Coronary Heart Disease in Patients With Diabetes: Part I: Recent Advances in Prevention and Noninvasive Management

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STATE-OF-THE-ART PAPERS

Coronary Heart Disease in Patients With Diabetes

Part I: Recent Advances in Prevention and Noninvasive Management

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Diabetes mellitus (DM) is a worldwide epidemic. Its prevalence is rapidly increasing in both developing and developed countries. Coronary heart disease (CHD) is highly prevalent and is the major cause of morbidity and mortality in diabetic patients. The purpose of this review is to assess the clinical impact of recent advances in the epidemiology, prevention, and management of CHD in diabetic patients. A systematic review of publications in this area, referenced in MEDLINE in the past 5 years (2000 to 2005), was undertaken. Patients with CHD and prediabetic states should undergo lifestyle modifications aimed at preventing DM. Pharmacological prevention of DM is also promising but requires further study. In patients with CHD and DM, routine use of aspirin and an angiotensin-converting enzyme inhibitor (ACE-I)—unless contraindicated or not tolerated—and strict glycemic, blood pressure, and lipid control are strongly recommended. The targets for secondary prevention in these patients are relatively well defined, but the strategies to achieve them vary and must be individualized. Intense insulin therapy might be needed for glycemic control, and high-dose statin therapy might be needed for lipid control. For blood pressure control, ACE-Is and angiotensin receptor blockers are considered as first-line therapy. Noncompliance, particularly with lifestyle measures, and underprescription of evidence-based therapies remain important unsolved problems. (J Am Coll Cardiol 2007;49:631–42) © 2007 by the American College of Cardiology Foundation

The population health burden of diabetes mellitus (DM) and diabetic coronary heart disease (CHD) remains considerable. Our group previously reviewed the published reports in this area (1); therefore, this work is restricted to publications from the years 2000 to 2005. We undertook a systematic Medline review with the keywords: diabetes, coronary heart disease, epidemiology, clinical trial, morbidity, mortality, myocardial infarction (MI), coronary angioplasty, stent, and coronary bypass surgery. In addition, contemporary guidelines from several national and international Societies were consulted (2–7). The present article constitutes the first installment of a 2-tier review that describes the contemporary epidemiology, prevention, and management of CHD in diabetic patients. Part II will describe the role and changing paradigm of coronary revascularization in the management of CHD in diabetic patients.

Recent Epidemiological Data

Changing prevalence and incidence of DM is a major public health and economic problem (8). Worldwide estimates of its prevalence are expected to rise from 2.8% (171 million people) in 2000 to 4.4% (366 million people) in 2030 (9). The prevalence of DM is growing rapidly in both developing and developed countries. The countries with the largest number of cases in 2030 will be China, India, and the U.S. The number of Americans with DM is projected to increase 165%, from 11 million people in 2000 to 20 million people in 2025 (prevalence of 4.0%) (10). On the basis of an estimated linear increase in prevalence from 4.0% in 2000 to 7.2% in 2050, the number of diabetic subjects in the U.S. population is projected to rise to at least 29 million people (10). Overall, the projected 18-million increase in 2050 can be attributed to demographic changes (37%), population growth (27%), and increasing prevalence rates (36%) (10).

Insulin resistance often precedes the onset of DM and already exists in the prediabetic states. Thus, abnormal glycoregulation is a spectrum where impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and obesity (mainly central or abdominal obesity) are the intermediate stages. All 3 increase the risk to develop type 2 DM. Recent epidemiological data estimate the prevalence of IFG and IGT to be between 8% and 12% of the adult population (11). Almost 20% of middle-aged adults and 35% of the older population in the U.S. have some degree of abnormal glycoregulation (12). In the year 2000, there were more than 300 million obese adults worldwide, and industrialized countries showed a prevalence of obesity of approximately 20%. Currently, more than one-half of the adult population

in the U.S. is overweight or obese (13). The prevalence of obesity in children is also dramatically increasing worldwide, and this contributes to adulthood obesity (14). The prevalence of the metabolic syndrome is estimated to be 10% to 60% (15). Although it occurs mainly in adults, it is also present in both childhood and adolescence. In the U.S., it reaches 50% in severely obese youngsters (16).

Metabolic Derangements Associated With DM

Insulin resistance. Type 2 DM is a multifactorial disease that combines hereditary and environmental factors. Two major metabolic derangements characterize DM: decreased insulin secretion by the pancreatic beta cells, and peripheral resistance to the action of insulin or insulin resistance. Insulin resistance or reduced insulin action on target tissues might not be responsible for DM in the absence of a deficit of insulin secretion (17). Insulin resistance results from environmental factors such as detrimental lifestyle habits, with progressive reduction of physical activity and energy expenditures and increased input of dietary calories, fats, and saturated fatty acids and from genetic or congenital susceptibility to pancreatic beta cell dysfunction with an inability to compensate for greater insulin requirements. Eighty percent of patients with type 2 DM are either obese or overweight (18). Obesity and the metabolic syndrome are linked to hyperinsulinemia and insulin resistance and independently predict cardiovascular disease (CVD) and coronary atherosclerosis (19–21).

The metabolic syndrome is a common metabolic disorder that is characterized by increases in waist circumference, blood pressure, and triglyceride levels combined with a reduction in high-density lipoprotein cholesterol (HDL-C) levels and evidence of glucose intolerance (22). Reaven initially proposed that insulin resistance was the main culprit (1), but Lemieux et al. (23) recently suggested that visceral obesity and the hypertriglyceridemic waist phenotype were its central components. When the fatty cells or adipocytes are full, they release cytokines and adipokynes that generate a systemic inflammatory state, damage blood vessels, and contribute to hypertension, dyslipidemia, and insulin resistance (24,25). Thus the metabolic syndrome can be seen as a disorder where central obesity leads to chronic systemic inflammation, systemic endothelial dys-

function, and insulin resistance, the main clinical components of the syndrome (12).

Hyperglycemia. Despite their high incidence in type 2 DM, CHD risk factors only partly account for the excessive risk of CVD (1,25). Thus, there seems to be an association between hyperglycemia and CVD. Epidemiological data suggest that there is no specific threshold for glycemia in relation with CV risk (26). However, the role of hyperglycemia per se in the excess CV risk is still controversial. The UKPDS (United Kingdom Prospective Diabetic Study) showed a significant relationship, although weak, between chronic hyperglycemia and the incidence of MI (27). In the EDIC/DCCT (Epidemiology of Diabetes Interventions and Complications/Diabetes Control and Complications Trial) study, the incidence of CV complications was significantly reduced in type 1 diabetic patients receiving intensive insulin therapy initially (28). In the DIGAMI (DIabetes mellitus, Glucose insulin infusion in Acute Myocardial Infarction) study, intensive insulin therapy improved CV prognosis in diabetic after MI patients (1). Although the DIGAMI-2 study confirmed that the glucose level was a strong predictor of mortality in these patients, it did not support the fact that early and continued insulin-based therapy improved survival (29). The PROACTIVE (PROspective pioglitAzone Clinical Trial In macroVascular Events) study evaluated pioglitazone versus placebo in the prevention of CV events in patients with type 2 DM and a history of CVD. Two types of results were obtained: a significant 16% reduction in the composite secondary end point of all-cause mortality, nonfatal MI, and stroke, as compared with placebo; and an increased risk of heart failure (30). The role of glitazones in CV prevention, although strongly supported by experimental and clinical data, must be better defined. This is being evaluated in ongoing clinical trials (Table 1).

Dyslipidemia. Post hoc analyses of diabetic subpopulations in lipid intervention trials before the year 2000 suggested that correction of lipoprotein abnormalities led to a decrease in CHD (1). More recently, additional clinical trials have reported similar results. For example, the HPS (Heart Protection Study) demonstrated that cholesterol-lowering therapy was beneficial for people with DM even if they did not already have a history of CHD or high cholesterol concentrations (31). Allocation to 40 mg of simvastatin daily reduced the rate of first major CV events by about one-quarter in a wide range of diabetic patients. The results from this trial supported the use of statin therapy in diabetic subjects with relatively normal plasma cholesterol concentrations (31). Several other trials have reported results consistent with the HPS (32–34). More recently, the CARDS (Collaborative Atorvastatin Diabetes Study) specifically compared atorvastatin 10 mg daily with a placebo in type 2 diabetic patients without symptomatic CHD who had relatively normal lipid concentrations (35). During a mean follow-up of 3.9 years, atorvastatin reduced major CV events by 37%. The ongoing ASPEN (Atorvastatin Study

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Table 1	**Glycemic Control in Patients With Diabetes Mellitus—Published and Ongoing Randomized Trials**						
Trial (Ref.)	**Status**	**Intervention**	**Population**	**Primary End Point**	**Enrolled (Randomized)**	**Follow-Up Period**	**Primary End Point Result**
DIGAMI (1)	Published	IGI after arrival in hospital followed by multi-dose insulin therapy for 3 months	Treated or new DM with acute MI	All-cause mortality	1,240 (620) Rx: 306 Control: 314	3 months 1 yr	Control: 15.6% Rx: 12.4% NS Control: 26.1% Rx: 18.6% $p < 0.03$
DIGAMI2 (29)	Published	1. 24 h IGI followed by SC insulin-based glucose control 2. 24 h IGI followed by standard glucose control 3. Routine metabolic management	Treated or new DM with acute MI	All-cause mortality	1,253 1. 474 2. 473 3. 306	Median 2.1 yrs	1. 23.4% 2. 21.2% 3. 17.9% NS
DCCT/EDIC (28)	Published	Intensive Rx: ≥3 insulin injections or external pump with dose adjustments; $HbA1_c$ goal <6.05% Conventional Rx: no specific glucose goals beyond those needed to prevent symptoms	Type I diabetes age 13–40 yrs	Time to first of: nonfatal MI or stroke, CV death, subclinical MI, angina, or coronary revascularization	1,441 randomized in DCCT 1,394 followed in EDIC	Mean 17 yrs	RR (95% CI): 42% (9%–63%); $p = 0.02$
PROACTIVE (30)	Published	Oral pioglitazone 15–45 mg daily vs. placebo	Type II DM $HbA1_c$ >6.5%	Time to all-cause mortality, nonfatal MI, stroke, ACS, endovascular or surgical intervention on the coronary or leg arteries, or above-ankle amputation	5,238 Active: 2,605 Placebo: 2,633	Mean 34.5 months	Active: 514 Placebo: 572 HR (95% CI): 0.90 (0.80–1.02); $p = 0.095$
BARI 2D (47)	Ongoing	a) Revascularization by PCI or surgery vs. aggressive medical Rx b) Insulin sensitization vs. insulin provision (target $HbA1_c$ <7.0% for each glycemic control strategy)	Type II DM Angiographic CAD amenable to revascularization Evidence of ischemia or mild angina and ≥50% stenosis of ≥1 coronary arteries Age ≥25 yrs	5-yr mortality	2,368	—	—
VADT (84)	Ongoing	Initial Rx with metformin (obese) or glimepiride (lean), followed by rosiglitazone, followed by insulin or other oral agents to achieve goals. Compares standard ($HbA1_c$ 8.0%–9.0%) with excellent control ($HbA1_c$ <6.0%) Goal of $HbA1_c$ separation >1.5% (expected 2%)	Age ≥45 yrs Type II DM with poor control ($HbA1_c$ ≥7.5%)	MI, CV mortality, stroke, new or worsening CHF, amputation from PVD, surgical coronary or PVD revascularization, and critical limb ischemia	1,792	—	—
IRIS (85)	Ongoing	Pioglitazone or placebo	DM + age ≥45 yrs History of non-embolic ischemic stroke Elevated FBG (insulin resistant)	Time to stroke or MI	3,136 expected	—	—
PPAR study (86)	Ongoing	Pioglitazone or: 1) instruct weight reduction, appropriate diet, regular exercise and/or 2) prescribe sulfonylurea agents	Age ≥45 yrs DM ($HbA1_c$ <6.5%) History of MI	1. CV mortality 2. CV hospitalization	3,000 expected	—	—

ACS = acute coronary syndrome; CAD = coronary artery disease; CHD = coronary heart disease; CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; DM = diabetes mellitus; FBG = fasting blood glucose; Hb = hemoglobin; HR = hazard ratio; IGI = insulin-glucose intravenous infusion; MI = myocardial infarction; NS = not significant; PCI = percutaneous coronary intervention; PPAR = peroxisome proliferator-activated receptor; PVD = peripheral vascular disease; RR = risk reduction; Rx = treatment; SC = subcutaneous.

for the Prevention of CHD ENdpoints) also compares atorvastatin and placebo specifically in type 2 diabetic patients.

Diabetic dyslipidemia has a characteristic lipid profile that includes elevated plasma triglycerides, normal or mildly elevated low-density lipoprotein cholesterol (LDL-C), and reduced plasma HDL-C concentrations (1). Although hypertriglyceridemia increases the risk of CHD in DM, the effect of statin therapy for the treatment of hypertriglyceridemia before the DALI (Diabetes Atorvastatin Lipid Intervention) study was uncertain (1). In the DALI study, high-dose atorvastatin therapy reduced total cholesterol, LDL-C, and apoB to a greater extent than low-dose atorvastatin. Plasma triglycerides decreased and HDL-C increased to a similar extent in both groups (36). In the DAIS (Diabetes Atherosclerosis Intervention Study), treatment with fenofibrate reduced angiographic progression of CHD in patients with type 2 DM, good glycemic control, and mild lipoprotein abnormalities (37). However, in the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) trial, although fenofibrate reduced plasma triglycerides and increased HDL-C concentrations, it did not significantly decrease the incidence of CV events (38). Thus, regardless of the lipid profile, current evidence does not warrant replacing statins as the first choice for prevention of CHD in patients with DM. The potential role of fenofibrate as part of combination therapy is the focus of the ongoing ACCORD (Action to Control CardiOvascular Risk in Diabetes) trial.

Particularities of CHD in DM

In a population-based autopsy study, coronary arteries were examined at 5-mm intervals with a semiquantitive grading system (39). High-grade atherosclerosis was defined as grade 3 (50% to 75%) left main stem disease or grade 4 (>75%) disease for other arteries. Coronary atherosclerosis was found in 49% of diabetic and 33% of nondiabetic decedents. Diabetic decedents more often had MI by autopsy, ventricular dilation, high-grade atherosclerosis, and multivessel disease. The global atherosclerotic burden and prevalence of multivessel disease were similar in diabetic patients without a history of CHD and in non-diabetic patients with a history of CHD. These findings revealed a high prevalence of subclinical atherosclerosis in diabetic subjects without a clinical history of CHD. Ledru et al. (40) recently compared coronary disease in consecutive diabetic and non-diabetic angiography referrals. Coronary disease, objectively evaluated with 3 severity score systems, was more severe in diabetic than in non-diabetic patients and included higher coronary occlusion rates. However, age, gender, LDL-C concentration, and hypertension were more powerful predictors of disease severity than DM. Recent case-control studies have found that, compared with non-diabetic patients, diabetic subjects typically have more severe coronary disease, more extensive coronary calcifications, a higher prevalence of left main stem disease, and reduced coronary collateral artery recruitment (41–43).

Accelerated atherosclerosis and thrombosis in patients with DM are mainly due to systemic inflammation, oxidative stress, and systemic endothelial dysfunction (25,44,45) combined with coagulation and platelet function abnormalities (25,46,47) and impaired fibrinolysis (47).

Epidemiology of CHD in DM

The prevalence of CHD rises from 2% to 4% in the general population to as high as 55% among adult diabetic patients (1). Diabetes mellitus is an independent risk factor for CVD in both men and women. Excess risk for CVD can be found in patients with type 1 and type 2 DM, in patients in the prediabetic stages, and in patients with obesity and with the metabolic syndrome (26).

Mortality in diabetic patients. The overall mortality from heart disease is twice as great in men and is 4 to 5 times higher in women with than without DM (1). Cardiovascular disease represents over one-half of all deaths in both type 1 and type 2 DM (48). In addition, non-CV mortality is greater in diabetic compared with non-diabetic subjects, and this excess risk remains constant during long-term follow-up (49,50). Diabetes mellitus has been considered as a CHD risk factor equivalent. In a prospective cohort study, the age-adjusted relative risk of death from any cause was 2.3 among men with DM but without CHD, 2.2 among men with CHD and without DM, and 4.7 among men with both DM and CHD (51). Patients with DM are more likely to die after an MI than patients without DM (26,52).

Morbidity in diabetic patients. Diabetes is associated with an increased risk of morbidity in patients with CHD (51). Diabetes mellitus and obesity are predictors of MI (52). About one-quarter of patients who present with an acute MI have DM (12). Diabetes mellitus is a predictor of ischemic stroke and heart failure, and diabetes increases the overall CV risk in patients with heart failure (53,54). Diabetic patients undergo invasive management less often, and when referred for coronary angiography, they wait longer (55,56). In addition, quality of life is reduced in DM patients compared with nondiabetic patients (57).

Mechanisms for the excess CV risk attributable to DM. The mechanisms responsible for the increased CV mortality and morbidity attributable to DM are multifactorial. In addition to a high prevalence of conventional risk factors, important contributing mechanisms include insulin resistance and hyperinsulinemia, hyperglycemia, subclinical atherosclerosis, congestive heart failure, acute coronary syndromes, and end-stage renal failure (12). The first 3 items have been previously discussed. Increased mortality in diabetic patients with left ventricular dysfunction and heart failure can be attributed to CHD, hypertension, left ventricular hypertrophy, obesity, autonomic dysfunction, and diabetic cardiomyopathy (12,58). Diabetes is a major risk factor for adverse outcomes in patients who suffer from

unstable angina or MI (12,26). Autonomic dysfunction lowers the threshold for life-threatening arrhythmias and increases the risk of hemodynamic instability. Coagulation and platelet abnormalities increase the risk of thrombosis at the site of plaque disruption and possibly increase the risk of reinfarction after thrombolytic therapy. Finally, diabetes has emerged as the leading cause of end-stage renal disease in the U.S., and this condition carries a 5-year survival of only 20% in patients with DM and CHD (12,59). Albuminuria is an important prognostic marker and a potential target for therapy in hypertensive diabetic patients with impaired renal function (60). Recent clinical trials have shown that both angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) are nephroprotective in patients suffering from type 2 DM, and these effects are independent from those attributable to blood pressure (BP) lowering (61–64).

Primary Prevention of DM in At-Risk Individuals

Screening. The American Diabetes Association recommends screening for type 2 DM in at-risk individuals (4). In particular, individuals ages 45 years or older who have a BMI $\geq$25 kg/m^2 should be assessed at 3 yearly intervals. The screening test should include a fasting blood glucose (FBG) or a 2-h oral glucose tolerance test (OGTT) (4). A diagnosis of DM is made if 2 consecutive FG levels are $\geq$7.0 mmol/l (126 mg/dl) or a 2-h post-load value is $\geq$11.1 mmol/l (200 mg/dl) within a 3-month period. In addition, community screening programs should be targeted to at-risk individuals (65).

Lifestyle modification. The hypothesis that type 2 DM is preventable is supported by recent clinical trials. At least 2 types of interventions have demonstrated their efficacy in terms of primary prevention of type 2 DM: lifestyle modification by dietary measures and physical exercise aiming at weight loss, and different pharmacological interventions.

Lifestyle modification, in patients with prediabetic states, has been shown in 3 placebo-controlled trials to markedly reduce the risk of new-onset DM (66–68) (Table 2). Nutritional therapy coordinated by dieticians had an important role in the lifestyle intervention, and individualized therapy is currently recommended in type 2 DM (4). Along with 1 earlier controlled trial of lifestyle changes for the prevention of DM in at-risk patients in China (68), the DPP (Diabetes Prevention Program) and Finnish trials support a strong recommendation for lifestyle intervention in patients with IGT (Table 2).

Pharmacological interventions. Recent trials in patients with hypertension and heart failure have indirectly shown the preventive effect of ACE-Is on DM (69–72). Similar results were reported with ARBs (73–76). These data must be interpreted with caution, however, because prevention of DM was not the primary end point in any of these trials. The effect of ACE-Is and ARBs on the progression to DM is now being tested as a primary outcome in ongoing randomized trials (77,78) (Table 2).

Other drugs that have also been shown to reduce the new onset of DM in at-risk subjects (obese or prediabetic individuals) include acarbose (79), bezafibrate (80), and peroxisome proliferator-activated receptor (PPAR) gamma inhibitors (81). In the DPP, the crude incidence of DM was 11 cases/100 person-years, 7.8 cases/100 person-years, and 4.8 cases/100 person-years for the placebo, metformin, and lifestyle-intervention groups, respectively (66). Compared with placebo, these interventions were also associated with increased time to DM onset, reduced glycosylated hemoglobin (HbA$_{1c}$), and reduced FG concentrations. Overall, metformin was less effective than lifestyle intervention (Fig. 1, Table 2).

Secondary Prevention and Management of CHD in Diabetic Patients

Screening for CHD in diabetic patients. Diabetes is commonly considered as a CHD risk equivalent (2,6). High-risk diabetic patients include those with typical or atypical symptoms, those 55 years or older, those with peripheral or carotid vascular disease, and those with 2 or more of the following risk factors: hyperlipidemia, hypertension, smoking, family history of premature CHD, microalbuminuria, and progressive retinopathy (82). Screening for CHD might be indicated in younger individuals, with a relatively short duration of DM and few risk or diabetic complications, because most guidelines recommend more aggressive management of risk factors in the presence of CHD. Detection of CHD involves the usual diagnostic methods, which include exercise stress testing and, as indicated, myocardial perfusion scintigraphy or stress echocardiography (82).

Pharmacological interventions to prevent CHD in diabetes. The implementation of lifestyle modification, including dietary measures and aerobic exercise aiming at long-term weight loss, are even more critical in patients with diabetic CHD than in those with DM alone, because of the higher risk of CV events in these patients.

ANTIPLATELET THERAPY. Primary prevention therapy with aspirin is recommended in diabetic patients >40 years of age, with additional risk factors, and/or with diabetes >10 years' duration (4). Contemporary guidelines recommend prophylactic therapy with aspirin for diabetic patients with CHD (4,46). In patients who do not tolerate or have a contra-indication to aspirin, clopidogrel can be used as an alternative antiplatelet agent.

A post hoc analysis of the diabetic patients randomized in the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) study found that clopidogrel therapy reduced the relative risk of death, MI, stroke, or repeat hospital stay compared with aspirin therapy (83). However, specific randomized trials will be needed to determine whether clopidogrel alone or clopidogrel plus
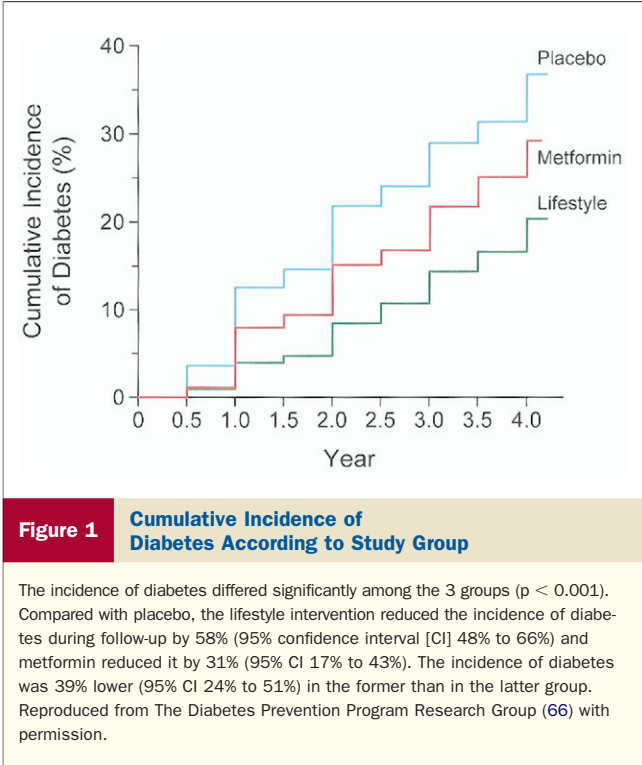
Table 2 Prevention of Diabetes Mellitus in At-Risk Individuals—Published and Ongoing Randomized Trials

Trial (Ref.)	Status	Intervention	Population	Primary End Point	Randomized	Mean Follow-Up Period	Primary End Point Result
DPP (66)	Published	1. Metformin 850 mg once–twice daily 2. Intensive lifestyle intervention 3. Standard lifestyle recommendations + placebo twice daily	≥25 yrs; BMI ≥24 kg/m² (≥22 in Asians) FBG 95–125 mg/dl (5.3–6.9 mmol/l) and 140–199 mg/dl (7.8–11.0 mmol/l) 2 h after 75 g OGL	New onset of DM	3,234 1. 1,073 2. 1,079 3. 1,082	2.8 yrs	Cases 100 patient yrs: 1. 7.8% 2. 4.8% 3. 11.0% Incidence reduction (95% CI): 1 vs. 3: 31% (17–43) 2 vs. 3: 58% (48–66)
FINNISH trial (67)	Published	Rx: dietary modification, exercise counseling and supervised exercise programs Usual care	40–64 yrs Overweight and IGT*	New onset of DM	522 Rx: 265 Placebo: 257	3.2 yrs	Cumulative incidence (95% CI) of DM at 4 yrs Intervention: 11% (6%–15%) Control: 23% (17%–29%) Risk reduction 0.4 (0.3–0.7); p < 0.001
CHINESE trial (68)	Published	Lifestyle intervention 1. Control 2. Diet 3. Exercise 4. Diet + exercise	IGT IR based on fasting insulin, and insulin sensitivity based on fasting glucose concentration	New onset of DM	284 1. 62 2. 81 3. 73 4. 68	6 yrs	1. 42/62 (67.4%) 2. 36/81 (44.4%)† 3. 38/73 (52.1%) 4. 26/68 (38.2%)†
LIFE (73)	Published	Losartan 50–100 mg daily Atenolol 50–100 mg daily	Age 55–80 yrs Hypertension (SBP 160–200 mm Hg; DBP 95–115 mm Hg) LVH on ECG	MI/stroke/CV death Incidence of DM was a predefined outcome	9,193 (13% DM) Losartan: 4,605 (12.7% DM) Atenolol: 4,588 (13.3% DM)	4.8 yrs	Losartan: 508 (11%) Atenolol: 588 (13%) HR (95% CI): 0.87 (0.77–0.98); p = 0.021 Incidence of DM: Losartan: 241 (6%) Atenolol: 319 (8%) HR (95% CI): 0.75 (0.63–0.88); p = 0.001
Acarbose (79)	Published	Acarbose 100 mg daily Placebo	Non-diabetic IGT, diagnosed with an OGTT	New DM	Acarbose: 714 Placebo: 715	3.3 yrs	Acarbose: 32% Placebo: 42% HR (95% CI): 0.75 (0.63–0.90); p = 0.0015
Bezafibrate (80)	Published	Bezafibrate 400 mg daily Placebo	Non-diabetic Obese (BMI ≥30 kg/m²) Age 42–74 yrs	New DM	339 15% with IFG	6.3 yrs	Bezafibrate: 42 (27%) Placebo: 56 (37%) p = 0.01 HR (95% CI): 0.59 (0.39–0.91)
PPAR inhibitors (81)	Published	1. Troglitazone 2. Placebo 3. Metformin 4. Lifestyle	Age ≥25 yrs IGT BMI ≥24 kg/m² (≥22 kg/m² in Native Americans)	New DM	1. 585 2. 582 3. 587 4. 589	Mean 0.9 yrs of troglitazone therapy	Cases 100 patient-yrs 1. 3.0 2. 12.0 3. 6.7 4. 5.1 p < 0.001, overall 1 vs. 2: p < 0.01 1 vs. 3: p = 0.02
DREAM (77)	Ongoing	1. ACE-I (ramipril 15 mg daily)/placebo 2. Thiazolidinedione (rosiglitazone 8 mg daily)/placebo 3. Combination 4. Placebo/placebo	Age ≥30 yrs No diabetes IFG or IGT or IFG + IGT	New-onset type 2 DM or all-cause mortality	5,269 IGT: 1,835 (35%) IFG: 739 (14%) IGT + IFG: 2,692 (51%)	—	—

Table 2   Continued

Trial (Ref.)	Status	Intervention	Population	Primary End Point	Randomized	Mean Follow-Up Period	Primary End Point Result
NAVIGATOR (78)	Ongoing	1. Valsartan 160 mg daily/placebo 2. Metiglinide (nateglinide 60 mg)/placebo 3. Combination 4. Placebo/placebo	IGT; IFG One-third age >50 yrs and 1 measure of CVD Two-thirds age >55 yrs and ≥1 CV risk factor	Time to major CV event (MI, stroke, CV death, revascularization, hospital stay for angina or heart failure) Time to progression to type 2 DM	7,400–11,000	—	—

*Impaired glucose tolerance (IGT) was defined as a blood glucose concentration of 140 to 200 mg/dl (7.8 to 11.0 mmol/l) 2 h after the oral administration of 75 g of glucose in subjects whose blood glucose concentration after an overnight fast was <140 mg/dl; †p < 0.001 versus controls.

ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; DBP = diastolic blood pressure; ECG = electrocardiogram; IFG = impaired fasting glucose; IR = insulin resistance; LVH = left ventricular hypertrophy; OGL = oral glucose load; OGTT = oral glucose tolerance test; other abbreviations as in Table 1.

Figure 1   **Cumulative Incidence of Diabetes According to Study Group**

The incidence of diabetes differed significantly among the 3 groups (p < 0.001). Compared with placebo, the lifestyle intervention reduced the incidence of diabetes during follow-up by 58% (95% confidence interval [CI] 48% to 66%) and metformin reduced it by 31% (95% CI 17% to 43%). The incidence of diabetes was 39% lower (95% CI 24% to 51%) in the former than in the latter group. Reproduced from The Diabetes Prevention Program Research Group (66) with permission.

aspirin is superior to aspirin alone in the prevention of cardiovascular events in diabetic patients with established CVD.

OPTIMIZATION OF GLYCEMIC CONTROL. The goal of antidiabetic drug therapy is to ensure optimal glycemic control (HbA$_{1c}$ <7% for all patients and, for the individual patient, an HbA$_{1c}$ as close to normal [<6%] as possible) with minimization of diabetes-related complications (4,6). There is no specific threshold for glycemia in relation to CV risk. Thus, optimal glycemic control must be a clear objective in diabetic patients, not only for prevention of microvascular but also of macrovascular events (1).

Multiple pharmacological interventions are often required, and there is still uncertainty on the best strategy to achieve glycemic control in diabetic patients with CHD. Intensive insulin therapy was effective in the prevention of CV events in the DIGAMI and EDIC/DCCT trials (Fig. 2) but not in the DIGAMI-2 trial. The PROACTIVE study has shown that pioglitazone also seems to be beneficial but should be given carefully to patients with CHD to avoid ventricular dysfunction or heart failure. Finally, it is not clear yet whether insulin-providing drugs such as insulin and sulfonylureas are more effective in the secondary prevention of CVD than insulin-sensitizers such as metformin and the glitazones. These questions are being examined in ongoing randomized trials (47,84–86) (Table 1).

ANTIHYPERTENSIVE THERAPY. The current antihypertension treatment targets are <130/<80 mm Hg in diabetic patients (120/80 mm Hg after MI) (4,5). In the UKPDS BP-lowering substudy, intensive therapy was associated
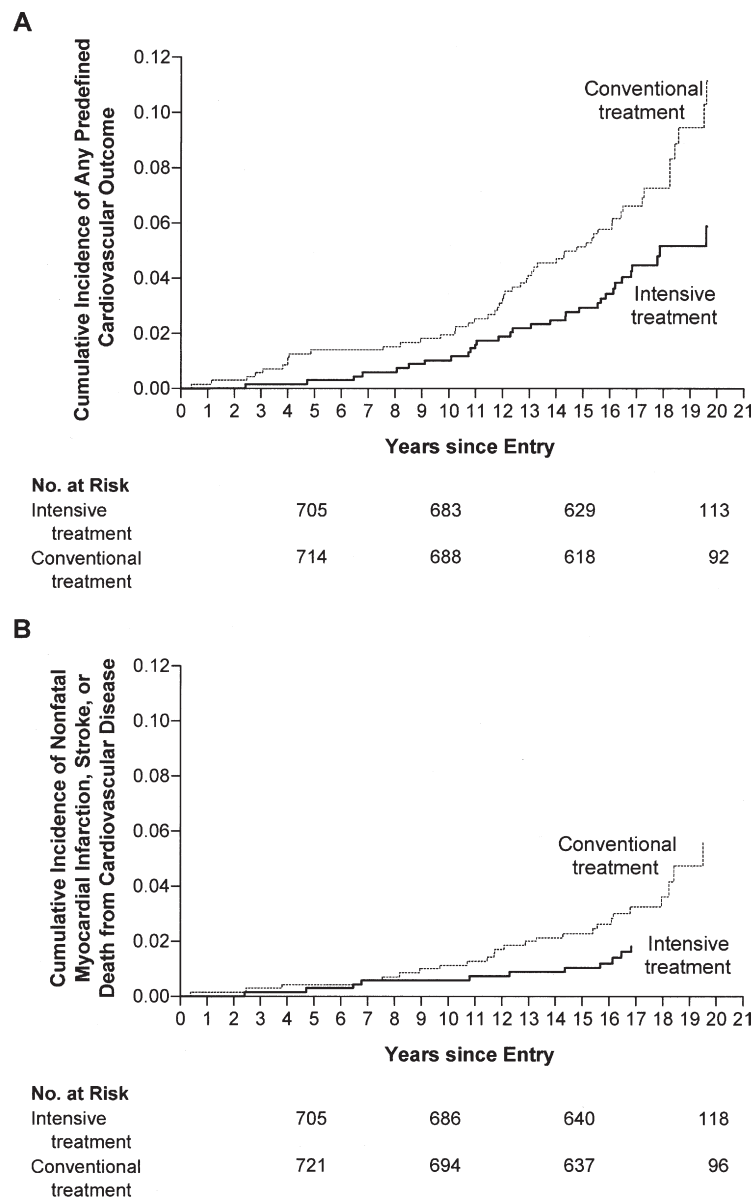
Figure 2   Cumulative Incidence of Cardiovascular Outcomes

Cumulative incidence of the first of any of the predefined cardiovascular disease (CVD) outcomes **(A)** and of the first occurrence of nonfatal MI, stroke, or death from CVD **(B)**. Compared with conventional treatment, intensive diabetic treatment reduced the risk of any predefined CVD outcome by 42% (95% confidence interval [CI] 9% to 63%; p = 0.02) **(A)** and reduced the risk of the first occurrence of nonfatal MI, stroke, or death from CVD by 57% (95% CI 12% to 79%; p = 0.02) **(B)**. Reproduced from Nathan et al. (28) with permission.

with reduced risks of stroke and MI (87). Greater risk reduction was achieved with lower BP levels, and there was no threshold for risk reduction (88). The evidence for drug efficacy in reducing CV events in high-risk patients with DM is largely derived from subgroup analyses of recent trials (71,89). In the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), the benefits of the amlodipine-based regimen (with or without perindopril) versus the atenolol-based regimen on rates of nonfatal MI and fatal CHD were similar for hypertensive patients with or without DM (89).

In the diabetic patients randomized in the MICRO-HOPE (Microalbuminuria, Cardiovascular, and Renal Outcomes-Heart Outcomes Prevention Evaluation) substudy, ramipril reduced the primary composite end point of MI, stroke, or CV death (61). Diabetic patients derived similar risk reductions with perindopril in the EUROPA (EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease) (90). In the LIFE (Losartan Intervention For Endpoints) study reduction in hypertension study, the primary composite end point of CV death,

stroke, or MI occurred less often in patients assigned to losartan than in those assigned to atenolol. Thus, compared with a beta-blocker–based regimen, losartan therapy conferred consistent CV risk reduction in hypertensive diabetic patients (91). Two ongoing ARB randomized trials assessing CV prevention trials will include diabetic patients (92).

Current clinical guidelines recommend primary prevention measures with ACE-I therapy in diabetic patients with 1 other CHD risk factor and secondary prevention with these drugs in diabetic patients with CHD (4,6). Recognizing that diabetic patients will usually need 3 or 4 antihypertensive drugs to lower BP to the recommended level, ACE-Is and ARBs (along with long-acting calcium channel blockers) are recommended as first-line therapy (4,6). Cardioselective beta-blockers and thiazide diuretic agents should be viewed as second-line anti-hypertensive therapy in DM.

LIPID-LOWERING THERAPY. Lipid lowering therapy is recommended for diabetic patients ≥40 years of age or subjects <40 years of age with additional risk factors (4). The current lipid target ranges are LDL-C <100 mg/dl or a reduction in LDL-C by 30% to 40%, triglycerides <150 mg/dl, and HDL-C >40 mg/dl (4). In women, an HDL-C goal of 10 mg/dl higher (50 mg/dl) might be considered. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines recommend lower LDL-C targets for patients suffering from both DM and CHD than for those suffering from DM alone (3). On the basis of the HPS and other trials (26,93,94), it is reasonable to target a LDL-C of 70 mg/dl for high-risk subjects such as diabetic patients (3).

There is a log-linear relationship between LDL-C concentration and relative risk of CHD. Recent trials have suggested that cholesterol-lowering therapy is beneficial for patients with DM even in the absence of a history of CHD or high cholesterol, suggesting that statin therapy should be initiated in DM regardless of LDL-C level (31–34,95). Should high-risk patients have concomitant hypertriglyceridemia or low HDL-C, it might be appropriate to add a fibrate or nicotinic acid (3,95). Combination therapy with lipid-modifying agents has not, however, been fully evaluated in CVD outcomes studies, and this approach has not yet achieved an expert consensus (4).

DIABETIC PATIENTS WITH UNSTABLE CAD. The established beneficial effects of reperfusion therapy, both with primary percutaneous coronary intervention and fibrinolytic therapy, and secondary post-reperfusion prevention with antiplatelet agents, beta-blockers, ACE-Is, and ARBs are discussed elsewhere.

Noncompliance and Underprescription of Medication

In the DPP trial, only 50% of the lifestyle intervention group achieved the goal of ≥7% weight reduction, and 74%

maintained at least 150 min/week of moderately intense physical activity (66).

In the NHANES (National Health and Nutrition Survey) 1999 to 2000, only 37% of participants achieved the target goal of HbA$_{1c}$ level <7.0% and another 37% were above the recommended "take action" HbA$_{1c}$ level of >8.0%. These percentages did not change significantly from the NHANES III (1988 to 1994) (96–98). Among the NHANES III participants ages >65 years, a target HbA1c concentration of <7% was achieved by 71%, 44%, and 2% of persons using no drug therapy, oral hypoglycemic agents, and insulin, respectively. In the NHANES 1999 to 2000, only 36% of patients achieved the BP target of <130/<80 mm Hg, and 40% had hypertensive levels (≥140 or ≥90 mm Hg) despite therapy. Over one-half of the participants in the NHANES 1999 to 2000 had cholesterol levels ≥200 mg/dl (52% vs. 66% in the NHANES III). In the LTAP (Lipid Treatment Assessment Project), only 41% of diabetic patients and 38% of nondiabetic patients attained the NCEP ATP III LDL-C guidelines (99).

Quite surprisingly, overall, only 7% of adults with DM in the NHANES 1999 to 2000 attained recommended goals of HbA$_{1c}$ <7%, BP <130/80 mm Hg, and cholesterol <200 mg/dl (98). Multiple sociodemographic factors might explain the low rate of treatment target achievement (100). In addition to noncompliance, underprescription of evidence-based preventive therapies is also a major issue (54,100). Thus, our efforts to jugulate the current epidemic of DM and its CV consequences must include, as a very high priority, improved compliance to lifestyle measures and drug therapy through patient and community counseling as well as sensibilization of the medical profession to the importance of primary and secondary CV prevention through appropriate long-term prescription of evidence-based therapies.

Conclusions

The global incidence and prevalence of DM is rapidly increasing in both developed and developing countries. CHD in diabetic individuals represents a major worldwide public health problem. Obesity, IFG, IGT, and DM form a continuous spectrum of risk of CVD. Glucose intolerance and the associated traditional risk factors for CVD, such as dyslipidemia and hypertension, might be present for many years before the diagnosis of DM. In patients with CHD and the prediabetic states, primary prevention of DM is now feasible and effective. In particular, lifestyle measures are recommended, and emerging evidence supports the role for therapeutic prevention of type 2 DM. Because of the epidemic proportions of DM worldwide, prevention of DM and prediabetic states might well be the most effective strategy to prevent serious CV events. Morbidity and mortality from CVD in diabetic patients with CHD are rapidly increasing. Screening for at-risk subjects can be a cost-effective intervention. Reduction of the increased risk

of CVD in patients with CHD and DM requires a multifactorial approach. The data currently available suggest that this can be achieved by intensive glycemic control and aggressive treatment of other CV risk factors, such as dyslipidemia, hypertension, and smoking. Noncompliance, particularly with lifestyle measures, and underprescription of evidence-based therapies, however, remain major unsolved problems.

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Coronary Heart Disease in Patients With Diabetes: Part I: Recent Advances in Prevention and Noninvasive Management

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