Coronary Artery Disease in Diabetes Mellitus

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A B S T R A C T

The twin epidemics of diabetes mellitus and heart disease are a major threat to the well-being as well as the economic development of India. It is believed that a combination of factors, genetic and environmental including newer risk factors like the metabolic syndrome and hypercoagulability in addition to traditional risk factors like smoking, hypertension and hypercholesterolemia is the culprit behind the explosive rise in the incidence of these diseases. CAD in DM is not only 2-4 times more frequent than non-diabetics and also has a worse prognosis. Many patients have subclinical or asymptomatic CAD which can have devastating consequences. Tight glycemic control alone only has a marginal effect in controlling CAD. This can be treated by a multifactorial approach which includes not only adequate glycemic control but also control of dyslipidemia, hypertension and microalbuminuria. Established CAD [acute and chronic] is largely treated by the usual methods, but the prognosis remains inferior to non-diabetics. ACE inhibitors, aspirin, beta-blockers and statins are useful in the majority of patients for reducing CVS end-points [in addition to glycemic control]. PTCA remains inferior to CABG in revascularization therapy in diabetics although advances in technology may help it to close the gap in the near future. Ultimately primary prevention of type 2 DM by exercise and lifestyle modification may help in preventing the development of type 2 diabetes and its complications; this may be very useful in stemming the epidemics of DM and CAD.

INTRODUCTION AND PREVALENCE OF DM AND CAD IN INDIA

The spreading cardiac and diabetes epidemic is a major health threat for India and holds the potential to bankrupt our nation. The unprecedented increase in diabetes and cardiovascular disease (CVD) prevalence is evident from the report of WHO which shows that India tops the world with the largest number of subjects. According to recent WHO reports presently India has 32 million diabetic subjects and this is projected to increase to 100 million i.e. a rise by 250 % by the year 2035; in addition there is also a growing incidence of metabolic syndrome. This syndrome is a deadly combination of hypertension, diabetes mellitus, dyslipidemia with abdominal obesity and often leads to heart disease. The cause of this is both bad genes and defective environmental influences.

Hence, in the coming decades the burden of CVD related to DM will increase significantly. Most diabetics die of CVD and atherosclerosis accounts for almost 80% of all diabetic mortality.[1] Presence of DM increases the risk of cardiovascular disease (CVD) 2-4 folds. Type 2 DM represents more than 90% of the diabetic population. However type 1 DM also have an independently higher risk of CVD and their disease develops at younger age.

Most data show that striking increase in the risk of a first or recurrent MI in diabetics as compared with non-diabetics in a population-based study in Finland[2] by Haffner et al over a seven year follow-up period these data also show that a diabetic patient without a history of MI has an approximately equal risk for a first MI as a non- diabetic subjects who has already sustained MI (Fig. 1). These data support recent recommendations by the American Diabetic Association to treat diabetic subjects as though they already have established CAD.

All the manifestations of CAD are at least two-fold more common in patients with DM than in non-diabetic individuals. Conversely, the prevalence of DM in CAD is approximately 20%.[1,2] As the recent statistics point out to a marked increase in diabetes worldwide[3] one can anticipate rising trends in prevalence of CAD associated with diabetes.

There is evidence from Indian data as well that CAD is more common in diabetic subjects. Studies conducted in south India by Mohan et al and Ramchandran et al in Chennai showed a prevalence of diabetes varying from 12-16%.
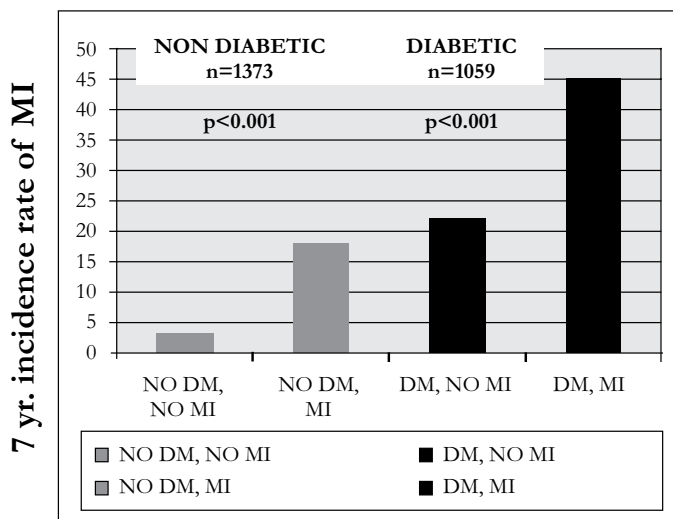
Fig. 1: Marked increase in the risk of coronary artery disease in Type 2 Diabetes

In a study done at MV Diabetes Centre, Madras the prevalence of CAD was assessed in a large cohort of 6597 NIDDM patients.[4] Overall 17.8% of patients had CAD. Its prevalence was not significantly different in males and females. The Chennai Urban Population Study (CUPS) reported that overall CAD prevalence was 11%. 12% of this population was diabetic. Among these 21.4% had CAD, more than the double that of non-diabetics.

All these data suggest that the epidemic of type 2 DM and CAD has already assumed alarming proportions and urgent measures are needed to stem it.

CARDIOVASCULAR RISK FACTORS AND PATHOPHYSIOLOGY OF CAD IN DIABETIC SUBJECTS

Diabetes mellitus and coronary artery disease share many common risk factors. According to Reaven, diabetes and CAD are constituents of the metabolic syndrome in which insulin resistance plays a contributory role. There is a clustering of several metabolic disorders like dyslipidemia, HTN, hyperglycemia and central abdominal obesity. This cluster has shown to predict death in Type 2 DM.[5] In addition, a number of other risk factors for CAD such as atherothrombotic factors, fibrinolytic factors, coagulation factors inflammatory markers, and autonomic neuropathy have also been described in diabetic patients.

Dyslipidemia

The classic triad of diabetic dyslipidemia consists of triglyceride elevation, low HDL cholesterol and small dense LDL particles [which are highly atherogenic]; total cholesterol and LDL cholesterol may be normal or mildly elevated. Dyslipidemia, a traditional risk factor has probably enhanced importance in diabetics as compared to non-diabetics.

Increased hepatic production of VLDL by the liver lies at the centre of the pathogenesis of diabetic dyslipidemia. Increased production of VLDL by the liver results from increased delivery of free fatty acids because of decreased utilization by muscle and increased delivery of fatty acids from visceral abdominal fat via the portal circulation.

Decreased catabolism of post-prandial TG-rich lipoprotein particles because of decreased lipoprotein lipase activity accelerates diabetic dyslipidemia.

Hyperglycemia and CAD

Increase in plasma glucose levels have long been recognized as a risk factor for CAD. In fact plasma glucose has been shown to have a continuous gradient relationship with CAD both in the diabetic range and in the non-diabetic range.[6] It is likely that post-prandial hyperglycemia may be more important in the development of CAD than fasting hyperglycemia (e.g. the DECODE study[7]).

HTN and CAD

Studies have shown that an increase BP by 5 mm of Hg is associated with 34% increase in risk for CVD,[8] this applies to diabetics as well as normoglycemic individuals. Up to 50% of type 2 diabetic individuals are also hypertensive, thereby multiplying the risk of CAD.

Hypercoagulation, Hypofibrinolysis and CAD

Diabetes in associated with various abnormalities of the haemostatic and fibrinolytic system. Indeed diabetes in considered to be a hypercoagulable and hypofibrinolytic state. An increased level of fibrinogen and PAI-1 has been indicated by both clinical and epidemiological studies among diabetic subjects.[9] Decreased fibrinolysis may predispose diabetic patients to deposit fibrin and this may exacerbate accumulation of LDL.[10]

Lipoprotein (a)

It is a complex of apolipoprotein (a) and LDL. Lipoprotein (a) has a striking homology and common genetic determinants with plasminogen and can competitively inhibit plasminogen activity leading to decreased fibrinolysis. Lipoprotein has also been implicated in enhanced oxidation and foam cell formation. Lipoprotein (a) had an independent association with CAD in Type-2 diabetic patients.[11] Several other studies have supported this association.[12]

The Metabolic Syndrome

The metabolic syndrome is a constellation of abnormalities including glucose intolerance, hyperinsulinemia, dyslipidemia, obesity [central or generalized], hypertension and microalbuminuria, often combined with hemostatic and fibrinolytic abnormalities. The WHO definition of this syndrome includes:[13]

1. Impaired glucose regulation or diabetes
2. Insulin resistance
3. Raised arterial pressure > 160/90
4. Raised plasma triglyceride > 150 mg/dl and/or low HDL cholesterol < 35 mg/dl in men or < 39 mg/dl in women
5. Central obesity (males : waist to hip ratio > 0.9 females ; waist to hip ratio > 0.85) and / or BMI / 30 kg/m²
6. Microalbuminuria

To satisfy the criterion of metabolic syndrome a patient needed to have either criterion (1) or (2) positive along with at least 2 of the 4 remaining criteria.[2-6]

Table 1: Risk factors more common in Asians in UK

1. Decreased physical activity
2. Increased central obesity
3. Hyperinsulinemia and increased insulin resistance
4. Decreased beta cell function
5. Increased prevalence of NIDDM
6. Increased lipoprotein(a)
7. Increased TG
8. Decreased HDL
9. Increased PAI-1

Two major studies on the metabolic syndrome include a recent population-based study by Isomaa and Coworkers[14] in Finland and Sweden concluded that the metabolic syndrome was present in 10% of subjects with normal glucose tolerance – 50% of subjects with impaired fasting glucose or impaired glucose tolerance and 80% of subjects with type 2 diabetes. The risk of coronary artery disease and stroke was markedly increased (nearly three-fold) in those with the syndrome and of the individual components microalbuminuria seemed the strongest predictor. A more recent study by Lakka and coworkers in Finnish males[15] indicated that the metabolic syndrome as per WHO criteria was associated with 2.6-3.0 times increased CVD mortality and 1.9-2.6 times all cause mortality. These were also the findings of the San Antonio Heart Study.[16]

Considering the fact that central obesity and hypertriglyceridemia are common in Indian diabetics, it is not surprising that the risk of CAD is considerably enhanced in Indians .

Homocysteine and CAD

Several studies on its association with CAD among Indians have produced conflicting results.[17,18] It's exact importance in diabetic with CAD in India remains doubtful.

Inflammatory Markers

There is emerging evidences that inflammatory processes and specific immune mechanism are involved in atherogenesis.[19] It has been shown that inflammatory markers predict future cardiovascular events. C-reactive protein [CRP] has recently gained lot of interest.[20] Another study have shown CRP to be associated with both DM and CAD.[21]

Additional risk factors specific for diabetic patients include, gross proteinuria, elevation in serum creatinine and altered platelet function.

Cardiovascular Autonomic Nervous System Dysfuction in Diabetes Mellitus

Cardiovascular autonomic neuropathy (CAN) probably contributes to the poor prognosis of CVD in both Type 1 and 2 DM.

Patients present with postural hypotension, resting tachycardia, exercise intolerance or painless myocardial ischemia or infarction.

CAN and Increased Cardiovascular Mortality and Morbidity in DM
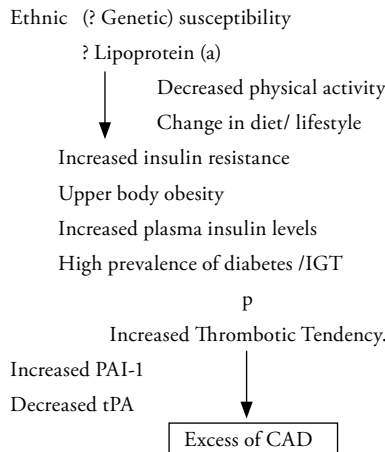
Numerous mechanisms are responsible

Fig. 2: Pathogenesis of CAD in Asians

Table 2: Mechanism of vascular abnormalities in DM

- Dyslipidemia – Small dense LDL, decreased HDL, increased TG.
- Hyperglycemia – Increased DAG, protein kinase C activation, increased sorbitol
- x Hyperinsulinemia
- x Oxidative stress – Reactive oxygen species, increased carbonyl overload.
- x Advanced glycation end-products – Activation of nuclear factor beta overproduction of inflammatory cytokines.
- x Procoagulant antifibrinolytic state – Elevated fibrinogen, increased PAF-1, heightened platelet function.
- x Genetic abnormalities
- x Metabolic syndrome - A combination of dyslipidemia, hypertension, glucose intolerance, obesity and microalbuminuria.

a. Impaired anginal perception leading to silent ischemia/ infarction
b. Altered threshold for ischemia
c. Causes abnormal systolic and diastolic dysfunction
d. Increased risk of ventricular arrhythmia
e. Loss of mechanical protection against myocardial infarction, and
f. Altered circadian BP regulation

It is clear that an excess of established risk factors for heart disease in not the only explanation for the increased IHD[CAD] among Asians. Perhaps a constellation of cardiovascular risk factors typical of these observed in insulin resistant status operates in Indians; notably n TG, p HDL, hyperinsulinemia, central obesity and a high prevalence of type 2 diabetes [as part of the metabolic syndrome or independently]. Recent findings suggest that part of this risk is inherited, probably linked to lipoprotein(a) and genetic polymorphism. This when combined with environmental influence of westernization including obesity, decreased physical activity, dietary changes, increased LDL cholesterol and diabetes can be transformed into very potent risk factor for IHD. This may be mediated through an increased thrombotic tendency related to increased plasminogen activator inhibitor-1 (PAI-1) and reduced tissue plasminogen levels. Table 1 and Fig. 2 outline the mechanisms and risk factors particularly applicable to South Asians.
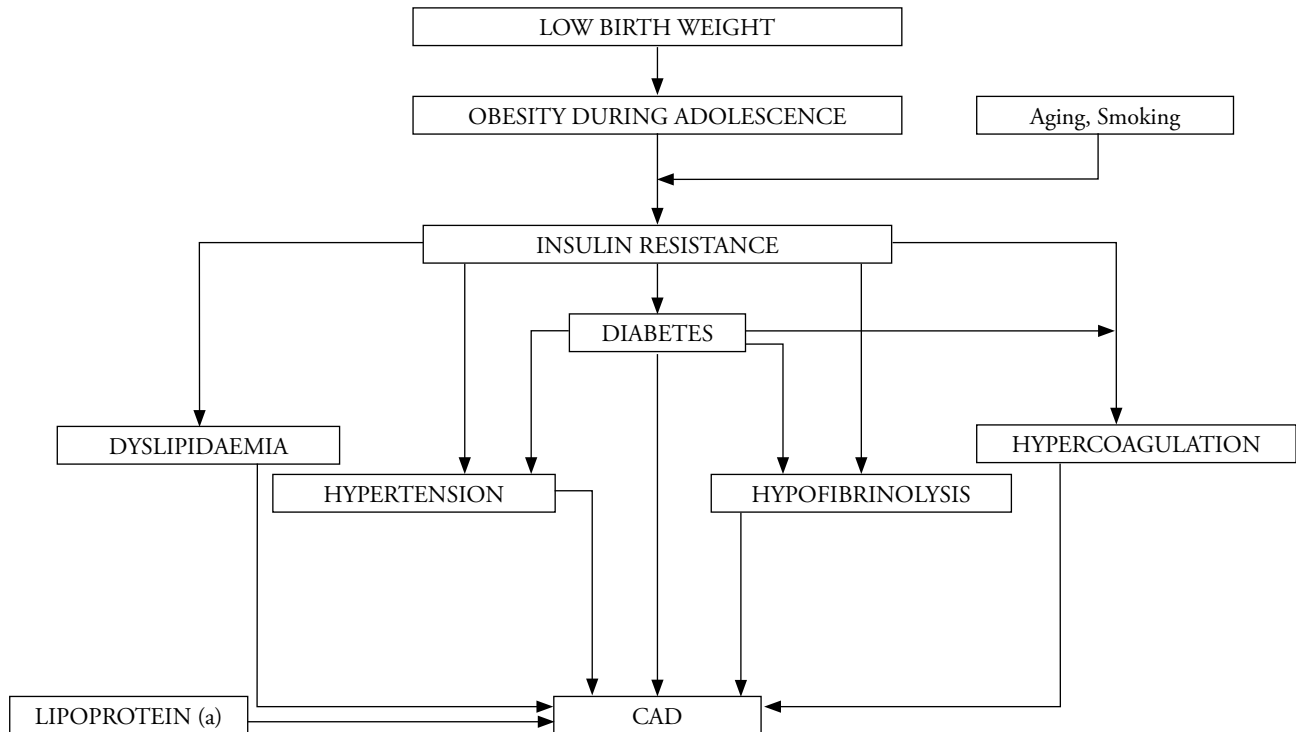
Fig. 3: Correlation of various risk factors leading to CAD in DM.

In sum, a combination of factors which includes traditional risk factors combined with emergence of newer risk factors like lipoprotein(a), decreased fibrinolysis, hyperinsulinemia and metabolic syndrome are likely to be responsible for the massive increase in CAD in diabetes. These are summarized in Table 2 and Fig. 3.

INTERVENTIONS TO DECREASE CAD MORTALITY

This may include:

A. Risk factor control for primary and secondary prevention - this has been extensively studied in type 1 DM [DCCT trial] and type2 DM [UKPDS].

B. Management of acute coronary syndromes in diabetics [including acute MI].

C. Interventional strategies [CABG or PTCA in acute or chronic situations].

D. Screening for CAD in asymptomatic individuals - especially type 2 diabetes.

E. Prevention of type 2 diabetes

A number of options are available as primary or secondary prevention of CAD in diabetic individuals.

Lifestyle modification

a. Cessation of smoking and exercise – Encourage moderate intensity activity for 30-60 minutes for at least 3-4 times a week

b. Weight reduction – Intensive dietary therapy and exercise in patient with BMI>25 Kg/m^2 esp. in patient with HTN, increased TG and increased glucose.

Intensive Glycemic Control

Numerous studies have shown a positive correlation between CAD endpoints and increasing glucose level in diabetes. In UKPDS trial HBA1c level above 6.2% were associated with increased risk of macrovascular disease[22] for each 1% increase in HbA1c CAD risk increased by 11%. However it also appeared that the relative risk of CAD did not increase in association with HbA1C < 7%, thus suggesting a threshold. In overweight diabetic patients metformin did have a lower risk of macrovascular disease including MI [30% and 39% reduction respectively compared to conventional therapy].[23] In the DCCT trials, intensive insulin therapy in Type 1 DM reduced the risk of macrovascular disease including CVD by 41%, although the difference between groups lacked statistical significance.[24]

In the UKPDS trial, improved glycemic control did not conclusively reduce cardiovascular mortality[25] with the exception of the overweight group mentioned earlier, although there was a marginal decrease in the incidence of MI of borderline statistical significance. Importantly with sulphonylureas and insulin did not appear to increase cardiovascular disease in Type 2 DM refuting prior claims of atherogenic potential of these agents. Glitazones may have anti-atherogenic properties although their utility is still not established in long-term clinical trials.

These data indicate that while glycemic control [maintaining HbA1c <7% as recommended by the ADA] is important , it alone is not enough to prevent and treat CAD [with the exception of metformin in overweight DM].

Dyslipidemia

Most common forms of dyslipidemia in diabetic include increased TG and decreased HDL. Though DM itself does not increase

LDL but small dense LDL particle found in diabetics are more atherogenic.

According to ADA guidelines lipid profile in diabetics without cardiovascular disease should be LDL < 130 mg/dl, HDL in Male > 35 mg/dl in female > 45 mg/dl and TG < 200 mg/dl. In diabetics, LDL should be < 100 mg/dl. Because of the high risk of CVD in diabetes most authorities recommend that optimal level of lipid profile in diabetics with or without CVD should be LDL < 100 mg/dl, HDL in male > 45 g and in female > 55 mg/dl, and TG < 200 mg/dl. Tight glycemic control can ameliorate features of lipoprotein profile associated with increased risk.

The order of priority in treatment of hyperlipidemia is to (1) decrease LDL (2), increase HDL, (3) decrease TG.

Eventhough LDL lies within normal limits in Type 2 DM treatment with statins reduces coronary risk. Several studies have proved the utility of statins in diabetics. These include Heart Protection Study (HPS) and the most recent CARDS study. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin has shown significant reduction of vascular events irrespective of baseline serum cholesterol in patients of diabetes

The CARDS study,[26] [Collaborative Atorvastatin Diabetes Study (CARDS)] were presented at the ADA 64th scientific session. Atorvastatin reduced cardiovascular events in diabetes with decreased acute coronary syndromes by 36%, stroke 48% and mortality 27%. This has firmly established the role of statins in diabetes with or without CAD; the major question is whether statins should be prescribed to all type 2 diabetics. Furthermore treatment with fibric acid derivatives targets low HDL and high TG, characteristic of diabetic dyslipidemia. The VA-HIT trial suggests that a population of individuals shows reduction in coronary events and strokes when treated with fibric acid derivatives.[27] DAIS trial showed delayed angiographic progression of coronary atherosclerosis in diabetics with fenofibrate.[28] However, statins remain the drug of first choice for treating diabetic dyslipidemia. This has been endorsed by ADA in its 2004 recommendations. Fibrates may be ancillary drugs especially in severe hypertriglyceridemia [triglycerides > 400mg/dl]. A more recent review of the subject by Grundy et al[29] suggests an optional LDL cholesterol of <70 mg/dl in diabetics.

Hypertension

The UKPDS trial studied tight BP control and the risk of macrovascular and microvascular complication in Type 2 DM and compared the effects of captopril vs. atenolol on these outcomes. Tight BP control reduces the risk for heart failure (RR = 0.44), microvascular complications (RR=0.63). This trial also suggests that intensive BP control may be more important than the drug itself[30] and also more important than glycemic control.

Hypertension can accelerate cardiovascular disease and nephropathy in DM. The goal is < 130/80 mmHg in diabetic individuals and < 125/75 mmHg with proteinuria. Antihypertensive agents should be selected on the basis of advantages and disadvantages of the agent in context of individual patient's risk factor profile.

ACE inhibitors are glucose and lipid neutral and also have vascular protective properties independent of their antihypertensive effect. If microalbuminuria or overt proteinuria is present,

the optimal antihypertensive is ACEI/ARBs. Alpha-blockers improve insulin resistance with positive impact on the lipid profile while beta-blockers and diuretics can increase insulin resistance and negative impact on lipid profile and slightly increases the risk of Type 2 DM. However after the results of the ALLHAT study which showed increased incidence of heart failure with alpha-blockers, the use of these drugs has been restricted. Cardioselective beta-blockers have minimal adverse profile. Sympathomimetic inhibitors and alpha-blockers cause postural hypotension in DM with autonomic dysfunction. Calcium channel blockers are lipid and glucose neutral and some evidence suggests that they decrease cardiovascular morbidity and mortality in Type 2 DM particularly in elderly with systolic HTN.[31] To summarize, ACE inhibitors are the drugs of first choice in hypertensive diabetics; ARBs, beta-blockers, diuretics and calcium channel blockers [preferably non-dihydropyridines like sustained release verapamil or diltiazem] may be used in addition for adequate control.

ACE Inhibitors

They reduce infarct size, limit ventricular remodeling improve survival after MI and also significant reduction in CHF may be of particular benefit in diabetics.[32] GISSI 3 trial revealed that early administration of lisinopril in acute MI reduce 6 months mortality more in diabetics than non-diabetics. ACE inhibitor treatment reduced nearly 50% the risk of sudden death, reinfarction and progression of CHF in diabetics whereas non-diabetics experienced only trends in protection against these secondary outcomes. HOPE and MICROHOPE trials investigated the effects of ramipril on the incidence of adverse cardiovascular and renal outcomes in people of DM. Ramipril (10mg/d) reduced the combined outcome of MI, stroke or death by 25%, total mortality by 24% and overt nephropathy by 24%.[33]

A recent study shows that intensive multifactorial intervention in type 2 diabetes may reduce cardiovascular risk by over 50%.[34] This highlights the importance of aggressively treating all aspects of diabetes and related risk factors [e.g. hypertension, dyslipidemia, microalbuminuria] rather than concentrating on glycemic control alone.

MANAGEMENT OF ACUTE CORONARY SYNDROMES

In general, treatment of acute manifestations of CAD is no different in diabetics than non-diabetics though overall prognosis is worse in diabetes. In addition to aspirin, beta-blockers, ACE-inhibitors, nitrates, fibrinolytic therapy is of particular benefit in diabetics.

Aspirin

Studies have consistently shown that patients with either Type 1 or Type 2 diabetics have enhanced platelet aggregation in response to a variety of agonists.[35] Diabetic patient exhibit increased production of thromboxane, a potent vasoconstrictor and platelet agonist.[36] The ADA currently recommends enteric-coated aspirin in a dose 81-325 mg/d(a) as secondary prevention in diabetics and evidence of macrovascular disease; and (b) as

primary prevention in persons with Type 1 and 2 diabetes and additional coronary risk factors.[37]

Beta-Blockers

These drugs produced an early and late post-MI survival advantage in comparison to placebo in patients with diabetics that exceeds the degree of benefit seen in their non-diabetic counterparts in several studies.[38]

Thrombolytic Therapy in ST elevation MI

Despite some concern that increased level of PAI-1, fibrinogen, coagulation factors and reactive platelets commonly seen in diabetes might reduce the likelihood of successful reperfusion[39] both TAMI and GUSTO-1. Thrombolysis trials demonstrated that similar infarct-related patency rates in both diabetes and non-diabetics.[41-43] Indeed, diabetic patients experience the same or greater benefit from thrombolysis than non-diabetics. ISIS-II trials shows diabetic patient receiving streptokinase had a 31% improvement in survival in comparison to placebo, greater than 23% improvement seen in non-diabetics. Pooled data from five recent major thrombolysis trials shows that 30 days mortality has been substantially reduced to 11% in diabetics and 6% in non-diabetics.

Glycoprotein IIb/IIIa Inhibitors

Based on the available data from randomised clinical trials, all three commercially available GP IIb/IIIa inhibitor have beneficial effect in diabetics undergoing PCI. This point was particularly exemplified in a recent meta-analysis by Roffi et al[44] that analysed the data from several trials involving abciximab, eptifibatide and tirofiban. This analysis found that GPIIb/IIa inhibitor significantly reduced 30 day mortality in diabetics with ACS whereas non-diabetics had no survival benefit. Of note, the majority of survival benefit was found in diabetics undergoing PCI.

CABG and PTCA in Diabetics

PTCA

Large scale trials have generally not shown a benefit of aggressive revascularisation after thrombolytic therapy for AMI even in diabetics.[45]

Although diabetics and non-diabetics have similar rate of initial angioplasty success, diabetics have higher restenosis rates after PTCA[46,47] and worse long-term outcome i.e. lower long-term patency and survival rates.[48] Although stenting has reduced restenosis rate both in diabetics and non-diabetics, overall smaller lumina in stented vessels and significantly higher restenosis rates (55 vs 20% P < 0.001) were seen in diabetics within 4 months of procedure.[49]

CABG

Most studies comparing outcomes in diabetic and non-diabetic patient undergoing CABG show an increased risk of post-operative death, 30 day and long term mortality and need for subsequent re-operation. Diabetic patients have a worse risk profile, tend to be older, and have more extensive CAD and poor LV function than non-diabetic patient's do.[50] This difference probably reflects accelerated disease progression in both the non-bypassed and bypassed native coronary vessels.

CABG vs PTCA

In general randomised trials comparing PTCA vs. CABG have reported similar outcomes. Diabetes, however, may alter the outcomes. The BARI trial found that bypass surgery in treated diabetics patients was associated with a higher survival rate at 5 year than PTCA.[51]

The ARTS[52] study compared the outcomes of CABG with those of multi-vessel PCI and coronary stenting in 1205 patients. The study found no significant difference between two groups in the primary end-point of freedom from death, stroke or MI at 1 year (91.3% for CABG vs. 90.6% PC1). However, 208 diabetic patients in this trial fared poorly with higher rate of mortality in the stenting arm than in CABG arm of trial (6.3% vs. 3.1% respectively).[53]

On initial review of the results of ARTS and SOS, CABG still appears to be superior to PCI in the era of bare metal stenting without the routine use of GP IIb/IIIa inhibitors. Only 3.5% of patients in ARTS received periprocedural abciximab during coronary stent implantation. Periprocedural abciximab reduced mortality compared with placebo in patient who received stents.[54] In fact, the mortality benefit of GP IIb/IIIa inhibitor is more pronounced in patients with diabetes. For example, a pooled analysis of the trials studying the use of abciximab in patients with PCI demonstrated that diabetic patients who received abciximab had a mortality rate similar to that of non-diabetic patients receiving placebo.[55]

The revascularisation option of choice for a diabetic patient with single vessel disease should be PCI. Several angiographic factors should be considered in determining the best revascularisation strategy in diabetic patients with multivessel disease for example, lesion characteristics should play role in determining whether a vessel is suitable for PCI.[56]

Because diabetic patients do have a higher incidence of left main CAD[57] and more severe and diffuse CAD[58] when presenting for CAG, it logically follows that a sizable percentage of diabetic patients would be better candidates for CABG than for multivessel PCI. However, determination of the best mode of revascularisation should not be made on the basis of diabetic status alone, but also on angiographic characteristics.

A recent study on impact of sirolimus eluting stents[59] in diabetic patients as reported by Mousa et al, showed that major adverse cardiac events were considerably decreased with the use of this drug, although they were still higher than non-diabetics.

It is possible therefore that with advances in stent technology PTCA may become comparable to CABG in diabetics as well.

SCREENING FOR CAD IN DM

Because diabetics have blunted anginal symptoms and a poor outcome following coronary events, a recent American College of Cardiology/ADA consensus development conference established guidelines for screening diabetic individuals for CAD; this includes many who do not have overt CAD; usually a treadmill test is initially recommended, other techniques are used when this is contraindicated.

Cardiac Testing for CAD[60]

1. Typical/atypical cardiac symptoms
2. Resting ECG suggestive ischemia/ infarction
3. Peripheral or carotid occlusive disease
4. Sedentary lifestyle, age > 35 yrs, intending vigorous exercise.
5. Two or more of the following risk factors in addition to DM
c. total cholesterol more than or equal to 240 mg/dl, LDL more than or equal to 160 mg/dl, HDL less than or equal to 35 mg/dl
d. BP >140/90 mmHg,
e. Smoking
f. Family history of premature CAD
g. Presence of microalbuminuria/ macroalbuminuria

PREVENTION OF TYPE 2 DIABETES

With the successful completion of the Diabetes Prevention Program (DPP) involving over 3000 individuals with IGT/IFG a reduction in the incidence of diabetes by 58% has been noted. This indicates that in certain groups lifestyle modification by [as part of the management of diabetes] cessation of smoking, regular exercise and weight reduction in overweight individuals may reduce the development of diabetes as well as deal with many other risk factors.[61]

FUTURE PROSPECTS

Cardiovascular complications have emerged over the last decade as the key target to reduce mortality and morbidity in diabetes. The focus in treatment of diabetes is shifting from blood sugar to the blood vessel.

Evaluation of the possible cardiovascular protective effects of newer drugs like insulin sensitizers (thiazolidinediones) is underway. The role of fibric acid derivatives in place of or in addition to statins for the treatment of diabetic dyslipidemia requires careful evaluation. The benefit of initiating treatment for individuals with IGT, IFG to slow the progression to diabetes has been well established by the DPP and other trials. Emphasis should be on primary prevention of diabetes and if already present on prevention of its complications rather than waiting for overt CAD to develop. This will go a long way in alleviating the devastating consequences of the diabetes epidemic.

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