



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Reviews

Review of Coronary Late Breaking Trials From the TCT Connect 2020 Virtual Meeting



Giorgio A. Medranda, Brian C. Case, Jason P. Wermers, Natalie Morrison, Charan Yerasi, Brian Forrestal, Chava Chezar-Azerrad, Ron Waksman *

Section of Interventional Cardiology, MedStar Washington Hospital Center, Washington, DC, United States of America

Contents

1. Introduction	65
2. Coronary	65
2.1. PROSPECT ABSORB: A randomized trial of interventional treatment of vulnerable plaques	65
2.2. NACMI: Outcomes from the North American COVID-19 STEMI registry	66
2.3. COMPARE CRUSH: A randomized trial of prehospital crushed vs uncrushed prasugrel in STEMI	66
2.4. TICO-STEMI: A randomized trial of ticagrelor monotherapy vs ticagrelor with aspirin in STEMI	67
2.5. Bivalirudin vs heparin in patients with myocardial infarction: An individual patient data pooled analysis.	67
2.6. Disrupt CAD III: Safety and effectiveness of intravascular lithotripsy for treatment of severe coronary calcification	67
2.7. XIENCE 90/28: Assessment of three-month and one-month DAPT after everolimus-eluting stents in high-bleeding-risk patients	68
2.8. HOST-REDUCE-POLYTECH-ACS: A randomized trial of durable-polymer vs bioabsorbable-polymer DES in patients with acute coronary syndromes	68
2.9. COBRA-REDUCE: A randomized trial of a thromboresistant polyzene F-coated stent with 14 days' DAPT in high-bleeding-risk patients	69
2.10. OPTIMIZE: A randomized trial of a novel, ultra-low-profile, fixed-wire DES.	69
Funding	70
Declaration of competing interest.	70
References	70

Abbreviations: ACS, acute coronary syndrome; ARC, Academic Research Consortium; BARC, Bleeding Academic Research Consortium; BVS, bioresorbable vascular scaffold; CAIC, Canadian Association of Interventional Cardiology; CK-MB, creatinine kinase-MB fraction; CI, confidence interval; COVID-19, coronavirus disease 2019; DAPT, dual antiplatelet therapy; DOCO, device-oriented composite outcome; ECG, electrocardiogram; GDMT, guideline-directed medical therapy; HBR, high-bleeding-risk; HR, hazard ratio; HOST-REDUCE-POLYTECH-ACS, Harmonizing Optimal Strategy for Treatment of coronary artery diseases – Comparison of Reduction of prasugrel or Polymer technology in ACS patients; IDS, Integrated Delivery System; ITT, intention-to-treat; IVL, intravascular lithotripsy; IVUS, intravascular ultrasound; LBBB, left bundle branch block; MACCE, major adverse cardiac or cerebrovascular events; MACE, major adverse cardiovascular events; MI, myocardial infarction; MLA, minimal lumen area; MSA, minimum stent area; NACE, net adverse clinical events; NACMI, North American COVID-19 ST-Segment Elevation Myocardial Infarction; NIRS, near-infrared spectroscopy; NSTEMI, non-ST-segment elevation myocardial infarction; OCT, optical coherence tomography; OR, odds ratio; PCI, percutaneous coronary intervention; POCO, patient-oriented composite outcome; PUJ, persons under investigation; SCAI, Society for Cardiovascular Angiography and Interventions; STEMI, ST-elevation myocardial infarction; TCT, Transcatheter Cardiovascular Therapeutics; TIMI, Thrombolysis in Myocardial Infarction; TLF, target lesion failure; TLR, target lesion revascularization; TVMI, target vessel myocardial infarction; UCL, upper confidence limit.

* Corresponding author at: Georgetown University, Cardiovascular Research and Advanced Education, MedStar Heart and Vascular Institute, MedStar Washington Hospital Center, 110 Irving St., NW, Suite 4B-1, Washington, DC 20010, United States of America.

E-mail address: ron.waksman@medstar.net (R. Waksman).

1. Introduction

Scientific meetings continue to migrate online amidst the coronavirus disease 2019 (COVID-19) pandemic. This has resulted in broader participation and access to highly anticipated clinical research. In this article, we present a brief overview of the coronary late-breaking clinical trials presented at the Transcatheter Cardiovascular Therapeutics (TCT) Connect 2020 virtual conference that carry significant clinical implications.

2. Coronary

2.1. PROSPECT ABSORB: A randomized trial of interventional treatment of vulnerable plaques

Presenter: Dr. Gregg W. Stone

Key Points: A randomized controlled trial embedded within the PROSPECT II natural history study assessing patients with non-flow-limiting vulnerable plaques, with severe plaque burden, found that percutaneous coronary intervention (PCI) with Absorb bioresorbable vascular

scaffolds (BVS) is safe and substantially enlarged lumen dimensions during follow-up.

The results were reported by study lead Gregg W. Stone, MD, of Mount Sinai Heart Health System, New York, New York [1]. The PROSPECT ABSORB results were simultaneously published online in the *Journal of the American College of Cardiology* [2]. Experts at the conference agreed that PROSPECT II lends further weight to the existing belief that non-culprit lesions with high lipid levels and plaque burden are a risk factor in future major adverse cardiovascular events (MACE).

PROSPECT ABSORB was devised in response to this question, recruiting a subset of 182 patients from the 898-patient PROSPECT II trial run in Scandinavia, which ran a combination intravascular ultrasound (IVUS) and suggests near-infrared spectroscopy (NIRS) intravascular catheter imaging analysis of culprit and non-culprit lesions following successful PCI. The 182-patient subgroup had angiographically non-obstructive stenosis not intended for PCI but with plaque burden of $\geq 65\%$ as defined by IVUS. These patients were randomized to treatment of the lesion with either a BVS plus guideline-directed medical therapy (GDMT) or GDMT alone (93 vs. 89, respectively). The median angiographic diameter stenosis of the randomized lesions was 41.6%, median plaque burden (as defined by NIRS-IVUS) was 73.7%, and the median minimum lumen area (MLA) was 2.9 mm². Median maximum lipid plaque content was 33.4%.

The primary powered effectiveness endpoint was the IVUS-derived MLA at protocol-driven 25-month follow-up in 167 patients. The non-powered primary safety endpoint was randomized target lesion failure (TLF; cardiac death, target vessel-related myocardial infarction [MI] or clinically driven target lesion revascularization [TLR]) at 24 months. Another non-powered secondary endpoint was randomized lesion-related MACE at latest follow-up. The MLA in BVS-treated lesions at follow-up was 6.9 ± 2.6 mm² compared with 3.0 ± 1.0 mm² in GDMT alone-treated lesions (least square means difference 3.9 mm², 95% confidence interval [CI]: 3.3, 4.5; $p < 0.0001$). The researchers marked this a “substantial” enlargement. This also appeared to be associated with favorable long-term clinical outcomes, they said. Although target lesion failure occurred at similar rates for both patient groups (4.3% vs. 4.5%), randomized lesion-related MACE was lower for the BVS group, with 4.3% incidence compared to 10.7% for GDMT alone, but this did not reach statistical significance (odds ratio [OR], 0.38; 95% CI: 0.11, 1.28; $p = 0.12$).

Although Stone conceded that, “provocatively,” PROSPECT ABSORB was a pilot trial meant to inform on a pivotal randomized trial that was “not powered for clinical effectiveness,” he stressed that the favorable randomized lesion-related MACE rates observed after BVS treatment versus medical therapy alone “warrants the performance of an adequately powered randomized trial” that determines whether PCI treatment of vulnerable plaques can improve patient prognosis as indicated. Still, despite the seeming successes of the BVS study, Stone said he would “want to see a more state-of-the-art scaffold” used in a pivotal trial. “I would be comfortable going ahead with a pivotal randomized trial with the state-of-the-art mechanical metallic drug-eluting stent,” he said.

The study received funding from Abbott Vascular, the manufacturer of Absorb BVS; InfraRedx; and The Medicines Company.

2.2. NACMI: Outcomes from the North American COVID-19 STEMI registry

Presenter: Dr. Timothy Henry

Key Points: A large multicenter registry of COVID-19-positive patients presenting with ST-segment elevation or new left bundle branch block (LBBB) on electrocardiogram (ECG) demonstrates that these patients had higher in-hospital mortality and in-hospital stroke with longer lengths of stay. In addition, these patients received primary PCI more commonly than fibrinolytics.

It has been established that patients with cardiovascular risk factors or established cardiovascular disease are more likely to experience severe or critical COVID-19 illness, and myocardial injury is a key extra-pulmonary manifestation. These patients frequently present with ST-elevation on an ECG because of multiple etiologies, including obstructive, non-obstructive, or angiographically normal coronary arteries. There are conflicting reports regarding the incidence of ST-elevation myocardial infarction (STEMI) mimics in COVID-19-positive hospitalized patients and the clinical outcomes. Also, it is known that these patients have a higher in-hospital mortality. Furthermore, there is considerable controversy regarding appropriate management. Thus, understanding the natural history and appropriate management of COVID-19 patients presenting with ST-elevation is essential to inform patient management decisions and protect healthcare workers.

The Society for Cardiovascular Angiography and Interventions (SCAI) and the Canadian Association of Interventional Cardiology (CAIC), in conjunction with the American College of Cardiology (ACC) Interventional Council, collaborated to create a multicenter observational registry, North American COVID-19 ST-Segment Elevation Myocardial Infarction (NACMI). This registry enrolled confirmed COVID-19-positive patients and those suspected of having COVID-19, known as persons under investigation (PUI), with new ST-segment elevation or new onset LBBB on the ECG. Timothy D. Henry, MD, The Christ Hospital, Cincinnati, Ohio, presented the results [3].

Included were 594 patients, of whom 171 were COVID-19-positive and the remaining 423 were PUI. The analysis shows that in both PUI and propensity-matched controls, STEMI occurred more frequently in Blacks, Hispanics, and diabetics. Also, COVID-19-positive patients with STEMI were more likely to present with cardiogenic shock (but not cardiac arrest) with lower left ventricular ejection fraction, more atypical symptoms, and slightly higher in-hospital presentation.

In terms of management, COVID-19-positive patients with ST-elevation were more likely not to receive angiography (21%) and to receive medical therapy, but still, 71% received primary PCI and treatment with fibrinolytics was uncommon. In terms of clinical outcomes, COVID-19-positive patients with ST-elevation had higher in-hospital mortality and in-hospital stroke with a longer length of stay.

Henry concluded that COVID-19-positive patients with ST-elevation represent a unique and high-risk patient population. Primary PCI is preferable (and feasible) in COVID-19-positive patients, with door-to-balloon times similar to those of PUI or COVID-19-negative patients, supporting current SCAI/ACC recommendations.

The registry is funded by SCAI and CAIC.

2.3. COMPARE CRUSH: A randomized trial of prehospital crushed vs uncrushed prasugrel in STEMI

Presenter: Dr. Georgios Vlachojannis

Key Points: Giving crushed prasugrel tablets to patients presenting with STEMI before PCI did not improve Thrombolysis in Myocardial Infarction (TIMI) 3 flow in the culprit artery during primary PCI in comparison with non-crushed tablets.

Georgios J. Vlachojannis, MD, PhD, of University Medical Center Utrecht, Den Haag, Netherlands, presented the results of the COMPARE CRUSH trial, which were also simultaneously published online in *Circulation* [4,5]. Guidelines currently recommend early treatment with a P2Y₁₂ inhibitor in STEMI patients undergoing primary PCI, as this has been found to reduce intraprocedural and postprocedural ischemic complications. Degree of myocardial damage, post-PCI arterial flow, and microvascular obstruction extent have been found to be associated with platelet reactivity. Crushed P2Y₁₂ inhibitor tablets have been shown to increase the drug's absorption and start platelet inhibition earlier than integral tablets.

In the COMPARE CRUSH study, patients presenting with STEMI where randomized in a 1-to-1 fashion to receive, while still in the ambulance, a loading dose (60 mg) of either crushed or non-crushed prasugrel and then taken to undergo primary PCI. Prasugrel tablets were crushed using a syringe crusher (Welcon, Fort Worth, Texas). All patients were additionally treated according to national ambulance STEMI protocol with 500 mg of aspirin and 5000 international units of heparin, both administered intravenously. The independent primary endpoints were TIMI 3 flow in the infarct-related artery at first angiography and $\geq 70\%$ ST-segment resolution 1 h after primary PCI. Key secondary endpoints included platelet reactivity; clinical outcomes including death, MI, urgent revascularization, and stent thrombosis; and a safety endpoint, bleeding.

A total of 727 STEMI patients were enrolled and randomized to receive either integral or crushed prasugrel in the ambulance. The study population had an average age of 62 years, 23% were women, and 40% were active smokers. The median time from treatment to wire crossing was 57 min, and the most common MI was anterior; 93% of cases were done via radial access. The primary endpoint occurred in 31% of the crushed prasugrel group and 32.7% of the non-crushed prasugrel group (OR, 0.92; 95% CI: 0.65, 1.30; $p=0.64$). One-hour post-PCI, complete resolution of the ST segment elevation was present in 59.9% of the crushed group and 57.3% of the integral group (OR, 1.11; 95% CI: 0.78, 1.58; $p=0.55$). There was a significant difference between the groups with respect to P2Y12 reactivity (crushed, 192 [95% CI: 132, 245] vs. integral, 227 [95% CI: 184, 254], $p<0.01$). There were no significant differences in TIMI major bleeding and Bleeding Academic Research Consortium (BARC) ≥ 3 bleeding between the groups. Finally, ischemic events at 30 days were not significantly different between the groups.

Vlachojannis concluded by saying that TIMI 3 flow in the infarct-related artery or 1-hour post-PCI ST-segment resolution was not improved with crushed prasugrel tablets compared to integral tablets in patients with STEMI planned for primary PCI. This is in spite of more potent platelet inhibition with crushed prasugrel. The question remains as to whether coronary reperfusion may be improved with the use of faster and more potent antiplatelet therapy in the setting of STEMI.

2.4. TICO-STEMI: A randomized trial of ticagrelor monotherapy vs ticagrelor with aspirin in STEMI

Presenter: Dr. Byeong-Keuk Kim

Key Points: In patients with STEMI who underwent PCI followed by 3 months of dual antiplatelet therapy (DAPT), 9 months of ticagrelor monotherapy reduced major bleeding risk and resulted in comparable ischemic risk as compared to DAPT with ticagrelor and aspirin.

The TICO-STEMI sub-study, presented by Byeong-Keuk Kim, MD, PhD, of Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, South Korea, focused on 1103 patients with STEMI; 546 were in the ticagrelor arm and 557 in the DAPT arm [6].

The TICO trial randomized 3056 patients with acute coronary syndromes (ACS) at 38 centers in South Korea to either ticagrelor monotherapy or DAPT after receiving 3 months of DAPT (ticagrelor and aspirin) following PCI with bioresorbable-polymer sirolimus-eluting stents (Orsiro, Biotronik) [7]. This study, presented at the ACC Scientific Sessions 2020 virtual conference, found that in patients with any type of ACS, including STEMI and non-ST-elevation myocardial infarction (NSTEMI), 9 months of ticagrelor monotherapy reduced bleeding without increasing ischemic risk. The primary outcome was net adverse clinical events (NACE), including bleeding and ischemic outcomes. Bleeding outcomes included TIMI major bleeding, and ischemic outcomes included major adverse cardiac and cerebrovascular events (MACCE), which was a composite of all-cause death, MI, stroke, or target vessel revascularization.

At 12 months, there was no significant difference in NACE between the two arms in the intention-to-treat population (ticagrelor 3.7% vs.

DAPT 5.0%; hazard ratio [HR], 0.73; 95% CI: 0.41, 1.29; $p=0.27$). However, the as-treated population did show a significant difference favoring the ticagrelor arm at 12 months (ticagrelor 2.3% vs. DAPT 5.2%; HR, 0.44; 95% CI: 0.23, 0.86; $p=0.01$). The ticagrelor monotherapy arm also showed less bleeding at 12 months in the intention-to-treat population (ticagrelor 0.9% vs. DAPT 2.9%; HR, 0.32; 95% CI: 0.12, 0.87; $p=0.02$). Finally, ischemic events were roughly equal between the two groups in the intention-to-treat analysis (ticagrelor 2.7% vs. DAPT 2.5%; HR, 1.09; 95% CI: 0.53, 2.27; $p=0.81$).

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

2.5. Bivalirudin vs heparin in patients with myocardial infarction: An individual patient data pooled analysis

Presenter: Dr. Gregg W. Stone

Key Points: Bivalirudin reduces 30-day risks of mortality, serious bleeding, and NACE in patients undergoing primary PCI after STEMI and lowers serious bleeding after PCI in NSTEMI, in comparison with heparin.

Gregg W. Stone, MD, of Mount Sinai Heart Health System, New York, New York, and colleagues pooled patient-level data from eight randomized controlled trials comparing bivalirudin and heparin in patients with myocardial infarction, whether STEMI or NSTEMI [8]. The prespecified primary safety endpoint was 30-day risk of serious bleeding, defined as either TIMI major or minor bleeding or BARC type 3 or 5 bleeding.

The final analyzed cohort included 27,409 patients (13,346 randomized to bivalirudin and 14,063 to heparin). Of these, 16,547 had STEMI and 12,152 had NSTEMI. In the bivalirudin arm, 7306 patients (54.7%) had STEMI and 6040 (45.3%) had NSTEMI. In the heparin arm, the distribution was similar, with 7948 (56.5%) STEMI patients and 6115 (43.5%) NSTEMI patients.

At 30 days, in the STEMI cohort, patients treated with bivalirudin had lower rates of serious bleeding than patients treated with heparin (3.5% vs. 6.0%; adjusted HR, 0.57; 95% CI: 0.47, 0.68). The same was true for NACE, which consisted of MACCE and serious bleeding (8.7% vs. 11.2%; adjusted HR, 0.78; 95% CI: 0.70, 0.88). In terms of ischemic events, the results were mixed. There was no significant difference between bivalirudin and heparin in all-cause death (2.5% vs. 2.9%; adjusted HR, 0.80; 95% CI: 0.64, 1.01), stroke, clinically driven target vessel revascularization, or MACCE. Bivalirudin showed higher rates of reinfarction (2.4% vs. 1.7%; adjusted HR, 1.29; 95% CI: 1.02, 1.64) and stent thrombosis (1.7% vs. 1.2%; adjusted HR, 1.45; 95% CI: 1.05, 1.91), and a lower rate of cardiac death (2.1% vs. 2.7%; adjusted HR, 0.72; 95% CI: 0.57, 0.91). Turning to NSTEMI patients, there was no significant difference between bivalirudin and heparin for any of the ischemic endpoints, but bivalirudin had significantly lower serious bleeding rates than heparin (3.3% vs. 5.3%; adjusted HR, 0.63; 95% CI: 0.52, 0.76). There was no significant difference in NACE between the two arms (12.8% vs. 14.1%; adjusted HR, 0.91; 95% CI: 0.82, 1.01).

Bivalirudin's benefits were most pronounced with infusions after PCI in STEMI patients, whether high or low dose, but not in NSTEMI patients. Post-PCI bivalirudin infusion led to reduced all-cause death (adjusted HR, 0.67; 95% CI, 0.50: 0.89) and cardiac death (adjusted HR, 0.60; 95% CI: 0.44, 0.81) as compared to heparin. But there were no significant differences between post-PCI bivalirudin and heparin in terms of all-cause or cardiac death among NSTEMI patients.

The study was funded by the Cardiovascular Research Foundation and the Medicines Company.

2.6. Disrupt CAD III: Safety and effectiveness of intravascular lithotripsy for treatment of severe coronary calcification

Presenter: Dr. Dean Kereiakes

Key Points: The Disrupt CAD III multicenter, single-arm study demonstrated safety and effectiveness of coronary intravascular lithotripsy (IVL)

as an adjunct to stent implantation in severely calcified coronary artery lesions.

These findings were presented by Dean Kereiakes, MD, of The Christ Hospital, Cincinnati, Ohio, and simultaneously published online in the *Journal of the American College of Cardiology* [9,10]. It has been well-known that significant coronary artery calcification hinders stent delivery and stent expansion, which results in adverse outcomes, including periprocedural myocardial infarction, stent thrombosis, and in-stent restenosis. Plaque modification of these calcified lesions is necessary to prevent these adverse outcomes. The Shockwave Medical IVL system is a new technology that delivers acoustic pressure waves to modify calcium, enhancing vessel compliance and optimizing stent deployment. Its role in treatment of peripheral vasculature calcified lesions has been well-established. The goal of the Disrupt CAD III study is to assess the safety and effectiveness of IVL in severely calcified *de novo* coronary lesions.

Disrupt CAD III was a prospective, single-arm, multicenter (47 sites in the US, UK, France, and Germany) study designed for regulatory approval of coronary IVL and included 431 patients, 384 in the intention-to-treat analysis and 47 roll-in patients. The primary safety endpoint was freedom from MACE (cardiac death, MI, or target vessel revascularization) at 30 days. The primary effectiveness endpoint was procedural success. Both endpoints were compared to a pre-specified performance goal. The mechanism of calcium modification was assessed in an optical coherence tomography (OCT) sub-study.

The primary safety endpoint was achieved in 92.2% of patients; the lower bound of the 95% CI was 89.5%, which exceeded the performance goal of 84.4% ($p < 0.0001$). The primary effectiveness endpoint was a 92.4% procedural success rate; the lower bound of the 95% CI was 90.2%, which exceeded the performance goal of 83.4% ($p < 0.0001$). Mean calcified segment length was 47.9 ± 18.8 mm, calcium angle was $292.5 \pm 76.5^\circ$, and calcium thickness was 0.96 ± 0.25 mm at the site of maximum calcification. OCT demonstrated multi-plane and longitudinal calcium fractures after IVL in 67.4% of lesions. Minimum stent area (MSA) was 6.5 ± 2.1 mm² and was similar regardless of demonstrable fractures on OCT.

There were some limitations to this study. First, the trial design was non-randomized and, thus, lacked a concurrent control group. Second, OCT identified calcium fractures in 67.4% of lesions after IVL; however, excellent MSA, area stenosis, and stent expansion outcomes were observed regardless of calcium fracture visualization. Finally, there was protocol exclusion of extremely tortuous vessels, true bifurcation lesions, and unprotected left main or ostial target lesions, precluding generalizability of study findings to these subgroups.

Nonetheless, the authors should be congratulated for their work in demonstrating that IVL safely and effectively facilitates stent delivery and optimizes stent expansion in patients with severely calcified coronary lesions. This technology offers a new way to tackle calcified plaque in the coronaries. Longer-term clinical follow up (ongoing in this study through 2 years) is required to determine the durability of clinical benefit associated with IVL-optimized stent implantation. In addition, future studies are required to determine whether there are any specific clinical or anatomic circumstances that are particularly suited to, and are more safely or effectively treated with, one or the other of these alternative lesion preparation strategies.

The study received funding support from Shockwave Medical Inc.

2.7. XIENCE 90/28: Assessment of three-month and one-month DAPT after everolimus-eluting stents in high-bleeding-risk patients

Presenter: Dr. Roxana Mehran

Key Points: Shorter DAPT regimens for high-bleeding-risk (HBR) patients who underwent successful PCI resulted in bleeding and thrombotic outcomes similar to the standard 12-month DAPT regimen in similar patients.

Roxana Mehran, MD, of Mount Sinai School of Medicine, New York, New York, and Marco Valgimigli, MD, PhD, of Bern University Hospital, Switzerland, presented the results of three trials that are part of the XIENCE Short DAPT program [11]. XIENCE 90 enrolled 2047 HBR patients across 106 US sites to evaluate the safety of 3-month DAPT. The two XIENCE 28 trials enrolled 1605 HBR patients at 111 international sites – 642 from 59 North American sites (XIENCE 28 USA) and 963 from 52 international sites (XIENCE 28 Global) to evaluate the safety of 1-month DAPT. All patients in all trials underwent PCI with the Xience everolimus-eluting stent (Abbott).

In XIENCE 90, patients were prescribed 3 months of DAPT after successful PCI. Those who were free from ischemic events and adhered to the DAPT regimen were eligible to be placed on aspirin monotherapy for 3 to 12 months. The primary endpoint was the composite rate of all-cause death or any MI from 3 to 12 months in this so-called “3-month clear” population of 1693 patients. In XIENCE 28, patients were prescribed 28 days of DAPT after PCI. Patients who complied with the DAPT regimen and were event free (no MI, repeat coronary revascularization, stroke, or stent thrombosis) were placed on aspirin monotherapy. The primary endpoint was the composite of all-cause death or any MI from 1 to 6 months in this so-called “1-month clear” population of 1392 patients.

Patients in the XIENCE 90 and XIENCE 28 trials were compared to historical, comparable controls from the XIENCE V USA post-approval study (which took place from 2008 through 2011) using propensity-score-stratified analysis. Patients in the XIENCE V USA study underwent DAPT for 12 months. Between 3 and 12 months, there was no difference between the XIENCE 90 and stratified XIENCE V USA patients in the incidence of the primary endpoint (5.4% vs. 5.4%; one-sided 97.5% upper confidence limit [UCL], 2.23%; noninferiority margin, 2.8%; p -noninferiority = 0.0063). Between 1 and 6 months, there was no statistically significant difference between the XIENCE 28 and stratified XIENCE V USA patients in the rate of the primary endpoint (XIENCE 28, 3.5%, vs. XIENCE V USA, 4.3%; one-sided 97.5% UCL, 0.97%; noninferiority margin, 2.5%; p -noninferiority = 0.0005).

Turning to a major secondary endpoint, BARC 2–5 bleeding, the shorter DAPT strategies yielded numerically lower bleeding rates, but they did not reach superiority compared to the historical 12-month DAPT controls (BARC 2–5 bleeding rates, 3–12 months: XIENCE 90, 5.1%, vs. XIENCE V USA, 7.0%; p -superiority = 0.0687. BARC 2–5 bleeding rates, 1–6 months: XIENCE 28, 4.9%, vs. XIENCE V USA, 5.9%; p -superiority = 0.19). Mehran also presented BARC 3–5 bleeding results, which she noted were not prespecified. These analyses did show superiority for the shorter DAPT strategies over 12-month DAPT (BARC 3–5 bleeding, 3–12 months: XIENCE 90, 2.2%, vs. XIENCE V USA, 6.3%; p -superiority < 0.0001. BARC 3–5 bleeding, 1–6 months: XIENCE 28, 2.2%, vs. XIENCE V USA, 4.5%; p -superiority = 0.0156).

The shorter DAPT regimens also did not appear to adversely affect stent thrombosis. Only 0.2% of XIENCE 90 patients experienced Academic Research Consortium (ARC) definite or probable stent thrombosis between 3 and 12 months, which was significantly below the 1.2% performance goal (two-sided 95% UCL, 0.63%; $p < 0.0001$). Finally, the ARC rates of stent thrombosis between 1 and 6 months were roughly the same between the XIENCE 28 patients and stratified XIENCE V USA patients (0.3% vs. 0.3%).

The study received funding from Abbott.

2.8. HOST-REDUCE-POLYTECH-ACS: A randomized trial of durable-polymer vs bioabsorbable-polymer DES in patients with acute coronary syndromes

Presenter: Dr. Hyo-Soo Kim

Key Points: DES with durable polymers are non-inferior to DES with bio-degradable polymers in patients with ACS in terms of patient-oriented adverse events at 1 year.

Hyo-Soo Kim, MD, PhD, of Seoul National University Hospital, South Korea, presented the results of the HOST-REDUCE-POLYTECH-ACS trial

[12]. DES have significantly improved outcomes amount patients undergoing PCI; however, the polymers used in first-generation DES were blamed as the cause of a chronic inflammatory response that leads to stent-oriented adverse clinical outcomes, such as stent thrombosis. Furthermore, biocompatible durable polymers and biodegradable polymers (which dissolve over time) were developed to help mitigate this adverse effect. The comparison of the two polymer technologies in patients with ACS (who have a heightened risk of thrombosis and delayed vascular healing after PCI) has not been previously performed in a large-scale randomized trial.

The aim of the HOST-REDUCE-POLYTECH-ACS (Harmonizing Optimal Strategy for Treatment of coronary artery diseases – Comparison of Reduction of prasugrel or Polymer technology in ACS patients) trial was to investigate the efficacy and safety of durable-polymer DES versus biodegradable-polymer DES in patients with ACS undergoing PCI. Patients with a culprit lesion in a native coronary artery or a graft vessel with significant stenosis eligible for stent implantation were randomized in a 1-to-1 fashion to durable-polymer or biodegradable-polymer DES. The primary endpoint was a patient-oriented composite outcome (POCO), consisting of all-cause death, nonfatal MI, stent thrombosis, and any repeat revascularization at 12 months. The key secondary endpoint was a device-oriented composite outcome (DOCO), consisting of cardiac death, target vessel MI, or target lesion revascularization.

In this investigator-initiated, randomized, open-label, multicenter trial, 3413 ACS patients with 4713 lesions from 35 centers were randomized to the durable-polymer DES group (1713 patients, 2367 lesions) or the biodegradable-polymer DES group (1700 patients, 2346 lesions). The rate of POCO was 5.2% in the durable-polymer DES group and 6.4% in the biodegradable-polymer DES group (HR, 0.81; 95% CI: 0.61, 1.08; $p=0.146$). The rate of DOCO was higher in the biodegradable-polymer group (durable polymer 2.6% vs. biodegradable polymer 3.9%; HR, 0.67; 95% CI: 0.46, 0.98; $p=0.038$).

The investigators concluded that durable-polymer DES were non-inferior to biodegradable-polymer DES in terms of 1-year POCO. Regarding DOCO, they observed a sign of higher clinical events in the biodegradable than durable polymer DES. In his presentation, Kim commented: “Most clinicians and industrial companies believe that biodegradable-polymer DES would be better than durable-polymer DES. Such belief is not confirmed by this study. On the other hand, the beneficial role of durable polymer, such as thrombo-resistance, may be real.”

The HOST-REDUCE-POLYTECH-ACS trial was sponsored by Seoul National University Hospital and received research funds from Biotronik, Boston Scientific, Daiichi Sankyo, Dio, Qualitech Korea Ltd., and Terumo.

2.9. COBRA-REDUCE: A randomized trial of a thromboresistant polyzene F-coated stent with 14 days' DAPT in high-bleeding-risk patients

Presenter: Dr. Robert Byrne

Key Points: As treatment for HBR patients with acute or chronic coronary syndromes, the Cobra PzF nanocoated coronary stent followed by 2 weeks of DAPT did not reduce bleeding and failed to demonstrate noninferiority to standard DES with 3 to 6 months of DAPT with respect to thrombotic events.

Robert A. Byrne, MB, BCh, PhD, of Mater Private Hospital, RCSI University of Medicine and Health Sciences, Dublin, Ireland, presented the results of COBRA-REDUCE [13]. The study was a randomized, open-label, active-controlled, assessor-blinded, multicenter trial that aimed to determine whether the Cobra PzF stent with a shorter-duration DAPT (14 days) results in a lower incidence of bleeding without increasing thrombotic events in comparison with US Food and Drug Administration-approved second-generation DES with standard DAPT (3 to 6 months) in patients taking oral anticoagulants. The Cobra PzF NCS (Celonova Biosciences) is made of a cobalt chromium alloy that is 71 μm thick. It is coated with polyzene-F, which is no more than 0.05 μm thick.

A total of 996 patients were enrolled between February 2016 and May 2020 at 59 sites in Europe and the US. Of those patients, who were deemed HBR because of a requirement for oral anticoagulants (vitamin K antagonist or non-vitamin K antagonist), 495 were randomized to the Cobra (treatment) group and 501 to the control (standard DES and DAPT). The patients' mean age was 74.4 years, 27% were women, 36.2% had diabetes, 12.1% had a history of stroke, and 6.6% had severe renal insufficiency; 29.3% of patients presented with acute coronary syndrome.

One co-primary endpoint was BARC 2–5 bleeding after 14 days. The two groups showed no difference in this outcome (treatment 7.5% vs. control 8.9%; $p=0.477$). The other co-primary endpoint was a thrombotic composite of death, MI, stent thrombosis, or ischemic stroke at 6 months. The Cobra stent failed to meet noninferiority (treatment 7.7% vs. control 5.2%; difference +2.5%; upper bound of 95% CI, 5.15%; prespecified noninferiority margin difference range, 0% to 5%; p -noninferiority = 0.061). Turning to secondary bleeding endpoints, there was no significant difference between the groups in BARC 3–5 bleeding after 14 days, BARC 3–5 bleeding after randomization, or BARC 2–5 bleeding after randomization; however, BARC 1–5 bleeding after randomization was significantly lower in the Cobra group (13% vs. 18.3%; $p=0.026$). A similar pattern was seen with secondary thrombo-embolic endpoints at 6 months. There were no significant differences between the groups in death, cardiac death, MI, definite or probable stent thrombosis, or ischemic stroke; however, the Cobra group did have a significantly higher rate of ischemia-driven target lesion revascularization (3.7% vs. 0.9%; $p=0.004$).

Byrne concluded that despite failing to reduce bleeding and failing to show noninferiority with regard to thrombotic events, the Cobra stent was safe, with stent thrombosis rates “considerably lower than those seen in earlier trials” with high-bleeding-risk patients, despite only 14 days of DAPT. He added that ongoing follow-up and planned analysis of the secondary outcomes at 12 months are anticipated to assess comparative efficacy of the treatment arms in relation to the study devices. During a press conference announcing the results, Byrne noted that the end of the study period coincided with the onset and early peak of the COVID-19 pandemic, which made it difficult to complete follow-up in a small number of patients.

The study received funding from Celonova Biosciences.

2.10. OPTIMIZE: A randomized trial of a novel, ultra-low-profile, fixed-wire DES

Presenter: Dr. Dean Kereiakes

Key Points: Two ultra-low-profile DES fell short of demonstrating the prespecified noninferiority criteria in comparison with more-established, commercially approved DES, even though “the totality of the evidence” shows that these new stents are, in fact, noninferior.

Dean J. Kereiakes, MD, of The Christ Hospital Heart and Vascular Center, Cincinnati, Ohio, presented the results of the OPTIMIZE trial [14]. The ultra-low-profile, fixed-wire Slender Integrated Delivery System (IDS) and rapid-delivery Direct RX DES systems, both manufactured by Svelte Medical Systems, are designed to facilitate transradial access and direct stenting. Kereiakes and co-authors wrote in an abstract presenting the OPTIMIZE study.

OPTIMIZE is a prospective, single-blind, randomized, international investigational device exemption trial comparing the safety and efficacy of the Slender IDS and RX with that of the Xience (Medtronic) or Promus (Boston Scientific) DES in patients with ischemic heart disease and no more than three *de novo* stenotic lesions that were no more than 34 mm long in no more than two native coronary arteries with reference vessel diameter of 2.25 to 4 mm that were amenable to PCI. A total of 1630 patients were randomized to receive the Svelte or control DES. The primary endpoint was to demonstrate noninferiority of the Svelte stent systems with regard to TLF, a composite of cardiac death, target vessel myocardial infarction (TVMI; including both Q-wave and

non-Q-wave), and clinically driven TLR at 12 months. The TVMI component of the endpoint also included periprocedural MI, which was defined as creatine kinase-MB fraction (CK-MB) or troponin more than 3 times the upper limit of normal within 48 h of the procedure. Secondary endpoints included components of TLF; target vessel failure; major adverse cardiac events; ARC-defined stent thrombosis; and lesion, device, procedure and direct-stent-strategy success.

The expected TLF rate based on the EVOLVE II trial was 6.5%. Noninferiority margin was set at 3.58%, and a one-sided alpha p -value <0.025 in the intention-to-treat (ITT) analysis would mean that the Svelte stents were noninferior to the control stents. Baseline characteristics between the control and Svelte DES groups were well-matched (mean age, control 65.8 years vs. Svelte 65.1 years; men, 70.8% vs. 72.7%; Caucasian 82.4% vs. 81.4%; Asian 11% vs. 10.9%; smoking history, 61.3% vs. 63.7%; diabetes, 30.7% vs. 28.5%). The same was mostly true of procedural characteristics, except that more patients in the Svelte group had three lesions treated (3.5% vs. control 1.6%), and the treated lesions were longer in the Svelte group (14.88 ± 7.04 mm vs. control 14.25 ± 7.52 mm). The Svelte stents failed to demonstrate noninferiority to the control stents with regard to the primary endpoint, TLF at 12 months (Svelte 10.3% vs. control 9.5%; difference +0.8%; upper bound of 95% CI, 3.8%; noninferiority margin, 3.58%; p -noninferiority = 0.034; prespecified p for noninferiority = 0.025). With regard to the TLF components at 12 months, the Svelte and control stents showed no significant differences.

Kereiakes noted that the TLF rate was driven by the TVMI rate (control stents 8.22% vs. Svelte stents 9.31%; $p=0.48$). Of the TVMIs in both arms, 90% were periprocedural MIs. He added that 25% of patients with troponin assays accounted for 80% of TVMIs. Of the troponin-positive patients, 3.8% had electrocardiogram changes and 87.5% were discharged without delay, he said. The overall study's TVMI rate of 8.8% was "unprecedented," Kereiakes said, reflecting the frequency of troponin use as a biomarker, which he said contributed to the study's high TLF rate (overall 9.9% vs. an expected 6.5% rate) and contributed to "effectively underpowering the OPTIMIZE study."

These findings prompted the investigators to analyze relative risk and assessment in OPTIMIZE in comparison with other investigational device exemption studies. An independent *post hoc* analysis was also conducted to determine whether the OPTIMIZE relative risk was within the prespecified protocol noninferiority margin of 1.55. This margin was assigned based on the ratio of noninferiority margin with estimated TLF. The analysis found that the relative risk was 1.09 (95% CI: 0.81, 1.46), meaning the upper bound of the CI was within the prespecified margin on the *post hoc* analysis. Based on this finding, Kereiakes said, the Svelte stents were noninferior to the control stents ($p=0.009$). Kereiakes speculated that future studies will probably not use the same protocols as OPTIMIZE because of how this study turned out.

Svelte Medical Systems provided all funding for this trial.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

Ron Waksman – Advisory Board: Abbott Vascular, Amgen, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips,

Pi-Cardia Ltd.; Consultant: Abbott Vascular, Amgen, Biotronik, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips, Pi-Cardia Ltd., Transmural Systems; Grant Support: AstraZeneca, Biotronik, Boston Scientific, Chiesi; Speakers Bureau: AstraZeneca, Chiesi; Investor: MedAlliance; Transmural Systems.

All other authors – None.

References

- [1] Stone GW. PROSPECT ABSORB: a randomized trial of interventional treatment of vulnerable plaques. Available from: <https://www.tctconnect.com/late-breaking-clinical-trial-session-i-co-sponsored-by-jacc-vulnerable-plaque-detection-and-treatment/>. [Accessed 19 October 2020].
- [2] Stone GW, Maehara A, Ali ZA, Held C, Matsumura M, Kjoller-Hansen L, et al. Percutaneous coronary intervention for vulnerable coronary atherosclerotic plaque. *J Am Coll Cardiol.* 2020;76:2289–301.
- [3] Henry T. NACMI: outcomes from the North American COVID-19 STEMI registry. Available from: <https://www.tctconnect.com/late-breaking-clinical-science-session-i-co-sponsored-by-circulation-acute-myocardial-infarction-interventions/>. [Accessed 19 October 2020].
- [4] Vlachojannis G. COMPARE CRUSH: a randomized trial of prehospital crushed vs uncrushed prasugrel in STEMI. Available from: <https://www.tctconnect.com/late-breaking-clinical-science-session-i-co-sponsored-by-circulation-acute-myocardial-infarction-interventions/>. [Accessed 19 October 2020].
- [5] Vlachojannis G, Wilschut JM, Vogel RF, Lemmert ME, Delewi R, Diletti R, et al. Effect of prehospital crushed prasugrel tablets in patients with ST-segment-elevation myocardial infarction planned for primary percutaneous coronary intervention: the randomized COMPARE CRUSH trial. *Circulation.* 2020;142:2316–28.
- [6] Kim B. TICO-STEMI: a randomized trial of ticagrelor monotherapy vs ticagrelor with aspirin in STEMI. Available from: <https://www.tctconnect.com/late-breaking-clinical-science-session-i-co-sponsored-by-circulation-acute-myocardial-infarction-interventions/>. [Accessed 19 October 2020].
- [7] Kim C, Hong SJ, Shin DH, Kim BK, Ahn CM, Kim JS, et al. Randomized evaluation of ticagrelor monotherapy after 3-month dual-antiplatelet therapy in patients with acute coronary syndrome treated with new-generation sirolimus-eluting stents: TICO trial rationale and design. *Am Heart J.* 2019;212:45–52.
- [8] Stone GW. Bivalirudin vs heparin in patients with myocardial infarction: an individual patient data pooled analysis. Available from: <https://www.tctconnect.com/late-breaking-clinical-science-session-i-co-sponsored-by-circulation-acute-myocardial-infarction-interventions/>. [Accessed 19 October 2020].
- [9] Kereiakes D. Disrupt CAD III: safety and effectiveness of intravascular lithotripsy for treatment of severe coronary calcification. Available from: <https://www.tctconnect.com/late-breaking-clinical-science-session-2-complex-pci-strategies/>. [Accessed 19 October 2020].
- [10] Hill JM, Kereiakes DJ, Shlofmitz RA, Klein AJ, Riley RF, Price MJ, et al. Intravascular lithotripsy for treatment of severely calcified coronary artery disease. *J Am Coll Cardiol.* 2020;76:2635–46.
- [11] Mehran R. XIENCE 90/28: assessment of three-month and one-month DAPT after everolimus-eluting stents in high-bleeding risk patients. Available from: <https://www.tctconnect.com/late-breaking-clinical-science-session-2-complex-pci-strategies/>. [Accessed 19 October 2020].
- [12] Kim HS. Host-Reduce-Polytech-ACS: a randomized trial of durable polymer vs bioabsorbable polymer DES in patients with acute coronary syndromes. Available from: <https://www.tctconnect.com/late-breaking-clinical-trial-session-iv-co-sponsored-by-european-heart-journal-stent-trials-and-high-bleeding-risk/>. [Accessed 19 October 2020].
- [13] Byrne RA. COBRA-REDUCE: a randomized trial of a thromboresistant polyzene F-coated stent with 14 days dapt in high-bleeding risk patients. Available from: <https://www.tctconnect.com/late-breaking-clinical-trial-session-iv-co-sponsored-by-european-heart-journal-stent-trials-and-high-bleeding-risk/>. [Accessed 19 October 2020].
- [14] Kereiakes D. OPTIMIZE: a randomized trial of a novel, ultra low profile fixed-wire DES. Available from: <https://www.tctconnect.com/late-breaking-clinical-trial-session-iv-co-sponsored-by-european-heart-journal-stent-trials-and-high-bleeding-risk/>. [Accessed 19 October 2020].