Under utilisation of evidence-based treatment partially explains for the unfavourable prognosis in diabetic patients with acute myocardial infarction

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Aims The prognosis after an acute myocardial infarction is worse for patients with diabetes mellitus than for those without. We investigated whether differences in the use of evidence-based treatment may contribute to the differences in 1-year survival in a large cohort of consecutive acute myocardial infarction patients with and without diabetes mellitus.

Methods We included patients below the age of 80 years from the Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA), which included all patients admitted to coronary care units at 58 hospitals during 1995–1998. In all 5193 patients had the combination of acute myocardial infarction and diabetes mellitus while 20 440 had myocardial infarction but no diabetes diagnosed. Multivariate logistical regression analyses were performed to evaluate the influence of diabetes mellitus on the use of evidence-based treatment and its association with survival during the first year after the index hospitalisation.

Results The prevalence of diabetes mellitus was 20.3% (males 18.5%; females 24.4%). The 1-year mortality was substantially higher among diabetic patients compared with those without diabetes mellitus (13.0 vs. 22.3% for males and 14.4 vs. 26.1% for female patients, respectively) with an odds ratio (OR) (95% confidence interval (CI)) in three different age groups: <65 years 2.65 (2.23–3.16); 65–74 years 1.81 (1.61–2.04) and >75 years 1.71 (1.50–1.93). During hospital stay patients with diabetes mellitus received significantly less treatment with heparins (37 vs. 43%; p<0.001), intravenous beta blockade (29 vs. 33%; p<0.001), thrombolysis (31 vs. 41%; p<0.001) and acute revascularisation (4 vs. 5%; p<0.003). A similar pattern was apparent at hospital discharge. After multiple adjustments for dissimilarities in baseline characteristics between the two groups, patients with diabetes were significantly less likely to be treated with reperfusion therapy (OR 0.83), heparins (OR 0.88), statins (OR 0.88) or to
be revascularised within 14 days from hospital discharge procedures (OR 0.86) while the use of ACE-inhibitors was more prevalent among diabetic patients compared to non-diabetic patients (OR 1.45). The mortality reducing effects of evidence-based treatment like reperfusion, heparins, aspirin, beta-blockers, lipid-lowering treatment and revascularisation were, in multivariate analyses, of equal benefit in diabetic and non-diabetic patients.

**Interpretation** Diabetes mellitus continues to be a major independent predictor of 1-year mortality following an acute myocardial infarction, especially in younger age groups. This may partly be explained by less use of evidence-based treatment although treatment benefits are similar in both patients with and without diabetes mellitus. Thus a more extensive use of established treatment has a potential to improve the poor prognosis among patients with acute myocardial infarction and diabetes mellitus.

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**Introduction**

Patients with diabetes mellitus have a more dismal prognosis following acute myocardial infarction than non-diabetic subjects. Despite considerable improvement in treatment of cardiovascular disease, a recent survey clearly showed that patients with diabetes mellitus have not benefited from this to the same extent as patients without diabetes mellitus.

Treatments that may be particularly effective in diabetic patients with myocardial infarction have often been withheld. One example is thrombolysis, which based on single case reports, was discouraged due to unverified worries for eye bleeding. Likewise, beta-blockade has often been withheld due to concerns about deterioration of metabolic control and blunting of warning signals of hypoglycaemia. Although only partly based on prospective trials, there is still evidence that aggressive treatment with beta-blockers and metabolic intervention improve the longevity in diabetic patients with acute myocardial infarction. In the DIGAMI-trial meticulous metabolic care offered promise for diabetic patients with myocardial infarction. In that study it was noted that the mortality in the control population was unexpectedly low. One possible reason for this finding could have been that the protocol stipulated extensive use of concomitant treatment e.g. beta-blockade, thrombolysis and aspirin. However, since the patients in the DIGAMI-trial represent a selected population it would be of interest to study the use of evidence-based treatment and their effect on treatment among diabetic and non-diabetic patients with acute myocardial infarction in an unselected patient population.

Today the Swedish Register of Information and Knowledge about Intensive Care Admission comprises data achieved from the majority of coronary care units in Sweden. Thus, this registry is well suited for a study of the actual prognosis for diabetic patients with acute myocardial infarction. It may also give an answer to the question whether a possible difference in outcome may relate to under utilisation of evidence-based treatment. The present study reports on these issues from a total cohort of 25,633 patients of whom 20.3% were known to have diabetes mellitus.

**Research design and methods**

The Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA), registers every patient admitted to the coronary care units of all participating hospitals. Information is reported on case record forms including 100 variables. On admission 30 variables are recorded including age, sex, smoking habits, hypertension, diabetes mellitus, hyperlipidemia, previous angina pectoris, previous myocardial infarction, previous coronary revascularisation, previous medication, symptoms, ECG changes at entry and key time points (‘previous’ refers to events occurring or medication started before the current admission). During the hospital stay another 37 variables are registered comprising biochemical markers, echocardiographic findings, thrombolytic and other pharmacological treatment, interventional procedures, serious arrhythmia and other major complications. At discharge 33 variables are recorded including complications, outcome and diagnosis during hospital stay and finally risk assessment with stress test, coronary angiography, revascularisation procedures and medication at discharge.

The criteria for the diagnosis of acute myocardial infarction are standardised and identical for all participating hospitals using the WHO criteria.
and the double upper level of normal of an appropriate biochemical marker (mainly CK-MB) as the biochemical criterion. ECGs are evaluated concerning the presence or development of Q-waves, ST-changes, T-wave inversions or bundle branch block. The criteria for the diagnosis of diabetes mellitus was based on either information from the patient of the disease at hospital admission or the prescription of insulin or oral anti-diabetic drugs at admission and/or at discharge. One-year mortality has been obtained by merging the RIKS-HIA database with the National Cause of Death Register covering the vital status of all Swedish citizens for the years 1995–1999. All recorded patients were informed and approved on participation in the register and the long-term follow-up. The National Board of Health and Welfare and the Swedish Data Inspection Board approved the register and the merging of registries.

Statistical analysis
Comparisons between different patient strata and different categories of hospitals were performed by chi-square tests for categorical variables, and Student’s t-test for continuous variables. Bivariate analyses and multiple covariate Cox regression analyses\(^{14}\) were used to identify any variable with a significant influence on treatment and mortality. All statistical analyses were performed with the SPSS 11.0 software program for personal computers.

Material
In 1995 19 hospitals participated in the register, increasing to 32 hospitals in 1996, 46 in 1997 and 58 in 1998. Data for this study was collected from 1995 to 1998 and comprised a total of 137 262 admissions at the 58 coronary care units. Because of an increased risk of concomitant disease among elderly patients, not covered by the registered variables, patients above 80 years of age were removed from the analysis. A total of 25 633 patients less than 80 years had a first recorded acute myocardial infarction in the registry, out of whom 5193 fulfilled our criteria for diabetes mellitus.

Source data verification was continuously performed by comparison of the register information to the patients’ hospital records in 50 randomly selected patients in 10 hospitals every year by an external monitor. In the first 1004 computer forms from 21 hospitals comprising 92 368 parameters there was an overall 94% agreement between the registered information and the source data in the patients’ records.

Results
The prevalence of diabetes mellitus in the total population was 20.3% (5193 out of 25 633 patients). This proportion was higher among females (24.4%) than in males (18.5%). The proportion of patients with diabetes mellitus increased with age and is presented in Fig. 1. Pertinent baseline characteristics from patients with and without diabetes mellitus are given in Table 1. The diabetic patients were somewhat older than the non-diabetic subjects. Previous cardiovascular diseases were significantly more common among diabetic patients who also were more frequently treated with cardiovascular drugs.

Treatment during hospitalisation and some important complications are given in Table 2, which demonstrates that several evidence-based types of treatment were less often administered to patients with diabetes mellitus. Serious events were, however, more common among the diabetic patients. At hospital discharge there was a similar pattern regarding several treatment modalities apart from ACE-inhibitors and diuretics that were more frequently used among the diabetic patients (Table 3) probably reflecting that these patients more often developed congestive heart failure during the...
hospital period (Table 2). Considering the discrepancies between patients with and without diabetes mellitus multiple regression analyses, including 27 variables of clinical relevance in this context, were applied regarding the use of treatment during hospitalisation and at hospital discharge. The outcome of this analysis is presented in Fig. 2, which reveals that thrombolytic treatment (also when adjusted for ST segment elevation) and the use of heparins, statins and revascularisation procedures were significantly less common even after adjustment for possible confounding factors, while the use of ACE-inhibitors remained significantly more common.

The crude mortality rate for diabetic patients was consistently higher than for those without diabetes in all age groups. This was particularly pronounced below the age of 65 years (Fig. 3). A Kaplan–Meyer survival analysis for all patients is presented in Fig. 4. The adjusted relative risk for mortality among diabetic patients during the first year of follow-up was 1.48 (95% confidence interval (CI) 1.30–1.60; *p* <0.001) compared with patients without diabetes. The mortality rate among male patients without diabetes was 13.0 % compared to 22.3 % among those with diabetes (odds ratio (OR) 1.92, 95% CI 1.74–2.11; *p* <0.001). The corresponding figures for female subjects were 14.4% and 26.1% (OR 2.10, 95% CI 1.85–2.38; *p* <0.001).

The impact of evidence-based treatment on 1-year mortality among diabetic and non-diabetic patients was tested in logistic regression models. This revealed beneficial effects of several types of treatment without any difference between diabetic and non-diabetic patients (Fig. 5).

**Discussion**

This study demonstrated that diabetes mellitus is common among unselected patients with acute myocardial infarction. It was an independent predictor of mortality during the first year of follow-up with the largest impact in younger age groups. The

<table>
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<th>Age (years, median, range)</th>
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<th>Diabetes n=5193</th>
<th>p-value</th>
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<th>Diabetes</th>
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<td>32</td>
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<tr>
<td>Statins</td>
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The mortality rate among male patients without diabetes was 13.0 % compared to 22.3 % among those with diabetes (odds ratio (OR) 1.92, 95% CI 1.74–2.11; *p* <0.001). The corresponding figures for female subjects were 14.4% and 26.1% (OR 2.10, 95% CI 1.85–2.38; *p* <0.001).

The impact of evidence-based treatment on 1-year mortality among diabetic and non-diabetic patients was tested in logistic regression models. This revealed beneficial effects of several types of treatment without any difference between diabetic and non-diabetic patients (Fig. 5).
study also demonstrated that several evidence-based treatment modalities seemed similarly efficacious in diabetic and non-diabetic patients, however, less well utilised among patients with diabetes mellitus.

The present population is an unselected and consecutive series of patients with myocardial infarction admitted to a large number of different hospitals. The only exclusion criterion was age above 80 years, a precaution taken to avoid influence of unrecorded co-morbidities that are in particular prevalent in an elderly population. Importantly there were no exclusions due to the presence or absence of specific risk factors, co-morbidities, anticipated adverse effects, participation in clinical trials or contraindications to certain medications. Moreover the representativeness of the present patient material was strengthened by the inclusion of all patients with myocardial infarction derived from a general population at centres.

### Fig. 2
Adjusted difference in treatment between patients with and without diabetes mellitus. The values are OR and 95% CI.

- **Reperfusion**: OR 0.83 (0.77-0.89), p <0.001
- **Heparin/Lwmh**: OR 0.88 (0.82-0.94), p <0.001
- **Aspirin**: OR 0.97 (0.87-1.08), p = 0.55
- **Betablockade**: OR 0.97 (0.87-1.07), p = 0.49
- **Statin**: OR 0.88 (0.80-0.97), p = 0.013
- **ACE-inhibition**: OR 1.45 (1.33-1.58), p <0.001
- **Revasc <14d**: OR 0.86 (0.75-0.98), p = 0.022

### Diabetes mellitus
- **No**
- **Yes**

### Fig. 3
One-year mortality (%) in three different age groups. Values above bars=OR; hatched bars=patients with diabetes mellitus; unfilled bars=patients without diabetes mellitus.

- **<65**: OR = 2.7
- **65-74**: OR = 1.8
- **≥75**: OR = 1.7

### Fig. 4
Kaplan–Meier curves showing cumulative mortality during 1-year follow-up. Dotted line=patients with diabetes mellitus; solid line=patients without diabetes mellitus.

- **Diabetes n = 4700**
- **No diabetes n = 19846**

Adjusted RR = 1.48 (1.3–1.60); p<0.001
with different levels of care including approximately two-thirds of all hospitals within Sweden. Many parameters were collected from these patients allowing for adjustment for confounding factors.

A disappointing finding was that the prognosis for diabetic patients with myocardial infarction continues to be considerably worse than in those without this disease. This finding was particularly evident in the youngest age groups. There were, however, no obvious gender related differences. Although the prevalence of diabetic patients increases by age it is notable that among patients with myocardial infarction, the prevalence already is high below the age of 65 (males=16%; females=21%). Thus, the total number of patients with the combination of diabetes mellitus and myocardial infarction is substantial and proper management of these patients will certainly influence the prognosis in myocardial infarction in a broad perspective. A reassuring finding was that many treatment modalities, accepted as the present standard as regards mortality reduction, seemed similarly effective for patients with and without diabetes mellitus. This finding was not surprising considering previous reports that for instance aspirin, beta-blockers, statins and ACE-inhibitors were beneficial in diabetic as well as non-diabetic populations. In this perspective it was discouraging to observe the less frequent use of several of these easily available therapies among diabetic patients. It is reasonable to assume that the prognosis for diabetic patients with myocardial infarction might improve by a more frequent utilisation of well-established therapeutic resources.

However, even if improved standards of treatment may favourably impact the prognosis it is unlikely that lack of utilisation of evidence-based therapy is the only or even most important explanation for the substantial over-mortality after an acute myocardial infarction in diabetic subjects already in younger age groups. Thus, there must be diabetes specific reasons contributing to the raised mortality. Among different possibilities, although, less amenable for treatment in the acute setting is a more diffuse and wide spread coronary artery disease and a possible diabetic cardiomyopathy. Also, metabolic factors may be of considerable importance as indicated by the beneficial effect of intensified insulin treatment in the DIGAMI-trial and a recent intensive care trial.

In conclusion diabetes mellitus is a common disease among patients with acute myocardial infarction. These patients account for a substantial

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<th>95% CI</th>
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Fig. 5 Multiple adjusted treatment effects on 1-year mortality in patients with and without diabetes mellitus. Values are OR and 95% CI.
over-mortality during the first year. This may partly be explained by less use of evidence-based treatment although it has similar beneficial effect on mortality in both patients with and without diabetes mellitus. A more extensive use of established treatment has a potential to improve the poor prognosis among people with diabetes and acute myocardial infarction. It is, however, also important that new treatment modalities, in particular directed towards improving the myocardial metabolism and hyperglycaemia, should be further explored.

Acknowledgements
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References