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REVIEW

Advances in Clinical Cardiology 2019: A Summary of Key Clinical Trials

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ABSTRACT

Introduction: A large number of important clinical trials in cardiology were published or presented at major international conferences during 2019. This paper aims to offer a concise overview of these significant advances and to put them into clinical context.

Methods: Trials presented at the major international cardiology meetings during 2019 were reviewed including The American College of Cardiology (ACC), Euro PCR, The European Society of Cardiology (ESC), Transcatheter Cardiovascular Therapeutics (TCT), and the American Heart Association (AHA). In addition to this a literature search identified several other publications eligible for inclusion based on their relevance to clinical cardiology, their potential impact on clinical practice and on future guidelines.

Results: A total of 70 trials met the inclusion criteria. New interventional and structural data include trials examining use of drug-coated balloons in patients with acute myocardial infarction (MI), interventions following shockable cardiac arrest, mechanical circulatory support in cardiogenic shock complicating MI, intervention in stable coronary artery disease, surgical or percutaneous revascularisation strategies in left main coronary artery disease, revascularisation strategy in ST elevation MI, transcatheter aortic valve replacement in low-risk patients, and percutaneous mitral or tricuspid valve interventions. Preventative cardiology data included the use of sodium–glucose cotransporter 2 (SGLT2) inhibitors (dapagliflozin), proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors (evolocumab), bempedoic acid, and novel approaches to the management of hypertension. Antiplatelet data included trials evaluating both the optimal length of course and combination of antiplatelet agents and regimes including combination antithrombotic therapies for patients with atrial fibrillation. Heart failure data included trials of sacubitril–valsartan in heart failure with preserved ejection fraction and the use of SGLT2 inhibitors in patients with heart failure but without diabetes. Electrophysiology data included trials examining alcohol in atrial fibrillation and the use of wearable fitness devices for identifying atrial fibrillation.

Conclusion: This article presents key clinical trials completed during 2019 and should be valuable to clinicians and researchers working in cardiology.

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Keywords: Acute coronary syndrome; Anticoagulation; Atrial fibrillation; Cardiology; Coronary revascularisation; Heart failure; Lipids; Mitral clip; Myocardial infarction; Transcatheter aortic valve implantation

Key Summary Points

Includes details of 70 important cardiology trials that were published or presented at key meetings during 2019.

A concise overview of the findings of these trials.

Research that will impact on and likely change clinical cardiology practice included.

Research into interventional and structural cardiology, acute coronary syndromes, heart failure, electrophysiology and disease prevention detailed.

INTRODUCTION

A multitude of clinical trials were published and presented during 2019, with the potential to impact on cardiology clinical practice and influence future guidelines, including presentations at The American College of Cardiology (ACC), EuroPCR, European Society of Cardiology (ESC), Euro PCR, Transcatheter Cardiovascular Therapeutics (TCT) and the American Heart Association (AHA). In this paper we review key studies within the categories of interventional cardiology, structural cardiology, cardiovascular (CV) prevention, acute coronary syndrome (ACS), electrophysiology and heart failure.

METHODS

The results of clinical trials presented at major international cardiology meetings in 2019 were reviewed. In addition to this 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 assessed for relevance to clinical cardiology and the potential impact on clinical practice and future guidelines. 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.

ADVANCES IN INTERVENTIONAL CARDIOLOGY

Identification of patients at high bleeding risk (HBR) is of utmost importance. The Academic Research Consortium for High Bleeding Risk (ARC-HBR) reviewed the available evidence and developed a consensus definition of HBR as patient with $\geq$ 4% risk of Bleeding Academic Research Consortium (BARC) grade 3–5 bleeding or $\geq$ 1% risk of intracranial haemorrhage (ICH) at 1 year [1]. Major and minor clinical predictors for HBR are listed in Table 1 (patients are considered to be at HBR if at least one major and two minor criteria are met).

The Randomised Controlled Trial with Resolute Onyx in One Month Dual Antiplatelet Therapy (DAPT) for high-bleeding risk patients (Onyx ONE) randomised 1996 patients to percutaneous coronary intervention (PCI) with either the Resolute Onyx durable polymer drug-eluting stent (DES) or BioFreedom polymer free drug-coated stent (DCS) [2]. All patients were at high risk of bleeding and all received 1 month of DAPT. The primary safety composite outcome of cardiac death, myocardial infarction (MI) or stent thrombosis for Resolute Onyx vs. BioFreedom was 17.1% vs. 16.9% respectively, which met criteria for non-inferiority. Further comparison of Resolute Onyx with the new-generation very thin-strut Biofreedom Ultra would be useful.

Use of very thin-strut or ultrathin-strut DES during PCI may reduce risk of major adverse cardiovascular events (MACE) compared with thicker strut stents, but previous data have been

Table 1 Major and minor criteria for HBR at the time of PCI [1]

Major criteria for high bleeding risk	Minor criteria for high bleeding risk
Anticipated long-term oral anticoagulation	Age $\geq$ 75 years
Severe or end-stage CKD (eGFR $<$ 30 ml/min)	Moderate CKD (eGFR 30–59 ml/min)
Haemoglobin $<$ 11 g/dl	Haemoglobin:
	11–12.9 g/dl for male patients
	11–11.9 g/dl for female patients
Spontaneous bleeding requiring hospitalisation or transfusion:	Spontaneous bleeding requiring hospitalisation or transfusion within the last 12 months not meeting the major criteria
Within 6 months if isolated	
Ever if recurrent	
Moderate or severe baseline thrombocytopenia ($< 100 \times 10^8$/l)	Long-term use of oral NSAIDs or steroids
Chronic bleeding diathesis	Ischaemic stroke at any time not meeting the major criteria
Liver cirrhosis with portal hypertension	
Active malignancy within the last 12 months (excluding non-melanoma skin cancer)	
ICH/stroke:	
Previous spontaneous ICH at any time	
Traumatic ICH within the last 12 months	
Presence of a bAVM	
Moderate or severe ischaemic stroke within the last 6 months	
Non-deferrable major surgery on DAPT	
Recent major surgery or major trauma within the 30 days before PCI	

bAVM brain arteriovenous malformation, *CKD* chronic kidney disease, *DAPT* dual antiplatelet therapy, *eGFR* estimated glomerular filtration rate, *ICH* intracranial haemorrhage, *NSAID* non-steroidal anti-inflammatory drug, *PCI* percutaneous coronary intervention

limited. First clinical outcomes of the thinner strut (84–88 μm) cobalt chromium biolimus-eluting Biomatrix Alpha stent (n = 400) were compared with the BioMatrix Flex (120 μm) arm (n = 857) of the LEADERS study as historical control [3].

The primary endpoint of cardiac death, MI or clinically indicated target vessel revascularisation (TVR) at 9 months for the Biomatrix Alpha stent was 3.94% (upper limit 5.98%) which met pre-specified criteria for non-inferiority compared with a 9.28% MACE rate reported for the Biomatrix Flex arm in LEADERS (P non-inferiority $<$ 0.001) (Fig. 1). Only one patient (0.25%) experienced definite or probable stent thrombosis. The low rate of MACE and stent thrombosis from an all comers population is

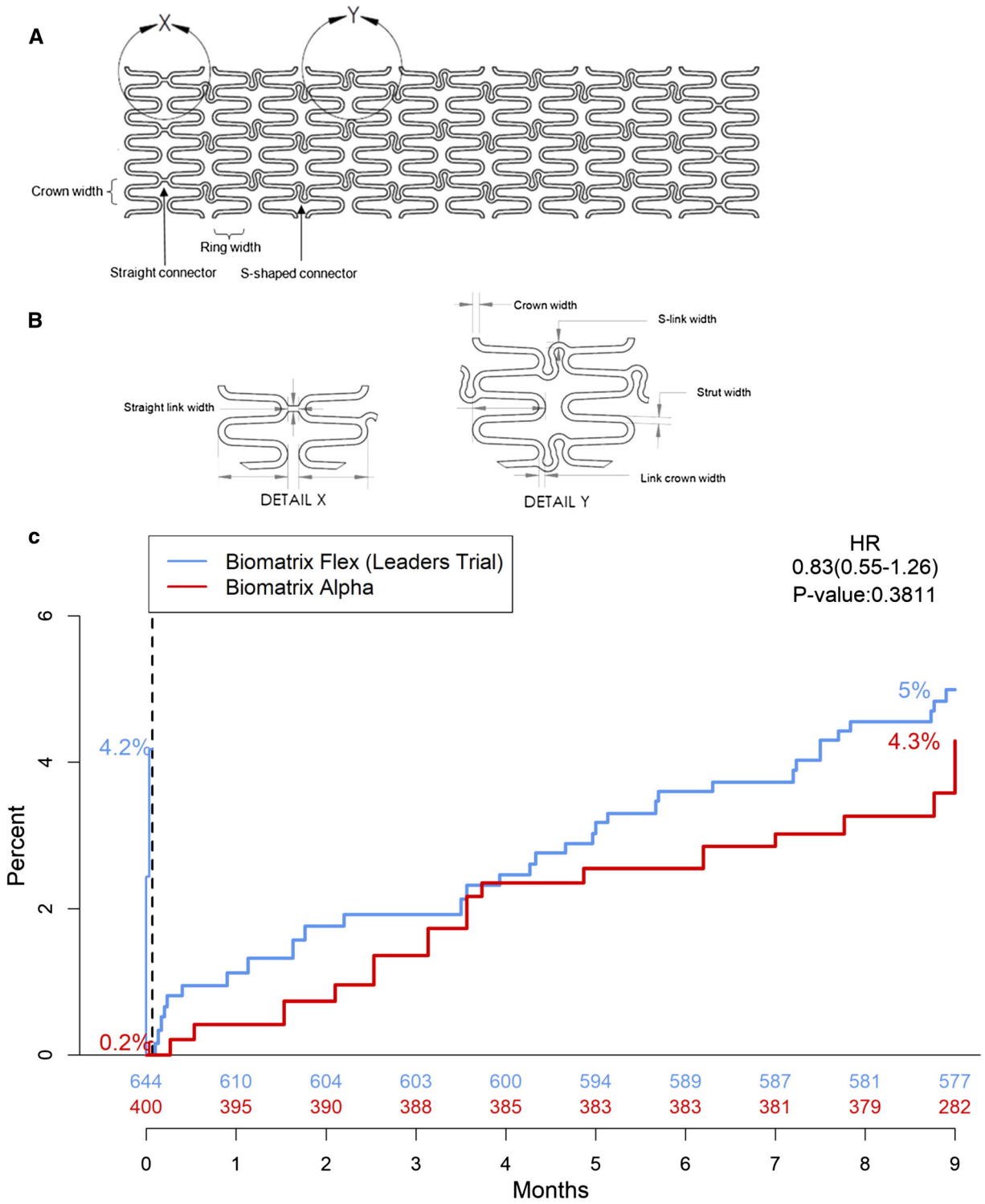

Fig. 1 **a** Flattened view of the cobalt chromium stent platform (small vessel model). **b** Details of the straight and curved link connectors. **c** Comparison with LEADERS (historical control), with propensity matching and landmark analysis at day 3 for the primary endpoint of major adverse cardiac events at 9 months [3]

encouraging and supports the clinical benefit of the new stent design.

A pre-specified analysis was undertaken in the subgroup of patients (n = 1506) undergoing small vessel (< 2.5 mm) PCI in the BIOdegradable Polymer and DuRablE Polymer Drug-eluting Stents in an All COmeRs PopulaTion (BIORESORT) trial as such patients might particularly benefit from thinner stent struts [4]. Target lesion revascularisation (TLR) at 3 years was significantly lower in those randomised to ultrathin-strut sirolimus-eluting stents vs. previous-generation thin-strut zotarolimus-eluting stents (2.1% vs. 5.3% adjusted HR 0.42; 95% CI 0.20–0.85; P = 0.02) and numerically although not significantly lower with very thin-strut everolimus-eluting stents vs. thin-strut zotarolimus-eluting stents (HR 0.74; 95% CI 0.41–1.34; P = 0.31).

In contrast, the TALENT study [5] randomised 1435 all comer patients to the ultrathin strut (60 μm) Supraflex sirolimus-eluting stent with biodegradable polymer vs. Xience. At 1 year, there was no difference in the primary device-oriented composite endpoint of cardiac death, target-vessel MI, or clinically indicated TLR (4.9% vs. 5.3%; P non-inferiority < 0.0001) and no difference in definite or probable stent thrombosis.

The TARGET All Comers study [6] randomised 1653 all comer patients to the thin strut (86 μm) Firehawk abluminal groove-filled biodegradable-polymer sirolimus-eluting coronary stent vs. Xience. At 2 years there was no difference in the incidence of target lesion failure (8.7% vs. 8.6%; P = 0.92) or incidence of very late definite or probable stent thrombosis (3 vs. 7 patients; P = 0.34). Longer follow-up will be interesting to see if a late safety advantage emerges for Firehawk.

Highly anticipated 5-year data from two trials of PCI vs. coronary artery bypass graft (CABG) for left main coronary disease provided contrasting results. In the Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease (EXCEL) trial [7] which studied low to intermediate left main complexity, the incidence of composite endpoint of death, stroke or MI (including peri-procedural MI) was similar in the PCI and CABG cohorts (22.0% vs. 19.2%; 95% CI − 0.9 to 6.5; P = 0.13). In contrast to previous 3-year data, EXCEL did note an excess of all-cause mortality at 5 years with PCI which attracted comment in the general media. Conversely, the NOBLE (Nordic–Baltic–British left main revascularisation study) [8], which included all-comer left main complexity, reported a higher incidence of the composite of death, MI (excluding peri-procedural MI), repeat revascularisation, and stroke for PCI (28% vs. 19%; P = 0.0002) (Fig. 2). However, NOBLE showed no difference in all-cause mortality with PCI (9% vs. 9%; HR 1.08; P = 0.68). Of note, neither EXCEL nor NOBLE showed an excess of CV death with PCI. Thus, PCI for left main coronary artery disease of low to intermediate complexity still appears reasonable, although best guided on a case by case basis with heart team consensus, advising patients of a likely reduction in perioperative MI but excess of later non-fatal cardiac events with PCI.

The SYNTAX Extended Survival (SYNTAXES), a 10-year follow-up of the multicentre randomised SYNTAX trial (PCI vs. CABG in patients with three-vessel or left main coronary artery disease), reported overall equivalence in all-cause mortality (27% PCI and 23.5% CABG) [9]. Subgroup analysis showed no difference for patients with left main disease (26.1% PCI and 26.7% CABG) or patients with diabetes (34.2% PCI and 32.1% CABG) but there was excess mortality with PCI in three-vessel disease (27.7% PCI and 20.6% CABG) with the differentiator being syntax score > 33. SYNTAXES thus confirms that PCI is a suitable option for patients with left main disease and three-vessel disease and low to intermediate syntax score (particularly considering that PCI was performed with first-generation paclitaxel-eluting stents and with relatively low use of intravascular physiology/imaging).

The Drug-coated Balloon Versus Drug-eluting Stent in Acute Myocardial Infarction (REVELATION) trial compared paclitaxel drug-coated balloon (DCB) angioplasty vs. new-generation DES in 120 patients presenting with ST elevation MI undergoing primary PCI. Culprit lesions were not heavily calcified and luminal stenosis was less than 50% after pre-dilatation [10]. The primary endpoint of 9-month target

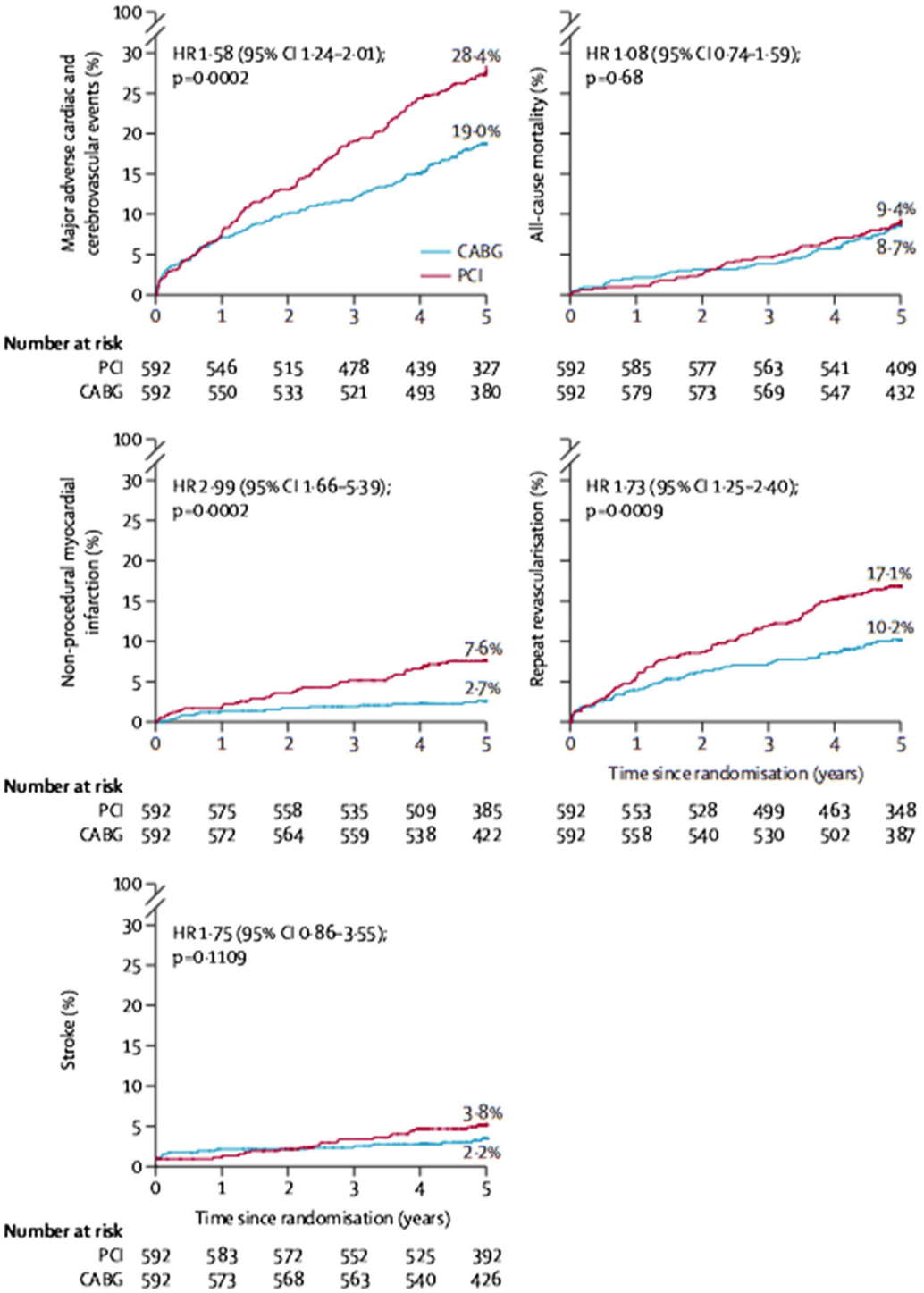

Fig. 2 Kaplan–Meier estimates of the 5-year outcomes in the NOBLE intention to treat population Reprinted from Holm et al. [8], with permission from Elsevier

vessel fractional flow reserve (FFR) was similar in DCB and DES groups (0.92 ± 0.05 vs. 0.91 ± 0.06) although given the relatively small numbers in the study, further confirmatory data are desirable.

It is often said that intracoronary physiology helps guide whether or not PCI should be done, and intracoronary imaging helps guide how best to optimise the PCI, if it needs to be done. Interesting, the FFR or OCT Guidance to RevasculariZe Intermediate Coronary Stenosis Using Angioplasty (FORZA) single-centre trial randomised 350 patients with 446 separate angiographically intermediate coronary lesions to either an FFR-guided strategy (PCI if FFR < 0.80) or an optical coherence tomography (OCT)-guided strategy (PCI if area stenosis ≥ 75%, if area stenosis 50–75% with minimal lumen area < 2.5 mm^2, or if visible plaque rupture) [11]. The primary endpoint (MACE or significant angina) was significantly higher with FFR vs. OCT guidance (14.8% vs. 8.0%; $P = 0.048$). The FORZA data are intriguing and support a larger multicentre trial of FFR vs. OCT-guided PCI.

With an aging population undergoing PCI, treatment of coronary calcium is increasingly common. The Shockwave Coronary Lithoplasty® Study (Disrupt CAD II) evaluated intravascular lithotripsy (IVL) for management of severe coronary artery calcification (CAC) in 120 patients undergoing PCI [12]. Successful delivery of the IVL catheter was achieved in all patients. Post-IVL, pre-stent angiographic luminal gain was 0.83 ± 0.47 mm. The primary endpoint (in-hospital MACE) occurred in 5.8% of patients. There were no cases of abrupt vessel closure, slow or no reflow, or perforations. In those with post-PCI OCT ($n = 47$), successful calcium fracture was demonstrated in 78.7% of lesions. IVL therefore appears to be a safe and effective strategy for the modification of severe CAC.

In patients with multivessel disease undergoing primary PCI, previous studies have suggested a benefit of PCI vs. conservative therapy for significant non-culprit lesions although the optimum timing of non-culprit PCI has been uncertain. In the Complete Revascularization with Multivessel PCI for Myocardial Infarction (COMPLETE) trial patients undergoing primary PCI were randomised to complete revascularisation (either in-hospital or staged up to 3 months) or to no further revascularisation. CV death or MI was significantly less frequent with complete revascularisation (7.8% vs. 10.5%; HR 0.74; 95% CI 0.60–0.91; $P = 0.004$) [13] as was the composite of CV death, MI or ischaemia-driven revascularisation (8.9% vs. 16.7%; HR 0.51; 95% CI 0.43–0.61; $P < 0.001$). There was no clinical benefit in delaying discharge to complete in-hospital PCI vs. returning for elective staged PCI up to 3 months.

The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial randomised 5179 patients with stable coronary artery disease and moderate to severe ischaemia on a non-invasive functional test to either a routine invasive revascularisation strategy or optimal medical therapy [14]. Notable exclusion criteria were left main stem stenosis ≥ 50%, severe left ventricular systolic dysfunction and unacceptable angina at baseline. The primary outcome of CV death, MI, resuscitated cardiac arrest, or hospitalisation for unstable angina or heart failure at 3.3 years occurred in 13.3% of the routine invasive group compared with 15.5% of the medical therapy group. The trial suggested no overall benefit to a routine invasive strategy in patients with stable coronary artery disease (with an absolute 2% early harm up to 6 months but a 2% late benefit by 4 years). A modest improvement of angina was noted at 3 months, especially among those with daily/weekly angina, which persisted at 12 and 36 months.

The ISCHAEMIA-CKD trial used the same design but included patients with chronic kidney disease (CKD). It enrolled 777 patients and the primary outcome of death or MI at 2.3 years occurred in 36.4% of the routine invasive group compared with 36.7% of the medical therapy group [15]. This trial therefore suggests no clear benefit to a routine invasive strategy in this subgroup of patients.

ADVANCES IN STRUCTURAL CARDIOLOGY

Transcatheter Aortic Valve Implantation

Transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis in

patients with high or intermediate operative risk is well established.

The PARTNER 2A trial previously reported that TAVI using the second-generation Sapien XT balloon expandable valve for treatment of severe aortic stenosis in intermediate-risk patients was non-inferior to surgical aortic valve replacement (SAVR) for the primary endpoint of death or disabling stroke at 2 years. New data showed that non-inferiority for TAVI was maintained up to 5 years [16] in those treated by transfemoral access but excess events were seen in those treated by transaortic access (59.3% vs. 48.3%; $P = 0.03$). Freedom from valve intervention was 96.8% in the TAVI group compared to 99.4% in the SAVR group ($P = 0.003$). Mean gradient on echocardiogram was similar; however, there were higher rates of moderate to severe paravalvular leak in the TAVI arm (6.5% vs. 0.4%; $P < 0.05$), which correlated with higher long-term mortality. The commercially available third-generation S3 valve, compared to the second-generation XT valve studied in this trial, has a skirt around the valve frame specifically to reduce the incidence of paravalvular leak. Further long-term data from the S3 cohort of the PARTNER 2 trial are awaited.

Two randomised controlled trials compared TAVI to SAVR in patients with low surgical risk. The Evolut Surgical Replacement and Transcatheter Aortic Valve Implantation in Low Risk Patients trial compared TAVI using a self-expanding bioprosthesis vs. SAVR in 1403 patients with severe symptomatic aortic stenosis [17]. At 2 years, TAVI vs. SAVR was associated with a similar incidence of the primary endpoint of death or disabling stroke (5.3% vs. 6.7%; $P < 0.05$ for non-inferiority, $P > 0.05$ for superiority), identical all-cause mortality (4.5% vs. 4.5%) and fewer disabling strokes (1.1% vs. 3.5%; $P < 0.05$). At 12 months, the TAVI group had a lower mean aortic valve gradient (8.6 mmHg vs. 11.2 mmHg) and larger mean effective orifice area (EOA) (2.3 cm^2 vs. 2.0 cm^2). However, TAVI was associated with a higher incidence of moderate or severe aortic regurgitation (3.5% vs. 0.5%) and pacemaker implantation (17.4% vs. 6.1%) at 30 days. The Placement of Aortic Transcatheter Valves (PARTNER) 3 trial randomised 1000 patients with severe calcific aortic stenosis and STS PROM risk score < 4% and suitable for transfemoral access to a third-generation balloon expandable TAVI (Edward's Sapien 3) vs. a bioprosthetic SAVR [18]. At 1 year, TAVI was associated with a lower incidence of the primary endpoint, a composite of death, stroke or rehospitalisation (8.5% vs. 15.1%; HR 0.54; 95% CI 0.37–0.79; $P = 0.001$). Importantly, there were no significant differences in major vascular complications, new permanent pacemaker insertions, or moderate or severe paravalvular regurgitation between the TAVI and SAVR groups. While short-term outcomes from Evolut Low Risk Trial and Partner 3 are promising, both trials plan to follow up for 10 years to assess durability. Of note, both trials excluded bicuspid aortic stenosis and were almost exclusively transfemoral access. Similar outcomes may or may not translate to patients with bicuspid aortic valves or those requiring alternative access.

Subclinical leaflet thrombosis characterised by hypoattenuated leaflet thickening (HALT) and reduced leaflet mobility has been observed in both transcatheter and surgical bioprosthetic aortic valves. The Partner 3 Low-Risk Computed Tomography (CT) Substudy compared HALT and reduced leaflet mobility in transcatheter and surgical aortic valves in a subset of 408 participants without a pre-existing indication for anticoagulation at the index procedure [19]. The incidence of HALT and reduced leaflet mobility was 10% at 30 days increasing to 24% at 1 year with significantly higher prevalence in the TAVI group at 30 days but not at 1 year. HALT and reduced leaflet mobility resulted in only a slight increase in valve gradients which was not associated with serious clinical events such as death, MI and stroke. Ten-year follow-up is planned which may improve understanding of the natural history of HALT and reduced leaflet mobility in the absence of anticoagulation (Fig. 3).

Given concerns regarding HALT, oral anticoagulation was studied in the Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy After TAVR to Optimize Clinical Outcomes

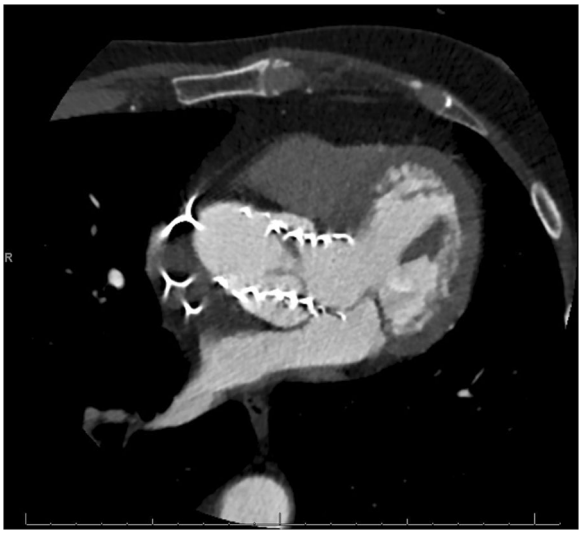

Fig. 3 Computed tomography image demonstrating hypoattenuation of the right cusp of TAVI prosthesis consistent with a focal area of thrombus

(GALILEO) trial which randomised 1644 patients without atrial fibrillation (AF) or other indication for anticoagulation to rivaroxaban 10 mg daily vs. clopidogrel 75 mg daily for 3 months (along with aspirin 75 mg in both arms) [20]. In an imaging subgroup (GALILEO 4D; $n = 231$), use of rivaroxaban was associated with reduced subclinical leaflet-motion abnormalities. However, the trial was terminated early as the rivaroxaban arm was associated with excess ischaemic and major bleeding events, including higher all-cause mortality (7.7% vs. 4.6%, $P = 0.009$). This trial suggests that use of direct factor Xa inhibitors after TAVI should be reserved for patients with AF or other indication for oral anticoagulation.

Commercially available TAVI systems differ in mechanism of deployment, size of vascular access, potential for repositionability, haemodynamic performance and risk of conduction disturbances, all of which help inform decisions in selecting the appropriate valve for individual patients. The Scope 1 trial is one of the few head to head comparisons between TAVI valves [21]. Patients with symptomatic severe aortic stenosis and increased surgical risk were randomised to TAVI with the self-expanding Acurate neo ($n = 372$) or Sapien 3 ($n = 367$). Although the Acurate neo valve achieved lower gradients and a larger EOA, it was associated with a higher incidence of the composite primary endpoint (death/stroke/bleeding/vascular complications/coronary obstruction/acute kidney injury (AKI)/rehospitalisation/repeat intervention/valve dysfunction) at 30 days (23.7% vs. 16.5%), driven by an excess of AKI and paravalvular regurgitation. Longer-term follow-up is awaited to see if this translates into a difference in mortality.

The France-TAVI nationwide registry included 12,141 patients undergoing balloon expandable TAVI (Edwards, $n = 8038$) or self-expanding TAVI (Medtronic, $n = 4103$) for native aortic stenosis in a propensity matched analysis [22]. The incidence of first co-primary outcome (moderate or greater paravalvular regurgitation and/or in-hospital mortality) was higher with self-expanding compared with balloon expandable TAVI (19.8% vs. 11.9%, $P < 0.0001$) as was mortality at 2 years (29.8% vs. 26.6%; $P = 0.003$). This registry data supports the need for a randomised controlled trial comparing the newest generations of self-expanding and balloon expandable valves.

Bicuspid aortic valve has an estimated prevalence of 1% and is prone to early degeneration often requiring surgery. Early TAVI trials excluded such patients but the Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapies Registry included 2691 propensity score matched pairs of bicuspid vs. tricuspid aortic stenosis undergoing TAVI with a balloon expandable valves [23]. There was no significant difference in 30-day or 1-year mortality between the two groups, valve haemodynamics or rates of moderate or severe paravalvular leak. However, bicuspid anatomy had an increased 30-day risk for stroke (2.5% vs. 1.6%; HR 1.57) and a higher risk of procedural complications requiring open heart surgery (0.9% vs. 0.4%). With the expanding indications for TAVI, adequately powered randomised trials are needed to compare TAVI vs. SAVR for bicuspid aortic stenosis.

Long-term durability of bioprosthetic transcatheter aortic valves in low-risk patients with longer life expectancies are unknown. It may be necessary for some patients to undergo valve-in-valve procedures. In a small feasibility study, a

novel percutaneous device, the Leaflex Performer catheter system (Pi-Cardia), was used to fracture calcium deposits in patients with degenerative calcific aortic stenosis to improve leaflet mobility in 16 patients [24]. This resulted in an increase in aortic valve area from baseline of 0.7 to 1.2 cm^2 after the procedure and lowered the mean pressure gradient from 34 to 18 mmHg with clinical significance met in both parameters. Of note, there were two non-embolic strokes and one death at 16 days, which was noncardiac and thought unrelated. Whilst this novel device appears promising, larger trials are needed to clarify if this strategy can delay the need for TAVI in certain patient subgroups (Fig. 4).

The management of asymptomatic severe aortic stenosis remains controversial with a paucity of randomised studies. Current ESC guidelines suggest that surgical aortic valve replacement should be considered in asymptomatic patients with low surgical risk but very severe stenosis defined as peak transvalvular velocity > 5.5 m/s [14] (Class IIa, level of evidence C). The Randomized Comparison of Early Surgery Versus Conventional Treatment in Very Severe Aortic Stenosis—RECOVERY trial compared early surgery vs. conservative care in 145 patients with asymptomatic very severe aortic stenosis defined as valve area ≤ 0.75 cm^2, peak transvalvular velocity ≥ 4.5 m/s or mean gradient ≥ 50 mmHg [25]. Early surgery was associated with a lower incidence of the primary outcome of operative mortality or CV mortality (1.4% vs. 15.3%; $P = 0.003$) and lower all-cause death (6.8% vs. 20.8%; $P = 0.03$). Importantly, this is the first randomised controlled trial to demonstrate a survival benefit (which extends out to 8 years) for early surgery vs. watchful waiting in such patients and is likely to inform a change in guidelines. The ongoing Early TAVR trial aims to assess whether benefits can be achieved with TAVI in asymptomatic patients.

Mitral Valve Interventions

While MitraClip (Abbott) is recognised as a treatment option for patients with primary mitral regurgitation (MR) and poor left ventricular (LV) ejection fraction (< 30%) refractory to medical therapy, its role in secondary MR is less clear with mixed results in previous randomised controlled trials. MITRA-FR previously reported no significant difference in death or hospitalisation for heart failure at 12 months

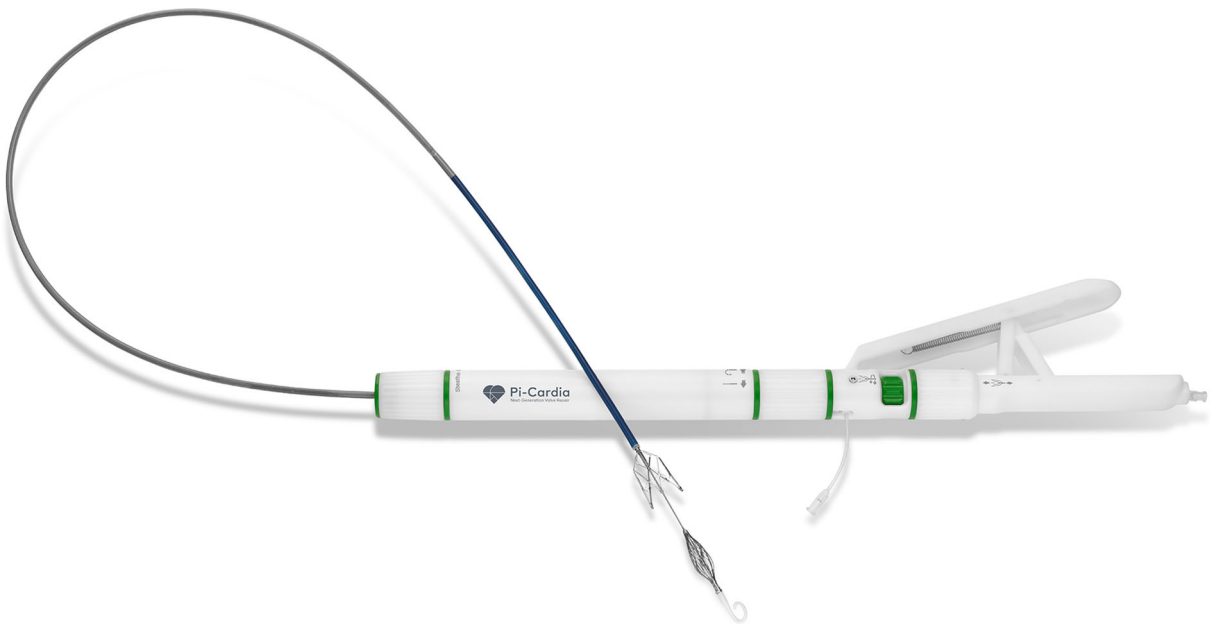

Fig. 4 Leaflex™ performer catheter system. Image courtesy of Pi-Cardia (Rehovot, Israel)

for MitraClip plus medical therapy vs. medical therapy alone [26]. At 24 months, again no significant difference in event rates was seen (64.2% for the MitraClip vs. 68.6% medical therapy alone) [27].

In contrast, the COAPT trial previously reported that MitraClip was associated with a reduction in death and in rehospitalisation for heart failure at 24 months [28]. At 3 years, this benefit remained (death 42.8% vs. 55.5%; $P = 0.001$ and annualised rate of rehospitalisation for heart failure 35.5% vs. 68.8%; $P < 0.001$) [29]. A COAPT echo substudy reported that the benefit of MitraClip was independent of the severity of left ventricular systolic dysfunction, left ventricular dilatation, pulmonary hypertension or severity of tricuspid regurgitation [30]. At 12 months, left ventricular ejection fraction decreased and left ventricular size progressively increased in both groups compared with baseline, but less so with MitraClip.

The different outcomes between MITRA-HF and COAPT may be due to COAPT having greater MR but smaller mean LV end-diastolic volume at baseline and requiring patients to already be on maximally tolerated medical therapy. The RESHAPE-HF2 study may provide further insight into the value of MitraClip in secondary MR [31].

The EXPAND registry evaluated third-generation MitraClip devices with greater coaptation surface area, and ease of use (NTR 41%, XTR 43% or both 16%) in 500 patients with symptomatic grade 3 or more mitral regurgitation [32]. Mitral regurgitation had reduced to grade 0/1 in 74% of patients by discharge, and was grade 0/1 in 66% at 30 days, along with encouraging improvement in New York Heart Association (NYHA) classification and quality of life. Adverse events at 30 days were relatively low in this high-risk population (death 2.8%, non-elective CV surgery for device-related complications 1.4% and stroke 0.4%).

Tricuspid Valve Interventions

Significant tricuspid regurgitation is associated with an increased risk of adverse events, including mortality and increased heart failure hospitalisation. Percutaneous tricuspid valve repair data were reported from the TriValve Registry—a propensity matched analysis of 268 pairs of patients either managed medically or with transcatheter tricuspid valve interventions using a variety of devices including MitraClip (80%), the Forma and Pascal repair systems and Cardioband [33]. Compared with medical management, patients undergoing transcatheter tricuspid valve intervention had lower 1-year mortality (23% vs. 36%; $P = 0.001$) and heart failure rehospitalisation (26% vs. 47%; $P < 0.0001$), which remained significant after adjusting for sex, NYHA functional class, right ventricular dysfunction and AF.

The Triluminate clinical trial prospectively evaluated the TriClip (Abbot) device in 85 patients with symptomatic moderate-to-severe tricuspid regurgitation [34]. No periprocedural deaths, conversions to open surgery, device embolization, MI or stroke were reported. Regurgitation severity at 30 days was reduced by at least one grade in 86%. By 6 months, there was significantly improved right ventricular function. Major adverse events occurred in 6% (less than the pre-specified performance goal of 39%; $P < 0.0001$) and CV mortality had occurred in 4%. Further randomised trials are required to assess the impact of tricuspid intervention on longer-term hard clinical outcomes.

ADVANCES IN CARDIOVASCULAR PREVENTION

Diabetes and CV Disease

Several studies have reported use of sodium–glucose cotransporter 2 (SGLT2) inhibitors in patients with type 2 diabetes (T2D) to be associated with reduction in CV events [35–38]. A substudy of the Dapagliflozin Effect on Cardiovascular Events trial (DECLARE-TIMI 58) reported that dapagliflozin reduced hospitalisation for heart failure both in patients with and without impaired left ventricular systolic function at baseline (HR 0.64; 95% CI 0.43–0.95 and HR 0.76; 95% CI 0.62–0.92, respectively) [39]. A suggestion of benefit for

SGLT2 inhibitors in patients with T2D and heart failure with preserved ejection fraction is of particular note and warrants further study.

Bariatric surgery may have metabolic benefits for obese patients with T2D. In an observational study of patients with T2D and body mass index (BMI) ≥ 30, 2287 patients who underwent bariatric surgery in the Cleveland Clinic were compared with 11,435 controls receiving usual care [40]. At a median follow-up of 3.9 years, patients receiving bariatric surgery had a significantly lower incidence of extended MACE (death, coronary artery events, cerebrovascular events, heart failure, nephropathy and AF) (30.8% vs. 47.7%; $P < 0.001$) suggesting that formal randomised trials of this approach are warranted.

Hypertension

Identifying patients with modifiable risk factors and commencing appropriate interventions is central to reducing CV event rates. The Heart Outcomes Prevention and Evaluation (HOPE 4) study randomised 1371 individuals from 30 communities to an intervention group with intensive, community-based CV risk detection and control programme implemented by non-physician health workers ($n = 644$ from 14 communities) vs. usual care ($n = 727$ from 16 communities) [41]. At 1 year the intervention group had a greater reduction in Framingham CV risk score (11.2% vs. 6.4% reduction; $P < 0.0001$), with greater absolute reductions in systolic blood pressure (11.45 mmHg; $P < 0.0001$) and LDL-C (0.41 mmol/; $P < 0.0001$) highlighting how the mode of delivery of care can significantly influence outcomes.

The Hygia Chronotherapy Trial looked at how the time of day of antihypertensive drug administration influenced CV disease events, randomising 19,084 patients to take their medication on wakening ($n = 9552$) or at bedtime ($n = 9532$) [42]. By a median of 6.3 years follow-up, the bedtime group experienced significantly fewer CV events (MI, coronary revascularisation, heart failure or stroke) (adjusted HR = 0.55; 95% CI 0.50–0.61; $P < 0.001$) suggesting that this small change may also be worth considering.

The importance of controlling hypertension in elderly patients was highlighted by results of the Effects of Intensive Versus Standard Ambulatory Blood Pressure Control on Cerebrovascular Outcomes in Older People (INFINITY) which randomised 199 patients > 75 years of age to either intensive hypertension treatment (aiming for 24-h mean systolic blood pressure ≤ 130 mmHg) or standard treatment (aiming for ≤ 145 mmHg) [43]. At 3-year follow-up, the intensive treatment group had less subcortical microvascular disease (less change in white matter hyperintensity on serial brain MRI 0.29% vs. 0.48%; $P = 0.03$) and fewer CV events (4 vs. 17; $P = 0.01$). Although no functional benefits in terms of gait speed and cognitive function were noted, further studies with a longer follow-up would be useful to assess how the imaging improvements may translate into functional benefits over time.

The Moderato is a novel dual chamber pacing device which may reduce blood pressure by reducing preload with an ultra-short atrioventricular (AV) delay and using neuromodulation to maintain the effect by preventing sympathetic nervous system activation hence reducing afterload (Fig. 5). In the MODERATO II trial, of 47 patients implanted with the device, 26 had the therapy turned on while 21 acted as sham controls [44]. In the active therapy group, mean systolic blood pressure was significantly reduced by 11.1 mmHg from baseline ($P < 0.001$) vs .only 3.1 mmHg in the control group (not significant). A larger trial is planned.

Lipids

The Odyssey Outcomes trial previously reported that alirocumab, a monoclonal antibody to proprotein convertase subtilisin–kexin type 9 (PCSK9), reduced risk of future CV events in patients with prior (1–12 months) ACS [45]. A new analysis from the trial suggests that patients with polyvascular disease benefit the most [46] with MACE in those with one, two or three diseased vascular beds being 10.0%, 22.2% and 39.7%, respectively. The corresponding

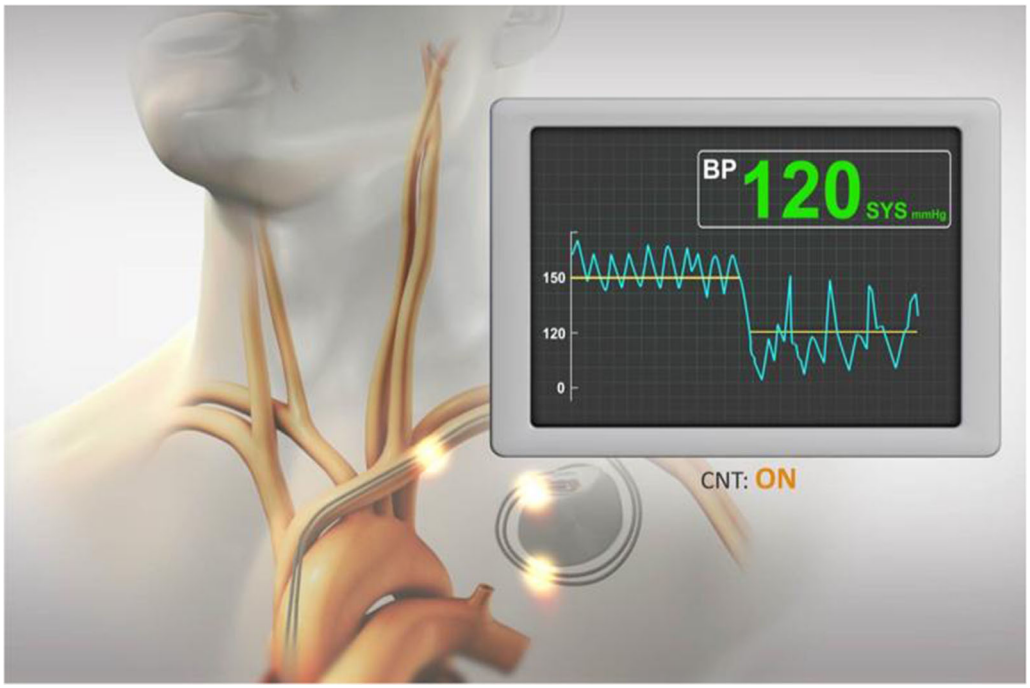

Fig. 5 The Moderato device, which reduces blood pressure using cardiac neuromodulation therapy. Image permitted and courtesy of Orchestra BioMed (New Hope, PA, USA)

absolute risk reductions with alirocumab were 1.4%, 1.9% and 13.0%, respectively ($P = 0.0006$ for interaction) suggesting that an aggressive approach to secondary prevention is particularly important in those with polyvascular disease.

In contrast to previous studies which studied PCSK9 inhibitors in patients with stabilised coronary disease [45, 47, 48], the EVOlocumab for Early Reduction of LDL-cholesterol Levels in Patients with Acute Coronary Syndromes (EVOPACS) trial evaluated evolocumab during the acute phase of ACS enrolled 308 patients with elevated LDL cholesterol (defined as ≥ 1.8 mmol/l on high intensity statin, ≥ 2.3 mmol/l on moderate intensity statin or ≥ 3.2 mmol/l on no statin) to atorvastatin and either evolocumab or placebo [49]. At 8 weeks, the evolocumab group showed significant reduction vs. placebo in total cholesterol (26.5%; $P < 0.001$), apolipoprotein B (34.2%; $P < 0.001$), non-high-density lipoprotein cholesterol (34.6%; $P < 0.001$) and triglycerides (20%; $P = 0.024$). Adverse events were similar suggesting that acute use is likely to be safe and further larger trials are underway.

Early trials with inclisiran, a small interfering RNA (siRNA), which switches off the gene for PCSK9, and only requires subcutaneous injection twice per year, have been discussed previously [50]. Phase 3 data have now been published. ORION-10 randomised 1561 patients with known atherosclerotic CV disease and already taking statins to either inclisiran ($n = 781$) or placebo ($n = 780$) [51]. After a follow-up of 18 months the inclisiran group had a mean percentage change in LDL cholesterol of − 56% vs. 1% in the placebo group ($P < 0.0001$). ORION-11 randomised 1617 patients with atherosclerotic CV disease at high risk of CV disease and already taking statins [52] to inclisiran ($n = 810$) or placebo ($n = 807$). The inclisiran group had a 49% reduction in LDL cholesterol vs. a 4% increase in the placebo group ($P < 0.00001$). No significant difference in serious adverse events was noted in either study and it is hoped that between the two groups a licence for clinical use may be granted during 2020.

Bempedoic acid, an oral ATP citrate lysase inhibitor, may be a further useful lipid-lowering agent, especially in those not candidates for PCSK9 inhibitors. In the CLEAR Wisdom trial, 779 patients with elevated LDL cholesterol and high CV risk and taking maximally tolerated statins were randomised (2:1) to receive bempedoic acid ($n = 522$) or placebo ($n = 257$) [53]. At 12 weeks the bempedoic acid group had a mean 15.1% reduction in LDL cholesterol whereas the placebo group had a 2.4% increase ($P < 0.001$ for comparison). While the study was not powered for outcomes, interestingly CV death, MI or stroke was observed in 2.7% of the bempedoic acid group at 1 year vs. 4.7% of the placebo group. In the CLEAR Harmony study 2230 patients with high CV risk and on maximally tolerated statins were randomised (2:1) to bempedoic acid or placebo [54]. At 12 weeks bempedoic acid was associated with an 18.1% reduction in LDL cholesterol vs. placebo ($P < 0.001$) (Table 2). There was no significant difference in adverse events between the two groups suggesting good tolerability.

Given the controversy surrounding the value of omega-3 supplementation, understanding the mechanism of benefit of high dose 4 g eicosapentaenoic acid (EPA) vs. placebo in the previously discussed Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) trial [50, 55] is of importance. The Effect of Vascepa on Progression of Coronary Atherosclerosis in Persons with Elevated Triglycerides (EVAPORATE) study randomised 80 patients on statins with elevated triglycerides, low LDL cholesterol levels and at least one stenosis of 20% or more of a coronary vessel on CT angiography to receive icosapent ethyl 4 g/day vs. placebo and to undergo serial CT imaging to assess plaque progression [56]. At 9-month interim analysis, mixed results were noted. Use of icosapent ethyl was associated with significantly less increase in total plaque volume (15% vs. 26%; $P = 0.0004$) although no significant difference in the increase of low-attenuated plaque (74% vs. 94%; $P = 0.469$) and numerically more increase in fibro-fatty plaque (87% vs. 25%; $P = 0.650$). Final results at 18 months are awaited.

Vascular Inflammation

Inflammation has a key role in the development of CV disease. Reduction in CV events has been reported with the interleukin-1 beta (IL-1β) inhibitor canakinumab [57] although not for methotrexate [50]. Of recent interest has been another anti-inflammatory drug colchicine, which inhibits tubulin polymerization and microtubule generation and may also have beneficial effects on cellular adhesion molecules, inflammatory chemokines and the inflammasome. The Colchicine Cardiovascular Outcomes (COLCOT) trial [58] randomised 4745 patients with recent MI (< 30 days) to low dose colchicine ($n = 2366$) or placebo ($n = 2379$). After a median follow-up of 22.6 months colchicine vs. placebo was associated with a 23% reduction in the composite primary endpoint of CV death, resuscitated cardiac arrest, MI, stroke or urgent hospitalisation for angina requiring revascularisation (5.5% vs. 7.1%; HR 0.77; 95% CI 0.61–0.96; $P = 0.02$). Each individual endpoint was numerically but non-significantly lower with colchicine. Gastrointestinal symptoms were the most commonly reported adverse events but

Table 2 Comparison of the changes in LDL cholesterol seen at 12 weeks in CLEAR HARMONY [54] and CLEAR WISDOM [53]

	CLEAR HARMONY			CLEAR WISDOM		
	Bempedoic acid	Placebo	*P* value	Bempedoic acid	Placebo	*P* value
Change in LDL cholesterol mg/dl (%)	− 19.2 (− 16.5)	+ 0.4 (+ 1.6)	< 0.001	− 21.8 (− 15.1)	+ 0.4 (+ 2.4)	< 0.001

were not significantly different between groups. Colchicine may offer a practical secondary prevention therapy for use in patients with recent MI and further studies are planned.

In a separate trial [59], 709 patients with suspected ischaemic heart disease or ACS scheduled for PCI were randomised to pre-procedure colchicine vs. placebo. While colchicine was associated with some attenuation in the rise of IL-6 and high sensitivity C-reactive protein (hsCRP) levels at 22–24 h post procedure there was no significant difference in the primary endpoint of peri-procedural MI < 24 h or in 30-day MACE. Further studies with earlier colchicine administration to optimise timing of peak anti-inflammatory effects are planned.

CV Medications Post CABG

In a concerning SWEDEHEART registry analysis of 28,812 patients undergoing isolated, first-time CABG analysis [60], while use of secondary prevention drugs was high immediately following surgery, use decreased significantly over follow-up (a median of 4.9 years). Renin–angiotensin system (RAS) inhibitors (HR 0.78; 95% CI 0.73–0.84; $P < 0.001$), statins (HR 0.56; 95% CI 0.52–0.60; $P < 0.001$) and antiplatelets (HR 0.74; 95% CI 0.69–0.81; $P < 0.001$) were all associated with reductions in mortality (Table 3). Interestingly, beta-blockers were not associated with survival benefit (HR 0.97; 95% CI 0.90–1.06; $P = 0.54$) regardless of left ventricular ejection fraction (LVEF) and further randomised study of this observation may be worthwhile.

ADVANCES IN ACS AND ANTITHROMBOTIC THERAPY

The optimal duration of dual antiplatelet therapy (DAPT) following PCI in both stable and unstable coronary artery disease is uncertain. Several trials published this year suggest that a shorter period of DAPT than in current guidelines may be reasonable.

The Ticagrelor With or Without Aspirin in High-Risk Patients After PCI (TWILIGHT) trial randomised patients (excluding ST elevation myocardial infarction, STEMI) at high bleeding risk (HBR) who had already received 3 months DAPT post PCI to either ticagrelor monotherapy vs. continued DAPT for a further 9 months [61]. (Patients with STEMI were excluded.) Bleeding Academic Research Consortium (BARC) type 2, 3 or 5 bleeding was significantly reduced with ticagrelor monotherapy (4.0% vs. 7.1%; $P < 0.001$) but with no difference in ischaemic events (3.9% vs. 3.9%) (Table 4).

The Effect of $P2Y_{12}$ Inhibitor Monotherapy vs. Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention (SMART-CHOICE) trial randomised 2993 patients undergoing PCI for either stable and unstable coronary syndromes to 3 months DAPT (followed by 9 months $P2Y_{12}$ inhibitor monotherapy) vs. 12 months DAPT [62]. At 12 months, bleeding was significantly lower in the 3 month DAPT group (2.0% vs. 3.4%) but there was no statistically significant difference in the rate of major adverse CV and cerebrovascular events (2.9% vs. 2.5%).

The ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 (STOPDAPT-2) trial

Table 3 Proportions of guideline recommended drug prescriptions in patients post CABG and adjusted hazard ratios for mortality associated with drug prescription [60]

Medication	Prescribed at baseline (%)	Prescribed at 8 years (%)	Overall HR for mortality (*P* value)
Statins	93.9	77.3	0.56, < 0.001
Beta-blockers	91.0	76.4	0.97, 0.54
RAS inhibitors	72.9	65.9	0.78, < 0.001
Antiplatelet	93.0	79.8	0.74, < 0.001

Table 4 Bleeding events in the TWILIGHT trial 1 year after randomization [61]

	Number of patients (%)		Hazard ratio (95% CI)	*P* value
	Ticagrelor plus placebo (*n* = 3555)	Ticagrelor plus aspirin (*n* = 3564)		
BARC 2, 3 or 5	141 (4.0)	250 (7.1)	0.56 (0.45–0.68)	< 0.001
BARC 3 or 5	34 (1.0)	69 (2.0)	0.49 (0.33–0.74)	
TIMI minor or major	141 (4.0)	250 (7.1)	0.56 (0.45–0.68)	
GUSTO moderate or severe	26 (0.7)	49 (1.4)	0.53 (0.33–0.85)	
ISTH major	39 (1.1)	72 (2.1)	0.54 (0.37–0.80)	

BARC Bleeding Academic Research Consortium, *TIMI* Thrombolysis In Myocardial Infarction, *GUSTO* Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries, *ISTH* International Society on Thrombosis and Haemostasis bleeding classifications

randomised 3045 patients undergoing PCI to 1-month DAPT (followed by 11 months clopidogrel monotherapy) vs. 12 months DAPT [63]. The 1-month DAPT arm was associated with significant reduction in the composite primary endpoint of CV death, MI, ischaemic or haemorrhagic stroke, definite stent thrombosis, or major or minor bleeding at 12 months (2.36% vs. 3.70%) largely driven by reduced bleeding outcomes.

The EVOLVE Short DAPT trial was a prospective single-arm study that examined outcomes from 1487 patients at high risk of bleeding whom had undergone PCI [64]. All patients discontinued $P2Y_{12}$ inhibitors following a 3-month DAPT. At 12 months the rate of definite/possible stent thrombosis was low at 0.3% and death/MI (adjusted) was 5.6% (although conclusions must be limited given the non-randomised design).

As discussed previously [50], GLOBAL LEADERS reported that 1-month aspirin plus ticagrelor followed by 23 months ticagrelor monotherapy vs. 12 months DAPT followed by 12 months aspirin monotherapy was associated with similar death or Q wave MI at 2 years and no difference in BARC 3–5 bleeding. The recent GLASSY substudy of GLOBAL LEADERS [65] reported outcomes based on independent clinical endpoint committee adjudicated events rather than investigator-reported events as it is recognised that investigators tend to over-report MI but under-report bleeding. A numerical reduction in the primary efficacy endpoint of all-cause death, MI, stroke and urgent TVR was noted (7.14% vs. 8.41%) but this did not achieve significance for superiority and there was no difference in major bleeding. Thus, conclusions remain similar to the overall study findings.

The role of DAPT in patients not undergoing PCI has also been of interest.

A Study Comparing Cardiovascular Effects of Ticagrelor Versus Placebo in Patients with Type 2 Diabetes Mellitus (THEMIS) randomised 19,220 patients with stable coronary artery disease (no recent PCI) and T2D to either DAPT with aspirin and ticagrelor vs. aspirin monotherapy [66]. The primary outcome of CV death, MI or stroke was lower in the DAPT arm (7.7% vs. 8.5%) albeit with an increase in TIMI major bleeding (2.2% vs. 1.0%). The THEMIS PCI subanalysis showed that the efficacy benefit was restricted to patients with prior PCI (n = 11,154; 58% of patients) who had a 15% reduction in events (7.3% vs. 8.6%; HR 0.85; 95% CI 0.74–0.97; P = 0.013). In contrast, those without prior PCI showed no significant benefit (8.2% vs. 8.4%; HR, 0.98; 95% CI 0.84–1.14; P = 0.76).

The Prospective, Randomized Trial of Ticagrelor Versus Prasugrel in Patients with Acute

Coronary Syndrome (ISAR REACT 5) undertook a head to head comparison of the two $P2Y_{12}$ inhibitors, randomising 4018 patients with ACS to ticagrelor vs. prasugrel, in addition to low dose aspirin [67] and powered for an assumed 22.5% superiority for ticagrelor. Patients with STEMI received immediate loading with ticagrelor or prasugrel. Patients with non-ST elevation acute coronary syndrome (NSTE-ACS) received immediate ticagrelor loading but prasugrel loading was delayed until after angiography in keeping with its licence. Unexpectedly the primary endpoint of death, MI or stroke at 1 year was significantly higher in the ticagrelor group (9.1% vs. 6.8%; $P = 0.006$). There was no significant difference in BARC 3–5 bleeding events (Table 5). Conclusions must be somewhat guarded following a single study with unexpected outcome, predominately telephone follow-up and higher than usual rate of drug discontinuation. Nevertheless, the National Institute for Health and Care Excellence (NICE) guideline draft update has recommended prasugrel instead of ticagrelor for STEMI [68].

In a novel approach to $P2Y_{12}$ inhibitor selection post STEMI, 2488 patients were randomised to either genotype-guided $P2Y_{12}$ inhibitor or standard ticagrelor or prasugrel [69]. In the genotype-guided group, carriers of *CYP2C19*2* or *CYP2C19*3* loss-of-function alleles received ticagrelor or prasugrel, and non-carriers received clopidogrel. At 12 months the rate of death from any cause, MI, stent thrombosis, stroke or major bleeding was 5.1% in the genotype-guided group and 5.9% in the control group. This raises the question whether some of the benefit of ticagrelor or prasugrel vs. clopidogrel in previous studies may have been due to inclusion of patients with genetic resistance to clopidogrel.

Previous studies with rivaroxaban and dabigatran have suggested a novel oral anticoagulants (NOAC)-based dual therapy is preferable to vitamin K antagonist (VKA)-based triple therapy for patients with AF undergoing PCI. Important new data were presented this year for apixaban and edoxaban shedding light on suitable timings for aspirin withdrawal and NOAC initiation. The Antithrombotic Therapy After Acute Coronary Syndrome or PCI in Atrial Fibrillation (AUGUSTUS) trial enrolled 4614 patients with AF and ACS managed either with PCI or medically [70]. All received a $P2Y_{12}$ inhibitor and were randomised in 2×2 design to apixaban vs. VKA and to placebo vs. aspirin. Apixaban vs. VKA was associated with a 31% reduction (10.5% vs. 14.7%; $P < 0.001$) and placebo vs. aspirin a 29% reduction (1.59 vs. 2.24; $P < 0.001$) in major or clinically relevant non-major bleeding. There was no significant difference in ischaemic events for apixaban vs. VKA, nor for placebo vs. aspirin. However, there was a non-significant increase in definite or probable stent thrombosis with placebo vs. aspirin (0.9% vs. 0.5%) despite the fact that patients where not enrolled for a mean of 1 week (and up to 2 weeks) after the index event, during which patients were receiving

Table 5 Clinical endpoints in the ISAR REACT 5 trial [68]

	Number of patients (%)		Hazard ratio (95% CI)	*P* value
	Ticagrelor group (*n* = 2012)	Prasugrel group (*n* = 2006)		
Death, myocardial infarction or stroke	184 (9.3)	137 (6.9)	1.36 (1.09–1.70)	0.006
Cardiovascular death	63 (3.2)	59 (3.0)		
Myocardial infarction	96 (4.8)	60 (3.0)	1.63 (1.18–2.25)	
Stroke	22 (1.1)	19 (1.0)	1.17 (0.63–2.15)	
BARC 3, 4 or 5 bleeding	95 (5.4)	80 (4.8)	1.12 (0.83–1.51)	0.46

aspirin. Thus, while dual therapy with NOAC (apixaban) and $P2Y_{12}$ appeared the optimum strategy, the safety of very early withdrawal of aspirin remains uncertain, and a short (2–4 week) initial use of aspirin appears prudent.

The Edoxaban-Based Versus Vitamin K Antagonist-Based Antithrombotic Regimen After Successful Coronary Stenting in Patients with Atrial Fibrillation (ENTRUST-AF PCI) trial investigated the safety of one NOAC, edoxaban, randomising 1506 patients undergoing PCI to dual therapy (edoxaban plus $P2Y_{12}$ inhibitor for 12 months) vs. triple therapy (VKA, $P2Y_{12}$ inhibitor for 12 months and aspirin for 1–12 months) [71]. The edoxaban strategy was associated with a non-significant 17% reduction in major or clinically relevant non-major bleeding (17.0% vs. 20%; *p* inferiority $P = 0.001$; *p* superiority $P = 0.11$). There was early bleeding excess with edoxaban. This is likely because patients were enrolled as early as 4 h post PCI after which those assigned to edoxaban achieved rapid full anticoagulation whereas those assigned to VKA were not bridged and thus had relatively little anticoagulation for the first 5 days. A post hoc landmark analysis at day 14 showed a 32% reduction in bleeding with edoxaban (HR 0.68; 95% CI [0.53–0.88]). This suggests that it may be prudent to defer starting the NOAC (edoxaban) for 1–2 days post PCI.

PB2452 is a novel monoclonal antibody that binds ticagrelor to reverse its effects. A small study examined its effects in 64 healthy volunteers pre-loaded with ticagrelor [72], 48 of who then received PB2452 vs. 16 who received placebo. Within 5 min of initiation of PB2452, a significant increase in platelet function vs. placebo was observed and was sustained for more than 20 h which was encouraging and supports further study.

The Coronary Angiography after Cardiac Arrest without ST-segment Elevation (COACT) trial aimed to establish the optimal timing for coronary angiography in patients successfully resuscitated from shockable cardiac arrest without post-arrest ST elevation, randomising 552 patients to immediate angiography vs. delayed angiography until neurological recovery [73]. No difference between the groups was noted for 90-day mortality (64.5% vs. 67.2%) or 1-year mortality. COACT thus supports use of a delayed strategy to facilitate the most effective post-arrest intensive care.

Remote ischaemic conditioning has previously been associated with reduction in MI size. The Effect of Remote Ischaemic Conditioning on Clinical Outcomes in STEMI Patients Undergoing PPCI (CONDI-2/ERIC-PPCI) trial randomised 5401 patients to remote ischaemic conditioning treatment before primary PCI vs. control (usual care). At 12 months, there was no difference in the rate of cardiac death or hospitalisation for heart failure between remote ischaemic conditioning and control groups (9.4% vs. 8.6%) [74]. Therefore, this large, well-designed trial does not suggest support for remote ischaemic conditioning for STEMI.

Previous studies have suggested that acute use of CT coronary angiography (CTCA) in ACS might reduce the length of stay compared with older-generation troponin protocols. The Trial of Cardiac CT in Acute Chest Patients with Intermediate Level Initial High-sensitivity Cardiac Troponin (PROTECCT) which randomised 250 intermediate-risk patients with suspected ACS, non-ischaemic ECG and high sensitivity troponin T (hs-TnT) of 5–50 ng/l to either CTCA or standard of care (repeat hs-TnT) [75]. In the CTCA group, patients with a coronary stenosis $< 25\%$ were deemed to have ACS excluded whereas those with stenosis $> 25\%$ were assigned to ongoing management as per the treating clinician. Use of CTCA did not shorten the median length of stay compared with standard of care (7.42 vs. 8.05 h; $P = 0.132$) or reduce hospital costs, although it did reduce subsequent cardiology referral/investigation (32 vs. 48%; $P = 0.01$).

The use of mechanical circulatory support devices in acute MI complicated by cardiogenic shock (AMI-CS) is controversial because of a lack of evidence of mortality benefit to date. The Impella LV support device is associated with greater augmentation of cardiac output than an intra-aortic balloon pump (IABP). Data from 237 patients with AMI-CS treated with an Impella device were compared with 237 matched patients from the IABP-SHOCK II trial [76]. Use of Impella was not associated with any

difference in 30-day all-cause mortality (48.5% vs. 46.4%). However, severe or life-threatening bleeding was more common with Impella (8.5% vs. 3.0%), as were peripheral vascular complications (9.8% vs. 3.8%). Separately, a propensity adjusted analysis of the Premier Healthcare Database registry (including 4782 Impella cases up to 2016) reported that Impella use was associated with higher odds of death, bleeding and stroke [77]. A large prospective randomised trial is thus urgently required.

ADVANCES IN ATRIAL FIBRILLATION AND ELECTROPHYSIOLOGY

Regular alcohol consumption is an important modifiable risk factor associated with AF and has been implicated in left atrial remodelling [78]. The Alcohol-AF trial randomised 140 patients with paroxysmal or persistent AF who consumed moderate alcohol (10 or more standard 12-g alcohol drinks per week) to abstinence vs. usual alcohol consumption [79]. By 6 months, abstinence was associated with a 27% reduction in AF recurrence (53% vs. 73%; $P = 0.004$) and 32% reduction in mean AF burden (5.6% vs. 8.2%; $P = 0.016$). This highlights the value of counselling patients with AF to limit alcohol consumption.

Despite guideline recommendations, there is limited randomised data evaluating oral anticoagulation (OAC) alone vs. OAC plus single antiplatelet (SAPT) in patients with AF beyond 1-year post revascularisation for stable coronary artery disease. The previously published OAC ALONE trial was underpowered and inconclusive because of the earlier than planned termination of enrolment [80]. The Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease (AFIRE) trial randomised 2236 patients with AF and stable coronary artery disease (≥ 1-year post PCI or CABG or stenosis ≥ 50% not requiring revascularisation) to rivaroxaban 15 mg vs. rivaroxaban plus SAPT of whom 70% received aspirin and 27% received a $P2Y_{12}$ inhibitor [81]. This trial was stopped early after a median treatment duration of 23 months because of excess mortality in the combination therapy arm. Rivaroxaban monotherapy was non-inferior for the primary efficacy endpoint of stroke, systemic embolism, MI, unstable angina requiring revascularisation, or death from any cause (4.14% vs. 5.75% per patient year; $P < 0.001$ for non-inferiority) and was associated with a 41% reduction in annualised major bleeding (1.62% vs. 2.76%; $P = 0.01$ for superiority). AFIRE thus supports current guidelines that anticoagulation monotherapy is preferred for patients with AF and stable coronary artery disease.

There is increasing interest in the general population regarding wearable fitness devices and healthcare apps. The Apple Watch uses optical sensors to detect pulse rate and algorithms to assess for pulse irregularity. In the Apple Heart Study [82] of more than 400,000 self-enrolled participants, 2161 (0.52%) received a notification of an irregular rhythm of whom 658 were sent an ECG patch after telehealth consultation, and 450 returned it for analysis. Overall, AF was detected in 34% of the ECG patches, more commonly in participants who were older and male. The positive predictive values for the tachogram and the notification were 0.71 and 0.84 respectively. As a result of notifications 57% contacted a healthcare provider outside the scope of the study and 28% were started on a new medication. While this wearable technology has shown promise in the detection of AF at a population level, the diagnostic accuracy is less than rhythm monitoring techniques currently used in practice. Further research to evaluate the additive clinical value of data from wearable technologies is ongoing.

ADVANCES IN HEART FAILURE

Sacubitril–Valsartan

We previously reviewed the PIONEER-HF study (Comparison of Sacubitril–Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized From an Acute HF Episode), which reported that initiation of sacubitril–valsartan in acute decompensated heart failure was safe and associated with greater reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP) [50]. In an extension of the initial

8-week trial, the investigators then studied patients for a further 4 weeks, with those already on sacubitril–valsartan continuing it and those originally on enalapril switching to sacubitril–valsartan [83].

Patients already on sacubitril–valsartan had a further 17.2% drop in NT-proBNP whereas patients switching from enalapril to sacubitril–valsartan had a 37.4% drop in NT-proBNP (between-group comparison $P < 0.001$).

Despite this, those with initial vs. late initiation of sacubitril–valsartan still had significantly lower NT-pro BNP measurements at 12 weeks ($P < 0.001$) and a lower rate of the composite of death, HF hospitalisation, transplant or use of left ventricular assist device (HR 0.67; 95% CI 0.48–0.94). Thus delaying initiation may reduce the full potential clinical effect of sacubitril–valsartan.

Heart failure with preserved ejection fraction (HFpEF) has been a difficult condition to manage with a lack of evidence-based treatment. The PARAGON HF trial (Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction) randomised 4822 patients with HFpEF, NYHA class II–IV and ejection fraction $\geq$ 45% to sacubitril–valsartan vs. valsartan alone [84]. Sacubitril–valsartan showed a 13% reduction in the primary endpoint of CV death or hospitalisations for heart failure, which just failed to meet significance (12.8% vs. 14.6% per year; 95% CI 0.75–1.01; $P = 0.06$). Subgroup analysis suggested that women may derive more benefit (27% risk reduction; 95% CI 0.59–0.90) which is of interest given that HFpEF is more common than heart failure with reduced ejection fraction (HFrEF) in women with HF but as the primary endpoint was negative this is only hypothesis generating [85].

The Effects of Sacubitril–Valsartan Therapy on Biomarkers, Myocardial Remodelling and Outcomes (PROVE-HF) study attempted to offer an explanation for the improvements seen in patients with heart failure taking sacubitril–valsartan by following 794 patients treated with sacubitril–valsartan for an average of 12 months [84]. Median NT-proBNP measurements fell from a baseline of 816–455 pg/ml ($P < 0.001$), which correlates with the findings from previous studies [84, 86]. LVEF increased by 5.2% from baseline at 6 months and 9.4% from baseline at 12 months. These results suggest that sacubitril–valsartan may benefit patients by inducing reverse cardiac remodelling. However, in some patients, improvements in LVEF can occur spontaneously, thus a prospective randomised study (vs. placebo or another drug) would be required to place the significance of these observations in context.

SGLT2 Inhibitors in Heart Failure

As previously discussed SGLT2 inhibitors have previously been found to be beneficial for patients with T2D and heart failure [35–38] but the DAPA-HF (Dapagliflozin on the Incidence of Worsening Heart Failure or CV Death in Patients with Chronic Heart Failure) trial [87] tested whether dapagliflozin 10 mg would be of benefit for 4744 patients with systolic heart failure (LVEF < 40%) whether they had (55%) or did not have (45%) T2D. At a median of 18.2 months, dapagliflozin was associated with a 26% reduction in CV death or worsening heart failure (16.3% vs. 21.2%; $P = 0.001$) regardless of diabetic status (Table 6) and a 17% reduction in all-cause mortality (11.6% vs. 13.9%; HR 0.83; 95% CI 0.71–0.97).

This benefit remained significant even for the 250 patients who were also on sacubitril–valsartan. The incidence of hypoglycaemia was no more frequent with dapagliflozin vs. placebo. It is fascinating that a drug originally designed for glycaemic control may now have an even more important role as a heart failure drug and studies are ongoing to further understand the mechanisms of benefit. Highly anticipated results from the EMPEROR-Preserved trial may help establish whether SGLT2 inhibitors are useful in patients with HFpEF [88].

Cessation of Medications in Recovered Dilated Cardiomyopathy

There is minimal evidence available to guide whether or not to stop treatment in patients with a diagnosis of dilated cardiomyopathy who have recovery of ejection fraction on follow-up. The TRED-HF trial identified 51 such patients

Table 6 Results for the overall primary composite endpoint and its component parts in the DAPA-HF trial [87]

	Dapagliflozin (%)	Placebo (%)	Hazard ratio (95% CI)	*P* value
Primary composite endpoint	16.3	21.2	0.74 (0.65–0.85)	< 0.001
Hospitalisation or urgent visit for HF	10.0	13.7	0.70 (0.59–0.83)	
Hospitalisation for HF	9.7	13.4	0.70 (0.59–0.83)	
Urgent HF visit	0.4	1.0	0.43 (0.20–0.90)	
CV death	9.6	11.5	0.82 (0.69–0.98)	

diagnosed with dilated cardiomyopathy (initial LVEF < 40%), but now with normalised LVEF (to > 50%), normalised LV end-diastolic volume and whose NT-pro-BNP had fallen to < 250 ng/l and randomised them to early phased withdrawal (n = 25) vs. continuation of treatment for 6 months before late phased withdrawal (n = 26) [89]. In the first 6 months, 11 (44%) patients in the early withdrawal group met the definition for a relapse. Between 6 and 12 months, late withdrawal was attempted in those initially continuing treatment and 9 (36%) patients met the definition for a relapse. Although small, this trial suggests that many patients deemed to have recovered from dilated cardiomyopathy will relapse following treatment withdrawal; thus, until robust predictors of relapse are defined, treatment should continue indefinitely.

Pulmonary Artery Pressure Sensor

The Abbott CardioMEMS pulmonary artery (PA) pressure sensor enables real-time PA pressure monitoring. We have previously discussed potential benefits seen with initial clinical experience [50]. Most recently, a post-approval study among 1214 patients reported a 58% reduction in hospitalisation for heart failure in the year following the implantation of the sensor vs. the year prior to implantation ($P < 0.0001$) [90]. The prospective randomised controlled trial of this device in a wider range of patients, GUIDE-HF, is expected to report in 2023.

Devices

For patients with reduced LVEF following ACS, current guidelines recommend reassessment of LVEF at 6–10 weeks to guide whether an implantable cardiac defibrillator (ICD) is indicated [91]. In the Defibrillator After Primary Angioplasty (DAPA) trial, 266 high-risk patients following primary PCI for STEMI were randomized to early ICD (at 30–60 days) vs. standard care [92]. High risk was defined as LVEF < 30% within 4 days, TIMI flow < 3 after PPCI, primary VF at < 24 h or Killip class ≥ 2. At 10 years, all-cause mortality was reduced by 42% in the ICD group (24.2% vs. 35.5%; HR 0.58; 95% CI 0.37–0.91; P = 0.02). Interestingly, the difference was not significant at 3 years (P = 0.4) and only reached significance at 9 years, driven by cardiac death. While DAPA suggests that there may be benefit to early ICD implantation in highly selected patients, larger studies are needed to evaluate this further.

Infection of implantable cardiac devices carries significant morbidity and mortality. The safety and efficacy of the TYRX^{TM}, absorbable, antibacterial envelope produced by Medtronic was assessed in the World-wide Randomised Antibiotic Envelope Infection Prevention Trial (WRAP-IT) which randomised 6983 patients to implantation with or without the envelope [93]. Use of TYRX^{TM} was associated with a 40% reduction in the primary endpoint of major device infection within 12 months (0.7% vs. 1.2%; P = 0.04). Although infection numbers were small is both study arms, given the significant clinical and economic implications of device infection, WRAP-IT supports considering

using an envelope in device implantations, and is currently being evaluated by NICE.

CONCLUSION

This article has highlighted and summarised the key trials that were published and presented in the field of cardiology during 2019. Many of these studies will help guide clinical practice and guideline updates. Others have shown encouraging early data to guide further trial development.

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