# ACC.14: Update on the Prevention, Diagnosis, and Treatment of Cardiovascular Disease

***Highlights From the 63rd Annual Scientific Sessions of the American College of Cardiology, March 29-31, 2014, Washington, DC***

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**KEY WORDS**

Transcatheter aortic valve replacement • Primary percutaneous coronary intervention • Stem cell therapy

Over 13,000 cardiovascular team members gathered to focus on the prevention, diagnosis, and treatment of cardiovascular disease at the 63rd Annual Scientific Sessions of the American College of Cardiology (ACC) from March 29 to 31, 2014, in Washington, DC. Here we examine important late-breaking clinical research studies and first reports of new data presented at ACC 2014 regarding pioneering developments in cardiology—ranging from transcatheter aortic valve replacement (TAVR), to the use of PCSK9 inhibitors in statin-intolerant patients, to the use of mesenchymal stem cells in patients with ischemic heart failure.

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## Primary Percutaneous Coronary Intervention

### *How Effective Are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention?*

Among patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI), with

selective use of abciximab (ie, bailout) and preprocedure dual antiplatelet therapy, the use of bivalirudin was found to be inferior to unfractionated heparin (UFH). Bivalirudin was associated with an increase in adverse cardiovascular events, due to an increase in myocardial infarction (MI)/stent thrombosis. There was no major bleeding reduction with bivalirudin, which is often touted as the predominant reason to use this agent; however, this may have been related to the lower vascular complication rate of radial arterial access which was commonly used in this study.[1]

Adeel Shahzad, MD, of Liverpool Heart and Chest Hospital (Merseyside, United Kingdom), presented the controversial findings, which randomized 1829 eligible patients and assigned 914 to UFH and 915 to bivalirudin for intraprocedural anticoagulation. The patients randomized to bivalirudin received a 0.75 mg/kg bolus followed by a 1.75 mg/kg/h infusion and those in the heparin arm received 70 units/kg body weight bolus prior to the procedure. Both groups followed the same protocol for selective use of abciximab bailout following the European Society of Cardiology guidelines. The primary efficacy endpoint was a composite of all-cause mortality, reinfarction, cerebrovascular accident, or unplanned target lesion revascularization (TLR) at 28 days; the primary safety endpoint was major bleeding.

At 28 days, there were 46 deaths, 11 strokes, 21 reinfarctions, and 1 TLR in the bivalirudin arm for a major adverse cardiovascular event (MACE) rate of 8.7% versus 36 deaths, 6 strokes, 7 reinfarctions, and no TLR in the heparin group, for a MACE rate of 5.7% (Figure 1). According to Shahzad, this event rate was similar to that observed in other large, multicenter randomized trials of bivalirudin, including EUROMAX (European Ambulance ACS Angiox) and HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction). Early stent thrombosis was the largest driver of events, with 24 in the bivalirudin arm and 6 in the heparin group, which was statistically significant with a wide confidence interval (relative risk [RR] = 3.91%, 95% confidence interval [CI], 1.6-9.5; $P = .001$).

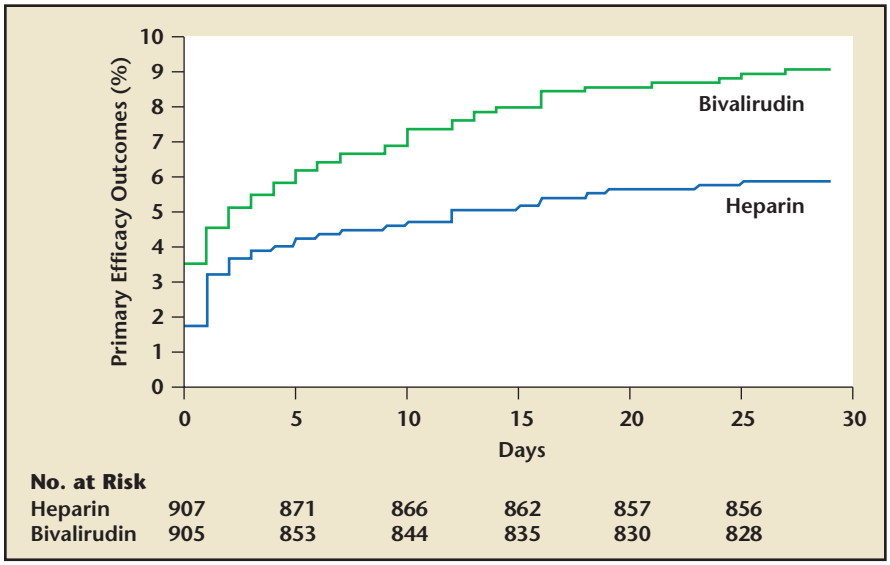


**Figure 1.** Rate of first major adverse cardiac event (MACE) event in the How Effective Are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention (HEAAT PPCI) trial. Reproduced with permission from CardioSource.

There was no clinically or statistically significant difference in major or minor bleeding rates: 83 minor bleeds and 113 major bleeds in the bivalirudin arm versus 98 and 122, respectively, in the heparin group. It was suggested that this lack of a bleeding rate benefit with bivalirudin was possible because of the high rate of radial procedures (80%-85%) in this study.

One of the aspects of this study that drew the strongest comments from the panel was the method the investigators used to consent patients for the study. The researchers treated the patients, evenly assigning them to either of the study arms, and then "when they were awake and feeling better" they asked them to consent to being in a research study and to consent to follow-up. Using this approach the authors were able to obtain consent from all but three of the patients initially randomized. Some panelists thought that this was a violation of the Helsinki accords but the authors defended their methods noting that three ethics committees had independently approved the study design and that both drugs are commercially approved and available for use for this indication.

### *Bavarian Reperfusion Alternatives Evaluation*

The majority of trials have separately assessed antiplatelet and antithrombotic therapy for the treatment of patients undergoing PPCI for STEMI. The Bavarian Reperfusion Alternatives Evaluation (BRAVE) 4 trial sought to study the safety and efficacy of combination therapy of prasugrel + bivalirudin compared with clopidogrel + UFH, according to trial presenter Gert Richardt, MD, from the German Heart Center (Munich, Germany).[2]

The targeted patient population included patients aged ≥ 18 years presenting with chest pain for ≥ 20 minutes but < 24 hours

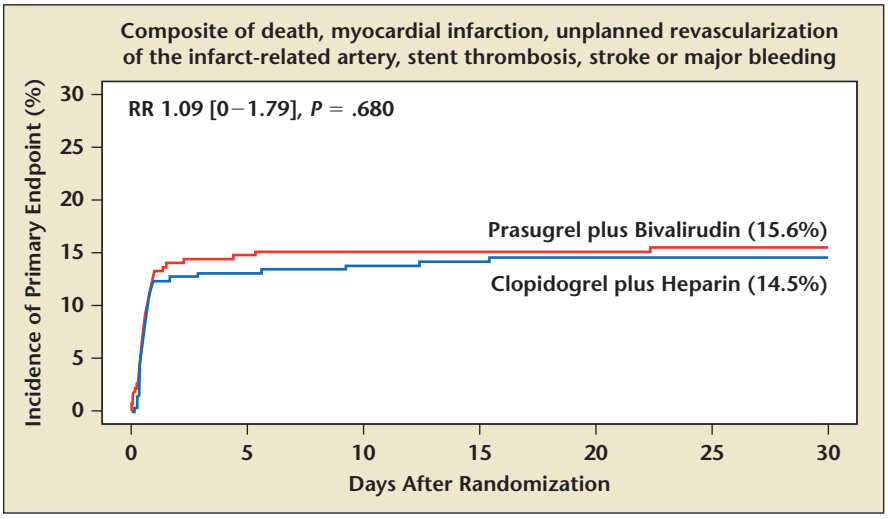


**Figure 2.** Primary endpoints in the Bavarian Reperfusion Alternatives Evaluation (BRAVE) 4 trial. RR, relative risk. Reproduced with permission from CardioSource.

from symptom onset who had ST-segment elevation ≥ 0.1 mV in ≥ two adjacent limb leads or ≥ 0.2 mV in ≥ two contiguous precordial leads or a new left bundle branch block, who were amenable to PPCI. Follow-up was out to 30 days. Mean patient age was 61 and mean left ventricular ejection fraction (LVEF) was 45%; 23% of the patients enrolled were women.

The investigator-initiated trial, conducted at three German centers, was originally designed to enroll over 1200 patients; the trial was stopped early, however, due to slow recruitment, with just 548 patients enrolled: 271 to prasugrel + bivalirudin and 277 to clopidogrel + UFH. Baseline characteristics were similar between the two arms. The majority of patients presented with inferior/posterior (50%) or anterior (42%) STEMI. Median systolic blood pressure (BP)/diastolic BP was 130/77 mm Hg and median ischemic time was 275 minutes. Baseline thrombolysis in MI flow grade was 0/1 in 63% of the patients. A stent was deployed in approximately 87% of patients, and 8% were conservatively managed. Crossover rates were low: prasugrel, 7%, and clopidogrel, 4%. In one arm, a 60-mg loading dose of prasugrel plus an intravenous bolus of bivalirudin, 0.75 mg/kg, was followed by an infusion of 1.75 mg/kg. In the other arm, clopidogrel was given at 600 mg, then heparin was given as a 70- to 100-IU/kg bolus.

The primary endpoint of death, MI, unplanned revascularization of the infarct-related artery, stent thrombosis, stroke, or major bleeding at 30 days was similar between the prasugrel + bivalirudin and the clopidogrel + UFH arms (15.6% vs 14.5%; $P = .68$) (Figure 2). Similarly, the secondary ischemic endpoint (death, MI, revascularization of the infarct-related artery, stent thrombosis, or stroke) was similar (4.8% vs 5.5%; $P = .89$). However, non–coronary artery bypass graft-related bleeding though numerically higher in the prasugrel + bivalirudin arm (14.1% vs 12.0%; $P = .54$) did not achieve statistical significance. Mortality at 30 days was virtually the same in both groups: 2.6% vs 2.5% ($P = .85$).

Thus, this suggests that there was no difference for ischemic or bleeding endpoints between a strategy of using prasugrel + bivalirudin compared with clopidogrel + UFH in patients with STEMI undergoing PPCI. Because the trial was terminated early, it was unfortunately underpowered to test its primary hypothesis.

Panelists agreed that the optimal antiplatelet/antithrombotic regimen in the patients undergoing PPCI remains an unanswered question because the majority of trials have been restricted to studying one pharmacologic agent versus another (either antithrombotic or antiplatelet), not the combination, which is why this trial is unique. In theory, use of more potent agents should be synergistic in high-risk PCIs such as STEMI, although that signal was not evident in the BRAVE 4 trial. This will need to be further assessed in future trials. Long-term follow-up of the BRAVE 4 trial is also awaited.

## Resistant Hypertension

### *SYMPLICITY HTN-3*

Although renal denervation with the Symplicity catheter (Medtronic, Minneapolis, MN) was found to be safe, it did not provide a significant advantage over a sham procedure for reducing office-based BP in the SYMPLICITY HTN-3 trial, according to presenter Deepak Bhatt, MD, MPH.[3]

The SYMPLICITY HTN-3 trial randomized 535 patients with resistant hypertension (systolic BP > 160 mm Hg despite taking maximal doses of at least three antihypertensive medications, one of which had to be a diuretic) in a 2:1 fashion to either renal denervation (intervention group) or renal angiography only (control group).

Through 6 months, office systolic BP dropped significantly from baseline in both the denervation group (14.13 mm Hg) and the sham-control group (11.74 mm Hg) yielding a nonsignificant between-group difference of only 2.39 mm Hg ($P = .26$ with a superiority margin of 5 mm Hg). Likewise, the reduction in average 24-hour

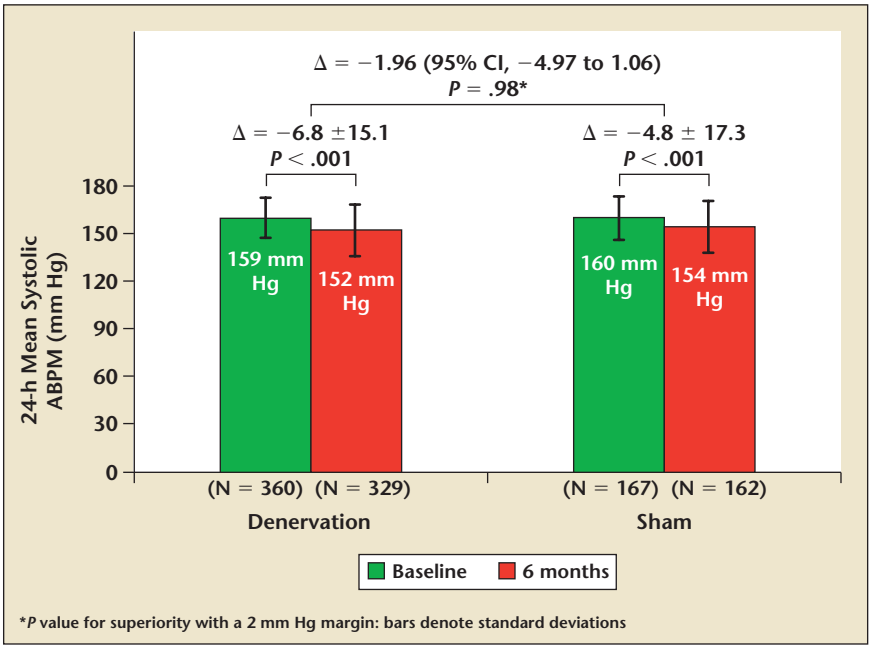


**Figure 3.** Secondary efficacy endpoints from the SYMPLICITY HTN-3 trial. ABPM, ambulatory blood pressure monitoring; CI, confidence interval. Reproduced with permission from CardioSource.

ambulatory BP in the denervation versus the sham-control group yielded a nonsignificant difference of only 1.96 mm Hg (6.75 vs 4.79 mm Hg; $P = .98$ with a superiority margin of 2 mm Hg). There was no difference in the rate of adverse events (Figure 3). All patients underwent renal artery angiography at the time of the study.

The trial, the first to include a sham-control group, did show that renal denervation was safe. The primary safety endpoint was a composite event rate of all-cause mortality, end-stage renal disease, embolic events resulting in end-organ damage, renovascular complications, or hypertensive crisis at 1 month or new renal-artery stenosis of more than 70% at 6 months. The composite event rate was no different in the denervation and control groups (1.4% vs 0.6%; $P = .67$) and there were no differences in renal function at any point during the study in either group.

The inclusion criteria for this trial were developed to ensure that only compliant patients with true treatment-resistant hypertension were enrolled. Patients had to undergo 24-hour ambulatory BP monitoring and also be assessed for medication adherence. After all these criteria were applied, only one-third of patients screened actually enrolled; this implies that the prevalence of true resistant hypertension may be less common than initially believed.

Some limitations of the study noted by the investigators include the fact that drug adherence was not confirmed (via blood tests), the follow-up period was short, the relative inexperience of operators with the renal denervation procedure, and an inability to directly assess if the renal arteries were actually denervated after the procedure.

There were many explanations for the lack of efficacy observed with renal denervation compared with the sham procedure. Some panelists noted that the technique used for denervation in this study may not have been adequate and that better devices are required for more complete and targeted denervation. Interestingly, the BP reduction observed in the denervation arm was less (14 mm Hg) than reported in earlier phase I/II renal denervation trials (20-25 mm Hg), including SYMPLICITY 1, SYMPLICITY 2, REDUCE HTN, and EnligHTN. Although the same catheter was used in this phase III study as was used in the earlier trials, there is a question as to whether adequate ablation was achieved or if a regression to the mean effect was seen with this larger sample size. It remains yet to be determined if newer-generation multipoint ablation catheters can achieve more complete denervation and greater BP reduction than observed in a sham-control arm. Along with the lower than expected BP response in the renal denervation arm, the sham-control group had a higher than expected BP response; this is thought to be from the use of aldosterone antagonists in this group (28.7% in the control group vs 22.5% in the intervention group).

Regardless, the majority of the panelists were still cautiously optimistic about the technology and believed that future investigations should be continued. The utility of renal denervation in patients with a higher sympathetic tone, such as those with concomitant chronic heart failure or atrial fibrillation, will need to be assessed in future trials.

## Transcatheter Aortic Valve Therapy

### *Comparison of Transcatheter Heart Valves in High-Risk Patients With Severe Aortic Stenosis*

The Comparison of Transcatheter Heart Valves in High Risk Patients With Severe Aortic Stenosis trial (CHOICE) was a randomized, placebo-controlled trial comparing the two US Food and Drug Administration (FDA)–approved

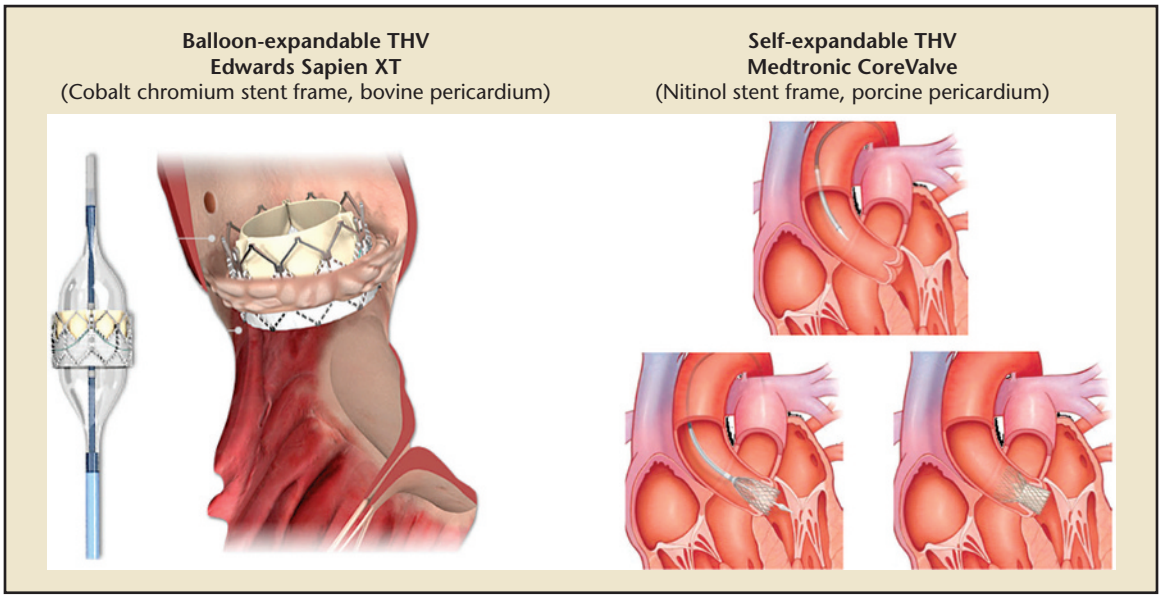


**Figure 4.** Transcatheter aortic valves. THV, transcatheter heart valve. The SAPIEN® valve is manufactured by Edwards Lifesciences, Irvine, CA. The CoreValve® is manufactured by Medtronic, Minneapolis, MN. Reproduced with permission from CardioSource.

devices (balloon expandable and self-expanding aortic bioprostheses) in patients with high-risk aortic stenosis undergoing TAVR. The use of a balloon-expandable valve (the second-generation SAPIEN® valve; Edwards Lifesciences, Irvine, CA) was compared with the self-expanding (CoreValve®; Medtronic), according to CHOICE investigator Mohamed Abdel-Wahab, MD, of the Universities of Kiel and Hamburg in Bad Segeberg, Germany.[4]

Overall, 241 patients were randomized in a 1:1 fashion to either the SAPIEN or CoreValve devices (Figure 4). The balloon-expandable valve was deployed during rapid ventricular pacing. The self-expandable valve was deployed without pacing or slow-rapid pacing. The mean age of the subjects studied was 82 years, 57% were women, mean logistic euroSCORE (European System for Cardiac Operative Risk Evaluation) was 21.5, mean Society of Thoracic Surgeons risk score was 5.6, 31% had diabetes, 60% had coronary artery disease, 22% had cerebrovascular disease, 60% had New York Heart Association (NYHA) class III heart failure, 17% had peripheral vascular disease, 22% had pulmonary disease, and 33% had atrial fibrillation. As measured by preprocedural echocardiography, the mean aortic valve area was 0.7 $cm^2$, mean aortic valve gradient was 43 mm Hg, mean LVEF was 53%, and a fraction of patients had concomitant $\geq$ moderate aortic, mitral, or tricuspid regurgitation.

The primary endpoint was device success, which was a composite endpoint of (1) successful vascular access, delivery, deployment, and retrieval of the delivery system; (2) correct position of the device; (3) mean gradient $<$ 20 mm Hg with $<$ moderate aortic regurgitation (determined by postprocedure angiography and corroborated by echocardiography); and (4) only one valve implanted in the proper location. Secondary endpoints included cardiovascular mortality, bleeding and vascular complications, postprocedural pacemaker placement, all-cause mortality, major stroke, or serious complications at 30 days.

The SAPIEN XT valve was found to have a 96% rate of technical success compared with 76% for the CoreValve (RR 1.24; $P < .001$). That primary composite endpoint included successful vascular access, deployment, and delivery system retrieval, as well as correct positioning, but was driven by fewer cases of moderate or severe aortic regurgitation (4.1% vs 18.3%; $P < .001$) and less use of more than one valve (0.8% vs 5.8%; $P = .03$) with SAPIEN XT compared with the CoreValve. In addition, in the SAPIEN XT arm fewer patients required a new permanent pacemaker (17.3% vs 37.6%; $P = .001$). There were no significant differences in 30-day cardiovascular mortality, bleeding and vascular complications, or overall safety on the composite endpoint of all-cause mortality, major stroke, and other serious complications.

Despite the instant comparisons that were drawn between the two valves and the head-to-head comparisons, some panelists believed that shorter duration of follow-up in this trial may have favored the balloon-expandable valve. Paravalvular leak was reported out to 30 days in CHOICE, but in the CoreValve pivotal trial, observations have revealed valve leakage to fall with time presumably because the device continued to expand over time.

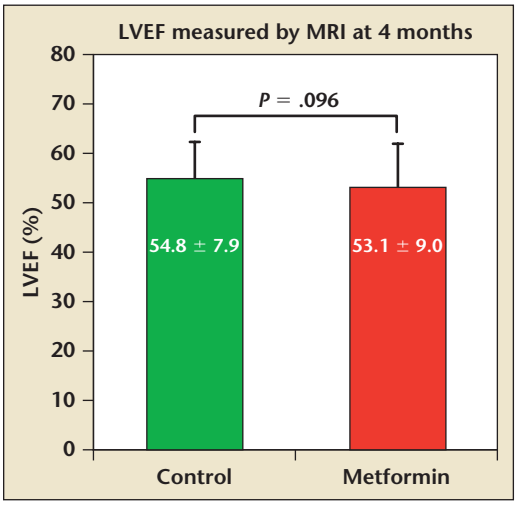


**Figure 5.** Primary endpoints in the Glycometabolic Intervention as Adjunct to Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction trial. LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging. Reproduced with permission from CardioSource.

## Acute MI

### *Glycometabolic Intervention as Adjunct to Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction*

The Glycometabolic Intervention as Adjunct to Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction (GIPS-III) trial was a double-blind, placebo-controlled single-center study conducted among 380 nondiabetic patients who underwent PPCI for STEMI at the University Medical Center Groningen, the Netherlands, between January 1, 2011, and May 26, 2013. Patients were randomized in a 1:1 fashion to receive either metformin hydrochloride, 500 mg, or placebo twice daily for 4 months.[5] The GIPS-III trial is the first double-blind, randomized, placebo-controlled study conducted to evaluate whether 4 months of metformin treatment preserved left ventricular function in nondiabetic patients with acute MI.

The primary endpoint was LVEF after 4 months, assessed by cardiac magnetic resonance imaging (MRI). Secondary endpoints included N-terminal pro-brain natriuretic peptide levels as well as the incidence of MACE (the combined endpoint of death, reinfarction, or TLR) out to 4 months after intervention. Chris Lexis, MD, noted that the results of the trial do not support the use of metformin in this acute setting as there was no significant difference between the two groups for either endpoint (Figure 5); however, it should also be noted that there were also no signals of increased harm with metformin use.

Although the results of this trial, which was conducted to test the pleiotropic effects of metformin in the post-MI healing process, were negative in this nondiabetic STEMI population, some of the panelists took a "glass half full" approach to interpreting the results. One way to interpret the results is that there may be no need (as previously thought and commonly practiced) to routinely hold metformin after angiography, as this trial demonstrates no difference in risk for acute renal failure or lactic acidosis between the two groups. Some noted that the trial failed as there is no longer much room for incremental improvement due to the many advances made in STEMI care over the past several decades, as evidenced by the average ejection fraction in both groups being $> 50\%$.

## Lipid Management

Important phase III clinical trial data on two monoclonal PCSK9 antibodies, alicrocumab and evolocumab, were presented at the 2014 ACC meeting. Here we review three of the blockbuster trials: ODYSSEY MONO, Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin-Intolerant Subjects (GAUSS-2), and Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels-2 (MENDEL-2).

### *ODYSSEY MONO*

Alirocumab demonstrated superior low-density lipoprotein (LDL) cholesterol lowering compared with ezetimibe over 24 weeks. The ODYSSEY MONO trial in a randomized, double-blind, double-dummy study in patients (mean age 50.5 and 59.8 years, 28% men, 47% white) with LDL cholesterol 100-190 mg/dL (2.6-4.9 mmol/L) and estimated 10-year risk of fatal cardiovascular events (SCORE)[3] 1% and $< 5\%$. Patients received ezetimibe 10 mg/d ($n = 51$) or alirocumab, 75 mg subcutaneously every 2 weeks ($n = 52$); the dose was uptitrated in a blinded manner to 150 mg every 2 weeks at week 12 if at week 8 LDL cholesterol was $\geq$ 70 mg/dL (1.8 mmol/L). Alirocumab and the alirocumab placebo in the ezetimibe arm were self-administered as single, 1-mL, subcutaneous injection using an autoinjector. The primary endpoint was mean percent change in LDL cholesterol from baseline to 24 weeks, analyzed using a mixed-effect model with repeated-measures approach (intent-to-treat population).

At baseline, mean (standard deviation) LDL cholesterol levels were 141.1 (27.1) mg/dL in the alirocumab arm and 138.3 (24.5) mg/dL in the ezetimibe arm; median

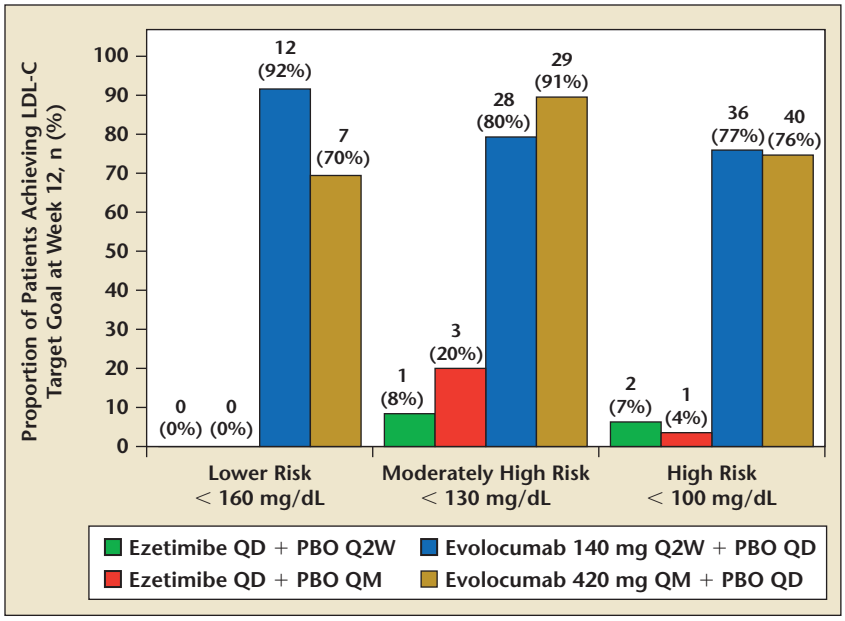


**Figure 6.** LDL-C achievement at 12 weeks in the GAUSS-2 trial. GAUSS-2, Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin-Intolerant Subjects; LDL-C, low-density lipoprotein cholesterol; PBO, placebo; Q2W, biweekly; QD, daily; QM, monthly. Reproduced with permission from CardioSource.

lipoprotein(a) was 13.0 and 16.0 mg/dL, respectively.

Overall, 44 of 52 (85%) and 44 of 51 (86%) patients in the alirocumab and ezetimibe arms, respectively, completed the 24-week treatment period. The least-squares mean (standard error) LDL cholesterol reduction from baseline to week 24 was 47.2% (± 3.0%) with alirocumab versus 15.6% (± 3.1%) with ezetimibe, representing a net treatment benefit of 31.6% (± 4.3%) over ezetimibe ($P < .0001$). Treatment-emergent adverse events occurred in 36 (69%) and 40 (78%) patients in the alirocumab and ezetimibe treatment arms, respectively. Injection site reactions occurred in < 4% of patients. There was no difference in muscle-related adverse events between the two groups occurring in approximately 3.8% to 3.9% in both groups.[6]

### *GAUSS-2*

The GAUSS-2 trial was a double-blind study that took place over 3 months. According to Erik Stroes, MD, PhD, of the Academic Medical Center in Amsterdam, it randomized 307 patients (mean [standard deviation] age 62 years [10], LDL cholesterol 193 [59] mg/dL) in a 2:2:1:1 fashion to one of four groups: evolocumab, 140 mg biweekly or evolocumab, 420 mg monthly, both with daily oral placebo; or subcutaneous placebo biweekly or monthly, both with daily oral ezetimibe, 10 mg.[7]

Co-primary endpoints were percent change from baseline in LDL cholesterol at week 12 and at the mean of weeks 10 and 12. Evolocumab reduced LDL cholesterol from baseline by 535 to 56%, corresponding to treatment differences versus ezetimibe of 37% to 39% ($P < .001$). Of evolocumab-treated patients at high risk, over 75% achieved LDL cholesterol < 100 mg/dL compared with < 10% of ezetimibe-treated patients. LDL cholesterol reductions are clinically equivalent with biweekly and monthly dosing regimens. (Figure 6).

Key safety endpoints included treatment-emergent and serious adverse events, muscle and hepatic enzyme elevations, and antievolocumab antibodies. Muscle adverse events occurred in 12% of evolocumab- and 23% of ezetimibe-treated patients. Treatment-emergent adverse events and laboratory abnormalities were comparable across treatment groups. Finally, there were no reports of antievolocumab antibodies.

The authors concluded that evolocumab administered over 3 months is a promising therapy for high-risk patients with elevated cholesterol who are statin intolerant because of evolocumab's efficacy combined with favorable tolerability. It yielded a significant reduction in LDL cholesterol in hypercholesterolemic patients unable to tolerate effective doses of at least two statins, reflecting a population with a true unmet need.

### *MENDEL-2*

MENDEL-2 evaluated evolocumab as a monotherapy in 614 randomized patients with heterozygous familial hypercholesterolemia not taking statins, noted study presenter and first author, Michael J. Koren, MD, of Florida's Jacksonville Center for Clinical Research. Patients aged 18 to 80 years with fasting LDL cholesterol ≥ 100 and < 190 mg/dL and Framingham risk scores ≤ 10% were randomized in a 1:1:1:1:2:2 fashion to one of six groups: oral placebo and subcutaneous placebo biweekly, oral placebo and subcutaneous placebo monthly, ezetimibe and subcutaneous placebo biweekly, ezetimibe and subcutaneous placebo monthly, oral placebo and evolocumab, 140 mg biweekly, or oral placebo and evolocumab, 420 mg monthly. The co-primary endpoints and key safety endpoints were the same as the aforementioned GAUSS-2 study.[8]

Mean age of study participants was 53 years, approximately 35% were men, average LDL cholesterol was 142 mg/dL, and high-density lipoprotein (HDL) cholesterol was 55 mg/dL. Similar to the GAUSS-2

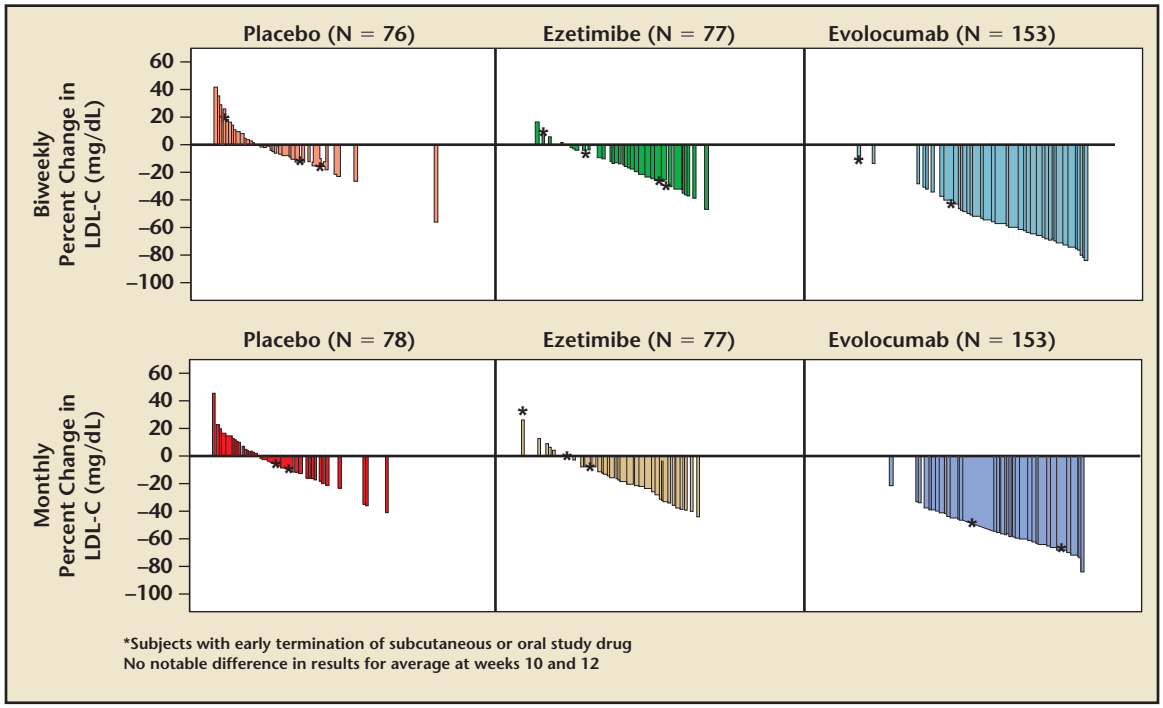


**Figure 7.** Change in LDL-C from baseline at week 12 in the MENDEL-2 study. LDL-C, low-density lipoprotein cholesterol; MENDEL-2, Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels-2. Reproduced with permission from CardioSource.

study findings, evolocumab treatment reduced LDL cholesterol from baseline, on average, by 55% to 57% more than placebo and 38% to 40% greater than ezetimibe ($P < .001$ for all comparisons). Evolocumab treatment also favorably altered other lipoproteins. Again, there was no difference between the groups in the primary safety endpoints and, again, the monthly and biweekly dosing regimens were found to be clinically equivalent (Figure 7). Treatment-emergent adverse events, muscle-related adverse events, and laboratory abnormalities were comparable across treatment groups. Importantly, evolocumab demonstrated consistent LDL cholesterol-lowering effects regardless of age, sex, race, region, or baseline levels of LDL cholesterol/triglycerides/PCSK9.

In the largest monotherapy trial using a PCSK9 inhibitor to date, evolocumab yielded significant LDL cholesterol reductions compared with placebo or ezetimibe, and was well tolerated. However, many panelists argued that enthusiasm about the new PCSK9 inhibitors should be tempered for a few reasons. The FDA recently expressed concern about the potential for neurocognitive side effects from a PCSK9 inhibitor that could potentially result from the drug per se, or the very low LDL cholesterol achieved. Although none of the studies on evolocumab presented at ACC 2014 indicated elevated risk of neurocognitive effects, neurocognitive stability will need to be part of the assessment in the large and long-term placebo-controlled studies of lipid-lowering agents. Moreover, the relatively high cost associated with biologic drugs may rule out use for primary prevention, although all attendees seemed to agree that, for cases where there really are no other options to drive cholesterol down sufficiently, such as in familial hypercholesterolemia, this drug cannot come to market soon enough.

Perhaps the most important question that remains is whether the FDA will approve this agent with surrogate endpoint data alone, especially in light of recent discoveries of other agents proven to successfully change biomarkers that did not confer clinical benefit in larger trials performed after they were given FDA approval. Such trials for alirocumab and evolocumab are already underway. The ODYSSEY Outcomes trial (in alirocumab) and Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial (in evolocumab) will together randomize approximately 40,000 higher-risk patients to the drug or placebo atop statin therapy and then monitor safety and impact on cardiovascular events.

## Stem Cell Therapies

### *Mesenchymal Stromal Cells in Chronic Ischemic Heart Failure*

A small randomized phase II trial from Denmark, not yet published, shows that injecting a patient's

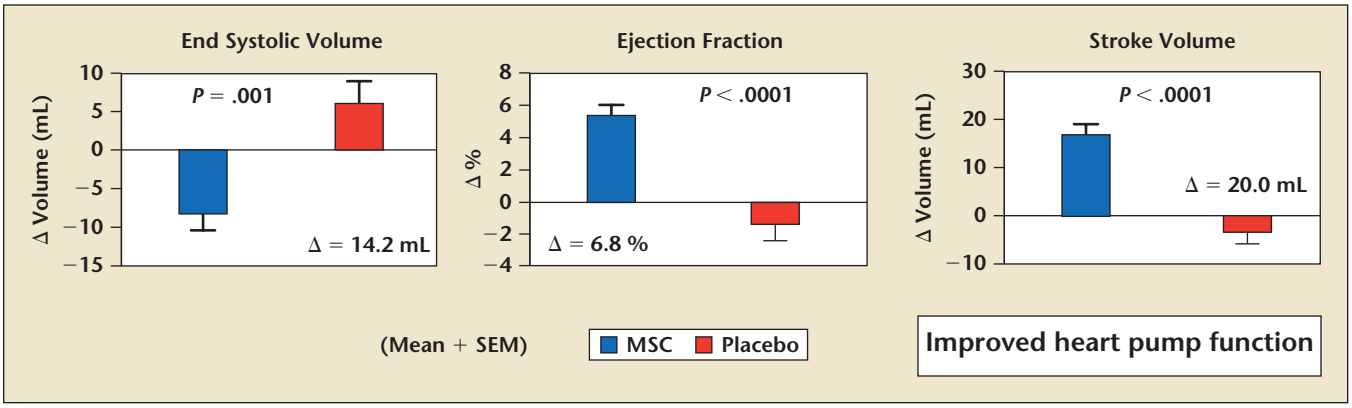


**Figure 8.** Results from the Mesenchymal Stromal Cells in Chronic Ischemic Heart Failure trial. MSC, mesenchymal stromal cells; SEM, standard error of the mean. Reproduced with permission from CardioSource.

own bone marrow–derived mesenchymal stem (stromal) cells directly into the patient's myocardium using a NOGA® XP (Cordis, Bridgewater, NJ) mapping system and injection catheter provided some improvements for patients with severe ischemic heart failure, according to Anders Bruun Mathiasen, MD, of Rigshospitalet-Copenhagen University Hospital.[9]

A total of 60 patients aged 30 to 80 years were randomized 2:1 to receive the stem cell or placebo injections. One patient was excluded before actually undergoing the procedure because of ventricular tachycardia, leaving 59 patients (mean age 66). All had chronic severe ischemic heart failure with NYHA class II or III symptoms and a LVEF below 45% (average 28%). The patients were not candidates for PCI or coronary artery bypass graft, and were taking maximum tolerated medications.

After the cells were taken from the patients, they were expanded in culture for 6 to 8 weeks. During the procedure, an average of 77.5 million stem cells or placebo was injected at spots surrounding scar tissue in the left ventricle in all 59 patients. Mathiasen reported that, compared with patients who received placebo injections, those who received stem cell injections in the left ventricle had significant improvement in end-systolic volume, LVEF, stroke volume, and new cardiac muscle within 6 months. The primary endpoint of the trial—end-systolic volume measured by MRI or computed tomography—improved in the stem-cell group and remained unchanged in the placebo group through 6 months, resulting in a significant between-group difference of 14.2 mL ($P = .001$). Also, the LVEF was an absolute 6.8% higher and stroke volume was 20 mL higher in the stem-cell group versus the placebo group ($P < .0001$ for both) (Figure 8). Finally, the end-systolic myocardial mass was 12.3 g larger in the stem-cell group by 6 months ($P < .0001$) compared with the placebo group. There was a signal toward reduction of scar tissue mass in the stem cell group but it did not reach statistical significance. The only difference in adverse events and safety between the two groups was the increased rate of hospitalizations for angina and pneumonia in the placebo arm.

However, those changes did not translate into superior clinical outcomes as measured by quality of life indices, NYHA class, or exercise capacity on the 6-minute walk test as patients in both groups experienced improvements, but panelists were quick to point out that the trial was not powered to meet these clinical outcomes. A phase III trial will be needed to determine whether the observed changes will influence clinical outcomes.

## Management of Cardiac Patients Undergoing Noncardiac Surgery

### *Perioperative Ischemic Evaluation-2*

The hunt for a preoperative strategy to reduce the risk of postoperative MI after noncardiac surgery continues after the negative results from the large randomized Perioperative Ischemic Evaluation (POISE) trials. In both randomized, blinded, placebo-controlled trials, neither aspirin nor clonidine administered just before surgery reduced the rate of nonfatal MI or death in patients at risk for vascular complications, according to P.J. Devereaux, MD, PhD, of McMaster University's Population Health Research Institute in Hamilton, Ontario.[10,11]

In POISE-2, 10,010 patients aged ≥ 45 years with or at risk for atherosclerotic cardiovascular disease (defined by a history of coronary disease, stroke, or peripheral arterial disease, being scheduled for vascular surgery, or having at least three of nine risk factors) undergoing various types of noncardiac

surgery from 2010 to 2013 were randomized at 135 centers in 23 countries. The mean age was 69 years, 47% were women, 38% had diabetes, 23% had coronary artery disease, 8.8% had peripheral arterial disease, and 5% had a history of stroke. Approximately two-thirds of patients received prophylactic anticoagulants for venous thromboembolism; a preoperative statin was used in 37% and a preoperative β-blocker in 23%.

In the aspirin trial, patients were stratified according to whether they had been taking any dose of aspirin daily for 4 of the 6 weeks before surgery (continuation stratum, n = 4382) or had not (initiation stratum, n = 5628). For the continuation stratum, aspirin use was stopped at least 72 hours before surgery. All patients received placebo or 200 mg of aspirin just before surgery. The initiation stratum continued 100 mg of aspirin or placebo daily for 30 days. The continuation stratum received 100 mg of aspirin or placebo for seven days and then resumed their previous aspirin regimen.

The primary outcome studied was the rate of death or nonfatal MI at 30 days and was not different between the aspirin and placebo groups (7% vs 7.1%; hazard ratio [HR] 0.99, 95% CI, 0.86-1.15). The components of the endpoint, as well as various other clinical outcomes, occurred at similar rates in the two groups, and there was no interaction with clonidine. Results were similar among the initiation and continuation stratum. Major bleeding occurred in significantly more patients who were taking aspirin (4.6% vs 3.7%; HR 1.23, 95% CI, 1.01-1.49) (Figure 9). Further, having a life-threatening or major bleed was an independent predictor of MI (HR 1.82, 95% CI, 1.40-2.36), which might explain the negative results of the trial.

**Results**

| Outcome | Aspirin (4998) | Placebo (5012) | HR (95% CI) | *P* |
|---|---|---|---|---|
| 1° outcome: death or MI | 351 (7.0) | 355 (7.1) | 0.99 (0.86-1.15) | .92 |
| 2° outcome: death, MI, or stroke | 362 (7.2) | 370 (7.4) | 0.98 (0.85-1.13) | .80 |
| death, MI, revasc, or VTE | 402 (8.0) | 407 (8.1) | 0.99 (0.86-1.14) | .90 |
| 3° outcomes: MI safety outcome | 309 (6.2) | 315 (6.3) | 0.98 (0.84-1.15) | .85 |
| Major bleeding | 229 (4.6) | 187 (3.7) | 1.23 (1.01-1.49) | .04 |

**Figure 9.** Results of the Perioperative Ischemic Evaluation (POISE)-2 trial. HR, hazard ratio; MI, myocardial infarction; VTE, venous thromboembolism. Reproduced with permission from CardioSource.

Patients were also randomized to perioperative clonidine 0.2 mg (n = 5009) versus placebo (n = 5001). Prior to study drug administration, patients were required to have a systolic BP ≥ 105 mm Hg and a heart rate ≥ 55 beats/min. The clonidine group (n = 5009) was given 0.2 mg oral clonidine just before surgery and a transdermal patch that delivered the same dose daily for 72 hours after surgery. The placebo group (n = 5001) was given matching tablets and patches. Patients were followed for 1 year.

Results showed clonidine compared with placebo also failed to improve the primary outcome of mortality and nonfatal MI at 30 days (367 and 339 respectively; 95% CI, 0.93-1.26; $P = .29$). The clonidine group had a nonsignificant increase in MI (329 clonidine vs 295 placebo; 95% CI, 0.95-1.30; $P = .18$). Two secondary measures were significant: clinically significant hypotension was seen in 48% of clonidine patients (n = 2385) versus 37% of placebo patients (n = 1854; 95% CI, 1.24-1.40; $P < .001$); and 16 clonidine patients had nonfatal cardiac arrest versus 5 in the placebo group (95% CI, 1.17-8.73; $P = .02$). Clinically important hypotension, in particular, was a strong predictor of MI (HR 1.37, 95% CI, 1.16-1.62).

Panelists debated on the various reasons the trials failed to show benefit but there was one point that was almost unanimous—everyone seemed to agree that neither one of these medications should be routinely prescribed for patients undergoing noncardiac surgery. ■

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