Vascular Disease, Hypertension, and Prevention

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The Vascular-Hypertension-Prevention (VHP) track includes data on vascular biology, hypertension, lipids, hormones, thrombosis, and cardiovascular epidemiology and provides insight into the prevention and treatment of coronary heart disease (CHD) and cerebrovascular and peripheral artery disease. On behalf of my colleagues on the Scientific Program Committee, I am privileged to present highlights on VHP from the Scientific Presentations at the Annual Scientific Sessions of the American College of Cardiology (ACC), held in New Orleans in March 2004.

Prevention. LIPIDS. The Thrombolysis In Myocardial Infarction (TIMI)-22 trial was presented by C. P. Cannon and was an international multi-center trial involving 4,162 patients with an acute coronary syndrome (ACS) who were randomized to moderate intensive lipid therapy with 40 mg pravastatin versus high-intensity therapy with 80 mg atorvastatin and followed for two years (1). Median low-density lipoprotein (LDL) cholesterol at baseline was 106 mg/dl in both groups and fell to 95 mg/dl in the pravastatin group and to 62 mg/dl with high-dose atorvastatin. At two years, 1,001 major cardiovascular (CV) events occurred, including all-cause mortality, myocardial infarction (MI), unstable angina, revascularizations, and stroke; there was a significant 16% reduction in major CV events in patients treated with intensive therapy (80 mg atorvastatin), including a 34% event reduction in those with baseline LDL cholesterol >125 mg/dl. A 17% benefit was noted as early as 30 days and became statistically significant by six months. These results challenged the current Adult Treatment Panel (ATP) III lipid guidelines to get LDL <100 mg/dl in patients with CHD and suggest that LDL should be lowered to <80 mg/dl and possibly as low as 60 to 70 mg/dl in patients with ACS.

In other late-breaking clinical trials on lipids, M. Koren presented the Alliance Study, in which 2,442 hyperlipidemic patients with CHD were randomized to atorvastatin to attain an LDL cholesterol <80 mg/dl versus usual care; atorvastatin lowered LDL cholesterol better (~34% vs. −23%, p < 0.0001) and was associated with a 17% reduction in major CV events (p = 0.02). P. S. Sever presented data on diabetes in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA). In the entire ASCOT trial, diabetic patients did not seem to obtain as much benefit as other patients. In 2,532 diabetic patients randomized to 10-mg atorvastatin versus placebo, LDL cholesterol was lowered by 40% with atorvastatin and total CV events were reduced by 23% (p = 0.04), clearly demonstrating the benefits of atorvastatin in diabetic patients (2).

Charakida et al. (3) presented data on 70 children with human immunodeficiency virus (HIV): 28 without antiretroviral treatment, 25 receiving treatment but no protease inhibitors (PIs), and 17 receiving PIs. Total cholesterol was elevated in both treatment groups, but endothelial function, as assessed by flow-mediated dilation (FMD), was only impaired in the PI group. This demonstrates that PIs are associated with both dyslipidemia and endothelial dysfunction. Because of a lack of metabolism by the cytochrome p450 system, pravastatin is theoretically the safest statin to combine with HIV medications (4). In another study of 20 HIV patients treated with PIs, Stein et al. (5) presented on the effects of 40 mg pravastatin versus placebo, demonstrating that pravastatin improves atherogenic lipoprotein fractions and endothelial function in HIV patients taking PIs.

OBESITY. In one of the late-breaking clinical trials, data on the endocannabinoid system was presented by L. Dale and R. Anthenelli, with discussion of rimonabant, a new cannabinoid-1 (CB) receptor antagonist used to aid smoking cessation and weight reduction. This drug was helpful in smoking cessation (28% vs. 15%) and prevented weight gain in these patients. In obesity, rimonabant led to a 20-lb weight loss, >3-inch waist reduction, 25% increase in high-density lipoprotein (HDL) cholesterol, 50% fall in triglycerides, and significant reductions in the metabolic syndrome and C-reactive protein (CRP) of 50% and 27%, respectively. Obesity is certainly not benign in the CV system (6). In addition to the adverse CV effects of obesity, Halcox et al. (7) reported on 418 patients and demonstrated the association of endothelial dysfunction with obesity, independent of CRP, atherosclerosis, and conventional CHD risk factors.

METABOLIC SYNDROME AND DIABETES MELLITUS (DM). Malik et al. (8) reported on 6,451 subjects and demonstrated that the odds of CV disease markedly increased when two metabolic risk factors were present, especially in those with DM. It was shown that CRP was an independent risk factor for CV disease, and CRP increased the risk even in those with DM. Desai et al. (9) reported on 6,142 individuals and demonstrated that the combination of metabolic syndrome and lack of physical activity was associated with an incremental increase in subclinical atherosclerosis, as determined by coronary calcium. Chen et al. (10) examined 1,474 children in the Bogalusa Heart Study with 16-year follow-up and determined that metabolic syndrome risk factors in childhood predicted the metabolic syndrome in adulthood and higher odds of parenteral CHD, hypertension, and DM, as well as increased carotid intimal medial

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thickness in adulthood. Deedwania et al. (11) reported on 811 patients with metabolic syndrome from Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR), who were randomized to various doses of four different statins. Although lipids improved with all agents, rosuvastatin had the most favorable effects on LDL, triglycerides, non-HDL, and HDL in these high-risk patients with the metabolic syndrome.

In 16,203 patients with DM in a registry, Lavasani et al. (12) reported that the use of trililazones (TZDs) and metformin was associated with marked reductions in mortality, as compared with those receiving sulfonylureas or insulin. In a late-breaking clinical trial, EUropean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA), K. M. Fox reported on 1,502 with DM with CHD and no heart failure, who were randomized to 8–mg perindopril versus placebo, and demonstrated a 19% reduction in major CV events with this angiotensin-converting enzyme (ACE) inhibitor in both those with and without DM (the number needed to treat was only 35 in those with DM). Similar to data with ACE inhibitors in Heart Outcomes Prevention Evaluation (HOPE), Yusuf et al. (13) reported on 5,436 patients with HF and without DM from Candesartan cilextil in Heart failure Assessment of Reduction Mortality and morbidity (CHARM) and demonstrated that candesartan, an angiotensin receptor blocker, reduced DM by 12% in those taking an ACE inhibitor and significantly reduced DM by 29% in those not taking an ACE inhibitor.

HORMONES. Currently, hormone replacement therapy has fallen on hard times. Despite benefits on lipids and endothelial function, high-dose estrogen therapy is associated with increased CRP, hypercoagulable states, and increases in major CV events. Koh et al. (14) randomized 57 women to either 0.625 mg or 0.3 mg of conjugated equine estrogen; both groups received 100 mg of micronized progesterone. Both high- and low-dose estrogen had comparable benefits on lipoproteins, FMD, and plasminogen activator inhibitor-1 levels. However, low-dose estrogen therapy did not increase CRP or prothrombin fragments and decreased anti-thrombin III to a lesser extent than did high-dose estrogen.

Malkin et al. (15) assessed 20 men with a testosterone deficiency and CHD and demonstrated that testosterone replacement therapy had modest and insignificant reductions in cholesterol, but significantly reduced inflammatory markers. Because 23% of men with CHD have hypogonadism, they concluded that testosterone replacement may improve CHD as well as quality of life. In 724 dialysis patients followed for two years, Itoh et al. (16) demonstrated that brain natriuretic peptide (BNP) was the strongest independent variable to predict mortality. Van de Werf et al. (17) reported the effects of pexelizumab, a C-5 complement inhibitor, in 3,631 bypass and 1,274 ACS patients treated with reperfusion and demonstrated that pexelizumab reduced mortality by 31% in these CHD patients.

HOLISTIC. The ATP III guidelines stress therapeutic lifestyle changes (TLC) as initial therapy for high-risk patients. Gordon et al. (18) studied TLC in patients with hypertension, hyperlipidemia, and elevated fasting glucose and demonstrated that two-thirds achieved their systolic and diastolic blood pressure (BP) goals, 27% achieved that ATP III LDL goal, and 41% achieved their fasting glucose goal with TLC. These data support the benefits of TLC without medications in preventive cardiology. The American Heart Association has focused on their Get With the Guidelines (GWTG) campaign in patients with CHD. Ellrodt et al. (19) studied data on 160 hospitals and demonstrated that GWTG programs improved quality of care in various age groups studied.

OTHER. Boger et al. (20) and Boger et al. (21) from Germany reported on two studies on asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase. In one study of 408 patients and 408 control subjects, CHD patients had high ADMA, and ADMA was significantly increased with established CHD risk factors and was an independent marker for CHD (20). In a second study of 15 elderly with elevated ADMA, 40 mg simvastatin did not improve endothelial function, but L-arginine, more so in combination with simvastatin, significantly improved endothelial function in these patients (21).

Hypertension (HTN). In 22,576 patients with HTN and CHD in data from the late-breaking clinical trial Internation Verapamil-Trandolapril Study (INVEST), F. H. Messerli evaluated levels of on treatment BP and outcome and demonstrated a J-shaped mortality curve with high events in BP strata >140/90 mm Hg and <110/70 mm Hg (and possibly <120/80 mm Hg). Low diastolic BP was associated with more MI, but not a high risk of stroke. These results increase our awareness of the potential adverse effects of an overzealous reduction in BP in patients with CHD. In 12,763 men from the Seven Country Study, Panagiotakos et al. (22) demonstrated that among all BP measurements, pulse pressure was the strongest predictor of CV mortality, with hazard ratios from 1.06 to 1.17 per 5 mm Hg (p < 0.05).

Two papers were highlighted from the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial (23,24). Wachtell et al. (23) presented data on 9,193 patients followed for five years, and 190 sudden cardiac deaths (SCDs) occurred. Baseline left ventricular hypertrophy (LVH) predicted SCD independent of CHD and other risk factors and remained predictive in patients without obvious atherosclerosis. Both losartan and atenolol protected equally against SCD. Okin et al. (24) looked at 8,254 hypertensive subjects, including 6% African Americans followed for five years, and demonstrated that African Americans had three times more LVH with strain (28% vs. 10%, p < 0.001). In the non-African Americans, LVH with strain was associated with higher event rates, but not in
African Americans. In 529 rural men from the Corfu cohort of the Seven Country Study during 40-year follow-up, Panagiotakos et al. (25) demonstrated that LVH increased the risk of stroke by fivefold (p < 0.001); high levels of fitness were associated with 35% lower risk of stroke (p < 0.05), and high fitness reduced stroke by 24% in those with LVH (p < 0.01). Shengyu et al. (26) presented data on 839 young adults from the Bogalusa Heart Study during a 27-year follow-up period and demonstrated that childhood systolic BP, adult systolic BP and triglycerides, and cumulative systolic BP and triglycerides predicted brachial–ankle pulse-wave velocity, and that childhood systolic BP was a consistent independent predictor of arterial stiffness in adults. Finally, Berman et al. (27) studied 39 patients with HTN and percutaneous renal artery intervention and demonstrated that this therapy reduced QT dispersion by >50% (p < 0.0001), improving ventricular refractoriness to a greater degree than the decrease in BP and LVH would suggest.

Vascular. VENOUS THROMBOSIS AND PULMONARY HYPERTENSION. Giovanni et al. (28) studied 458 patients randomized to control, aspirin for three days, or low-molecular-weight heparin (LMWH) 2 to 3 h before a long flight and found 5.6% deep venous thrombosis (DVT) events in controls, 4.3% in those taking aspirin, and no events in those receiving LMWH, thus demonstrating the potential benefits of one fixed dose of LMWH as an option for high-risk patients during long-haul flights. Kucher et al. (29) reported for the DVT Free Steering Committee on a 183-center U.S. registry of 5,451 consecutive patients (47% men) that demonstrated the men received more DVT prophylaxis than did women (34% vs. 29%, p = 0.001). Although this year’s ACC meeting emphasized heart disease prevention and treatment in women, this study identified a gender bias against women, with failure to administer DVT prophylaxis to high-risk women who subsequently developed DVT.

Pulmonary hypertension has major effects on morbidity and mortality. Lang et al. (30) studied 112 patients with pulmonary hypertension treated with long-term treprostinil, a prostacyclin analog. This therapy improved exercise capacity, reduced symptoms, and significantly improved overall mortality.

OTHER VASCULAR. Kipshidze et al. (31) reported on 23 patients with significant limb ischemia who received either control therapy (saline), intramuscular fibrin, or fibrin plus deferoxamine and added growth factor. Below-the-knee amputation occurred in 70% in the control group, 33% with fibrin, and only 10% with fibrin and growth factor, suggesting that fibrin is a safe and potentially novel method for inducing therapeutic angiogenesis in limb ischemia. In a study of mice treated with or without rosiglitazone, a peroxisome proliferator–activated receptor agonist, Wang et al. (32) demonstrated that rosiglitazone promoted differentiation of bone marrow–derived angiogenic progenitor cells (APCs) toward endothelial lineage, enhanced APC homing to injured vascular sites, and attenuated restenosis with angioplasty. Arterial stiffness was measured in 118 African Americans and 285 Caucasian young adults in the Bogalusa Heart Study, and Chen et al. (33) reported that G894T polymorphism at the endothelial nitric oxide synthase gene locus was associated with lower arterial wall stiffness, independent of BP, and was especially present in the African American cohort. Finally, Kunz et al. (34) studied 122 patients undergoing cardiac catheterization and demonstrated that circulating endothelial progenitor cells predicted the severity of disease in patients with multivessel disease and DM, as well as in post-MI patients.

REFERENCES


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