Reducing low-density lipoprotein-cholesterol (LDL-C) to very low levels should be considered for patients with peripheral artery disease (PAD) to mitigate their risk of major adverse cardiovascular events (MACE) and major adverse limb events (MALE). That conclusion emerged from analysis of FOURIER, presented as an oral session by Dr. Bonaca, who noted that patients with lower-extremity PAD are at high risk of MACE. Earlier research has shown that statins (versus placebo) reduce cardiovascular risk and peripheral revascularization risk in this population, with observational studies also suggesting reduced amputation rates. FOURIER tested whether further reducing LDL-C with the proprotein convertase subtilisin/kexin type 9 inhibitor evolocumab (Repatha, Amgen) would reduce cardiovascular or MALE risk.

The overall FOURIER trial revealed a 59% reduction in LDL-C with subcutaneous evolocumab (140 mg once every two weeks or 420 mg once monthly) compared with placebo to a median of 30 mg/dL over a median follow-up of 2.2 years. It also showed a 20% reduction in combined cardiovascular death, myocardial infarction, and stroke. FOURIER was conducted among 27,564 high-risk, stable patients with established cardiovascular disease.

In FOURIER, PAD was defined as intermittent claudication and an ankle brachial index of less than 0.85 or prior peripheral revascularization or amputation for ischemia. The FOURIER PAD analysis included 3,642 patients with asymptomatic lower-extremity PAD, 1,505 of them with no prior myocardial infarction or stroke. Mean patient age was 64 years, and 72% were women.

Among patients receiving placebo, the rate of combined cardiovascular death, myocardial infarction, and stroke was 13.0% in patients with PAD and 7.6% in those with no PAD and prior myocardial infarction and stroke (adjusted hazard ratio [HR], 1.81; \( P < 0.001 \)). For those with prior myocardial infarction/stroke and PAD, the rate was 14.9%.

Treatment with evolocumab reduced the combined endpoint in patients with PAD to 9.5%, a 27% relative risk reduction (\( P = 0.0040 \)), with a number needed to treat (NNT) for 2.5 years of 29. In those with no PAD, the combined endpoint rate was reduced to 6.2% (NNT = 72).

The MALE (acute limb ischemia, major amputation, or urgent revascularization) rate in all patients was reduced by 42%, from 0.45% with placebo to 0.27% with evolocumab (HR, 0.58; \( P = 0.0093 \)). Evolocumab benefits extended to those PAD patients without prior myocardial infarction or stroke. The absolute risk reduction for MACE or MALE was 6.3% (NNT = 16) at 2.5 years.

Dr. Bonaca concluded that “LDL-C reduction to very low levels should be considered in patients with PAD, regardless of history of myocardial infarction or stroke.”

### FOURIER: Evolocumab and Outcomes in Patients With Peripheral Artery Disease

- Marc P. Bonaca, MD, Brigham and Women’s Hospital, Boston, Massachusetts

The randomized EMPA-REG OUTCOME trial investigated the effects of empagliflozin versus placebo on cardiovascular outcomes, mortality, and renal outcomes in patients with type-2 diabetes and established cardiovascular disease. All patients (N = 7,020) received standard of care with the addition of placebo in 2,333 patients and empagliflozin (10 mg or 25 mg) in 4,687 patients. They were treated for a median observation period of 3.1 years. The primary outcome was adjudicated combined cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. PAD was defined as 1) the presence of limb angioplasty, stenting, or bypass surgery; 2) limb or foot amputation due to circulatory insufficiency; 3) evidence of significant peripheral artery stenosis (greater than 50% on angiography or hemodynamically significant via noninvasive methods) in one limb; or 4) ankle brachial index of less than 0.9 in one or more ankle. At baseline, PAD was present in 21% (982 of 4,687) of patients treated with empagliflozin and in 21% (479 of 2,333) of patients treated with placebo. Dr. Verma noted that in recent PAD trials, diabetes has been found in about 40% of patients, while in recent diabetes trials, PAD has been present in about 20% of participants.

### Empagliflozin Reduces Mortality and Hospitalization for Heart Failure in Patients With Type-2 Diabetes and Peripheral Artery Disease: A Subanalysis of the EMPA-REG OUTCOME Trial

- Subodh Verma, MD, University of Toronto, Toronto, Canada

Peripheral artery disease (PAD), one of the most common cardiovascular complications of type-2 diabetes, is a predictor of cardiovascular death. In the EMPA-REG OUTCOME trial, empagliflozin (Jardiance, Boehringer Ingelheim) reduced adjudicated combined cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke in type-2 diabetes mellitus patients with and without PAD, Dr. Verma said in an oral presentation. Empagliflozin is a selective inhibitor of sodium-glucose cotransporter 2.

Prior empagliflozin research showed risk of cardiovascular death reduced by 38%, all-cause mortality by 32%, hospitalization for heart failure by 35%, and incident or worsening nephropathy by 38%.

The randomized EMPA-REG OUTCOME trial investigated the effects of empagliflozin versus placebo on cardiovascular outcomes, mortality, and renal outcomes in patients with type-2 diabetes and established cardiovascular disease. All patients (N = 7,020) received standard of care with the addition of placebo in 2,333 patients and empagliflozin (10 mg or 25 mg) in 4,687 patients. They were treated for a median observation period of 3.1 years. The primary outcome was adjudicated combined cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. PAD was defined as 1) the presence of limb angioplasty, stenting, or bypass surgery; 2) limb or foot amputation due to circulatory insufficiency; 3) evidence of significant peripheral artery stenosis (greater than 50% on angiography or hemodynamically significant via noninvasive methods) in one limb; or 4) ankle brachial index of less than 0.9 in one or more ankle. At baseline, PAD was present in 21% (982 of 4,687) of patients treated with empagliflozin and in 21% (479 of 2,333) of patients treated with placebo. Dr. Verma noted that in recent PAD trials, diabetes has been found in about 40% of patients, while in recent diabetes trials, PAD has been present in about 20% of participants.
Empagliflozin treatment in EMPA-REG OUTCOME resulted in cardiovascular death reductions that appeared early and persisted for the duration of the trial. In patients with PAD at baseline, empagliflozin reduced cardiovascular death by 43%, all-cause mortality by 38%, and the primary outcome by 16% compared with placebo.

In general, overall and serious adverse events were balanced between the empagliflozin and placebo groups in patients with and without PAD. In patients with PAD, however, lower-limb amputations occurred in 5.5% of those treated with empagliflozin and in 6.3% among those treated with placebo (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.54–1.32). In patients without PAD, lower-limb amputations occurred in 0.9% treated with empagliflozin and in 0.7% of those treated with placebo (HR, 1.30; 95% CI, 0.69–2.46).

“The substantial risk reductions observed in the vulnerable subgroup of patients with type-2 diabetes and PAD from the EMPA-REG OUTCOME trial have important translational implications,” Dr. Verma said.

The lack of a signal for increased lower-limb amputation with empagliflozin in this trial, compared with the nearly doubling of risk with a drug of the same class, canagliflozin (Invokana, Janssen) versus placebo in the CANVAS trial, is favorable, according to AHA discussant Renato D. Lopes, MD, MHS, PhD, of Duke University Medical Center. At this point, he commented, the finding remains unexplained.

Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events in Type-2 Diabetes: Results From the CANVAS Program

- Kenneth W. Mahaffey, MD, Stanford University School of Medicine, Stanford, California

In both primary and secondary prevention populations with type-2 diabetes, canagliflozin (Invokana, Janssen), an inhibitor of sodium-glucose cotransporter 2 (SGLT2), improved cardiovascular and renal primary and secondary outcomes, according to CANVAS trial results.

Inhibitors of SGLT2, such as canagliflozin, have shown favorable effects on biomarkers, including glycemia, blood pressure, weight, intrarenal hemodynamics, and albuminuria, Dr. Mahaffey said at an AHA press briefing. They may also reduce risk of serious cardiovascular complications, kidney disease, and death. Type-2 diabetes mellitus is associated with a high risk for cardiovascular and renal disease.

The CANVAS objective was to compare the effects of canagliflozin versus placebo on cardiovascular, renal, and safety outcomes among secondary and primary prevention participants. Participants at 667 centers in 30 countries (N = 10,142) were men and women with type-2 diabetes (glycated hemoglobin level, 7.0% or greater and 10.5% or less) and were either 30 years of age or older with a history of symptomatic atherosclerotic cardiovascular disease or 50 years of age or older with two or more of the following risk factors for cardiovascular disease: duration of diabetes of at least 10 years; systolic blood pressure greater than 140 mm Hg while they were receiving one or more antihypertensive agents; current smoking; microalbuminuria or macroalbuminuria; or high-density lipoprotein-cholesterol level of less than 1 mmol/L (38.7 mg/dL). Participants were required to have an estimated glomerular filtration rate (eGFR) at entry greater than 30 mL/minute per 1.73 m² of body-surface area and to meet a range of other criteria.

CANVAS investigators randomized patients to canagliflozin (300 mg or 100 mg) or placebo after a two-week placebo run-in. Initial CANVAS results presented previously for the primary composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke favored canagliflozin over placebo with a 14% reduction (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.75–0.97; P = 0.02). The current analysis compared canagliflozin effects among secondary (n = 6,656) and primary prevention (n = 3,486) participants. Mean follow-up was 188 weeks.

At baseline, rates of prior myocardial infarction (44%), hospitalization for unstable angina (11%), coronary revascularization (54%), percutaneous coronary intervention (38%), bypass graft surgery (21%), and stroke (19%) were high in the secondary prevention analysis population. HRs for the primary endpoint for canagliflozin versus placebo in the secondary and primary prevention groups were 0.82 (95% CI, 0.72–0.95) and 0.98 (95% CI, 0.74–1.30), respectively, without a significant interaction (P = 0.18). HRs for heart failure were 0.68 and 0.64, respectively, and for renal composite were 0.59 and 0.63, respectively. Interactions were not significant.

Dr. Mahaffey reported that the number of events prevented in 1,000 patients over five years was 23 for the primary endpoint, 16 for heart failure hospitalization, and 18 for renal improvement (40% reduction in eGFR, renal replacement therapy, or renal death), with an increase of 15 lower-extremity amputations (10 toe or metatarsal, five above the ankle) (HR, 2.85; 95% CI, 1.95–4.16). The mechanism for this unexpected increase is not understood, he said.

Dr. Mahaffey concluded that to improve cardiovascular and renal outcomes, canagliflozin should be considered for the management of diabetes mellitus in patients at high risk for cardiovascular events. He also noted that caution needs to be exercised with canagliflozin in patients at risk for amputations.

Does High-Intensity Pitavastatin Therapy Further Improve Clinical Outcomes? The REAL-CAD Study In Patients With Stable Coronary Artery Disease

- Hiroaki Shimokawa, Tohoku University Graduate School of Medicine, Sendai, Japan

In the open-label REAL-CAD trial, high-dose pitavastatin (4 mg per day) reduced cardiovascular events significantly compared with low-dose pitavastatin (1 mg per day) therapy. The trial included Japanese patients with stable coronary artery disease, and its findings support administration of higher doses of statins in this population, Dr. Shimokawa said.

American College of Cardiology (ACC)/AHA guidelines recommend a “fire-and-forget” strategy of high-intensity statin therapy (atorvastatin 40/80 mg, rosuvastatin 20/40 mg, or simvastatin 80 mg) for lipid lowering in patients with established coronary artery disease, while European Society of
Cardiology guidelines recommend a “treat-to-target” strategy of 70 mg/dL or lower, he explained.

In daily practice, especially in Asia, high-intensity statins are not widely prescribed, and supportive clinical evidence in Asian populations is lacking. Furthermore, the doses cited in the ACC/AHA guidelines are not approved in Japan, and cardiovascular event rates are lower in Asian patients than in Western patients, according to Dr. Shimokawa.

While the clinical relevance of benefits shown for high-intensity statins in Western patients may not persist for the lower-event-risk Asian patient, he said, in Japanese patients, significant dose-related reductions in low-density lipoprotein-cholesterol (LDL-C) levels have been shown at 33.6% for pitavastatin 1 mg and 41.8% and 47.0% for pitavastatin 2 mg and 4 mg, respectively. Also, while reduced plaque volume and carotid intima-media thickness have been demonstrated in Asian studies, no studies have shown high-dose statin mortality benefits.

The REAL-CAD trial included 13,054 stable coronary artery disease patients who were randomized 1:1 (after a pitavastatin 1 mg daily one-month run-in) to pitavastatin 1 mg daily or 4 mg daily with 36–60 months of follow-up. Mean patient age was 68 years, and approximately 83% were men. All patients included had LDL-C of less than 120 mg/dL on 1 mg pitavastatin daily. Dr. Shimokawa noted that the pitavastatin 1-mg and 4-mg doses are equivalent to atorvastatin 5-mg and 20-mg doses, respectively.

LDL-C reductions were significantly greater in the pitavastatin 4 mg daily group ($P < 0.001$) at follow-up, as were reductions in triglycerides ($P < 0.001$) and high-sensitivity C-reactive protein ($P < 0.001$). High-density lipoprotein-cholesterol increased significantly in the pitavastatin 4 mg daily group ($P < 0.001$). After five years, the primary endpoint of combined cardiovascular death, myocardial infarction, ischemic stroke, or unstable angina was lower in the 4-mg dose group (4.3%) compared with the 1-mg group (5.4%) (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.69–0.95; $P = 0.01$). The number needed to treat (NNT) was 63. The secondary endpoint, which added the need for coronary revascularization to the primary endpoint, was also reduced in the 4-mg group at 7.9% compared with 9.7% in the 1-mg group (HR, 0.83; 95% CI, 0.73–0.93; $P = 0.002$). The number needed to treat was 41. The pattern persisted across numerous subgroups.

Safety analysis showed that muscle complaints were more frequent in the pitavastatin 4 mg group (1.9%) compared with the 1-mg group (0.7%) ($P < 0.001$). There was no difference in the rate of rhabdomyolysis or any other adverse event in the two groups.

AHA discussant Karol E. Watson, MD, PhD, Co-Director of the UCLA Program in Preventive Cardiology, commented, “This trial should give comfort that this strategy is safe, well tolerated, and beneficial.” She added that whether greater LDL-C reductions would yield further benefits and remain well tolerated remains unknown for this population.

For prevention of serious outcomes or acute kidney injury after angiography, the standard of care should be intravenous (IV) isotonic sodium chloride, Dr. Weisbord said in an AHA press briefing. Analysis of PRESERVE trial data did not show acetylcysteine to be effective, nor did it show IV sodium bicarbonate to confer benefit compared with sodium chloride.

Accelerated progression of underlying chronic kidney disease, the need for dialysis, and death are possible consequences of contrast-induced acute kidney injury during angiography, Dr. Weisbord said. The use of the standard prophylaxis of procedural isotonic sodium chloride is based on the notion that urinary alkalization and scavenging of reactive oxygen species reduces iodinated contrast-material–induced renal tubular epithelial cell injury. Multiple studies have assessed the use of acetylcysteine and have compared IV sodium bicarbonate with IV sodium chloride. Trials, however, have been underpowered, and results have been inconsistent. Both sodium chloride and sodium bicarbonate are in widespread use.

PRESERVE, a double-blind, placebo- and comparator-drug-controlled trial, was conducted at 53 medical centers in the United States (mostly Veterans Affairs sites), and in Australia (13 sites), Malaysia (three sites), and New Zealand (two sites). The trial included 4,993 patients undergoing angiography who were at high risk for renal complications. The primary composite outcome was prevention of death, need for dialysis, or persistent decline in kidney function at 90 days. Contrast-associated acute kidney injury was a secondary endpoint. All included patients were scheduled for angiography (emergent angiography excluded) and had estimated glomerular filtration rates of 15–44.9 mL/minute per 1.73 m² of body surface area for nondiabetic patients and 45–59.9 mL/minute per 1.73 m² for those with diabetes. Equal groups were randomized to IV 1.26% sodium bicarbonate (150 mmol/L) or IV 0.9% sodium chloride (154 mmol/L) and oral acetylcysteine capsules or matched placebo. Mean patient age was approximately 70 years and about 94% were men.

Based on a planned conditional power analysis after 67% of planned enrollment was complete, PRESERVE was terminated upon recommendation of the Veterans Administration. At that time, it was clear that the primary outcome was similar in the groups, occurring in 4.4% and 4.7% of patients in the sodium bicarbonate and sodium chloride groups, respectively ($P = 0.62$). For the secondary outcome of contrast-associated acute kidney injury, the rates were also similar ($P = 0.13$) at 9.5% and 8.3% for sodium bicarbonate and sodium chloride, respectively.

In the acetylcysteine versus placebo comparison, the rates for the primary endpoint were 4.6% and 4.5%, respectively for acetylcysteine and placebo ($P = 0.88$). The rates for contrast-associated acute kidney injury were also similar at 9.1% and 8.7%, respectively ($P = 0.58$). In addition, multiple prespecified subgroup analyses detected no differences.
"The current standard of care should be intravenous isotonic sodium chloride," Dr. Weisbord concluded. "This is an important study," said AHA discussant Nuria M. Pastor-Soler, MD, PhD, of the University of Southern California’s Keck School of Medicine, “that helps resolve the uncertainty of how best to manage and preserve kidney function in patients undergoing angiography who receive contrast dye.”

**Aspirin in Patients With Previous Percutaneous Coronary Intervention Undergoing Noncardiac Surgery: The POISE-2 PCI Substudy**

- Michelle M. Graham, MD, University of Alberta and Mazankowski Alberta Heart Institute, Edmonton, Canada

While aspirin did not prevent the primary outcome of death/myocardial infarction versus placebo at 30 days in patients undergoing noncardiac surgery, benefit was more likely in the subgroup of patients who had undergone prior percutaneous coronary interventions (PCIs) in the overall results of the POISE-2 trial. Aspirin did, however, increase risks of major bleeding, Dr. Graham said in an oral presentation.

Ten million of the more than 200 million noncardiac surgeries performed annually entail major vascular complications that lead to mortality, hospitalizations, and concomitant costs. While it is known that those who have had prior PCI are at higher risk for major perioperative complications, the effects of aspirin in this group remain unknown. Within the population of 10,010 patients randomized in POISE-2, 470 with prior PCI were included in the present post-hoc analysis.

Patients were randomized to 200 mg aspirin or placebo just before surgery and continued daily at 100 mg for 30 days in those patients who had not been taking daily aspirin before surgery (the initiation stratum) and for seven days in those who had (the continuation stratum).

Mean patient age was about 68 years and 22% were women, with 59% of all patients undergoing major surgery. Most patients were in the continuation stratum (approximately 86%). About half of the patients had received bare metal stents (54.3%), about one-quarter received drug-eluting stents (25.3%), with others unknown or none. The median duration between PCI and noncardiac surgery was 64 months.

Analysis revealed primary outcome (death/myocardial infarction) rates of 7.0% and 7.1% for aspirin and placebo, respectively, in the overall trial. In the no-prior-PCI/prior-PCI analysis, the rates for those without prior PCI were 7.1% for aspirin and 6.9% for placebo. For those with prior PCI, however, the rates were 6.0% for aspirin and 11.4% for placebo. The interaction for all three analyses was significant (P = 0.036).

Differences also appeared in an analysis of the primary outcome components taken separately among patients with prior PCI. Among the overall trial population and among those without prior PCI, there were no differences between aspirin and placebo for either myocardial infarction or death. In the prior PCI group, the myocardial infarction rate was 5.1% for aspirin and 11.0% for placebo (P = 0.033; interaction P = 0.021); for death it was 0.9% for aspirin and 1.3% for placebo (interaction P = 0.61).

Major bleeding with aspirin was increased in the overall population (hazard ratio [HR], 1.22; 95% confidence interval [CI], 1.01–1.48) and in no-prior-PCI patients (HR, 1.24; 95% CI, 1.02–1.51). For those with prior PCI, major bleeding occurred in 3.4% of the aspirin group and in 3.8% of the placebo group (HR, 0.85; 95% CI, 0.33–2.20). The interaction P value overall was 0.50. Analysis of a variety of stenting factors showed no significant interactions.

An interaction analysis discounted the possibility that the differences in the prior-PCI group were simply attributable to coronary artery disease history (interaction P > 0.45), Dr. Graham said. “Among those with prior PCI, perioperative aspirin may be more likely to benefit than to harm patients,” she concluded. She added that for every 1,000 patients with prior PCI undergoing noncardiac surgery, perioperative aspirin will prevent 59 myocardial infarctions, but will cause eight major bleeds.

The POISE-2 conclusions are hypothesis-generating, said AHA discussant Bernard Gersh, MD, of the Mayo Clinic in Rochester, Minnesota, because while the numbers are “quite persuasive,” the numbers are very small and the confidence intervals are wide. He also commented that the finding is biologically plausible because the perioperative period encompasses a prothrombotic state. Dr. Gersh was impressed that the post-PCI vulnerability persisted despite the three to 10 years between stent procedures and the noncardiac surgery when stents would have already been fully endothelialized. "This is my clinical practice and the clinical practice of most [surgeons]. I’m not going to stop aspirin for noncardiac surgery.”

**ABRIDGE-J: Clinical Benefit of Minimally Interrupted Dabigatran Versus Uninterrupted Warfarin for Catheter Ablation of Atrial Fibrillation: A Prospective, Randomized, Multicenter Trial**

- Kazutaka Aonuma, MD, PhD, University of Tsukuba, Tsukuba, Ibaraki, Japan

Patients undergoing ablation for nonvalvular atrial fibrillation who received anticoagulation with minimally interrupted dabigatran with or without heparin bridging had fewer bleeding complications than those treated with uninterrupted warfarin. In addition, said Dr. Aonuma, the ABRIDGE-J trial lead investigator, there was no increase in thromboembolic events with minimally interrupted dabigatran.

Dr. Aonuma noted that in the RE-CIRCUIT trial, uninterrupted dabigatran was shown to be effective for reducing stroke at the time of ablation for nonvalvular atrial fibrillation, with lower bleeding risk than uninterrupted warfarin. However, five major bleeding events (two within four hours; three within four to eight hours) occurred in the patients who received the final dose of dabigatran less than eight hours before ablation. Although in wide use, minimally interrupted direct oral anticoagulants have not been subject to sufficient controlled study, he said in an oral presentation.

ABRIDGE-J investigators enrolled 500 patients with paroxysmal or persistent nonvalvular atrial fibrillation scheduled for initial catheter ablation in a prospective randomized, open-label, multicenter, controlled trial with blinded assessments after 12-month follow-up. The objective was to compare the
efficacy and safety of minimally interrupted dabigatran as an anticoagulant therapy with that of uninterrupted warfarin. Patients were randomly assigned to receive either minimally interrupted dabigatran or uninterrupted warfarin. Dabigatran was administered at 150 mg or 110 mg twice daily. The 110-mg twice-daily dose was administered in patients with moderate renal disorders (creatinine clearance 30–50 mL/min). In the warfarin group, warfarin was continued without interruption. Target prothrombin time/international normalized ratio was 2.0–3.0 for patients younger than 70 years of age and 1.6–2.6 for patients 70 years of age and older, according to the Japanese guidelines. During the procedure, achieving and maintaining an activated clotting time of 300–400 seconds was recommended. Anticoagulation was continued in both treatment groups for three months after the procedure, and all of the patients were followed up for 12 months. The primary endpoint was the incidence of adjudicated major bleeding events up to three months after ablation.

Dr. Aonuma reported that among the 442 evaluable patients who underwent ablation (mean age, 64 years; 75% male), there was only one thromboembolic event (0.5%), which occurred in the warfarin group. The probability of major bleeding events at three months, however, was significantly lower with dabigatran (1.4 ± 0.8%) than with warfarin (5.0 ± 1.5%; P = 0.032).

Pericardial hemorrhage was reported in one dabigatran-treated patient and in three warfarin-treated patients. Gastro bleeding events were also more common in the warfarin group (one dabigatran, five warfarin). A significant reduction in major bleeding risk in the dabigatran group compared with the warfarin group was consistently observed across the subgroups: age 65 to younger than 75 years, male gender, CHA2DS2-VASc score of 1, and radiofrequency energy ablation.

“Anticoagulation with minimally interrupted dabigatran with or without heparin bridging was associated with fewer bleeding complications than uninterrupted warfarin with no increase in thromboembolic events,” Dr. Aonuma concluded.

Subgroup Analysis From the RE-DUAL PCI Trial: Dual Antithrombotic Therapy With Dabigatran In Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention

• Jonas Oldgren, MD, Uppsala University, Uppsala, Sweden

The benefit of dabigatran dual therapy versus warfarin triple therapy in patients with atrial fibrillation (AF) undergoing percutaneous coronary interventions (PCIs) was consistent with the benefit shown in the trial’s main results. Those results, Dr. Oldgren said in an oral presentation, demonstrated benefit in patients with acute coronary syndrome (ACS) and nonacute ACS index events, in those receiving drug-eluting stents (DES) or bare metal stents (BMS), and those receiving either of two P2Y12 inhibitors—ticagrelor (Brilinta, AstraZeneca) or clopidogrel.

A high risk of bleeding is associated with triple antithrombotic therapy consisting of warfarin and two antiplatelet agents, the standard of care for post-PCI patients with AF, Dr. Oldgren said. To test dual antithrombotic therapy with dabigatran, RE-DUAL PCI investigators randomized 2,725 patients post-PCI to dabigatran 150 mg twice daily plus a P2Y12 inhibitor, dabigatran 110 mg twice daily plus a P2Y12 inhibitor, or warfarin (international normalized ratio, 2.0–3.0) plus a P2Y12 inhibitor and aspirin for a minimum of six months. Mean follow-up was approximately 14 months.

The hazard ratio (HR) for dabigatran 110-mg dual therapy versus warfarin triple therapy for the primary endpoint (time to first International Society on Thrombosis and Hemostasis [ISTH] major or clinically relevant non-major [CRNM] bleeding event) was 0.52 (95% confidence interval [CI], 0.42–0.63; P < 0.0001). For dabigatran 150-mg dual therapy, the HR was 0.72 (95% CI, 0.58–0.88; P = 0.002). The rates for the composite efficacy outcome (all-cause death, myocardial infarction, stroke, systemic embolism, or unplanned revascularization) were similar for dabigatran (combined dose) and warfarin triple therapy at 13.7% and 13.4%, respectively.

While bleeding event rates (ISTH major or CRNM) generally favored dabigatran, they were similar among ACS and non-ACS patients and for those patients with BMS or DES. Death and thromboembolic events were also similar among ACS and non-ACS patients. Analysis showed no significant interactions.

Although bleeding rates were generally higher for ticagrelor versus clopidogrel (e.g., in the dabigatran 110-mg twice-daily group, combined ISTH major and CRNM rates were 21.2% for ticagrelor and 14.5% for clopidogrel), interactions were not significant. Only 12% of patients received ticagrelor.

While bleeding was more frequent in the ticagrelor group, the AHA discussant for RE-DUAL PCI, Mark A. Hlatky, MD, of the Stanford University School of Medicine, cautioned that the ticagrelor versus clopidogrel comparison was not randomized or adjusted for confounders.

Effects of Bariatric Surgery in Obese Patients With Hypertension: The GATEWAY Randomized Trial

• Carlos Aurelio Schiavon, MD, HCor Research Institute, Sao Paulo, Brazil

In the GATEWAY trial, gastric bypass surgery reduced need for antihypertensive medications by at least 30% in nearly 84% of patients. In addition, remission from hypertension was reported in about half of the patients, Dr. Schiavon said in an AHA press briefing.

About 40% of Americans are obese. Adult hypertension is attributable to adiposity in about 60% to 70% of cases. Observational and clinical trial evidence, mostly from type-2 diabetes research, has shown that bariatric surgery leads to a reduction or discontinuation of antihypertensive medication and an overall reduction in cardiovascular events, he said.

According to Dr. Schiavon, GATEWAY was launched because randomized, controlled trials in a broad population of hypertensive obese patients have not been conducted. GATEWAY is a single center, open-label, randomized trial evaluating the efficacy of gastric bypass for reducing prescription of antihypertensive drugs and assessing effects on hypertension and other cardiovascular risk factors. Patients were randomized to gastric bypass plus medical therapy (n = 49) or to medical therapy with lifestyle intervention (cardiologist, nutritionist, and psychologist visits) (n = 47). The included patients had

continued on page 57
hypertension, body mass index (BMI) between 30.0 and 39.9 kg/m², and were treated with at least two antihypertensive drugs at maximum doses or more than two at moderate doses. The blood pressure target was systolic blood pressure (SBP) of less than 140 mm Hg and diastolic blood pressure (DBP) of less than 90 mm Hg. Patients with SBP of 180 mm Hg or greater or DBP of 120 mm Hg or greater were excluded. Patients in the medical therapy group, if above target, were treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers plus a calcium-channel blocker, and with a thiazide diuretic and spironolactone or clonidine as needed. Dosage and/or the number of antihypertensive medications were reduced if SBP was less than 110 mm Hg and/or DBP was greater than 70 mm Hg. Need for reintroduction of medication in the gastric bypass group was checked daily in the post-operative period. The primary endpoint was a reduction of at least 30% of the total antihypertensive medications while maintaining SBP and DBP lower than 140 mm Hg and 90 mm Hg, respectively, at 12 months.

The mean number of baseline antihypertensive drugs was approximately three in both groups. Mean baseline age was about 44 years, approximately 70% of the patients were women, and mean BMI was 37.4 kg/m² in the gastric bypass group and 36.4 kg/m² in the medical therapy group.

The primary endpoint was achieved in the gastric bypass group by 83.7% of patients and in the medical therapy group by 12.8%. Dr. Schiavon emphasized, “Most importantly, the remission of hypertension by office measurement was present in 51% of gastric bypass patients and in none of the medical therapy patients.” He pointed out that the reduction in medications occurred in the gastric bypass patients before they had lost significant weight. “That raises a question as to how bariatric surgery improves hypertension.”

Increases in anemia (20% in the gastric bypass group versus 10% in the medical therapy group) and hypervitaminosis B₁₂ were reported in the gastric bypass group, with six patients needing hospitalization.

“Bariatric surgery represents a safe and effective way to treat obesity. Hypertension amelioration is a potential beneficial effect. Reduction in antihypertensive medications can help in adherence to treatment,” Dr. Schiavon said. Improved metabolic and inflammatory profiles, he added, can potentially reduce major cardiovascular events.

REFERENCE