 13	6/ 14						
Bergenstal et al. (2009) - 0.46yr			76/ 124	69/ 124				36/ 124																					
Janka et al. (2005) - 0.46yr															109/ 177										127/ 187				
Kilo et al. (2003) - 0.23yr	13/ 47		20/ 46																	15/ 47									
Fritsche et al. (2003) - 0.46yr																330/ 463													173/ 232
Riddle & (1998) - 0.46yr																										27/ 73	37/ 72		
Liu et al. (2013) - 0.46yr																							5/ 59	6/ 60					
Count data																													
Zinman et al. (2011) - 0.31yr												23/ 19264		12/ 6608															
Heise et al. (2011) - 0.31yr											61/ 12656			12/ 6440															
Lund et al. (2009) - 1.00yr			1238/ 19477			1418/ 17310																							
Russell-Jones et al. (2009) - 0.50yr															202/ 41041				109/ 39767										

	Metformin-NPH insulin	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide (once weekly)-Metformin-Sulfonylurea	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/ aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/ 50-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin mix 70/ 30	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin	NPH insulin mix 70/ 30	NPH insulin mix 70/ 30-Sulfonylurea	NPH insulin-repaglinide	NPH insulin-Sulfonylurea
Milicevic et al. (2009) - 0.46yr																	124/ 10080												31/ 10248
Civera et al. (2008) - 0.46yr	6/ 2016																				10/ 2016								
Ushakova et al. (2007) - 0.31yr		23/ 11424	21/ 10920																										
Robbins et al. (2007) - 0.46yr														247/ 24696				586/ 25116											
Pan et al. (2007) - 0.46yr																682/ 36960													1019/ 37464
Nauck et al. (2007) - 1.00yr				1315/ 85722				1059/ 82264																					
Eliaschewitz et al. (2006) - 0.46yr																517/ 37716													819/ 41496
Yki-Jarvinen et al. (2006) - 0.69yr	268/ 12222													226/ 15246															
Raz et al. (2005) - 0.34yr		221/ 11718			134/ 11277																								
Heine et al. (2005) - 0.50yr								928/ 46410							799/ 46319														
Aljabri et al. (2004) - 0.31yr																						79/ 3220	34/ 3416						
Stehouwer et al. (2003) - 0.69yr																									355/ 22176				253/ 21672
Goudswaard et al. (2004) - 1.00yr																						89/ 12012				133/ 11284			
Furlong et al. (2002) - 0.25yr	64/ 3609																											38/ 3381	
Furlong et al. (2003) - 0.25yr																												94/ 3458	115/ 3549

	Metformin-NPH insulin	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide (once weekly)-Metformin-Sulfonylurea	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/ aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/ 50-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin mix 70/ 30	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin	NPH insulin mix 70/ 30	NPH insulin mix 70/ 30-Sulfonylurea	NPH insulin-repaglinide	NPH insulin-Sulfonylurea
Kvapil et al. (2006) - 0.31yr		62/ 11648	64/ 11480																										
Riddle et al. (1992) - 0.31yr																										69/ 1120	97/ 1232		
Yki-JaŸˆrvinen et al. (1999) - 1.00yr	25/ 7826																					73/ 8554			94/ 8736				68/ 8372
Meneghini et al. (2013) - 0.50yr													329/ 37644	457/ 37824															
Park et al. (2014) - 0.54yr														64/ 5698	83/ 5940	95/ 5978													

Values given are number of events / number of participants (for dichotomous proportion data) and number of events / total patient-days (for count data). Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 109: SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations

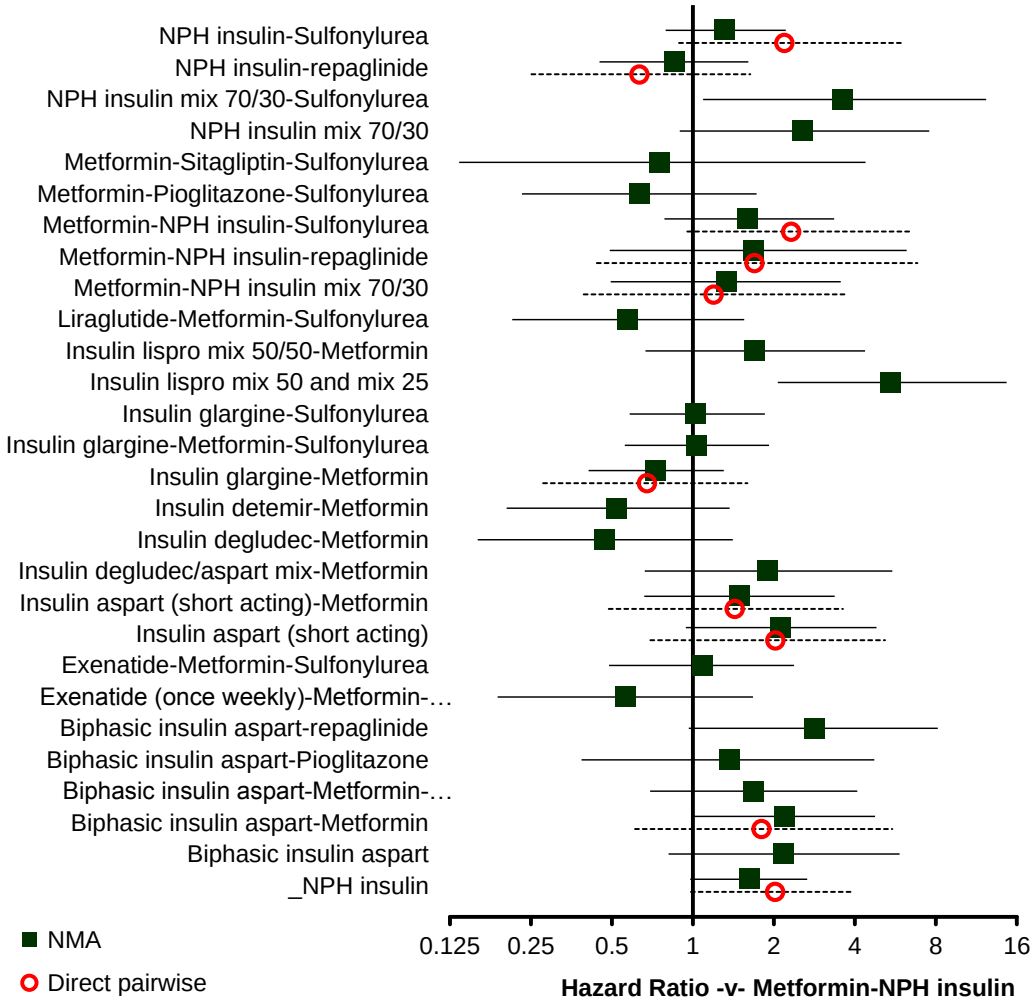
	Metformin-NPH insulin	_NPH insulin	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide (once weekly)-Metformin-Sulfonylurea	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin mix 70/30	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin mix 70/30	NPH insulin mix 70/30-Sulfonylurea	NPH insulin-repaglinide
Metformin-NPH insulin		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
_NPH insulin	1.62 (0.98, 2.66)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Biphasic insulin aspart	2.17 (0.81, 5.87)	1.34 (0.48, 3.79)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Biphasic insulin aspart-Metformin	2.19 (1.00, 4.75)	1.35 (0.58, 3.11)	1.00 (0.55, 1.85)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Biphasic insulin aspart-Metformin-Sulfonylurea	1.68 (0.69, 4.08)	1.04 (0.42, 2.57)	0.77 (0.31, 1.96)	0.77 (0.38, 1.57)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Biphasic insulin aspart-Pioglitazone	1.37 (0.39, 4.72)	0.85 (0.23, 3.04)	0.63 (0.29, 1.35)	0.63 (0.24, 1.65)	0.81 (0.24, 2.67)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Biphasic insulin aspart-repaglinide	2.83 (0.96, 8.13)	1.74 (0.57, 5.33)	1.29 (0.50, 3.37)	1.29 (0.61, 2.71)	1.68 (0.60, 4.60)	2.07 (0.59, 6.99)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Exenatide (once weekly)-Metformin-Sulfonylurea	0.56 (0.19, 1.67)	0.35 (0.12, 0.99)	0.26 (0.07, 0.98)	0.26 (0.08, 0.86)	0.33 (0.10, 1.13)	0.41 (0.09, 1.92)	0.20 (0.05, 0.82)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	Metformin-NPH insulin	_NPH insulin	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide (once weekly)-Metformin-Sulfonylurea	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin mix 70/30	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin mix 70/30	NPH insulin mix 70/30-Sulfonylurea	NPH insulin-repaglinide
Exenatide-Metformin-Sulfonylurea	1.09 (0.49, 2.38)	0.68 (0.30, 1.46)	0.50 (0.20, 1.22)	0.50 (0.26, 0.96)	0.65 (0.37, 1.10)	0.80 (0.24, 2.59)	0.39 (0.14, 1.04)	1.94 (0.62, 5.76)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin aspart (short acting)	2.12 (0.94, 4.81)	1.31 (0.58, 2.94)	0.97 (0.28, 3.41)	0.97 (0.32, 2.88)	1.27 (0.40, 3.95)	1.55 (0.35, 6.70)	0.75 (0.20, 2.79)	3.77 (1.03, 13.77)	1.95 (0.67, 5.72)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin aspart (short acting)-Metformin	1.50 (0.66, 3.37)	0.92 (0.41, 2.06)	0.69 (0.19, 2.40)	0.68 (0.23, 2.05)	0.89 (0.28, 2.86)	1.10 (0.25, 4.75)	0.53 (0.14, 1.96)	2.65 (0.73, 9.71)	1.37 (0.48, 4.08)	0.70 (0.29, 1.73)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin degludec/aspart mix-Metformin	1.90 (0.66, 5.51)	1.17 (0.39, 3.54)	0.87 (0.21, 3.54)	0.87 (0.25, 3.08)	1.13 (0.31, 4.12)	1.40 (0.28, 7.04)	0.68 (0.16, 2.92)	3.37 (0.83, 14.00)	1.75 (0.53, 6.09)	0.89 (0.25, 3.31)	1.27 (0.35, 4.71)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin degludec-Metformin	0.47 (0.16, 1.41)	0.29 (0.09, 0.90)	0.22 (0.05, 0.92)	0.21 (0.06, 0.79)	0.28 (0.07, 1.06)	0.35 (0.07, 1.76)	0.17 (0.04, 0.74)	0.83 (0.20, 3.59)	0.43 (0.13, 1.55)	0.22 (0.06, 0.85)	0.31 (0.08, 1.18)	0.25 (0.07, 0.88)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin detemir-Metformin	0.52 (0.20, 1.37)	0.32 (0.12, 0.88)	0.24 (0.06, 0.90)	0.24 (0.07, 0.79)	0.31 (0.09, 1.06)	0.38 (0.08, 1.77)	0.19 (0.05, 0.74)	0.93 (0.24, 3.52)	0.48 (0.16, 1.56)	0.24 (0.07, 0.84)	0.35 (0.10, 1.17)	0.28 (0.09, 0.87)	1.11 (0.34, 3.64)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin glargine-Metformin	0.73 (0.41, 1.30)	0.45 (0.23, 0.86)	0.33 (0.11, 0.99)	0.33 (0.14, 0.82)	0.43 (0.16, 1.13)	0.53 (0.14, 2.04)	0.26 (0.08, 0.83)	1.29 (0.43, 3.98)	0.66 (0.29, 1.60)	0.34 (0.13, 0.90)	0.49 (0.19, 1.25)	0.38 (0.16, 0.92)	1.55 (0.61, 3.83)	1.39 (0.65, 2.91)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin glargine-Metformin-Sulfonylurea	1.03 (0.56, 1.92)	0.64 (0.36, 1.12)	0.47 (0.17, 1.29)	0.47 (0.21, 1.05)	0.61 (0.28, 1.37)	0.75 (0.22, 2.70)	0.37 (0.12, 1.08)	1.84 (0.75, 4.53)	0.94 (0.50, 1.87)	0.49 (0.19, 1.26)	0.69 (0.27, 1.78)	0.54 (0.18, 1.60)	2.20 (0.70, 6.75)	1.98 (0.72, 5.29)	1.43 (0.74, 2.71)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin glargine-Sulfonylurea	1.02 (0.58, 1.85)	0.63 (0.37, 1.11)	0.47 (0.16, 1.37)	0.47 (0.20, 1.13)	0.61 (0.24, 1.57)	0.74 (0.20, 2.86)	0.36 (0.12, 1.17)	1.82 (0.63, 5.48)	0.94 (0.42, 2.22)	0.48 (0.19, 1.23)	0.68 (0.28, 1.75)	0.54 (0.18, 1.59)	2.19 (0.72, 6.69)	1.96 (0.74, 5.27)	1.41 (0.76, 2.68)	0.99 (0.55, 1.84)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	Metformin-NPH insulin	_NPH insulin	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide (once weekly)-Metformin-Sulfonylurea	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin mix 70/30	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin mix 70/30	NPH insulin mix 70/30-Sulfonylurea	NPH insulin-repaglinide
Insulin lispro mix 50 and mix 25	5.41 (2.07, 14.65)	3.34 (1.30, 8.71)	2.49 (0.66, 9.61)	2.47 (0.76, 8.34)	3.21 (0.95, 11.31)	3.94 (0.86, 18.99)	1.92 (0.48, 7.95)	9.65 (2.54, 38.08)	4.95 (1.60, 16.24)	2.56 (0.77, 8.67)	3.61 (1.10, 12.00)	2.84 (0.72, 11.39)	11.55 (2.84, 46.67)	10.31 (2.83, 37.85)	7.44 (2.66, 21.65)	5.24 (1.89, 14.64)	5.29 (2.13, 13.18)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin lispro mix 50/50-Metformin	1.70 (0.67, 4.37)	1.05 (0.39, 2.85)	0.78 (0.21, 2.92)	0.77 (0.24, 2.50)	1.01 (0.30, 3.44)	1.24 (0.27, 5.86)	0.60 (0.15, 2.43)	3.02 (0.80, 11.51)	1.55 (0.52, 5.00)	0.80 (0.24, 2.70)	1.13 (0.34, 3.76)	0.89 (0.28, 2.84)	3.62 (1.12, 11.65)	3.26 (1.12, 9.43)	2.34 (1.10, 4.95)	1.65 (0.61, 4.41)	1.66 (0.61, 4.36)	0.31 (0.08, 1.12)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Liraglutide-Metformin-Sulfonylurea	0.57 (0.21, 1.55)	0.35 (0.14, 0.92)	0.26 (0.07, 0.93)	0.26 (0.09, 0.79)	0.34 (0.11, 1.05)	0.42 (0.10, 1.83)	0.20 (0.05, 0.77)	1.01 (0.32, 3.39)	0.52 (0.19, 1.48)	0.27 (0.08, 0.93)	0.38 (0.11, 1.30)	0.30 (0.08, 1.14)	1.22 (0.31, 4.84)	1.10 (0.31, 3.86)	0.79 (0.29, 2.17)	0.55 (0.26, 1.20)	0.56 (0.21, 1.50)	0.11 (0.03, 0.38)	0.34 (0.10, 1.18)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Metformin-NPH insulin mix 70/30	1.34 (0.49, 3.54)	0.83 (0.28, 2.39)	0.62 (0.20, 1.89)	0.61 (0.23, 1.56)	0.80 (0.26, 2.43)	0.98 (0.25, 3.79)	0.47 (0.14, 1.56)	2.38 (0.58, 9.39)	1.23 (0.42, 3.58)	0.63 (0.18, 2.17)	0.89 (0.25, 3.15)	0.70 (0.17, 2.88)	2.84 (0.66, 12.13)	2.57 (0.66, 9.64)	1.84 (0.60, 5.48)	1.30 (0.44, 3.71)	1.31 (0.43, 3.81)	0.25 (0.06, 0.95)	0.79 (0.20, 2.96)	2.34 (0.63, 8.55)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Metformin-NPH insulin-repaglinide	1.69 (0.49, 6.23)	1.05 (0.28, 4.27)	0.78 (0.16, 3.97)	0.77 (0.18, 3.49)	1.01 (0.22, 4.85)	1.24 (0.22, 7.54)	0.60 (0.12, 3.26)	2.99 (0.58, 16.38)	1.56 (0.36, 7.14)	0.80 (0.18, 3.72)	1.13 (0.26, 5.32)	0.89 (0.17, 4.75)	3.61 (0.70, 19.97)	3.23 (0.68, 16.32)	2.33 (0.58, 9.83)	1.64 (0.41, 6.94)	1.65 (0.42, 6.88)	0.31 (0.06, 1.59)	1.00 (0.21, 5.05)	2.97 (0.60, 15.29)	1.27 (0.26, 6.59)		N/A	N/A	N/A	N/A	N/A	N/A
Metformin-NPH insulin-Sulfonylurea	1.60 (0.78, 3.35)	0.99 (0.49, 2.03)	0.74 (0.23, 2.44)	0.73 (0.27, 2.06)	0.96 (0.33, 2.83)	1.17 (0.30, 4.92)	0.57 (0.17, 2.03)	2.85 (0.85, 9.83)	1.47 (0.56, 4.13)	0.76 (0.28, 2.15)	1.08 (0.39, 3.03)	0.84 (0.25, 2.90)	3.43 (0.97, 12.04)	3.06 (0.99, 9.61)	2.21 (0.95, 5.26)	1.55 (0.68, 3.63)	1.56 (0.73, 3.43)	0.30 (0.10, 0.87)	0.94 (0.30, 2.98)	2.79 (0.90, 8.94)	1.20 (0.37, 4.05)	0.95 (0.21, 4.02)		N/A	N/A	N/A	N/A	N/A
Metformin-Pioglitazone-Sulfonylurea	0.63 (0.23, 1.72)	0.39 (0.15, 1.06)	0.29 (0.07, 1.16)	0.29 (0.09, 0.99)	0.38 (0.11, 1.37)	0.46 (0.10, 2.22)	0.22 (0.06, 0.95)	1.13 (0.28, 4.66)	0.58 (0.18, 2.00)	0.30 (0.09, 1.04)	0.42 (0.13, 1.47)	0.33 (0.08, 1.37)	1.36 (0.32, 5.64)	1.22 (0.32, 4.60)	0.87 (0.29, 2.65)	0.61 (0.21, 1.86)	0.62 (0.22, 1.74)	0.12 (0.03, 0.42)	0.37 (0.10, 1.41)	1.11 (0.29, 4.27)	0.47 (0.12, 1.92)	0.37 (0.07, 1.85)	0.40 (0.20, 0.78)		N/A	N/A	N/A	N/A
Metformin-Sitagliptin-Sulfonylurea	0.75 (0.14, 4.38)	0.47 (0.08, 2.69)	0.34 (0.05, 2.57)	0.34 (0.05, 2.32)	0.45 (0.07, 3.13)	0.55 (0.07, 4.63)	0.27 (0.04, 2.02)	1.34 (0.19, 10.21)	0.69 (0.11, 4.60)	0.35 (0.05, 2.39)	0.50 (0.08, 3.34)	0.40 (0.05, 2.99)	1.62 (0.21, 12.43)	1.45 (0.21, 10.24)	1.04 (0.17, 6.46)	0.73 (0.13, 4.49)	0.74 (0.13, 4.36)	0.14 (0.02, 0.96)	0.44 (0.06, 3.19)	1.32 (0.19, 9.63)	0.56 (0.08, 4.16)	0.44 (0.05, 3.81)	0.47 (0.10, 2.37)	1.18 (0.29, 5.04)		N/A	N/A	N/A
NPH insulin mix 70/30	2.56 (0.89, 7.55)	1.58 (0.56, 4.57)	1.18 (0.29, 5.01)	1.17 (0.33, 4.32)	1.53 (0.41, 6.02)	1.87 (0.38, 9.64)	0.91 (0.21, 4.02)	4.54 (1.11, 19.95)	2.35 (0.69, 8.71)	1.21 (0.34, 4.42)	1.71 (0.49, 6.26)	1.35 (0.32, 5.76)	5.44 (1.26, 24.21)	4.90 (1.24, 19.46)	3.53 (1.12, 11.51)	2.47 (0.83, 7.89)	2.49 (0.85, 7.58)	0.47 (0.12, 1.80)	1.51 (0.39, 6.02)	4.47 (1.14, 18.28)	1.92 (0.46, 8.09)	1.52 (0.29, 7.88)	1.60 (0.74, 3.45)	4.05 (1.44, 11.52)	3.41 (0.58, 19.24)		N/A	N/A

	Metformin-NPH insulin	_NPH insulin	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide (once weekly)-Metformin-Sulfonylurea	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin mix 70/30	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin mix 70/30	NPH insulin mix 70/30-Sulfonylurea	NPH insulin-repaglinide
NPH insulin mix 70/30-Sulfonylurea	3.59 (1.09, 12.30)	2.23 (0.68, 7.41)	1.65 (0.36, 7.70)	1.64 (0.40, 6.85)	2.14 (0.51, 9.35)	2.61 (0.48, 14.89)	1.27 (0.27, 6.32)	6.35 (1.39, 31.26)	3.29 (0.85, 13.79)	1.69 (0.42, 7.02)	2.40 (0.61, 9.96)	1.88 (0.39, 9.09)	7.65 (1.58, 38.55)	6.82 (1.56, 30.95)	4.92 (1.37, 18.45)	3.48 (0.99, 12.69)	3.49 (1.03, 12.08)	0.66 (0.15, 2.86)	2.11 (0.48, 9.51)	6.26 (1.44, 28.66)	2.69 (0.58, 12.63)	2.12 (0.36, 12.21)	2.24 (0.87, 5.89)	5.66 (1.77, 18.57)	4.76 (0.74, 30.21)	1.40 (0.78, 2.51)		N/A
NPH insulin-repaglinide	0.86 (0.45, 1.61)	0.53 (0.26, 1.07)	0.39 (0.12, 1.24)	0.39 (0.15, 1.03)	0.51 (0.18, 1.43)	0.62 (0.16, 2.50)	0.30 (0.09, 1.03)	1.52 (0.46, 5.07)	0.78 (0.31, 2.05)	0.40 (0.15, 1.08)	0.57 (0.21, 1.54)	0.45 (0.14, 1.46)	1.82 (0.53, 6.16)	1.64 (0.54, 4.89)	1.18 (0.52, 2.59)	0.83 (0.37, 1.82)	0.84 (0.40, 1.67)	0.16 (0.06, 0.45)	0.50 (0.17, 1.48)	1.48 (0.50, 4.54)	0.64 (0.20, 2.04)	0.51 (0.12, 2.02)	0.53 (0.22, 1.26)	1.35 (0.43, 4.07)	1.13 (0.18, 6.80)	0.33 (0.10, 1.06)	0.24 (0.06, 0.86)	
NPH insulin-Sulfonylurea	1.31 (0.79, 2.22)	0.81 (0.51, 1.30)	0.60 (0.21, 1.74)	0.60 (0.26, 1.43)	0.78 (0.31, 1.97)	0.96 (0.26, 3.61)	0.47 (0.15, 1.48)	2.34 (0.80, 6.93)	1.20 (0.55, 2.80)	0.62 (0.26, 1.52)	0.87 (0.37, 2.15)	0.69 (0.23, 2.04)	2.80 (0.91, 8.51)	2.51 (0.93, 6.77)	1.81 (0.96, 3.44)	1.27 (0.70, 2.35)	1.28 (0.87, 1.87)	0.24 (0.11, 0.55)	0.77 (0.29, 2.08)	2.29 (0.86, 6.13)	0.98 (0.34, 2.94)	0.77 (0.19, 3.01)	0.82 (0.40, 1.64)	2.07 (0.77, 5.64)	1.74 (0.30, 9.66)	0.51 (0.18, 1.43)	0.37 (0.11, 1.19)	1.53 (0.83, 2.89)

Values given are hazard ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.

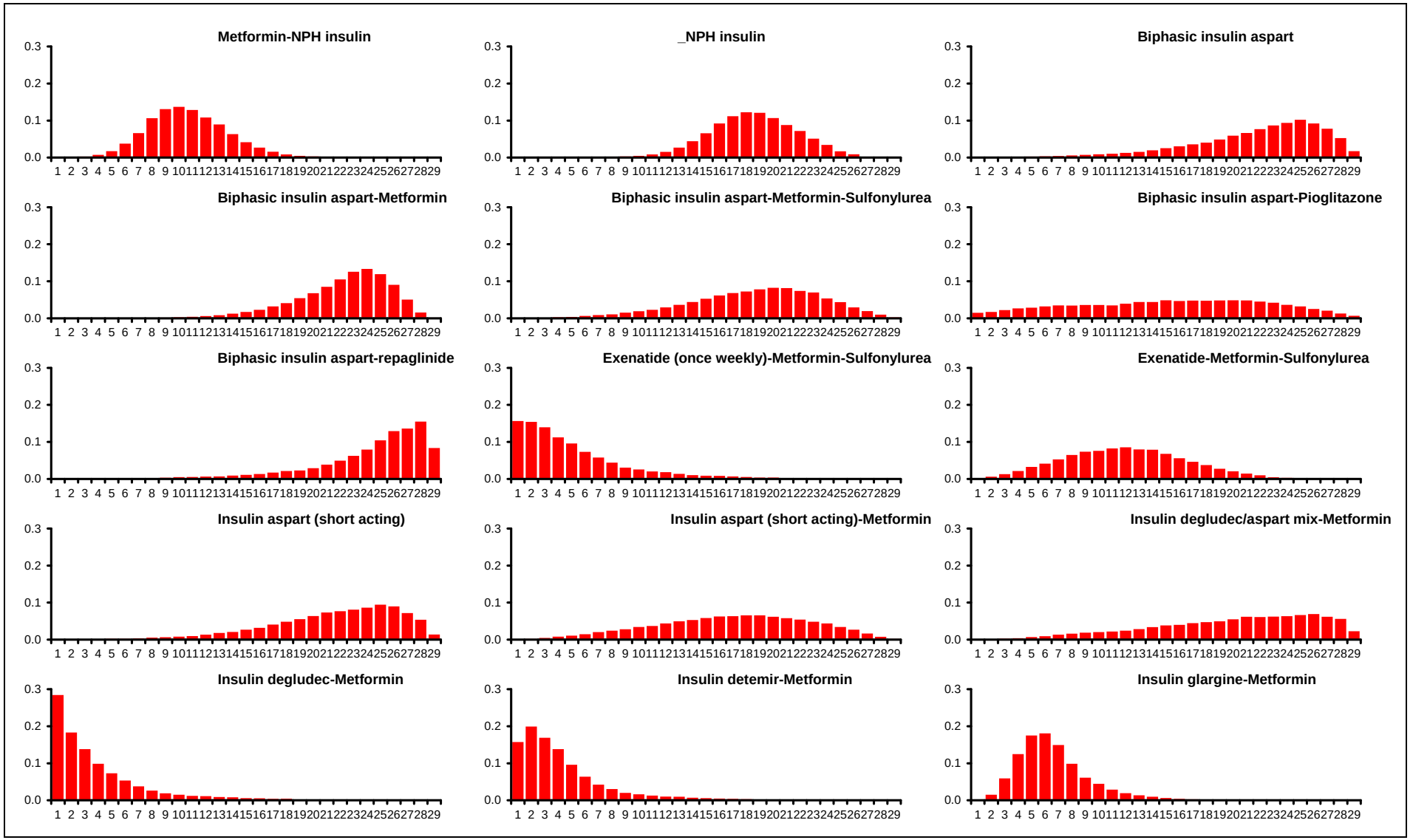


Values greater than 1 favour metformin-NPH insulin; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 65: SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effect of all options versus reference treatment

Table 110: SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – rankings for each comparator

	Probability best	Median rank (95%CI)
Metformin-NPH insulin	0.000	10 (5, 17)
_NPH insulin	0.000	19 (12, 25)
Biphasic insulin aspart	0.000	23 (9, 28)
Biphasic insulin aspart-Metformin	0.000	23 (13, 27)
Biphasic insulin aspart-Metformin-Sulfonylurea	0.000	19 (8, 27)
Biphasic insulin aspart-Pioglitazone	0.015	16 (2, 27)
Biphasic insulin aspart-repaglinide	0.000	26 (12, 29)
Exenatide (once weekly)-Metformin-Sulfonylurea	0.156	4 (1, 17)
Exenatide-Metformin-Sulfonylurea	0.001	12 (4, 21)
Insulin aspart (short acting)	0.000	22 (10, 28)
Insulin aspart (short acting)-Metformin	0.001	17 (5, 27)
Insulin degludec/aspart mix-Metformin	0.000	21 (7, 28)
Insulin degludec-Metformin	0.284	3 (1, 16)
Insulin detemir-Metformin	0.157	3 (1, 15)
Insulin glargine-Metformin	0.001	6 (3, 14)
Insulin glargine-Metformin-Sulfonylurea	0.000	11 (5, 19)
Insulin glargine-Sulfonylurea	0.000	11 (5, 19)
Insulin lispro mix 50 and mix 25	0.000	29 (22, 29)
Insulin lispro mix 50/50-Metformin	0.000	19 (7, 28)
Liraglutide-Metformin-Sulfonylurea	0.120	4 (1, 16)
Metformin-NPH insulin mix 70/30	0.005	15 (3, 26)
Metformin-NPH insulin-repaglinide	0.009	19 (3, 29)
Metformin-NPH insulin-Sulfonylurea	0.000	18 (8, 26)
Metformin-Pioglitazone-Sulfonylurea	0.075	5 (1, 18)
Metformin-Sitagliptin-Sulfonylurea	0.164	7 (1, 27)
NPH insulin mix 70/30	0.000	24 (10, 28)
NPH insulin mix 70/30-Sulfonylurea	0.000	27 (14, 29)
NPH insulin-repaglinide	0.009	8 (2, 19)
NPH insulin-Sulfonylurea	0.000	15 (9, 22)


Metformin-NPH insulin
_NPH insulin
Biphasic insulin aspart
Biphasic insulin aspart-Metformin
Biphasic insulin aspart-Metformin-Sulfonylurea
Biphasic insulin aspart-Pioglitazone
Biphasic insulin aspart-repaglinide
Exenatide (once weekly)-Metformin-Sulfonylurea
Exenatide-Metformin-Sulfonylurea
Insulin aspart (short acting)
Insulin aspart (short acting)-Metformin
Insulin degludec/aspart mix-Metformin
Insulin degludec-Metformin
Insulin detemir-Metformin
Insulin glargine-Metformin
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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29

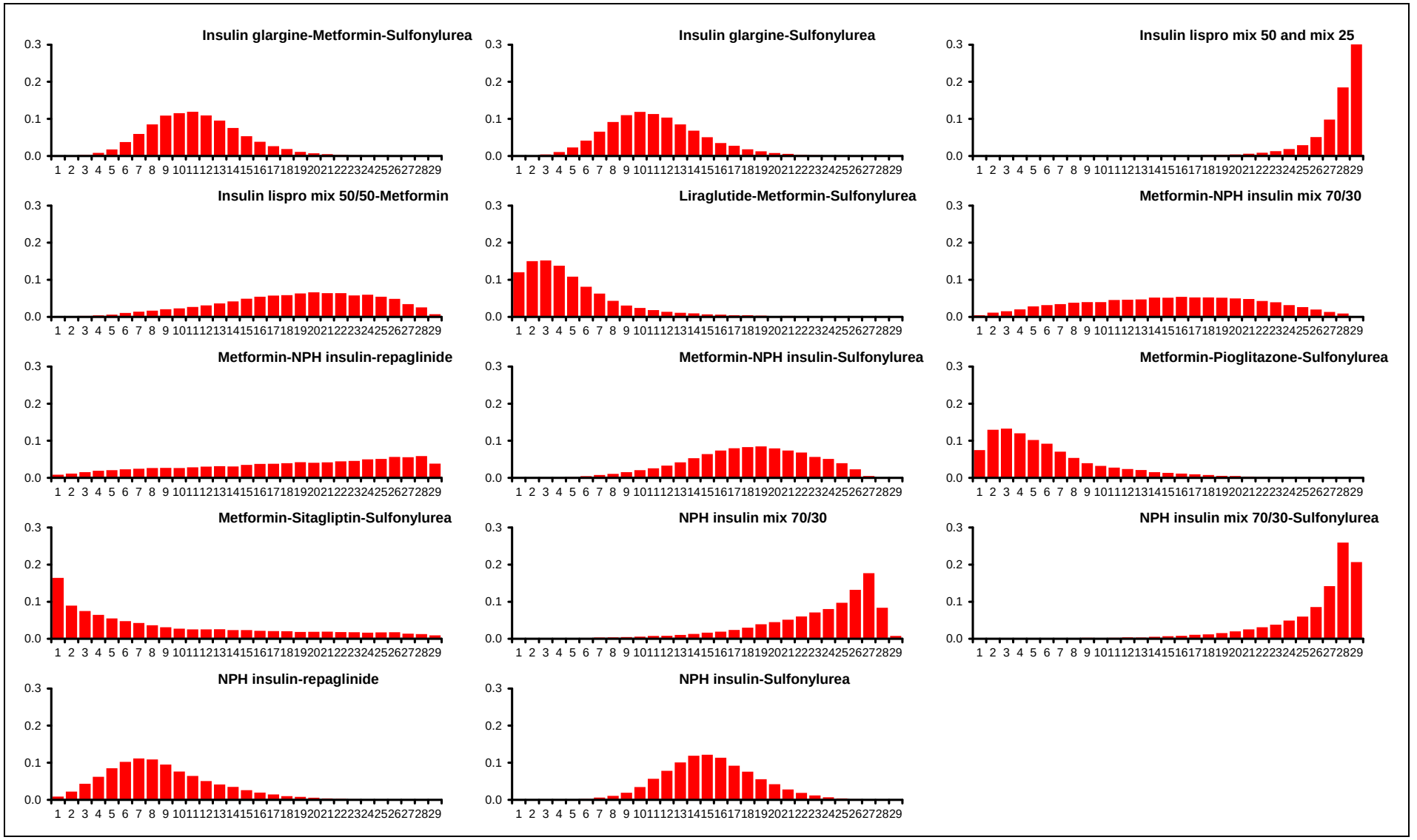


Figure 66: SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – rank probability histograms

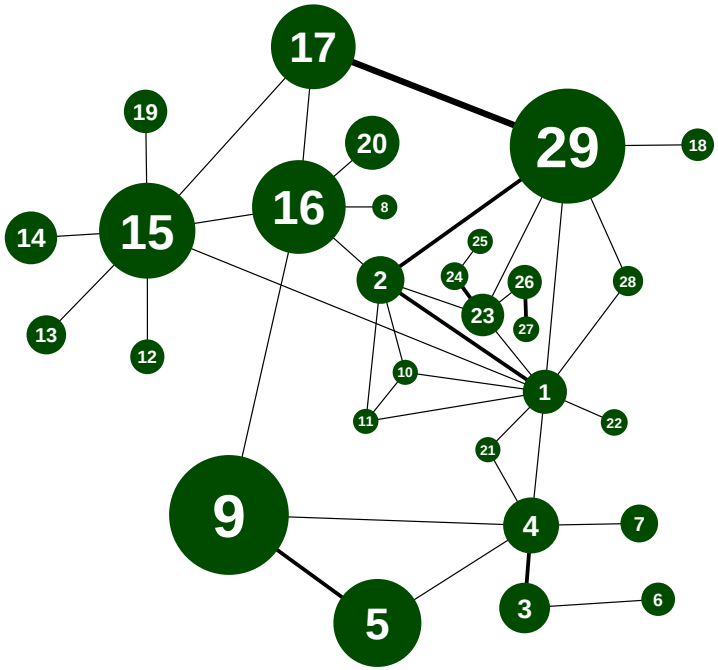
Table 111: SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
79.94 (compared to 77 datapoints)	125.496	104.158	21.338	606.632	0.335 (95%CI: 0.183, 0.590)

Table 112: SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – notes

- Hybrid cloglog--Poisson model for count/dichotomous data; random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

J.2.3.3 Dropouts due to adverse events at study endpoint



1 Metformin-NPH insulin
2 _NPH insulin
3 Biphasic insulin aspart
4 Biphasic insulin aspart-Metformin
5 Biphasic insulin aspart-Metformin-Sulfonylurea
6 Biphasic insulin aspart-Pioglitazone
7 Biphasic insulin aspart-repaglinide
8 Exenatide (once weekly)-Metformin-Sulfonylurea
9 Exenatide-Metformin-Sulfonylurea
10 Insulin aspart (short acting)
11 Insulin aspart (short acting)-Metformin
12 Insulin degludec/aspart mix-Metformin
13 Insulin degludec-Metformin
14 Insulin detemir-Metformin
15 Insulin glargine-Metformin
16 Insulin glargine-Metformin-Sulfonylurea
17 Insulin glargine-Sulfonylurea
18 Insulin lispro mix 50 and mix 25
19 Insulin lispro mix 50/50-Metformin
20 Liraglutide-Metformin-Sulfonylurea
21 Metformin-NPH insulin mix 70/30
22 Metformin-NPH insulin-repaglinide
23 Metformin-NPH insulin-Sulfonylurea
24 Metformin-Pioglitazone-Sulfonylurea
25 Metformin-Sitagliptin-Sulfonylurea
26 NPH insulin mix 70/30
27 NPH insulin mix 70/30-Sulfonylurea
28 NPH insulin-repaglinide
29 NPH insulin-Sulfonylurea

Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 67: SECOND INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – evidence network

Table 113: SECOND INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – input data

	Metformin-NPH insulin	Acarbose-Metformin-Sulfonylurea	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin mix 70/30	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-repaglinide-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin	NPH insulin-Sulfonylurea
Zinman et al. (2011) - 0.31yr												1/183		1/62													
Heise et al. (2011) - 0.31yr											1/118			0/60													
Gram et al. (2011) - 1.99yr	5/45								3/48	2/45																0/46	
Derosa et al. (2010) - 0.73yr		16/175																					16/175				
Lund et al. (2009) - 1.00yr				0/52			2/49																				
Hartemann-Heurtier et al. (2009) - 0.46yr																						1/14	1/14				
Russell-Jones et al. (2009) - 0.50yr															5/232				11/230								
Milicevic et al. (2009) - 0.46yr																	1/68										5/67
Derosa et al. (2009) - 0.29yr		2/52																						1/51			
Bergenstal et al. (2009) - 0.46yr				6/124	1/124			9/124																			
Civera et al. (2008) - 0.46yr	0/12																				1/12					0/13	
Ushakova et al. (2007) - 0.31yr														1/158				5/157									
Robbins et al. (2007) - 0.46yr					0/248			20/253																			
Nauck et al. (2007) - 1.00yr																2/231											0/250
Eliaschewitz et al. (2006) - 0.46yr	1/49													1/61													
Yki-Jarvinen et al. (2006) - 0.69yr			2/97			1/93																					
Raz et al. (2005) - 0.34yr															1/177											6/187	
Janka et al. (2005) - 0.46yr			1/107	2/108																							
Heine et al. (2005) - 0.50yr																9/463											7/232
Kilo et al. (2003) - 0.23yr																							2/59		1/60		
Kvapil et al. (2006) - 0.31yr			1/100	1/100																							
Fritsche A,Schweitzer MA,Haring (2003) - 0.46yr								27/282							2/267												
Yki-JaŶˆrvinen et al. (1999) - 1.00yr	0/47			2/46																0/47							
Liu et al. (2013) - 0.46yr	4/24																					1/24				0/24	1/24
Meneghini et al. (2013) - 0.50yr													5/228	3/229													

Values given are number of events / number of participants. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

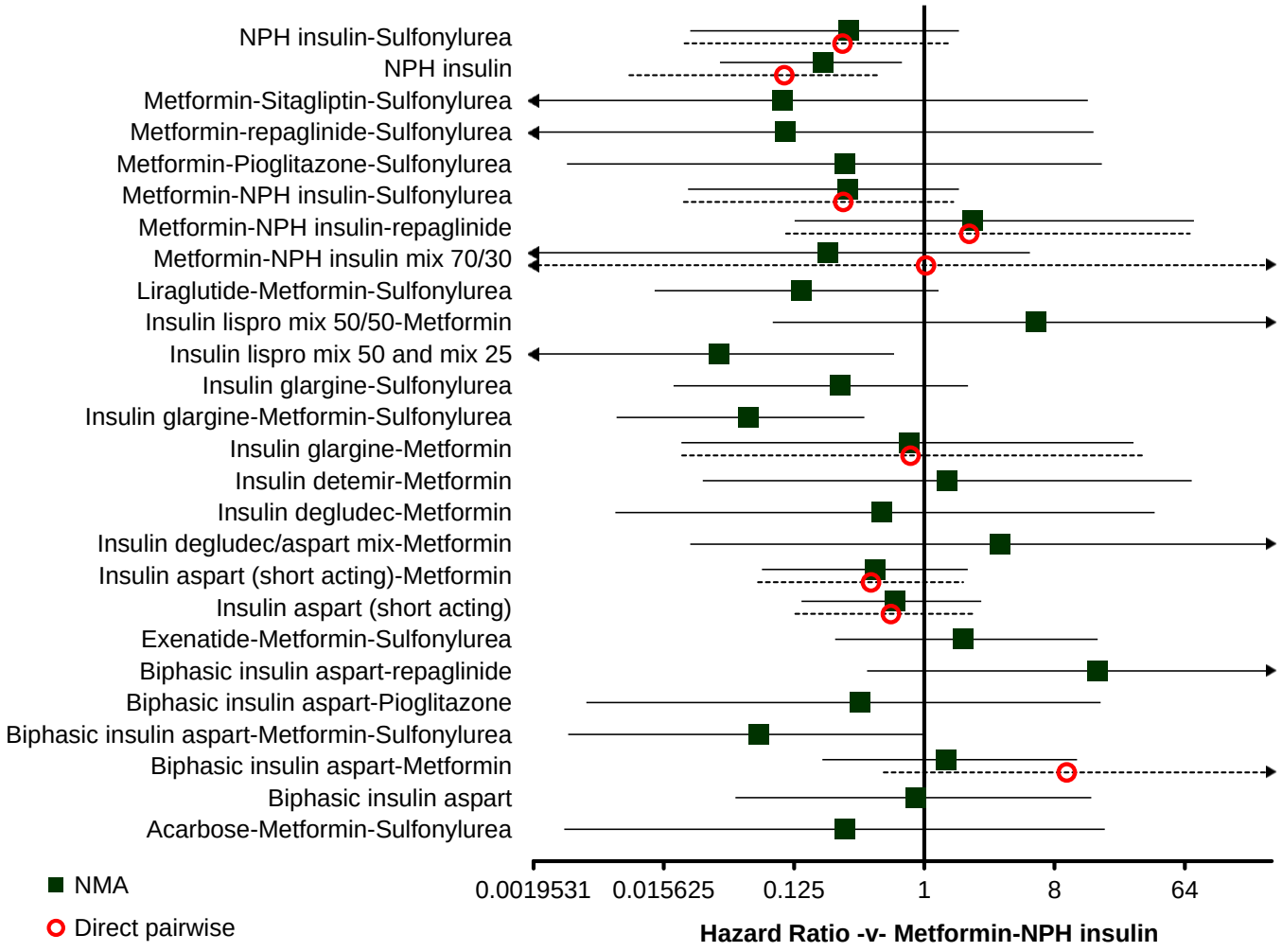
Table 114: SECOND INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations

	Metformin-NPH insulin	Acarbose-Metformin-Sulfonylurea	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin mix 70/30	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-repaglinide-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin
Metformin-NPH insulin		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Acarbose-Metformin-Sulfonylurea	0.28 (0.00, 17.84)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Biphasic insulin aspart	0.88 (0.05, 14.37)	3.17 (0.02, 581.50)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Biphasic insulin aspart-Metformin	1.42 (0.20, 11.47)	5.15 (0.05, 641.50)	1.59 (0.24, 13.55)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Biphasic insulin aspart-Metformin-Sulfonylurea	0.07 (0.00, 0.99)	0.25 (0.00, 42.12)	0.08 (0.00, 1.34)	0.05 (0.00, 0.30)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Biphasic insulin aspart-Pioglitazone	0.36 (0.00, 16.68)	1.27 (0.00, 428.60)	0.43 (0.01, 5.35)	0.25 (0.01, 6.47)	5.08 (0.07, 283.30)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Biphasic insulin aspart-repaglinide	15.94 (0.40, 10090.00)	65.49 (0.22, 121200.00)	17.79 (0.48, 11140.00)	10.20 (0.56, 5283.00)	224.90 (6.17, 147300.00)	49.42 (0.48, 52500.00)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Exenatide-Metformin-Sulfonylurea	1.86 (0.24, 15.90)	6.76 (0.07, 853.40)	2.10 (0.25, 22.13)	1.31 (0.50, 3.63)	24.41 (5.91, 278.20)	5.21 (0.18, 320.50)	0.13 (0.00, 2.89)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin aspart (short acting)	0.63 (0.14, 2.48)	2.22 (0.03, 221.80)	0.71 (0.03, 16.27)	0.44 (0.04, 4.63)	8.80 (0.44, 231.00)	1.76 (0.03, 168.70)	0.04 (0.00, 1.98)	0.33 (0.03, 3.66)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin aspart (short acting)-Metformin	0.46 (0.07, 2.00)	1.59 (0.02, 172.50)	0.51 (0.02, 12.49)	0.32 (0.02, 3.60)	6.37 (0.28, 179.70)	1.26 (0.02, 123.00)	0.03 (0.00, 1.49)	0.24 (0.02, 2.78)	0.72 (0.11, 4.04)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	Metformin-NPH insulin	Acarbose-Metformin-Sulfonylurea	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin mix 70/30	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-repaglinide-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin
Insulin degludec/aspart mix-Metformin	3.37 (0.02, 3135.00)	12.91 (0.02, 42000.00)	4.11 (0.01, 6011.00)	2.44 (0.01, 2658.00)	50.76 (0.17, 79410.00)	10.75 (0.02, 27400.00)	0.19 (0.00, 450.20)	1.86 (0.01, 2128.00)	5.52 (0.03, 6023.00)	7.86 (0.04, 8307.00)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin degludec-Metformin	0.51 (0.01, 39.48)	1.83 (0.00, 869.10)	0.58 (0.00, 106.20)	0.36 (0.00, 43.06)	7.35 (0.05, 1391.00)	1.49 (0.00, 657.80)	0.03 (0.00, 10.14)	0.27 (0.00, 32.77)	0.81 (0.01, 80.38)	1.16 (0.01, 120.00)	0.16 (0.00, 9.91)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin detemir-Metformin	1.44 (0.03, 71.34)	5.07 (0.02, 1750.00)	1.62 (0.01, 202.70)	1.01 (0.01, 79.68)	20.52 (0.18, 2735.00)	4.14 (0.02, 1413.00)	0.08 (0.00, 19.81)	0.76 (0.01, 61.10)	2.31 (0.04, 147.20)	3.27 (0.05, 224.60)	0.46 (0.00, 16.57)	2.84 (0.15, 43.66)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin glargine-Metformin	0.79 (0.02, 28.18)	2.84 (0.01, 818.20)	0.91 (0.01, 86.46)	0.56 (0.01, 32.89)	11.45 (0.13, 1131.00)	2.25 (0.01, 608.10)	0.04 (0.00, 8.74)	0.43 (0.01, 24.60)	1.27 (0.03, 59.71)	1.79 (0.03, 92.05)	0.27 (0.00, 6.00)	1.62 (0.12, 13.84)	0.57 (0.11, 2.42)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin glargine-Metformin-Sulfonylurea	0.06 (0.01, 0.38)	0.21 (0.00, 24.66)	0.07 (0.00, 1.03)	0.04 (0.00, 0.23)	0.84 (0.06, 13.39)	0.17 (0.00, 12.75)	0.00 (0.00, 0.13)	0.03 (0.00, 0.14)	0.10 (0.01, 0.92)	0.13 (0.01, 1.52)	0.02 (0.00, 3.66)	0.12 (0.00, 12.12)	0.04 (0.00, 3.11)	0.07 (0.00, 4.54)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin glargine-Sulfonylurea	0.26 (0.02, 2.01)	0.88 (0.01, 96.82)	0.29 (0.01, 10.11)	0.18 (0.01, 3.13)	3.55 (0.09, 138.10)	0.70 (0.01, 82.69)	0.01 (0.00, 1.16)	0.14 (0.01, 2.45)	0.41 (0.02, 5.25)	0.57 (0.03, 8.41)	0.07 (0.00, 16.38)	0.49 (0.00, 57.24)	0.17 (0.00, 15.25)	0.31 (0.00, 21.04)	4.24 (0.19, 75.58)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin lispro mix 50 and mix 25	0.04 (0.00, 0.62)	0.12 (0.00, 21.53)	0.04 (0.00, 2.36)	0.03 (0.00, 0.83)	0.51 (0.00, 31.88)	0.10 (0.00, 18.35)	0.00 (0.00, 0.27)	0.02 (0.00, 0.64)	0.06 (0.00, 1.46)	0.08 (0.00, 2.29)	0.01 (0.00, 3.28)	0.07 (0.00, 12.41)	0.02 (0.00, 3.34)	0.04 (0.00, 4.60)	0.62 (0.01, 19.69)	0.16 (0.00, 1.49)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin lispro mix 50/50-Metformin	5.99 (0.09, 734.90)	22.52 (0.06, 13500.00)	7.07 (0.04, 1811.00)	4.26 (0.04, 755.00)	90.38 (0.58, 23120.00)	18.18 (0.06, 10880.00)	0.34 (0.00, 169.80)	3.28 (0.03, 601.30)	9.72 (0.12, 1496.00)	13.61 (0.16, 2155.00)	1.90 (0.00, 178.00)	11.69 (0.44, 566.20)	4.06 (0.29, 144.60)	6.92 (0.94, 211.90)	102.20 (0.99, 18920.00)	24.77 (0.20, 5727.00)	177.20 (1.03, 85900.00)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Liraglutide-Metformin-Sulfonylurea	0.14 (0.01, 1.26)	0.51 (0.00, 68.62)	0.16 (0.01, 3.13)	0.10 (0.01, 0.80)	2.01 (0.12, 38.90)	0.40 (0.01, 34.33)	0.01 (0.00, 0.37)	0.08 (0.01, 0.51)	0.23 (0.02, 2.80)	0.32 (0.02, 4.62)	0.04 (0.00, 9.50)	0.28 (0.00, 33.15)	0.10 (0.00, 8.30)	0.18 (0.00, 12.21)	2.33 (0.85, 7.58)	0.57 (0.03, 16.22)	3.93 (0.10, 336.60)	0.02 (0.00, 2.67)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Metformin-NPH insulin mix 70/30	0.22 (0.00, 5.40)	0.64 (0.00, 189.40)	0.23 (0.00, 10.83)	0.15 (0.00, 3.37)	2.92 (0.01, 156.40)	0.54 (0.00, 96.10)	0.01 (0.00, 1.22)	0.11 (0.00, 2.83)	0.33 (0.00, 12.22)	0.46 (0.00, 18.67)	0.05 (0.00, 24.47)	0.36 (0.00, 86.23)	0.13 (0.00, 23.60)	0.24 (0.00, 34.54)	3.55 (0.01, 118.80)	0.80 (0.00, 51.20)	5.42 (0.01, 947.60)	0.03 (0.00, 7.56)	1.45 (0.00, 59.76)		N/A	N/A	N/A	N/A	N/A	N/A
Metformin-NPH insulin-repaglinide	2.18 (0.13, 73.91)	8.33 (0.05, 1983.00)	2.58 (0.05, 217.40)	1.58 (0.05, 78.91)	32.43 (0.65, 2798.00)	6.54 (0.05, 1556.00)	0.13 (0.00, 20.91)	1.19 (0.03, 63.03)	3.55 (0.15, 150.60)	5.02 (0.19, 236.10)	0.63 (0.00, 294.20)	4.44 (0.02, 1021.00)	1.59 (0.01, 275.60)	2.89 (0.03, 421.00)	37.56 (1.26, 1868.00)	8.98 (0.25, 655.00)	63.61 (1.03, 11130.00)	0.38 (0.00, 83.31)	15.89 (0.45, 920.00)	11.94 (0.13, 10590.00)		N/A	N/A	N/A	N/A	N/A

	Metformin-NPH insulin	Acarbose-Metformin-Sulfonylurea	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin mix 70/30	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-repaglinide-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin
Metformin-NPH insulin-Sulfonylurea	0.30 (0.02, 1.74)	1.00 (0.02, 43.28)	0.32 (0.01, 9.58)	0.20 (0.01, 2.85)	3.99 (0.11, 133.60)	0.78 (0.01, 86.95)	0.02 (0.00, 1.11)	0.15 (0.01, 2.26)	0.46 (0.03, 4.67)	0.64 (0.04, 7.85)	0.08 (0.00, 16.43)	0.54 (0.00, 56.65)	0.19 (0.00, 14.12)	0.34 (0.01, 20.94)	4.79 (0.23, 70.81)	1.12 (0.06, 20.46)	7.46 (0.24, 491.90)	0.05 (0.00, 4.66)	2.01 (0.08, 36.34)	1.39 (0.02, 753.40)	0.12 (0.00, 3.77)		N/A	N/A	N/A	N/A
Metformin-Pioglitazone-Sulfonylurea	0.28 (0.00, 17.02)	1.00 (0.50, 2.00)	0.31 (0.00, 47.45)	0.19 (0.00, 17.87)	4.01 (0.02, 587.00)	0.80 (0.00, 305.90)	0.02 (0.00, 4.32)	0.15 (0.00, 13.96)	0.45 (0.00, 34.58)	0.62 (0.01, 53.08)	0.08 (0.00, 51.06)	0.55 (0.00, 196.00)	0.20 (0.00, 54.12)	0.36 (0.00, 80.29)	4.72 (0.04, 424.90)	1.14 (0.01, 116.10)	8.04 (0.05, 1778.00)	0.04 (0.00, 16.77)	1.98 (0.02, 204.80)	1.55 (0.01, 1745.00)	0.12 (0.00, 18.97)	1.01 (0.02, 41.25)		N/A	N/A	N/A
Metformin-repaglinide-Sulfonylurea	0.11 (0.00, 14.91)	0.42 (0.01, 5.44)	0.12 (0.00, 37.31)	0.07 (0.00, 15.59)	1.55 (0.00, 483.70)	0.31 (0.00, 225.10)	0.01 (0.00, 3.21)	0.06 (0.00, 11.90)	0.17 (0.00, 29.91)	0.24 (0.00, 46.48)	0.03 (0.00, 36.81)	0.21 (0.00, 142.90)	0.07 (0.00, 40.84)	0.13 (0.00, 58.95)	1.81 (0.01, 366.90)	0.44 (0.00, 90.19)	3.10 (0.01, 1365.00)	0.02 (0.00, 11.59)	0.76 (0.00, 177.10)	0.62 (0.00, 1092.00)	0.05 (0.00, 14.15)	0.40 (0.00, 37.54)	0.42 (0.01, 6.12)		N/A	N/A
Metformin-Sitagliptin-Sulfonylurea	0.10 (0.00, 13.61)	0.40 (0.01, 5.89)	0.12 (0.00, 34.71)	0.07 (0.00, 14.81)	1.52 (0.00, 454.70)	0.29 (0.00, 198.80)	0.01 (0.00, 3.01)	0.05 (0.00, 11.60)	0.17 (0.00, 28.45)	0.23 (0.00, 41.72)	0.03 (0.00, 31.03)	0.20 (0.00, 126.40)	0.07 (0.00, 36.10)	0.13 (0.00, 57.94)	1.79 (0.01, 335.20)	0.43 (0.00, 88.11)	3.06 (0.01, 1317.00)	0.02 (0.00, 10.34)	0.73 (0.00, 161.10)	0.59 (0.00, 994.00)	0.04 (0.00, 14.41)	0.38 (0.00, 35.10)	0.40 (0.01, 5.30)	0.95 (0.01, 73.01)		N/A
NPH insulin	0.20 (0.04, 0.70)	0.67 (0.01, 67.47)	0.22 (0.01, 3.97)	0.14 (0.02, 0.99)	2.65 (0.19, 55.24)	0.53 (0.01, 45.94)	0.01 (0.00, 0.47)	0.10 (0.01, 0.75)	0.31 (0.04, 1.87)	0.43 (0.06, 3.25)	0.06 (0.00, 9.91)	0.38 (0.00, 32.40)	0.13 (0.00, 8.58)	0.24 (0.01, 12.11)	3.08 (0.68, 19.04)	0.75 (0.06, 12.49)	5.14 (0.23, 317.60)	0.03 (0.00, 2.71)	1.32 (0.20, 10.79)	0.90 (0.03, 418.30)	0.09 (0.00, 1.92)	0.67 (0.07, 9.83)	0.67 (0.01, 64.60)	1.76 (0.01, 466.50)	1.82 (0.01, 503.70)	
NPH insulin-Sulfonylurea	0.30 (0.02, 1.74)	0.98 (0.01, 103.90)	0.32 (0.01, 9.92)	0.20 (0.01, 2.94)	4.02 (0.12, 136.60)	0.78 (0.01, 90.54)	0.02 (0.00, 1.14)	0.15 (0.01, 2.27)	0.46 (0.03, 4.74)	0.64 (0.04, 7.94)	0.08 (0.00, 16.99)	0.55 (0.00, 59.57)	0.19 (0.00, 15.77)	0.36 (0.01, 21.56)	4.78 (0.24, 69.90)	1.13 (0.42, 2.86)	7.02 (0.95, 214.70)	0.05 (0.00, 4.84)	1.98 (0.08, 36.58)	1.39 (0.02, 708.30)	0.13 (0.00, 3.85)	1.00 (0.07, 16.14)	0.99 (0.01, 99.28)	2.58 (0.01, 695.00)	2.62 (0.01, 756.90)	1.53 (0.10, 14.13)

Values given are hazard ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.



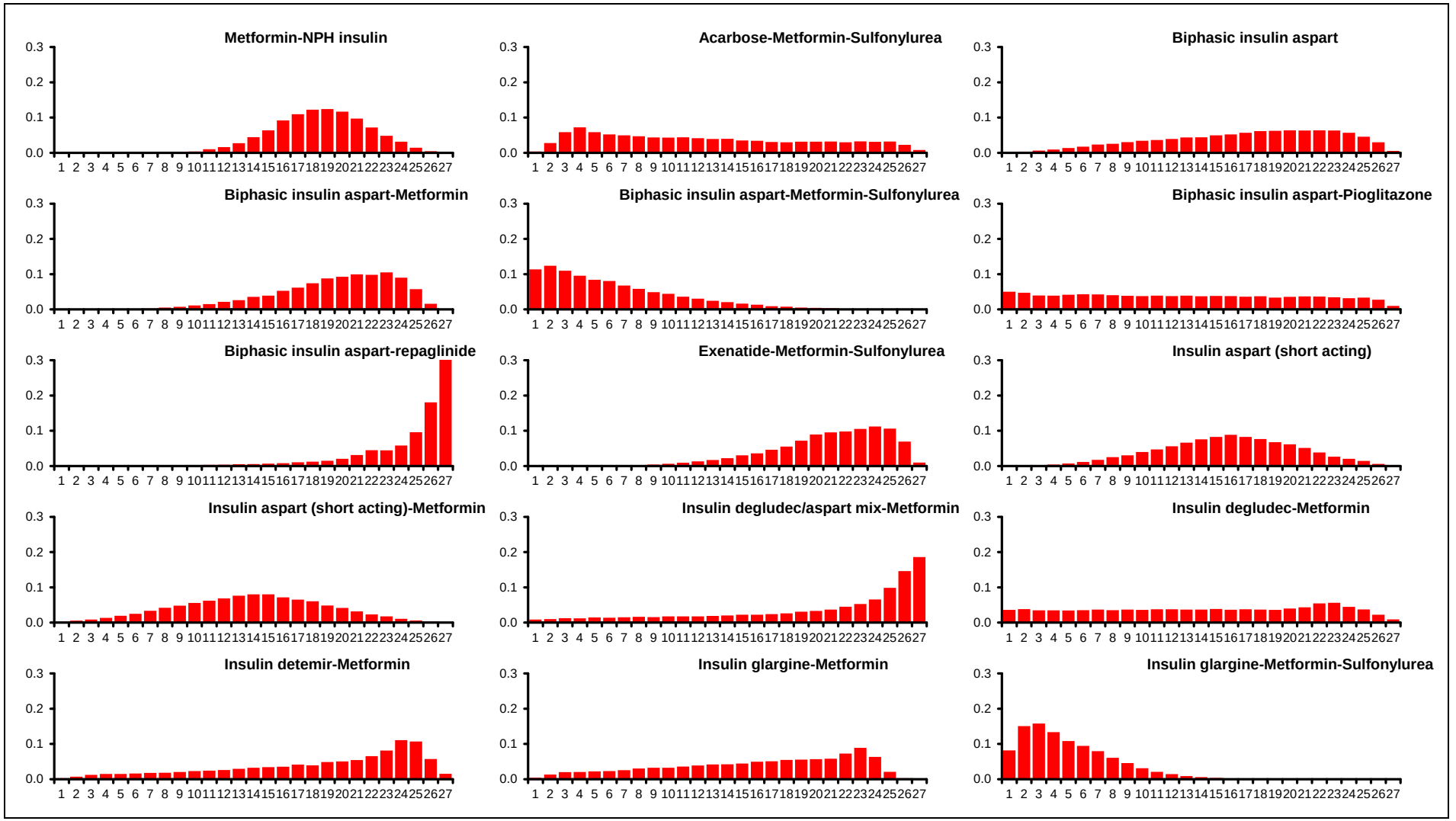
Values greater than 1 favour metformin-NPH insulin; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 68: SECOND INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – relative effect of all options versus reference treatment

Table 115: SECOND INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – rankings for each comparator

	Probability best	Median rank (95%CI)
Metformin-NPH insulin	0.000	19 (12, 24)
Acarbose-Metformin-Sulfonylurea	0.004	12 (2, 26)
Biphasic insulin aspart	0.000	18 (5, 26)
Biphasic insulin aspart-Metformin	0.000	20 (10, 25)
Biphasic insulin aspart-Metformin-Sulfonylurea	0.114	5 (1, 17)
Biphasic insulin aspart-Pioglitazone	0.050	13 (1, 26)
Biphasic insulin aspart-repaglinide	0.000	26 (14, 27)
Exenatide-Metformin-Sulfonylurea	0.000	22 (12, 26)
Insulin aspart (short acting)	0.000	16 (6, 24)
Insulin aspart (short acting)-Metformin	0.003	14 (4, 23)
Insulin degludec/aspart mix-Metformin	0.008	23 (3, 27)
Insulin degludec-Metformin	0.036	14 (1, 26)
Insulin detemir-Metformin	0.003	20 (4, 26)
Insulin glargine-Metformin	0.004	17 (3, 24)
Insulin glargine-Metformin-Sulfonylurea	0.082	4 (1, 12)
Insulin glargine-Sulfonylurea	0.003	11 (2, 22)
Insulin lispro mix 50 and mix 25	0.268	3 (1, 15)
Insulin lispro mix 50/50-Metformin	0.000	25 (8, 27)
Liraglutide-Metformin-Sulfonylurea	0.006	8 (2, 19)
Metformin-NPH insulin mix 70/30	0.119	10 (1, 25)
Metformin-NPH insulin-repaglinide	0.002	22 (7, 27)
Metformin-NPH insulin-Sulfonylurea	0.005	12 (3, 21)
Metformin-Pioglitazone-Sulfonylurea	0.003	12 (3, 26)
Metformin-repaglinide-Sulfonylurea	0.146	7 (1, 26)
Metformin-Sitagliptin-Sulfonylurea	0.143	6 (1, 25)
NPH insulin	0.001	9 (3, 17)

	Probability best	Median rank (95%CI)
NPH insulin-Sulfonylurea	0.000	12 (3, 22)


Metformin-NPH insulin
Acarbose-Metformin-Sulfonylurea
Biphasic insulin aspart
Biphasic insulin aspart-Metformin
Biphasic insulin aspart-Metformin-Sulfonylurea
Biphasic insulin aspart-Pioglitazone
Biphasic insulin aspart-repaglinide
Exenatide-Metformin-Sulfonylurea
Insulin aspart (short acting)
Insulin aspart (short acting)-Metformin
Insulin degludec/aspart mix-Metformin
Insulin degludec-Metformin
Insulin detemir-Metformin
Insulin glargine-Metformin
Insulin glargine-Metformin-Sulfonylurea
0.0
0.1
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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27

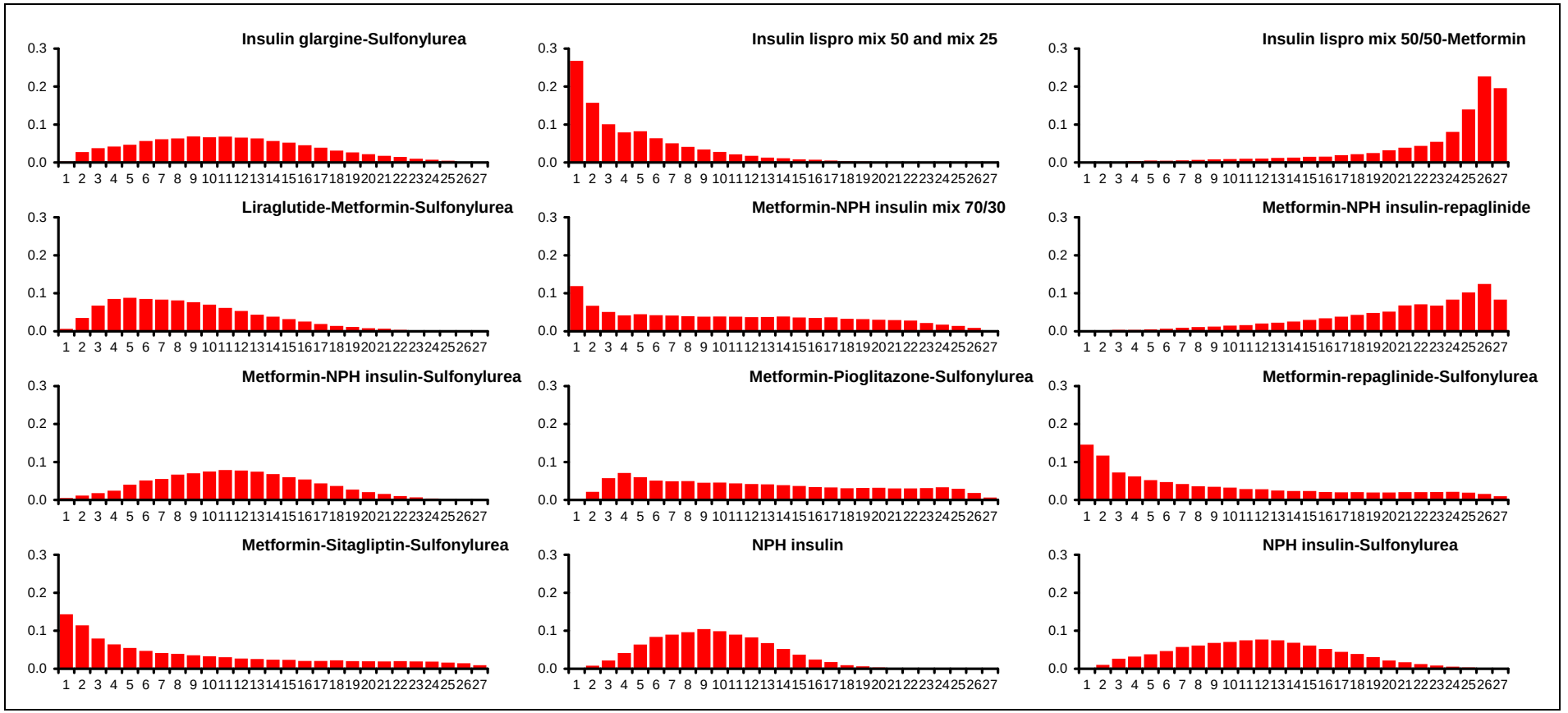


Figure 69: SECOND INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – rank probability histograms

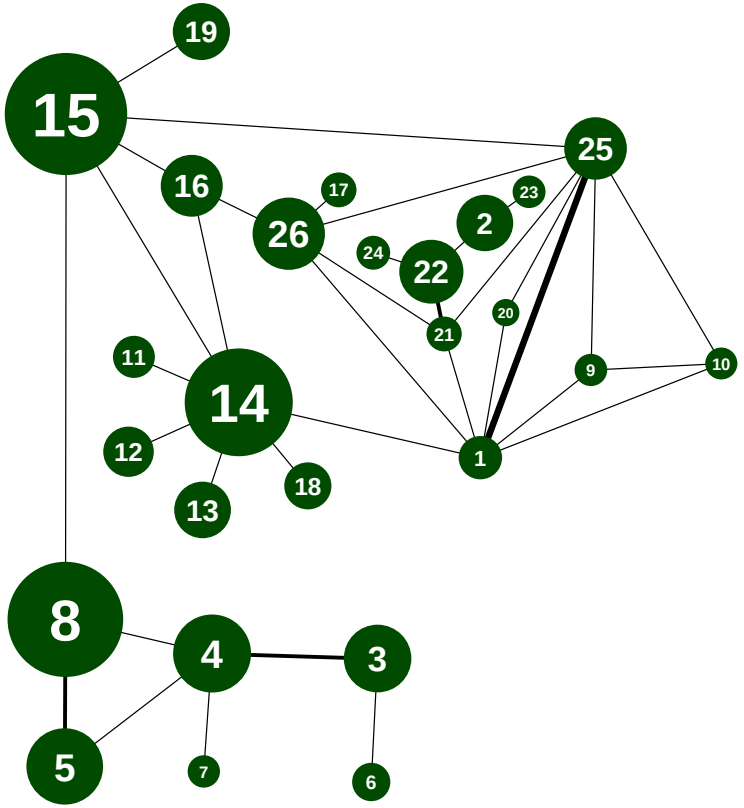
Table 116: SECOND INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	
63.34 (compared to 61 datapoints)	218.857	171.644	47.212	266.069	

Table 117: SECOND INTENSIFICATION: DROPOUTS DUE TO ADVERSE EVENTS AT STUDY ENDPOINT – notes

- Dichotomous diachronic (binomial; cloglog link); fixed effects
- 50000 burn-ins; 10000 recorded iterations

J.2.3.4 Total dropouts at study endpoint



1 Metformin-NPH insulin
2 Acarbose-Metformin-Sulfonylurea
3 Biphasic insulin aspart
4 Biphasic insulin aspart-Metformin
5 Biphasic insulin aspart-Metformin-Sulfonylurea
6 Biphasic insulin aspart-Pioglitazone
7 Biphasic insulin aspart-repaglinide
8 Exenatide-Metformin-Sulfonylurea
9 Insulin aspart (short acting)
10 Insulin aspart (short acting)-Metformin
11 Insulin degludec/aspart mix-Metformin
12 Insulin degludec-Metformin
13 Insulin detemir-Metformin
14 Insulin glargine-Metformin
15 Insulin glargine-Metformin-Sulfonylurea
16 Insulin glargine-Sulfonylurea
17 Insulin lispro mix 50 and mix 25
18 Insulin lispro mix 50/50-Metformin
19 Liraglutide-Metformin-Sulfonylurea
20 Metformin-NPH insulin-repaglinide
21 Metformin-NPH insulin-Sulfonylurea
22 Metformin-Pioglitazone-Sulfonylurea
23 Metformin-repaglinide-Sulfonylurea
24 Metformin-Sitagliptin-Sulfonylurea
25 NPH insulin
26 NPH insulin-Sulfonylurea

Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 70: SECOND INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – evidence network

Table 118: SECOND INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – input data

	Metformin-NPH insulin	Acarbose-Metformin-Sulfonylurea	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-repaglinide-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin	NPH insulin-Sulfonylurea
Zinman et al. (2011) - 0.31yr												22/183		6/62												
Heise et al. (2011) - 0.31yr											10/118			5/60												
Gram et al. (2011) - 1.99yr	8/45								15/48	7/45															6/46	
Derosa et al. (2010) - 0.73yr		39/175																				37/175				
Lund et al. (2009) - 1.00yr				1/52			3/49																			
Hartemann-Heurtier et al. (2009) - 0.46yr																					1/14	1/14				
Russell-Jones et al. (2009) - 0.50yr															13/232				23/230							
Milicevic et al. (2009) - 0.46yr																	16/68									12/67
Derosa et al. (2009) - 0.29yr		3/52																					1/51			
Bergenstal et al. (2009) - 0.46yr				24/124	20/124			37/124																		
Civera et al. (2008) - 0.46yr	0/12																			1/12					1/13	
Ushakova et al. (2007) - 0.31yr														22/158				15/157								
Robbins et al. (2007) - 0.46yr					25/248			54/253																		
Nauck et al. (2007) - 1.00yr																13/231										6/250
Eliaschewitz et al. (2006) - 0.46yr	1/49													1/61												
Yki-Jarvinen et al. (2006) - 0.69yr			8/97			7/93																				
Raz et al. (2005) - 0.34yr															7/177										28/187	
Janka et al. (2005) - 0.46yr																					3/31	1/31				
Heine et al. (2005) - 0.50yr			6/107	11/108																						
Aljabri et al. (2004) - 0.31yr																						8/60		6/60		
Kvapil et al. (2006) - 0.31yr			4/104	5/100																						
Yki-JaÝˆrvinen et al. (1999) - 1.00yr								54/282							25/267											
Liu et al. (2013) - 0.46yr	5/24																				1/24				0/24	2/24
Meneghini et al. (2013) - 0.50yr													38/228	41/229												
Park et al. (2014) - 0.54yr														7/33	8/32	7/34										

Values given are number of events / number of participants. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms

	Metformin-NPH insulin	Acarbose-Metformin-Sulfonylurea	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-repaglinide-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin	NPH insulin-Sulfonylurea
have been pooled here, whereas each arm is entered separately into the NMAs.																										

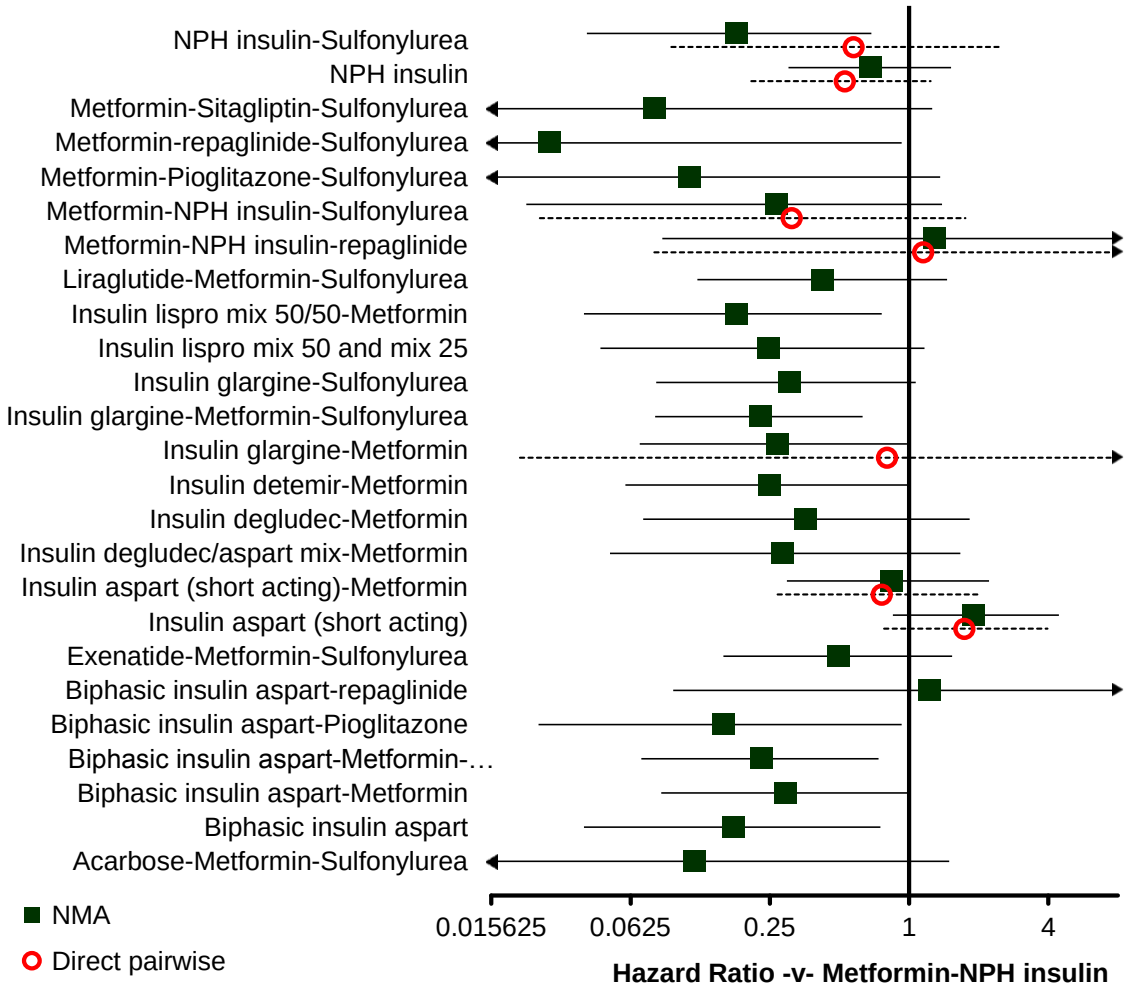
Table 119: SECOND INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations

	Metformin-NPH insulin	Acarbose-Metformin-Sulfonylurea	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-repaglinide-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin
Acarbose-Metformin-Sulfonylurea	0.12 (0.01, 1.49)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Biphasic insulin aspart	0.17 (0.04, 0.75)	1.48 (0.09, 43.68)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Biphasic insulin aspart-Metformin	0.29 (0.08, 0.99)	2.49 (0.16, 65.37)	1.67 (0.75, 3.83)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Biphasic insulin aspart-Metformin-Sulfonylurea	0.23 (0.07, 0.74)	1.94 (0.13, 50.37)	1.31 (0.51, 3.52)	0.78 (0.46, 1.37)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Biphasic insulin aspart-Pioglitazone	0.16 (0.02, 0.93)	1.35 (0.06, 45.69)	0.90 (0.31, 2.55)	0.54 (0.14, 1.98)	0.69 (0.16, 2.83)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Biphasic insulin aspart-repaglinide	1.23 (0.10, 47.17)	11.43 (0.30, 1153.00)	7.11 (0.65, 246.30)	4.16 (0.45, 138.70)	5.30 (0.53, 178.30)	7.97 (0.56, 311.10)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Exenatide-	0.50	4.24	2.83	1.69	2.16	3.14	0.41		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	Metformin-NPH insulin	Acarbose-Metformin-Sulfonylurea	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-repaglinide-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin
Metformin-Sulfonylurea	(0.16, 1.53)	(0.28, 105.30)	(1.12, 7.49)	(1.05, 2.83)	(1.52, 3.12)	(0.79, 13.23)	(0.01, 4.09)																		
Insulin aspart (short acting)	1.91 (0.85, 4.44)	16.32 (1.15, 404.50)	10.96 (2.40, 51.78)	6.57 (1.85, 24.73)	8.37 (2.40, 30.13)	12.15 (1.94, 80.82)	1.55 (0.04, 20.83)	3.86 (1.17, 13.08)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin aspart (short acting)-Metformin	0.84 (0.30, 2.22)	7.11 (0.48, 187.60)	4.80 (0.94, 24.91)	2.87 (0.69, 12.03)	3.65 (0.91, 14.58)	5.31 (0.78, 38.04)	0.67 (0.02, 9.93)	1.69 (0.44, 6.40)	0.44 (0.16, 1.07)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin degludec/aspart mix-Metformin	0.29 (0.05, 1.67)	2.44 (0.12, 79.60)	1.64 (0.26, 11.08)	0.98 (0.19, 5.47)	1.25 (0.25, 6.61)	1.82 (0.22, 15.73)	0.23 (0.01, 4.08)	0.58 (0.12, 2.96)	0.15 (0.02, 0.93)	0.34 (0.05, 2.36)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin degludec-Metformin	0.36 (0.07, 1.83)	3.06 (0.17, 95.42)	2.05 (0.36, 12.63)	1.23 (0.26, 6.03)	1.56 (0.34, 7.35)	2.29 (0.30, 18.41)	0.28 (0.01, 4.53)	0.72 (0.16, 3.24)	0.19 (0.03, 1.04)	0.43 (0.07, 2.67)	1.25 (0.29, 5.38)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin detemir-Metformin	0.25 (0.06, 0.98)	2.12 (0.13, 59.42)	1.42 (0.30, 6.89)	0.85 (0.23, 3.26)	1.08 (0.30, 3.90)	1.58 (0.24, 10.57)	0.20 (0.01, 2.80)	0.50 (0.15, 1.71)	0.13 (0.03, 0.57)	0.30 (0.06, 1.48)	0.87 (0.25, 2.81)	0.70 (0.23, 1.84)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin glargine-Metformin	0.27 (0.07, 0.98)	2.29 (0.15, 62.92)	1.54 (0.35, 7.02)	0.92 (0.27, 3.24)	1.17 (0.35, 3.90)	1.70 (0.28, 10.86)	0.22 (0.01, 2.89)	0.54 (0.17, 1.71)	0.14 (0.03, 0.57)	0.32 (0.07, 1.50)	0.95 (0.29, 2.74)	0.76 (0.27, 1.79)	1.08 (0.70, 1.69)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin glargine-Metformin-Sulfonylurea	0.23 (0.08, 0.63)	1.92 (0.14, 48.20)	1.30 (0.46, 3.80)	0.78 (0.39, 1.54)	0.99 (0.54, 1.80)	1.44 (0.33, 6.51)	0.19 (0.01, 1.94)	0.46 (0.28, 0.73)	0.12 (0.04, 0.35)	0.27 (0.08, 0.97)	0.79 (0.17, 3.63)	0.63 (0.15, 2.56)	0.92 (0.30, 2.88)	0.85 (0.30, 2.43)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin glargine-Sulfonylurea	0.31 (0.08, 1.07)	2.58 (0.17, 66.72)	1.73 (0.40, 7.49)	1.04 (0.31, 3.52)	1.32 (0.42, 4.19)	1.93 (0.33, 11.73)	0.24 (0.01, 3.15)	0.61 (0.20, 1.83)	0.16 (0.04, 0.61)	0.36 (0.08, 1.65)	1.06 (0.23, 4.59)	0.85 (0.21, 3.22)	1.21 (0.41, 3.67)	1.12 (0.42, 3.07)	1.33 (0.49, 3.61)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin lispro mix 50 and mix 25	0.25 (0.05, 1.17)	2.12 (0.11, 61.36)	1.41 (0.23, 8.36)	0.84 (0.17, 4.12)	1.07 (0.22, 5.07)	1.55 (0.20, 12.31)	0.19 (0.00, 3.18)	0.49 (0.10, 2.24)	0.13 (0.02, 0.67)	0.29 (0.05, 1.71)	0.85 (0.13, 5.31)	0.68 (0.11, 3.80)	0.98 (0.20, 4.61)	0.91 (0.20, 4.04)	1.08 (0.25, 4.55)	0.81 (0.25, 2.55)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Insulin lispro mix 50/50-Metformin	0.18 (0.04, 0.76)	1.52 (0.09, 42.71)	1.02 (0.20, 5.28)	0.61 (0.15, 2.52)	0.78 (0.20, 3.05)	1.13 (0.16, 7.93)	0.14 (0.00, 2.11)	0.36 (0.10, 1.34)	0.09 (0.02, 0.44)	0.22 (0.04, 1.12)	0.63 (0.16, 2.20)	0.51 (0.15, 1.50)	0.72 (0.32, 1.59)	0.66 (0.34, 1.28)	0.79 (0.23, 2.68)	0.59 (0.18, 1.93)	0.73 (0.14, 3.75)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Liraglutide-Metformin-Sulfonylurea	0.42 (0.12, 1.46)	3.57 (0.23, 96.12)	2.40 (0.69, 8.62)	1.44 (0.55, 3.89)	1.84 (0.74, 4.63)	2.68 (0.54, 14.01)	0.34 (0.01, 4.11)	0.85 (0.37, 1.98)	0.22 (0.06, 0.80)	0.50 (0.12, 2.16)	1.48 (0.27, 7.70)	1.18 (0.24, 5.54)	1.70 (0.46, 6.47)	1.57 (0.45, 5.59)	1.85 (0.94, 3.78)	1.40 (0.41, 4.65)	1.73 (0.36, 8.77)	2.36 (0.59, 9.76)		N/A	N/A	N/A	N/A	N/A	N/A
Metformin-NPH insulin-repaglinide	1.29 (0.09,	11.04 (0.28,	7.32 (0.37,	4.37 (0.26,	5.59 (0.33,	8.09 (0.35,	0.97 (0.01,	2.59 (0.15,	0.67 (0.04,	1.52 (0.09,	4.46 (0.20,	3.53 (0.17,	5.15 (0.27,	4.73 (0.26,	5.67 (0.35,	4.20 (0.24,	5.21 (0.26,	7.15 (0.37,	3.05 (0.17,		N/A	N/A	N/A	N/A	N/A

	Metformin-NPH insulin	Acarbose-Metformin-Sulfonylurea	Biphasic insulin aspart	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-Pioglitazone	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-Sulfonylurea	Insulin aspart (short acting)	Insulin aspart (short acting)-Metformin	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-repaglinide-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin
	13.88)	521.40)	108.60)	57.97)	70.88)	148.30)	32.26)	32.13)	7.73)	19.28)	75.32)	58.74)	75.44)	67.60)	66.93)	58.50)	84.64)	109.70)	39.14)						
Metformin-NPH insulin-Sulfonylurea	0.27 (0.02, 1.39)	2.10 (0.36, 17.72)	1.50 (0.10, 12.56)	0.90 (0.06, 6.28)	1.15 (0.09, 7.78)	1.65 (0.09, 18.20)	0.20 (0.00, 4.14)	0.53 (0.04, 3.45)	0.14 (0.01, 0.83)	0.31 (0.02, 2.12)	0.91 (0.05, 9.01)	0.73 (0.04, 6.70)	1.06 (0.07, 8.39)	0.98 (0.07, 7.34)	1.17 (0.09, 7.01)	0.87 (0.06, 6.15)	1.06 (0.07, 9.65)	1.47 (0.09, 12.28)	0.63 (0.04, 4.29)	0.20 (0.01, 4.91)		N/A	N/A	N/A	N/A
Metformin-Pioglitazone-Sulfonylurea	0.11 (0.00, 1.36)	0.94 (0.60, 1.48)	0.64 (0.02, 10.63)	0.38 (0.01, 5.64)	0.49 (0.02, 6.94)	0.71 (0.02, 14.40)	0.08 (0.00, 3.11)	0.22 (0.01, 3.18)	0.06 (0.00, 0.77)	0.13 (0.01, 1.93)	0.39 (0.01, 7.26)	0.31 (0.01, 5.26)	0.44 (0.02, 6.97)	0.41 (0.02, 6.13)	0.49 (0.02, 6.45)	0.37 (0.01, 5.44)	0.45 (0.02, 8.04)	0.62 (0.02, 10.31)	0.26 (0.01, 3.87)	0.09 (0.00, 3.34)	0.45 (0.06, 2.50)		N/A	N/A	N/A
Metformin-repaglinide-Sulfonylurea	0.03 (0.00, 0.93)	0.26 (0.01, 2.42)	0.16 (0.00, 6.56)	0.10 (0.00, 3.60)	0.12 (0.00, 4.55)	0.18 (0.00, 8.62)	0.02 (0.00, 1.70)	0.06 (0.00, 2.09)	0.01 (0.00, 0.53)	0.03 (0.00, 1.26)	0.10 (0.00, 4.23)	0.08 (0.00, 3.32)	0.11 (0.00, 4.51)	0.10 (0.00, 4.04)	0.12 (0.00, 4.37)	0.09 (0.00, 3.50)	0.11 (0.00, 4.99)	0.16 (0.00, 6.40)	0.07 (0.00, 2.52)	0.02 (0.00, 1.76)	0.12 (0.00, 2.18)	0.27 (0.01, 2.72)		N/A	N/A
Metformin-Sitagliptin-Sulfonylurea	0.08 (0.00, 1.26)	0.68 (0.20, 2.20)	0.45 (0.01, 9.46)	0.27 (0.01, 5.07)	0.35 (0.01, 6.24)	0.50 (0.01, 12.71)	0.06 (0.00, 2.55)	0.16 (0.01, 2.87)	0.04 (0.00, 0.71)	0.09 (0.00, 1.73)	0.28 (0.01, 6.66)	0.22 (0.01, 4.78)	0.32 (0.01, 6.28)	0.29 (0.01, 5.59)	0.35 (0.01, 5.97)	0.26 (0.01, 4.91)	0.32 (0.01, 7.13)	0.44 (0.01, 8.91)	0.19 (0.01, 3.43)	0.06 (0.00, 2.76)	0.32 (0.03, 2.42)	0.72 (0.23, 2.14)	2.66 (0.20, 95.87)		N/A
NPH insulin	0.68 (0.30, 1.52)	5.74 (0.46, 136.50)	3.89 (1.12, 14.40)	2.33 (0.88, 6.44)	2.94 (1.17, 7.75)	4.32 (0.86, 23.30)	0.55 (0.02, 6.49)	1.36 (0.58, 3.36)	0.36 (0.15, 0.84)	0.81 (0.29, 2.40)	2.39 (0.45, 12.21)	1.90 (0.41, 8.76)	2.74 (0.77, 10.07)	2.52 (0.78, 8.67)	2.97 (1.49, 6.45)	2.24 (0.73, 7.21)	2.75 (0.64, 13.32)	3.80 (0.99, 15.18)	1.61 (0.59, 4.49)	0.53 (0.05, 8.06)	2.55 (0.47, 31.07)	6.05 (0.50, 136.90)	24.10 (0.74, 2195.00)	8.50 (0.55, 231.90)	
NPH insulin-Sulfonylurea	0.18 (0.04, 0.69)	1.52 (0.09, 41.03)	1.02 (0.20, 5.02)	0.61 (0.15, 2.43)	0.78 (0.19, 2.97)	1.13 (0.17, 7.65)	0.14 (0.00, 2.06)	0.36 (0.09, 1.31)	0.09 (0.02, 0.40)	0.21 (0.04, 1.03)	0.62 (0.11, 3.28)	0.50 (0.10, 2.31)	0.72 (0.18, 2.74)	0.66 (0.18, 2.36)	0.79 (0.22, 2.62)	0.59 (0.24, 1.37)	0.73 (0.34, 1.55)	0.99 (0.23, 4.19)	0.42 (0.10, 1.67)	0.14 (0.01, 2.59)	0.68 (0.09, 9.52)	1.61 (0.10, 42.15)	6.42 (0.16, 638.00)	2.22 (0.11, 69.53)	0.26 (0.07, 0.92)

Values given are hazard ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.

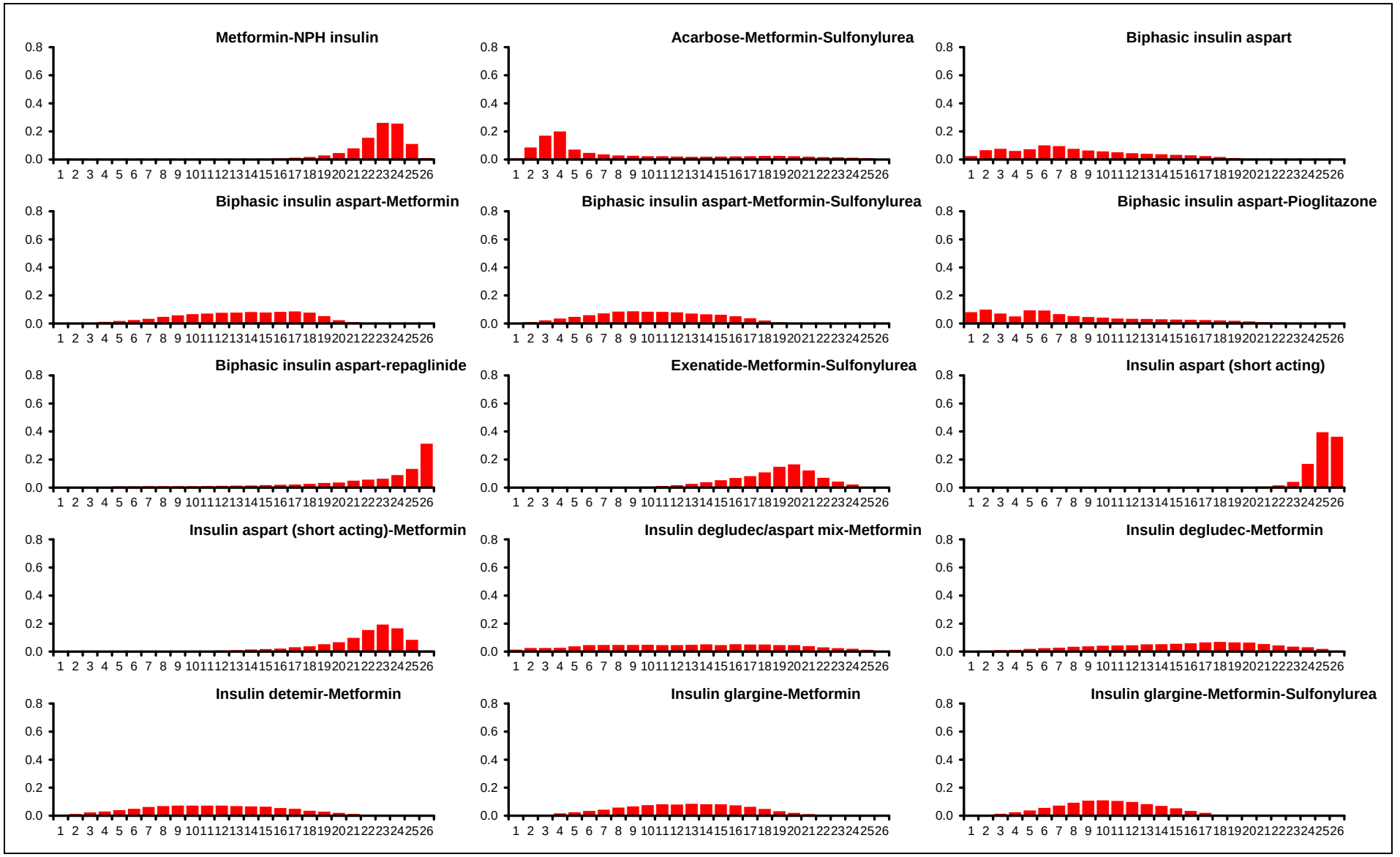


Values greater than 0 favour metformin- NPH insulin; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 71: SECOND INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – relative effect of all options versus reference treatment

Table 120: SECOND INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – rankings for each comparator

	Probability best	Median rank (95%CI)
Metformin-NPH insulin	0.000	23 (17, 25)
Acarbose-Metformin-Sulfonylurea	0.009	5 (2, 24)
Biphasic insulin aspart	0.025	8 (2, 18)
Biphasic insulin aspart-Metformin	0.000	14 (5, 20)
Biphasic insulin aspart-Metformin-Sulfonylurea	0.003	10 (3, 18)
Biphasic insulin aspart-Pioglitazone	0.081	7 (1, 21)
Biphasic insulin aspart-repaglinide	0.005	24 (5, 26)
Exenatide-Metformin-Sulfonylurea	0.000	19 (11, 24)
Insulin aspart (short acting)	0.000	25 (22, 26)
Insulin aspart (short acting)-Metformin	0.000	22 (11, 25)
Insulin degludec/aspart mix-Metformin	0.014	13 (2, 24)
Insulin degludec-Metformin	0.003	16 (4, 25)
Insulin detemir-Metformin	0.003	11 (3, 21)
Insulin glargine-Metformin	0.000	13 (4, 20)
Insulin glargine-Metformin-Sulfonylurea	0.002	10 (4, 17)
Insulin glargine-Sulfonylurea	0.001	14 (5, 22)
Insulin lispro mix 50 and mix 25	0.015	11 (2, 23)
Insulin lispro mix 50/50-Metformin	0.038	8 (1, 18)
Liraglutide-Metformin-Sulfonylurea	0.000	17 (7, 24)
Metformin-NPH insulin-repaglinide	0.010	24 (3, 26)
Metformin-NPH insulin-Sulfonylurea	0.005	12 (3, 24)
Metformin-Pioglitazone-Sulfonylurea	0.013	4 (2, 23)
Metformin-repaglinide-Sulfonylurea	0.610	1 (1, 21)
Metformin-Sitagliptin-Sulfonylurea	0.130	3 (1, 22)
NPH insulin	0.000	21 (14, 24)
NPH insulin-Sulfonylurea	0.033	8 (1, 18)


Metformin-NPH insulin
Acarbose-Metformin-Sulfonylurea
Biphasic insulin aspart
Biphasic insulin aspart-Metformin
Biphasic insulin aspart-Metformin-Sulfonylurea
Biphasic insulin aspart-Pioglitazone
Biphasic insulin aspart-repaglinide
Exenatide-Metformin-Sulfonylurea
Insulin aspart (short acting)
Insulin aspart (short acting)-Metformin
Insulin degludec/aspart mix-Metformin
Insulin degludec-Metformin
Insulin detemir-Metformin
Insulin glargine-Metformin
Insulin glargine-Metformin-Sulfonylurea
0.0
0.2
0.4
0.6
0.8
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26

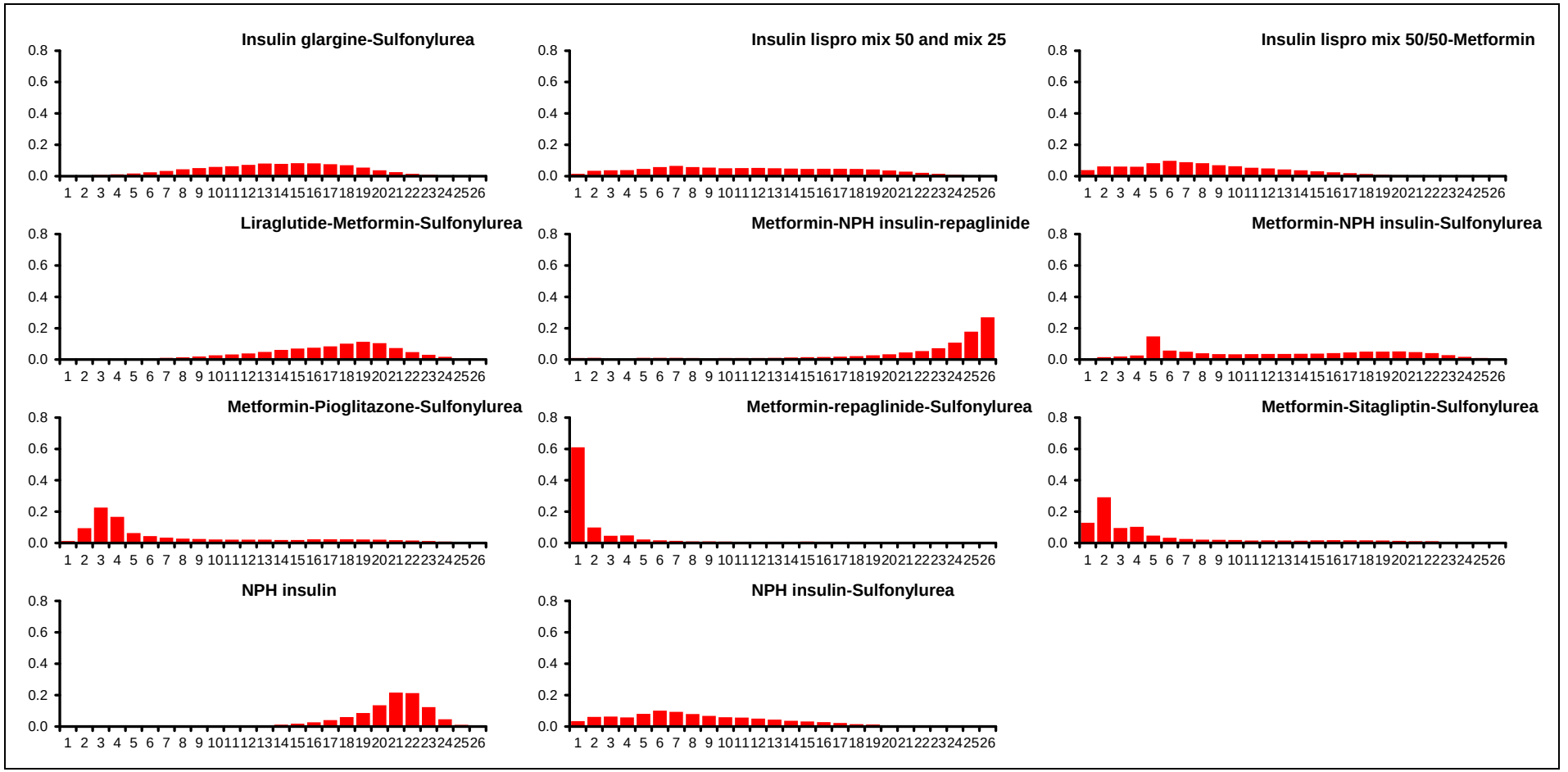


Figure 72: SECOND INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – rank probability histograms

Table 121: SECOND INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – model fit statistics

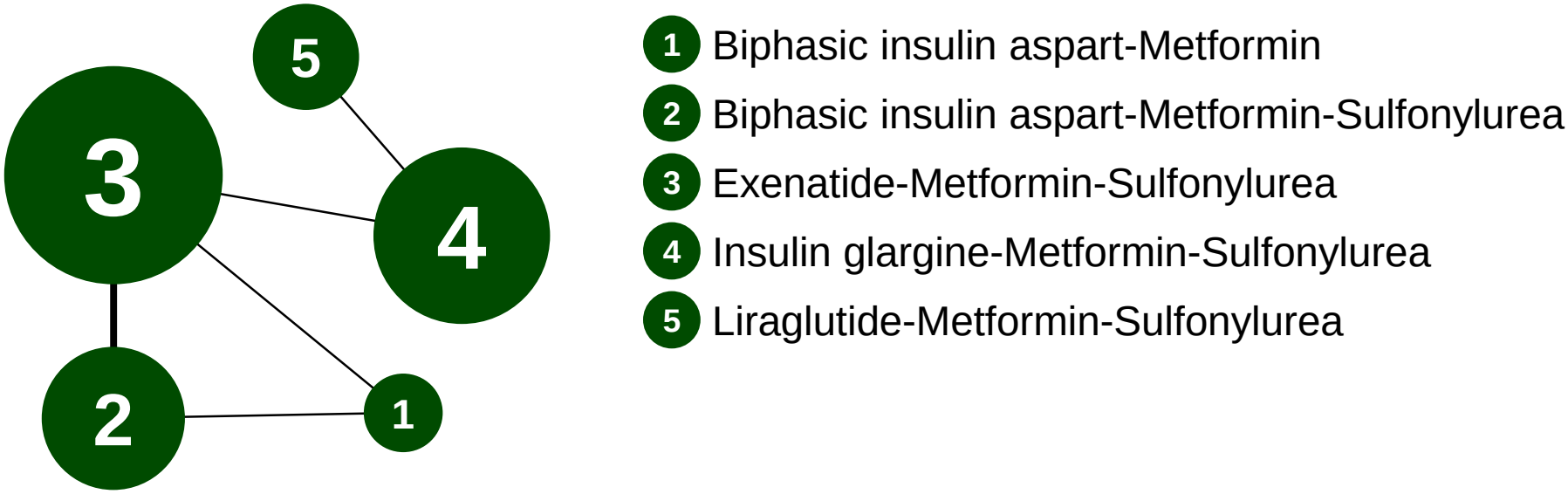
Residual deviance	Dbar	Dhat	pD	DIC	
65.34	284.271	235.257	49.013	333.284	

Residual deviance	Dbar	Dhat	pD	DIC	
(compared to 60 datapoints)					

Table 122: SECOND INTENSIFICATION: TOTAL DROPOUTS AT STUDY ENDPOINT – notes

- Dichotomous diachronic (binomial; cloglog link); fixed effects
- 50000 burn-ins; 10000 recorded iterations

J.2.3.5 Nausea at study endpoint



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 73: SECOND INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – evidence network

Table 123: SECOND INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – input data

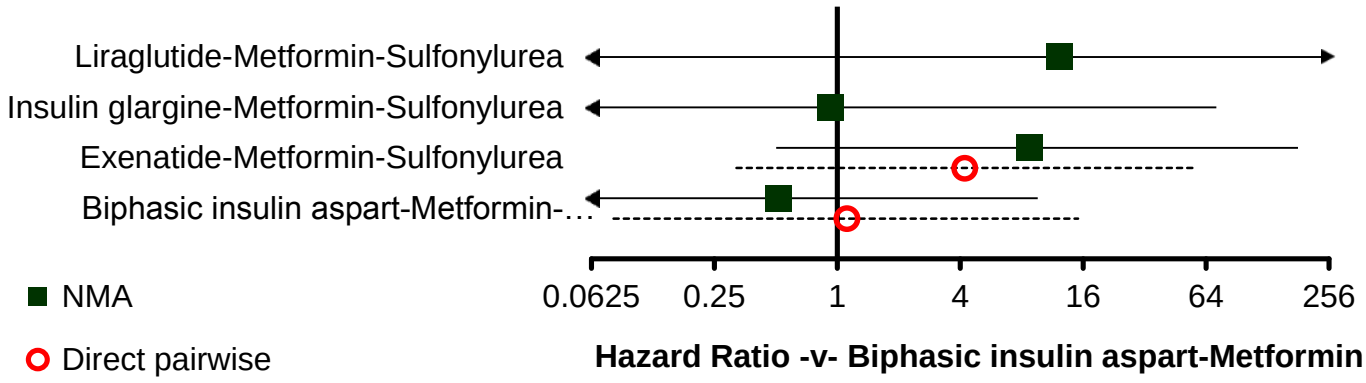
	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Exenatide-Metformin-Sulfonylurea	Insulin glargine-Metformin-Sulfonylurea	Liraglutide-Metformin-Sulfonylurea
Russell-Jones et al. (2009) - 0.50yr				3/232	32/230
Bergenstal et al. (2009) - 0.46yr	10/124	11/124	36/124		
Nauck et al. (2007) - 1.00yr		1/248	84/253		
Heine et al. (2005) - 0.50yr			161/282	23/267	

Values given are number of events / number of participants. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 124: SECOND INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations

	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Exenatide-Metformin-Sulfonylurea	Insulin glargine-Metformin-Sulfonylurea	Liraglutide-Metformin-Sulfonylurea
Biphasic insulin aspart-Metformin		N/A	N/A	N/A	N/A
Biphasic insulin aspart-Metformin-Sulfonylurea	0.52 (0.03, 9.60)		N/A	N/A	N/A
Exenatide-Metformin-Sulfonylurea	8.78 (0.50, 180.50)	16.96 (1.81, 199.20)		N/A	N/A
Insulin glargine-Metformin-Sulfonylurea	0.93 (0.01, 72.03)	1.79 (0.04, 100.60)	0.11 (0.00, 2.41)		N/A
Liraglutide-Metformin-Sulfonylurea	12.36 (0.06, 2925.00)	23.65 (0.16, 4448.00)	1.38 (0.02, 143.10)	13.16 (0.52, 355.20)	

Values given are hazard ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.



Values greater than 1 favour Biphasic insulin aspart-metformin; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 74: SECOND INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – relative effect of all options versus reference treatment

Table 125: SECOND INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – rankings for each comparator

	Probability best	Median rank (95%CI)
Biphasic insulin aspart-Metformin	0.222	2 (1, 5)
Biphasic insulin aspart-Metformin-Sulfonylurea	0.460	2 (1, 4)
Exenatide-Metformin-Sulfonylurea	0.000	4 (3, 5)
Insulin glargine-Metformin-Sulfonylurea	0.292	2 (1, 4)
Liraglutide-Metformin-Sulfonylurea	0.025	5 (1, 5)

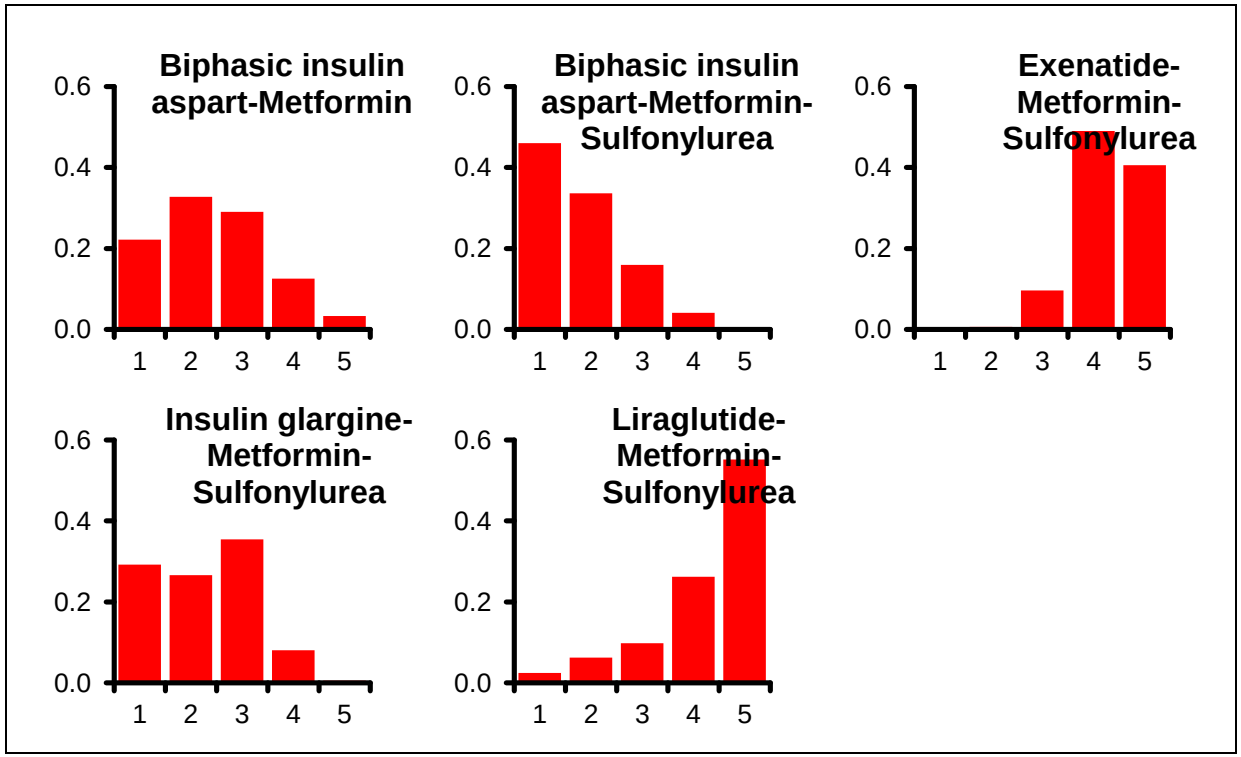


Figure 75: SECOND INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – rank probability histograms

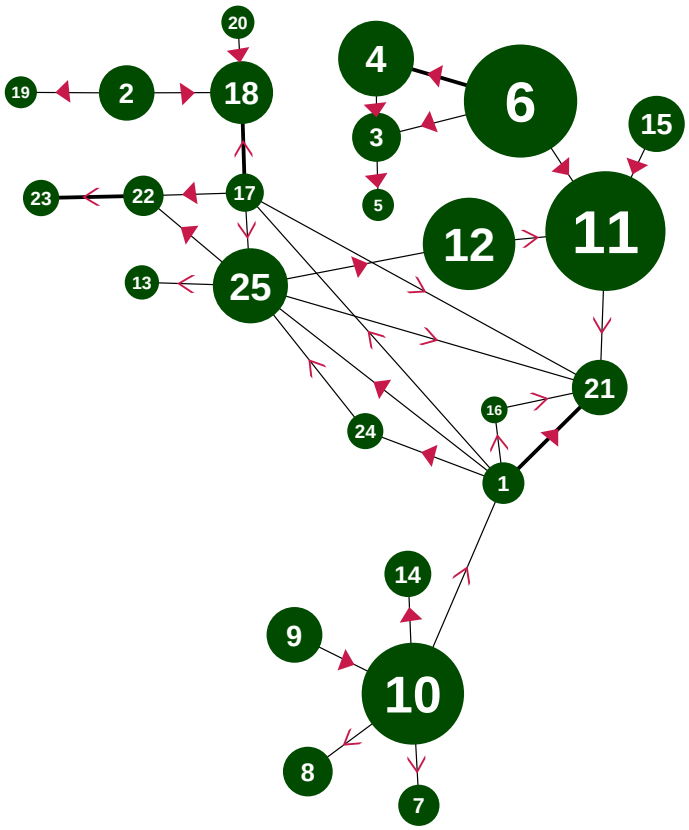
Table 126: SECOND INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
9.227 (compared to 9 datapoints)	49.509	40.69	8.818	58.327	1.523 (95%CI: 0.694, 1.978)

Table 127: SECOND INTENSIFICATION: NAUSEA AT STUDY ENDPOINT – notes

- Dichotomous diachronic (binomial; cloglog link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

J.2.3.6 Change in body weight up to 12 months



1 Metformin-NPH insulin
2 Acarbose-Metformin-Sulfonylurea
3 Biphasic insulin aspart-Metformin
4 Biphasic insulin aspart-Metformin-Sulfonylurea
5 Biphasic insulin aspart-repaglinide
6 Exenatide-Metformin-Sulfonylurea
7 Insulin degludec/aspart mix-Metformin
8 Insulin degludec-Metformin
9 Insulin detemir-Metformin
10 Insulin glargine-Metformin
11 Insulin glargine-Metformin-Sulfonylurea
12 Insulin glargine-Sulfonylurea
13 Insulin lispro mix 50 and mix 25
14 Insulin lispro mix 50/50-Metformin
15 Liraglutide-Metformin-Sulfonylurea
16 Metformin-NPH insulin-repaglinide
17 Metformin-NPH insulin-Sulfonylurea
18 Metformin-Pioglitazone-Sulfonylurea
19 Metformin-repaglinide-Sulfonylurea
20 Metformin-Sitagliptin-Sulfonylurea
21 NPH insulin
22 NPH insulin mix 70/30
23 NPH insulin mix 70/30-Sulfonylurea
24 NPH insulin-repaglinide
25 NPH insulin-Sulfonylurea

Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 76: SECOND INTENSIFICATION: BODY WEIGHT UP TO 12 MONTHS – evidence network

Table 128: SECOND INTENSIFICATION: BODY WEIGHT UP TO 12 MONTHS – input data

	Metformin-NPH insulin	Acarbose-Metformin-	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-	Insulin degludec/aspart	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Liraglutide-Metformin-	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-	Metformin-repaglinide-	Metformin-Sitagliptin-	NPH insulin	NPH insulin mix 70/30	NPH insulin mix 70/30-Sulfonylurea	NPH insulin-repaglinide	NPH insulin-Sulfonylurea
Zinman et al. (2011)								0.27 (2.36)		-0.30 (2.40)															
Heise et al. (2011)							-0.05 (2.25)			-0.10 (3.20)															
Derosa et al. (2010)		-0.60 (1.34)																0.90 (1.41)							
Lund et al. (2009)			2.22 (3.89)		4.73 (3.99)																				
Hartemann-Heurtier et al. (2009)																	2.40 (1.70)	3.70 (3.50)							
Russell-Jones et al. (2009)											1.60 (5.03)				-1.80 (5.00)										
Milicevic et al. (2009)													1.42 (3.52)												1.20 (2.50)
Derosa et al. (2009)		-1.40 (1.32)																	1.70 (1.58)						
Bergenstal et al. (2009)			4.10 (5.40)	2.80 (3.60)		-1.90 (3.80)																			
Civera et al. (2008)	1.70 (2.60)															2.90 (2.80)					3.00 (2.80)				
Robbins et al. (2007)										-0.50 (2.80)				1.20 (3.20)											
Nauck et al. (2007)				2.90 (3.15)		-2.50 (3.18)																			
Yki-Jarvinen et al. (2006)	2.60 (2.80)									2.00 (2.34)															
Janka et al. (2005)											1.40 (3.40)										2.10 (4.20)				
Olsson & (2002)																						5.80 (2.69)			1.90 (2.83)

	Metformin-NPH insulin	Acarbose-Metformin-	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-	Insulin degludec/aspart	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Liraglutide-Metformin-	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-	Metformin-repaglinide-	Metformin-Sitagliptin-	NPH insulin	NPH insulin mix 70/30	NPH insulin mix 70/30-Sulfonylurea	NPH insulin-repaglinide	NPH insulin-Sulfonylurea
Heine et al. (2005)						-2.30 (3.65)					1.80 (3.55)														
Aljabri et al. (2004)																	2.50 (2.80)	2.60 (4.30)							
Goudswaard et al. (2004)																	1.30 (3.90)					4.20 (4.30)			
Furlong et al. (2002)	0.90 (2.56)																							2.70 (2.50)	
Furlong et al. (2003)																								3.40 (2.56)	4.10 (3.12)
Fritsche A,Schweitzer MA,Haring (2003)												3.80 (4.08)													2.90 (4.30)
Riddle et al. (1992)																						3.30 (3.79)	4.90 (3.32)		
Riddle & (1998)																						4.00 (3.76)	4.30 (3.00)		
Yki-JaÝˆrvinen et al. (1999)	0.90 (5.23)																3.60 (3.84)				4.60 (4.90)				3.90 (3.28)
Liu et al. (2013)																		1.34 (2.46)		-0.26 (2.48)					
Meneghini et al. (2013)									-0.49 (3.30)	1.00 (3.10)															
Park et al. (2014)											1.38 (2.97)	1.26 (2.60)													

Values given are mean change in body-weight(SD), in kilograms. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

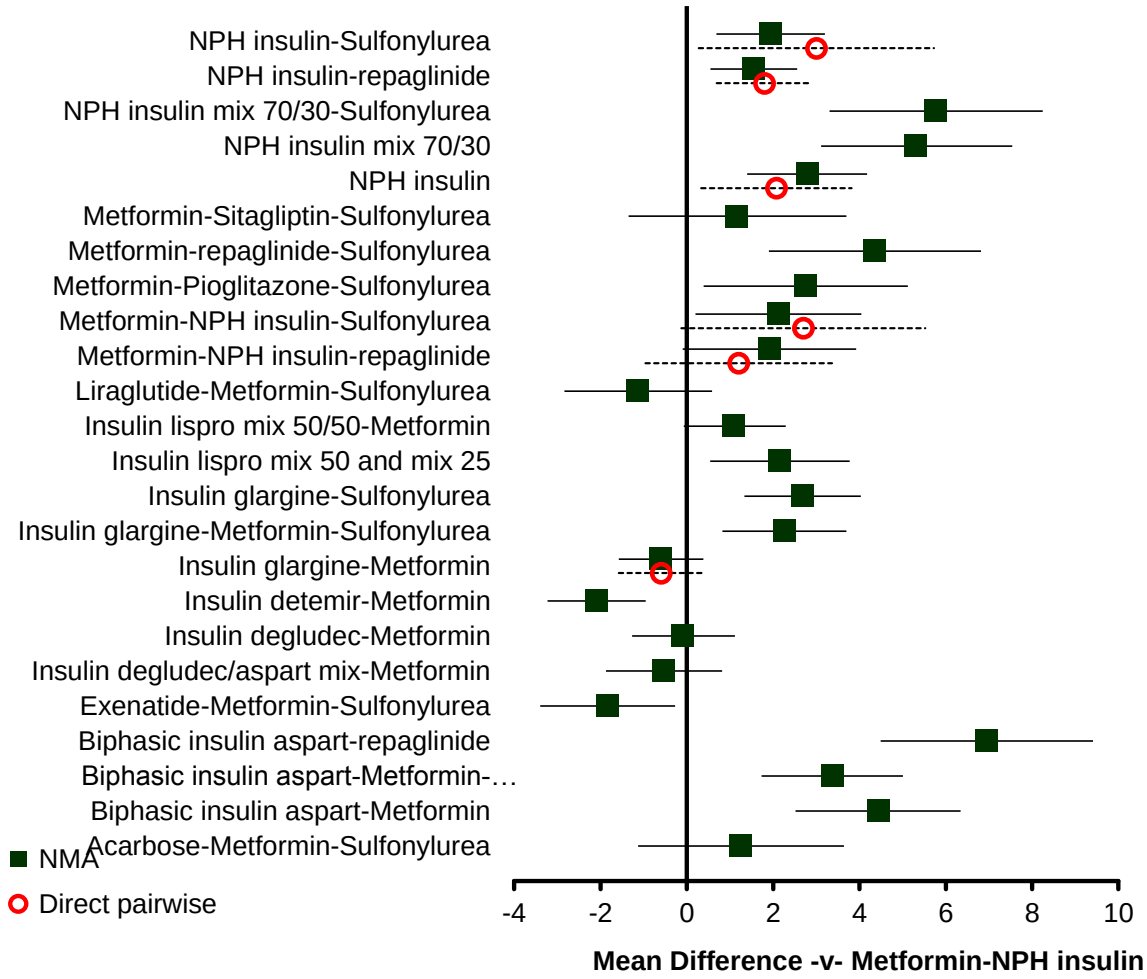
Table 129: SECOND INTENSIFICATION: BODY WEIGHT UP TO 12 MONTHS – relative effectiveness of all pairwise combinations

	Metformin-NPH insulin	Acarbose-Metformin-Sulfonylurea	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-Sulfonylurea	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-repaglinide-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin	NPH insulin mix 70/30	NPH insulin mix 70/30-Sulfonylurea	NPH insulin-repaglinide
Acarbose-Metformin-Sulfonylurea	1.26 (-1.13, 3.64)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1.50 (1.21, 1.79)	3.10 (2.53, 3.67)	-	-	-	-	-
Biphasic insulin aspart-Metformin	4.44 (2.52, 6.34)	3.18 (0.50, 5.85)		-1.30 (-2.44, -0.16)	2.51 (0.97, 4.05)	-6.00 (-7.16, -4.84)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Biphasic insulin aspart-Metformin-Sulfonylurea	3.38 (1.73, 5.01)	2.12 (-0.36, 4.61)	-1.05 (-2.15, 0.03)		-	-5.21 (-5.69, -4.74)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Biphasic insulin aspart-repaglinide	6.95 (4.49, 9.41)	5.70 (2.61, 8.79)	2.51 (0.97, 4.06)	3.57 (1.71, 5.46)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Exenatide-Metformin-Sulfonylurea	-1.83 (-3.40, -0.27)	-3.09 (-5.53, -0.66)	-6.27 (-7.37, -5.19)	-5.21 (-5.69, -4.74)	-8.78 (-10.66, -6.90)		-	-	-	-	4.10 (3.49, 4.71)	-	-	-	-	-	-	-	-	-	-	-	-	-
Insulin degludec/aspart mix-Metformin	-0.54 (-1.87, 0.82)	-1.80 (-4.54, 0.95)	-4.97 (-7.31, -2.65)	-3.91 (-6.03, -1.82)	-7.48 (-10.27, -4.71)	1.31 (-0.75, 3.35)		-	-	-0.05 (-0.96, 0.86)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Insulin degludec-Metformin	-0.09 (-1.27, 1.11)	-1.35 (-4.00, 1.35)	-4.52 (-6.77, -2.27)	-3.47 (-5.49, -1.45)	-7.02 (-9.76, -4.32)	1.75 (-0.22, 3.68)	0.45 (-0.68, 1.57)		-	-0.57 (-1.26, 0.12)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Insulin detemir-Metformin	-2.09 (-3.23, -0.95)	-3.35 (-5.99, -0.68)	-6.53 (-8.74, -4.29)	-5.48 (-7.48, -3.49)	-9.04 (-11.73, -6.33)	-0.25 (-2.21, 1.65)	-1.56 (-2.64, -0.48)	-2.00 (-2.90, -1.09)		1.49 (0.90, 2.08)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Insulin glargine-Metformin	-0.60 (-1.58, 0.38)	-1.86 (-4.43, 0.74)	-5.04 (-7.18, -2.89)	-3.98 (-5.91, -2.09)	-7.55 (-10.18, -4.90)	1.24 (-0.61, 3.08)	-0.06 (-0.98, 0.84)	-0.51 (-1.20, 0.17)	1.49 (0.91, 2.08)		-	-	-	1.70 (1.04, 2.36)	-	-	-	-	-	-	-	-	-	-
Insulin glargine-Metformin-Sulfonylurea	2.27 (0.82, 3.70)	1.01 (-1.35, 3.39)	-2.17 (-3.41, -0.91)	-1.11 (-1.89, -0.34)	-4.68 (-6.66, -2.71)	4.10 (3.49, 4.70)	2.80 (0.83, 4.75)	2.36 (0.50, 4.23)	4.36 (2.54, 6.21)	2.87 (1.12, 4.61)		-0.12 (-1.47, 1.23)	-	-	-3.40 (-4.31, -2.49)	-	-	-	-	-	0.70 (-0.08, 1.48)	-	-	-
Insulin glargine-Sulfonylurea	2.69 (1.33, 4.03)	1.43 (-0.82, 3.70)	-1.76 (-3.43, -0.07)	-0.70 (-2.08, 0.67)	-4.27 (-6.53, -2.01)	4.52 (3.24, 5.80)	3.22 (1.30, 5.12)	2.77 (0.96, 4.57)	4.77 (3.02, 6.56)	3.28 (1.62, 4.97)	0.41 (-0.71, 1.53)		-	-	-	-	-	-	-	-	-	-	-	-

	Metformin-NPH insulin	Acarbose-Metformin-Sulfonylurea	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-Sulfonylurea	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-repaglinide-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin	NPH insulin mix 70/30	NPH insulin mix 70/30-Sulfonylurea	NPH insulin-repaglinide
Insulin lispro mix 50 and mix 25	2.16 (0.54, 3.77)	0.90 (-1.52, 3.34)	-2.28 (-4.29, -0.26)	-1.22 (-2.98, 0.53)	-4.80 (-7.34, -2.26)	3.99 (2.31, 5.66)	2.70 (0.60, 4.81)	2.24 (0.24, 4.25)	4.25 (2.29, 6.24)	2.75 (0.88, 4.65)	-0.11 (-1.68, 1.45)	-0.53 (-1.73, 0.68)		-	-	-	-	-	-	-	-	-	-	-
Insulin lispro mix 50/50-Metformin	1.10 (-0.07, 2.29)	-0.16 (-2.82, 2.53)	-3.34 (-5.59, -1.09)	-2.28 (-4.32, -0.26)	-5.85 (-8.57, -3.12)	2.93 (0.95, 4.89)	1.64 (0.53, 2.75)	1.18 (0.23, 2.14)	3.19 (2.31, 4.08)	1.70 (1.04, 2.36)	-1.18 (-3.04, 0.70)	-1.58 (-3.39, 0.23)	-1.05 (-3.06, 0.94)		-	-	-	-	-	-	-	-	-	-
Liraglutide-Metformin-Sulfonylurea	-1.13 (-2.84, 0.58)	-2.38 (-4.91, 0.15)	-5.56 (-7.12, -4.00)	-4.51 (-5.72, -3.31)	-8.07 (-10.24, -5.90)	0.71 (-0.41, 1.81)	-0.59 (-2.76, 1.58)	-1.04 (-3.13, 1.05)	0.96 (-1.11, 3.03)	-0.53 (-2.51, 1.45)	-3.40 (-4.31, -2.48)	-3.81 (-5.26, -2.37)	-3.29 (-5.10, -1.48)	-2.22 (-4.33, -0.14)		-	-	-	-	-	-	-	-	-
Metformin-NPH insulin-repaglinide	1.92 (-0.10, 3.92)	0.66 (-2.32, 3.65)	-2.52 (-4.96, -0.07)	-1.47 (-3.71, 0.79)	-5.03 (-7.93, -2.13)	3.75 (1.56, 5.96)	2.46 (0.05, 4.85)	2.00 (-0.34, 4.32)	4.02 (1.71, 6.31)	2.52 (0.29, 4.74)	-0.35 (-2.47, 1.76)	-0.77 (-2.93, 1.44)	-0.24 (-2.63, 2.19)	0.83 (-1.49, 3.12)	3.05 (0.72, 5.38)		-	-	-	-	0.10 (-2.10, 2.30)	-	-	-
Metformin-NPH insulin-Sulfonylurea	2.12 (0.20, 4.04)	0.86 (-0.56, 2.28)	-2.32 (-4.58, -0.03)	-1.27 (-3.28, 0.78)	-4.83 (-7.56, -2.10)	3.95 (1.99, 5.94)	2.66 (0.29, 5.00)	2.21 (-0.07, 4.45)	4.21 (1.98, 6.47)	2.73 (0.55, 4.88)	-0.16 (-2.02, 1.75)	-0.56 (-2.32, 1.20)	-0.03 (-2.01, 1.95)	1.02 (-1.25, 3.27)	3.24 (1.17, 5.35)	0.20 (-2.39, 2.84)		0.64 (-0.74, 2.02)	-	-	1.00 (-1.51, 3.51)	2.90 (0.88, 4.92)	-	-
Metformin-Pioglitazone-Sulfonylurea	2.76 (0.39, 5.12)	1.50 (1.21, 1.79)	-1.68 (-4.32, 0.99)	-0.62 (-3.09, 1.84)	-4.19 (-7.27, -1.11)	4.59 (2.18, 7.02)	3.30 (0.56, 6.03)	2.85 (0.17, 5.49)	4.85 (2.20, 7.48)	3.36 (0.77, 5.92)	0.49 (-1.86, 2.83)	0.08 (-2.18, 2.32)	0.61 (-1.83, 3.00)	1.66 (-1.02, 4.31)	3.88 (1.36, 6.41)	0.83 (-2.13, 3.80)	0.64 (-0.75, 2.03)		-	-1.60 (-2.49, -0.71)	-	-	-	-
Metformin-repaglinide-Sulfonylurea	4.36 (1.90, 6.81)	3.10 (2.52, 3.67)	-0.08 (-2.81, 2.68)	0.97 (-1.58, 3.53)	-2.59 (-5.73, 0.56)	6.19 (3.70, 8.69)	4.90 (2.07, 7.68)	4.44 (1.69, 7.15)	6.45 (3.72, 9.16)	4.95 (2.28, 7.59)	2.10 (-0.34, 4.52)	1.67 (-0.67, 4.00)	2.20 (-0.30, 4.70)	3.26 (0.51, 5.98)	5.49 (2.87, 8.08)	2.44 (-0.61, 5.49)	2.24 (0.72, 3.77)	1.60 (0.96, 2.24)		-	-	-	-	-
Metformin-Sitagliptin-Sulfonylurea	1.15 (-1.35, 3.69)	-0.10 (-1.04, 0.84)	-3.29 (-6.06, -0.48)	-2.23 (-4.85, 0.37)	-5.80 (-9.00, -2.61)	2.98 (0.43, 5.55)	1.69 (-1.18, 4.55)	1.24 (-1.57, 4.02)	3.25 (0.47, 5.99)	1.76 (-0.95, 4.45)	-1.12 (-3.62, 1.37)	-1.53 (-3.95, 0.85)	-1.01 (-3.58, 1.55)	0.06 (-2.73, 2.84)	2.27 (-0.37, 4.95)	-0.77 (-3.88, 2.31)	-0.97 (-2.60, 0.68)	-1.60 (-2.50, -0.71)	-3.20 (-4.30, -2.11)		-	-	-	-
NPH insulin	2.79 (1.40, 4.18)	1.53 (-0.83, 3.89)	-1.65 (-3.09, -0.19)	-0.59 (-1.65, 0.47)	-4.15 (-6.27, -2.06)	4.63 (3.66, 5.58)	3.32 (1.40, 5.25)	2.88 (1.06, 4.71)	4.88 (3.09, 6.69)	3.39 (1.70, 5.09)	0.52 (-0.23, 1.26)	0.11 (-1.09, 1.30)	0.63 (-0.95, 2.22)	1.69 (-0.13, 3.52)	3.92 (2.74, 5.10)	0.87 (-1.16, 2.91)	0.68 (-1.20, 2.54)	0.03 (-2.29, 2.38)	-1.57 (-3.96, 0.87)	1.64 (-0.85, 4.14)		-	-	-
NPH insulin mix 70/30	5.31 (3.11, 7.54)	4.06 (1.81, 6.29)	0.88 (-1.62, 3.42)	1.94 (-0.36, 4.27)	-1.63 (-4.56, 1.36)	7.15 (4.90, 9.43)	5.86 (3.26, 8.44)	5.40 (2.89, 7.89)	7.42 (4.91, 9.91)	5.92 (3.51, 8.34)	3.04 (0.87, 5.23)	2.63 (0.61, 4.66)	3.16 (0.97, 5.37)	4.23 (1.71, 6.74)	6.44 (4.11, 8.81)	3.39 (0.57, 6.18)	3.20 (1.47, 4.93)	2.56 (0.35, 4.76)	0.96 (-1.37, 3.26)	4.16 (1.78, 6.54)	2.53 (0.36, 4.69)		0.47 (-0.63, 1.56)	-
NPH insulin mix 70/30-Sulfonylurea	5.78 (3.30, 8.25)	4.53 (2.02, 6.98)	1.33 (-1.38, 4.09)	2.39 (-0.18, 4.97)	-1.19 (-4.29, 2.01)	7.60 (5.10, 10.12)	6.32 (3.45, 9.12)	5.86 (3.10, 8.61)	7.88 (5.13, 10.59)	6.38 (3.71, 9.03)	3.49 (1.06, 5.96)	3.09 (0.79, 5.39)	3.61 (1.14, 6.11)	4.68 (1.93, 7.41)	6.89 (4.31, 9.50)	3.85 (0.81, 6.88)	3.66 (1.60, 5.69)	3.03 (0.54, 5.48)	1.43 (-1.18, 3.96)	4.62 (1.99, 7.24)	2.98 (0.54, 5.41)	0.45 (-0.63, 1.55)		-

	Metformin-NPH insulin	Acarbose-Metformin-Sulfonylurea	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Biphasic insulin aspart-repaglinide	Exenatide-Metformin-Sulfonylurea	Insulin degludec/aspart mix-Metformin	Insulin degludec-Metformin	Insulin detemir-Metformin	Insulin glargine-Metformin	Insulin glargine-Metformin-Sulfonylurea	Insulin glargine-Sulfonylurea	Insulin lispro mix 50 and mix 25	Insulin lispro mix 50/50-Metformin	Liraglutide-Metformin-Sulfonylurea	Metformin-NPH insulin-repaglinide	Metformin-NPH insulin-Sulfonylurea	Metformin-Pioglitazone-Sulfonylurea	Metformin-repaglinide-Sulfonylurea	Metformin-Sitagliptin-Sulfonylurea	NPH insulin	NPH insulin mix 70/30	NPH insulin mix 70/30-Sulfonylurea	NPH insulin-repaglinide
NPH insulin-repaglinide	1.55 (0.54, 2.56)	0.29 (-2.07, 2.70)	-2.89 (-4.80, -0.96)	-1.83 (-3.46, -0.19)	-5.40 (-7.85, -2.95)	3.38 (1.82, 4.96)	2.09 (0.42, 3.77)	1.64 (0.06, 3.19)	3.64 (2.13, 5.17)	2.15 (0.75, 3.56)	-0.72 (-2.16, 0.74)	-1.14 (-2.35, 0.10)	-0.61 (-2.10, 0.89)	0.45 (-1.11, 2.01)	2.68 (0.96, 4.39)	-0.36 (-2.55, 1.79)	-0.58 (-2.47, 1.34)	-1.21 (-3.57, 1.17)	-2.81 (-5.23, -0.34)	0.39 (-2.11, 2.93)	-1.24 (-2.65, 0.20)	-3.77 (-5.93, -1.59)	-4.22 (-6.65, -1.77)	
NPH insulin-Sulfonylurea	1.94 (0.69, 3.20)	0.68 (-1.53, 2.88)	-2.50 (-4.22, -0.77)	-1.45 (-2.87, -0.03)	-5.02 (-7.31, -2.72)	3.77 (2.45, 5.11)	2.48 (0.63, 4.30)	2.03 (0.29, 3.76)	4.03 (2.35, 5.73)	2.53 (0.94, 4.14)	-0.33 (-1.51, 0.84)	-0.74 (-1.38, -0.11)	-0.22 (-1.25, 0.81)	0.84 (-0.91, 2.57)	3.06 (1.57, 4.56)	0.02 (-2.16, 2.17)	-0.19 (-1.86, 1.50)	-0.82 (-3.01, 1.37)	-2.42 (-4.72, -0.15)	0.78 (-1.58, 3.13)	-0.86 (-2.08, 0.37)	-3.38 (-5.33, -1.42)	-3.83 (-6.07, -1.60)	0.39 (-0.71, 1.47)

Values given are mean differences in body-weight in kilograms.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist FE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.

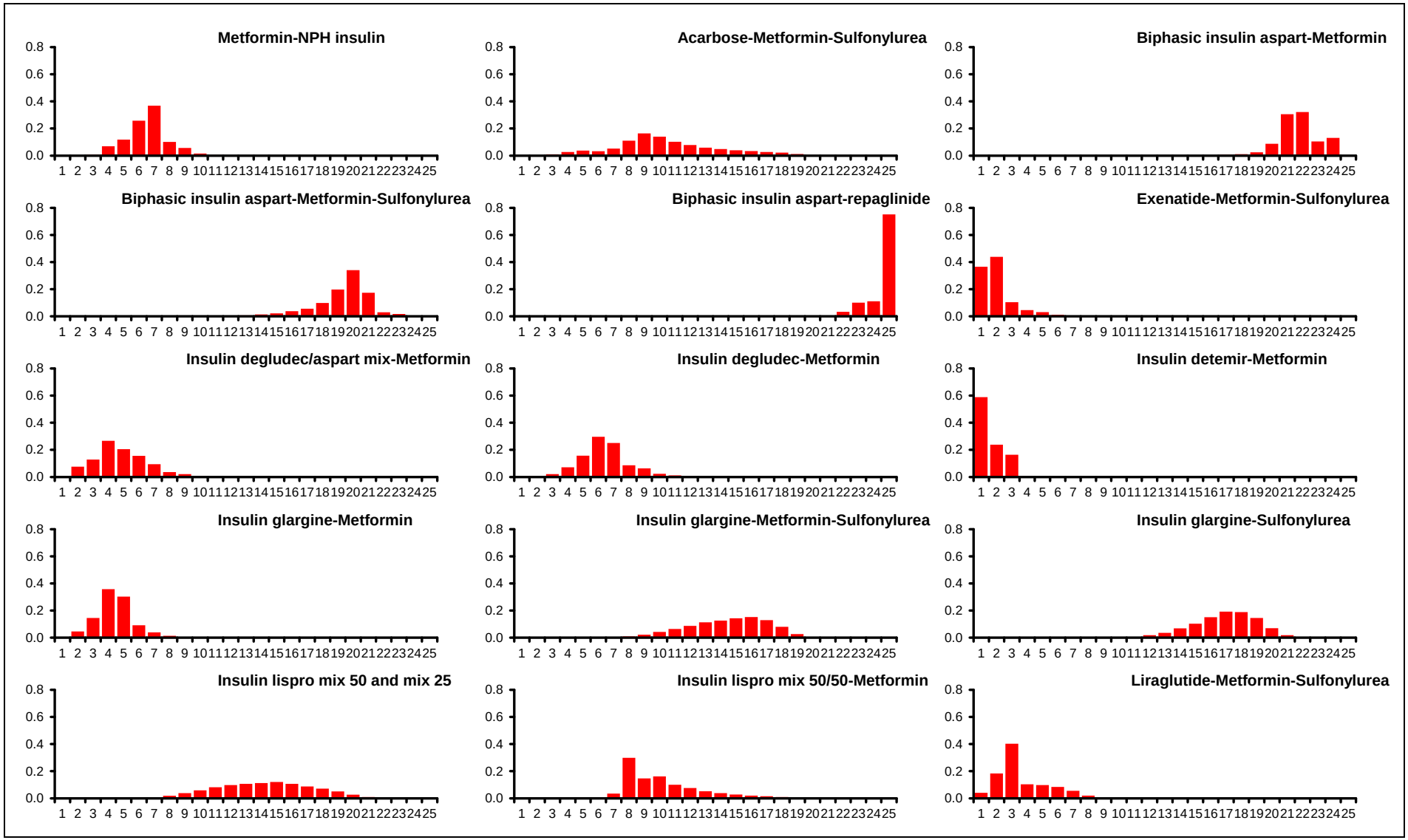


Values greater than 0 favour metformin-NPH insulin; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 77: SECOND INTENSIFICATION: BODY WEIGHT UP TO 12 MONTHS – relative effect of all options versus reference treatment

Table 130: SECOND INTENSIFICATION: BODY WEIGHT UP TO 12 MONTHS – rankings for each comparator

	Probability best	Median rank (95%CI)
Metformin-NPH insulin	0.000	7 (4, 9)
Acarbose-Metformin-Sulfonylurea	0.001	10 (4, 18)
Biphasic insulin aspart-Metformin	0.000	22 (19, 24)
Biphasic insulin aspart-Metformin-Sulfonylurea	0.000	20 (14, 22)
Biphasic insulin aspart-repaglinide	0.000	25 (22, 25)
Exenatide-Metformin-Sulfonylurea	0.366	2 (1, 5)
Insulin degludec/aspart mix-Metformin	0.001	5 (2, 9)
Insulin degludec-Metformin	0.000	6 (3, 10)
Insulin detemir-Metformin	0.589	1 (1, 3)
Insulin glargine-Metformin	0.000	4 (2, 7)
Insulin glargine-Metformin-Sulfonylurea	0.000	15 (9, 19)
Insulin glargine-Sulfonylurea	0.000	17 (12, 20)
Insulin lispro mix 50 and mix 25	0.000	14 (8, 20)
Insulin lispro mix 50/50-Metformin	0.000	10 (7, 17)
Liraglutide-Metformin-Sulfonylurea	0.041	3 (1, 8)
Metformin-NPH insulin-repaglinide	0.000	13 (7, 21)
Metformin-NPH insulin-Sulfonylurea	0.000	14 (9, 20)
Metformin-Pioglitazone-Sulfonylurea	0.000	18 (10, 21)
Metformin-repaglinide-Sulfonylurea	0.000	22 (16, 24)
Metformin-Sitagliptin-Sulfonylurea	0.003	10 (3, 18)
NPH insulin	0.000	18 (12, 20)
NPH insulin mix 70/30	0.000	23 (20, 25)
NPH insulin mix 70/30-Sulfonylurea	0.000	24 (21, 25)
NPH insulin-repaglinide	0.000	11 (8, 17)
NPH insulin-Sulfonylurea	0.000	13 (9, 17)


Metformin-NPH insulin
Acarbose-Metformin-Sulfonylurea
Biphasic insulin aspart-Metformin
Biphasic insulin aspart-Metformin-Sulfonylurea
Biphasic insulin aspart-repaglinide
Exenatide-Metformin-Sulfonylurea
Insulin degludec/aspart mix-Metformin
Insulin degludec-Metformin
Insulin detemir-Metformin
Insulin glargine-Metformin
Insulin glargine-Metformin-Sulfonylurea
Insulin glargine-Sulfonylurea
Insulin lispro mix 50 and mix 25
Insulin lispro mix 50/50-Metformin
Liraglutide-Metformin-Sulfonylurea
0.0 0.2 0.4 0.6 0.8
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25

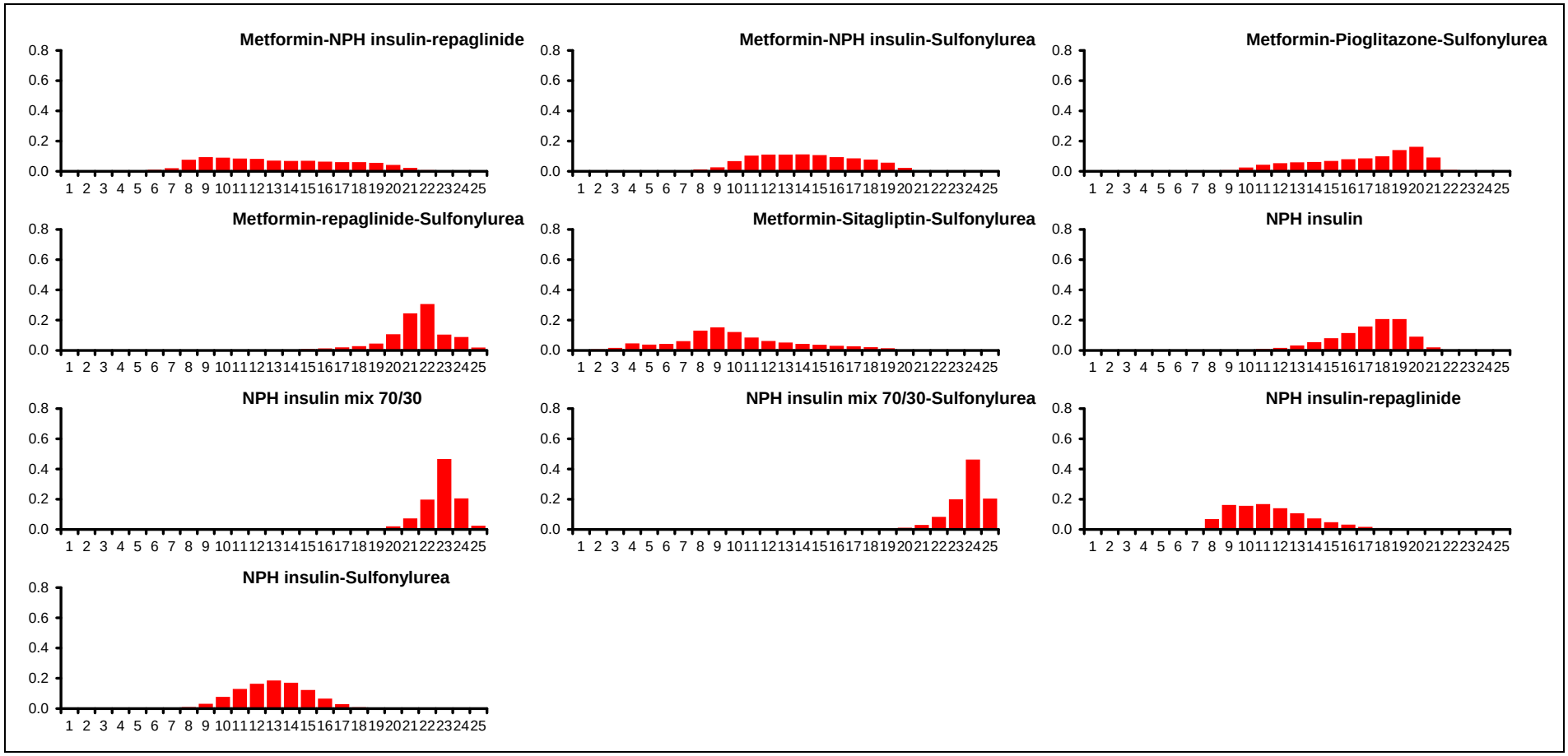


Figure 78: SECOND INTENSIFICATION: BODY WEIGHT UP TO 12 MONTHS – rank probability histograms

Table 131: SECOND INTENSIFICATION: BODY WEIGHT UP TO 12 MONTHS – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	
64.49 (compared to 62 datapoints)	63.763	12.733	51.029	114.792	

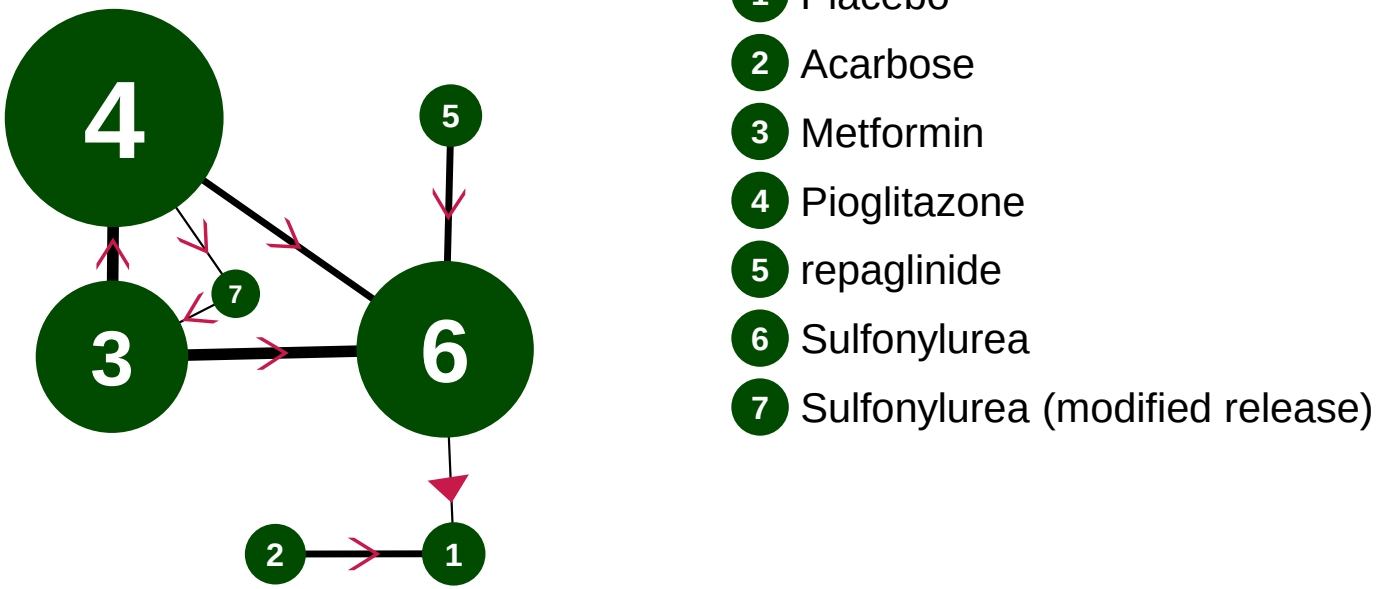
Table 132: SECOND INTENSIFICATION: BODY WEIGHT UP TO 12 MONTHS – notes

- Continuous (normal; identity link); fixed effects
- 50000 burn-ins; 10000 recorded iterations (thinned from 200000)

J.3 SENSITIVITY ANALYSES

J.3.1 RESULTS FOR INITIAL THERAPY – TRULY DRUG NAÏVE INDIVIDUALS

J.3.1.1 Change in HbA1c at 12 months



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 79: SENSITIVITY ANALYSIS INITIAL THERAPY: HbA1c AT 12 MONTHS – evidence network

Table 133: SENSITIVITY ANALYSIS INITIAL THERAPY: HbA1c AT 12 MONTHS – input data

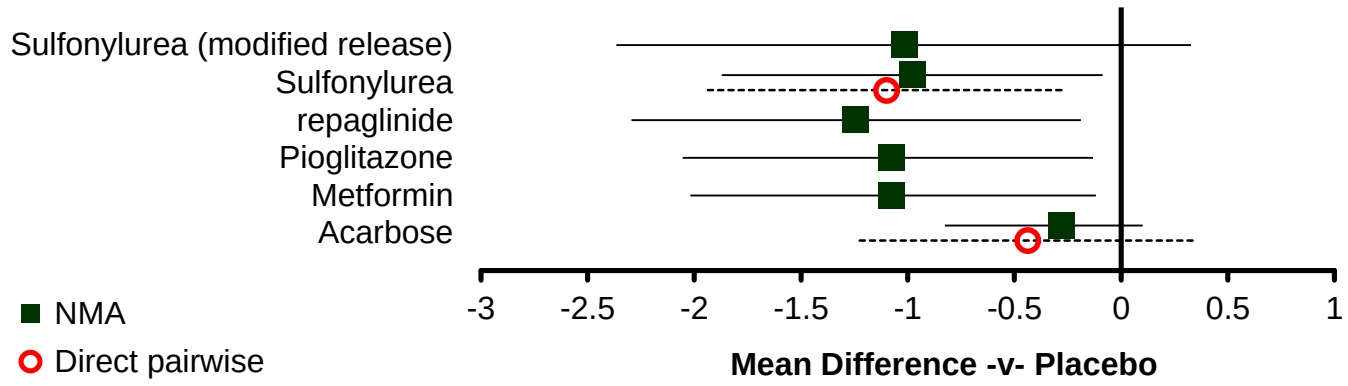
	Placebo	Acarbose	Metformin	Pioglitazone	repaglinide	Sulfonylurea	Sulfonylurea (modified release)
Kirkman et al. (2006)	-0.10 (0.81)	-0.19 (0.92)					
Yoon et al. (2011)			-0.92 (0.96)			-0.89 (0.76)	
Abbatecola et al. (2006)					-0.75 (1.12)	-0.50 (1.84)	
Schernthaner et al. (2004)			-1.50 (0.97)	-1.41 (0.97)			
Campbell et al. (1994)			-2.82 (2.15)			-2.03 (2.68)	
Yamanouchi et al. (2005)			-2.10 (1.15)	-2.30 (1.21)		-2.10 (1.08)	
Chiasson JL,Josse RG,Hunt JA,Palmason C,Rodger NW,Ross (1994)	0.40 (1.09)	-0.50 (1.54)					
Birkeland et al. (1994)	0.45 (1.30)					-0.65 (1.51)	
Charbonnel et al. (2005)				-1.50 (1.42)		-1.40 (1.48)	
Saleem et al. (2011)					-1.10 (2.20)	-0.80 (2.07)	
Erem et al. (2014)			-1.22 (1.20)	-1.57 (1.73)			-1.28 (1.67)

Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 134: SENSITIVITY ANALYSIS INITIAL THERAPY: HbA1c AT 12 MONTHS – relative effectiveness of all pairwise combinations

	Placebo	Acarbose	Metformin	Pioglitazone	repaglinide	Sulfonylurea	Sulfonylurea (modified release)
Placebo		-0.44 (-1.22, 0.35)	-	-	-	-1.10 (-1.94, -0.26)	-
Acarbose	-0.28 (-0.83, 0.10)		-	-	-	-	-
Metformin	-1.07 (-2.02, -0.12)	-0.78 (-1.80, 0.31)		0.07 (-0.04, 0.18)	-	0.04 (-0.16, 0.24)	-0.06 (-0.98, 0.86)
Pioglitazone	-1.08 (-2.06, -0.13)	-0.79 (-1.81, 0.29)	0.01 (-0.38, 0.29)		-	0.11 (-0.04, 0.26)	0.29 (-0.79, 1.37)
repaglinide	-1.24 (-2.29, -0.19)	-0.95 (-2.07, 0.24)	-0.17 (-0.80, 0.47)	-0.17 (-0.78, 0.51)		0.26 (-0.15, 0.68)	-
Sulfonylurea	-0.97 (-1.87, -0.09)	-0.68 (-1.65, 0.36)	0.10 (-0.25, 0.45)	0.09 (-0.21, 0.50)	0.27 (-0.28, 0.81)		-
Sulfonylurea (modified release)	-1.01 (-2.37, 0.33)	-0.72 (-2.12, 0.72)	0.06 (-0.91, 1.03)	0.06 (-0.90, 1.05)	0.23 (-0.93, 1.38)	-0.04 (-1.05, 0.97)	

Values given are mean differences in HbA1c in percentage-points.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 80: SENSITIVITY ANALYSIS INITIAL THERAPY: HbA1c AT 12 MONTHS – relative effect of all options versus reference treatment

Table 135: SENSITIVITY ANALYSIS INITIAL THERAPY: HbA1c AT 12 MONTHS – rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.000	7 (5, 7)
Acarbose	0.023	6 (2, 7)
Metformin	0.101	3 (1, 5)
Pioglitazone	0.094	3 (1, 5)
repaglinide	0.490	2 (1, 5)
Sulfonylurea	0.011	4 (2, 6)
Sulfonylurea (modified release)	0.281	4 (1, 7)

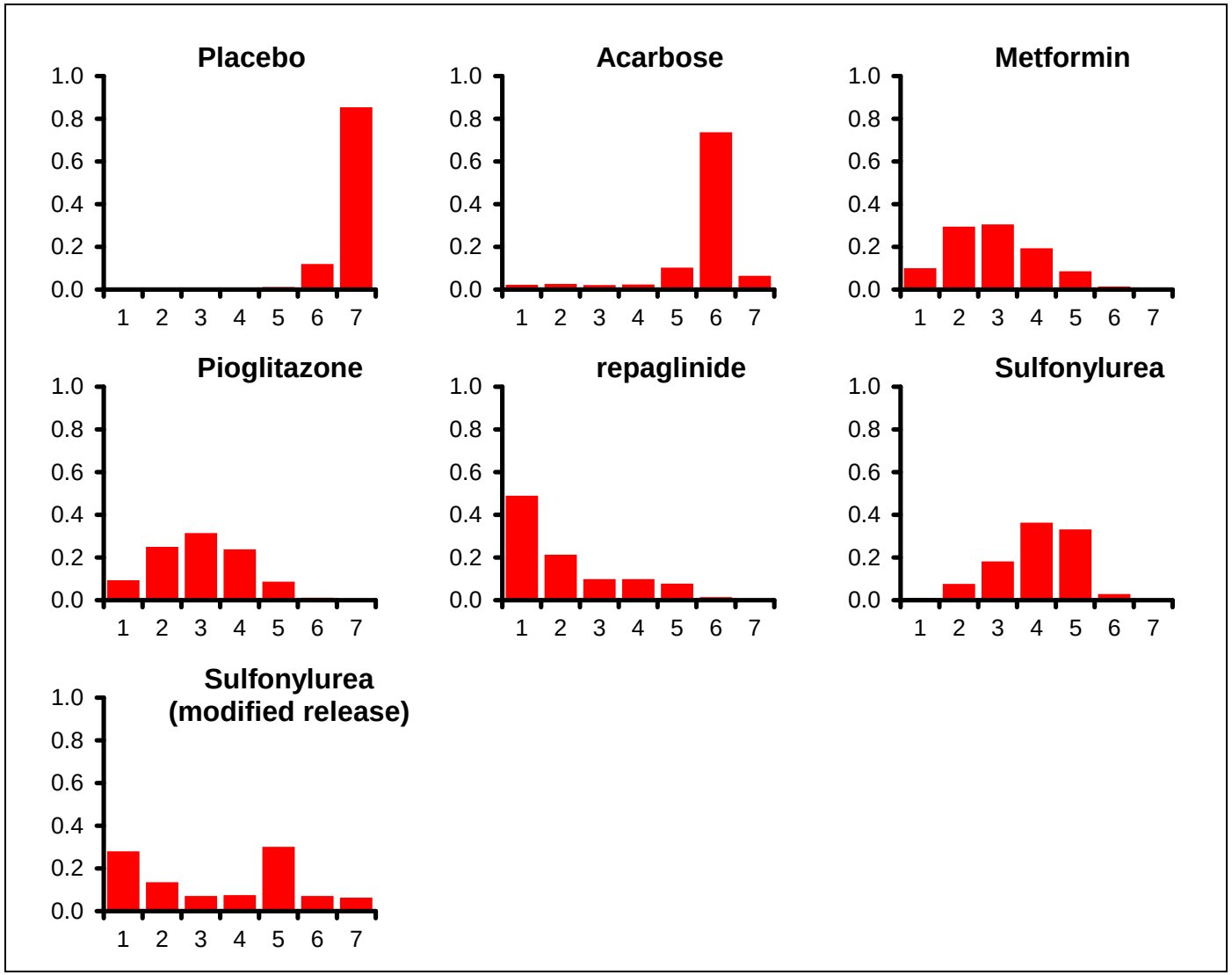


Figure 81: SENSITIVITY ANALYSIS INITIAL THERAPY: HbA1c AT 12 MONTHS – rank probability histograms

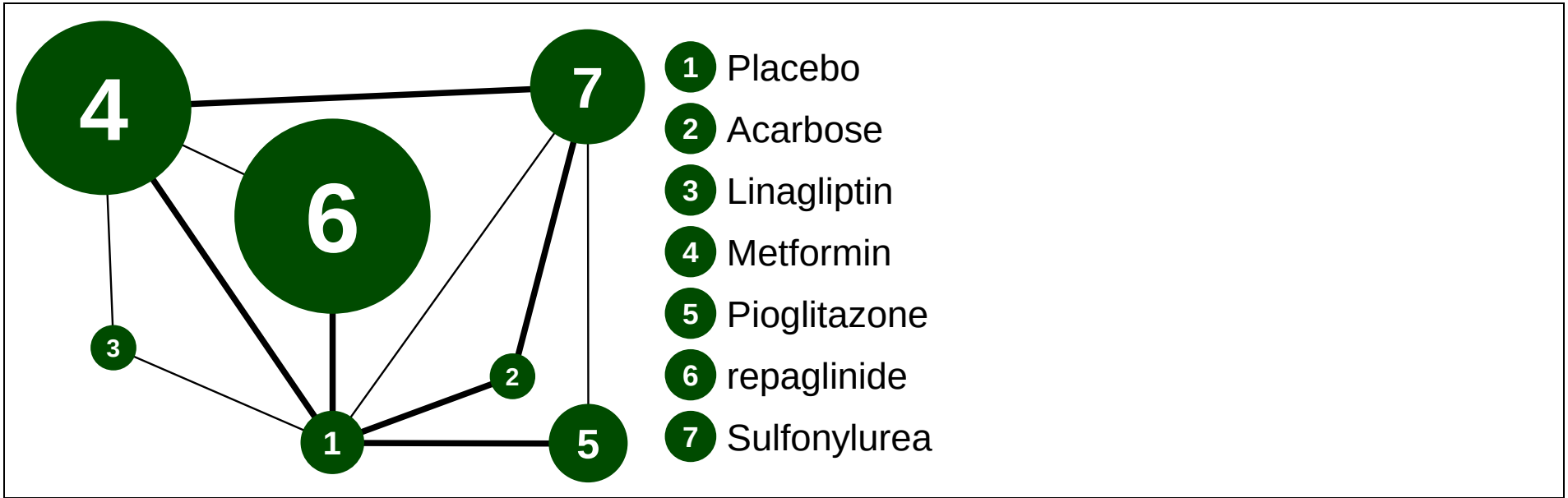
Table 136: SENSITIVITY ANALYSIS INITIAL THERAPY: HbA1c AT 12 MONTHS – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
25.16 (compared to 25 datapoints)	-16.168	-36.059	19.891	3.723	0.154 (95%CI: 0.008, 0.570)

Table 137: SENSITIVITY ANALYSIS INITIAL THERAPY: HbA1c AT 12 MONTHS – notes

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 200000)

J.3.1.2 Hypoglycaemia at study endpoint



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 82: SENSITIVITY ANALYSIS INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – evidence network

Table 138: SENSITIVITY ANALYSIS INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – input data

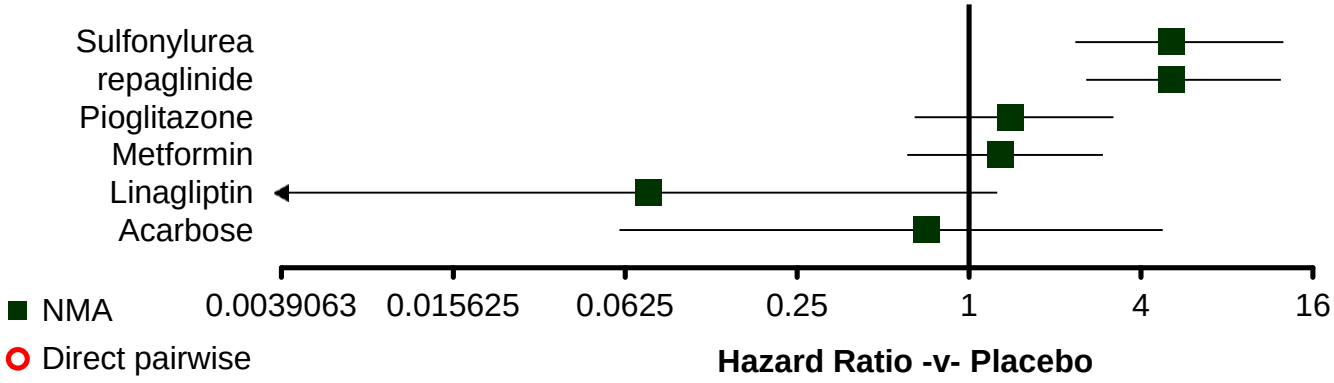
	Placebo	Acarbose	Linagliptin	Metformin	Pioglitazone	repaglinide	Sulfonylurea
Dichotomous proportion data							
Yoon et al. (2011) - 0.92yr				4/114			23/118
Haak et al. (2012) - 0.46yr	1/72		0/142	7/291			
Derosa et al. (2011) - 0.54yr	0/87	0/88					
Herz et al. (2003) - 0.31yr	11/96				21/191		
Horton et al. (2000) - 0.46yr	3/104			11/104			
Jovanovic et al. (2000) - 0.46yr	8/75					89/286	
Aronoff et al. (2000) - 0.50yr	0/79				4/329		
Hoffmann & (1994) - 0.46yr	0/30	0/28					2/27
Salman et al. (2001) - 0.46yr		0/27					3/30
Viberti et al. (2002) - 3.99yr				168/1454			557/1441
Charbonnel et al. (2005) - 1.00yr					22/624		63/626
Moses et al. (2001) - 0.31yr	4/134					44/260	
Count data							
Fang et al. (2014) - 0.29yr				0/2100		10/4147.5	

Values given are number of events / number of participants (for dichotomous proportion data) and number of events / total patient-days (for count data). Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 139: SENSITIVITY ANALYSIS INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations

	Placebo	Acarbose	Linagliptin	Metformin	Pioglitazone	repaglinide	Sulfonylurea
Placebo		N/A	N/A	N/A	N/A	N/A	N/A
Acarbose	0.71 (0.06, 4.76)		N/A	N/A	N/A	N/A	N/A
Linagliptin	0.08 (0.00, 1.25)	0.10 (0.00, 3.99)		N/A	N/A	N/A	N/A
Metformin	1.30 (0.61, 2.94)	1.82 (0.29, 21.87)	16.86 (1.14, 8532.00)		N/A	N/A	N/A
Pioglitazone	1.40 (0.64, 3.20)	1.98 (0.30, 25.17)	18.50 (1.07, 9188.00)	1.09 (0.44, 2.62)		N/A	N/A
repaglinide	5.11 (2.57, 12.34)	7.46 (1.00, 97.67)	70.06 (3.85, 36660.00)	3.96 (1.49, 11.89)	3.65 (1.30, 11.73)		N/A
Sulfonylurea	5.14 (2.36, 12.59)	7.24 (1.26, 85.76)	67.95 (4.34, 33440.00)	3.98 (2.18, 7.86)	3.67 (1.74, 8.51)	1.01 (0.33, 2.90)	

Values given are hazard ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.



Values greater than 1 favour placebo; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 83: SENSITIVITY ANALYSIS INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effect of all options versus reference treatment

Table 140: SENSITIVITY ANALYSIS INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – rankings for each comparator

	Probability best	Median rank (95%CI)
Placebo	0.015	3 (2, 5)
Acarbose	0.113	2 (1, 6)
Linagliptin	0.866	1 (1, 3)
Metformin	0.002	4 (2, 5)
Pioglitazone	0.004	4 (2, 5)
repaglinide	0.000	6 (5, 7)
Sulfonylurea	0.000	7 (6, 7)

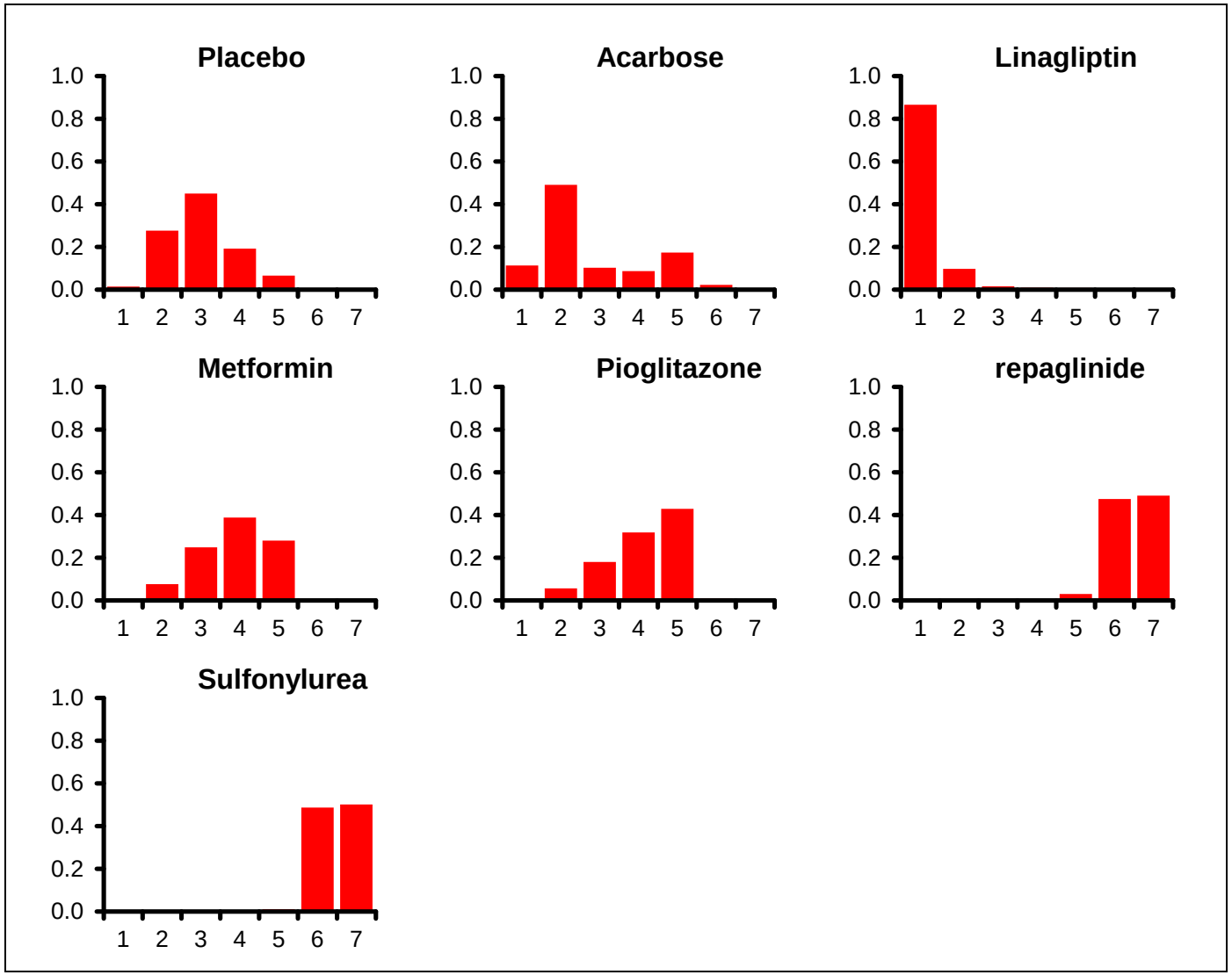


Figure 84: SENSITIVITY ANALYSIS INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – rank probability histograms

Table 141: SENSITIVITY ANALYSIS INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – model fit statistics

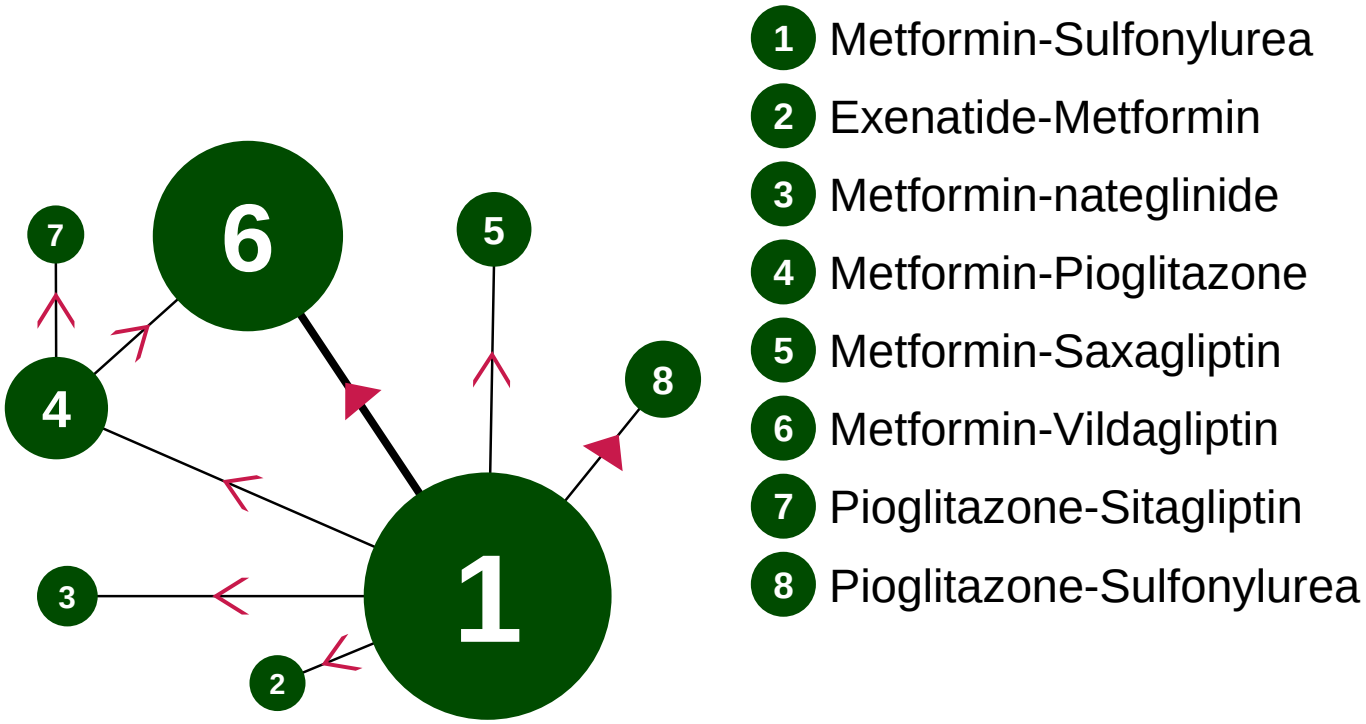
Residual deviance	Dbar	Dhat	pD	DIC	tau
28.2 (compared to 31 datapoints)	129.942	109.874	20.068	158.983	0.280 (95%CI: 0.018, 0.919)

Table 142: SENSITIVITY ANALYSIS INITIAL THERAPY: HYPOGLYCAEMIA AT STUDY ENDPOINT – notes

- Hybrid cloglog--Poisson model for count/dichotomous data; random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

J.3.2 RESULTS FOR FIRST INTENSIFICATION – PEOPLE PREVIOUSLY ON 1 ORAL ANTIDIABETIC MEDICINE

J.3.2.1 Change in HbA1c at 12 months



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 85: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – evidence network

Table 143: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – input data

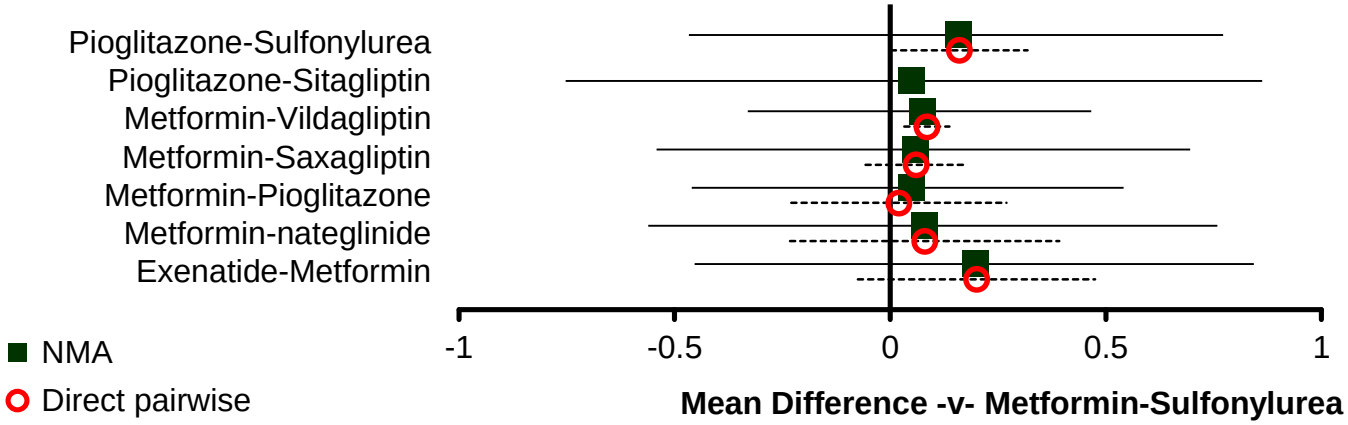
	Metformin-Sulfonylurea	Exenatide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Vildagliptin	Pioglitazone-Sitagliptin	Pioglitazone-Sulfonylurea
Goke et al. (2010)	-0.80 (0.86)				-0.74 (0.57)			
Derosa et al. (2011)	-1.40 (0.75)	-1.20 (0.65)						
Filozof & (2010)	-0.85 (1.19)					-0.81 (1.18)		
Derosa et al. (2010)				-1.40 (0.75)			-1.40 (0.84)	
Ferrannini et al. (2009)	-0.53 (0.65)					-0.44 (0.67)		
Bolli et al. (2008)				-0.60 (1.45)		-0.60 (0.96)		
Ristic et al. (2006)	-0.20 (1.22)		-0.12 (1.07)					
Matthews et al. (2005)	-1.01 (1.59)			-0.99 (1.60)				
Hanefeld et al. (2004)	-1.36 (1.02)							-1.20 (1.02)

Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 144: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – relative effectiveness of all pairwise combinations

	Metformin-Sulfonylurea	Exenatide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Vildagliptin	Pioglitazone-Sitagliptin	Pioglitazone-Sulfonylurea
Metformin-Sulfonylurea		0.20 (-0.08, 0.48)	0.08 (-0.23, 0.39)	0.02 (-0.23, 0.27)	0.06 (-0.06, 0.18)	0.09 (0.03, 0.14)	-	0.16 (0.00, 0.32)
Exenatide-Metformin	0.20 (-0.45, 0.84)		-	-	-	-	-	-
Metformin-nateglinide	0.08 (-0.56, 0.76)	-0.12 (-1.02, 0.86)		-	-	-	-	-
Metformin-Pioglitazone	0.05 (-0.46, 0.54)	-0.15 (-0.99, 0.66)	-0.03 (-0.89, 0.76)		-	0.00 (-0.20, 0.20)	0.00 (-0.27, 0.27)	-
Metformin-Saxagliptin	0.06 (-0.54, 0.70)	-0.14 (-1.01, 0.77)	-0.02 (-0.93, 0.88)	0.01 (-0.74, 0.82)		-	-	-
Metformin-Vildagliptin	0.08 (-0.33, 0.47)	-0.13 (-0.90, 0.62)	-0.01 (-0.81, 0.74)	0.02 (-0.48, 0.51)	0.01 (-0.75, 0.72)		-	-
Pioglitazone-Sitagliptin	0.05 (-0.75, 0.86)	-0.15 (-1.18, 0.90)	-0.03 (-1.09, 1.01)	0.00 (-0.63, 0.66)	-0.01 (-1.04, 1.02)	-0.02 (-0.81, 0.80)		-
Pioglitazone-Sulfonylurea	0.16 (-0.47, 0.77)	-0.04 (-0.97, 0.84)	0.08 (-0.86, 0.95)	0.11 (-0.70, 0.90)	0.10 (-0.80, 0.96)	0.09 (-0.67, 0.81)	0.11 (-0.90, 1.11)	

Values given are mean differences in HbA1c in percentage-points.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 86: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – relative effect of all options versus reference treatment

Table 145: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – rankings for each comparator

	Probability best	Median rank (95%CI)
Metformin-Sulfonylurea	0.163	3 (1, 6)
Exenatide-Metformin	0.067	7 (1, 8)
Metformin-nateglinide	0.206	5 (1, 8)
Metformin-Pioglitazone	0.091	4 (1, 8)
Metformin-Saxagliptin	0.126	4 (1, 8)
Metformin-Vildagliptin	0.036	5 (1, 7)
Pioglitazone-Sitagliptin	0.259	4 (1, 8)
Pioglitazone-Sulfonylurea	0.053	6 (1, 8)

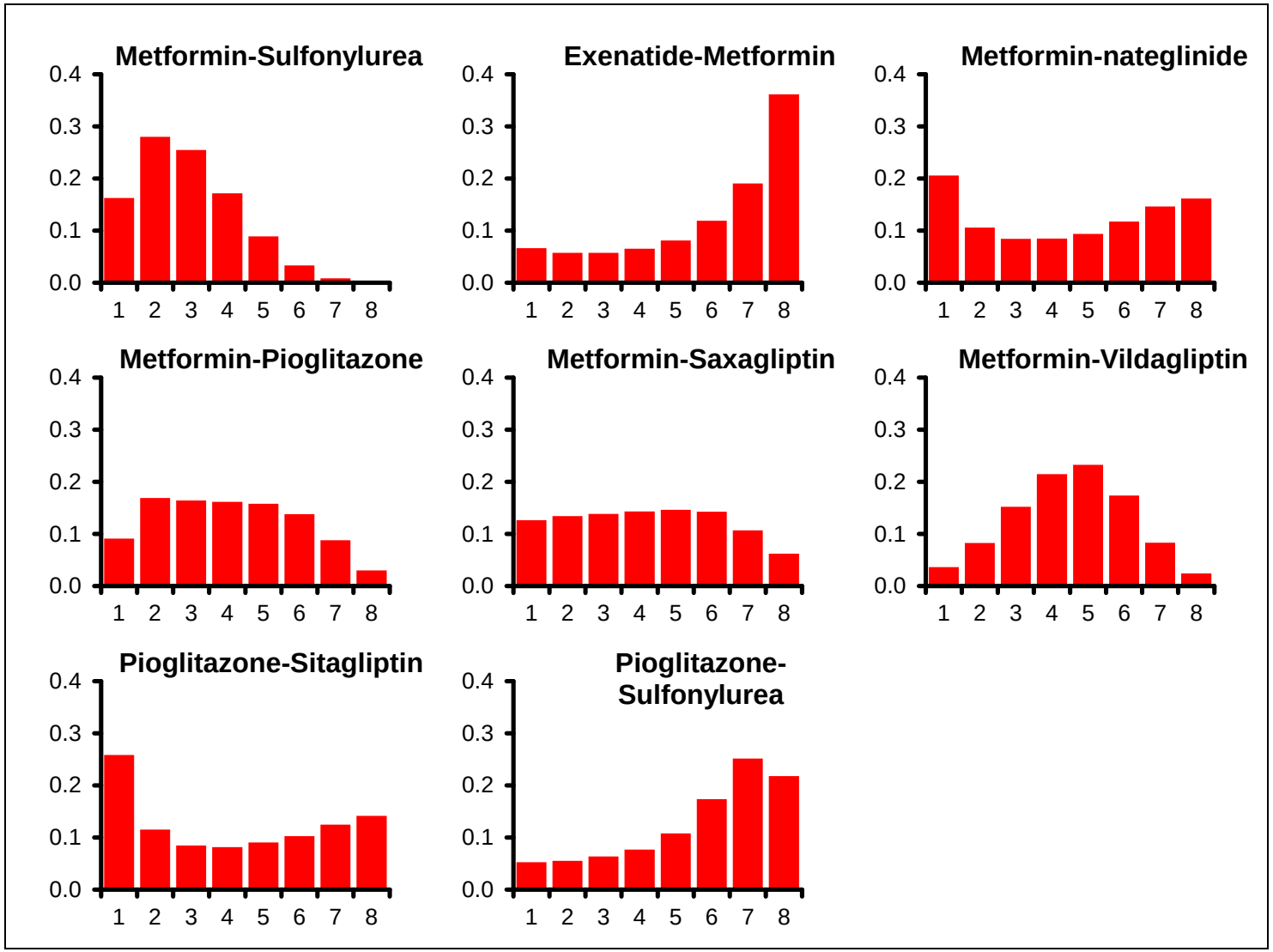


Figure 87: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – rank probability histograms

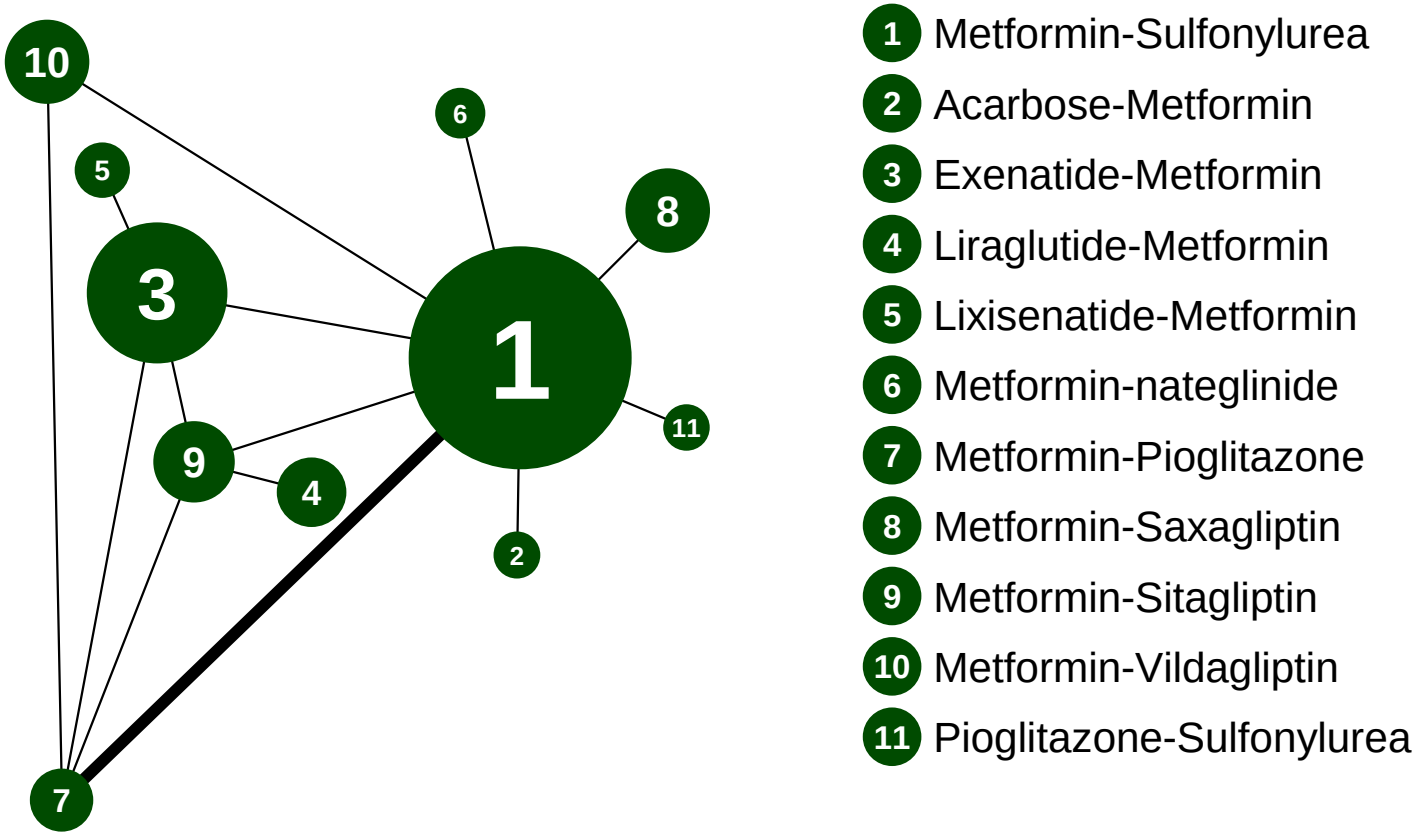
Table 146: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
17.12 (compared to 18 datapoints)	-48.664	-65.697	17.033	-31.631	0.086 (95%CI: 0.003, 1.099)

Table 147: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HbA1c AT 12 MONTHS – notes

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

J.3.2.2 Hypoglycaemia at study endpoint



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 88: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – evidence network

Table 148: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – input data

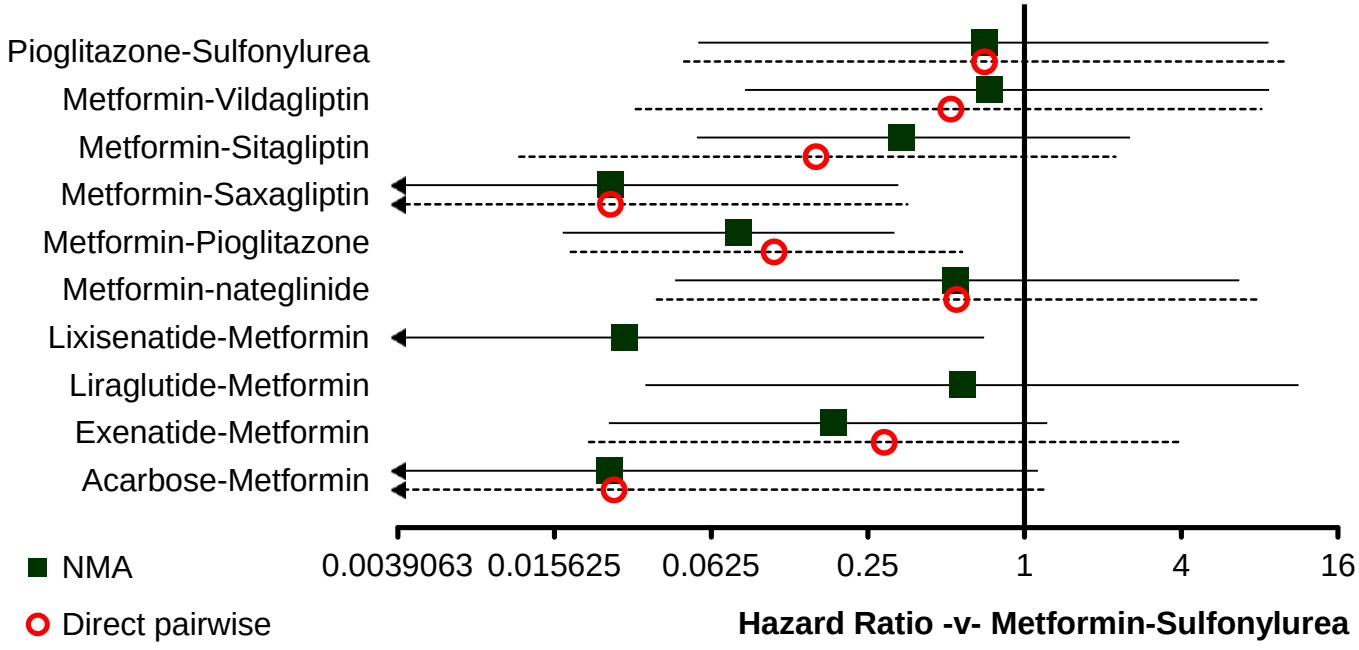
	Metformin-Sulfonylurea	Acarbose-Metformin	Exenatide-Metformin	Liraglutide-Metformin	Lixisenatide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Sitagliptin	Metformin-Vildagliptin	Pioglitazone-Sulfonylurea
Dichotomous proportion data											
Wang et al. (2011) - 0.31yr	6/26	0/29									
Matthews et al. (2005) - 1.99yr	36/313						7/317				
Umpierrez et al. (2006) - 0.50yr	32/96						1/107				
Hanefeld et al. (2004) - 1.99yr	50/320										36/319
Count data											
Gallwitz et al. (2012) - 2.99yr	7162/491400		1946/467376								
Goke et al. (2010) - 1.99yr	896/210028							24/215852			
Pfutzner et al. (2011) - 0.46yr	5/22764						2/23352				
Bergenstal et al. (2010) - 0.50yr			2/26117				1/26936		9/28210		
Filozof & (2010) - 1.00yr	11/164892									6/167440	
Bolli et al. (2008) - 0.46yr							0/44100			3/46788	
Ristic et al. (2006) - 0.46yr	188/19992					110/21252					
Arechavaleta et al. (2010) - 0.57yr	460/103441								73/103441		
Pratley et al. (2010) - 1.00yr				94/133042					25/67340		
Rosenstock et al. (2013) - 0.46yr			48/49308		8/49980						

Values given are number of events / number of participants (for dichotomous proportion data) and number of events / total patient-days (for count data). Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 149: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations

	Metformin-Sulfonylurea	Acarbose-Metformin	Exenatide-Metformin	Liraglutide-Metformin	Lixisenatide-Metformin	Metformin-nateglinide	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Sitagliptin	Metformin-Vildagliptin
Acarbose-Metformin	0.03 (0.00, 1.13)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Exenatide-Metformin	0.18 (0.03, 1.22)	7.44 (0.10, 5579.00)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Liraglutide-Metformin	0.58 (0.03, 11.29)	25.12 (0.21, 26080.00)	3.12 (0.15, 83.46)		N/A	N/A	N/A	N/A	N/A	N/A
Lixisenatide-Metformin	0.03 (0.00, 0.70)	1.20 (0.01, 1308.00)	0.16 (0.01, 2.05)	0.05 (0.00, 2.60)		N/A	N/A	N/A	N/A	N/A
Metformin-nateglinide	0.55 (0.05, 6.68)	22.89 (0.24, 20240.00)	2.97 (0.13, 73.54)	0.95 (0.02, 40.53)	18.72 (0.33, 1242.00)		N/A	N/A	N/A	N/A
Metformin-Pioglitazone	0.08 (0.02, 0.32)	3.15 (0.05, 2189.00)	0.43 (0.05, 3.72)	0.14 (0.01, 2.54)	2.75 (0.09, 81.50)	0.15 (0.01, 2.37)		N/A	N/A	N/A
Metformin-Saxagliptin	0.03 (0.00, 0.33)	1.06 (0.01, 1045.00)	0.14 (0.01, 3.72)	0.04 (0.00, 1.92)	0.89 (0.01, 57.75)	0.05 (0.00, 1.63)	0.32 (0.02, 6.57)		N/A	N/A
Metformin-Sitagliptin	0.34 (0.06, 2.54)	13.96 (0.21, 9787.00)	1.82 (0.23, 19.95)	0.58 (0.06, 5.28)	11.69 (0.44, 407.80)	0.61 (0.03, 14.57)	4.22 (0.61, 42.01)	13.19 (0.58, 335.00)		N/A
Metformin-Vildagliptin	0.73 (0.08, 8.69)	31.17 (0.38, 28030.00)	4.00 (0.24, 93.59)	1.26 (0.03, 53.34)	26.02 (0.57, 1549.00)	1.34 (0.05, 44.44)	9.21 (0.93, 148.20)	29.05 (1.06, 975.20)	2.18 (0.12, 43.23)	
Pioglitazone-Sulfonylurea	0.70 (0.06, 8.64)	29.12 (0.30, 27940.00)	3.80 (0.17, 94.03)	1.20 (0.02, 50.23)	24.18 (0.44, 1479.00)	1.27 (0.04, 44.92)	8.78 (0.50, 174.70)	27.31 (0.75, 892.90)	2.08 (0.08, 46.40)	0.95 (0.03, 25.71)

Values given are hazard ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.



Values greater than 1 favour metformin-sulfonylurea; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 89: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effect of all options versus reference treatment

Table 150: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – rankings for each comparator

	Probability best	Median rank (95%CI)
Metformin-Sulfonylurea	0.000	10 (7, 11)
Acarbose-Metformin	0.391	2 (1, 9)
Exenatide-Metformin	0.002	5 (3, 9)

	Probability best	Median rank (95%CI)
Liraglutide-Metformin	0.005	8 (3, 11)
Lixisenatide-Metformin	0.279	2 (1, 8)
Metformin-nateglinide	0.004	8 (3, 11)
Metformin-Pioglitazone	0.027	4 (1, 7)
Metformin-Saxagliptin	0.287	2 (1, 7)
Metformin-Sitagliptin	0.001	7 (4, 10)
Metformin-Vildagliptin	0.001	9 (4, 11)
Pioglitazone-Sulfonylurea	0.003	9 (3, 11)

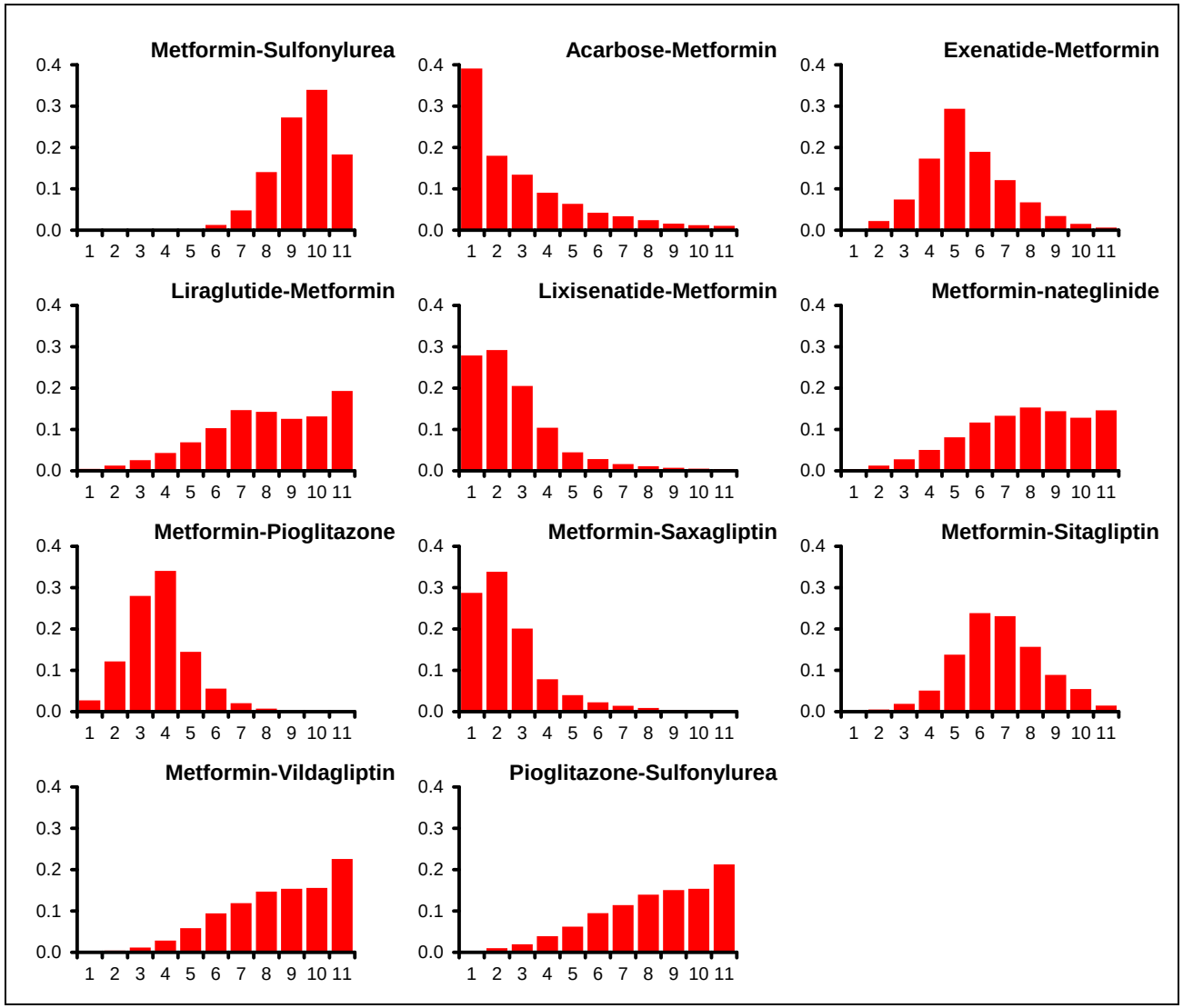


Figure 90: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – rank probability histograms

Table 151: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – model fit statistics

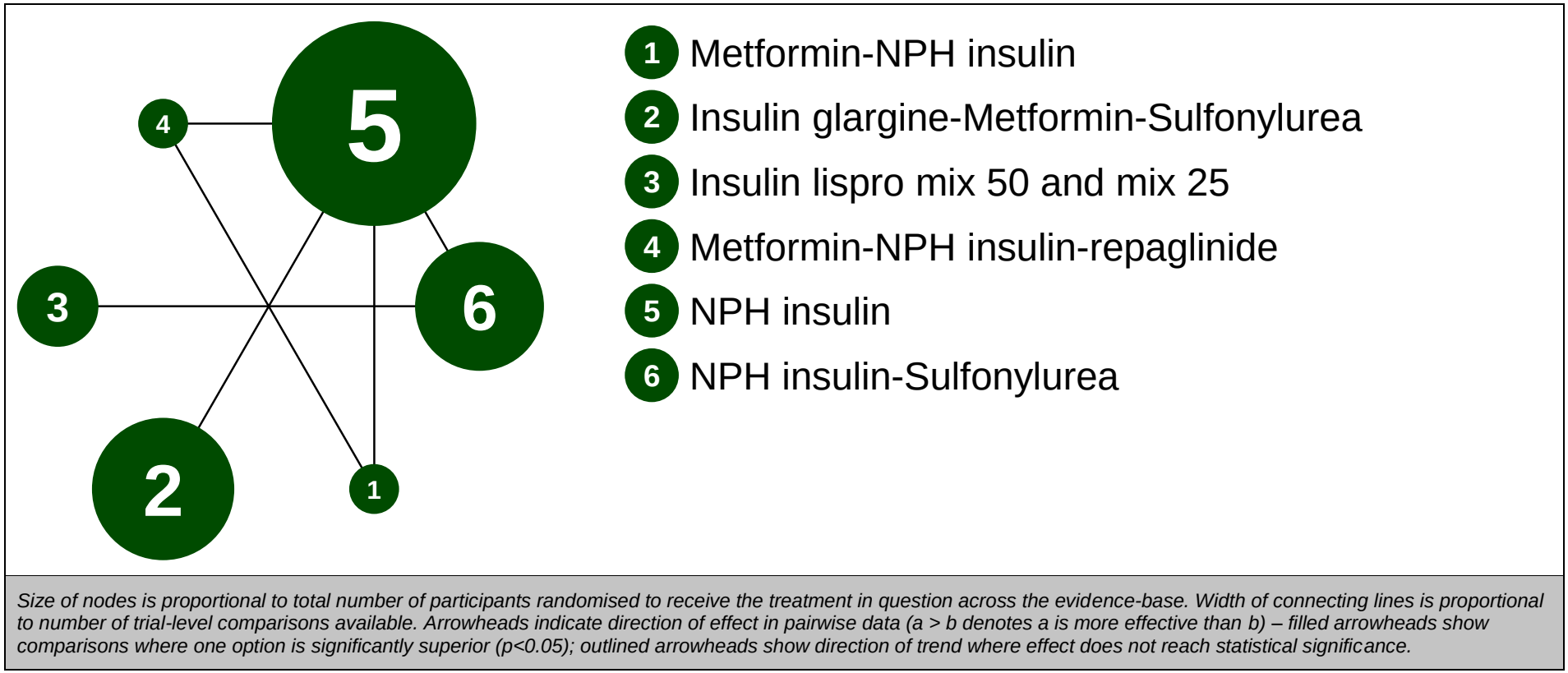
Residual deviance	Dbar	Dhat	pD	DIC	tau
30.32 (compared to 30 datapoints)	40.088	32.724	7.364	146.372	1.120 (95%CI: 0.502, 1.912)

Table 152: SENSITIVITY ANALYSIS FIRST INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – notes

- Hybrid cloglog--Poisson model for count/dichotomous data; random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

J.3.3 RESULTS FOR SECOND INTENSIFICATION – INDIVIDUALS PREVIOUSLY ON 2 NON-INSULIN BASED MEDICINES

J.3.3.1 Change in HbA1c up to 12 months



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 91: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – evidence network

Table 153: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – input data

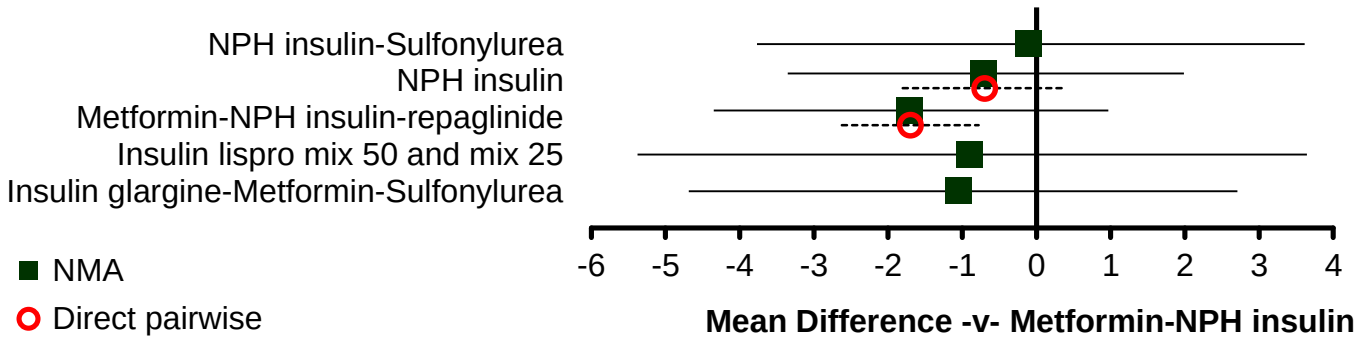
	Metformin-NPH insulin	Insulin glargine-Metformin-Sulfonylurea	Insulin lispro mix 50 and mix 25	Metformin-NPH insulin-repaglinide	NPH insulin	NPH insulin-Sulfonylurea
Milicevic et al. (2009)			-1.30 (2.00)			-0.50 (1.60)
Civera et al. (2008)	-0.70 (1.20)			-2.40 (1.10)	-1.40 (1.60)	
Janka et al. (2005)		-1.64 (0.92)			-1.31 (0.94)	
Stehouwer et al. (2003)					-1.10 (1.24)	-0.50 (1.30)

Values given are mean change in HbA1c (SD), in percentage-point units. Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 154: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – relative effectiveness of all pairwise combinations

	Metformin-NPH insulin	Insulin glargine-Metformin-Sulfonylurea	Insulin lispro mix 50 and mix 25	Metformin-NPH insulin-repaglinide	NPH insulin	NPH insulin-Sulfonylurea
Metformin-NPH insulin		-	-	-1.70 (-2.62, -0.78)	-0.70 (-1.80, 0.40)	-
Insulin glargine-Metformin-Sulfonylurea	-1.05 (-4.69, 2.71)		-	-	0.33 (0.14, 0.52)	-
Insulin lispro mix 50 and mix 25	-0.90 (-5.38, 3.65)	0.14 (-4.29, 4.58)		-	-	0.80 (0.19, 1.41)
Metformin-NPH insulin-repaglinide	-1.71 (-4.35, 0.97)	-0.68 (-4.36, 3.07)	-0.81 (-5.34, 3.60)		1.00 (-0.07, 2.07)	-
NPH insulin	-0.70 (-3.35, 1.99)	0.33 (-2.18, 2.89)	0.20 (-3.47, 3.79)	1.01 (-1.70, 3.70)		0.60 (0.22, 0.98)
NPH insulin-Sulfonylurea	-0.11 (-3.77, 3.61)	0.94 (-2.60, 4.54)	0.80 (-1.79, 3.35)	1.61 (-2.08, 5.29)	0.60 (-1.94, 3.15)	

Values given are mean differences in HbA1c in percentage-points.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (frequentist RE pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values greater than 0 favour metformin-NPH insulin; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 92: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – relative effect of all options versus reference treatment

Table 155: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – rankings for each comparator

	Probability best	Median rank (95%CI)
Metformin-NPH insulin	0.025	5 (1, 6)
Insulin glargine-Metformin-Sulfonylurea	0.190	3 (1, 6)
Insulin lispro mix 50 and mix 25	0.212	3 (1, 6)
Metformin-NPH insulin-repaglinide	0.530	1 (1, 5)
NPH insulin	0.024	4 (2, 6)
NPH insulin-Sulfonylurea	0.018	5 (2, 6)

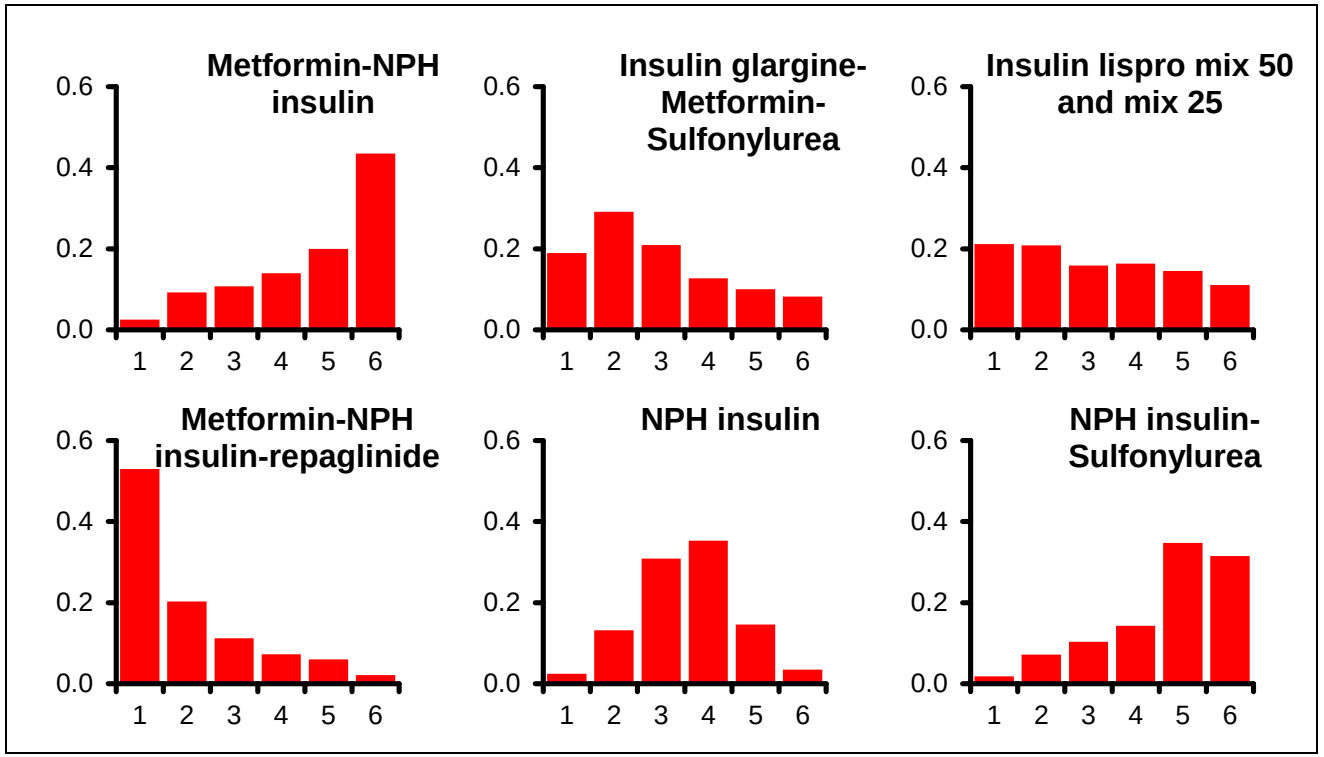


Figure 93: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – rank probability histograms

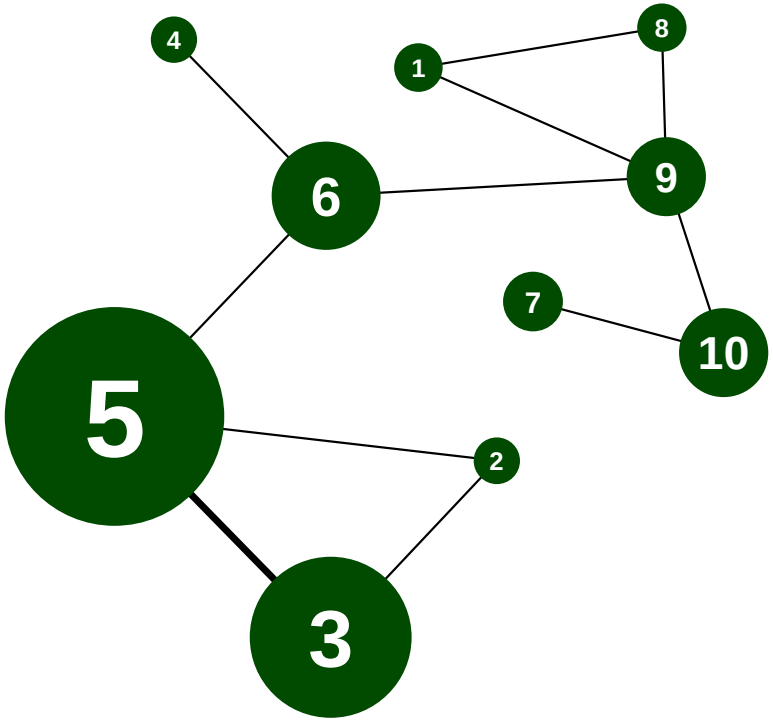
Table 156: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
9.004 (compared to 9 datapoints)	-5.256	-14.259	9.003	3.747	1.009 (95%CI: 0.058, 1.952)

Table 157: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HbA1c UP TO 12 MONTHS – notes

- Continuous (normal; identity link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)

J.3.3.2 Hypoglycaemia at study endpoint



1 Metformin-NPH insulin
2 Biphasic insulin aspart-Metformin
3 Biphasic insulin aspart-Metformin-Sulfonylurea
4 Exenatide (once weekly)-Metformin-Sulfonylurea
5 Exenatide-Metformin-Sulfonylurea
6 Insulin glargine-Metformin-Sulfonylurea
7 Insulin lispro mix 50 and mix 25
8 Metformin-NPH insulin-repaglinide
9 NPH insulin
10 NPH insulin-Sulfonylurea

Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 94: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – evidence network

Table 158: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – input data

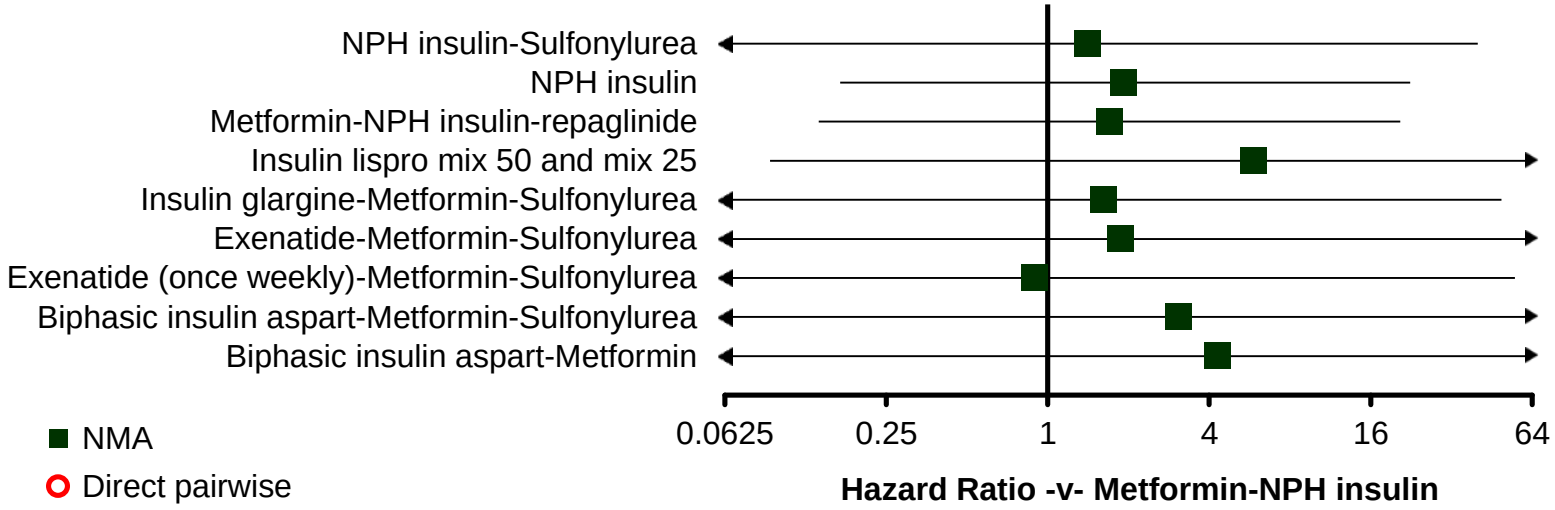
	Metformin-NPH insulin	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Exenatide (once weekly)-Metformin	Exenatide-Metformin-Sulfonylurea	Insulin glargine-Metformin-Sulfonylurea	Insulin lispro mix 50 and mix 25	Metformin-NPH insulin-repaglinide	NPH insulin	NPH insulin-Sulfonylurea
Dichotomous proportion data										
Diamant et al. (2010) - 1.61yr		76/124	69/124		36/124					
Bergenstal et al. (2009) - 0.46yr						109/177			127/187	
Janka et al. (2005) - 0.46yr				25/69		37/66				
Milicevic et al. (2009) - 0.46yr							124/10080			31/10248
Count data										
Civera et al. (2008) - 0.46yr	6/2016							10/2016	12/2184	
Nauck et al. (2007) - 1.00yr			1315/85722		1059/82264					
Heine et al. (2005) - 0.50yr									355/22176	253/21672
Stehouwer et al. (2003) - 0.69yr					928/46410	799/46319				

Values given are number of events / number of participants (for dichotomous proportion data) and number of events / total patient-days (for count data). Note that, for ease of comparison, any data from trials in which the same treatment is represented in multiple arms have been pooled here, whereas each arm is entered separately into the NMAs.

Table 159: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effectiveness of all pairwise combinations

	Metformin-NPH insulin	Biphasic insulin aspart-Metformin	Biphasic insulin aspart-Metformin-Sulfonylurea	Exenatide (once weekly)-Metformin-Sulfonylurea	Exenatide-Metformin-Sulfonylurea	Insulin glargine-Metformin-Sulfonylurea	Insulin lispro mix 50 and mix 25	Metformin-NPH insulin-repaglinide	NPH insulin
Biphasic insulin aspart -Metformin	4.30 (0.04, 469.00)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
Biphasic insulin aspart -Metformin-Sulfonylurea	3.07 (0.04, 251.00)	0.71 (0.08, 6.66)		N/A	N/A	N/A	N/A	N/A	N/A
Exenatide (once weekly) -Metformin-Sulfonylurea	0.90 (0.01, 55.29)	0.21 (0.00, 10.36)	0.29 (0.01, 11.60)		N/A	N/A	N/A	N/A	N/A
Exenatide-Metformin -Sulfonylurea	1.87 (0.03, 112.70)	0.44 (0.05, 3.93)	0.62 (0.12, 3.15)	2.11 (0.08, 59.03)		N/A	N/A	N/A	N/A
Insulin glargine-Metformin -Sulfonylurea	1.61 (0.06, 49.19)	0.38 (0.02, 8.94)	0.54 (0.03, 9.29)	1.83 (0.18, 19.69)	0.86 (0.09, 8.84)		N/A	N/A	N/A
Insulin lispro mix 50 and mix 25	5.88 (0.09, 355.00)	1.36 (0.01, 249.70)	1.91 (0.01, 277.80)	6.54 (0.06, 748.20)	3.11 (0.03, 334.70)	3.60 (0.07, 217.00)		N/A	N/A
Metformin-NPH insulin -repaglinide	1.71 (0.14, 20.65)	0.40 (0.00, 43.22)	0.55 (0.01, 47.13)	1.93 (0.03, 119.60)	0.90 (0.02, 56.23)	1.06 (0.04, 30.98)	0.29 (0.01, 17.27)		N/A
NPH insulin	1.92 (0.17, 22.48)	0.45 (0.01, 23.17)	0.64 (0.02, 25.86)	2.16 (0.08, 59.49)	1.02 (0.04, 28.41)	1.19 (0.12, 11.80)	0.33 (0.01, 9.74)	1.12 (0.10, 12.84)	
NPH insulin-Sulfonylurea	1.42 (0.05, 40.10)	0.33 (0.00, 35.38)	0.46 (0.01, 38.42)	1.58 (0.03, 98.46)	0.75 (0.01, 46.19)	0.87 (0.03, 23.65)	0.24 (0.02, 2.54)	0.83 (0.03, 23.05)	0.74 (0.07, 7.50)

Values given are hazard ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells is left blank, as it is not straightforward to derive estimates of direct effect in a frequentist context that are comparable to those estimated in the NMA.



Values greater than 1 favour metformin-NPH insulin; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 95: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – relative effect of all options versus reference treatment

Table 160: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – rankings for each comparator

	Probability best	Median rank (95%CI)
Metformin-NPH insulin	0.271	3 (1, 10)
Biphasic insulin aspart-Metformin	0.030	9 (1, 10)
Biphasic insulin aspart-Metformin-Sulfonylurea	0.032	8 (1, 10)
Exenatide (once weekly)-Metformin-Sulfonylurea	0.340	2 (1, 10)
Exenatide-Metformin-Sulfonylurea	0.058	5 (1, 9)
Insulin glargine-Metformin-Sulfonylurea	0.022	5 (2, 9)
Insulin lispro mix 50 and mix 25	0.022	9 (2, 10)
Metformin-NPH insulin-repaglinide	0.087	5 (1, 10)
NPH insulin	0.011	6 (2, 9)
NPH insulin-Sulfonylurea	0.127	4 (1, 9)

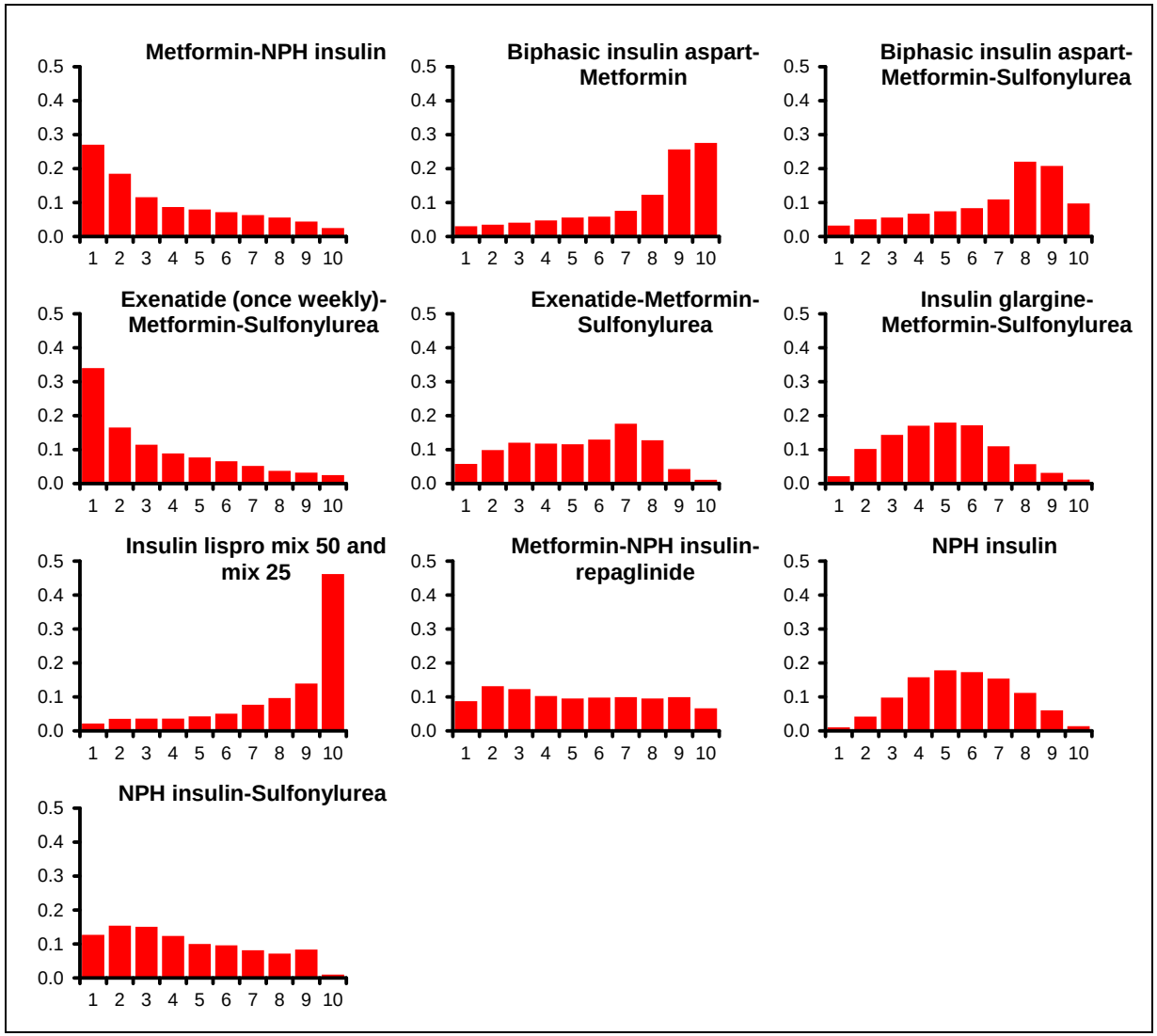


Figure 96: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – rank probability histograms

Table 161: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
18.2 (compared to 18 datapoints)	43.058	36.009	7.049	50.107	0.868 (95%CI: 0.203, 1.924)

Table 162: SENSITIVITY ANALYSIS SECOND INTENSIFICATION: HYPOGLYCAEMIA AT STUDY ENDPOINT – notes

- Hybrid cloglog--Poisson model for count/dichotomous data; random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations (thinned from 100000)