Articles

Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview

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Summary

Background High blood glucose concentration may increase risk of death and poor outcome after acute myocardial infarction. We did a systematic review and meta-analysis to assess the risk of in-hospital mortality or congestive heart failure after myocardial infarction in patients with and without diabetes who had stress hyperglycaemia on admission.

Methods We did two searches of MEDLINE for English-language articles published from 1966 to October, 1998, a computerised search of Science Citation Index from 1980 to September, 1998, and manual searches of bibliographies. Two searchers identified all cohort studies or clinical trials reporting in-hospital mortality or rates of congestive heart failure after myocardial infarction in relation to glucose concentration on admission. We compared the relative risks of in-hospital mortality and congestive heart failure in hyperglycaemic and normoglycaemic patients with and without diabetes.

Findings 14 articles describing 15 studies were identified. Patients without diabetes who had glucose concentrations more than or equal to range 6·1–8·0 mmol/L had a 3·9-fold (95% CI 2·9–5·4) higher risk of death than patients without diabetes who had lower glucose concentrations. Glucose concentrations higher than values in the range of 8·0–10·0 mmol/L on admission were associated with increased risk of congestive heart failure or cardiogenic shock in patients without diabetes. In patients with diabetes who had glucose concentrations more than or equal to range 10·0–11·0 mmol/L the risk of death was moderately increased (relative risk 1·7 [1·2–2·4]).

Interpretation Stress hyperglycaemia with myocardial infarction is associated with an increased risk of in-hospital mortality in patients with and without diabetes; the risk of congestive heart failure or cardiogenic shock is also increased in patients without diabetes.

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Introduction

An unusually high prevalence of glucosuria in patients without diabetes who have acute myocardial infarction was noted as far back as 1931.[1] Since then, up to half of these patients with acute myocardial infarction have been recognised as having raised blood glucose concentrations.[2,3] Moreover, a positive association between hyperglycaemia at the time of the event and mortality from myocardial infarction has been noted.[4]

Although the mechanisms underlying this association are not fully understood, evidence that use of insulin to lower glucose concentrations decreases mortality in patients with diabetes who have myocardial infarction[5] suggests that hyperglycaemia is not simply an epiphenomenon of the stress response mediated by cortisol and noradrenaline. In patients who have had myocardial infarction, the lack of insulin associated with hyperglycaemia may lead to a decrease of glycolytic substrate for cardiac muscle and excessive free fatty acids. These changes may reduce myocardial contractility at increased oxygen cost, lead to pump failure, and promote arrythmias.[6] Consequently, hyperglycaemia at the time of myocardial infarction in patients with and without diabetes may be an important and potentially modifiable risk factor for poor outcome.

We systematically searched for, reviewed, and assessed published evidence on the association between stress hyperglycaemia and in-hospital mortality and congestive heart failure in patients with and without diabetes, admitted with myocardial infarction.

Methods

Selection of articles

Two independent researchers did a computerised MEDLINE search of published articles (from 1966 to October, 1998). One researcher was assisted by a medical librarian experienced in literature searches. We searched by the subject headings "blood glucose" and "myocardial infarction", text words "hyperglycemia", "euglycemia", and "hypoglycemia", and methodology terms (including subject headings "incidence", "mortality", "follow-up studies", "cohort studies", and "prognosis", and text words "natural history", "course", and "predict") to try to achieve maximum sensitivity.[7]

In addition, we did a computerised search of the Science Citation Index from 1980 to September, 1998, to retrieve all articles citing any one of three key studies.[3,8,9] The bibliographies of all relevant articles were searched manually for additional articles, and experts in the field were contacted to identify any further citations. English-language articles reporting original data were eligible for inclusion in the study. Letters and review articles were searched for additional references, but were not included in the meta-analysis.

Study reference	Year of myocardial infarction	Year published	Number of patients with myocardial infarction	Number excluded from analysis	Definition of hyperglycaemia (mmol/L)	Number of patients without diabetes who had stress hyperglycaemia	Number of patients with diabetes who had stress hyperglycaemia	Reported outcome	Blood glucose
Patients without diabetes									
3	NS	1986	397	161*†	⩾8	112 (47%)	..	Died	Admission/plasma
21	1967	1975	169	0	>6·7	80 (47%)	..	Died	Fasting/NS
22	1985–87	1989	330	3†	>6·7‡	119 (36%)	..	CHF, died	Admission/plasma
23	NS	1981	99	6†	⩾6·1	66 (71%)	..	Died	Fasting/plasma
24§	1980–85	1991	714	0	>8	23 (3%)	..	CHF or shock, died	Fasting/NS
25	1981–83	1993	2802	0	>10	129 (5%)	..	Shock	Admission/NS
26	NS	1989	277	0	⩾8‖	118 (43%)	..	Died	Admission/plasma
27	NS	1979	40	0	⩾6·7¶	17 (43%)	..	CHF or shock, died	Fasting/plasma
Patients with diabetes									
17**	1984–87	1994	208	68†	⩾10	..	97 (69%)	Died	Admission/NS
17**	1990–92	1994	115	6†	⩾10	..	86 (79%)	Died	Admission/NS
25	1981–83	1993	663	0	>10	..	306 (46%)	Shock	Admission/NS
26	NS	1989	143	0	⩾11‖	..	120 (84%)	Died	Admission/plasma
28	1967–83	1984	417	121†	⩾10	..	203 (69%)	Died	Admission/NS

CHF=congestive heart failure; Shock=cardiogenic shock; NS=not stated.
*Patients with newly diagnosed diabetes excluded.
†Patients excluded because glucose not drawn on admission.
‡Paper reported data with cut-off values of 6·7 mmol/L and 10·0 mmol/L; lower cut-off was chosen for consistency.
§Patients with diabetes excluded because outcomes reported in relation to glucose on admission only for those without diabetes.
‖Paper reported data with cut-off values of 8 mmol/L and 11 mmol/L; lower cut-off used for patients without diabetes and higher for patients with diabetes.
¶Paper reported glucose concentration for each patient; cut-off values of 6·7 mmol/L (for relative risk of mortality) and 8·0 mmol/L (for relative risk of congestive heart failure) chosen for consistency with other studies.
**Patients without diabetes excluded because outcomes were reported in relation to glucose on admission only for patients with diabetes.

Table 1: **Prospective studies included in meta-analysis**

The full text of all articles thought by either of the two searchers to be relevant was obtained. We deleted details of the investigators and their institution, funding, sources of articles, and any acknowlegments, and the modified text was assessed independently for relevance by the two searchers. An article was judged relevant if it was a cohort study or clinical trial of patients admitted with acute myocardial infarction, in which baseline blood glucose concentrations had been measured on or soon after admission, and in which outcomes (in-hospital mortality, or development of congestive heart failure or cardiogenic shock after myocardial infarction) were reported in relation to the baseline blood glucose concentration. Agreement between the two searchers on selection of relevant studies was measured, and any disagreements were resolved by consensus.

Retrieved studies were included in the review if they: assembled and prospectively followed an inception cohort; explicitly stated that blood glucose was drawn within 24 h of admission; reported follow-up of at least 70% of patients to discharge; and reported outcomes according to glucose cocentrations at admission. Studies that did not explicitly report the proportion of patients followed up or the timing of blood glucose measurement, and those that followed up less than 70% of patients were excluded.

Definition of diabetes and hyperglycaemia

Data for patients with and without diabetes were analysed separately. Patients were classified as having diabetes if they had a reported history of diabetes. We did not try to integrate glycated haemoglobin on admission, or glucose concentrations, because glycated haemoglobin was not measured in all studies and assays are not standard across laboratories, and because stress glucose concentrations that correspond to diabetes cut-off values (ie, fasting plasma glucose 7·0 mmol/L or 2 h glucose 11·1 mmol/L on a 75 g oral glucose tolerance test) are undefined. We defined hyperglycaemia according to the definitions used in the individual studies, and therefore the threshold glucose concentration used to define hyperglycaemia varied from study to study.

Statistical analysis

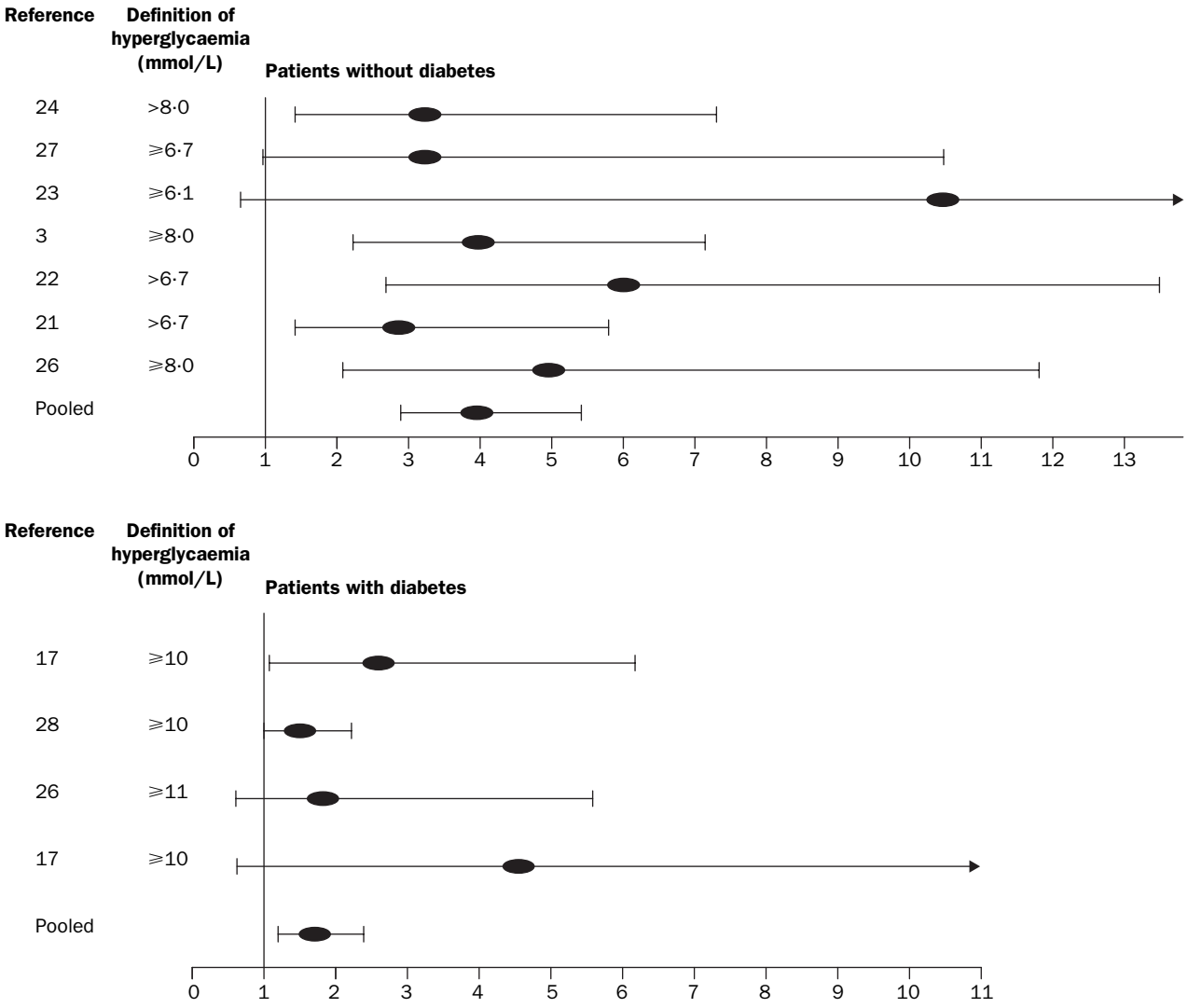
We calculated κ coefficients for agreement between the two searchers on the inclusion of studies. For each study, the relative risk and 95% CI for death or congestive heart failure or cardiogenic shock in hyperglycaemic compared with non-hyperglycaemic patients after myocardial infarction was calculated. We calculated relative risks separately for patients with and without diabetes. The approach of DerSimonian and Laird[10] (random-effects model) was used to generate a summary estimate of relative risk. We assessed statistical heterogeneity among the studies by χ^2 analysis.

Results

The two MEDLINE searches yielded 49 and 217 citations, respectively. From the titles, abstracts, or both, 49 of the 266 citations were thought to be relevant by one or both of the searchers (κ=0·77), and the full text of these articles was retrieved. After review of the full text, 19 articles from the MEDLINE search were judged relevant (for agreement between searchers κ=0·83). Two additional relevant articles were found by searching the bibliographies; the Science Citation Index search yielded no additional relevant articles.

Seven of the 21 relevant articles were excluded because of methods and reporting issues: the proportion of patients followed up was not reported in three articles,[11–13] the relation between glucose and an outcome was not expressed quantitatively in one article[14] or was described only for patients treated intensively with insulin in one randomised controlled trial,[15] and the timing of death[8,16] or glucose measurement[8] could not be determined in two articles. 14 papers, representing 15 cohort studies (one paper described two cohorts[17]), were included in the overview.

Four of the 15 selected cohort studies reported only the mean glucose concentration in patients with and without outcome events. Mean glucose concentration on admission was consistently higher in patients who did not survive myocardial infarction than in those who did. In patients with diabetes who survived myocardial infarction in two studies,[18,19] mean glucose concentrations on admission were 16·3 mmol/L and 10·0 mmol/L, respectively, compared with 19·7 mmol/L and 17·9 mmol/L in patients who died ($p<0·05$). In patients without diabetes in two other studies,[9,20] mean glucose concentrations on admission in survivors of myocardial infarction were 7·55 mmol/L and 7·8 mmol/L, respectively, compared with 9·85 mmol/L and 11·3 mmol/L in patients who did not survive ($p<0·01$).



Unadjusted relative risk of in-hospital mortality in patients with and without stress hyperglycaemia on admission

Furthermore, one study reported a higher mean glucose concentration on admission in patients with diabetes who developed heart failure than in those who did not (19·7 *vs* 16·3 mmol/L, p<0·05).[18] The data reported from these four studies were insufficient to calculate the relative risk of mortality or heart failure in patients with and without stress hyperglycaemia on admission. Therefore, they were not included in the quantitative meta-analysis.

The remaining 11 studies reported outcomes in patients with and without stress hyperglycaemia[3,17,21–28] (table 1). The mean age for patients in these studies ranged from 50 years to 68 years. Threshold glucose concentrations used to define stress hyperglycaemia ranged from 6·7 mmol/L to 11·0 mmol/L (on admission) or from 6·1 mmol/L to 8·0 mmol/L (fasting, the morning after admission). The proportion of patients who had stress hyperglycaemia ranged from 3% to 71% in patients without diabetes and from 46% to 84% in patients with diabetes. Relative risks for mortality and pump failure were calculated separately for patients with and without diabetes in each study and the results were combined to generate a summary risk estimate.

The pooled unadjusted relative risk of in-hospital mortality after myocardial infarction in 1856 patients without diabetes who had stress hyperglycaemia on admission was 3·9 (95% CI 2·9–5·4, figure and table 2) compared with patients without diabetes and no hyperglycaemia on admission. In 688 patients with diabetes who had stress hyperglycaemia on admission, the pooled unadjusted relative risk was 1·7 (1·2–2·4, figure) compared with patients who had diabetes but no hyperglycaemia on admission. There was no significant heterogeneity in these results (p>0·1). Adjusted relative risks of mortality after myocardial infarction in patients with stress hyperglycaemia compared with those without stress hyperglycaemia were reported in two of the ten studies. In one study,[24] patients without diabetes who had hyperglycaemia on admission had a 2·8-fold (0·9–8·30) higher risk of mortality than those without hyperglycaemia on admission, after adjustment for age. In the second study,[26] the relative risk of mortality after myocardial infarction associated with stress hyperglycaemia in patients without diabetes was 2·48 (1·52–4·97) after adjustment for age and Killip class.

Congestive heart failure or cardiogenic shock, were reported in four studies. Stress hyperglycaemia was associated with an increased risk of congestive heart failure or cardiogenic shock in patients without diabetes; this association was not seen in patients with diabetes

Study (reference)	Definition of hyperglycaemia (mmol/L)	Number of events/patients at risk		Unadjusted relative risk (95% CI)
		Patients with hyperglycaemia on admission	Patients without hyperglycaemia on admission	
Patients without diabetes				
O'Sullivan (24)*	>8	5/23	47/691	3·20 (1·40–7·28)
Sewdarsen (26)*	⩾8	22/118	6/159	4·94 (2·07–11·80)
Ravid (21)	>6·7	23/80	9/89	2·84 (1·40–5·78)
Bellodi (22)	>6·7	24/119	7/208	5·99 (2·66–13·49)
Oswald (3)	⩾8	43/112	12/124	3·97 (2·21–7·13)
Soler (23)	⩾6·1	12/66	0/27	10·45 (0·64–170·45)
Lewandowicz (27)	⩾6·7	7/17	3/23	3·16 (0·95–10·46)
Pooled relative risk				3·93 (2·86–5·39)
Diabetic patients				
Lynch (17)	⩾10	29/97	5/43	2·57 (1·07–6·19)
Lynch (17)	⩾10	17/86	1/23	4·55 (0·64–32·39)
Sewdarsen (26)†	⩾11	29/120	3/23	1·85 (0·62–5·58)
Gwilt (28)	⩾10	75/203	23/93	1·49 (1·00–2·22)
Pooled relative risk	. .	. .	. .	1·71 (1·22–2·40)

*Excludes patients with diabetes.
†Excludes patients without diabetes.

Table 2: **Relative risk of in-hospital mortality after myocardial infarction in patients with hyperglycaemia on admission compared with patients without hyperglycaemia**

(table 3). Results of these four studies could not be pooled because of statistical heterogeneity. Adjusted relative risk of mortality was reported in one study, in which patients without diabetes who had stress hyperglycaemia had a 3·1-fold (1·2–7·4) higher risk of congestive heart failure or cardiogenic shock than those without stress hyperglycaemia after adjustment for age.[24]

Discussion

We showed that patients without diabetes who have stress hyperglycaemia on admission for acute myocardial infarction are at increased risk of in-hospital mortality and congestive heart failure or cardiogenic shock. Several possible mechanisms may explain this observation.

First, hyperglycaemia is a reflection of relative insulin deficiency, which is associated with increased lipolysis and excess circulating free fatty acids; this effect may be exaggerated in cases of acute stress such as myocardial infarction.[29,30] Free fatty acids, although normally the substrate of choice for healthy myocardium, are toxic to ischaemic myocardium and may lead to damaged cardiac-cell membranes, calcium overload, and arrythmias.[6] Moreover, in animal studies, high concentrations of free fatty acids during myocardial ischaemia increase myocardial oxygen demands and reduce myocardial contractility.[31] β-blockers suppress the increase in free fatty acids in patients with myocardial infarction, and may lessen the harmful effects of hyperglycaemia and insulin deficiency.[32] We did not explore this hypothesis in the overview because the only study that stated that β-blockers were administered provided no information about the interaction between these drugs and stress hyperglycaemia on the risk of outcomes after myocardial infarction.[25] Insulin deficiency may also limit the ability of cardiac muscle to take up glucose for anaerobic metabolism. In animal studies, preservation of myocardial function during ischaemia correlates with increased uptake and metabolism of glucose.[33] The potential importance of insulin deficiency is also highlighted by randomised controlled trials in which insulin administered to patients without diabetes who have had acute myocardial infarction improved clinical outcomes.[34] A similar observation was reported by the DIGAMI study,[35] in which 620 patients with diabetes who had acute myocardial infarctions were randomly assigned an insulin infusion followed by multidose subcutaneous insulin treatment for at least 3 months, or conventional management. In that study, insulin lowered mortality by 28% (p=0·011) after a mean follow-up of 3·4 years, and higher glucose concentrations on admission predicted higher risk of mortality.[36]

Second, acute hyperglycaemia may precipitate an osmotic diuresis. The resulting volume depletion may interfere with the Frank-Starling mechanism, an important compensatory mechanism for the failing left ventricle in which increased end-diastolic volume leads to increased stroke volume.[37,38]

Third, stress hyperglycaemia may be a marker of more extensive cardiac damage in acute myocardial infarction.[39] More extensive cardiac damage may lead to a greater rise in stress hormones (promoting glycogenolysis and hyperglycaemia) and may also

Study	Outcome (CHF/Shock)	Definition of hyperglycaemia (mmol/L)	Number of events/patients at risk		Unadjusted relative risk (95% CI)
			Patients with hyperglycaemia on admission	Patients without hyperglycaemia on admission	
Patients without diabetes					
Bellodi (22)	CHF	>10	18/21	88/306	2·98 (2·33–3·82)
Leor (25)	Shock	>10	20/129	47/2673	8·82 (5·39–14·43)
Lewandowicz (27)	CHF or shock	>8	4/6	15/34	1·51 (0·77–2·98)
O'Sullivan (24)	CHF or shock	>8	13/23	181/691	2·16 (1·48–3·15)
Patients with diabetes					
Leor (25)	Shock	>10	10/306	12/357	0·97 (0·43–2·22)

CHF=congestive heart failure; Shock=cardiogenic shock.

Table 3: **Relative risk of pump failure after myocardial infarction in patients with hyperglycaemia on admission compared with patients without hyperglycaemia**

increase the risk of congestive heart failure and mortality. Thus, stress hyperglycaemia could simply be an epiphenomenon reflecting the most severe cardiac damage. However, stress hyperglycaemia is an imperfect marker of the extent of cardiac damage, since many other factors in addition to stress hormones (such as insulin resistance and the capacity of the pancreas to secrete insulin) contribute to the regulation of glucose concentrations. Indeed, other research on the relation between glucose concentration and infarct size is inconclusive, with some studies showing no correlation[40] or weak correlation.[3] Moreover, the clinical-trial data we have summarised, which suggest that insulin may be cardioprotective, support the view that stress hyperglycaemia is of pathophysiological importance in patients with acute myocardial infarction.

Fourth, patients who develop stress hyperglycaemia are likely to be dysglycaemic when not stressed. Patients with dysglycaemia (who have blood glucose concentrations higher than the normal range but lower than the threshold for diabetes) are at a higher risk of cardiovascular disease than patients who have normal blood glucose,[41] and may have a worse prognosis after acute myocardial infarction because of more extensive underlying coronary artery disease.

Stress hyperglycaemia was also associated with an increased risk of mortality in patients with diabetes who had myocardial infarction, but the effect was smaller than that in patients without diabetes. There are several possible reasons. First, the threshold values that defined hyperglycaemia in the individual studies may have been too low to distinguish between patients with diabetes who did and did not have stress hyperglycaemia. For example, in the DIGAMI study, a striking increase was seen in long-term mortality in patients who had very high glucose concentrations on admission; patients in the upper tertile of whole-blood glucose concentrations (>16·5 mmol/L, equivalent to plasma glucose of 18·0 mmol/L) had about a 50% higher risk of death than those in the lowest and middle tertiles (⩽13·0 mmol/L and >13·0–16·5 mmol/L, respectively).[36] Moreover, the definition of stress hyperglycaemia is intrinsically difficult in patients with diabetes because the unstressed baseline concentration of glucose is not known. The observation in patients with diabetes that higher mean glucose concentrations were associated with higher mortality strongly supports this possibility.

Second, patients with diabetes are more likely to receive insulin for hyperglycaemia during and after myocardial infarction. This treatment may lessen the rise in free fatty acids during myocardial infarction, promote myocardial uptake of glucose for anaerobic metabolism and decrease coagulability because of reduced production of thromboxane A[42] and PAI-1 activity.[43]

Third, many adverse factors, in addition to hyperglycaemia, contribute to poor outcome in patients with diabetes who have myocardial infarction. For example, patients with diabetes have worse ventricular function in non-infarcted myocardium than patients without diabetes, which limits the ability of the non-infarcted myocardium to compensate.[44] In addition, the higher prevalence of hypertension in patients with diabetes[45] contributes to left-ventricular diastolic dysfunction, which may lead to congestive heart failure even with minimum impairment of left-ventricular systolic function. Patients with diabetes may also be less likely than those without diabetes to receive thrombolytic agents.[46]

Our results are limited by several factors: the definition of hyperglycaemia, concomitant treatment, and use of thrombolytic agents differed in each study; relative risks were not adjusted for other prognostic factors; the total number of outcome events in the pooled studies was small; and only published studies were included. Nevertheless, the strong and consistent association between stress hyperglycaemia on admission and poor prognosis seen in patients with and without diabetes suggests that glucose is an important risk factor for morbidity and mortality after myocardial infarction. Further research is needed to find out whether reversal of stress hyperglycaemia and the associated flux of free fatty acids at the time of myocardial infarction can improve the clinical outcome for these patients.

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