Appendix E Evidence tables

Review question 1: What is the optimal inpatient metabolic management of patients presenting with hyperglycaemia and acute coronary syndrome (ACS) who have diagnosed diabetes mellitus and hyperglycaemia

Evidence table 1

<table>
<tr><th>Bibliographic Reference (Ref ID)</th><th>Study type/aim</th><th>Patient characteristics</th><th>Definitions</th><th>Intervention</th><th>Comparator</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Comments</th></tr>
<tr>
<td>Malmberg et al 1995 (Ref ID: 396)</td>
<td>Multicenter RCT/To test how insulin-glucose infusion followed by multidose insulin treatment in diabetic patients</td>
<td>620 (control = 314, intervention = 306) patients with AMI and diabetes. 1240 fulfilled inclusion criteria but</td>
<td><u>Diabetes:</u> Patient has been informed of diagnosis and was on prescribed treatment (diet, tablets or insulin). <u>Newly detected</u></td>
<td><u>Insulin-glucose infusion:</u> 500 ml 5% glucose with 80 IU of soluble insulin (~1 IU/6ml). Started as soon as possible after</td>
<td><u>Control:</u> Treated according to standard coronary care unit practice and did not receive insulin unless it</td>
<td>Mean time of follow-up was 344days (range 91 to 365 days).</td>
<td>Mortality:
<table>
<tr><th>Time</th><th>Control (%)</th><th>Infusion (%)</th><th>Mortality reduction</th></tr>
<tr><td>In hospital</td><td>35 (11.1)</td><td>28 (9.1)</td><td>18% (ns)</td></tr>
<tr><td>3 months</td><td>49 (15.6)</td><td>38 (12.4)</td><td>21% (ns)</td></tr>
<tr><td>1 year</td><td>82 (26.1)</td><td>57 (18.6)</td><td>29% (p = 0.03)</td></tr>
</table>
The relative reduction in mortality was 29% by crude method and 31% with Cox model (CI 4% to 51%).</td>
<td>Swedish Heart-Lung Foundation, Karolinska Institutet and Hoechst Marion Roussel Sweden</td>
<td>DIGAMI 1 study. Patients received treatment other than glucose-insulin infusion according to predefined guidelines.</td>
</tr>
</table>

<table>
<tr><th>Bibliographic Reference (Ref ID)</th><th>Study type/aim</th><th>Patient characteristics</th><th>Definitions</th><th>Intervention</th><th>Comparator</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Comments</th></tr>
<tr>
<td></td>
<td>with Acute Myocardial Infarction (AMI) affected mortality during 12 months of follow up.</td>
<td>620 excluded. <u>Inclusion criteria:</u> suspected AMI within preceding 24 hours and previously known diabetes and blood glucose > 11mmol/l or blood glucose > 11mmol/l without diabetes. <u>Stratification:</u> based on risk and previous use of insulin. High risk patients fulfilled ≥</td>
<td><u>diabetes</u>: Admission blood glucose ≥ 11 mmol/litre. <u>AMI:</u> ≥ 2 of following criteria fulfilled; 1) chest pain for ≥ 15 mins; 2) ≥ 2 values of serum creatine kinase (S-CK) and S-CK isoenzyme B (S-CKB) or serum lactic dehydrogenase (S-LD) above the normal range (normal</td>
<td>arrival. Infusion was continued until stable normoglycaemia was attained for ≥ 24 hours. <u>Subcutaneous insulin:</u> administration of soluble insulin using insulin pen 3 times daily before meals combined with medium long acting insulin in the evening.</td>
<td>was deemed clinically indicated.</td>
<td></td>
<td>
<table>
<tr><td></td><td colspan="4">Strata*</td></tr>
<tr><td>Time</td><td>1</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td>Control 3m</td><td>18 (13.5)</td><td>10 (15.2)</td><td>8 (12.3)</td><td>13 (26.0)</td></tr>
<tr><td>Control 1yr</td><td>24 (18.0)</td><td>21 (31.8)</td><td>14 (21.5)</td><td>23 (46.0)</td></tr>
<tr><td>Insulin 3m</td><td>9 (6.5)</td><td>11 (17.5)</td><td>7 (13.0)</td><td>11 (22.0)</td></tr>
<tr><td>Insulin 1yr</td><td>12 (8.6)</td><td>17 (27)</td><td>10 (18.5)</td><td>18 (36.0)</td></tr>
<tr><td>Mortality reduction (3m)</td><td>52%**</td><td>-11%</td><td>0%</td><td>15%</td></tr>
<tr><td>Mortality reduction (1yr)</td><td>52%**</td><td>15%</td><td>14%</td><td>22%</td></tr>
</table>
* As defined in patient characteristics, **p = 0.046, p = 0.02 log rank test
In stratum 1 the mortality reduction was 52% after 3 months (p = 0.046) and this difference persisted at one year
</td>
<td></td>
<td>Possible AMI defined in 3% of infusion group and 7% in control. Fasting blood glucose also available for 3 month follow-up but not reported in table. Authors note that revascularisation procedures did not differ between groups. There</td>
</tr>
</table>

Bibliographic Reference (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
		2 of following criteria; age > 70 years, history of previous AMI and/or congestive heart failure (CHF) or ongoing treatment with digitalis. Pre defined strata; 1) no insulin & low risk, 2) no insulin & high risk, 3) insulin & low risk and 4) insulin & high risk.	+2SD), including an LD-isoenzyme pattern typical of myocardial damage; and 3) development of new Q waves in ≥ 2 standard ECG leads. **Possible AMI:** typical chest pain with only 1 S-CK or S-LD value above normal range and/or new Q waves in one ECG only. **Reinfarction:** new AMI	This was started immediately after cessation of infusion, according to regime, with aim of achieving normoglycaemia. Subcutaneous insulin was given 4 times daily for ≥ 3 months.			with mortality rate of 8.6% in infusion group and 18.0% in control (relative risk reduction 52%, p = 0.02). **Morbidity:** During the hospital period the control group did not significantly differ from the infusion group regarding reinfarction (4% vs. 5%), ventricular fibrillation (5% vs. 3%), high degree atrioventricular conduction disturbances (3% vs. 7%) or CHF (48% vs. 50%). There was a significant difference between hospital stay (11.3 ± 13.3 days in infusion group vs. 9.5 ± 9.4 days in control, p = 0.04). **Measures of blood glucose and adverse events:** Significantly higher numbers of patients experienced hypoglycaemia in the infusion group compared to control during the first 24 hours (46 vs. 0, p < 0.0001).		were no sub group analyses for those who had reperfusion and those who didn't and those who were suffering from heart failure and those who weren't.

<table>
<tr><th>Bibliographic Reference (Ref ID)</th><th>Study type/aim</th><th>Patient characteristics</th><th>Definitions</th><th>Intervention</th><th>Comparator</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Comments</th></tr>
<tr><td></td><td></td><td><u>Baseline characteristics</u>: 62% male & 38% female. Mean age for control = 68 ± 9 and for infusion = 67 ± 9. Mean blood glucose shown in outcome measures. Diabetes status: non insulin (control = 265 84%, infusion = 251 82%), insulin dependent (control = 49 16%,</td><td>> 72 hours after index infarct.</td><td></td><td></td><td></td><td>
<table>
<tr><td>Blood glucose (mmol/litre)</td><td>Control</td><td>Infusion</td><td>p-value</td></tr>
<tr><td>At randomisation</td><td>15.7±4.2</td><td>15.4±4.1</td><td>NS</td></tr>
<tr><td>24 hrs after randomisation</td><td>11.7±4.1</td><td>9.6±3.3</td><td>< 0.0001</td></tr>
<tr><td>At discharge</td><td>9.0±3.0</td><td>8.2±3.1</td><td>< 0.01</td></tr>
</table>
</td><td></td><td></td></tr>
</table>

<table>
<tr><th>Bibliographic Reference (Ref ID)</th><th>Study type/aim</th><th>Patient characteristics</th><th>Definitions</th><th>Intervention</th><th>Comparator</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Comments</th></tr>
<tr><td></td><td></td><td>infusion = 55 18%) and previously unknown diabetes (control = 47 15%, infusion = 31 10%). The groups were well matched in terms of baseline characteristics.</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Malmberg et al 1996 (Ref ID: 378)</td><td>Analysis of DIGAMI 1 to report the influence of insulin therapy on early and long-term</td><td>For details please see above DIGAMI 1 study. Groups were well balanced for patient characteristics. 50%</td><td>See above for DIGAMI 1 study. <u>Ventricular tachyarrhythmias</u>: The presence of either ventricular premature</td><td>See above for details of DIGAMI 1 study. Insulin group received insulin-glucose infusion followed by</td><td><u>Control:</u> Treated according to standard coronary care unit practice and did not receive</td><td></td><td><u>Mortality:</u><table><tr><td>Mortality</td><td>Total (%)</td><td>Control (%)</td><td>Infusion (%)</td><td>P-value</td></tr><tr><td>Hospital</td><td>63 (10)</td><td>35 (11)</td><td>28 (9)</td><td>ns</td></tr><tr><td>Discharge (12 months)</td><td>77 (13)</td><td>47 (15)</td><td>30 (10)</td><td>< 0.05</td></tr><tr><td>Total</td><td>140 (23)</td><td>82 (26)</td><td>58 (19)</td><td>< 0.05</td></tr></table>After one year the total mortality had</td><td>Swedish Heart-Lung Foundation, Karolinska Institutet and Hoechst Marion Roussel</td><td>The authors concluded that insulin-glucose infusion followed by subcutaneous insulin treatment</td></tr>
</table>

Bibliographic Reference (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
	cause-specific mortality and morbidity, with special reference to fatal and non-fatal reinfarction	were thrombolysed, 54% received intravenous nitro-glycerine & 17% were fully heparinised during the acute period in hospital.	beats or ventricular tachycardia requiring antiarrhythmic treatment, or documented ventricular fibrillation (VF) was included. VF defined as early if within 48 hrs of symptom onset and late if after. **Atrioventricular block**: Only high grade AV-blocks (II-III) were considered. The	multidose subcutaneous insulin treatment for at least 3 months.	insulin unless it was deemed clinically indicated.		decreased by 30% in the infusion group (p = 0.027). During 1 year follow-up the specific causes of death included HF, sudden death, myocardial rupture, stroke, non classified and non cardiovascular. Most died of CHF (66%). There was a trend towards less cardiovascular deaths of all kinds, and specifically for sudden death, in the infusion group compared to controls but these were non-significant. Among strata 1 patients, mortality had significantly reduced during the hospital phase and this was maintained throughout follow-up (in hospital p < 0.05, 3-month p < 0.05 and 1 year p = 0.020). **Morbidity:** During hospitalisation the control group did not differ from the infusion group regarding the incidence of reinfarction (4% vs. 5%), ventricular fibrillations (5% vs. 3%), high degree atrioventricular conduction disturbances (3% vs. 7%) or CHF (48% vs. 50%). During 1 year follow-up 108 (18%) patients suffered reinfarction (55 in control vs. 53 in infusion group, ns).	Sweden	in patients with diabetes and AMI favourably influences 1 year mortality by reducing all cardiovascular causes of death. This therapeutic regimen seems to have particular impact on fatal reinfarctions.

Bibliographic Reference (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
			conduction defect had to be treated to be noted in case record. **CHF:** clinical and/or radiological signs of pulmonary congestion resulting in the institution of treatment.				After 1 year there were 25 fatal reinfarctions in control compared to 15 in infusion group. This corresponds to reduction of 40% (CI -15% to 68%, p = 0.12). In all, 45% of reinfarctions were fatal in control group compared to 28% in infusion group (ns). **Measures of blood glucose and adverse events:** Fasting blood glucose after 1 year did not differ between groups. After 1 year 3 patients in control group and 8 in infusion group had hypoglycaemia but this difference was not significant.		
Malmberg et al 1997 (Ref ID: 367)	Analysis of DIGAMI 1 for long-term survival	For details please see above DIGAMI 1 study. The 2 groups were well balanced at the time of randomisat	For details please see above DIGAMI 1 study.	For details please see above DIGAMI 1 study.	For details please see above DIGAMI 1 study.	The mean (range) follow-up was 3.4 years (1.6-5.6 years) and no patients were lost	**Hospital and 1 year mortality:** During the initial year of follow-up, including deaths in hospital, 82 (26%) patients died in the control group compared with 58 (19%) in the insulin group. This corresponds to a relative reduction in mortality of 30% (p = 0.027). Most of the reduction occurred after hospital discharge. Only in patients without previous insulin treatment and at low cardiovascular	Swedish Heart-Lung Foundation, Karolinska Institutet and Hoechst Marion Roussel	The authors concluded that insulin-glucose infusion followed by intensive subcutaneous insulin

<table>
<tr><th>Bibliographic Reference (Ref ID)</th><th>Study type/aim</th><th>Patient characteristics</th><th>Definitions</th><th>Intervention</th><th>Comparator</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Comments</th></tr>
<tr><td></td><td></td><td>ion.</td><td></td><td></td><td></td><td>to follow-up as regards mortality.</td><td>risk (strata 1, 44% of all patients) was this reduction already significant during the hospital phase (from 12% in control group to 5% in the insulin group, relative reduction = 58%, p < 0.05). Absolute reduction in risk was 11%, relative risk 0.72 (CI 0.55-0.92), p = 0.011).
<u>Long-term mortality:</u>
During continued follow-up there were 138 (44%) deaths in the control group compared with 102 (33%) in the infusion group. The relative reduction in mortality at the end of follow-up was 28% by the Cox model (CI 8% to 45%, p = 0.011)
<u>Long-term mortality by strata:</u>
<table>
<tr><td></td><td colspan="4">Strata*</td></tr>
<tr><td>Detail</td><td>1 (n = 272)</td><td>2 (n = 129)</td><td>3 (n = 119)</td><td>4 (n = 100)</td></tr>
<tr><td>Mean follow up (yrs)</td><td>3.4</td><td>3.3</td><td>3.4</td><td>3.5</td></tr>
<tr><td>Total mortality</td><td>69</td><td>69</td><td>42</td><td>60</td></tr>
<tr><td colspan="5">Mortality by group</td></tr>
<tr><td>Control</td><td>44</td><td>35</td><td>26</td><td>33</td></tr>
</table></td><td>Sweden</td><td>treatment in diabetic patients with AMI improves long-term survival by nearly a third and the effect seems to last for at least 3.5 years. One limitation is that exact information about insulin treatment during long-term follow-up is not available.</td></tr>
</table>

Bibliographic Reference (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
							<table><tr><td></td><td>(33)</td><td>(53)</td><td>(40)</td><td>(66)</td></tr><tr><td>Insulin</td><td>25 (18)</td><td>34 (54)</td><td>16 (30)</td><td>27 (54)</td></tr><tr><td>P-value</td><td>0.004</td><td>> 0.2</td><td>> 0.2</td><td>> 0.2</td></tr></table> As defined in patient characteristics in DIGAMI 1 above. The most apparent effect was achieved in strata 1, with an absolute reduction in mortality of 15%, from 33% in control to 18% in insulin group. This corresponds to a relative reduction of 51% (19% to 70%, p = 0.004) by Cox model		

Bibliographic Reference (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
Malmberg et al 1997 (Ref ID: 2181)	The present report describes the short and long-term prognostic factors in diabetic patients with AMI by applying multivariate statistics on the DIGAMI cohort.	For details please see above DIGAMI 1 study. 38% were female and 62% were male. The female group was older than the male (70 ± 9 vs. 66 ± 9 years; p < 0.001) and had fewer previous infarctions (28 vs. 44%, p < 0.001). Hypertension was more prevalent among women	For details please see above DIGAMI 1 study	For details please see above DIGAMI 1 study	For details please see above DIGAMI 1 study	All patients were followed prospectively for 1 year with scheduled visits at 3 months and 12 months after randomisation. No patient was lost to follow-up.	**Mortality:** The overall 1 year mortality tended to be higher among females than males (26.3 vs. 20.4%, p = 0.092) **Univariate prediction of mortality**: In the entire patient group age, previous CHF, previous MI, previous angina pectoris, previous treatment with digitalis or insulin and the duration of diabetes were associated with mortality after 1 year. Patients who were smokers had a significantly better prognosis at 1 year than non-smokers. In the entire patient group the most powerful predictors for an unfavourable outcome were high blood glucose at admission (RR 1.08, CI 1.04-1.12, p = 0.0001) and new onset heart failure during hospitalisation (RR 2.87, CI 1.99-4.13, p = 0.0001). Thrombolytic therapy during the hospital phase (RR 0.60, CI 0.43-0.85, p = 0.004) and beta-blocker at discharge (RR 0.45, CI 0.31-0.66, p = 0.0001) were associated with survival. **Multivariate prediction of mortality:** Independent effects of concomitant treatment on 1 year mortality (following correction for age, gender and	Swedish Heart-Lung Foundation, Karolinska Institutet and Hoechst Marion Roussel Sweden	Specific RRs for the univariate predictors of mortality are not presented in the evidence table. The authors concluded that good metabolic control and not conventional risk factors is of major importance for diabetic patients sustaining AMI. Also treatment with beta blockade

Bibliographic Reference (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
		than men (56 vs. 44%, p < 0.01) and the duration of diabetes was longer in the female group (11 ± 11 vs. 9 ± 9 years, p < 0.05). With these exceptions there were no sex differences regarding baseline characteristic.					intensive insulin by multivariate Cox regression) showed that among all patients; thrombolysis (RR 0.61, CI 0.41-0.92, p = 0.018) and treatment with beta blockers at hospital discharge (RR 0.53, CI 0.36-0.78, p = 0.001) besides intensive insulin treatment (RR 0.65, CI 0.44-0.96, p = 0.0327) independently reduced 1 year mortality. Independent effects of baseline characteristics on 1 year mortality showed that in the entire patient group age (RR 1.07, CI 1.04-1.10, p = 0.0001), previous CHF (RR 2.10, CI 1.37-3.21, p = 0.0007) and previous insulin treatment (RR 1.58, CI 1.05-2.39, p = 0.028) were independent predictors for fatal outcome during the first year of follow-up. It was also found that elevated HbA_{1c} (p < 0.0001), tachycardia (p < 0.0001), presence of pulmonary rales at admission (p < 0.01) and a high body weight (p < 0.01) were all independently linked to hyperglycaemia at admission in multivariate analysis.		seems to be of special importance in this category of patients.
Malmberg et al 1999	Analysis of DIGAMI 1	For details please see above	For details please see above	For details please see above	For details please	The mean time of	**Mortality:** During long-term follow-up there were 240 deaths (39%), 138 in control group	Swedish Heart-Lung	The authors concluded

Bibliographic Reference (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
(Ref ID: 207a)	to describe factors influencing the long-term prognosis and effects of concomitant treatment by applying univariate and multivariate statistical analyses.	DIGAMI 1 study. The 2 groups were well balanced at the time of randomisation.	DIGAMI 1 study. **Type of diabetes:** dependent on clinical history. **Non-insulin dependent diabetes (NIDDM):** > 40 years at diagnosis and did not need insulin for ≥ 2 years after diagnosis and not prone to ketoacidosis.	DIGAMI 1 study.	see above DIGAMI 1 study. **Control group:** received conventional treatment at the discretion of the physician in charge.	follow-up was 3.4 years (range 1.6 to 5.6 years) and did not differ between patients within the 4 strata.	(mortality 44%) and 102 in infusion group (mortality 33%, p = 0.011). This corresponds to a relative mortality reduction (at the end of follow-up) of 28% (CI 8% to 45%) using Cox model. Patients in strata 1 had an absolute mortality reduction of 15%, from 44 deaths (33%) in control group to 25 deaths (18%) in infusion group. This corresponds to a relative reduction of 51% (CI 19% to 70%, p = 0.004). **Univariate prediction:** In the control group the following factors were found to be significantly associated with long-term mortality; age RR = 1.07 (1.04-1.10, p < 0.001), male sex RR = 0.70 (0.50-0.98, p < 0.05), previous MI RR = 1.42 (1.01-1.99, p < 0.05), previous CHF RR = 2.37 (1.67-3.38, p < 0.001), previous hypertension RR = 1.45 (1.04-2.03, p < 0.05), smoking RR = 0.58 (0.37-0.92, p < 0.05), blood glucose at admission RR = 1.09 (1.05-1.13, p < 0.001), HbA_{1c} RR = 1.13 (1.04-1.25, p < 0.01), CHF during hospitalisation RR = 2.59 (1.82-3.68, p < 0.001), thrombolysis RR = 0.69 (0.49-0.97, p < 0.05) and beta blockers at discharge RR = 0.45 (0.31-	Foundation, Karolinska Institutet and Hoechst Marion Roussel Sweden	that mortality is predicted by age, previous HF and the severity of the gluco-metabolic state at admission. Institution of intensive insulin reduces this risk considerably. Beta blockers also have striking preventative effect in diabetics with MI. Those prescribed ACE may

Bibliographic Reference (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
							0.65, p < 0.001). In the infusion group the following factors were found to be significantly associated with long-term mortality; age RR = 1.07 (1.05-1.10, p < 0.001), previous MI RR = 2.01 (1.36-2.97, p < 0.001), previous CHF RR = 2.90 (1.95-4.30, p < 0.001), diabetes duration RR = 1.02 (1.01-1.04, p < 0.01), blood glucose at admission RR = 1.05 (1.01-1.11, p < 0.05), CHF during hospitalisation RR = 2.40 (1.59-3.62, p < 0.001) and thrombolysis RR = 0.44 (0.29-0.67, p < 0.001). **Multivariate prediction:** In the control group the following factors were found to be significantly associated with long-term mortality using Cox regression; age RR = 1.09 (1.06-1.12, p < 0.001), previous CHF RR = 2.37 (1.50-3.74, p < 0.001), admission blood glucose + 1mmol/litre RR = 1.06 (1.01-1.11, p < 0.05) and HbA_{1c} on admission RR = 1.15 (1.03-1.29, p < 0.05). In the infusion group the following factors were found to be significantly associated with long-term mortality; age RR = 1.08 (1.05-1.12, p < 0.001), previous history of CHF RR = 2.28		have more severe CHF

Bibliographic Reference (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
							(1.33-3.73, p < 0.01) and diabetes duration (1 added yr) RR = 1.03 (1.01-1.05, p < 0.01). **Effects of treatment:** Independent effects of concomitant treatment on long-term mortality after correction for age, sex and CHF during the hospital period found thrombolysis RR = 0.63 (1.43-0.92, p < 0.05), beta-blockade at discharge RR = 0.55 (0.38-0.79, p < 0.01) and ACE inhibitor at discharge RR = 1.50 (1.04-2.30, p < 0.05) were significant predictors in the control group. Only thrombolysis RR = 0.44 (0.28-0.72, p < 0.001) was a significant predictor in the infusion group. Overall, intensive insulin RR = 0.67 (0.51-0.88, p < 0.01) was also associated with long-term mortality.		

Bibliographic Reference (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
Malmberg 2004 (Ref ID: 144a)	Analysis of DIGAMI 1 for findings regarding effects on mortality and morbidity.	For details please see above DIGAMI 1 study. The 2 groups were well balanced at the time of randomisation	For details please see above DIGAMI 1 study. **Hypoglycaemia:** blood glucose level < 3 mmol/litre with or without symptoms.	For details please see above DIGAMI 1 study.	For details please see above DIGAMI 1 study.	For details please see above DIGAMI 1 study.	**Mortality:** Overall, the intensive approach reduced the long-term relative mortality (at 3.4 years of follow-up) by 25% in the insulin treated group (p = 0.011). This corresponds to an absolute mortality reduction of 11%. **Mortality of strata 1:** At dismissal patients in strata 1 had a 58% reduction in mortality (p < 0.05). This benefit was sustained throughout follow-up with a 50% reduction at 12 months. At longer term follow-up (3.4 years) there was a highly significant 45% reduction in mortality (33% vs. 18%, p = 0.004).		The author acknowledges that as patients were given both immediate infusion and long-term metabolic control, it is impossible to determine which part contributes most to the favourable outcome or whether both elements were important.
Malmberg et al 2005	DIGAMI 2-multicentr	1253 patients were	**Hyperglycaemia:** patients	**Group 1:** Insulin-glucose	**Group 3:** the glucose	All patients were	**Mortality (intention to treat):** Overall there were 277 deaths (21.3%) and mortality did not significantly differ	The Swedish Heart-	Concomitant therapy was used

Bibliographic Reference (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
(Ref ID: X)	e, prospective, randomised open trial comparing three different management strategies in patients with type 2 diabetes and AMI.	allocated to 3 groups (group 1 = 474, group 2 = 473, and group 3 = 306). At discharge 84, 84 and 84% of patients in groups 1, 2 and 3 fulfilled the diagnosis of MI- almost all remaining patients had coronary artery disease. **Inclusion criteria:** patients with	with established type 2 diabetes or an admission blood glucose > 11.0mmol/litre were eligible for inclusion. **MI:** diagnosed according to joint recommendation of ESC and ACC. **Reinfarction:** new event > 72 hours from index infarction. **Stroke:** unequivocal signs of	infusion 500 ml 5% glucose with 80 IU of soluble insulin (~1 IU/6ml) was given with the objective to decrease blood glucose as fast as possible and keep it within 7 and 10mmol/litre. The infusion lasted until stable normoglycaemia and at least for 24 hours. Subcutaneous insulin	lowering treatment was at the discretion of the responsible physician and according to local routines. Target values were not defined in this group.	followed up for a minimum of 6 months and the maximum time of follow-up was 3 years. No patients were lost to follow-up.	between the 3 groups. After 2 years of follow-up, the Kaplan-Meier estimated mortality was 23.4% among patients in group 1 when compared with 21.2% in group 2 (HR = 1.03, CI = 0.79-1.34, p = 0.832). The corresponding proportion in group 3 was 17.9% (group 1 vs. 3 HR = 1.26, CI = 0.92-1.72, p = 0.157). Adjusted HR for difference in previous diseases between groups 1 and 3 was 1.19 (CI 0.86-1.64, p = 0.29). Comparing groups 2 and 3, the HR = 1.23 (CI 0.89-1.69, p < 0.203). Cardiovascular causes of death were most common without any significant differences among the groups, whereas a lower incidence of non-cardiovascular deaths in group 3 explained the trend towards a somewhat lower overall mortality in this group compared with groups 2 and 3 (group 1 vs. 3, p = 0.021). There was a slight difference in mortality from malignancies, with a higher incidence in group 1 (n = 16) compared with group 2 (n = 5) and group 3 (n = 2, group 1 vs. 2, p = 0.016, group 1 vs. 3, p = 0.011). **Multivariate predictors of mortality:**	Lung Foundation, AFA Insurance, The King Gustav V and Queen Victoria Foundation, The Swedish Medical Research Council, The Swedish Diabetes Association and unconditional research grants from Aventis Sweden and Novo Nordisk Denmark.	based on evidence based international guidelines for AMI. 14% of group 3 were administered insulin-glucose infusion. During follow-up, multidose insulin was used in < 50% of patients in group 1& in between 15 and 20% in groups 2 & 3 whereas ~10% in group 1

Bibliographic Reference (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
		established type 2 diabetes or an admission blood glucose > 11.0mmol/l admitted to coronary care units. **Baseline characteristics:** baseline characteristic, biochemical and clinical data were well balanced in most respects. However, there were significantly fewer	focal or global neurological deficit of sudden onset and a duration of > 24 hours that were judged to be of vascular origin. **Sudden cardiovascular deaths**: those that occurred within 24 hours following onset of symptoms and without any obvious reason for the fatal outcome.	was initiated at the cessation of infusion. Insulin was given as short-acting insulin before meals and intermediate long-acting insulin in the evening. The treatment goal in group 1 was a fasting blood glucose level of 5-7 mmol/litre and a non-			Updated blood glucose during the time of follow up (HR = 1.20 for 3mmol/litre, p < 0.001) was a significant and independent predictor together with increasing age (HR = 2.14 for 10 years, p < 0.001), previous HF (HR = 1.71, p < 0.001) and elevated serum creatinin (HR = 1.13 for 40µmol/litre, p < 0.001). **Morbidity:** There was a trend towards fewer secondary events in groups 2 and 3 compared to group 1. However, this difference did not reach statistical significance for stroke or myocardial reinfarction. The combined total event rate was high in the magnitude of 35-40% but did not significantly differ between the 3 groups. **Glucose lowering treatment and adverse events:** Blood glucose with or without symptoms < 3mmol/litre (hypoglycaemia) was more frequent during the initial 24 hours in group 1 (12.7%, symptomatic 27%) and 2 (9.6%, symptomatic 39%) than in group 3 (1.0%, symptomatic 33%). Apart from slightly but statistically significant lower blood glucose after 24 hours in groups		and ~15-20% of those in groups 2 and 3 did not receive any glucose lowering drugs. Authors concluded that DIGAMI 2 did not support the use of acute, long-term insulin treatment to improve survival in patients with type 2 diabetes and AMI when compared

Bibliographic Reference (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
		previous MIs and a trend towards less hypertension and HF in group 3. Mean age (group 1 = 68.1, group 2 = 68.6, and group 3 = 68.4). 67% were male. Blood glucose at randomisation (1 = 12.8, 2 = 12.5, 3 = 12.9, p = 0.414).	**Hypoglycaemia:** blood glucose level < 3 mmol/litre with or without symptoms.	fasting level of < 10mmol/litre. **Group 2:** initial insulin-glucose infusion was given as above and glucose lowering treatments at the discretion of the responsible physician and according to local routines. Target values were not defined in this group.			1 and 2 compared with group 3 (1 = 9.1, 2 = 9.1, 3 = 10.0, p = 0.0001), blood glucose and HbA_{1c} did not differ significantly among any of the 3 groups when comparing the area under the curve of blood glucose over time. The absolute difference between these groups and group 3 was only 0.9mmol/l. The levels did not reach the targeted level between 5 and 7mmol/litre in group 1.		with conventional management at similar levels of glucose control. However, glucose level was found to be a strong, independent predictor of long-term mortality suggesting that glucose control is still an important factor.

<table>
<tr><th>Bibliographic Reference (Ref ID)</th><th>Study type/aim</th><th>Patient characteristics</th><th>Definitions</th><th>Intervention</th><th>Comparator</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mellbin et al 2009 (Ref ID: 3363)</td><td>Analysis of DIGAMI 2 to explore whether hypoglycaemic episodes during hospitalisation had an impact on total mortality and the rate of non-fatal re-infarctions and stroke during follow-up.</td><td>See DIGAMI 2 above for details. 1253 patients randomised to 3 groups. Patients experiencing hypoglycaemia were older, had a lower body weight and body mass index and more often presented with a history of HF. Moreover they were less</td><td>See DIGAMI 2 above for details. <u>Updated hypoglycaemia:</u> relates to when the hypoglycaemic event occurred, during 0-24 hours, 24-48 hrs or 48hrs-9 days.</td><td>See DIGAMI 2 above for details. <u>Group 1:</u> 24 hour insulin-glucose infusion followed by subcutaneous insulin based long-term glucose control (n = 474). <u>Group 2:</u> Same initial treatment as group 1 followed by standard glucose control (n = 473).</td><td>See DIGAMI 2 above for details. <u>Group 3:</u> Glucose lowering treatment according to local practice (n = 306)</td><td>Patients were followed up during a median of 2.1 years (interquartile range 1.03-3.00 yrs).</td><td>Mortality & morbidity:<table><tr><th>Endpoint</th><th>Patients with Hypoglycaemia (n = 153)</th><th>Patients with symptomatic hypoglycaemia (n = 45)</th></tr><tr><td>Death</td><td>39 (25.5%)</td><td>16 (35.6%)</td></tr><tr><td>Cardiovascular death</td><td>35 (22.9%)</td><td>14 (31.1%)</td></tr><tr><td>Stroke</td><td>7 (4.6%)</td><td>3 (6.7%)</td></tr><tr><td>Re-infarction</td><td>19 (12.4%)</td><td>4 (8.9%)</td></tr></table>Besides a somewhat higher total (unadjusted HR = 1.99, CI 1.20-3.29, p = 0.0076) and cardiovascular mortality (unadjusted HR = 2.06, CI 1.20-3.53, p = 0.0009) among patients with symptomatic hypoglycaemia the event rate showed a similar pattern in those with and without hypoglycaemic episodes. However this mortality difference disappeared following adjustment for confounders (p > 0.05). <u>Predictors of subsequent</u></td><td>The Swedish Heart-Lung Foundation, AFA Insurance and unconditional research grants from Aventis Sweden and Novo Nordisk Denmark.</td><td>Further regression analyses among patients receiving glucose-insulin infusion testing an even lower cut off level 2.7 mmol/litre for hypoglycaemia did not change these results. The authors concluded that hypoglycaemia during the initial</td></tr>
</table>

Bibliographic Reference (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
		treated with lipid lowering drugs but more often with diuretics. HbA_{1c}, admission blood glucose and glucose lowering treatment at admission did not differ. The duration of diabetes was longer among patients with than those without hypoglycaemic					**<u>hypoglycaemic events:</u>** Hypoglycaemia was experienced by 153 (12%) patients out of whom 45 (29%) were symptomatic. Most episodes in insulin treated patients occurred during the first 24 hours (n = 111, 12%, symptomatic n = 26, 23%). The corresponding numbers in patients on routine treatment were three (1.0%) and one, respectively. Bodyweight (+1kg; OR 0.97, CI0.95-0.98, p < 0.0001) and diabetes duration (+1 year; OR 1.03, CI 1.01-1.05, p = 0.0085) remained independent predictors for subsequent hypoglycaemic events following a step-wise logistic regression.		hospitalisation was not an independent risk factor for future morbidity or mortality in patients with type 2 diabetes and MI. Such episodes were however, more prevalent in patients at high risk for other reasons.

Bibliographic Reference (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
		episodes							
Cheung et al 2006 (Ref ID: 103a)	The HI-5 study was a multicenter open-label randomised controlled trial aimed to determine whether tight glycaemic control improves outcomes for hyperglycaemic patients with AMI	240 patients (126 in infusion therapy group and 114 in conventional therapy group). **Inclusion criteria:** 1) evidence of AMI within last 24 hours and 2) known diabetes or not diabetic with an admission blood glucose level ≥ 7.8mmol/litre	**Hypoglycaemia:** finger prick blood glucose < 3.5mmol/l, irrespective of the occurrence of symptoms. **Reinfarction:** new AMI occurring > 72 hours following index infarct. Cardiac failure: dyspnoea with radiographic evidence of pulmonary or interstitial	**Infusion Therapy Group (ITG):** patients placed on insulin at 2 units/h and 5% dextrose at 80ml/h. Insulin was titrated to maintain blood glucose between 4 and 10mmol/litre for at least 24 hours. For patients with cardiac failure, 10% dextrose	**Conventional Therapy Group (CTG):** remained on their usual diabetes therapy but metformin was temporarily discontinued. Supplemental subcutaneous short-acting insulin was permitted if blood glucose	Patients were contacted to obtain information regarding the occurrence of cardiovascular events following discharge. Outcomes were measured during the index hospital admission and after 3 and 6 months. There	**Mortality and morbidity:** There was no difference in mortality between the groups at the inpatient stage (ITG = 4.8%, CTG = 3.5%, p = 0.75), 3 months (ITG = 7.1%, CTG = 4.4%, p = 0.42) or 6 months (ITG = 7.9%, CTG = 6.1%, p = 0.62). There was lower incidence of cardiac failure during the inpatient period (12.7 vs. 22.8%, p = 0.04) and of reinfarction within 3 months (2.4 vs. 6.1%, p = 0.05) in the ITG group. There were no other differences in any of the secondary cardiac outcomes or in the occurrence of composite end points. **Sub-group analysis by diabetes status:** Among patients with diabetes there was a lower reinfarction rate in the ITG (0 vs.7.7%, p = 0.04) and a lower occurrence of composite end points (21.9 vs. 40.4%, p = 0.03) at 3 months. There were no differences in other outcome variables. Among those without diabetes, there was an incidence of cardiac failure in the ITG during the inpatient period (11.3 vs. 27.4%, p = 0.02). There were no	National Health and Medical Research Council of Australia Project Grant and Novo Nordisk Pharmaceuticals	Data for glycaemic control in the first 24 hours were collected for 97.5% of patients. The mean 24 hr blood glucose was distributed around a median level of 8.1mmol/l so the cohort was divided into ≤ 8 mmol/l and ≥ 8.1mmol/l. The authors concluded that insulin

<table>
<tr><th>Bibliographic Reference (Ref ID)</th><th>Study type/aim</th><th>Patient characteristics</th><th>Definitions</th><th>Intervention</th><th>Comparator</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Comments</th></tr>
<tr>
<td></td>
<td></td>
<td>(140mg/dl). <u>Baseline characteristics:</u> There were no differences in baseline characteristics. There was no difference between patients given PTCA (infusion = 32%, control = 39%), thrombolysis (32% vs. 32%) or no reperfusion (37% vs. 29%). The mean age was 63 ± 11 years</td>
<td>edema. <u>Cardiogenic shock:</u> cardiac failure with a systolic blood pressure < 80mmHg. <u>Composite end point:</u> death or any major cardiac event. <u>Evidence of AMI:</u> troponin-T > 0.1 µg/l or electrographic criteria of ST elevation in two limb leads.</td>
<td>was administered at 40 ml/h. All diabetes medications were discontinued temporarily. Upon cessation of infusion, patients resumed their usual diabetes medication.</td>
<td>was > 16mmol/l.</td>
<td>was no information relating to mean follow-up period but it was reported that follow-up at 6 months was successful for 94% of subjects.</td>
<td>differences in other outcome variables
<u>Sub-group analysis by 24 hr glycaemic control</u>:
The mean 24 hour blood glucose was associated with risk of death in hospital (p = 0.03) and borderline at 6 months (p = 0.06).
<table>
<tr><th></th><th>24 hr mean blood glucose ≤ 8 mmol/l</th><th>24 hr mean blood glucose ≥ 8.1 mmol/l</th><th>Adjusted OR (CI)*</th><th>P-value</th></tr>
<tr><td>Inpatient mortality</td><td>0%</td><td>7%</td><td>7.2 (0.9-58.9)</td><td>0.07</td></tr>
<tr><td>3-month mortality</td><td>2%</td><td>9%</td><td>4.7 (1.0-22.4)</td><td>0.05</td></tr>
<tr><td>6-month</td><td>2%</td><td>11%</td><td>5.6 (1.2-26.1)</td><td>0.03</td></tr>
</table>
</td>
<td></td>
<td>infusion did not reduce short-term mortality following AMI using an intention to treat analysis. The mean duration of symptom onset to commencement of insulin was 13 hrs and this may have been too late for significant myocardial salvage. The authors concluded that a</td>
</tr>
</table>

Bibliographic Reference (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
		and 116 (48%) participants had known diabetes (all type 2). 78% were male. The baseline blood glucose was 10.8 ±4.1 in the infusion group and 11.1 ±3.5 in the control group (p = 0.23). **Stratification:** 1) known diabetes or admission blood glucose ≥ 11					mortality * adjusted for age, sex and cardiac intervention (PTCA or thrombolysis) The mortality among patients with a mean 24h blood glucose ≥ 8.1 mmol/l was higher than those with mean blood glucose ≤ 8 mmol/l. **Adverse events:** There were 13 episodes of hypoglycaemia among the ITG and 2 episodes in the CTG (p = 0.02). No patient developed significant symptoms.		variable rate insulin infusion protocol aimed at controlling hyperglycaemia did not reduce short term mortality following AMI using an intention to treat analysis.

Bibliographic Reference (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
		mmol/litre without known diabetes (n = 142). 2) admission blood glucose 7.8-11 mmol/litre without known diabetes (n = 98).							

Mortality predictor tables

Independent associations between cardiovascular risk factors and glucometabolic markers with long-term mortality by multivariate Cox regression analysis. Observational data extracted from DIGAMI 1 study

	Patient Groups					
	All (240 of 620)		**Control (138 of 314)**		**Intensive insulin (102 of 306)**	
Parameter	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Age (1 added year)	1.08 (1.06-1.11)	< 0.001	1.09 (1.06-1.12)	< 0.001	1.08 (1.05-1.12)	< 0.001
Male sex	1.12(0.82-1.54)	0.46	0.97 (0.63-1.49)	0.88	1.44 (0.88-2.32)	0.15
Previous disease Myocardial infarction	1.22 (0.87-1.70)	0.25	1.10 (0.69-1.77)	0.68	1.40 (0.86-2.28)	0.16
Congestive heart failure	2.24 (1.60-3.14)	< 0.001	2.37 (1.50-3.74)	< 0.001	2.28 (1.33-3.73)	< 0.01
Hypertension	1.01 (0.75-1.35)	0.96	1.15 (0.78-1.71)	0.48	0.86 (0.55-1.36)	0.52
Smoker	1.08 (0.69-1.68)	0.74	1.05 (0.57-1.93)	0.87	1.25 (0.62-2.52)	0.53
Diabetes duration (1 added year)	1.02 (1.01-1.03)	< 0.01	1.01 (0.99-1.03)	0.21	1.03 (1.01-1.05)	< 0.01
Admission Blood glucose +1mmol/l	1.06 (1.03-1.10)	< 0.01	1.06 (1.01-1.11)	< 0.05	1.05 (0.99-1.11)	0.065
HbA_{1c} +1%	1.09 (1.00-1.18)	0.054	1.15 (1.03-1.29)	< 0.05	1.03 (0.90-1.17)	0.66

Independent influence of different treatments on long-term mortality by multivariate Cox regression analysis correcting for age, sex and congestive heart failure during hospital stay. Observational data extracted from DIGAMI 1 study

	Patient Groups					
	All (240 of 620)		Control (138 of 314)		Intensive insulin (102 of 306)	
Parameter	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Intensive insulin treatment	0.67 (0.51-0.88)	< 0.01	-	-	-	-
Thrombolysis	0.54 (0.41-0.72)	< 0.001	0.63 (0.43-0.92)	< 0.05	0.44 (0.28-0.72)	< 0.001
β-Blockade at discharge	0.68 (0.50-0.88)	< 0.01	0.55 (0.38-0.79)	< 0.01	0.81 (0.52-1.27)	0.36
ACE inhibitor at discharge	1.36 (1.01-1.83)	< 0.05	1.50 (1.04-2.30)	< 0.05	1.20 (0.76-1.88)	0.45

Mortality when cohort divided into those with a mean glucose level in first 24 h above and below 8mmol/l. Observational data on mortality extracted from HI-5 STUDY

	24h mean BGL < 8mmol/l	24h mean BGL > 8mmol/l	Significance	Adjusted Odds ratio 95% CI	P Value
Inpatient Mortality	0	7	0.05	7.2(0.9-58.9)	0.07
3month mortality	2	9	0.05	4.7(1.0-22.4)	0.05
6 month mortality	2	11	0.02	5.6(1.2-26.1)	0.03

Adjusted for age, gender and cardiac intervention (PTCA or Thrombolysis)

Mortality when cohort divided into those with a glucose level below 8mmol/l seven out of eight times and above 8mmol/l on more than 20% of the time when measured at 8 standard time points in the first 24 hours (0700, 0900,1200,1400,1700,1900,2200,0300). Observational data on mortality extracted from HI-5 STUDY

	Below 8mmol/l 7/8 times	Above 8mmol/l on more than 20% of the time	P Value
Inpatient mortality	0%	5.4%	0.053
3 month mortality	1.5%	7.2%	0.08
6 month mortality	1.6%	9.1%	0.047

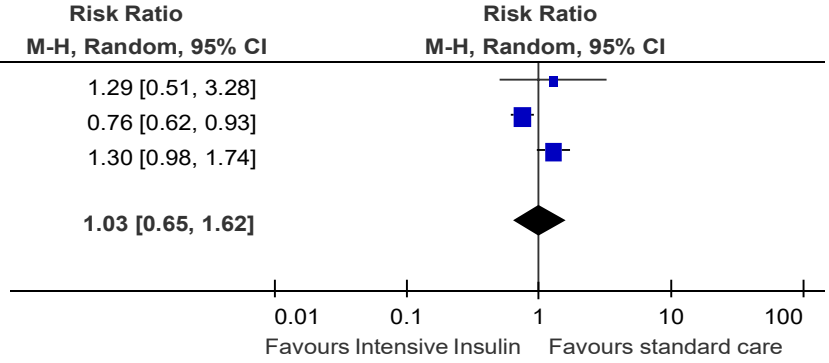
Adjusted for age, gender, diabetes status, creatine kinase, ST elevation infarct and randomisation group

Forest Plots for Review Question 1

Overall Mortality

Study or Subgroup	Intensive Insulin therapy Events	Total	Standard Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cheung 2006(103a)	10	126	7	114	16.0%	1.29 [0.51, 3.28]
Malmberg 1996(378)	102	306	138	314	43.8%	0.76 [0.62, 0.93]
Malmberg 2005(RefID)	111	474	55	306	40.2%	1.30 [0.98, 1.74]
Total (95% CI)		**906**		**734**	**100.0%**	**1.03 [0.65, 1.62]**
Total events	223		200			

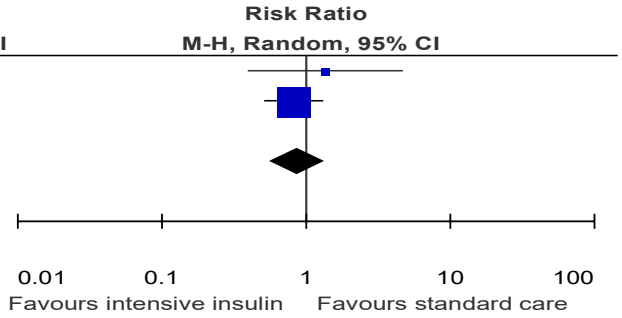
Heterogeneity: Tau² = 0.11; Chi² = 9.78, df = 2 (P = 0.008); I² = 80%
Test for overall effect: Z = 0.11 (P = 0.91)



Inpatient Mortality

Study or Subgroup	Intensive Insulin therapy Events	Total	Standard Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cheung 2006(103a)	6	126	4	114	12.6%	1.36 [0.39, 4.69]
Malmberg 1995(396)	28	306	35	314	87.4%	0.82 [0.51, 1.32]
Total (95% CI)		**432**		**428**	**100.0%**	**0.87 [0.56, 1.36]**
Total events	34		39			

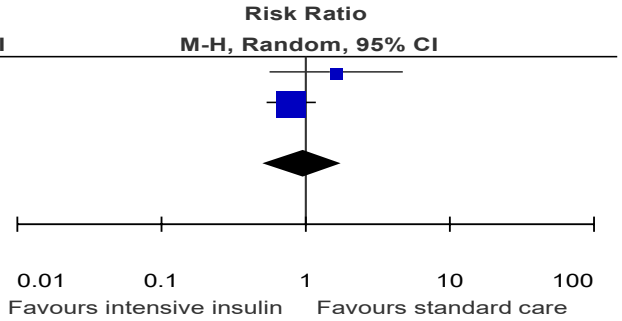
Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)



Three month Mortality

Study or Subgroup	Intensive Insulin therapy Events	Total	Standard Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cheung 2006(103a)	9	126	5	114	25.3%	1.63 [0.56, 4.72]
Malmberg 1995(396)	38	306	49	314	74.7%	0.80 [0.54, 1.18]
Total (95% CI)		**432**		**428**	**100.0%**	**0.95 [0.52, 1.76]**
Total events	47		54			

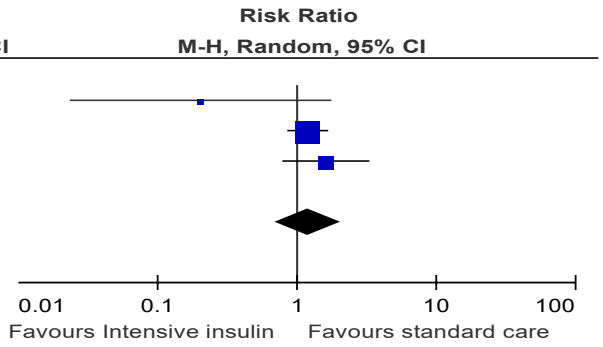
Heterogeneity: Tau² = 0.09; Chi² = 1.54, df = 1 (P = 0.22); I² = 35%
Test for overall effect: Z = 0.15 (P = 0.88)



Reinfarction

Study or Subgroup	Intensive Insulin therapy Events	Total	Standard Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cheung 2006(103a)	1	64	4	52	5.7%	0.20 [0.02, 1.76]
Malmberg 1996(378)	53	253	55	314	61.3%	1.20 [0.85, 1.68]
Malmberg 2005(RefID)	25	474	10	306	33.0%	1.61 [0.79, 3.31]
Total (95% CI)		**791**		**672**	**100.0%**	**1.19 [0.70, 2.04]**
Total events	79		69			

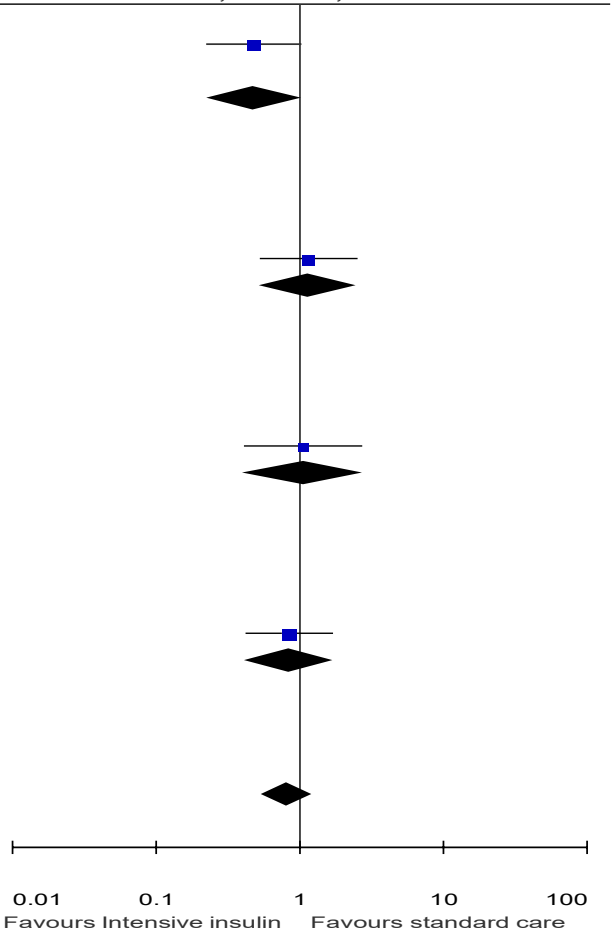
Heterogeneity: Tau² = 0.09; Chi² = 3.24, df = 2 (P = 0.20); I² = 38%
Test for overall effect: Z = 0.65 (P = 0.52)



Three month mortality of subgroups stratified by risk

Study or Subgroup	Intensive Insulin therapy Events	Total	Standard Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 no insulin low risk						
Malmberg 1995(396)	9	139	18	133	26.4%	0.48 [0.22, 1.03]
Malmberg 1995(396)	0	0	0	0		Not estimable
Subtotal (95% CI)		**139**		**133**	**26.4%**	**0.48 [0.22, 1.03]**
Total events	9		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.89 (P = 0.06)						
1.5.2 no insulin high risk						
Malmberg 1995(396)	11	63	10	66	25.1%	1.15 [0.53, 2.52]
Subtotal (95% CI)		**63**		**66**	**25.1%**	**1.15 [0.53, 2.52]**
Total events	11		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.35 (P = 0.72)						
1.5.3 prev insulin low risk						
Malmberg 1995(396)	7	54	8	65	17.1%	1.05 [0.41, 2.72]
Subtotal (95% CI)		**54**		**65**	**17.1%**	**1.05 [0.41, 2.72]**
Total events	7		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.11 (P = 0.91)						
1.5.4 prev insulin high risk						
Malmberg 1995(396)	11	50	13	50	31.4%	0.85 [0.42, 1.71]
Subtotal (95% CI)		**50**		**50**	**31.4%**	**0.85 [0.42, 1.71]**
Total events	11		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
Total (95% CI)		**306**		**314**	**100.0%**	**0.82 [0.55, 1.21]**
Total events	38		49			

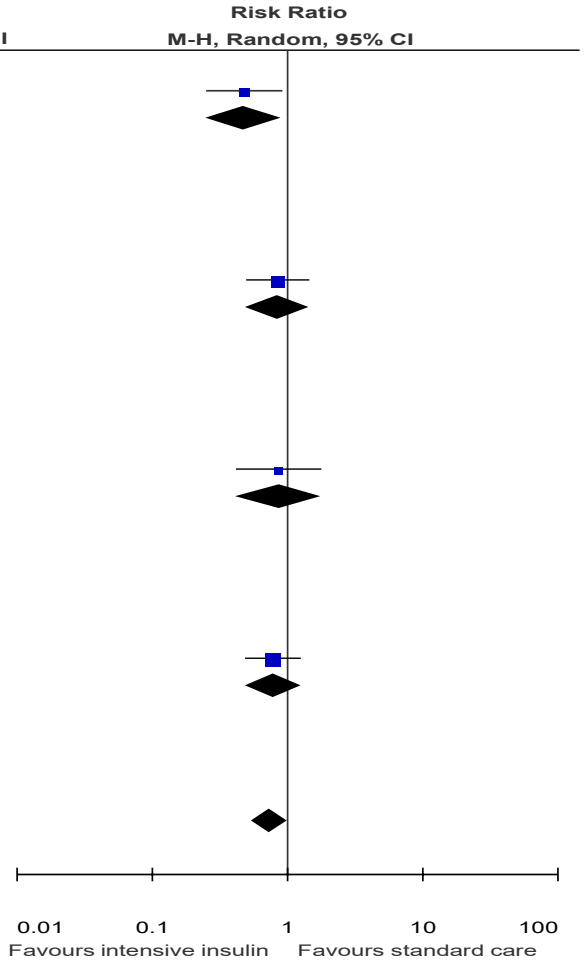
Heterogeneity: Tau² = 0.00; Chi² = 2.92, df = 3 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)



One year mortality of subgroups stratified by risk

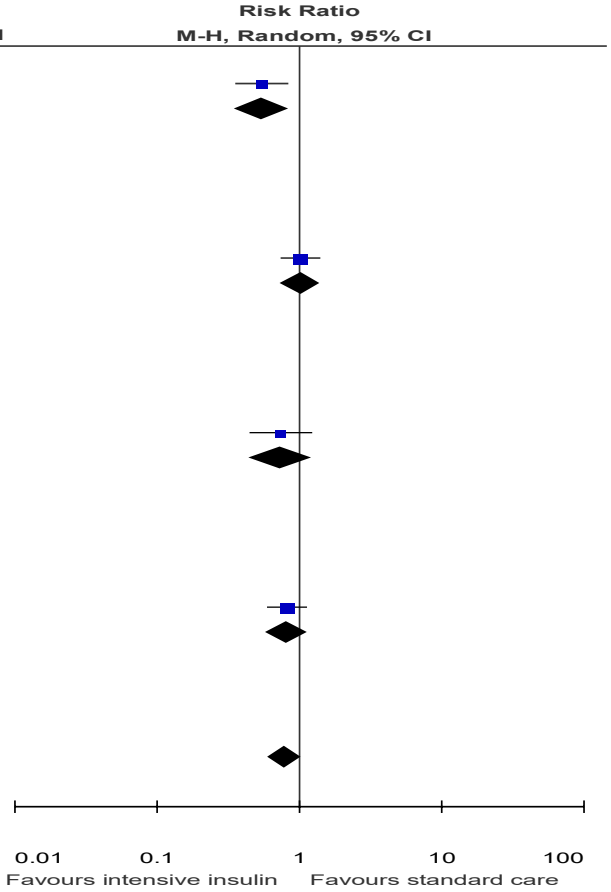
Study or Subgroup	Intensive Insulin therapy Events	Total	Standard Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 no insulin low risk						
Malmberg 1995(396)	12	139	24	133	19.5%	0.48 [0.25, 0.92]
Subtotal (95% CI)		**139**		**133**	**19.5%**	**0.48 [0.25, 0.92]**
Total events	12		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.22 (P = 0.03)						
1.6.2 no insulin high risk						
Malmberg 1995(396)	17	63	21	66	28.5%	0.85 [0.50, 1.45]
Subtotal (95% CI)		**63**		**66**	**28.5%**	**0.85 [0.50, 1.45]**
Total events	17		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
1.6.3 prev insulin low risk						
Malmberg 1995(396)	10	54	14	65	15.6%	0.86 [0.42, 1.78]
Subtotal (95% CI)		**54**		**65**	**15.6%**	**0.86 [0.42, 1.78]**
Total events	10		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
1.6.4 prev insulin high risk						
Malmberg 1995(396)	18	50	23	50	36.4%	0.78 [0.49, 1.26]
Subtotal (95% CI)		**50**		**50**	**36.4%**	**0.78 [0.49, 1.26]**
Total events	18		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
Total (95% CI)		**306**		**314**	**100.0%**	**0.74 [0.55, 0.98]**
Total events	57		82			

Heterogeneity: Tau² = 0.00; Chi² = 2.22, df = 3 (P = 0.53); I² = 0%
Test for overall effect: Z = 2.07 (P = 0.04)
Test for subgroup differences: Not applicable



Long term mortality (follow up 3.4 years) of subgroups stratified by risk

Study or Subgroup	Intensive Insulin therapy Events	Total	Standard Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 no insulin low risk						
Malmberg 1995(396)	25	139	44	133	22.2%	0.54 [0.35, 0.84]
Subtotal (95% CI)		**139**		**133**	**22.2%**	**0.54 [0.35, 0.84]**
Total events	25		44			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.78 (P = 0.005)						
1.7.2 no insulin high risk						
Malmberg 1995(396)	34	63	35	66	30.0%	1.02 [0.74, 1.40]
Subtotal (95% CI)		**63**		**66**	**30.0%**	**1.02 [0.74, 1.40]**
Total events	34		35			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.11 (P = 0.91)						
1.7.3 prev insulin low risk						
Malmberg 1995(396)	16	54	26	65	18.0%	0.74 [0.45, 1.23]
Subtotal (95% CI)		**54**		**65**	**18.0%**	**0.74 [0.45, 1.23]**
Total events	16		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.16 (P = 0.25)						
1.7.4 prev insulin high risk						
Malmberg 1995(396)	27	50	33	50	29.8%	0.82 [0.59, 1.13]
Subtotal (95% CI)		**50**		**50**	**29.8%**	**0.82 [0.59, 1.13]**
Total events	27		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.21 (P = 0.22)						
Total (95% CI)		**306**		**314**	**100.0%**	**0.78 [0.60, 1.02]**
Total events	102		138			
Heterogeneity: Tau² = 0.03; Chi² = 5.65, df = 3 (P = 0.13); I² = 47%						
Test for overall effect: Z = 1.81 (P = 0.07)						
Test for subgroup differences: Not applicable						



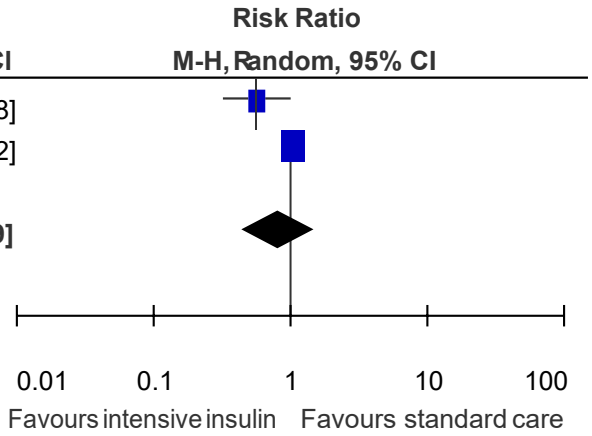
High risk: At least two of the following: Above 70 years, previous Myocardial infarction, previous congestive heart failure and current treatment with digitalis(digoxin)

Heart Failure

Study or Subgroup	Intensive Insulin therapy Events	Total	Standard Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cheung 2006(103a)	16	126	26	114	40.4%	0.56 [0.32, 0.98]
Malmberg 1995(396)	153	306	151	314	59.6%	1.04 [0.89, 1.22]
Total (95% CI)		**432**		**428**	**100.0%**	**0.81 [0.44, 1.49]**
Total events	169		177			

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 4.42$, df = 1 (P = 0.04); $I^2 = 77\%$

Test for overall effect: Z = 0.68 (P = 0.49)

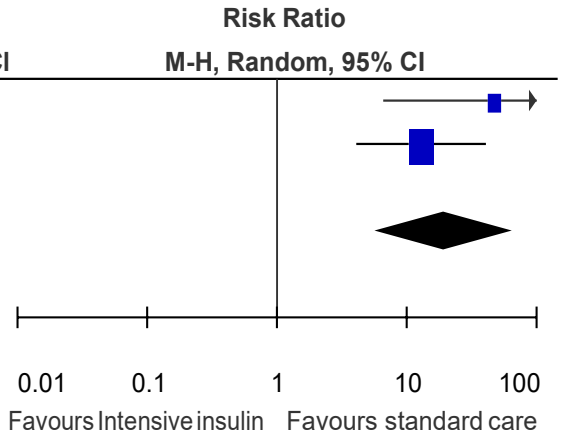


Hypoglycaemia after 24 hours

Study or Subgroup	Intensive Insulin therapy Events	Total	Standard Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Malmberg 1995(396)	46	306	1	315	31.0%	47.35 [6.57, 341.22]
Malmberg 2005(RefID)	60	474	3	306	69.0%	12.91 [4.09, 40.80]
Total (95% CI)		**780**		**621**	**100.0%**	**19.32 [5.79, 64.41]**
Total events	106		4			

Heterogeneity: Tau² = 0.20; Chi² = 1.30, df = 1 (P = 0.25); I² = 23%

Test for overall effect: Z = 4.82 (P < 0.00001)

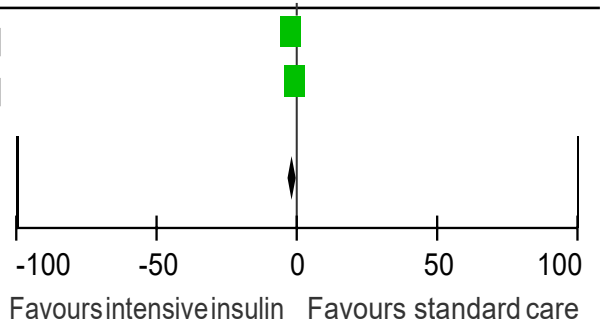


Difference in Blood glucose levels after 24 hours

	Intensive insulin			standard care				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
Malmberg 1995(396)	9.6	3.3	306	11.7	4.1	314	49.0%	-2.10 [-2.69, -1.51]	
Malmberg 2005(RefID)	9.1	3	474	10	3.6	306	51.0%	-0.90 [-1.39, -0.41]	
Total (95% CI)			**780**			**620**	**100.0%**	**-1.49 [-2.66, -0.31]**	

Heterogeneity: Tau² = 0.64; Chi² = 9.57, df = 1 (P = 0.002); I² = 90%

Test for overall effect: Z = 2.48 (P = 0.01)



Review question 2: What is the optimal inpatient metabolic management of patients presenting with hyperglycaemia and acute coronary syndrome (ACS) without a diagnosis of diabetes mellitus?

Evidence table 2

<table>
<tr><th>Study ref (Ref ID)</th><th>Study type/aim</th><th>Patient characteristics</th><th>Definitions</th><th>Intervention</th><th>Comparator</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Comments</th></tr>
<tr>
<td>Weston et al 2007 (Ref ID:312a)</td>
<td>An observational study from the MINAP database to determine the effect of insulin for the management of hyperglycaemia in non-diabetic patients with ACS.</td>
<td>2642 patients (any insulin treatment = 872, no treatment = 1770). The following patient characteristics were reported mean age (insulin = 72 yrs, no treatment = 76 yrs). Admission blood glucose was also recorded for each group; insulin = 14.8 mmol/l (12.3-18.6), no</td>
<td><u>Hyperglycaemia:</u> study included patients without a diagnosis of diabetes and who presented to hospital with ACS and an admission blood glucose of ≥ 11.0 mmol/l</td>
<td><u>Insulin:</u> The majority of those receiving insulin were given the DIGAMI insulin/glucose regime 607/872 (69.6%) or an insulin pump 225/872 (25.8%). The remaining 40 (4.6%) insulin treated patients</td>
<td><u>No treatment:</u> no diabetic treatment in hospital and treatment strategy was not recorded.</td>
<td>There was an absence of follow-up data so analyses of outcomes were based on an assumption that medication prescribed at discharge was continued after discharge.</td>
<td><u>Mortality at 7 and 30 days:</u>
In order to negate any bias resulting from deaths occurring prior to treatment or before any potential treatment effect of insulin had occurred, regression analyses were also performed after excluding 79 deaths occurring on the day of admission (median interval 12 hours). The adjusted RR of death was slightly reduced, but remained statistically significant (see table below).
<table>
<tr><th>All deaths</th><th>No treatment (%)</th><th>Insulin</th><th>RR</th><th>Adjusted RR*</th><th>P-value</th></tr>
<tr><td>7 days</td><td>290/1761 (16.5)</td><td>101/868 (11.6)</td><td>1.42</td><td>1.56</td><td>< 0.001</td></tr>
<tr><td>30 days</td><td>389/1761 (22.1)</td><td>137/868 (15.8)</td><td>1.40</td><td>1.51</td><td>< 0.001</td></tr>
<tr><td colspan="6">Deaths on day of admission excluded</td></tr>
</table>
</td>
<td>The Healthcare Commissions.</td>
<td>Mortality at 7 and 30 days compared those who were treated with insulin (this was by any regime) with those who did not receive any treatment and those who did not have treatment recorded. The authors concluded that non-diabetic patients presenting with hyperglycaemia in association with ACS have</td>
</tr>
</table>

<table>
<tr><th>Study ref (Ref ID)</th><th>Study type/aim</th><th>Patient characteristics</th><th>Definitions</th><th>Intervention</th><th>Comparator</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Comments</th></tr>
<tr>
<td></td>
<td></td>
<td>treatment = 12.9 (11.7-14.9) and treatment strategy not recorded = 13.0 (12.0-16.0). Gender, ST elevation infarction, length of stay, admission cholesterol, heart rate on admission, blood pressure and current smoking habits are also presented</td>
<td></td>
<td>received single dose insulin regimes.</td>
<td></td>
<td></td>
<td>
<table>
<tr><td>1-7 days</td><td>228/1682 (13.6)</td><td>80/841 (9.5)</td><td>1.43</td><td>1.43</td><td>0.011</td></tr>
<tr><td>1-30 days</td><td>327/1682 (19.4)</td><td>116/841 (13.8)</td><td>1.41</td><td>1.41</td><td>0.004</td></tr>
</table>
* adjustments for age, gender, HF, renal failure, admission blood glucose, presence of ST elevation infarction and history of previous angina or MI

The effect of insulin treatment on risk of death was examined separately for ST segment (STEMI) and non-ST segment elevation infarction (NSTEMI).
7 and 30 day mortality by AMI type:
<table>
<tr><th>MI type</th><th>No treatment (%)</th><th>Insulin (%)</th><th>RR</th><th>Adjusted RR</th><th>P-value</th></tr>
<tr><td>STEMI (7 days)</td><td>164/755 (21.7)</td><td>67/509 (13.2)</td><td>1.64</td><td>1.62</td><td>0.003</td></tr>
<tr><td>STEMI (30 days)</td><td>193/755 (25.6)</td><td>80/509 (15.7)</td><td>1.63</td><td>1.58</td><td>0.002</td></tr>
<tr><td>NSTEMI (7 days)</td><td>126/1006 (12.5)</td><td>34/359 (9.5)</td><td>1.32</td><td>1.30</td><td>0.211</td></tr>
<tr><td>NSTEMI (30 days)</td><td>196/1006 (19.5)</td><td>57/359 (15.9)</td><td>1.23</td><td>1.25</td><td>0.188</td></tr>
</table>
</td>
<td></td>
<td>a better short-term prognosis when they are treated with insulin.</td>
</tr>
</table>

Study ref (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
							* covariates as described above were used for adjustments. For STEMI patients the use of reperfusion was added as they were more likely to receive reperfusion. The crude mortality was greater in both groups for patients who did not receive insulin, but the mortality difference between insulin-treated and those without treatment was more marked for patients with STEMI. The adjusted RR for those with NSTEMI who did not receive insulin was also greater, but this did not achieve statistical significance.		

Study ref (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
Cheung et al 2006 (Ref ID: 103a)	The HI-5 study was a multicenter open-label randomised controlled trial aimed to determine whether tight glycaemic control improves outcomes for hyperglycaemic patients with AMI	240 patients (126 in infusion therapy group and 114 in conventional therapy group). **Inclusion criteria:** 1) evidence of AMI within last 24 hours and 2) known diabetes or not diabetic with an admission blood glucose level ≥ 7.8mmol/litre (140mg/dl). **Baseline characteristics:** There were no differences in baseline characteristics. There was no difference between patients given	**Hypoglycaemia:** finger prick blood glucose < 3.5mmol/l, irrespective of the occurrence of symptoms. **Reinfarction:** new AMI occurring > 72 hours following index infarct. Cardiac failure: dyspnoea with radiographic evidence of pulmonary or interstitial edema. **Cardiogenic shock:** cardiac	**Infusion Therapy Group (ITG):** patients placed on insulin at 2 units/h and 5% dextrose at 80ml/h. Insulin was titrated to maintain blood glucose between 4 and 10mmol/litre for at least 24 hours. For patients with cardiac failure, 10% dextrose was administered at 40	**Conventional Therapy Group (CTG):** remained on their usual diabetes therapy but metformin was temporarily discontinued. Supplemental subcutaneous short-acting insulin was permitted if blood glucose was > 16mmol/l	Patients were contacted to obtain information regarding the occurrence of cardiovascular events following discharge. Outcomes were measured during the index hospital admission and after 3 and 6 months. There was no information relating to mean follow-up period but	**Sub-group analysis by diabetes status:** Among patients with diabetes there was a lower reinfarction rate in the ITG (0 vs.7.7%, p = 0.04) and a lower occurrence of composite end points (21.9 vs. 40.4%, p = 0.03) at 3 months. There were no differences in other outcome variables. Among those without diabetes, there was an incidence of cardiac failure in the ITG during the inpatient period (11.3 vs. 27.4%, p = 0.02). There were no differences in other outcome variables	National Health and Medical Research Council of Australia Project Grant and Novo Nordisk Pharmaceuticals	Data for glycaemic control in the first 24 hours were collected for 97.5% of patients. The mean 24 hr blood glucose was distributed around a median level of 8.1mmol/l so the cohort was divided into ≤ 8 mmol/l and ≥ 8.1mmol/l. The authors concluded that insulin infusion did not reduce short-term mortality following AMI using an intention to treat analysis. The mean duration of symptom onset to

Study ref (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
		PTCA (infusion = 32%, control = 39%), thrombolysis (32% vs. 32%) or no reperfusion (37% vs. 29%). The mean age was 63 ± 11 years and 116 (48%) participants had known diabetes (all type 2). 78% were male. The baseline blood glucose was 10.8 ±4.1 in the infusion group and 11.1 ±3.5 in the control group (p = 0.23). **Stratification:** 1) known diabetes or admission	failure with a systolic blood pressure < 80mmHg. **Composite end point:** death or any major cardiac event. **Evidence of AMI:** troponin-T > 0.1 µg/l or electrographic criteria of ST elevation in two limb leads.	ml/h. All diabetes medications were discontinued temporarily. Upon cessation of infusion, patients resumed their usual diabetes medication.		at 3 months 125 and 112 patients in the intervention and standard care group were assessed and at 6 months 121 and 109 were assessed in the intervention and standard care group.			commencement of insulin was 13 hrs and this may have been too late for significant myocardial salvage. The authors concluded that a variable rate insulin infusion protocol aimed at controlling hyperglycaemia did not reduce short term mortality following AMI using an intention to treat analysis.

Study ref (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
		blood glucose ≥ 11 mmol/litre without known diabetes (n = 142). 2) admission blood glucose 7.8-11 mmol/litre without known diabetes (n = 98).							
Van der Horst et al 2003 (Ref ID: 5001)	Single-center randomised controlled trial to investigate whether adjunction of glucose-insulin-potassium (GIK) infusion to primary coronary transluminal angioplasty (PTCA) is	940 patients (infusion = 476, control = 464). **Inclusion criteria:** all patients with symptoms consistent with AMI of > 30 mins, presenting within 24 hours after the onset of symptoms and with ST elevation of more than		**GIK infusion:** a continuous infusion of 80 mmol potassium chloride in 500ml 20% glucose with a rate of 3 ml/kg body weight /hr over an 8 to 12 hr period was given as	**Non-infusion group:** no details given	Main outcome was 30-day mortality. No further details were given on mean follow-up period.	Results are based on sub-group analysis by diabetes status, however outcomes for reinfarction and composite end-point are based on all patients **30-day mortality:** 23 patients (4.8%) in the GIK group vs. 27 (5.8%) in the control group had died at 30 days (RR 0.82, CI 0.46-1.46, p = 0.50). In 856/940 patients without signs of heart failure (Killip class 1), the mortality rate was 5/426 (1.2%) in the GIK group versus 18/430 patients (4.2%) in the control group (RR 0.28, CI 0.1-0.75, p = 0.01). In this subgroup of patients, a higher number of patients died of HF in the control group (0.7% in GIK group vs. 2.8% in the control group). Non-significant differences between the GIK and control groups were also found for sub groups based on age (< 60 years and ≥ 60	Not reported.	The authors concluded that GIK as adjunctive therapy to PTCA in AMI did not result in a significant mortality reduction in all patients. However, in the large subgroup of patients without signs of HF (over 90% of the population), a significant

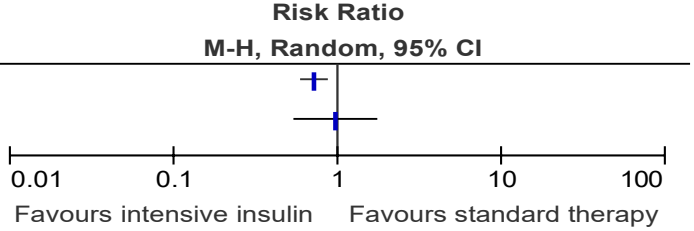
Study ref (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
	effective in patients with AMI.	1mm in 2 or more leads or new onset left bundle branch block were evaluated for inclusion. **Baseline characteristics:** With the exception of male gender, there were no statistically significant differences between both groups. After coronary angioplasty, 90.5% underwent PTCA, 4% were referred for CABG within 7 days after initial stabilisation and 4.5% were treated conservatively		soon as possible. A continuous infusion of short acting insulin (50 U Actrapid HM, Novo Nordisk, Copenhagen Denmark) in 50 ml 0.9% sodium chloride was started using a pump (Perfusor-FM, B. Braun Germany). Baseline infusion-infusion dose and hourly adjustment			years), gender, time to admission (≤ 180 mins and > 180 mins) and diabetes status (with diabetes RR = 0.30, 0.06-1.56, p = 0.16, without diabetes RR = 0.97, 0.52-1.81, p = 1.00). **Clinical end-points at 30 days:** There were no significant differences between the GIK group and control group in terms of recurrent infarction (adj RR 0.42, CI 0.12-1.5, p = 0.19), repeat angioplasty (adj RR 0.74, CI 0.38-1.44, p = 0.37) and composite end point (adj RR 0.68, CI 0.44-1.05, p = 0.08). However, In patients without HF (Killip class 1), the composite end point showed a significant advantage of GIK (adj RR 0.47, CI 0.27-0.83, p = 0.01). In this group without HF there was also a beneficial effect of GIK on mortality (adj RR 0.28, CI 0.10-0.77, p = 0.01). **Adverse events:** Side effects such as hypoglycaemia, hyperkaliemia and severe phlebitis were not observed. **Blood glucose levels:** There were no major differences in blood glucose levels between the GIK group and control group at admission (median blood glucose 8.5 mmol/l in both groups) and 16 hours after admission (median blood glucose 7.7 mmol/l in the GIK and 8.1 mmol/l in the control group)		reduction was seen.

Study ref (Ref ID)	Study type/aim	Patient characteristics	Definitions	Intervention	Comparator	Length of follow-up	Outcome measures and effect size	Source of funding	Comments
		(there were no sig differences between groups). 50 (10.5%) in infusion group and 49 (10.6%) in control group had diabetes.		s of the insulin dose were based on a normogram to obtain blood glucose levels between 7.0 and 11.0 mmol/l.					

Forest plots for Review Question 2

Forest plot of 30 day mortality in patients without diagnosed diabetes

Study or Subgroup	Intensive insulin Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
MINAP (Weston 2007)	116	841	327	1682		0.71 [0.58, 0.86]
Van Der Horst 2003	21	426	21	415		0.97 [0.54, 1.76]

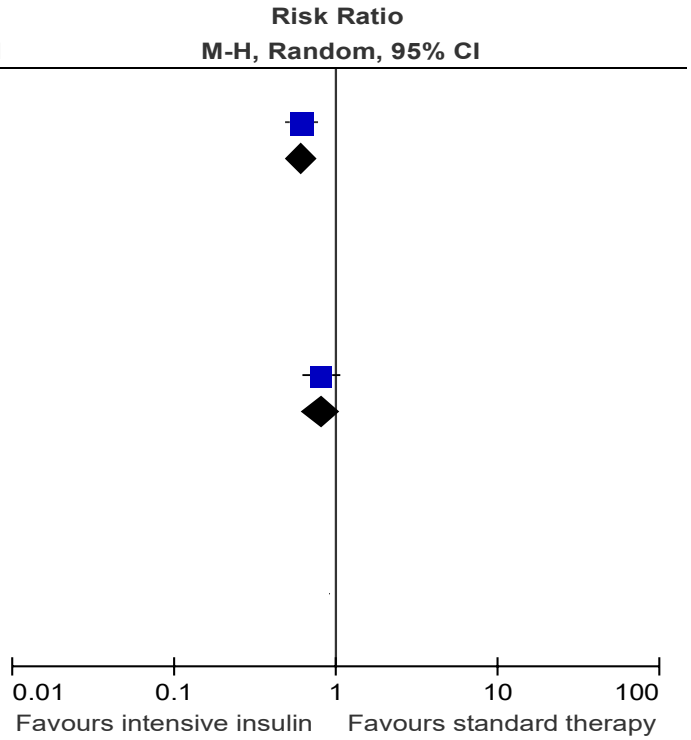


Interpretation

The forest plot above shows a significant 29% reduction in mortality in patients without diabetes who were administered intensive insulin in comparison to standard therapy using observational data from MINAP (deaths on day of admission were excluded). However, the RCT (Van der Horst 2003) shows no significant reduction in mortality in patients without previous diabetes who were given intensive insulin in comparison to standard therapy. The HI-5 study (Cheung et al 2006) reported that subgroup analysis by diabetes status showed no differences in mortality at any stage. These studies were not combined to provide a single summary estimate as there is a high risk of heterogeneity. The intervention in the Van der Horst paper was glucose-insulin-potassium infusion while the MINAP cohort received any insulin intervention (approx 70% were given the glucose-insulin regime as used in the DIGAMI study). It should also be noted that the relative risks used in the forest plot relate to crude unadjusted estimates (available adjusted values will be presented in GRADE where possible).

Forest plot of 30 day mortality, sub-grouped by type of infarction

Study or Subgroup	Intensive insulin Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 STEMI						
MINAP (Weston 2007)	80	509	193	755	52.8%	0.61 [0.49, 0.78]
Subtotal (95% CI)		**509**		**755**	**52.8%**	**0.61 [0.49, 0.78]**
Total events	80		193			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.05 (P < 0.0001)						
1.3.2 NSTEMI						
MINAP (Weston 2007)	57	359	196	1006	47.2%	0.81 [0.62, 1.07]
Subtotal (95% CI)		**359**		**1006**	**47.2%**	**0.81 [0.62, 1.07]**
Total events	57		196			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.49 (P = 0.14)						

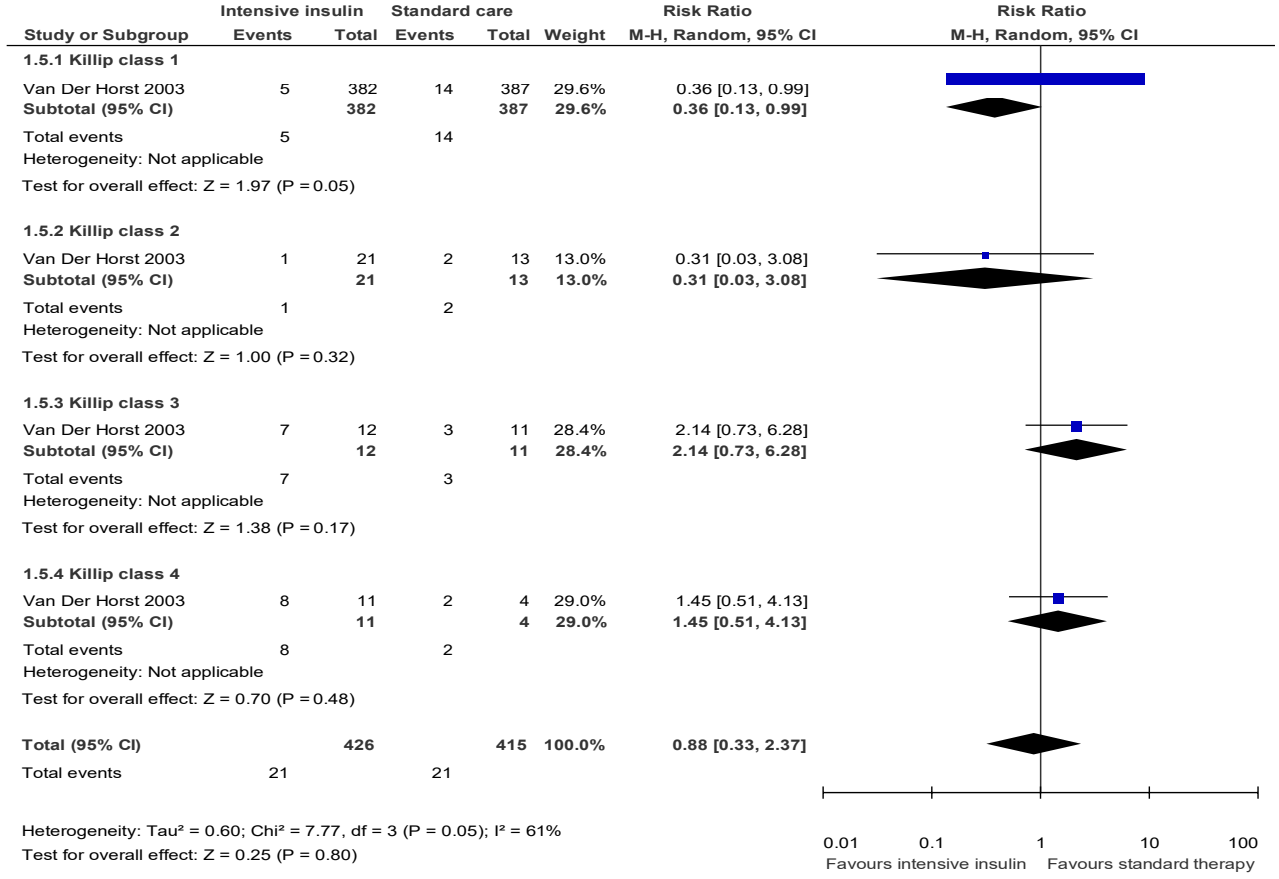


Interpretation

The forest plot above illustrates a statistically significant 39% reduction in overall mortality (after 30 days) in patients who had a STEMI and were administered intensive insulin in comparison to no diabetic therapy. There was no significant effect for patients who had an NSTEMI. Th is suggests that intensive therapy may be more effective in reducing mortality in patients who have had a STEMI in comparison to an NSTEMI.

However, it should be noted that this is a sub-group analysis from a single observational study and may be prone to bias, therefore needs to be interpreted with caution. The relative risks used in the forest plot relate to crude unadjusted estimates.

Forest plot of 30 day mortality, sub-grouped by Killip class

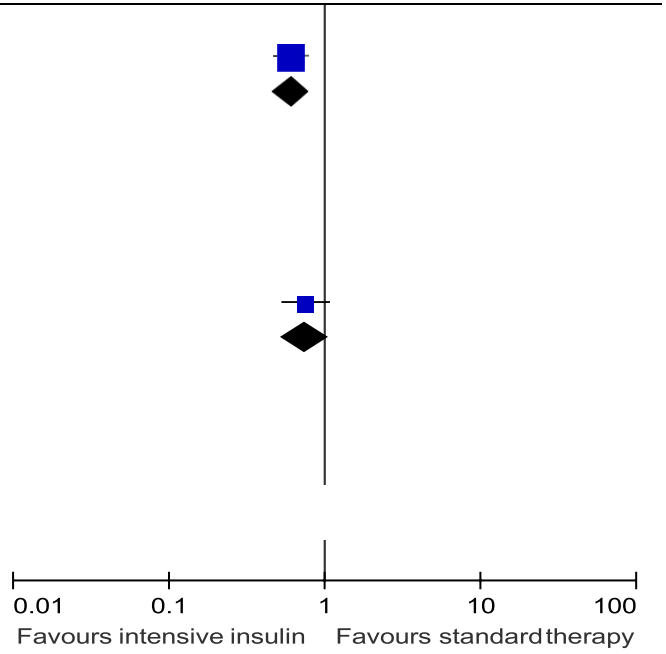


Interpretation

The forest plot above shows that the only statistically significant reduction in mortality occurred in patients without previous diabetes who were classified as having Killip class 1 (no clinical signs of heart failure). The other groups (that indicate increasing risk of heart failure) showed no significant effect of intensive insulin on risk of death. As above it should be noted that this is a sub-group analysis from a single trial and may be prone to bias, therefore needs to be interpreted with caution. The relative risks used in the forest plot relate to crude unadjusted estimates.

Forest plot of 7 day mortality by type of infarction

Study or Subgroup	Intensive insulin Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 STEMI						
MINAP (Weston 2007)	67	509	164	755	65.4%	0.61 [0.47, 0.79]
Subtotal (95% CI)		**509**		**755**	**65.4%**	**0.61 [0.47, 0.79]**
Total events	67		164			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.76 (P = 0.0002)						
1.4.2 NSTEMI						
MINAP (Weston 2007)	34	359	126	1006	34.6%	0.76 [0.53, 1.08]
Subtotal (95% CI)		**359**		**1006**	**34.6%**	**0.76 [0.53, 1.08]**
Total events	34		126			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.53 (P = 0.13)						



Interpretation

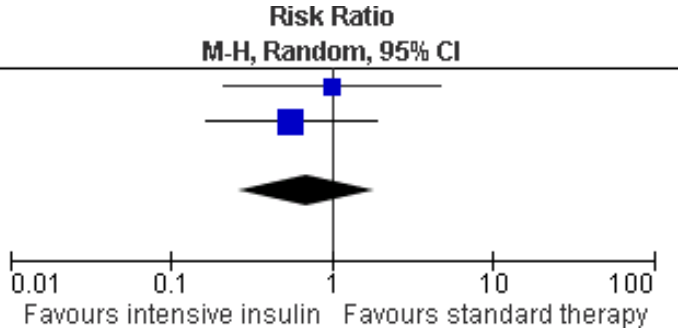
The forest plot above shows a significant 39% reduction in mortality at 7 days in patients who had a STEMI and were administered intensive insulin in comparison to standard therapy. There was no significant reduction in mortality for patients who had a NSTEMI and were given intensive insulin treatment in comparison to standard therapy. This is a sub-group analysis from a single observational study and may be prone to bias. It should also be noted that the relative risks used in the forest plot relate to crude unadjusted estimates.

Forest plot of reinfarction (after up to 3 months)

	Intensive insulin		Standard therapy			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
HI-5 (Cheung 2006)	3	62	3	62	38.0%	1.00 [0.21, 4.76]
Van Der Horst 2003	4	476	7	464	62.0%	0.56 [0.16, 1.89]
Total (95% CI)		**538**		**526**	**100.0%**	**0.70 [0.27, 1.82]**
Total events	7		10			

Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%

Test for overall effect: Z = 0.74 (P = 0.46)



Interpretation

The forest plot above shows no significant reduction in reinfarction. It should be noted that for this outcome the Van der Horst paper included some patients with diabetes (10%, n = 99) and crude unadjusted estimates of relative risks have been presented here for this study.

Review question 3: At what stage should patients with hyperglycaemia and ACS without diagnosed diabetes be referred for subsequent investigations for possible diabetes?

Evidence table 3

<table>
<tr><th>Bibliography (Ref ID)</th><th>Study type/aim</th><th>Number of patients and characteristics</th><th>Definitions and outcome measures</th><th>Risk factors/results</th><th>Length of follow-up</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr>
<td>Tenerz et al 2003 (1593)</td>
<td>To characterise the glucometabolic profile of patients with AMI without diabetes and to see if sustained glucometabolic perturbations are predictable during the hospital phase of the disease.</td>
<td>145 patients with AMI and no previous diagnosis of diabetes were defined as having normal glucose tolerance (NGT, 34%, n = 61, mean age 50), impaired glucose tolerance (IGT, 41%, n = 59, mean age 64) or diabetes (25%, n = 36, mean age 65). Treatment for hypertension</td>
<td>During hospitalisation FBG was measured on first morning after admission. OGTT performed immediately before discharge (usually on day 5) and repeated 3 months after hospital discharge. OGTT including FBG and blood glucose measurement after 60 (BG-60) and 120 mins (BG-120). Classifications were based on</td>
<td><u>Blood glucose levels at admission (first morning) and discharge (usually day 5)</u>
<table>
<tr><th>Blood glucose (mmol/litre)</th><th>NGT</th><th>IGT</th><th>Diabetes</th><th>P valu</th></tr>
<tr><td>Admission</td><td>6.0 (1.4)</td><td>6.2 (1.6)</td><td>7.1 (2.2)</td><td>0.04</td></tr>
<tr><td>Discharge</td><td>5.0 (0.65)</td><td>5.1 (.93</td><td>5.6 (0.83</td><td>0.00</td></tr>
</table>
Data are median (interquartile range)
Blood glucose for all patients taken together decreased during hospital stay with no further decrease until follow-up.
<u>Results of OGTT in patients with AMI at discharge from hospital and 3 months after (n = 142)</u>
<table>
<tr><th></th><th></th><th colspan="3">OGTT at 3 months</th></tr>
<tr><th></th><th>OGTT at discharge</th><th>NGT</th><th>IGT</th><th>Diabetes</th></tr>
<tr><td>NGT</td><td>48 (100)</td><td>23 (48)</td><td>23 (48)</td><td>2 (4)</td></tr>
<tr><td>IGT</td><td>47 (100)</td><td>18 (38)</td><td>21 (45)</td><td>8 (17)</td></tr>
<tr><td>Diabetes</td><td>47 (100)</td><td>7 (15)</td><td>15 (32)</td><td>25 (53)</td></tr>
</table>
Data are n (%)</td>
<td>3 month follow-up (142 results available for OGTT after 3 months- no further details given for drop-outs)</td>
<td>Swedish Heart-Lung Foundation, the Swedish Medical Research Council and the Center for Clinical Research, Central Hospital, Vasteras, Uppsala University, the research foundation of Vastmanland county council, the Karolinska Institute and Aventis U.S</td>
<td>Authors conclude that readily available routine tests such as an OGTT or a single blood glucose value taken 60 minutes after ingestion of 75g glucose at discharge predict the diagnosis of abnormal glucose tolerance after 3 months. Other components</td>
</tr>
</table>

Bibliography (Ref ID)	Study type/aim	Number of patients and characteristics	Definitions and outcome measures	Risk factors/results	Length of follow-up	Source of funding	Additional comments
		was most common amongst those with IGT. **Exclusion:** known diabetes and residence outside catchment area	WHO definitions from 1998. **Normal glucose tolerance (NGT):** fasting blood glucose (FBG) < 6.1mmol/litre, 120 minute blood glucose (BG-120) < 7.8mmol/litre **Impaired glucose tolerance:** FBG < 6.1mmol/litre, BG-120 7.8-11.0mmol/litre **Diabetes:** FBG ≥ 6.1mmol/litre and/or BG-120 ≥ 11.1mmol/litre	**Agreement** 49% of the OGTT performed at discharge and after 3 months allocated the patients into the same glucose tolerance category (NGT, IGT or diabetes) on both occasions. The agreement between the OGTT classification at discharge and after 3 months could be expressed as k = 0.23 (p < 0.001). **Predictors of abnormal glucose tolerance** The hospital derived variables that predicted diabetes after 3 months were OGTT (p = 0.001) and a single BG-60 (p = 0.008). Adding age, BMI, antihypertensive treatment, and HbA_{1c} at admission, fasting triglycerides or HDL cholesterol on day 2, and a single FBG, fasting insulin, fasting proinsulin, HOMA-IR, and PAI-1 on day 5 to the logical regression model did not improve the predictive value. BG-60 was the only predictive variable (P < 0.001) when a similar analysis was performed aiming at the prediction of IGT or diabetes after 3 months. The odds ratio for a 1 mmol/litre increase in BG-60 was 1.38 (CI 1.16-1.64). With a cutoff value of 8.6mmol/litre for BG-60, 70% of the patients were correctly predicted as either belonging to the NGT group or the IGT/diabetes group after 3 months, using cross-validation.			of the metabolic syndrome do not add further predictive value.
Ishihara et al 2006	To investigate whether	200 non-diabetic	Plasma glucose was measured at	**Results of OGTT at admission and at discharge (1 week after admission)**	Only assessed	No financial support for	Authors conclude that

<table>
<tr><th>Bibliography (Ref ID)</th><th>Study type/aim</th><th>Number of patients and characteristics</th><th>Definitions and outcome measures</th><th>Risk factors/results</th><th>Length of follow-up</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr>
<td>(634)</td>
<td>admission hyperglycaemia in non-diabetic patients with AMI is a surrogate for previously undiagnosed abnormal glucose tolerance</td>
<td>patients with AMI were categorised at admission into 3 groups:
<u>Group 1</u>: (no or mild admission hyperglycaemia < 7.8 mmol/litre)
<u>Group 2:</u>
(moderate admission hyperglycaemia ≥ 7.8 and < 11.1 mmol/litre)
<u>Group 3:</u>
(severe admission hyperglycaemia ≥ 11.1mmol/litre).
<u>Exclusions:</u> patients with previous diagnosis of</td>
<td>time of hospital admission and patients were divided into groups 1, 2 or 3. OGTT was performed before hospital discharge (one week after admission). Definitions were
according to WHO 1998. The American Diabetes Association (ADA) criteria for diabetes were also assessed.
<u>Diabetes:</u> FBG ≥ 7.0mmol/litre and/or 2-h post-load glucose ≥ 11.1 mmol/litre
<u>IGT:</u> FBG < 7.0mmol/litre and 2h glucose of 7.8-11.0 mmol/litre</td>
<td>
<table>
<tr><td></td><td colspan="3">Discharge OGTT</td><td></td></tr>
<tr><td>Admission</td><td>Diabetes</td><td>IGT</td><td>NGT</td><td>Total</td></tr>
<tr><td>no/mild (group 1)</td><td>15 (19%)</td><td>39 (48%)</td><td>27 (33%)</td><td>81</td></tr>
<tr><td>moderate (group 2)</td><td>21 (25%)</td><td>31 (37%)</td><td>31 (37%)</td><td>83</td></tr>
<tr><td>severe (group 3)</td><td>17 (47%)</td><td>8 (22%)</td><td>11 (31%)</td><td>36</td></tr>
<tr><td>P-value</td><td>0.002</td><td>0.008</td><td>n.s</td><td>200</td></tr>
</table>
OGTT identified diabetes in 53 patients (27%), IGT in 78 patients (39%) and normal glucose tolerance in 69 (35%) patients. When the fasting glucose criteria were applied, however, only 14 patients (7%) were diagnosed as having diabetes.
There was no significant difference in admission glucose between patients with normal glucose tolerance and patients with abnormal glucose tolerance (8.9±2.4 vs. 8.9±2.4, p = 0.93).
<u>Predictors of abnormal glucose tolerance at discharge</u>
Multivariate analysis showed that fasting glucose (OR 5.00, CI 1.97-12.50, P < 0.001) and Hb_{A1c} (OR 5.76, CI 1.50-22.16, P = 0.01) were independent predictors of abnormal glucose tolerance, but admission glucose was not (OR 0.98, CI 0.84-1.16, P = 0.85). Other significant predictors include fasting insulin (OR 1.17, CI 1.04-1.31, P = 0.007)
</td>
<td>at admission and one week after (discharge)</td>
<td>this study</td>
<td>admission hyperglycaemia in non-diabetic patients with AMI does not represent previously undiagnosed abnormal glucose tolerance. Fasting glucose and $Hb_{A1c,}$ rather than admission glucose, may be useful to predict abnormal glucose tolerance</td>
</tr>
</table>

Bibliography (Ref ID)	Study type/aim	Number of patients and characteristics	Definitions and outcome measures	Risk factors/results	Length of follow-up	Source of funding	Additional comments
		diabetes, those who died during hospitalisation and those who underwent coronary bypass surgery. The mean admission glucose concentration was 8.9 mmol/litre. There were 81 patients in group 1, 83 in group 2 and 36 in group 3.There were no significant differences in baseline characteristics , except lower prevalence of prior MI,	**NGT:** FBG < 7.0 mmol/litre and 2h glucose < 7.8 mmol/litre The values of 7.8mmol/litre and 11.1mmol/litre were also used for classification of admission hyperglycaemia. **Abnormal glucose tolerance**: was used to describe the presence of newly diagnosed diabetes or IGT. **AMI:** diagnosed by chest pain consistent with ongoing myocardial ischaemia persisting longer than 30 mins and concomitant electrocardiographic changes.	and time to angiography (OR 1.17, CI 1.04-1.32, P = 0.01). ROC curves assessing the ability of baseline variables to detect newly diagnosed diabetes showed area under the curve (AUC) for fasting glucose of 0.90 (P < 0.001), 0.85 for Hb_{A1c} (P < 0.001) and 0.65 for admission glucose (P = 0.003). ROC curves assessing the ability of baseline variables to detect abnormal glucose tolerance showed AUC of 0.76 for fasting glucose (P < 0.001) and 0.71 for Hb_{A1c} (P < 0.001), but it was 0.50 for admission glucose (P = 0.93).			

<table>
<tr><th>Bibliography (Ref ID)</th><th>Study type/aim</th><th>Number of patients and characteristics</th><th>Definitions and outcome measures</th><th>Risk factors/results</th><th>Length of follow-up</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td>higher Killip class and higher HbA_{1c} in patients with higher admission glucose levels.</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Norhammar et al 2002 (1020)</td><td>To ascertain the prevalence of impaired glucose metabolism in patients without diagnosed diabetes but with MI and to assess whether such abnormalities can be identified in the early course of an MI.</td><td>144 patients (181 initially but only 144 tested at discharge and 3 months later) with suspected AMI with baseline blood glucose < 11.1mmol/litre. Patients had a mean age 63.5 years, 68% were male and mean blood glucose at admission</td><td>Blood glucose was analysed as soon as possible after admission. An OGTT was taken at discharge (day 4 or 5). 3 months after discharge, FBG and a new OGTT after 12h fasting was carried out. Definitions for diabetes and IGT were taken from WHO 1998 classification and the fasting blood glucose criteria was adopted from</td><td><u>Mean blood glucose</u>
Mean blood glucose at admission was 6.5mmol/litre, mean 2-h postload blood glucose OGTT was 9.2mmol/litre at discharge (day 4 or 5) and 9.0mmol/litre 3 months later.
<u>Multiple logistic regression of independent predictors of diabetes and abnormal glucose tolerance 3 months after discharge</u>
<table>
<tr><td></td><td colspan="2">Diabetes</td><td colspan="2">IGT and diabetes</td></tr>
<tr><td>Parameter</td><td>Odds Ratio (CI)</td><td>P</td><td>Odds Ratio (CI)</td><td>P</td></tr>
<tr><td>Previous hypertension</td><td>0.53 (0.29-0.91)</td><td>0.03</td><td>0.88 (0.56-1.37)</td><td>0.57</td></tr>
<tr><td>BMI (for increase of 1kg/m^2)</td><td>1.13 (1.01-1.29)</td><td>0.04</td><td>1.06 (0.96-1.17)</td><td>0.26</td></tr>
<tr><td>HbA_{1c} (for increase in 1%)</td><td>2.32 (1.11-5.18)</td><td>0.03</td><td>2.55 (1.23-5.64)</td><td>0.02</td></tr>
</table>
<u>Predictors of diagnosis at 3 months:</u></td><td>Patients were tested before hospital discharge and 3 months later.</td><td>Swedish Heart and Lung Foundation and Aventis Pharmaceuticals</td><td>Authors conclude that fasting and postchallenge hyperglycaemia in the early phase of AMI could be used as early markers of high-risk individuals.</td></tr>
</table>

<table>
<tr><th>Bibliography (Ref ID)</th><th>Study type/aim</th><th>Number of patients and characteristics</th><th>Definitions and outcome measures</th><th>Risk factors/results</th><th>Length of follow-up</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td>was 6.5mmol/litre.
<u>Exclusion:</u> patients with known diabetes and aged > 80 years or serum creatinine concentration of 200µmol/litre</td><td>the ADA 1997
<u>Diabetes:</u> fasting blood glucose > 6.0mmol/litre or 2 hour postload blood glucose > 11.0mmol/litre or both.
<u>Impaired glucose tolerance:</u> fasting blood glucose < 6.1mmol/litre and 2 hour blood glucose 7.8-11.0 mmol/litre
<u>Normal glucose tolerance:</u> fasting blood glucose < 6.1mmol/litre and 2 hour blood glucose < 7.8mmol/litre
<u>AMI:</u> defined as European Society of Cardiology and the American</td><td>The area under the curve was 0.710 (P < 0.0001) for fasting blood glucose and 0.685 (P = 0.001) for $HbA_{1c.}$ A fasting glucose of > 5.3mmol/litre on day 4 (discharge) was able to predict newly detected diabetes at 3 months with a sensitivity of 80% and a specificity of 57%. The corresponding sensitivity and specificity values for HbA_{1c} of more than 4.9% were 79% and 49%. When entering fasting blood glucose concentration on day 4 in the analysis, this parameter was the only remaining independent predictor of diabetes.
<u>Multiple logistic regression of independent predictors of diabetes and abnormal glucose tolerance 3 months after discharge</u>
<table>
<tr><td></td><td colspan="2">Diabetes</td><td colspan="2">IGT and diabetes</td></tr>
<tr><td>Parameter</td><td>Odds Ratio (CI)</td><td>P</td><td>Odds Ratio (CI)</td><td>P</td></tr>
<tr><td>FBG day 4 (for increase in 1mmol/litre in blood glucose</td><td>2.97 (1.55-6.40)</td><td>0.002</td><td>1.90 (1.05-3.69)</td><td>0.04</td></tr>
<tr><td>HbA_{1c} (for increase in 1%)</td><td>1.73 (0.72-4.31)</td><td>0.220</td><td>2.58 (1.17-6.09)</td><td>0.02</td></tr>
</table>
Since some patients were discharged on day 4 rather than day 5, the FBG obtained on this day was used in analyses. Inclusion of the fasting blood glucose on day 4 in the model rendered both</td><td></td><td></td><td></td></tr>
</table>

<table>
<tr><th>Bibliography (Ref ID)</th><th>Study type/aim</th><th>Number of patients and characteristics</th><th>Definitions and outcome measures</th><th>Risk factors/results</th><th>Length of follow-up</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td>College of Cardiology.</td><td>HbA_{1c} and fasting blood glucose as independent predictors of abnormal glucose tolerance.</td><td></td><td></td><td></td></tr>
<tr><td>Okosieme et al 2008 (1329)</td><td>To clarify the prevalence of unrecognised abnormal glucose tolerance in population of patients with ACS in South Wales, UK and to analyse the performance of fasting and admission glucose (applied individually or in combination) as markers of previously undiagnosed diabetes in patients with ACS.</td><td>140 patients admitted to coronary care unit with diagnosis of ACS. There were no significant differences between in age, sex and ethnic distribution between the various categories of glucose tolerance.
<u>Exclusion:</u> patients with previously known diabetes or IGT.</td><td>Casual blood glucose was taken on the day of admission (when one admission glucose level was available the highest reading was selected for analysis). An OGTT was performed before discharge (usually between day 5 and 7). Glycaemic status was classified on basis of 2-h postload (2-h plasma glucose) glucose values of the OGTT according to WHO 1998 definition and FPG on the basis</td><td><u>Prevalence of abnormal glucose tolerance at discharge</u>
The prevalence of diabetes and IGT on the basis of OGTT were 27% and 39% respectively
<u>Diagnostic accuracy of APG and FPG to diagnose diabetes in patients with ACS at discharge</u>
<table>
<tr><th></th><th>Prevalence</th><th>Sensitivity</th><th>Specificity</th><th>PPV</th></tr>
<tr><td>FPG ≥ 5.6 mmol/litre</td><td>48</td><td>81.6%</td><td>64.7 %</td><td>46.3%</td></tr>
<tr><td>APG ≥ 7.8 mmol/litre</td><td>30</td><td>65.8%</td><td>83.3 %</td><td>59.5%</td></tr>
<tr><td>FPG ≥ 5.6 or APG ≥ 7.8 mmol/litre</td><td>52</td><td>89.5%</td><td>56.9 %</td><td>43.6%</td></tr>
</table>
The AUCs for diagnosing diabetes were 0.83 (P < 0.001) for FPG, 0.79 (P < 0.001) for APG and 0.84 (P < 0.001) for FPG and APG applied in combination. The optimal cut-off point for diagnosing diabetes with FPG was 5.8mmol/litre. This is the FBG value with the best sensitivity and</td><td>Blood glucose was measured on admission and OGTT before discharge (usually days 5 and 7)</td><td>Not reported.</td><td>The authors conclude that the combination of FPG ≥ 5.6mmol/litre and/or APG ≥ 7.8mmol/litre was highly sensitive for identifying diabetes. Although weakly specific, this simple algorithm could offer a practical initial screening tool at the acute setting in the high risk population with ACS.</td></tr>
</table>

Bibliography (Ref ID)	Study type/aim	Number of patients and characteristics	Definitions and outcome measures	Risk factors/results	Length of follow-up	Source of funding	Additional comments
			of American Diabetes Association 2004 criteria: **Normal Glucose Tolerance:** 2-h plasma glucose < 7.8mmol/litre or FPG < 5.6mmol/litre **Impaired Glucose Tolerance:** 2-h plasma glucose 7.8-11.0mmol/litre or **Impaired Fasting Glucose:** FPG 5.6-6.9mmol/litre **Diabetes:** 2-h plasma glucose ≥ 11.1mmol/litre or FPG > 7.0mmol/litre **Admission Plasma Glucose (APG)** was stratified into 3	specificity for identifying diabetes in this setup. At this cut-off the sensitivity and specificity of FPG in detecting diabetes were 69.2 and 77.2% respectively. The optimal cut-off point for identifying diabetes with APG was 7.7mmol/litre; this cut-off point was associated with sensitivity of 65.8% and specificity of 82.4%.			

Bibliography (Ref ID)	Study type/aim	Number of patients and characteristics	Definitions and outcome measures	Risk factors/results	Length of follow-up	Source of funding	Additional comments
			groups: < 7.8mmol/litre, 7.8-11.0mmol/litre and ≥ 11.1mmol/litre. **AMI:** diagnosis based on joint recommendations by European Society of Cardiology and American College of Cardiology.				
Oswald & Yudkin 1987 (Ref ID:	Clinical audit (prognostic design)/ to investigate validated levels of HbA_{1c} indicative of diabetes in order to assess the contribution of undiagnosed diabetes to admission	397 patients with confirmed AMI (463 initially but 66 had known diabetes and were excluded). In 248 patients an admission plasma glucose level was estimated before administration	Categorisation of HbA_{1c} **Clearly normal (group 1):** < 6.9% **Borderline (group 2):** 6.9-7.8% **Clearly abnormal HbA_{1c} (group 3):** > 7.8% Diabetes and IGT were defined according to the	**HbA_{1c}** A level of HbA_{1c} > 7.8% (classified as clearly abnormal) was 100% sensitive and 99% (CI 97-100%) specific for overt diabetes, but when all diabetes at follow-up was included, the sensitivity fell to 67% (CI 36-97%) with the same specificity. IGT was more common in group 2 than group 1 ($p < 0.001$). **Admission plasma glucose (APG)** APG was detailed in 248 patients before administration of glucose. The level was ≥ 11mmol/litre in 49 (20%) of these patients. Sensitivity for DM was 33% (CI 3-64%), specificity for DM was 91% (CI 85-97%). For overt diabetes the sensitivity is 50% (CI 9 to 91%) and specificity	293/397 patients survived. 117 patients had an OGTT at 7-10 days (before discharge). 61 of these patients went on		In four patients with fasting plasma glucose < 8mmol/litre but with 2h plasma glucose ≥ 11mmol/litre at 3 months follow-up, the OGTT was repeated at 6 months from

Bibliography (Ref ID)	Study type/aim	Number of patients and characteristics	Definitions and outcome measures	Risk factors/results	Length of follow-up	Source of funding	Additional comments
	hyperglycaemia after AMI	of glucose solution. There were no significant difference between patients sampled for plasma glucose and those not sampled in terms in gender, age or outcome. OGTT was carried out in 117/293 survivors between 7-10 days after infarction and before discharge.	WHO criteria using venous plasma. 2 elevated glucose values were required in the absence of symptoms.	91% (CI 85 to 97%).	to have an OGTT at 3 months and 49 randomly selected patients had their first OGTT at 3 months so a total of 110 had a follow-up at 3 months.		AMI. Paper does not report specific definitions of overt diabetes and diabetes but assumption that overt diabetes refers to symptomatic diabetes.

Review question 4: What information should patients with peri ACS and hyperglycaemia (who are at high risk of developing diabetes) be provided while waiting for a referral for diagnostic investigations for diabetes?

No studies were identified for this question.