American College of Cardiology Update 2021

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Learning objectives

You will learn the current evidence on:

- The prevention of major adverse cardiovascular events (MACE) in patients with established cardiovascular disease
- Coronary event risk prediction in chronic coronary artery disease (CAD) and the role of complete revascularisation
- Best practice in the management of acute myocardial infarction (MI)
- Percutaneous coronary intervention (PCI) and antiplatelet therapy
- The medicines used to treat patients with heart failure (HF)
- Therapeutic anticoagulation during COVID-19.

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Introduction

ACC 2021 was a virtual meeting presented on several channels simultaneously. All sessions kept strictly to time and in all cases the presenters' slides were available immediately for downloading and reference. Below are summaries of the presentations that I found to be of particular interest.

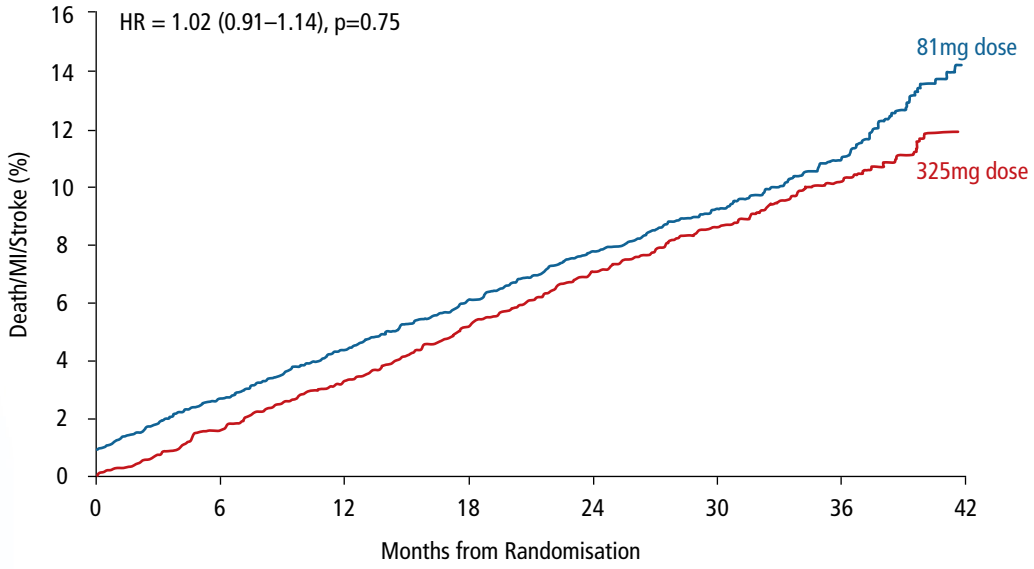
Prevention

Which aspirin dose is best for patients with established cardiovascular disease?

Using an open-label design, the ADAPTABLE trial compared the safety and effectiveness of two aspirin doses (81mg and 325mg) in 15 000 high-risk patients with CAD, including patients with prior MI, prior revascularisation, angiography demonstrating CAD or a history of chronic ischaemic heart disease. Patients were recruited through blogs, Facebook or engagement at meetings, and after granting consent electronically they self-randomised one-to-one on the portal to receive either 81mg or 325mg aspirin OD. Patients with a history of aspirin allergy, gastrointestinal bleeding in the last 12 months, a bleeding disorder, current or planned use of an oral anticoagulant or ticagrelor, and female patients who were pregnant or nursing were excluded.

The primary effectiveness endpoint was the composite of all-cause mortality, hospitalisation for MI or hospitalisation for stroke. The primary safety endpoint was hospitalisation for major bleeding associated with blood transfusion. Endpoints were confirmed by participant report, electronic health record data or insurance claim data. Average age at randomisation was 68 years and 31% of participants were women. Of the cohort, 85% had used 81mg aspirin a day before entering the study and 22% had received dual antiplatelet therapy (DAPT) at baseline; 6.5% reported prior gastrointestinal haemorrhage and 1.4% had had an intracranial haemorrhage previously. At 42 months there was no significant difference in the primary effectiveness endpoint between the two doses (Figure 1) and there was no significant difference between the groups for the primary safety endpoint (0.63% versus 0.60%). Subgroup analysis revealed no significant differences between the two groups. Of those receiving 325mg, 41.6% switched to 81mg during the trial. Discontinuation of aspirin was numerically higher in the 325mg OD group.[1]

In the group receiving 325mg, 41.6% switched to 81mg during the trial



At risk								
81mg dose	7 540	7 357	7 177	5 627	4 190	2 712	1 558	636
325mg dose	7 536	7 297	7 095	5 544	4 090	2 613	1 489	592

(All-cause death, hospitalisation for MI, or hospitalisation for stroke)

Figure 1. Primary effectiveness endpoint outcome of the ADAPTABLE trial in patients with CAD

Omega-3 fatty acids to reduce MACE – balancing the evidence

These findings cast uncertainty on whether any net benefit or harm occurs with any omega-3 preparation

A secondary analysis of the STRENGTH trial[2,3] attempted to explain the discordant results of the REDUCE-IT and STRENGTH trials that both evaluated higher doses of omega-3 fatty acids; the former found a reduction in MACE of 25% and the latter did not detect a difference. Three hypotheses have been put forward to explain the difference. Firstly, the mineral oil placebo in REDUCE-IT raised LDL cholesterol by 10.9% and the high-sensitivity C-reactive protein (hs-CRP) by 32.3% whereas the corn oil placebo used in STRENGTH exhibited neutral effects. Secondly, REDUCE-IT used purified eicosapentaenoic acid (EPA), achieving moderately higher levels of EPA. Thirdly, a mixture of EPA and docosahexaenoic acid (DHA) was used in STRENGTH, raising the question of whether the effect of DHA could have counterbalanced the effects of EPA. In STRENGTH, in the top tertile of the responders a 443% increase in EPA was not associated with any benefit. There was also a 68% increase in DHA in the top tertile that was not associated with any demonstrable harm. These findings cast uncertainty on whether any net benefit or harm occurs with any omega-3 preparation.[3]

Benefits of IL-6 inhibition

Ziltivekimab markedly reduced multiple biomarkers of systemic inflammation and thrombosis including hs-CRP, fibrinogen, serum amyloid A, sPLA2 and lipoprotein(a)

The CANTOS trial with canakinumab, which targets the central interleukin (IL)-1β to IL-6 to hs-CRP pathway, found cardiovascular event rates were reduced independent of LDL lowering; subgroup analysis found that the magnitude of clinical benefit in individual trial participants related directly to the magnitude of downstream IL-6 reduction achieved. Dr Paul Ridker presented the results of RESCUE, a phase II trial of the IL-6 inhibitor ziltivekimab conducted in 264 participants with chronic kidney disease (CKD) stage 3-5 and an hs-CRP >2mg/l.[4] Ziltivekimab is a narrow-spectrum fully human monoclonal antibody targeting the IL-6 ligand. Ziltivekimab markedly reduced multiple biomarkers of systemic inflammation and thrombosis including hs-CRP, fibrinogen, serum amyloid A, secretory phospholipases A2 (sPLA2) and lipoprotein(a).

Evinacumab in severe hypertriglyceridaemia

Angiopoietin-like protein 3 (ANGPLT3) inhibits lipoprotein lipase and endothelial lipase. Evinacumab is a fully human monoclonal antibody that in turn inhibits ANGPLT3. Its safety and efficacy in reducing severe hypertriglyceridaemia was evaluated in a phase II trial comprising three patient groups previously hospitalised for acute pancreatitis. Evinacumab substantially reduced fasting triglyceride levels though it was ineffective in those with familial chylomicronaemia syndrome.

Hypertension

The RADIANCE-HTN TRIO trial evaluated the effect of ultrasound renal denervation in 136 patients with hypertension resistant to combination triple medication (an angiotensin receptor blocker + amlodipine + hydrochlorothiazide) whose blood pressure was ≥140/90mmHg on treatment, randomised one-to-one to renal denervation or a sham procedure.[5] Renal denervation resulted in a 4.5mmHg greater decrease in blood pressure than in the sham-operated controls. This effect was consistent across 24 hours.

Chronic CAD

Biomarker score to predict coronary events

For selected patients with chronic CAD and at least moderate ischaemia, the outcome of an invasive strategy may be better if anatomical complete revascularisation is achieved

Two years ago a biomarker-based strategy identified a gradient of risk for cardiovascular death, MI and stroke among patients who had had an acute coronary syndrome,[6] and a biomarker score was developed comprising hs-troponin I, NT-proBNP, growth differentiation factor 15 (GDF-15) and hs-CRP (Table 1). The relationship of the score and hs-CRP to major coronary events in patients with stable coronary atherosclerosis, using data from the FOURIER trial, identified a significant gradient of risk for clinical coronary events including MI and complex revascularisation procedures, high-risk coronary anatomy at the time of revascularisation and revascularisation for in-stent restenosis (Figure 2).[7]

Table 1. Biomarker score

Biomarkers	Points
hs-TnI ≥6ng/l	1
NT-proBNP ≥450pg/ml	1
GDF-15 >1800pg/ml	1
hs-CRP ≥2mg/l	1
Score	
Low risk	0
Intermediate risk	1-2
High risk	3-4

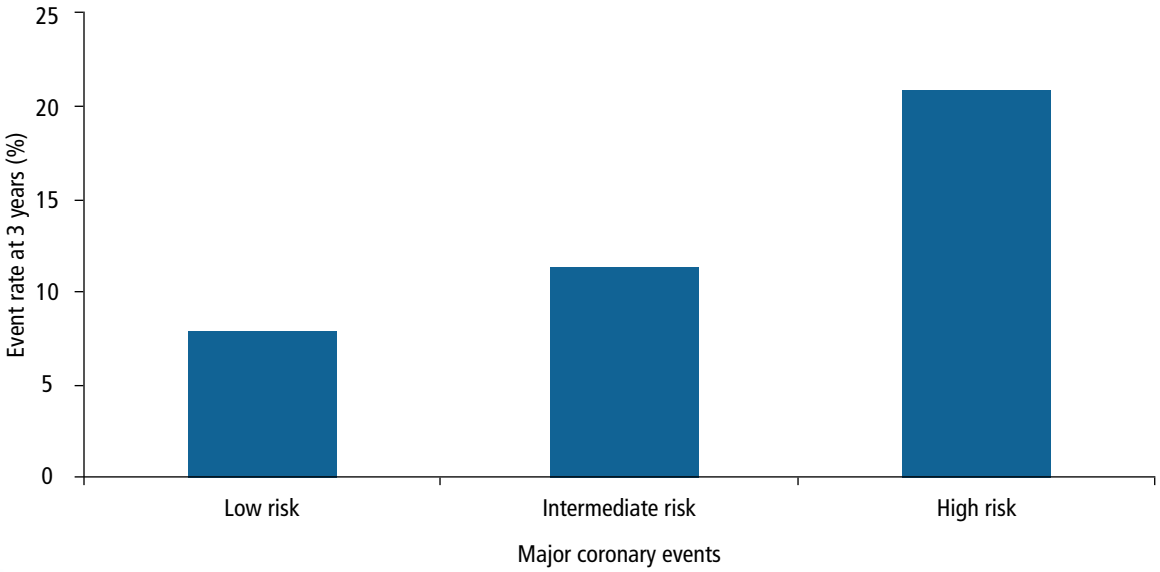


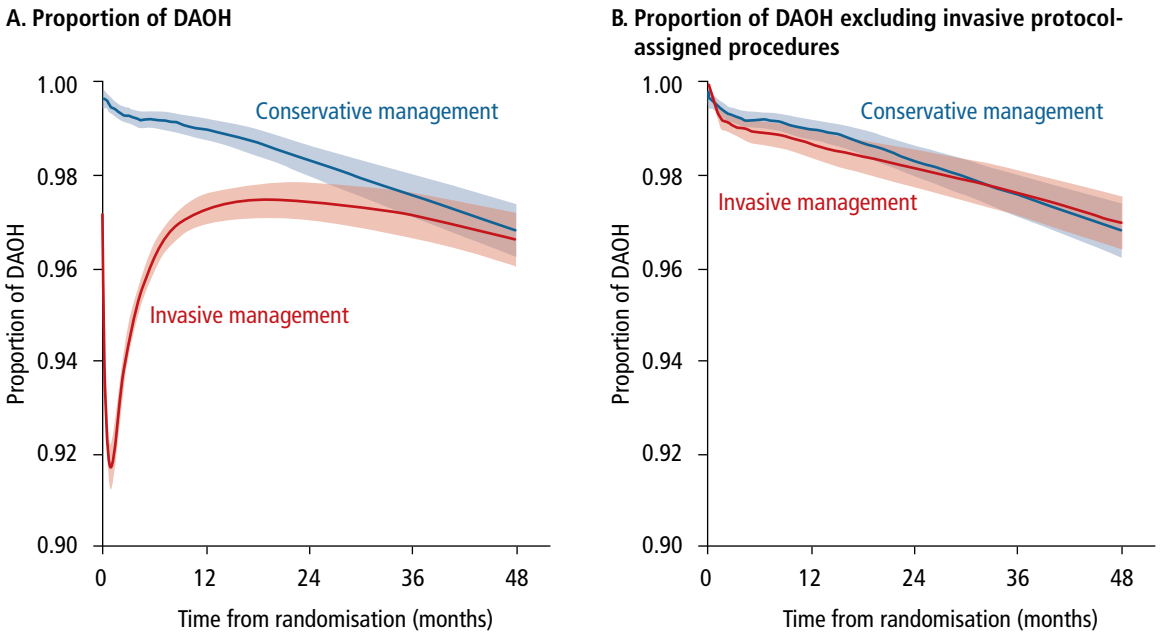
Figure 2. Gradient of biomarker-derived assessment of risk for clinical coronary events

Role of complete revascularisation in the ISCHEMIA trial

Dr Gregg Stone reported on the impact of the completeness of revascularisation on the clinical outcomes in patients with stable ischaemic heart disease treated with an invasive versus conservative strategy in the ISCHEMIA trial. He concluded that for selected patients with chronic CAD and at least moderate ischaemia, the outcome of an invasive strategy may be better if anatomical complete revascularisation is achieved, having shown lower rates of cardiovascular death and MI (as yet unpublished). All-cause mortality was similar between the invasive and conservatively treated groups, even if complete revascularisation was achieved.

Assessment of the quality-of-life of patients in the ISCHEMIA trial found that there was a greater improvement in angina- related quality-of-life when complete revascularisation was achieved, particularly in those patients who had more frequent angina, compared to conservative management. The functional assessment of complete revascularisation was shown to be at least as effective as anatomical assessment in improving the quality-of-life. The ischaemic burden from non-invasive testing and the presence of chronic total occlusions did not identify patients who would benefit more or less from complete revascularisation.

Professor Harvey White reported that during the first two years of the ISCHEMIA trial, the conservative group had significantly more days alive out-of-hospital than the invasive group. There were no significant differences between the groups beyond two years (Figure 3).[8]



Proportion of DAOH for assigned patients, with follow-up up to 4 years. B. Proportion of DAOH excluding protocol-assigned procedures for assigned patients, with follow-up up to 4 years. The shaded areas indicate 95% CIs.

Figure 3. Proportion of days alive out-of-hospital with follow-up up to four years among randomised participants vs those excluding protocol-assigned procedures

Coronary microvascular dysfunction

Integration of hs-troponin T into the clinical evaluation was not associated with a reduction in late death or MI over 12 months

Coronary microvascular dysfunction is common in women. Resolvins are small lipid cell-signalling molecules that are metabolites of omega-3 fatty acids. They inhibit neutrophil functions and promote macrophage anti-inflammatory actions. The WARRIOR study obtained peripheral blood samples from women with ischaemia and no obstructive CAD. Their coronary microvascular dysfunction was documented by measuring coronary flow reserve. Resolvin D and E series, DHA and EPA were measured by mass spectrometry. Elevated resolvin levels and lower levels of EPA and DHA were found in patients with coronary microvascular dysfunction, leading to the hypothesis that coronary microvascular dysfunction may be associated with insufficient omega-3 fatty acid substrate, biologically ineffective resolvins, or a combination of both. Resolvins may mediate microvascular dysfunction by failing to inhibit vascular inflammation.[9]

Acute MI

In the RAPID-TnT study, 3 378 patients presenting with suspected acute coronary syndrome without evidence of ischaemia in their electrocardiogram (ECG) were randomised to either standard care or a 0/1-hour protocol based upon their hs-troponin T level. The 0/1-hour protocol was associated with a reduction in functional stress testing and an increase in coronary angiography and revascularisation.[10] Integration of hs-troponin T into the clinical evaluation was not associated with a reduction in late death or MI over 12 months. Among patients with an hs-troponin T level ≤29ng/l there was a suggestion of an increase in the rate of death or MI when the result was not integrated into clinical management.

Fractional flow reserve-guided or angiography-guided multivessel PCI in STEMI?

FLOWER MI randomised 1 171 patients with multivessel disease to compare the use of fractional flow reserve (FFR)-guided to angiography-guided revascularisation in the treatment of ST segment elevation MI (STEMI). The aim was to provide complete revascularisation in the two groups. Investigators preferred a staged strategy for the treatment of non-culprit lesions. The one-year incidence of MACE was low; FFR did not reduce the composite risk of death, reinfarction or urgent revascularisation at one year compared with an angiographically guided strategy.[11] Cost-effectiveness and cost-utility favoured angiography-guided revascularisation.

When to transfuse in acute MI with anaemia?

The REALITY trial randomised patients with anaemia and acute MI to a blood transfusion strategy that was either restrictive, triggered by HbA_{1c} <8g/dl, or liberal, triggered by HbA_{1c} <10g/dl. The one-year outcome of MACE demonstrated that the restrictive strategy, initially found to be noninferior to the liberal strategy, was no longer noninferior at a year. Freedom from MACE was less in those treated with a restrictive strategy.[12]

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A 'hyperinvasive' pre-hospital care strategy for cardiac arrest improves outcomes

A 'hyperinvasive' approach to refractory out-of-hospital cardiac arrest was shown to be both feasible and effective in comparison to the standard approach in the Prague OHCA study which randomised 264 patients in 94 months.[13] Characteristics of the hyperinvasive approach include highly effective pre-hospital care, a high percentage of bystander cardiopulmonary resuscitation, dispatch centre-directed cardiopulmonary resuscitation and close cooperation with an experienced coronary angiography centre. Beneficial effects were observed in the 30-day neurological outcome, 180-day mortality and in patients resuscitated for more than 45 minutes.

Mild hypothermia for comatose patients after out-of-hospital cardiac arrest – beneficial or not?

The CAPITAL-CHILL trial randomised comatose survivors of out-of-hospital cardiac arrest presumed to be cardiac in origin to moderate versus mild hypothermia. The respective temperature targets were 31°C and 34°C. The outcome was similar in the two groups.[14]

Cardiogenic shock – do US women experience worse outcomes?

A US nationwide registry was used to evaluate outcomes in 1 780 men and 1 339 women older than 65 years who presented with cardiogenic shock and survived their index hospitalisation. The women were older, had a higher prevalence of comorbidity and worse kidney function; they were less likely to receive guideline-directed medical care, cardiac catheterisation or any revascularisation for non-STEMI, and in-hospital mortality and major bleeding rates were higher. No differences were detected in the outcomes between the sexes at one year.

PCI and antiplatelet therapy

Are there benefits in genotype-guided oral P2Y12 inhibitor selections?

The TAILOR-PCI study found that whereas there was benefit from genotype-guided P2Y12 inhibitor therapy using ticagrelor instead of clopidogrel within the first three months after PCI, there was no significant reduction in ischaemic events over a median follow-up of 39 months.[15]

De-escalation of DAPT beneficial

The investigators concluded that a uniform unguided de-escalation of DAPT, switching from ticagrelor to clopidogrel at 30 days, was superior to continuing ticagrelor-based therapy

The TALOS-AMI investigators reported the effect of ticagrelor versus clopidogrel in 2 697 stabilised patients with acute MI following successful PCI without adverse events. They were treated with aspirin and ticagrelor for the first month and then randomised to DAPT with aspirin plus clopidogrel or aspirin plus ticagrelor. Adherence to therapy was high, although slightly lower in the aspirin plus ticagrelor group. There was a 45% increase in bleeding in the ticagrelor group. The investigators concluded that a uniform unguided de-escalation of DAPT, switching from ticagrelor to clopidogrel at 30 days, was superior to continuing ticagrelor-based therapy. The de-escalation strategy was associated with significantly less bleeding, without an increase in ischaemic events.[16]

Chronic maintenance therapy post-PCI

The primary outcome of cardiovascular death, first HF hospitalisation or outpatient treatment for HF was no different between the two groups at three years

The HOST-EXAM trial randomised patients to aspirin or clopidogrel as chronic maintenance monotherapy after PCI in 5 438 patients who had been event-free for 16-18 months post-MI. Almost all completed 24-month follow-up. Clopidogrel reduced the primary outcome of all-cause death, non-fatal MI, stroke, readmission for acute coronary syndrome and major bleeding by 27% over 24 months. The absolute difference in risk was 2.0%. Thrombotic composite outcomes and any bleeding were reduced by 32% in the clopidogrel group.[17]

Heart failure

Prospective ARNI versus ACE inhibitor therapy for HF reduction after MI

The PARADISE-MI trial investigated angiotensin receptor neprilysin inhibition (ARNI) versus ACE inhibitor therapy following acute MI in 5 661 patients, followed for a median of 23 months.[18] Sacubitril/valsartan was compared to ramipril 5mg BD. Patients with a left ventricular ejection fraction (LVEF) <40% and/or pulmonary venous congestion were included up to seven days post-MI; 76% of patients had sustained a STEMI, 92% received DAPT, 85% a beta-blocker, 94% statin treatment and 40% a mineralocorticoid antagonist.

The primary outcome of cardiovascular death, first HF hospitalisation or outpatient treatment for HF was no different between the two groups at three years. Discontinuations for cough were more frequent with ramipril, whereas discontinuations for hypotension were more frequent with sacubitril/valsartan. Analysis of first and recurrent adjudicated events suggested incremental clinical benefits of sacubitril/valsartan. Three-year mortality rate in this trial was 10%, compared to ~23% in the earlier trials involving ACE inhibitors and valsartan.

LIFE trial of sacubitril/valsartan in advanced HFrEF

The LIFE trial was conducted in patients with advanced HF, comparing sacubitril/valsartan to valsartan with regard to lowering NT-proBNP levels. Sacubitril/valsartan was not superior to valsartan and did not improve the clinical composite of numbers of days alive out-of-hospital and free from HF events, HF hospitalisation or cardiovascular or all-cause death. Compared to the PARADIGM-HF trial, these patients were sicker, used lower doses of sacubitril/valsartan and the comparator was valsartan and not enalapril. These results are consistent with observations that as HF advances, chronic excessive activation of the renin-angiotensin-aldosterone system blunts or overrides the effect of natriuretic peptides on the heart, vasculature and kidneys.[19]

Sotagliflozin in HFpEF

Sotagliflozin is an SGLT-1/-2 inhibitor that was shown in both the SOLOIST-WHF[20] and SCORED[21] trials to reduce the incidence of total cardiovascular death, hospitalisations for HF and urgent visits for HF by ~30%. A subgroup analysis of patients with reduced ejection fraction (rEF) (<40%), mid-range ejection fraction, and preserved ejection fraction (pEF) (>50%) revealed a robust and significant reduction in the composite endpoint in all three groups. An on-treatment analysis revealed a significant reduction in cardiovascular death. These are the first randomised data to show a significant effect of SGLT-2 inhibitor therapy in HFpEF. A consistent and significant benefit in women was noted.

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Selective cardiac myosin activator therapy in HFrEF

GALACTIC-HF showed that omecamtiv mecarbil, a selective cardiac myosin activator, reduced HF events or cardiovascular death by 8% in patients with HFrEF whose LVEF was <35%. A substudy showed that the treatment effect increased with decreasing EF, with no difference in serious adverse events across the entire range of EF. There were no adverse effects on blood pressure, heart rate, potassium homeostasis or kidney function. Dr JR Teerlink concluded that omecamtiv mecarbil reduces the risk of HF events or cardiovascular death and might be useful in a broad range of appropriate patients at any point in their clinical course, in many of whom therapeutic options may be limited, without interfering with other life-saving therapies.[22]

Patients developing HF while receiving standard care

The VICTORIA trial[23] studied patients with symptomatic chronic HF following a worsening HF event. All patients were in NYHA class II to IV with an EF <45% who, while taking available guideline-directed HF therapies, had experienced a recent episode of decompensated HF and had elevated natriuretic peptides. Vericiguat was compared to placebo and achieved a 10% reduction in the time to cardiovascular death or first HF hospitalisation over 36 months. The annual number needed to treat was 24. Vericiguat was safe and well tolerated. In the armamentarium of HF therapies, vericiguat treatment is appropriate in patients who develop HF while receiving standard of care and may also be useful in those who are unable to tolerate standard therapy.

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Antifibrotic agent reduces myocardial fibrosis in patients with HFpEF

Pirfenidone is an antifibrotic agent licensed for idiopathic pulmonary fibrosis. It inhibits the synthesis and secretion of transforming growth factor (TGF)-β1, fibroblast proliferation and function and pro-fibrotic pathways. The PIROUTTE trial[24] investigated the effect of pirfenidone in patients with HFpEF with myocardial fibrosis assessed by cardiac magnetic resonance imaging. Pirfenidone reduced myocardial fibrosis, suggesting that it might have a favourable effect in HFpEF. Further trials are required.

PRADA study: LVEF decline in breast cancer patients

In the PRADA study, candesartan and metoprolol failed to protect against the long-term decline in LVEF in patients eligible for treatment of early breast cancer.[25]

Rehabilitation of older patients after acute decompensated HF hospitalisation

REHAB-HF[26] was an intervention in older patients hospitalised for acute decompensated HF, who had a high comorbidity burden with markedly impaired physical function, poor quality-of-life and high rates of depression and frailty. The patients were randomised to a three-week in-facility rehabilitation followed by five weeks of unsupervised maintenance exercise at home or to standard care. There was excellent retention of patients in the trial with excellent adherence to the intervention. The intervention produced

a large improvement in the Short Physical Performance Battery accompanied by large improvements in six-minute walk distance, quality-of-life, frailty score and depression.

Peer-audit and feedback did not improve HF outcomes in CONNECT-HF

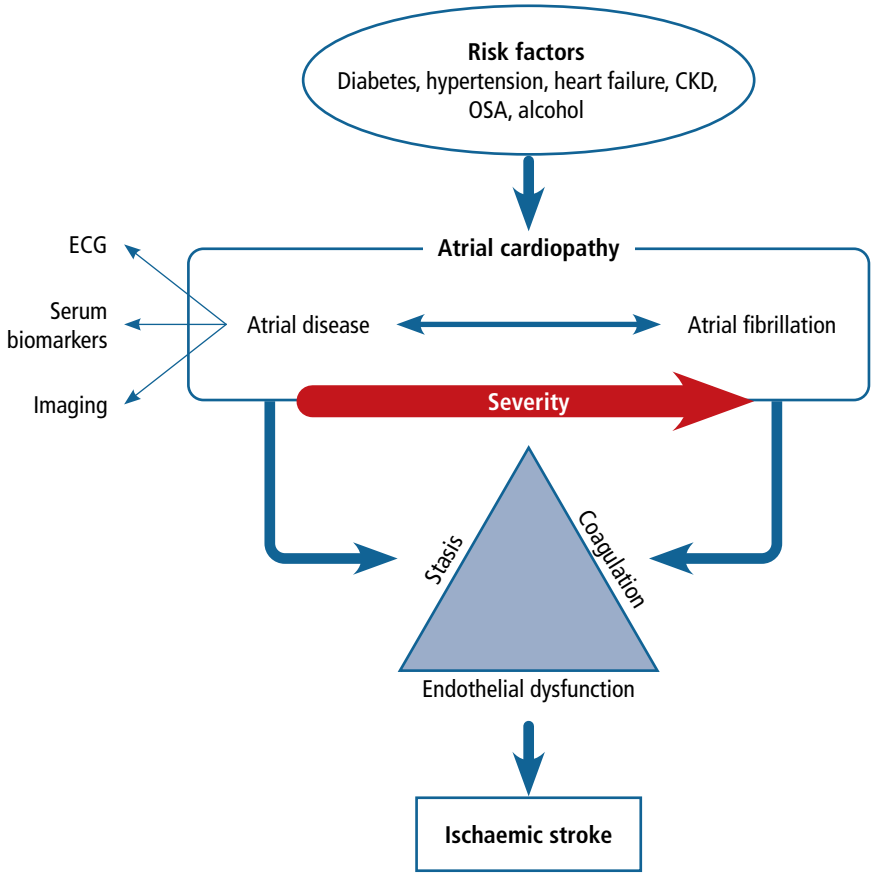
In CONNECT-HF patients who were hospitalised for HFrEF, an in-hospital and post-discharge quality improvement intervention that focused on both clinical education and audit and feedback of HF quality of care did not meaningfully impact on HF outcomes as compared to standard care.

There was speculation that atrial cardiopathy might result in systemic embolism in the absence of AF and that high-risk groups could therefore benefit from anticoagulant therapy

Atrial fibrillation

Atrial cardiopathy

One session was devoted to the discussion of atrial cardiopathy as the substrate for atrial fibrillation (AF). Intrinsic disease of the atrium arises from risk factors such as hypertension, diabetes mellitus, HF, CKD and alcohol consumption and results in AF. The converse may also be operative when the presence of AF promotes fibrosis within the atrium. Atrial cardiopathy can be detected by changes in the surface ECG, biomarkers and by imaging. A negative P-terminal force in V1 is associated with AF and stroke, and is a marker of left atrial fibrosis, elevated filling pressures and dilatation of the atrium. Downstream, the interactions of Virchow's triad, viz. circulatory stasis, endothelial dysfunction and a hypercoagulable state, result in thrombus formation, ischaemic stroke and cognitive impairment (Figure 4). There was speculation that atrial cardiopathy might result in systemic embolism in the absence of AF and that high-risk groups could therefore benefit from anticoagulant therapy.



CKD, Chronic kidney disease; OSA, obstructive sleep apnoea

Figure 4. Factors contributing to atrial cardiopathy

Left atrial appendage occlusion in patients with AF undergoing open heart surgery for another indication

In a landmark analysis, left atrial appendage occlusion reduced the risk of ischaemic stroke or systemic embolism by 42% noted from 30 days after surgery. The benefit of left atrial appendage occlusion was additive to that of oral anticoagulation

The LAAOS-III trial randomised 4 811 patients with AF undergoing cardiac surgery and with a CHA_2DS_2-VASc ≥2 to left atrial appendage occlusion or no occlusion. This multicentre study included patients from 27 countries.[27] The primary endpoint was ischaemic stroke or systemic embolism and the primary safety outcome was hospitalisation for HF, with a mean follow-up of 3.8 years. The mean age of patients was 71 years and the mean CHA_2DS_2-VASc score 4.2. Of the cohort, 68% were male and 57% had a history of HF. All forms of cardiac surgery were included. An average of 33% of patients underwent concurrent AF ablation.

The 30-day mortality rate was close to 4%. Anticoagulants were employed during follow-up; 77% were still on anticoagulation after three years.

The incidence of ischaemic stroke and systemic embolism was 4.8% with left atrial appendage occlusion and 7% in those who were not treated. In a landmark analysis, left atrial appendage occlusion reduced the risk of ischaemic stroke or systemic embolism by 42%, noted from 30 days after surgery. The benefit of left atrial appendage occlusion was additive to that of oral anticoagulation.

Ablation-based rhythm control versus rate control trial in HF patients with AF

The RAFT-AF trial[28] randomised patients with HF and a high burden of AF to ablation-based rhythm control versus rate control, with approximately 200 patients in each group. The composite of all-cause mortality and HF events with ablation did not achieve a statistically significant difference compared to rate control. Subgroup analysis found a differential effect between patients with a LVEF <45% and those whose EF was >45%. In the ablation group there were numerically fewer primary outcome events and greater improvements in LV function, quality-of-life and reduction of NT-proBNP.

AF after one alcoholic drink

The HOLIDAY Monitors study enrolled 100 patients with paroxysmal AF who consumed at least one alcoholic drink a month. These patients were continuously monitored for episodes of AF and 56 participants had at least one AF episode. The AF episodes were seen most commonly 3-4 hours following the consumption of at least one drink. Alcohol consumption appeared to heighten the risk of a discrete AF event, although there was no clear threshold to indicate the amount of alcohol required to precipitate AF.

Peripheral arterial disease

It was estimated that rivaroxaban treatment avoided 4.4 primary and 12.5 total vascular events per 100 participants over a three-year period

The VOYAGER PAD trial[29] examined the reduction in first ischaemic events with rivaroxaban in 6 564 patients with symptomatic peripheral arterial disease after revascularisation. Following lower extremity revascularisation there is a four-fold increase in the risk of acute limb ischaemia; these events have a poor outcome and repeat revascularisation is frequently required. Patients were randomised to rivaroxaban 2.5mg BD plus aspirin 100mg OD versus aspirin plus placebo and followed for a median of 2.5 years. Clopidogrel was added at the discretion of the investigator. The primary efficacy endpoint was the time to the first acute limb ischaemic event, major amputation of vascular aetiology, MI, ischaemic stroke or cardiovascular death. The principal safety outcome was TIMI major bleeding. Rivaroxaban effected an absolute risk reduction of 2.6% with an increase in major bleeding of 0.8%. Unplanned limb revascularisation for ischaemia and venous thromboembolism were decreased. The accrual of total vascular events over three years was evaluated, showing a significant 14% reduction. It was estimated that rivaroxaban treatment avoided 4.4 primary and 12.5 total vascular events per 100 participants over a three-year period.

SAFE-PAD[30] assessed the safety of femoropopliteal endovascular treatment with paclitaxel-coated devices as previous studies have suggested that they are associated with an increase in mortality. Among more than 160 000 Medicare beneficiaries, drug-coated devices were shown to be noninferior to non-drug-coated devices in respect of mortality.

CKD

Cardiorenal protection in type 2 diabetes mellitus (T2DM) and CKD

Finerenone is a non-steroidal selective mineralocorticoid antagonist that reduces the risk of cardiovascular disease and CKD progression in patients with CKD and T2DM. The FIDELIO-DKD[31] trial randomised 5 734 patients with T2DM and impaired kidney function to finerenone or placebo; over 48 months of follow-up, finerenone lowered the incidence of new-onset AF by 29% consistently across prespecified patient subgroups. Finerenone demonstrated cardiorenal protection in patients with CKD and T2DM, irrespective of the history of AF.

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Routine coronary angiography for patients undergoing kidney transplantation

In a sub-analysis of the ISCHEMIA-CKD trial, outcomes were examined based on the renal transplant listing status of the patients. Similar outcomes were noted for those on an initial invasive strategy compared to the conservative strategy. Patients listed for transplantation were more likely to undergo coronary angiography. The authors concluded that the data do not support routine coronary angiography or revascularisation to improve outcomes in patients listed for kidney transplantation who are receiving optimal medical therapy.[32]

Transfemoral aortic valve replacement (TAVR)

ATLANTIS[33] sought to demonstrate the superiority of apixaban 5mg BD after successful TAVR in comparison to the standard of care comprising either antiplatelet or vitamin K antagonist therapy. The study included 1 510 patients, with an average age of 82 years, who were randomised into two strata. When there was an indication for oral anticoagulant therapy, they were randomised to a vitamin K antagonist or apixaban 5mg BD. Those without an indication for anticoagulation were randomised to either apixaban 5mg BD or the standard of care (dual or single antiplatelet therapy). Apixaban 2.5mg BD was used in 34% of patients. The primary endpoint was the composite of death, MI, stroke, systemic embolism, intracardiac or bioprosthetic thrombus, deep venous thrombosis (DVT), or pulmonary embolism (PE) or major bleeding over one year. A four-dimensional CT scan was mandated by the protocol to identify subclinical valve thrombosis as a component of the primary endpoint.

There was no significant difference in the primary outcome when apixaban was compared to standard of care. Bioprosthetic thrombosis, DVT and PE were numerically less with apixaban than with standard of care. There was no significant difference in the bleeding risk between the two strategies. In the apixaban-treated group *without* the need for oral anticoagulation there were significant increases in the rates of death, stroke, TIA or systemic embolism (56%), death alone (86%) and non-cardiovascular death (299%) whereas any valve thrombosis was reduced by 81%.

COVID-19

Therapeutic anticoagulation during COVID-19

In the ACTION trial,[34] patients hospitalised with COVID-19 with elevated d-dimer levels received in-hospital therapeutic anticoagulation with rivaroxaban 20mg OD for stable patients, or enoxaparin 1mg/kg BD for unstable patients followed by rivaroxaban through 30 days. Rivaroxaban increased the risk of bleeding compared with in-hospital prophylactic anticoagulation.

A trial of atorvastatin 20mg OD compared to placebo in patients with COVID-19 admitted to intensive care did not significantly reduce the risk of adjudicated venous or arterial thrombosis, the requirement for treatment with extracorporeal membrane oxygenation, or all-cause mortality.

Dapagliflozin in non-critically ill hospitalised patients with COVID-19

The DARE-19 trial[35] in patients hospitalised with COVID-19 and with associated cardiometabolic risk factors found that treatment with dapagliflozin did not achieve a significant reduction in the combination of the prevention of organ failure or death (although these were numerically reduced) or the recovery from the infection. Regarding safety, there was no evidence to support discontinuing SGLT-2 inhibition during COVID-19 infection.

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Key learnings

- The IL-6 inhibitor, ziltivekimab, markedly reduced multiple biomarkers of systemic inflammation and thrombosis
- The ANGPLT3 inhibitor, evinacumab, substantially reduced fasting triglyceride levels in severe hypertriglyceridaemia
- Completeness of revascularisation impacts clinical outcomes in patients with stable ischaemic heart disease
- De-escalation of DAPT is associated with significantly less bleeding without an increase in ischaemic events
- The PARADISE-MI trial showed no difference in MACE at three years between ARNI and ACE inhibitor therapy
- There is a significant effect of SGLT-2 inhibitor therapy (sotagliflozin) in HFpEF
- Finerenone demonstrates cardiorenal protection in patients with CKD and T2DM irrespective of the history of AF.

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