Vascular Disease, Hypertension, and Prevention

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There were 411 presentations related to vascular disease, hypertension, and prevention during the American College of Cardiology 2006 Scientific Sessions, including the results of the Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID), numerous substudies of the Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) trial, and a number of new trials evaluating risk factors and treatments. These presentations were selected from a total of 1,278 abstracts submitted to the program committee.

CLOPIDOGREL

Just before Labor Day weekend in 2004, former U.S. President Bill Clinton presented with chest pain to a local hospital. Angiography showed extensive multivessel coronary artery disease, but his coronary artery bypass surgery was reportedly delayed several days because he had taken clopidogrel during his initial hospitalization. One of the abstracts from the Scripps Clinic sheds some light on how we may address this clinical scenario in the future.

Drs. Matthew Price and Garrett Wong studied the effects of clopidogrel 75 mg administered daily to 44 volunteers for a mean of 13 days after a loading dose (1). The percent inhibition of platelet aggregation mediated by the P2Y12 receptor was measured by point-of-care testing using the VerifyNow assay (Accumetrics, San Diego, California). Platelet aggregation was measured before the initial dose, 24 h after the last dose, and 4 days thereafter. A substantial proportion of subjects had low platelet inhibition at each time point; but interestingly, at day 5, two of the subjects still had persistent platelet inhibition. Clearly, further study is needed to investigate the utility of point-of-care testing to better identify patients on clopidogrel who can either undergo surgery earlier or who may need to wait even longer before surgical intervention.

In a study using Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction-22 (PROVE IT–TIMI-22) patients, Schweiger et al. (2) sought to determine whether high-dose atorvastatin attenuated the efficacy of clopidogrel, given that both atorvastatin and clopidogrel are metabolized through the cytochrome p450 3A4 system. In this evaluation of 4,161 patients with acute coronary syndrome (ACS), each subject received either high-dose atorvastatin 80 mg daily or standard-dose pravastatin 40 mg daily; 3,038 of 4,161 patients were receiving clopidogrel at study entry, whereas 1,123 were not. At both 30 days and 2 years there was no difference in the incidence of death or myocardial infarction among those on statin therapy when analyzed by the presence or absence of clopidogrel (Table 1). Thus, the combination of high-dose atorvastatin and clopidogrel produced no meaningful interaction or reduction in efficacy of treatment.

The addition of clopidogrel to aspirin has been shown to be more beneficial than aspirin alone in a number of secondary prevention studies. For example, trials evaluating clopidogrel in acute ST-segment elevation myocardial infarction include the Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis In Myocardial Infarction-28 (CLARITY–TIMI-28) trial (3) and the Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study (COMMIT/CCS-2) (4). In ACS patients, available data include the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study (5). In the setting of percutaneous coronary intervention (PCI), we have data from the Clopidogrel for Reduction of Events During Observation (CREDO) study (6).

At ACC.06, the main results were presented from the Clopidogrel for High Atherothrombotic Risk, Ischemic Stabilization, Management, and Avoidance (CHARISMA) study. The trial involved 15,603 patients 45 years old or more who were deemed to be at high risk of atherothrombotic events. All subjects were treated with aspirin, and half were randomized to once-daily clopidogrel 75 mg (7). The primary end point was a composite of myocardial infarction, stroke, or cardiovascular death.

Surprisingly, in the primary prevention group with multiple risk factors, dual-platelet inhibition was associated with a trend toward a higher cardiac event rate than therapy with aspirin alone (6.6% vs. 5.5%, 95% confidence interval 0.91 to 1.59; p = 0.20). Conversely, in the much larger subgroup with a history of atherothrombosis, the event rates were 6.9% in the dual antiplatelet inhibition group and 7.9% in the aspirin-only group (95% confidence interval 0.77 to 0.998; p = 0.046) (8). Further cost-effectiveness analyses are required to identify any subgroup that may benefit from dual-antiplatelet therapy in the secondary prevention setting, aside from the standard scenarios of post-PCI or post-ACS for 9 to 12 months.

THE CAMELOT SUBSTUDIES

The CAMELOT study looked at the effect of amlodipine (10 mg) and enalapril (20 mg) on cardiovascular (CV) events in normotensive coronary artery disease (CAD)

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Abbreviations and Acronyms

ACS	= acute coronary syndrome
ASTEROID	= A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden
CAD	= coronary artery disease
CAMELOT	= Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis
CHARISMA	= Clopidogrel for High Atherothrombotic Risk, Ischemic Stabilization, Management, and Avoidance
CLARITY	= Clopidogrel as Adjunctive Reperfusion Therapy
COMMIT/CCS-2	= Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study
CREDO	= Clopidogrel for Reduction of Events During Observation
CURE	= Clopidogrel in Unstable Angina to Prevent Recurrent Events
CV	= cardiovascular
HDL	= high-density lipoprotein
hsCRP	= high-sensitivity C-reactive protein
IMT	= intima-media thickness
IVUS	= intravascular ultrasound
LDL	= low-density lipoprotein
Lp(a)	= lipoprotein(a)
MACE	= major adverse cardiac events
MESA	= Multi-Ethnic Study of Atherosclerosis
MetS	= metabolic syndrome
NHANES	= National Health And Nutrition Examination Survey
PCI	= percutaneous coronary intervention
PROVE IT–TIMI-22	= Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction-22
PWV	= pulse wave velocity
TAV	= total atheroma volume

a reduction in coronary revascularization and hospitalization from angina. These reductions were not seen with enalapril compared with placebo, despite a similar reduction in blood pressure.

In a post-hoc analysis of CAMELOT study subjects who were treated with any statin, amlodipine was associated with a 44% relative reduction in major adverse cardiac events (MACE) versus placebo (25% vs. 17%; p = 0.002) and a 26% risk reduction versus enalapril (22% vs. 17%; p = 0.03) (10). The investigators concluded that treatment with amlodipine 10 mg for two years reduced the risk of MACE compared with placebo and enalapril in normotensive patients treated with a statin. There was a suggestion of synergy related to the combination of amlodipine and atorvastatin (p = 0.029).

Another study by the same group looked at 363 patients with diabetes mellitus, 822 patients with metabolic syndrome (MetS), and 350 patients with impaired fasting glucose (11). Among patients with diabetes mellitus, amlodipine reduced MACE compared with enalapril (hazard ratio = 0.58; p = 0.04), and the results were similar for patients with MetS; amlodipine reduced the incidence of MACE significantly compared with placebo (hazard ratio = 0.62; p = 0.02) and enalapril (hazard ratio = 0.59; p = 0.008). Amlodipine also reduced CV events in normotensive patients with impaired fasting glucose compared with placebo (Table 2). We do not know whether the results would have been different if the angiotensin-converting enzyme inhibitor enalapril had been given twice per day or perhaps if a more lipophilic angiotensin-converting enzyme inhibitor had been used instead of enalapril.

In an economic analysis of CAMELOT study data, normotensive patients with CAD treated with amlodipine had fewer CV hospitalizations and lower associated costs (12). This seems to address most of the concerns first raised in the mid-1990s regarding short-acting calcium channel blockers, which were associated with higher event rates in patients with acute coronary syndromes; apparently, longer-acting calcium channel blockers are safe and effective in reducing CV events.

The CAMELOT study investigators also looked at the effect of beta-blockers on progression of coronary atherosclerosis using intravascular ultrasound (IVUS), which was performed on a single artery at baseline and after two years of treatment with amlodipine, enalapril, or placebo (13). The change in total atheroma volume (TAV) was compared for those treated with and without beta-blockade, with results adjusted for study treatment, blood pressure, and lipids.

patients (n = 1,991) (9). Treatment with amlodipine was associated with a reduction in the composite end point of CV events compared with placebo; this was largely driven by

Table 1. The PROVE IT–TIMI-22 Trial: Statins With or Without Clopidogrel

Outcome	Atorvastatin/Clopidogrel (n = 1,542)	Atorvastatin/No Clopidogrel (n = 557)	p	Pravastatin/Clopidogrel (n = 1,496)	Pravastatin/No Clopidogrel (n = 566)	p	Interaction p
30-day death/MI	1.1%	1.8%	0.21	1.3%	1.1%	0.70	0.27
2-year death/MI	7.7%	9.9%	0.15	9.7%	10.7%	0.33	0.68

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   MI = myocardial infarction.

Table 2. Effect of Amlodipine and Enalapril on Major Adverse Cardiac Events in Normotensive Patients With Coronary Artery Disease in the CAMELOT Trial

Subgroup/Outcome	Amlodipine Event Rate (%)	Enalapril Event Rate (%)	Placebo Event Rate (%)	Amlodipine vs. Placebo Hazard Ratio	p Value	Amlodipine vs. Enalapril Hazard Ratio	p Value	Enalapril vs. Placebo Hazard Ratio	p Value
Diabetes mellitus (n = 363)	19%	30%	29%	0.62	0.067	0.58	0.043	1.06	0.796
Metabolic syndrome (n = 822)	15%	23%	23%	0.62	0.015	0.59	0.008	1.05	0.779
Impaired fasting glucose (n = 350)	12%	18%	23%	0.47	0.018	0.64	0.192	0.75	0.339

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Beta-blockers were associated with significantly lower progression of TAV (p = 0.03) compared with patients not on beta-blocker therapy who had significantly greater increases in TAV. This observational analysis suggests that beta-blockers may slow CAD progression as part of their cardioprotective effects in the secondary prevention setting.

Another CAMELOT substudy suggests that normal blood pressure (<125 mm Hg systolic) also may slow CAD progression compared with either high normal or high systolic blood pressure (14). Investigators used IVUS of a single artery; progression of coronary disease was measured as the change in TAV. The mean blood pressure in all subjects was 127/76 mm Hg, and the change in TAV was higher in patients with a systolic blood pressure >140 mm Hg (p < 0.001) and in patients with a systolic reading of 125 to 140 mm Hg (p = 0.02). Indeed, although the TAV increased in both of these groups, there was a small decrease in TAV among those with a systolic pressure <125 mm Hg. The results support the epidemiologic evidence that there is a continuous risk reduction with lower blood pressure levels. Thus, in addition to aggressive lipid-lowering therapy, we should also advocate aggressive blood pressure control for our patients with coronary heart disease.

THE ASTEROID TRIAL

The goal of the ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial was to assess whether intensive statin therapy could actually regress coronary atherosclerosis (15). This was a prospective, open-label,
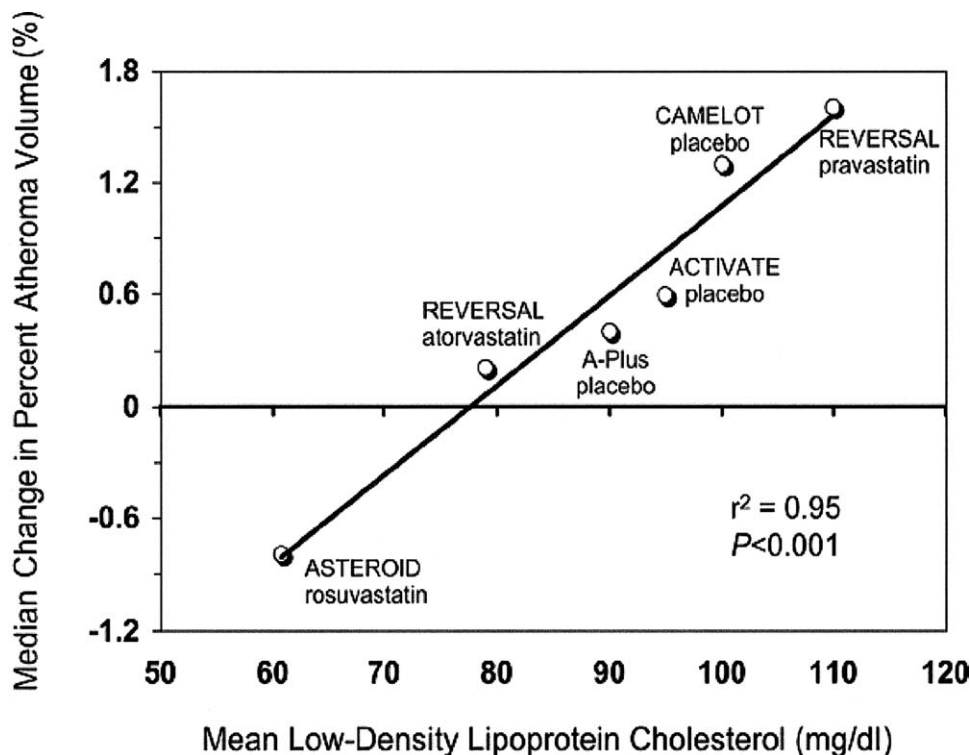

Figure 1. Use relationship between mean low-density lipoprotein cholesterol and median percent atheroma volume in intravascular ultrasound trials. Adapted with permission from JAMA, March 13, 2006 [e pub ahead of print], Copyright © 2006 American Medical Association. All rights reserved.

multicenter, blinded-end-points trial involving motorized IVUS pullback to assess the atheroma burden at baseline and after 24 months. At the end of two years, 349 patients had evaluable serial IVUS studies. All patients received rosuvastatin 40 mg per day with no comparator group. The primary end point included change in percent atheroma volume and change in nominal atheroma volume in a selected 10-mm (most diseased) subsegment of the study artery.

After treatment, a 53% mean reduction in low-density lipoprotein (LDL) cholesterol levels was observed. On-treatment mean LDL decreased from 130 to 61 mg/dl (p < 0.001), with high-density lipoprotein (HDL) cholesterol values increasing 15% from 43 to 49 mg/dl (p < 0.001). After 24 months, the mean change in percent atheroma volume was −1% compared with baseline (p < 0.001). The change in atheroma volume of the most-diseased 10-mm subsegment was −6 mm³ compared with baseline (p < 0.001). Moreover, there was a 7% median reduction compared with baseline in the secondary efficacy measure of change in TAV. Interestingly, the coronary artery lumen cross-sectional area did not change.

Although it may be hypothesized that the increase in HDL was responsible for this regression, the r² value in this analysis was 0.95 (Fig. 1), suggesting that the very low LDL levels achieved alone may account for this modest regression in percent atheroma volume.

METABOLIC SYNDROME

In a study of global risk assessment, investigators at the University of California, Irvine, led by Dr. Nathan D. Wong, used the National Health And Nutrition Examination Survey (NHANES) database to calculate the Framingham risk score for individuals with MetS (16). Among all patients with MetS, one-half were classified at intermediate to high risk for CHD, and one-half were classified at low risk. These low-risk subjects would not qualify for aspirin therapy, and they would not qualify for lipid-lowering therapy unless their LDL level was >160 mg/dl. Of note, among those classified at intermediate to high risk, the majority were men or African American.

The investigators suggested that given the growing recognition of MetS as an indicator of increased CV risk, greater risk assessment using measurements of subclinical atherosclerosis or measurement of high-sensitivity C-reactive protein (hsCRP) may be useful in selected people with MetS to more appropriately target treatment intensity. Although the Framingham risk score classifies many middle-aged people with MetS as low risk, clinicians need to motivate these individuals to improve their lifestyle habits and consider further risk stratification to determine whether they are suitable candidates for aspirin and lipid-lowering therapy.
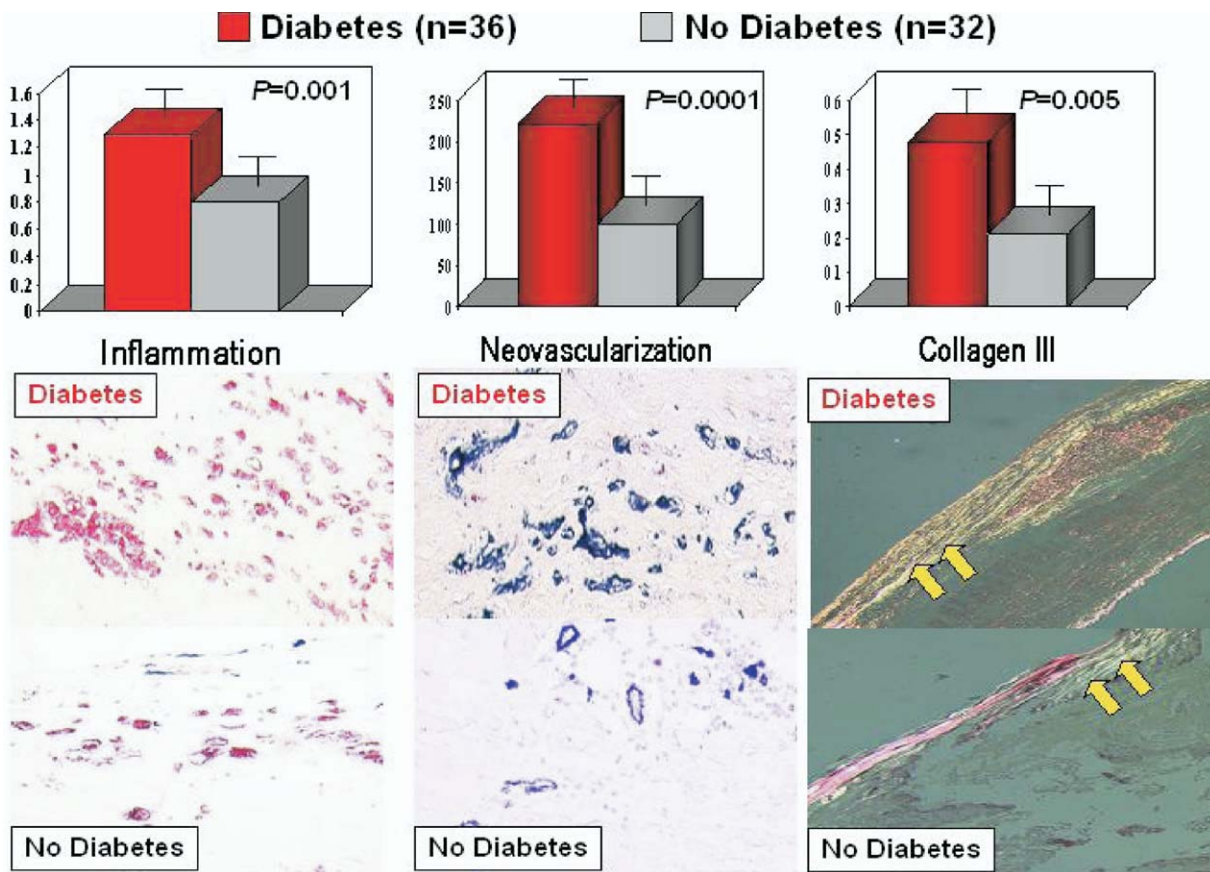

Figure 2. Comparison of diabetic and nondiabetic plaques. Reprinted with permission from Purushothaman et al. (20).

Investigators from Japan evaluated the impact of MetS and diabetes in long-term outcomes after PCI in 748 consecutive patients, who were characterized based on the presence or absence of MetS (17). They found that patients with MetS, but not necessarily with frank diabetes, were at the highest risk (p < 0.0001). Clearly, the presence of MetS at discharge after PCI is an indicator of high risk, and clinicians should place a greater emphasis on improving the dietary and exercise habits of MetS patients, including increased efforts to reduce obesity.

The theme of seemingly high-risk patients not being identified by traditional risk assessment emerged again in the German Heinz Nixdorf Recall study, which is being conducted in parallel to the ongoing Multi-Ethnic Study of Atherosclerosis (MESA) in the U.S. The Heinz Nixdorf Recall study group is a population-based unselected European cohort. The investigators sought to determine how risk assessment may be affected by the extent of inflamed plaque burden, which they defined as a combination of elevated hsCRP and coronary calcium score (Agatston method) (18).

Many clinicians have come to realize that if a woman is younger than 65 years old, it is nearly impossible for her to reach the 10% 10-year Framingham risk score that would make her eligible for aspirin or lipid-lowering therapy (if her LDL-cholesterol is <160 mg/dl). In this analysis, the investigators defined risk as being elevated if the calcium score was >100 and hsCRP was >3 mg/dl, or if the calcium score was >400 and hsCRP was at least 1 mg/dl. They concluded that the extent of subclinical CAD inflammatory activity may be significantly underestimated in selected Framingham low-risk patients. Individuals with a high calcium score and elevated hsCRP levels also tend to have other components of MetS; these patients specifically need more thorough investigation from their physicians, as well as more lifestyle modification, and consideration for earlier institution of aspirin and lipid-lowering therapy.

NOVEL AGENTS/NOVEL RISK FACTORS

Among several ongoing studies considering the effects on cardiac events of thiazolidinediones, a group from Japan reported on their efforts to see whether pioglitazone slowed progression of atherosclerosis by measuring intima-media thickness (IMT) of the common carotid artery and arterial stiffness by the brachial-to-ankle pulse wave velocity (PWV) (19). Both IMT and PWV decreased significantly in patients taking pioglitazone, although the improvement in IMT and PWV did not correlate well with levels of hemoglobin A1c. They concluded that pioglitazone may reduce arterial wall thickness and stiffness in a manner that may be partly independent of glucose lowering.

Cardiovascular researchers from the Mount Sinai School of Medicine hypothesized that sustained injury may induce a reparative process including increased collagen synthesis and accelerated CAD progression in diabetics (20). Inves-

tigators obtained lipid-rich plaques from the aorta at autopsy from those with and without diabetes, and compared levels of inflammation, neovascularization, intraplaque hemorrhage, and reparative collagen. The levels of inflammation, neovascularization, and reparative collagen were increased significantly in plaques taken from patients with diabetes. The levels of type III collagen also were increased in plaques with intraplaque hemorrhage (Fig. 2) and correlated with the total microvessel content. The investigators concluded that increased inflammation and neovascularity in diabetes is associated with a reparative process that is mediated by type III collagen and likely contributes to aggressive plaque progression in diabetes.

Using data from the Women's Health Study, which followed up 27,000 healthy women for 10 years, Suk Danik et al. (21) attempted to assess the future risk of CV events based on baseline lipoprotein(a) [Lp(a)] levels. They found that median levels of Lp(a) and the overall distribution of Lp(a) differed among women in whom CV disease did and did not develop. A median level of 66 mg/dl in the top quintile was associated with a 60% higher likelihood of developing CV disease than those in the first quintile, in which the median level was only 2 mg/dl (p < 0.0001). They concluded that only very high levels of Lp(a) were associated with an increased risk of CV disease in their predominantly Caucasian female cohort.

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