Primary Results of the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) Trial

- Marc Steven Sabatine, MD, TIMI Study Group, and Brigham and Women’s Hospital, Boston, Massachusetts

When added to statin therapy, PCSK9 inhibition with evolocumab (Repatha, Amgen) significantly and safely reduced major cardiovascular events in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial. “Benefit was achieved with [low-density lipoprotein] cholesterol [LDL-C] levels well below current targets,” Dr. Sabatine said. “FOURIER is the first large-scale clinical trial to test whether the addition of a PCSK9 inhibitor to statin therapy reduces major adverse cardiovascular events in patients with vascular disease.”

Risk for major adverse cardiovascular events remains high in patients with cardiovascular disease despite current therapies. LDL-C is a well-established modifiable cardiovascular risk factor. Evolocumab is a fully human monoclonal antibody inhibitor of PCSK9 that reduces LDL-C by about 60%.

The randomized, double-blind, placebo-controlled, multinational (49 countries) FOURIER trial enrolled patients with histories of myocardial infarction (MI), nonhemorrhagic stroke, or symptomatic peripheral artery disease (PAD) who had either LDL-C of 70 mg/dL or greater or non-high-density lipoprotein-cholesterol of 100 mg/dL or greater on optimized statin therapy. They were randomized 1:1 to evolocumab (140 mg subcutaneously [SC] every two weeks or 420 mg SC every month, based on patient preference) or matching placebo. The primary endpoint was a composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization.

The mean patient age was 62.4 years, and 75% were men, with histories of MI (81%), nonhemorrhagic stroke (19%), and symptomatic PAD (13%). Median time from prior MI or stroke was approximately three years. Hypertension was reported in 80% and diabetes in 37%. At baseline, median LDL-C was 91.5 mg/dL, and more than two-thirds were receiving high-intensity statins. Median follow-up was 26 months.

Dr. Sabatine reported a mean reduction in LDL-C of 59% (95% confidence interval [CI], 58–60; P < 0.00001) and an absolute reduction of 56 mg/dL for evolocumab (median, 30 mg/dL; interquartile range, 19–46 mg/dL) compared with placebo. The impact on the primary composite outcome was positive and significant, with rates of 14.6% for placebo and 12.6% for evolocumab (hazard ratio [HR], 0.85; 95% CI, 0.79–0.92; P < 0.0001). For the key secondary endpoint of combined cardiovascular death, MI, or stroke, the rates were 9.9% for placebo and 7.9% for evolocumab (HR, 0.80; 95% CI, 0.73–0.88; P < 0.00001).

Looking specifically at the relationship between intensive LDL-C lowering and cardiovascular death in a summary of six trials failed to reveal a clear benefit (HR, 0.96; 95% CI, 0.90–1.03). In FOURIER, all-cause death rates were 4.8% for evolocumab and 4.3% for placebo (HR, 1.04; 95% CI, 0.91–1.19).

Landmark analysis showed increasing benefit for combined cardiovascular death, MI, or stroke over time for evolocumab versus placebo (16% relative risk reduction [RRR] at 12 months; 25% RRR at 36 months). Similarly, for fatal or nonfatal stroke, RRR was 19% for evolocumab versus placebo at 12 months and 33% at 36 months (P < 0.00001). “An important point here that we’ve seen for all the statin trials, as well, is that it takes time for LDL-lowering to translate into healthier arteries,” Dr. Sabatine stressed.

The long-term benefit, Dr. Sabatine said, was consistent for benefits seen with statins per mmol/L LDL-C reductions. Better outcomes also tracked closely with LDL-C level reductions, down to unprecedented low LDL levels.

Rates of adverse events (AEs) were essentially identical between evolocumab and placebo, with any AEs and serious AEs at 77.4% and 24.8%, respectively, for evolocumab and 77.4% and 24.7% for placebo.

ACC discussant Professor Valentin Fuster, MD, of Mount Sinai Medical School in New York, commented: “It was a positive trial, but it was only a 2% [absolute] difference, which could become 4% in two years, however. The caution is cost-effectiveness. … This is very expensive stuff, and we have to be sure that we identify the right people in which this type of approach would be meaningful.”

EBBINGHAUS: A Cognitive Study of Patients Enrolled in the FOURIER Trial

- Robert P. Giugliano, MD, Brigham and Women’s Hospital, Boston, Massachusetts

Based on a case series and two small six-month randomized controlled trials (RCTs) with statins that raised concerns regarding statin-induced cognitive deficits (such as memory loss and confusion), the Food and Drug Administration required a warning about potential adverse cognitive deficits to be added to statin labeling in 2012. Subsequent analyses of large-scale statin RCTs did not support that finding, and the 2014 Statin Cognitive Safety Task Force concluded that statins are not associated with cognitive side effects. More recently, however,
a meta-analysis by Lipinski and colleagues\(^1\) of six trials in 958 patients receiving PCSK9 inhibitors suggested an increased risk (hazard ratio, 2.3; 95% confidence interval, 1.1–4.9), but with low event rates (less than 1%). Dr. Giugliano noted that monoclonal antibody molecules are too large to cross an intact blood–brain barrier, however.

In the FOURIER study of the PCSK9 inhibitor evolocumab (Repatha, Amgen) among 27,564 stable patients (40 to 85 years of age) with cardiovascular disease and additional cardiovascular risk factors (low-density lipoprotein-cholesterol (LDL-C) of at least 70 mg/dL or non-high-density lipoprotein-cholesterol of at least 100 mg/dL), patients were randomized double-blind to either matching placebo or subcutaneous evolocumab (140 mg every two weeks or 420 mg once a month). All were on a background regimen of moderate-to-high-intensity statin therapy. Analysis showed a 59% reduction in LDL-C, with a concomitant significant reduction in cardiovascular outcomes after 26 months mean follow-up. Treatment was safe and well tolerated.

The Ebbinghaus substudy of the FOURIER findings is based on the 1,024 patients who had baseline and follow-up cognitive testing (tests, patient surveys, and investigator-reported adverse events). The Ebbinghaus hypothesis was: “The addition of evolocumab to statin therapy in patients with clinically evident vascular disease does not adversely affect cognitive function.”

Patients’ mean age was 63 years; 72% were men. High-intensity statin doses were reported in 71%, and median LDL-C levels were 92 mg/dL. The primary endpoint was the spatial working memory strategy index of executive function component of the Cambridge Neuropsychological Test Automated Battery. A patient survey and investigator reports of cognitive adverse events were also included.

Dr. Giugliano reported that, in patients with known cardiovascular disease on background statins followed for 20 months, there were no differences between evolocumab and placebo in either the battery of cognitive tests, patient-reported everyday cognition, or adverse cognitive events reported by investigators. Furthermore, the lack of difference in cognitive tests persisted in patients who achieved a nadir LDL-C level of less than 25 mg/dL.

ACC discussant Sandra Lewis, MD, of Oregon Health and Science University, commented: “In my office, every day, my patients say that statins make them dumb. I can comfortably tell my patients that we actually studied whether this makes you dumb, and it didn’t.”

### Safety and Cardiovascular Event Efficacy of Bococizumab Among 27,000 High-Risk Patients: Studies of PCSK9 Inhibition and the Reduction in Vascular Events (SPIRE) and SPIRE 1 and SPIRE 2 Cardiovascular Outcomes Trials

- Paul M. Ridker, MD, MPH, Brigham and Women’s Hospital, Boston, Massachusetts

While PCSK9 inhibition with bococizumab (Pfizer) reduces low-density lipoprotein-cholesterol (LDL-C) by 55% to 60% when given as an adjunct to statin therapy, the effect is significantly attenuated over time in 10% to 15% of patients. The cause—development of antidrug antibodies—is specific to bococizumab, a humanized monoclonal antibody. The effect has not been seen in either evolocumab (Repatha, Amgen) or alirocumab (Praluent, Sanofi/Regeneron), both of which are fully human monoclonal antibodies.

The SPIRE bococizumab development program included 4,449 patients in its lipid-lowering trials and 27,438 in its cardiovascular outcomes trials. The lipid-lowering trials compared bococizumab (150 mg subcutaneously every two weeks) versus placebo, both with the addition of maximally tolerated statin doses. The trials enrolled patients with a range of risk factors for heart disease (known cardiovascular disease or a combination of diabetes, chronic kidney disease, or peripheral vascular disease with additional cardiovascular risk factors).

Among patients with LDL-C lower than 100 mg/dL at baseline, bococizumab did not improve cardiovascular event rates. In those at high cardiovascular risk (baseline LDL-C greater than 100 mg/dL), however, risk compared with placebo for cardiovascular events was reduced by 21%.

The trials’ sponsor, Pfizer, announced on November 1, 2016, that bococizumab development would be discontinued based on the attenuated LDL-C lowering over time and evidence of immune responses in some patients. Safety was similar between bococizumab and placebo with the exception of injection site reactions with bococizumab, evidence of the agent’s immunogenicity.

“The findings add to what we know about PCSK9 inhibitors,” Dr. Ridker said, “and it is encouraging that we found a statistically significant reduction in events among the highest-risk patients who had the highest LDL levels.”

Valentin Fuster, MD, the ACC discussant, commented with respect to the approved drugs in this class: “The appropriate patients to treat would belong to two groups, those with familial hypercholesterolemia and those with intolerance to statins and high levels of LDL-C. These studies here are in much lower-risk populations.” Treatment of the populations tested in FOURIER and SPIRE will await cost-effectiveness studies, he said.

Several experts at the ACC press conference decried the highly time-consuming process of getting PCSK9 reimbursement approval for appropriate patients.

### Reduced-Dose Rivaroxaban in the Long-Term Prevention of Recurrent Symptomatic VTE (EinsteinChoice)

- Philip S. Wells, MD, Chief of the Department of Medicine, University of Ottawa, Ottawa, Canada

In the EinsteinChoice trial, low-dose rivaroxaban (Xarelto, Janssen) reduced the risk of blood clot recurrence by threefold compared with aspirin without increasing bleeding.

Dr. Wells noted that in patients without reversible risk factors, venous thromboembolism (VTE) risk goes up to 10% in the first year if anticoagulation therapy is discontinued. While recurrent VTE is prevented by extended anticoagulation therapy, bleeding concerns often cause reluctance to continue treatment beyond six to 12 months. He pointed out further that the most common risk factors for VTE are cancer and immobility due to surgery or illness. In addition, some patients...
develop what are known as “unprovoked” VTEs that occur in the absence of known risk factors.

EinsteinChoice was designed to determine the relative efficacy and safety of aspirin (100 mg every day) versus lower-dose anticoagulant therapy (rivaroxaban 20 mg or 10 mg every day) for 12 months. The randomized (1:1:1), double-blind, active-comparator trial included 3,396 patients with confirmed symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) who completed six to 12 months of anticoagulation. The primary efficacy outcome was symptomatic recurrent VTE (nonfatal DVT or PE, fatal PE, or unexplained death where PE cannot be excluded). Major bleeding (as defined by the International Society of Thrombosis and Hemostasis) was the principal safety outcome.

Patients’ mean age was about 59 years. Approximately 55% were men; 77% were Caucasian, 14% were Asian, and 4% were African-American. The index event was DVT in about 51% of patients, PE in about 34%, and both in 15%. About 41% of index events were unprovoked.

Dr. Wells reported recurrent VTE rates of 4.4% for aspirin, 1.5% for rivaroxaban 20 mg, and 1.2% for rivaroxaban 10 mg, with both rivaroxaban doses showing statistically significant benefit versus aspirin ($P < 0.001$). Hazard ratios for rivaroxaban were 0.34 and 0.26 for 20 mg and 10 mg, respectively, versus aspirin. Results were generally consistent across subgroups.

Major bleeding rates were similar for both rivaroxaban doses and for aspirin (20 mg, 0.5%; 10 mg, 0.4% and aspirin, 0.3%).

Dr. Wells noted that the number needed to treat with rivaroxaban 20 mg and 10 mg for one year to prevent one VTE without an increase in bleeding was 33 and 30, respectively.

“Both rivaroxaban regimens are superior to aspirin for the primary and other efficacy outcomes and are associated with similar rates of bleeding,” he said.

“We have shown that practitioners can safely prescribe rivaroxaban for patients at risk for a recurrent VTE without being concerned that doing so will increase risk for bleeding side effects,” Dr. Wells commented. Patients requiring full-dose anticoagulation, he noted, were excluded and may need extended treatment with the 20-mg once-daily rivaroxaban regimen. The investigators plan to conduct a follow-up study to examine whether low-dose rivaroxaban is equally effective in other patient populations.

**GEMINI ACS-1: Rivaroxaban Versus Aspirin, In Addition to P2Y$_{12}$ Inhibition, for Patients After Acute Coronary Syndromes**

- **Erik Magnus Ohman, MD, Duke Clinical Research Institute, Durham, North Carolina**

Compared with acute coronary syndrome (ACS) patients who received standard aspirin plus an antiplatelet agent, those treated with the Xa inhibitor rivaroxaban (Xarelto, Janssen) plus an antiplatelet P2Y$_{12}$ inhibitor (clopidogrel or ticagrelor [Brilinta, AstraZeneca]) had similar rates of clinically significant non-coronary artery bypass graft (CABG) bleeding complications, according to phase 2 GEMINI ACS-1 results.

While aspirin and dual antiplatelet therapy (DAPT, aspirin plus a P2Y$_{12}$ inhibitor) are standard ACS therapy, nearly 10% of patients still suffer major cardiovascular events during follow-up, Dr. Ohman observed. Cardiovascular events have been shown to be reduced by triple antithrombotic therapy consisting of rivaroxaban added to DAPT. That benefit, however, has come at the cost of significant twofold increases in major bleeding complications. *In vivo* research into thrombosis and bleeding potential with a rivaroxaban/P2Y$_{12}$ combination has demonstrated efficacy similar to DAPT, but with lower bleeding risk. In addition, studies of this rivaroxaban/P2Y$_{12}$ combination in patients with atrial fibrillation after percutaneous coronary intervention (PCI) have suggested this strategy as one with potential to enhance overall outcomes in ACS.

**GEMINI ACS-1** enrolled 3,037 patients within 10 days of hospitalization for acute myocardial infarction (89%) or unstable angina (11%). A history of impaired kidney function, long-term anticoagulant therapy, active bleeding, or bleeding in the brain or gastrointestinal tract within the previous year were exclusion criteria. Following stable doses of clopidogrel (75 mg daily) (n = 1,333) or ticagrelor (90 mg twice daily) (n = 1,704) for more than 48 hours, the patients were randomly assigned to receive either low-dose rivaroxaban (2.5 mg twice daily) or aspirin (100 mg daily). The primary endpoint was non-CABG clinically significant bleeding risk based on Thrombolysis in Myocardial Infarction (TIMI) score.

Patients’ mean age was approximately 62 years, 75% were men, and 93% were Caucasian. Myocardial infarctions (MIs) were ST-segment elevation in 49% and non-ST-segment elevation in 40%, with unstable angina in 11%.

Rates of TIMI non-CABG clinically significant bleeding were similar between the two treatment arms at three years at 4.9% for aspirin and 5.3% for rivaroxaban (hazard ratio, 1.09; 95% confidence interval, 0.80–1.50; $P = 0.5840$). No differences were observed in any subgroups (gender, age, creatinine clearance, index diagnosis, index PCI, diabetes, prior MI, prior PCI, prior CABG, current smoking, Global Registry of Acute Coronary Events risk score). Dr. Ohman noted that the most common type of bleeding was minor, such as a nosebleed for which the patient needed to see a doctor.

Similarly, the ischemic composite endpoint of cardiovascular death, MI, stroke or definite stent thrombosis occurred at similar rates (4.7% for aspirin, 5.0% for rivaroxaban [hazard ratio, 1.09; 95% confidence interval, 0.80–1.50; $P = 0.5840$]). No significant differences were detected for any of the components.

Dr. Ohman pointed out that a limited *post hoc* multivariate model for the primary bleeding endpoint noted a higher association with bleeding and ticagrelor use ($P = 0.0006$), but was also associated with region ($P < 0.02$).

“...In this phase 2 trial, we observed similar risk of TIMI non-CABG clinically significant bleeding with the combination of rivaroxaban and a P2Y$_{12}$ inhibitor compared with DAPT. The ischemic composite outcomes were also similar, but the trial was not powered for assessing this endpoint,” Dr. Ohman said. “This study is important because it is the first to show that replacing aspirin with a newer, more targeted drug—low-dose rivaroxaban, an anticoagulant—presents no additional risk of bleeding complications when given as dual therapy with an antiplatelet drug.”

Dr. Ohman suggested that more research is needed to define the best intensity of antithrombotic therapy for patients transitioning from the acute thrombotic setting to chronic prevention.
Safety and Efficacy of Uninterrupted Anticoagulation With Dabigatran Etexilate Versus Warfarin in Patients Undergoing Catheter Ablation Of Atrial Fibrillation: The RE-CIRCUIT Study

Hugh Calkins, MD, Johns Hopkins Medical Institutions, Baltimore, Maryland

Compared with performing atrial fibrillation (AF) ablation with uninterrupted warfarin, uninterrupted dabigatran (Pradaxa, Boehringer Ingelheim) is a better strategy, according to RE-CIRCUIT study results.

Stroke risk is increased fivefold in patients with AF. Catheter ablation of AF, Dr. Calkins noted, is the most common ablation procedure performed today in major medical centers throughout the world. Among AF ablation’s most feared complications are thromboembolic and bleeding events, including cardiac tamponade. Risk of these complications has been shown to be minimized when patients are on uninterrupted anticoagulation with a vitamin K antagonist (VKA). This approach, however, is cumbersome because most AF patients are anticoagulated with a non-VKA oral anticoagulant (NOAC) prior to AF ablation, requiring transition to VKA therapy prior to ablation.

Dr. Calkins explained that dabigatran has established efficacy and safety for stroke prevention in patients with AF. Outcomes data on AF ablation when performed on uninterrupted NOAC therapy, however, are limited. The RE-CIRCUIT study aim, therefore, was to investigate the safety and efficacy of uninterrupted dabigatran versus warfarin for periprocedural anticoagulation in patients undergoing catheter ablation of AF.

Investigators randomized 678 patients with paroxysmal or persistent nonvalvular AF scheduled for catheter ablation across 104 sites in 11 countries. Patients were randomized to uninterrupted dabigatran (150 mg twice daily) or uninterrupted warfarin (international normalized ratio, 2.0–3.0) for four to eight weeks before ablation and eight weeks after ablation. The primary endpoint was incidence of adjudicated International Society on Thrombosis and Hemostasis major bleeding events (MBEs) from venous access up to eight weeks post-ablation.

Patients’ mean age was 59.2 years. AF was paroxysmal in approximately 68% and persistent in approximately 26%, with longstanding persistent AF in approximately 6%. Dr. Calkins reported that patients on uninterrupted dabigatran had significantly fewer MBEs compared with warfarin patients: five versus 23 (1.6% versus 6.9%, a 5.3% absolute risk reduction [95% confidence interval [CI], –8.4 to –2.2; P = 0.0009]). The relative risk reduction with dabigatran was 77.2% and the hazard ratio was 0.22 (95% CI, 0.08–0.59). Pericardial tamponade was reported in one dabigatran patient and six warfarin patients. Overall, medical action for MBEs was necessary in four dabigatran patients and 21 warfarin patients.

Thromboembolic events were rare, with no strokes or systemic embolic events in either treatment group. One transient ischemic attack occurred in a warfarin patient. Minor bleeding event rates were similar at 18.6% for dabigatran and 17.0% for warfarin. No deaths were reported. Also, severe adverse events were less frequent for dabigatran (3.3%) than for warfarin (6.2%), as were adverse event–related discontinuations (2.4% versus 5.6%). Need for hospitalization (7.7% versus 10.1%) and prolonged hospitalizations (3.8% versus 6.5%) were also less common in the dabigatran group.

“RE-CIRCUIT demonstrates that uninterrupted dabigatran is a better anticoagulation strategy than uninterrupted warfarin for performing AF ablation,” Dr. Calkins concluded. He noted that the availability of the specific reversal agent idarucizumab (Praxbind, Boehringer Ingelheim), although not needed by any subjects in RE-CIRCUIT, further motivates the adoption of this dabigatran regimen as the preferred anticoagulation strategy for patients undergoing AF ablation. “I expect these findings will encourage clinicians to quickly shift to doing this procedure with uninterrupted use of NOACs,” Dr. Calkins said.

REFERENCE