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PEER-REVIEWED CONFERENCE REPORT

Vericiguat Benefits High-Risk HF Patients

The phase 3 VICTORIA trial, which included very high-risk heart failure patients, showed that vericiguat was superior to placebo at improving heart failure outcomes.

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Rivaroxaban + Aspirin Reduces Risk in PAD

VOYAGER PAD: rivaroxaban + aspirin significantly reduced the risk of adverse limb ischaemia and cardiovascular events in patients with symptomatic peripheral artery disease after revascularisation.

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Evinacumab Reduces LDL-C in Homozygous FH

A phase 3 trial demonstrated that PCSK9 inhibitor evinacumab substantially lowers low-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia, regardless of LDL receptor function.

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Editor Prof. Marc Peter Bonaca, University of Colorado, USA

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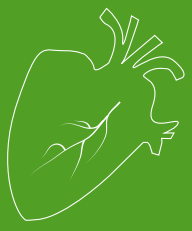

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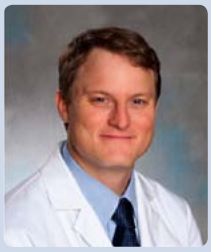
Letter from the Editor



Prof. Marc Peter Bonaca

Dear Reader,

The 2020 American College of Cardiology Scientific Sessions occurred in the context of an incredibly challenging period where all were and continue to be impacted by the COVID pandemic. The implications of COVID were broad in that many participants and attendees are on the frontline helping patients; all of us are impacted personally no matter where we live; travel was impossible; and scientific priorities were largely focused on COVID. These implications rapidly unfolded in the weeks preceding the planned Scientific Sessions in Chicago and required the rapid and dynamic pivot to a virtual meeting that would enable the scientific community to come together and disseminate high-quality science in an effective format. In spite of these challenges, landmark trials including VOYAGER PAD, VICTORIA, and CARVAGGIO as well as many other studies were presented online with panel discussion, QA, and dynamic chat.

In the following pages you will find a comprehensive review of this landmark virtual meeting and summaries of pivotal trials and impactful studies. We hope you find this report to be useful and informative. Thank you for your interest and most of all we wish you all the best, hope you and your families are safe and healthy, and express our thanks to all who are doing what they can to help in this critical and challenging time.

Best Regards,
Marc Bonaca

Biography

Marc P. Bonaca, MD, MPH, is a Cardiologist and Vascular Medicine Specialist who serves as the Executive Director of CPC Clinical Research and CPC Community Health at the University of Colorado Anschutz Medical Campus. He is the Director of Vascular Research and an Associate Professor of Medicine at the University of Colorado School of Medicine and the inaugural holder of the William R. Hiatt Endowed Chair in Cardiovascular Research.

Dr Bonaca earned his medical degree from the University of Connecticut School of Medicine and his Masters in Public Health at Harvard University. He served as a Medical House Officer at Brigham and Women's Hospital and Harvard Medical School. After completion of his training he joined the faculty of the Cardiovascular Division and Vascular Medicine section of Brigham and Women's Hospital and Harvard Medical School and became an Investigator at the TIMI Study Group.

Dr Bonaca's research focus is on ischemic risk in patients with atherosclerotic vascular disease, risk prediction, and risk modification through the use of pharmacologic and biologic therapies. His key areas of interest include patients with peripheral artery disease, polyvascular disease and diabetes with a focus on the breadth of risk including ischemic limb outcomes, microvascular complications and major adverse cardiovascular events.

COI statement Prof. Marc Bonaca (Editor)
Grant support to BWH from AstraZeneca, MedImmune, Merck, Pfizer
Grant support to CPC from Amgen, AstraZeneca, Bayer, Janssen, NovoNordisk, Sanofi

COI statement Prof. Menno Huisman (Reviewer)
Dr Huisman reports grants from ZonMW Dutch Healthcare Fund; and grants and personal fees from Boehringer-Ingelheim, Pfizer-BMS, Bayer Health Care, Aspen, Daiichi-Sankyo.

COI statement Prof. Patrizio Lancellotti (Reviewer)
Nothing to declare.

Heart Failure and Cardiomyopathies

Vericiguat shows beneficial effects in a very high-risk HF population

Results from the phase 3 VICTORIA trial –which included high-risk heart failure (HF) patients– showed that vericiguat was superior to placebo at improving heart failure outcomes [1].

Prof. Paul Armstrong (University of Alberta, Canada) presented the results of the 42-country *Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction* (VICTORIA) trial, which was designed to evaluate vericiguat compared with placebo among patients with chronic heart failure due to reduced ejection fraction (HFrEF). Vericiguat is a first-in-class stimulator of soluble guanylate cyclase (sGC) activity that also enhances sGC sensitivity to endogenous nitric oxide (NO). Deficiency in sGC-derived cyclic guanosine monophosphate (cGMP) causes both myocardial dysfunction and impaired endothelium-dependent vasomotor regulation. Hence, restoration of sufficient NO-sGC–cGMP signalling has been proposed as an important treatment target in HF.

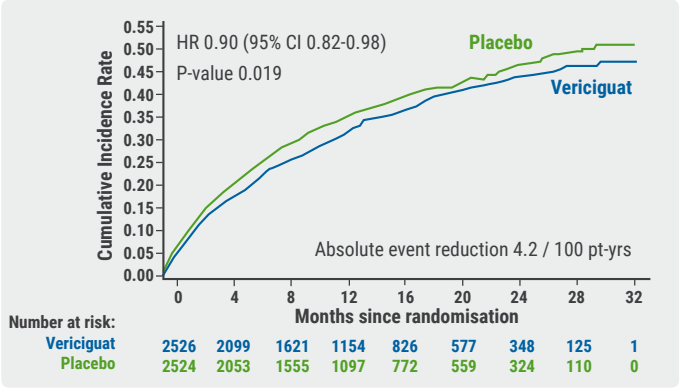
The primary composite outcome of this trial was cardiovascular death or first HF hospitalisation. The phase 3, randomised, double-blind, placebo-controlled trial included 5,050 patients with chronic HF (defined as New York Heart Association [NYHA] functional class II-IV, left ventricular ejection fraction <45%, and guideline-based HF therapies), after a worsening event (defined as an HF hospitalisation or receiving an intravenous diuretic for HF without hospitalisation) with very elevated natriuretic peptides (i.e. brain natriuretic peptide [BNP] or N-terminal [NT]-proBNP). They were randomly assigned to receive either vericiguat (n=2,526) or placebo (n=2,524) + guideline-based HF therapy. Patients received vericiguat initially at 2.5 mg/day, titrated over a month to a target dose of 10 mg/day. Baseline characteristics were evenly balanced between the 2 groups. Median follow-up was 10.8 months.

The primary composite endpoint was reached by 35.5% of vericiguat patients and 38.5% of placebo patients (HR 0.90; 95% CI 0.82-0.98; P=0.019), a 10% lower risk of cardiovascular death or HF hospitalisation (see Figure). However, the individual component analysis showed that these data were primarily driven by the reduction of total hospitalisations for heart among patients taking vericiguat (HR 0.91; 95% CI 0.84–0.99; P=0.02). These data indicate an absolute risk reduction of 4.2 per 100 patient-years in the vericiguat arm. Roughly 24 patients with chronic HFrEF would need to be treated to prevent 1 cardiovascular death/HF hospitalisation. No significant difference in cardiovascular death was observed: 12.9% for the vericiguat arm versus 13.9% for the placebo arm (HR 0.93; 95% CI 0.81-1.06; P=0.269). Regarding safety, vericiguat titrated to 10 mg was generally safe and well-tolerated, although reports of hypotension and syncope were numerically higher with vericiguat.

In conclusion, vericiguat may represent an expansion of options for patients with a recent worsening HF event, especially because it is a once-daily oral medicine, easy to titrate, generally safe and well tolerated, and does not require monitoring of renal function or electrolytes. These data are particularly relevant because hospitalisation for worsening HF represents a "major inflection point" in the natural history of the condition, which is characterised by a marked change in the risk of future hospitalisations and mortality. To date, no prior therapies have attenuated this risk, but vericiguat might be the first to alter the natural history of HF after a patient has had a worsening event. Furthermore, this trial represents the feasibility of modulating the bioavailability of NO as a novel therapeutic approach for HF, as well as potentially other cardiovascular conditions characterised by insufficient NO-sGC–cGMP signalling.

1. Armstrong PW, et al. Abstract 402-08. ACC/WCC 28-30 March 2020.

Figure: Primary composite endpoint: Cardiovascular death or first heart failure hospitalisation [1]



Mavacamten shows promising results in non-obstructive hypertrophic cardiomyopathy

Results from the phase 2 MAVERICK-HCM trial showed that treatment with mavacamten in patients with non-obstructive hypertrophic cardiomyopathy was well tolerated and reduced biomarkers of cardiac injury and wall stress, according to Dr Carolyn Y. Ho (Brigham and Women's Hospital, USA) [1].

Mavacamten is a first-in-class, selective allosteric inhibitor of cardiac myosin, which reduces the number of myosin-actin cross bridges and decreases the excessive contractility that characterises hypertrophic cardiomyopathy. The MAVERICK-HCM study analysed 59 patients with symptomatic non-obstructive hypertrophic cardiomyopathy. After a 28-day screening period, patients were assigned to either once-daily mavacamten with a drug concentration target of 200 ng/mL (n=19), once-daily mavacamten with a drug concentration target of 500 ng/mL (n=21), or once-daily placebo (n=19). Patients were treated during a period of 16 weeks, followed by monitoring for 8 weeks after completion.

During treatment and wash-out (to 24 weeks), 89.7% of patients who received mavacamten had ≥1 treatment-emergent adverse event –76% had mild adverse events– versus 68.4% of patients on placebo. Furthermore, 10.3% of mavacamten patients had ≥1 serious adverse event versus 21.1% with placebo. Mean reduction in left ventricular ejection fraction from baseline to 16 weeks in the pooled mavacamten group was -4.1%. This was -2.3% for patients receiving 200 ng/mL mavacamten, -5.6% for those on 500 ng/mL mavacamten, and -2.3% for placebo. In addition, mavacamten reduced N-terminal pro-brain natriuretic peptide (NT-proBNP) by 53% compared with 1% with placebo (P=0.0005). The drug also decreased cardiac troponin I by 34% versus a 4% increase with placebo (P=0.009). The change in NT-proBNP at 4 weeks in patients assigned mavacamten correlated with the change in cardiac troponin I at 16 weeks (P=0.006). Dr Ho pointed out that patients with more severe disease may derive a greater benefit from treatment with mavacamten. The MAVERICK-HCM results set the groundwork for future larger-scale studies in non-obstructive hypertrophic cardiomyopathy and potentially heart failure with preserved ejection fraction.

1. Ho CY, et al. Abstract 412-16. ACC/WCC 28-30 March 2020.

No role for sodium nitrite in out-of-hospital cardiac arrest

The use of sodium nitrite during active resuscitation by emergency medical services (EMS) was not associated with improved chances of survival to hospital admission or to discharge among patients with out-of-hospital cardiac arrest [1]. It was also not associated with substantial or significant adverse effects on haemodynamics.

As the survival of out-of-hospital cardiac arrest is less than 20% and an animal model has demonstrated increased survival by nearly 50% with the administration of sodium nitrite during resuscitation, Dr Francis Kim (University of Washington, USA) and colleagues investigated whether sodium nitrite given during resuscitation improves outcomes in out-of-hospital cardiac arrest. The study enrolled 1,492 patients who received ether 60 mg sodium nitrite (n=497), 45 mg sodium nitrate (n=499), or placebo (n=496). Patients were aged 18 years and over, had cardiac arrest with life support by paramedics, had intravenous/intraosseous access, and were unconscious. Baseline characteristics were comparable between groups, with an average age of 64 years. The primary endpoints were safety (i.e. survival to hospital admission) and efficacy (i.e. survival to discharge).

Return of spontaneous circulation (ROSC) was seen in 53% of patients who received 45 mg sodium nitrite, 58% of patients who received 60 mg sodium nitrite, and 58% in the placebo group. Re-arrest was observed in 48%, 53%, and 48% per arm, respectively. Survival to admission occurred in 41%, 43%, and 44% per arm, respectively. Survival to discharge for ventricular fibrillation, the secondary endpoint, occurred in 43.2%, 41.3%, and 42.4% of patients, while the rates for survival to discharge for non-ventricular fibrillation were 6.2%, 5.4%, and 6.3%, respectively. Thus, no statistically significant improvement was seen in the primary and secondary outcomes with the use of sodium nitrite (45 mg or 60 mg) compared with placebo during resuscitation in out-of-hospital cardiac arrest. However, sodium nitrite therapy did not result in significant haemodynamic adverse events.

1. Kim F, et al. Abstract 406-17. ACC/WCC 28-30 March 2020.

Vascular Medicine and Thromboembolism

Rivaroxaban and aspirin effective and safe for PAD patients

Results from the VOYAGER PAD trial showed that rivaroxaban 5 mg (2.5 mg twice daily) + aspirin significantly reduced the risk of adverse limb ischaemia and cardiovascular events in patients with symptomatic peripheral artery disease (PAD) after peripheral artery revascularisation [1]. Although there was a numerical increase in thrombolysis in myocardial infarction (TIMI) major bleeding and significantly increased International Society on Thrombosis and Haemostasis (ISTH) major bleeding, no excess was observed in intracranial or fatal bleeding.

The multicentre, randomised, double-blind VOYAGER PAD trial was presented by Prof. Marc Bonaca (University of Colorado, USA), and simultaneously published in the *New England Journal of Medicine* [2]. The purpose of this trial was to investigate whether the benefits of a treatment strategy of rivaroxaban added to background antiplatelet therapy, which has been shown to reduce ischaemic risk in patients following recent acute coronary syndromes, could extend to patients with symptomatic PAD who had recently undergone lower limb revascularisation.

The trial enrolled 6,564 participants from 34 countries with moderate-to-severe symptomatic PAD in the lower extremities. Of these participants, 65% underwent endovascular revascularisation within 10 days before starting study treatment. The remaining 35% had undergone surgical revascularisation. Patients received either rivaroxaban 2.5 mg twice daily added to low-dose aspirin (n=3,286) or placebo + aspirin (n=3,278). The primary endpoint was a composite of acute myocardial infarction, ischaemic stroke, cardiovascular death, acute limb ischaemia, or major amputation. Median follow-up was 28 months.

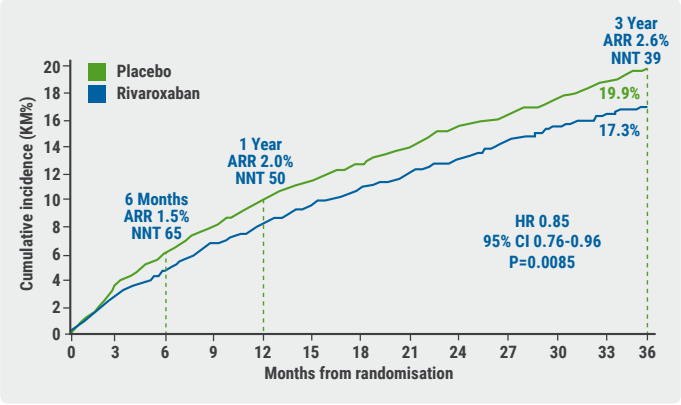
The primary endpoint occurred in 508 patients in the rivaroxaban group, compared with 584 patients in the placebo group. The Kaplan-Meier estimates of incidence at 3 years were 17.3% of patients who received rivaroxaban + aspirin and 19.9% of those on placebo + aspirin (HR 0.85; 95% CI 0.76-0.96; P=0.0085; see Figure), translating to a 15% relative risk reduction in the rivaroxaban arm. The absolute risk reduction was 1.5% at 6 months, 2.0% at 1 year, and 2.6% at 3 years. This endpoint was primarily driven by a reduction in acute limb ischaemia.

Regarding safety, the rate of TIMI major bleeds was 2.7% for patients treated with rivaroxaban versus 1.9% for patients on placebo (HR 1.43; 95% CI 0.97-2.10; P=0.07). Although this result did not reach statistical significance, it did demonstrate a small but important increased risk for bleeding events of this combined regimen, which was underscored by the secondary safety outcome, ISTH major bleeding score, occurring in 5.9% and 4.1% of the rivaroxaban and placebo groups, respectively (HR 1.42; 95% CI 1.10-1.84; P=0.007). Despite bleeding events being more common in the patients receiving rivaroxaban, the rate of ischaemic events prevented by rivaroxaban + aspirin exceeded the excess bleeding rate by 3- to 6-fold (depending on the definition of the bleeding episodes).

In conclusion, PAD patients who have undergone lower-extremity revascularisation and take rivaroxaban plus aspirin have a lower incidence of major adverse limb and cardiovascular events than patients who take aspirin alone in this population and setting. In addition, the benefit of rivaroxaban was apparent early in treatment and was consistent over time across all major subgroups, including patients with critical limb-threatening ischaemia, and reduced the need for unplanned index limb revascularisation.

1. Bonaca MP, et al. Abstract 402-10. ACC/WCC 28-30 March 2020.
2. Bonaca MP, et al. N Engl J Med. 2020; DOI: 10.1056/NEJMoa2000052.

Figure: Cumulative incidence of the primary endpoint versus time [1]



ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; NNT, number needed to treat.
Figure kindly provided by Prof. Bonaca.

Subgroup analysis VOYAGER PAD

A prespecified subgroup analysis of VOYAGER PAD demonstrated that background clopidogrel in patients with peripheral artery disease (PAD) receiving rivaroxaban and low dose aspirin after lower extremity revascularisation does not modify the benefit of rivaroxaban but appears to increase bleeding [1].

The VOYAGER PAD trial was the largest evidence base of patients with revascularised symptomatic PAD, which demonstrated that the combination of twice-daily rivaroxaban and once-daily aspirin was safe and more effective than aspirin alone for reducing future thrombotic and ischaemic events [2]. In the current subgroup analysis of VOYAGER PAD, presented by Prof. William Hiatt (University of Colorado, USA), investigators aimed to evaluate whether efficacy and safety of rivaroxaban were consistent regardless of background clopidogrel use.

The rationale for this particular subgroup analysis was that the dual-antiplatelet therapy (DAPT) in PAD patients who have just undergone endovascular lower-extremity revascularisation usually consists of aspirin and clopidogrel, although this choice is not based on any Class I evidence and instead is "an extrapolation from the coronary artery literature, where it does have some benefit, particularly after percutaneous coronary intervention," Prof. Hiatt explained.

Here, half of the 6,564 randomised patients enrolled in VOYAGER PAD also received clopidogrel at the time of their lower extremity revascularisation procedure, which was at the discretion of their treating physician and was allowed for up to 6 months. Patients receiving clopidogrel were more likely to undergo endovascular procedures (90.7%) than undergo surgery (9.3%), consistent with the common use of clopidogrel in endovascular procedures.

Results of this pre-specified subgroup analysis demonstrated that the benefit of rivaroxaban + aspirin versus aspirin alone in patients with symptomatic PAD undergoing revascularisation is consistent, regardless of background clopidogrel. The primary efficacy endpoint had a hazard ratio ~0.85 with rivaroxaban, regardless of clopidogrel with number needed to treat <50 with or without clopidogrel. The safety of rivaroxaban + aspirin versus aspirin alone was also consistent regardless of background clopidogrel overall. The principal safety outcome of Thrombolysis in Myocardial Infarction (TIMI) major bleeding had a hazard ratio of ~1.3 to 1.5 regardless of clopidogrel, with number needed to harm >90 with or without clopidogrel.

In an exploratory analysis of early bleeding, exposure to clopidogrel was associated with higher rates of bleeding while used, particularly with longer durations (e.g. >30 days). Prof. Hiatt concluded: "In the absence of clear benefit, clopidogrel exposure along with aspirin and rivaroxaban should be minimised or avoided to reduce this risk." It should be noted that VOYAGER PAD was not designed to assess whether clopidogrel provides any benefit in this setting, a question that remains unanswered.

1. Hiatt WR, et al. Abstract 406-13. ACC/WCC 28-30 March 2020.
2. Bonaca MP, et al. N Engl J Med. 2020. DOI:10.1056/NEJMoa2000052.

TAILOR-PCI misses endpoint but still provides valuable insights

Although it missed its primary endpoint of a 50% reduction in cardiovascular (CV) events at 1 year, the TAILOR-PCI trial demonstrated a 34% reduction in CV events, alongside a statistically significant 40% reduction in the total number of events per patient receiving genetically-guided treatment versus patients receiving standard treatment [1].

TAILOR-PCI, presented by Prof. Naveen Pereira (Mayo Clinic, USA), is the largest trial to date to investigate the clinical utility of using genetic testing to detect the clopidogrel loss-of-function (LOF) genotype to guide antiplatelet therapy in patients undergoing percutaneous coronary intervention (PCI). The trial enrolled 5,302 patients who had had PCI with stenting. Patients received standard antiplatelet therapy with clopidogrel 75 mg/day without genetic testing or antiplatelet therapy prospectively guided by genotyping for the clopidogrel reduced-function *CYP2C19* alleles. Of the tested patients, 35% was found to have the clopidogrel LOF variant. They received ticagrelor 90 mg daily, whereas patients without the LOF variant were treated with clopidogrel. The primary composite endpoint consisted of CV death, myocardial infarction, stroke, definite or probable stent thrombosis, and severe recurrent ischaemia.

After 1 year, 4% of patients receiving genetically guided treatment experienced a primary endpoint event versus 5.9% of patients who were treated conventionally (adjusted HR 0.66; 95% CI 0.43- 1.02; P=0.56), showing a neutral result for the primary endpoint. An exploratory analysis indicated that there was a lower rate of 40% associated with those who were genotyped (HR 0.60; 95% CI 0.41-0.89; P=0.011). Interestingly, the rate of adverse events was significantly reduced by 79% in the first 3 months of treatment among patients who received genetically-guided therapy compared with those who did

not. Prof. Pereira pointed out that, as the risk of adverse events is highest immediately after PCI, the potential benefit of genetically-guided therapy has the largest impact in this particular period. The study might have been underpowered as a result of recent improvements in care, such as the use of drug-coated stents, which may have reduced the expected rates of adverse events. Further studies are planned, including a cost-effectiveness analysis of genetically-guided therapy based on long-term follow-up of these patients.

1. Pereira NL, et al. Abstract 402-12. ACC/WCC 28-30 March 2020.

Edoxaban: alternative to warfarin after surgical aortic or mitral valve procedures?

After surgical or mitral valve replacements or repair, 3 months of edoxaban was non-inferior to warfarin for preventing thromboembolism and major bleeding.

Dr Geu-Ru Hong (Yonsei University College of Medicine, South Korea) presented the results of the open-label, parallel group, randomised Korean ENAVLE study, which aimed to explore the efficacy of edoxaban in patients after mitral valve repair or bioprosthetic valve implantation [1]. Dr Hong pointed out that 3 months of warfarin administration after surgical or transcatheter valve therapy is common practice in Korea. The problem is that a Korean diet typically includes high levels of vitamin K that can interfere with the efficacy of warfarin. Thus, the investigators in this trial sought to identify an alternative among the direct oral anticoagulants (DOACs).

The primary efficacy endpoint was the occurrence of thromboembolic and any thrombus at repaired ring or bioprosthetic valves at week 12. Patients (n=220) were randomised, 5 to 9 days after surgical aortic or mitral valve replacement or repair, to receive edoxaban (60 mg or 30 mg once daily; n=110) or warfarin for 3 months (standard care; n=110). Baseline characteristics were well balanced; both arms had similarly high levels of hypertension, hyperlipidaemia, and/or atrial fibrillation. Outpatient clinic visits occurred at 2, 4, and 12 weeks. Echocardiography and CT scans were performed during the final visit at 12 weeks.

In total, 4 patients from the warfarin group and 0 patients in the edoxaban group experienced a primary outcome event. Additionally, there were 3 ISTH bleeds with edoxaban versus 1 with warfarin. Dr Hong noted that a higher risk for gastrointestinal bleeding was observed in the edoxaban group, which may warrant further consideration. Session co-moderator Dr Martin Leon (New York Presbyterian Hospital, USA) summarised: "If we are going to change the guideline recommendation and begin using a DOAC post-valve therapy, we need more data. We need larger numbers of patients to be assured of safety, and to be at least somewhat confident that there really is an efficacy benefit relevant to no therapy, which is generally the standard in the United States."

1. Hong GR, et al. Abstract 412-14. ACC/WCC 28-30 March 2020.

Table: Efficacy outcomes in the intention-to-treat cohort [1]

Outcomes	Edoxaban (n=109)	Warfarin (n=109)	Risk difference (95% CI)	P-value*
Primary efficacy outcome	**0 (0)**	**4 (3.67)**	**-0.0367 (-0.0720, -0.0014)**	**<0.001**
Death	0 (0)	0 (0)		
Clinical thromboembolic event	0 (0)	1 (0.92)	-0.0093 (-0.0271, 0.0087)	<0.001
Asymptomatic intracardiac thrombus	0 (0)	3 (2.75)	-0.0275 (-0.0582, 0.0032)	<0.001
Subclinical leaflet thrombosis	0 (0)	1 (0.92)	-0.0093 (-0.0271, 0.0087)	<0.001
Thrombus within cardiac chambers	0 (0)	2 (1.83)	-0.0183 (-0.0435, 0.0068)	<0.001

* P for non-inferiority

Bleeding reduction post-TAVI with OAC alone vs OAC + clopidogrel

In patients with an established indication for oral anticoagulation (OAC) undergoing transcatheter aortic valve implantation (TAVI), OAC alone as compared with OAC + clopidogrel reduced the rate of bleeding events, including major life-threatening bleeding events, without increasing the rate of thrombotic events [1,2].

The POPular TAVI trial is an investigator-initiated, randomised, open-label trial conducted in 17 centres in Europe. The purpose of this trial was to investigate whether extra antithrombotic protection post-TAVI was coupled with extra safety issues. Dr Vincent Nijenhuis (St. Antonius Hospital, the Netherlands) presented the results for 1 of the 2 study cohorts. This cohort consists of patients who were undergoing TAVI and had an established indication for long-term OAC. Patients were randomised to receive clopidogrel on top of their existing oral anticoagulation therapy (n=156) or oral anticoagulation therapy alone (n=157), which was either a direct oral anticoagulant (DOAC) or a vitamin K antagonist. The co-primary endpoints were all bleeding complications (Valve Academic Research Consortium [VARC-2]) and non-procedural bleeding complications (Bleeding Academic Research Consortium type 4 [BARC]) at 1 year after TAVI. Secondary endpoints consisted

of cardiovascular (CV) mortality, non-procedural bleeding, all-cause stroke, or myocardial infarction (MI) as well as the efficacy endpoint defined as CV mortality, ischaemic stroke, or MI at 1 year after TAVI. Mean age of the patients was 81 years and 95% had atrial fibrillation. The adherence for 3 months clopidogrel was 95.5%.

At 1 year after TAVI, results showed that OAC alone was superior with regard to the primary endpoint with rates of 21.7% for OAC alone versus 34.6% for OAC + clopidogrel (risk ratio [RR] 0.63; 95% CI 0.43-0.90; P=0.011). Non-procedural bleeding occurred in 21.7% versus 34.0%, respectively (RR 0.64; 95% CI 0.44-0.92; P=0.015). The rates for CV mortality, non-procedural bleeding, stroke, or MI were 31.2% versus 45.5% (RR 0.69; 95% CI 0.51-0.92), and 13.4% versus 17.3% for the efficacy endpoint of CV mortality, ischaemic stroke, or MI (RR 0.77; 95% CI 0.46-1.31). In brief, the trial data argued against adding clopidogrel on top of oral anticoagulation in TAVR patients with a DOAC indication in order to reduce their risk of bleeding. It is important to note that while the authors evaluated antithrombotic therapy in this cohort, the primary endpoint was bleeding, not efficacy. Therefore, the trial was not powered to understand differences in ischaemic outcomes and the upper confidence interval for risk was 1.31. Thus, the conclusions should be limited to safety.

1. Nijenhuis VJ, et al. Abstract 405-08. ACC/WCC 28-30 March 2020.
2. Nijenhuis VJ, et al. N Engl J Med 2020; DOI: 10.1056/NEJMoa1915152.

Apixaban offers new perspective for cancer patients in need of anticoagulation

Oral apixaban has shown to be non-inferior to subcutaneous dalteparin for the treatment of cancer-associated venous thromboembolism (VTE) in the phase 3, open-label, multinational CARAVAGGIO trial [1]. Of interest was that no increase was observed in the risk of major bleeding at the gastrointestinal (GI) sites. These reassuring results, which were simultaneously published in the *New England Journal of Medicine*, open up opportunities for patients with cancer-associated thrombosis who are eligible for treatment with direct oral anticoagulants (DOACs), including patients with GI cancer [2].

Patients with cancer run a high risk of recurrent VTE and bleeding. Although major guidelines recommend low-molecular-weight heparin and have recently added edoxaban and rivaroxaban, the high risk of bleeding (mainly at GI sites) poses a serious issue and limits the clinical benefit of these drugs. The CARAVAGGIO trial, presented by Prof. Giancarlo Agnelli (University of Perugia, Italy), assessed whether oral apixaban (10 mg twice daily for the first 7 days, 5 mg twice daily thereafter) was non-inferior to subcutaneous dalteparin (200 IU/kg once daily for the first month and then 150 IU/kg once daily) in the treatment of proximal deep-vein thromboembolism (DVT) and/or pulmonary embolism (PE) in patients suffering from cancer.

The study was conducted in Europe, Israel, and the United States and enrolled 1,170 patients with cancer who had newly diagnosed, objectively confirmed symptomatic or incidental proximal lower-limb DVT, or symptomatic or incidental PE in a segmental or more proximal pulmonary artery. The primary endpoint was recurrent proximal DVT or PE over 6 months, as assessed by a central, independent adjudication committee unaware of study treatment allocation. The primary safety outcome was major bleeding defined according to the guidelines of the International Society of Thrombosis and Haemostasis (ISTH). Patients were randomised to apixaban (n=585) or dalteparin (n=585). Baseline characteristics were comparable between both groups. The most common type of cancer was colorectal cancer, followed by lung cancer, and breast cancer.

Recurrent VTE occurred in 5.6% of apixaban patients and 7.9% of dalteparin patients (HR 0.63; 95% CI 0.37-1.07; P<0.001 for non-inferiority and P=0.08 for superiority, see Table). This was 2.3% and 2.6% for recurrent DVT, and 3.3% and 5.5% for PE, respectively. Fatal PE occurred in 0.7% and 0.5% of patients, respectively. The primary safety endpoint of major bleeding was observed in 3.8% of patients on apixaban and 4.0% of patients on dalteparin (HR 0.82; 95% CI 0.40-1.69; P=0.60). Major GI bleeding occurred in 1.9% and 1.7% of patients, respectively. In conclusion, the CARAVAGGIO study provided compelling evidence that while apixaban could provide comparable protection from recurrence of VTE as compared with low-molecular-weight heparin, no substantial increase in bleeding hazard was observed.

1. Agnelli G, et al. Abstract 406-09. ACC/WCC 28-30 March 2020.
2. Agnelli G, et al. N Engl J Med. 2020; DOI: 10.1056/NEJMoa1915103.

Table: Primary efficacy outcomes of the CARAVAGGIO trial [1]

	Apixaban (n=576)	Dalteparin (n=579)	Hazard ratio (95% CI)	P-value
Recurrent VTE n (%)	**32 (5.6)**	**46 (7.9)**	**0.63 (0.37-1.07)**	**<0.001 for non-inferiority; 0.08 for superiority**
Recurrent DVT n (%)	13 (2.3)	15 (2.6)	0.87 (0.34-2.21)	
Recurrent PE n (%)	19 (3.3)	32 (5.5)	0.54 (0.29-1.03)	
Fatal PE n (%)	4 (0.7)	3 (0.5)	1.93 (0.40-9.41)	

CI, confidence interval; DVT, deep-vein thromboembolism; PE, pulmonary embolism; VTE, venous thromboembolism.

Rivaroxaban superior to enoxaparin in preventing VTE in non-major orthopaedic surgery

Oral rivaroxaban has shown to be superior to subcutaneous enoxaparin in preventing venous thromboembolism (VTE) in patients undergoing non-major orthopaedic surgery with a period of immobilisation [1,2]. No significant difference was observed in major bleeding with rivaroxaban versus enoxaparin.

Prof. Nadia Rosencher (Paris Center University Hospital, France) and colleagues in the PRONOMOS trial aimed to compare the effect of rivaroxaban with that of enoxaparin in preventing major VTE during immobilisation after lower-limb non-major orthopaedic surgery [1]. The trial enrolled 3,604 adult patients who underwent non-major orthopaedic surgery of the lower limbs and who required thromboprophylaxis for >2 weeks (investigator's assessment). The primary efficacy endpoint of the study was major VTE, a composite of symptomatic distal or proximal deep-vein thromboembolism (DVT), pulmonary embolism, or VTE-related death during the treatment period, or asymptomatic proximal DVT at the end of treatment. Safety outcomes were major and clinically relevant non-major bleeding. Participants were enrolled between December 2015 and April 2018 at 200 sites in 10 countries. As recruitment of patients was slower than expected, enrolment was terminated early due to drug supply issues. Participants had a mean age of 41 years and median body mass index of 26.3 kg/m². Many types of surgery were included in the study (median duration 60 minutes), with the most common being ligament repair of the knee, ankle fracture, and knee arthroscopy. A prophylactic dose of low-molecular-weight heparin was given prior to surgery to 13.8% of patients. The patients were randomised to receive 10 mg oral rivaroxaban and a placebo injection (n=1,809) or enoxaparin (40 mg in 0.4 mL of diluent) plus a placebo oral tablet (n=1,795).

The results showed that 0.2% of patients on rivaroxaban experienced VTE (n=4) versus 1.1% of patients receiving enoxaparin (n=18; risk ratio [RR] 0.25; 95% CI 0.09-0.75; P<0.001 for non-inferiority, P=0.01 for superiority). Symptomatic VTE was seen in 0.2% versus 0.6% of patients, respectively (RR 0.28; 95% CI 0.08-1.00). Asymptomatic proximal DVT was seen in 0.1% of the rivaroxaban group versus 0.4% of the enoxaparin group. Major and non-major clinically relevant bleeding occurred in 1.1% of rivaroxaban patients and 1.0% of enoxaparin patients (RR 1.04; 95% CI 0.55-2.00). Although this study was prematurely stopped because of low accrual, and is therefore limited in impact, the net clinical benefit of VTE + major bleeding was 0.8% for rivaroxaban and 1.8% for enoxaparin (RR 0.48; 95% CI 0.26-0.90). These findings suggest that rivaroxaban could replace enoxaparin to prevent VTE during postoperative reduced mobility after non-major orthopaedic surgery in at-risk patients.

1. Samama CM, et al. Abstract 406-11. ACC/WCC 28-30 March 2020.
2. Samama CM, et al. N Engl J Med. 2020. DOI:10.1056/NEJMoa1913808.

Interventional Cardiology

TAVR safe and effective in low-risk bicuspid aortic stenosis patients

Low-risk bicuspid aortic stenosis patients who underwent transcatheter aortic valve replacement (TAVR) with Evolut supra-annular, self-expanding valve achieved promising early results with low early rates of death or disabling stroke, according to Dr Basel Ramlawi (Valley Health System, USA) [1].

The objective of the study was to assess safety and efficacy of TAVR in patients with bicuspid aortic valve stenosis and low surgical risk with a follow-up of 10 years. The primary safety endpoint was all-cause mortality or disabling stroke at 30 days; the primary efficacy endpoint was device success. The study was performed in high-volume experienced centres, which recommended annular sizing and strongly encouraged pre-TAVR balloon dilatation (91.3%). The study included 150 patients with bicuspid aortic valve anatomy confirmed by multi-slice CT. They were either symptomatic or asymptomatic and their predicted risk of mortality was <3%. Mean age of the patients was 70 years, and 147 individuals completed follow-up.

At 30 days after the procedure, 1.3% of patients had died (1 patient was excluded due to coronary obstruction), and 3.3% of patients had experienced a non-disabling stroke. The device's success rate at 30 days was 95.3%. Valve haemodynamics were centrally adjudicated by a core echocardiographic laboratory; mean aortic valve gradient was 7.6 mmHg and the effective orifice area was 2.3 cm^2. Mild aortic regurgitation occurred in 40.4% of patients. However, no moderate or severe aortic regurgitation was seen in this population. In this study, TAVR was shown to be safe and effective. However, Dr Ramlawi concluded, the choice between TAVR and surgery remains a complicated one and should be based on a multidisciplinary heart team discussion that includes anatomic, clinical, and patient social factors.

1. Ramlawi B, et al. Abstract 405-10. ACC/WCC 28-30 March 2020.

TAVR model reveals differences in hospital outcomes

A novel, patient-centric, composite-outcome model for transcatheter aortic valve replacement (TAVR) based on 30-day outcomes and their ranked association with both 1-year mortality and quality of life has shown significant site-level variation in mortality and major complications after TAVR procedures in the United States [1].

Dr Nimesh Desai (Hospital of the University of Pennsylvania, USA) presented the results of the STS/ACC TVT Registry. The purpose of the study was to determine whether site-level variation exists in TAVR quality of care in the USA using a novel, patient-centric, 30-day, composite-outcome measure, comparing each hospital to the national average. The patient cohort consisted of patients who underwent transfemoral TAVR for symptomatic aortic stenosis between 1 January 2015 and 31 December 2017. Data from hospitals with >10% missing data for the outcome variable and other key study variables was excluded. A ranked composite outcome selection was developed consisting of periprocedural complications determined by their adjusted association with 1-year mortality and patient quality of life, based on the Kansas City Cardiomyopathy Questionnaire (KCCQ); and any outcome with significant hazard ratio was maintained. When ranking the endpoints, the outcome with the highest rank was assigned if patients had more than 1 outcome. The overall model was a hierarchical, multi-category, logistic regression model that estimates a set of hospital-specific odds ratios. Site difference was defined as a random patient doing worse at an average hospital and a random patient doing better at an average hospital.

It emerged that 11% of the 301 included sites performed worse than expected, 80% performed as expected, and 8% better than expected. The reliability of the model was tested, and it showed moderate-to-high reliability even when including lower-volume programmes. However, the researchers acknowledged that the analysis had its limitations including that it did not examine the quality of care of patients who underwent TAVR using non-femoral access as well as missing baseline KCCQ-12 and gait speed data, which limited the number of sites included in this analysis. The steering committee of the STS/ACC TVT registry commissioned the composite metric, said Dr Desai, and it has already been approved for use.

1. Desai N, et al. Abstract 405-12. ACC/WCC 28-30 March 2020.

TAVR versus surgery in older patients

In a new, real-world study evaluating patients aged 70 years or older, transcatheter aortic valve replacement (TAVR) was not inferior to surgery with respect to death from any cause at 1 year.

Dr William Toff (University of Leicester, UK) presented 1-year follow-up data from UK TAVI study, which involved participants treated at 34 UK sites who were ≥70 years (with additional risk factors) or ≥80 years (with or without additional risk factors) [1]. The mean age was 81 years. The unmet need this trial attempted to address was that although previous clinical trials have found TAVR to be non-inferior or superior to open-heart surgery, most trials have been limited to a younger cohort and mostly only evaluated outcomes from high-volume TAVR centres.

The UK TAVI trial enrolled 913 patients who had been referred for treatment of severe aortic stenosis between 2014 to 2018 at any UK centre that performed TAVR, regardless of volume. Participants were randomly assigned to receive TAVR or open-heart surgery and will be followed up for at least 5 years.

At 1 year, the prespecified threshold for non-inferiority of TAVR was met. Th e primary endpoint, the rate of death from any cause, was 4.6% in the TAVR group and 6.6% in the surgery group (HR 0.69; 95% CI 0.38-1.26; P=0.23). This treatment effect was similar in subgroup analyses, accounting for coronary artery disease requiring revascularisation, age, gender, Society of Thoracic Surgeons (STS) score, and frailty. Rates of death from cardiovascular disease or stroke were also similar between the 2 groups.

Major bleeding events in the TAVR group were lower compared with surgery (6.3% vs 17.1%; P< 0.001). TAVR was also associated with a shorter hospital stay, fewer days in intensive care, and a faster improvement in functional capacity and quality of life. At 6 weeks after the procedure, functional capacity and quality-of-life measures were better in the TAVR group, but by 1 year they were similar in the 2 groups. However, patients in the TAVR arm did have a significantly higher rate of vascular complications (4.8%) than those receiving surgery (1.3%). TAVR patients were also more likely to have a pacemaker implanted compared with those undergoing surgery (12.2% vs 6.6%). Furthermore, mild aortic regurgitation occurred at 1 year in 38.3% of the TAVR group and 11.7% of the surgery group, whereas moderate regurgitation occurred in 2.3% of TAVR patients and 0.6% of surgery patients.

In conclusion, both TAVR and surgery were safe in older patients, although each procedure had its particular benefits and risks. Prof. Toff said the findings support those of earlier TAVR trials while being "more reflective of the real world."

1. Toff WD, et al. Abstract 405-14. ACC/WCC 28-30 March 2020.

Real-world evidence for MitraClip

The EXPAND G4 study confirmed the safety and efficacy of the next generation MitraClip NTR/XTR system in primary mitral regurgitation (MR) patients in a real-world setting, according to Dr Scott Lim (University of Virginia, USA) [1].

The 1,000+ patient global EXPAND study is a post-market, multi-centre, single-arm, prospective study to assess the safety and performance of the next generation MitraClip G4 System. Also, it is the first trial to use Echo Core Lab and Clinical Events Committee adjudicated 30-day clinical outcomes in patients with primary mitral regurgitation treated with the next generation NTR and XTR MitraClips.

The primary objective was to determine the percentage of participants with MR reduction to ≤2+ at 30 days. Secondary objectives of the study were to evaluate MR reduction outcomes as a function of mitral valve anatomic complexity and to confirm the safety (including single leaflet device attachments and leaflet injuries) and efficacy of the NTR and XTR systems. Eligible patients had symptomatic MR (≥3+) and were eligible to receive the MitraClip per the current approved indications for use in their respective country of residence. The overall study subject population consisted of 413 subjects with secondary MR aetiology and 422 subjects with primary or mixed aetiology; this last group was the focus of this analysis.

All-cause death occurred in 2.4% of patients, stroke in 1.2% (ischaemic stroke in 1.0% and haemorrhagic stroke in 0.2%), and non-elective cardiovascular surgery for device-related complications in 0.9%. Regarding the device-related leaflet adverse events, single leaflet device attachment occurred in 1.9% and leaflet injury (i.e. leaflet tear or perforation) in 0.2%. It was concluded that approximately one third of patients had a complex mitral valve anatomy, reflecting the difference in patients treated in the real world in comparison with those included in past clinical trials. Results show that MR ≤1+ is being achieved more often with MitraClip NTR and XTR than previously observed in the EVEREST II trials [2]. MitraClip XTR was associated with greater MR reduction compared with NTR in more complex anatomies.

1. Lim DS, et al. Abstract 412-12. ACC/WCC 28-30 March 2020.
2. Feldman T, et al. N Engl J Med. 2011;364(15):1395-1406.

2-year results show non-significant outcomes TAVR vs surgery in severe aortic stenosis

In a defined population of severe symptomatic aortic stenosis patients who were at low surgical risk, transcatheter aortic valve replacement (TAVR) compared with surgery showed a reduction in death, stroke, or cardiovascular (CV) rehospitalisation at 2 years. Between 1 and 2 years, however, TAVR patients experienced more stroke/death events, which resulted in no significant differences between both groups [1].

Prof. Michael Mack (Baylor Scott & White Heart Hospital, USA) presented the 2-year clinical and echocardiographic outcomes of the PARTNER 3 trial for low-risk patients with severe symptomatic aortic stenosis who were treated with the SAPIEN 3 TAVR system compared with surgery. A thousand patients were randomised 1:1 to TAVR and surgery; follow-up was done at 30 days, 6 months, and continuing annually through 10 years. The primary endpoint was a composite of all-cause mortality, stroke, or CV rehospitalisation at 1 year post-procedure. Participants had severe calcific aortic stenosis and low surgical risk, mean age was 73 years, and mean Society of Thoracic Surgeons (STS) score was 1.9. At 2 years, 96.5% of participants were available for primary endpoint analysis.

At 1 year, a primary endpoint event occurred in 15.6% of surgery patients and in 8.5% of TAVR patients; at 2 years, these

numbers rose to 17.4% versus 11.5%, respectively. Death at 1 year occurred in 2.5% of surgery patients versus 1.0% of TAVR patients; at 2 years, this was 3.2% and 2.4%, respectively. The rates for stroke at 1 year were 3.3% and 1.2%, respectively, and 3.6% versus 2.4% at 2 years. The results were complex; because the patients experienced more CV events/deaths between 1-2 years, the benefits were offset by 2 years. At 1 year, the incidence of new-onset atrial fibrillation was lower in the TAVR arm (7.9% vs 41.8%; P<0.001) and the incidence of new-onset left bundle branch block was higher (24.4% vs 9.4%; P<0.001). Likewise, at 2 years, 2.6% of TAVR patients had valve thrombosis compared with 0.7% of surgery patients (P=0.02).

Limitations of the study included that the results only apply to the enrolled selected population, which excluded a large number of patients. Also, there was less follow-up data available in the surgical group as more patients withdrew from the study. Finally, it was pointed out that valve thrombosis definitions by Valve Academic Research Consortium (VARC) 2 criteria are outdated and may be exaggerated by recent CT imaging leaflet thickening studies, and that results reflect only 2-year outcomes, which makes long-term assessment of structural valve deterioration necessary.

Prof. Mack concluded that the main take-home messages were "that there are 2 good options for low-risk patients and that there should be shared decision-making with the patient as to which option is best for them." He pointed out that PARTNER 3 was not an all-comers trial, "so if you put it in that framework and have patients who were studied in the trial, both options are good options based upon 2-year data. However, extending the findings of this trial to the population outside of that study is a bridge too far."

1. Leon MB, et al. Abstract 405-16. ACC/WCC 28-30 March 2020.

Renal denervation better than sham for blood pressure

The SPYRAL PIVOTAL - SPYRAL HTN-OFF MED trial showed that renal denervation was superior to a sham procedure at reducing blood pressure in patients with uncontrolled high blood pressure at 3 months follow-up.

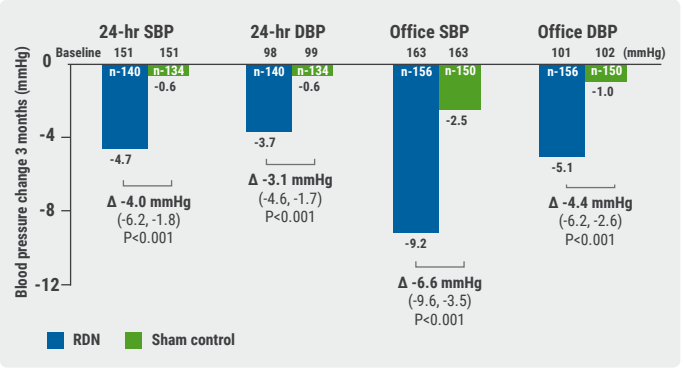
Prof. Michael Böhm (Saarland University Medical Center, Germany) presented the international, prospective, single-blinded, sham-controlled trial, which was designed to assess the efficacy of renal denervation in the absence of antihypertensive medications [1]. The findings were simultaneously published in *The Lancet* [2].

This trial was instigated based on observational data suggesting that catheter-based renal denervation significantly reduced blood pressure. Following a positive pilot trial, the SPYRAL PIVOTAL-SPYRAL HTN-OFF MED trial was powered to evaluate the efficacy of catheter-based renal denervation in the absence of medications. Participants (n=331) from 46 sites had a systolic blood pressure (average over 24 hours) between 140 -170 mmHg and had either never taken any blood pressure-reducing medications or had discontinued those medications for at least 3 weeks prior to study entry. Characteristics were similar between both groups; 67% were men, the average age was 53, and the average body mass index was 31. Patients were randomised to either renal denervation (n=166) or a sham procedure (n=165), during which a catheter was inserted and angiography was performed.

The primary efficacy endpoint was the change in average 24-hour systolic blood pressure at 3 months post-procedure, adjusted for systolic blood pressure at study entry. The secondary efficacy endpoint was the change in average blood pressure measured in the doctor's office at 3 months, adjusted for office blood pressure at study entry. Major adverse safety events were also assessed at 3 months, including rates of death, stroke, changes in kidney function, or any injury to the arteries surrounding the kidney.

Both endpoints were met. At 3 months, a significant 4.7 mmHg reduction was observed in patients' 24-hour systolic ambulatory blood pressure and a 9.2 mmHg reduction in office systolic blood pressure. Change in 24-hour systolic blood pressure was 3.9 mmHg (P<0.001) and change in office systolic blood pressure at was 6.6 mmHg (P<0.001; see Figure). No deaths, strokes, or decreases in kidney function occurred during the first 3-months of follow-up.

Figure: Primary analysis of blood pressure at 3 months over 24-hours at home or the office [1]



DBP, diastolic blood pressure; RDN, renal denervation; SBP, systolic blood pressure.
Figure kindly provided by Prof. Blöm.

Prof. Böhm concluded: "The findings show that renal denervation lowers blood pressure not just during the day but also through the night and early morning periods when risk is highest for clinical events and the effect of some medications on blood pressure is reduced. This study establishes renal denervation as an additional option beyond exercise or lifestyle modification for patients with high blood pressure who are unwilling to take or cannot tolerate medication."

Results from a companion study, the SPYRAL HTN-ON MED trial, which is testing the safety and effectiveness of renal denervation in patients who are taking up to 3 blood pressure-reducing medications, are expected at the end of 2021.

1. Böhm M, et al. Abstract 406-15. ACC/WCC 28-30 March 2020.
2. Böhm M, et al. Lancet 2020;Mar 29. DOI: 10.1016/S0140-6736(20)30554-7.

Radial artery best for second bypass

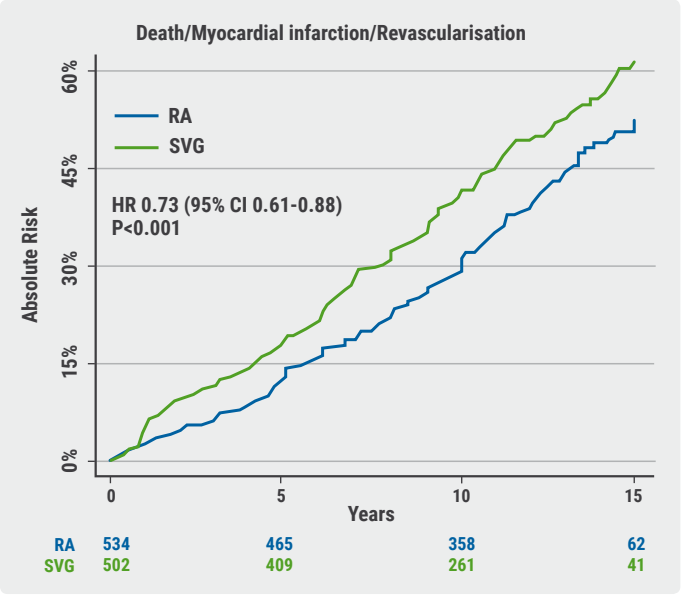
After 10 years of follow-up, data showed that using the radial artery rather than the saphenous vein for a second bypass was associated with a statistically significant decrease in the combined rate of death, heart attacks, and revascularisation procedures.

Prof. Mario Gaudino (Weill Cornell Medicine, USA) presented the results of the RADIAL study, which was a patient-level combined meta-analysis of 5 clinical trials held in Australia, Korea, Italy, Serbia, and the United Kingdom [1]. The rationale of this combined analysis stems from the fact that the use of >1 arterial grafts for coronary-artery bypass grafting (CABG) has not been widely adopted despite current guidelines recommendations. It is generally accepted that radial artery grafts have a better patency rate compared with saphenous vein grafts. Yet, evidence has shown that patients frequently receive saphenous vein grafts in addition to an internal thoracic artery graft to the left anterior descending coronary artery [2]. "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," Prof. Gaudino said.

For the RADIAL meta-analysis, the investigators combined the results from 5 trials in which patients receiving bypass surgery were randomly assigned to get a second bypass from either the radial artery (n=534) or the saphenous vein (n=502). Participants had an average age of 67 years at the time of surgery; 70% were male. The primary endpoint was the combined rate of death, heart attack, or need for a second procedure to treat the same artery. The co-primary endpoint was the combined rate of death or heart attack.

In 2018, this team previously reported in the *New England Journal of Medicine* that after an average 5-year follow-up, patients who received radial artery versus saphenous vein bypasses had significantly fewer heart attacks and repeat revascularisation procedures, although the death rate was similar in the 2 groups [3]. The current study extends that study by an additional 5 years of follow-up from the same patient cohorts. At a median of 10 years follow-up, patients who received radial artery bypasses had a 23% reduced risk of experiencing the primary or secondary endpoint event when compared with the saphenous vein group (HR 0.77; 95% CI 0.63-0.94). Use of the radial artery was associated with a 27% reduction in deaths (HR 0.73; 95% 0.61-0.88; see Figure), a 26% reduction in heart attacks, and a 38% reduction in repeat procedures. In a subgroup analysis, females had better survival with radial artery grafts compared with saphenous vein grafts (HR 0.51; 95% CI 0.36-0.72) than males (HR 0.84; 95% CI 0.68-1.05).

Figure: Cumulative incidence of the primary composite outcome in the radial artery (RA) versus saphenous vein graft (SVG) groups [1]



Prof. Gaudino concluded that although the results from RADIAL are a pooled analysis of several small trials rather than 1 large trial, the ongoing ROMA trial will hopefully confirm these data in a larger and more homogenous setting. ROMA aims to test whether outcomes are better for patients who receive 2 or more arterial bypasses compared with patients who receive just 1 in a cohort of 4,300 patients. Initial results are expected in 2025.

1. Gaudino M, et al. Abstract 410-12. ACC/WCC 28-30 March 2020.
2. ElBardissi AW, et al. J Thorac Cardiovasc Surg 2012;143:273-281.
3. Gaudino M, et al. N Engl J Med. 2018;378(22):2069-2077.

PCI and CABG are equal in left main CAD

With a median follow-up of 11.3 years, the PRECOMBAT trial showed that percutaneous coronary intervention (PCI) with sirolimus-eluting stents was non-inferior to coronary-artery bypass grafting (CABG) among patients with severe left main disease.

Dr Duk-Woo Park (Asan Medical School, South Korea) presented the results of the *open-label Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease* (PRECOMBAT) trial [1]. PRECOMBAT was the first randomised study to compare PCI (n=300) with CABG (n=300) in patients with left main coronary artery disease. The results were simultaneously published online in *Circulation* [2]. At 10 years, there was no difference between the 2 groups; the primary composite endpoint of all-cause mortality, myocardial infarction, stroke, or ischaemia-driven revascularisation occurred in 29.8% of patients treated with PCI and 24.7% of patients in the CABG surgery group (HR 1.25; 95% CI 0.93-1.69). However, looking at individual components, the rate of revascularisation was significantly higher in patients treated with PCI (16.1% vs 8.0%; HR 1.98; 95% CI 1.21-3.21).

The study was not powered for clinical outcomes at 10 years. Dr Park cautioned that the results should be considered hypothesis-generating only and pointed out that the open-label nature of this study may have influenced some of the non-fatal outcomes. Further research is warranted for data concerning extended follow-up.

1. Park S-J, et al. Abstract 410-14. ACC/WCC 28-30 March 2020.
2. Park DW, et al. Circulation. 2020. DOI:10.1161/CIRCULATIONAHA.120.046039.

Infusion of ethanol in the vein of Marshall for persistent AF

The infusion of ethanol via the vein of Marshall (VOM), coupled with catheter ablation, leads to improved outcomes for patients with persistent atrial fibrillation (AF).

Presented by Dr Miguel Valderrabano (Baylor College of Medicine, USA), the VENUS trial addressed the challenge of treating persistent AF, which is limited by the imperfect success of catheter ablation procedures, and the consequent need for repeat procedures [1]. The investigators hypothesised that by ablating AF triggers in the VOM through retrograde ethanol infusion, coupled with a catheter ablation approach, the restoration of normal rhythm could be achieved in more patients with persistent AF.

Participants (n=343) with symptomatic persistent AF and refractory to at least 1 anti-arrhythmic agent were randomised to receive either catheter ablation alone (n=158) or catheter ablation combined with VOM ethanol (n=185). The investigators anticipated that approximately 15% of the patients randomised to the VOM group would have a VOM difficult to cannulate; those patients would continue in the study receiving only catheter ablation.

Outcomes were measured at 1, 3, 6, 9, and 12 months post-procedure, with continuous month-long monitoring taking place at the 6- and 12-month time points. Prior to catheter ablation, patients in the VOM group received a coronary sinus venogram to identify the VOM and angioplasty balloon cannulation with 4 retrograde injections of 1 cc of ethanol (from distal to proximal). Left atrial voltage maps were performed before and after the ethanol injection to assess the scar induced by the alcohol administration. Catheter ablation for both groups included pulmonary vein isolation. The extent of the total tissue ablated was determined by a final left atrial voltage map. The primary endpoint at 3 months was resolution of either AF or atrial tachycardia (AT) for more than ≥30 seconds, without anti-arrhythmic medication.

A total of 142 participants were included in the per-treatment analysis; the VOM procedure was unsuccessful in 30 patients, 3 patients died, and 10 participants had missing data. Notably, more patients in the VOM group had hypertension (77% vs 66%) and the atrial diameter was larger in the catheter ablation-only group (44.8 mm vs 47 mm). These distinctions should be considered in the results interpretation. Resolution of AF or AT for more than 30 seconds after 3 months was achieved in 38% of the patients randomised to the catheter ablation group, and 51.6% among those in the VOM plus catheter ablation group (P=0.015, see Table). AF/AT recurrence was seen in 51.9% of the catheter ablation group, compared with 40% of those undergoing VOM infusion plus catheter ablation.

Dr Valderrabano concluded: "In persistent AF, VOM ethanol added to catheter ablation reduces the recurrence of AF and AT, reduces the AF, and may reduce the need for repeat procedures."

1. Valderrabano M et al. Abstract 409-12, ACC/WCC 28-30 March 2020.

Table: Ablation success: Resolution of AF or AT ≥30 seconds after 3 months

	Intention-to-treat			PER treatment		
Catheter ablation n=158	**VOM-Catheter Ablation n=185**			**VOM-Catheter Ablation n=155**		
n(%)	n(%)	Odds Ratio (95% CI)	P-value	n(%)	Odds Ratio (95% CI)	P-value
60 (38)	91 (49.2)	**0.63 (0.41-0.97)**	0.037	80 (51.6)	**0.57 (0.37-0.90)**	0.015

AF, atrial fibrillation; AT, atrial tachycardia; CI, confidence interval; VOM, vein of Marshall.

Atrial Fibrillation/Acute Coronary Syndrome

Fewer adverse events with ticagrelor monotherapy after 3 months DAPT

Ticagrelor monotherapy after 3-month dual antiplatelet therapy (DAPT) has shown a significantly lower risk of net adverse clinical events (NACE) than the currently recommended 12-month DAPT with ticagrelor and aspirin, with the reduced risk mainly due to decreased major bleeding [1].

The objective of the TICO trial, presented by Prof. Yang Soo Jang (Yonsei University, South Korea), was to investigate ticagrelor monotherapy after 3 months of DAPT versus ticagrelor-based, 12-month DAPT for patients with acute coronary syndrome (ACS) after percutaneous coronary intervention (PCI) with new-generation, drug-eluting stents. The study enrolled 3,065 ACS patients (mean age 61 years) undergoing PCI with second-generation, ultrathin, biodegradable, polymer-coated, sirolimus-eluting stents. All patients received ticagrelor plus aspirin for 3 months after which they were randomised to continue treatment with ticagrelor alone (n=1,527) or ticagrelor and aspirin (n=1,529). The primary study endpoint was a net clinical benefit composite of death, myocardial infarction, stroke, stent thrombosis, revascularisation, or Thrombolysis in Myocardial Infarction (TIMI) major bleeding at 12 months.

The results showed that 3.9% of patients on ticagrelor monotherapy experienced a primary endpoint event compared with 5.9% of patients continuing DAPT (HR 0.66; P=0.01). Interestingly, there was a clear difference in event rate at 3 months after randomisation with 1.4% of ticagrelor monotherapy patients achieving the composite endpoint versus 3.5% of those continuing DAPT (HR 0.41; P=0.001). At 12 months, TIMI major bleeding was present in 1.7% of patients on ticagrelor monotherapy versus 3% of continuing DAPT patients (HR 0.56; P=0.02). No difference was observed in ischaemic events between the 2 groups (2.3% with ticagrelor monotherapy vs 3.4% with 12-month DAPT; HR 1.51; 95% CI 0.43-5.33; P=0.53). Although the study had some limitations, such as the open-label design, no placebo group, and exclusion of patients with an elevated risk for bleeding, the authors concluded that ticagrelor monotherapy could be an optimal strategy balancing both ischaemic and bleeding risks for patients with ACS. It should be noted that this study was not powered for ischaemic endpoints and therefore observations and conclusions should be limited to safety.

1. Kim B-K, et al. Abstract 410-08. ACC/WCC 28-30 March 2020.

Apixaban in AF patients with recent ACS/PCI: Drop aspirin after 30 days

Patients with atrial fibrillation (AF) and recent acute coronary syndrome (ACS) and/or percutaneous coronary intervention (PCI) who receive a $P2Y_{12}$ inhibitor are better off with apixaban than a vitamin K antagonist (VKA) as the use of aspirin for up to 30 days results in an equal trade-off between an increase in severe bleeding and reduction in severe ischaemic events [1].

The AUGUSTUS trial was a large, prospective, randomised trial with a two-by-two factorial design that showed that AF patients with recent ACS or PCI who used a $P2Y_{12}$ inhibitor and apixaban had significantly less bleeding compared with warfarin (10.5% vs 14.7%, respectively; P<0.0001) [2]. No significant difference was seen between patients who received additional aspirin versus placebo in the secondary outcomes of composites death or hospitalisation and ischaemic events: death or ischaemic event for apixaban versus VKA (6.7% vs 7.1%; P>0.05); death or hospitalisation for aspirin versus placebo (26.2% vs 24.7%; P>0.05); death or ischaemic event for aspirin versus placebo (6.5% vs 7.3%; P>0.05); ICH for apixaban versus VKA (0.2% vs 0.6%; P>0.05); ICH for aspirin versus placebo (0.4% vs 0.4%; P>0.05).

The objective of this post-hoc secondary analysis, presented by Prof. John Alexander (Duke University, USA) was to explore the balance of risk (i.e. bleeding) and benefit (i.e. ischaemic events) between randomisation and 30 days, and between 30 days and 6 months, with aspirin and placebo, in a cohort of 4,614 patients enrolled in AUGUSTUS. Although the choice of $P2Y_{12}$ inhibitor was left to the treating physician, more

than 90% of the patients were treated with clopidogrel, which is consistent with most guidance statements.

From randomisation to 30 days, the risk of severe bleeding was 2.1% with aspirin versus 1.1% with placebo (absolute risk difference 0.97%; 95% CI 0.23-1.70). Severe ischaemic events occurred in 1.7% patients on aspirin versus 2.6% on placebo (absolute risk difference -0.91; 95% CI -1.74 to -0.08). From 30 days to 6 months, the risk of severe bleeding with aspirin was 3.7% versus 2.5% with placebo (risk ratio 1.25; 95% CI 0.23- 2.27) while the risk of severe ischaemic event was 3.8% versus 4.0%, respectively (absolute risk difference -0.17; 95% CI -1.33 to 0.98).

Prof. Alexander pointed out some limitations of the study, such as patients receiving aspirin prior to randomisation (median 6 days) in both arms, which could have influenced subsequent bleeding or ischaemic outcomes. Also, severe, intermediate, and broad composite bleeding and ischaemic event outcomes may not be of completely comparable severity, and the number of events was small, especially regarding the more severe outcomes.

In conclusion, apixaban with or without aspirin seems to balance the bleeding risk with possible ischaemic benefit in the first 30 days of treatment; continued aspirin is associated with more bleeding.

1. Alexander JH, et al. Abstract 409-08. ACC/WCC 28-30 March 2020.
2. Lopes RD, et al. N Engl J Med. 2019;380:1509-1524.

TWILIGHT sub-study: same outcomes for diabetes patients

A pre-specified sub-analysis of the TWILIGHT trial demonstrated that participants with diabetes mellitus (DM) who had had a recent percutaneous coronary intervention (PCI) did not differ in death, myocardial infarction (MI), or stroke between the arms (i.e. ticagrelor with either aspirin or placebo) when compared with participants who were not diabetic.

The parent TWILIGHT trial took patients who had just undergone PCI and treated them with ticagrelor plus aspirin for 3 months and, if event-free and adherent, randomly assigned them to ticagrelor plus aspirin or plus placebo for an additional 12 months. The main conclusion of that trial was that dropping aspirin after 3 months of dual antiplatelet therapy (DAPT) following PCI among high-risk patients was associated with lower rates of bleeding but no increased risk of death, MI, or stroke.

The current sub-analysis asked whether those findings hold true for the patients in that cohort who also had DM. Prof. Dominick Angiolillo (University of Florida -Jacksonville, USA) presented the findings of the TWILIGHT-DM sub-study [1]. The results were simultaneously published online in the *Journal of the American College of Cardiology* [2]. TWILIGHT participants with DM comprised 37% (n=2,620; mean age 64.8 years) of the randomised cohort. They had more comorbidities and a higher prevalence of multivessel disease when compared to non-diabetic patients (n=4,499) randomised in that cohort.

At 1-year follow-up, no significant interaction was found for the primary endpoint when compared with non-diabetic patients (P=0.23). Patients with DM had a higher rate of bleeding in the ticagrelor + aspirin arm, similar to the parent study. The incidence of Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding was 4.5% in the ticagrelor + placebo group and 6.7% in the ticagrelor + aspirin group among patients with DM (HR 0.65; 95% CI 0.47-0.91; P=0.012). DM patients assigned to ticagrelor monotherapy also had significant reductions in other bleeding definitions: BARC 3 or 5 (1.1% vs 1.3%), Thrombolysis in Myocardial Infarction (TIMI) minor or major (4.5% vs 6.7%), Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) moderate-to-severe (0.7% vs 2.3%), and International Society on Thrombosis and Haemostasis (ISTH) major (1.4% vs 3.1%). The interaction was positive only for GUSTO bleeding (P=0.03).

Also similar to the parent study, although the ticagrelor monotherapy was associated with numerically fewer all-cause death, MI, or stroke events compared with ticagrelor + aspirin, these data did not reach statistical significance (4.6% vs 5.9%; HR 0.77; 95% CI 0.55 to 1.09; P=0.14; P for interaction=0.05).

In conclusion, this sub-analysis shows consistency with the overall trial and that dropping aspirin after 3 months from PCI reduces bleeding.

1. Angiolillo D, et al. Abstract 410-16, ACC/WCC 28-30 March 2020.
2. Angiolillo DJ, et al. Am Coll Cardiol. 2020. DOI:10.1016/j.jacc.2020.03.008.

TWILIGHT sub-study: complex PCI patients

New data from a post-hoc analysis of the TWILIGHT trial showed that, in patients who underwent a complex percutaneous coronary intervention (PCI), ticagrelor monotherapy after an initial 3 months of dual antiplatelet therapy (DAPT) with ticagrelor plus aspirin was associated with

significantly lower clinically relevant bleeding without increasing the risk of ischaemic events compared with continuing the DAPT. The TWILIGHT-COMPLEX sub-study was presented by Prof. George Dangas (Icahn School of Medicine at Mount Sinai, USA) and published simultaneously [1,2].

The original randomised, double-blind, placebo-controlled TWILIGHT trial recently determined that dropping aspirin after 3 months of DAPT with ticagrelor following PCI is associated with lower rates of bleeding but no increased risk of death, myocardial infarction (MI), or stroke [3]. The aim of this sub-study was to evaluate the effect of ticagrelor monotherapy versus ticagrelor + aspirin in patients undergoing complex PCI, defined as a combination of high-risk angiographic and procedural features.

Of the original 9,006 participants in the original TWILIGHT trial, investigators considered 2,342 (33%) as requiring complex PCI. Complex PCI was defined as 3 or more lesions or vessels treated, total stent length greater than 60 mm, bifurcation with 2 stents implanted, atherectomy device use, left main PCI, surgical bypass graft, or chronic total occlusion as target lesions.

All participants underwent 1:1 randomisation to either ticagrelor + placebo or to ticagrelor + aspirin and had a 1-year follow-up. All patients received aspirin before randomisation for the first 3 months following PCI. Like the TWILIGHT trial, the primary endpoint of this post-hoc analysis was Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding, and investigators also assessed for a composite ischaemic endpoint of all-cause death, MI, or stroke.

Of the 2,342 patients who had had complex PCI, 1,158 were randomised to ticagrelor + placebo and 1,184 were randomised to ticagrelor + aspirin. Ticagrelor + placebo resulted in significantly lower rates of BARC type 2, 3, or 5 bleeding than ticagrelor + aspirin: 4.2% versus 7.7%, respectively (HR 0.54; 95% CI 0.38-0.76; P<0.001). BARC type 3 or 5 bleeding was also significantly reduced with ticagrelor + placebo (1.1%) compared with ticagrelor + aspirin (2.6%; HR 0.41; 95% CI 0.21-0.80; P=0.009).

This subgroup was not powered to assess differences in ischaemic outcomes between the 2 groups with results of death, MI, or stroke (3.8% vs 4.9%; HR 0.77; 95% CI 0.52-1.15) as well as cardiovascular death, MI, or stroke (3.6% vs 4.8%; HR 0.75; 95% CI 0.50-1.12). There were also no significant differences in all-cause deaths between groups (0.9% vs 1.5%; HR 0.59; 95% CI 0.27-1.29; see Table). In conclusion, this subset analysis established that withdrawing aspirin after complex PCI reduced bleeding.

1. Dangas GD, et al. Abstract 410-10. ACC/WCC 28-30 March 2020.
2. Dangas G, et al. J Am Coll Cardiol. 2020. DOI:10.1016/j.jacc.2020.03.011.
3. Mehran R, et al. N Engl J Med. 2019;381(21):2032-2042.

Table. Bleeding and ischaemic events 1 year after randomisation. Modified from [2]

Outcomes	ticagrelor + placebo (n=1,158)	ticagrelor + aspirin (n=1,184)	Hazard ratio (95% CI)
Bleeding endpoints			
BARC type 2, 3, or 5	48 (4.2)	90 (7.7)	0.54 (0.38-0.76)
BARC type 3 or 5	12 (1.1)	30 (2.6)	0.41 (0.21-0.80)
TIMI minor or major	48 (4.2)	90 (7.7)	0.54 (0.38-0.76)
GUSTO moderate or severe	10 (0.9)	20 (1.7)	0.51 (0.24-1.09)
ISTH major	13 (1.1)	32 (2.7)	0.41 (0.22-0.79)
Ischaemic endpoints			
Death, MI, or stroke	43 (3.8)	56 (4.9)	0.77 (0.52-1.15)
CV death, MI, or ischaemic stroke	41 (3.6)	55 (4.8)	0.75 (0.50-1.12)
All-cause death	10 (0.9)	17 (1.5)	0.59 (0.27-1.29)
CV death	9 (0.8)	17 (1.5)	0.53 (0.24-1.20)
Myocardial infarction	33 (2.9)	40 (3.5)	0.83 (0.52-1.32)
Ischaemic stroke	1 (0.1)	2 (0.2)	0.50 (0.05- 5.56)
Def/prob stent thrombosis	5 (0.4)	9 (0.8)	0.56 (0.19-1.67)
Definite stent thrombosis	5 (0.4)	9 (0.8)	0.56 (0.19-1.67)

BARC, Bleeding Academic Research Consortium; CI, confidence interval; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

LAAO Watchman registry data positive

Real-world evidence from the National Cardiovascular Data Registry (NCDR) Left Atrial Appendage Occlusion (LAAO) registry of patients implanted percutaneously with the Watchman device reveals a high implant success rate in addition to a low rate of in-hospital complications.

Dr James Freeman (Yale University School of Medicine, USA) presented the observational, non-randomised, post-approval analysis from the registry of periprocedural outcomes of the Watchman LAAO device, which includes data from >38,000 patients, [1]. The study was simultaneously published by the *Journal of the American College of Cardiology* [2].

The approval of LAAO to prevent stroke in patients with atrial fibrillation (AF) was established in 2015, based on 2 randomised trials, yet post-approval clinical data are limited [3,4]. To qualify for Medicare reimbursement in the USA, hospitals have been required to report all Watchman device procedures to the NCDR LAAO registry, with the intent to capture patient, hospital, and physician characteristics and in-hospital adverse event rates.

Table: Patient characteristics LAAO registry compared with other trials [1]

Characteristics	LAAO Registry 2016-2018 (n=38,158)	Protect AF Trial 2005-2008 (n=462 intervention arm)	PREVAIL Trial 2011-2013 (n=268 intervention arm)	EWOLUTION Registry 2013-2015 (n=1,025)
Demographics				
Age, years	76.1 ± 8.1	71.7 ± 8.8	74.0 ± 7.4	73.4 ± 8.9
Women	15,672 (41.1)	137 (29.6)	87 (32.3)	411 (40.1)
Race				
White/European	35,345 (92.6)	425 (91.8)	253 (94.1)	NA
Black/African American	1,768 (4.6)	6 (1.3)	6 (2.2)	NA
Asian/Pacific Islanders	670 (1.7)	5 (1.1)	1 (0.4)	NA
Hispanic ethnicity	138 (0.4)	25 (5.4)	6 (2.2)	NA
Medical history				
CHA_2DS_2-VASc score	4.6 ± 1.5	3.4 ± 1.5	3.8 ± 1.2	4.5 ± 1.6
Prior ischaemic stroke/transient ischaemic attack	11,389 (29.9)	82 (17.7)	74 (27.5)	312 (30.5)
Prior congestive heart failure	14,266 (37.4)	124 (26.8)	63 (23.4)	350 (34.2)
Prior diabetes mellitus	14,396 (37.7)	113 (24.4)	91 (33.8)	304 (29.7)
Prior hypertension	35,148 (92.1)	413 (89.2)	238 (88.5)	885 (86.4)
HAS-BLED score	3.0 ± 1.1	NA	NA	2.3 ± 1.2
Prior intracranial bleeding	4,550 (11.9)	NA	NA	155 (15.1)
Prior clinically relevant bleeding	26,466 (69.4)	NA	NA	396 (38.7)

Compared with the original trials, the registry cohort was older (mean patient age was 76.1±8.1 years) and had more comorbidities (see Table). Furthermore, the mean CHA_2DS_2-VASc score for AF stroke risk determination was 4.6±1.5 (approximately 10-12% risk of stroke), and the mean HAS-BLED score for major bleeding was 3.0±1.1.

Hospitals performed a median number of 30 annual LAAO procedures, with a median of 12 per physician. Procedures were cancelled or aborted in 7% of cases; among cases in which a device was deployed, 98.1% were implanted with <5 mm leak. Major in-hospital adverse event rates were lower when compared to the original trials, occurring in 2.16% of patients, with the most common complications being pericardial effusion requiring intervention (1.39%) and major bleeding (1.25%), while stroke (0.17%) and death (0.19%) were rare.

The registry suggests that this procedure and device are safe and effective in managing stroke risk in a real-world setting with heterogeneous patient characteristics and comorbidities. However, without a control group, Dr Freeman cautioned, unmeasured confounders could influence the interpretation. For example, the adverse events reporting relies on site-reported data, which may be under-reported. Consequently, adverse events may be underestimated in this registry. However, overall, these registry data support the clinical trial data.

1. Freeman JV, et al. Abstract 409-10. ACC/WCC 28-30 March 2020.
2. Freeman JV, et al. J Am Coll Cardiol. 2020;75(13):1503-1518.
3. Holmes DR Jr, et al. [Published correction appears in J Am Coll Cardiol. 2014 Sep 16;64(11):1186]. J Am Coll Cardiol. 2014;64(1):1–12.
4. Reddy VY, et al. Circulation. 2013;127(6):720–729.

Genetics and Prevention

Homozygous FH responds to alirocumab

In the ODYSSEY HoFH study, alirocumab significantly reduced low-density lipoprotein cholesterol (LDL-C) in the largest randomised, placebo-controlled clinical trial looking at lipid-lowering in adults with homozygous familial hypercholesterolaemia (HoFH) to date.

The primary objective of the study, presented by Prof. Dirk Blom (University of Cape Town, South Africa), was to demonstrate the reduction of LDL-C after subcutaneous alirocumab every 2 weeks compared with placebo after 12 weeks of treatment [1].

The double-blinded trial included 69 adults with genetically confirmed HoFH randomised 2:1 to the PCSK9 inhibitor alirocumab dosed at 150 mg every 2 weeks or placebo while on concurrent intensive background lipid lowering with statins and/or other agents including ezetimibe. Patients' LDL-C levels at baseline were 300 mg/dL, which is approximately 350% the target level.

Although no patient reached target LDL-C levels, the average observed reduction in LDL-C in the alirocumab arm was 63 mg/dL, which met the primary endpoint and is clinically relevant in this patient group. Of the patients on alirocumab, 57% had at least a 30% reduction in LDL at 12 weeks, and 27% had at least a 50% reduction. Alirocumab also affected other atherogenic lipids, with an approximate 20% reduction from baseline in lipoprotein(a), a 23% decrease in apolipoprotein B, and a 25% reduction in non-HDL cholesterol.

Invited discussant Prof. Raul Santos (University of São Paulo, Brazil) concluded: "Certainly, PCSK9 inhibitors should be the next step after statins and ezetimibe. They are much less expensive and more available than apheresis."

1. Blom D, et al. Abstract 411-10. ACC/WCC 28-30 March 2020.

Evinacumab significantly reduces LDL-C in homozygous FH patients

Results from a phase 3 trial demonstrated that evinacumab substantially lowered low-density lipoprotein cholesterol (LDL-C) in patients with homozygous familial hypercholesterolemia (FH), regardless of LDL receptor function. The PCSK9 inhibitor evinacumab may provide an effective treatment option for patients with homozygous FH who are unable to reach target LDL-C despite multiple conventional lipid lowering therapies with or without apheresis.

Dr Frederick Raal (University of the Witwatersrand, South Africa), who presented the results of this study, explained that evinacumab is a fully human monoclonal antibody inhibitor of ANGPTL3 and reduces LDL-C regardless of the LDL receptor [1]. Patients were eligible if they were 12 years or older and on a stable maximally tolerated lipid-lowering therapy with LDL-C ≥70 mg/dL. Participants were randomised to evinacumab 15 mg/kg IV every 4 weeks (n=43) or placebo (n=22). The primary endpoint of the study was LDL reduction from baseline at 24 weeks.

At 24 weeks, the mean LDL reduction was 47.1% with evinacumab compared with an increase of 1.9% with placebo. This translates into an average relative reduction of 49% in patients receiving evinacumab, meeting the trial's primary endpoint (P<0.001). For patients who received evinacumab, LDL reductions were similar for those with null/null alleles (n=15) and non-null/null mutations (n=28). At 24 weeks, the absolute change in LDL was 134.7 mg/dL for patients receiving evinacumab versus 2.6 mg/dL for those on placebo (difference of 132.1 mg/dL; P<0.0001).

Adverse events occurred in 65.9% of evinacumab patients versus 81% of placebo patients. Serious adverse events occurred in 4.5% of evinacumab patients while no placebo patients experienced serious adverse events. According to the researchers, events occurring in the evinacumab group were unrelated to the study drug. Several study limitations were pointed out, including the duration, particularly for conclusions regarding the long-term safety of evinacumab, which would presumably be taken life-long. The safety of evinacumab is being further assessed in the open-label treatment period of the trial.

1. Raal FJ, et al. Abstract 411-12. ACC/WCC 28-30 March 2020.

Higher serum levels of eicosapentaenoic acid correlate with reduced CV events

Compared with placebo, icosapent ethyl (IPE) 4 g/day has shown to significantly reduce first and total cardiovascular (CV) events, which is beyond what can be explained by the degree of triglyceride or other biomarker changes. It seems that serum levels of eicosapentaenoic acid (EPA) play an important role here [1].

Dr Deepak Bhatt (Brigham and Women's Hospital, USA) presented the results REDUCE-IT EPA analysis, which was based on the initial study including 8,179 patients at 473 sites in 11 countries who had elevated CV risk and were using statins. They were randomised to IPE 2 g twice daily (n=4,089) or placebo (n=4,090) with a mean duration of 4.9 years of follow-up. Results showed that icosapent ethyl 4 grams daily compared with placebo resulted in a reduced combined rate of first and subsequent non-fatal myocardial

infarction, stroke, CV death, coronary revascularisation, or hospitalisations for unstable angina by 25% and 30%, respectively. Subsequently, serum EPA levels were measured and compared with the placebo group. Patients were grouped by EPA level tertiles (<20, 20-34, >34 µg/mL) and averaged across visits.

Results suggest that higher EPA serum levels within the IPE group were strongly associated with reduced CV events; significant associations were found with all measured CV outcomes. The higher the serum EPA level was, the lower the rate of the various CV events, CV deaths, and even total mortality (P for interaction=0.91). Overall, the drug significantly increased serum EPA levels by 386% from baseline to 1-year when compared with placebo, and was sustained out to 5 years in the IPE arm (P<0.0001), while it remained more or less unchanged in the placebo arm. Docosahexaenoic acid (DHA) was also measured and its level decreased (-2.9%), suggesting that it plays no role in the observed CV benefits, which are considered to be the result of EPA. Also, patients with highest on-treatment EPA levels had a significant reduction in hospitalisations for new onset heart failure with the drug compared with placebo. Furthermore, significant associations were observed between on-treatment EPA levels and a lower risk of sudden cardiac death and cardiac arrest.

The results of this trial indicate that the use of IPE 2 g twice daily was superior to placebo in reducing triglycerides, CV events, and CV death among patients with high triglycerides and either known CV disease or those at high risk for developing it, and who were already on statin therapy with relatively well-controlled LDL levels. Dr Bhatt concluded that these are exciting findings that may open a new field of study and hopefully treatment options.

1. Bhatt DL, et al. Abstract 411-14. ACC/WCC 28-30 March 2020.

Quit smoking: vaping + counselling helps

Vaping on top of counselling doubled short-term smoking quit rate when compared with counselling alone, and reduced the number of daily cigarettes at 12 weeks, according to data from a randomised controlled trial.

Presenting the first large trial to address the added value of e-cigarettes for smoking cessation, Prof. Mark J. Eisenberg (McGill University, Canada) described *The Evaluating the Efficacy of E-Cigarette Use for Smoking Cessation* E3 study [1]. The trial randomly assigned participants to receive nicotine e-cigarettes and minimal counselling, non-nicotine e-cigarettes and minimal counselling, or only minimal counselling for 12 weeks. Participants will be followed for 1 year to see which (if any) group is more likely to have quit or reduced their cigarette consumption. The primary outcome measure was the 7-day prevalence of self-reported smoking abstinence at 12 weeks, coupled with a measurement of exhaled carbon monoxide less than 11 ppm.

E3 enrolled 376 people (mean age 52 years; 53% men) at 17 sites in Canada. On average, these individuals had smoked 21 cigarettes a day for the previous 35 years. Of the participants, 91% had tried to quit smoking before but had failed. Most had already tried smoking cessation medications or behavioural therapy; about 1/3 had previously tried e-cigarettes.

All participants received 100 minutes of smoking cessation counselling over the 12-week study period. Participants self-reported their progress during 3 phone calls. Twice during the 12 weeks, they visited a clinic to undergo a breath test for carbon monoxide to confirm smoking behaviour.

In the nicotine e-cigarette group, there was a 12.8% absolute difference in 12-week quit rates compared with counselling alone (relative risk [RR] 2.4; 95% CI 1.3-4.6). The e-cigarette group without nicotine was 8.2% more likely to quit than the counselling group, which was not quite a significant difference (RR 1.9; 95% CI 1.0-3.8).

No adverse events were noted, except for 1 patient in the nicotine e-cigarette group whose pre-existing chronic pulmonary disease worsened.

Because of a manufacturing delay in the e-cigarettes, the researchers halted enrolment at 77% of their target. To compensate for the reduced statistical power, the study had to change its planned primary endpoint from 52-week follow-up, to only analysing the end of the 12-week treatment period. Six- and 12-month data are still forthcoming and will help determine the long-term effect of the intervention and whether it promotes permanent cessation.

1. Eisenberg MJ, et al. Abstract 11-08. ACC/WCC 28-30 March 2020.