ACTION-COALITION IV

Insights: Carlos Aguiar

COVID-19 patients may experience venous and arterial thromboembolic events. Elevated biomarkers of thrombosis, such as D-dimer, are associated with disease progression and higher mortality in COVID-19. ACTION-COALITION IV was designed to assess whether a strategy of therapeutic anticoagulation is superior to prophylactic anticoagulation in preventing complications in 615 adult patients hospitalized with COVID-19 and presenting elevated D-dimer at admission. Key exclusion criteria included an indication for therapeutic anticoagulation, estimated creatinine clearance <30 ml/min, platelet count <50,000/mm3, and a very high risk of bleeding. Patients were randomized to full-dose anticoagulation for 30 days with rivaroxaban 20 mg once daily (or enoxaparin 1 mg/kg twice daily if oral administration is not feasible) versus standard of care with any approved venous thromboembolism prophylaxis regimen during hospitalization only. The therapeutic anticoagulation strategy did not improve clinical outcomes and increased bleeding compared with in-hospital prophylactic anticoagulation.

ATLANTIS

Insights: Mamas Mamas

Thrombotic events following TAVR are a major concern, with subclinical leaflet thrombosis occurring in up to 15% of cases but are often asymptomatic and are not associated with transvalvular pressure gradients outside the expected range. There have been conflicting studies around the future clinical impact of subclinical leaflet thrombosis. The ATLANTIS trial was an open label RCT that randomized 1,510 people following successful TAVR for aortic stenosis to apixaban 5 mg twice a day or standard of care (single or dual antiplatelet therapy or warfarin). The primary composite endpoint of death, MI, stroke, systemic emboli, intracardiac or bioprosthesis thrombus, deep vein thrombosis or pulmonary embolism, and major bleeding over 1 year occurred in 18.4% of patients treated with apixaban and 20.1% in patients treated with standard of care (HR 0.92, 95% CI 0.73-1.16) with no significant interaction by indication for oral anti-coagulant. Interestingly, patients with no indication for oral anticoagulation had a higher rate of non-cardiovascular death in the apixaban arm (2.66% vs 0.96%; HR 2.99; 95% CI, 1.07-8.35). The ATLANTIS study suggests that there is no clinical benefit for anticoagulation for patients who do not have a formal indication, although it still remains unclear whether higher-risk patients such as those with valve-in-valve procedures or small aortic roots may benefit from such an approach.
Coronavirus disease 2019 (COVID-19) can lead to multiorgan failure, including respiratory and CV decompensation, and kidney injury, with significant associated morbidity and mortality, particularly in patients with underlying metabolic, CV, respiratory or kidney disease. Dapagliflozin, a sodium-glucose cotransporter-2 inhibitor (SGLT2i), has shown significant cardi- and renoprotective benefits in patients with type 2 diabetes, heart failure (HF) and chronic kidney disease. DARE-19 enrolled 1,250 adult patients hospitalized with COVID-19, but not critically ill on admission, and presenting at least one cardiometabolic risk factor for COVID-19 complications, who were randomized to dapagliflozin 10 mg daily or placebo. Dapagliflozin did not significantly reduce the primary efficacy endpoint consisting of time to development of new or worsened organ dysfunction during the index hospitalization, or all-cause mortality. However, dapagliflozin was well tolerated, with numerically fewer serious adverse events (including acute kidney injury) than placebo. This finding is relevant as it does not support discontinuation of SGLT2i in a setting of COVID-19, as long as patients are monitored.

**BEST OF BASIC AND TRANSLATIONAL SCIENCE**

**Insights: Carol Ann Remme**

In the Young Investigator Awards session on Basic and Translational Science at ACC 2021, six excellent studies were presented. Rohan Bhandari (Cleveland, US) showed that targeted inhibition of gut microbiota-dependent trimethylamine N-oxide (TMAO) production promotes regression of pre-existing cardiac dysfunction and adverse ventricular remodelling in mice with renal dysfunction. Hoda Hatoum (Michigan, US) presented a novel model that links patient-specific anatomic, valve, and flow parameters to predict leaflet thrombosis following transcatheter aortic valve replacement. Using a rat model of pulmonary arterial hypertension, Sasha Prisco (Minnesota, US) demonstrated that antagonism of glycoprotein 130 signalling normalizes the microtubule-junctophilin-2 pathway, restores t-tubule architecture, and improves right ventricular function and survival. Jacob Scherba (Durham, US) identified the epigenetic chromatin modifying enzyme BRG1 as a novel biomarker of hypertrophic cardiomyopathy and BRG1 inhibition as a potential novel therapeutic avenue. Fotios Spyropoulos (Boston, US) presented a new rat model of heart failure employing chemogenetically induced production of reactive oxygen species, which has a distinct metabolomic and transcriptomic signature. Finally, Carla Valenzuela Ripoll (Saint Louis, US) showed that dapagliflozin attenuates endothelial leak in a murine lipopolysaccharide-induced model of systemic inflammation via an apolipoprotein-M dependent pathway.

**DARE-19**

**Insights: Carlos Aguiar**

Coronavirus disease 2019 (COVID-19) can lead to multiorgan failure, including respiratory and CV decompensation, and kidney injury, with significant associated morbidity and mortality, particularly in patients with underlying metabolic, CV, respiratory or kidney disease. Dapagliflozin, a sodium-glucose cotransporter-2 inhibitor (SGLT2i), has shown significant cardi- and renoprotective benefits in patients with type 2 diabetes, heart failure (HF) and chronic kidney disease. DARE-19 enrolled 1,250 adult patients hospitalized with COVID-19, but not critically ill on admission, and presenting at least one cardiometabolic risk factor for COVID-19 complications, who were randomized to dapagliflozin 10 mg daily or placebo. Dapagliflozin did not significantly reduce the primary efficacy endpoint consisting of time to development of new or worsened organ dysfunction during the index hospitalization, or all-cause mortality. However, dapagliflozin was well tolerated, with numerically fewer serious adverse events (including acute kidney injury) than placebo. This finding is relevant as it does not support discontinuation of SGLT2i in a setting of COVID-19, as long as patients are monitored.
**FLOWER-MI**

*Insights: Stephan Achenbach*

FLOWER-MI was presented on Sunday May 16 at ACC Scientific Sessions 2021 by Etienne Puymirat from Paris. After some recent trials provided evidence to support complete revascularization in acute coronary syndromes, the FLOWER-MI trial was designed to assess whether, in patients with STEMI and multivessel disease, FFR-guided revascularization is superior to angiography-guided revascularization of non-culprit lesions. In 41 French centres experienced in FFR, FLOWER MI randomized 1171 patients with STEMI, successful culprit lesion PCI, and at least one further ≥50% stenosis, to either angiography-guided PCI or FFR-guided PCI. Non-culprit revascularizations were almost uniformly performed staged, at a mean interval of 2 days after STEMI. In the angiography guided group, 97% of patients underwent non-culprit PCI as compared to 66% when guided by FFR. The primary endpoint was a combination of mortality, MI, and urgent revascularization after one year. There was no significant difference in this endpoint, with a rate of 5.5% in the FFR group and 4.2% in the angiography guided group. Potentially, the trial was too small: event rates of around 5% after 12 months were low. Also, peri-procedural MI, which drove much of the benefit of FFR-guided revascularization in chronic coronary syndrome trials was undetectable in the STEMI setting. Also of note is the fact that in only 33% of patients, PCI was deferred based on FFR and the mean FFR of lesions that underwent revascularization was only 0.79. In fact, numerous lesions with an FFR between 0.80 and 0.85 received a stent. In the discussion however, the trialists mentioned a sub-analysis of lesions with FFR ≤0.80 only which yielded no different result. In summary, the trial was robust and failed to demonstrate an advantage of FFR-guided non-culprit PCI over angiography-guided non-culprit PCI in STEMI. It therefore does not imply any compelling need to change clinical practice or to deviate from current ESC guidelines.

**EXPLORER-HCM**

*Insights: Carlos Aguiar*

EXPLORER-HCM randomized 251 adult patients with symptomatic obstructive hypertrophic cardiomyopathy (gradient ≥50 mm Hg and NYHA class II-III) to mavacamten, a first-in-class cardiac myosin inhibitor, or placebo for 30 weeks, followed by an 8-week washout period. Mavacamten significantly improved the primary functional composite outcome of improved peak oxygen uptake and NYHA class. A secondary analysis was reported at ACC.21 focusing on patients’ health status. The Kansas City Cardiomyopathy Questionnaire (KCCQ) was administered at baseline and weeks 6, 12, 18, 30 (end of treatment), and 38 (end of study). At 30 weeks, the change in KCCQ overall summary (OS) score was greater with mavacamten than placebo (difference +9.1 [95% CI, 5.5-12.8]; p<0.0001). The proportion of patients with a very large change (KCCQ-OS ≥20 points) was 36% in the mavacamten group versus 15% in the placebo group, with an estimated absolute difference of 21% and number needed to treat of five. These gains returned to baseline after treatment was stopped. These findings support a role for mavacamten as a new strategy for improving symptoms, physical and social function, and quality of life in symptomatic obstructive hypertrophic cardiomyopathy.
**GALACTIC-HF**

**Insights: Carlos Aguiar**

Myotropes represent a new class of drugs that improve myocardial function by directly augmenting cardiac sarcomere function. The cardiac myosin activator, omecamtiv mecarbil, is the first of this class and it increases systolic function by selectively facilitating the actin-myosin interaction, increasing contractile force without altering the cardiomyocyte calcium transient. In GALACTIC-HF, omecamtiv mecarbil significantly reduced the primary composite endpoint of time-to-first HF event or CV death in 8256 patients with HF and EF ≤35%. The influence of baseline EF on the therapeutic effect of omecamtiv mecarbil was reported at ACC.21. This analysis found that EF was a strong modifier of the treatment effect of omecamtiv mecarbil on the primary composite endpoint. Patients receiving omecamtiv mecarbil had a progressively greater relative and absolute treatment effect as baseline EF decreased with a 17% relative risk reduction for the primary composite endpoint in patients with baseline EF ≤22% (HR 0.83; 95% CI, 0.73-0.95) compared to patients with EF ≥33% (HR 0.99; 95%CI, 0.84-1.16; interaction as EF by quartiles, p=0.013). These findings are consistent with the drug's mechanism of selectively improving systolic function and may present an important opportunity to improve the outcomes in a selected group of patients at greatest risk.

**HOST-EXAM**

**Insights: Mamas Mamas**

Whilst there have been numerous randomized controlled trials focused around both the optimal regime and duration of antiplatelet therapy post PCI, the question around optimal maintenance antiplatelet therapy is less clear. CAPRI has previously shown superiority of clopidogrel over aspirin in patients at high risk from cardiovascular events, but this has never been tested in patients following PCI in a large trial. The HOST-EXAM trial was an investigator-initiated, prospective, randomized, open-label, multicenter trial at 37 study sites in South Korea. Patients following a PCI at 6 to 18 months were randomized to receive either clopidogrel 75 mg once daily or aspirin 100 mg once daily for 24 months. The primary endpoint was a composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and Bleeding Academic Research Consortium (BARC) bleeding type 3 or greater, in the intention-to-treat population. 5438 patients were randomized and at 24-months follow-up, the primary outcome occurred in 152 (5.7%) patients in the clopidogrel group and 207 (7.7%) in the aspirin group (HR 0.73; 95% CI, 0.59-0.90, P=0.0035). Clopidogrel was associated with better composite secondary ischemic and major bleeding endpoints. HOST-EXAM provides us important data for treatment strategies in the more chronic phase post PCI.
**LIFE**

**Insights: Carlos Aguiar**

Sacubitril/valsartan (S/V), an angiotensin receptor-neprilysin inhibitor, significantly reduces mortality and HF hospitalization in chronic HF patients with a reduced ejection fraction (HFrEF), but data are lacking in patients with advanced HF. LIFE (LCZ696 in Hospitalized Advanced Heart Failure) was a 24-week trial that compared the safety, efficacy, and tolerability of S/V with those of valsartan in patients with advanced HFrEF. Patients had an EF ≤ 35%, New York Heart Association (NYHA) functional class IV symptoms, elevated natriuretic peptide concentration, systolic blood pressure ≥ 90 mmHg, and ≥1 objective finding of advanced HF. Following an open label run-in period with S/V (24 mg/26 mg twice daily), patients were randomized to S/V titrated to 97 mg/103 mg twice daily versus 160 mg of valsartan twice daily. The primary endpoint was the proportional change from baseline in the area under the curve for NT-proBNP levels measured through week 24. Neither treatment decreased the median NT-proBNP levels below baseline through 24 weeks, and S/V was not superior to valsartan with respect to the primary endpoint. This surprising result raises several questions that deserve further investigation.

**PARADISE MI**

**Insights: Mamas Mamas**

The PARADIGM-HF trial demonstrated that sacubitril/valsartan was superior to enalapril in reducing the risks of death and of hospitalization for heart failure in patients with NYHA class II-IV HF and an ejection fraction < 40%. The PARADISE-MI trial aimed to investigate whether sacubitril/valsartan was superior to ramipril in an acute AMI population. 5,669 patients from 495 sites in 41 countries presenting with an acute MI within the previous 0.5-7 days (mean 4.3 days) were randomized to receive either ramipril (target dose of 5 mg BD) or sacubitril/valsartan (target dose 97/103 mg BD). Inclusion criteria included LVEF ≤ 40% and / or pulmonary congestion, plus at least one additional risk factor for HF or death including diabetes, prior MI, atrial fibrillation, age ≥ 70 years, estimated glomerular filtration rate < 60 mL/min/1.73m², LVEF < 30%, Killip class ≥ III or STEMI without reperfusion. The primary endpoint of CV death, HF hospitalization, outpatient development of HF occurred in 11.9% of the sacubitril/valsartan group and 13.9% of the ramipril group (HR 0.90; 95% CI, 0.78-1.04) which was not significantly different. Interestingly, in an exploratory secondary endpoint analysis, CV death and total hospitalizations for HF, MI or stroke were reduced in the sacubitril/valsartan arm (HR 0.84; 95% CI, 0.70-1.00; P=0.045). The standard of care should remain as ramipril in this population, although it will be interesting to see whether further exploratory secondary analyses are able to identify high risk populations that may potentially benefit form sacubitril/valsartan.
PIROUETTE

Insights: Carlos Aguiar

HF with preserved EF (HFpEF) accounts for up to 50% of all HF, is associated with high morbidity and mortality, and represents a major unmet need in CV medicine. Myocardial fibrotic burden has been associated with the risk of death and HF hospitalization in HFpEF. Pirfenidone is an antifibrotic agent without hemodynamic effects. PIROUETTE was designed to test the hypothesis that pirfenidone will cause regression of myocardial fibrosis and hence improve cardiac structure and function, fluid status and quality of life in HFpEF. This phase 2 study randomized 94 patients with HF, EF ≥ 45%, and elevated natriuretic peptides, to 52 weeks of pirfenidone (target dose 2,403 mg daily) versus placebo. All patients had evidence of myocardial fibrosis defined as an extracellular matrix volume (ECV) of ≥ 27% measured using cardiac magnetic resonance. Pirfenidone was associated with a significant reduction in myocardial ECV (primary outcome) compared to placebo over 52 weeks. No differences were observed in secondary outcomes, including diastolic function, atrial size and function, 6-minute walk distance, and quality of life assessed by the KCCQ. Further studies are needed to assess the clinical effectiveness and safety of pirfenidone in HFpEF.

PRADA

Insights: Carol Ann Remme

The PRADA trial is a randomized, placebo-controlled, double-blind study, aimed at investigating whether concomitant treatment with the angiotensin receptor blocker candesartan or the β-blocker metoprolol may attenuate cardiac dysfunction associated with adjuvant therapy in patients with early breast cancer. At ACC.21, Dr Heck from Norway presented the results of an extended study of PRADA which assessed the long-term effects of this strategy. Patients (n=120) were randomized to either candesartan, metoprolol, or placebo during the course of adjuvant therapy, and left ventricular ejection fraction (LVEF) was assessed during a follow-up period of approximately 2 years. The decline in LVEF was found to be lower than 2% in all groups, indicating a limited impact of adjuvant therapy on cardiac function in these patients. Second, candesartan and metoprolol had no significant effect on LVEF during long-term follow-up suggesting that their routine use during adjuvant breast cancer treatment is not indicated in patients without any pre-existing cardiovascular disease. It remains to be seen whether there are any subgroups of patients who are at higher risk of cardiotoxicity and who may still benefit from cardioprotective treatment during adjuvant therapy, but this will require additional studies in larger cohorts.
RADIANCE HTN TRIO

Insights: Sanjay Sharma

RADIANCE HTN TRIO is a double-blind randomized study that assessed the effect of ultrasound-based renal denervation (RDN) in patients with resistant hypertension (HT). Enrollment criteria included a 24-hour ambulatory BP $\geq 135/85$ mm Hg on a fixed dose 3 drug combination regime. Patients with secondary HT (except obstructive sleep apnoea), cardiovascular or cerebrovascular event within 3 months, type 1 diabetes, uncontrolled type 2 diabetes mellitus and unsuitable renal artery anatomy were excluded. The primary endpoint was a change in daytime ambulatory systolic blood pressure (ASBP). Sixty-seven patients were randomized to RDN and 67 to a sham procedure. The demographics of both groups was similar with a mean age of 53-years-old, 80% male prevalence and median BMI of 32.7. During a two month follow-up period there was an 8 mm Hg median reduction in ASBP in the denervation group, which was 4.5 mm Hg lower than in the sham group. Furthermore, there was a median drop of 9 mm Hg in office BP and 6 mm Hg in home BP in the treatment group which was 6 mm Hg and 4 mm Hg lower than the sham group respectively. The results are promising, however longer-term efficacy and safety data is required.

RAFT-AF

Insights: Carol Ann Remme

RAFT-AF was designed to compare catheter ablation-based rhythm control compared with rate control in patients with atrial fibrillation and heart failure. A total of 411 patients were included with either reduced or preserved ejection fraction and a high burden of AF. The primary outcome was a composite of all-cause mortality and hospitalization for heart failure. After a mean follow-up of 37 months, no significant differences were observed in primary outcome between the rhythm and rate control group, but the trial was stopped early due to futility concerns and, as a result, had limited statistical power. Nevertheless, numerically there were lower event rates in the rhythm control group, particularly in patients with an ejection fraction below 45%. Rhythm control also significantly improved secondary outcome measures of heart failure in patients with reduced ejection fraction. Overall, the trial showed that ablation-based rhythm-control is not superior to rate-control in heart failure patients with atrial fibrillation. Nevertheless, the study does provide some additional indication that rhythm control may be of benefit specifically in patients with reduced ejection fraction. Studies with longer follow-up may be required to confirm these observations.
**RESCUE**

**Insights: Carlos Aguiar**

The CANTOS trial demonstrated that inflammation inhibition targeting the central interleukin (IL)-1 beta to IL-6 to C-reactive protein (CRP) pathway of innate immunity using canakinumab, a monoclonal antibody against IL-1 beta, reduces CV event rates independently of cholesterol lowering. Moreover, in CANTOS, the magnitude of clinical benefit was directly related to the magnitude of downstream IL-6 reduction achieved, suggesting that IL-6 may be the primary target for atheroprotection. The RESCUE trial addressed whether ziltivekimab, a fully human monoclonal antibody directed against the IL-6 ligand, safely and effectively reduces biomarkers of inflammation and thrombosis among 264 patients with high CV risk, high-sensitivity CRP ≥2 mg/L, and moderate to severe chronic kidney disease. RESCUE randomized participants to subcutaneous administration of placebo or ziltivekimab 7.5 mg, 15 mg, or 30 mg every 4 weeks up to 24 weeks. The primary outcome was percentage change from baseline in high-sensitivity CRP after 12 weeks of treatment with ziltivekimab compared with placebo, with additional biomarker and safety data collected over 24 weeks of treatment. At 12 weeks after randomisation, median high-sensitivity CRP levels were reduced by 77% for the 7.5 mg group, 88% for the 15 mg group, and 92% for the 30 mg group compared with 4% for the placebo group (all p<0.0001). Dose-dependent reductions were also observed for fibrinogen, serum amyloid A, haptoglobin, secretory phospholipase A2, and lipoprotein(a). Ziltivekimab was well tolerated, did not affect the total cholesterol to HDL cholesterol ratio, and there were no serious injection-site reactions, sustained grade 3 or 4 neutropenia or thrombocytopenia. A large-scale CV outcomes trial (ZEUS) will investigate the effect of ziltivekimab in patients with chronic kidney disease, increased high-sensitivity CRP, and established CV disease.

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**REHAB-HF Trial**

**Insights: Sanjay Sharma**

Exercise programmes in heart failure (HF) exclude elderly frail patients with multiple comorbidities. Such patients have the highest re-admission and mortality rates, resulting in substantial health care costs. Long admissions also reduce functional independence. This rehabilitation trial aimed to improve deficits in 4 functional components, notably strength, balance, mobility and endurance. 175 patients were randomised to the programme which started during admission and consisted of 3 out-patient visits for 12 weeks. The results were compared with 174 patients assigned to usual care. The primary aim was to assess whether the program could improve physical function within 3 months. Patients were aged 73 years old; just over 50% were female and just over 50% had HF with preserved ejection fraction. 80% were in NYHA class III or IV and 97% were pre frail or frail. At 3 months, adherence was maintained in 82%. The short performance physical battery score, a measure of physical function increased by 1.6. The 6 min walking distance improved by 34 metres. The Kansas City Cardiomyopathy Questionnaire score, which is a measure of general wellbeing, improved by 7.1 points, and there was reduced depression. There was no change in readmissions from heart failure.
SOLOIST/SCORED

Insights: Carol Ann Remme

D. Bhatt and colleagues presented a combined analysis of the previously published SOLOIST and SCORED trials as a “late breaker” at ACC.21 on Monday, May 17. SOLOIST had analyzed the impact of the SGLT2 inhibitor sotagliflozin in patients with diabetes and recent heart failure hospitalization, and SCORED had investigated the impact of sotagliflozin in patients with diabetes and chronic kidney disease. Both had shown a robust reduction in heart failure events. By combining the two trials, 11784 patients became available and the investigators analyzed the effect of sotagliflozin versus placebo on outcomes in patients with reduced ejection fraction (EF less than 40%), mid-range EF (40 to 50%) and what is called “preserved EF” (HFpEF, EF of 50% or more). They demonstrated a significant benefit of sotagliflozin on the combined endpoint of cardiovascular death, heart failure hospitalization, and urgent heart failure visits in all EF strata, including patients with EF > 50%, and patients with HFpEF (clinical heart failure and EF > 50%). In sub-analyses, benefits were shown for female patients and, in an on-treatment analysis, a benefit in cardiovascular mortality. This combined analysis was performed in diabetic patients who at least either had heart failure or chronic kidney disease. As such, the results strictly only apply to individuals with diabetes and the respective concomitant conditions. All the same, they do present a first signal that a drug can be useful in heart failure with what we call “preserved EF”. And they certainly add to the constantly growing amount of data that support strong beneficial effects of SGLT2 inhibitors.

STRENGTH

Insights: Carlos Aguiar

The REDUCE-IT and STRENGTH trials reported divergent results for treatment of patients at high CV risk with high doses of n-3 fatty acids. In an attempt to explain this difference, a post hoc analysis of the STRENGTH trial was conducted to assess the association between CV outcomes and achieved levels of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), or changes in levels of these fatty acids. STRENGTH enrolled 13,078 patients at high CV risk with elevated triglyceride levels and low levels of high-density lipoprotein cholesterol who were randomized to receive 4 g daily of n-3 carboxylic acid or an inert comparator, corn oil. EPA and DHA levels were available at both baseline and 12 months after randomization in 10,382 participants. There was no association between achieved or change in level of either n-3 fatty acid and major adverse CV events (composite of CV death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization). Achieving higher EPA plasma levels was not associated with benefits on CV outcomes, nor were higher DHA levels associated with harm. These findings strengthen the concerns that the choice of comparator may have influenced the divergent results observed in the two afore-mentioned trials.
Insights: Carlos Aguiar

Patients with peripheral artery disease (PAD) are at increased risk for major adverse limb and cardiovascular (CV) events. Moreover, a history of lower extremity revascularization (LER) is associated with a significantly higher risk of adverse limb events, even years after the procedure. The VOYAGER PAD study of patients undergoing LER demonstrated that the addition of rivaroxaban 2.5 mg twice daily to aspirin versus aspirin alone reduced first primary endpoint events (acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke or CV death) by approximately 15%. A pre-specified analysis from VOYAGER PAD was reported at ACC.21, evaluating the efficacy of rivaroxaban on total (first and subsequent) limb and CV events. Among 6,564 patients there were 4,714 total vascular events, including 1,614 primary endpoint events and 3,100 other vascular events (namely peripheral revascularizations and venous thromboembolisms). These numbers testify the very high total event burden in symptomatic PAD patients who undergo LER. The most significant burden of risk is driven by vascular limb outcomes with recurrent peripheral revascularization being a particularly frequent event. Rivaroxaban reduced total primary endpoint events (HR 0.86, 95% CI 0.75-0.98; p=0.02) and total vascular events (HR 0.86, 95% CI 0.79-0.95; p=0.003).