Diabetes and Cardiovascular Disease

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This is the second of a series of articles based on presentations at the American Diabetes Association (ADA) 70th Scientific Sessions, held 25–29 June 2010 in Orlando, Florida, pertaining to cardiovascular disease (CVD).

At a symposium on the relationship between diabetes and CVD, Silvio E. Inzucchi, New Haven, CT, reviewed findings of the Detection of Ischemia in Asymptomatic Diabetes (DIAD) study. Coronary artery disease (CAD) is a leading cause of morbidity and mortality, but a concern is that myocardial ischemia may be silent, with its first presentation an acute myocardial infarction or sudden death. If CAD can be identified in a preclinical stage, identifying patients with silent ischemia might lead to benefits beyond that from intensive risk factor reduction, perhaps leading to "more serious" risk factor treatment, both on the part of the physician and on the part of the patient, or, perhaps, to benefits beyond that from recommending revascularization. Screening can involve electrocardiographic exercise testing, myocardial perfusion imaging or stress echocardiography after adenosine or exercise, or computed tomography angiography. There were three portions to the DIAD study; the first described the prevalence and predictors of silent ischemia, the second identified which factors were associated with progression and which with regression of CAD, and the third addressing the question of whether cardiac event rates were affected by screening versus not screening among individuals with type 2 diabetes.

With adenosine-sestamibi single photon emission computed tomography myocardial perfusion imaging (MPI), DIAS endeavored to identify high-risk patients based on conventional risk factors. The study included 1,123 eligible type 2 diabetic patients age 50–75 years without a history of CAD and with a normal resting electrocardiogram, randomized to undergo or not undergo MPI (1). Of 522 screened, 113 (22%) had abnormalities, substantially fewer than the 50–60% anticipated, with 83 showing perfusion abnormality, and 30 showed electrocardiogram change or lung uptake without perfusion abnormality. Among those with perfusion abnormality, 50 were mild and 33 were moderate or large, comprising just 6% of the screened cohort. Inzucchi pointed out that the conventional risk factors typically used to determine whether an individual should be screened were not predictive of abnormal MPI. This included findings such as blood pressure, BMI, diabetes duration, A1C, lipids, and C-reactive protein (CRP) in univariate analysis, although in multivariate analysis cardiac autonomic neuropathy, diabetes duration, and male sex were predictive of moderate-to-large defects. There were no differences in prevalence of silent ischemia in those with <2 or ≥ 2 risk factors (so, the ADA consensus statement recommendation that only the latter be screened appears to be incorrect). If silent ischemia is not as common as previously reported, if most of the perfusion defects are small, and if baseline characteristics are not predictive, a recommendation for screening becomes difficult to justify.

In the second part of DIAD, 358 of the 522 screened individuals were included, with the others lost to follow-up. Of those with MPI abnormalities on the initial study, 79% had resolved, whereas in the normal group ~10% became abnormal (2). It appeared that the combination of ACE inhibitors, statins, and aspirin was associated with resolution of MPI defects, suggesting the benefit of current risk factor reduction approaches. The question of whether screening improved clinical outcome was addressed in the third part of the study (3). The observed CAD event rate was 3% over 5 years, or 0.6% per year, which is considerably less than the traditional Framingham CVD equivalent risk of >2% per year (4). As expected, the presence of perfusion defects did predict events; other predictors were male sex, peripheral arterial disease, LDL cholesterol, serum creatinine, abnormal heart rate response to standing, moderate-to-large MPI defects, and nonperfusion abnormalities. Inzucchi commented, "The surprise was that there was absolutely no difference in clinical outcomes in the screened versus not screened groups." He acknowledged that this was "a low-risk group of patients" and noted that participants in clinical trials tend to be healthier but pointed out that they had an average diabetes duration of 8 years and were obese, that 25% were treated with insulin, that 60% had more than two risk factors, and that 34% were not active at all and 50% were unable to exercise. A post hoc analysis stratifying based on Framingham Risk Score, UK Prospective Diabetes Study (UKPDS) risk engine score, Association de Langue Française pour l'Etude du Diabète et des Maladies Métaboliques/Société Française de Cardiologie (ALFEDIAM/SFC) score (5), or the presence of metabolic syndrome showed no benefit of screening in either the low-risk or the high-risk groups. Inzucchi concluded that approximately one-fifth of diabetic patients will have CAD and that approximately one-sixteenth will have major abnormalities but that ischemia appears frequently to resolve and that stress testing "does not appear to favorably alter outcome rates in the context of modern practice." "Routine screening," he suggested, "cannot be recommended at this time."

Siu et al. (abstract 869) reported from the DIAD group that the baseline electrocardiogram showed axis deviation in 5%, a conduction defect in 10%, and left ventricular hypertrophy in 2%; none of these were associated with MPI abnormality or with development of acute coronary syndrome, congestive heart failure (CHF), or cardiac death. However, abnormal T-waves were present in 14%, minor Q waves in 10%, ST depression in 4%, and ST elevation in 5%; all were associated with doubling or greater likelihood of MPI or clinical CAD events. Kawasaki et al. (abstract 832) reported the prevalence of CAD among 622 outpatients and 573 inpatients with type 2 diabetes without cardiac symptoms, undergoing resting and treadmill electrocardiogram,

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with MPI based on these findings; only 1.4% of the 1,195 screened patients had coronary angiography–proven CAD, corroborating the DIAD findings. Jinnouchi et al. (abstract 835) studied multidetector computed tomography angiography of the coronary arteries in 500 diabetic patients, finding that 34% of those symptomatic and 31% of those asymptomatic for CAD had >75% stenosis. Kawai et al. (abstract 836) reported 64-slice multidetector computed tomography angiography results in 140 asymptomatic patients, however, finding that 51% had evidence of significant coronary artery stenosis or calcification, which occurred more often in those with diabetes duration >11 years, hypertension, or increased carotid intima-media thickness (IMT).

Bypass Angioplasty Revascularization Investigation 2 Diabetes study

Darren K. McGuire, Dallas, TX, analyzed the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) study to review its findings on outcome of revascularization versus medical therapy for CAD. Diabetic patients comprise one-third to one-half of subjects in cardiovascular studies, with approximately one-half not previously diagnosed (6,7), "so not only is diabetes common, it is probably much more common than previously recognized" in patients with CVD, and when not recognized or appropriately treated it is particularly associated with increased risk (8,9). McGuire reviewed evidence from the UKPDS of the high prevalence of CAD, with fewer than 10% having a microvascular end point but CVD during ~25% of the 40,000 patient-years of observation (10). He suggested a number of treatment goals once a diabetic patient develops CAD to prolong life; to prevent myocardial infarction, CHF, arrhythmia, and angina; and to optimize cost-efficiency and avoid unnecessary procedures, particularly those requiring hospitalization.

The original BARI study compared coronary artery bypass graft (CABG) with angioplasty, without stents or antiplatelet treatment, and showed that in the diabetic cohort CABG led to better survival than percutaneous transluminal coronary angioplasty (11), although this was a relatively small population. Advances in technology may, however, make these findings obsolete. Intensified medical treatment of lipids, blood pressure, and glucose and better integrated systems to improve adherence are available, as are drug-eluting stents, closure devices, and adjuvant therapies, and improvements in CABG as well with greater use of arterial conduits, improved glucose control, off-pump options, and improved cardioplegia techniques require that clinical trial findings be updated.

In BARI-2D, 2,368 patients were randomized, all of whom were candidates for revascularization but who did not immediately require the procedures because of unstable angina, to medical treatment with or without intervention. Baseline A1C was 7.6%, diabetes duration was 10 years, and approximately one-third had a history of myocardial infarction and 10% cerebrovascular disease. Revascularization had no benefit over optimal medical therapy in death, myocardial infarction, or stroke. McGuire pointed out that although 42% of the medical group did cross over to revascularization, because the majority consequentially did not require such treatment the choice not to operate or perform a procedure should usually be considered correct.

Overall, then, optimal medical treatment is comparable to revascularization, but it is noteworthy that in certain areas CABG was preferable. Among those in the percutaneous coronary intervention (PCI) stratum, there was no benefit in death, myocardial infarction, or stroke, although angina appears to have improved. In fact, McGuire continued, "we've never demonstrated that stents affect event rates." In the CABG stratum, there was, however, reduction in myocardial infarction and a trend to reduction in death and stroke. The bypass group had more advanced disease than those in the PCI stratum, but the outlook of those undergoing CABG became comparable with that of those assigned to PCI.

Revascularization is challenging in diabetes because of increased likelihood of restenosis as well as accelerated atherosclerosis beyond the target lesion. There is a 40% greater likelihood of 30-day mortality after CABG among individuals with diabetes (12) and 80% greater 1-year mortality among diabetic patients after PCI with 40% greater need for revascularization (13). After 2 years, major coronary events are more likely to occur at sites different from that of the PCI, perhaps explaining the benefit of more thorough vascular reconstruction with CABG than that with PCI; another factor may be greater clopidogrel resistance (14) and greater likelihood of thrombosis of drug-eluting stents (15) in diabetic patients. The suggestion that bypass surgery is superior is being prospectively tested in the ongoing FREEDOM (Future REvascularization Evaluation of patients with Diabetes mellitus: Optimal management of Multivessel disease) trial (16). For now, however, McGuire concluded that in this group, with a very high risk of events (occurring annually in 4–5% of individuals randomized either to intervention or to control in the BARI-2D study), "we have a lot of work to do" in risk factor reduction but must recognize that the presence of an obstructive lesion does not necessarily mean that revascularization is required. Certainly, it is a concern that only 47% of individuals in the trial had an A1C <7% and only 71% had blood pressure <130/80 mmHg, although 93% achieved LDL cholesterol <100 mg/dL.

In a presentation at the ADA meeting, Lavis et al. (abstract 403) reported outcome in insulin-treated patients in BARI-2D. Overall, the results showed no advantage of insulin-sensitizing over insulin-providing treatment with sulfonylureas or insulin with respect to mortality, myocardial infarction, or stroke over 5 years. Those taking insulin at baseline had higher rates of mortality, myocardial infarction, CHF, and hypoglycemia, and their requirement for late revascularization was twice as great as that for subjects not taking insulin at baseline. Severe hypoglycemia rates were more than twice as great in these patients and were not reduced with the insulin-sensitizing strategy, as was the case in patients not taking insulin at baseline.

Biomarkers and CVD

Peter W.F. Wilson, Atlanta, GA, discussed the use of biomarkers for CVD in diabetes. How, he asked, do we incorporate novel biomarker information, recognizing that "there's a biomarker every week" and that many will not be found to be useful. In the assessment of a new biomarker, the initial (and lowest cost) approach is to perform a cross-sectional study, analyzing its association with other vascular risk factors or with subclinical vascular disease such as carotid IMT or coronary artery calcification (CAC). Because one needs to take into account multiple other conditions and parameters, regression models are used, factoring in age, sex, A1C, lipids, and many other variables, hence, requiring a large study.

Even with nested case-control or cohort studies, thousands of person-years of observation are required. To assess the predictive accuracy of a biomarker, Wilson discussed the notion of discrimination/reclassification. Discrimination is measured with the C-statistic, the area under the curve of receiver operating characteristic analysis, to define the ability of a test to distinguish disease from nondisease. Calibration refers to the ability of a test to match predicted and observed outcome. Finally, he noted the importance of test characteristics, including laboratory variability, biologic variability, and cost. "Most tests as we have done them over time," Wilson pointed out, "get cheaper and cheaper," an argument for use of older markers. However, over time some markers will be replaced, an example being the use of apolipoprotein B or non-HDL to replace LDL cholesterol.

With such an approach to analysis of tests, the increment in discrimination of CRP and most other proposed markers is minimal over that from existing measures (17). It may, however, be optimal to add several biomarkers in improving the discrimination accuracy. In a study using the Framingham data of new biomarker determinants for CVD risk, B-type natriuretic peptide level, CRP, the urinary albumin-to-creatinine ratio, homocysteine, and renin levels predicted mortality and CVD events, with a panel of multiple markers giving a small increase in overall accuracy (18). Wilson commented that although the improvement in test discrimination was modest, such information may be useful in other ways, with natriuretic peptide indicating the prognostic importance of CHF and the urine albumin-to-creatinine ratio the importance of chronic kidney disease. However, there, too, older markers are usually sufficient to assess risk (19). Similar conclusions apply to most new lipid markers, such as small, dense LDL particle distribution, which does not give better discrimination than use of the LDL and HDL cholesterol levels (20). Similar questions have been raised about whether use of LDL particle number rather than LDL and HDL cholesterol measurements is effective (21). Glycated albumin, CRP, and tumor necrosis factor-α were associated with severity of CAD in a study of type 2 diabetic individuals in Shanghai (22). Other studies have investigated adiponectin, although Wilson did not find this convincing as a risk marker.

Wilson discussed the use of serial testing for risk estimation/reclassification based on estimates of prior probability. A test may be particularly important if its use leads to reclassification of an individual from, say, a 10–20% risk to a level >20% or <10%. Such an analysis pertains to the question of whether diabetic patients are truly at high CAD risk in the modern era of statins and blood pressure and glycemic treatment. With such an analysis, a study of 1,135 Swedish men without CVD followed for a decade from age 71 showed that adding natriuretic peptide, CRP, and cystatin C did have advantages in predicting CVD mortality over the use of blood pressure, lipid, diabetes, cigarette, and obesity measures (23). Another useful approach is to validate a set of biomarkers in several populations; with this approach, the combination of troponin I, natriuretic peptide, and CRP was associated with increased risk (24).

Several studies have applied new biomarkers for CAD risk prediction in type 1 diabetes. The use of carboxymethyl lysine and soluble receptor for advanced glycation end products was associated with CVD in one study, but an evaluation including all the standard risk factors was not done, and Wilson suggested it likely would not add to traditional markers. In another study of type 1 diabetic individuals with proteinuria, both CRP and lipoprotein-associated phospholipase A2 were associated with risk (25).

Most data with all the biomarkers is from cohorts that include both diabetic and nondiabetic patients, and although the new biomarkers provide information about the pathophysiology of CVD, their use in isolation from traditional markers is not very helpful, and the new biomarkers appear unlikely to enhance CVD prediction. Wilson suggested that a reasonable strategy is to use diabetes factors, age, sex, HDL and total cholesterol, cigarette use, blood pressure, A1C, a measure of renal function, albuminuria, and perhaps greater consideration of markers of CHF.

A number of studies presented at the ADA meeting discussed biomarkers and CVD. Resl et al. (abstract 868) found that among 308 diabetic patients, both baseline and follow-up natriuretic peptide levels were the most accurate predictors of 29-month outcome when compared with A1C, LDL cholesterol, microalbuminuria, sex, duration of diabetes, and age. Mori et al. (abstract 855) reported that erythrocyte distribution width, which reflects the variability in size of circulating erythrocytes, was associated with CVD events and carotid IMT and was greater in patients receiving sulfonylureas and lower in those treated with thiazolidinediones. Vonbank et al. (abstract 858) measured fasting insulin in 986 individuals undergoing coronary angiography, finding that homeostasis model assessment (HOMA) of insulin sensitivity was associated with metabolic syndrome but not with CAD. Similarly, Kim et al. (abstract 860) found that an insulin sensitivity index did not correlate with carotid IMT, adjusting for age, sex, BMI, smoking, systolic pressure, A1C, and HDL and LDL cholesterol. Kim et al. (abstract 793), however, reported that lower levels of HOMA of insulin sensitivity were associated with carotid IMT in a study of 876 nondiabetic healthy individuals. In a study of type 1 diabetic patients, Pambianco et al. (abstract 784) reported that both cardiovascular autonomic neuropathy and distal symmetrical polyneuropathy were associated with CHD and mortality in an 18-year follow-up, although neither was independently predictive in multivariate analysis. Waters et al. (abstract 803) reported analysis of 1,433 diabetic individuals with stable CAD followed for 4.9 years, finding major CVD events in 19.5% of those with baseline heart rate ≥70 bpm but in 13.6% of those with a lower heart rate. Mortality increased 69% and likelihood of CHF hospitalization increased 149% in the more tacchycardic group, with differences remaining after adjustment for standard risk characteristics, suggesting that heart rate should be considered an independent risk factor. An interesting observation by Takata et al. (abstract 295) was that postprandial glucose-dependent insulinotrophic polypeptide levels increased with increasing prevalence of hypertension and CVD in a cohort of 122 individuals after adjustment for age, sex, smoking, BMI, postprandial glucose, hypertension, and LDL cholesterol. Son et al. (abstracts 806 and 833) studied 174 type 2 diabetic individuals without known CVD, finding bone morphogenic protein-4 to correlate inversely with carotid IMT after adjustment for age, duration of diabetes, systolic blood pressure, BMI, A1C, lipid profiles, and CRP.

Limits of glycemic control in reducing CVD

Peter D. Reaven, Phoenix, AZ, addressed the question of whether the benefit of

glycemic control in its ability to reduce microvascular and macrovascular disease might be outweighed by negative effects, particularly in the presence of CVD, hypoglycemia, and weight gain. Further, he suggested the concept of "vascular age," which may limit the ability of glycemic control to improve outcome. In the Diabetes Control and Complications Trial in younger type 1 diabetic patients and in the Kumamoto and UKPDS studies of type 2 diabetic patients, all microvascular end points decreased, while CVD outcomes "were less clear," although posttrial follow-up of both the DCCT (26,27) and UKPDS (28), despite loss of glycemic separation, did show CVD benefit, leading to the concept of metabolic memory. Reaven asked whether there may be "negative glycemic memory of poor glycemic control" of diabetes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial, and Veterans Affairs Diabetes Trial (VADT) endeavored to assess cardiovascular effects of glycemic control. The intensively treated group in ACCORD had increased mortality, although subset analysis showed that individuals without CVD and those with A1C <8% at entry had evidence of reduction in the primary cardiovascular outcome. In ADVANCE, there was no overall macrovascular benefit in an older population with a high prevalence of CVD. In the VADT, A1C separation was 6.9 vs. 8.4%, but the reduction in composite CVD outcome was not significant. Post hoc analysis showed that diabetes duration was related to benefit, with a 0–15 year hazard ratio (HR) of 0.74 but a ≥16 year HR of 1.24 in CVD outcome. "Intensive glycemic control does not come without a cost," Reaven said: a threefold increase in hypoglycemia in the VADT, and severe and recent hypoglycemia was a very important predictor of cardiovascular death in the study. A meta-analysis including ACCORD, ADVANCE, UKPDS, and VADT showed a significant 9% reduction in major macrovascular events, but those with a history either of macrovascular or of microvascular disease did not benefit (29). Reaven recalled the findings of the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study of 620 diabetic individuals allocated to intensive insulin after myocardial infarction, prerandomized into four groups based on risk. Only the low-risk subgroup not treated with insulin, and without CAD history, had benefit (30). Glucose lowering among newly detected diabetic patients with glycemic treatment in the Euro Heart Survey suggested benefit in reducing mortality (31). Similarly, in a 5-year follow-up of type 2 diabetic patients, those with a high comorbidity score who had lower A1C did not do better than those with higher A1C, but with a low comorbidity score, lower A1C was associated with better outcome (32).

Another approach is to directly assess the level of atherosclerosis burden; this approach was taken in a VADT substudy, with CAC measured at onset and at 5 years (33). Those with lower CAC had evidence of better cardiovascular outcome with intensive glycemic treatment, but with higher CAC glycemic treatment did not produce cardiovascular benefit, which Reaven interpreted as "suggesting perhaps that if you have . . . extensive disease you are less well able to respond." The follow-up of CAC showed that less progression occurred in individuals with lower baseline CAC scores (34).

"We don't exactly understand," Reaven commented, why poor prior glycemic control would be associated with less benefit of improved control during the study. A suggestion has been advanced that "you may not be able to overcome" advanced glycemic end product protein cross-linking, lesion necrosis, excess mitochondrial reactive oxidant stress and damage, glycemia-induced renal disease, vasa vasorum angiogenesis, expanded vascular smooth muscle, or epigenetic changes in gene transcription occurring with long-standing hyperglycemia (35). A study of the effect of prior control in type 1 diabetic patients with new onset, those with diabetes for 5 years with mean A1C <7%, and those with diabetes for 5 years with mean A1C >7% found improvement in flow-mediated vasodilation when normal glucose levels were maintained only in the former two groups (36), further suggesting the existence of this adverse effect of poor glycemic control.

Reaven concluded that optimal A1C should be individualized based on the patient's risk for and from hypoglycemia, their potential for benefit of lower A1C, the difficulty of attaining control, and vascular age based on prior CVD and long diabetes duration (37). With none of these factors, an A1C of 6.5–7% may be appropriate; with one factor, the goal might be 7.5%; and with two or more factors, a goal of 7.5–8% might be most appropriate.

Is diabetes a CVD risk equivalent?

At a debate on whether diabetes should be considered a cardiovascular disease equivalent, Eberhard Standl, Munich, Germany, argued in the affirmative, although admitting that "we do not know the ultimate answer." The concept began with the East-West study findings (38) suggesting that diabetic patients without CAD history had risk levels similar to those of nondiabetic individuals with a history of myocardial infarction. A meta-analysis of this and 12 other studies showed, however, that there were lower CAD rates in individuals with diabetes than in those with a history of myocardial infarction (39). Standl noted, however, that the investigators excluded >300 other papers on the topic for various reasons, leading one to be uncertain as to whether the analysis could have been carried out in a different fashion. Examples of the omitted studies (which would have supported the CAD equivalent argument) include a population study of 3.3 million individuals in Denmark showing that diabetic patients requiring glucose-lowering treatment had the same cardiovascular risk as nondiabetic individuals with a prior myocardial infarction (40); a study of >9 million individuals living in Ontario, Canada (41); and an update of the original East-West study population continuing to show increased risk in diabetic individuals (42). Standl suggested, then, that there are important and contradictory data missing and that there is certainly evidence that CAD risk is high in diabetic patients. Further, Standl noted that if diabetes is considered a CAD equivalent then no expensive screening is needed. There has been evidence for a long time of a high prevalence of CAD in diabetic individuals (43). A concern is, however, that the Framingham and UKPDS risk equations may be inaccurate and may overestimate risk in diabetic individuals (44–46). Particular underestimation of cardiovascular risk occurs among individuals at lower risk, with diabetes amplifying the adverse effects of metabolic syndrome (47).

Further evidence comes from studies of both type 1 and type 2 diabetic individuals for several decades. Standl pointed out that over the first 5 years of diabetes, there is little evidence of adverse outcome (48). Furthermore, he stated, 20–35% of diabetic individuals without

CAD signs or symptoms have silent myocardial ischemia (43), as confirmed in the DIAD study (described above), and silent myocardial ischemia is associated with a 10-year risk of ~30%. Of further note are studies of 5-year outcomes in 8,357 Australian individuals (49) and in the 9,306-person Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial (50) suggesting a dose-effect relationship between the degree of hyperglycemia and CVD outcome. In ADVANCE, the total population without prior macrovascular disease history was 7,502 individuals and their estimated 10-year CVD risk was 33%, with 15% major CVD, 14% CAD, and 8% major CAD (not including CHF) risks (44). Those without a history of macrovascular disease in VADT, ACCORD, and ADVANCE had 10-year risks of CAD events of ~18%, Standl stated, despite unusually good control of blood pressure and lipids. He noted that the DIAD study suggests it is not necessary to screen for silent myocardial ischemia and that multifactorial therapy was appropriate, with evaluation if symptoms occur. Similar conclusions can be drawn from the Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation (COURAGE) trial, in which 33% of enrolled patients had diabetes (51) and BARI-2D (discussed above), leading Standl to conclude that individuals with diabetes are still at high CAD risk (around 15–20% at 10 years), with CVD prognosis markedly improved by intensive multifactorial treatment. Studies such as DIAD suggest that screening does not change prognosis, which underscores the importance of regarding diabetic patients as requiring aggressive medical treatment.

Iskandar R. Idris, Sheffield, U.K., took the contrary position, that diabetes is not really a cardiovascular risk equivalent, while recognizing that it is a major risk factor for developing CVD (52) and that after myocardial infarction, diabetes increases risk (53). The question is whether diabetes is a CAD risk equivalent, which would mean 10-year risk for major coronary events >20%. This would imply, Idris stated, a need for statins in almost all patients. Further, he pointed out that the 10-year 20% CAD risk applies to individuals with stable angina and that those with major CAD have a 10-year risk of 26%, while most studies show that risk levels are lower with diabetes (54). He compared a high-risk strategy of "treating the most needy" with a "population strategy," in which a whole population receives treatment, suggesting the former to be more beneficial (55). In the Strong Heart Study, Idris stated, diabetes alone was consistently a lesser risk factor than CAD alone, although diabetes with multiple risk factors was associated with much higher risk, particularly with diabetic dyslipidemia. He pointed out that in the East-West study, patients were self-selected and had pharmacologically treated diabetes. Other studies suggesting that diabetes may not be equivalent to CAD are the Nurses' Health Study (56), a prospective cohort study of U.S. physicians (57), and the Atherosclerosis Risk in Communities study (58). In one of the studies cited by Standl, Idris stated, at above age 50 years the CAD mortality risk became similar for diabetes alone versus prior CVD in males, but not in females, and was interpreted by the authors to suggest that diabetes did not convey risk equivalent to CAD but, rather, could be equated with 15 years of aging (41). His similar study in the U.K. primary care cohort suggests that the age of transition from low to high risk was approximately 52 years in men and 49 years in women (54), but in Asian Indian patients the ages were 37 and 50 years, respectively (59). He reviewed his meta-analysis, as previously discussed by Standl, and explained that it showed that patients with diabetes without prior CVD had significantly lower risk than patients with prior myocardial infarction without diabetes (39). Diabetes as a true CVD equivalent would require routine use of aspirin, clopidogrel, ACE inhibitors or angiotensin receptor blockers, β-blockers, and high-dose statins, but evidence to justify this is lacking. Furthermore, risk reduction in patients with diabetes in lipid-lowering trials is similar to that in nondiabetic patients, also suggesting little specific adverse effect of diabetes. Idris concluded that there is significant heterogeneity in cardiovascular risk among diabetic patients, that a primary prevention strategy to prevent CVD in diabetic patients should be based on individual risk assessment, and that the blanket statement of diabetes as a cardiovascular risk equivalent is unproven and, perhaps, unhelpful.

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