Best of the ESC Congress 2008

Highlights From the European Society of Cardiology Congress, August 30-September 3, 2008, Munich, Germany

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Key words: Aortic stenosis • Coronary artery bypass grafting • C-reactive protein • Drug-eluting stents • Fish oil • Heart failure • Percutaneous coronary intervention • STEMI

The 2008 European Society of Cardiology (ESC) Congress featured studies on many important topics, including percutaneous coronary intervention (PCI) in high-risk ST-elevation myocardial infarction (STEMI) patients, the use of fish oil in patients with heart failure, drug-eluting stents (DES) in patients with multivessel or left main (LM) disease, and PCI versus coronary artery bypass grafting (CABG). There were also new trial data on rosuvastatin, combination ezetimibe-simvastatin, darapladib, and telmisartan.

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CARESS-in-AMI

The Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI) 30-day and 1-year results were presented by Carlo Di Mario, MD, of Royal Brompton Hospital and Imperial College (London, UK).[1] The 600 study subjects had STEMI and presented within 12 hours from symptom onset to a hospital without primary PCI capabilities. All patients had at least 1 high-risk characteristic (summation of ST elevation in all 12 leads, new left bundle branch block, previous myocardial infarction [MI], Killip class II or III, or left ventricular ejection fraction [EF] $\leq$ 35%). All patients received therapy with heparin, half-dose reteplase, and abciximab, and then were randomized to immediate transfer for PCI or standard therapy and rescue PCI if needed. The door-to-balloon time in the immediate transfer group was still 300 minutes.

The primary endpoint of the composite of death, reinfarction, or refractory ischemia at 30 days was less frequent in the immediate transfer group (4.4% vs 10.7%; P = .005) (Figure 1). There was no significant difference in major bleeding. At 1-year, there was a trend for benefit with immediate transfer (11.4% vs 16.4%; P = .07). PCI was performed in 86% of patients in the urgent transfer group and 30% of patients in the standard care group. This study would support the use of the heparin-reteplase-abciximab therapy in high-risk STEMI patients presenting to hospitals without primary PCI capabilities before urgent transfer for PCI.

GISSI-HF: n-3 PUFA

Results from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Heart Failure (GISSI-HF) trial on fish oil were

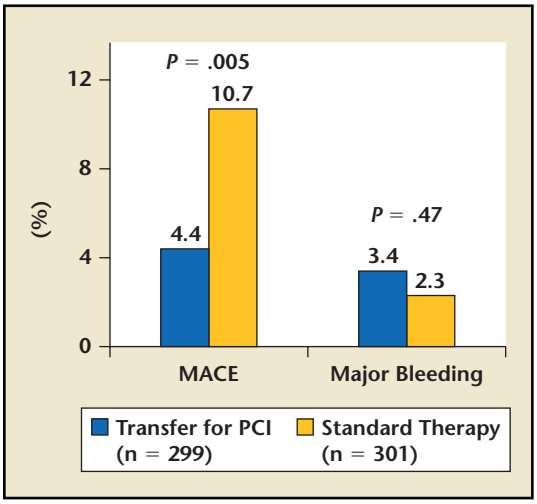

Figure 1. *In the CARESS-in-AMI trial, the primary endpoint of MACE (death, reinfarction, or refractory ischemia) at 30 days was less frequent in patients who were immediately transferred to PCI than in patients who received standard therapy and rescue PCI if needed. There was no significant difference in major bleeding. CARESS-in-AMI, Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction; MACE, major adverse coronary events; PCI, percutaneous coronary intervention. Data from Di Mario C et al.[1] Adapted with permission from Cardiosource.*

presented by Luigi Tavazzi, MD, of the University of Pavia (Pavia, Italy).[2] This study evaluated the effects of n-3 polyunsaturated fatty acids (n-3 PUFA) (1 g/d of 850-882 mg eicosapentaenoic acid) on mortality and morbidity in patients with symptomatic heart failure. Among the 6975 study subjects, 63.5% were categorized as New York Heart Association (NYHA) class II, 33.9% were in class III, and 2.6% were in class IV. The mean EF was 33%; half the patients had an ischemic cardiomyopathy and 29% had a dilated cardiomyopathy. Patients with an EF exceeding 40% were enrolled if they had been admitted to a hospital for heart failure within the previous 12 months. The primary endpoints of the trial included time to death and time to death or admission to a hospital for cardiovascular causes. Secondary endpoints included cardiovascular mortality; admission for heart failure, MI, or stroke; and cardiovascular mortality or all-cause mortality.

The 2 study groups did not significantly differ in the primary endpoint of death, but patients in the fish oil group had fewer arrhythmia-related hospital admissions (Figure 2). Patients receiving fish oil had an absolute 1.8% reduction of all-cause mortality (hazard ratio, 0.91; $P = .041$) and an 8% reduction in the combined primary endpoint of mortality and cardiovascular admissions ($P = .009$). There was no difference in study drug discontinuation rates between the placebo and fatty acid groups. These data are consistent with those from other investigators who have found that patients with heart failure benefit from n-3 PUFA in conjunction with optimal medical therapy.

GISSI-HF: Rosuvastatin

Results from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Heart Failure: Rosuvastatin Study were presented by Gianni Tognoni, MD, of Consorzio Mario Negri Sud (Santa Maria Imbaro, Italy).[3] The 4631 patients had chronic symptomatic heart failure (patients who had an EF > 40% had been admitted to a hospital with heart failure at least once in the preceding 12 months). They were studied to determine the effect of rosuvastatin in patients with chronic heart failure who lack a primary indication for the use of a statin.

The mean low-density lipoprotein cholesterol (LDL-C) levels were 56 to 57 mg/dL for both groups at baseline. LDL-C levels dropped to 42 mg/dL in the rosuvastatin group and remained the same in the control group. The primary endpoints were time to death and time to death or hospital admission for a cardiovascular condition, with a mean follow-up of 3.9 years.

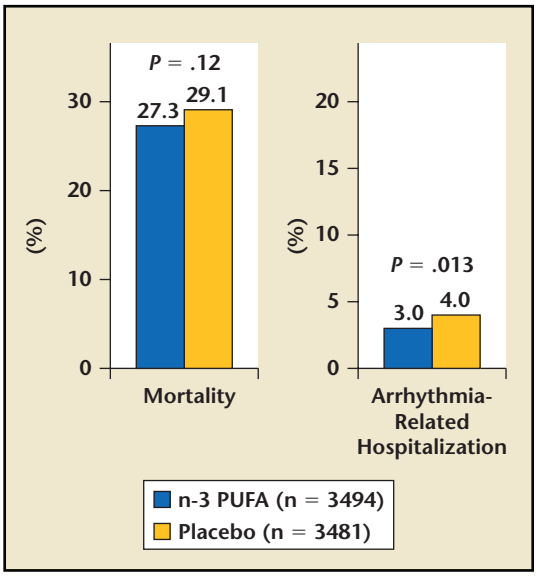

Figure 2. *In the GISSI-HF n-3 PUFA trial, fish oil supplements did not significantly reduce mortality as compared with placebo in patients with symptomatic heart failure. Patients in the fish oil group did experience fewer hospital admissions for arrhythmia-related issues. GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Heart Failure; n-3 PUFA, n-3 polyunsaturated fatty acids. Data from the GISSI-HF investigators.[2] Adapted with permission from Cardiosource.*

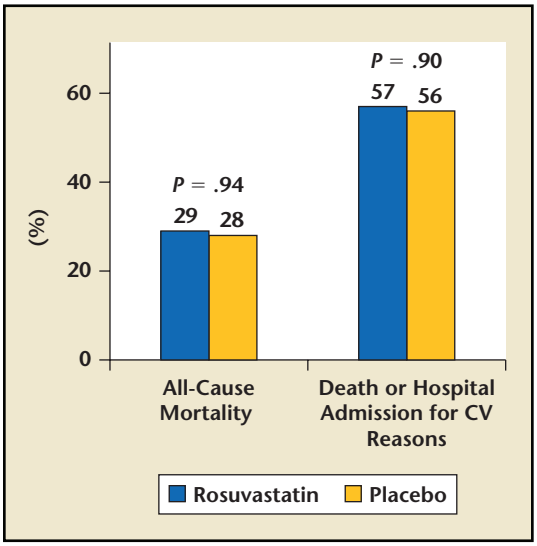

Figure 3. *The GISSI-HF Rosuvastatin study showed no significant difference in the incidence of all-cause mortality or the endpoint of death or CV-related hospital admissions among patients with chronic symptomatic heart failure who received rosuvastatin or placebo. GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Heart Failure; CV, cardiovascular. Data from the GISSI-HF investigators.[3] Adapted with permission from Cardiosource.*

There was no difference in the incidence of all-cause mortality or the endpoint of death and cardiovascular-related hospital admission (Figure 3). There was no difference in cardiac mortality, sudden cardiac death, stroke, or MI rates. These trial results would indicate that there is no benefit from the use of statins in a heart failure population of patients who do not have a primary indication for lipid-lowering therapy, particularly when their LDL-C levels are low at baseline. This study does not at all change our approach to aggressive lipid modification in patients who have atherosclerotic coronary and vascular disease or in other heart failure patients whose baseline lipids do not meet current guideline goals.

The SEAS Trial

The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial evaluated the ability of combination ezetimibe-simvastatin (EA) to prevent the progression of aortic stenosis in patients with asymptomatic mild-to-moderate aortic stenosis as compared with placebo.[4] Aortic stenosis seems to have pathologic similarities to atherosclerotic disease, with inflammatory cells and compounds playing a prominent role in its development and progression. This study tested the hypothesis that lipid reduction therapy would slow the progression of aortic stenosis.

There was no difference in the primary endpoint of aortic valve replacement and cardiovascular events between the treatment group and the placebo group (Figure 4). There was a reduction of a secondary endpoint, a composite of ischemic events, in the EA group. Of interest is the finding that EA as compared with placebo was associated with higher rates of cancer and deaths from cancer. There was no specific type of cancer associated with EA.

The finding of higher rates of cancer with EA has not been observed in other EA trials, and therefore this question remains an open and important one. Clinical outcome trials with EA are ongoing and will be key for clinicians to understand the advantage side of the equation and balance it with any proven shortcomings of this approach. There is, however, general consensus when it comes to LDL-C that "lower is better," whether it be the result of using a statin, a resin binder, or lifestyle modification. In patients who do not achieve goal LDL-C reduction with lifestyle modification and statin therapy or who do not tolerate statin therapy, the use of ezetimibe seems to be a reasonable option along with niacin and resins. Until the cancer

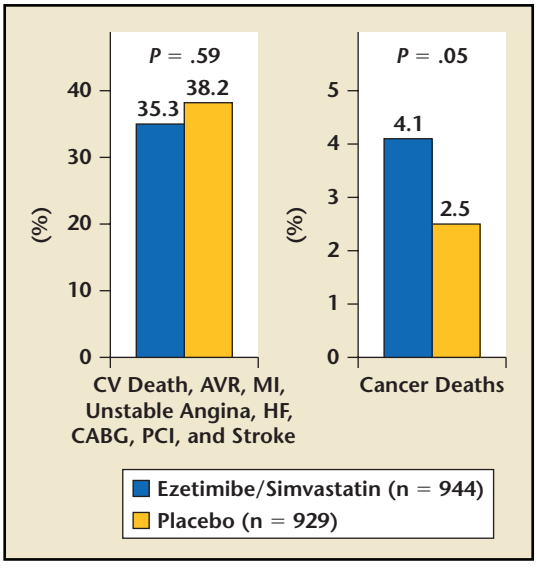

Figure 4. *The SEAS trial evaluated the ability of combination ezetimibe-simvastatin to prevent the progression of aortic stenosis in patients with asymptomatic mild-to-moderate aortic stenosis as compared with placebo. There was no significant difference in the primary endpoint, but ezetimibe-simvastatin treatment was associated with higher rates of cancer deaths. SEAS, Simvastatin and Ezetimibe in Aortic Stenosis; CV, cardiovascular; AVR, aortic valve replacement; MI, myocardial infarction; HF, heart failure; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention. Data from Rossebø AB et al.[4] Adapted with permission from Cardiosource.*

concern is resolved, ezetimibe should be reserved as add-on therapy and not as a first-line approach to LDL-C modification in patients who can tolerate treatment with statins, niacin, or resin.

The LEADERS Trial

Results from the Limus Eluted From A Durable vs Erodable Stent Coating (LEADERS) trial were presented by Stephan Windecker, MD, of the University Hospital Bern (Bern, Switzerland).[5] This randomized study examined a stainless steel stent coated with a polylactic acid biodegradable polymer delivering a semi-synthetic analog of sirolimus, biolimus (BioMatrix™, Biosensors, Int., Newport Beach, CA) in comparison with the sirolimus-eluting Cypher® stent (Cordis Corp./Johnson & Johnson, Inc., Miami Lakes, FL). By 9 months, the polymer degrades to lactic acid, leaving a bare stainless steel stent.

The primary endpoint of the study was the composite of cardiovascular death, MI, or urgent target vessel revascularization within 9 months. The primary composite event outcome was not significantly different between the biolimus group and the sirolimus group (9.2% vs 10.5%; P = .39 for superiority and P = .003 for noninferiority) (Figure 5). Biolimus was also noninferior with regard to in-stent diameter stenosis and late loss compared with the sirolimus stent. Cumulative stent thrombosis rates out to 9 months were similar between the 2 stents, suggesting that the biodegradable polymer had no incremental benefit compared with the sirolimus-eluting stent.

How the biolimus stent would have performed compared with other commercially available stents with different drug-delivery systems (polymer and drug) remains unanswered. Comparisons of very late thrombosis rates would also be important and remain unknown for now. This study illustrates that the biolimus stent is noninferior to a sirolimus-eluting stent.

IBIS-2

The Integrated Biomarker and Imaging Study–2 (IBIS-2) results were presented by Willem Wijns, MD, PhD, of the Cardiovascular Centre, Onze-Lieve-Vrouw Hospital (Aalst, Belgium).[6] The goal of the trial was to study the effect of the lipoprotein-associated phospholipase A_2 inhibitor (Lp-PLA_2) darapladib on coronary artery deformability and levels of high-sensitivity C-reactive protein (hsCRP) in patients with coronary artery disease. Lp-PLA_2 is present within the necrotic core of atherosclerotic plaques and may play an important role in plaque instability. It is a circulating enzyme secreted by inflammatory cells such as macrophages that binds to lipoproteins containing apolipoprotein B. Lp-PLA_2 rapidly degrades oxidatively modified phospholipids in LDL-C, leading to formation of proinflammatory and cytotoxic compounds. The direct inhibition of Lp-PLA_2 by an oral agent offers a novel method to stabilize atherosclerotic plaque.

The 330 study subjects were undergoing diagnostic coronary angiography for either chronic coronary artery disease or an acute coronary syndrome indication. They were randomized to receive 160 mg of darapladib or placebo. Patients underwent intravascular ultrasound on a nonintervened segment of the coronary artery.

The coprimary endpoints of plaque deformability and hsCRP levels were similar between the 2 groups. Patients treated with darapladib experienced no significant change in the necrotic core volume, whereas the placebo group had further expansion over the 12 months (Figure 6). Concern was raised when the darapladib group experienced a 3–mm Hg increase in blood pressure relative to placebo. Further study is warranted to determine the implications of this mode of plaque-stabilizing therapy on rates of cardiovascular events and on the progression and morphology of atherosclerotic plaques, particularly in patients who

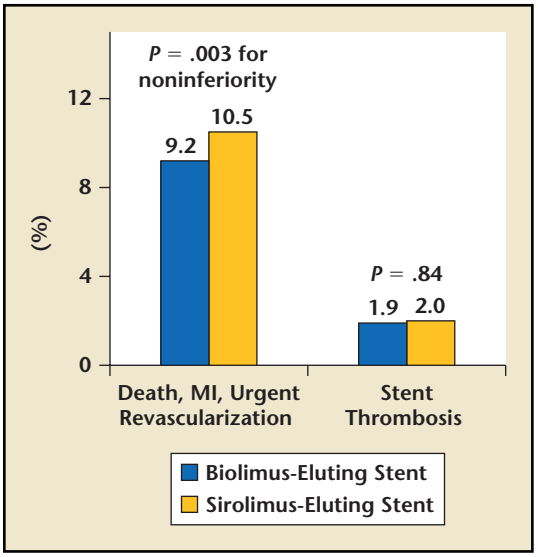

Figure 5. *The LEADERS trial compared the use of a stainless steel stent coated with a polylactic acid biodegradable polymer delivering a semi-synthetic analog of sirolimus, biolimus, with a sirolimus-eluting stent. The primary composite event outcome and rates of stent thrombosis were not significantly different between the biolimus patients and the sirolimus patients. LEADERS, Limus Eluted From A Durable vs Erodable Stent Coating; MI, myocardial infarction. Data from Windecker S et al.[5] Adapted with permission from Cardiosource.*

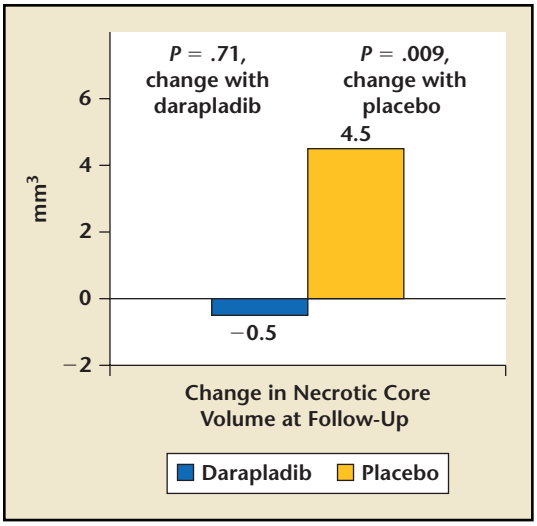

Figure 6. *The IBIS-2 study examined the effects of darapladib in patients undergoing diagnostic coronary angiography for either chronic coronary artery disease or an acute coronary syndrome indication. Patients treated with darapladib experienced no significant change in the necrotic core volume, whereas the placebo group had further expansion at 12 months. IBIS-2, Integrated Biomarker and Imaging Study–2. Data from Wijns W.[6] Adapted with permission from Cardiosource.*

have not progressed to the point of developing obstructive coronary artery disease.

SYNTAX

The Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) trial 1-year follow-up data were presented by Patrick Serruys, MD, PhD, of Thoraxcenter (Rotterdam, the Netherlands).[7] SYNTAX compared CABG with a PCI strategy using the Taxus® paclitaxel-eluting stent (Boston Scientific Corp., Natick, MA). The patients in this trial had multivessel or LM coronary artery disease and were considered by both surgeons and interventional cardiologists to be appropriate candidates for either revascularization strategy.

A total of 1800 patients were randomized to CABG or DES-PCI. Among the study group, 66% had triple vessel disease without LM involvement, 3.4% had isolated LM disease, 5.3% had LM with single-vessel disease, 11.8% had LM with double-vessel disease, and 13.7% had LM with triple-vessel disease. There were similar numbers of bifurcation lesions (73%) and trifurcation lesions (11%) in the 2 groups.

In the DES group, there was an increase in the primary endpoint of major adverse cardiac and cardiovascular events (all-cause death, cerebrovascular event, MI, or repeat revascularization) (12.1% vs 17.8%; $P = .0015$). This increase was driven by a higher rate of revascularization in the DES group versus the CABG group (5.9% vs 13.7%; $P < .0001$). There was no difference in the "harder" cumulative event rates of death, MI, and stroke between the 2 groups. However, the risk of stroke was more than 3 times greater in the CABG group as in the DES group (2.2% vs 0.6%; $P = .003$). Symptomatic graft-occlusion and stent thrombosis rates were between 3.3% and 3.4% for both groups.

The major difference in the composite event rate between DES and CABG was driven by an absolute increase in the revascularization rate of 7.8% with DES. However, this event must be compared with an absolute increase in stroke risk of 1.6% with CABG. How a clinician applies the results of this trial will be determined by how he or she ranks the impact of the incidence of stroke versus revascularization on a patient's well-being.

The CARDia Study

The Coronary Artery Revascularization in Diabetes (CARDia) study was designed to demonstrate the noninferiority of PCI compared with CABG in diabetes patients with multivessel coronary artery disease.[8] On an intention-to-treat basis, the 12-month event rates of death, MI, and stroke were no different between CABG and PCI (10.2% vs 11.6%; $P = .63$) (Figure 7). There was a strong trend towards an increase in stroke with CABG, with a similar magnitude difference observed in the SYNTAX trial (2.5% vs 0.4%; $P = .09$) and an

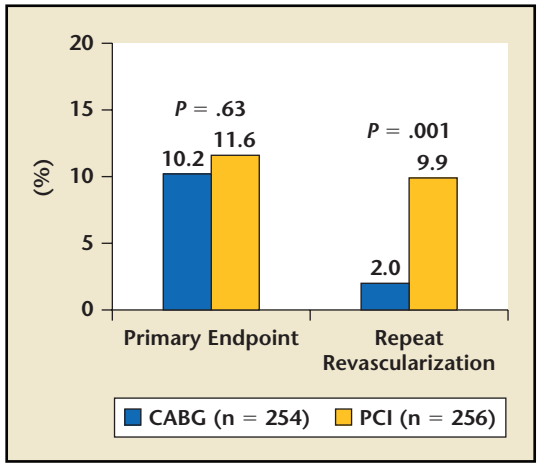

Figure 7. *The CARDia study was designed to demonstrate the noninferiority of PCI compared with CABG in diabetes patients with multivessel coronary artery disease. The 12-month event rates of death, myocardial infarction, and stroke were no different between CABG and PCI groups. The PCI group had a significantly higher rate of repeat revascularization. CARDia, Coronary Artery Revascularization in Diabetes; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft. Data from Kapur A.[8] Adapted with permission from Cardiosource.*

increased rate of revascularization with PCI compared with CABG (9.9% vs 2.0%; $P = .001$). In the PCI group, 71% of the stents were DES. This trial, although underpowered, does support a PCI approach to patients with diabetes who have multivessel coronary artery disease.
[Norman E. Lepor, MD, FACC, FAHA, FSCAI]

The TRANSCEND Trial

The concept of general cardiovascular protection began with the Heart Outcomes Prevention Evaluation (HOPE) study published in 2000.[9] That trial studied patients with clinical histories of coronary disease, stroke, peripheral arterial disease, and complex diabetes and compared the effects of the angiotensin-converting enzyme (ACE) inhibitor ramipril with placebo during a 54-month period. The primary endpoint in that trial was a composite of cardiovascular death, MI, and stroke, and ramipril produced a relative reduction of 22% in this outcome compared with placebo.

Since that time, ramipril has been recommended in the wide range of patients who fit the HOPE profile. More recently, the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), which was performed in patients similar to those in HOPE, established that the benefits of the angiotensin receptor blocker telmisartan were similar to those of ramipril.[10] Most recently, the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (TRANSCEND) compared telmisartan with placebo in patients similar to those in HOPE, but characterized by ACE-inhibitor intolerance. Results from TRANSCEND were presented by Koon K. Teo, MB, PhD, of McMaster University (Hamilton, Ontario, Canada).[11]

Methods

The study was performed in 5926 ACE inhibitor–intolerant patients who were randomized to telmisartan 80 mg/d (n = 2954) or placebo (n = 2972). Importantly, all patients continued to receive appropriate therapies for their underlying coronary, stroke, hypertension, and diabetic conditions. Patients were evaluated at 6-month periods throughout the trial (median duration: 56 months). The primary endpoint of the study was a variant on the original HOPE endpoint: it retained the 3 individual components of cardiovascular death, MI, and stroke, but—presumably in an attempt to enhance the power of the study—added hospitalization for heart failure. Outcome events were rigorously adjudicated by a blinded endpoints committee.

Results

Demographic and clinical features of the patients were similar in the 2 treatment arms. The average age was 67 years, and 43% of the patients were women. There were previous histories of hypertension in 76% of patients and of diabetes in 36% of patients. The mean blood pressure at baseline was 141/82 mm Hg in both groups.

By the end of the study, vital data were available in 99.7% of patients. Of note, of the 81% of telmisartan patients who were still taking this drug, almost all (2086 out of 2122) were receiving the full 80-mg dose. However, there were some potentially important differences between the telmisartan and placebo arms in their concomitant therapies. Of note, more patients in the placebo group finished taking diuretics (40% vs 34%) and more received calcium channel blockers (46% vs 38%). Almost certainly, these differences reflected the intention of the study investigators to adequately control blood pressure in their patients.

During the study, blood pressure was lower in the telmisartan group than in the placebo group; the weighted difference between the groups was approximately 4.0/2.2 mm Hg. The event rates for the primary composite endpoint were 15.7% in the telmisartan group and 17.0% in the placebo group. This relative risk reduction of 8% was not statistically significant.

The principal secondary endpoint for TRANSCEND was the original HOPE triad of cardiovascular death, MI, and stroke (but excluding hospitalization for heart failure). The event rate for this secondary outcome was 13.0% in the telmisartan group and 14.8% in the placebo group. This relative risk reduction of 13% reached statistical significance ($P = .048$). A further secondary endpoint of total hospitalization for cardiovascular events demonstrated an 8% advantage for the telmisartan arm, a finding that again achieved significance. None of the 4 individual components of the primary composite endpoint demonstrated a significant difference between the telmisartan and placebo arms.

Interpretation

The results from TRANSCEND are completely consistent with the conclusions that came from the HOPE trial. The apparent reduction in the magnitude of benefit for the original HOPE endpoint—a 22% risk reduction with ramipril in HOPE to a 13% reduction with telmisartan in TRANSCEND—can readily be explained by the secular changes in underlying cardiovascular medicine. For example, the use of lipid-lowering agents, particularly statins, had doubled during the time period between the 2 studies. The relatively greater proportion of women and patients with hypertension in TRANSCEND might also have somewhat affected the outcomes.

Confirming this conclusion are the results of ONTARGET, which was conducted simultaneously with TRANSCEND and established the close similarity in cardioprotection of ramipril and telmisartan. This provides useful information because it establishes that for the large numbers of patients who fit the profile of the study cohorts in HOPE and TRANSCEND, treatment with this angiotensin receptor blocker provides benefits comparable with those produced by ramipril.

The use of heart failure as an addition to the primary endpoint in TRANSCEND had the unfortunate effect of confounding interpretation of the study. In fact, some critiques of the trial—including a formal commentary given at the time of the presentation of the trial at the ESC Congress—might have led to some confusion. It should be emphasized that from a clinical trials point of view, there are 2 separate aspects of heart failure: prevention and treatment.

The trials utilizing telmisartan that have addressed prevention of heart failure have been TRANSCEND and ONTARGET. Although the effect of telmisartan on heart failure prevention did not differ from placebo in TRANSCEND, the effect of telmisartan on heart failure in ONTARGET did not differ from ramipril. Based on these observations, it is reasonable to conclude that the ability of telmisartan to prevent new heart failure is not established in the types of patients studied in these trials, but that it does not appear to be different from that of a widely used ACE inhibitor.

These findings have no relevance to the use of ACE inhibitors or angiotensin receptor blockers in the treatment of patients with heart failure. Not only was this question not studied in ONTARGET or TRANSCEND, but patients with any evidence of heart failure were specifically excluded from entry into these trials. Any comments based on TRANSCEND comparing the relative values of telmisartan and other angiotensin receptor blockers for treating hypertension are therefore invalid.

Following TRANSCEND, it seems reasonable to regard telmisartan as a useful alternative to ramipril in patients at high cardiovascular risk. Choosing either of these agents for cardioprotection can now be fully justified based on recent clinical trials; some clinicians might prefer to select the angiotensin receptor blocker because of its tolerability and, where hypertensive patients at high risk are concerned, its blood pressure–lowering efficacy. ■

[Michael A. Weber, MD, FACC, FAHA]

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Main Points

- A study of high-risk ST-elevation myocardial infarction patients supports the use of the heparin-reteplase-abciximab therapy in patients who present to hospitals without primary percutaneous coronary intervention (PCI) capabilities before urgent transfer for PCI.
- Data from a new trial supports previous studies suggesting that patients with heart failure benefit from fish oil in conjunction with optimal medical therapy.
- Ezetimibe should be reserved as add-on therapy and not as a first-line approach to low-density lipoprotein cholesterol modification in patients who can tolerate treatment with statins, niacin, or resin.
- In a study of patients with coronary artery disease, those treated with darapladib experienced no significant change in the necrotic core volume, whereas a placebo group had further expansion.
- A new study supports a PCI approach to patients with diabetes who have multivessel coronary artery disease.
- Telmisartan can be considered a useful alternative to ramipril in patients at high cardiovascular risk.

TAXUS and cardiac surgery: the SYNTAX study. Paper presented at: European Society of Cardiology Congress; August 30-September 3, 2008; Munich, Germany.
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