Dithering over the treatment of diabetics with acute myocardial infarction

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In this issue Gustafsson et al.\(^1\) describe 6676 consecutive patients with acute myocardial infarction who were enrolled in the Trandolapril Cardiac Evaluation (TRACE) Study Registry between 1990 and 1992. Despite having a similar incidence of ST-segment elevation and a similar admission delay, diabetic patients were less likely to be given thrombolytic therapy and aspirin than non-diabetics. These findings are supported by a large registry of 272 651 patients with acute myocardial infarction (84 663 of whom were eligible for reperfusion) in the United States from 1994 to 1996, in which diabetics were 50% less likely to receive reperfusion therapy than non-diabetics (adjusted odds ratio 0·67, 95% confidence interval 0·52–0·87)\(^2\).

It is not clear why diabetics are so often denied effective treatment. In the Fibrinolytic Therapy Trialists’ overview\(^3\), the relative reduction in mortality with thrombolytic therapy was non-significantly higher in diabetics than in non-diabetics (27% vs 15%), but because the higher absolute risk of mortality was greater in diabetics, the number of lives saved was also greater than in non-diabetics (37 vs 15 per 1000 patients treated, \(P<0·001\)). In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) Trial\(^4\), diabetics had a similar rate of major bleeding to that of non-diabetics. No intracocular haemorrhages were reported, although it was estimated that 200 of the 6011 diabetic patients probably had non-proliferative retinopathy and 300 probably had proliferative retinopathy.

The use of thrombolytic therapy and aspirin in the TRACE Registry also varied among diabetic subgroups. Thrombolytic therapy was used in 28% of diet-treated diabetics, 30% of tablet-treated diabetics and 19% of insulin-treated diabetics (vs 42% of non-diabetics). Aspirin was used in 62% of diet-treated diabetics, 62% of tablet-treated diabetics and 50% of insulin-treated diabetics (vs 70% of non-diabetics). These differences may partly account for the higher long-term mortality rate among diabetics in the registry\(^1\).

Diabetics still fare worse even when they do receive thrombolytic therapy for acute myocardial infarction\(^5,6\). In a recent review of over 80 000 patients given thrombolytic therapy for acute myocardial infarction\(^7\), the 1-month mortality rate was 1·7 times higher in diabetics than in non-diabetics, and this difference persisted throughout the first year. As was the case in the TRACE Registry, insulin-treated diabetics had the worst prognosis, with a mortality rate 1·3 times higher than that of non-insulin-treated diabetics. Apart from a longer delay to treatment in diabetic patients (even under clinical trial conditions), other possible explanations for the excess mortality include reduced efficacy of thrombolytic regimens, more extensive underlying coronary disease, and worse left ventricular function due to diabetes and its metabolic derangement. These issues were partly addressed by the GUSTO-I Angiographic Substudy\(^8\), but it should be noted that high-risk patients (who are more likely to die before angiography can be performed) were under-represented in the analysis. Although microvascular blood flow may be impaired in diabetics\(^6\), their rates of infarct artery blood flow were found to be no different from those of non-diabetics. The rates of angiographic reclosure and global systolic ejection fractions were also no different between diabetics and non-diabetics, although diabetics had an attenuated hyperkinetic response in the non-infarct zones. This finding is consistent with the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Study results\(^9\), and may have been due to concomitant multivessel disease or microcirculatory and cellular dysfunction caused by diabetes. In the GUSTO-I Angiographic Substudy\(^8\), the difference in wall motion in the non-infarct zones of diabetics was no longer apparent after the acute phase of myocardial infarction.

Metabolic derangement occurs during the acute stress of myocardial infarction. There is anaerobic metabolism of glucose and free fatty-acid accumulation, and insulin deficiency or resistance reduces cellular glucose uptake even further. Stress hyperglycaemia during myocardial infarction increases the risk of in-hospital mortality in both diabetics and non-diabetics\(^10\). The benefit of metabolic modulation may depend on restoration of cellular perfusion in the infarct zone and the degree of metabolic derangement in the non-infarct zone, both of which may be affected by concomitant multivessel coronary artery disease.

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A meta-analysis of 1932 patients in the pre-thrombolytic era showed that metabolic modulation with glucose, insulin and potassium (GIK) reduced in-hospital mortality by 28%[11]. A prospective study in which patients received either high- or low-dose GIK solution found that GIK was incrementally beneficial, particularly in the subgroup of patients who received reperfusion therapy (relative risk of in-hospital death 0.34, 95% confidence interval 0.15–0.78, \( P=0.008 \))[12]. In the Diabetic Patients with Acute Myocardial Infarction (DIGAMI) Study of 620 patients[13], the use of insulin-glucose infusions in the acute phase, followed by multi-dose subcutaneous insulin for at least three months, reduced mortality by 29% at one year.

Diabetics in the TRACE Registry had higher mortality rates at 7 years (62% in diet-treated diabetics, 73% in tablet-treated diabetics and 79% in insulin-treated diabetics) than non-diabetics (46%)[11]. On multivariate analysis, the mortality increase persisted in diabetics treated with insulin or tablets, but not in those treated with diet alone. Cardiac and non-cardiac mortality rates were not defined, and relevant prognostic data such as creatinine levels and measures of glycaemic control were not recorded. In the United Kingdom Prospective Diabetes (UKPDS 33) Study[14], tighter control of diabetes (with a haemoglobin A1c level of 7.0% vs 7.9% in the conventionally-treated group) substantially reduced the risk of microvascular complications, and was associated with a trend towards reduced mortality. In the TRACE Registry[1], the ACE inhibitortrandolapril was markedly more beneficial in diabetics than in non-diabetics, saving one life per six diabetics treated for 26 months compared with one life per 17 non-diabetics treated. This finding is consistent with the Heart Outcomes Prevention Evaluation (HOPE) Study, which reported positive vasculoprotective and renoprotective effects with ramipril[15]. The prognosis of diabetic patients can also be substantially improved by reduction of cholesterol levels[16], long-term use of cardioprotective drugs such as beta-blockers and aspirin, and judicious use of revascularization procedures[17].

With increasing influence and the spread of Westernized eating habits in developing countries, the global prevalences of diabetes and coronary disease are increasing dramatically[18]. The nature of coronary disease may differ between diabetics and non-diabetics, as may their metabolic responses during acute coronary syndromes. Further knowledge of these aspects will help to refine future management. In the meantime, we must not dither over the implementation of therapies that are known to benefit diabetics with acute myocardial infarction.

C.-K. WONG
H. D. WHITE
Green Lane Hospital, Auckland, New Zealand

References

The management of refractory angina

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The term ‘refractory unstable angina’ needs to be defined precisely, if one is to learn anything from different management strategies. In my opinion, refractory unstable angina should be considered only when there is ongoing chest pain associated with ongoing significant changes such as transient ST segment depression in the setting of maximum aggressive antiischaemic, anticoagulation, and general medical therapy.

Maximum antiischaemic and anticoagulation therapy also needs to be defined. Maximum antiischaemic therapy should consist of the following: (1) oral beta-blockers up to a maximum tolerated dose resulting in a decrease in heart rate to around 60 beats min\(^{-1}\); (2) oral calcium channel blockers, if chest discomfort persists despite beta-blockade, to a maximum tolerated or prescribable dose. My own preference is to use calcium antagonists that slow the heart rate, but dihydropyridines can be used when combined with a beta-blocker; (3) nitrates to maximum tolerable dose, i.e. a dose that does not decrease blood pressure excessively; (4) anticoagulant therapy with aspirin plus intravenous unfractionated heparin to raise the accelerated prothrombin time 1·5 to 2 times normal, or subcutaneous low molecular weight heparin, 100–120 units per kilogram, twice daily.

Based on recent studies, patients who continue to have recurrent ischaemia despite the above therapy should be treated with a glycoprotein IIb/IIIa receptor blocker\(^{[1]}\). The goal of therapy, of course, is to stabilize the clinical situation, i.e. decrease the episodes of chest discomfort to zero, and theoretically stabilize the underlying pathology, i.e. plaque disruption.

One can be alerted about a potentially refractory state and poor prognosis in this type of patient if biochemical markers such as troponin T or troponin I are elevated. Increased levels of C-reactive protein may also portend a poorer prognosis.

In the acute situation, my own preference is to use an intravenous nitrate, since the intravenous preparation is easy to adjust if hypotension or bradycardia occurs. Beta-blockers, oral or intravenous, still remain the mainstay of therapy for acute myocardial ischaemia. In my practice, calcium antagonists, although effective, are not first line therapy in unstable angina unless the patient has already received nitrates and beta-blockers prior to presentation and continues to have ischaemic chest pain.

Since the pathogenesis of this condition in most instances is related to non-occlusive thrombus at the site of a disrupted plaque, it makes good sense to anticoagulate the patient. How long a patient should be anticoagulated is not clear, but most recommend anticoagulation in refractory patients until a revascularization procedure is accomplished. At the present time, it is not my practice to use low molecular weight heparins routinely in the usual patient with unstable angina, but I certainly admit that long-term use might be beneficial if chronic stabilization of a disrupted plaque would occur. Perhaps the patient with elevated troponin T or I or C-reactive protein might benefit most from long-term therapy with low molecular weight heparin.

One tends to forget using lipid lowering agents in the acute phase of any patient’s illness, but there is evidence that statins alter vascular reactivity quite early. Thus, it seems reasonable to use these agents as one is trying to stabilize the disrupted plaque.

In this issue Michalis and colleagues report on a common problem, that is, treatment of patients with ‘refractory’ angina in parts of the world that do not have cardiac surgery\(^{[2]}\). Believe it or not, this situation also exists in the United States. The investigators report a trial entitled, ‘TRUCS’ which stands for Treatment of Refractory Unstable angina in geographically isolated areas without Cardiac Surgery.

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