Best of the ACC 2007 Scientific Sessions

Highlights From the American College of Cardiology Scientific Sessions, March 24-27, 2007, New Orleans, LA

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Key words: Valvular disease • Percutaneous coronary intervention • Hypertension • Drug-eluting stents • Atherosclerosis • Hypercholesterolemia • Lipids

This year's meeting of the American College of Cardiology (ACC) presented important new data on a variety of topics. Our board members discuss studies of valvular and adult congenital disease, non-ST elevation myocardial infarction (non-STEMI), percutaneous coronary intervention (PCI) in stable angina patients, acute postoperative hypertension, drug-eluting stents, hypercholesterolemia, coronary atherosclerosis, lipid level management to reduce cardiovascular events, and more.

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Valvular and Adult Congenital Disease

Further Efforts to Understand a Cause for Calcific Aortic Stenosis

In 1999, the Cardiovascular Health Study revealed that the risk of death was increased in patients with echocardiographic aortic valve thickening (aortic sclerosis),[1] a condition found in about 25% of the population, with frank aortic stenosis occurring in 1% to 2% of people older than 65. The risk factors associated with these findings were found to be similar to those observed with coronary artery disease (CAD),[2] and the hunt for the pathophysiology of the calcium deposition in this disease has been on since. Animal models have shown histochemical effects of cholesterol on the valve that result in the expression of bone matrix markers. Oxidative stress, similar to that in atherosclerosis, has been found in valvular tissue, and the signaling mechanism for the deposition of calcium within the valve is under active investigation. Animal models have also suggested that the reduction in cholesterol afforded by statins may even prevent the lesion, although small studies in humans have had mixed results, and it is a hypothesis yet to be proven clinically. One of the concerns is that most studies in humans have tried therapies at a time when the disease

is well established, and the current thought is that intervention earlier in the disease process might be more fruitful.

Several studies at the ACC meeting reported on this continuing effort to define a mechanism for the development of calcific aortic stenosis in hopes of interfering with the process. Since oxidized low-density lipoprotein (LDL) is a known inflammatory factor in atherosclerosis, the group from Laval Hospital in Canada[3] looked at the amount of oxidized LDL and tumor necrosis factor–alpha found in 75 explanted aortic valves and compared the results with associated inflammatory cells in the leaflets and with plasma LDL particles. They found that the level of oxidized LDL content in the valves correlated with the presence of leucocytes, macrophages, and T cells. In addition, the higher the oxidized LDL content in the valves, the more small-molecule LDL (but not total or LDL cholesterol) was present in the plasma. The authors concluded that simply lowering the LDL cholesterol, without reducing the small-size LDL, may not be enough to prevent calcium buildup in the aortic valve.

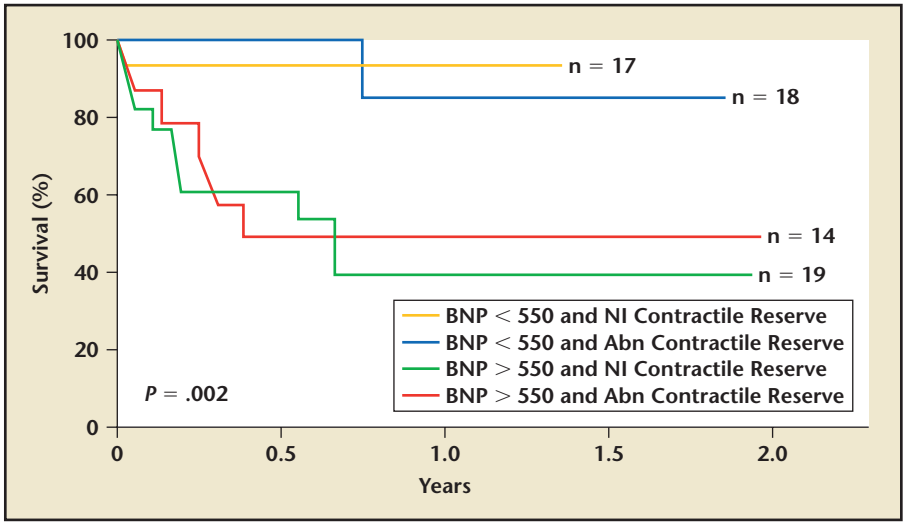
Bicuspid aortic valves also undergo the same calcium deposition. Prior studies have suggested that mutations in the transcription regulator Notch1 gene may cause an early developmental defect in the aortic valve and later a de-repression of calcium deposition that could lead to calcific aortic stenosis. The group led by Nalini Rajamannan, MD, at Northwestern University, compared tissue from 23 bicuspid valve patients versus 20 normal controls from cardiac transplantation for mutations in Notch1.[4] They found that Notch1 was expressed in the bicuspid valves and resulted in a decrease in normal protein expression. Then, in a mouse model, they looked for Notch1 gene expression in the aortic valves of control mice versus cholesterol-fed mice without atorvastatin versus cholesterol-fed mice on atorvastatin. They found that only the cholesterol-fed mice without atorvastatin expressed the Notch1 gene, suggesting it was triggered by high cholesterol but its expression may be prevented by the use of statins.

In another effort to search for a serum protein associated with calcium deposition in aortic stenosis, the level of a potent circulating inhibitor of vascular and soft-tissue calcification, human fetuin-A, was examined in 35 patients and compared to semi-quantitative calcium scores using multislice computed tomography.[5] The authors found that those patients with the lowest amount of human fetuin-A had the highest progression in aortic valve calcium, suggesting a deficiency in this inhibitor of tissue calcification.

Low-Output, Low-Gradient Aortic Stenosis

The decision on whether to operate on patients with aortic stenosis and poor left ventricular (LV) systolic function plus low output presents a continuing challenge. Most patients are given dobutamine or nitroprusside to see if the cardiac outputs can be raised without increasing the valve area before surgical aortic valve replacement (AVR) is considered. Patients who have little improvement in cardiac output or who increase their valve area are generally thought to have more of a cardiomyopathy than severe aortic stenosis and usually do not undergo AVR. In the multicenter Truly or Pseudo-severe Aortic Stenosis (TOPAS) trial, the added value of a serum B-type natriuretic peptide (BNP) on prognosis in these patients was evaluated.[6] Sixty-nine patients with low-output, low-gradient aortic stenosis undergoing dobutamine challenge were followed for an average of 411 days. The results revealed that patients with a BNP above 550 pg/mL had a poor prognosis, regardless of the results of the cardiac reserve assessment or whether the patients went on to AVR or not (Figure 1). The use of BNP as a surrogate for exercise testing in the evaluation of aortic stenosis patients has been ongoing

Figure 1. *Survival in patients with low-gradient, low-output aortic stenosis based on B-natriuretic peptide (BNP) and response to dobutamine testing in the Truly or Pseudo-severe Aortic Stenosis (TOPAS) trial. Adapted with permission from Bergler-Klein J et al.[6] Abn, abnormal.*



for some time now. This study is the first to suggest that high levels of BNP bode such an adverse prognosis in this disease.

Dropout Rates Extraordinarily High in Transitioning Children With Congenital Heart Disease to Adult Cardiology

As the number of patients with adult congenital heart disease continues to balloon, Mackie and colleagues[7] from Montreal provide a sobering snapshot of how poorly we are doing in transitioning these patients from pediatrics to adulthood—even in a system with national health insurance. They looked at Canadian individuals born in 1983 with congenital heart disease who were under a cardiologist's care by age 6 and were alive at age 22 (n = 563). They divided them into 2 groups: patients with complex congenital disease whom one would expect to be alive and eligible for follow-up as an adult, and patients with only an atrial septal defect or ventricular septal defect. They then looked to see if the patients were currently followed as adults by a cardiologist.

The dropout rate for the entire group was a remarkable 72%. Only 56% of the patients with complex disease were being followed, and a paltry 17% in the atrial septal defect/ventricular septal defect group were being followed. The dropout began to occur at quite an early age—between 6 and 12 years.

There are likely many reasons for such a dropout in care, but as there is a growing national movement to develop adult congenital heart disease programs in the United States, it is important to realize that such programs cannot be effective unless there is access and appropriate referral for care. Education regarding the importance of close medical follow-up must start with the parents and caregivers when the patients are at a very young age.

[Thomas M. Bashore, MD, FACC, FAHA]

Ranolazine in Non-STEMI: Results of the MERLIN TIMI-36 Trial

Pharmacological therapy for angina has until recently been confined to beta-blockers, calcium channel blockers, and nitrates, and only beta-blockers have been shown to improve mortality in both stable patients and patients with acute coronary syndromes. Recently, ranolazine, a late Na+ current inhibitor, was approved by the Food and Drug Administration (FDA) as a second-line therapy for the treatment of chronic angina. Ranolazine is a unique agent in that it has few hemodynamic effects but has been shown, in a small percentage of patients, to prolong QT intervals, although without known proarrhythmic effects. The role of ranolazine in acute coronary syndrome, however, has not been established. The Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes Thrombosis in Myocardial Infarction–36 (MERLIN TIMI-36) trial was a large, multicenter, randomized trial of 6560 patients with non-STEMI.[8] The study results were presented at the ACC meeting by David Morrow, MD, from the TIMI group. Patients were started on standard care and randomized to ranolazine or placebo. The drug was initially given intravenously for up to 96 hours and then orally (1000 mg twice daily) for 12 months. The primary endpoint was cardiovascular death, myocardial infarction (MI), or recurrent ischemia.

The study demonstrated no significant difference between the groups, with the primary endpoint occurring in 23.5% of the placebo group and 21.8% of the ranolazine group (hazard ratio [HR] .92; $P = .11$) (Figure 2). In addition, no significant differences were seen in the endpoint of cardiovascular death and MI (10.5% with placebo vs 10.4% with ranolazine) or in recurrent ischemia (16.1% with placebo vs 13.9% with ranolazine). The main safety endpoints were death, sudden death, symptomatic arrhythmias, and

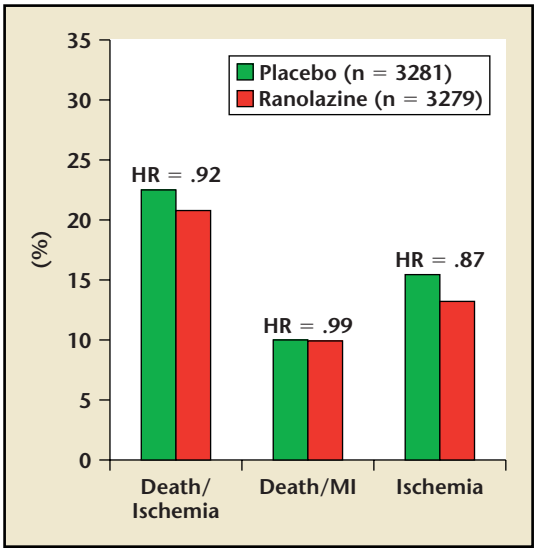


Figure 2. *The MERLIN TIMI-36 results demonstrated no difference in the primary endpoint of cardiovascular death or MI, or in the secondary endpoints of death and MI and recurrent ischemia. MI, myocardial infarction; HR, hazard ratio; MERLIN TIMI-36, Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes Thrombosis in Myocardial Infarction–36. Adapted with permission from Morrow DA et al.*[8]

significant arrhythmias on Holter monitoring. Although there was no difference in mortality, sudden cardiac death, or symptomatic arrhythmias, there was a significantly lower incidence of significant arrhythmias on Holter monitoring (83.1% with placebo vs 73.1% with ranolazine; HR 0.89; $P < .001$). Significant arrhythmias were defined as ventricular tachycardia exceeding 3 beats, supraventricular tachycardia exceeding 12 beats per minute, new atrial fibrillation, bradycardia less than 45 beats per minute, complete heart block, or pauses exceeding 2.5 seconds.

The findings are disappointing but reassuring. The lack of further relief with ischemia contrasts with the results of prior trials in stable angina. The Combination Assessment of Ranolazine In Stable Angina (CARISA) trial showed a 36% decrease in angina with 1000 mg bid of ranolazine in patients with stable angina.[9] This disparity may be due to the difference in mechanisms that are responsible for recurrent ischemia in patients with acute coronary syndrome as compared with stable angina, in which plaque rupture and thrombosis play a major role. The lack of an effect on mortality and recurrent MI is consistent with the prior trials, but it is also disappointing, even though this result is not unlike that of other antianginal agents, such as calcium channel blockers and nitrates.

The effect on arrhythmias is interesting and potentially important. Myocardial ischemia is known to increase late Na channel influx, which can lead to sodium and, thus, calcium overload. Calcium overload results in LV dysfunction and increased electrical instability. Ranolazine might be expected to have antiarrhythmic effects as a result. The prolongation of QT, however, might be expected to increase torsade de pointes. This result was not seen in prior studies or in the MERLIN trial. The reduction of arrhythmias on Holter is suggestive of an antiarrhythmic effect, but the study did not show any reduction in symptomatic arrhythmias or sudden death. The findings provide reassurance that the drug is safe in the setting of acute coronary syndrome, and the study will undoubtedly increase use of ranolazine in patients with stable angina. The role of ranolazine in patients with acute coronary syndrome is less certain given the results of this trial, however, so the drug should probably be reserved for patients who demonstrate chronic angina following the unstable event.

The Use of PCI in Stable Angina Patients Is More Clearly Defined by the COURAGE Trial

The ACC/American Heart Association (AHA) guidelines for stable angina recommend that patients be initially treated with intensive medical therapy, reduction of risk factors, and lifestyle modification.[10] Patients who continue to be symptomatic or who have high-risk features on noninvasive testing should be considered for cardiac catheterization and revascularization. The type of revascularization (PCI or coronary artery bypass graft [CABG]) does not appear to have an impact on long-term mortality, except in patients with diabetes—although this finding has been debated as well. With the growth of angioplasty, more patients are now offered PCI prior to or concomitant with intensive medical therapy, based upon the belief that treatment of high-grade stenosis will affect long-term mortality and morbidity. Until now, this approach has not been tested against modern medical therapy.

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial is a multicenter, randomized trial comparing intensive medical therapy versus intensive medical therapy and PCI. The study was presented at the ACC meeting by William Boden, MD,[11] and simultaneously published in *The New England Journal of Medicine*.[12] The 2287 patients were randomized at 50 US and Canadian centers, of which 40% were veterans affairs centers. Patients with stable CAD, at least a 70% stenosis, and objective evidence of myocardial ischemia (unless they had classic angina and $> 80\%$ stenosis) were randomized. More than 35,000 patients were screened.

More than 40% of the patients had no or mild angina, but more than 65% had multiple perfusion defects. On angiography, two thirds had multivessel disease. Intensive medical therapy including aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, and statins effectively reduced risk factors and improved angina. The primary endpoint was death and nonfatal MI, and the secondary endpoints included death, MI, stroke, and hospitalization for unstable angina. The trial was sized to determine a 22% relative difference in the primary endpoint at an average of 3 years.

The study demonstrated that there was no difference in the primary endpoint, which occurred in 19% of the PCI group and 18.5% of the medical group at 4.6 years (Figure 3). There were no differences in the secondary endpoints as well. The PCI group did have better relief of angina for most of the study period, but at 5 years the groups had an equal percentage of patients who were asymptomatic (74% in the PCI group vs 72% in the medical group) (Figure 4). However, one third of the patients in the

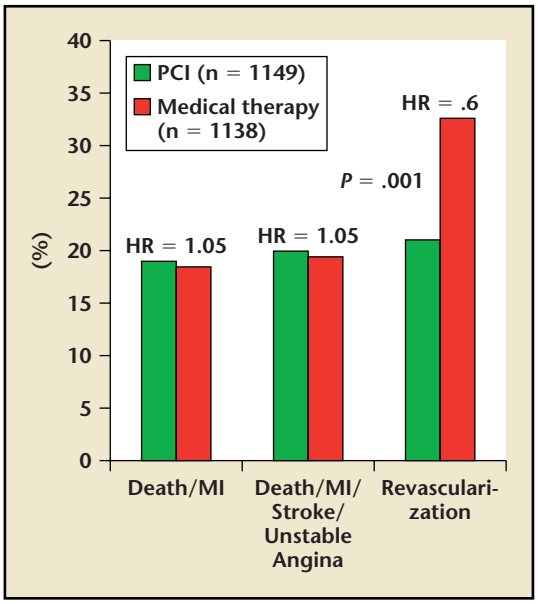


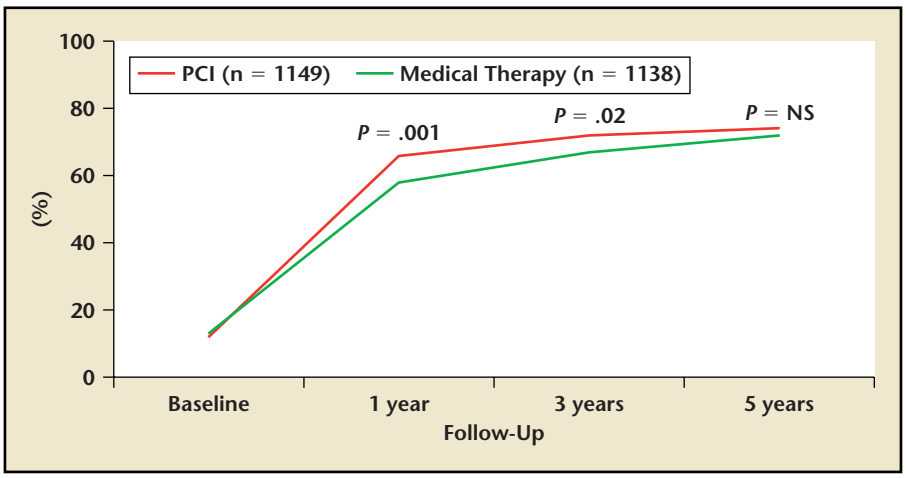
Figure 3. *The COURAGE trial compared intensive medical therapy with and without PCI.[11,12] The primary endpoint of death and MI was not different, nor was the secondary endpoint of death, MI, stroke, and re-hospitalization for unstable angina. Revascularization was significantly less in the PCI group. PCI, percutaneous coronary intervention; HR, hazard ratio; MI, myocardial infarction; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation.*

medical group crossed over and received a revascularization procedure.

The results of the study are not surprising. They are consistent with prior studies that have demonstrated that PCI relieves angina but does not reduce death or MI in patients with stable CAD who do not have some high-risk markers or severe CAD, such as left main or 3-vessel disease and reduced LV function. The impact of intensive medical therapy in this study was impressive. Although blood pressure and cholesterol were dramatically reduced, other risk factors such as weight reduction and cigarette smoking were not. The trial must be interpreted with caution, however, because the eligible patients represented only 8.6% of all the patients screened, which raises concerns about the applicability of the study to the larger group of patients with CAD. In addition, the group was relatively asymptomatic, with more than 40% of the patients either asymptomatic or in class I.

Studies starting in the 1980s have established that PCI is primarily useful in reducing angina and myocardial ischemia. Although this trial did demonstrate that ischemia was reduced with PCI, the reduction was modest and not different at 5 years. This finding is likely due to the mild angina at baseline and the need for revascularization in one third of the patients in the medical group. In addition, the study was done prior to the use of drug-eluting stents (DES), which have been shown to reduce restenosis and the subsequent need for revascularization. It is likely that if DES had been used, a larger difference in symptom relief and a lower need for repeat revascularization would have resulted. Older studies have demonstrated that PCI does not reduce mortality compared with medical therapy, and, unfortunately, the findings of this study do not help us understand the issue any further. In contrast, coronary artery bypass surgery has been shown to reduce mortality, but in a meta-analysis it prolonged life only in patients with 3-vessel disease or left main disease. In the Bypass Angioplasty Revascularization Investigation (BARI) trial, PCI with balloon angioplasty was comparable with CABG over 7 years, except in patients with diabetes.[13] This finding would suggest that in patients with severe CAD, either revascularization strategy would be expected to prolong life. Why then didn't the COURAGE trial show a survival benefit? The explanation could be that medical therapy is now so effective that these prior studies are obsolete. Alternatively, high-risk

Figure 4. *In the COURAGE trial, the percentage of patients who were free of angina rose in both the PCI and the intensive medical therapy groups, but the percentage was higher in the PCI group at 1 and 3 years.[11,12] It was not different at 5 years. PCI, percutaneous coronary intervention; NS, not significant; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation.*



subgroups such as patients with 3-vessel disease and reduced LV function were under-represented in this trial. One of the exclusion criteria in this study was an ejection fraction of less than 30%, and very few patients had an ejection fraction under 50%. It is likely that the subgroup with 3-vessel disease and low ejection fraction was too small to determine the effect of PCI on mortality.

The study will have an impact, however, since it confirms that PCI does not prolong life in many patients and that intensive medical therapy is effective in relieving symptoms and improving risk factors. Initial therapy for patients with stable angina or ischemia should be medical therapy, except in those with very severe disease or high-risk markers, and this trial supports the recommendations of the guidelines in this regard. [David P. Faxon, MD, FACC, FAHA]

Acute Postoperative Hypertension

The results of the Evaluation of Clevidipine in the Perioperative Treatment of Hypertension Assessing Safety Events (ECLIPSE) trials evaluating the efficacy of intravenous clevidipine compared with intravenous nitroglycerin, nitroprusside, or nicardipine for the treatment of perioperative hypertension were presented by Solomon Aronson, MD, from the Duke University Health System in Durham, NC.[14] Clevidipine is a dihydropyridine calcium antagonist with a half-life of about 1 minute, making it suitable for rapid up and down titration. The primary endpoint of the trial was the cumulative incidence of death, MI, stroke, and renal dysfunction within 30 days. Secondary endpoints included serious adverse events through day 7 and blood pressure control during the first 24 hours of the infusions.

Clevidipine was found to be a safe and effective alternative to therapy with other intravenous agents for the treatment of acute postoperative hypertension (Figure 5).

Distal Protection in PCI

The goal of the Randomized Comparison of the Effect of Distal Protection and Drug Eluting Stent Versus Bare Metal Stent Implantation During Percutaneous Coronary Intervention For ST-elevation Myocardial Infarction (DEDICATION) trial was to determine the utility of the FilterWire® (Boston Scientific, Natick, MA) distal protection device compared with conventional PCI without distal protection in patients presenting with ST elevation MI.[15] The 616 patients were randomized to either FilterWire or conventional PCI. Most of the patients (96%) were treated with glycoprotein (GP) IIb/IIIa inhibitors. The primary endpoint was ST resolution through 90 minutes post-PCI. Of the patients randomized to the FilterWire cohort, only 81% had successful placement of the device.

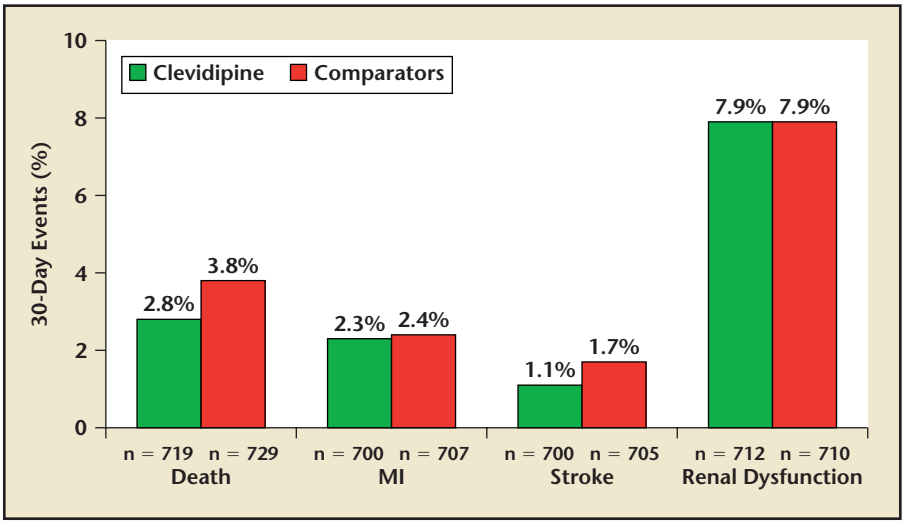
There was no significant difference in the endpoint of ST resolution at or greater than 70% through 90 minutes post-PCI between the FilterWire cohort and the conventional PCI group (76% vs 72%; $P = .29$). There was a significant improvement in TIMI III flow at the completion of the procedure in the FilterWire group versus the conventional PCI group (95% vs 88%; $P = .01$), but no difference in peak creatine kinase MB release or 30-day major adverse cardiac event rates.

In contrast to the FilterWire's utility in PCI of saphenous vein grafts, there was no significant improvement with the use of the FilterWire in the outcomes of patients presenting with STEMI treated with PCI (Figure 6).

Treatment of Chronic Decompensated Heart Failure

The Follow-Up Serial Infusions of Nesiritide for the Management of Patients with Heart Failure (FUSION II) trial evaluated the ability of serial outpatient treatment with nesiritide compared with placebo in patients with chronic decompensated heart failure.[16] Patients were randomized to serial outpatient nesiritide once or

Figure 5. *In the ECLIPSE trial,[14] clevidipine was found to be safe and effective for the treatment of acute postoperative hypertension. MI, myocardial infarction; ECLIPSE, Evaluation of Clevidipine in the Perioperative Treatment of Hypertension Assessing Safety Events. Adapted with permission from Cardiosource.*



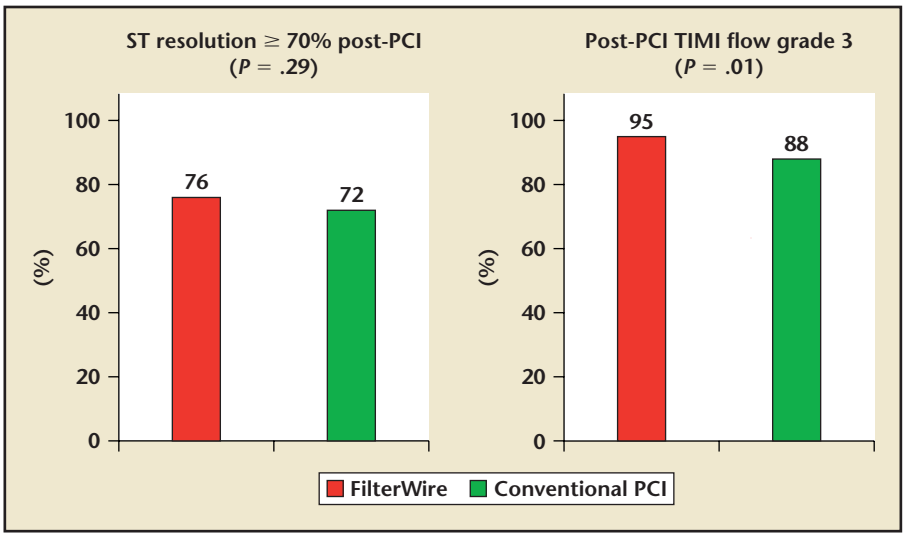


Figure 6. *In the DEDICATION trial, there was no significant improvement with the use of a distal protection device as compared to conventional PCI.[15] PCI, percutaneous coronary intervention; TIMI, Thrombosis in Myocardial Infarction; DEDICATION, Randomized Comparison of the Effect of Distal Protection and Drug Eluting Stent Versus Bare Metal Stent Implantation During Percutaneous Coronary Intervention for ST-elevation Myocardial Infarction. Adapted with permission from Cardiosource.*

twice weekly (2 μ/kg bolus and 0.01 μ/kg/min infusion for 4 to 6 hours; n = 605) or placebo (n = 306) for 12 weeks. All patients were also treated with standard heart failure therapy at the discretion of the treating physician. At study entry, 47% of patients were New York Heart Association (NYHA) III and 53% were class IV. The average left ventricular ejection fraction (LVEF) was 25%.

There was no difference in the primary endpoint of all-cause death or cardiovascular or renal hospitalization between groups (36.7% for nesiritide vs 36.8% for placebo; P = .79). Among the individual components of the composite endpoint, there was no difference in mortality (9.5% vs 9.6%; P = 0.98) or cardiovascular or renal hospitalizations (32.9% vs 33.9%; P = 0.95). Frequency of increase in serum creatinine of more than 0.5 mg/dL was lower with nesiritide than placebo (32% vs 39%; $P < .05$).

Although this trial failed to show a significant benefit of nesiritide in patients with chronic decompensated heart failure, it does shed light on the safety of nesiritide, particularly in regard to its effect on mortality and renal function. The lack of a detrimental effect on mortality and an actual reduction of renal dysfunction in this randomized trial should allay many of the concerns about nesiritide raised by a previous meta-analysis.

Drug-Eluting Stents

The goal of the randomized SPIRIT III trial was to evaluate treatment with an everolimus-eluting stent (EES) compared with a paclitaxel-eluting stent (PES) among 1002 patients undergoing elective PCI for de novo coronary lesions.[17] Intravascular ultrasound (IVUS) was also performed in 240 patients.

The primary endpoint of in-segment late lumen loss at 8 months was less in the EES group than in the PES group (0.14 mm vs 0.28 mm; $P < .001$ for noninferiority and P = .004 for superiority). Binary in-segment restenosis was observed in 4.7% of the EES group and 8.9% of the PES group (P = .07). IVUS analysis showed neointimal hyperplasia volume of 10.1 in the EES group and 20.9 in the PES group. There was no significant difference in the major secondary endpoint of target vessel failure (cardiac death, MI, or target vessel revascularization) at 9 months. (It occurred in 7.2% of the EES group and 9.0% of the PES group; $P < .001$ for noninferiority and P = .31 for superiority). Target lesion revascularization at 9 months occurred in 2.6% of the EES group and 5.0% of the PES group (P = .053). Stent thrombosis through 9 months occurred in 0.5% of the EES group and in no patients in the PES group. Among patients undergoing elective PCI for de novo lesions, treatment with the EES was associated with a reduction in late lumen loss compared with treatment with the PES at 8-month angiographic follow-up (Figure 7).

Hypertensive Therapy

The Aliskiren and Valsartan for Antihypertensive Therapy trial evaluated the efficacy of the combination of the recently FDA-approved direct renin inhibitor aliskiren added to the angiotensin receptor blocker valsartan.[18] Following a 1- to 2-week period of washout from prior hypertensive therapy and a run-in period of 3 to 4 weeks, patients were randomized in a double-blind manner to aliskiren (150 mg; n = 437), valsartan (160 mg; n = 455), the combination of the 2 (n = 446), or placebo (n = 459). Treatment was to continue for 4 weeks, at which time the doses were doubled for the following 4 weeks. Blood pressure was evaluated at baseline, 4 weeks, and 8 weeks.

Mean blood pressure at baseline was 154/100 mm Hg. At 8-week follow-up, diastolic blood pressure declined by 4.1 mm Hg in the placebo group, 9.0 mm Hg in the aliskiren group, 9.7 mm Hg in the valsartan

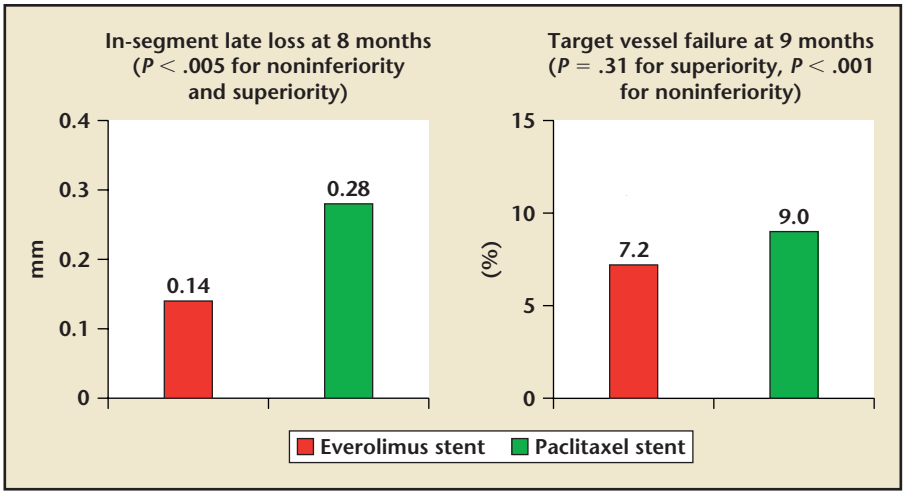


Figure 7. *In the SPIRIT III trial, treatment with an everolimus stent was associated with a reduction in late lumen loss as compared with a paclitaxel stent.[17] Adapted with permission from Cardiosource.*

group, and 12.2 mm Hg in the combination group ($P < .001$ for combination vs placebo and for combination vs each treatment individually). Systolic blood pressure declined by 4.6 mm Hg in the placebo group, 13.0 mm Hg in the aliskiren group, 12.8 mm Hg in the valsartan group, and 17.2 mm Hg in the combination group ($P < .001$ for combination vs placebo and for combination vs each treatment individually). Blood pressure response rate was highest in the combination group (65.8% vs 19.9% for placebo, 53.5% for aliskiren, and 55.2% for valsartan; $P < .05$ for combination vs placebo and for combination vs each treatment individually), as was blood pressure control (49.3% vs 16.5% for placebo, 37.4% for aliskiren, and 33.8% for valsartan) (Figure 8).

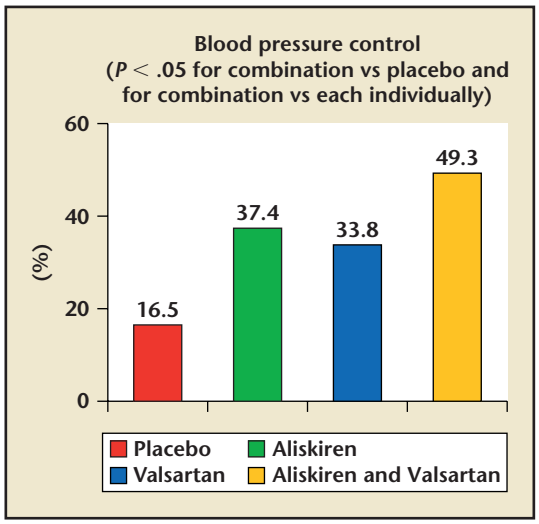
The addition of the angiotensin receptor blocker valsartan to the direct renin inhibitor aliskiren does lead to greater reductions in blood pressure and greater blood pressure than either drug alone.

ACUITY at 1 Year

The Acute Catheterization and Urgent Intervention Triage Strategy Trial (ACUITY) compared heparin plus GP IIb/IIIa inhibition (control) versus bivalirudin with or without GP IIb/IIIa inhibition.[19] A total of 13,819 patients were randomized to unfractionated heparin or enoxaparin plus a GP IIb/IIIa inhibitor (n = 4603), bivalirudin plus a GP IIb/IIIa inhibitor (n = 4604), or bivalirudin alone (n = 4612). At 30 days, bivalirudin plus a GP IIb/IIIa inhibitor versus heparin plus a GP IIb/IIIa inhibitor was noninferior in each of the primary endpoints. Bivalirudin alone, as compared with heparin plus GP IIb/IIIa inhibitors, was noninferior in terms of the composite ischemia endpoint, plus it significantly reduced rates of major bleeding ($P < .001$) and the net clinical outcome endpoint ($P = .02$). At 1 year, approximately 98% of all ACUITY patients were available for follow-up. There was no significant difference among the arms in terms of the composite ischemia endpoint or the rate of stent thrombosis. Although there was no change in 1-year all-cause mortality, the trend was in favor of bivalirudin (Figure 9).

An interesting finding in the 1-year analysis of ACUITY was the impact of major bleeding during the first 30 days of follow-up on 1-year mortality. Patients with major bleeding had more than 3 times the mortality risk of patients who did not have a major bleed or MI (Figure 10). In addition, the occurrence of a major bleed in those patients who suffered an MI during the first 30-day follow-up experienced a tripling of mortality risk as compared with those patients who suffered an MI without the occurrence of a major bleed. The association of bleeding and mortality risk in patients undergoing

Figure 8. *The trial on Aliskiren and Valsartan for Antihypertensive Therapy showed that in patients with mild to moderate hypertension, aliskiren, valsartan, and the combination were associated with greater reductions in blood pressure as compared with placebo.[18] Adapted with permission from Cardiosource.*



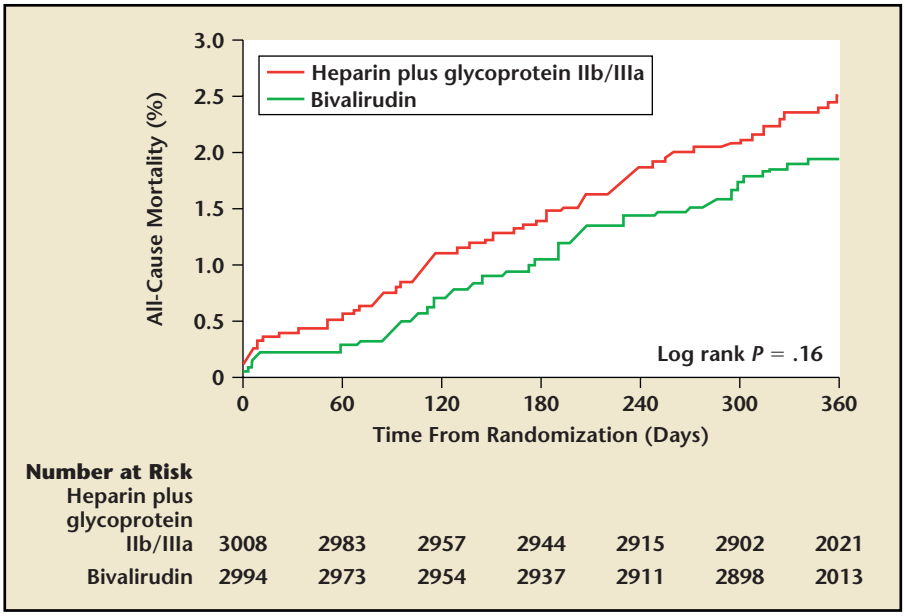


Figure 9. *Cumulative incidence of 1-year all-cause mortality in the ACUITY trial. ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy Trial. Reprinted with permission from Stone GW.*[19]

PCI has been a persistent finding of a variety of clinical trials. This risk has been attributed to a range of possible factors, including the adverse effects of transfusions and the need to discontinue antiplatelet therapy in patients until the bleeding has resolved.

[Norman E. Lepor, MD, FACC, FAHA, FSCAI]

Effects of a PPAR–Alpha Agonist in Patients With Atherogenic Dyslipidemia or Hypercholesterolemia

In a 12-week, placebo-controlled, randomized, double-blind study involving a total of 309 patients, Nissen and colleagues[20] evaluated the effects of a novel peroxisome proliferator-activated receptor (PPAR) alpha agonist, LY518674, which is nearly 10,000 times more potent than fenofibrate as a PPAR alpha agonist. The drug was evaluated at various doses (10 µg/d, 25 µg/d, 50 µg/d, and 100 µg/d) compared with placebo and fenofibrate (200 mg/d). The study examined effects on dyslipidemia and hypercholesterolemia.

Dyslipidemia

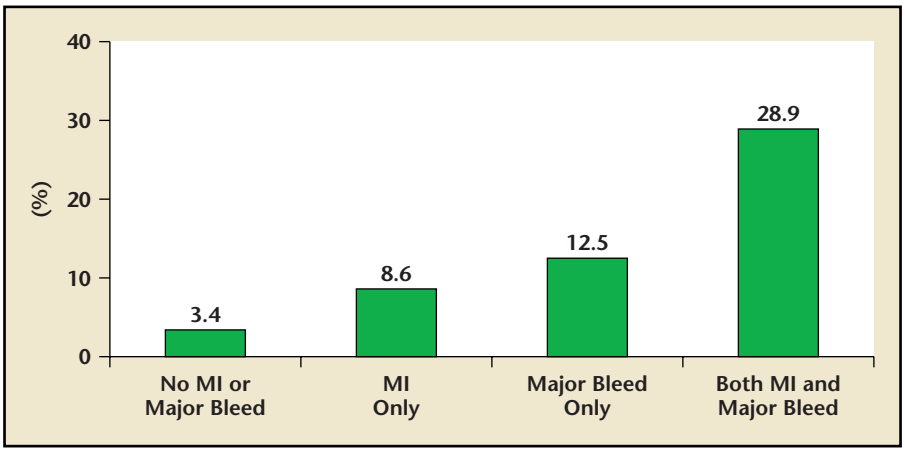
Atherogenic dyslipidemia is characterized by a cluster of risk factors that include elevated levels of triglycerides and small, dense LDL particles, and reduced levels of high-density lipoprotein (HDL) cholesterol. Fenofibrate and gemfibrozil are 2 fibric acid derivatives that are commonly used to treat this form of dyslipidemia.

LY518674 and fenofibrate produced comparable increases in HDL cholesterol (15.8% and 14.4%, respectively) and comparable reductions in triglycerides (34.9% and 41.7%, respectively). However, unlike fenofibrate, LY518674 produced a dose-dependent increase in LDL cholesterol (19.5% at the highest dose), whereas fenofibrate did not significantly change LDL cholesterol levels. In both groups, 37% to 38% of patients had serum creatinine levels increase above the normal range. Fenofibrate, but not LY518674, increased serum creatine phosphokinase levels.

Hypercholesterolemia

This study included subjects with LDL cholesterol levels of 100 mg/dL to 160 mg/dL on statins or 130 mg/dL to 190 mg/dL without statins. Following a 4- to 6-week washout period, patients were entered into a 4-week active treatment period during which they were randomized to receive placebo or atorvastatin 10 mg or 40 mg. These groups were subsequently stratified

Figure 10. *Impact of MI and major bleeding (non-CABG) in the first 30 days on risk of death over 1 year in ACUITY. MI, myocardial infarction; CABG, coronary artery bypass graft; ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy Trial. Reprinted with permission from Stone GW.*[19]



into patients with an LDL cholesterol level below or above 160 mg/dL. The patients were enrolled into a 12-week active treatment period, during which those within each of the previous treatment groups were randomized to receive placebo or LY518674 at 10 μg/d or 50 μg/d.

Both doses of LY518674 reduced triglycerides by about 37%, reduced LDL cholesterol by 13.2% to 15.8%, and increased HDL cholesterol by 12.5% to 15%. When added to atorvastatin, LY518674 produced minimal additional change in HDL cholesterol (−0.6% to +11.9%) and had no additional effect on LDL cholesterol; triglyceride levels were significantly reduced by 20.4% to 42%. Increases in alanine aminotransferase (ALT) levels above 1.5 to 3 times the upper limit of normal were observed in 16.7% of patients receiving atorvastatin 40 plus LY518674 50 μg/d.

Comments

Thus, despite the substantially greater PPAR alpha-agonist activity of LY518674 as compared with fenofibrate, the novel PPAR alpha agonist did not show superiority over fenofibrate in terms of triglyceride reduction and HDL cholesterol elevation. It had worse effects on LDL cholesterol levels. Both agents raised safety concerns with respect to renal function. Although clinical outcomes were not evaluated in this trial, previous studies of fibric acid derivatives have shown inconsistent results. Nuclear hormone receptors, such as PPAR alpha, PPAR gamma, and PPAR delta, play an important role in lipid and glucose metabolism. Many agonists that activate various PPARs singly or in combination have been previously evaluated and most have been discarded (except for glitazones, which act as PPAR gamma agonists) because of toxicity involving the muscles, heart, and liver, and oncogenic potential. These 2 studies add to the body of evidence that activation of PPARs for therapeutic benefit remains an unfulfilled promise.

Effect of Reconstituted HDL Infusions on Coronary Atherosclerosis

Preclinical experimental studies from Cedars-Sinai Medical Center (Los Angeles, CA) and the University of Milan in Italy, followed by a pilot phase II clinical trial from the Cleveland Clinic in Ohio, have shown that short-term infusions of recombinant HDL containing apolipoprotein (Apo) A-Imilano (ETC-216), a naturally occurring mutant, rapidly regress atherosclerosis. Two studies at the ACC provided new data.

A Different Form of HDL

Tardif and colleagues[21] used a different form of HDL: human plasma–derived wild type Apo A-I linked to the soybean phosphatidylcholine carrier (molar ratio of 1:150) (CSL-111). The study enrolled 183 patients who were within 2 weeks of admission for acute coronary syndrome and in whom coronary angiography showed at least 1 segment with narrowing of 20% or more. Patients were randomized to receive 4 weekly infusions of volume-matched placebo (n = 60) or HDL (40 mg/kg [n = 111] or 80 mg/kg [n = 12]). Before infusion, a baseline IVUS of the designated unintervened target coronary artery was performed. The procedure was repeated 2 to 3 weeks after the last infusion. Quantitative coronary angiography was also performed at baseline and during follow-up. The primary efficacy was assessed by the percent change (from baseline to follow-up) in atheroma volume as measured by IVUS. Secondary endpoints included absolute change in atheroma volume, the change in plaque composition as assessed by IVUS, and change in angiographic coronary score (as defined by per patient mean of the minimal lumen diameter for all lesions measured).

A total of 145 patients remained in the study (47 in the placebo group, 9 in the HDL 80 mg/kg group, and 89 in the HDL 40 mg/kg group). After a planned interim analysis, the 80 mg/kg dose was abandoned because of significant liver function test abnormalities, and the patients in this group were assigned to placebo or HDL 40 mg/kg until the original target number of patients was reached.

Patients in the HDL group experienced a −3.4% change in atheroma volume (Table 1). The absolute change in atheroma volume was −5.3 mm^3. Other secondary endpoints, such as plaque characterization indexes on qualitative IVUS and stenosis by angiography, showed small but favorable changes in the HDL group.

Adverse Events. Liver function test abnormalities, in general transient and reversible, were common in the HDL group and, to a lesser extent, in the placebo group. However, none resulted in clinical adverse outcomes. Hypotension was noted in 13.8% of HDL patients versus 7.1% of placebo patients. Marked liver function test abnormalities, including a case of a 100-fold increase in ALT levels, were noted in the HDL 80 mg/kg group.

Comments. This interesting study attempted to duplicate the results of the Apo A-I milano infusion study (with 4 infusions rather than 5). However, the results were mixed and somewhat inconclusive. The primary endpoint of the study was negative, but secondary endpoints suggest a potential benefit in terms of possible rapid coronary plaque regression and change in plaque composition with human plasma–derived wild-type Apo A-I linked to a phospholipid

Table 1
Effects of Short-term Infusions of Recombinant HDL

	Percent Change in Atheroma Volume* (*P* Value)	Absolute Change in Atheroma Volume† (*P* Value)
Placebo	−1.6	−2.3 mm^3
	(*P* = .07 [baseline vs follow-up])	(*P* = .04 [baseline vs follow-up])
HDL 40	−3.4	−5.3 mm^3
	(*P* = .48 [HDL vs placebo])	(*P* = .39 [HDL vs placebo])
	(*P* = < .001 [baseline vs follow-up])	(*P* = < .001 [baseline vs follow-up])

*Primary endpoint.
†Secondary endpoint.
HDL, high-density lipoprotein. Data from Tardif JC.[21]

carrier. Concerns include the product's human plasma origin, side effects such as liver function abnormalities (especially at higher doses), and the potential efficacy, especially in comparison with the recombinant Apo A-I milano containing HDL (ETC 216). Larger studies, possibly with longer periods of treatment and observation, may be necessary to validate this approach.

Recombinant Apo A-I Milano

Ibanez and colleagues[22] also presented data on whether short-term infusions of a recombinant HDL containing Apo A-I milano (ETC-216) could rapidly regress atherosclerosis. The study subjects were 3-month-old New Zealand white rabbits fed a high-cholesterol diet, which underwent double balloon injury to the aorta to accelerate plaque formation. When the rabbits reached 36 weeks of age, magnetic resonance imaging of the abdominal aorta was performed to quantitate the size of the abdominal aortic plaque. The rabbits received 2 weekly injections of either placebo or recombinant Apo A-I milano (ETC 216) at 75 mg/kg/dose. Magnetic resonance imaging of the aorta was repeated when the rabbits were 38 weeks old.

Two weekly injections of recombinant Apo A-I milano led to a significant regression of plaque (from 29.5 mm^3 to 27.8 mm^3; $P = .003$) (primary endpoint), whereas placebo treatment was associated with a trend towards progression of lesion size (from 29 mm^3 to 29.9 mm^3; P = not significant [NS]). There were no significant changes in lumen size in either group. In a secondary endpoint of regression of the most diseased lesions (consisting of 3 consecutive slices), recombinant Apo A-I milano treatment led to significant regression (from 99 mm^3 to 92 mm^3; $P = .002$), whereas subjects in the placebo group showed a trend towards progression (from 101 mm^3 to 103 mm^3; P = NS).

Histological examination and immunocytochemistry of plaques showed that the plaques of rabbits treated with recombinant Apo A-I milano had less macrophage immunoreactivity than those of the placebo subjects (0.7% vs 1.5%; $P = .008$) and a higher smooth muscle to macrophage ratio (34% vs 17%; $P < .05$), which indicates a more stable plaque phenotype. Treatment with recombinant Apo A-I milano was also associated with significantly reduced tissue factor and monocyte chemotactic protein-1 mRNA levels, and with reduced matrix metalloproteinase-2–mediated gelatinolytic activity in the plaques.

Comments. This study corroborates previous observations in animals and humans that short-term infusions of recombinant Apo A-I milano can rapidly regress plaques and induce plaque composition changes that would favor plaque stability. Further human investigation of this promising approach is warranted, and such studies are in the planning stages.

[Prediman K. Shah, MD, FACC, FACP, FCCP]

Lipid Level Management to Reduce Cardiovascular Events

Prospective epidemiologic studies have consistently shown that higher HDL levels are associated with a lower risk of cardiovascular events. For this reason, HDL-based therapy has received much recent attention. The cholesteryl ester transfer protein (CETP) inhibitor torcetrapib had been widely believed to be the next breakthrough in cardiovascular medicine because inhibition of CETP was found to increase HDL levels up to 80% over baseline. Inhibition of CETP promotes the transfer of cholesteryl esters from antiatherogenic HDL to Apo B–containing lipoproteins, including very-low-density lipoproteins (VLDL), VLDL remnants, and LDL. The net effect of CETP inhibition, therefore, is to raise HDL levels, lower VLDL levels (triglycerides), and lower LDL levels. Enthusiasm for this approach was almost universal. However, a few investigators suggested that this mechanism of raising HDL cholesterol might not work, perhaps because it could lead to a dysfunctional HDL particle.

The large-scale clinical trial Investigation of Lipid Level management

to Understand its Impact in Atherosclerotic Events (ILLUMINATE)[23] sought to evaluate the efficacy of torcetrapib. It enrolled approximately 15,000 patients at high coronary heart disease risk who were randomized to treatment with torcetrapib (60 mg) plus atorvastatin versus atorvastatin alone (10 mg to 80 mg). The study was terminated abruptly and unexpectedly after a little more than a year of treatment, because of an excess of deaths in the torcetrapib/atorvastatin (82 deaths) versus the atorvastatin group (51 deaths).[23] Increases in heart failure, angina, and revascularization procedures were also observed.[24]

At the same time that ILLUMINATE was ongoing, another trial investigating torcetrapib's effect on coronary atherosclerosis was also being performed. Results from this trial, the Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE), were presented at the ACC meeting.[25]

The goal of the ILLUSTRATE trial was to evaluate the effect of treatment with torcetrapib in combination with atorvastatin as compared with atorvastatin alone on disease progression among patients with coronary stenoses. The primary endpoint was change in percent atheroma volume as detected by IVUS. The secondary endpoints included normalized total atheroma volume and change in atheroma volume in the most diseased 10-mm segment.

Study subjects were 1188 CAD patients aged 18 to 75 years (mean age 57 years); 30% were female. All patients had a clinical indication for cardiac catheterization, and were found to have at least 1 coronary stenosis of at least 20%. Exclusion criteria for the study included a left main coronary stenosis of more than 50%, blood pressure greater than 140/90 mm Hg despite treatment, triglycerides above 500 mg/dL, or creatinine above 1.7 times the upper limit of normal.

All subjects had a baseline IVUS and received 10 g to 80 g of atorvastatin titrated during a 2- to 10-week period to achieve an LDL level of 85 mg/dL to 115 mg/dL. After the run-in, patients were randomized to receive either 60 mg/d of torcetrapib (n = 591) or a matching placebo (n = 597) for 2 years. At the end of the treatment period, a second IVUS was performed, examining the same coronary artery segments. Researchers measured the change in plaque volume in the artery, comparing the baseline to the follow-up ultrasound. They also measured lipids and biomarkers of inflammation at several points during the trial.

Results

The mean atorvastatin dose was 23 mg in both groups. HDL cholesterol at follow-up was higher in the torcetrapib group than in the atorvastatin alone group (72.1 mg/dL vs 43.9 mg/dL; $P < .001$). LDL levels were lower in the torcetrapib group (70.1 mg/dL vs 87.2 mg/dL; $P < .001$). Median C-reactive protein levels at follow-up were higher in the torcetrapib group than in the atorvastatin alone group (1.8 mg/L vs 1.5 mg/L; $P = .02$). Systolic blood pressure was higher at follow-up in the torcetrapib group (126.4 mm Hg vs 122.0 mm Hg; $P < .001$), as was diastolic blood pressure (76.0 mm Hg vs 74.3 mm Hg; $P < .001$), representing an increase in blood pressure in the torcetrapib group of 6.5/2.8 mm Hg.

The primary endpoint of change from baseline in percent atheroma volume did not differ between treatment groups (0.12% for torcetrapib vs 0.19% for atorvastatin alone; $P = .72$), nor did change in atheroma volume of the most diseased 10-mm segment (-4.1 mm^3 for torcetrapib vs -3.3 mm^3 for atorvastatin alone; $P = .12$). Reduction in normalized total atheroma volume was greater in the torcetrapib group compared with atorvastatin alone (-9.4 mm^3 vs -6.3 mm^3; $P = .02$).

All-cause mortality occurred in 1.4% of the torcetrapib group and 1.0% of the atorvastatin alone group. The composite of death from coronary heart disease, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, or coronary revascularization did not differ between groups (21.0% for torcetrapib vs 19.6% for atorvastatin alone). Blood pressure–related adverse events occurred more frequently in the torcetrapib group (23.7% vs 10.6%), as did an increase in blood pressure of more than 15 mm Hg (9.0% vs 3.2%).

Among patients with coronary disease, treatment with the CETP inhibitor torcetrapib in addition to atorvastatin therapy was not associated with a difference in change in percent atheroma volume compared with atorvastatin alone at 24-month follow-up.

Torcetrapib was very effective in raising the level of HDL in the present study.[26] However, effects on atherosclerosis progression were modest or nonexistent, despite the increased HDL and lowered LDL.

The Future of CETP Inhibitors

The results of ILUSTRATE are consistent with those from ILLUMINATE. The cause for the increase in mortality is not known at this time because full results of the safety trial have not yet been presented or published. It is also not known if the increase in blood pressure and mortality is a class effect of the CETP inhibitors or if it is specific to torcetrapib. The possibilities for increased mortality

with torcetrapib are many, and the following 2 hypotheses have been widely proposed:

1. CETP inhibition generates abnormal HDL particles.
2. The elevated blood pressure levels seen with torcetrapib (up to 4 mm Hg to 5 mm Hg) countered any favorable lipid-altering effects and were primarily responsible for the increased mortality.

So what is the future of CETP inhibitors? Although the development of torcetrapib has been abandoned, other pharmaceutical companies have CETP inhibitors in their portfolios. Whether or not these agents will continue to be developed is unknown. Also unknown is the future of HDL-raising therapies. Despite this apparent blow to HDL-raising therapies, most experts believe this approach will be beneficial in the future. There are several other HDL-targeted therapies in development, and future clinical trials will be needed to validate their efficacy.

[Karol E. Watson, MD, PhD]

Echocardiography and Valvular Heart Disease

Percutaneous techniques for treating valvular heart disease in adults have recently been developed as alternatives to surgical valve replacement or repair. Percutaneous mitral valvuloplasty is well established, with excellent results in a large percentage of patients with over a decade of follow-up (discussed below). Percutaneous aortic valvuloplasty, although technically feasible, has been less successful due to limited increases in valve area, procedure-related complications, and early restenosis. It is generally reserved for patients with severe disease who are not considered candidates for surgical intervention. More recently, several groups have been investigating percutaneous methods for aortic valve replacement, and short-term results are now appearing. Several percutaneous approaches to the treatment of mitral regurgitation (MR) have also been described, the most advanced of which is the use of the clip device to appose the tips of the mitral leaflets. Preliminary results from several studies evaluating the feasibility and short-term results of percutaneous aortic valve replacement and mitral valve repair were presented at this year's ACC meeting.

Percutaneous Aortic Valve Replacement

The treatment of severe aortic stenosis in patients who are not suitable candidates for cardiac surgery due to complicating medical disease remains a major therapeutic challenge. Grube and colleagues[27] reported the experience of percutaneous AVR using the CoreValve Revalving™ system, a self-expandable porcine bioprosthesis within a nitinol frame (CoreValve Corporation, Irvine, CA). The study subjects were 60 patients (49 high-risk and 11 inoperable) with a mean aortic valve area (AVA) of 0.64 ± 0.2 cm^2. A multidisciplinary approach involving general anesthesia, surgical peripheral arterial access, and femoral vein–femoral artery cardiopulmonary bypass was employed. Valve deployment failed for technical reasons in 5 cases, with 3 resulting in immediate conversion to surgery. Immediate results in the 55 cases with successful deployment by transesophageal echocardiography showed a mean valve area of 1.6 ± 0.4 cm^2, with a small paravalvular leak (Grade 0 to 1) in 45 patients. In-hospital mortality occurred in 8 out of 60 patients (13%) (4 out of 11 in the inoperable group and 4 out of 49 (8%) in the high-risk group). Follow-up (mean 5.0 ± 2.5 months) confirmed continued hemodynamic and functional improvement in all discharged patients.

In a second study using the CoreValve Revalving system, Berry and colleagues[28] described 11 patients with an AVA of 0.56 ± 0.19 cm^2 who were turned down for cardiac surgery, underwent percutaneous AVR, and were followed for 1 month. The postprocedure valve area was more than 1.2 cm^2, with 2 or fewer episodes of paravalvular regurgitation. There were 2 deaths (18%), and 3 patients required permanent pacemaker implantation. Follow-up of survivors for up to 8 months confirmed functional and hemodynamic improvement in all cases. (The mean AVA was 1.3 ± 0.4 cm^2, with a mean increase in LVEF from 49 ± 17% pre-percutaneous AVR to 56 ± 11% at 1 month).

Two additional studies reported on the results of percutaneous AVR using the Edwards percutaneous heart valve (PHV) (Edwards Lifesciences Corporation, Irvine, CA), an equine pericardial bioprosthesis sutured into a balloon expandable stent. A study presented by Eitchaninoff and colleagues[29] included 37 patients with end-stage aortic stenosis and multiple comorbidities, who were declined for surgical valve replacement and included on a compassionate basis in 2 consecutive studies (Initial Registry of Endovascular Implantation of Valves in Europe [I-REVIVE] and Registry of Endovascular Critical Aortic Stenosis Treatment [RECAST]) to determine the feasibility, efficacy, and durability of PHV implantation. Clinical and echocardiographic outcomes were assessed serially at 1 day, 1 week, 1 month, 3 months, and every 6 months thereafter. Successful implantation was obtained in 27 patients with a final AVA of 1.7 ± 0.1 cm^2 and a transvalvular gradient of 9.0 ± 2.0 mm Hg. Adverse events occurred in 26% of patients, including 6 deaths of noncardiac cause within the first month. No PHV dysfunction

was observed. Although the patients were critically ill at the time of implantation, at follow-up of at least 18 months (and of 3 years in 2 patients), 9 patients were alive, in NYHA class 1, and had returned to a normal life. PHV function remained unchanged during follow-up in 27 patients.

In a second report using the Edwards PHV, Kodali and colleagues[30] described the results of the REVIVAL-II trial, in which 28 patients with a mean age of 83 years and a mean AVA of 0.5 cm^2 underwent percutaneous AVR. Percutaneous AVR was successfully performed in 24 patients (86%) (23 mm valve [10] and 26 mm valve [14]). Two implantation failures resulted in death from type A dissection and 2 failures resulted from the inability to insert the PHV sheath due to severe vascular disease. In patients with successful percutaneous AVR, the mean gradient was reduced to less than 5 mm Hg, with postprocedure valve areas greater than 1.7 cm^2. Only 1 patient had greater than 2+ para-valvular aortic regurgitation (4%). Periprocedural mortality occurred in 2 out of 28 patients (7%), with death, MI, major stroke, or major vascular complication in 6 out of 28 (21%). NYHA functional class was reduced from 3.1 at baseline to 1.5 at 1 month ($P < .01$).

In the aggregate, these studies prove that percutaneous AVR is feasible, and although the rates of periprocedural mortality and morbidity remain high, they are less than the rates predicted for surgical valve replacement in this high-risk population. For survivors of percutaneous AVR, the short-term hemodynamic and functional improvement appears encouraging.

Percutaneous Mitral Valve Repair

Correction of MR has recently been attempted using a percutaneously inserted clip (MitraClip™; Evalve®, Inc, Menlo Park, CA) to achieve apposition of the tips of the anterior and posterior mitral leaflets. In a 6-month follow-up study of 55 patients with moderately severe or severe baseline MR (degenerative = 47, functional = 8) who underwent percutaneous clip apposition of their mitral leaflets, Foster and colleagues[31] examined 4 echocardiographic variables: regurgitant volume, regurgitant fraction, pulmonary vein flow pattern, and color flow Doppler grade. The clip was successfully implanted in 49 out of 55 patients (89%). Eight patients required surgery for MR within 6 months, there was 1 unrelated death, and 1 echocardiogram was unavailable. At 6-months follow-up in the remaining 28 patients (24 degenerative and 4 functional), all measures of MR severity decreased significantly (regurgitant volume 48.2 ± 20.3 mL to 22.0 ± 13 mL, regurgitant fraction 45.1 ± 12.3 to 25.5 ± 12.9, and color flow Doppler grade 3.1 ± 0.7 to 1.4 ± 0.5; all $P < .0001$). Thus, percutaneous mitral valve repair resulted in sustained reduction in MR severity to moderate or less in the majority of patients.

This series of studies, although reporting on preliminary work with early generation devices, offers the hope that alternative types of repair will be available for individuals whose clinical status makes them unsuitable candidates for surgical valve replacement or repair. In many cases, this approach may offer a definitive correction, whereas in others it will offer a bridge solution until the patient's condition improves.

3D Echocardiography

A number of studies have shown that real-time 3-dimensional echocardiography (3DE) is feasible in a variety of conditions. However, most investigators believe that the greatest early promise lies in the quantitation of left and right ventricular volumes. Although research studies generally involving small groups of patients have shown 3DE to be a more accurate method of assessing LV volumes and ejection fraction than conventional 2-dimensional echocardiography (2DE), there is limited information regarding the feasibility and incremental value of 3DE in clinical practice. To address this issue, Marwick and colleagues[32] studied 168 unselected patients referred to 2 hospital-based echocardiography laboratories using both 2DE and 3DE, with measurement of acquisition and analysis time. Feasibility was defined by the ability to measure LV end-diastolic volume, end-systolic volume, and ejection fraction. The potential of 3DE to alter clinical decisions based on 2DE was evaluated by the ability to identify 4 clinically relevant thresholds:

- LVEF less than 40% (indication for heart failure treatment).
- LVEF less than 35% (indication for ICD).
- LV end-systolic volume (LVESV) greater than 30 mL/m^2 (prognosis post-MI).
- LVESV greater than 50 mL/m^2 (indication for surgery in regurgitant valve disease).

Of 168 patients, 3DE was feasible in 150 (89.3%), with 2-dimensional and 3-dimensional data available in 148 patients (88.1%). Time for 3-dimensional sample acquisition and analysis was 5.3 ± 1.9 minutes. The proportion of patients in which 3DE changed categorization above or below a threshold as defined by 2DE was 5.4% (8 out of 148) for LVEF less than 40%, 2.7% (4 out of 148) for LVEF less than 35%, 11.5% (17 out of 148) for LVESV greater than 30 mL/m^2, and 2.7% (4 out of 148) for LVESV greater than 50 mL/m^2, with

82% of impact for ejection fraction in the range of 30% to 45%, and 75% for LVESV in the range of 20 mL/m^2 to 40 mL/m^2. Although there was no gold standard to which both measures were compared, these data do show that 3DE is feasible in clinical practice and has the potential to alter clinical decision-making in a small but potentially important percentage of cases.

Echocardiographic Detection of Dyssynchrony and Prediction of Response to Cardiac Resynchronization Therapy in Patients With Severe Impairment in LV Function

Echocardiography is widely used to determine the presence of LV dyssynchrony and to evaluate the immediate and long-term response to cardiac resynchronization therapy (CRT). Several echo-Doppler criteria have been described to define dyssynchrony and predict a favorable response; however, there has been no agreement as to the best approach. In a study by Tanabe and colleagues,[33] color-coded longitudinal velocities were recorded in the apical 2, 4, and long-axis views at the basal and mid-ventricular levels (12 segments) in 100 patients. Time-to-peak velocity was analyzed either by including post-systolic peak velocities after aortic valve closure or were limited to the peak velocity during systolic ejection. Dyssynchrony was calculated using each of the 3 most common approaches: Yu index (12-site standard deviation), opposing wall delay (by view), and maximal delay (all segments). A positive response to CRT, defined as more than a 15% increase in ejection fraction at about 4 months occurred in 74% of patients. Inclusion of post-systolic peaks by all approaches weakened the ability to predict a positive response to CRT. Yu index (34 ms cut-off), opposing wall delay (65 ms cut-off), and maximum delay (110 ms cut-off) during ejection all showed similar favorable sensitivities (82% to 88%) and specificities (73% to 81%) to predict a favorable response to CRT and were linearly related to one another (r = .88 to .92). The authors concluded that by limiting analysis to the systolic ejection period, the 3 approaches appeared clinically equivalent in predicting response to CRT. This finding may explain why none of the approaches has become established as optimal.

Current criteria suggest that CRT is appropriate in patients with a reduced ejection fraction (< 35%) and left bundle branch block, and with a QRS interval of at least 130 ms. However, several recent echocardiographic studies have identified dyssynchrony in many patients with QRS intervals less than 130 ms, and preliminary data suggest that many of these patients may also benefit from CRT. To further examine the role of CRT in patients with echocardiographic evidence of dyssynchrony and narrow QRS, Rafique and colleagues[34] studied 90 patients, 38 with narrow QRS less than 130 ms (nQRS) and 52 with wide QRS at least 130 ms (wQRS) cardiomyopathy who had presence of mechanical asynchrony immediately before CRT and underwent a follow-up echocardiography after CRT. Mean age was 65 ± 16 years, mean NYHA class was 3 ± 1, and 53% had ischemic cardiomyopathy. Mean follow-up time was 4 ± 7 weeks. Almost all patients (98%) met at least 1 criterion for asynchrony (standard deviation of time to peak velocity [Tp] in 12 LV segments [> 33 ms], basal septolateral wall delay [> 60 ms], Max diff Tp 6 basal segments [> 110 ms], septoposterior wall delay M-mode [> 130 ms], sum of basal LV and regurgitant volume asynchrony [> 102 ms], delayed longitudinal contraction [2 or more basal LV segments]); 2 criteria were met by 92%. Responders were defined as patients in whom end-systolic volume was reduced by 10% after CRT. There was no difference in the presence and severity of asynchrony in the 2 groups before CRT. In both groups, 70% of patients had more than 4 criteria for presence of mechanical asynchrony. There was no difference in the response to CRT in the 2 groups. (The percent change in end-systolic volume was 12 ± 17 in the nQRS group vs 15 ± 29 in the wQRS group [P = .6]. The change in LVEF was 26 ± 46 in the nQRS group vs 38 ± 48% in the wQRS group [P = .3]. The percentage of responders was 57% in the nQRS group vs 73% in the wQRS group [P = .22].) Among nonresponders, 23% in the nQRS group and 91% in the wQRS group had ischemic cardiomyopathy (P = .001). The authors concluded that in patients with cardiomyopathy with comparable mechanical asynchrony, response to CRT in the nQRS group was similar to patients with wQRS, and that mechanical and not electrical asynchrony should be used in patients with nQRS for CRT. ■

[Arthur E. Weyman, MD, FACC]

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Main Points

- In one study, patients with a B-type natriuretic peptide level above 550 pg/mL had a poor prognosis, regardless of the results of the cardiac reserve assessment or whether the patients went on to aortic valve replacement or not. This study is the first to suggest that high levels of B-type natriuretic peptide bode such an adverse prognosis in this disease.
- The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial demonstrated that there was no difference in death or non-fatal myocardial infarction between a patient group undergoing percutaneous coronary intervention and another group receiving medical therapy.
- Data show that the addition of the angiotensin receptor blocker valsartan to the direct renin inhibitor aliskiren leads to greater reductions in blood pressure and greater blood pressure than either drug alone.
- A study in rabbits corroborates previous observations in animals and humans that short-term infusions of recombinant apolipoprotein A-I milano can rapidly regress plaques and induce plaque composition changes that would favor plaque stability.
- In one study, torcetrapib raised levels of high-density lipoprotein and reduced levels of low-density lipoprotein. However, the effects on atherosclerosis progression were modest or nonexistent.
- A new study suggests that 3-dimensional echocardiography is feasible in clinical practice and has the potential to alter clinical decision-making in a small but potentially important percentage of cases.

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