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Reviews

Review of ACC 2020 Late-Breaking Trials in Interventional Cardiology

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Contents

The American College of Cardiology Scientific Sessions (ACC) is one of the largest cardiology conferences in the world, sharing the latest research in the field. The ACC conference was unique this year, as it was a virtual meeting given the novel coronavirus 2019 pandemic. In this article, we provide a brief overview of the late-breaking trials (LBTs) presented at the ACC 2020 conference that will have significant impact on clinical practice in the field of interventional cardiology.

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1. Structural

1.1. Transcatheter Aortic Valve Replacement in Patients With Severe Bicuspid Aortic Valve Stenosis at Low Predicted Risk of Mortality

Presenter: Dr. Basel Ramlawi

Key points: Transcatheter aortic valve replacement (TAVR) with a self-expanding prosthesis is safe and effective in low-risk patients with bicuspid aortic valves.

TAVR using a self-expanding prosthesis is safe in low-risk patients with bicuspid aortic stenosis. Basel Ramlawi, MD, a cardiothoracic surgeon and chairman of The Heart & Vascular Center at Valley Health System in Virginia, presented the results on behalf of the Medtronic Low-Risk Bicuspid investigators.

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The prospective registry enrolled 150 patients at 25 high-volume centers across the United States. Enrolled patients had an average age of 70 years and a Society of Thoracic Surgeons (STS) mortality risk score of 1.4%. Patients with Sievers type 0 and 1 bicuspid valves were included.

Patients were treated with Medtronic's Evolut R (23, 26, 29, or 34 mm) or the Evolut Pro (23, 26, or 29 mm) self-expanding transcatheter heart valve (THV). Key anatomical exclusion criteria were significant ascending aortopathy requiring surgical repair, an ascending aorta diameter >4.5 cm and age <60 years.

At 30 days of follow-up after the procedure, 1.3% of patients had died or experienced a disabling stroke. Procedural success was also high at 95.3%, indicating a low complication rate. The design improvements from Evolut R to Evolut Pro, which added a sealing skirt on the bottom cells of the device, showed impressive results, with 100% of patients demonstrating mild or no aortic regurgitation within 7 days.

Commenting about the results, Ramlawi said: "This is the first study that shows the self-expanding valve works well for patients with both type 1 and type 0 bicuspid valves. The medical community has perceived type 0 bicuspid valves as more challenging to treat, so those data are especially encouraging."

Of note, the trial was funded by Medtronic, maker of the self-expanding valves used in the study.

1.2. Two-year Clinical and Echocardiographic Outcomes From the PARTNER 3 Low-Risk Randomized Trial

Presenter: Dr. Michael J. Mack

Key points: Transcatheter aortic valve replacement (TAVR) with a balloon-expandable valve holds on to its advantage over surgical aortic valve replacement (SAVR) at 2 years. However, the primary-outcome gap shrinks after the first year, with increased valve thrombosis noted in the TAVR arm between years 1 and 2.

Patients at low surgical risk for mortality who underwent TAVR with a balloon-expandable valve continued to show significantly better outcomes at 2 years than those who underwent SAVR, but the differences between the two groups began to narrow from year 1 to year 2.

Michael J. Mack, MD, a cardiothoracic surgeon at Baylor Scott & White Health, Dallas, Texas, presented the 2-year results of the PARTNER 3 trial, which randomized low-risk patients with severe, symptomatic aortic stenosis to undergo TAVR with the balloon-expandable Sapien 3 THV (Edwards Lifesciences) or SAVR.

The PARTNER 3 trial at 1 year showed superiority of TAVR over SAVR for the primary composite outcome of death, stroke or rehospitalization. That outcome occurred in 8.5% of TAVR patients and 15.1% of SAVR patients, according to results presented at ACC 2019 and published in *The New England Journal of Medicine* [1].

At 2 years, the difference in the composite rate remained statistically significant but narrowed between TAVR (11.5%) and SAVR (17.4%), mostly due to an increase in late events in the TAVR arm, including more late deaths and stroke, between years 1 and 2. There was also an increase in valve thrombosis in the TAVR group at 2 years. The improvement in hemodynamics and the frequency of moderate or mild paravalvular regurgitation were unchanged between 1 and 2 years in both TAVR and SAVR patients.

Mack concluded that there was a 37% relative reduction in death, stroke and rehospitalization in the TAVR arm but that there were more death and stroke events in TAVR patients from 1 to 2 years, and there were reduced cardiovascular-related hospitalizations in favor of TAVR.

The relevance of valve thrombosis on long-term outcomes, particularly structural valve deterioration, needs longer-term follow-up, but there are no early signals of poor outcomes, and the risks and benefits of anticoagulation need to be assessed on a patient-to-patient basis, Mack said.

"Longer-term outcomes are particularly important for this patient population because younger, low-risk patients have longer to live with this valve than patients that have been previously studied," Mack said in a news release accompanying the study results. "Therefore, the durability of the valve is of utmost importance."

The PARTNER 3 trial was funded by Edwards Lifesciences.

1.3. Antithrombotic Therapy After Transcatheter Aortic Valve Implantation in Patients With a Long-Term Indication for Oral Anticoagulation (POPular TAVI Trial - Cohort B)

Presenter: Dr. Jurrien ten Berg

Key points: POPular TAVI demonstrated that treatment with an anticoagulation-alone strategy has a lower rate of serious bleeding than oral anticoagulation (OAC) plus clopidogrel for 3 months after transcatheter aortic valve replacement (TAVR).

Patients with atrial fibrillation on OAC therapy who underwent TAVR and continued treatment with OAC alone had a lower rate of serious bleeding at 1-year follow-up than patients who received OAC plus clopidogrel for 3 months after TAVR. Jurrien ten Berg, MD, PhD, MSc, of St. Antonius Hospital, Nieuwegein, Netherlands, presented the results of Cohort B of the POPular TAVI trial. This study was simultaneously published online in *The New England Journal of Medicine* [2].

A significant percentage of patients undergoing TAVR, also known as transcatheter aortic valve implantation (TAVI), have concomitant atrial fibrillation, requiring them to be on chronic OAC. Current guidelines do not specify a treatment strategy for these patients after TAVR, and the question of whether the addition of an antiplatelet to treatment with OAC is beneficial is not yet understood.

POPular TAVI is a prospective, 1:1 randomized, parallel-group, open-label, multicenter trial performed at 17 European sites. Cohort A randomized patients without an indication for OAC after TAVR to aspirin or aspirin and clopidogrel. Cohort B, which was presented at ACC 2020, randomized patients on chronic OAC therapy to treatment with OAC alone or to clopidogrel for 3 months in addition to OAC after TAVR. The main exclusion criteria were drug-eluting stent implantation 3 months before TAVR, bare metal stent implantation 1 month before TAVR or clopidogrel allergy.

The trial had two primary outcomes: all bleeding and non-procedural bleeding. The Valve Academic Research Consortium-2 was used to classify bleeding events and vascular complications, and Bleeding Academic Research Consortium type 4 severe bleeding was used to define procedure-related events.

A total of 326 patients (mean age 81 years, 45.4% women) underwent randomization; 164 were assigned to receive OAC alone (157 completed 12 months of follow-up). In the second arm, 162 were assigned to receive OAC plus clopidogrel for 3 months (156 patients completed 12 months of follow-up). There were no significant differences between the groups in baseline characteristics.

The OAC-alone group was less likely to experience all-cause bleeding than the group taking OAC and clopidogrel (21.7% vs. 34.6%; relative risk [RR], 0.63; 95% confidence interval [CI], 0.43–0.90; $p = 0.01$). Access-site bleeding was the most common cause of bleeding.

The secondary composite outcome (cardiovascular-related death, non-procedure-related bleeding, all-cause stroke, or myocardial infarction [MI]) occurred in 31.2% of the OAC-alone group and in 45.5% of the OAC-plus-clopidogrel group (95% CI for noninferiority, -25.0 to -3.6; RR, 0.69; 95% CI for superiority, 0.51 to 0.92). Another secondary composite outcome (cardiovascular-related death, ischemic stroke, or MI) occurred in 13.4% receiving OAC alone and in 17.3% receiving OAC plus clopidogrel (95% CI for noninferiority, -11.9 to 4.0; RR, 0.77; 95% CI for superiority, 0.46 to 1.31). Both of these outcomes showed noninferiority for OAC alone, but the authors wrote in the *New England Journal of Medicine* manuscript, "No clinical inferences can be drawn for these secondary outcome results because of the lack of a plan for correction for multiple comparisons."

"The rates of complications for TAVR — especially complications related to bleeding — remain high," commented Vincent Nijenhuis, MD, of St. Antonius Hospital and the study's lead author, in a news release accompanying the trial results. "This study helps physicians to better understand the risks of adding antiplatelet therapy to oral anticoagulants — namely, that doing so leads to more bleeding without reducing the rate of ischemic events. I think once physicians are aware of this, they will not treat patients undergoing TAVR so aggressively, leading to better outcomes."

The trial was funded by The Netherlands Organization for Health Research and Development.

1.4. A Composite Metric for Benchmarking Site Performance in Transcatheter Aortic Valve Replacement: Results From the STS/ACC TVT Registry

Presenter: Dr. Nimesh D. Desai

Key points: Novel TAVR measure shows 80% of centers meet expectations for patient outcomes.

The vast majority of U.S. centers that perform transcatheter aortic valve replacement (TAVR), 80%, saw patient outcomes that were expected in terms of survival and quality of life, while 8% performed better than expected, and 11 performed worse than expected.

Nimesh D. Desai, MD, PhD, co-director of the Penn Thoracic Aortic Surgery Program and an associate professor of surgery at the Hospital of the University of Pennsylvania, presented the results of the novel, patient-centric composite outcome measure. The measure was designed to better reflect the patient experience than mortality alone.

Data were collected from 301 sites and 54,217 patients using the Society of Thoracic Surgeons/ACC Transcatheter Valve Therapy Registry. The selection and rank order of the periprocedural complications for the composite was determined by their adjusted association with 1-year mortality and patient quality of life (assessed through the Kansas City Cardiomyopathy Questionnaire). The ranking of endpoints was as follows: death, stroke, major bleeding, acute kidney injury, and moderate or severe paravalvular leak.

Site differences were assessed using this novel composite outcome. The model's reliability was assessed according to site volume, showing acceptable mortality in sites with as few as 25 cases per year, meaning that it performed better than mortality alone. Desai concluded that this 30-day composite metric was appropriate for high-stakes applications such as public reporting.

Howard Herrmann, MD, director of Cardiac Catheterization Laboratories at the Hospital of the University of Pennsylvania, commented that it is important to report quality, but he expressed concern that missing data may impact validity for public reporting. Mayra Guerrero, MD, an interventional cardiologist at the Mayo Clinic, Rochester, Minnesota, said it was interesting to note that new permanent pacemaker implantation did not have a major impact on quality of life.

Desai warned that the patient cohort did not include low-risk patients and did not report on the very long-term implications of having a permanent pacemaker.

1.5. The United Kingdom Transcatheter Aortic Valve Implantation (UK TAVI) Trial

Presenter: Dr. William Toff

Key points: TAVR, SAVR show comparable 1-year mortality results in UK TAVI Trial.

Transcatheter aortic valve replacement (TAVR) was shown to be non-inferior to surgical aortic valve replacement (SAVR) in terms of mortality in patients age 70 and older deemed to be at increased surgical mortality risk.

The UK TAVI trial was designed to assess the clinical effectiveness and cost utility of TAVR, compared with SAVR, in patients age 70 years and older with severe, symptomatic aortic stenosis. The design was an open-label, non-inferiority, randomized controlled trial. The trial enrolled patients at intermediate or high surgical risk for mortality as determined by the multi-disciplinary heart team.

A total of 913 patients from 34 UK centers were randomized to undergo TAVR or SAVR. William Toff, MD, a professor of clinical cardiology at the University of Leicester, UK, stressed in presenting the results that the study had a pragmatic design with minimal exclusion criteria and took place in a real-world setting with all CE-marked TAVR valves allowed.

The primary endpoint was all-cause mortality at 1 year. The trial also measured several key secondary outcomes, including all-cause mortality at 2, 3, 4, and 5 years; stroke; and death from any cause or stroke.

Baseline characteristics were similar between the two arms, including mean age (TAVR 81.1 years, SAVR 81.0 years), male sex (TAVR 53.9%, SAVR 53.2%), and median Society of Thoracic Surgeons risk score (TAVR 2.6%, SAVR 2.7%).

At 1 year, all-cause death rates were similar between the two groups (TAVR 4.6% vs. SAVR 6.6%; hazard ratio [HR], 0.69; 95% CI, 0.38–1.26; $p = 0.23$).

TAVR was associated with a significantly higher rate of vascular complications, (TAVR 4.8% vs. SAVR 1.3%; HR, 3.39; 95% CI, 1.79–7.60; $p < 0.001$), higher rate of permanent pacemaker implantation (TAVR 12.2% vs. SAVR 6.6%; HR, 1.92; 95% CI, 1.33–2.76; $p = 0.02$) and higher rate of aortic regurgitation (mild regurgitation, TAVR 38.3% vs. SAVR 11.7%; moderate regurgitation, TAVR 2.3% vs. SAVR 0.6%).

However, TAVR was associated with less major bleeding (TAVR 6.3% vs. SAVR 17.1%; HR, 0.34; 95% CI, 0.25–0.46; $p < 0.001$), shorter hospital stay (TAVR 3 days vs. SAVR 8 days), fewer days in intensive care (TAVR 0 days vs. SAVR 1 day), and more rapid improvement in functional capacity and quality of life.

Toff concluded that non-inferiority of TAVR compared to SAVR was met in patients older than 70 years and deemed at intermediate or high surgical risk in a real-world setting with minimal exclusion criteria.

The UK TAVI trial was funded by the National Institute for Health Research Technology Assessment Programme with support from the institute's Leicester Biomedical Research Centre.

2. Coronary

2.1. Clinical Implementation of Clopidogrel Pharmacogenetics: The Tailor PCI Trial

Presenter: Dr. Naveen L. Pereira

Key points: Ticagrelor reduces ischemic events after percutaneous coronary intervention (PCI), but falls short of goal versus clopidogrel.

TAILOR PCI, an international clinical trial that used genetic testing to guide which antiplatelet medication was given to patients following PCI, did not meet its stated goal for cutting in half the incidence of serious ischemic events in the year following the procedure.

The trial aimed to provide evidence showing whether CYP2C19 loss-of-function (LOF) allele carriers treated with ticagrelor in the prospective genotyping arm would have improved clinical outcomes as compared to those in the conventional treatment arm, who received clopidogrel. The LOF carriers have a genetic variant that makes them less able to metabolize clopidogrel, reducing the medication's effectiveness, according to a press release accompanying the trial results.

Patients were enrolled at 40 centers in the US, Canada, Mexico, and South Korea. Eligible patients were adults age 18 years and older who underwent PCI for acute coronary syndromes or stable coronary artery disease and required 12 months of dual antiplatelet therapy.

A total of 5302 patients were randomized to genotype-guided therapy ($n = 2650$) or conventional therapy ($n = 2652$). The primary analysis cohort was CYP2C19 *2/*3 LOF carriers in both arms of the trial, which totaled 1849 patients (903 genotype-guided therapy [ticagrelor], 946 conventional therapy [clopidogrel]). The non-carriers in both arms received clopidogrel.

The primary endpoint was to demonstrate a 50% reduction in the composite of cardiovascular death, myocardial infarction, stroke, definite or probable stent thrombosis, and severe recurrent ischemia within 1 year of the index PCI. The secondary endpoints were major or minor bleeding as defined by the Thrombolysis in Myocardial Infarction (TIMI) criteria.

At 1 year, genotype-guided therapy missed the 50% reduction goal; however, it did show a 34% reduction in ischemic events in comparison with conventional therapy (adjusted hazard ratio [HR], 0.66; 95% CI, 0.43–1.02; p = 0.056; number needed to treat = 55).

A prespecified sensitivity analysis examining multiple recurring ischemic events instead of "time to first event" also showed a 40% reduction in these events in the genotype-guided therapy group (HR, 0.60; 95% CI, 0.41–0.89; p = 0.011).

Bleeding rates were similar between the two groups.

"Although these results fell short of the effect size that we predicted, they nevertheless provide a signal that offers support for the benefit of genetically guided therapy, with approximately one-third fewer adverse events in the patients who received genetically guided treatment compared with those who did not," said Naveen L. Pereira, MD, of Mayo Clinic, Rochester, Minnesota, co-principal investigator of the study, who presented the results.

A *post hoc* landmark analysis did show a 79% reduction in ischemic events in the genotype-guided therapy group at 90 days (Δ = 2.1% [1.0, 3.4]; HR = 0.21; p = 0.001).

Extended follow-up funded by the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health is ongoing. The study received funding from the NHLBI and Mayo Clinic. Spartan Bioscience Inc. supplied the genetic tests.

2.2. Ticagrelor With or Without Aspirin in Acute Coronary Syndrome After Percutaneous Coronary Intervention: Randomized Evaluation of Ticagrelor Monotherapy After 3-Month Dual Antiplatelet Therapy in Acute Coronary Syndrome

Presenter: Dr. Yongsoo Jang

Key points: Ticagrelor without aspirin following percutaneous coronary intervention (PCI) lowers bleeding risk and does not raise thromboembolic risk in comparison with ticagrelor-plus-aspirin therapy in patients presenting with acute coronary syndrome (ACS).

The TICO investigators evaluated whether ticagrelor monotherapy after 3 months of dual antiplatelet therapy (DAPT) improved upon ticagrelor-based 12-month DAPT for ACS in patients undergoing PCI with bioresorbable-polymer sirolimus-eluting stents (Orsiro, Biotronik). This was a prospective, randomized, multicenter trial conducted at 38 centers in Korea and included 3056 patients.

The primary outcome was the composite of net adverse clinical events at 12 months, defined as Thrombolysis in Myocardial Infarction (TIMI) major bleeding, all-cause death, myocardial infarction, stent thrombosis, stroke, or target vessel revascularization.

The primary outcome occurred in 59 patients (3.9%) in the ticagrelor monotherapy group and in 89 patients (5.9%) in the conventional therapy group (HR, 0.66; 95% CI, 0.48–0.92; p = 0.014). The difference was mainly driven by a lower risk of major bleeding in the ticagrelor monotherapy group (1.7% vs. 3.0%; HR, 0.56; 95% CI 0.34–0.91; p = 0.019). The rates of major adverse cardiac and cerebrovascular events and death were similar between the two groups.

The TICO trial demonstrated that ticagrelor monotherapy after 3 months of DAPT showed a significantly lower risk of net adverse clinical events than currently recommended ticagrelor-based 12-month DAPT. This finding indicates that ticagrelor monotherapy could be an optimal strategy, balancing both ischemic and bleeding risks for patients with ACS treated by biodegradable-polymer sirolimus-eluting stents.

The TICO trial was supported by the Cardiovascular Research Center, Seoul, Korea, and funded by Biotronik, Bülach, Switzerland.

2.3. Safety and Efficacy of Ticagrelor Monotherapy After Complex PCI: The TWILIGHT-COMPLEX Substudy

Presenter: Dr. George D. Dangas

Key points: Ticagrelor without aspirin following percutaneous coronary intervention (PCI) lowers bleeding risk and does not raise thromboembolic risk in comparison with ticagrelor-plus-aspirin therapy in patients with complex PCI.

In this prespecified sub-analysis of the TWILIGHT randomized, double-blind, placebo-controlled trial, the investigators assessed the effect of antiplatelet monotherapy specifically in patients who had been treated with complex PCI. Patients with at least 1 clinical and 1 angiographic criterion for complex PCI were treated with ticagrelor plus aspirin for 3 months followed by either aspirin or placebo and continued on ticagrelor for an additional 12 months.

Complex clinical criteria included age ≥65 years, female sex, troponin-positive acute coronary syndrome (ACS), established vascular disease, diabetes, or chronic kidney disease. Complex angiographic criteria included multivessel coronary artery disease, target lesions requiring total stent length >30 mm, thrombotic target lesion, bifurcation lesions requiring ≥2 stents, left main or proximal left anterior descending artery lesions, and calcified target lesions requiring atherectomy.

Among 7119 patients randomized in the main TWILIGHT trial, complex PCI was performed in 2342 patients. Compared to ticagrelor plus aspirin, ticagrelor plus placebo resulted in significantly lower rates of Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding (4.2% vs. 7.7%; hazard ratio [HR], 0.54; 95% CI, 0.38–0.76). BARC type 3 or 5 bleeding was also significantly reduced in the ticagrelor-plus-placebo group (1.1% vs. 2.6%; HR, 0.41; 95% CI, 0.21–0.80). There were no significant differences in death, myocardial infarction, or stroke (ticagrelor 3.8% vs. DAPT 4.9%; HR, 0.77; 95% CI, 0.52–1.15), nor in stent thrombosis, Dangas and colleagues reported in a manuscript simultaneously published online in the *Journal of the American College of Cardiology* [3].

Among patients who underwent complex PCI, a regimen of ticagrelor monotherapy (after an initial 3 months of dual antiplatelet therapy [DAPT] with ticagrelor and aspirin) was associated with significantly lower clinically relevant bleeding without increasing the risk of ischemic events in comparison with continuing the DAPT. This effect was consistent across the individual components of the complex PCI definition.

These results comport with the main TWILIGHT findings, which were first presented at Transcatheter Cardiovascular Therapeutics (TCT) 2019 in September and published in *The New England Journal of Medicine* [4].

2.4. Radial Artery Versus Saphenous Vein for Coronary Bypass Surgery at Long-Term Follow-Up

Presenter: Dr. Mario F.L. Gaudino

Key points: New data show survival benefit of radial artery grafting in coronary bypass at 10 years.

Patients who underwent coronary artery bypass grafting (CABG) with radial artery grafts showed improved survival and a lower rate of adverse cardiovascular events in comparison with those who underwent bypass surgery with saphenous vein grafts.

Mario F.L. Gaudino, MD, of New York Presbyterian Weill Cornell Medical Center, presented the data on behalf of the Radial Artery Database International Alliance (RADIAL) investigators.

The study consolidated five separate randomized controlled trial databases into one centralized patient-level dataset. The included trials were performed across five countries (Serbia, Australia, UK, Italy, and South Korea) from 1997 to 2009. When pooled together, 1036 patients were included in the final patient-level meta-analysis to a median

follow-up of 10 years (534 in the radial artery grafting group, 502 in the saphenous vein graft group).

Patients across the two study arms were similarly matched, with a mean age of 66 years and similar comorbidities at entry to the study; 70% of the included participants were men. An average of 3.1 grafts were performed in each group, and 77% of patients in the radial artery group had a successful radial artery graft to the left circumflex coronary artery.

The risk of the primary composite outcome of death, myocardial infarction (MI), or repeat revascularization was significantly decreased in the radial artery graft patients compared to the patients with saphenous vein grafts (hazard ratio [HR], 0.730; 95% CI, 0.61–0.88; $p < 0.001$). A similar result in the secondary composite outcome of death or MI was also seen, with radial grafting faring better than saphenous vein grafting at 10 to 15 years of follow-up (HR, 0.77; 95% CI, 0.63–0.94; $p = 0.01$). A subgroup analysis suggested that radial artery grafting showed a particular benefit in women (HR, 0.51; 95% CI, 0.36–0.72; $p = 0.03$).

These data demonstrate for the first time the long-held belief that radial artery grafting offers improved outcomes compared with saphenous vein grafting in CABG.

"The choice of an artery or a vein to create the second bypass is one of the most important unresolved questions in contemporary bypass surgery," Gaudino said in a news release accompanying the results. "This study offers the first evidence from randomized trials to show that patients live longer and have better outcomes when surgeons use the radial artery instead of the saphenous vein to create the second bypass."

2.5. Ten-Year Outcomes After Drug-Eluting Stents Versus Coronary Artery Bypass Grafting for Left Main Coronary Disease

Presenter: Dr. Duk-Woo Park

Key points: Ten years later, study shows similar outcomes between CABG and PCI in patients with unprotected left main disease.

In the longest randomized controlled trial to compare drug-eluting stents and coronary artery bypass grafting (CABG) in patients with unprotected left main coronary artery (LMCA) disease, there were no significant differences in the rates of major adverse cardiac or cerebrovascular events, serious composite outcomes, and mortality over 10 years.

These findings were presented by Duk-Woo Park, MD, PhD, of Asan Medical Center, University of Ulsan College of Medicine, Seoul. The results were also simultaneously published online in *Circulation* [5].

Long-term outcomes after percutaneous coronary intervention (PCI) with drug-eluting stents and CABG in patients with LMCA disease are limited. From April 2004 to August 2009, 600 patients with LMCA disease were randomly assigned to undergo either PCI with sirolimus-eluting stents (300 patients) or CABG (300 patients). The primary outcome was major adverse cardiac or cerebrovascular events (MACCE: death from any cause, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization). The study patients' average age at treatment was 62.3 years, 76.5% were men, and 32% were being treated for diabetes.

At 10-year follow-up (median 11.3 years), the primary outcome occurred in 29.8% of the PCI group and 24.7% of the CABG group (hazard ratio [HR] with PCI vs. CABG, 1.25; 95% CI, 0.93–1.69; $p = 0.14$). In addition, the 10-year incidence of a composite of death, myocardial infarction, or stroke, as well as death from any cause, was not significantly different between the PCI and CABG groups. Finally, ischemia-driven target vessel revascularization was more frequent after PCI than after CABG (16.1% vs. 8.0%; HR, 1.98; 95% CI, 1.21–3.21; $p = 0.006$).

In this long-term randomized cohort of patients with LMCA disease who underwent either PCI with a drug-eluting stent or CABG, there was no significant difference in the rates of MACCE, serious composite outcome, and mortality at 10 years. These findings provide extended follow-up and important insights on long-term outcomes, which may aid in decision-making about the optimal treatment strategy for patients with LMCA disease.

However, Park noted that the study is underpowered, so "the results should be considered hypothesis-generating, highlighting the need for further research."

The PRECOMBAT study was funded by the Cardiovascular Research Foundation.

2.6. Ticagrelor With and Without Aspirin in High-Risk Patients With Diabetes Mellitus Undergoing Percutaneous Coronary Intervention: Insights From the TWILIGHT Trial

Presenter: Dr. Dominick Angiolillo

Key points: Ticagrelor without aspirin following percutaneous coronary intervention (PCI) lowers bleeding risk and does not raise thromboembolic risk in comparison with ticagrelor-plus-aspirin therapy in patients with diabetes who receive a PCI.

This prespecified sub-analysis of the TWILIGHT trial provided important data, as patients with diabetes are known to be at high risk for both ischemic and bleeding complications after PCI. Randomization was not stratified, however, by the presence of diabetes, and diabetes presence was based upon physician diagnosis.

Patients with diabetes comprised 37% ($n = 2620$) of the randomized TWILIGHT cohort and were characterized by more frequent comorbidities and a higher prevalence of multivessel disease. The incidence of Bleeding Academic Research Consortium 2, 3, or 5 bleeding was lower among patients with diabetes randomized to ticagrelor plus placebo (ticagrelor 4.5% vs. DAPT 6.7%; HR, 0.65; 95% CI, 0.47–0.91; $p = 0.012$). Ticagrelor monotherapy was not associated with an increase in ischemic events in these patients (4.6% vs. 5.9%; HR, 0.77; 95% CI, 0.55–1.09; $p = 0.14$). In the overall trial population, there was no significant interaction between diabetes status and treatment group for the primary bleeding or ischemic endpoints, Angiolillo and colleagues reported in a manuscript simultaneously published online in the *Journal of the American College of Cardiology* [6].

The TWILIGHT investigators concluded that the effect of ticagrelor monotherapy in reducing the risk of clinically relevant bleeding without any increase in ischemic events was consistent among patients with or without diabetes undergoing PCI. These findings support such a bleeding avoidance strategy, which can be implemented without any signals for harm even in high-risk patients, such as those with diabetes.

3. Peripheral

3.1. Rivaroxaban for Prevention of Cardiovascular and Limb Events After Lower–Extremity Revascularization: Primary Results of the VOYAGER PAD Randomized Trial

Presenter: Dr. Marc P. Bonaca

Key points: Rivaroxaban plus aspirin reduces adverse events after revascularization in lower-extremity peripheral arterial disease (PAD) patients.

A twice-daily regimen of 2.5 mg of rivaroxaban plus aspirin significantly reduced lower-limb and cardiovascular adverse events in comparison with placebo in patients who underwent revascularization for lower-extremity PAD.

Marc P. Bonaca, MD, presented the VOYAGER PAD (Vascular Outcomes Study of ASA Along with Rivaroxaban in Endovascular or Surgical Limb Revascularizations for Peripheral Artery Disease) results, which were simultaneously published online in *The New England Journal of Medicine* [7].

The objective of the study was to assess rivaroxaban, 2.5 mg twice daily, compared with placebo among patients with lower-extremity PAD undergoing revascularization. This was a randomized, parallel, double-blind study that included 6564 patients. Patients age 50 years

or older with PAD as demonstrated by ischemic symptoms, disease evidenced by imaging or an abnormal ankle brachial index, who underwent successful revascularization were included in the study.

The primary efficacy outcome (composite of acute limb ischemia, major amputation for vascular cause, myocardial infarction, ischemic stroke, or cardiovascular death) occurred in 17.3% of the rivaroxaban group compared with 19.9% of the placebo group ($p = 0.0085$). The primary safety outcome, Thrombolysis in Myocardial Infarction (TIMI) major bleeding, occurred in 2.7% of the rivaroxaban group compared with 1.9% of the placebo group ($p = 0.069$). The International Society on Thrombosis and Haemostasis (ISTH) major bleeding occurred in 5.94% of the rivaroxaban group compared with 4.06% of the placebo group ($p = 0.007$).

The authors concluded that in patients with symptomatic PAD after lower-extremity revascularization, 2.5 mg of rivaroxaban twice daily with aspirin was associated with significantly reduced incidence of the composite outcome of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes. There was no significant difference in TIMI major bleeding among the two groups, whereas ISTH major bleeding was significantly increased in the rivaroxaban group in comparison with the aspirin group.

The VOYAGER PAD study received funding from Bayer and Janssen Pharmaceuticals.

3.2. The Benefit and Risk of Rivaroxaban Plus Aspirin in Patients With Peripheral Artery Disease After Lower-Extremity Revascularization With and Without Concomitant Clopidogrel: A Key Subgroup Analysis From VOYAGER-PAD

Presenter: Dr. William R. Hiatt

Key points: Substudy demonstrates that rivaroxaban benefits PAD patients with or without clopidogrel.

A substudy from the VOYAGER PAD trial shows that low-dose rivaroxaban is safe and effective in patients with peripheral artery disease (PAD) undergoing revascularization, irrespective of clopidogrel use.

William R. Hiatt, MD, of the University of Colorado School of Medicine, presented the study.

The primary VOYAGER PAD study shows that low-dose rivaroxaban, 2.5 mg twice daily, is effective in lowering the primary efficacy endpoint in patients with PAD undergoing revascularization (hazard ratio [HR], 0.85; 95% CI, 0.76–0.96; $p = 0.008$). At 3 years, the absolute risk reduction (ARR) with rivaroxaban was 2.6%, with a number needed to treat of 39. The primary efficacy endpoint was a composite of acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke, or cardiovascular death.

In this study, clopidogrel was used at the investigator's discretion, and the substudy was performed to evaluate whether the safety and efficacy of rivaroxaban would remain with the background use of clopidogrel.

A total of 3313 patients were on clopidogrel, and 3234 were not. The mean age of the patients in the clopidogrel group was 67.1 ± 8.6 years, 28% were women, and about 80% were Caucasian. The clopidogrel group had significantly more women, Caucasians, patients with diabetes mellitus, hyperlipidemia, coronary artery disease, prior coronary artery bypass grafting, heart failure and prior coronary intervention. Also, there was a higher percentage of prior limb revascularization in the clopidogrel group; however, there was a higher percentage of patients with a history of critical limb ischemia in the group with no clopidogrel. Almost 91% of patients in the clopidogrel group underwent revascularization via an endovascular approach. In the no-clopidogrel group, only 42% underwent revascularization via an endovascular approach, and 58% underwent revascularization surgically. At the time of randomization, 50.5% of patients were using clopidogrel in both groups.

At 3 years, rivaroxaban was effective in lowering the primary efficacy endpoint, both with clopidogrel (HR, 0.85; 95% CI, 0.71–1.01; ARR 2.3%) and without clopidogrel (HR, 0.86; 95% CI, 0.73–1.01; ARR, 2.8%). Similar results were seen through 180 days (rivaroxaban 4.1% vs. placebo 5.7% with clopidogrel; rivaroxaban 5.5% vs. placebo 7% without clopidogrel). The primary endpoint results were driven primarily by lower rates of acute limb ischemia in both groups with rivaroxaban. The secondary endpoints of myocardial infarction, stroke, and hospitalization for coronary or peripheral event showed lower rates with the rivaroxaban group, irrespective of clopidogrel use.

In terms of the safety endpoint, Thrombolysis in Myocardial Infarction (TIMI) major bleeding, fatal bleeding, intracranial hemorrhage, or International Society on Thrombosis and Haemostasis (ISTH) major bleeding did not differ between both groups, irrespective of clopidogrel, although numerically higher rates of ISTH or TIMI major bleeding were seen in patients taking rivaroxaban and clopidogrel. In the first 6 months, which is referred to as the period when clopidogrel triple therapy was allowed, the absolute risk increase (ARI) was 1.2% with clopidogrel vs. 0.4% without clopidogrel. After 6 months, there was only a 0.2% ARI with clopidogrel and 0.3% without clopidogrel.

Hiatt concluded that in patients with lower-extremity PAD undergoing revascularization, the benefit and safety of 2.5 mg of rivaroxaban twice daily with aspirin vs. aspirin alone was not affected by clopidogrel use. He also questioned the benefit of clopidogrel, as, he said, all the clinical trials showed no benefit. He added that there is more bleeding with background clopidogrel, and therefore, clopidogrel should be minimized or avoided.

The VOYAGER PAD trial was co-sponsored by Bayer AG (Leverkusen, Germany) and Janssen Pharmaceuticals (Beerse, Belgium).

3.3. Catheter-Based Renal Denervation in the Absence of Antihypertensive Medications: Primary Results From the SPYRAL HTN-OFF MED Pivotal Trial

Presenter: Dr. Michael Böhm

Key points: Renal denervation lowers blood pressure without medication.

Catheter-based renal denervation is effective in reducing blood pressure in the absence of antihypertensive medications.

Michael Böhm, MD, of the University of Saarland, Germany, presented results from the SPYRAL HTN-OFF MED study.

Currently, 1 in 3 adults have hypertension, and there is an unmet need for hypertension treatment. The initial SPYRAL HTN-OFF MED pilot trial showed that renal denervation (RDN) effectively reduces blood pressure, thus leading to this pivotal trial.

The Symplicity Spyral catheter is a 6-French-compatible, multielectrode catheter with a quadrantic vessel contact for simultaneous ablation in up to four electrodes. Flexibility of the catheter allows for branch treatment.

SPYRAL HTN-OFF MED is a prospective, multicenter, randomized, sham-controlled study performed in 44 recruiting sites worldwide. All the patients were screened during two office visits, separated 3 to 4 weeks apart, to check office blood pressure and for drug testing. The main inclusion criteria were patients with confirmed elevated blood pressure as per guidelines and not on antihypertensive medications, and the main exclusion criteria were patients with ineligible renal artery anatomy, type 1 diabetes mellitus, estimated glomerular filtration rate <45 mL/min/1.73 m^2, secondary causes of hypertension and patients with systolic blood pressure (SBP) >180 mmHg or diastolic blood pressure (DBP) <90 mmHg.

A total of 251 patients were randomized to receive RDN or a sham procedure. Follow-up was performed every 2 weeks. The primary efficacy endpoint was change in 24-hour SBP/DBP and office SBP/DBP at 3 months. The primary safety endpoint was any major adverse event at 1 and 3 months.

For the primary analysis, 80 patients in the initial pilot trial were included, bringing the total to 331 randomized patients, 166 to RDN and 165 to the sham control. In the RDN group, the patients' mean age was 52.4 years, 64.5% were men, and 3.6% had type 2 diabetes. In the control group, the mean age was 52.6 years, 68.5% were men, and 5.5% had type 2 diabetes. At baseline, office SBP was around 162 mmHg and 24-hour SBP was 151 mmHg in both groups. In the RDN group, about 2.2 ± 0.6 renal arteries were treated and 5.8 ± 2.7 branches were treated. A total of 46.9 ± 15.6 ablations were performed, of which 18.3 ± 9.9 were in the main arteries. The procedure was successful in all patients.

At 1 month, there were no major adverse events in either group. At 3 months, one patient in the RDN group was hospitalized for hypertensive crisis and one patient in the sham-control group experienced stroke. At 3 months, 91% of RDN patients had no anti-hypertensive drug identified by drug testing, compared to 95% in the sham group.

In terms of the primary efficacy endpoint, at 3 months, both office SBP and DBP were significantly lower in the RDN group (office SBP: D: 6.6 mmHg [-9.6, -3.5, $p < 0.001$], office DBP: D: 4.4 mmHg [-6.2, -2.6, $p < 0.001$]). Similar results were seen with 24-hour ambulatory SBP and DBP at 3 months. Treatment effects were consistent in both the pilot and pivotal trials. By Bayesian, primary endpoint analysis, RDN met the primary efficacy endpoint with >99.9% probability of superiority. The subgroup analysis showed a positive trend, though nonsignificant, with RDN reducing blood pressure in most groups. Although antihypertensive drugs were detected in 36 patients, the results were also consistent in the per-protocol analysis, which excluded patients on medications.

Böhm concluded that catheter-based RDN is effective in lowering blood pressure in patients with uncontrolled hypertension in the absence of antihypertensive medication, with no major device- or procedure-related safety events through 3 months. He added that a large study with patients on medications, SPYRAL HTN-ON MED, is currently enrolling.

The results of the SPYRAL HTN-OFF MED study were simultaneously published online in *The Lancet* [8].

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Declaration of competing interest

Ron Waksman – Advisory Board: Amgen, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips, Pi-Cardia Ltd.; Consultant: Amgen, Biotronik, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips, Pi-Cardia Ltd.; Grant Support: AstraZeneca, Biotronik, Boston Scientific, Chiesi; Speakers Bureau: AstraZeneca, Chiesi; Investor: MedAlliance.

All other authors – None.

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