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REVIEW

Advances in Clinical Cardiology 2023: A Summary of Key Clinical Trials

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ABSTRACT

Introduction: Over the course of 2023, numerous key clinical trials with valuable contributions to clinical cardiology were published or presented at major international conferences. This review seeks to summarise these trials and reflect on their clinical context.

Methods: The authors collated and reviewed clinical trials presented at major cardiology conferences during 2023 including the American College of Cardiology (ACC), European Association for Percutaneous Cardiovascular Interventions (EuroPCR), European Society of Cardiology (ESC), Transcatheter Cardiovascular Therapeutics (TCT), American Heart Association (AHA), European Heart Rhythm Association (EHRA), Society for Cardiovascular Angiography and Interventions (SCAI), TVT-The Heart Summit (TVT) and Cardiovascular Research Technologies (CRT). Trials with a broad relevance to the cardiology community and those with potential to change current practice were included.

Results: A total of 80 key cardiology clinical trials were identified for inclusion. Key trials in acute coronary syndrome (ACS) and antiplatelet management such as HOST-IDEA, T-PASS and STOP-DAPT3 were included in addition to several pivotal interventional trials such as ORBITA 2, MULTISTARS-AMI, ILUMIEN-IV, OCTIVUS and OCTOBER. Additionally, several trials evaluated new stent design and technology such as BIOSTEMI, PARTHENOPE and TRANSFORM. Structural intervention trials included long-term data from PARTNER 3, new data on the durability of transcatheter aortic valve intervention (TAVI), in addition to major new trials regarding transcatheter tricuspid valve intervention from TRISCEND II. Heart failure (HF) and prevention covered several key studies including DAPA-MI, STEP-HF, ADVOR, DICTATE HF and CAMEO-DAPA. In cardiac devices and electrophysiology, several trial exploring novel ablation strategies in atrial fibrillation (AF) such as PULSED AF and ADVENT were presented with further data evaluating the efficacy of anticoagulation in subclinical AF in NOAH-AFNET 6, FRAIL AF and AZALEA-TIMI 71.

Conclusion: This article presents a summary of key clinical cardiology trials published and presented during the past year and should be of interest to both practising clinicians and researchers.

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Key Summary Points

This review paper presents a concise summary of over 80 key cardiology trials presented at major international conferences during 2023 with the potential to impact and change current practice.

Updates included in this article extend across the spectrum of cardiology including structural and coronary intervention, acute coronary syndrome, antiplatelet therapies, electrophysiology, atrial fibrillation, preventative therapies and heart failure (HF).

Key areas of interest are major updates with long-term data for transcatheter aortic valve intervention and promising new data for transcatheter mitral and tricuspid interventions in addition to important new evidence regarding abbreviated anti-platelet strategies and intravascular imaging in percutaneous coronary intervention (PCI).

Additionally, important new evidence is presented regarding HF therapies including glucagon-like peptide-1 (GLP-1) receptor agonists for modification of cardiovascular (CV) risk and HF outcomes as well as mechanistic insights into the action of sodium-glucose co-transporter-2 (SGLT2) inhibitors in heart failure.

INTRODUCTION

In 2023, several landmark trials with the potential to change clinical practice were presented at major international meetings including the American College of Cardiology (ACC), European Association for Percutaneous Cardiovascular Interventions (EuroPCR), European Society of Cardiology (ESC), Transcatheter Cardiovascular Therapeutics (TCT), American Heart Association (AHA), European Heart Rhythm Association (EHRA), Society for Cardiovascular Angiography and Interventions (SCAI), TVT-The Heart Summit (TVT) and Cardiovascular Research Technologies (CRT). In this article we review key studies across the spectrum of cardiovascular subspecialties including ACSs, interventional and structural, electrophysiology and atrial fibrillation (AF), heart failure (HF) and preventative cardiology.

METHODS

The results of clinical trials presented at major international cardiology meetings in 2023 were reviewed. Additionally, a literature search of PubMed, Medline, Cochrane Library and Embase was completed including the terms “acute coronary syndrome”, “atrial fibrillation”, “coronary prevention”, “electrophysiology”, “heart failure” and “interventional cardiology”. Trials were selected based on their relevance to the cardiology community and the potential to change future clinical guidelines or guide further phase 3 research. This article is based on previously completed work and does not involve any new studies of human or animal subjects performed by any of the authors.

Acute Coronary Syndromes and Antiplatelets

The latest iteration of the European Society of Cardiology guidelines in acute coronary syndromes were published this year. Previous guidance regarding antiplatelet strategies was consolidated with dual antiplatelet therapy (DAPT) remaining recommended for 12 months. Additionally, in patients presenting with an ACS and undergoing subsequent coronary artery bypass grafting (CABG), maintenance of DAPT for 12 months was conferred a class I level of evidence. Conversely, despite favourable outcomes of multiple studies using abbreviated DAPT of 3–6 months (including new studies below), this strategy was given a IIB rating based on potential generalisability of trial data to real-world practice. Complete revascularisation in ST elevation myocardial infarction (STEMI) at index procedure or within 45 days was upgraded to class IA

and use of angiographic severity for assessment of non-culprit revascularisation was favoured over epicardial functional assessment (class IB). Important expansions to this year's guidance also included specific strategies for management of patients with concurrent malignancy presenting with ACS in addition to focusing on holistic care and lifestyle modification [1].

Several important studies were published this year which have added to the evidence base for abbreviated antiplatelets strategies (Table 1). Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis (HOST-IDEA) was an open-label, multicentre, randomised controlled trial (RCT) ($n=2013$, mean age 65.7 ± 10.5 years, 73.9% male) comparing short-duration DAPT (3 months) vs 12 months after implantation of an ultrathin strut drug-eluting stent (DES) (Orsiro biodegradable polymer sirolimus-eluting stents or the Coroflex ISAR polymer-free sirolimus-eluting stents). At 1 year the primary outcomes of NACE (cardiac death, target vessel MI [TV MI], target lesion revascularisation [TLR], stent thrombosis and BARC3/5 bleeding) were similar between the two groups, (3.7% vs 4.1%; hazard ratio [HR] 0.93; 95% CI 0.60–1.45; $p<0.001$ [non-inferiority]). Antiplatelet choice was not mandated; however, aspirin and clopidogrel were most common (89%). Oddly, there was no difference in major bleeding (BARC 3 or 5; 1.5% vs 1.9%; HR 0.82; 95% CI 0.41–1.61) [2].

The same group also extended results from previously published Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-Extended Antiplatelet Monotherapy (HOST-EXAM), a study comparing long-term clopidogrel monotherapy vs aspirin post PCI. At 5.8 years clopidogrel monotherapy met the primary endpoint (a composite of all-cause death, nonfatal myocardial infarction, stroke, readmission attributable to acute coronary syndrome and Bleeding Academic Research Consortium type 3 or greater bleeding) at a rate of 12.8% vs 16.9%. Thus, long-term follow-up confirmed the initial findings that clopidogrel monotherapy vs aspirin was associated with lower rates of the composite clinical outcome [3].

Other ACS antiplatelet strategies currently being explored include aspirin cessation in favour of P2Y12 inhibition. Building on previously published data, extended results from the previously discussed Ticagrelor With Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) study were published this year [4]. At 1 year, no difference in clinically driven revascularisation in the ticagrelor monotherapy group was noted vs control (7.1% vs 6.6%, $p=0.363$) with lower NACE rates at 1 year also noted the ticagrelor monotherapy group (12.2% vs 14.6%: HR 0.83; 95% CI 0.73–0.94) [5]. Similarly, the Ticagrelor Monotherapy in Patients Treated With New-Generation Drug-Eluting Stents for Acute Coronary Syndrome (T-PASS) study randomised patients with ACS (mean age 61 years: 17% female) undergoing treatment with a bioresorbable polymer sirolimus-eluting stent (BP-SES; Orsiro series, Biotronik) to < 1 month DAPT with ticagrelor followed by 11 months ticagrelor monotherapy ($n=1426$) vs 12 months DAPT ($n=1424$). The primary outcome of net CV events was lower in the monotherapy group (2.8% vs 5.2% HR 0.54, 95% CI 0.37–0.80, $p<0.001$ non-inferiority: $p=0.002$ superiority) [6]. Additionally, rates of BARC bleeding were significantly lower 1.2% vs 3.4% (HR 0.35, 95% CI 0.20–0.61; $p<0.001$). These findings are in keeping with previous data gleaned from TICO and STOP-DAPT-2 [4].

Given the growing evidence for abbreviated strategies, Stopping Aspirin Within 1 Month After Stenting for Ticagrelor Monotherapy in Acute Coronary Syndrome (STOP-DAPT 3) randomised patients with ACS post angiography ($n=5966$, mean age 71.6 years; 23.4% women) to prasugrel monotherapy vs DAPT. At 1 month, prasugrel monotherapy was associated with higher rates of stent thrombosis (0.58% vs 0.17%; HR 3.40; 95% CI 1.26–9.23) but no difference in major bleeding (4.47% vs 4.71%; HR 0.95; 95% CI 0.75–1.20). Notably, a lower dose of prasugrel was used in the trial (3.75 mg), which is standard practice in Japan due to intrinsic differences in thrombotic/bleeding risks vs Western populations [7]. This adds much needed data to this area and suggests perhaps that shortening of DAPT must be restricted to a minimum of 1 month.

Despite the widespread acceptance as gold standard care, primary-PCI (PPCI) for STEMI may not always be available, such as in remote areas.

Table 1 Summarising the major antiplatelet trials relating to percutaneous coronary intervention

Major antiplatelet trials 2023											
Study	**Year**	**Design**	**Size (*n*)**	**Mean age (years)**	**Cohort**	**Intervention**	**Control**	**Follow-up**	**Stent used**	**Primary end-point**	**Outcome**
HOST-IDEA	2023	RCT	2013	65.7	Stable and ACS (STEMI exlcuded)	3 or 6 month DAPT (antiplatelet used at physician discretion)	Conventional 12-month DAPT (antiplatelet used at physician discretion)	12 months	Orsiro biodegradable polymer sirolimus-eluting stents or Coroflex ISAR polymer-free sirolimus-eluting stents	NACE (composite of cardiac death, target vessel myocardial infarction, clinically driven target lesion revascularisation, stent thrombosis, or BARC bleeding type 3 or 5 at 12 months)	3.7% (3–6 month DAPT) vs 4.1% (HR 0.93; 95% CI 0.60–1.45; $p = 0.75$)
HOST-EXAM	2023	RCT	5530	63.5	Stable and ACS (STEMI exlcuded)	Clopidogrel monotherapy post completion of standard DAPT	Aspirin monotherapy	24 months	Drug eluting stents	All-cause mortality, MI, stroke, readmission due to acute coronary syndrome (ACS), major bleeding,	5.7% (clopidogrel) vs 7.7% (HR 0.73, 95% CI 0.59–0.90, $p = 0.003$)
TWLIGHT-extended	2023	RCT	7039	65.2	Stable and ACS (STEMI exlcuded)	Clopidogrel monotherapy post completion of standard DAPT	Conventional 12-month DAPT (ticagrelor based)	12 months	Drug eluting stents	Clinically driven revascularisation	7.1% (ticagrelor monotherapy) vs 6.6% (HR 1.09, 95% CI 0.90–1.30, $p = 0.363$)

Table 1 continued

Major antiplatelet trials 2023

Study	Year	Design	Size (*n*)	Mean age (years)	Cohort	Intervention	Control	Follow-up	Stent used	Primary endpoint	Outcome
T-PASS	2023	RCT	2850	61	Acute coronary syndromes	DAPT < 1 month followed by ticagrelor monotherapy	Conventional 12-month DAPT (ticagrelor based)	12 months	Bioresorbable polymer sirolimus-eluting stent (BP-SES; Orsiro series, Biotronik)	NACE (composite of all-cause death, nonfatal MI, in-stent thrombosis, stroke, and BARC bleeding type 3 or 5 at 12 months)	2.8% (< 1 month DAPT) vs 5.2% (HR 0.54, 95%[CI] 0.37–0.80; *p* for noninferiority < 0.001, *p* for superiority = 0.002)
STOP-DAPT 3	2023	RCT	5966	71.6	Stable and ACS (STEMI exlcuded)	Prasugel monotherapy	DAPT with aspirin and prasugel	1 month	Everolimus-eluting stent (Xience)	Bleeding endpoint- BARC 3 or 5 CV endpoint (composite of CV death, MI, definite stent thrombosis or stroke)	Bleeding endpoint: 4.47% (monotherapy) vs 4.71% (HR 0.95, 95% CI 0.75–1.20; *p* = 0.66) CV endpoint: 4.12% vs 3.69% (HR 1.12; 95% CI 0.87–1.45; *p* = 0.01: noninferiority)

RCT randomised controlled trial; *ACS* acute coronary syndrome; *STEMI* ST elevation myocardial infarction; *NACE* net adverse cardiovascular events; *BARC* Bleeding Academic Research Consortium; *MI* myocardial infarction; *HR* hazard ratio; *CI* confidence interval; *DAPT* dual antiplatelet therapy; *CV* cardiovascular

The Strategic Reperfusion in Elderly Patients Early After Myocardial Infarction (STREAM-2) study ($n=604$, mean age 71 years: 32% female) was a randomised (2:1) controlled trial comparing half-dose Tenecteplase (TNK) with PPCI. At 30 days, the primary composite outcome of death, myocardial infarction and shock was reached in 12.8% TNK group vs 13.3% in PPCI (RR 0.96, 95% CI 0.62–1.48). Higher rates of intracranial haemorrhage (ICH) were noted in the NTK group (1.5% vs 0%, $p=$ns) although this did not reach statistical significance. This study suggests that half-dose TNK has a similar efficacy to PPCI though with a trend to higher rates of ICH [8].

The optimum timing of non-culprit lesion revascularisation in ACS remains unclear. Immediate Versus Staged Complete Revascularisation in Patients Presenting with Acute Coronary Syndrome and Multivessel Coronary Disease (BIOVASC) was an open-label trial in patients with ACS and multi-vessel disease (MVD) randomised to immediate ($n=764$) vs staged within 6 weeks ($n=761$) complete revascularisation. Non-inferiority for the primary outcome (MI, unplanned revascularisation, cerebrovascular events) was met at 1 year in the immediate group (7.6% vs 9.4%, p for noninferiority = 0.0011, p for superiority = 0.17). Immediate revascularisation was associated with similar incidence of death (1.9% vs 1.2%; $p=0.30$) but lower rates of myocardial infarction (MI) (1.9% vs 4.5%, $p=0.0045$) and unplanned revascularisation (4.2% vs 6.7%, $p=0.030$). This study suggests that both strategies are viable options depending on patient characteristics although an immediate strategy may confer additional benefits [9].

Similarly, the Timing of Complete Revascularization with Multivessel PCI for Myocardial Infarction (MULTISTARS AMI) non-inferiority study randomised 840 patients with STEMI to immediate vs staged PCI (in 19–45 days) of non-culprit disease. At 1 year, immediate PCI was associated with reduction in the primary composite endpoint (death MI, stroke, unexplained ischaemia-driven revascularisation or hospitalisation for heart failure; 8.5% vs 16.3%; RR 0.52, 95% CI 0.38–0.72; $p<0.001$ for non-inferiority and $p<0.001$ for superiority) with no difference in death (2.9% vs 2.6%) but reduction in MI (2.0% vs 5.3%; $p<0.05$) [10]. In contrast to the COMPLETE trial [11], which found similar benefit for immediate vs staged complete revascularisation up to 45 days, MULTISTARS AMI suggests that immediate complete revascularisation is preferable although it remains unclear whether urgent non-culprit PCI during the index hospitalisation but not in the same acute setting would be equally effective.

Transfusion targets in ischaemic heart disease (IHD) are traditionally higher but randomised data in ACS are limited. The Myocardial Ischaemia and Transfusion (MINT) study was an international trial which randomised 3504 patients admitted with MI and concurrent anaemia (Hb < 10 g/dl) to a restrictive (aiming for Hb ≥ 7–8 g/dl) vs liberal (aiming Hb ≥ 10 g/dl) blood transfusion strategy. At 30 days a restrictive strategy was associated with non-significant trend to increase in the primary outcome of all-cause death or recurrent nonfatal MI (16.9% vs 14.5%: RR 1.15, 95% CI 0.99–1.34, $p=0.07$), and increased type 1 MI RR 1.32 (95% CI 1.04–1.67), but no difference in death (9.9% vs 8.3%, RR 1.19, 95% CI 0.96–1.47) or heart failure (5.8% vs 6.3%, RR 0.92, 95% CI 0.71–1.20). Thus, a liberal transfusion strategy in MI may be reasonable to consider without an appreciably increased risk of harm [12].

There is increasing interest in streamlined out-of-hospital cardiac arrest (OOHCA) care with the use of dedicated centres. The Expedited Transfer to a Cardiac Arrest Center for Non-ST-Elevation Out-of-Hospital Cardiac Arrest (ARREST) study was a multicentre open-label trial across 35 London hospitals which randomised 862 patients after OOHCA without STEMI identified on post-resuscitation ECG to immediate transfer to a cardiac arrest centre vs standard of care (i.e. transfer to the nearest emergency department). At 30 days, an immediate transfer strategy did not show any difference in all-cause mortality (63% vs 63%, $p=0.96$); despite increased use of early angiography, haemodynamic support and ventilation. Interestingly, this contradicts prior observational data (which were likely confounded by selection bias) although this study was focused in one large city and might not be generalisable to the more rural areas [13].

The use of early mechanical circulatory support in acute MI complicated by cardiogenic shock (AMI-CS) remains controversial. The Extracorporeal Life Support in Infarct-Related Cardiogenic Shock (ECLS-SHOCK) study randomised 420 patients (median age 63 years; 81.3%) with AMI-CS undergoing revascularisation to extracorporeal life support (ECLS) vs standard care. At follow-up, ECLS was not associated with any reduction in the primary outcome of 30-day mortality (47.8% vs 49.0%, $p=0.81$) but was associated with excess moderate to severe bleeding (23.4% vs 9.6%, RR 2.44; 95% CI 1.50–3.95; $p<0.05$) and vascular complications requiring intervention (11.0% vs 3.8%; $p<0.05$) [14]. Further to this, a meta-analysis conducted by Zeymer et al. also failed to show any reduction in 30-day mortality with VA-ECMO (OR, 0.93; 95% CI, 0.66–1.29) but showed increased major bleeding (OR, 2.44; 95% CI 1.55–3.84) and vascular complications (OR, 3.53; 95% CI 1.70–7.34) [15]. Taken collectively, these data suggest that the increased use of VA-ECMO being seen in the management of AMI-CS should be reconsidered.

Advances in Percutaneous Coronary Intervention

Coronary Revascularisation

Previous trials such as *COURAGE*, *ISCHAEMIA* and *ORBITA-1* raised the possibility that the benefit of PCI observed in stable angina might be primarily a placebo effect [4, 16]. The widely anticipated, placebo-controlled Trial of Percutaneous Coronary Intervention for Stable Angina (*ORBITA*) 2 study randomised (1:1, double blind) 301 patients with ischaemia and ≥ 1 severe lesion to PCI with complete revascularisation vs a sham placebo procedure. At enrolment, all patients had their anti-anginal medications stopped. At 12 weeks, use of PCI was associated with significant reduction in the primary endpoint of mean angina symptom score (2.9 vs 5.6; OR 2.21; 95% CI 1.41–3.47; $p<0.001$), reduced daily angina frequency (0.3 vs 0.7; OR 3.44, 95% CI 2.00–5.91), reduced CCS class (0.9 vs 1.7), improved mean treadmill exercise time (700.9 vs 641.4 s) and improved freedom from angina on the Seattle Angina Questionnaire (80.6 vs 66.2). Thus, in contrast to ORBITA-1, this trial confirms the antianginal benefit of PCI for stable coronary artery disease (CAD) in a sham-controlled design [17].

The possibility of excess non-cardiac mortality in patients with chronic coronary syndromes (CCS) undergoing PCI had been observed in the ISCHAEMIA trial. This question was directly assessed in a meta-analysis by Navarese et al. of 18 trials ($n=16{,}908$) which compared non-cardiac mortality in patients with CCS randomised to either PCI plus medical therapy vs medical therapy alone. At an average follow-up of 5.7 years, no significant excess non-cardiac mortality was seen with PCI (RR 1.09; 95% CI 0.94–1.26) [18], which was conclusively reassuring.

Guidelines recommend revascularisation of intermediate coronary artery stenosis should be guided by evidence of ischaemia (by either fractional flow reserve [FFR] or a validated resting index such as instantaneous wave-free ratio [iFR]). Initial 1- and 5-year follow-up of the iFR-SWEDEHEART trial showed no significant difference in MACE or death [19]. Similarly, DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization) showed non-inferiority of an iFR vs FFR strategy for MACE (death, MI or unplanned revascularisation) at 1 year (6.8% vs 7.0%: $p<0.001$ for noninferiority) [20]. However, 5-year follow-up of DEFINE-FLAIR reported that iFR was associated with a trend to higher MACE (21.1% vs 18.4%; HR 1.18; 95% CI 0.99–1.42; $p=0.06$), although the excess was only seen in the subgroup treated by PCI (HR 1.36; 95% CI 1.07–1.72; $p=0.01$) and not in the deferred subgroup [21]. A study-level meta-analysis of 5-year pooled data from iFR-SWEDEHEART and DEFINE FLAIR reported similar findings whereby iFR was associated with increased MACE (HR 1.18; 95% CI 1.04–1.34) and all-cause mortality (HR 1.34; 95% CI 1.08–1.67) although again the excess was only seen in the subgroup undergoing PCI [22]. This is surprising in that excess MACE risk would be expected to be mainly in the deferred group, for example if iFR had led to deferral of PCI for a prognostically significant left main or

LAD lesion. The SWEDEHEART investigators thus undertook a new large analysis of 42,887 patients from the SWEDEHEART registry and reported that iFR vs FFR was not associated with increased risk of MACE at 5 years (adjusted HR 0.99; 95% CI 0.93–1.05; $p=0.72$) or risk of death (adjusted HR 1.04; 95% CI 0.94–1.14; $p=0.43$), nor was they any difference between treated or deferred subgroups [23]. The registry data are reassuring but the debate is likely to continue particularly for larger vessels subtending large areas of myocardium.

Intravascular Imaging

Intravascular imaging has been associated with improved outcomes compared with angiography only guided PCI. Most clinical outcome studies to date have been with IVUS. The Optical Coherence Tomography (OCT) Guided Coronary Stent Implantation Compared with Angiography (ILUMIEN-IV) trial randomised 2487 high-risk patients to OCT-guided vs angiography only-guided PCI. The OCT group achieved a significantly greater acute minimal stent area (primary imaging endpoint; 5.72 vs 5.36 mm^2; $p<0.001$) but, disappointingly, this did not translate into significant reduction in the primary clinical endpoint of 2-year target vessel failure (7.4% vs 8.2%; HR 0.90; 95% CI 0.67–1.19; $p=0.45$). The observation of fewer stent thromboses in the OCT group (0.5% vs 1.4%; HR 0.36; 95% CI 0.14–0.91) was encouraging but only hypothesis generating [24].

However, the OCT or Angiography Guidance for PCI in Complex Bifurcation Lesions (OCTOBER) trial randomised 1201 patients undergoing complex true bifurcation PCI to OCT-guided vs angiography-guided PCI. At a median follow-up of 2 years, OCT was associated with a significant reduction in the primary endpoint of cardiac death, target lesion MI or ischemia-driven TLR (10.1% vs 14.1%; HR 0.70; 95% CI 0.50–0.98; $p=0.035$) [25].

A meta-analysis of 20 randomised trials ($n=12,428$) including ILUMIEN-IV and OCTOBER reported intravascular imaging (IVUS or OCT)-guided vs angiography only-guided PCI was associated with a 31% reduction in the primary endpoint of cardiac death, target-vessel MI or TLR) [26]. While OCT provides additional near-field resolution vs IVUS, the comparative effectiveness for improving clinical outcomes is unknown. The Optical Coherence Tomography–guided versus IntraVascular UltraSound-guided percutaneous coronary intervention (OCTIVUS) multicentre, open-label trial randomised 2008 patients with significant coronary artery lesions undergoing PCI to OCT vs IVUS. At 1-year, the primary composite endpoint (CV death, target vessel MI or ischaemia-driven TVR) was similar in OCT and IVUS groups (2.5% vs 3.1%; p for noninferiority <0.001) [27]. At 2 years, a pre-specified sub-analysis of patients with complex coronary lesions ($n=1475$; 73.5% of cohort) again reported OCT to have a similar incidence of the composite outcome (6.5% vs 7.4%; HR 0.87; 95% CI 0.59–1.29; $p=0.50$) although lower target vessel MI (0.8% vs 2.4%, HR 0.35; 95% CI 0.14–0.88; $p=0.03$) and lower procedural complications (1.7% vs 3.4%; $p=0.03$), which may have been related to more aggressive stent sizing and periprocedural MI in the IVUS group [28].

Bifurcation Stenting and New Stent Technology

PCI of bifurcation lesions continues to be frequently required in routine practice. Contemporary thin strut stents may improve clinical outcomes and facilitate more complex stent techniques in complex lesions [29]. The European Bifurcation Club LM (left main) Coronary Stent (EBC MAIN) study randomised 467 patients from from 11 European countries with left main bifurcation lesions to a provisional strategy vs systematic two-stent approach (using Resolute Onyx stents). Kissing balloon inflation and proximal optimisation techniques (POT) were mandated in both arms although the choice of two-stent technique was left to operator discretion [30]. At 3 years, the composite of death, MI and TVR was similar for provisional vs systematic two-stent approach (23% vs 29%; $p=0.13$).

Similarly, the European Bifurcation Coronary (EBC) 2 trial randomised 200 patients with non-LM bifurcations to provisional T-stenting vs a two-stent culotte strategy (Nobori stents; 16% of

the provisional group proceeded to T stenting). Procedure time, x-ray dose and cost all favoured the simpler procedure. At 5-year follow-up, the incidence of death, MI or TVR remained similar for provisional vs systematic culotte arms (18.4% vs 23.7%; $p=0.36$) [31]. These data, even with latest generation thin strut stents, continue to support starting with a provisional strategy rather than upfront two-stent strategy in most cases.

Ultrathin stent struts (< 70 µm thick) may be less thrombogenic and have more rapid endothelialisation. The COMPARE 60/80 trial randomised 732 patients at high bleeding risk to an ultrathin (60 µm) strut stent (Supraflex Cruz; SMT) vs a thicker (80 µm) strut stent (Ultimaster, Terumo) although with an abbreviated DAPT duration (mean duration 30 days). The ultrathin Supraflex stent met criteria for non-inferiority of 4.0% with similar incidence of the primary outcome of CV death, MI, TVR, stroke or major bleeding (17.1% 15.4% vs 17.1%; HR 0.89; 95% CI 0.62–1.28) [32].

Biodegradable polymer stents were developed in response to excess stent thrombosis noted with first-generation durable polymer stents. However, new durable polymer designs are associated with much lower rates of stent thrombosis. The long-term results of the Biodegradable Polymer Sirolimus-Eluting Stents Versus Durable Polymer Everolimus-Eluting Stents in Patients With STEMI (BIOSTEMI) study are thus relevant. BIOSTEMI randomised 1300 patients with STEMI to a sirolimus-eluting biodegradable polymer stent (Orsiro) vs an everolimus-eluting durable polymer stent (Xience Prime/Xpedition). At 5-year follow-up (data available for 85% of patients), the Orsiro stent was associated with a significant reduction in the primary outcome of cardiac death, target-vessel MI or TLR (8% vs 11%; RR 0.70, 95% Bayesian credible interval [BCI] 0.51–0.95; Bayesian posterior probability for superiority 0.988); interestingly, rates of stents thrombosis were lower in the biodegradable polymer group (1.7% vs 2.6%) [33]. This suggests biodegradable polymer stents may indeed be superior to durable polymer stents (although further studies using identical drugs and identical stents other than the polymer subtype would be needed to evaluate precisely).

Polymer-free stent designs may also shorten stent healing and facilitate abbreviated DAPT but data vs biodegradable polymer DES remain limited. The Polymer-free vs Biodegradable-polymer Drug-eluting stents and Personalized vs Standard Duration of Dual Antiplatelet Therapy in All-comers Undergoing PCI (PARTHENOPE) study randomised patients to the Cre8 polymer-free stent ($n=1051$) vs the Synergy bioabsorbable polymer everolimus-eluting stent (Boston Scientific; $n=1056$) with further randomisation to personalised DAPT vs standard 12 months DAPT. While the Cre8 polymer-free stent met criteria for noninferiority with a similar incidence of CV death, target vessel MI or TLR at 1 year (8.2% vs 7.2%; p for noninferiority = 0.04), more Cre8 patients had definite or probable stent thrombosis (11 vs 3 patients, $p=0.04$) [34]; thus, further studies are required to define the optimum DAPT strategy with this device.

Drug-coated Balloons and Stent Technology

The management of in-stent restenosis (ISR) remains a challenging issue. European and international data have supported use of drug-coated balloons (DCBs). The first multicentre US DCB for coronary ISR study, A Clinical Trial to Assess the Agent Paclitaxel Coated PTCA Balloon Catheter for the Treatment of Subjects with In-Stent Restenosis (AGENT-IDE), randomised (2:1) 480 patients with in-stent restenosis to a pacliataxel-coated balloon vs balloon angioplasty. At 1 year, the Agent DCB was associated with significant reduction in the primary endpoint death, target-vessel MI or TLR (17.9% vs 28.7%; $p=0.0063$), driven as expected by reduction in TLR and target-vessel MI [35]. This trial may provide a basis for FDA approval.

Although limus drugs are preferred to paclitaxel for drug-eluting stents, their use in DCBs has been limited by need of a suitable excipient given their lower lipophilicity vs paclitaxel. Chen et al. randomised 258 patients with ischaemic in-stent restenosis from 16 Chinese centres to a sirolimus-coated balloon SCB (SeQuent SCB) vs paclitaxel-coated balloon PCB (SeQuent Please Neo; both B. Braun Melsungen AG). At 9 months, the SeQuent SCB met non-inferiority for the primary endpoint of in-stent late lumen

loss (0.35 vs 0.31 mm; absolute difference 0.05 mm; 95% CI 0.0523–0.1476; non-inferiority margin 0.2 mm) [36].

This was further assessed in the TRANSFORM study (Multicenter Randomized Trial to Assess the Effectiveness of the MagicTouch Sirolimus-Coated Balloon in Small Vessels) which randomised 121 patients with small-vessel coronary disease (reference vessel diameter < 2.75 mm) to the MagicTouch SCB (Concept Medical) vs SeQuent Please Neo PCB. In this study the SCB failed to achieve noninferiority for 9-month net lumen gain (0.25 vs 0.48, *p* noninferiority = 0.173; absolute difference − 0.23 mm [95% CI: − 0.37 to − 0.09]; noninferiority margin 0.3 mm), which was in part due to more frequent late lumen enlargement with the PCB [37].

Advances in Structural Cardiology

Transcatheter Aortic Valve Interventions (TAVI)

The role of TAVI is firmly established in patients with high-risk aortic stenosis (AS) and emerging data continue to support its role in lower risk patients (STS PROM ≤ 3%). The Evolut Low Risk study randomised patients at low surgical risk (mean age 74 years; 35.3% female) to TAVI (Medtronic CoreValve, Evolut R or Evolut PRO, [*n* = 691, mean STS 2.0%]) vs surgical aortic valve replacement (SAVR) (*n* = 610, mean STS 1.9%. At 4 years (data available in 94%); there was a trend in favour of TAVI for the primary endpoint of death or disabling stroke (10.7% vs 14.1%; HR 0.74, 95% CI 0.54–1.00 [*p* = 0.05]) with no difference in valve re-intervention (1.3% vs 1.7%, *p* = 0.63) or in clinical or subclinical valve thrombosis (0.7% vs 0.6%, *p* = 0.84) but permanent pacemaker implantation was more frequent (24.6% vs 9.9%, *p* < 0.001) [38] (Fig. 1).

In addition, 5-year results from the Placement of Aortic Transcatheter Valves 3 (PARTNER 3) study, which randomised low surgical risk patients (*n* = 1000, mean age 73 years: 30% female) with severe symptomatic aortic stenosis to TAVI (SAPIEN 3 valve; *n* = 503) vs SAVR (*n* = 497), reported no difference in the primary outcome (death, stroke or rehospitalisation related to the procedure/valve/HF; 22.8% vs 27.2%, *p* = 0.07), mortality (10.0% vs 8.2%, *p* = 0.35), stroke (5.8% vs 6.4%, *p* = 0.6) or valve failure (3.3% vs 3.8%, *p* = NS) but TAVI was associated with a lower incidence of serious bleeding (10.2% vs 14.8%, *p* < 0.05) and AF (13.7% vs 42.4%, *p* < 0.05) [39]. These two important trials add to the increasing evidence for TAVI in aortic stenosis with low surgical risk.

Cerebral protection devices may reduce the risk of peri-procedural stroke during TAVI but robust data are limited. The Carbon Dioxide (CO_2) Flushing Reduces Vascular Brain Injury in TAVI (INTERCEPTavi) study was a single-centre pilot study of 60 patients (mean age 81 years; 53% men) undergoing TAVI with valve flushing pre-procedure using CO_2 plus saline vs saline alone. Although no cerebrovascular events were noted, at 7 days, the average number of acute cerebral lesions visualised on brain magnetic resonance imaging (MRI) post procedure was lower with CO_2 flushing (4.2 vs 9.0 per patient; *p* = 0.032). Larger multicentre studies are now planned [40].

Some concern persists regarding transcatheter valve durability [16]. O'Hair et al. conducted a secondary analysis of 2000 pooled patients (mean age 81 years; 55% male) from the previously discussed CoreValve US Pivotal and SURTAVI trials [4]. Interestingly, at 5 years, bioprosthetic valve dysfunction (BVD) was significantly lower in the TAVI group (7.8% vs 14.2%; HR 0.50; 95% CI 0.38–0.66) with an advantage particularly in the subgroup with smaller baseline annuli of < 23 mm (8.6% vs 19.7%; HR 0.31; 95% CI 0.18–0.55), suggesting the BVD excess with SAVR may possibly be related prosthesis undersizing [41].

Treatment for patients with severe aortic stenosis and small aortic annuli (mean diameter < 23 mm) remains unclear. Rodes-Cabu et al. conducted a multicentre, randomised (1:1) trial (*n* = 151, mean age 75 ± 5 years, 93% female) comparing TAVI vs SAVR. There was no difference in rates of pacemaker (PPM) implantation at 30 days (TAVI 5.6% vs SAVR 10.3%, *p* = 0.30) or a median of 2 years for mortality (TAVI 9.1%, SAVR 8.1%, *p* = 0.89) or stroke (TAVI 3.9% vs SAVR 4.1%, *p* = 0.95). However, the study was

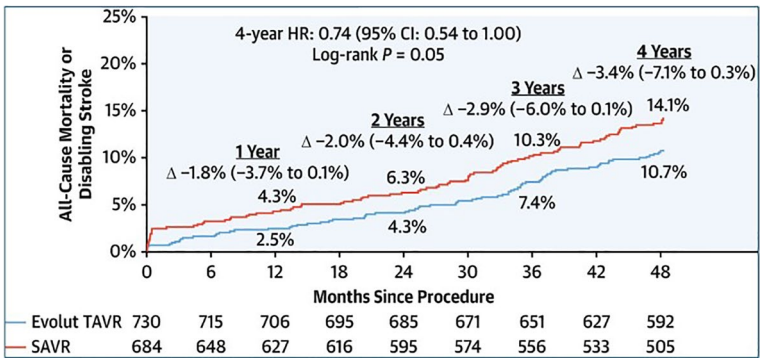

Fig. 1 Kaplan-Meier curve demonstrating the time to primary endpoint of all-cause mortality or disabling stroke through 4 years in patients treated with SAVR vs Evolut TAVR in the Evolut Low Risk study (citation). At 4 years, there was a 26% RR in the hazard for death or disabling stroke with TAVR vs SAVR Reproduced with permission from Journal of the American College of Cardiology. *SAVR* surgical aortic valve replacement; *TAVR* transcatheter aortic valve replacement; *CI* confidence interval; *RR* relative reduction; *HR* hazard ratio

stopped prior to reaching sufficient numbers to achieve appropriate power; therefore, the data, which are much needed in this area, should be interpreted with caution [42].

The role of TAVI in patients with severe AS and cardiogenic shock was evaluated by Dhoble et al. who identified 309,505 patients from the STS/ACC TVT Registry (2015–2022) undergoing TAVI with Sapien 3 and Sapien 3 Ultra balloon-expandable valves (Edwards Lifesciences) of whom 5006 had cardiogenic shock (CS) (1.6%, mean STS 10.76 ± 10.4). At 30 days, mortality was notably higher in the CS group (12.9% vs 4.9%, $p < 0.0001$) vs a control group of all other patients undergoing TAVI without CS. Interestingly, landmark analysis found that if patients with CS survived the first 30 days, the risk of 1-year mortality was similar (HR 1.07; 95% CI 0.95–1.21) supporting intervention in this high-risk group despite the early hazard [43].

Implementation of protocolised pathways may help expedite discharge without compromising patient care. The FAST-TAVI multicentre French RCT compared an early discharge protocol (including patient and staff education and algorithmic pathways to identify complications) vs standard of care in patients undergoing TAVI ($n = 1829$, mean age 89.9 +/6.6 years: 55.9% male, mean Euroscore II 4.4%). The early discharge protocol enabled a higher rate of discharge < 3 days (58.1% vs 42.3%; $p < 0.0001$) with no difference in 30-day mortality (1% vs 0.5%; $p = 0.29$) or re-admission (4.6% vs 2.8%, $p = 0.28$) [44].

Interventional options for patients with severe symptomatic aortic regurgitation not amenable to surgery are urgently needed. The ALIGN-AR single-arm, multicentre study evaluated use of the novel Trilogy heart valve system (JenaValve) in patients with symptomatic moderate-to-severe or severe AR (mean age 75.5 years; 47.2% women: mean STS 4.1%). At 30 days, the primary safety endpoint of all-cause mortality (observed rate 26.7%) was met, falling below the prespecified 40.5% ($p < 0.001$, non-inferiority). Efficacy was defined using 1-year mortality, the observed rate (7.8%) of which fell significantly below the prespecified performance goal (25%, $p < 0.0001$). These data are encouraging, given the clinical need for specific devices in this patient group; however, randomised data are still needed [45].

Mitral and Tricuspid Valve Interventions

The landmark Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) previously reported transcatheter mitral valve repair with MitraClip in moderate-to-severe or severe secondary mitral regurgitation (MR) refractory to

medical therapy was superior to medical therapy alone [4]. New data at 5-year follow-up reported Mitraclip was associated with lower rates of all-cause mortality (57.3% vs 67.2% HR 0.72; 95% CI 0.58–0.89) and heart failure (33.1% vs 57.2% HR 0.53; 95% CI 0.41–0.68). While these data are encouraging, they contrast with the MITRA-FR study (which failed to demonstrate significant benefit) and do not fully account for advances in medical therapy in the interim [46].

Long-term data STS/ACC TVT registry data are now available from 19,088 patients with primary MR treated by MitraClip between January 1, 2014, and June 30, 2022 (mean age 82 years, 49% female: mean STS score 4.6%). The composite primary endpoint of MR success (defined as ≤ moderate residual MR and mean mitral gradient < 10 mmHg at 30 days) was obtained in 88.9% of patients overall, although procedural success improved over time, which may reflect improved expertise and/or technology. Achieving the MR success definition vs suboptimal procedural result was associated with significantly lower 1-year mortality (14.0% vs 26.7%; adjusted hazard ratio [HR], 0.49; 95% CI 0.42–0.56; $p < 0.001$) [47].

The Edwards PASCAL TrAnScatheter Valve RePair System Pivotal Clinical (CLASP IID) trial randomised patients (2:1) with symptomatic severe degenerative MR to treatment with PASCAL ($n = 204$) vs MitraClip ($n = 96$). Both devices were associated with functional improvement from baseline and the PASCAL device met criteria for non-inferiority vs Mitraclip with no significant differences in mortality, heart failure hospitalisation or major adverse events between groups at 1 year ($p > 0.05$) [48].

The Mitral Implantation of Transcatheter Valves (MITRAL) multicenter prospective study evaluated use of a transcatheter balloon-expandable aortic valve to treat patients with severe MR ($n = 91$, 74.3 ± 8.9 years) and failed surgical bioprostheses (mitral valve-in-valve [MViV], $n = 30$), annuloplasty rings (valve-in-ring [MViR], $n = 30$), or severe mitral annular calcification (valve-in-mitral annular calcification [ViMAC], $n = 31$). Survival at 5 years was higher with MViV (79%) vs MViR (36%) or ViMAC (33%). Among those surviving to 5 years ($n = 85$), excellent outcomes were seen (New York Heart Association [NYHA] I in 28% NYHA II in 47% and no or only trivial MR on echo in 79%) [49].

Tricuspid Valve Interventions

Several important trials in the field of tricuspid intervention have been published this year. The Transcatheter Repair for Patients with Tricuspid Regurgitation (TRILUMINATE) trial randomised 350 patients with severe tricuspid regurgitation (TR) (mean age 78 years: 56% female) to percutaneous tricuspid transcatheter edge-to-edge repair (TEER) ($n = 175$) vs medical therapy alone ($n = 175$) [50]. TEER was associated with notably more frequent reduction of TR severity to moderate or less at 30 days (87.0% vs 4.8%; $p < 0.001$), significant reduction in the primary outcome (all-cause mortality, TV surgery, heart failure hospitalisation and Kansas City Cardiomyopathy Questionnaire (KCCQ) score at 1 year; TEER win ratio = 1.48; $p = 0.02$) and significantly lower mortality or heart failure hospitalisation at 1 year (74.8% vs 45.9%; $p < 0.001$), with quality of life (QoL) benefits seen early (mean between-group difference in KCCQ-OS at 1 month = 9.4 points, 95% CI 5.3–13.4) [51]. However, long-term data are still needed to evaluate treatment durability. The Edwards transcatheter tricuspid replacement device for the treatment of severe TR has been previously evaluated the single-arm prospective TRISCEND study [4]. The sequel to this was the TRISCEND II trial, which randomised 400 patients with severe TR (mean age 79 years: 80% female; STS 10%) to the Evoque (Edwards Lifesciences, Fig. 2) transcatheter tricuspid valve vs medical therapy. Preliminary data at 6 months from the first 150 patients recruited reported use of Evoque was associated with significant reduction in TR (98.8% achieving ≤ moderate TR) and improved QOL outcomes (a composite of KCCQ, NYHA class and 6 MWT; win ratio 4.6) [52]. While encouraging, full trial cohort data and hard clinical outcomes are still awaited.

Left Atrial Appendage Occlusion

Interest in left atrial appendage occluder (LAAO) devices has continued to grow since the

approval of the Watchman (Boston Scientific) in 2015 [4]. Thirteen-month data from the SWISAPERO trial which randomised patients undergoing LAAO to an Amulet vs Watchman device reported no difference in the composite primary clinical outcome (CV death, ischaemic stroke or systemic embolism) (9.5% vs 10.2%, $p=0.829$) and no difference in device-related thrombus (DRT) (2.4% vs 3.8%, $p=0.610$). Of note, the rate of residual leaks as assessed by computed tomography (CT) was high at 50% [53]. Previous studies utilised trans-oesophageal echocardiography (TOE), which may be less sensitive, and longer follow-up is needed to understand the clinical implications of this finding.

The Concomitant Left Atrial Appendage Occlusion and Transcatheter Aortic Valve Replacement Among Patients with Atrial Fibrillation (WATCH TAVR) multicentre study randomised 349 patients (mean age 81 years: female 39%) with severe AS and concomitant AF to TAVI + LAAO (Watchman) ($n=177$) vs TAVI alone ($n=172$). TAVI + LAAO was not associated with any reduction in the primary composite outcome of death, stroke or major bleeding at 2 years (22.7 vs 27.3 events per 100 patient-years; HR 0.86, 95% CI 0.60–1.22; p for noninferiority <0.001, p for superiority $=0.40$). TAVI + LAAO did facilitate a lower rate of anticoagulation at 2 years (14% vs 67%) but this did not translate into a reduction in major bleeding (HR 1.10, 95% CI 0.67–1.79). Notably, in contrast to TAVI, TAVI + LAAO requires a general anaesthetic, which adds to procedural duration and risk. However, data from longer term follow-up and from use of the newer Watchman FLX (which does not require anticoagulation in the first 6 weeks) may be of interest [54].

Electrophysiology and Cardiac Devices

Atrial Fibrillation

AF prevalence continues to increase [55]. Pulsed field ablation (PFA), which may avoid some thermally mediated complications seen with conventional catheter ablation, was evaluated in the Pulsed Field Ablation to Irreversibly Electroporate Tissue and Treat AF (PULSED AF) prospective, paired, single-arm study in patients with paroxysmal ($n=150$) or persistent ($n=150$) symptomatic AF, refractory to class I or III antiarrhythmics [56]. At 12 months, the primary composite efficacy endpoint (freedom from of acute procedural failure, arrhythmia recurrence or escalation of antiarrhythmic therapy) was met in 66.2% (95% CI 57.9–73.2) of patients with paroxysmal AF and 55.1% (95% CI 46.7–62.7) of patients with persistent AF. The primary safety endpoint (a composite of serious procedure or device related adverse incidents) occurred in only one patient from each cohort (0.7%; 95% CI 0.1–4.6).

The Safety and Effectiveness of Pulsed Field Ablation to Treat Atrial Fibrillation (MANIFEST-PF) registry evaluated 1758 patients undergoing PFA for AF. Successful pulmonary vein isolation was achieved in 99.9% with an average procedure time of 65 min. Major complications occurred in 1.6% (including pericardial tamponade 0.97% and stroke 0.4%) and minor complications occurred in 3.9% (including vascular 3.3%, transient phrenic nerve paresis 0.46% and TIA 0.11%). No oesophageal or phrenic nerve complications persisted past hospital discharge [57].

While the above single-arm data are of interest, randomised data were provided by the Pulsed Field or Conventional Thermal Ablation for Paroxysmal Atrial Fibrillation (ADVENT) study, which assigned patients to PFA ($n=305$) vs conventional catheter ablation ($n=302$). Use of PFA met non-inferiority for the primary efficacy outcome at 1 year (procedural failure, AF recurrence, antiarrhythmic drug use, cardioversion or repeat ablation) occurring in 73.3% vs 71.3% (between-group difference 95% Bayesian credible interval −5.2 to 9.2; p noninferiority >0.999) and the primary safety outcome (acute or chronic device and procedure related serious adverse events) occurring in 2.1% vs 1.5% (between-group difference 95% Bayesian credible interval, −1.5 to 2.8; p noninferiority >0.999) [58]. Although these data are reassuring, larger adequate studies are still needed to test whether PFA provides safety or efficacy advantages.

Another novel technique is hybrid ablation (a combination of endocardial and epicardial

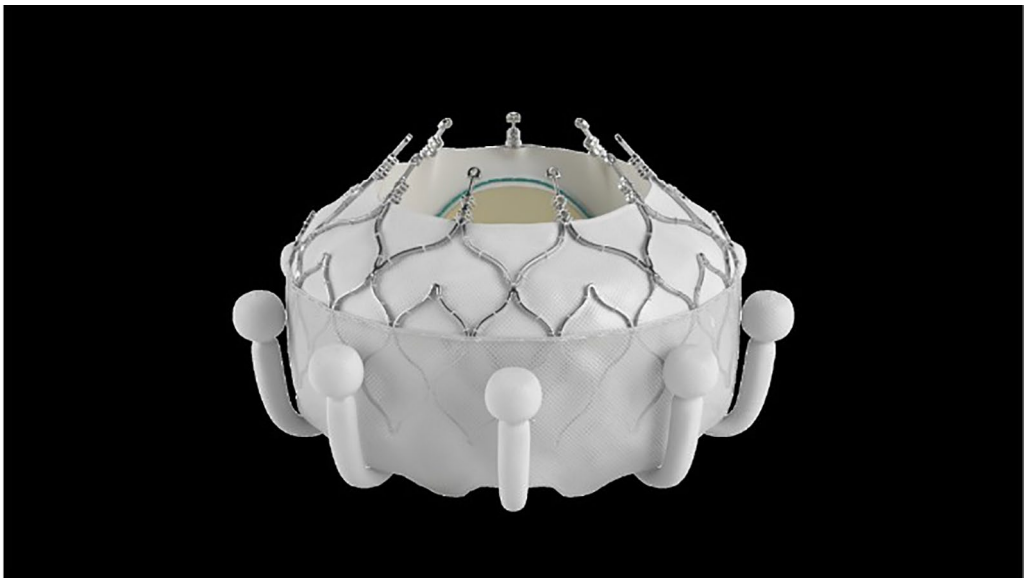

Fig. 2 Edwards EVOQUE transcatheter tricuspid valve replacement system. Figure published with permission from Edwards Lifesciences

ablation). The Efficacy and Safety of Hybrid Epicardial and Endocardial Ablation versus Endocardial Ablation in Patients with Persistent and Long-standing Persistent Atrial Fibrillation (CEASE-AF) study randomised 154 patients with AF (2:1 ratio) to hybrid vs conventional endocardial ablation. At 1 year, the hybrid approach was associated with a marked improved in the primary efficacy endpoint (freedom from AF/atrial flutter/atrial tachycardia > 30 s, absent class I/III anti-arrhythmic drugs except those not exceeding previously failed doses; 71.6% vs 39.2%; absolute increase 32.4% [95% CI 14.3–48.0%], $p < 0.001$) but no difference in the primary safety outcome (major complications within 30 days; 7.8% vs 5.8%; $p = 0.75$) [59]. Given these encouraging findings, larger trials are planned.

The feared complication of atrial-oesophageal fistula following AF ablation was evaluated in a Worldwide Survey on Incidence, Management, and Prognosis of Oesophageal Fistula Formation following Atrial Fibrillation Catheter Ablation (POTTER-AF), which studied data from 553,729 procedures across 214 centres (radiofrequency 62.9%, cryoballoon 36.2%, other 0.9%). In total, 138 patients (0.025%) developed oesophageal fistula (more commonly after radiofrequency 0.038% vs cryoballoon 0.0015%; $p < 0.0001$) with a median time to diagnosis of 21 (range 2–63) days. Oesophageal surgery was performed in 47.4%, direct endoscopic treatment in 19.8% and conservative treatment in 32.8% of patients. Overall mortality was 65.8% but lower following surgical (51.9%) or endoscopic treatment (56.5%) vs conservative management (89.5%) (OR 7.463 [2.414, 23.072], $p < 0.001$) [60]. This highlights the rare but significant mortality of this complication.

AF may worsen outcomes in heart failure patients, but the benefit of catheter ablation remains unclear. The Catheter Ablation in End-Stage Heart Failure with Atrial Fibrillation (CASTLE-HTX) single-centre open-label trial randomised patients to catheter ablation ($n = 97$) vs medical therapy ($n = 97$). Catheter ablation was associated with a 76% reduction in the primary endpoint (composite of death from any cause, implantation of a left ventricular [LV] assist device, or urgent heart transplantation) (8% vs 30%; HR 0.24; 95% CI 0.11–0.52; $p < 0.001$) and 71% reduction of all-cause death (6% vs 20%; HR 0.29; 95% CI 0.12–0.72) [61]. Given the marked benefit in this small study, further larger multicentre studies in this population are warranted.

In patients with LV dysfunction secondary to AF, catheter ablation is recommended as a first-line therapy but it is difficult to predict which patients will have recovery of LV function [55]. A New Prediction Model for Left Ventricular Systolic Function Recovery after Catheter Ablation of Atrial Fibrillation in Patients with Heart Failure (ANTWOORD II) externally validated a previously proposed ANTWERP score employing a retrospective analysis of patients undergoing AF ablation for persistent AF with HFREF ($n=605$). A lower Antwerp score was associated with higher probability of LV function recovery (90% probability if Antwerp score ≤ 2, 47% if score 3 or 4 and 14% if ≥ 5 fewer HF hospitalisations [OR 0.09, 95% CI 0.05–0.18, $p<0.001$] and lower mortality [OR 0.11, 95% CI 0.04–0.31, $p<0.001$]) [62]. This simple scoring system may prove useful to guide which patients with LV dysfunction secondary to AF stand to gain the most from catheter ablation.

High body mass index (BMI) can limit the utility of direct current cardioversion (DCCV) for restoring sinus rhythm and dual defibrillation (400J delivered utilising two sets of pads) may improve efficacy. Aymond et al. randomised 152 patients with AF and obesity (mean BMI 41.2 kg/m²) to dual vs single defibrillator DCCV. Use of dual DCCV was associated with marked reduction in failure to achieve the primary outcome (reversion to sinus rhythm after the first shock) occurring in only 2% vs 14% ($p=0.015$) [63]. Dual DCCV may thus be a useful option in such patients refractory to conventional approaches.

Anticoagulation

Oral anticoagulation is recommended for patients with AF and an elevated CHADSVASC score (2 ≥ in men or 3 ≥ in women) [55]. Improved detection of subclinical AF poses the difficult question of whether to start anticoagulation. The Anticoagulation with Edoxaban in Patients with Atrial High-Rate Episodes (NOAH-AFNET 6) study randomised 2608 patients aged ≥ 65 years with subclinical atrial high rate episodes (AHREs) lasting ≥ 6 min but no prior history of AF to edoxaban 60 mg vs placebo [64]. After a median of 21 months, edoxaban was associated with a numerical but non-significant reduction in the primary efficacy outcome of CV death, stroke or systemic embolism (3.2% vs 4.0%; HR 0.81; 95% CI 0.6–1.08; $p=0.15$) yet an increased primary safety outcome of all cause death or major bleeding (5.9% vs 4.5%; HR 1.31; 95% CI 1.02–1.67; $p=0.03$). However, the trial was stopped early and may thus have been underpowered to detect a small reduction in stroke. The Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Subclinical Atrial Fibrillation (ARTESiA) study randomised 4012 patients with subclinical AF lasting ≥ 6 min to ≤ 24 h and CHADSVASc ≥ 3 to apixaban vs aspirin for a median follow-up of 3.5 ± 1.8 years. Use of apixaban was associated with a 37% reduction in the primary efficacy outcome of stroke or systemic embolus (HR 0.63; 95% CI 0.45–0.88; $p=0.007$) although a higher incidence of major bleeding (1.71% vs 0.94% per patient year; HR 1.80; 95% CI 1.26–2.57; $p=0.001$) [65]. Subsequent metanalysis of NOAH-AFNET 6 and ARTESiA reported a 32% reduction in ischaemic stroke (RR 0.68; 95% CI 0.5–0.92) but no difference in all-cause mortality and increased major bleeding (RR 1.62; 95% CI 1.05–1.17) [66].

Given the increased intracranial haemorrhage with vitamin K antagonists (VKAS) vs oral anticoagulants (OACS), it has been suggested that there may be benefit in switching from VKA to non-VKA OACs (NOACS), especially in patients who are frail, with an inherently higher bleeding risk and more likely to fall. The Safety of Switching from a Vitamin K Antagonist to a Non-Vitamin K Antagonist Oral Anticoagulant in Frail Older Patients with Atrial Fibrillation (FRAIL-AF) multicentre study randomised 1330 patients > 75 (mean age 83) years, taking VKA for AF, switching to NOAC vs ongoing VKA [67]. The trial was stopped early because of futility, with 101 primary outcome events (major or clinically relevant bleeding) versus 62 in the continue arm (HR 1.69, 95% CI 1.23–2.32) suggesting that continuation of a VKA may be preferable in this patient group.

Major bleeding remains a limitation of current OAC strategies. The Abelacimab, a Novel Factor XI/XIa Inhibitor, vs Rivaroxaban in Patients with Atrial Fibrillation (AZALEA-TIMI 71) study randomised 1282 patients with AF to subcutaneous

Abelacimab (either 150 or 90 mg once a month) vs rivaroxaban 20 mg once daily. Abelacimab was associated with significant reduction in the primary outcome of major and clinically relevant nonmajor bleeding (abelacimab 150 mg 2.7/100 patient-years HR 0.33; abelacimab 90 mg 1.9/100 patient-years HR 0.23; vs rivaroxaban 8.1/100 patient-years) but no significant difference in ischaemic stroke (abelacimab 150 mg 1.1/100 patient-years $p=0.42$; abelacimab 90 mg 1.3/100 patient-years; $p=0.28$ vs rivaroxaban 0.7/100 patient-years) [68]. These findings are encouraging although a larger trial fully powered for efficacy endpoints is now needed.

Cardiac Devices and Pacing

Right ventricular (RV) pacing may be associated with late reduction in LV function. The Upgrade of Right Ventricular Pacing to Cardiac Resynchronization Therapy (CRT) in Heart Failure (BUDAPEST CRT UPGRADE) study randomised 360 patients with symptomatic HF with reduced ejection fraction (HFREF) (NYHA III/IV), an ICD or PPM in situ with > 20% RV pacing burden and QRS > 150 ms to CRT-D upgrade vs ICD. At 12 months, use of CRT-D was associated with a marked reduction in the primary composite outcome of all-cause mortality, heart failure hospitalisation or < 15% reduction of left ventricular end-systolic volume (32.4% vs 78.9%; OR 0.11; 95% CI 0.06–0.19; $p<0.001$ and in the secondary outcome of all-cause mortality and heart failure hospitalisation [10.2% vs 31.7%; HR 0.27; 95% CI 0.16–0.47, $p<0.001$]) [69] supporting an upgrade to CRT-D in patients with HFREF and high % RV burden.

The Adaptive versus Conventional Cardiac Resynchronisation Therapy in Patients with Heart Failure (ADAPT RESPONSE) trial randomised 3617 patients to adaptive CRT (LV pacing synchronised to fuse with intrinsic right bundle conduction vs conventional CRT). The trial was stopped early because of futility after a median follow-up of 59 months with adaptive CRT failing to show significant reduction in the primary composite outcome of all-cause death or intervention for heart failure decompensation (23.5% vs 25.7% at 60 months; HR 0.89, 95% CI 0.78–1.01; $p=0.077$) [70].

Sudden Cardiac Death and Arrhythmia

People identified with genetic heart conditions associated with increased sudden cardiac death have historically been restricted from competitive sports. Martinez et al. investigated outcomes in 76 elite athletes with a diagnosis of genetic heart disease (hypertrophic cardiomyopathy [53%], long QT syndrome [23%], others [26%]) of whom 63% were asymptomatic and 72% had initially been disqualified from sport but after clinical evaluation had unrestricted return to play policies [71]. After a mean of 7 ± 6-year follow-up there was only one (1.3%) exercise-related and two non-exercise-related adverse cardiac events, none of which were fatal. This small study suggests that if appropriate return to play policies are implemented, the risk of adverse cardiac events may be low.

Similarly, the Vigorous Exercise in Patients with Hypertrophic Cardiomyopathy (LIVE-HCM) study [72] prospectively evaluated 1660 patients with clinical HCM ($n=1534$) or gene-positive, phenotype-negative status ($n=126$) according to their level of physical activity: vigorous exercise (42%) vs non vigorous (moderate 43%, sedentary 15%). Interestingly, after follow-up of between 3–7 years, participation in vigorous exercise was not associated with any difference in the composite endpoint of death, resuscitated sudden cardiac arrest, arrhythmic syncope or appropriate shock from an ICD (4.7% vs 4.6%; HR 1.01; 95% CI 0.68–1.48; $p=0.98$).

PREVENTION

Consensus statements from the American Heart Association in 2023 have highlighted the emerging importance of fully capturing patient multimorbidity to improve prediction of CV risk, such as development of PREVENT risk equations to evaluate cardio-kidney-metabolic syndrome (CKMS) [73–75] and consideration of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) [76].

Indeed, targeting cardio-metabolic pathways as a treatment target has been the focus of must interest with new therapies such as

GLP-1 receptor agonists for weight reduction gaining much attention. While their effectiveness for weight reduction in patients with or without diabetes is well recognised, it has been unclear whether such weight reduction is associated with CV outcome benefit. The Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) study randomised 17,604 patients without diabetes (mean age 61.6; 72.3% men, mean BMI of 33.3 kg/m^2, mean HbA1c 5.8%) to semaglutide vs placebo. At an average follow-up of 39.8 months, semaglutide was associated with a 20% reduction in the primary composite outcome of CV death, MI or stroke (6.5% vs 8.0%; HR 0.80, 95% CI 0.72–0.90, $p<0.001$). Aside from increased GI side effects leading to higher treatment discontinuation (16.6% vs 8.2%; $p<0.001$), there were no unexpected safety concerns [77] (Fig. 3).

In addition to weight reduction, increased exercise is often encouraged to reduce CV risk. The MASTER@HEART study evaluated coronary atherosclerosis in lifelong endurance athletes ($n=191$), late onset (after 30 years) endurance athletes ($n=191$) and healthy non-athletes ($n=176$). Interestingly, lifelong endurance athletes vs non-athlete controls had a higher incidence of coronary atherosclerosis (≥1 coronary plaque OR 1.86; 95% CI 1.17–2.94) including proximal non-calcified plaque (OR 2.80; 95% CI 1.39–5.65) (Fig. 4). In addition, lifelong vs late onset endurance athletes had a higher athlete incidence of ≥50% stenosis in any coronary segment (OR 2.79; 95% CI 1.20–6.50) including ≥50% stenosis in a proximal segment (OR 5.92; 95% CI 1.22–28.80). These data highlight the importance of not underestimating CV risk in apparently fit athletes and may even suggest moderate rather than endurance exercise is preferable from a CV perspective although larger prospective, ideally randomised, trials with hard outcomes are needed [78].

With a class IA indication in ESC guidance, statins remain the cornerstone of lipid-lowering therapy [79]. However, many patients are intolerant of or do not wish to take statin therapy. Effective low-density lipoprotein (LDL) cholesterol lowering may also be achieved using the ATP citrate lyase inhibitor bempedoic acid but, until now, outcome data have been lacking [11]. The Bempedoic Acid and Cardiovascular Outcomes in Statin-intolerant Patients (CLEAR-Outcomes) study randomised 13,970 statin-intolerant patients with or at high risk of CV disease to oral bempedoic acid 180 mg vs placebo. At a median follow-up of 40.6 months, bempedoic acid was associated with a 13% reduction in the primary composite endpoint of CV death MI, stroke or coronary revascularisation (11.7% vs 13.3%; HR 0.87; 95% CI 0.79–0.96; $p=0.004$) and a 23% reduction in MI (3.7% vs 4.8%, HR 0.77; 95% CI 0.66–0.91; $p=0.002$) [80].

While current pro-protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are highly efficacious for LDL cholesterol lowering, patient acceptability may be limited the need for frequent (every 2–4 weeks) subcutaneous injections. Recaticimab is a long-acting PCSK9 inhibitor, which may enable less frequent injections. The Recaticimab Add-on Therapy in Patients with Non-familial Hypercholesterolaemia and Mixed Hyperlipidemia (REMAIN-2) multicentre study undertaken in China randomised 692 patients not at their lipid goal despite moderate to high intensity statin plus ≥ one other lipid-lowering drug to (1) recaticimab 150 mg vs placebo every 4 weeks, (2) recaticimab 300 mg vs placebo every 8 weeks or (3) recaticimab 450 mg vs placebo every 12 weeks. Recaticimab achieved marked between-group differences in LDL cholesterol vs placebo at 24 weeks whether given at 4, 8 or 12 weekly intervals (–62.2%, –59.7% and –53.4%, respectively) [81].

MK-0616 is a new oral, renally excreted, macrocyclic peptide, which binds to PCSK9. In a phase 2b trial 381 patients were randomised (1:1:1:1:1) to one of four MK-0616 doses (6, 12, 18 or 30 mg daily) vs placebo. At 8 weeks, all MK-0616 doses showed significant ($p<0.001$) reduction in LDL from baseline but similar rates of adverse events. Although oral treatment may be cheaper and more acceptable to patients, further studies are required to assess long-term efficacy, safety, adherence and clinical event reduction [82].

Lipoprotein (a) is associated with increased CV risk but has been difficult to treat with conventional lipid-lowering therapy [4]. Lepodisiran, a small interfering RNA which targets *LPA* (the gene encoding for apolipoprotein(a) from

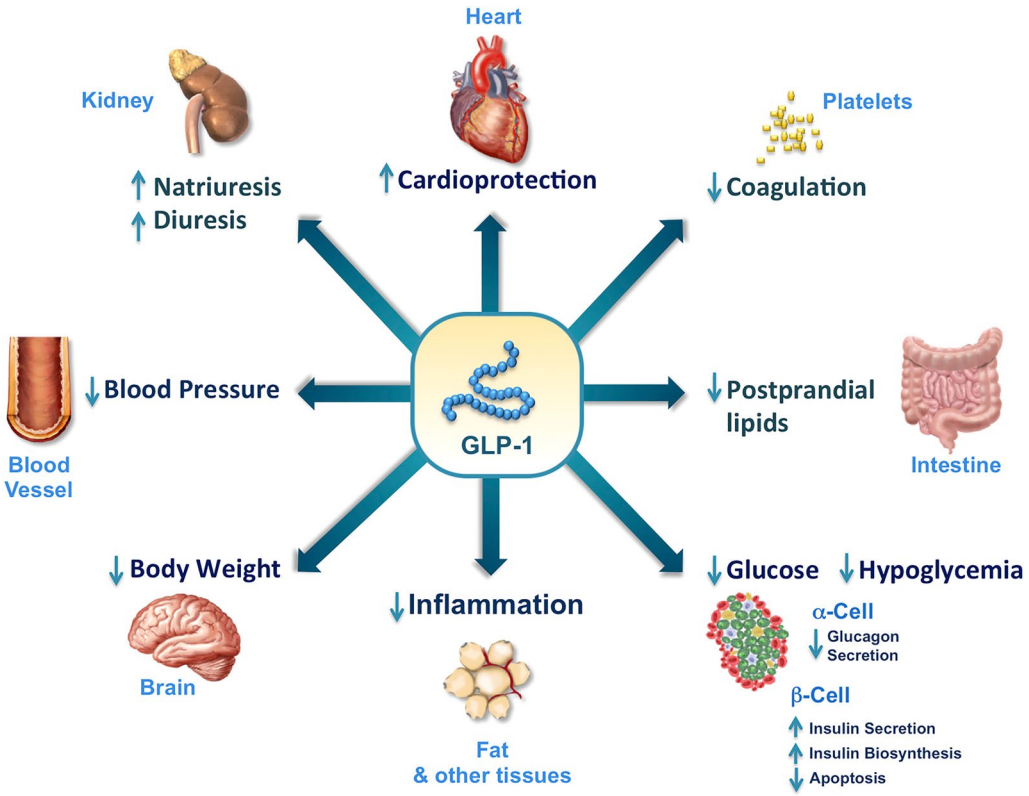

Fig. 3 Illustrating demonstrating the various end organ effects mediated by GLP-1 agonism regarding cardiovascular risk modification. Illustration reproduced with permission from Cell Metabolism, 24, DJ Drucker, The cardiovascular biology of glucagon-like peptide-1, 15–30, copyright (2016), with permission from Elsevier. *GLP-1* glucagon-like peptide-1

which the liver synthesises liprotein[a]) underwent a phase 1, dose-escalating study, in which 48 patients were randomised to lepodisiran vs placebo. Lepodisiran was associated with a marked reduction of lipoprotein(a) from baseline vs placebo (–41% [IQR, –47% to –20%] and –5% [IQR, –16% to + 11%], respectively). Lepodisiran was well tolerated and further studies are awaited [83].

Retrospective clinical data have suggested that atorvastatin may reduce cardiac dysfunction associated with anthracycline use. The Statin Therapy Associated with Reduced Heart Dysfunction from Anthracyclines (STOP-CA) multicentre trial [84] randomised 300 patients with lymphoma undergoing anthracycline treatment to atorvastatin 40 mg vs placebo, of whom 286 (95%) completed the study. Baseline LV ejection fraction (LVEF) was 63 ± 4.6%. Use of atorvastatin was associated with significant reduction in the primary endpoint of ≥ 10% fall in LVEF where the final LVEF was < 55% (9% vs 22%; $p = 0.002$) and in the secondary outcome of ≥ 5% fall in LVEF where the final LVEF was < 55% (13% vs 29%; $p = 0.001$) but with no significant difference in adverse events. These findings strongly support the use of atorvastatin in this setting. Whether it extends to other cancers/chemotherapies is unknown.

Hypertension remains poorly managed at a global level. The Effect of Dietary Sodium on Blood Pressure: a Crossover Trial (CARDIA-SSBP) randomised 213 patients to a low-sodium (500 mg/day) vs high-sodium (usual diet plus 2.2 g [~ 5 g total]/day) diet for 1 week before being switched to the other diet for another week. At the end of the first week, the low vs high sodium diet was associated with

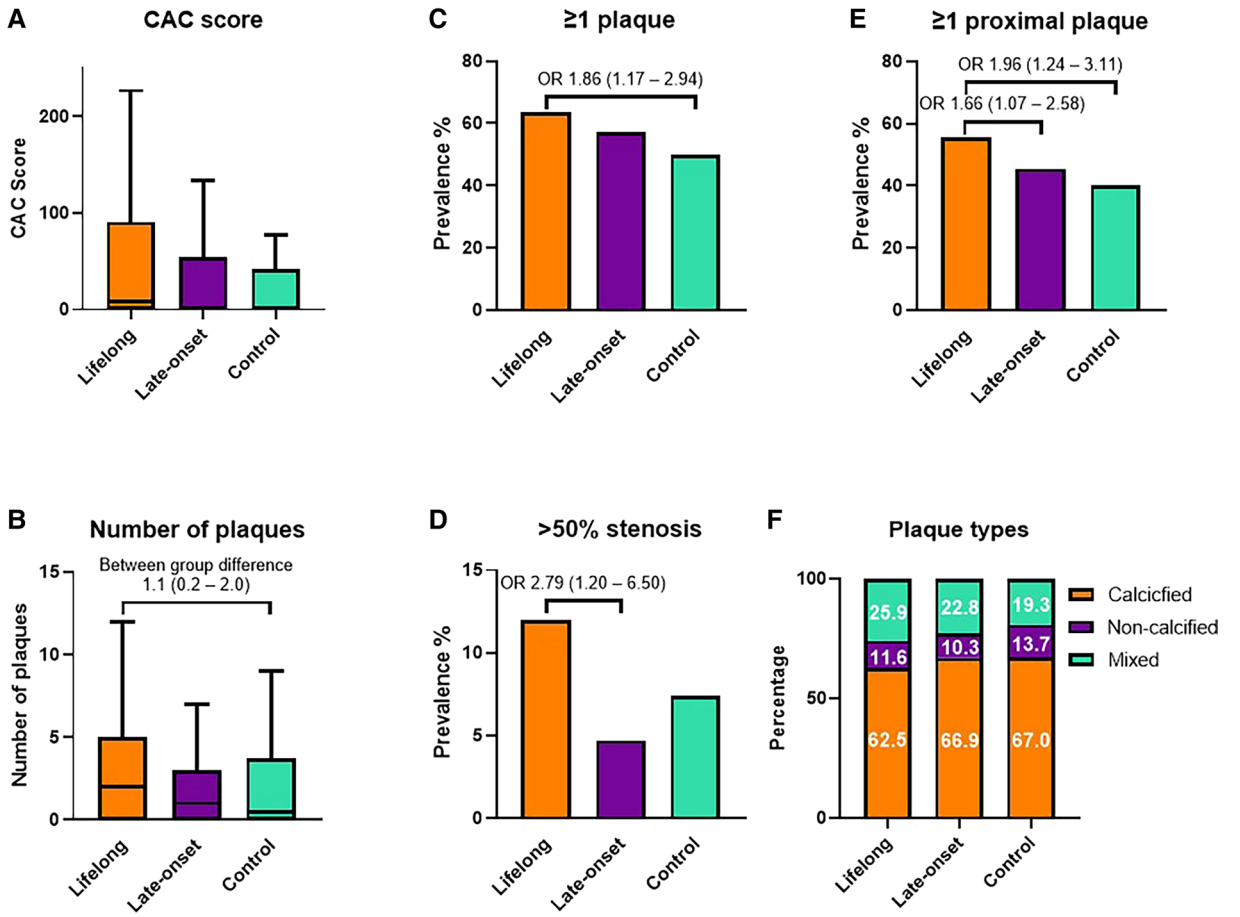

Fig. 4 Simple and cluster bar charts demonstrating differences in multiple markers of coronary atherosclerosis as evidenced on CTCA relative to level of exercise (lifelong athletes, late-onset athletes and non-athletic controls). Illustration reproduced with permission from European Heart Journal, 44, R De Bosscher et al., Lifelong exercise and its relation to coronary atherosclerosis, 2388–2399, copyright (2023), reprinted under Creative Commons CC-BY-NC, with permission from Oxford University Press. *CTCA* computed tomography coronary angiography; *CAC* coronary artery calcification score; *OR* odds ratio

significantly lower mean systolic BP (between group difference – 8 mmHg (95% CI –4 to –11 mmHg; $p<00.0001$). Overall, the low-sodium diet reduced systolic blood pressure from baseline in 73.4% of patients, with 46% having > 5 mmHg reduction (meeting the definition of being salt sensitive) and highlighting the importance of reducing dietary salt as part of hypertension management [85].

Hypertensive disorders of pregnancy are associated with increased CV risk. The Physician-Guided Self-Monitoring Improves Blood Pressure (BP) after Hypertensive Pregnancy (POP-HT) study randomised 220 women from a single UK centre requiring post-natal antihypertensive medication (preeclampsia 60%, gestational hypertension 40%) to an intervention group (self-monitoring plus research physician-optimised antihypertensive titration) vs usual care (from primary care physician and midwife). At 9 months postpartum, those assigned to the intervention group had significantly lower mean 24-h BP (114/71.2 vs 120.3/76.6 mmHg) and fewer women required readmission for blood pressure (7% vs 27%; $p<0.001$; number needed to prevent = 5) [86]. In an imaging substudy [87], those assigned to the intervention group by echo ($n=101$ of 187) had lower LV relative

wall thickness (ratio 0.06; 95% CI 0.07–0.05, $p = < 0.001$) and by cardiac MRI ($n = 93$ or 174) had lower LV mass (–6.37 g/m^2; $p < 0.001$), lower end diastolic volume (–3.87 ml/m^2, $p = 0.009$), lower end systolic volume (–3.25 ml/m^2, $p < 0.001$) and higher LVEF (2.6%, $p < 0.001$) supporting the need to enhance supervision of postnatal hypertension management.

The importance of hypertension management in cerebrovascular health was illustrated in the China Rural Hypertension Control Project. This previously discussed trial [16] published new data reporting that the intervention group, in which a large, sustained reduction in BP was obtained, had a 15% reduction in the annual rate of all-cause dementia vs the usual care group (1.12% vs 1.31%; HR 0.85; 95% CI 0.76–0.95) and lower annual rate of cognitive impairment without dementia (4.19% vs 5.02%; HR 0.84; 95% CI 0.80–0.87) [88].

HEART FAILURE

The mechanism of benefit for SGLT2 inhibitors in heart failure remains poorly understood. Despite having a class Ia recommendation. The Cardiac and Metabolic Effects of Dapagliflozin in Heart Failure with Preserved Ejection Fraction (CAMEO-DAPA) single-centre study randomised 38 patients with NYHA II/III, EF > 50% and elevated pulmonary capillary wedge pressure (PCWP) to dapagliflozin 10 mg OD vs placebo. At 24 weeks, dapagliflozin vs placebo resulted in a 3.5 mmHg lower resting PCWP ($p = 0.029$) and 6.1 mmHg lower exercise PCWP ($p = 0.019$) pointing to one potential mechanism of benefit in HFpEF [89].

The Dapagliflozin in Myocardial Infarction without Diabetes or Heart Failure (DAPA-MI) registry-based trial randomised 4017 patients (mean age 63 years; 20% female; mean eGFR 83.5 ml/min/1.73 m^2) presenting with acute MI and impaired LV function (but no prior heart failure or diabetes) to dapagliflozin 10 mg vs placebo. At 1 year, dapagliflozin did not significantly reduce CV death or hospitalisation for heart failure (HFh) (2.5% vs 2.6%; HR 0.95; 95% CI 0.64–1.40). Given low event rates, the primary analysis was changed mid-trial to a win ratio analysis of a hierarchical composite of CV plus cardiometabolic outcomes resulting in more wins for dapagliflozin (win ratio, 1.34; 95% CI, 1.20–1.50; $p < 0.001$) [90].

The potential benefit of natriuresis with a SGLT2 inhibitor was assessed in the Early Initiation of Dapagliflozin Benefits Patients with Acute Heart Failure (DICTATE-HF) multicentre open-label trial which randomised 240 patients (median age 64 years; 39% female; 71% T2DM) admitted with acute decompensated heart failure (with or without type 2 diabetes, eGFR ≥ 25 ml/min/1.73 m^2) to intravenous loop diuretics plus dapagliflozin vs intravenous loop diuretics alone. Use of dapagliflozin significantly increased 24-h natriuresis ($p = 0.025$), increased 24-h urine output ($p = 0.005$), decreased time to completing IV diuretic therapy ($p = 0.006$) and decreased time to hospital discharge ($p = 0.007$). However, dapagliflozin failed to improve the primary outcome of diuretic efficiency at 5 days (defined as cumulative weight change divided by cumulative loop diuretic dose; $p = 0.06$) [91].

In addition to beneficial CV risk data discussed earlier, new data were presented for semaglutide in heart failure. The Semaglutide in Patients With Obesity and Heart Failure Across Mildly Reduced or Preserved Ejection Fraction (STEP-HF) study randomised 529 patients (median age 69 years; 56.1% female; median body weight 105.1 kg) without diabetics but with obesity (BMI ≥ 30 kg/m^2), LVEF ≥ 45% and ≥ 1 heart failure risk marker to semaglutide 2.4 mg/week vs placebo. At 1 year, semaglutide vs placebo improved the co-primary endpoints of KCCQ clinical summary score (+ 7.8 points; 95% CI 4.8–10.9; $p < 0.001$) and body weight (– 10.7%; 95% CI – 11.9 to – 9.4; $p < 0.001$) and the secondary endpoint of 6-min walk distance (21.5 vs 1.2 m; $p < 0.001$) with reductions noted in C-reactive protein and NT-proBNP. There was no heterogeneity across LVEF groups [92].

The safety and efficacy of starting sacubitril valsartan soon after heart failure decompensation were assessed in the Prospective Comparison of ARNI with ARB Given Following StabiLization In DEcompensated HFpEF (PARAGLIDE

HF) study which randomised 466 patients (LVEF > 40%, within 30 days of worsening heart failure) to sacubitril-valsartan vs valsartan. Over 8-week follow-up, sacubitril-valsartan was associated with a 15% greater time-averaged reduction in NT-proBNP ($p = 0.049$) and reduced worsening renal function (OR 0.61; 95% CI 0.40–0.93) but increased symptomatic hypotension (OR 1.73; 95% CI 1.09–2.76) [93] (Fig. 5). The Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies (STRONG-HF) trial previously reported that rapid up-titration of heart failure therapy (within 2 weeks) vs usual care was associated with reduced death/HF hospitalisation but at a cost of a 10% increase in adverse events [16]. A post hoc analysis of the rapid up-titration arm of the trial was thus undertaken to assess whether safety concerns would negatively impact up-titration speed and hence possibly outcomes. Over 6-week follow-up, 57.7% of patients triggered one or more safety indicators (eGFR < 30 ml/min/1.73 m^2, potassium > 5.0 mmol/l, SBP < 95 mmHg, heart rate < 55 bpm, NT pro-BNP > 10% higher than pre-discharge), which was associated with achieving a lower mean percentage of optimal drug doses (–11.0%; 95% CI –13.6 to –8.4%; $p < 0.001$) and a lower EURO-QoL score ($p = 0.015$) but no difference in the primary endpoint of 180-day death/HF readmission (15.0% vs 14.2%; HR 0.84, 95% CI 0.48–1.46, $p = 0.540$) [94] (Fig. 6).

A virtual care team approach may help facilitate timely heart failure therapy optimisation. The Virtual Optimization of Guideline-directed Medical Therapy in Hospitalized Patients with Heart Failure with Reduced Ejection Fraction (IMPLEMENT-HF) randomised 252 in-hospital encounters in patients with LVEF ≤ 40% to a virtual team vs usual care approach. A virtual team approach was associated with an increased new initiations (44% vs 23%; $p = 0.001$) and drug dose intensifications (44% vs 24%; $p = 0.002$) but with no significant difference in adverse events ($p = 0.30$) suggesting virtual teams represent a centralised and scalable approach to optimise heart failure therapy [95].

Natriuresis-guided therapy has been suggested to as a method of individualising optimum patient treatment. The Pragmatic Urinary Sodium-Based Algorithm in Acute Heart Failure (PUSH-AHF) study randomised 310 patients with acute decompensated heart failure requiring intravenous loop diuretics to natriuresis-guided therapy (with additional diuretic if urine sodium < 70 mmol/l at 2, 6, 12, 18, 24 and 36 h) vs usual care. The natriuresis-guided group achieved the co-primary endpoint of higher natriuresis at 24 h (409 vs 345 mmol; $p = 0.0061$) but no difference in death/heart failure hospitalisation at 180 days (31% vs 31%; $p = 0.70$) or any reduction in length of hospital stay [96].

Evaluating another method optimising diuresis and natriuresis, a prespecified analysis of the Renal Function and Decongestion with Acetazolamide in Acute Decompensated Heart Failure (ADVOR) study assessed whether the beneficial decongestion effects of acetazolamide were consistent in lower vs higher renal function cohorts. Within the 519 randomised patients, median eGFR was 40 ml/min/1.73 m^2. While acetazolamide consistently increased the likelihood of decongestion across the entire spectrum of eGFR (p-interaction = 0.977), natriuresis and diuresis were more pronounced in patients with low eGFR (p-interaction < 0.007). Although acetazolamide was associated with a higher incidence of worsening renal function (rise in creatinine ≥ 0.3 mg/dl) (40.5% vs 18.9%; $p < 0.001$), there was no difference in creatinine after 3 months ($p = 0.565$) [97]. Of note, ADVOR excluded concurrent SGLT2 inhibitor use as it also acts at the proximal tubule; hence, the efficacy of acetazolamide in conjunction with SGLT2 inhibition requires further study.

Current ESC guidelines recommend intravenous (IV) iron in symptomatic patients with HFrEF or HFmrEF and iron deficiency to improve quality of life but its effects on clinical events remain unclear. The Ferric Carboxymaltose in Heart Failure with Iron Deficiency (HEART-FID) study randomised 3065 patients with HFrEF ≤ 40% and iron deficiency to IV ferric carboxymaltose vs placebo. While ferric carboxymaltose had an acceptable adverse-event profile and was associated with modest numerical reduction in death at 12 months (8.6% vs 10.3%), heart failure hospitalisation at 12 months (297 vs 332 patients) and greater change in 6-min walk duration from baseline to

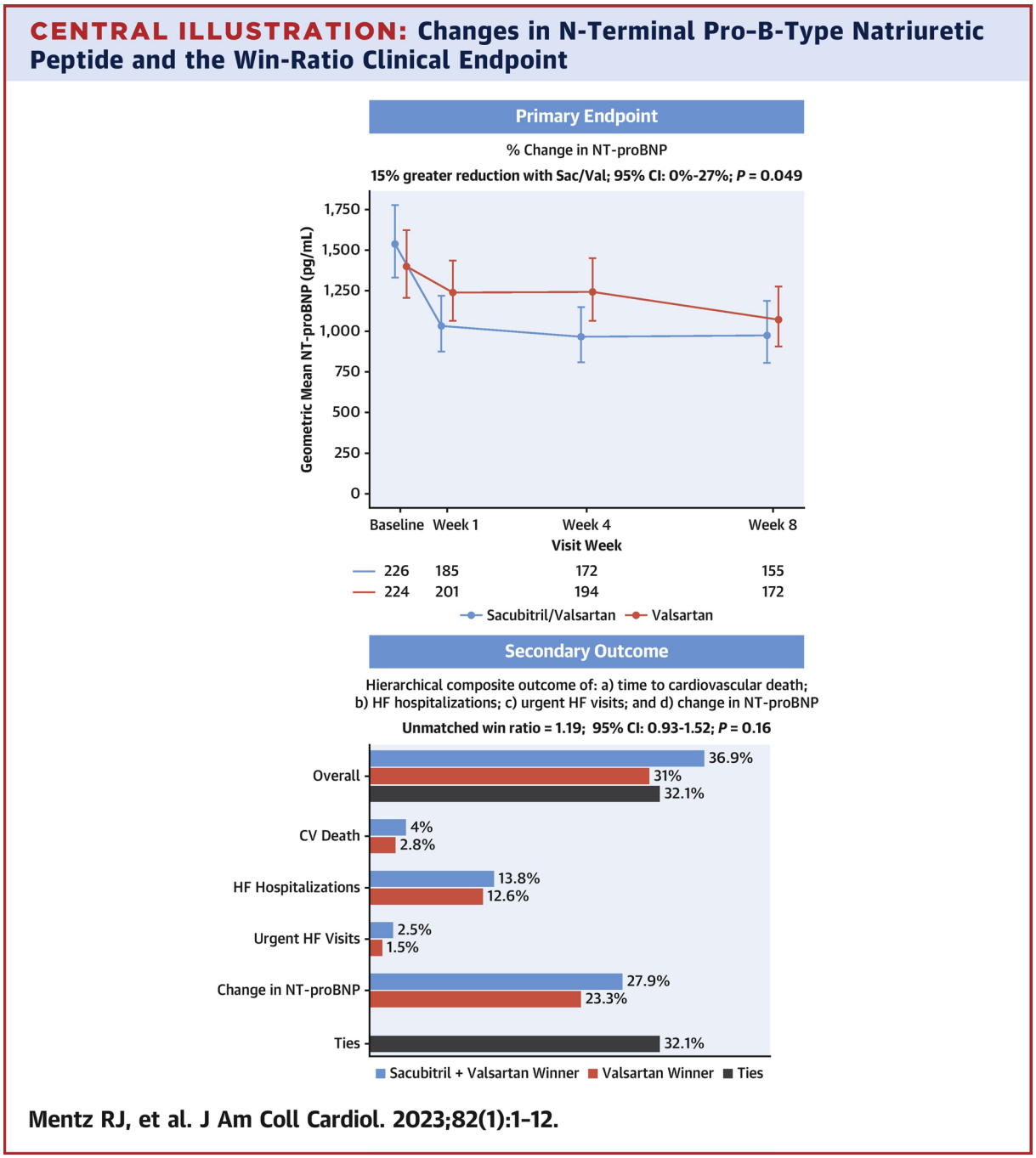

Fig. 5 Central illustration reproduced from the PARAGLIDE-HF study demonstrating mean change in NT-proBNP in patients treated with sacubitril/valsartan versus valsartan control group. Mentz et al. Angiotensin-neprilysin inhibition in patients with mildly reduced or preserved ejection fraction and worsening heart failure. J Am Coll Cardiol. 2023 Jul, 82 (1) 1–12. Reproduced with permission from Elsevier under the Creative Common license. *NT-pro BNP* N-terminal pro-B type natriuretic peptide; *CI* confidence interval; *HF* heart failure; *CV* cardiovascular

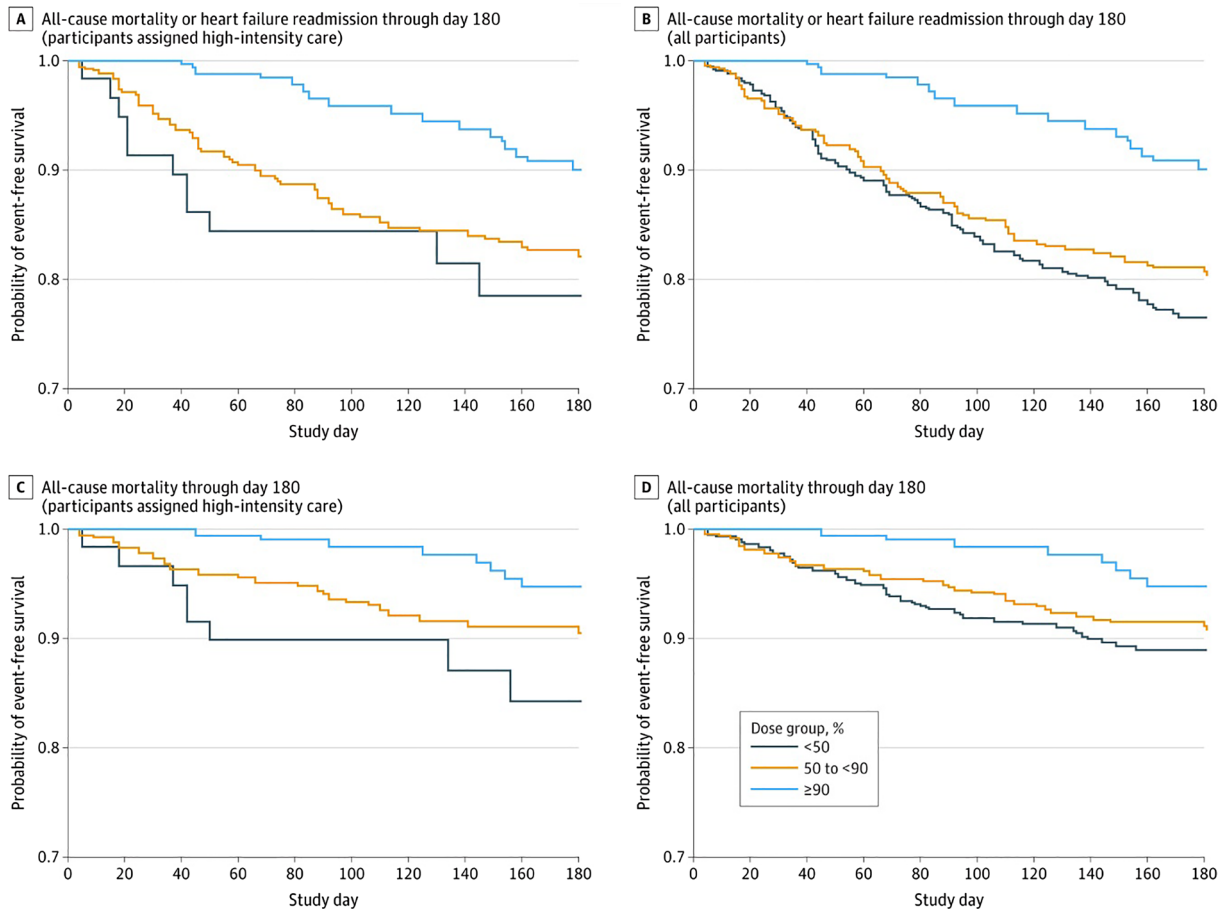

Fig. 6 A post hoc analysis of the STRONG-HF trial with Kaplan-Meier curves demonstrating relationship of event-free survival from the primary outcome (composite of first HF rehospitalisation or all-cause death at day 180) and % dose of GDMT achieved in patients with HF. **A** All-cause mortality or heart failure readmission through day 180 (patients assigned high-intensity care). **B** All-cause mortality or heart failure readmission through day 180 (all patients). **C** All-cause mortality through day 180 (patients assigned high-intensity care). **D** All-cause mortality through day 180 (all patients). Cotter G et al. Optimization of evidence-based heart failure medications after an acute heart failure admission: A secondary analysis of the STRONG-HF randomized clinical trial. JAMA Cardiol. 2024. Reproduced under creative common license with permission of Journal American Medical Association. *GDMT* guideline-directed medical therapy; *HF* heart failure

6 months (8 vs 4 m), unfortunately the primary hierarchical composite did not meet the prespecified significance level of $p<0.01$ (Wilcoxon-Mann-Whitney $p=0.02$; unmatched win ratio, 1.10; 99% CI 0.99–1.23) [98].

Current treatment options for transthyretin amyloid cardiomyopathy (ATTR-CM) are limited. Tafamidis has a 1B ESC recommendation but is not currently recommended by NICE because of uncertainty regarding cost-effectiveness (further review is expected in 2024). Acoramidis is a new oral high-affinity transthyretin stabiliser (>90% stabilisation). The Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy (ATTRIBUTE-CM) study randomised (2:1) patients with ATTR-CM to acoramidis HCl 800 mg BD vs placebo. At 30 months, a hierarchical analysis consisting of death, CV-related hospitalisation, change in NT-proBNP and change in 6-min walk distance had an overall win ratio favouring acoramidis (win ratio 1.77, 95% CI

1.42–2.22; $p<0.0001$), including a 50% reduction in CV hospitalisation but no significant reduction in death [99]. As with tafamidis, the adoption of acoramidis may depend on estimated cost-effectiveness.

LIMITATIONS

While all summarised trials were presented at major cardiology conferences in 2023, not all trials were published in peer-reviewed journals at time of publication of this review paper.

CONCLUSION

This paper has highlighted and summarised the key cardiology trials that were published and presented during 2023 with many trials likely to impact on clinical practice and influence guideline development. This year, emerging evidence for the use of abbreviated anti-platelet strategies in PCI as well robust data supporting the use of intravascular imaging to guide coronary interventions has been presented. Additionally, long-term data supporting TAVI in patients with low surgical risk as well as data supporting transcatheter TEER in patients with severe TR was noted. Notable data in HF and prevention included the positive data for GLP-1 receptor agonism in both prevention of CV events and HF events in the SELECT and STEP-HF trials respectively.

Future research into expanding technological advancement in structural intervention as well as evolving iterations in stent design are anticipated. Additionally, greater evaluation of metabolic pathways and their implications in CV disease are likely to be of interest along with new therapies which may lead to paradigm shifts in the management of dyslipidaemias, such as targeted therapies for reduction of lipoprotein (a).

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Author Contributions. Patrick Savage—Lead author, collated clinical trials for review and divided sections across authors. Wrote structural, ACS and antiplatelet sections as well as abstract, introduction and compilation of all sections into one document. Implemented final edits from supervising consultant and reviewers. Brian Cox—Wrote intervention section. Bronagh Kelly—Wrote Heart failure and prevention section; Michael Shahmohammadi—Wrote EP/Devices section; Ian Menown—Supervising consultant. Guided style and format of review paper. Reviewed and edited final document with changes fed back to and incorporated into final paper by lead author.

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Declarations

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