Temporal trends in mortality of patients with diabetes mellitus suffering acute myocardial infarction: a comparison of over 3000 patients between 1995 and 2003

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Aims Over the last decade, advances in treatment for patients sustaining an acute myocardial infarction (AMI) have reduced mortality rates. We aimed to assess whether patients with diabetes mellitus (DM) have derived similar benefits as patients without DM.

Methods and results We compared characteristics, management, and survival of patients with and without DM who sustained an AMI in 1995 (n = 1762) with a second group of patients who sustained an AMI in 2003 (n = 1642). All patients were followed up for 18 months or until death. Between 1995 and 2003 the prevalence of DM in AMI patients increased from 12.5 to 16.6% (P, 0.001). Involvement of cardiologists, provision of secondary prevention agents and early revascularization rates improved in both groups. Thirty-day mortality improved significantly in patients with and without DM [40% (P = 0.006) and 30% (P < 0.001) relative reductions, respectively]. Despite this, there was no significant change in mortality at 18 months in patients with DM when comparing 1995 and 2003 (absolute mortality 38.0 vs. 36.4%, P = 0.71). The interaction between DM and study period in predicting long-term mortality was highly significant (P = 0.008); this persisted after adjustment for baseline characteristics and treatment variables.

Conclusion Although early post-AMI mortality has fallen in patients with and without DM, these improvements were only maintained in the longer term in those without DM; more effective diabetes-related management strategies are required post-AMI.

INTRODUCTION

Over the last decade management of acute myocardial infarction (AMI) has advanced significantly; randomized controlled trials have guided the introduction of increasingly advanced reperfusion, revascularization, and secondary prevention strategies with resulting improvements in mortality.¹,² During this period, there has also been a substantial rise in the prevalence and incidence of type 2 diabetes mellitus (DM), a trend that is predicted to continue over the next 25 years.³ Whether patients with DM have benefited from the improvements in outcome to a similar extent as patients without DM is unclear. It is therefore timely and important to evaluate the effect of improved therapies for AMI in patients with DM outside the setting of a randomized controlled trial.

We therefore sought to compare the temporal changes in short and long-term mortality using well-characterized groups of patients, the first recruited during 1995 and the second cohort in 2003.

METHODS

Data collection

We performed a comparative analysis of the Evaluation of Methods and Management of Acute Coronary Events (EMMACE)-1 and EMMACE-2 prospective cohort studies.⁴,⁵ Both examined outcomes in consecutively admitted, unselected patients with confirmed acute coronary syndromes (ACS) in multiple adjacent hospitals (within the catchment area of one tertiary centre, performing all
interventional procedures) in Yorkshire, UK. Patients were recruited over a 3-month period during 1995 in EMMACE-1 and a 6-month period during 2003 in EMMACE-2. Baseline patient characteristics, inpatient and discharge treatment variables, and all-cause mortality over 18 months from hospital admission were recorded. All patients provided written informed consent to participate in the studies, which were approved by the appropriate regional and local research Ethics Committees, in accordance with the declaration of Helsinki.

Data collection was performed as previously described. In brief, potential participants in both cohorts were identified through clinical coding, coronary care registers, and biochemistry laboratory cardiac biomarker assay databases. All consenting patients were enrolled in the study at which point their medical records were used for data collection. The UK Office of National Statistics provided long-term mortality data; 18-month mortality data are presented for all patients.

In keeping with the evolving definitions of ACS, the recruitment criteria for both EMMACE studies differed. In order to allow direct comparison of cohorts, we selected only validated cases of AMI using World Health Organisation (WHO) criteria, stipulating the need for any two of ischaemic chest pain, cardiac enzyme, or biomarker elevation [creatinine kinase or the MB fraction of this more than twice the upper reference range or troponin I (Beckman Coulter Ltd) ≥ 0.5 ng/mL] and serial ECG changes.

Outcomes and measures
The following definitions are used in the characteristic data. Age, heart rate, and systolic blood pressure refer to measurements taken at the point of admission. Individuals with DM were identified on the basis of past history documented in the medical records or the receipt of DM-related dietary or pharmacological intervention prior to the index event. Killip class (grades 1–4 indicating increasingly severe signs of heart failure) pertains to the highest recording during admission. Hypertension and hyperlipidaemia are defined as the use of anti-hypertensive or lipid-lowering medication at admission and heart failure, respectively, to any pre-admission diagnosis. Smoking is classified as present in current or previous smokers and ischaemic heart disease (IHD) is a composite of previous myocardial infarction, angina, or coronary revascularization. Reperfusion refers to the use of primary angioplasty or intravenous thrombolysis; revascularization refers to percutaneous coronary intervention or coronary artery bypass grafting performed in-hospital or planned prior to outpatient follow-up. Specialist cardiology input was defined as a recognized cardiologist taking direct responsibility for the management of a patient during their hospital admission. Secondary prevention agent use was assessed at patient discharge from hospital.

Statistical analysis
All statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). Continuous data are presented as mean (standard error) and categorical data as number (percentage). Groups were compared using analysis of variance for continuous data and Pearson’s $x^2$ for categorical data using two-sided tests. Survival of groups was compared with log-rank tests. Data from Kaplan–Meier curves were used to calculate quantitative mean survival improvements between 1995 and 2003 in cohorts with and without DM. Statistical significance was accepted at $P < 0.05$, though the multiple comparisons of cohort characteristics displayed in Table 1 should be interpreted with more caution; specific correction of this figure is difficult given the non-independence of test variables. The interaction between diabetes status and study period in predicting mortality was assessed using logistic regression analysis with additional adjustment for all baseline risk and treatment factors included in Table 1.

Results
A total of 2096 patients with a discharge diagnosis of AMI were recruited in the EMMACE-1 study in 1995. After applying WHO diagnostic criteria to medical record data, 1770 cases were validated for inclusion in our analysis. Within the 2499 cases of confirmed ACS in EMMACE-2 in 2003, 1642 suffered AMI according to WHO diagnostic criteria and were included in this study.

Patient characteristics
Table 1 summarizes the characteristics of patients presenting with AMI in the years 1995 and 2003. Over this period, the prevalence of DM in patients with AMI increased from 12.5–16.6% ($P < 0.001$). The mean age of the DM group was unchanged, though in 2003, it remained greater than that of non-diabetic patients ($P = 0.04$). Hypertension and hyperlipidaemia increased, though this may well relate to lowered diagnostic thresholds. Although significant declines in the prevalence of pre-existing IHD and heart failure were noted in the non-diabetic group, this was not the case in those with DM. Killip class fell by around one-third in each group. This may reflect the decreasing prevalence of AMI with ST-segment elevation between the two study periods, which is in agreement with other observers. Interestingly, this decline was much more apparent in DM sufferers (20% absolute decline compared with 10% in the non-diabetic group), resulting in proportionally fewer ST-segment elevation AMIs in DM patients in 2003 ($P < 0.001$). In-hospital cardiac arrest rates fell by 25–35% between study periods, though this reached significance only in the non-diabetic cohort.

Treatment
As expected, trends in the management of AMI have generally paralleled widely disseminated guidance. The provision of anti-platelet agents, HMGCoA reductase inhibitors, angiotensin-converting enzyme-inhibitors and beta-adrenergic receptor blockers rose significantly in both groups between 1995 and 2003; in 2003, these factors achieved parity between those with and without DM. Reperfusion rates declined over the study period, in parallel with the lower rates of ST-segment elevation AMI, though in 2003, around one-fifth of patients with ST-segment elevation AMI did not receive reperfusion. Primary angioplasty was not used during 1995 and rates remained almost negligible (one patient with DM, three patients without DM) in 2003. However, referral for revascularization increased five-fold in both groups.

Mortality
Absolute mortality data at 30 days and 18 months after hospital admission are shown in Table 2. Even with contemporary management strategies, the unselected AMI cohort in 2003 exhibited an 18-month mortality of 27%, half of this occurring in the first month. However, impressive declines in early mortality occurred overall and particularly so in those with DM (40.4% relative 30-day mortality reduction between 1995 and 2003 $P = 0.006$). These improvements were not sustained at 18 months in patients with DM, however, with no significant improvement in absolute
The most striking observation from our work is that, despite advances in evidence-based therapies and their delivery between 1995 and 2003, early mortality gains noted in all AMI patients were not sustained over the longer term in those without DM. Even in those without DM, the longer-term mortality reductions were less impressive than the early improvements after 18 months in those without DM, but not those with DM (P = 0.003 and P = 0.506, respectively).

The differential improvement in 18-month mortality for patients with and without DM is confirmed by the strong interaction between diabetes status and study period (P = 0.008); equitable gains in short-term survival are also verified (P for interaction 0.341). Given the complex changes in the baseline risk and management strategy of study cohorts between 1995 and 2003, further analyses adjusting for such factors were performed. Inclusion of variables (in Table 1) accounting for baseline and index event risk results in persistent significance of the interaction term at 18 months, but not at 30 days (P = 0.017 and P = 0.475, respectively); further addition of all treatment-related variables produces similar values (P = 0.028 and P = 0.87).

In order to quantify 18-month survival improvements over the study period, mean survival for the 1995 group with or without DM was subtracted from the respective group in 2003. This difference is demonstrated as the yellow highlighted area between the two survival curves for the groups with or without DM in Figure 1. Table 3 lists the absolute and relative improvements in each cohort. Between 1995 and 2003, no significant improvement in survival over 18 months was noted in patients with DM. This contrasts with a significant 27.3-day, or almost 20%, improvement in the survival of patients without diabetes.

### Discussion

The most striking observation from our work is that, despite advances in evidence-based therapies and their delivery between 1995 and 2003, early mortality gains noted in all AMI patients were not sustained over the longer term in those without DM. Even in those without DM, the longer-term mortality reductions were less impressive than the early improvements. Few studies have compared temporal
trends in short and long-term survival after AMI in prospectively followed patients with and without DM. Gandhi et al.11 studied a smaller sample of AMI sufferers with and without DM, comparing mortality in 1979 and 1998; unadjusted 5-year survival showed improvement in patients without DM, but no improvement for patients with DM. Consistent with this some population, studies have also suggested smaller improvements in the cardiovascular mortality of patients with DM compared with those without.12

A number of factors could contribute to the disappointing results observed in patients with DM. First, one could speculate that the cohort of AMI sufferers with DM has become ‘higher risk’ over the study period. Certainly, the prevalence of hypertension and hyperlipidaemia increased in this group, though diagnostic thresholds have also been lowered over the study period.8,9 The proportion of patients with pre-existing ischaemic heart disease increased in patients with DM, contrasting with the non-diabetic group. This was driven by greater rates of previous AMI or longstanding angina (data not shown), which would be expected to increase the risk of mortality over long-term follow-up. The accompanying adjusted analyses provide an assessment of how changes in such factors between study periods have impacted upon the observed differential long-term survival gains in patients with and without DM. These suggest that neither differing baseline risk patterns nor treatment factors entirely account for the poorer outcomes in patients with DM. Equally, adjusted analyses of 30-day outcome suggest that we cannot attribute the equitable early survival gains to changes in the baseline risk or treatment factors that we have measured.

Short-term post-AMI mortality is predominantly related to left ventricular dysfunction and ventricular arrhythmias. It is re-assuring to see a decline in Killip class and cardiac arrest rate in the entire study cohort and this is reflected in the 30-day survival improvements between 1995 and 2003. Longer-term mortality is often related to recurrent ischaemic events. Despite the recent move towards invasive management of ACS with early revascularization,13,14 the presence of DM remains a strong independent predictor of

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**Table 3** Quantitative survival improvements

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<th>Diabetes</th>
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<th>No diabetes</th>
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<tr>
<td>Mean number of patient-days lost in 18 months (confidence interval)</td>
<td>170 (136.9–203.2)</td>
<td>150 (121.7–178.8)</td>
<td>137.5 (125.7–149.2)</td>
<td>110.2 (98.7–121.7)</td>
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<td>Absolute improvement (confidence interval)</td>
<td>20 (–41.9 to 81.5)</td>
<td>27.3 (4–50.5)</td>
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death or recurrent ischaemia.\textsuperscript{15} Our analysis has also highlighted a larger increase in the proportion of AMI without ST-elevation in the diabetic population. Non-ST-segment elevation AMI has been associated with a poorer long-term prognosis than ST-segment elevation AMI,\textsuperscript{16} which may contribute to the poor long-term improvements in DM patients in our study, especially in the face of a trend towards lower rates of early revascularization in this group during 2003 ($P = 0.078$; data not shown). It is important to note that patients with DM have been shown to benefit from an early invasive strategy after non-ST-elevation ACS.\textsuperscript{15} Primary angioplasty has emerged as an important treatment modality for patients with ST-elevation AMI.\textsuperscript{17} In the present study, this was performed in a limited number of patients. The effect on outcome of early percutaneous approaches to patients with DM suffering AMI warrants future assessment.

Another potentially important factor in the management of AMI in patients with DM is attention to glycometabolic control. Although the evidence for hyperglycaemia as an adverse glucose lowering in the setting of AMI is controversial.\textsuperscript{18} Nonetheless, the publication of the DIGAMI study in 1995 is likely to have led to more patients with DM receiving insulin in the 2003 cohort.\textsuperscript{19} Whether this contributed to the decline in early mortality witnessed in those with DM is uncertain.

Our analysis highlights improvements in in-hospital management of AMI and the equality of provision of secondary prevention measures in patients with and without DM over the last decade. It is likely that these improvements were driven by the publication of randomized controlled trials and the synthesis of comprehensive management guidelines and audit targets. Within the UK, for example, coronary heart disease and DM were targeted for particular attention with the publication of disease-specific National Service Frameworks (NSF).\textsuperscript{20–22} Such guidelines correctly focus on modifying traditional risk factors in order to reduce the incidence of cardiovascular events, though this may be insufficient to protect large numbers of individuals, particularly those with diabetes.\textsuperscript{23} It remains to be seen whether attention to non-traditional risk factors which cluster with DM, including visceral adiposity, oxidant stress, and inflammation, is also necessary to improve the long-term prognosis of this group.\textsuperscript{24}

The NSF for Diabetes recommends screening for DM in high-risk groups, yet we appear to be poor at doing so, given the relatively low proportion of AMI sufferers with a diagnosis of DM in our analysis. Norhammar \textit{et al.}\textsuperscript{25} provided important insights in this area, showing in their series of AMI patients with random glucose levels below 11.1 mmol/L that approximately one-third have overt diabetes and a further third impaired glucose tolerance, at discharge and 3 months later. In Europe, abnormal glucose regulation is demonstrable in the majority of individuals presenting with coronary artery disease.\textsuperscript{26} The low rate of DM observed in our study may have spuriously elevated non-diabetic mortality by inclusion of patients with undiagnosed DM. Should one-third of our 2003 study cohort have been diagnosed with DM and observed 18-month mortality persisted, corresponding non-diabetic mortality would fall by 5–20.7%, almost half that of those with DM. These data put into perspective the potential scale of the issue and the need to actively diagnose abnormal glucose homeostasis in patients suffering from AMI.

**Study limitations**

In the present report, we did not specify the mode of death. Data on cardiovascular mortality and non-cardiovascular mortality would be useful and enable us to assess the reasons for the disparity between short and long-term survival gains. Moreover, we were also unable to differentiate between patients presenting with type 1 and type 2 DM; these data would also be of interest. Nevertheless, despite these limitations, our study still represents an observation of major importance to patients and healthcare providers.

In summary, we have demonstrated that despite improvements in management of AMI, with a corresponding reduction in 30-day mortality between 1995 and 2003, the longer-term survival of AMI patients with DM has remained unchanged over this period. Given the rapidly increasing global burden of DM, and the high absolute risk to which affected individuals are exposed, ongoing research to optimize the prevention and management of cardiovascular complications reaches critical importance.

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**Conflict of interest:** none declared.

**References**

Clinical vignette

Coronary artery perforation complicated by cardiac rupture during conventional PCI

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A 65-year-old female hypertensive, hypercholesterolaemic patient on medical therapy for stable angina presented with worsening symptoms. Coronary angiography revealed a left coronary artery (LCA) with a 50% stenosis and a right coronary artery (RCA) suboclusion (Panel A). The patient underwent RCA angioplasty.

The RCA suboclusion was crossed with guide wire, and multiple dilations were performed using 2.0/18 and 2.5/20 mm balloons (-Maverick, Boston Scientific). Two driver stents (24/3.5 and 30/4.0 mm, Medtronic) were deployed. On angiogram, there was evidence of extravasation of contrast in the pericardium (Panel B). Afterwards, the patient presented ventricular fibrillation, cardiogenic shock, and cardiac tamponade requiring cardiopulmonary resuscitation and pericardiocentesis. Two GraftMaster polytetrafluoroethylene-coated stents (12/3.0 and 19/4.0 mm, Abbott Laboratories) were deployed to seal the rupture. Because severe blood extravasation still persisted, an occlusive coronary balloon was inflated and an intra-aortal balloon pump (IABP) was inserted (Panel C). The patient underwent emergency cardiac surgery operation.

Active bleeding from the RCA in the atiroventricular groove was documented and cardiopulmonary bypass was started. The vessel’s wall presented an extensive defect exposing a covered stent (Panel D). The stent was removed (Panel E) but the wall damage was too extensive to be repaired. A right ventricular tear was identified and repaired. The proximal and distal ends of the coronary rupture were ligated and a saphenous vein bypass graft to the posterior intraventricular artery was performed. With difficulty, the patient was weaned from cardiopulmonary bypass with inotropic drugs and IABP support. She could not be recovered from severe right ventricular failure and died after 48 h.

Panel A. Coronary angiography shows multiple severe stenosis in the middle portion of the right coronary artery.
Panel B. Coronary angiography shows the site of rupture after balloon dilatation and multiple stenting of the RCA with bare metal stents and two covered stents.
Panel C. Coronary angiography shows the right coronary artery occluded by an angioplasty balloon and a left coronary artery with a 50% stenosis of middle portion lesion.
Panel D. Intra-operative image showing the right coronary artery rupture exposing one of the covered stents.
Panel E. The covered stent removed with pieces of bare metal stent inside.

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