Management of acute myocardial infarction in the diabetic patient

Peter Hammond

Introduction

Ischaemic heart disease is the major cause of death in type 2 diabetes and acute myocardial infarction (AMI) carries a particularly poor prognosis. Hyperglycaemia is an important determinant of poor outcome, even in non-diabetic patients sustaining a myocardial infarct. The DIGAMI study has shown the benefit of intensive insulin therapy for hyperglycaemic patients who suffer an AMI. To improve the prognosis for diabetic patients, this intervention should be combined with others that have been proven to benefit all patients with AMI.

Ischaemic heart disease affects up to 50% of people with diabetes, and is the cause of death in about 35% of patients with type 2 diabetes. Diabetic patients are affected at an earlier age than non-diabetics, and postmenopausal women with diabetes, who have lost the protective effect of premenopausal oestrogen, are affected to the same extent as men.

Acute myocardial infarction (AMI) carries a particularly poor prognosis, the risk of death at one year post-infarction in the diabetic population being three times that in the non-diabetic population. The re-infarction rate in the patient with diabetes is 60% at 6 months (Smith et al, 1984).

A number of factors may contribute to the poor prognosis following AMI in the diabetic patient (*Table 1*). Hyperglycaemia is an important determinant of poor outcome, and this is true in patients not previously known to have diabetes. In one study the mortality rate was 3% in patients with an admission blood glucose of <6.7 mmol/l, compared with 15% in those with blood glucose in the range 6.7–10 mmol/l, and 43% where blood glucose was >10 mmol/l (Bellodi, 1989). The elevated blood glucose levels are associated with elevated free fatty acid levels, and together they have an adverse effect on myocardial function, resulting in an increase in infarct size.

Table 1. Factors contributing to the worse prognosis of myocardial infarction in diabetic patients

- Severity of atherosclerosis — triple- and small-vessel disease
- Diabetic cardiomyopathy
- Larger infarct size
- Autonomic dysfunction — arrhythmia, vasoconstriction
- Impaired fibrinolysis
- Increased platelet adhesion
- Metabolic toxicity (glucose, fatty acids)

The Diabetes Mellitus Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study

Control of hyperglycaemia would be expected to improve prognosis, given the adverse consequences of high blood glucose concentrations on myocardial function. In the DIGAMI study (Malmberg, 1995), 620 patients with AMI and an admission blood glucose of >11 mmol/l, whether or not they had a previous diagnosis of diabetes, were randomised to one of two regimens:

- Insulin-glucose infusion for at least 24 hours, then subcutaneous insulin four times daily for at least 3 months
- Standard care.

Over 12% of the study patients did not have a previous diagnosis of diabetes. By 24 hours, glycaemic control was better in the intensively treated group and this

ARTICLE POINTS

1 Ischaemic heart disease is the major cause of death in type 2 diabetes.

2 Intensive insulin therapy has been shown to improve the prognosis in patients with hyperglycaemia who suffer an AMI.

3 Secondary prevention of myocardial infarction in diabetes is effective.

4 Insulin therapy should be routinely used for all patients with AMI and an admission blood glucose of >11mmol/litre.

KEY WORDS

- **Type 2 diabetes**
- **Myocardial infarction**
- **Prognosis**
- **Insulin therapy**

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Table 2. Relative reduction in mortality in patients in the DIGAMI study stratified according to cardiovascular risk* and insulin usage on admission

	Not using insulin	Using insulin
Low risk	52%	14%
High risk	15%	22%

* High cardiovascular risk = two of the following: age >70, previous myocardial infarction, history of congestive cardiac failure, current treatment with digoxin

Table 3. Possible explanations for efficacy of DIGAMI intervention protocol

- Withdrawal of oral hypoglycaemic agents
- Initial correction of hyperglycaemia
- Reduced levels of non-esterified fatty acids
- Improved fibrinolysis, reduced platelet adhesion
- Long-term improvement in glycaemic control
- Reduced dyslipidaemia

persisted for the duration of the study. After 12 months there was a significant 29% relative reduction in mortality in the intensively treated group, and the benefit was greatest in those at low risk, who were not previously taking insulin (*Table 2*) (Malmberg et al, 1995). At 3 years the benefits were sustained, with an absolute reduction in mortality of 11% overall, and a 15% absolute reduction in the low risk, non-insulin group (Malmberg, 1997). Thus for every nine patients treated with intensive insulin therapy, one life was saved.

Implementation of DIGAMI

There are a number of possible explanations for the efficacy of the intensive insulin regimen in the DIGAMI study (*Table 3*). It is interesting to speculate on the possible benefit of withdrawing sulphonylureas, whose action in closing cardiac potassium channels may have deleterious effects. This may explain why the low-risk patients who were not previously taking insulin did best.

If the crucial factors in the success of DIGAMI are the acute interventions, such as withdrawal of oral hypoglycaemic agents or the suppression of circulating glucose and fatty acid levels, then the introduction of treatment protocols to coronary care units to reproduce the initial insulin infusion therapy should have a similar impact on prognosis. Even if, as seems likely, lower glycaemic thresholds for using an insulin infusion are accepted in the future, these interventions will still be restricted to coronary care units.

However, if there is widespread acceptance of the principle of intensive insulin therapy for all these patients post-AMI for at least 3 months, this will add a considerable burden to the workload of diabetes care teams, particularly specialist nurses. Reassuringly, almost 50% of the standard care group were on insulin at 12 months post-discharge. This lends support to the concept that it is the early intervention that is most important, and suggests that any increased workload may not be quite as great as anticipated.

Other interventions

The results of DIGAMI compare very well to those of other therapies that have been used following AMI in patients with diabetes (*Table 4*). However, most patients in the study received at least one other therapeutic intervention, with no differences in these interventions between standard and intensive insulin groups (*Table 5*). DIGAMI can thus be regarded as a trial of intensive insulin therapy added to standard management for patients with AMI.

It is important that patients with diabetes are not denied other therapies when they are appropriate.

Thrombolysis for AMI is even more effective in patients with diabetes than in non-diabetics (Fibrinolytic Therapy Trialists Collaborative Group, 1994). However, it is a consistent finding that patients with diabetes are less likely to receive thrombolysis; in some cases, this is because the diagnosis is delayed, possibly when the diabetic patient does not experience classic symptoms, but in many patients it is because of concerns about haemorrhage from proliferative retinopathy. In practice this has been reported only once worldwide, and retinopathy, regardless of the severity, must not be regarded as even a relative contraindication to thrombolysis.

Aspirin given acutely and continued long term after AMI is slightly less effective

in patients with diabetes. However, the increased mortality in the diabetic population means that the absolute benefit is greater, with 38 cardiac events being prevented for every 1,000 patients treated (Antiplatelet Trialists Collaboration, 1994).

Beta-blockers given acutely or long term after AMI are as effective at reducing the risk of death and cardiac events in the diabetic population as in non-diabetics (Tse and Kendall, 1994). Theoretical concerns about diminished awareness of hypoglycaemia and adverse effects on lipid profiles are of little clinical significance and should not deter the use of beta-blockers. Co-morbid conditions may be relative contraindications to beta-blockade, but careful consideration should be given as to whether they are serious enough to deprive the patient of the potential benefits of this form of therapy.

Angiotensin-converting enzyme (ACE) inhibitors have been shown, in a number of large randomised controlled trials, to be of benefit when given to patients following AMI. They are particularly effective in patients with evidence of heart failure post-AMI, which is more likely to be present in patients with diabetes.

There is little evidence as to the benefits of ACE inhibitor therapy in patients with diabetes suffering AMI, as only a small percentage of the patients in the large trials had diabetes; what data are available suggest a relative reduction in mortality of about 30% in those with diabetes (Zuanetti and Latini, 1997).

The 4S and CARE studies have shown the benefits of statin therapy started at 3 months post-AMI in patients with low-density lipoprotein (LDL)-cholesterol >3.2 mmol/l — roughly equivalent to a total cholesterol of >4.8 mmol/l. The risk reduction for further cardiac events in the patients with diabetes included in these studies was 55% in the 4S and 25% in the CARE study, compared with 32% and 23% respectively in the non-diabetic patients (Sacks et al, 1996; Pyorala et al, 1997).

These benefits are substantial when the greater risk of further events in diabetic patients is considered. Diabetic patients often have a mixed hyperlipidaemia, with elevated triglycerides in addition to LDL-cholesterol. Fibrates are usually more effective than statins in reducing triglyceride levels in these patients, but the priority for treatment post-AMI must be LDL-cholesterol. Evidence from these large trials supports the use of statins as first-line therapy in diabetic patients as well as non-diabetic patients following AMI.

Table 4. Benefit of interventions post-AMI in patients with diabetes

Intervention	Number needed to treat per life saved
DIGAMI — intensive insulin therapy	9
Beta-blockade — acute	29
Beta-blockade — long term	11
Thrombolysis	27
Statin therapy (4S trial)	10

Table 5. Percentage of patients receiving other therapies in the DIGAMI study

Thrombolysis	50%
Aspirin*	80%
Beta-blocker*	70%
ACE inhibitor*	31%

***Taking on discharge**

Publisher's note: This image is not available in the online version.

Conclusion

Patients of either sex with diabetes are more likely to suffer an AMI and this carries a poorer prognosis than in the non-

PAGE POINTS

1 Intensive insulin therapy in hyperglycaemic patients with AMI reduced the mortality at 3 years by 11% overall, in the DIGAMI study.

2 The benefits of insulin therapy were greatest in the low-risk patients, not previously taking insulin.

3 Thrombolysis for AMI is even more effective in patients with diabetes than in non-diabetic patients.

4 It is important that patients with diabetes suffering an AMI are not denied other therapies when appropriate.

5 Retinopathy, whatever the severity, is not a contraindication to thrombolysis.

diabetic population. Existing strategies for improving the prognosis post-AMI, including thrombolysis, aspirin, beta-blocker, ACE inhibitor and statin therapy, are of proven benefit in patients with diabetes and should be routinely used where appropriate.

The DIGAMI study has shown that the addition of intensive insulin therapy to this management strategy is of significant benefit. Insulin infusion therapy should be used routinely for all patients with AMI and an admission glucose >11 mmol/l, but local strategies will be needed, to determine whether and how to implement the longer-term use of intensive insulin therapy. ■

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