Best of the ACC 2008 Scientific Session

Highlights From the 57th Annual American College of Cardiology Scientific Session, March 29-April 1, 2008, Chicago, IL

[Rev Cardiovasc Med. *2008;9(2):125-136*]

Key words: Cardiac resynchronization therapy • Cardiovascular disease • Clopidogrel loading • Distal protection devices • Drug-eluting stents • Embolic protection systems • Fibrinolytic therapy • Hypertension • Percutaneous coronary intervention

This year's meeting of the American College of Cardiology presented important new data on many topics. Here we discuss key studies on percutaneous coronary intervention (PCI), use of an embolic protection system during stenting, use of a clopidogrel loading dose prior to PCI, drug-eluting stents, thrombus aspiration during primary PCI, cardiac resynchronization therapy, and treatment of hypertension in the elderly. Several trials focused on the efficacy and safety of drugs, including bivalirudin versus unfractionated heparin, pioglitazone versus glimepiride, binodenoson versus adenosine, istaroxime, rolofylline, aliskiren alone or in combination with losartan, amlodipine/benazepril compared with hydrochlorothiazide (HCTZ)/benazepril, low-dose versus high-dose atorvastatin, and telmisartan versus ramipril.

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TRANSFER-AMI

Although primary PCI has emerged as the preferred reperfusion strategy for patients with ST-segment elevation myocardial infarction (STEMI), it is performed in just over 50% of STEMI patients worldwide because timely access to a PCI-capable facility is not widely available. Therefore, numerous strategies with the potential to allow a safe and effective delay prior to definitive PCI continue to be evaluated.

Facilitated PCI, which involves urgent, planned performance of PCI after an initial preparatory pharmacological regimen intended to improve coronary patency rates, has not been proven to be an effective or safe alternative to primary PCI. A hybrid strategy, referred to as pharmaco-invasive reperfusion, that involves initial treatment with fibrinolytic therapy followed routinely by coronary angiography and PCI as indicated (on a non-urgent basis) has also been proposed as an approach to treatment for STEMI, but to date, the evidence supporting such a strategy has been limited. In fact, "immediate" balloon angioplasty following fibrinolytic therapy prior to the contemporary use of thienopyridines, IIb/IIIa platelet receptor antagonists, and stents did not appear to salvage myocardium, improve left ventricular (LV) function, or prevent re-infarction and death, and was associated

with an increased incidence of adverse events.

The goal of the Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI) was to test the hypothesis that routine, early PCI within 6 hours after fibrinolysis is safe and superior to the standard treatment of fibrinolytic therapy with rescue PCI or delayed coronary angiography in patients with STEMI who do not undergo primary PCI.[1] Accordingly, 1059 patients within 12 hours of symptom onset of STEMI and at least 1 high-risk feature (systolic blood pressure $<$ 100 mm Hg, heart rate $>$ 100 beats per minute, Killip class II-III, $\geq$ 2 mm of ST-segment depression in the anterior leads, $\geq$ 1 mm of ST elevation in right-sided lead V4 indicative of right ventricular involvement) presenting to non–PCI-capable hospitals and treated with fibrinolytic therapy were randomized to a pharmaco-invasive strategy (emergent transfer for PCI within 6 hours of fibrinolysis) or to standard treatment after fibrinolysis (which included rescue PCI as required for ongoing chest pain and $<$ 50% resolution of ST-elevation at 60 to 90 minutes or hemodynamic instability). For standard-treatment patients who did not require rescue PCI, coronary angiography after 24 hours in successfully reperfused patients or within the first 2 weeks was encouraged.

All patients received standard-dose tenecteplase (TNK) and aspirin (160 to 325 mg). Either unfractionated heparin (UFH) or enoxaparin was used based on a weight-adjusted dose consistent with published guidelines. Clopidogrel loading (300 mg for patients 75 years or younger, and 75 mg for patients older than 75 years) was strongly encouraged in all study patients. Glycoprotein IIb/IIIa inhibitors were administered at the PCI-capable hospitals according to standard practice at the institution. PCI of the culprit lesion was performed for stenosis at or exceeding 70% or high-risk features (thrombus, ulceration, dissection), and stents were used whenever technically feasible. The primary endpoint of the trial was the 30-day composite of death, re-infarction, recurrent ischemia, heart failure (HF), or shock.

The results of TRANSFER-AMI were based on the 1030 patients with complete data, of whom 522 were randomized to the pharmaco-invasive strategy and 508 to standard treatment. Just over half the study cohort had an anterior myocardial infarction (MI). The median time to administration of TNK from onset of symptoms was 2 hours in both arms, whereas the median time from TNK to catheterization was 3 hours in the pharmaco-invasive group and 27 hours in the standard treatment group. Coronary angiography was performed in 97% versus 82% and PCI in 84% versus 62% of the pharmaco-invasive and standard treatment groups, respectively. Glycoprotein IIb/IIIa platelet receptor antagonists were used in 73% of the pharmaco-invasive group and 47% of the standard treatment group whereas stents were used in 98% of patients in both groups.

The primary endpoint of the trial occurred in 10.6% of the pharmaco-invasive group compared with 16.6% in the standard treatment group. In addition, although there was no difference in mortality between groups, the incidence of re-infarction, recurrent ischemia, and death/MI/ischemia was significantly lower in patients receiving the pharmaco-invasive strategy. However, it should be noted that the study was not powered to evaluate the components of the primary endpoint. Importantly, the incidence of bleeding, using both Thrombolysis In Myocardial Infarction (TIMI) and Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) definitions, was not different between groups. The authors concluded that following treatment with fibrinolytic therapy, STEMI patients presenting to hospitals without PCI-capability should be transferred immediately to a PCI center to undergo coronary angiography and PCI without waiting to determine whether reperfusion has occurred.

Comments

The purpose of this trial was to evaluate a strategy of fibrinolytic therapy followed by routine urgent transfer for contemporary PCI within 6 hours in high-risk patients with STEMI presenting to hospitals without PCI-capability (and presumably where primary PCI could not be achieved in a timely fashion). Exclusion of patients with (new) left bundle branch block, cardiogenic shock, renal insufficiency, and prior coronary bypass surgery notwithstanding, the results suggest that this specific pharmaco-invasive strategy is safe, effective, and superior to a standard treatment with rescue PCI and/or coronary angiography and PCI after 24 hours. Perhaps the inherent delay (median time, 3 hours) to PCI achieves a balance between the increased bleeding associated with immediate or facilitated PCI and recurrent ischemia/re-infarction associated with the standard treatment following successful fibrinolysis. Yet to be determined (from these data) is the optimal or allowable delay between treatment with fibrinolytic agents and planned PCI (especially with respect to time from symptom onset). It will also be important to determine whether this strategy will be superior to delayed primary PCI in high-risk STEMI patients, particularly in patients who

present late after symptom onset. Nonetheless, this important trial suggests that this pharmaco-invasive strategy appears promising for STEMI patients without access to timely primary PCI.

[Alice K. Jacobs, MD, FACC, FAHA]

The ISAR-REACT 3 Trial

The Bivalirudin Versus Unfractionated Heparin in Troponin-Negative Patients Undergoing Percutaneous Coronary Interventions After Pre-Treatment With 600 mg of Clopidogrel (ISAR-REACT 3) trial was designed to determine whether bivalirudin is superior to UFH in terms of ischemic and hemorrhagic endpoints.[2] The 4750 biomarker-negative subjects were randomized to receive either UFH (bolus of 140 U/kg) or bivalirudin (bolus of 0.75 mg/kg, followed by infusion of 1.75 mg/kg/h) during the procedure, in addition to 600 mg of clopidogrel and 325 mg or more of aspirin taken at least 2 hours prior to the procedure. The majority of patients (82%) had stable angina; the rest had unstable angina. Patients were excluded if they had an acute coronary syndrome (ACS) with positive biomarkers or STEMI within the previous 48 hours, cardiogenic shock, history of heparin-induced thrombocytopenia or other bleeding diatheses, and serum creatinine exceeding 3 mg/dL.

The primary endpoint, a composite rate of death, MI, urgent target vessel revascularization, or in-hospital major bleeding, was similar between the 2 cohorts (8.3% for bivalirudin vs 8.7% for UFH [P = .57]) (Figure 1). The secondary endpoint of death, MI, and urgent revascularization was 5.9% in the bivalirudin arm and 5.0% in the UFH arm (P = .23). The incidence of major bleeding was significantly reduced by 33% with bivalirudin (3.1%) compared with UFH (4.6%) (P = .008). Similarly, the incidence of minor bleeding was significantly reduced with bivalirudin (P = .0001).

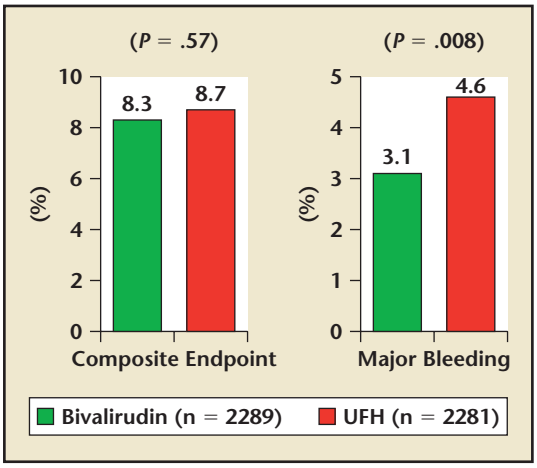

Figure 1. *Results from the ISAR-REACT 3 trial. The primary endpoint was a composite rate of death, myocardial infarction, urgent target vessel revascularization, and in-hospital major bleeding. ISAR-REACT 3, Bivalirudin Versus Unfractionated Heparin in Troponin-Negative Patients Undergoing Percutaneous Coronary Interventions After Pre-Treatment With 600 mg of Clopidogrel; UFH, unfractionated heparin; PCI, percutaneous coronary intervention. Data from Kastrati A.[2] Adapted with permission from Cardiosource.*

The PERISCOPE Trial

In the Comparison of Pioglitazone Versus Glimepiride on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes (PERISCOPE) trial, 543 subjects were randomized to receive either 1 to 4 mg of glimepiride, a third-generation sulfonylurea agent, or pioglitazone at 15 to 45 mg to start and, if tolerated, titrated to maximum dosage by 16 weeks.[3] Mean follow-up was 18 months. Baseline intravascular ultrasound (IVUS) was performed to determine atheroma volume.

After 18 months, IVUS of the originally examined coronary artery was performed in 360 patients. Patients were included for study if their baseline glycohemoglobin levels were 6.0% to 9.0% with antidiabetic medication or 6.5% to 10% without it. Coronary angiography was performed for clinical indications that demonstrated at least 1 angiographic stenosis exceeding 20%. Exclusion criteria included type 1 diabetes, concurrent use of 3 or more antidiabetic medications, use of a thiazolidinedione within the previous 3 months, serum creatinine exceeding 2.0 mg/dL, triglyceride level exceeding 500 mg/dL, uncontrolled hypertension (blood pressure < 160/100 mm Hg despite treatment), active liver disease, or left main disease exceeding 50%.

The primary efficacy endpoint, least square mean change in percent atheroma volume from baseline, increased significantly in the glimepiride arm but decreased slightly in the pioglitazone arm (Figure 2). Compared with baseline, there was a greater reduction in fasting insulin levels, a greater increase in high-density lipoprotein cholesterol, a greater reduction in triglycerides and high-sensitivity C-reactive protein, a smaller increase in systolic blood pressure, and a greater decrease in diastolic blood pressure in the pioglitazone arm compared with the glimepiride arm. The composite endpoint of cardiovascular death, nonfatal MI, or stroke was similar between the glimepiride and pioglitazone arms (2.2% vs 1.9%, respectively; P = not significant [NS]). Similarly, the incidence of hospitalization for congestive HF was 1.8% in the glimepiride group and 1.5% in the pioglitazone group (P = NS). Hospitalization for coronary revascularization

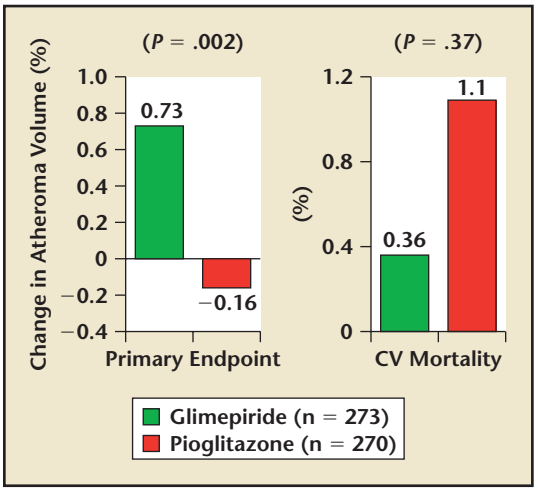

Figure 2. *The PERISCOPE trial compared the effectiveness of pioglitazone with glimepiride in reducing progression of atherosclerosis in patients with type 2 diabetes and coexisting CAD. PERISCOPE, Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation; CAD, coronary artery disease; CV, cardiovascular. Data from Nissen SE.[3] Adapted with permission from Cardiosource.*

was 11.0% in the glimepiride group and 10.7% for the pioglitazone group (P = NS). The incidence of hypoglycemia and angina was greater with glimepiride, whereas the incidence of bone fractures, anemia, and peripheral edema was greater with pioglitazone.

Comment

Although these 2 classes of oral hyperglycemic therapies have their own adverse effects consistent with their modes of action, it is comforting that this trial did not show any increase in the composite cardiovascular event rate for pioglitazone compared with glimepiride.

The A-F Trial

The Vascular Protection in High-Risk Non–ST-Elevation Acute Coronary Syndromes: The Angioplasty Balloon-Associated Coronary Debris and the EZ FilterWire (A-F) trial examined the safety of the FilterWire EZ™ Embolic Protection System (Boston Scientific, Natick, MA), a 110-micron–pore filter that permits continuous blood flow while maintaining embolic capture efficiency.[4] The study subjects were 151 patients with non–ST-elevation ACS who were randomized to receive the FilterWire before stenting or to undergo stenting alone. The patients were considered to be at a heightened risk of distal embolization according to clinical criteria (dynamic ischemic electrocardiographic changes, rest angina, elevated cardiac enzymes) or angiographic criteria (visible thrombus, ulceration, eccentric lesion, irregular border, abrupt lesion edges, lesion length > 20 mm). The primary endpoint was a composite of in-hospital major adverse cardiac events (MACE): death, MI, or emergency repeat revascularization.

There was evidence of embolic material recovery in 42% of patients. The primary endpoint of in-hospital MACE was similar in both groups (11.7% of the FilterWire group vs 9.5% of the control group [P = NS]) (Figure 3).

Comment

Distal protection devices have been found to be effective in reducing cardiovascular events in patients undergoing saphenous vein graft interventions. Recovery of embolic material occurred in a significant proportion of these patients, but without translating to a reduction in cardiovascular events. Perhaps these patients had a lower distal embolic burden and, therefore, did not reach the embolic threshold that would cause the distal capillary plugging leading to myocardial necrosis that is observed in vein graft interventions.

The VISION Trial

The Vasodilator Induced Stress in Concordance With Adenosine (VISION) trial was designed to evaluate the safety and efficacy of the selective adenosine A_{2A}-receptor

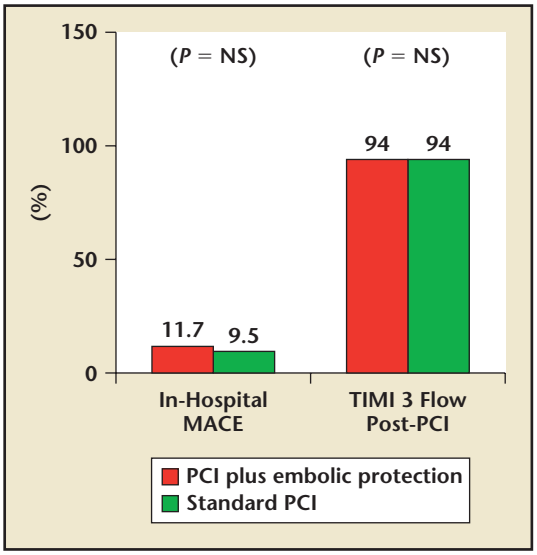

Figure 3. *The A-F trial examined the safety of the FilterWire EZ Embolic Protection System, a 110-micron–pore filter that permits continuous blood flow while maintaining embolic capture efficiency. A-F, Vascular Protection in High-Risk Non–ST-Elevation Acute Coronary Syndromes: The Angioplasty Balloon-Associated Coronary Debris and the EZ FilterWire; NS, not significant; MACE, major adverse coronary events; TIMI, Thrombolysis In Myocardial Infarction; PCI, percutaneous coronary intervention. Data from Webster M.[4] Adapted with permission from Cardiosource.*

agonist binodenoson against that of adenosine for pharmacologic stress in patients at risk of coronary artery disease (CAD) or with known CAD.[5] There are a number of adverse events associated with the use of adenosine, including flushing and heart block, that limit use of this agent in many patients undergoing myocardial perfusion studies. These events may be reduced with the use of a selective adenosine receptor antagonist.

The 804 patients completed 2 double-blind, double-dummy myocardial perfusion imaging procedures in random order within 7 days: one with bolus 1.5 μg/kg binodenoson along with a 6-minute placebo infusion, and one with bolus placebo along with a 6-minute adenosine infusion at 140 μg/kg/min. After 2 to 7 days, the patients crossed over and received another scan with the other agent.

The primary endpoint of the trial was the mean paired summed difference scores. The difference of binodenoson versus adenosine was −0.09 (95% confidence interval, −0.44-0.27), well within the prespecified 1.5 summed difference score units for noninferiority showing similar abilities to induce ischemia. The incidence of second- or third-degree atrioventricular block was 0% for binodenoson versus 3% for adenosine ($P = .004$) (Figure 4). Patients taking binodenoson experienced less flushing (50% vs 32% [$P < .05$]), chest pain (61% vs 38% [$P < .05$]), and dyspnea (51% vs 42% [$P < .05$]). In addition, these adverse effects were considered less intense by the binodenoson patients as compared with the adenosine patients. It is likely that binodenoson will be a useful pharmacologic stress agent in the exercise laboratory because of its improved adverse event profile.

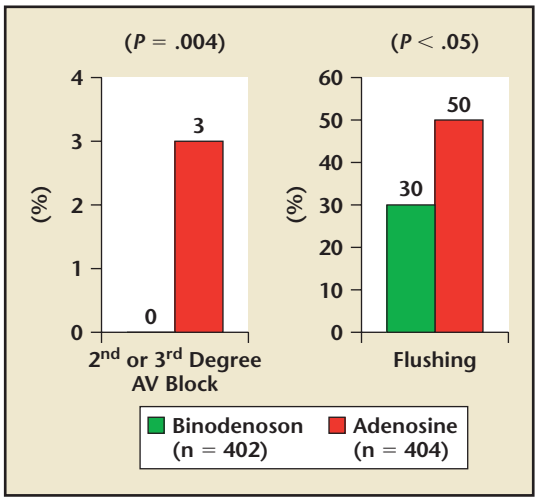

Figure 4. *The VISION trial was designed to evaluate the safety and efficacy of binodenoson against that of adenosine for pharmacologic stress in patients at risk of CAD or with known CAD. VISION, Vasodilator Induced Stress in Concordance With Adenosine; CAD, coronary artery disease; AV, atrioventricular. Data from Udelson JE.[5] Adapted with permission from Cardiosource.*

The ARMYDA-Reload Trial

The Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty-Reload (ARMYDA-Reload) trial evaluated the safety and efficacy of an additional 600-mg clopidogrel loading dose prior to PCI in patients undergoing revascularization.[6] This issue is important in the cardiac catheterization laboratory because clinicians may be uncertain whether patients who have been on chronic clopidogrel therapy would benefit from a re-bolus dose.

The patients in this study underwent PCI for stable angina or non–ST-elevation ACS and had been taking chronic clopidogrel therapy for at least 10 days. The primary endpoint was a composite of MACE (death, MI, or target vessel revascularization). The incidence of the primary endpoint was 7% in the reload group versus 9% in the placebo group ($P = .70$) (Figure 5). Among stable angina patients, MACE was 8% in the reload group versus 4% in the placebo group ($P = .23$). Among ACS patients, MACE was 7% in the reload patients versus 18% in the placebo patients ($P = .035$). Minor bleeding was 5% in both groups ($P = 1.0$), and there were no major bleeds.

Comment

This trial shows that there is no benefit to a reload of clopidogrel in stable patients undergoing PCI, although there is a suggestion of a benefit in patients presenting with an ACS. This effect may be related to the heightened state of platelet activation in this syndrome.

The ALLAY Trial

The Aliskiren Left Ventricular Assessment of Hypertrophy (ALLAY) trial was designed to determine whether aliskiren, alone or in combination with losartan, was more effective than losartan alone in reducing LV hypertrophy in overweight hypertensive patients.[7] The 460 study patients were randomized to 3 treatment arms: aliskiren 150 mg/d, losartan 50 mg/d, or a combination of the 2 medications. After 2 weeks, these medications were force-titrated to aliskiren 300 mg/d, losartan 100 mg/d, or the combination for 34 weeks. Other antihypertensive agents were added as necessary to meet blood pressure goals. All patients had evidence of LV hypertrophy, as indicated by a mean baseline LV mass index (LVMI) of 78.5 g/m^2, and were followed for a mean of 36 months.

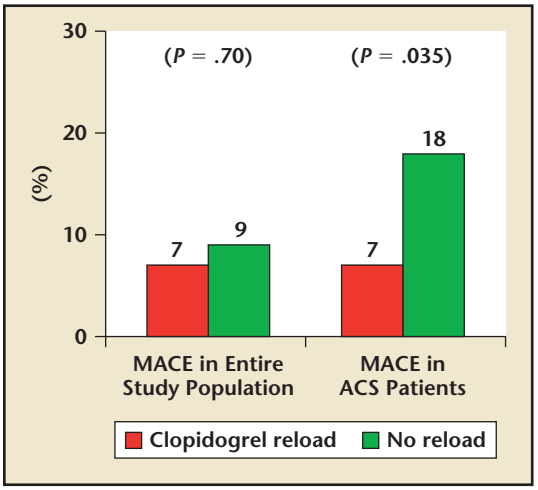

Figure 5. *The ARMYDA-Reload trial evaluated the safety and efficacy of an additional 600-mg clopidogrel loading dose prior to percutaneous coronary intervention in patients undergoing revascularization. The primary endpoint was a composite of MACE (death, myocardial infarction, or target vessel revascularization). ARMYDA-Reload, Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty-Reload; MACE, major adverse coronary events. Data from Di Sciascio G.[6] Adapted with permission from Cardiosource.*

The primary endpoint was a change in LVMI, as assessed by cardiac magnetic resonance imaging (MRI) from baseline to week 36.

Mean reductions in blood pressure did not differ among the 3 groups (6.5/3.8 mm Hg in the aliskiren group, 5.5/3.7 mm Hg in the losartan group, and 6.6/4.6 mm Hg in the combination group). The primary endpoint of change in LVMI was 4.9 ± 1, 4.8 ± 1, and 5.8 ± 0.9 with aliskiren, losartan, and the combination, respectively (all $P < .0001$ compared with baseline) (Figure 6). Aliskiren was noninferior to losartan (P for inferiority $< .0001$) for the primary endpoint, and the combination of losartan and aliskiren was not superior to losartan alone ($P = .52$).

The HORIZON-HF Study

Istaroxime (PST-2744) is a first-in-class Na,K-ATPase inhibitor chemically unrelated to cardiac glycosides that enhances myocardial contractility by stimulating calcium entry via the sarcolemmal Na/Ca exchanger. Preliminary data suggest that istaroxime may permit cytosolic calcium accumulation while avoiding the proarrhythmic state seen with other inotropes. The Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Inotropic Agent With Lusitropic Properties, in Acute Heart Failure Syndromes (HORIZON-HF) trial tested 3 istaroxime dosages (0.5 μg/kg/min [n = 29]; 1.0 μg/kg/min [n = 30]; 1.5 μg/kg/min [n = 30]) against placebo (n = 31).[8]

The primary endpoint was the change in pulmonary capillary wedge pressure. The mean change in pulmonary capillary wedge pressure at 6 hours was −3.2, −3.3, and −4.7 for the 0.5, 1.0, 1.5 μg/kg/min infusions, respectively, and 0.0 mm Hg for placebo ($P < .05$ for all doses compared with placebo). In addition, improvement in hemodynamics and diastolic function was observed in the high-dose cohort (Figure 7). Further study is needed to show the impact of this agent on clinical events.

The PROTECT Pilot Trial

Rolofylline is an adenosine A1-receptor antagonist that exerts its effect by blocking adenosine-mediated constriction of the afferent glomerular arteriole, leading to an increase in glomerular blood flow and filtration and inhibition of sodium reabsorption in the proximal tubule. The Effects of Rolofylline, a New Adenosine A1 Receptor Antagonist, on Symptoms, Renal Function, and Outcomes in Patients With Acute Heart Failure (PROTECT) pilot trial compared rolofylline with a placebo.[9] Patients were included in the study if they had acute HF requiring intravenous diuretic therapy within 24 hours of

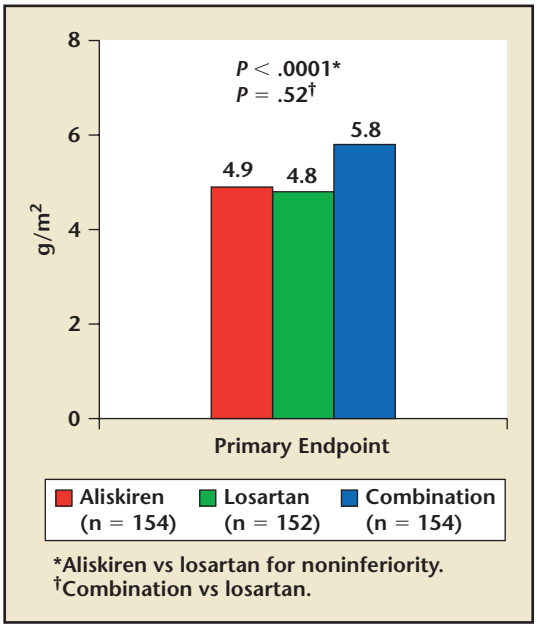

Figure 6. *The ALLAY trial examined whether aliskiren, alone or in combination with losartan, was more effective than losartan alone in reducing left ventricular hypertrophy in overweight hypertensive patients. The primary endpoint was a change in left ventricular mass index, as assessed by cardiac magnetic resonance imaging from baseline to week 36. ALLAY, Aliskiren Left Ventricular Assessment of Hypertrophy. Data from Solomon SD.[7] Adapted with permission from Cardiosource.*

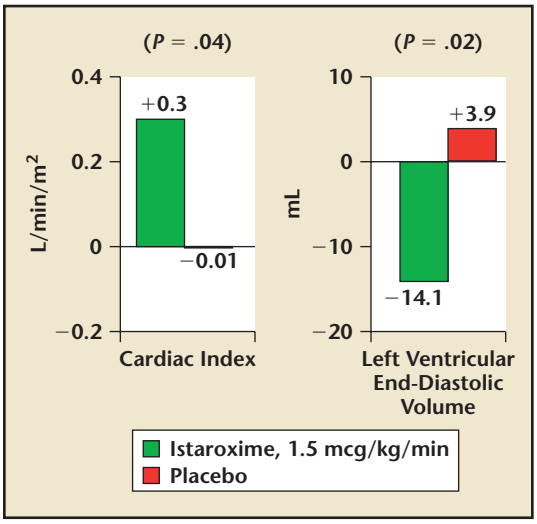

Figure 7. *Results from the HORIZON-HF trial suggest that high-dose istaroxime improves hemodynamics and diastolic function in patients with decompensated heart failure. HORIZON-HF, Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Inotropic Agent With Lusitropic Properties, in Acute Heart Failure Syndromes. Data from Gheorghiade M.[8] Adapted with permission from Cardiosource.*

admission, an estimated creatinine clearance of 20 to 80 mL/min, and systolic blood pressure exceeding 95 mm Hg. Patients were excluded if their B-type natriuretic peptide (BNP) levels were less than 250 pg/mL or their N-terminal proBNP levels were less than 1000 pg/mL, or if they had severe pulmonary disease, significant valve stenosis, ACS in the 2 weeks prior to screening, or a high risk for seizure (history of seizure, stroke, brain tumor, or brain surgery within 2 years).

Fewer patients in the 30-mg rolofylline group experienced an increase in serum creatinine of more than 0.3 mg/dL compared with placebo ($P < .05$). Increases in serum creatinine during HF therapy are associated with a poor prognosis. Death or rehospitalization for HF occurred in 19%, 24%, and 32% for the 30 mg, 20 mg, and 10 mg groups, respectively, and 33% for placebo, with a strong trend towards this endpoint reduction with rolofylline (Figure 8). Larger randomized trials will be needed to confirm whether important clinical endpoint reductions are achieved with this agent.

The SPIRIT II Study

The goal of the SPIRIT II study was to evaluate the safety and efficacy of the XIENCE™ V everolimus-eluting cobalt chromium coronary stent (Abbott Laboratories, Abbott Park, IL) compared with the TAXUS® paclitaxel-eluting stent (Boston Scientific, Natick, MA) among patients with de novo coronary lesions.[10] The 300 study subjects were randomized in a 3:1 ratio to everolimus-eluting stents or paclitaxel-eluting stents, with follow-up coronary angiography performed at 6 months. A subset of 152 patients also underwent IVUS and angiography at 6 months and 2 years. Patients were included in this study if they had 1 or 2 de novo coronary target lesions, stable angina, target vessel reference diameter 2.5 to 4.0 mm, lesion length of 28 mm or more, and stenosis of at least 50%.

The primary endpoint of in-stent late loss in a single lesion per patient at 6 months met the criteria for noninferiority and superiority for the everolimus-eluting stent group compared with the paclitaxel-eluting stent group (0.11 mm for everolimus vs 0.36 mm for paclitaxel [$P < .001$ for both noninferiority and superiority]) (Figure 9). However, this difference was not statistically significant at 2 years (0.33 mm for everolimus vs 0.34 for paclitaxel [$P = .61$]) in the subset of patients with 2-year data. The more recent SPIRIT III data also showed less in-segment late lumen loss in the everolimus group than in the paclitaxel group (0.14 mm vs

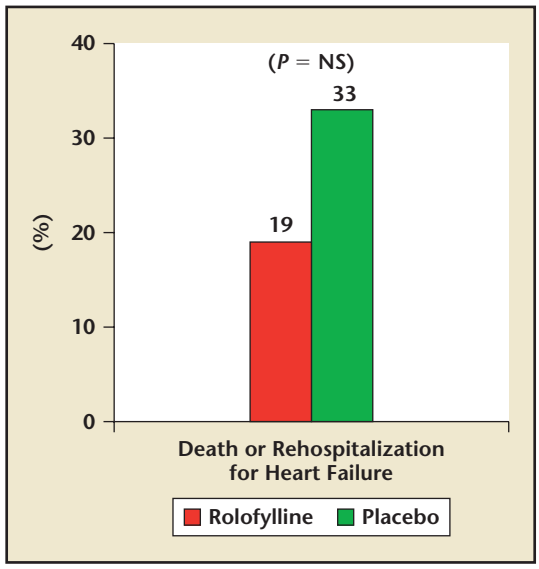

Figure 8. *The PROTECT pilot trial compared rolofylline with a placebo in patients with decompensated heart failure. PROTECT, Effects of Rolofylline, a New Adenosine A1 Receptor Antagonist, on Symptoms, Renal Function, and Outcomes in Patients With Acute Heart Failure; NS, not significant. Data from Massie BM.[9] Adapted with permission from Cardiosource.*

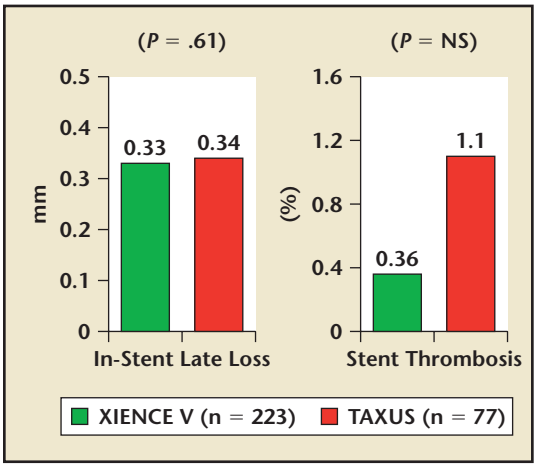

Figure 9. *The SPIRIT II study evaluated the safety and efficacy of the XIENCE V everolimus-eluting cobalt chromium coronary stent compared with the TAXUS paclitaxel-eluting stent among patients with de novo coronary lesions. NS, not significant. Data from Serruys PW.[10] Adapted with permission from Cardiosource.*

0.28 mm [$P < .001$ for noninferiority and $P = .004$ for superiority]) and confirms the reduction of late lumen loss with everolimus-eluting stents compared with paclitaxel-eluting stents.[11]

The ACCOMPLISH Trial

The Avoiding Cardiovascular Events through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial was designed to evaluate the safety and efficacy of the combination of amlodipine/benazepril compared with HCTZ/benazepril.[12] To be included in the trial, patients had systolic hypertension at or higher than 160 mm Hg or were currently on antihypertensive therapy, were 55 years or older, and had evidence of end-organ damage. The study participants (N = 11,462) were randomized to a fixed-dose combination of either amlodipine 5 mg/benazepril 20 mg or HCTZ 12.5 mg/benazepril 20 mg. After 1 month, the benazepril dose was increased to 40 mg in both arms. After further uptitration of HCTZ to 25 mg and of amlodipine to 10 mg in the respective groups, other antihypertensive agents could be added-on as needed to achieve a blood pressure target of less than 140/90 mm Hg, or, in patients with diabetes or chronic kidney disease, less than 130/80 mm Hg. The mean follow-up was 36 months.

The primary endpoint, a composite of cardiovascular mortality, stroke, MI, coronary revascularization, unstable angina, and resuscitation from sudden death, was reduced by 20% in the amlodipine/benazepril arm (9.2%) compared with the HCTZ/benazepril arm (11.4%) ($P = .0002$) (Figure 10). Cardiovascular death, stroke, and MI were also reduced by 20% ($P = .007$) in the amlodipine/benazepril arm. All other endpoints, including cardiovascular mortality, nonfatal MI, nonfatal stroke, and resuscitated sudden death, were similar between the 2 study groups.

Comment

This study is important because it confirms that combining an agent that affects the renin-angiotensin-aldosterone system with a calcium channel blocker is superior to combining it with a diuretic in reducing not only blood pressure, but also cardiovascular endpoints. These results run counter to those guidelines that recommend a diuretic as initial therapy for hypertension.

The TAPAS Trial

The Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction (TAPAS) trial evaluated the efficacy of thrombus aspiration during primary PCI compared with conventional PCI in patients with STEMI.[13] The primary endpoint was the post-procedural incidence of myocardial blush grade 0 or 1, an indicator of poor myocardial cell perfusion.

A post-procedural myocardial blush grade of 0 or 1 was observed in

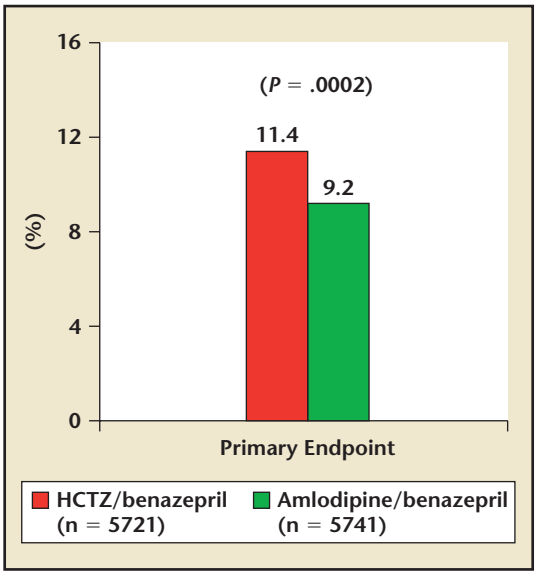

Figure 10. *In the ACCOMPLISH trial, the primary endpoint, a composite of cardiovascular mortality, stroke, MI, coronary revascularization, unstable angina, and resuscitation from sudden death, was reduced by 20% in the amlodipine/benazepril arm compared with the HCTZ/benazepril arm. ACCOMPLISH, Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension. Data from Jamerson K.[12] Adapted with permission from Cardiosource.*

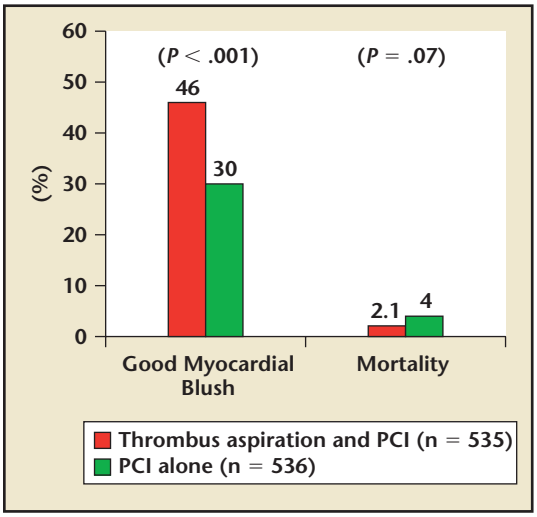

Figure 11. *The TAPAS trial evaluated the efficacy of thrombus aspiration during primary PCI compared with conventional PCI in patients with STEMI. TAPAS, Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction. Data from Zijlstra F.*[13] *Adapted with permission from Cardiosource.*

17% of the aspiration group and 26% of the conventional PCI group ($P < .001$), with complete ST-segment resolution observed in 57% of the aspiration group and 44% of the conventional PCI group ($P < .001$) (Figure 11). There was a trend in reduction of mortality from 4.0% to 2.1% with aspiration.

The ATHEROMA Study

The Atorvastatin Therapy: Effects on Reduction Of Macrophage Activity (ATHEROMA) trial compared the effects of low-dose (10 mg) versus high-dose (80 mg) atorvastatin on macrophage activity in carotid atherosclerotic plaques using ultrasmall super-paramagnetic iron oxide (USPIO)-enhanced T2*-weighted MRI, a marker for inflammation and perhaps of plaque vulnerability.[14] The 40 subjects had a carotid stenosis exceeding 40% on duplex examination and intraplaque accumulation of USPIO on MRI at baseline. Patients were randomized in a double-blind manner to either 10 mg or 80 mg atorvastatin daily for 12 weeks. Follow-up MRI imaging was performed at 6 and 12 weeks.

At 12 weeks, total cholesterol was reduced by 15.4% in the high-dose group and 3.3% in the low-dose group. Low-density lipoprotein cholesterol was reduced by 28.7% in the high-dose group and 14% in the low-dose group. A significant reduction from baseline in USPIO-defined signal intensity was observed in the 80-mg group at both 6 weeks ($P = .0003$) and 12 weeks ($P < .0001$) (Figure 12). No significant difference was observed in the low-dose arm at 6 weeks ($P = 1.5$) and 12 weeks ($P = .3$). At 12 weeks, the mean signal difference between the 2 groups was 0.24 ($P < .0001$).

Comment

This study provides very important insights into the ability of aggressive cholesterol modification to reduce plaque inflammation and provides a peek into the future of assessing plaque vulnerability. This approach may be a more important assessment of cardiovascular risk modification therapy effectiveness than models that simply measure changes in plaque volume. It also confirms the theory of cholesterol modification that "less is better." Further studies are needed to show that this assessment of plaque vulnerability corresponds to actual cardiovascular event reduction.

The REVERSE Trial

The Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial is the first large, randomized, double-blind study to include patients with both New York Heart Association (NYHA) class I and II HF.[15] The study was conducted to determine if cardiac resynchronization therapy (CRT) can

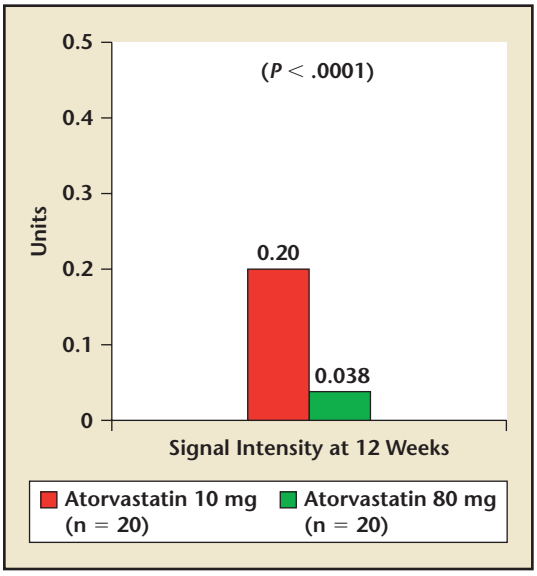

Figure 12. *The ATHEROMA trial compared the effects of low-dose (10 mg) versus high-dose (80 mg) atorvastatin on macrophage activity in carotid atherosclerotic plaques using USPIO-enhanced T2*-weighted magnetic resonance imaging, a marker for inflammation and perhaps of plaque vulnerability. ATHEROMA, Atorvastatin Therapy: Effects on Reduction Of Macrophage Activity; USPIO, ultra-small super-paramagnetic iron oxide. Data from Tang TY.*[14] *Adapted with permission from Cardiosource.*

prevent or slow HF progression in patients with asymptomatic LV dysfunction or mildly symptomatic disease. Patients with LV dysfunction (LV ejection fraction ≤ 40%), LV end-diastolic dimension of 55 mm or more, prolonged QRS duration (≥ 120 ms), and no indication for permanent pacing and who were taking optimal medical therapy were randomized to CRT ON (n = 419) or CRT OFF with optimal medical therapy (n = 191). The primary endpoint was the HF clinical composite response, which was defined as the percentage of patients who worsened with CRT ON versus CRT OFF. The composite endpoint included all-cause mortality, HF hospitalization, crossover due to worsening HF, NYHA class, and patient global assessment.

The primary endpoint, the percentage of patients who clinically worsened, was 16% for those with CRT ON versus 21% for those with CRT OFF (P = NS). The LV end-systolic volume index decreased 18.4 mL/m^2 for CRT ON compared with a decrease of only 1.3 mL/m^2 for medical therapy alone ($P < .0001$). The risk of HF hospitalization was reduced with CRT ON. This trial provides some insights into a potential benefit of early CRT in patients with less severely symptomatic HF.

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

Powerful New Data From HYVET

Information on treating hypertension in the elderly—in particular, people older than 80 years—has been incomplete and maybe even discouraging. Data extracted from large, clinical outcomes trials have indicated that effective antihypertensive therapy in older patients appears to reduce the incidence of stroke, but perhaps at the cost of an increase in mortality.

Before undertaking what would become a definitive prospective trial, the investigators of the Hypertension in the Very Elderly Trial (HYVET) conducted a pilot study that appeared to confirm the earlier conclusions: namely, that the stroke benefits of blood pressure reduction in the elderly might be offset by a corresponding increase in all-cause mortality.[16] HYVET studied hypertensive patients ages 80 or older. It was conducted in Europe, North Africa, Asia, and Australia. To enter the trial, patients were required to discontinue any previous antihypertensive drugs and to have a systolic blood pressure between 160 and 199 mm Hg during a placebo run-in period. Patients were excluded if they had evidence of HF or a history of recent hemorrhagic stroke, dementia, renal dysfunction, or accelerated hypertension.

Treatment was targeted to reduce blood pressure to below 150/80 mm Hg. Eligible patients were randomized to placebo or active treatment with the diuretic indapamide SR 1.5 mg/d, to which perindopril 2 mg/d, and then 4 mg/d, could be added if needed to achieve the goal blood pressure. The primary study endpoint was stroke, fatal and nonfatal; secondary endpoints included all-cause death as well as cardiovascular outcomes, other fatal outcomes, and HF.

A total of 1933 patients were randomized to active treatment and 1912 to placebo. The characteristics of the 2 groups were very similar: mean age was 83.5, 60% of patients were women, 90% had a previous history of hypertension, 12% had histories of previous cardiovascular events, and 7% were diabetic. The baseline blood pressure was 173/91 mm Hg in each group. The median follow-up time in the trial was 20 months, by which time blood pressure in the active-treatment group was 15/6 mm Hg lower than in the placebo group.

The primary endpoint of fatal plus nonfatal stroke was 30% lower in the active-treatment group (P = .055), but this finding was overshadowed by a significant reduction in total mortality of 21% (P = .019) with active treatment. Other noteworthy endpoints included reductions in the treated group of 39% in fatal stroke (P = .046), 64% in HF (P = .001), 19% in noncardiovascular death (P = NS), 23% in cardiovascular death (P = NS), 29% in cardiac death (P = NS), and 34% for all cardiac events ($P < .05$). Using a prespecified per-protocol analysis (based on patients remaining on therapy), the findings were even more powerful, including a 34% reduction in the total stroke primary endpoint (P = .025) and a 28% reduction in total mortality (P = .001). The treatment was well tolerated, and there was no evidence of differences between the 2 study groups in measures of glucose, renal function, or potassium.

Comments

These findings clearly have strong clinical implications. HYVET is the first trial to prospectively study the outcome effects of antihypertensive therapy in patients older than 80 years. Of particular importance, the previous concerns that such therapy might reduce strokes but increase fatal events can now be refuted. Indeed, the most compelling result of HYVET was the reduction in total mortality. In addition, all key cardiovascular endpoints were reduced or showed trends toward reduction.

In their presentation, the investigators pointed out that the criteria for patient selection for this trial might have favored a relatively healthy elderly hypertension cohort. Also, the patients achieved a mean systolic blood pressure only in the

Table 1
Results From the ONTARGET Trial

Outcome	Ramipril n = 8576 (%)	Telmisartan n = 8542 (%)	Combination n = 8502 (%)	Risk Ratio (95% CI), Telmisartan vs Ramipril	Risk Ratio (95% CI), Combination Therapy vs Ramipril
CV death/MI/stroke/ CHF hospitalization	16.5	16.7	16.3	1.01 (0.94-1.09)	0.99 (0.92-1.07)
CV death/MI/stroke	14.1	13.9	14.1	0.99 (0.91-1.07)	1.00 (0.93-1.09)
MI	4.8	5.2	5.2	1.07 (0.94-1.22)	1.08 (0.94-1.23)
Stroke	4.7	4.3	4.4	0.91 (0.79-1.05)	0.93 (0.81-1.07)
CHF hospitalization	4.1	4.6	3.9	1.12 (0.97-1.29)	0.95 (0.82-1.10)
CV death	7.0	7.0	7.3	1.00 (0.89-1.12)	1.04 (0.93-1.17)
Any death	11.8	11.6	12.5	0.98 (0.90-1.07)	1.07 (0.98-1.16)
Renal impairment	10.2	10.6	13.5	1.04 (0.96-1.14)	1.33 (1.22-1.44)

ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; CHF, congestive heart failure.
Reprinted with permission from Yusuf S et al.[18]

high 150s, so the study did not really address whether guideline recommendations for goal blood pressures below 140/90 mm Hg are justified. Still, the effect of this research will be to revitalize attention on diagnosing and treating hypertension in people older than 80 years.
[Michael A. Weber, MD, FACC, FAHA]

The ONTARGET Trial

Angiotensin-converting enzyme (ACE) inhibitors are standard therapy for the treatment of patients with coronary heart disease or HF, or who are at high risk of developing cardiovascular disease. These agents have extensive clinical trial evidence documenting their benefit in decreasing morbidity and mortality in these patient populations. Angiotensin receptor blockers (ARB) were developed in anticipation that they would have similar clinical benefits to ACE inhibitors, perhaps with a more favorable adverse event profile. The ARBs, however, currently do not have an evidence base demonstrating benefit that is comparable to that of the ACE inhibitors.

The goal of the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) was to determine whether the ARB telmisartan was noninferior to the ACE inhibitor ramipril, and whether a combination of the 2 drugs was superior to ramipril alone as a treatment to prevent vascular events in high-risk patients.[17] The trial enrolled 25,620 patients at high risk for coronary heart disease. All participants were at least 55 years old and had no evidence of HF. Patients were randomized to receive ramipril 10 mg/d, telmisartan 18 mg/d, or a combination of the 2. The mean duration of follow-up was 55 months.

Blood pressure was lower in the telmisartan group (by 0.9/0.6 mm Hg) and the combination-therapy group (by 2.4/1.4 mm Hg) than in the ramipril group. The primary endpoint (a composite of cardiovascular death, MI, stroke, or hospitalization for HF) occurred in a similar number of patients in all 3 treatment groups (Table 1). Compared with the ramipril group, telmisartan patients had lower rates of cough and angioedema but a higher rate of hypotensive symptoms. Patients given the combination treatment had higher rates of hypotensive symptoms, syncope, renal dysfunction, and hyperkalemia. In addition, they showed a trend toward an increased risk of renal function requiring dialysis.

Comments

The ARB telmisartan is similar to the ACE inhibitor ramipril in preventing cardiovascular events in patients at high risk for coronary heart disease. In this trial, as in other trials before it, patients receiving both the ACE inhibitor and the ARB were more likely to suffer adverse events, including hypotension, syncope, and worsening renal function.

These results indicate that in patients at high risk for coronary heart disease, either the ARB telmisartan or

the ACE inhibitor ramipril is equally effective in reducing future cardiovascular events. This study also confirms prior studies that suggest the combination of an ACE inhibitor and an ARB may produce increased adverse events.

[Karol E. Watson, MD, PhD]

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Main Points

- A pharmaco-invasive strategy appears promising for ST-segment elevation myocardial infarction patients without access to timely primary percutaneous coronary intervention (PCI).
- Distal protection devices have been found to be effective in reducing cardiovascular events in patients undergoing saphenous vein graft interventions.
- There was no benefit to a reload of clopidogrel in stable patients undergoing PCI, although there was a suggestion of a benefit in patients presenting with an acute coronary syndrome.
- Combining an agent that affects the renin-angiotensin-aldosterone system with a calcium channel blocker is superior to combining it with a diuretic in reducing blood pressure and cardiovascular endpoints.
- In a study of patients 80 years and older, treatment of hypertension significantly reduced rates of total mortality, fatal and nonfatal stroke, heart failure, and all cardiac events.
- The angiotensin-receptor blocker telmisartan was similar to the angiotensin-converting enzyme inhibitor ramipril in preventing cardiovascular events in patients at high risk for coronary heart disease.