HOSPITAL CHRONICLES 2021, 16(1): 34–42

CARDIOLOGY CORNER

Cardiology News/Literature Review/2021

Antonios Chalapas MD, PhD, FESC
Interventional Cardiology and THV Program, Athens Medical Center, Greece

CORONARY ARTERY DISEASE

1. Stable ischemic heart disease Coronary Revascularization vs. Medical Therapy Alone: A SCAI Statement

An international group of investigators performed a rigorous meta-analysis of 25 randomized clinical trials (RCTs) with an enrolment of 19,806 patients conducted between 1979 and 2020 that compared the effects of medical therapies alone with medical therapies plus revascularization in patients with stable ischemic heart disease (SIHD). Strict entry criteria were established to assure the analysis was restricted to studies involving elective, deferrable treatments of patient with SIHD. The analysis found that use of revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting surgery (CABG) was linked to a statistically important 21% reduction in late cardiovascular death. Furthermore, the magnitude of benefit appeared to increase over time. In fact, meta-regression techniques indicated that prior studies might have missed this finding principally due to short follow up. The research team performed multiple sensitivity analyses to determine how certain conditions influenced the results of the meta-analysis such as treatment in the context of a recent acute coronary syndrome, inclusion of patients requiring treatment of chronic total occlusions, or studies in which >30% of patients received CABG. Also, a few studies were judged to have a meaningful risk of bias. Exclusion of these studies did not alter the significance of the cardiovascular mortality risk reduction with an initial invasive strategy. The meta-analysis also found that an initial invasive approach was associated with a 24% reduction in spontaneous MI, which had a larger impact on survival than peri-procedural MI. In fact, the meta-analysis found that peri-procedural MI in the RCTs did not impact reported cardiac death rates. Furthermore, the meta-analysis linked a survival advantage to lower spontaneous MI rates especially among patients with extensive disease. An especially important observation from this report evolved from a meta-regression analysis which found that longer follow up was associated with increased observed benefit with an invasive strategy, and that differences in conclusions between RCTs could be explained largely by differences in follow up duration. While total MI rates may not appear to be different between treatment strategies in the short run, revascularization helps over a long timeline by more effectively lowering the risk of spontaneous MI; this observation may be overwhelmed by the effects of peri-procedural MI associated with undergoing revascularization if follow up is relatively short. Therefore, this meta-analysis indicates that coronary revascularization with PCI or CABG provides a long-term cardiovascular survival advantage over an initial conservative approach in patients with stable ischemic heart disease by lowering rates of spontaneous MI, providing a biologically plausible explanation for the observed benefit. Eliano Navarese, *Euro-PCR,* May 2021.

2. PCI vs. CABG in 3VD or UPLMD: 10-Year All-Cause Death According to Completeness of Revascularization in Patients with Three-Vessel Disease or Left Main Coronary Artery Disease: Insights from the SYNTAX Extended Survival Study

Ten-year all-cause death according to incomplete (IR) versus complete revascularization (CR) has not been fully investigated in patients with three-vessel disease (3VD) and/or left main coronary artery disease (LMCAD) undergoing percutaneous coronary intervention (PCI) vs. coronary artery bypass grafting (CABG). The SYNTAX Extended Survival Study evaluated vital status up to 10 years in patients who were originally enrolled in the SYNTAX trial. In the present sub-study, outcomes of the CABG CR group were compared with the CABG IR, PCI CR, and PCI IR groups. In addition, in the PCI cohort, the residual SYNTAX score (rSS) was used to quantify the extent of IR and to assess its association with fatal late outcome. The rSS of 0 suggests CR, whereas a rSS >0 identifies degree of IR. IR was more frequently observed in patients with PCI vs. CABG (56.6% vs. 36.8%) and more common in those with 3VD than LMCAD in both PCI (58.5% vs. 53.8%) and CABG arm (42.8% vs. 27.5%). Patients undergoing PCI with CR had no significant difference in 10-year all-cause death compared with those undergoing CABG (22.2% for PCI with CR vs. 24.3% for CABG with IR vs. 23.8% for

CABG with CR). In contrast, those with PCI and IR had a significantly higher risk of all-cause death at 10 years compared with CABG and CR (33.5% vs. 23.7%; adjusted hazard ratio [aHR]: 1.48; 95% confidence interval [CI]: 1.15–1.91). When patients with PCI were stratified according to the rSS, those with a rSS ≤8 had no significant difference in all-cause death at 10 years as the other terciles (22.2% for rSS=0 vs. 23.9% for rSS >0–4 vs. 28.9% for rSS >4–8), whereas a rSS >8 had a significantly higher risk of 10-year all-cause death as compared with those undergoing PCI with CR (50.1% vs. 22.2%; aHR: 3.40; 95% CI: 2.13–5.43). IR is common after PCI, and the degree of incompleteness was associated with 10-year mortality. If it is unlikely that complete (or nearly complete; rSS <8) revascularization can be achieved with PCI in patients with 3VD, CABG should be considered. Kuniaki Takahashi, et al. *Circulation.* 2021 12;394(10206):1325–1334. 021 May 20. doi: 10.1161/CIRCULATIONAHA.120.046289.

3. Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent versus Durable Polymer Everolimus-Eluting Stent for Patients With Acute ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. Data from BIOSTEMI trial

Two-year results from the BIOSTEMI trial*,* which were presented during a late-breaking trial session at the 2021 Cardiovascular Research Technologies meeting. In BIOSTEMI the Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent compared with durable Polymer Everolimus-Eluting Stent in patients with STEMI undergoing Primary Percutaneous Coronary Intervention. It was an investigator-initiated, multicenter, assessor-blind, randomized superiority trial using Bayesian methods. Patients with STEMI undergoing primary PCI within 24 h of symptom onset were randomized in a 1:1 ratio to receive BP-SES (n=649) or DP-EES (n=651). The primary endpoint was: target lesion failure (TLF), a composite of cardiac death, target vessel myocardial re-infarction, and clinically indicated target lesion revascularization (TLR), at 2 years. Between April 2016 and March 2018, 1,300 patients were included. Baseline characteristics were comparable between the 2 treatment groups. Follow-up through 2 years was complete in 1,221 patients (94%). At 2 years, TLF occurred in 33 patients (5.1%) treated with BP-SES and in 53 patients (8.1%) treated with DP-EES (rate ratio: 0.58; 95% Bayesian credible interval: 0.40 to 0.84; posterior probability of superiority = 0.998). The difference was driven by a lower incidence of clinically indicated TLR in patients treated with BP-SES compared with DP-EES (2.5% vs. 5.1%; rate ratio: 0.52; 95% Bayesian credible interval: 0.30 to 0.87; posterior probability of superiority = 0.993). There were no significant differences in rates of cardiac death, target vessel myocardial re-infarction, and definite stent thrombosis between the 2 treatment arms. Therefore, in patients with STEMI undergoing primary PCI, BP-SESs were superior to DP-EESs with respect to TLF at 2 years. The difference was driven by lower rates of ischemia-driven TLR. David Kandzari, 2021 Cardiovascular Research Technologies meeting.

4. Acute myocardial infarction and cardiogenic shock. Outcomes of mechanical circulatory support for acute myocardial infarction complicated by cardiogenic shock

The objective of this retrospective cohort study was to describe trends and outcomes of Impella usage in acute myocardial infarction complicated by cardiogenic shock (AMICS) treated with MCS (Impella or IABP) using real-world observational data from the National Inpatient Sample (NIS). The study included 54,480 hospitalizations (10.5%, utilizing Impella) for AMICS managed with MCS, between January 2012 and December 2017. Throughout the study period, Impella usage increased yearly to 19.9% of AMICS cases in 2017. After propensity score matching, Impella was associated with higher in-hospital mortality (odds ratio [OR] 1.74, 95% confidence interval [CI] 1.41–2.13) and transfusions (OR 1.97, 95% CI 1.40–2.78) than IABP, without association with acute kidney injury or stroke. Impella use was associated with higher hospital costs (mean difference $22,416.80 [95% CI $17,029–27,804]). Impella usage for AMICS increased significantly from 2012 to 2017 and was associated with increased in-hospital mortality and costs. In addition, Impella has been associated with higher in-hospital mortality than intra-aortic balloon pump (IABP) in the Premier Healthcare Database and National Cardiovascular Data Registry. Therefore, further data are needed to support the use of MCS in acute MI combined with cardiogenic shock. Yeunjung Kim et al. *Cath. Cardiov. Intervention,* 2021 ahead of print. doi.org/10.1002/ccd.29834.

STRUCTURAL HEART DISEASE

1. Global epidemiology of valvular heart disease

This is an interesting review article discussing the global burden of Valvular heart disease (VHD), the geographical variation in the presentation and clinical management, and finally the temporal trends in the disease burden. VHD is a major contributor to loss of physical function, quality of life and longevity. The epidemiology of VHD varies substantially around the world, with a predominance of functional and degenerative disease in high-income countries, and a predominance of rheumatic heart disease in low-income and middle-income countries. Reflecting this distribution, rheumatic heart disease remains by far the most common manifestation of VHD worldwide and affects approximately 41 million people. By contrast, the prevalence of calcific aortic stenosis and degenerative mitral valve disease is 9 and 24 million people, respectively. Despite a reduction in global mortality related to rheumatic heart disease since 1900, the death rate

has remained fairly static since 2000. Meanwhile, deaths from calcific aortic stenosis have continued to rise in the past 20 years. Epidemiological data on other important acquired and congenital forms of VHD are limited. An ageing population and advances in therapies make an examination of the changing global epidemiology of VHD crucial for advances in clinical practice and formulation of health policy. The most important key points highlighted are:

- The prevalence of VHD is growing worldwide as a consequence of improved survival and the ageing population.
- Rheumatic heart disease (RHD) remains the most prevalent form of VHD and contributes to substantial premature mortality and reduced quality of life; RHD is primarily encountered in middle-income and low-income countries and specific (usually indigenous) groups in high-income countries. Calcific aortic valve disease is highly age-related, and its prevalence is increasing rapidly in high-income countries.
- Endocarditis is increasing in incidence and prevalence as a consequence of improved diagnosis and an ageing, susceptible population undergoing an increasing range and complexity of medical interventions.
- Valve abnormalities are a frequent component of congenital heart disease; bicuspid aortic valve is most commonly encountered, and its prevalence seems to be uniform across the world.
- Epidemiological information on patients who have undergone surgical or transcatheter valve intervention is limited, but this population is growing exponentially (especially in high-income countries); forecasting trends is difficult owing to the rapid evolution of these interventions and of therapies that might reduce the need for interventional treatment. Coffey S, et al. *Nat Rev Cardiol.* 2021, ahead of print. doi: 10.1038/s41569-021-00570-z.

2. Impact of Surgical and Transcatheter Aortic Valve Replacement in Low-Gradient Aortic Stenosis: a meta-analysis

Severe aortic stenosis (AS) associated with a low (LG) transaortic gradient (AVA <1cm^2, mean gradient <40mmHg) seen in up to one-third of patients put forward for TAVI. LG severe AS encompasses a wide variety of pathophysiology, including classical low-flow, LG (LF-LG), paradoxical LF-LG, and normal-flow, LG (NF-LG) AS. An uncertainty exists regarding the impact of AVR on each subclass of LG AS. PubMed and Embase were queried through October 2020 to identify studies comparing survival with different management strategies (SAVR, TAVR, and conservative) in patients with LG AS. Pairwise meta-analysis comparing AVR versus conservative management and network meta-analysis comparing SAVR versus TAVR versus conservative management were performed. The aim of this study was to assess the impact of aortic valve replacement (AVR) on survival in patients with each subclass of low-gradient (LG) aortic stenosis (AS) and to compare outcomes following surgical AVR (SAVR) and transcatheter AVR (TAVR). 32 studies with a total of 6,515 patients and a median follow-up time of 24.2 months (interquartile range: 36.5 months) were included. AVR was associated with a significant decrease in all-cause mortality in classical LF-LG (hazard ratio [HR]: 0.42; 95% confidence interval [CI]: 0.36 to 0.48), paradoxical LF-LG (HR: 0.41; 95% CI: 0.29 to 0.57), and NF-LG (HR: 0.41; 95% CI: 0.27 to 0.62) AS compared with conservative management. SAVR and TAVR were each associated with a decrease in all-cause mortality in classical LF-LG (HR: 0.46 [95% CI: 0.38 to 0.55] and 0.49 [95% CI: 0.37 to 0.64], respectively), paradoxical LF-LG (HR: 0.42 [95% CI: 0.28 to 0.65] and 0.42 [95% CI: 0.25 to 0.72], respectively), and NF-LG (HR: 0.40 [95% CI: 0.21 to 0.77] and 0.46 [95% CI: 0.26 to 0.84], respectively) AS compared with conservative management. No significant difference was observed between SAVR and TAVR. In all subclasses of LG AS, AVR was associated with a significant decrease in all-cause mortality regardless of surgical or transcatheter approach. Ueyama H, et al. *JACC Cardiovasc Interv.* 2021 Apr 28;S1936-8798(21)00813-X. doi: 10.1016/j.jcin.2021.04.038.

3. TAVI and low surgical risk patients: 8-year outcomes for patients with aortic valve stenosis at low surgical risk randomized to transcatheter vs. surgical aortic valve replacement. Data from the Notion Trial

In the NOTION trial, patients with symptomatic severe aortic valve stenosis were randomized to TAVI or SAVR. Clinical status, echocardiography, structural valve deterioration, and failure were assessed using standardized definitions. In total, 280 patients were randomized to TAVI (n=145) or SAVR (n=135). Baseline characteristics were similar, including mean age of 79.1±4.8 years and a mean STS score of 3.0±1.7%. At 8-year follow-up, the estimated risk of the composite outcome of all-cause mortality, stroke, or myocardial infarction was 54.5% after TAVI and 54.8% after SAVR (P=0.94). The estimated risks for all-cause mortality (51.8% vs. 52.6%; P=0.90), stroke (8.3% vs. 9.1%; P=0.90), or myocardial infarction (6.2% vs. 3.8%; P=0.33) were similar after TAVI and SAVR. The risk of structural valve deterioration was lower after TAVI than after SAVR (13.9% vs. 28.3%; P=0.0017), whereas the risk of bioprosthetic valve failure was similar (8.7% vs. 10.5%; P=0.61). Therefore, in patients with severe aortic valve stenosis at low surgical risk randomized to TAVI or SAVR, there were no significant differences in the risk for all-cause mortality, stroke, or myocardial infarction, as well as the risk of bioprosthetic valve failure after 8 years of follow-up. Troels Højsgaard Jørgensen, et al. *European Heart Journal* (2021) 00, 1–8. doi:10.1093/eurheartj/ehab375.

4. Mitral Surgery After Transcatheter Edge-to-Edge Repair: Society of Thoracic Surgeons Database Analysis

As the number of Transcatheter edge-to-edge (TEER) mitral repair progressively increase passing to younger patients often may complicated by residual or recurrent mitral regurgitation. Therefore, an increasing need for surgical re-intervention has been reported, but operative outcomes are not well defined. The Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database was used to identify 524 adults who underwent mitral surgery after TEER between July 2014 and June 2020. Emergencies (5.0%; n=26), previous mitral surgery (5.3%; n=28), or open implantation of transcatheter prostheses (1.5%; n=8) were excluded. The primary outcome was 30-day or in-hospital mortality. In the study cohort of 463 patients, the median age was 76 years (interquartile range [IQR]: 67 to 81 years), median left ventricular ejection fraction was 57% (IQR: 48% to 62%), and 177 (38.2%) patients had degenerative disease. Major concomitant cardiac surgery was performed in 137 (29.4%) patients: in patients undergoing isolated mitral surgery, the median STS-predicted mortality was 6.5% (IQR: 3.9% to 10.5%), the observed mortality was 10.2% (n=23 of 225), and the ratio of observed to expected mortality was 1.2 (95% confidence interval [CI]: 0.8 to 1.9). Predictors of mortality included urgent surgery (odds ratio [OR]: 2.4; 95% CI: 1.3 to 4.6), non-degenerative/unknown etiology (OR: 2.2; 95% CI: 1.1 to 4.5), creatinine of >2.0 mg/dl (OR: 3.8; 95% CI: 1.9 to 7.9) and age of >80 years (OR: 2.1; 95% CI: 1.1 to 4.4). In a volume outcomes analysis in an expanded cohort of 591 patients at 227 hospitals, operative mortality was 2.6% (n=2 of 76) in 4 centers that performed >10 cases versus 12.4% (n=64 of 515) in centers performing fewer (p=0.01). The surgical repair rate after failed TEER was 4.8% (n=22) and was 6.8% (n=12) in degenerative disease. In conclusion, this study indicates that mitral repair is infrequently achieved after failed TEER, which may have implications for treatment choice in lower-risk and younger patients with degenerative disease. These findings should inform patient consent for TEER, clinical trial design, and clinical performance measures. Joanna Chikwe, et al. *J Am Coll Cardiol.* 2021 Jul 6;78(1):1–9. doi: 10. Mitral regurgitation and MITRA-FR vs. COAPT:1016/j.jacc.2021.04.062. Epub 2021 May 1.

5. Incidence and clinical relevance of persistent iatrogenic atrial septal defect after percutaneous mitral valve repair

Percutaneous mitral valve repair (PMVR) requires transseptal puncture resulting in iatrogenic atrial septal defect (iASD). The impact of persistent iASD was previously investigated. However, data were diverse and inconclusive. 53 patients who underwent MITRACLIP were retrospectively included. Based on the presence of iASD in transesophageal echocardiography (TEE) after 6 months, patients were divided in two groups (iASD group vs. non-iASD group). Impact of iASD on outcome at 6 months and at two years was evaluated. Persistent iASD was detected in 62% of patients. Independent predictors for persistent iASD were female gender and reduced left ventricular ejection fraction. At 6-month follow-up, there was no difference in reduction of NYHA class (ΔNYHA = 1.3±1 in iASD group vs. 0.9±1 in non-iASD group, p=0.171). There was a significant difference in right ventricular end diastolic diameter (RVEDd) (42±8 mm in iASD-group vs. 39±4 mm in non-iASD group, p=0.047). However, right ventricular systolic function (TAPSE) (14±7 mm in iASD group vs. 16±8 mm in non-iASD group, p=0.176) and right ventricular systolic pressure (RVSP) (40±12 mmHg in iASD group vs. 35±10 mmHg in non-iASD group, p=0.136) were still comparable between both groups. At 2 years follow-up, there was no significant difference regarding rate of rehospitalization (24% vs 15%, p=0.425) or mortality (12% vs 10%, p=0.941) between both groups. Incidence of persistent iASD after MITRACLIP is markedly high. Despite the increase in right ventricular diameter in patients with persistent iASD, these patients were not clinically compromised compared to patients without persistent iASD. Mhd Nawar Alachkar, et al. *Sci Rep.* 2021 Jun 16;11(1):12700. doi: 10.1038/s41598-021-92255-3.

6. European position paper on the management of patients with patent foramen ovale. Part II - Decompression sickness, migraine, arterial deoxygenation syndromes and select high-risk clinical conditions

Patent foramen ovale (PFO) is implicated in the pathogenesis of a number of medical conditions. However, the high prevalence of a PFO in the normal population (20-30%) implies that PFO can often be an incidental finding rather than a causative one. To help clinicians with decision making, the European Association of Percutaneous Cardiovascular Interventions (EAPCI) Scientific Documents and Initiatives Committee invited eight European scientific societies and international experts to develop interdisciplinary position statements on the management of PFO, based on systematic assessments of the literature. A previous position paper has been published addressing issues related to cryptogenic thromboembolism. The present interdisciplinary paper reports the approach to patients with PFO and decompression sickness, desaturation syndromes, migraine, and other clinical presentations. We present the most important key points:

- *Decompression sickness (DCS):* A PFO can allow paradoxical embolization of venous gaseous emboli (VGE) when there is a rise in right heart pressures due to pulmonary gas embolism or physical exercise; however, in large PFOs with spontaneous right-to-left (R-T-L) shunts, paradoxical VGE can also occur without other provoca-

tion. No evidence-based statements can be formulated regarding PFO closure as primary prevention of DCS. In professional divers, primary screening for PFO can be foreseen in accurately selected cases with high-risk work activity, in order to evaluate the possibility of a primary percutaneous closure. Primary screening for PFO could be carried out in select military pilots performing intensive very high-altitude flight activities. However, primary PFO closure in pilots should be weighed against the possibility of disqualification from flight activity. When a PFO is an incidental finding in pilots or divers with no history of DCS, no restriction in conventional altitude flights is required, while recreational divers should be counselled by an experienced diving physician.

- *Migraine:* Factors that may suggest a pathogenic role of PFO in migraine are the presence of: 1) an aura and 2) previous stroke. Older age and small shunts through the PFO would suggest a less likely causative relationship between a PFO and migraine.
- *Pregnancy:* In asymptomatic women planning a pregnancy or during a normal pregnancy, PFO should not be systematically screened. In women with a known PFO but otherwise without coagulation diseases, no primary prevention for thrombotic systemic embolism should be foreseen.
- *Neurosurgery:* All patients scheduled for neurosurgery in the sitting position should routinely undergo screening for a PFO prior to surgery. Christian Pristipino et al. *Eur Heart J.* 2021 Apr 21;42(16):1545-1553. doi: 10.1093/eurheartj/ehaa1070.

7. Transcatheter strategies for tricuspid valve disease

The tricuspid valve (TV), which is commonly referred to as the ''forgotten valve'' has received increasing attention in recent years. Anatomical challenges include the large annulus, paucity of valve/annular calcification, adjacency of the right coronary artery, and fragility of the valve tissue. Current approaches under investigation in feasibility and early phase clinical trials include edge-to-edge repair, coaptation enhancement, annuloplasty, heterotopic caval valve implantation, and percutaneous tricuspid valve replacement. Transcatheter therapies for TVD continue to gain momentum, as evidenced by three studies presented at EuroPCR 2021: TRISCEND, TriBAND, and CLASP TR. On the whole, the early data suggest these devices are a viable treatment for tricuspid regurgitation (TR), investigators told the meeting's virtual audience, yet they also speak to the diverse approaches—annular reduction, transcatheter edge-to-edge repair (TEER), and valve replacement—aimed at addressing this clinical niche. Although recent studies have suggested potential advantages of transcatheter intervention compared with medical therapy, major questions that need to be addressed by future trials include whether earlier intervention for tricuspid regurgitation may be beneficial, and whether combined mitral and tricuspid procedures improve procedural success and clinical outcomes. We present the most recent data:

- **The TRISCEND study and Evoque device:** Evoque is a self-expanding from nitinol valve engages the leaflets, chords, and annulus to achieve secure placement. It is "designed to be delivered from a transfemoral approach over a stiff wire placed in the RV apex. The TRISCEND study enrolled 56 patients, 84% of whom were NYHA functional class III-IV and 92% had at least severe TR. In 68% the etiology of TR was functional, whereas 11% had degenerative TR and the rest had mixed/other origins. Nearly half (43%) had undergone a prior valve surgery or intervention. By 30-day follow-up all patients had a reduction of at least one TR grade and 95% had a decrease of two or more grades. Three-quarters were NYHA class I-II. There were significant improvements in 6-minute walk distance and Kansas City Cardiomyopathy Questionnaire (KCCQ) score. At 30-day follow-up, one patient (1.9%) had died of a cardiovascular cause. There were no strokes or MIs. Severe bleeding, the most-common complication, was seen in 22.6%, while 3.8% required nonelective tricuspid valve reintervention and one 1.9% had major access-site/vascular complications. Two patients died in total, for an all-cause mortality rate of 3.8%. Based on the results of this study, a pivotal trial evaluating this therapy—TRISCEND II—has been initiated. A possible limitation could be the potential of bioprosthesis degeneration and durability. Susheel Kodali. EuroPCR 2021.
- **The CLASP TR study and Pascal device:** Pascal device is similar to mitra clip leading to edge-to-edge repair of the valve. The study presented the latest results from CLASP TR for TEER with the Pascal device, showed that much like at 30 days, 6-month results in these challenging cases of tricuspid valve disease are encouraging. Pascal device received CE Mark approval for TR last year in Europe. Seventy percent of the 63 patients had started out with NYHA class III-IV at baseline. Six months later, 84% were NYHA class I-II. At baseline, TR was categorized in 69% as "massive or torrential", a proportion that dropped to 8% by 6 months. Within 6 months, 89% improved by at least one TR grade and 70% saw at least a two-grade reduction in TR. There were significant gains in quality life on the KCCQ. At 6-month follow-up, two patients each (2.3%) had died of CV causes or experienced stroke, and there were no MIs. Severe bleeding occurred in five patients (7.9%), while reintervention related to the device and major access-site/vascular complications requiring intervention were seen in one patient (1.6%) each. Other events included all-cause death (3.2%), heart failure hospitalization (6.3%), and single-leaflet device attachment assessed by a core lab (4.8%). Based on the above mentioned data in USA the CLASP-II TR pivotal trial is underway. However one can mention as a limitation the possibility of an incom-

plete solution, because usually the disease makes the gap very large in the tricuspid setting and usually you cannot eliminate TR completely and therefore there is high risk for recurrence. Mackram Eleid. Euro-PCR 2021.

- **The TriBAND study and Cardioband device:** This device is designed to reduce annular dilation, allowing better leaflet coaptation, "which is the key pathology of functional tricuspid regurgitation. Cardioband —originally developed for mitral regurgitation— was the first device, in 2018, to receive CE Mark approval for the tricuspid indication. In this single-arm, multicenter study the safety and effectiveness of the Cardioband tricuspid valve reconstruction system was evaluated. TriBAND study included 61 patients with severe and symptomatic functional TR who hadn't responded to diuretic therapy. Most (85%) were NYHA class III-IV at baseline. By discharge, 59% had reached moderate-or-lower-grade TR, with 78% showing a reduction of at least one grade. Septolateral annular diameter decreased by 20% pointing out that these changes were "accompanied by early evidence of right heart remodeling." At 30-day follow-up, there was one MI (1.6%) but no CV mortality or stroke. There was one all-cause death. The most common complications were severe bleeding, in seven patients (11.5%); major access-site/vascular complications and coronary artery injury requiring intervention, each seen in four patients (6.6%); and new need for renal replacement therapy, in two patients (3.3%). The majority (74%) were now in NYHA class I-II, and overall KCCQ score had improved by 17 points. Results showed significant reductions in annular diameter and TR severity, accompanied by early evidence of right heart remodeling and improvements in functional status and quality of life and by addressing the annulus and maintaining the native tricuspid leaflets, the Cardioband tricuspid system preserves the option for future interventions such as leaflet repair or valve replacement. Georg Nickenig et al. *Euro Intervention* 2021; Epub ahead of print. DOI: 10.4244/EIJ-D-21-00300.

ARTERIAL HYPERTENSION

Blood Pressure Levels in Young Adulthood and Midlife Stroke Incidence in a Diverse Cohort

We examined the longitudinal association between blood pressure (BP) and stroke incidence in young and middle-aged adults. BP measured during 9 examinations of the CARDIA study (Coronary Artery Risk Development in Young Adults) from 1985–1986 to 2015–2016 was used to classify participants (n=5079) according to the 2017 Hypertension Clinical Practice Guidelines. We used the highest BP obtained through the third examination (1990–1991) to define baseline BP categories; time-dependent categories (accounting for change in BP over time) were determined incorporating follow-up measurements. BP groups at ages 30 and 40 years were also defined. Stroke events were adjudicated until 2018. Mean age at baseline was 29.8 years. Stroke occurred in 100 participants. Stroke incidence was higher (P<0.001) in Black versus White participants. After adjustment with Cox models for sociodemographic and cardiovascular risk factors, stage 2 hypertension was associated with a higher risk of stroke at baseline (hazard ratio, 3.72 [95% CI, 2.12–6.54]), as a time-dependent variable (hazard ratio, 5.84 [95% CI, 3.43–9.95]), at age 30 (hazard ratio, 4.14 [95% CI, 2.19–7.82]) and at age 40 (hazard ratio, 5.59 [95% CI, 3.35–9.31]), compared with normal BP. Elevated BP and stage 1 hypertension showed more modest increases in risk. As a continuous variable, systolic BP ≥90 mmHg at age 40 was directly associated with stroke risk. These findings call for primordial prevention strategies to reduce population BP levels among young and middle-aged adults, particularly in Black young adults given ≈4-fold higher stroke incidence, including within values traditionally considered to be normal. Yarin Gerber, et al. *Hypertension* 2021 5;77(5):1683-1693. doi: 10.1161/HYPERTENSIONAHA.120.16535.

HEART FAILURE

Update on Heart Failure: Revised universal definition and classification of heart failure, 2021

In 2019 the ESC has published new guidelines on heart failure (HF). Recently, the members of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society, Writing Committee of the Universal Definition of Heart Failure, endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association and with the participation from total 14 different countries and 6 continents written this expert consensus report regarding the definitions of HF. The majority of the HF care is provided by non-cardiologists, including general practitioners, internal medicine or family medicine clinicians, hospitalists, emergency room providers, and other specialists, therefore, this report provides a universal definition of HF that is clinically relevant, simple but conceptually comprehensive, with the ability to sub-classify and to encompass stages within, with universal applicability globally, and with prognostic and therapeutic validity and acceptable sensitivity and specificity. This document proposes:

- A **universal definition of HF** as a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion.
- A **revised stages of HF** as: At risk for HF (Stage A), for patients at risk for HF but without current or prior symptoms or signs of HF and without structural or biomarker evidence of heart disease. Pre-heart failure (Stage B), for

patients without current or prior symptoms or signs of HF but evidence of structural heart disease or abnormal cardiac function, or elevated natriuretic peptide levels. HF (Stage C), for patients with current or prior symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality. Advanced HF (Stage D), for patients with severe symptoms and/or signs of HF at rest, recurrent hospitalizations despite guideline-directed medical therapy (GDMT), refractory or intolerant to GDMT, requiring advanced therapies such as consideration for transplant, mechanical circulatory support, or palliative care.

- A new and **revised classification of HF according to left ventricular ejection fraction** (LVEF), including: HF with reduced ejection fraction (HFrEF): symptomatic HF with LVEF ≤40%; HF with mildly reduced ejection fraction (HFmrEF): symptomatic HF with LVEF 41–49%; HF with preserved ejection fraction (HFpEF): symptomatic HF with LVEF ≥50%; and HF with improved ejection fraction (HFimpEF): symptomatic HF with a baseline LVEF ≤40%, a ≥10 point increase from baseline LVEF, and a second measurement of LVEF >40%. Biykem Bozkurt, et al. *European Journal of Heart Failure* 2021; 23:352–380, doi:10.1002/ejhf.2115.

ARRYTHMIAS

2021, European Heart Rhythm Association (EHRA) Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

This Practical Guide is an update of the 2018 version provided by the collaboration of members of EHRA, Heads of the National Cardiac Societies, and medical experts from the manufacturers of the NOACs and intends to provide support for safe and effective use of NOACs in every daily clinical practice. Although NOACs have demonstrated an improved efficacy/safety ratio, there are practical aspects to the proper use of the individual NOACs in many clinical situations. In addition, there are aspects of NOACs which are not well-researched, but may be relevant in clinical practice. Finally, the use of NOACs in daily clinical practice does not require monitoring of coagulation since all four phase-III RCTs comparing NOACs to VKAs have been conducted without dose adjustments based on plasma level measurements. However, assessment of the anticoagulant effect of NOACs may be desirable in certain, rare situations. Most routine coagulometers are capable of measuring NOAC plasma levels within ≤30min. Institutions should strongly consider 24/7 availability of these tests for emergency situations. We describe the use of NOACs in various clinical scenarios:

- **In patients with Mechanical Valves:** NOACS are contraindicated since they have been excluded form pivotal RCTs.
- **After bioprosthetic valve implantation or valve repair**: Traditionally, VKA have been the anticoagulants of choice during the first 1–3 months post-surgery in patients with AF. NOACs appear as a valid option after this period (given data from the pivotal phase III studies as well as the dedicated RIVER trial). Results of the latter imply that patients may be treated with a NOAC even earlier after biological valve replacement however more solid data are needed.
- **Post transcatheter aortic valve implantation** (**TAVI):** For TAVI patients, who have an indication for anticoagulation (e.g. AF), a small RCT of 157 patients comparing OAC alone with a combination of OAC + clopidogrel, indicated a benefit from OAC alone in terms of reduced bleeding without compromising ischemic events. It is important to remember that OAC (including NOAC) monotherapy may be considered after TAVI in patients with AF.
- **Patients with AF and HCM:** Patients with HCM may be eligible for NOAC therapy.
- **Patients with AF after coronary artery bypass grafting (CABG)**: In patients with concomitant AF, the combination of a single antiplatelet agent (aspiring or clopidogrel) with a NOAC appears reasonable but —in contrast to patients after percutaneous coronary intervention (PCI)/acute coronary syndrome (ACS)— randomized trial data are lacking. The combination of DAPT with a NOAC seems undesirable due to its inherent bleeding risk, but again, no prospective evidence is available.
- **After percutaneous coronary intervention (PCI)/acute coronary syndrome (ACS):** According to the current ESC guidelines for AF as well as for NSTEMI/ACS, a short course of triple therapy is recommended for up to 1 week in all patients with AF undergoing PCI. Therefore, a low threshold for prolonging triple therapy with DAPT and NOAC up to 30 days may be advisable in patients with a high thrombotic risk. In contrast, continuation of triple therapy beyond 30 days rarely seems warranted.
- **In patients with a recent ACS (<1 year) who develops new-onset AF**: ACS guidelines recommended DAPT for up to 1 year after the acute event in patients without indication for OAC, and high-risk patients might require an even longer DAPT duration. In patients with a recent acute coronary syndrome (<1 year) who develops new-onset AF NOAC should be started and the need for continuing DAPT should be carefully weighed against the increased bleeding risk. Beyond 1 month after the event, aspirin can be stopped in the majority of such patients.
- **In patients with chronic coronary syndrome or acute coronary syndrome >1 year) who develops atrial fibrillation:** Patients with a CCS developing AF should receive anticoagulation, depending on their CHA_2DS_2-VASc score (which per definition will be ≥1). A NOAC without any antiplatelet agent appears to be the preferred strategy for

these patients, based on the results of the four landmark NOAC trials and the 'Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease' (AFIRE) trial. An additional antiplatelet agent should only be considered in individual patients with a very high ischemic- and low bleeding risk.

- **In patients with atrial fibrillation who develop left ventricular (LV) thrombus after myocardial infarction**: In the absence of randomized studies, it remains uncertain whether a NOAC is effective in the treatment of LV thrombi complicating a large infarction. One observational study suggests that NOACs were associated with a higher incidence of thromboembolic events compared to VKA in (mostly non-AF) patients with a LV thrombus, while others showed a similar rate of thrombus resolution. Although residual confounding can never be excluded in these settings, VKA should be viewed as standard of care for the treatment of patients with LV thrombus until more data. If a thrombus persists during follow-up despite confirmed good adherence to the NOAC regimen an individualized management strategy is required. This may include switching to a different type of NOAC (direct thrombin inhibitor to FXa-inhibitor or vice versa) or INR-tailored VKA-therapy.
- **Old patients with AF:** This group of patients have more favorable outcomes on OAC than without, and on NOACs than on VKA.
- **Frail patients with AF:** Frailty and pre-frail states are common with advancing age and raise specific considerations regarding the risk-benefit of OAC. Frailty is associated with weight loss and a risk for deterioration in renal function. As a result, patients need to be weighed and their renal function monitored regularly to ensure safe NOAC dosing. There may be no benefit to OAC in states of severe frailty or where life expectancy is likely to be limited.
- **Patients with AF and risk for falling:** Falling per se is not a contraindication to NOAC use but precautions should be taken and modifiable bleeding risk factors assessed including, importantly, co-use of antiplatelet agents.
- **Patients with AF and low Body weight (BW):** Low BW (BMI <18.5 kg/m^2) may increase the exposure to NOACs increasing the risk of bleeding. Moreover, renal function may be overestimated in underweight patients due to their reduced muscle mass, BW ≤60 kg requires dose reduction of apixaban [in patients with age ≥80 years and/or serum Creatinine ≥1.5 mg/dl] as well as for edoxaban, whereas it is in itself not a factor for dose reduction of rivaroxaban or use of lower dose dabigatran. Both apixaban and edoxaban showed consistent efficacy and safety compared to warfarin in underweight patients when compared with the overall study population. Drug concentrations and inhibition of Factor Xa did not differ in patients with low BW (range 30–55 kg) from patients with middle body weight in an analysis from ENGAGE AF-TIMI 48. As such, both drugs may be a preferred choice for patients ≤60 kg. If therapy with a NOAC is warranted in low and very low weight individuals, measurement of trough levels may be considered to check for accumulation of the drug. However, no evidence-based recommendations can be given regarding dose reduction in cases where trough levels are above the expected range.
- **Black, Hispanic, or other ethnicities patients with AF** - Black patients have been shown to have a lower incidence of AF but appear to be at higher risk of stroke. The rate of stroke in AF equally appears higher and outcomes may be worse in Hispanics vs. non-Hispanic patients. NOACs should also be the preferred therapy for Black or Hispanic patients, particularly due to the oftentimes difficult and suboptimal alternative of VKA therapy.
- **Patients in pregnancy:** NOACs are contraindicated.
- **Pediatric patients**. Pediatric patients have been excluded from the pivotal stroke prevention RCTs and AF with need for OAC is rare in this population. NOAC therapy should be discouraged in children but can be considered in fully grown adolescents with body weight >50 kg.
- **Patients with AF in thrombocytopenia** - There is no 'safe' cut-off above which NOAC therapy is without risk in patients with thrombocytopenia. In addition to the absolute number of platelets the dynamics of the platelet count, the underlying reason for thrombocytopenia, and special risk factors (including the likelihood of dysfunctional platelets as well as other coagulation abnormalities) need to be considered. As a general advice – PLT <20.000/µl -> Avoid NOAC therapy, PLT >50.000/µl. -> proceed with caution and close monitoring, PLT >20.000/µl and <50.000/µl. -> proceed with very caution, close monitoring and half dose Given the lack of a large evidence base for guidance the decision for NOAC treatment needs to follow an individualized, team-based approach including the patient and his/her needs and expectations (shared decision-making).
- **NOACs and heparin-induced thrombocytopenia (HIT)**: Thrombocytopenia is an uncommon side effect of NOACs, but isolated cases have been reported. In HIT ± thrombosis (HIT/HITT) there is growing evidence that NOACs are not recognized by pre-existing HIT antibodies, do not complex with platelet factor 4 and do not cause platelet aggregation. NOAC therapy may hence constitute a viable less expensive and easier to administer alternative to parenteral heparin substitutes (e.g. argatroban, fondaparinux) especially if the latter are not available or are deemed unsuitable.
- **Anticoagulant therapy and malignancy:** Overall, NOACs may appear as a valid option in patients with AF and malignancy based on the few available data from RCTs as well as using extrapolations from cancer-related VTE treatment. Antithrombotic therapy in patients with AF

suffering from a malignancy needs a dedicated interdisciplinary team approach. Especially when myelosuppressive chemotherapy or radiation therapy is planned, temporary dose reduction or cessation of NOAC therapy needs to be evaluated, taking into account full blood counts including platelets, renal/liver function, and physical signs of bleeding. Gastric protection with PPI or H2 blockers should be considered in all such patients.

- **Post kidney transplantation** - there are no data on the use of NOACs in AF patients. Jan Steffel et al. *Europace* 2021; 00:1–65. doi:10.1093/europace/euab065.

PREVENTIVE CARDIOLOGY

Participation in exercise-based cardiac rehabilitation is related to reduced total mortality in both men and women post myocardial infarction: results from the SWEDEHEART registry

Although, meta-analyses consistently report that participation in exercise-based cardiac rehabilitation (exCR) reduces the cardiovascular mortality, there are conflicting results regarding effects on total mortality. Presently, many eligible patients do not receive exCR in clinical practice. This is a longitudinal, observational cohort study including 20.895 patients from the SWEDEHEART registry with a mean follow-up of 4.5 years. Mortality data were obtained from the Swedish National Population Registry. Using Cox regression for proportional odds and taking a wide range of potential confounders into consideration, participation in exCR was related to significantly lower total mortality [hazard ratio (HR) 0.72, 95% confidence interval 0.62–0.83]. Exercise-based CR participation was related to lowered total mortality in most of the investigated subgroups. The risk reduction was more pronounced in women than in men (HR 0.54 vs. 0.81, respectively). The above-mentioned results support the recommendations to participate in exCR, and hence we argue that exCR should be a mandatory part of comprehensive CR programs, offered to all patients post-MI. Örjan Ekblom, et al. *European Journal of Preventive Cardiology*, https://doi.org/10.1093/eurjpc/zwab083.

CARDIAC ARREST and CARDIOPULMONARY RESUSCITATION

European Resuscitation Council Guidelines 2021: Cardiac arrest in special circumstance

The European Resuscitation Council (ERC) Cardiac Arrest in Special Circumstances guidelines based on the 2020 International Consensus on Cardiopulmonary Resuscitation Science with Treatment Recommendations. This section provides guidelines on the modifications required to basic and advanced life support for the prevention and treatment of cardiac arrest in special circumstances; specifically special causes (hypoxia, trauma, anaphylaxis, sepsis, hypo/hyperkalemia and other electrolyte disorders, hypothermia, avalanche, hyperthermia and malignant hyperthermia, pulmonary embolism, coronary thrombosis, cardiac tamponade, tension pneumothorax, toxic agents), special settings (operating room, cardiac surgery, catheter laboratory, dialysis unit, dental clinics, transportation (in-flight, cruise ships), sport, drowning, mass casualty incidents), and special patient groups (asthma and COPD, neurological disease, obesity, pregnancy). Carsten Lott, et al. *Resuscitation*. 2021;161:152–219. doi: 10.1016/j.resuscitation.2021.02.011.