Abstract

Diabetic subjects are more likely to experience a myocardial infarction and have worse outcomes compared to non-diabetic subjects. The underlying pathophysiology of the atherosclerotic process is not significantly different in diabetic subjects, but the prothrombotic and procoagulant state with which diabetes is associated is thought to contribute to the higher incidence of and worse prognosis after myocardial infarction. Difficulties of re-establishing vessel patency by thrombolytic or mechanical means contribute to the high morbidity and mortality. The diffuse nature of arterial disease with accompanying metabolic derangement contribute to impaired compensatory mechanisms, increased infarct size and a disproportionately more substantial impairment of left ventricular function. The newer adjuvant antithrombotic and anticoagulant agents have particular roles in management therefore and careful modulation of glucose metabolism in the acute and follow-up phase of an infarct may favourably influence outcome.

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Key words: diabetes mellitus, myocardial infarction, acute management.

Introduction

Diabetes mellitus is a major risk factor for coronary artery disease and is associated with a higher incidence of myocardial infarction (MI) and sudden death. Mortality, morality and reinfarction rate are higher following MI in diabetic than non-diabetic subjects, with one-year mortality in this population as high as 50%. Similarly the acute and long-term efficacy of reperfusion strategies, has, historically, been worse in patients with diabetes. Despite evidence for improvement in outcomes from cardiovascular disease in the general population over the past 30 years, these benefits have not been paralleled in the diabetic (particularly female) population. This is despite clear evidence of at least equal benefit from acute interventions, such as thrombolysis, and suggests the possibility of a failure of implementation of the evidence base (table 1).

Type 2 diabetes is present in 10–30% of patients presenting with MI and, given the expected doubling in the incidence of diabetes over the next 25 years, represents a major public health concern. In addition, MI may be associated with the first presentation of glucose intolerance or overt diabetes, early diagnosis providing an opportunity for appropriate intensive management and risk stratification.
REVIEW

**Table 1.** Treatment associated with known or possible benefit in the management of diabetic patients with myocardial infarction

<table>
<thead>
<tr>
<th>Established treatment</th>
<th>Possible benefit</th>
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<tbody>
<tr>
<td>Thrombolysis</td>
<td>Streptokinase/rtPA</td>
</tr>
<tr>
<td>Anti-platelet</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Anticoagulant therapy</td>
<td>Stent deployment GpIIb/IIIa inhibitors</td>
</tr>
<tr>
<td>Interventional management</td>
<td>Glucose and insulin infusion and sc insulin regimen (DIGAMI)</td>
</tr>
<tr>
<td>Metabolic management</td>
<td>Ramipril</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Beta blockers</td>
</tr>
</tbody>
</table>

**Pathophysiological factors**

Increased platelet activation, increased expression of coagulation factors and reduced intrinsic thrombolytic activity, contribute to a prothrombotic and procoagulant state.

Endothelial dysfunction, a manifestation of reduced nitric oxide bioavailability and an early marker of the subsequent development of atheroma, is associated with insulin resistance, the metabolic syndrome and the chronic inflammatory state seen in diabetes. In combination these factors are thought also to be responsible for the diffuse nature of the coronary atheroma, and impairment of cardiac function that marks diabetic heart disease (figure 1). This diffuse coronary disease may limit collateralisation, potentially increasing infarct size, which may be exacerbated by the suggested detrimental effect of sulphonureas on protective ischaemic preconditioning. Standard pharmacological approaches which are known to improve endothelial function, such as the use of angiotensin-converting enzyme (ACE) inhibitors, statins and thiazolidinediones, may have a particular role in the perinfarct management of people with diabetes.

**Presentation and delivery of thrombolysis**

Although thrombolysis benefits diabetic more than non-diabetic patients, fewer diabetic patients receive thrombolysis, and those that do, receive it later. Possibly through autonomic neuropathy, reduced pain sensation or atypical symptoms, diabetic patients present approximately 15 minutes later than non-diabetic patients after the onset of symptoms. The delivery of thrombolysis is also delayed, this being compounded by the suggested reduced sensitivity of the standard 12-lead ECG in patients taking sulphonureas, because of changes in T-wave morphology. Patient education regarding symptoms is therefore of great importance, although even patients who have had one MI, fail to present earlier in the face of a second. In the absence of standard ECG criteria for ST elevation in MI, thrombolysis cannot be recommended, but the clinician should clearly have a high index of suspicion. In the presence of atypical presentation and non-diagnostic ECGs, the use of troponin measurements has aided the identification of high-risk subjects in whom aggressive alternative management should be instituted.

Through a perceived increased risk of haemorrhagic complications or the existence of co-morbidities, diabetic patients are less likely to be considered appropriate candidates for thrombolysis. This supposed risk has not been borne out by major thrombolytic trials. A number of other confounding factors may be relevant, such as later presentation and less clearly met clinical and
ECG diagnostic criteria, but despite the lack of supportive evidence, the presence of diabetes has been shown by multivariate analysis to be an independent predictor of the less frequent use of thrombolysis.20

### Thrombolytic therapy

Despite the greater relative and absolute benefits of thrombolysis in diabetic patients sustaining MI, re-occlusion rates (9.2% vs. 5.3%13), and 30-day (11.3% vs. 5.9%13) and 1-year (14.5% vs. 8.9%) mortality measures remain worse in diabetic than non-diabetic patients.

Enhanced platelet activation and the procoagulant state associated with diabetes increase the likelihood of a thrombotic event, encourage thrombus propagation, impair the action of thrombolytic drugs and increase the chance of re-occlusion.21 Despite this, in several studies, vessel patency following thrombolysis, as measured by the Thrombolysis in Myocardial Infarction (TIMI) flow grade (a marker of the efficacy of thrombolysis), was not significantly different between diabetic and non-diabetic subjects, nor was the incidence of re-occlusion.7,13 However, TIMI flow may not be a sensitive enough marker of overall myocardial (including microvascular) perfusion, which is also impaired in diabetes. There may also be an issue of selection bias, with a higher incidence of early death prior to angiography in the diabetic group.13 Recurrent ischaemia was, however, shown to occur more frequently in the diabetic group.

Due to the small numbers of diabetic subjects involved in the major thrombolytic trials and the lack of trials looking only at diabetic subjects, there are few data to suggest specific regimens. However, given the delay in thrombolysis delivery, and reduced efficacy, early vessel patency assumes even greater importance, and accelerated administration of t-PA may be of particular benefit in diabetic patients.8

### Adjunctive antithrombotic therapy

It is clear that aspirin is of equal benefit in diabetic and non-diabetic patients and meta-analyses have not demonstrated any additional risk.22 The use of additional anti-platelet agents has been advocated, and, specifically, clopidogrel has been shown to be of benefit in addition to aspirin in the setting of unstable angina and non-Q-wave MI.23 Current evidence supports clopidogrel use only in this setting. But evidence of benefit after MI is lacking.

Several studies have demonstrated a benefit from low molecular weight heparins (LMWH) over unfractionated heparin in the management of unstable angina and non-Q-wave MI. Neither the ESSENCE trial24 nor TIMI Ib25 demonstrated additional benefit in diabetic subjects, although the latter showed a greater advantage in a 'high-risk' group, identified on the basis of raised troponin I, which had a greater proportion of diabetic patients. The GUSTO Ib study suggested a marginal additional benefit from the use of hirudin, a direct thrombin inhibitor in diabetic subjects.26

The glycoprotein (Gp) IIb/IIIa antagonists, tirofiban and eptifibatide, have been used in the setting of unstable angina/non-Q-wave MI and have been shown to improve both short and medium-term outcomes. The risks of death and MI were more significantly reduced in diabetic patients in both PRISM-PLUS27 and PURSUIT28 studies, although this benefit was limited to insulin-requiring diabetic patients in PURSUIT.22 A meta-analysis of the major Gp IIb/IIIa studies in unstable coronary syndromes suggests that the absolute benefit in diabetic patients is twice that of non-diabetic patients.29 The National Institute of Clinical Excellence (NICE) guidelines support their use in high risk and particularly troponin positive patients, but their integration into the management of acute coronary syndromes has yet to be fully defined, with factors such as cost-effectiveness, use of clopidogrel and proposed interventional management influencing their use. In resistant unstable angina, and possibly as a bridging measure to definitive revascularisation procedures, the IIb/IIIa antagonists may have a particularly important role in diabetes.

### The role of intensive glycaemic control

The metabolic derangement that occurs at the time of MI leads to anaerobic glucose metabolism and a shift towards free fatty acid production. This derangement, together with the proinflammatory state of diabetes, has been shown to have a deleterious effect on myocardial function.30-32 The role of intensive glycaemic control is, therefore, of paramount importance. The management of diabetes in this setting involves the use of insulin-based regimens, which are designed to mimic the normal response to post-prandial feeding (Figure 2).30

Figure 2. Mechanisms of poor outcome following myocardial infarction in diabetic patients
acid utilisation, this being exacerbated by insulin deficiency or resistance. This shift increases oxygen demand, worsens ischaemia, increases superoxide production, promotes sympathetic activity and reduces myocardial contractility. This change affects both ischaemic and non-ischaemic territories, increasing infarct size, and reducing the compensatory response of viable myocardial tissue. Insulin therapy in the setting of MI promotes glucose oxidation, and the enhanced availability of glycolytic substrate counters these adverse effects, particularly in the diabetic patient, where it may also improve the prothrombotic state.

Although early studies were contradictory, a meta-analysis of nine more recent studies using glucose, insulin and potassium (GIK) infusions peri-infarction, demonstrated a marked reduction in mortality. An unblinded but randomised pilot study from the ECLA group recruited 407 patients to a high- or low-dose GIK strategy or to standard therapy as control. The high-dose infusion comprised a 25% glucose solution, with 50 IU of insulin and 80 mmol KCl per litre, infused at a rate of 1.5 ml/kg/hour for 24 hours. This demonstrated a trend towards reduced mortality in the high-dose treated group, a reduction in mortality in those receiving concomitant reperfusion therapy, and a consistent beneficial trend in other in-hospital events. A larger definitive study is on-going.

The DIGAMI study demonstrated benefits from a glucose and insulin infusion, to achieve early improved metabolic control, followed by at least three months therapy with a four-times daily subcutaneous insulin regimen. The study enrolled MI patients presenting with a blood glucose > 11 mmol/L, regardless of whether diabetes had previously been diagnosed. A 5% glucose solution with 160 IU of soluble insulin was delivered at a rate to maintain blood glucose at 7–10.9 mmol/L. Control subjects received best ‘standard’ therapy, including the continuation of pre-existing insulin regimes if appropriate. At discharge, 90% of the infusion group and 44% of the control group were receiving subcutaneous insulin; at one year the figures were 70% and 50% respectively. At one year the relative risk reduction of death in the infusion group was 29%, with a 52% reduction at one year being seen in those not previously diagnosed as requiring insulin. The benefit was maintained to beyond three years. It is possible that some benefit may have been accrued through the withdrawal of potentially detrimental oral hypoglycaemic agents, particularly the sulphonylureas. The on-going DIGAMI II study aims to assess the relative importance of the acute and follow-up management of diabetes on this improved outcome.

Despite significant benefits of treatment, the practicalities of initiation of insulin therapy have led to a slow uptake of the DIGAMI protocol in coronary care units. Because of a lack of familiarity, incorrect or poorly monitored regimens may be implemented or ‘standard’ sliding scales prescribed by default. In our unit pre-printed proformas have been developed in collaboration with the diabetes team in order to address this. Careful co-ordination of patient education programmes for post-discharge management is also essential.

**Key messages**

- Diabetes is associated with a higher risk of and worse outcome from MI
- Pathophysiological factors may reduce the efficacy of thrombolysis and impair left ventricular compensatory mechanisms
- Diabetes and its complications per se should not be considered contraindications to the delivery of thrombolysis
- Careful control of glucose metabolism during and after MI may limit myocardial damage
- There is a role for early invasive investigation and management, particularly with the advent of adjuvant antithrombotic therapies and advances in interventional techniques

**Beta blockade**

Beta blockers have consistently been under-prescribed in diabetes. The DIGAMI study showed a positive influence on long-term outcome in diabetic patients post-MI. Beta blockers not only reduce myocardial oxygen demand, but they may also shift energy production from fatty acids to glucose usage. Their effect is in proportion to the magnitude of the reduction in heart rate, which in diabetic patients is higher following MI, possibly through a free fatty acid-mediated increase in sympathetic drive. The benefit of beta blockers may therefore be more marked in this group of patients.

**Invasive strategies**

Studies have demonstrated a benefit from direct angioplasty compared to thrombolysis in MI, high-risk patients in general and diabetic patients specifically gaining most, although complication and restenosis rates are higher in diabetic patients in both the elective and acute settings. Stent deployment in non-diabetic patients has been shown to be feasible and is associated with a lower restenosis rate than Percutaneous Transluminal Coronary Angioplasty (PTCA) in MI. Stenting is also associated with improved outcomes in diabetic patients. Current UK practice supports the use of primary angioplasty in cases of cardiogenic shock, where thrombolysis may be contraindicated or the early presentation of MI where interventional facilities are readily available.

The debate regarding the role of an early invasive strategy in the management of post-MI patients remains active, and has evolved in parallel with the development in interventional strategies and adjuvant therapies. Apparently poorer outcomes in groups undergoing an early invasive approach reflect the fact that higher risk and sicker patients are more likely to be man-
aged in this way. Improved outcome from intervention has shifted the balance in favour of early investigation, and increasingly refined risk stratification criteria are defining more clearly those that would benefit from such an approach.46 Following MI, symptoms suggestive of ongoing ischaemia or demonstration of residual ischaemia on exercise testing should prompt early investigation.

A further shift in favour of mechanical reperfusion in acute MI has been prompted by a series of trials examining the role of adjunctive therapy with the GpIIb/IIIa inhibitor, Abciximab.48,49 These have demonstrated improved achievement of TIMI grade III flow following intervention, evidence of better microcirculatory perfusion, an associated improvement in echocardiographic left ventricular wall-motion scores and better clinical outcome at 30 days and six months. Given the concerns regarding distal embolisation of platelet thrombi and microcirculatory dysfunction such benefits may be of particular importance in the diabetic patient. This has been borne out by the findings of subgroup analysis of the ADMIRAL study,50,51 which showed a reduction in the primary end point of death (0 vs. 16.7% p=0.02) and the combined end point of death, re-infarction or revascularisation (20.7 vs. 50.0% p=0.02) at six months in diabetic subjects treated with Abciximab.

Conclusion
A number of pathophysiological factors adversely affect the incidence of and outcomes from acute MI in diabetic patients. The failure of delivery of well-established therapies may add to this. Thrombolytic therapy is as appropriate to diabetic as non-diabetic patients, and may carry greater benefit. Anti-platelet treatment with aspirin should be instituted early and may be augmented with clopidogrel. With the prothrombotic state associated with diabetes, additional benefit may be gained from LMWH and GpIIb/IIIa inhibition. Metabolic manipulation has now established itself in mainstream treatment, although the exact regimen will vary. The emerging pharmacological agents may continue to be refined. With the evolution of coronary intervention, primary and early intervention in diabetic patients may offer advantageous outcomes in appropriately selected patients.

Diabetic patients remain a high-risk group for MI, with poorer outcomes, whilst having a sound pathophysiological basis for aggressive treatment and intervention with greater benefits than non-diabetic patients. An increased awareness and appropriate delivery of established therapies to this group is essential in the face of a rising diabetic population worldwide.

References


