Ibrahim Card Med J 2021; 11 (2): 91-96

Updates from Important Trials in Cardiology of 2022 (January – June)

F. Aaysha Cader[1], Md Minhaj Arefin[2], Sahela Nasrin[3], Saidur Rahman Khan[3]

INTRODUCTION

In this edition of the Ibrahim Cardiac Medical Journal's "Journal Scan", we present an overview of important randomised controlled trials presented at the American College of Cardiology (ACC.22) scientific sessions and Euro PCR 2022, with a brief critical appraisal.

In keeping with a critical appraisal format, each trial is introduced with its background and aims, PICO (Population, Intervention, Comparator, Outcomes) Criteria, main results and concluding remarks.

Authors' information:

[1] ***Dr. F. Aaysha Cader,*** *MD, MRCP, Assistant Professor & Associate Consultant, Department of Cardiology, Ibrahim Cardiac Hospital & Research Institute, Dhaka, Bangladesh.*

[2] ***Dr. Md Minhaj Arefin****, MD, Assistant Registrar, National Institute of Cardiovascular Diseases, Dhaka.*

[3] ***Dr. Sahela Nasrin****, MCPS, MD, Associate Professor & Consultant, Department of Cardiology, Ibrahim Cardiac Hospital & Research Institute, Dhaka, Bangladesh.*

[4] ***Dr. Saidur Rahman Khan****, MD, PhD, Professor & Senior Consultant, Department of Cardiology, Ibrahim Cardiac Hospital & Research Institute, Dhaka, Bangladesh.*

Correspondence: ***Dr. F. Aaysha Cader,*** *Mobile : 01749419893, Email: aaysha.cader@gmail.com*

TRIALS IN HEART FAILURE & CARDIOMYOPATHY

Study of Dietary Intervention under 100 mmol in Heart Failure (SODIUM-HF)

Presented at ACC 2022

Background:

Dietary restriction of sodium for patients with heart failure has been practiced, with little evidence, on the basis that it prevents fluid overload and adverse outcomes. The Study of Dietary Intervention under 100 mmol in Heart Failure (SODIUM-HF) was designed to test the efficacy of a reduction in dietary sodium on cardiovascular-related hospital admissions, emergency department visits and all-cause mortality at 12 months.[1]

PICO (Population, Intervention, Comparator, the Outcomes) Criteria:

This international, open-label, randomised, controlled trial enrolled 806 patients with chronic heart failure (NYHA functional class 2–3), and receiving optimally tolerated guideline-directed medical treatment, at 26 sites in six. Recruitment was stopped early by the Data and Safety Monitoring Board (DSMB), owing to limitations of trial operational feasibility and the impact of the COVID 19 pandemic. As such, total of 806 patients were randomly assigned (1:1) to either low sodium diet of less than 100 mmol (ie, <1500 mg/day) (intervention arm; n=397) or usual care according to local guidelines (comparator arm; n=409). The composite primary endpoint was cardiovascular-related hospital admissions, emergency department visits and all-cause mortality within 12 months. Secondary Endpoints included quality of life (by KCCQ), exercise capacity (by 6MWT) and New York Heart Association [NYHA] class.

Results:

The median age of the patients was 67 (IQR: 58–74) years with male-to-female ratio being 2:1. There were no differences in the composite primary outcome at 12 months (15% vs 17% for low-sodium vs usual care; hazard ratio [HR] 0·89 [95% CI 0·63–1·26]; p=0·53), which were assessed by

intention-to-treat (ITT). No differences were observed in the individual components of the composite either.[1] A modest effect on quality-of-life assessed by KCCQ and a very modest effect on NYHA improvement by 1 class were seen, which are of limited value given the open label design. There were also no differences in 6-minute walk distance between the low sodium and the usual care groups.[1]

Conclusion:

Dietary intervention to reduce sodium intake beyond current recommendations of 2000 mg/ day did not reduce clinical events in ambulatory patients with heart failure. These results ought to be interpreted on the background of what is a potentially underpowered trial: the estimated effect size was optimistic, fewer patients that needed were enrolled owing to premature termination of the trial and event rates were lower than anticipated.

Mavacamten as an Alternative to Surgical Septal Myectomy or Alcohol Ablation in Patients with Severely Symptomatic Obstructive Hypertrophic Cardiomyopathy (VALOR HCM trial)

Presented at ACC 2022

Background:

Mavacamten, a targeted inhibitor of cardiac myosin improves left ventricular outflow tract (LVOT) gradient, quality of life and physical functioning in obstructive HCM. Septal reduction therapies (SRT), is recommended for patients with intractable symptoms despite maximal medical therapy. As such, there is a lack of approved medical therapies for obstructive hypertrophic cardiomyopathy (HCM). VALOR-HCM, a phase 3, double-blind placebo-controlled trial was designed to assess if addition of mavacamten to maximally-tolerated medical therapy would allow severely symptomatic obstructive HCM patients to improve sufficiently such that they no longer met guideline criteria for SRT or chose not to undergo SRT for 16 weeks.[2]

PICO (Population, Intervention, Comparator, Outcomes) Criteria:

A hundred and twelve patients were randomised 1:1 to Mavacamtem vs placebo and followed up for 16 weeks. The population included patients with severely symptomatic obstructive HCM on maximally tolerated medical therapy meeting guideline criteria of eligibility for septal reduction therapy (SRT). The primary endpoint was a composite of patient decision to proceed with SRT or SRT guideline eligibility after 16 weeks. Mavacamtem dose was titrated to a maximally tolerated dose of 16 mg QD at weeks 8 and 12, using core-lab measured echo LV ejection fraction and LVOT gradient.

Results:

The study cohort had a mean age of 60 years, 49% were women, and 92% met criteria for NYHA class 3 heart failure. The trial met its primary endpoint: significantly fewer patients on Mavacamtem decided to undergo SRT or otherwise still met guideline-recommended criteria for receiving SRT, as compared with placebo (17.9% vs 76.8%; P < .0001). Mavacamten also led to a reduction in resting LVOT gradient (Difference:-33.4 mmHg [95% CI, -42.3 to -24.5]), greater improvements in NYHA class, and improved quality of life, evidenced by a greater change in KCCQ-23 clinical summary score (Difference: 9.4 mmHg [95% CI, 4.9-14.0]), as compared with placebo.[2]

Conclusion:

Mavacamten may be a reasonable option for patients with highly symptomatic obstructive HCM. Additionally, significant improvement in quality-of-life measures was also observed with mavacamten, and no serious adverse events were reported.

A Cluster Randomized Pragmatic Trial Aimed at Improving Use of Guideline Directed Medical Therapy in Our Patients with Heart Failure: PROMPT HF

Presented at ACC 2022

Background:

Guideline Directed Medical Therapy (GDMT) improves clinical outcomes in heart failure patients with reduced ejection fraction (HFrEF), however it

remains under-prescribed. The PROMPT HF trial was a pragmatic cluster-randomised comparative effectiveness trial designed to investigate if timely and targeted alerts embedded in electronic health records (EHR) systems and specifically tailored to the patient would improve GDMT prescriptions in eligible patients with HFrEF, compared to usual care.[3]

PICO (Population, Intervention, Comparator, Outcomes) Criteria:

A total of 1310 patients achieved 91% power to detect a 10% difference between study arms at α of 0.05 and an intra-cluster correlation coefficient of 0.05. Randomisation occurred at the provider level with 100 experienced providers randomised to the intervention group (alert) or usual care (No Alert), creating 100 clusters to which eligible participants were assigned on their first clinic visit. The intervention was an EHR-embedded best practice alert that triggered for the patient which notified providers of individualized GDMT recommendations and relevant clinical and laboratory parameters. The comparator arm was usual care with no alert. The primary endpoint was an increase in the number of GDMT classes prescribed at 30 days post-randomization.

Results:

The median age of patients was 72 years. Almost one-third (31%) of the patients were female and median LVEF was 32%. The study met its primary endpoint, with a 25.7% increase in the alert arm, as compared with 18.7% of the usual care arm [adjusted RR: 1.41, 95% CI (1.03, 1.93), P=0.03]. This was consistent across pre-specified subgroups. Improved secondary outcomes of increase in dose or number of GDMT classes at 30 days were also seen in the intervention arm. However, there were no significant differences in mortality, emergency department (ED) visits, or hospitalizations via the ED.[3]

Conclusion:

The authors concluded that a personalized EHR-triggered alert during office visits led to significantly higher number of HFrEF patients on appropriate GDMT. This low-cost tool can be rapidly embedded into the EHR. Although PROMPT-HF was a pragmatic trial, limitations included that it was single centre, tested exclusively in an outpatient setting, via experienced providers with outcomes assessment limited to 30 days.

TRIALS IN INTERVENTIONAL & STRUCTURAL CARDIOLOGY

Effects of Complete Revascularization on Angina-related Quality of Life in Patients with St-segment Elevation Myocardial Infarction

Presented at ACC 2022

Background:

The COMPLETE trial demonstrated that complete revascularization reduced major CV events and this led to a Class 1A recommendation for complete revascularization for STEMI in the 2021 ACC/AHA/AATS/STS/SCAI Guidelines for Coronary Artery Revascularization.[4] In this COMPLETE trial Quality of Life (QOL), a pre-specified analysis of the COMPLETE trial, the effect of complete revascularization on angina-related quality of life was evaluated.

PICO (Population, Intervention, Comparator, Outcomes) Criteria:

PICO is as for the COMPLETE trial. Patients with STEMI and multivessel coronary disease were randomized to complete revascularization (n=2,016) versus culprit-only revascularization (n=2,025). Seattle Angina Questionnaire (SAQ) was administered at baseline (randomization), 6 months and final visit (median 3 years). Endpoints were residual angina or proportion that was angina-free.

Results:

The change in Seattle Angina Questionnaire (SAQ) summary score from baseline to 3 years was 9.8 in the complete revascularization group vs. 9.6 in the culprit-only group (p = 0.003). The benefit was confined to those with a non-culprit lesion ≥80%. Residual angina at the study end was observed in 12.5% in the complete revascularization group vs. 15.7% in the culprit-only group (p = 0.013)

Conclusions:

Both a complete revascularization and a culprit-lesion-only strategy improved angina-related QOL compared with baseline. At a median follow-up of 3 years, a complete revascularization may result in an improved angina-related QOL vs culprit only PCI, translating into a number needed to treat 31 patients to prevent one patient from experiencing angina at a median follow-up of 3 years.

Edoxaban versus Dual Antiplatelet Therapy for Leaflet Thrombosis & Cerebral Thromboembolism after TAVR: The ADAPT TAVR Randomized Clinical Trial

Presented at ACC 2022

Background:

The primary objective of ADAPT TAVR was to investigate the effect of edoxaban compared to dual antiplatelet therapy (DAPT) for the prevention of leaflet thrombosis and the potential risks of cerebral thromboembolization and neurological or neurocognitive dysfunction in patients without an oral anticoagulation (OAC) indication after Transcatheter aortic valve replacement (TAVR).[5]

PICO (Population, Intervention, Comparator, Outcomes) Criteria:

The investigators randomised 229 patients who had undergone TAVR, and did not have any indications for anticoagulation to receive either edoxaban (intervention arm) or DAPT (comparator arm) for six months. Patients underwent magnetic resonance imaging (MRI) scans and neurological and neurocognitive function tests within one week of their TAVR procedure and again at six months. At six-month follow up, patients received computed tomography (CT) scans to detect subclinical leaflet thrombosis (SLT). The primary endpoint was the incidence of leaflet thrombosis on 4D-volume rendered CT at 6 months. The secondary objective was to determine the causal association of subclinical leaflet thrombosis with cerebral thromboembolism & neurological or neurocognitive dysfunction.

Results:

Among a total of 229 patients who had undergone TAVR, 10(9.8%) patients in the edoxaban group developed SLT that was detectable on the CT scan, compared with 20(18.4%) of those in the DAPT group; however, this difference was not statistically significant. Rates of death, stroke, transient ischemic attack, blood clotting in the brain and problems with thinking or memory were similar between the groups.[5]

Conclusion:

The overall incidence of leaflet thrombosis on CT scans was less frequent (8.5% difference; risk ratio of 0.53) with the edoxaban therapy than with the DAPT therapy, and it did not reach statistical significance. There was no causal association of leaflet thrombosis with temporal related changes of new cerebral thromboembolism and neurological end points.

Distal Versus Conventional Radial Access for Coronary Angiography & Intervention (DISCO RADIAL)

Presented at EURO PCR 2022

Background:

Transradial access (TRA) is the recommended access for coronary procedures owing to its increased safety and convenience. However, radial artery occlusion (RAO) is its most frequent complication, which will increasingly affect patients undergoing multiple procedures during their lifetimes. Distal radial access (DRA) has emerged as a promising alternative access to minimize RAO risk. A large-scale, international, randomized trial comparing RAO with TRA and DRA is lacking.

PICO (Population, Intervention, Comparator, Outcomes) Criteria:

DISCO RADIAL was an international, multicenter (Europe & Japan), randomized controlled trial. A total of 1307 patients with indications for percutaneous coronary procedure using a 6-F Slender sheath was randomized to DRA or TRA with

systematic implementation of best practices to reduce RAO.[6] The primary endpoint was the incidence of forearm RAO assessed by vascular ultrasound at discharge. Secondary endpoints included crossover, hemostasis time, and access site-related complications.

Results:

Overall, 657 patients underwent TRA, and 650 patients underwent DRA. Forearm RAO did not differ between groups (0.91% vs 0.31%; P = 0.29). Patent hemostasis was achieved in 94.4% of TRA patients. Crossover rate was higher with DRA than that with TRA (7.4% vs 3.5%; P = 0.002), and median hemostasis time was shorter for DRA (153 vs. 180 minutes; P < 0.001). Radial artery spasm occurred more frequently with DRA (5.4% vs 2.7%; P=0.015). Overall bleeding events and vascular complications did not differ between groups.

Conclusions:

With the implementation of a rigorous hemostasis protocol, DRA and TRA have equally low RAO rates. DRA is associated with a higher crossover rate & radial artery spasm but a shorter hemostasis time.

Comparison of Fractional Flow Reserve and Intravascular ultrasound-guided Intervention Strategy for Clinical Outcomes in Patients with Intermediate Stenosis: The FLAVOUR randomized clinical trial

Presented at ACC 2022

Background:

Coronary angiography has limitations in defining the ischemia-causing stenotic lesion, especially in cases with intermediate coronary stenosis. Fractional flow reserve (FFR) is a current standard method to define the presence of ischemia physiologically. On the other hand, intravascular ultrasound (IVUS) is the most commonly used intravascular imaging tool that can provide the lesion geometry and provide important information on plaque vulnerability. The primary aim of the FLAVOUR study was to compare the safety and efficacy of FFR-guided versus IVUS-guided percutaneous coronary intervention (PCI) strategies in patients with intermediate coronary stenosis.[7]

PICO (Population, Intervention, Comparator, Outcomes) Criteria:

The FLAVOUR trial was an international, multicenter, prospective, randomized clinical trial. It was powered for non-inferiority. A total of 1682 consecutive patients with intermediate stenosis (defined as 40-70% by angiographic visual estimation) in a major epicardial coronary artery were included. They were randomized 1:1 to receive either FFR-guided or IVUS-guided PCI strategy. Patients were treated with PCI according to the predefined criteria for revascularization; FFR ≤ 0.80 in the FFR-guided group and Minimal Lumen Area (MLA) ≤3 mm^2 (or 3 mm^2<MLA ≤4 mm^2 and plaque burden >70%) in the IVUS-guided group. The primary endpoint was the patient-oriented composite outcome (POCO), which was a composite of all-cause death, myocardial infarction, and any repeat revascularization at 24 months after randomization.

Results:

Compared with patients who were evaluated by IVUS, significantly fewer patients evaluated by FFR underwent PCI (65.3% vs. 44.4%, respectively). The primary outcome, all-cause death, myocardial infarction, or revascularization at 24 months, occurred in 8.1% of the FFR group vs. 8.5% of the IVUS group (p for noninferiority = 0.015), which was consisted across tested subgroups. Among secondary outcomes, myocardial infarction at 24 months were 1.9% of the FFR arm vs. 1.7% of the IVUS arm (p =0.70), Revascularization at 24 months was 5.7% of the FFR arm vs. 5.3% of the IVUS arm (p=0.71). There were no differences in patient-reported outcomes (Seattle Angina Questionnaire) between treatment groups.

Conclusions:

Among patients with an intermediate coronary stenosis, FFR-guided PCI was noninferior to IVUS-guided PCI. FFR-guided PCI was associated

with a similar incidence of adverse cardiovascular events at 24 months compared with IVUS-guided PCI. Patient-reported outcomes were similar between the treatment groups. These results apply to patients with non–left main native coronary artery stenoses.

Efficacy of Diltiazem to Improve Coronary Vasomotor Dysfunction in Angina and Nonobstructive Coronary Arteries: Results of the EDIT-CMD Randomized Clinical Trial

Presented at ACC 2022

Background:

Diltiazem is recommended and frequently prescribed in patients with angina and non-obstructive coronary artery (ANOCA) disease, suspected of Coronary Vasomotor Dysfunction (CVDys). However, studies substantiating its effect are this patient group are lacking. Efficacy of Diltiazem to Improve Coronary Microvascular Dysfunction (EDIT-CMD) was randomized clinical trial which evaluated the effect of diltiazem on coronary vasomotor dysfunction, as assessed by repeated coronary function testing (CFT), angina, and quality of life.[8]

PICO (Population, Intervention, Comparator, Outcomes) Criteria:

A total of 126 patients with ANOCA were included and underwent CFT. CVDys, defined as the presence of vasospasm (after intracoronary acetylcholine provocation) and/or microvascular dysfunction (coronary flow reserve: <2.0, index of microvascular resistance: ≥25), was confirmed in 99 patients, of whom 85 were randomized to receive either oral diltiazem or placebo up to 360 mg/d. After 6 weeks, a second CFT was performed. The primary end point was the proportion of patients having a successful treatment, defined as normalization of 1 abnormal parameter of CVDys and no normal parameter becoming abnormal. Secondary end points were changes from baseline to 6-week follow-up in vasospasm, index of microvascular resistance, coronary flow reserve, symptoms (Seattle Angina Questionnaire), or quality of life (Research and Development Questionnaire 36).

Results:

In total, 73 patients (38 diltiazem vs 35 placebo) underwent the second CFT. Improvement of the CFT did not differ between the groups (diltiazem vs placebo: 21% vs 29%; P=0.46). However, more patients on diltiazem treatment progressed from epicardial spasm to microvascular or no spasm (47% vs 6%; P=0.006). No significant differences were observed between the diltiazem & placebo group in microvascular dysfunction, Seattle Angina Questionnaire, or Research and Development Questionnaire.[8]

Conclusions:

This first performed randomized, placebo-controlled trial in patients with ANOCA showed that 6 weeks of therapy with diltiazem, when compared with placebo, did not substantially improve CVDys, symptoms, or quality of life, but diltiazem therapy did reduce prevalence of epicardial spasm

Effects of Alirocumab on Coronary Atherosclerosis Assessed by Serial Multimodality Intracoronary Imaging in Patients with Acute Myocardial Infarction: A Double-blind, Placebo-controlled, Randomized Trial (PACMAN AMI)

Presented at ACC 2022

Background:

The risk for cardiovascular adverse events after acute myocardial infarction (AMI) remains high despite potent medical treatment including low-density lipoprotein cholesterol (LDL-C) lowering with statins. Proprotein convertase subtilisin/kexin type 9 (PCSK9) antibodies substantially reduce LDL-C when added to statin. Alirocumab, a monoclonal antibody to PCSK9, reduces major adverse cardiovascular events (MACE) after AMI. The effect of alirocumab on coronary atherosclerosis including plaque burden, plaque composition and fibrous cap thickness in patients presenting with AMI remains unknown.

PICO (Population, Intervention, Comparator, Outcomes) Criteria:

This was a multicenter, double-blind, placebo-controlled trial. Four hundred fifty patients undergoing PCI for AMI were randomised to receive biweekly subcutaneous alirocumab (150 mg; n=148) or placebo (n=152), initiated less than 24 hours after urgent PCI of the culprit lesion, for a total of 52 weeks.[9] All patients received high-intensity statin therapy (rosuvastatin 20 mg). The primary efficacy endpoint was the change in IVUS-derived percent atheroma volume from baseline to week 52. Secondary endpoints included changes in near-infrared spectroscopy-derived maximum lipid core burden index within 4 mm, as well as optical coherence tomography-derived minimal fibrous cap thickness from baseline to week 52.[9]

Results:

The mean change in percent atheroma volume was -2.13% with alirocumab vs. -0.92% with placebo at 52 weeks. In addition, the mean change in maximum lipid core burden index within 4 mm was -79.42 in the alirocumab group compared with -37.60 in the placebo group (95% CI−70.71 - −11.77, p = 0.006), while the mean change in minimal fibrous cap thickness was 62.67 μm with alirocumab vs. 33.19 μ m with placebo (95% CI 11.75-47.55; p=0.001). All other secondary imaging outcomes showed a significant difference in favour of alirocumab. Ischaemia-driven revascularisation rates were lower in the alirocumab arm, as compared with the placebo arm (4.8% vs. 11%, p = 0.04) with no other difference in clinical events. Overall adverse event rates were low in both groups with general allergic reaction found in the alirocumab group alone (3.4% vs. 0.0%, p=0.03).[9]

Conclusions:

Following early initiation of alirocumab on top of high-intensity statin therapy in a high-risk population with AMI, we observed a 2 fold regression of coronary atherosclerosis & stabilization of high-risk plaques when compared with treatment with statins alone. These findings provide insights to support more-frequent, early and targeted use of alirocumab on top of high-intensity statin therapy in patients who have had a heart attack and are at high risk for a second one.

The ROLEX Registry (Revascularization of Left Main with Resolute ony X): A Multicenter Prospective Registry of the Resolute Onyx Stent for the Treatment of Unprotected Left Main Coronary Artery Disease

Presented at EURO PCR 2022

Background:

The primary objective of this study is to assess the safety & efficacy of the new-generation zotarolimus-eluting stent Resolute Onyx in the treatment of unprotected left main coronary artery disease (ULMCAD), both isolated or in association with two- or three-vessel coronary artery disease.[10]

PICO (Population, Intervention, Comparator, Outcomes) Criteria:

The ROLEX study was a prospective, non-randomized, European, multi-center registry. A total of 450 patients with ULMCAD with low or intermediate anatomical complexity (SYNTAX score <32), were enrolled at up to 40 European sites. One-third of patients had left main CAD plus an additional stenosis, while nearly 60% had left main disease with multivessel CAD. Patients received a PCI procedure with Resolute Onyx DES and 45% of them (200 patients) received intravascular imaging guidance. Resolute Onyx DES was chosen as the study stent because of its 4.5- & 5.0-mm diameter sizes, which expand to 6.0 mm, & its single-wire design that enables conformability to achieve optimal strut apposition. The primary endpoint was 1 year target lesion failure (TLF).

Results:

At 1 year, the primary endpoint of TLF was 5.1% in the 450 patients who underwent PCI. Rate of cardiac death, target-vessel MI, and ischemia-driven target lesion revascularization (ID-TLR) were 2.7, 2.7, & 2.0%, respectively. The rate of Stent Thrombosis

(ST) was 1.1%. Periprocedural MI occurred in 3.8% of cases. The risks of Target Lesion Failure (TLF) were significantly lower among those treated with intracoronary imaging compared with those treated with angiography alone. Among the 200 patients in whom operators used either IVUS or OCT, the rate of TLF was 2.0%, ID-TLR was 1% & ST 0.5%. In contrast, the TLF rate among 250 patients treated with angiography-guided PCI was 7.6%. In majority (98.7%) of cases, device success was demonstrated, including 53.4% with ACS, 58.5% with multivessel disease, and 30.4% with diabetes.

Conclusions:

The data of the ROLEX study supports the use of the Resolute Onyx DES in left main stenting, as well as the benefits of imaging-guided procedures in combination with a conformable DES platform to help reduce adverse events.

REFERENCES

1. Ezekowitz JA, Colin-Ramirez E, Ross H, Escobedo J, Macdonald P, Troughton R et al. Reduction of dietary sodium to less than 100 mmol in heart failure (SODIUM-HF): an international, open-label, randomised, controlled trial. *The Lancet* 2022;399:1391-1400.
2. Desai MY, Wolski K, Owens A, Naidu SS , Geske JB , Smedira NG et al. Study design and rationale of VALOR-HCM: evaluation of mavacamten in adults with symptomatic obstructive hypertrophic cardiomyopathy who are eligible for septal reduction therapy. *Am Heart J* 2021;239:80-89.
3. Ghazi L, Desai NR, Simonov M, Yamamoto Y, O'Connor KD, Riello RJ et al. Rationale and design of A cluster-randomized pragmatic trial aimed at improving use of guideline directed medical therapy in outpatients with heart failure: Pragmatic trial of messaging to providers about treatment of heart failure (PROMPT-HF). *Am Heart J.* 2022 Feb;244:107-115. doi: 10.1016/j.ahj.2021.11.010. Epub 2021 Nov 20.
4. Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyenet H al. Complete Revascularization with Multivessel PCI for Myocardial Infarction. *N Engl J Med* 2019; 381:1411-1421.
5. Park DW, Ahn JM, Kang DY, Kim KW, Koo HJ, Yanget DH et al. Edoxaban versus Dual Antiplatelet Therapy for Leaflet Thrombosis and Cerebral Thromboembolism after TAVR: The ADAPT-TAVR Randomized Clinical Trial. *Circulation* 2022;0.
6. Aminian A, Sgueglia GA, Wiemer M, Kefer J, Gasparini GL, Ruzsa Z et al. Distal Versus Conventional Radial Access for Coronary Angiography and Intervention (DISCO RADIAL). *Cardiovasc Interv*. 2022:S1936-8798(22)00897-4
7. Kang J, Koo BK, Hu X, Lee JM, Hahn JY, Yang HM et al. Comparison of Fractional Flow Reserve And Intravascular ultrasound-guided Intervention Strategy for Clinical Outcomes in Patients with Intermediate Stenosis (FLAVOUR): Rationale and design of a randomized clinical trial. *Am Heart J.* 2018;199:7-12.
8. Jansen TPJ, Konst RE, Annemiek de Vos, Paradies V, Teerenstra S, van den Oord SCH et al. Efficacy of Diltiazem to Improve Coronary Vasomotor Dysfunction in ANOCA: The EDIT-CMD Randomized Clinical Trial. *JACC Cardiovasc Imaging.* 2022:S1936-878X(22)00177-2.
9. Zanchin C, Koskinas KC, Ueki Y, Losdat S, Häner JD, Bär S et al. Effects of the PCSK9 antibody alirocumab on coronary atherosclerosis in patients with acute myocardial infarction: a serial, multivessel, intravascular ultrasound, near-infrared spectroscopy and optical coherence tomography imaging study-Rationale and design of the PACMAN-AMI trial. *Am Heart J.* 2021;238:33-44.
10. The ROLEX Registry (Revascularization of Left Main with Resolute ony X) A Multicenter Prospective Registry of the Onyx Resolute Stent for the Treatment of Unprotected Left Main Coronary Artery Disease. Clinical Trials.gov Identifier: NCT03316833.