National Institute for Health and Clinical Excellence **NICE short clinical guideline on [title]** **Document cover sheet**			
Date	**Version number**	**Worked on by**	**Action**
11/04/11	V0.0	Vicky	Set up Appendices
11/04/11	V1.0	Vicky	Insert Evidence Tables, Forrest plots and other tables

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 X

<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 620</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 arrival.</td>
<td><u>Control:</u> Treated according to standard coronary care unit practice and did not receive insulin unless it was</td>
<td>Mean time of follow-up was 344days (range 91 to 365 days).</td>
<td><u>Mortality:</u>
<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</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. Possible</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>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 ≥2 of following</td><td><u>diabetes</u>: Admission blood glucose ≥11 mmol/L. <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</td><td>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. This was</td><td>deemed clinically indicated.</td><td></td><td>model (CI 4% to 51%).
<table>
<tr><th></th><th colspan="4">Strata*</th></tr>
<tr><th>Time</th><th>1</th><th>2</th><th>3</th><th>4</th></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 with mortality rate of 8.6% in infusion group and 18.0% in control (relative risk reduction 52%, p=0.02).</td><td></td><td>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 were no</td></tr>
</table>

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<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>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. <u>Baseline characteri</u></td><td>the normal range (normal +2SD), including an LD-isoenzyme pattern typical of myocardial damage; and 3) development of new Q waves in ≥2 standard ECG leads. <u>Possible AMI:</u> typical chest pain with only 1 S-CK or S-LD value</td><td>started immediately after cessation of infusion, according to regime, with aim of achieving normoglycaemia. Subcutaneous insulin was given 4 times daily for ≥3 months.</td><td></td><td></td><td><u>Morbidity:</u>
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).
<u>Measures of blood glucose and adverse events:</u>
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).
<table><tr><td>Blood glucose (mmol/L)</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>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.</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
		stics: 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%, infusion=55 18%)	above normal range and/or new Q waves in one ECG only. **Reinfarction:** new **AMI >72 hours after index infarct.**						

<table>
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<tr><td></td><td></td><td>and previously unknown diabetes (control=47 15%, infusion=3 1 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 cause-specific mortality</td><td>For details please see above DIGAMI 1 study. Groups were well balanced for patient characteristics. 50% were thrombolysed, 54%</td><td>See above for DIGAMI 1 study. <u>Ventricular tachyarrhyth-mias</u>: The presence of either ventricular</td><td>See above for details of DIGAMI 1 study. Insulin group received insulin-glucose infusion followed by multidose subcutaneous insulin</td><td><u>Control:</u> Treated according to standard coronary care unit practice and did not receive insulin unless it was</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</td><td>82</td><td>58</td><td><0.0</td></tr>
</table></td><td>Swedish Heart-Lung Foundation, Karolinska Institutet and Hoechst Marion Roussel Sweden</td><td>The authors concluded that insulin-glucose infusion followed by subcutaneous insulin treatment in patients with</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 morbidity, with special reference to fatal and non-fatal reinfarction	received intravenous nitro-glycerine & 17% were fully heparinised during the acute period in hospital.	premature beats or ventricular tachycardia requiring antiarrhythmic treatment, or documented ventricular fibrillation (VF) was included. VF defined as early if within 48 hrs of	treatment for at least 3 months.	deemed clinically indicated.		(23) (26) (19) 5 After one year the total mortality had 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		diabetes and AMI favourably influences one year mortality by reducing all cardiovascular causes of death. This therapeutic regimen seems to have particular impact on fatal reinfarctions.

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			symptom onset and late if after. **Atrioventricular block**: Only high grade AV-blocks (II-III) were considered. The conduction defect had to be treated to be noted in case record. **CHF:** clinical				(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). 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.		

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			and/or radiological signs of pulmonary congestion resulting in the institution of treatment.						

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: 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 randomisation.	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 to follow-up as regards mortality.	**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 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). **Long-term mortality:** During continued follow-up there were	Swedish Heart-Lung Foundation, Karolinska Institutet and Hoechst Marion Roussel Sweden	The authors concluded that insulin-glucose infusion followed by intensive subcutaneous insulin 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

<table>
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<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>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 (33)</td><td>35 (53)</td><td>26 (40)</td><td>33 (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</td><td></td><td>information about insulin treatment during long-term follow-up is not available.</td></tr>
</table>

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							18% in insulin group. This corresponds to a relative reduction of 51% (19% to 70%, p=0.004) by Cox model		

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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	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	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

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		women 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.					correction for age, gender and 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 HbA1c (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.		blockade 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	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.	240 deaths (39%), 138 in control group (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	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

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							admission RR=1.09 (1.05-1.13, p<0.001), HbA1c 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 (0.31-0.65, 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/L RR=1.06 (1.01-1.11, p<0.05) and HbA1c on admission RR=1.15 (1.03-1.29, p<0.05).		ACE may have more severe CHF

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							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 (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.		

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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/L 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	DIGAMI 2-	1253 patients	**Hyperglycaemia:**	**Group 1:** Insulin-	**Group 3:** the	All patients	**Mortality (intention to treat):**	The Swedish	Concomitant therapy

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
2005 (Ref ID: X)	multicentre, prospective, randomised open trial comparing three different management strategies in patients with type 2 diabetes and AMI.	were 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	patients with established type 2 diabetes or an admission blood glucose >11.0mmol/L were eligible for inclusion. **MI:** diagnosed according to joint recommendation of ESC and ACC. **Reinfarction:** new event >72 hours from index	glucose 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/L. The infusion lasted until stable normoglycaemia and at least for 24 hours.	glucose lowering treatment was at the discretion of the responsible physician and according to local routines. Target values were not defined in this group.	were 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.	Overall there were 277 deaths (21.3%) and mortality did not significantly differ 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	Heart-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	was used 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

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	infarction. **Stroke:** unequivocal signs of 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	Subcutaneous insulin 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			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:** Updated blood glucose during the time of follow up (HR=1.20 for 3mmol/L, 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/L, 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	Nordisk Denmark.	group 1 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

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).	and without any obvious reason for the fatal outcome. **Hypoglycaemia:** blood glucose level <3 mmol/L with or without symptoms.	mmol/L and a non-fasting level of <10mmol/L. **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			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/L (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 1 and 2 compared with group 3 (1=9.1, 2=9.1, 3=10.0, p=0.0001), blood glucose and HbA1c 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/L in group 1.		compared 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>defined in this group.</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</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</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><u>Mortality & morbidity:</u>
<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,</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/L for hypoglycaemia did not change these results. The authors concluded that hypoglycaemia</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
		they were less treated with lipid lowering drugs but more often with diuretics. Hba1c, admission blood glucose and glucose lowering treatment at admission did not differ. The duration of diabetes was longer among patients with than those without		standard glucose control (n=473).			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). **Predictors of subsequent hypoglycaemic events:** 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.		during the initial 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
		hypoglycaemic episodes					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.		
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	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	**Hypoglycaemia:** finger prick blood glucose <3.5mmol/l, irrespective of the occurrence of symptoms. **Reinfarction:** new AMI occurring >72 hours following index infarct.	**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/L for at least 24 hours. For	**Conventional Therapy Group (CTG):** remained on their usual diabetes therapy but metformin was temporarily discontinued. Supplemental subcutaneous	Patients were contacted to obtain information regarding the occurrence of cardiovascular events following discharge. Outcomes were measured during the index	**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	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

<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 AMI</td>
<td>admission blood glucose level ≥7.8mmol/L (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</td>
<td>Cardiac failure: dyspnoea with radiographic evidence of pulmonary or interstitial 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</td>
<td>patients with cardiac failure, 10% dextrose was administered at 40 ml/h. All diabetes medications were discontinued temporarily. Upon cessation of infusion, patients resumed their usual diabetes medication.</td>
<td>short-acting insulin was permitted if blood glucose was >16mmol/l.</td>
<td>hospital admission and after 3 and 6 months. There 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>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
<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 mortal</td><td>0%</td><td>7%</td><td>7.2 (0.9-58.9)</td><td>0.07</td></tr>
</table>
</td>
<td></td>
<td>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 commencement of insulin was 13 hrs and this may have been too late for</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>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). <u>Stratification:</u> 1)</td>
<td>electrographic criteria of ST elevation in two limb leads.</td>
<td></td>
<td></td>
<td></td>
<td>
<table>
<tr><td>ity</td><td></td><td></td><td></td><td></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 mortality</td><td>2%</td><td>11%</td><td>5.6 (1.2-26.1)</td><td>0.03</td></tr>
</table>
* 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.
<u>Adverse events:</u>
There were 13 episodes of hypoglycaemia among the ITG and 2 episodes in the CTG (p=0.02). No patient developed significant symptoms.
</td>
<td></td>
<td>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.</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>known diabetes or admission blood glucose ≥11 mmol/L without known diabetes (n=142). 2) admission blood glucose 7.8-11 mmol/L without known diabetes (n=98).</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>CREATE-ECLA trial group investigators (Ref ID: 951)</td><td>Randomised Controlled Trial/ to determine the effect of high dose GIK infusion</td><td>20195 (20201 were randomised) patients with AMI. 8060 from India, 7510 from</td><td></td><td><u>Infusion group:</u> usual care and GIK infusion for 24 hours. GIK consisted of 25%</td><td><u>Standard therapy:</u> usual care alone</td><td>Only 30 (0.15%) of 20201 patients randomised were lost to follow-up and</td><td><u>Primary and secondary outcomes:</u>
<table>
<tr><th>Outcome</th><th>Usual care</th><th>GIK</th><th>Hazard ratio (CI)</th><th>P-value</th></tr>
<tr><td colspan="5">30 days</td></tr>
<tr><td>Death</td><td>979/</td><td>1004</td><td>1.03</td><td>0.45</td></tr>
</table></td><td>No external funding. Aventis Pharma donated human insulin in India and</td><td>Non-study GIK was used in 152 (1.9%) control patients randomised (ECLA did not</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>on mortality in patients with STEMI</td><td>China, 3804 from ECLA centers and 827 from Pakistan. Median time from symptom onset to randomisation was 4.7 hours. Baseline characteristic were similar in both groups. Mean age was 58.6 years with 7.9% older than 75 years. A total of 17.7% had diabetes</td><td></td><td>glucose, 50U/L of regular insulin and 80 mEq/L of potassium. GIK was initiated immediately after randomisation (this was within 1 hour of randomisation in 90% of patients). The full 24 hour infusion was completed in 84.2% with 92.2% receiving at least 10 hours of</td><td></td><td>analyses were performed using an intention to treat approach.</td><td>
<table>
<tr><td></td><td>1010 7</td><td>/ 1008 8</td><td>(0.95-1.13)</td><td></td></tr>
<tr><td>Reinfarction</td><td>246/ 1010 7</td><td>236/ 1008 8</td><td>0.98 (0.82-1.17)</td><td>0.81</td></tr>
<tr><td>Death or reinfarction</td><td>1154 / 1010 7</td><td>1179 / 1008 8</td><td>1.03 (0.95-1.12)</td><td>0.49</td></tr>
<tr><td colspan="5">7 days</td></tr>
<tr><td>Death</td><td>771/ 1010 7</td><td>816/ 1008 8</td><td>1.06 (0.96-1.17)</td><td>0.22</td></tr>
<tr><td>Reinfarction</td><td>202/ 1010 7</td><td>190/ 1008 8</td><td>0.96 (0.79-1.17)</td><td>0.70</td></tr>
<tr><td>Death or reinfarction</td><td>920/ 1010 7</td><td>965/ 1008 8</td><td>1.06 (0.97-1.16)</td><td>0.23</td></tr>
</table>
</td><td>had no role in design or conduct of the study, collection, analysis or interpretation of data or approval of the manuscript.</td><td>collect these data). CREATE ECLA was a partial 2X2 factorial design with one randomisation to GIK infusion or standard care and a second randomisation to double-blind therapy with reviparin or matching placebo (in India and China). In India 5127</td></tr>
</table>

<table>
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<tr><td></td><td></td><td>and 37.1% had known history of hypertension. The majority of patients presented as Killip class 1 (84.7%) and 15.4% presented as Killip class II, III or IV. Medications in the hospital were similar between groups. 766 of 1438 with type 2 diabetes in control group and</td><td></td><td>therapy.</td><td></td><td></td><td><u>Safety outcomes at 7 days:</u>
<table>
<tr><th>Outcome</th><th>Usual care (n=10107)</th><th>GIK (n=10088)</th><th>Hazard ratio (CI)</th><th>P-value</th></tr>
<tr><td>Heart failure</td><td>1711</td><td>1721</td><td>1.01 (0.95-1.08)</td><td>0.72</td></tr>
<tr><td>Hyperkalemia (>5.5 mEq/L)</td><td>161</td><td>431</td><td>2.76 (2.30-3.31)</td><td><0.001</td></tr>
<tr><td>Significant phlebitis</td><td>17</td><td>339</td><td>20.64 (12.07-33.62)</td><td><0.001</td></tr>
<tr><td>Symptomatic hypoglycaemia</td><td>11</td><td>34</td><td>3.11 (1.57-6.13)</td><td><0.001</td></tr>
</table></td><td></td><td>patients were initially randomised using sealed opaque envelopes, although subsequent patients (n=2933) had central telephone randomisation. Randomisation errors occurred in 1.1% of patients and these patients were included in their originally</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>720 of 1436 with type 2 diabetes in GIK group received nonstudy insulin.</td><td></td><td></td><td></td><td></td><td>At 30 days, the rates of heart failure were 17.4% (1761/10107) in usual care group and 17.4% (1758/10088) in GIK group (HR 1.00, CI 0.94-1.07, P=0.88).
<u>Sub-group analyses:</u>
<table>
<tr><th>Group</th><th>GIK</th><th>Usual care</th><th>P value for interaction</th></tr>
<tr><td colspan="4">Killip class</td></tr>
<tr><td>I</td><td>605/ 8490</td><td>607/ 8606</td><td rowspan="2">0.91</td></tr>
<tr><td>II-IV</td><td>399/ 1592</td><td>368/ 1499</td></tr>
<tr><td colspan="4">Diabetes</td></tr>
<tr><td>Present</td><td>249/ 1780</td><td>240/ 1802</td><td rowspan="2">0.81</td></tr>
<tr><td>Absent</td><td>752/ 8258</td><td>729/ 8246</td></tr>
<tr><td colspan="4">Baseline Blood Glucose Level (mmol/L)</td></tr>
<tr><td><7</td><td>268/ 3247</td><td>219/ 3302</td><td rowspan="3">0.01</td></tr>
<tr><td>7 to <8</td><td>259/ 3481</td><td>302/ 3547</td></tr>
<tr><td>≥8</td><td>477/ 3360</td><td>455/ 3258</td></tr>
<tr><td colspan="4">Time to randomisation (h)</td></tr>
<tr><td><4</td><td>366/</td><td>350/</td><td></td></tr>
</table></td><td></td><td>intended allocations for analyses. Results are also available for non fatal cardiac arrest, cardiogenic shock, death or cardiac arrest and death or cardiogenic shock but they are not reported in the evidence tables.</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>4124</td><td>4218</td></tr><tr><td>4 to <8</td><td>419/ 3886</td><td>407/ 3775</td></tr><tr><td>≥8</td><td>219/ 2078</td><td>219/ 2114</td></tr></table> NB: sub group analyses are also available for age, sex, reperfusion, thrombolytic therapy and primary percutaneous coronary intervention but are not reported in the evidence table. **Serum BGL:** Mean glucose levels were 9.0mmol/L in the GIK and control group at baseline. At 6 hours after randomisation the mean BGL in the GIK group increased to 10.4mmol/L; in the control group it decreased to 8.2mmol/L. By 24 hours after randomisation, the mean BGL was 8.6mmol/L in the GIK group and 7.5mmol/L in the control group. When the baseline BGL in the control group were divided into tertiles, higher baseline BGL were associated with higher mortality at 30 days (see sub group analysis).		

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
HbA1c +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

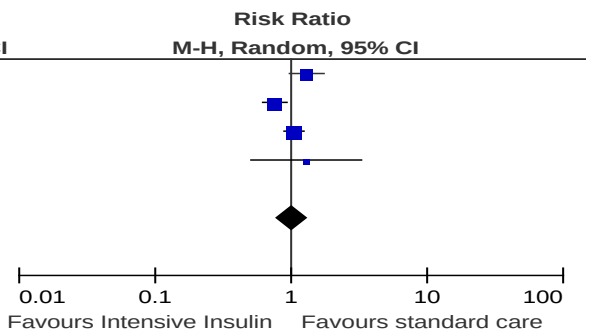
Adjusted for age, gender, diabetes status, creatine kinase, ST elevation infarct and randomisation group

Forrest Plots on Outcomes

Overall Mortality

Study or Subgroup	Intensive Insulin therapy Events	Total	Standard Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Malmberg 2005(6053)	111	474	55	306	26.8%	1.30 [0.98, 1.74]
Malmberg 1996(378)	102	306	138	314	32.2%	0.76 [0.62, 0.93]
CREATE-ECLA 2005 (951)	249	1780	240	1802	34.3%	1.05 [0.89, 1.24]
Cheung 2006(103a)	10	126	7	114	6.7%	1.29 [0.51, 3.28]
Total (95% CI)		**2686**		**2536**	**100.0%**	**1.02 [0.78, 1.32]**
Total events	472		440			

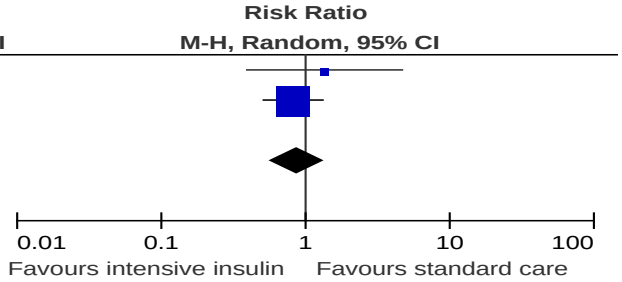
Heterogeneity: Tau² = 0.05; Chi² = 11.10, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 0.12 (P = 0.91)



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)

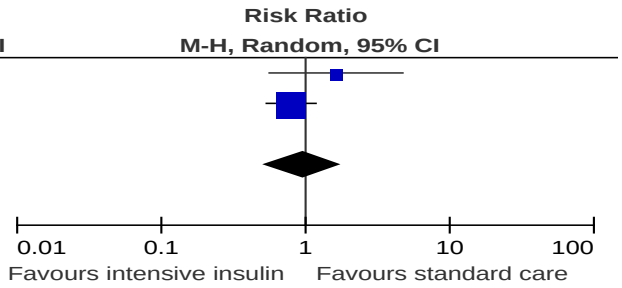


Three month Mortality

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)

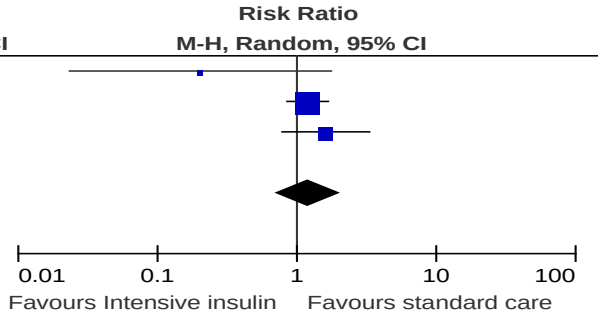


Reinfarction

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			

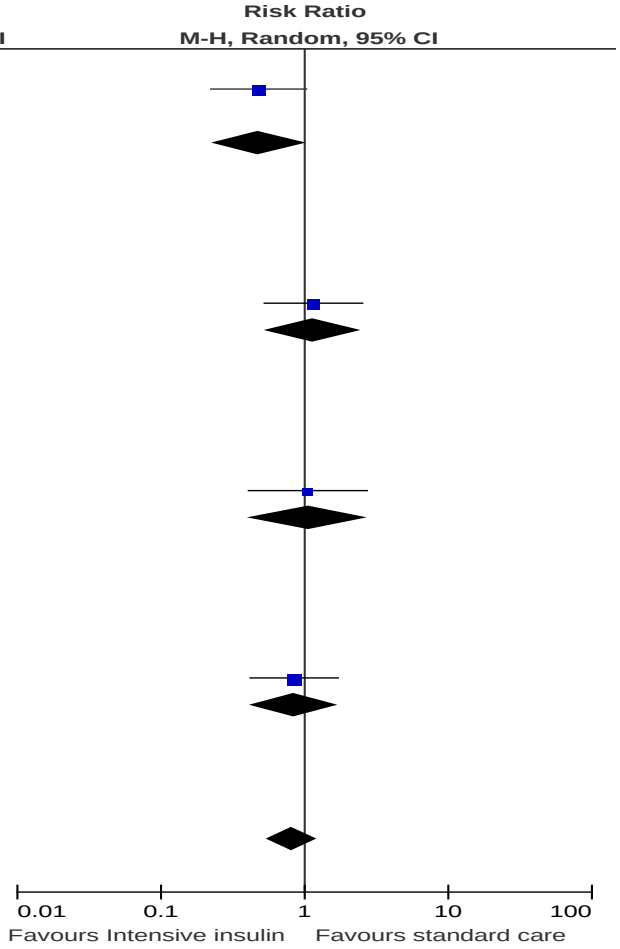
Heterogeneity: Tau² = 0.09; Chi² = 3.24, df = 2 (P = 0.20); I² = 38%

Test for overall effect: Z = 0.65 (P = 0.52)



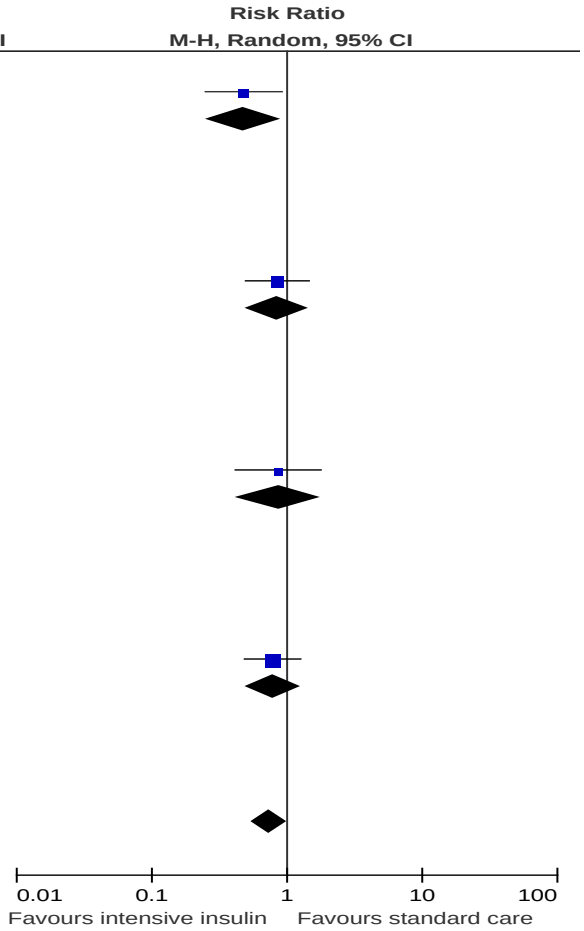
Three month mortality of subgroups stratified by risk

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)						

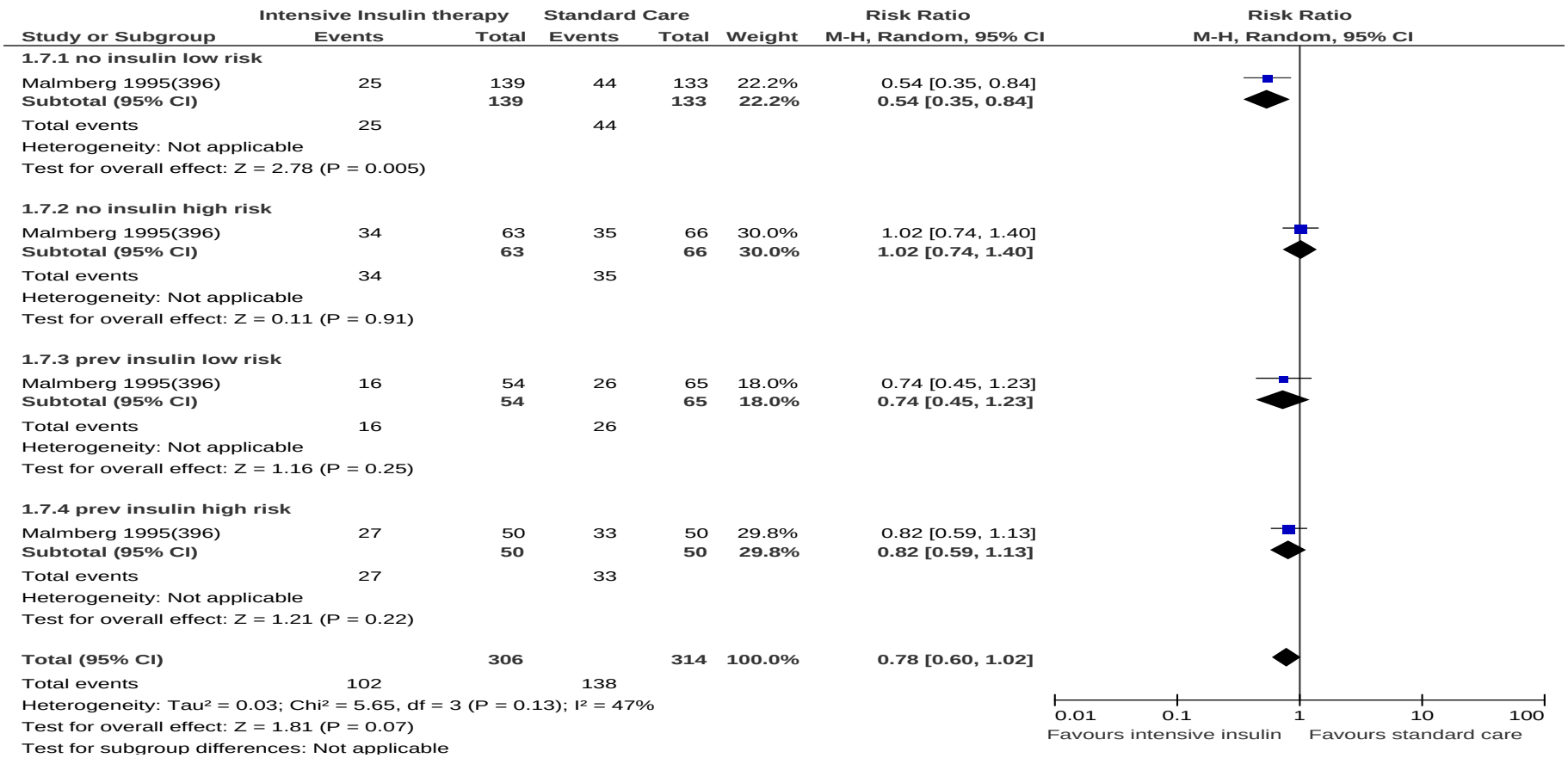


One year mortality of subgroups stratified by risk

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



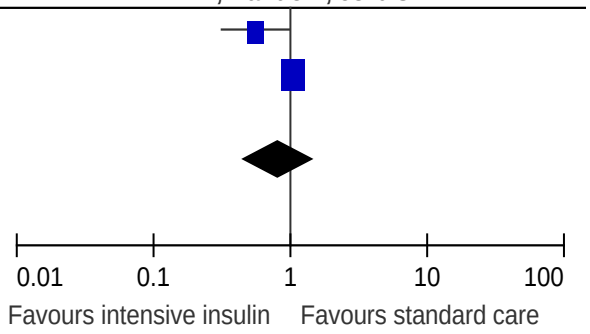
High risk: At least two of the following: Above 70 years, previous Myocardial infarction, previous congestive heart failure and current treatment with digitalis(digoxin)

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)

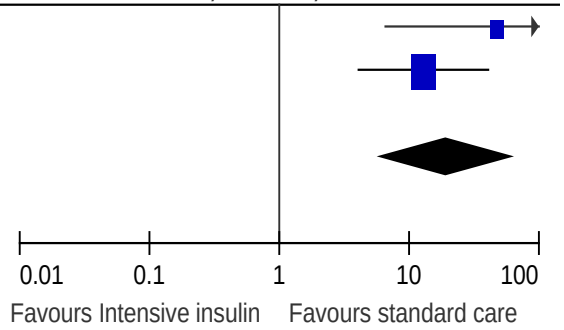


Hypoglycaemia after 24 hours

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: $Tau^2 = 0.20$; $Chi^2 = 1.30$, df = 1 (P = 0.25); $I^2 = 23\%$

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

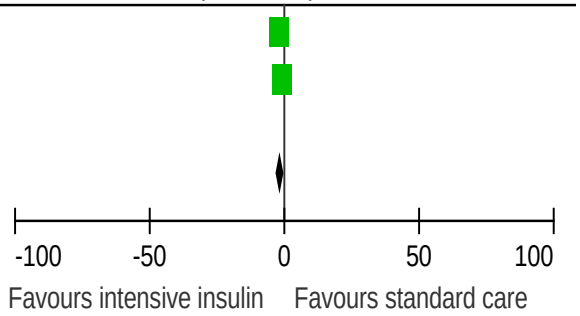


Difference in Blood glucose levels after 24 hours

Study or Subgroup	Intensive insulin Mean	SD	Total	standard care Mean	SD	Total	Weight	Mean Difference 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?

Table [X Add brief title; style = Unnumbered bold heading]

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
Weston et al 2007 (Ref ID:312a)	An observational study from the MINAP database to determine the effect of insulin for the management of hyperglycaemia in non-diabetic patients with ACS.	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	**Hyperglycaemia:** 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	**Insulin:** 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	**No treatment:** no diabetic treatment in hospital and treatment strategy was not recorded.	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.	**Mortality at 7 and 30 days:** 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). All deaths / No treatment (%) / Insulin / RR / Adjusted RR* / P-value 7 days / 290/1761 (16.5) / 101/868 (11.6) / 1.42 / 1.56 / <0.001	The Healthcare Commissions.	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

<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>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>
<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).
<u>7 and 30 day mortality by AMI type:</u>
<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>STEM</td><td>193/75</td><td>80/5</td><td>1.6</td><td>1.58</td><td>0.0</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
							<table><tr><td>I (30 days)</td><td>5 (25.6)</td><td>09 (15.7)</td><td>3</td><td></td><td>02</td></tr><tr><td>NSTE MI (7 days)</td><td>126/10 06 (12.5)</td><td>34/3 59 (9.5)</td><td>1.3 2</td><td>1.30</td><td>0.2 11</td></tr><tr><td>NSTE MI (30 days)</td><td>196/10 06 (19.5)</td><td>57/3 59 (15.9)</td><td>1.2 3</td><td>1.25</td><td>0.1 88</td></tr></table> * 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/L (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/L 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/L without known diabetes (n=142). 2) admission blood glucose 7.8-11 mmol/L 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 translumina l angioplasty (PTCA) is effective in	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 1mm in 2 or more leads or		**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 soon 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	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 reduction was

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
	patients with AMI.	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 (there were no sig differences		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 adjustments of the			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 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		seen.

<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>between groups). 50 (10.5%) in infusion group and 49 (10.6%) in control group had diabetes.</td><td></td><td>insulin dose were based on a normogram to obtain blood glucose levels between 7.0 and 11.0 mmol/l.</td><td></td><td></td><td>observed.
<u>Blood glucose levels:</u>
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)</td><td></td><td></td></tr>
<tr><td>CREATE-ECLA trial group investigators (Ref ID: 951)</td><td>Randomised Controlled Trial/ to determine the effect of high dose GIK infusion on mortality in patients with STEMI</td><td>20195 (20201 were randomised) patients with AMI. 8060 from India, 7510 from China, 3804 from ECLA centers and 827 from Pakistan. Median time from symptom onset to randomisation was 4.7 hours. Baseline characteristic</td><td></td><td><u>Infusion group:</u> usual care and GIK infusion for 24 hours. GIK consisted of 25% glucose, 50U/L of regular insulin and 80 mEq/L of potassium. GIK was initiated immediatel</td><td><u>Standard therapy:</u> usual care alone</td><td>Only 30 (0.15%) of 20201 patients randomised were lost to follow-up and analyses were performed using an intention to treat approach.</td><td><u>Primary and secondary outcomes:</u>
<table>
<tr><th>Outcome</th><th>Usual care</th><th>GIK</th><th>Hazard ratio (CI)</th><th>P-value</th></tr>
<tr><td colspan="5">30 days</td></tr>
<tr><td>Death</td><td>979/10107</td><td>1004/10088</td><td>1.03 (0.95-1.13)</td><td>0.45</td></tr>
<tr><td>Reinfarction</td><td>246/10107</td><td>236/10008</td><td>0.98 (0.82-1.17)</td><td>0.81</td></tr>
</table></td><td>No external funding. Aventis Pharma donated human insulin in India and had no role in design or conduct of the study, collection, analysis</td><td>Non-study GIK was used in 152 (1.9%) control patients randomised (ECLA did not collect these data). CREATE ECLA was a partial 2X2 factorial design with one randomisation to GIK infusion or standard care and a second randomisation to double-blind</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>were similar in both groups. Mean age was 58.6 years with 7.9% older than 75 years. A total of 17.7% had diabetes and 37.1% had known history of hypertension. The majority of patients presented as Killip class 1 (84.7%) and 15.4% presented as Killip class II, III or IV. Medications in the hospital were similar between groups. 766 of 1438 with type 2 diabetes in control group and 720 of</td><td></td><td>y after randomisation (this was within 1 hour of randomisation in 90% of patients). The full 24 hour infusion was completed in 84.2% with 92.2% receiving at least 10 hours of therapy.</td><td></td><td></td><td>
<table>
<tr><td></td><td></td><td>8</td><td></td><td></td></tr>
<tr><td>Death or reinfarction</td><td>1154/10107</td><td>1179/10088</td><td>1.03 (0.95-1.12)</td><td>0.49</td></tr>
<tr><td colspan="5">7 days</td></tr>
<tr><td>Death</td><td>771/10107</td><td>816/10088</td><td>1.06 (0.96-1.17)</td><td>0.22</td></tr>
<tr><td>Reinfarction</td><td>202/10107</td><td>190/10088</td><td>0.96 (0.79-1.17)</td><td>0.70</td></tr>
<tr><td>Death or reinfarction</td><td>920/10107</td><td>965/10088</td><td>1.06 (0.97-1.16)</td><td>0.23</td></tr>
</table>
</td><td>or interpretation of data or approval of the manuscript.</td><td>therapy with reviparin or matching placebo (in India and China). In India 5127 patients were initially randomised using sealed opaque envelopes, although subsequent patients (n=2933) had central telephone randomisation. Randomisation errors occurred in 1.1% of patients and these patients were included in their originally intended allocations for analyses. Results are</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>1436 with type 2 diabetes in GIK group received nonstudy insulin.</td><td></td><td></td><td></td><td></td><td><u>Safety outcomes at 7 days:</u>
<table>
<tr><td>Outcome</td><td>Usual care (n= 10107)</td><td>GIK (n= 10088)</td><td>Hazard ratio (CI)</td><td>P-value</td></tr>
<tr><td>Heart failure</td><td>1711</td><td>1721</td><td>1.01 (0.95 - 1.08)</td><td>0.72</td></tr>
<tr><td>Hyperkalemia (>5.5 mEq/L)</td><td>161</td><td>431</td><td>2.76 (2.30 - 3.31)</td><td><0.001</td></tr>
<tr><td>Significant phlebitis</td><td>17</td><td>339</td><td>20.64 (12.07- 33.62)</td><td><0.001</td></tr>
<tr><td>Symptomatic hypoglycaemia</td><td>11</td><td>34</td><td>3.11 (1.57 - 6.13)</td><td><0.001</td></tr>
</table>
At 30 days, the rates of heart failure were 17.4% (1761/10107) in usual care group and 17.4% (1758/10088) in GIK group (HR 1.00, CI 0.94-1.07, P=0.88).</td><td></td><td>also available for non fatal cardiac arrest, cardiogenic shock, death or cardiac arrest and death or cardiogenic shock but they are not reported in the evidence tables.</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></td><td></td><td></td><td></td><td></td><td><u>Sub-group analyses:</u>
<table>
<tr><td>Group</td><td>GIK</td><td>Usual care</td><td>P value for interaction</td></tr>
<tr><td colspan="4">Killip class</td></tr>
<tr><td>I</td><td>605/ 8490</td><td>607/ 8606</td><td rowspan="2">0.91</td></tr>
<tr><td>II-IV</td><td>399/ 1592</td><td>368/ 1499</td></tr>
<tr><td colspan="4">Diabetes</td></tr>
<tr><td>Present</td><td>249/ 1780</td><td>240/ 1802</td><td rowspan="2">0.81</td></tr>
<tr><td>Absent</td><td>752/ 8258</td><td>729/ 8246</td></tr>
<tr><td colspan="4">Baseline Blood Glucose Level (mmol/L)</td></tr>
<tr><td><7</td><td>268/ 3247</td><td>219/ 3302</td><td rowspan="3">0.01</td></tr>
<tr><td>7 to <8</td><td>259/ 3481</td><td>302/ 3547</td></tr>
<tr><td>≥8</td><td>477/ 3360</td><td>455/ 3258</td></tr>
<tr><td colspan="4">Time to randomisation (h)</td></tr>
<tr><td><4</td><td>366/ 4124</td><td>350/ 4218</td><td rowspan="3">0.79</td></tr>
<tr><td>4 to <8</td><td>419/ 3886</td><td>407/ 3775</td></tr>
<tr><td>≥8</td><td>219/ 2078</td><td>219/ 2114</td></tr>
</table>
NB: sub group analyses are also available</td><td></td><td></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
							for age, sex, reperfusion, thrombolytic therapy and primary percutaneous coronary intervention but are not reported in the evidence table. **Serum BGL:** Mean glucose levels were 9.0mmol/L in the GIK and control group at baseline. At 6 hours after randomisation the mean BGL in the GIK group increased to 10.4mmol/L; in the control group it decreased to 8.2mmol/L. By 24 hours after randomisation, the mean BGL was 8.6mmol/L in the GIK group and 7.5mmol/L in the control group. When the baseline BGL in the control group were divided into tertiles, higher baseline BGL were associated with higher mortality at 30 days (see sub group analysis).		

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

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>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,</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</td>
<td><u>Blood glucose levels at admission (first morning) and discharge (usually day 5)</u>
<table>
<tr><th>Blood glucose (mmol/L)</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 (0.93)</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>Diabete</td><td>47 (100)</td><td>7 (15)</td><td>15 (32)</td><td>25 (53)</td></tr>
</table>
</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</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</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
		mean age 65). Treatment for hypertension was most common amongst those with IGT. **Exclusion:** known diabetes and residence outside catchment area	(BG-120). Classifications were based on WHO definitions from 1998. **Normal glucose tolerance (NGT):** fasting blood glucose (FBG) <6.1mmol/L, 120 minute blood glucose (BG-120) <7.8mmol/L **Impaired glucose tolerance:** FBG <6.1mmol/L, BG-120 7.8-11.0mmol/L **Diabetes:** FBG≥6.1mmol/L and/or BG-120 ≥11.1mmol/L	s Data are n (%) **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/L increase in BG-60 was 1.38 (CI 1.16-1.64). With a cutoff value of 8.6mmol/L 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.		Karolinska Institute and Aventis U.S	months. Other components of the metabolic syndrome do not add further predictive value.
Ishihara	To investigate	200 non-	Plasma glucose	**Results of OGTT at admission and at discharge**	Only	No financial	Authors

<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>et al 2006 (634)</td>
<td>whether admission hyperglycaemia in non-diabetic patients with AMI is a surrogate for previously undiagnosed abnormal glucose tolerance</td>
<td>diabetic patients with AMI were categorised at admission into 3 groups:
<u>Group 1</u>: (no or mild admission hyperglycaemia <7.8 mmol/L)
<u>Group 2:</u> (moderate admission hyperglycaemia ≥7.8 and <11.1 mmol/L)
<u>Group 3:</u> (severe admission hyperglycaemia ≥11.1mmol/L).
<u>Exclusions:</u> patients with</td>
<td>was measured at 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/L and/or 2-h post-load glucose ≥11.1 mmol/L</td>
<td><u>(1 week after admission)</u>
<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</td>
<td>assessed at admission and one week after (discharge)</td>
<td>support for this study</td>
<td>conclude that 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
		previous diagnosis of diabetes, those who died during hospitalisation and those who underwent coronary bypass surgery. The mean admission glucose concentration was 8.9 mmol/L. There were 81 patients in group 1, 83 in group 2 and 36 in group 3.There were no significant differences in	**IGT:** FBG< 7.0mmol/L and 2h glucose of 7.8-11.0 mmol/L **NGT:** FBG<7.0 mmol/L and 2h glucose <7.8 mmol/L The values of 7.8mmol/L and 11.1mmol/L 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	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) 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>baseline characteristics, except lower prevalence of prior MI, higher Killip class and higher HbA_{1c} in patients with higher admission glucose levels.</td><td>myocardial ischaemia persisting longer than 30 mins and concomitant electrocardiographic changes.</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</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/L.</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.</td><td><u>Mean blood glucose</u>
Mean blood glucose at admission was 6.5mmol/L, mean 2-h postload blood glucose OGTT was 9.2mmol/L at discharge (day 4 or 5) and 9.0mmol/L 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</td><td>0.53</td><td>0.0</td><td>0.88</td><td>0.5</td></tr>
</table></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>abnormalities can be identified in the early course of an MI.</td>
<td>Patients had a mean age 63.5 years, 68% were male and mean blood glucose at admission was 6.5mmol/L.
<u>Exclusion:</u> patients with known diabetes and aged >80 years or serum creatinine concentration of 200µmol/L</td>
<td>Definitions for diabetes and IGT were taken from WHO 1998 classification and the fasting blood glucose criteria was adopted from the ADA 1997
<u>Diabetes:</u> fasting blood glucose >6.0mmol/L or 2 hour postload blood glucose >11.0mmol/L or both.
<u>Impaired glucose tolerance:</u> fasting blood glucose <6.1mmol/L and 2 hour blood glucose 7.8-11.0 mmol/L
<u>Normal glucose</u></td>
<td>
<table>
<tr><td>hypertension</td><td>(0.29-0.91)</td><td>3</td><td>(0.56-1.37)</td><td>7</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>
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/L 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>
</table>
</td>
<td></td>
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<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><u>tolerance:</u> fasting blood glucose <6.1mmol/L and 2 hour blood glucose <7.8mmol/L
<u>AMI:</u> defined as European Society of Cardiology and the American College of Cardiology.</td><td>
<table>
<tr><td>FBG day 4 (for increase in 1mmol/L 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>0.044</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>0.024</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 HbA1c 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</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</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</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><td></td><td>Prevalence</td><td>Sensitivity</td><td>Specificity</td><td>PPV</td></tr>
<tr><td>FPG≥5.6 mmol/L</td><td>48</td><td>81.6%</td><td>64.7 %</td><td>46.3%</td></tr>
<tr><td>APG≥7.8 mmol/L</td><td>30</td><td>65.8%</td><td>83.3 %</td><td>59.5%</td></tr>
</table></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/L and/or APG≥ 7.8mmol/L was highly sensitive for identifying diabetes. Although</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 fasting and admission glucose (applied individually or in combination) as markers of previously undiagnosed diabetes in patients with ACS.	between the various categories of glucose tolerance. **Exclusion:** patients with previously known diabetes or IGT.	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 of American Diabetes Association 2004 criteria: **Normal Glucose Tolerance:** 2-h plasma glucose <7.8mmol/L or FPG <5.6mmol/L **Impaired Glucose Tolerance:** 2-h	FPG≥5.6 or APG≥7.8 mmol/L: 52 / 89.5% / 56.9 % / 43.6% 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/L. This is the FBG value with the best sensitivity and 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/L; this cut-off point was associated with sensitivity of 65.8% and specificity of 82.4%.			weakly specific, this simple algorithm could offer a practical initial screening tool at the acute setting in the high risk population with ACS.

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
			plasma glucose 7.8-11.0mmol/L or **Impaired Fasting Glucose:** FPG 5.6-6.9mmol/L **Diabetes:** 2-h plasma glucose ≥11.1mmol/L or FPG >7.0mmol/L **Admission Plasma Glucose (APG)** was stratified into 3 groups: <7.8mmol/lL, 7.8-11.0mmol/L and ≥11.1mmol/L. **AMI:** diagnosis based on joint recommendations by European Society of Cardiology and American College				

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 Cardiology.				
Oswald & Yudkin 1987 (Ref ID:	Clinical audit (prognostic design)/ to investigate validated levels of hba1c indicative of diabetes in order to assess the contribution of undiagnosed diabetes to admission hyperglycaemia after AMI	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 of glucose solution. There were no significant difference between patients sampled for plasma	Categorisation of Hba1c **Clearly normal (group 1):** <6.9% **Borderline (group 2):** 6.9-7.8% **Clearly abnormal hba1c (group 3):** >7.8% Diabetes and IGT were defined according to the WHO criteria using venous plasma. 2 elevated glucose values were required in the absence of symptoms.	**Hba1c** A level of Hba1c >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/L 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 91% (CI 85 to 97%).	293/397 patients survived. 117 patients had an OGTT at 7-10 days (before discharge). 61 of these patients went on to have an OGTT at 3 months and 49 randomly selected patients had their		In four patients with fasting plasma glucose <8mmol/L but with 2h plasma glucose ≥11mmol/L at 3 months follow-up, the OGTT was repeated at 6 months from AMI. Paper does not report specific definitions of overt diabetes and diabetes but assumption that overt

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
		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.			first OGTT at 3 months so a total of 110 had a follow-up at 3 months.		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