Scholars LITERATURE

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Review Article

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A Systematic Review on Emerging Trials in Clinical Cardiology 2020-2023

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Abstract

Introduction: Several key clinical trials with valuable contributions to clinical cardiology were published or presented in 2023. The purpose of this review is to summarize these trials and reflect on their clinical context.

Methods: During 2023, the authors reviewed clinical trials presented at major cardiology conferences or events organized by American Heart Association, the European Heart Rhythm Association, American College of Cardiology, the European Society of Cardiology, TCT summit, Society for Cardiovascular Angiography, and Interventions. A wide range of trials relevant to the cardiology community were included, as well as those with the potential to change current practice.

Results: For this study, 210 key cardiology clinical trials were identified. New intravascular physiology strategies such as quantitative flow ratio was evaluated in interventional cardiology trials evaluating new generation novel stent technology. Acute coronary syndrome (ACS) trials have examined shock, out-of-hospital cardiac arrest (OOHCA), the impact of COVID-19 on ST-elevation myocardial infarction (STEMI) networks, and the optimal duration/type of antiplatelet treatment. Trials involving structural interventions included the latest data on transcatheter aortic valve replacement (TAVR) as well as mitral, tricuspid, and pulmonary valve interventions. For hypertrophic cardiomyopathy (HCM), sodium-glucose cotransporter 2 (SGLT2) inhibitors, sacubitril/valsartan and mavacamten were studied. Inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) were investigated in prevention trials. There was new data regarding atrial fibrillation screening and evidence for rhythm vs. rate control strategies in electrophysiology. A summary of key clinical cardiology trials published during the last few years is presented in this article.

Keywords: Cardiology, Coronary revascularization, Acute coronary syndrome, Antiplatelets, Atrial fibrillation, Heart failure, Lipids, Mitral clip, Transcatheter aortic valve implantation, Left atrial appendage closure

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Introduction

At major international meetings in 2023, including American Heart Association, the European Heart Rhythm Association, American College of Cardiology, the European Society of Cardiology, TCT summit, the Society for Cardiovascular Angiography, and Interventions, multiple clinical trials were presented that may influence future guidelines and current practice [1, 2]. This article provides a review of key studies in a variety of cardiovascular (CV) subspecialties including ACS, interventional and structural cardiology, electrophysiology and atrial fibrillation, heart failure (HF), and preventive cardiology [3-9].

Methods

An assessment of clinical trials presented at major international cardiology meetings in 2023 was conducted. Moreover, a literature search was carried out in PubMed, Medline, Cochrane library, and Embase, including the terms "ACS", "atrial fibrillation", "coronary prevention", "electrophysiology", "HF", and "interventional cardiology" [10-16]. Clinical trials were selected for their relevance to the cardiology community and their potential to alter clinical guidelines or guide further phase 3 research. All of the authors have completed previously completed work for this article. There have been no new studies performed on humans or animals for this article [17-22].

Interventional Cardiology: Recent Advancements

There is still an ongoing strain on global healthcare systems caused by COVID-19. It has been shown that patients with STEMI and concurrent COVID-19 infection were more likely to have complex presentations, have higher mortality rates, and are less likely to undergo primary percutaneous coronary intervention (PCI) compared to historical matched controls. An analysis of 456 STEMI patients (86 with COVID-19 positives, 160 suspected COVID-19 positives, and 210 controls) showed that COVID-19 carriers had a higher incidence of cardiogenic shock and cardiac arrest. A significant difference in mortality between those with COVID-19 who received angiography was also noted in the 47% of patients with COVID-19 who did not receive angiography [23-26].

Coronary artery lesion physiological assessment

A combination of complete revascularization and culprit lesion PCI has been found to be superior to STEMI-only PCI, with increasing evidence for multivessel PCI (either acutely, at the beginning of the

hospital stay or within 45 days, however it is unclear whether fractional flow reserve (FFR) is superior to angiography-only guidance in guiding complete revascularization) [27]. A multicenter study called FLOW-ER-MI (FLOW evaluation to guide revascularization in multi-vessel STEMI) randomized 602 STEMI patients with successful PCI to FFR or only angiography guided complete revascularization [28-32]. There was no significant difference between FFR and angiography-only guidance for the primary outcomes of death, MI, and unplanned hospitalization leading to urgent revascularizations at 10 - 12 months' time [33]. According to a sub-analysis, patients with at least one PCI had lower event rates at 1 year compared with patients who had deferred PCI. However, future randomized studies must confirm that deferring lesions judged relevant by visual estimation but with FFR > 0.80 might not be optimal in this context [34]. Prior fractional flow reserve versus angiography in multivessel evaluation trials have demonstrated that FFR is more effective than angiography alone or medical therapy alone in treating coronary artery disease (CAD) (Figure 1) [35].

Recent updates on stent technology

In the biodegradable polymer sirolimus-eluting stents (BP-SES) versus durable polymer everolimus-eluting stents (DP-EES) in patients with STEMI, ultrathin strut BP-SES were compared to DP-EES. 900 patients were randomized between BP-SES and DP-EES. The use of BP-SES at 2 years reduced target lesion failure (TLF) significantly, but the single endpoints of cardiac death, target vessel MI and definite stent thrombosis were not significantly different [37-39]. Whereas uncertainty persists regarding the mechanism of TLF reduction. Despite the fact that thinner struts are associated with improved clinical outcomes in bare metal stents, reducing strut thickness may affect drug delivery in drug-eluting stents (DES) [40]. However, to fully assess the potential benefits of thinner struts in DES, it is important to compare DES that are otherwise similar with regard to the stent design, polymer, and drug eluted. Using the prospective biomatrix alpha registry, Fazel and Grann [41] compared 400 patients who received at least one thin strut (84 - 88 meters) with cobalt chromium, biodegradable polymer, biolimus A9-eluting stents [41]. There is a significant clinical benefit in DES from thinner stunts. In certain situations, direct stenting may be beneficial. Seto, et al. randomized more than 1000 patients to the Svelte DES and Slender integrated delivery system versus conventional EE-DES in the optimize trial (optical coherence tomography compared to intravascular ultrasound and angiography to guide coronary stent implantation) [42-47]. It was found that the Svelte system displayed an excess of periprocedural troponin elevation at 1 year, but at 2 years, using a stricter, more clinically relevant definition of periprocedural MI, there was no significant difference between conventional EE-DES. Hence, minimal elevations of high-sensitive troponin in clinical trials are no longer considered clinically relevant. Patients with diabetes may benefit from amphilimus-eluting stents that were shown in the ASTUTE (amphilimus Italian multicentre registry) and INSPIRE-1 (Italian nobori stent prospective registry-1) trials to be non-inferior to zotarolimus-eluting stents due to their ability to enable higher drug diffusion across the vessel wall [48-50].

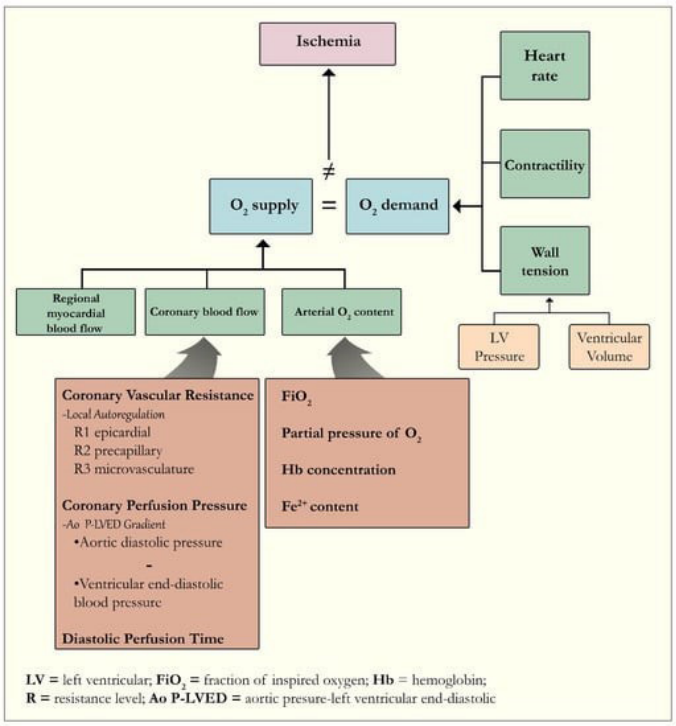

Figure 1: The coronary supply and myocardial demand relationship [36].

The advancements in structural cardiology

Transcatheter aortic valve implantation (TAVI)

In the UK, TAVI trial and placement of aortic transcatheter valves (PARTNER) 2A trial, data have firmly established that TAVI is effective in intermediate to high-risk aortic stenosis [51]. In surgical replacement and TAVI trial, self-expanding core valve TAVI was compared with surgical aortic valve replacement (SAVR) in intermediate-risk patients and the study reported non-inferiority for the endpoint of death or stroke and no difference in valve thrombosis, although higher re-intervention, more paravalvular leak, smaller effective orifice areas and higher gradients [52, 53]. It is noteworthy that only a small percentage of patients received the second-generation core valve evolut R valve, which may have underestimated the effectiveness of TAVI [54-57]. As of now, watchful waiting is the recommended strategy for asymptomatic severe as with preserved left ventricular (LV) function; however, studies such as recovery suggest that early intervention may reduce CV death rates [58].

A new procedure's economic Cost vs Benefit is becoming increasingly relevant in modern healthcare. Based on the PARTNER 3 low-risk data set, cohen performed a cost analysis of more than 1000 TAVI patients with the SAPIEN 3 device [59]. In spite of shorter procedure durations, shorter hospitalization times, and shorter intensive care unit times, the initial hospitalization cost for both TAVI and surgery was comparable, largely due to the costs associated with TAVR devices. A significant reduction in follow-up costs was present in the TAVR group at 2 years compared with SAVR. There is a possibility that the cost divergence will widen as more devices enter the market and costs fall due to competition. Efforts to streamline TAVI to reduce costs have resulted in dedicated next-day discharge pathways, such as the Vancouver 3M pathway. Due to the increasing robustness of data for TAVI, patient selection vs. surgery has become increasingly contentious. TAVI should be offered to patients over the age of 75 as opposed to SAVR according to the updated 2023 European Society Cardiology guidelines published this year. Many patients undergoing TAVI have concomitant atrial fibrillation. With the results of the popular TAVI trial in mind, the ESC now recommends oral anticoagulation without antiplatelets for patients with an underlying coagulation indication (Figure 2) [60-62].

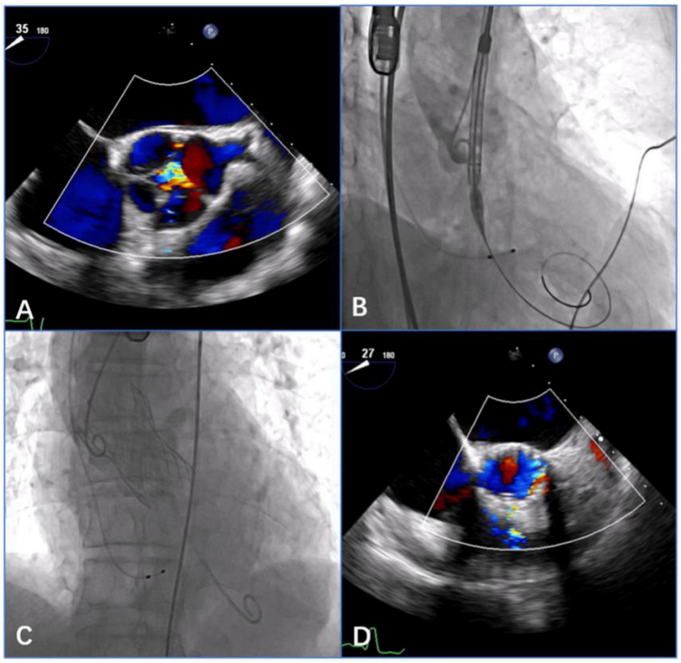

Figure 2: Procedural details of transcatheter aortic valve replacement [63].

Interventions in transcatheter mitral valve (TCMV)

The landmark COAPT trial (CV outcomes assessment of the MitraClip percutaneous therapy for HF patients with functional mitral valve regurgitation (MR)) demonstrated that TCMV repair with the abbot MitraClip was superior to medical therapy alone in moderate-to-severe or severe secondary MR refractory to medical therapy [64]. An Edwards PASCAL™ transcatheter valve repair system feasibility study sought to assess its safety and efficacy in patients with severe symptomatic MR (functional and degenerative). As a result of cytoplasmic linker-associated protein 2 (CLASP2's) positive 1-year results (92% survival and 88% free from HF hospitalizations), the 2-year outcomes showed an 80% survival rate with 84% free from HF hospitalization [65, 66]. Several feasibility studies have endorsed TCMV edge-to-edge repair; however, real-world data on procedural and device failures requiring surgical intervention is limited. The feasibility of replacing the TCMV has also been examined in recent studies [67-69]. Intrepid transfemoral transseptal TCMV replacement trial was a prospective multicenter feasibility study of the Intrepid™ TTMVR system (Medtronic) in patients with moderate-severe/severe MR at high surgical risk. Post-procedure MR was not present in 14 of the implants. It was necessary to convert one to a sternotomy. At 30 days, no deaths, strokes or re-interventions were reported. Despite its favorable results, longer follow-up is needed to validate this new technology [70].

Often, patients undergoing mitral valve surgery also have severe tricuspid regurgitation (TR), requiring double valve surgery. The rationale for intervention is less clear in patients with a dilated tricuspid valve (TV) annulus but only moderate or less regurgitation [71].

Transcatheter tricuspid and pulmonary interventions

A number of trials have investigated novel approaches to transcatheter TV intervention, including valve replacement, tricuspid edge-to-edge repair and annuloplasty ring repair. As part of the triband study, Edwards lifesciences evaluated the cardio band TV reconstruction system, which reduces annular dilation in severe functional TR and facilitates leaflet coaptation by reducing functional annular dilation. Patients with severe functional TR despite the best medical treatment participated in this multicenter prospective study [72]. There was a 1.6% all-cause mortality rate and a 19.7% major adverse events rate at 30 days, with 85% of patients achieving one grade reduction in TR and 69% achieving a TR grade of moderate or lower at 30 days [73]. 63 patients with symptomatic severe TR despite optimal medical therapy were included in CLASP TR, a single-arm, multicenter US feasibility study that evaluated the PASCAL transcatheter valve repair system. Over the course of 6 months, 89% of patients showed improvement in at least one TR grade, and 70% showed improvement in at least two TR grades. In 2 - 3% of cases, the cause of death was all-cause and in 2 - 3% of cases, it was CV. There were five patients with severe bleeding, of whom one required intervention [74]. Based on these feasibility studies, the CLASP II TR trial is currently enrolling patients to compare PASCAL with standard medical treatment. An evaluation of transfemoral TV replacement (TTVR) was conducted in TRISCEND, a single-arm, multicenter and prospective study of 56 patients with severe TR evaluating the EVOQUE TTVR system (Edwards Lifesciences, Irvine, CA, USA). TR has a mixed etiology, with 43% of patients having undergone a prior valve intervention [75-80]. At 6 months, 94% of patients remained free from hospitalization for HF, with a survival rate of 96%. This exciting new mode of transcatheter intervention awaits future data. Surgical replacement or repair of the pulmonary valve is often required in patients with significant pulmonary regurgitation and right ventricular dysfunction (RV). In many cases, these are young patients with congenital abnormalities who have already undergone open-heart surgery. Thus, novel transcatheter options are being explored [81].

An Overview of Cardiogenic Shock, Antiplatelet Therapies and ACS

ACS

In early reports, messenger RNA (mRNA) COVID-19 vaccines appeared to be associated with myocarditis. A recent review of a large Israeli healthcare database showed an estimated incidence of post-vaccine myocarditis of 2.13 cases per 100,000 patients [82]. Incidences were highest among male patients aged 16 to 29 years; however, the majority of cases were mild and only one case had cardiogenic shock. Despite these data, myocarditis is still rare and mild among most patients. It is well known that COVID is associated with myocardial injury and troponin release; however, its relative impact on survival is unknown. An observational, retrospective analysis of troponin levels was performed by Kini and her authors 72 h before and 48 h after patients tested positive for COVID-19. Patients with acutely elevated troponin as well as chronic myocardial injury had a higher mortality risk, however if patients were younger than 65 years or did not have CAD, the prognosis was worse. In spite of the well-established relationship between troponin elevation and mortality, these results suggest that troponin analysis plays a role in COVID-19 when it comes to risk stratification and prognosis. Young patients are less likely to experience MI than older individuals, and the pathophysiology is not necessarily the same. In spite of this, the diagnosis of this disease is associated with significant morbidity and mortality [83, 84].

Cardiogenic shock

In patients with OOHCA, the optimal time for angiography remains unclear. Coronary angiography after cardiac arrest previously found no difference in mortality between immediate and delayed angiography. There was only 5% evidence of a true thrombotic lesion

on angiography for patients who achieved return of spontaneous circulation without evidence of STEMI. Prior research suggests a link between air pollution and CV disease, but little is known about pollution and OOHCA [85]. An analysis conducted by several authors showed daily pollution concentrations throughout 2023 and its association was conducted. The analysis demonstrated that all pollutants examined, benzene, carbon monoxide, nitrogen dioxide, sulfur dioxide and ozone, were associated with an increased incidence of OOHCA. Further impetus is provided to improve city air quality with this association. Many centers lack unified pathways to treat refractory cardiac arrest, resulting in a high mortality rate. PRAGUE OOHCA randomized 264 patients undergoing on-scene chest compressions to a hyperinvasive approach with extracorporeal membrane oxygenation and mechanical cardiopulmonary resuscitation (CPR) as opposed to standard care. In the hyperinvasive group, resuscitation times and neurological recovery were longer, but survival rates were not different. At 180 days, patients with prolonged CPR showed a significant improvement in their cerebral performance category. The trial was terminated early because of improved secondary endpoints of neurological recovery. It may therefore be beneficial to implement invasive management for patients with prolonged downtime; however, its implementation remains a challenge (Figure 3) [86].

As part of international resuscitation guidelines, therapeutic hypothermia is recommended for the management of unconscious post cardiac arrest survivors in order to minimize the risk of death and poor neurological outcomes [2, 87].

Antiplatelets

A number of major trials were conducted in 2023 to test whether shortened dual antiplatelet therapy (DAPT) reduced bleeding risk without increasing the risk of further ischemic events. There were patients with high bleeding risk randomly assigned to 1-month DAPT or ongoing DAPT for at least 3 months standard therapy. Each patient underwent PCI with a BP-SES [88]. After 335 days, abbreviated therapy met non-inferiority for the primary outcomes of net adverse clinical events (NACE; death, MI, stroke or major bleeding) and major adverse CV events (MACVE) (death, MI or stroke). A subsequent analysis revealed that the abbreviated strategy reduced major or clinically relevant non-major bleeding significantly. In a pre-specified sub-analysis of participants with acute or recent MI, NACE and MACVE were similar to outcomes in the overall trial. Although the results are very encouraging when a biodegradable-polymer stent is used, it is not clear whether the findings apply to all stents [89, 90].

The twilight trial (Ticagrelor with or without aspirin in high-risk patients after PCI) in patients post PCI deemed at high risk of bleeding or ischemic events previously reported a reduction in bleeding, without an increase in ischemic events, associated with ticagrelor monotherapy after 3 months of DAPT. After adjusting for differences in baseline characteristics, the investigators found similar bleeding event and ischemic event risks between sexes [91-93]. Those who continued DAPT for more than 12 months vs those who stopped earlier about 350 days had a lower incidence of death, MI, or stroke at 30 months, with no significant difference in bleeding outcomes. A potential issue with ticagrelor is its potent antiplatelet properties, which can increase the risk of bleeding, particularly when surgery is urgent. A phase III trial, reverse-IT (rapid and sustained reversal of ticagrelor-intervention), evaluated bentracimab as an intravenous ticagrelor reversal agent. The platelet inhibition results were consistent among patients with major bleeding and those requiring urgent surgery. This agent may be useful in clinical settings, especially when surgery cannot be delayed until ticagrelor's antiplatelet effects subside [94].

Cardiogenic Shock Stage	Study Definition
Stage A: **A**t Risk	Neither hypotension/tachycardia nor hypoperfusion
Stage B: **B**eginning	Hypotension/tachycardia without hypoperfusion
Stage C: **C**lassic	Hypoperfusion WITHOUT deterioration
Stage D: **D**eteriorating	Hypoperfusion WITH deterioration NOT refractory shock
Stage E: **E**xtremis	Hypoperfusion WITH deterioration AND refractory shock

Figure 3: Cardiogenic shick stages

Advances in HF

HF with reduced ejection fraction (HFrEF)

Sacubitril/valsartan

In recent years, sacubitril/valsartan has become an important component of the treatment of patients with HFrEF. Paradise-MI (Prospective ARNI vs ACE inhibitors to determine superiority in reducing HF events after MI) examined sacubitril/valsartan in 5661 patients with acute MI complicated by reduced EF and/or pulmonary congestion, with 2830 patients receiving sacubitril/valsartan whereas the remaining 2831 received ramipril. In the sacubitril/valsartan group, 338 deaths were reported, in the ramipril group, 373 deaths were reported [95]. It appears that further research is necessary to identify whether there is a subgroup of patients who may benefit from this drug following a MI. As part of the LIFE study, 335 patients with HFrEF and NYHA class IV symptoms were randomized to receive sacubitril/valsartan or valsartan alone and followed up for 24 weeks [96]. There was no significant difference between the groups in terms of days alive outside hospital and without HF events, 111 in the valsartan group and 103 in the sacubitril/valsartan group ($p = 0.45$). In addition, neither group had a significant difference in NT-proBNP compared to baseline. In this trial, patients were sicker than in previous studies, and the results do suggest that this drug may be beneficial to patients at an earlier stage in their disease [97].

Novel therapies

Previously, mecamtiv mecarbil has been shown to improve cardiac performance by acting on cardiac myosin. In a recent study, it was found that Omecamtiv-Mecarbil had a greater benefit for patients with very low EF when compared with patients with higher EF in the GALACTIC-HF trial. For inclusion in the trial, all participants had HFrEF with an LVEF less than 35%, and for further analysis, their LVEF was divided into quartiles. It was found that omecamtiv mecarbil compared to placebo resulted in a 17% reduction in the risk of CV death or HF in the lower quartile [98-100]. The benefit failed to reach significance in the highest quartile. According to these results, patients with the most advanced stages of HF should consider taking this drug.

CardioMEMS implantable pulmonary artery pressure monitors did not appear to improve outcomes in patients with HF and NYHA II–IV symptoms in the GUIDE-HF study (Hemodynamic-Guided Management of HF). Among the 1022 patients enrolled in the study, 253 primary endpoint events (a composite of all-cause mortality and HF events) occurred among 497 patients in the haemodynamics-guided management group, while 289 events occurred among 503 patients in the control group. When a pre-COVID-19 impact analysis was conducted, there were some suggestions of the monitor's benefits. Although it is unclear why this occurred, it has been hypothesized that increased compliance due to the pandemic may have led to the loss of benefit [101].

SGLT2 inhibitors

Chronic HF has well-established use of SGLT2 inhibitors, but the safety of these drugs in acute HF has yet to be established. As part of the empulse trial (Effect of dapagliflozin on CV death or worsening HF in patients with chronic HFrEF), 530 patients with acute HF were randomly assigned to empagliflozin or placebo. A greater incidence of clinical benefit was associated with empagliflozin use (as measured by mortality, HF events, time to first HF event, or change in Kansas city cardiomyopathy questionnaire-total symptom score. We found no safety concerns, suggesting that SGLT2 inhibitors could be started during acute HF. Dapagliflozin was previously reported to reduce CV death and worsening HF in patients with HFrEF in the DAPA-HF trial. An analysis of dapagliflozin versus placebo showed a significant reduction in the composite of serious ventricular arrhythmia, resuscitated cardiac arrest, or sudden death. Currently, the mechanism of action is unclear, but it could be related to positive effects on cardiac metabolism, hemodynamics, and reverse remodeling [102].

HCM

According to the explorer-HCM trial (Clinical study to evaluate mavacamten (MYK-461) in adults with symptomatic obstructive HCM), mavacamten, a cardiac myosin inhibitor, significantly improved peak oxygen consumption (pVO_2) and NYHA class of symptoms in patients with HCM with significant LV outflow tract obstruction. The quality of life has now also been studied by explorer-HCM. Over a period of 30 weeks, 251 patients with NYHA class II–III symptoms and symptomatic obstructive HCM were assessed with mavacamten (n = 123) or placebo (n = 128). Compared to placebo, mavacamten produced a greater change in KCCQ-OS (overall summary) score (14.9 [SD 15.8]) at 30 weeks (difference + 9.1, 95% CI 5.5 - 12.8) and the beneficial effect disappeared after stopping the medication [2]. For this group of patients, previous efficacy data and quality of life data support its use.

Chemotherapy-related HF

Breast cancer therapy containing anthracyclines and anti-human epidermal growth factor receptor 2 antibodies, as well as radiotherapy may result in cardiac dysfunction. 120 patients were randomized to receive candesartan and metoprolol or placebo during a prada trial (Prevention of cardiac dysfunction during adjuvant breast cancer therapy). A median of 23 months follow-up showed no significant differences in LVEF between the four groups. Cardioprotective medications administered alongside breast cancer therapy are unlikely to be beneficial and should instead be tailored to each patient's risk profile [103].

Cardiac devices and arrhythmia advances

There was no screening or prevention of arrhythmias in patients with less than 35% EF prior to MI. In the SMART-MI-ICM trial (Implantable cardiac monitors in high-risk post-infarction patients with cardiac autonomic dysfunction and moderately reduced LV EF), arrhythmia screening was examined in patients with LVEFs between 35% and 50%. ICM detected more arrhythmias than control. A high percentage of serious arrhythmias in this patient group makes it unclear whether earlier detection would reduce morbidity or mortality. Permanent AF can be treated more aggressively with AVN ablation and biventricular pacing [58]. A study conducted by APAF-CRT found that this approach reduced hospital admissions for HF. AVN ablation and biventricular pacing were evaluated as a sub-study of the APAF-CRT mortality trial. In comparison of cardiac resynchronization therapy (CRT) versus pharmacological therapy was conducted in patients with severe symptomatic AF, narrow QRS, and at least one HF admission in the previous 12 months. The study showed efficacy after a median follow-up of 29 months with 11% of intervention patients reaching an endpoint compared to 29% of control patients. In patients regardless of EF, ablating and biventricular pacing were found to have similar survival benefits to medications. CRT should be preferred over RV pacing in patients undergoing AVN ablation for AF according to the updated 2023 ESC guidelines on cardiac pacing and CRT. Using His bundle pacing as a treatment option for CRT patients in whom coronary sinus leads can't be implanted was also added to the 2023 guidelines with a class 2a recommendation and level of evidence B. A subcutaneous implantable cardioverter defibrillator (S-ICD) is an alternative to a transvenous cardioverter defibrillator (ICD), which is especially useful in young or at-risk patients. A 5-year follow-up study known as effortless (Evaluation of factors impacting clinical outcome and cost effectiveness of the S-ICD) assessed complication rates and rates of inappropriate shocks among patients who received an S-ICD. A system or procedure-related complication was experienced by 10% of patients, and an inappropriate shock was received by 17% of patients. At 5 years, complication rates were relatively low for S-ICDs, with older generation devices experiencing the majority of inappropriate shocks [66].

Advances in Prevention

Hypertension

Renal artery denervation (RDN) has now been proven to be effective for the treatment of resistant hypertension, and trials are currently underway to determine its optimal role. With a blood pressure greater than 140/90 mmHg, 136 patients were randomized to either ultrasound RDN (n = 69) or a sham procedure (n = 67) in the RADIANCE-HTN TRIO study. The RDN group had a greater decrease in their ambulatory systolic blood pressure than the sham group (- 8.0 mmHg vs - 3.0 mmHg) with a median between group difference of - 4.5 mmHg (95% CI - 8.5 to - 0.3; $p = 0.022$). Further evidence suggests that RDN may be a viable option for patients with truly resistant hypertension and that ultrasound is both safe and effective when used instead of radiofrequency ablation. An examination of the combination pill containing four BP-lowering agents (irbesartan, amlodipine, indapamide, and bisoprolol) in 591 hypertensive patients who were either on no or monotherapy at enrollment was conducted in the QUARTET study (Quadruple ultra-low-dose treatment for hypertension). The quadpill treatment was given to 300 patients, while the monotherapy was given to 291 others. There was a significant difference between the quadpill group and the control group at 12 weeks with blood pressure control rates in the quadpill group being higher than the control group (76%) and systolic blood pressures in the quadpill group being lower than the control group (58%) (RR 1.30, 95% CI 1.15–1.47; p = 0.01). It may be possible to achieve better blood pressure control and simplify treatment for patients by using this approach. In treating hypertension aggressively, tolerability of medications is always considered, and it is unclear what the target blood pressure should be for older adults. As compared to the standard treatment group, the intensive treatment group had a lower mean systolic blood pressure at 1 year. The primary composite endpoints of stroke, ACS, acute HF, coronary revascularization, AF or CV death occurred significantly fewer in the intensive treatment group over a median follow-up of 3.34 years. A 95% confidence interval was found in the standard treatment group. Hypotension occurred more frequently in the intensive treatment group, but syncope, dizziness, and fracture were not significantly different, indicating the intensive control strategy was safe. Based on an analysis of the NHANES cohort, 18.5% of patients with known hypertension were co-prescribed drugs that increased blood pressure. Among these medications were

antidepressants, nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, and oestrogens, all of which have alternatives. Among patients with hypertension, it is important to review other medications in addition to antihypertensives [104].

Lipids

The PCSK9 inhibitors reduce LDL cholesterol levels and CV events significantly, but they must be administered subcutaneously until now. SPIRE-1 and SPIRE-2 are two phase 1 trials evaluating PCSK9 inhibitors. The SPIRE-1 study enrolled 16K patients with low-density lipoprotein (LDL) levels below 70 mg/dl, and the SPIRE-2 study enrolled 10K patients with high-density lipoproteins. As compared to SPIRE-1, SPIRE-2 had a higher incidence of familial hypercholesterolemia. Using daily doses of MK-0616, the agent significantly reduced plasma PCSK9 levels and LDL-C levels in 100 patients already on statin therapy for two weeks. Additionally, no significant increase in adverse events or deaths was observed in the treatment groups with the drug. Patients who require this treatment may benefit from an oral PCSK9 inhibitor, which is certainly more convenient for them. Because of immunogenicity issues, both trials were prematurely ended by the sponsor. High doses of eicosapentoic acid (EPA) have been debated for their potential to enhance CV risk in recent years. Compared to other omega-3 studies, the REDUCE-IT trial reported that this agent reduced CV events, possibly because higher serum EPA levels were achieved. It appears, however, that higher plasma levels of EPA were not associated with reduced cardiac events in a new analysis of the STRENGTH trial (Outcomes Study to assess statin residual risk reduction with EpaNova in high CV risk patients with hypertriglyceridemia). Thirteen thousand seven hundred and eighty-eight patients were randomized to receive either ω-3 carboxylic acid (CA) or an inert comparator, corn oil. A composite endpoint of CV death, MI, stroke, coronary revascularization, or unstable angina with hospital admission was associated with an adjusted hazard ratio of 0.98. As a result of these findings, questions remain regarding REDUCE-IT's mechanism of action, as well as the role of fish oils [3, 4].

Several trials evaluated the use of fixed-dose combination pills containing at least two antihypertensive agents, a statin, and sometimes aspirin, compared to either placebos or usual care. In this analysis, 18K participants were randomized to receive the polypill, and those receiving the polypill had a significantly lower incidence of CV death, MI, stroke or arterial revascularization than those receiving standard care. Participants taking aspirin preparations experienced the greatest risk reduction, but this group also had higher rates of gastrointestinal bleeding. CV risk management requires basic interventions. In another study, participants with a previous stroke or those aged 60 or older with hypertension were randomly assigned to receive either a salt substitute or regular salt. In the salt substitute group, major CV events, strokes, and deaths were lower after a mean follow-up period of 4.74 years compared with the regular group. The undertreatment of hypertension and hyperlipidemia increases CV risk, and novel ways to manage these risk factors with the help of technology need to be examined. Earlier this year, a study described an algorithm-based remote digital care programme run by pharmacists and navigators for patients with high CV risk. 92% of participants reached their BP goals and 94% achieved their LDL goals after completing the program [104]. Using this approach, CV risk profiles were improved, face-to-face contacts were limited, and physician time was reduced.

Conclusion

The purpose of this paper is to provide a summary of the key advances in cardiology trials published and presented during the year 2023 and we believe it should be of interest to both practicing clinicians and researchers.

Acknowledgements

None.

Conflict of Interest

None.

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