The American Diabetes Association's 48th Annual Advanced Postgraduate Course

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This article covers symposia presented at the American Diabetes Association's 48th Annual Advanced Postgraduate Course, which was held in New York in January 2001. Topics include management of cardiovascular disease and diabetes, management of diabetes and hypertension, estrogen therapy and cardiovascular disease, and use of ACE inhibitors.

At the American Diabetes Association's 48th Annual Advanced Postgraduate Course in New York, 19–21 January 2001, much emphasis was devoted to cardiovascular disease (CVD) management in patients with diabetes. Henry Ginsberg, New York, NY, discussed diabetic dyslipidemia as a part of the hyperglycemia syndrome and, more importantly, the insulin resistance syndrome. Central to diabetic dyslipidemia is the elevation of fatty acid levels, with consequent elevated total triglycerides, reduced HDL cholesterol levels, and normal or mildly elevated levels of LDL cholesterol of abnormal composition. Thus, triglyceride levels exceed 235 mg/dl in 9 vs. 19% of nondiabetic vs. diabetic men and are >200 mg/dl in 8 vs. 17% of women. HDL cholesterol levels <31 mg/dl are seen in 12 vs. 21% of the two groups of men, and levels <41 mg/dl are seen in 10 vs. 25% of the respective groups of women. LDL cholesterol levels are similar in individuals with and without diabetes, exceeding 190 mg/dl in 11 vs. 9% and 16 vs. 15% of men and women, respectively (1). Similarly, in the U.K. Prospective Diabetes Study (UKPDS), HDL levels were lower and triglyceride levels were higher in both men and women with diabetes, although among women with diabetes, LDL cholesterol levels were higher (2). Insulin resistance is associated with a 30–40% higher free fatty acid (FFA) level because of decreased adipocyte uptake and increased release, leading to an increase in hepatic triglyceride synthesis, with increased VLDL production. In the circulation, cholesterol ester transfer protein, which resides mainly on HDL particles, transfers cholesterol from HDL to VLDL and triglyceride from VLDL to HDL particles. Under the action of hepatic lipase, HDL triglyceride is metabolized and apolipoprotein (apo)-A1 is lost. Similarly, VLDL and LDL exchange cholesterol and triglyceride, with formation of small dense LDL as the triglyceride is metabolized by hepatic lipase or lipoprotein lipase, although apoB is not lost and is retained in the particles. In addition to nonpharmacologic treatment with diet, exercise, and weight loss, a number of pharmacologic treatments are available.

There are currently six hydroxymethylglutaryl (HMG)-CoA reductase inhibitors ("statins"). Recalling that the average LDL level among patients with diabetes is ~140 mg/dl, a level similar to that observed in nondiabetic subjects, Ginsberg suggested that, on average, to reduce LDL to 100 mg/dl, administration of 10 mg atorvastatin, 20 mg simvastatin, 40 mg lovastatin or pravastatin, 80 mg fluvastatin, or 0.4 mg cerivastatin would all be effective. In the Scandinavian Simvastatin Survival Study (4S) trial with simvastatin (3) and the Cholesterol and Recurrent Events (CARE) trial with pravastatin (4), the improvement with treatment of individuals with diabetes was similar to that of nondiabetic subjects. Given that individuals with diabetes continue to show higher event rates than those without diabetes, Ginsberg noted that there is still "much more to do." This may be accomplished in part by the use of combinations with additional lipid-modifying agents. The bile acid binding resins cholestyramine, colestipol, and colesevelam are not absorbed systemically and can lead to a 10–20% lowering of LDL, although triglyceride levels may increase. With colesevelam, gastrointestinal side effects and drug interactions are lesser in degree, and these may be useful as adjuncts. The fibrates (gemfibrozil and fenofibrate are available in the U.S.) activate peroxisome proliferator–activated receptor (PPAR)-α, leading to a 35–50% reduction in triglyceride, a 10–20% increase in HDL cholesterol, and variable LDL effects. In the Helsinki Heart Study in the late 1980s, the 5-year incidence of coronary heart disease (CHD) fell from 10 to 3% among patients with diabetes, similar to the decrease in nondiabetic subjects (5). In the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT), approximately one-quarter of patients had diabetes and another one-quarter had impaired glucose tolerance (IGT). The baseline LDL, HDL, and triglyceride levels were 111, 32, and 160 mg/dl, respectively. HDL increased by 7.5% and triglycerides decreased by 25%, with a 24% reduction in CVD (decreasing from 36 to 28% in those with diabetes and from 23 to 18% in those without diabetes) (6). The Diabetes Atherosclerosis Intervention Study (DAIS)

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Abbreviations: 4S, Scandinavian Simvastatin Survival Study; A2, angiotensin 2; ACEI, angiotensis-converting enzyme inhibitor; Ach, acetylcholine; AN, autonomic neuropathy; apo, apolipoprotein; AAV, adeno-associated virus; BARI, Bypass Angioplasty Revascularization Investigators; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCB, calcium channel blocker; CHD, coronary heart disease; CHF, congestive heart failure; CMV, cytomegalovirus; CVD, cardiovascular disease; FFA, free fatty acid; HOPE, Heart Outcomes Prevention Evaluation; HRT, hormone replacement therapy; HSP, heat shock protein; IGT, impaired glucose tolerance; MAPK, mitogen-activated protein kinase; MCP-1, macrophage chemoattractant protein-1; MMP9, Matrix metaloproteinase-9; NO, nitric oxide; NOS, NO synthase; PAI-1, plasminogen activator inhibitor-1; PDGF, platelet-derived growth factor; PPAR, peroxisome proliferator–activated receptor; PTCA, percutaneous transluminal coronary angioplasty; SHEP, Systolic Hypertension in the Elderly Program; SMC, smooth muscle cell; SPECT, single-photon emission computed tomography; Syst-Eur, Systolic Hypertension in Europe; UKPDS, U.K. Prospective Diabetes Study.

with fenofibrate showed a 27% decreased triglyceride level, a 6% decreased LDL level, and a 7% increased HDL level among 418 patients with diabetes, with a 40% reduction in angiographic progression of coronary disease (7). One should be aware of the risk of myositis, which is ~1% per year with combination statin-fibrate treatment (8). This risk is medically acceptable, Ginsberg suggested, given the lipid benefits (9) and, hence, the predictable decrease in CVD. Lipid data for rosiglitazone show variable effects on triglyceride, with a fibrate-like increase in LDL but a definite increase in HDL; pioglitazone more consistently lowers triglyceride with less of an increase in LDL and with a similar increase in HDL. Fish oils lower triglycerides effectively, but only when high doses are given, and they show little HDL effect. They may raise LDL cholesterol levels, as do fibrates in certain patients. Available evidence shows a reduction in sudden death by antiarrhythmic mechanisms, which led Ginsberg to state that "there may be reasons to tell people to eat a lot of fish." The short-acting niacins, and in particular the agent Niaspan, appear to show overall the best lipid effects. In the Arterial Disease Multiple Intervention Trial (ADMIT) of 468 patients (125 having diabetes), there was a 10% decrease in LDL cholesterol, a 30% increase in HDL cholesterol, and a 30% decrease in triglycerides, while—with appropriate adjustment in treatment—glycemia remained controlled (10). Interestingly, niacin acutely reduces FFA release from adipocytes, which, as one would anticipate, could actually lower glucose levels; however, there is a tendency for glucose to increase, "so there's something it's doing somewhere else." The objectives for lipid treatment in diabetic patients are to first lower LDL cholesterol levels and then to decrease triglycerides to <200 mg/dl (and <150 mg/dl if possible) and finally to get HDL "as high as you can."

Norman Kaplan, Dallas, TX, discussed the management of diabetes and hypertension. According to the target levels of <130/80 mmHg, 70% of patients with diabetes need treatment for hypertension, and although it is possible that even lower blood pressure levels may be desirable, "it may not be practical to achieve [such levels]." The recent Dietary Approaches to Stop Hypertension (DASH) study of nonpharmacologic treatment showed that dietary sodium levels of 65, 107, and 140 mmol/l per day were associated with progressively higher blood pressure levels (11). Kaplan stated that all drugs are beneficial when compared with placebo, that he believed there was no conclusively greater benefit from any class, and that multiple drugs are usually needed to reach the target. In the Hypertension Optimal Treatment (HOT) trial, which had diastolic goals of 90, 85, or 80 mmHg, there were no differences observed in nondiabetic subjects, but there were ~38, 30, and 43% reductions in CHD/congestive heart failure (CHF), stroke, and total mortality in diabetic patients, comparing the <80 mmHg group (who achieved a mean level of 140/81 mmHg) with the 90 mmHg group (who achieved a level of 144/85 mmHg) (12). In the UKPDS, the randomized blood pressure study of 1,148 patients randomized to goals of 150/85 vs. 180/105 mmHg achieved a 10/5 mmHg difference of 154/87 vs. 144/82 mmHg in the two groups, which led to decreases of 21, 56, 44, and 18% in major cardiovascular events, CHF, stroke, and mortality, respectively (13). Epidemiologic analysis of the overall group of 3,642 patients in the UKPDS showed that a systolic 10-year mean blood pressure <120 mmHg was associated with less than half of the end points of those with systolic mean levels >160 mmHg (14). "As long as the patient can stand up," Kaplan suggested, "the lower their blood pressure should be." Kaplan also noted that there is very little evidence suggesting that, regarding the treatment of diabetic hypertensive subjects, there is any difference among the various types of drugs available. Chlorthalidone (which was used in the Systolic Hypertension in the Elderly Program [SHEP] [15]), nitrendipine (which was used in the Systolic Hypertension in Europe [Syst-Eur] [16] and the Systolic Hypertension in China [Syst-China] [17]) studies, and ramipril (which was used in the Heart Outcomes Prevention Evaluation [HOPE] study [18]) all showed benefit, with a suggestion that the nitrendipine treatment of Syst-Eur led to greater benefit among patients with diabetes than the thiazide treatment among patients with diabetes in SHEP. Although some authors (19) have suggested that calcium channel blockers (CCBs) lead to adverse outcomes, the trials in question "were relatively small in aggregate" and patients often switch treatment between agents in trials (20). Kaplan stated that "the scares about the dangers of the CCBs are mistaken" and that comparisons suggest lesser degrees of mortality with CCBs. He showed an analysis of seven trials with a total of 5,000 patients, showing no evidence of benefit of any one class. In both the UKPDS and the Captopril Prevention Project (CAPPP), captopril and β-blocker treatment led to similar outcomes. The Swedish Trial of Old People (STOP-2) compared CCBs, angiotensin-converting enzyme inhibitors (ACEIs), and thiazide/β-blocker treatment, showing little difference, although ACEIs may have somewhat decreased myocardial infarction (21). Overall, 1,903 patients were treated with diuretics and/or β-blockers, 1,368 were treated with ACEIs, and 1,657 were treated with CCBs, with mortality in 12.5, 12, and 8.2%, CHD in 8.5, 8.4, and 6.9%, and stroke in 6.2, 6.6, and 5.3%. However, these trials are "in a sense irrelevant" because most patients require multiple drugs for adequate treatment. For example, in the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET), although the CCB amlodipine was of less benefit than the ACEI fosinopril, the use of both agents was associated with the greatest degree of benefit (22).

Hertzel Gerstein, Toronto, Canada, followed Kaplan's presentation by discussing the contrasting, though not entirely opposing, question of whether all patients with diabetes should receive an ACEI. Factors arguing against such treatment include the cost, annoyance, and potential distraction from other treatment, as well as the frequent cough and rare angioedema seen with these agents. In favor of treatment, one can argue that ACE mediates the conversion of angiotensin 1 to angiotensin 2 (A2), thereby increasing adrenal aldosterone production, having direct vasoconstrictive effects, and acting as a growth factor for the left ventricle, vascular smooth muscle, and mesangial cells. Bradykinin is inactivated by ACE and has vasodilatory effects. Decreased A2 will lower blood pressure, myocardial demand, left ventricular mass, smooth muscle proliferation, endothelin, plasminogen activator inhibitor-1 (PAI-1), and platelet aggregation. Individuals with higher rennin have higher future myocardial infarction risk (23), and those with the ACE DD genotype have higher ACE and increased myocardial infarction risk (24). These consider-

ations led to the HOPE study, which prespecified diabetes as a subgroup for separate analysis and recruited 3,654 patients with diabetes whose age was >55 years and who had a history of the following: prior CVD, blood pressure >160/90 mmHg or blood pressure treatment (half of the participants did not have hypertension), microalbuminuria (32% of participants), cigarette use, cholesterol >200 mg/dl, or of HDL cholesterol <35 mg/dl (18). Patients with CHF or with dipstick proteinuria were excluded from the study. Ramipril decreased mortality, stroke, and cardiac events by ~25%. Development of macroalbuminuria decreased 22%, and there was no significance effect on laser treatment. The most frequent cause of discontinuation was cough (7 vs. 2% of treated vs. placebo patients). Gerstein pointed out that the most important consideration in administering ACEI (or any other agent) is the number of patients that must be treated to avoid each adverse event, which depends on the baseline risk. Thus, with a 25% decrease in event rates, if the baseline 5-year risk is 25%, then 16 patients would need to be treated for 5 years to prevent one event. If the baseline risk is 20, 10, or 4, then these numbers increase to 20, 40, and 100 patients. In the HOPE study, 5-year event rates in individuals with diabetes ranged from 11% in those without CVD at baseline to 26.5% in those with CVD. For younger individuals with diabetes, these rates might be lower. The risk of adverse events, however, does not change with the different scenarios; therefore, one must "make trade-offs."

Richard Cannon, Bethesda, MD, discussed the role of estrogen therapy for improving CVD outcomes among women with diabetes. In regard to examining CVD outcomes among diabetic women, the major question to be addressed is what illnesses are responsible for death in women? As women age, the risk of CVD death increases considerably, but the risk of breast cancer mortality decreases. This case is particularly more prevalent among women with diabetes. The fact that the increase in CVD begins around the time of menopause suggests that estrogen deficiency is associated with accelerated CVD risk. In the Nurses Health Study, women who were using hormone replacement therapy (HRT) had approximately half the risk of a CVD event or CVD death than those who had never taken or had formerly taken estrogen (25). This may be an indicator of good health instead of a mediator per se. However, among 1,178 women with >70% stenosis on coronary angiography, those taking HRT had 97 vs. 60% 10-year survival (26). Estrogen lowers LDL, increases HDL, lowers lipoprotein(a), acts as an antioxidant, increases nitric oxide (NO), decreases endothelin-1, increases fibrinolysis, and may have an anti-inflammatory effect. In animal studies, estrogen decreases the proliferative response to arterial injury and decreases atheroscleosis with a high-cholesterol diet. Effects of estrogen on NO production are of particular interest. The enzyme NO synthase (NOS) is stimulated by acetylcholine (Ach) or by increasing shear stress. Intracoronary Ach infusion in women with CHD paradoxically causes a vasoconstrictive effect, which can be prevented by coinfusion of 17-β estradiol in a process mediated by NO. NO regulates vasomotor tone, inhibits platelet aggregation and attachement, inhibits inflammatory cell attachment, and inhibits the release of procoagulant factors.

In the context of this data, the Heart and Estrogen/Progestin Replacement Study (HERS) assessed 2,763 women with coronary artery disease (CAD) whose age was <80 years and who had their uterus intact and were treated with conjugated equine estrogen 0.625 mg plus medroxyprogesterone acetate 2.5 mg daily in a randomized, placebo-controlled trial with an average 4.1 years of follow-up (27). CHD events occurred in 172 vs. 176 of patients treated with estrogen vs. placebo. Nonfatal myocardial infarction occurred in 116 vs. 129 patients, CHD death occurred in 71 vs. 58 patients, pulmonary emboli occurred in 34 (2 fatal) vs. 12 patients, gallbladder disease events occurred in 84 vs. 62 patients, and persistent vaginal bleeding occurred in 30 vs. 4 patients. Fractures occurred in 130 vs. 136 and breast cancer in 32 vs. 25. Analysis of the time course of events showed lower CHD event rates among placebo-treated patients during the first 3 years; after 4 years, the estrogen group appeared to have lower event rates. Thus, at least initially, despite the extensive experimental and epidemiological evidence that suggested benefit, it appears that estrogen treatment may do harm to women with coronary disease. Cannon reviewed findings from the Coronary Drug Project, a study performed more than three decades ago that randomized 8,341 men with prior myocardial infarction to estrogen, clofibrate, d-thyroxine, niacin, or placebo treatment (28). At 18 months, 1,119 men randomized to high-dose estrogen had 6.2 vs. 3.2% reinfarction and 9.7 vs. 8.2% total mortality.

Estrogen does augment both production of procoagulant factors in a dose-dependent fashion, including fibrinopeptide A, and prothrombin conversion to thrombin, whereas the antithrombotic factors antithrombin III and protein S decrease with this treatment. Inflammation is increasingly recognized to be a component of atherosclerosis. Over time, chronic injury caused by hypertension, dyslipidemia, cigarettes, and diabetes causes injury to the arterial wall, leading to cytokine and growth factor production. In this setting, inflammatory cell attraction further contributes to atherosclerosis. Estrogen may have anti-inflammatory properties via elaboration of NO, antioxidant, and increased HDL levels. Although estogen decreases levels of cell adhesion factors, it increases levels of C-reactive protein, interleukin-6, and Matrix metaloproteinase-9 (MMP9); the latter potentially weakens the fibrous cap of a vulnerable atherosclerotic plaque, causing rupture. The primary activator of MMP9 is plasmin, which in turn is activated by thrombin. Estrogens enhance fibrinolysis, decreasing PAI-1 and D-dimer, perhaps allowing tissue plasminogen activator activation that leads to MMP9 activation.

Thus, at this point there is no clear evidence of benefit of estrogen treatment for women with diabetes, and there may be an adverse effect, given the frequency of underlying coronary disease. "At the present time," Cannon concluded, "we have to keep an open mind [and] make greater use of the drugs which we know can reduce cardiovascular risk." The Women's Health Initiative is a multicenter study of 161,000 postmenopausal women, 28,000 of whom are participating in a controlled study of HRT vs. placebo. The Women's International Study of Long Duration Oestrogen after Menopause (WISDOM) study is a similar European study of 20,000–30,000 women. These studies may provide important additional information.

Aaron Vinik, Norfolk, VA, addressed the question of whether neuropathy plays a role in CVD in patients with diabetes, stating, "A limp penis predicts a heart attack!" Autonomic neuropathy (AN) is a common complication that is seen clinically in 10–50% of patients. With more

sophisticated assessment, it is present in 90% of patients and affects every system in the body, having a major impact on morbidity and mortality. AN seriously affects quality of life, is easy to diagnose, and is preventable, treatable, and, Vinik suggested, reversible. The condition may occur functionally with either hyperglycemia or hypoglycemia, may affect sympathetic, parasympathetic, or neuropeptidergic pathways, and may be either symptomatic or asymptomatic. Risk factors for AN include hypertension, increased LDL cholesterol, decreased HDL cholesterol, female sex, age, obesity, hyperinsulinemia, and PAI-1. Peripheral abnormalities include decreased temperature regulation with abnormal sweating and edema, which may increase the risk of lower-extremity ulceration. The initial damage is to the parasympathetic system, so that tacchycardia is an early manifestation attributable to unopposed sympathetic activity. Central cardiovascular effects of AN include systolic and diastolic dysfunction, orthostasis, and the syndrome of cardiac denervation with consequent arrhythmias. Vinik noted the association of AN with prolonged QT interval, which is perhaps caused by an imbalance in regional sympathetic innervation, and suggested that adrenergic supersensitivity may be a cause of arrhythmia. The increase in cardiac output during exercise is less pronounced with AN, further potentially causing adverse cardiac outcome. Normally, the heart rate varies with deep respiration resulting from changes in activity of the vagal nerve, and this is lost with neuropathy. Tests include the expiratory-inspiratory ratio, the Valsalva ratio, and the ratio of the RR interval at the 15th and 30th heartbeats after standing, all three of which are sensitive and specific, with high positive and negative predictive values. More than half of type 1 and type 2 diabetic patients show evidence of AN.

Only 25–50% of people with diabetes who have symptomatic AN survive 10 years, suggesting this to be a major cause of adverse outcome, with abnormal heart rate variability associated with more than a fivefold increase in mortality in type 1 diabetes (29). Myocardial infarction may present in patients with diabetes with cough, nausea, dyspnea, fatigue—or in diabetic patients with no symptoms. Survival after myocardial infarction is decreased in patients with AN. A number of studies have shown improved survival with β-blockers, which potentially restore sympathetic-parasympathetic balance. ACEIs may also be effective, with quinapril particularly effective with mild to moderate disease (30). Another potential treatment is physical exercise. Vinik suggested that these patients need care with heat exposure, and that if surgery is needed one should alert the anesthesiologist because of potential adverse interactions with general anesthesia. Spironolactone (31), amiodorone, CCBs, antioxidants (e.g., α-lipoic acid, aldose reductase inhibitors, and protein kinase C inhibitors), and neurotrophic agents may also be of benefit. Furthermore, the Diabetes Control and Complications Trial showed a 60% decrease in the risk of abnormal E:I ratio with intensive treatment, suggesting the importance of glycemic control.

Ami Iskandrian, Birmingham, AL, discussed the diagnosis of CHD in patients with diabetes, giving the audience two marvelous caveats. He began by recalling that Einstein said, "Not everything that counts can be counted, and not everything that can be counted counts," and concluded with Hippocrates, who advised, "There are two things: science and opinion; the first leads to knowledge, the second to ignorance."

Finnish data shows 7-year survival and event rates of 20.2 and 45% vs. 3.5 and 18.8% among diabetic vs. nondiabetic individuals (32). Diabetes is associated with more severe stenosis, longer lesions, more ulcerated plaques, more vessel clot burden, more progression, more total occlusions, more diffuse disease, and smaller vessel caliber. "Every single one of these," Iskandrian said, "is important." Unlike the nondiabetic, patients with type 2 diabetes without angiographic CAD have decreased peak hyperemic flow response, which is particularly seen in patients with microvascular disease or AN and may indicate decreased tissue perfusion (33). Clinical evaluation includes treadmill testing, Holter, and angiography. With all of these, one needs to consider a given patient's pretest probability of disease, but the nature of the patient's anginal symptoms is more difficult to assess in the patient with diabetes because of the frequency of silent disease. The electron beam–computed tomography measure of coronary calcification is of interest (34), but Iskandrian commented, "The incremental value of electron beam–computed tomography over traditional risk models has not yet been established. We have even less data in patients with diabetes."

Sestamibi–single-photon emission computed tomography (SPECT) appears to have similar sensitivity and specificity in patients with and without diabetes. The event rate in those with normal images, regardless of diabetic status, is low (although higher with diabetes than without diabetes). Because treadmill testing does not localize the disease, does not allow estimation of left ventricular function, and does not allow follow-up assessment, SPECT testing appears to be preferable. In comparison with stress echocardiography, SPECT is more accurate, is more sensitive, and has a higher technical success rate, with sensitivity >90% and specificity >60%, suggesting SPECT to be the optimal noninvasive approach. Since adenosine produces a consistent maximal hyperemic response, exceeding that of maximal exercise, and because submaximal tests decrease sensitivity with all modalities, adenosine should be used for all patients unable to perform maximal exercise, with gated SPECT imaging. An important question concerns whether we should try to detect all disease or just severe disease. For the latter, treadmill testing may be more sensitive, although, again, with diabetes there are many obstacles to the use of an exercise study.

Katherine Detre, Pittsburgh, PA, discussed current treatments for CHD. The Bypass Angioplasty Revascularization Investigators (BARI) study was designed to compare coronary artery bypass grafting (CABG) with percutaneous transluminal coronary angioplasty (PTCA) in patients with multivessel disease, with angina or other objective evidence of ischemia, and without prior revascularization (35). Thus, a somewhat atypical population was studied, as "every patient had to be eligible for the less invasive percutaneous procedure." Of >12,000 patients screened, only one-third were angiographically eligible and less than half of these were randomized. The average age was 62 years, three quarters were male, more than half had a history of myocardial infarction, 41% had triple vessel disease, and 22% had ejection fraction <50%. Of the patients, 19% were treated diabetics. Bypass was performed to a mean of 3.1 arteries, with 82% having an internal mammary artery graft. On average, PTCA was performed on in two vessels. The 7-year survival was similar in

86% of patients without diabetes but was 76 vs. 54% at 7 years in those with diabetes. Patients with diabetes who received oral hypoglycemic agents and had CABG did almost as well as those without diabetes, but those treated with insulin had worse survival even with CABG. Patients with diabetes also required more repeat procedures after PTCA. Q-wave myocardial infarction was more common in patients with diabetes. Patients not having myocardial infarction during the follow-up period had relatively good survival, but those who had Q-wave myocardial infarction had much higher mortality after PTCA than after CABG. Thus, symptomatic diabetic patients with multivessel coronary disease who require revascularization benefit more from CABG, although they have worse prognosis, particularly if they are treated with insulin.

The BARI-2 study, which is now beginning, will use a double randomization to study less severely symptomatic patients with type 2 diabetes and stable CAD, to test whether 5-year mortality is lower with an immediate revascularization (using the procedure "of choice," either CABG or PTCA) plus aggressive medical therapy versus medical therapy alone, and to test insulin sensitizer versus insulin-providing treatment. Detre speculated on the problem with revascularization in diabetes. Patients with diabetes have more comorbidity, such as peripheral and carotid arterial insufficiency, more peri-procedure complications, more myocardial infarction and stroke, and excessive restenosis, with more intimal hyperplasia, which is caused by abnormal endothelial function, decreased endothelial regeneration, a prothrombotic state, more negative remodeling, protein glycosylation, increased vascular matrix deposition, and decreased collateral formation. An important goal of BARI-2 will be to address the roles of insulin and insulin resistance in the pathogenesis of vascular disease. The goal of treatment will be to attain an HbA_{1c} of 7% in both groups while avoiding combination treatment that would lead to crossovers. Patients in the study will be assigned to treatment either with insulin sensitizers or with insulin secretagogues; α-glucosidase inhibitors will be considered "insulin neutral" and will be available for use in both groups. Detre stated that "PTCA these days is more sophisticated," thus leading to the decision of the investigators to not compare PTCA and bypass, particularly in the target study population of patients with less severe disease, despite the findings of their previous study.

Michael Conte, Boston, MA, reviewed genetic approaches to treating peripheral vascular disease. Vascular gene transfer can, in principle, replace or augment functional genes by delivering a transcriptional unit or use gene blockade with antisense oligonucliotides, with ribozymes to degrade mRNA, or with inhibitors of transcription. Systemic treatment might be applied to disorders of lipid metabolism, coagulation, or other arteriopathies, whereas local treatment could be used for atherosclerosis, restenosis, bypass graft failure, or chronic ischemia of the lower extremities. Multiple aspects of pathophysiology, including thrombosis, ischemia, reperfusion, inflammation, endothelial dysfunction, and smooth muscle cell (SMC) migration, can be targeted. Barriers to gene transfer include the difficulty of efficient delivery leading to integration without causing injury, the need to cause stable and regulable gene expression, and the difficulty of targeting specific cells or tissues, either with ex vivo isolation, purification, and maintenance or with in vivo approaches. Ex vivo approaches can be applied to endothelial cells, SMCs, or cardiac myocytes or perhaps to stem cells or endothelial cell progenitors. Ex vivo gene therapy can be highly reproducible, and seeding itself may have benefits, with control of vector distribution. There are, however, risks of contamination, and a denuding injury to the vasculature is required for reimplantation of vascular cells. Direct in situ treatment can transduce cardiac myocytes, vascular cells, or other tissues. However, the delivery efficiency may be poor, immunity to the delivery vehicle (e.g., an adenovirus) may be a problem, and there is need to minimize injury and to minimize ischemia to tissues perfused by the treated vessel. The atherosclerotic vessel has anatomic barriers, and delivery to deeper layers of the wall may require injury of the endothelium. Bypass grafts are particularly amenable to genetic transduction, with animal studies suggesting that this can be done using these vectors in a stable fashion.

The ideal vector would be safe and efficient and would not elicit a local or systemic response. Nonviral vectors include "naked" (plasmid) DNA, ligand-DNA complexes, and liposomes. Viruses being studied include retroviral derivatives of HIV, which is capable of delivery to replicating cells and is therefore more effective for ex vivo treatment, and adenovirus and adeno-associated virus (AAV). The normal retrovirus life cycle involves a single-stranded RNA surrounded by a capsid and an envelope, attaching to a target cell via specific receptors and converting its RNA via viral reverse transcriptase to DNA, which is then transferred to the nucleus for replication. Modified retroviral particles for gene transfer use "packaging cells" to make "empty" virus particles without viral RNA, to which the RNA to be added is used, while the lack of viral RNA leads to safety and inability to cause infection. Replication-deficient adenoviral vectors can be produced and concentrated to high titer to efficiently infect quiescent cells, such as endothelial cells. However, these do lead to a significance local inflammatory response. AAV vectors being studied are nonpathogenic members of the parvovirus family with single-stranded DNA genome, but production of these vectors is still difficult without a "stable" packaging line. Clinical trials include attempts at therapeutic angiogenesis and restenosis treatment with vascular endothelial growth factor via plasmid delivery and treatment of vein graft failure using a genetic strategy of a "decoy" gene. Vein graft failure is a significant problem in the heart and lower extremities, affecting the majority of patients after 5–10 years. The ideal vector would be safe and efficient at reversing a critical target mechanism of atherosclerosis, such as thrombosis. There are two pathways of vein graft healing, with injury causing neointimal hyperplasia, whereas the more physiological hemodynamic stress leads to medial hypertrophy. By bathing a vein graft in an oligonucleotide-containing solution, the Project of Ex-vivo Vein graft Engineering via Transfection (PREVENT) trial studied gene therapy using a decoy oligodeoxynucleotide, which bound and inactivated the pivotal cell-cycle transcription factor E2F. A total of 41 patients were treated with E2F decoy, a "scrambled DNA" oligonucleotide, or placebo (36). There was no systemic abnormality or complication, and graft failure appeared to occur less frequently with active treatment. Thus, the development of gene therapy approaches appears to be feasible and may be relevant for the treatment of CVD in patients with diabetes.

Stephen Epstein, Washington, DC, discussed the interrelationships among inflammation and atherosclerosis, observing that many patients with atherosclerosis lack known risk factors and that atherosclerosis shows evidence of being an inflammatory disease. Changes within the vessel wall suggesting involvement of immune and inflammatory processes include the presence of T-cells and macrophages and expression of tumor necrosis factor and interferon as well as inflammatory products by cells in the atherosclerotic lesion. Infection may play a role. A large number of studies have shown epidemiological association of chlamydia pneumonia and cytomegalovirus (CMV) seropositivity with vascular disease, with those individuals having both increased C-reactive protein and positive CMV antibodies at particularly increased CAD risk. CMV is a persistent virus like the related herpes viruses. In a study of restenosis lesions, half were found to be CMV positive using polymerase chain reaction and cell culture. To assess whether CMV-seropositive patients undergoing angioplasty had a higher rate of restenosis, a group of patients was studied prospectively, showing ~45 vs. 5% restenosis in the two groups. Using a rat carotid injury model, with infection at and before the time of injury, greater neointimal hyperplasia and carotid stenosis were seen in both models of infection. In ApoE knockout mice, CMV infection is also associated with greater propensity to development of atherosclerotic lesions. Migration of SMC to form the neointima after injury is important in restenosis and in atherosclerosis. CMV infection increases the SMC migration response to platelet-derived growth factor (PDGF), increases the density of PDGF receptors, increases cellular proliferative response to injury, and promotes lipid accumulation, endothelial dysfunction, expression of chemokines, cytokines, and adhesion molecules. The increased inflammation is targeted to both infective agents and their products. Neointima development increases despite the absence of virus in the injured vessel wall, suggesting that infection-induced circulating cytokines potentiate the atherosclerotic process. Indeed, infection leads to persistent elevation in factors, including interleukin-2 and -4, and serum from uninfected cells increases macrophage chemoattractant protein-1 (MCP-1) production by endothelial cells. There is also evidence suggesting an infection-induced autoimmune response involved in atherogenesis, perhaps because certain endothelial peptides are homologous to virally expressed peptides, thereby leading to antibody and cell-mediated autoimmunity. Heat shock proteins (HSPs) are highly conserved intracellular proteins with increased expression and expression on the cell surface when cells are exposed to stressful stimuli, such as inflammation and infection, potentially another cause of autoimmunity. HSP60 antibody titers are associated with increased CVD risk, and HSPs induced by chlamydial infection cause endothelial cell cytotoxicity.

Willa Hsueh, Los Angeles, CA, concluded the symposium with a discussion of the influence of PPAR-γ on vascular function. All major cell types involved in vascular lesion formation (SMCs, endothelial cells, and monocytes/macrophages) express PPAR-γ. Dominant-negative mutations in PPAR-γ in humans are associated with severe insulin resistance, diabetes, and quite severe hypertension, without obesity, suggesting that vascular PPAR-γ is involved in the mediation of vascular tone. In human coronary artery SMCs, the PPAR-γ ligands troglitazone, rosiglitazone, and 15-deoxy prostaglandin-J2 inhibit both fibroblast growth factor–induced proliferation and PDGF-directed SMC migration. Vascular SMC migration involves attachment, locomotion (with phosphorylation and activation of myosin light-chain kinase [cytosolic]), and invasion, requiring induction of MMP production. A variety of chemoattractants and cytokines are involved in this process; all act via mitogen-activated protein kinase (MAPK). PDGF-induced phosphorylation of myosin light-chain kinase is blocked by an inhibitor of MAPK, and PDGF-induced Ets-1 expression is MAPK-dependent and is inhibited by PPAR-γ ligands. PPAR-γ ligands also inhibit MCP-1–directed migration of monocytes via a MAPK-dependent process. This may decrease foam cell formation and the initiation of atherosclerotic lesions. MCP-1 knockout models do indeed appear to show less atherosclerosis development. In atherosclerotic models of LDL receptor knockout mice given a high-fat or high-fructose diet, troglitazone administration decreases the atherosclerotic process by more than half. Evidence of decreased cytokine production and other anti-inflammatory effects of troglitazone have been reported. In an arterial injury model, troglitazone inhibits neointimal proliferation, suggesting an in vivo correlate of the above in vitro observations. Clinical studies using intravascular ultrasound after troglitazone administration to individuals receiving PTCA also suggest inhibition of intimal hyperplasia. A study is being carried out to determine whether rosiglitazone can inhibit stenosis of Gortex graft AV shunts for dialysis access. A2 may mediate many aspects of atherosclerosis, including PAI-1, adhesion factors, the vasoconstrictor endothelin, and MMPs. In the LDL receptor knockout mouse receiving a high-fat diet and given A2 parenterally, there is markedly increased atherosclerosis, with advanced plaques similar to those seen clinically. With rosiglitazone administration in this model, atherosclerosis decreases by ~60%, without improvement in lipid or blood pressure levels, suggesting a nonmetabolic action of the PPAR-γ ligand.

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