The clinical implications of diabetic heart disease

Introduction

Epidemiological studies have shown that diabetes mellitus is a potent independent risk factors for cardiovascular disease\cite{1,2}. The Framingham Study demonstrated that the subsequent risk of cardiovascular disease for 239 diabetic subjects at baseline was doubled for men and tripled for women after adjustment for other risk factors (dyslipidaemia, hypertension and smoking). Although hypertension was the best predictor of subsequent coronary artery disease, the next most predictive were smoking in men and diabetes in women. More recently, the First National Health And Nutrition Survey (NAHANES 1)\cite{3} also showed that the diabetic population was twice as likely to develop coronary artery disease as the non-diabetic population. Indeed, 75% of the excess mortality in men with diabetes in this study was due to coronary artery disease. Whilst the burden of cardiovascular disease is obvious, the causes and implications in patients with diabetes are not. There are therefore cogent reasons to review the current state of knowledge and understanding of coronary artery disease in diabetes in order to identify therapeutic avenues to reduce this adverse risk. Diabetes may affect the heart in four major ways:

1. Earlier and more severe coronary artery disease.
2. Autonomic neuropathy.
4. Microvascular disease.

In this article we discuss the clinical implications of these manifestations of diabetic heart disease. The evidence that drugs are effective in improving the morbidity and mortality from cardiac disease in people with diabetes is discussed.

What is the natural history of coronary artery disease in diabetes?

The incidence of many manifestations of coronary artery disease (angina, myocardial infarction and sudden death) are increased in patients with Type 1 and Type 2 diabetes. These manifestations are more marked in women\cite{1,2}, who have a higher mortality than men\cite{4}. Indeed, cardiovascular disease may be present at diagnosis of diabetes before other macro or microvascular complications are evident. In the London cohort of the WHO Multinational Study of Vascular Disease in Diabetes, 21% of Type 1 diabetic subjects and 27% of Type 2 diabetic subjects showed evidence of coronary artery disease at study inception, which had increased to 43% by the end of the 8.3 years follow-up\cite{5}.

The diabetic heart often develops atherosclerotic disease in a different distribution compared with non-diabetic subjects. Some data suggest that diabetics who warrant cardiovascular intervention (angioplasty or bypass grafting) usually have diffusely diseased, inoperable vessels\cite{6}. However, data to support or refute this assertion are conflicting, for example, left main disease was reported more commonly (13% vs 6%) in some papers\cite{7}, but not in others. Veska et al.\cite{8} suggested that there is no difference between the distribution of coronary disease between non-diabetic and diabetic subjects. However, Dortimer et al.\cite{9} demonstrated that diabetic subjects had more triple vessel disease (43% vs 25%), more significantly affected vessels (68% vs 46%) and fewer normal vessels (11% vs 27%). Others suggest that disease may also be more diffuse and extend more peripherally in diabetic subjects\cite{10,11}.

Diabetes, silent ischaemia and angina

The patient with diabetes may have more severe coronary artery disease, but this may not lead to more angina because ischaemia may well be silent and only discovered at exercise testing or nuclear medicine imaging. Naka et al.\cite{12} compared 132 patients with diabetes with no previous myocardial infarction, symptomatic angina or heart failure, with 140 non-diabetic controls. He reported no difference between the two groups in the overall number of positive exercise tests, but showed that in those patients who had a positive treadmill test, diabetics had a 2-2 times higher prevalence of silent ischaemia ($P<0.05$). In addition, those who were taking insulin or had retinopathy were at greater risk of silent ischaemia than those who did not. The Coronary Artery Surgery Study (CASS)\cite{13} examined this issue and found that in a cohort of patients with >70% stenosis of a coronary artery, those with silent ischaemia and diabetes did worse than those who had silent ischaemia and were not diabetic (6 year survival 59 vs 82% $P=0.001$). Interestingly, if no ischaemia was demonstrated then the survival rate was the same for...
diabetics and non-diabetics. A proportion of this same patient group then underwent coronary artery bypass grafting. The patients with diabetes and asymptomatic ischaemia had a trend towards improved survival when compared with conservative therapy (6 year survival 85% vs 52% P=0.08). An important point was that the survival advantage was present whether left ventricular function was normal or impaired. This is supported by other work which showed that patients with type 2 diabetes had more electrocardiographic evidence of asymptomatic coronary artery disease\[14\].

The explanation for silent ischaemic episodes may be related to autonomic neuropathy. Langer et al.\[15\] investigated both exercise induced ischaemia and ischaemia on 48 h ambulatory ECG monitoring. If ischaemia was found, thallium scintigraphy scanning was used to determine the site in addition to autonomic function tests. It was found that the overall prevalence of silent ischaemia was 10%, and that asymptomatic ischaemic episodes were much more common in those subjects who had evidence of cardiac autonomic neuropathy, 38% vs 5% (P<0.003).

In contrast, data from the Asymptomatic Cardiac Ischaemia Pilot (ACIP) study\[16\] found no significant difference between the incidence of ischaemic episodes during ambulatory ECG monitoring or exercise testing. However, the diabetic subgroup was comparatively small, and the results would have been significant if the numbers in the diabetic group were arbitrarily raised to the same as the control groups\[17\].

**Unstable angina**

There are few conclusive data concerning the impact of diabetes on the prevalence or outcome of unstable angina. However, patients with diabetes who have unstable angina have increased morbidity compared with their non-diabetic counterparts. A prospective study in Malta evaluated 166 Type 2 diabetic and 162 non-diabetic subjects\[18\] and found diabetes conferred a greater than three-fold increase in mortality at three months (8-6% vs 2-5%, Type 2 diabetes vs control, P=0.014) which was maintained at one year (16-7% vs 8-6%, Type 2 diabetes vs control, P=0.029). A key feature of this study was that the incidence of unstable angina, myocardial infarction and coronary artery bypass were equal in both groups during the follow-up period. The uptake of beta-blocker use, coronary angiography and coronary angioplasty was lower in the patients with diabetes. The suggestion that diabetes worsens the prognosis of unstable angina, but does not increase the incidence, is supported by other data\[19,20\] that examine diabetic patients as sub-groups in studies of unstable angina.

**Myocardial infarction**

Patients with diabetes who suffer a myocardial infarction have a poorer prognosis both acutely\[21,22\] and in the long term\[23–28\]. The Gotebo¨rg Trial\[25\] showed that the 5-year mortality post-myocardial infarction was 46% in diabetic population compared with 27% in normoglycaemic controls. A meta-analysis by Kereiakes\[23\] showed that diabetes increased the risk of fatal myocardial infarction (31% vs 19-5%), diabetic subjects vs normoglycaemic patients.

**Gender differences; diabetes and myocardial infarction**

It has been increasingly recognised that the incidence of cardiovascular disease is higher in men than in women; this is particularly obvious prior to the menopause, but persists after it as well. The coexistence of risk factors like cholesterol, left ventricular hypertrophy and hypertension does not alter this sex bias, but diabetes does. Diabetes removes the protection that pre-menopausal subjects have and it is generally agreed that diabetic women develop atherosclerotic disease more frequently than diabetic men. This may or may not lead to a higher incidence of myocardial infarction. The London cohort of the WHO Multinational Study of Vascular Disease in Diabetes\[5\] demonstrated that the risk of myocardial infarction was higher for men than women. This conflicts with a study by Uusitupa et al\[29\] that demonstrated an increase in major Q wave abnormalities or myocardial infarction in 133 newly diagnosed patients with Type 2 diabetes. They showed that the relative risk was significantly increased only in women (4-4 (P=0.007) vs 1·7 (ns), female vs male). Interestingly, complaints of chest pain were more common in Type 2 diabetic patients than in normal controls, which is surprising considering the previous data suggesting chest pain may be less common for a given degree of ischaemia. In the meta-analysis by Kereiakes et al\[23\], the risk of myocardial infarction was the same in men and women with diabetes but women had a 40% greater mortality. This is supported by data from Framingham, where Abbott et al\[26\] demonstrated that diabetes doubled the risk of recurrent myocardial infarction in women, compared with both normoglycaemic women and diabetic men.

**Prognostic factors in myocardial infarction**

**Heart failure**

Survival is closely linked to residual left ventricular pump function following acute myocardial infarction\[30,31\]. The increased susceptibility to cardiac failure (fourfold increase (16% vs 3.8%) in diabetic vs
non-diabetic women) was an important factor in determining survival in the Framingham study\cite{26} and is supported by other data in men and women\cite{24,27,28,32}.

Two reasons have been suggested to explain the increased incidence of heart failure post-myocardial infarction. Firstly, it has been proposed that more severe and diffuse coronary disease limits the coronary reserve causing watershed, non-infarcted segments to be rendered more ischaemic by an infarct of comparable size. Secondly, it has been proposed that a specific co-existent disease of diabetic heart muscle disease, which is independent of the coronary disease, impairs myocardial relaxation and contractility.

Infarction site

Anterior infarction may be more common\cite{24} and may explain the increased incidence of heart failure. Other data\cite{32} from a study involving 54 subjects and 270 normoglycaemic controls, also showed that anterior infarcts were more common (43% vs 13%) and had a significant adverse impact, the 60 day mortality being 55% in diabetic vs 31% in non-diabetic subjects. Other complications which appear more common are anterior wall rupture which is 2.7 times more likely and cardiogenic shock. Arrhythmias have been found more commonly in some studies\cite{23} but not in others\cite{22,33,34}.

There are conflicting data, for example, Lehto et al\cite{35} showed that the immediate post-myocardial infarction mortality did not differ between patients with or without diabetes, but the 28 day mortality was twice as high in diabetic subjects, with cardiac failure being the principal explanation for the excess deaths. The magnitude of rise in cardiac enzymes and QRS-score was equivalent in both groups, suggesting that in this group of 1622 patients, people with diabetes neither had larger infarcts nor excess of anterior myocardial infarctions.

Ketoacidosis

Fatty acids normally provide the metabolic fuel for the heart but as oxygen concentration falls the heart becomes reliant more on glucose. Insulin’s ability to enhance glucose supply to the myocardium is antagonized by the stress hormones released, adrenal steroids, glucagon and catecholamines\cite{24,36}. This increases the degree of fatty acid oxidation, increases oxygen utilization and reduces myocardial performance. The occurrence of ketoacidosis is likely to worsen the prognosis of myocardial infarction, although the number of cases of diabetic ketoacidosis generated by myocardial infarction compared with other precipitants such as infection remains small.

**Autonomic neuropathy**

Diabetes mellitus is associated with loss of both sympathetic and parasympathetic innervation to the heart. Perhaps the most important clinical consequence of this is the increased prevalence of silent myocardial ischaemia and infarction. In some studies 32–42% patients with diabetes are reported to have had more silent or less painful infarctions compared with 6–15% in non-diabetic subjects\cite{37}. The Framingham Study showed the same trend in men but not in women, though the mechanism remains unclear\cite{38}.

Therefore impaired pain perception might suggest that angina is a poor discriminating symptom in the diabetic patient with ischaemic heart disease. On exercise and thallium scanning there is a higher incidence of silent ischaemia in diabetics compared to non-diabetic subjects, further suggesting that significant episodes of ischaemia are missed by symptoms alone\cite{39,40}. In some series, the 5-year survival for patients with autonomic neuropathy may be as low as 50%\cite{41}.

Other features of cardiac autonomic neuropathy are postural hypotension, cardiac denervation leading to a loss of an exercise or stress-induced heart rate rise, impaired systolic and diastolic function and changes in blood pressure. Blood pressure variability and the normal nocturnal dip in pressure are lost in diabetic autonomic neuropathy, leading to an increased average blood pressure and relative nocturnal hypertension\cite{42} and this may increase cardiovascular risk. More recent developments which may reflect autonomic neuropathy include increased QT dispersion in these patients and reduced heart rate variability\cite{43,44}.

**Type 1 diabetes**

Cardiac autonomic neuropathy may be present very early in the disease process. A new technique for the evaluation of cardiac autonomic dysfunction is the use of $^{123}$I-Meta-iodobenzylguanidine (\textsuperscript{123}I-MIBG) as marker for adrenaline in the terminal portion of sympathetic neurones; the capture of the iodine decay is then analysed by single photon emission computer tomography (SPECT). A study by Schnell et al\cite{45} looked at 22 newly diagnosed patients with Type 1 diabetes with $^{123}$I-MIBG scanning and found that 77% of the diabetic subgroup had abnormalities compared with none of the control group. Using more conventional measures of autonomic function only 9% demonstrated any disturbance of cardiac autonomic function. The demonstration of cardiac autonomic neuropathy is associated with increased mortality in type 1 diabetes patients\cite{46}.
**Type 2 diabetes**

In Type 2 diabetic subjects, Murata *et al.* [47] compared $^{123}$I-MIBG scanning to power spectral analysis of heart rate variability and found that there was a significant correlation between the two methods. A ten year follow-up by Toyry *et al.* [48] studied a population of 133 newly diagnosed Type 2 diabetes patients and compared the prevalence of both parasympathetic and sympathetic dysfunction at baseline, 5 and 10 years. They found that abnormalities of parasympathetic function advanced more quickly (4.9% vs 2.2% at baseline and 65 vs 28% after 10 years. Type 2 diabetic subject vs control) and was a predictor of the 10 year mortality. It was also related to the metabolic control of diabetes, hyperinsulinaemia and the female sex. The overall increase in combined cardiac autonomic dysfunction was from 2.1% vs 1.8% at 5 years to 15.2% vs 4.2% at ten years (Type 2 diabetic subject vs control respectively).

Heart failure

Heart failure is common in patients with diabetes mellitus and is more common than expected following myocardial infarction [21,27,33]. Two reasons which have been postulated to explain this are firstly, the extent and severity of the occlusive coronary artery disease (as discussed above), and secondly, the presence of a specific diabetic heart muscle disease.

There is increasing evidence to support the presence of a specific heart muscle disease in diabetes. Epidemiological data from the Framingham Study [26] show that diabetic subjects have a much higher risk of developing heart failure. Men aged 45–74 had a twofold increased risk and women had a fivefold increase in risk which persisted even when age, cholesterol, ischaemic heart disease, blood pressure and weight were taken into account. Abnormalities in both diastolic and systolic function occur without evidence of coronary artery disease being present very early in the disease process.

In an intriguing study, heart failure has also been reported in the neonate of mothers with diabetes mellitus. This presented either with signs similar to hypertrophic or dilated cardiomyopathy [49]. Both defects appeared to resolve spontaneously over the year following birth.

Patients with newly diagnosed Type 2 diabetes demonstrate left ventricular diastolic [50] and systolic dysfunction [51] but at 15 months follow-up, the degree of systolic dysfunction had diminished as glycaemic control improved. Diabetic cardiomyopathy presents with features of systolic and diastolic dysfunction, although the diastolic filling defect predates the development of systolic ventricular dysfunction. Diastolic dysfunction is not related to the presence of coronary artery disease [52], but may be related to the duration of diabetes [53]. The pathological abnormality seems to be collagen deposition within the heart muscle increasing ventricular wall stiffness [54]. Animal studies have found p-aminosalicylic acid-positive material among the muscle fibres and the presence of cholesterol and triglycerides in the myocardium [55–57], changes which appear not to resolve with better glycaemic control, although other reports are conflicting [58]. The increased incidence of bradyarrhythmia has been thought to be due to the microvascular effects of diabetes damaging the cardiac conduction system. The microvascular changes in the heart are the same as those throughout the rest of the body such as interstitial fibrosis, perivascular thickening and fibrosis and micro-aneurysm formation [59].

**Treatment issues**

**Drug therapy in myocardial infarction**

**Beta-blockers**

These agents have been demonstrated to be of significant benefit to diabetic patients with ischaemic heart disease [60,61]. Fears of reduced perception of hypoglycaemic symptoms are probably unfounded with the use of beta-blockers [62]. Beta-blockers reduce fatty acid oxidation and may reduce sudden death in diabetic subgroups at least as much if not more than non-diabetic subjects [62,63]. Interestingly, two studies; the First International Study of Infarct Survival (ISIS 1) [64], and the Metoprolol in Acute Myocardial Infarction study (MIAMI) [61] showed a non-significant differences with acute beta-blockade in the peri-infarct period between diabetic and non-diabetic subjects. Two trials [65–67] which looked at beta-blockers 5–28 days following a myocardial infarction, The Beta Blocker Heart Attack Trial (BHAT) [65] and the Norwegian Timolol Multicentre study [66] showed non-significant trends towards improved outcome with beta-blockade. A beneficial effect was also seen in one observational study [63]. However, meta-analysis demonstrated a significant reduction in mortality in both acute trials (37% vs 13%; diabetic vs non-diabetic subjects) [68] and those started later (48% vs 33%; diabetic vs non-diabetic subjects) [62].

The evidence is compelling that beta-blockers are at least equally effective in diabetic subjects and therefore their use should be actively encouraged.
This is particularly the case as a secondary prevention measure post-myocardial infarction. The usage of beta-blockers in the management of stable angina pectoris and unstable angina has not been particularly evaluated in diabetes and we are left to assume that the efficacy in diabetes is similar to that seen in non-diabetic subjects.

Aspirin therapy
Aspirin’s effect in primary prevention trials has been investigated in a subgroup analysis of the Early Treatment Diabetic Retinopathy Study\textsuperscript{[69]}, which showed a non-significant reduction in myocardial infarction but no conclusive impact on all-cause mortality. Although the role of aspirin in myocardial infarction is well documented, little data directly addresses the specific problems of diabetes. Evidence suggests that the dose of aspirin may be critical in diabetic subjects, with ISIS 2\textsuperscript{[70]} demonstrating no benefit from 160 mg of aspirin daily in diabetics and these data are supported by some\textsuperscript{[71]} but not all\textsuperscript{[72,73]} reports. Increased platelet turnover may be one explanation for this disparity, as 300 mg of aspirin may be necessary to effectively suppress thromboxane A\textsubscript{2}\textsuperscript{[74]}. The Antiplatelet Trialists Collaboration\textsuperscript{[75]} performed a meta-analysis of secondary prevention studies and showed that aspirin benefited diabetic and non-diabetic subjects to the same degree (38 per 1000 vs 36 per 1000 vascular events avoided, diabetic and non-diabetic subjects respectively).

There appears to be an interaction between aspirin and angiotensin converting enzyme inhibitors, this being seen in the CONSENSUS II\textsuperscript{[76]} and SOLVD studies\textsuperscript{[77]}. The case seems sound for aspirin post myocardial infarct, however some data suggest that a dose of at least 300 mg may be needed rather than the 160 mg used in ISIS 2\textsuperscript{[70]} which may be less effective.

ACE inhibition
There are two areas of interest with ACE inhibition; firstly, the impact of early use post myocardial infarction with introduction of the ACE inhibitor within 4 to 6 weeks. Secondly, the introduction of ACE inhibitors in patients who have demonstrable heart failure following the index infarct.

The earliest introduction of an ACE inhibitor post myocardial infarction was in CONSENSUS II\textsuperscript{[78]}, where intravenous enalaprilat was given within the first 24 h of a myocardial infarction. This strategy was associated with an 11% increase in mortality. However, data from the GISSI-3\textsuperscript{[79]} and ISIS 4\textsuperscript{[80]} demonstrated that diabetic patients benefit from ACE inhibition in the short term when introduced orally some days following myocardial infarction (12% and 7%, GISSI-3 and ISIS 4, respectively). Subgroup analysis of GISSI-3\textsuperscript{[79]} demonstrated that diabetics benefited more than non-diabetic subjects (44%, 27% and 22%; Type 1 diabetes, Type 2 diabetes and non-diabetic groups respectively). The impact of ACE inhibition initiated chronically to patients with evidence of heart failure has been extensively investigated. However, the major trials which include the Survival and Ventricular Enlargement (SAVE) Trial\textsuperscript{[80]}, The Acute Infarction Ramipril Efficacy (AIRE) Study\textsuperscript{[82]} and the Trandolapril Cardiac Evaluation (TRACE) Study\textsuperscript{[83]} have failed to publish subgroup data in diabetic subjects. Therefore, we have to assume that the reduction seen in non-diabetics (approximately 22%) is also applicable to diabetic subjects. Some help is available from the Studies of Left Ventricular Dysfunction (SOLVD) trials\textsuperscript{[84,85]} which found that the benefit was similar in both diabetic and non-diabetic subjects.

Lipid lowering therapy
Reducing lipid levels has been demonstrated to improve endothelial function in both animal\textsuperscript{[86]} and human models\textsuperscript{[87]}. This improvement in endothelial function appears to be tracked by improvements in morbidity and mortality trials in post-myocardial infarction subjects\textsuperscript{[88,89]}. However no prospective evaluation has investigated whether improvements in endothelial function precede a reduction in the severity of occlusive cardiac disease and ultimately improve morbidity and mortality.

Primary prevention studies such as the West of Scotland Coronary Prevention Study (WOSCOPS)\textsuperscript{[90]} have demonstrated mortality benefits with lipid reduction using pravastatin. However, the WOSCOPS group have not published subgroup analysis looking at diabetic patients and instead we must rely on the fall in all cause mortality of 22% and assume that a similar effect is seen in diabetic subjects. The Air Force Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)\textsuperscript{[91]} is still in process and is enrolling subjects with normal or mildly raised cholesterol and LDL-cholesterol. Although the effect of lovastatin in diabetic subjects has not been set as an a priori hypothesis, some preliminary data from AFCAPS/TexCAPS were presented at the 47th Scientific Sessions of the American College of Cardiology (Atlanta, Georgia, U.S.A.; March 1998). Lovastatin was found to reduce the first cardiovascular event by 37% (P=0.00008), bypass grafts by 18%, angioplasty by 37% and to produce a 29% fall in hospital admissions. The full publication of the data are awaited.

Most primary prevention studies have investigated the effects of statin therapy. The notable
exception was the Helsinki Heart Study[71] which demonstrated a 10% fall in serum cholesterol levels accompanied by a 34% reduction in coronary heart disease with gemfibrozil. These encouraging findings were not supported by a fall in total mortality.

Three major studies looking at secondary prevention in the post myocardial infarction period have demonstrated significant benefits in diabetic patient subgroups. The Scandinavian Simvastatin Study (4S)[88] included 204 diabetics out of a total of 4444 subjects. It demonstrated that cholesterol lowering therapy following myocardial infarction was highly effective therapy with significant reductions in cardiovascular deaths, cardiovascular events and the need for revascularization procedures. These benefits appeared even more marked with diabetic than non-diabetic subjects (risk reduction 55% vs 32%)[92,93]. Similar results were reported by the Cholesterol and Recurrent events (CARE) trial[89], which included 586 diabetic subjects. The reduction in mortality was comparable in both diabetic and non-diabetic subjects (25% vs 23% respectively). More recently, preliminary data from the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study, presented at the American Heart Association’s Scientific Sessions, 12th November 1997 suggested an overall fall in mortality of 23%, with a fall in myocardial infarction of 29%. The full publication of the results are awaited.

In summary, there appears to be compelling evidence for the use of statin therapy post myocardial infarction in diabetic subjects. There is also growing evidence for lipid lowering therapy in the primary prevention of cardiovascular disease, although we are restricted to drawing conclusions from subgroups analysis of large trials. However, further work is required to evaluate the cost implications of adopting a primary prevention strategy. Perhaps identifying patient groups at higher baseline risk, such as people with diabetes, may limit the overall health care cost implications of primary prevention.

**Delivering benefits to patients**

The Action on Secondary Prevention through Intervention to Reduce Events (ASPIRE) study highlighted that drugs effective for secondary prevention of cardiovascular disease are often not used in everyday clinical practice. This United Kingdom survey performed under the auspices of the British Cardiac Society showed that of the patients who had suffered a myocardial infarction, only 38% of patients were receiving a beta-blocker, 17% ACE inhibitor, 10% lipid lowering but 75% aspirin[94]. Data specific to diabetes are available from the DARTS/MEMO Collaboration[95] which is a research database of all diabetic patients in Tayside, Scotland (population 390 000, diabetic population 7596; prevalence 1·94%, sensitivity 95%, positive predictive value 96%) and records all drugs encashed at community pharmacies. During the same period as ASPIRE we found that 208 diabetic patients were admitted to Tayside hospitals with a first myocardial infarction. Of the patients that survived 3 months, 25% were taking a beta-blocker, 68% were taking aspirin and 25% were taking ACE inhibitors and despite cholesterol being measured in 21% of subjects, only 2% were discharged taking lipid lowering therapy[96]. It is therefore clear that diabetic patients who have suffered a myocardial infarction often do not receive these highly beneficial treatments.

**Hormone replacement therapy**

Oestrogen withdrawal at the menopause is associated with increased low density lipoprotein cholesterol concentration, insulin resistance, impaired endothelial dependent vasodilatation and increased blood pressure[97]. The evidence for the use of hormone replacement therapy is significant and more than 30 studies have been conducted to establish the relationship between oestrogen supplementation/replacement therapy and cardiovascular disease. A meta-analysis of these data suggest an overall reduction in the risk of coronary artery disease of approximately 40%[98]; unfortunately only one of these studies reached statistical significance in its own right[99]. The benefit appears to be greater for those who have established cardiovascular disease or those with other risk factors[100] and is thought to accrue mainly through changes in lipid metabolism[97].

Therefore there are cogent reasons to recommend the use of oestrogen replacement therapy in post menopausal women who either have established coronary artery disease or who have cardiovascular risk factors. There are few data concerning diabetes specifically.

**Insulin-glucose infusion**

The metabolic changes in diabetes increase lipolysis which acts to inhibit glycolysis both in ischaemic and non-ischaemic tissue[101]. Two therapeutic options are available to reduce fatty acid oxidation; blockade and insulin-glucose infusion[102]. We already know beta-blockers are beneficial in diabetic subjects, particularly following myocardial infarction.
Insulin and glucose therapy was first suggested to have beneficial effects in a study by Clark et al. in 1985 which showed a reduction in mortality following a myocardial infarction in diabetic patients who were given intravenous insulin and glucose following admission[34]. More recently, the diabetes glucose insulin acute myocardial infarction (DIGAMI) study randomized 620 patients to receive traditional therapy (not treated with insulin unless clinically indicated) or insulin-glucose infusion followed by multidose insulin (SSI) regimen[103,104]. The insulin regimen improved the prognosis for diabetic patients (mortality 8.6% vs 18.0%, intensive vs traditional treatment, \( P=0.020 \) at one year). Long-term follow-up data from this study[105] suggest this benefit was maintained over the mean follow-up period of 3-4 years with a mean absolute reduction in death of 11%. Interestingly, the most marked benefit was seen in the group who were not previously treated with insulin therapy and were considered to be at low cardiovascular risk (relative risk, 0.49, 95% CI 0.30-0.80, \( P=0.004 \)).

The DIGAMI Study[103,104] is compromised by a lack of data concerning cigarette consumption and other risk factors. There is also concern that infarct size appeared smaller in the intensive treatment arm and whether this affects mortality rather than the intensive therapy itself is unclear. Furthermore, the finding that those who benefit from this therapy most were those not previously treated with insulin suggests two possibilities. Either the benefit is due to the withdrawal of oral hypoglycaemic agents or it is due to the intensive insulin regimen itself.

Diabetes is a hypercoaguable state[105] and insulin therapy has also been shown to reduce some hypercoagulation parameters[106], though the clinical relevance of this finding is far from clear. Though intuitively one would expect that reducing hypercoagulability would be beneficial in unstable angina and myocardial infarction.

**Thrombolysis**

Data drawn from the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Study[111] supported evidence presented earlier that patients with diabetes had more multivessel disease that was more severe, died more frequently and had more cardiac failure. Initial patency and re-occlusion rates following thrombolysis were equivalent between patients with and without diabetes (71% vs 70% respectively). However, once more severe coronary artery disease had been adjusted for, diabetes was not an independent risk factor for mortality, suggesting that the secondary complications of diabetes are responsible for the increase in mortality. The conclusion was that poorer contractile function of the peri-infarct zone in the diabetic group was due to more extensive coronary artery disease. Other groups have suggested that worse cardiac function and regional wall abnormalities may in fact be due to the presence of a specific diabetic heart muscle disease. Data from the International Study of Infarct Survival (ISIS) II[70] showed that patients with diabetes had more benefit that non-diabetics following thrombolyis, although this was based on sub-group analysis rather than an a priori hypothesis.

**Implications of diabetes for coronary revascularization**

Patients with diabetes benefit less from coronary revascularization. In diabetic subjects the peri-operative mortality is doubled from 4% to 9% and surgery is associated with a reduced long term survival[24]. This is supported by a substantial Swedish study[107] which showed similar results. The post-operative period is more stormy with increased arrhythmias, infections and respiratory problems[108]. However, previous data have suggested that bypass time and occlusion time were similar[108] and the number of grafts were also similar for both diabetics and non-diabetics[109] although others suggest the number of grafts may be greater in diabetic subjects[110].

The TIMI II trial[111] suggested that a more conservative approach produced better survival figures. When patients were randomized to either aggressive (coronary angiography and angioplasty) or conservative (wait and see) groups, the conservatively treated group did better. Other work has demonstrated a poorer outcome for diabetic patients with coronary artery bypass graft (CABG)[109] and percutaneous transluminal angioplasty (PTCA)[112].

When symptoms or prognostic indications necessitate interventional strategies, the question as to whether CABG or PTCA has any advantage over the other has only recently been addressed. The Bypass Angioplasty Revascularization Investigation (BARI) is a multicentre study of 1829 patients, designed to investigate long-term mortality differences comparing an initial strategy of CABG vs PTCA. A physicians’ alert was issued in December 1995[113] when the 5 year mortality rate for 353 patients treated with insulin or oral hypoglycaemic drugs was analysed. In the PTCA arm the mortality rate was found to be 35% compared with 19% in the CABG arm of the trial. The mortality rate in diet
controlled diabetics was found to be similar to the 5 year mortality rate for all patients undergoing CABG (9% vs 9.2%).

PTCA is a successful, low risk treatment of coronary disease, but the BARI alert raised significant questions about its validity in the patient with diabetes mellitus. The main determinant of an unsuccessful angioplasty remains restenosis of the angioplasty site. Many factors play a role in increasing the likelihood of restenosis occurring including age, hypertension, diabetes, more severe angina, multivessel disease and poorer initial results. The impact of increased stent usage and better technical skill in stent placement may alter this apparent deleterious effect of angioplasty in diabetic patients and more studies are required to address this issue.

Conclusion

Cardiovascular disease in diabetes is an area of key importance. Patients with diabetes have a much higher risk of coronary disease, heart failure, myocardial infarction and death. The specific problems of diabetic subjects suggest that a universal management plan cannot be applied to all patients. Diabetic patients may need specific interventions which contrast with current practice in non-diabetic subjects. Evidence supports the use of many drugs and procedures in diabetic subjects, often in cases where there appears to be more benefit in diabetic compared to non-diabetic subjects, but where usage is not as high as perhaps it could be.

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