AHA Scientific Sessions 2018

American Heart Association

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PEER-REVIEWED CONFERENCE REPORT

Late-Breaking Clinical Trials
The most impactful trials presented at the conference include DECLARE-TIMI 58, CIRT, and REDUCE-IT. Their results are presented and discussed in this report.

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Safety and Efficacy of Acute CVD Treatment
Different strategies to improve survival after acute myocardial infarction are being investigated. These include haemodynamic optimisation, mechanical unloading of the left ventricle, and intra-arrest cooling.

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2018 AHA/ACC Cholesterol Clinical Practice Guidelines
Updated guidelines are based on latest science in prevention, diagnosis, and treatment. They recommend more personalised risk assessment and emphasise importance of healthy lifestyle. Statins remain an effective treatment approach.

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MEDICOM MEDICAL PUBLISHERS

Editor: Prof. Marc Bonaca, University of Colorado, USA

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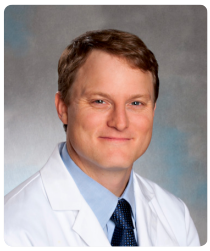
Letter from the Editor



Prof. Marc Peter Bonaca

Dear Reader,

The 2018 American Heart Association Scientific Sessions included high impact late breaking trials, innovation and discussion of cutting edge science and the future of cardiovascular treatment and prevention.

The DECLARE-TIMI 58 trial demonstrates the important benefits of the SGLT-2 inhibitor dapagliflozin for heart failure and extends the findings beyond secondary prevention to patients with diabetes and primary prevention. The REDUCE-IT trial demonstrated robust cardiovascular benefits for icosapent ethyl on top of statin therapy. Finally, the CIRT trial demonstrated that targeting inflammation is complex and that methotrexate did not reduce cardiovascular events.

The details of these late breaking trials and much more are covered in the following pages as we explore the exciting activities of AHA 2018!

Best,
Marc Bonaca

Biography

Marc P. Bonaca, MD, MPH is a Cardiologist and Vascular Medicine Specialist who serves as the Executive Director of CPC Clinical Research and CPC Community Health which is an Academic Research Organization created by and affiliated with the University of Colorado Anschutz Medical Campus. He is the Director of Vascular Research and an Associate Professor of Medicine at the University of Colorado School of Medicine and the inaugural holder of the William R. Hiatt Endowed Chair in Cardiovascular Research. CPC is a core resource of the University of Colorado research and community outreach infrastructure.

Dr. Bonaca earned his medical degree from the University of Connecticut School of Medicine and his Masters in Public Health at Harvard University. He served as a Medical House Officer at Brigham and Women's Hospital and Harvard Medical School. Following his medical residency training, he served as a Cardiology Fellow at Brigham and Women's Hospital and subsequently completed a fellowship in Vascular Medicine at Brigham and Women's Hospital under the mentorship of Mark A. Creager MD. He then served as a Cardiovascular Research Fellow with the TIMI Study Group with the Cardiovascular Division of Brigham and Women's Hospital.

After completion of his training he joined the faculty of the Cardiovascular Division and Vascular Medicine section of Brigham and Women's Hospital and Harvard Medical School and became an Investigator at the TIMI Study Group. At Brigham and Women's Hospital he founded the Aortic Syndrome Program and served as the Medical Director of the Aortic Center. At the TIMI Study Group he was the Chairman of the TIMI Safety Desk and oversaw pharmacovigilance activities for more than 8 large, multinational clinical trials. At TIMI he was an investigator on the TRA2P-TIMI 50 Trial, co-Principal Investigator of the PEGASUS-TIMI 54 Trial, co-investigator and United States National Lead Investigator of the DECLARE-TIMI 58 trial, and Principal Investigator of the REAL-TIMI 63B trial. At TIMI he led investigation in multiple datasets evaluating vascular outcomes including major adverse limb events and venous thromboembolism. He is currently the Center Director and Clinical Project Principal Investigator of the Brigham and Women's Hospital and Dartmouth Hitchcock Center in the American Heart Association Strategically Focused Research Network in Peripheral Vascular Disease.

Dr. Bonaca's research focus is on ischemic risk in patients with atherosclerotic vascular disease, risk prediction, and risk modification through the use of pharmacologic and biologic therapies. He has extensive experience in the design and conduct of large multicenter randomized clinical trials as well as analyses in registries and real-world datasets. His key areas of interest include patients with peripheral artery disease, polyvascular disease and diabetes with a focus on the breadth of risk including ischemic limb outcomes, microvascular complications and major adverse cardiovascular events. In addition, he is actively investigating the cardiac, vascular and thrombotic complications associated with novel oncologic therapies. Other clinical research interests include the evaluation of novel antithrombotic, lipid lowering and glucose lowering drugs, and the use of established and novel biomarkers or risk prediction and personalization of therapy. He is a member of the Society of Vascular Medicine, American College of Cardiology (ACC) and American Heart Association (AHA). He currently serves on the ACC PVD Leadership Council and is an associate editor for the Vascular Medicine.

Conflict of Interest Statement:

Grant support to BWH from AstraZeneca, MedImmune, Merck, Pfizer

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State-of-the-Art: The Cutting Edge of Cardiovascular Science

AHA Scientific Sessions, past and present, drive home the critical role of science and technology in reducing the global morbidity and mortality caused by cardiovascular disease. This year's Sessions focused on the research that will inform the prevention, diagnosis, and treatment of CVD in the global community of nations. The first AHA meeting took place on 26 May 1925 in Atlantic City, USA. There were 200 attendees and 10 presentations. This year's 91st AHA Scientific Sessions brought together over 10,000 attendees from more than 100 countries and featured 4,000 scientific presentations. The meeting opened with a review of recent ideas and topics that form the cutting edge of today's cardiovascular science.

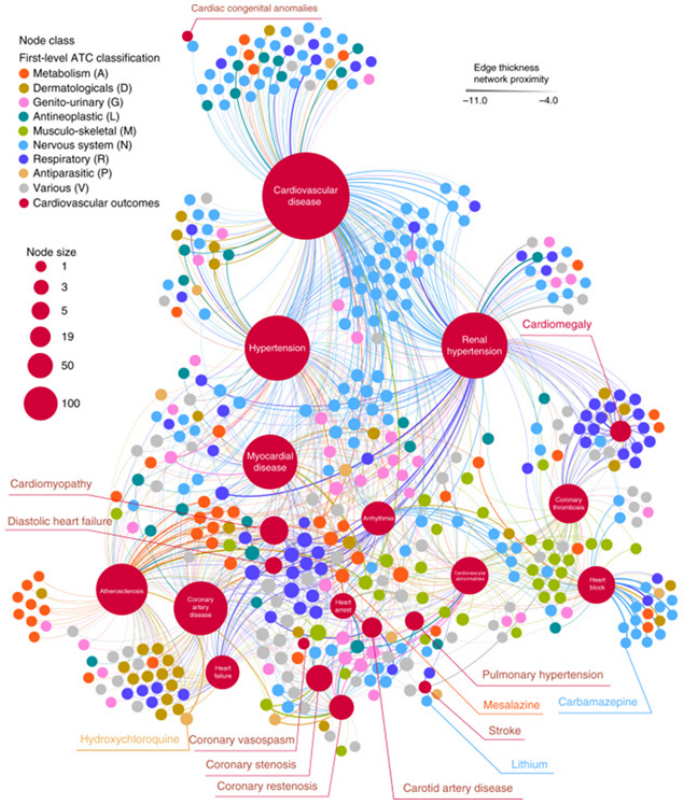
Network medicine: From systems biology to rapid drug development

A critical need exists for new and more effective drugs for the prevention and treatment of cardiovascular disease (CVD). Repurposing existing medications can reduce the costs and accelerate the development process. Dr Joseph Loscalzo (Brigham and Women's Hospital and Harvard Medical School, USA) discussed the use of systems- and network-based analysis to speed up and refine the process of identifying already-approved drugs for the treatment of new indications.

Discrete protein-protein networks scattered throughout the physical interactome link to mechanisms that underlie unique diseases [1]. The interplay and overlap between disease proteins and drug targets in the human protein-protein interactome serve as the basis for exploring new indications for existing therapeutics (Figure 1). Drug targets are typically explored in isolation, then *in situ*. However, precise drug-target interactions are highly unlikely [1]. An average of 32 targets per drug suggests that many drugs already approved for non-CVD indications can be repurposed to treat heart disease. In addition, the identification of multiple targets may identify many side effects that do not reach measured adverse effects.

Dr Loscalzo highlighted a study by Cheng et al. [2] that identified hundreds of new drug-disease associations for over 900 FDA-approved drugs by quantifying the network proximity of disease genes and drug targets in the human (protein-protein) interactome. Cheng et al. tested the causal relationships of four network-predicted associations using large healthcare databases with over 220 million patients and state-of-the-art pharmacoepidemiologic analyses. Comparator drugs treated the same diseases but had targets remote from the coronary disease module. The primary endpoint was new or worsening coronary heart disease in patients with pre-existing disease 18 months after the initiation of therapy.

Figure 1 The predicted drug-disease network [2]



The high-confidence predicted drug-disease association network connects 22 types of cardiovascular disease outcomes (red circles) and 431 FDA-approved non-cardiac drugs. Four selected drug-disease pairs tested in patient data are highlighted. Drugs are coloured by the first-level anatomical therapeutic chemical (ATC) classification system codes. The node size indicates the degree (connectivity) of nodes in the network.
Reprinted from: Cheng F, et al. Nat Commun 2018;9:2691. This figure is licensed under a Creative Commons Attribution 4.0 International License.

Propensity score matching validated two of four network-based predictions in patient-level data: carbamazepine was associated with an increased risk of coronary artery disease (CAD) (HR 1.56, 95% CI 1.12-2.18), and hydroxychloroquine with a decreased risk (HR 0.76, 95% CI 0.59-0.97). *In vitro* experiments showed that hydroxychloroquine attenuated pro-inflammatory cytokine-mediated activation in human aortic endothelial cells, a mechanism that supports its potential beneficial effect in CAD.

This network-based approach has broad application. It demonstrates that protein-protein interaction network proximity and large-scale patient-level longitudinal data can identify targets for novel drug repurposing [2]. Complemented by mechanistic *in vitro* studies, such analyses can facilitate the development of repurposed drugs for many new indications, including heart disease.

The heart-brain connectome: From neurovascular diseases to neurodegeneration

The most vital 'connectome' links the heart to the brain via blood vessels. Dr Constantino Iadecola from Cornell Medicine, USA, reviewed data on components of the neurovascular unit that alter vascular function in ways that lead to neurodegeneration and dementia, including the recently identified role of peripheral vascular macrophages in hypertension-induced neurovascular and cognitive dysfunction.

The health of the cerebrovascular system is vital for the brain's functional and structural integrity. The brain has no energy reserves and requires a continuous supply of blood matched to its dynamic regional metabolic needs. Neurons, glia, and vascular cells are key components of the neurovascular unit; they work in concert to assure that the brain is always adequately perfused. Brain activation increases cerebral blood flow to support energy demands and remove potentially harmful byproducts of cerebral metabolism. At the same time, endothelial cells regulate the trafficking of molecules and cells at the blood brain barrier and coordinate microvascular flow by releasing vasoactive agents.

Hypertension is the most important risk factor for stroke and vascular cognitive impairment [3]. It has also been linked to Alzheimer's disease, the leading cause of dementia in the elderly population. Most cases of Alzheimer's disease, especially in older individuals, are mixed dementia caused by neurodegenerative changes driven by amyloid pathology and vascular alterations. Hypertension disrupts all major factors that regulate cerebral circulation [3]. Structural changes (e.g. hypertrophy, remodelling, stiffening) and alterations in cerebrovascular regulation promote vascular insufficiency. As a result, the brain becomes more susceptible to the neuronal dysfunction and damage that underlie vascular cognitive impairment.

Angiotensin II plays an important role in human hypertension, inducing profound alterations in neurovascular coupling and endothelium-dependent vasodilation [4]. Cerebrovascular dysfunction is mediated by activation of angiotensin II type 1 receptors and vascular oxidative stress produced by a NOX2-containing NADPH oxidase. The downstream mechanisms by which angiotensin II-induced oxidative stress alters cerebrovascular function involve nitrosative stress and nitric oxide depletion.

Recent research has identified previously unrecognised peripheral vascular macrophages (PVMs) as a critical factor in brain health and a novel pathogenic component in the neurovascular unit [3]. This distinct population of resident brain macrophages play key homeostatic roles. However, they also have the potential to generate large amounts of reactive oxygen species (ROS).

In mouse models of hypertension, Faraco et al. [4] found that PVMs are critical drivers of alterations in neurovascular regulation and attendant cognitive impairment. An increase in blood-brain barrier permeability allows angiotensin II to enter the perivascular space and activate angiotensin type 1 receptors in PVMs, leading to production of ROS through the superoxide-producing enzyme NOX2.

The discovery that PVMs play a key pathogenic role in hypertension has resolved an area of controversy surrounding which vascular cell types produce ROS and initiate neurovascular dysfunction. Faraco et al. [4] implicate brain PVMs in hypertension-induced neurovascular dysfunction and cognitive deficits. As critically important components in the development of neurovascular diseases associated with vascular oxidative stress, including dementia, they represent a new therapeutic target.

Anti-atherosclerosis vaccines for cardiovascular disease prevention

Scientific evidence indicates that the immune system plays a major role in the development and progression of atherosclerosis. Prof. Klaus Ley (La Jolla Institute for Allergy

and Immunology, USA) presented review data that supports the potential of the immune system to prevent or treat atherosclerosis.

Atherosclerosis is a chronic inflammatory disease with a secondary autoimmune response. The main atherosclerosis auto-antigen is apolipoprotein B (apoB), which holds LDL-C together. Research into immunisation with major histocompatibility complex II-restricted apoB peptides in mice identified 6 apoB-100-derived peptide candidates for atherosclerotic vaccine antigens [5]. For example, vaccination with apoB P3, P6 was shown to reduce lesions by 40% to 50% [6]. Kimura et al. [7] found that apoB P18-specific CD4+ T cells are mainly regulatory T cells in healthy donors but co-express other CD4 lineage transcription factors in donors with subclinical cardiovascular disease.

Mouse models demonstrate that CD11c+ cells enable antigen presentation in the aorta. Kolsova et al. [8] found that antigen presentation by antigen-presenting cells to CD4+ T cells in the arterial wall causes local T cell activation and production of proinflammatory cytokines. These promote atherosclerosis by maintaining chronic inflammation and inducing foam cell formation.

Human studies show that most apoB-tetramer+ CD4 T cells in women without cardiovascular disease are regulatory T cells; that 1% of CD4 T cells from healthy subjects spontaneously make the anti-inflammatory IL-10; and that many apoB-tetramer+ CD4 T cells in women with atherosclerosis express RORγt and other pro-inflammatory transcription factors.

The CANTOS trial [8] offers a rationale for immunotherapy in the prevention or treatment atherosclerosis. It reported that canakinumab, an antibody to the inflammatory cytokine IL-1, was atheroprotective in subjects with CRP ≥2 mg/l. This benefit came at the cost of impaired host defence with increased risk of fatal infection. However, immunotherapy is narrowly antigen specific, and therefore, spares host defence.

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Novel Approaches to Cardiovascular Disease Prevention

Heart disease is a leading global cause of morbidity and mortality. Clinical trials are the proving grounds of innovative tools, therapeutics, and interventions that can be used to prevent cardiovascular disease in diverse populations of men, women, and children. This year's AHA Scientific Sessions was the stage for late-breaking clinical trials such as DECLARE-TIMI 58, CIRT, and REDUCE-IT.

DECLARE-TIMI 58 trial

The DECLARE–TIMI 58 trial [1] showed that dapagliflozin, a selective sodium-glucose co-transporter-2 inhibitor (SGLT-2i), was noninferior to placebo with respect to the primary safety outcome of a composite of major adverse cardiovascular events (MACE), defined as cardiovascular death, MI, or ischaemic stroke; and was superior to placebo for reducing the composite of CV death or heart failure. This trial is the largest of the SGLT-2i trials presented so far and includes the broadest population extending the benefits to patients with diabetes and risk factors alone. Additional findings support a possible lower rate of adverse renal outcomes consistent with those seen with the other SGLT-2i.

Dapagliflozin reduces blood glucose, weight, and blood pressure by promoting glycosuria via the inhibition of urinary glucose reabsorption. Previous SGLT-2i trials have

demonstrated statistically significant reductions in the combined primary outcome of MACE, mainly in patients with known atherosclerotic cardiovascular disease (CVD). These trials have also demonstrated reductions in hospitalisation for heart failure (HHF).

DECLARE-TIMI 58 was a phase 3b, randomised, double-blind, placebo-controlled trial to evaluate the CV safety and efficacy of dapagliflozin in patients with type 2 diabetes and either CVD or multiple risk factors for CVD. It tested the hypotheses that dapagliflozin is safe and will reduce the occurrence of important CV events. It was the largest trial with an SGLT-2i to address these questions in a broad population of patients with type 2 diabetes.

The study included 17,160 patients with type 2 diabetes and established CVD and those without CVD and multiple CV risk factors, including 10,186 without atherosclerotic CVD. They were randomised 1:1 to dapagliflozin 10 mg or matching placebo and followed for a median of 4.2 years. The primary safety outcome was a composite of MACE. The dual primary efficacy outcomes were MACE and the composite of HHF or CV death.

In the primary safety outcome analysis, dapagliflozin met the prespecified criterion for noninferiority to placebo with respect to MACE (upper boundary 95% CI <1.3; P<0.001 for noninferiority). In the two primary efficacy analyses, dapagliflozin did not lower the rate of MACE (8.8% in the dapagliflozin group vs 9.4% in the placebo group; HR 0.93; 95% CI 0.84 to 1.03; P=0.17). However, it significantly reduced the co-primary endpoint of CV death or HHF (4.9% vs 5.8%; HR 0.83; 95% CI 0.73 to 0.95; P=0.005).

This outcome was driven by a reduction in hospitalisation for heart failure (HR 0.73; 95% CI 0.61 to 0.88) relative to CV death (HR 0.98; 95% CI 0.82 to 1.17). Renal complications occurred in 4.3% in the dapagliflozin group and in 5.6% in the placebo group (HR 0.76; 95% CI 0.67 to 0.87); death from any cause occurred in 6.2% and 6.6%, respectively (HR 0.93; 95% CI 0.82 to 1.04). Diabetic ketoacidosis was more common with dapagliflozin than with placebo (0.3% vs 0.1%, P=0.02) (Table 1). So was the rate of genital infections that led to discontinuation of the regimen or were considered serious adverse events (0.9% vs 0.1%, P<0.001) and no increases were found in fractures or bladder cancer.

In conclusion, the DECLARE-TIMI 58 study confirms that the benefit for SGLT-2i treatment is primarily for CV death or heart failure. The study provides important safety information and broadens the indication for patients with CVD or multiple risk factors for CVD.

Table 1 Key safety events DECLARE-TIMI 58 [1]

	Dapagliflozin (%)	Placebo (%)	Between Group Comparison
Treatment emergent SAE	34.1	36.2	P<0.001
Treatment emergent DAE	8.1	6.9	P=0.01
Major Hypoglycemia	0.7	1.0	P=0.02
Diabetic Ketoacidosis* (DKA)	0.3	0.1	P=0.02
Amputation	1.4	1.3	NS
Fracture	5.3	5.1	NS
Acute Kidney Injury	1.5	2.0	P=0.002
Symptoms of volume depletion	2.5	2.4	NS
Genital infection (SAE, DAE)	0.9	0.1	P<0.001
Urinary tract infection (SAE, DAE)	1.5	1.6	NS
Fournier's Gangrene	0.01	0.08	NS
Cancer of Bladder*	0.3	0.5	P=0.02

* CEC adjudicated

No apparent effect of low-dose methotrexate for the prevention of atherosclerotic events

Treatment with canakinumab, a monoclonal antibody that inhibits inflammation by neutralising interleukin-1β, has been shown to reduce CV events relative to placebo [2]. The Cardiovascular Inflammation Reduction Trial (CIRT) examined whether using generic low-dose methotrexate would reduce CV event rates among patients with atherosclerosis and either diabetes or metabolic syndrome [3]. Its results were presented at the AHA Scientific Sessions 2018 by Dr Paul Ridker (Brigham and Women's Hospital, USA).

CIRT was a randomised, double-blind, controlled trial of low-dose methotrexate (at a target dose of 15-20 mg weekly) or matching placebo. A total of 4,786 patients with previous MI or multivessel coronary disease, and either type 2 diabetes or the metabolic syndrome, were randomised to low-dose methotrexate (n=2,391) or placebo (n=2,395). All participants received 1 mg of folate daily. Primary endpoint was a composite of nonfatal MI, nonfatal stroke, or CV death (MACE). The combination of these major adverse CV events plus hospitalisation for unstable angina requiring urgent revascularisation (MACE+) was added later in the trial.

The results showed that methotrexate did not lower interleukin-1β, interleukin-6, or C-reactive protein levels

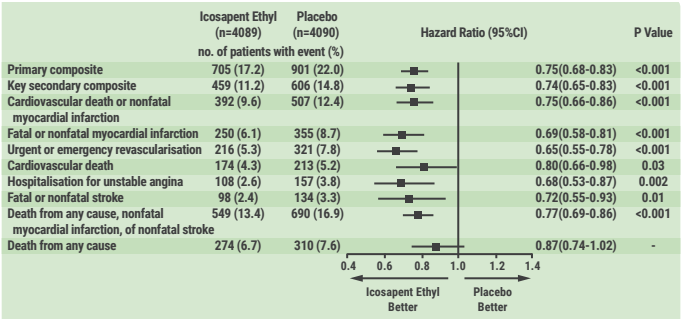
relative to placebo. The final primary endpoint (MACE+) occurred in 201 patients in the methotrexate group and 207 patients in the placebo group (incidence rate 4.13 vs 4.31 per 100 person-years). The original primary endpoint (MACE) occurred in 170 patients in the methotrexate group and in 167 in the placebo group (incidence rate 3.46 vs 3.43 per 100 person-years). Methotrexate was also associated with elevations in liver-enzyme levels, reductions in leukocyte counts and haematocrit levels, and a higher incidence of non-basal-cell skin cancers than placebo. The Independent Data and Safety Monitoring Board recommended early termination of the trial after a median follow-up of 2.3 years for futility. The CIRT was formally stopped on 2 April 2018, with final safety visits scheduled to conclude in September 2018. As such, it can be concluded that targeting inflammation is a complex process, and results are likely to be target specific.

Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia

The Japan EPA Lipid Intervention Study (JELIS) identified significantly reduced risk of major coronary events in patient with hypercholesterolemia who received low-intensity statin therapy plus 1.8 g of eicosapentaenoic acid (EPA) vs statin therapy alone [6]. These findings led to the design of the REDUCE-IT trial [7]. This multicentre, randomised, double-blind, placebo-controlled trial tested whether icosapent ethyl therapy would reduce the risk of CV events in patients with residual risk vs placebo. Its primary results were presented at the AHA 2018 meeting by Dr Deepak Bhatt (Brigham and Women's Hospital, USA).

The trial included patients with established CVD or diabetes and other risk factors who had been receiving statin therapy. They had a fasting triglyceride level of 135-499 mg/dL (1.52-5.63 mmol/L) and an LDL-C level of 41-100 mg/dL (1.06-2.59 mmol/L). A total of 8,179 patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total daily dose, 4 g) or placebo. The primary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularisation, or unstable angina. The main secondary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Patients were followed for a median of 4.9 years.

Figure 2 Hierarchical testing of endpoints according to the prespecified plan [7]



The primary endpoint event occurred in 17.2% of the patients in the icosapent ethyl group vs 22% of those in the placebo group (HR 0.75; P<0.001). Corresponding rates of the main secondary endpoint were 11.2% and 14.8% (HR 0.74; P<0.001). The rates of additional ischaemic endpoints were significantly lower in the icosapent ethyl group than in the placebo group, including the rate of CV death (4.3% vs 5.2%; HR 0.80; P=0.03). A larger percentage of patients in the icosapent ethyl group than in the placebo group were hospitalised for atrial fibrillation or flutter (3.1% vs 2.1%, P=0.004). Serious bleeding events occurred in 2.7% of the patients in the icosapent ethyl group and in 2.1% in the placebo group (P=0.06).

Data demonstrated that the risk of ischaemic events, including CV death, was significantly lower in patients who received 2 g of icosapent ethyl twice daily than among those who received placebo (Figure 2). This was a very positive outcome beyond that expected for patients with high triglyceride levels. While there are still questions regarding the responsible mechanisms, the REDUCE-IT trial led to an important discovery for this high-risk group of patients with promise of reducing complications.

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Coronary Revascularisation: Leading Edge Science

Chronic total occlusions (CTOs) are found in about a third of patients with coronary artery disease and can pose a significant challenge during percutaneous revascularisation. Advances in vein-graft techniques, stent technology, and percutaneous coronary intervention (PCI) strategies, devices, and algorithms have led to significant improvements in the success of CTO treatment.

Endoscopic vein harvest for coronary bypass surgery

Endoscopic harvesting reduces the incidence of leg-wound healing complications, but evidence to evaluate major adverse cardiac events is limited [1,2]. In addition, vein-graft patency is consistently lower with endoscopic harvesting compared with non-endoscopic harvesting [3]. The multicentre, randomised REGROUP trial assessed the influence of the vein-graft harvesting technique on long-term clinical outcomes in coronary artery bypass graft (CABG) surgery.

Eligible patients were ≥18 years with planned elective or urgent (but not emergency) CABG. The median sternotomy approach was used with the use of at least one saphenous vein graft as a conduit. The saphenous vein graft is the most common conduit for CABG. The SYNTAX score was used to quantify the severity of coronary artery disease. The score for low anatomical complexity was ≤22. The respective scores for intermediate and high anatomical complexity were 23-32 and ≥32. A total of 1,150 patients underwent randomisation; 99.5% were male. In the endoscopic group (n=574), 48.8% had diabetes; 51.7% of those in the open group (n=576) had the disease. There were no significant differences between the groups.

Only expert endoscopic vein graft harvesters (e.g. surgeons or physician assistants) from established endoscopic vein harvesting programmes were invited to participate in the trial. Each had more than 2 years of experience with the endoscopic as well as open approaches. Minimum expertise was defined as more than 100 endoscopic vein harvesting cases with a certified low (<5%) conversion rate to open harvesting.

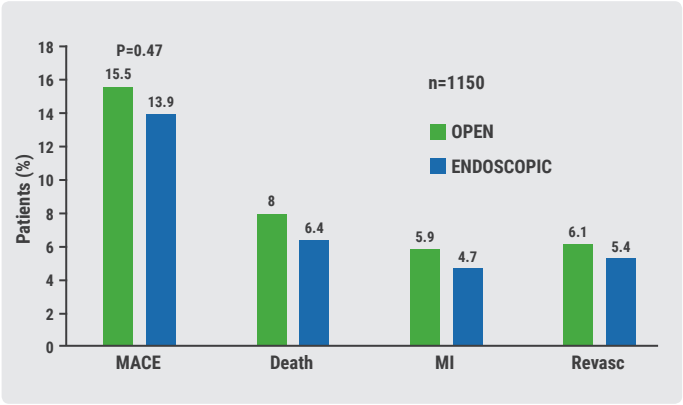
Patients undergoing CABG at 16 Veterans Affairs cardiac surgery centres were randomly assigned to either open or endoscopic saphenous vein graft harvesting. The primary outcome was a composite of major adverse cardiac events, including death from any cause, nonfatal myocardial infarction (MI), and repeat revascularisation in a time-to-event analysis over the active follow-up period of the trial. Leg-wound complications were also evaluated.

Over a median follow-up of 2.78 years, the primary outcome occurred in 89 patients (15.5%) in the open-harvest group and 80 patients (13.9%) in the endoscopic-harvest group (HR 1.12; 95% CI 0.83 to 1.51; P=0.47). A total of 46 patients (8.0%) in the open-harvest group and 37 patients (6.4%) in the endoscopic-harvest group died (HR 1.25; 95% CI 0.81 to 1.92). MI occurred in 34 patients (5.9%) in the open-harvest group and 27 (4.7%) in the endoscopic-harvest group (HR 1.27; 95% CI 0.77 to 2.11). Revascularisation occurred in 35 patients (6.1%) in the open-harvest group and 31 (5.4%) in the endoscopic-harvest group (HR 1.14; 95% CI 0.70 to 1.85). Leg-wound infections occurred in 18 patients (3.1%) in the open-harvest group and 8 patients (1.4%) in the endoscopic-harvest group (RR 2.26; 95% CI 0.99 to 5.15).

Among patient who underwent CABG, there was no significant difference between open vein-graft harvesting and endoscopic vein-graft harvesting in the risk of major adverse cardiac over a median follow-up of 2.78 years (Figure 3). Harvest-site healing was better among endoscopic harvesting patients than among those in the open approach group.

The REGROUP trial included only experienced harvesters, and its results may not apply to other populations. The learning curve for vein-graft harvesting is steep, and proficiency is required for good outcomes. Inexperienced operators may cause unnecessary stretching and trauma to the vein graft

Figure 3 Primary outcomes in the REGROUP trial [4]



during harvesting, leading to endothelial injury and possible early vein-graft failure [5, 6]. To ensure the safety of patients and effectiveness of the procedure, further studies are needed to establish standards for harvester expertise.

Long-term survival following multivessel revascularisation in patients with diabetes

The FREEDOM trial demonstrated that for patients with diabetes mellitus and multivessel coronary disease (MVD), CABG is superior to percutaneous coronary intervention with drug-eluting stents (PCI-DES) in reducing the rate of major adverse cardiovascular and cerebrovascular events after a median follow-up of 3.8 years [7]. Dr Valentin Fuster (Icahn School of Medicine at Mount Sinai, USA) presented results of the FREEDOM Follow-On study, which evaluated the long-term survival of diabetes patients with MVD who underwent coronary revascularisation in the FREEDOM trial [8,9].

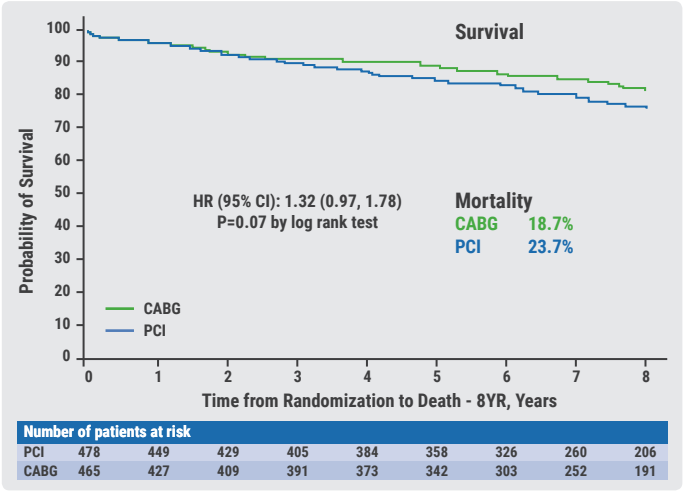
Between April 2005 and April 2010, the FREEDOM trial randomised 1,900 patients from 140 centres worldwide with diabetes and MVD to undergo either PCI with sirolimus or paclitaxel eluting stents or CABG on a background of optimal medical therapy [7]. All patients had angiographically confirmed MVD, defined as a diameter stenosis of more than 70% in 2 or more major epicardial vessels involving at least 2 separate coronary artery territories and without left main coronary artery disease. Most (83%) had 3-vessel disease that included involvement of the left anterior descending coronary artery (99%), with a mean SYNTAX score of 26.2 ±8.6. They were deemed suitable for both PCI-DES and CABG based on the judgment of the local Heart Team. Of the 1,900 patients, there were 314 deaths during the entire follow-up period (204 deaths in the original trial and 110 deaths in the FREEDOM Follow-On). The all-cause mortality rate was significantly higher in the PCI-DES group than in the CABG group (24.3% [159 deaths] vs 18.3% [112 deaths]; HR 1.36; 95% CI 1.07 to 1.74; P=0.01).

After completion of the FREEDOM trial in 2012, patients and centres were invited to participate in the FREEDOM Follow-On study. Twenty-five centres agreed to participate, with a total of 943 patients (49.6% of the original population). Patients consented to be contacted annually by phone or mail or to ascertain their vital status by the medical record or national death registries. Centres followed 97.05% of the patients. Baseline characteristics were similar between groups. A total of 478 patients in the FREEDOM Follow-on study underwent PCI and 465 underwent CABG. The median follow-up for all patients was 4.9 years (range 0.0-13.2). The median follow-up of the FREEDOM Follow-On cohort was 7.5 years (range 0.0-13.2). Survival was evaluated using Kaplan-Meier analysis, and Cox proportional hazards models were used for subgroup and multivariate analyses.

The FREEDOM Follow-On study provides the longest follow-up data on all-cause mortality after randomisation of patients with diabetes and MVD, without left main disease, to PCI-DES or CABG. The outcomes show that, at 8 years, mortality is numerically lower with CABG relative to PCI in a pattern consistent with the overall trial results (18.7% [72 deaths] vs 23.7% [99 deaths]; HR 1.32; 95% CI 0.97-1.78; P=0.07) (Figure 4).

These findings support current recommendations that CABG be considered the preferred revascularisation strategy

Figure 4 All-cause mortality in the FREEDOM extended follow-up cohort (n=943) [9]



patients with diabetes and MVD. Medical therapy, PCI technology, and CABG strategies have advanced since the beginning of the FREEDOM trial. These need to be considered in future revascularisation studies in this population.

Ten-year clinical outcomes drug-eluting stents with biodegradable or permanent polymer coating

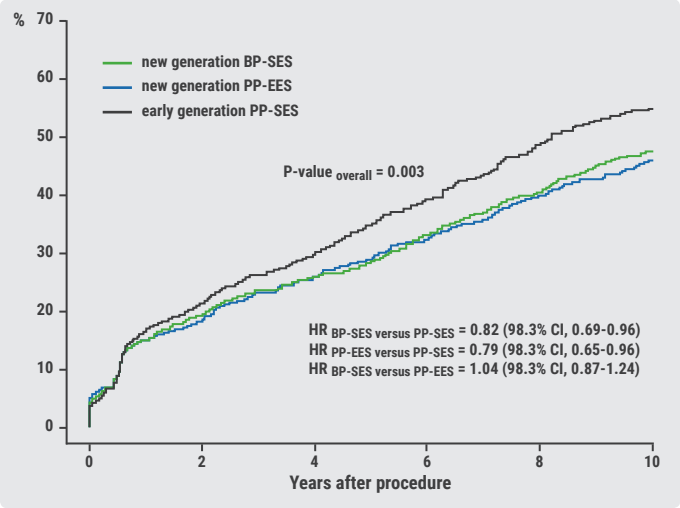
New-generation drug-eluting stents (DES) offer the potential for enhanced late outcomes in comparison with early-generation DES. However, long-term follow-up data on new-generation DES with different polymer coating strategies remains a notable gap in the literature.

The ISAR-TEST 4 trial was a multicentre, randomised trial to compare the efficacy and safety of 3 limus-eluting stents with different polymer coatings in patients with coronary artery disease [10, 11]. All patients had ischaemic symptoms or evidence of myocardial ischaemia plus the presence of on ≥50% stenosis in native coronary arteries. The primary endpoint was MACE (combined incidence of all-cause death, MI, or target lesion revascularisation) at 10 years. Secondary endpoints were individual components of the primary endpoint at 10 years and definite or probable stent thrombosis at 10 years.

A total of 2,603 patients were enrolled in two centres in Munich, Germany, between September 2007 and August 2008. They were randomised in a 2:1:1 allocation to a new generation sirolimus-eluting stent with biodegradable polymer (Yukon Choice PC, n=1,299); a new-generation everolimus-eluting stent with permanent polymer (Xience, n=652); or an early-generation sirolimus-eluting stent with permanent polymer (Cypher, n=652). There were no significant differences in patient or lesion characteristics between the groups at baseline. Patient were assessed annually, and 2,153 (83%) completed the trial with a median follow-up interval of 10.6 years.

The new-generation stents showed superior outcomes compared with the early generation stent for the primary outcome of MACE at 10 years. The HR for the BP-SES vs the PP-SES was 0.82. It was 0.79 for the PP-EES vs the PP-SES, and 1.04 for the BP-SES vs the PP-EES. The differences were statistically significant (P<0.003) as shown in Figure 5.

Figure 5 ISAR-TEST 4 outcomes for the primary endpoint MACE at 10 years [10]



BP-SES, biodegradable polymer sirolimus-eluting stent;
PP-EES, permanent polymer everolimus-eluting stent

BP-SES, biodegradable polymer sirolimus-eluting stent; PP-EES, permanent polymer everolimus-eluting stent

Differences between the new-generation and early-generation stents for all-cause mortality at 10 years were also significant (P=0.02; BP-SES 31.8% vs PP-EES 30.3% vs PP-SES 37.2%). There were no significant differences in target lesion revascularisation or definite or probable stent thrombosis at 10 years. Major cardiac events were significantly lower at 10 years for the new generation vs early generation stents (P=0.003) and all-cause death (P=0.02).

The benefit of new-generation DES over early-generation DES is driven by increasing event rates over time in patients treated with early generation DES. Biodegradable polymer-based sirolimus stents and permanent polymer-based everolimus stents had comparable clinical outcomes at 10 years.

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Groundbreaking Studies in the Practice of Cardiovascular Medicine

The AHA 2018 Scientific Sessions showcased basic, translational, and clinical research. The last decade has seen marked progress in reducing cardiovascular disease deaths. The latest science promises to further reduce the burden of global cardiovascular disease.

Resource use and cost implications of a left ventricular assist device

The MOMENTUM 3 trial compared resource use and cost-effectiveness of the centrifugal HeartMate 3 (HM3) with the axial HeartMate II (HMII) continuous-flow left ventricular assist system in patients with advanced heart failure [1,2]. Outcomes from the 2-year clinical trial [3], presented by Dr Mandeep Mehra (Brigham and Women's Hospital and Harvard Medical School, USA), demonstrated superiority of the HM3 compared with the HMII for rehospitalisations, hospital days spent during rehospitalisations, and cost savings following discharge.

All hospitalisations (n=366) for implantation and their post-discharge costs were monitored until censoring (i.e. study withdrawal, heart transplantation, pump exchange with a non-study device, or death). Each adjudicated episode of hospital-based care was used to calculate device-attributable and non-device-attributable event costs. These were estimated from trial data and payer administrative claims databases. Cost savings were stratified by subgroups: study outcome (i.e. transplant, death, or ongoing on device); intended goal of therapy; type of insurance; and sex. In total, 366 patients were randomly assigned to HM3 or HMII groups. The as-treated group included 361 patients (189 in the HM3 group and 172 in the HMII group). Of these individuals, 337 (177 in the HM3 group and 160 in the HMII group) were successfully discharged following implantation.

The economic analysis of the 2-year outcome of the MOMENTUM 3 trial showed fewer total hospitalisations per patient-year (HM3: 2.1±0.2 vs HMII: 2.7±0.2; P=0.015) and 8.3 fewer hospital days per patient-year on average in the HM3 arm vs the HMII arm (HM3: 17.1 days vs HMII: 25.5 days; P=0.003). These differences were driven by patients hospitalised for suspected pump thrombosis (HM3: 0.6% vs HMII: 12.5%; P<0.001) and stroke (HM3: 2.8% vs HMII: 11.3%; P=0.002). Controlled for time spent in the study (average cumulative cost per patient-year), costs in the post-discharge HM3 arm were 51% lower than those in HMII group (HM3: $37,685±4,251 vs HMII: $76,599±11,889, P<0.001).

This trial demonstrated a reduction in rehospitalisations, hospital days spent during rehospitalisations, and significant cost savings following discharge for the HM3 model compared with the HMII model. This was so regardless of the intended goal of therapy [3]. Overall costs after discharge were 51% lower with the HeartMate 3 than with the HeartMate II pump. The greater cost-effectiveness of left ventricular assist systems for advanced heart failure might prompt more widespread use across different healthcare systems.

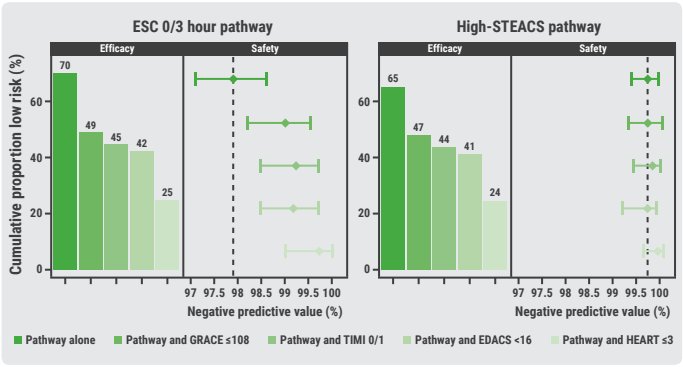
Limited value for adding risk scores to high-sensitivity troponin tests in acute coronary syndrome

High-sensitivity cardiac troponin test can help to identify patients who are at low risk of myocardial infarction (MI) in the emergency department. Prof. Nicholas Mills (University of Edinburgh, United Kingdom) presented results of a study that analysed whether adding clinical risk scores improved the safety of early rule-out pathways for MI [4].

A total of 1,935 patients with suspected acute coronary syndrome (ACS) were included in the analysis of the safety and efficacy of 2 rule-out pathways alone or in combination. The European Society of Cardiology (ESC) 3-hour pathway uses one diagnostic threshold (99th percentile); the High-STEACS pathway uses different thresholds to rule out (<5 ng/L) and rule in (>99th percentile) MI. They were used in conjunction with low-risk TIMI (0 or 1); GRACE (≤108); EDACS (<16), or HEART (≤3) scores.

Data showed that 14.3% of patients (276/1935) experienced MI or cardiac death during index presentation or at 30 days.

Figure 6 Proportion of patients classified as low-risk based on the ESC 3-hour or High-STEACS pathway alone or in combination with the TIMI, GRACE, EDACS, or HEART scores [4]



The ESC pathway ruled out 70% and missed 27 events. It had a negative predictive value (NPV) of 97.9% (95% CI, 97.1-98.6). Inclusion of a HEART score ≤3 reduced the percentage of patients ruled out by ESC pathway to 25% but improved the NPV to 99.7% (95% CI, 99.0-100; P<0.001). The High-STEACS pathway ruled out 65% and missed 3 events. Its NPV was 99.7% (95% CI, 99.4-99.9). No risk score improved the NPV of the High-STEACS pathways, but all of them reduced the percentage of patients ruled out (24% to 47%; P<0.001 for all) [4].

Thus, safety of the ESC 3-hour pathway was significantly improved by adding clinical risk scores. Results showed no benefit to using risk scores with pathways that use low concentrations of cardiac troponin to risk-stratify patients (e.g. High-STEACS or ESC 1-hour pathways) (Figure 6).

In-hospital cardiac arrest: Recommendations for resuscitation teams

Dr Brahmajee Nallamothu (University of Michigan Medical School, USA) presented the results of a qualitative study that set out to better understand how resuscitation teams at top-performing hospitals achieve high in-hospital cardiac arrest (IHCA) survival rates [5].

Risk-standardised IHCA survival-to-discharge rates were calculated for registry hospitals across the American Heart Association Get with the Guidelines–Resuscitation. Hospitals were in the top, middle, and bottom quartiles of survival. A total of 158 individuals across 9 geographically and academically diverse hospitals were interviewed between 2012 and 2014. Disciplines included physicians (17.1%), nurses (45.6%), other clinical staff (17.1%), and administrators (20.3%). Top-performing hospitals had dedicated or designated resuscitation teams that included diverse disciplines. The roles and responsibilities of team members were clearly defined. All teams showed strong leadership and clear communication during IHCA events using in-depth mock codes.

Table 2 Recommendations for resuscitation teams. Modified from Nallamothu et al. [5]

Theme	Recommendations
Team design	Establish dedicated or designated teams for in-hospital cardiac arrest.
Team composition and roles	Ensure the participation of diverse disciplines, including physician, nursing, respiratory therapy, and pharmacy expertise. Develop systems to include trainees while ensuring the availability of advanced expertise as needed. Define clear roles, tasks, and responsibilities of team members before or at the start of an in-hospital cardiac arrest event; focus on core skills, including chest compressions, airway management, and IV access.
Communication and leadership	Encourage the development of approaches that improve communication (e.g., closed-loop communication) and stress respect across multiple disciplines; have a communication system in place to correct behavioural issues without being punitive. Leadership during in-hospital cardiac arrest requires focus. Identifying high-quality and clearly identified leaders within resuscitation teams is essential for successful teamwork.
Training/education	Implement mock codes that are regular and unscheduled; occur in actual patient rooms and high-risk areas; are multidisciplinary; and include post-mock code debriefing.

Qualitative, thematic analysis identified 4 broad themes related to resuscitation teams at top-performing hospitals, as summarised in Table 2.

A simple, evidence-based diagnostic tool of HFpEF

The current gold standard for diagnosing heart failure with preserved ejection fraction (HFpEF) is catheter lab exercise testing. Yet, catheter lab tests are not universally available, and noninvasive methods generally lack sensitivity [6]. The aim of a recent retrospective study [7] was to derive and validate non-invasive diagnostic criteria using clinical and echocardiographic variables that are widely available in clinical practice. Dr Barry Borlaug (Mayo Clinic, USA) presented findings at the AHA Scientific Session 2018.

A total of 414 consecutive patients with unexplained dyspnoea were diagnosed for HFpEF (267 cases) or noncardiac dyspnoea (147 controls) by invasive haemodynamic exercise testing (HFpEF prevalence 64%). The ability of clinical findings to discriminate cases from controls was evaluated using logistic regression. A scoring system was developed and

then validated in a separate test cohort with 100 consecutive patients (61 with HFpEF; prevalence 61%). The final set of predictive variables included obesity, atrial fibrillation, age >60 years, treatment with ≥2 antihypertensives, echocardiographic E/e' ratio >9, and echocardiographic pulmonary artery systolic pressure >35 mmHg. A weighted score based on the 6 variables was used to create a composite score (H2FPEF score) ranging from 0 to 9. The odds of HFpEF doubled for each 1-unit score increase (odds ratio, 1.98; 95% CI, 1.74–2.30; P<0.0001), with an area under the curve of 0.841 (P<0.0001).

The H_2FPEF score was found to be superior to a currently used algorithm based on expert consensus (increase in area under the curve of 0.169; 95% CI, 0.120–0.217; P<0.0001). Performance in the independent test cohort was maintained (area under the curve, 0.886; P<0.0001). The H2FPEF score discriminated HFpEF from noncardiac causes of dyspnoea and can help determine the need for further diagnostic testing in patients with unexplained exertional dyspnoea.

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Harnessing Technology and Improving Systems for Global Health

The growing burden of chronic disease combined with rising healthcare costs and explosive growth in the literature have created an urgent need for easy-to-use clinical e-tools and educational resources for physicians and their patients [1]. E-health care applications are becoming more common but are still largely unable to connect across platforms or users. Nonetheless, clinical decision support systems (CDSS) have wide-ranging functionality that could improve the safety and efficacy of cardiovascular care.

Clinical decision support systems (CDSS) can proactively identify potential adverse events based on the presence of abnormal parameters; help clinicians stay current with guideline-based recommendations; engage patients with personalised content; and support individual care plans for chronic disease self-management. Advances in health informatics technologies have already made such systems available to physicians at the point-of-care. Growing numbers of patients are also able to access CDSS to better track and manage their own health [1]. These trends are paving the way toward more equitable and effective healthcare systems.

Efficacy of electronic clinical decision support in atrial fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac rhythm abnormality, with a lifetime risk of 1 in 4 [2, 3]. It is an important and independent risk factor for stroke, increasing the risk of such events by 5-fold and accounting for approximately 15-20% of all strokes [4]. At least a third of AF patients are asymptomatic [5]. Management of AF in the primary care setting can be challenging. A typical physician is called on to treat a wide swath of conditions. He or she is also expected to stay abreast of exponential growth in medical information [6]. CDSS's monitor patient-specific clinical data, proactively identify potential adverse events, and provide diagnostic and therapeutic recommendations to clinicians [1].

The prospective, randomised, cluster-design IMPACT-AF trial assessed the efficacy of a CDSS to improve AF management in primary care settings. Conducted in Nova Scotia, Canada, its primary aim was to evaluate whether a web-based CDSS could improve clinical and patient-reported outcomes compared with usual care. The trial included physicians

in full-time practice. All had high-speed internet access and were managing adult patients. Participants were Nova Scotia residents aged ≥18 years with electrographically-confirmed AF or a documented past diagnosis and management. Primary efficacy outcome was a composite of AF-related emergency department visits or unplanned cardiovascular hospitalisation. The primary safety outcome was major bleeding over 12 months per ISTH criteria. The study included 117 primary care practices randomised 1:1 to usual care (n=56) or CDSS (n=61). A total of 1,145 patients (n=548 usual care; n=597 CDSS) participated in the study. Their mean age was 72 years. Over 50% were male and came from rural areas.

At 12 months, physician use of the CDSS had no significant effect on time to AF-related emergency department visits or unplanned hospitalisations vs usual care. However, incident rate ratios suggest that CDSS's might lead to large reductions with more and better training over a longer span of time. Differences in safety outcomes at 12 months were also not significant. Many real-world preferences and conditions could account for the outcomes.

Increased anticoagulation prescription with alert-based computerised decision support in atrial fibrillation

Chronic anticoagulation is recommended for AF patients with thromboembolic risk factors regardless of AF duration or frequency [7]. Despite widely available risk stratification tools, safe and effective anticoagulant options, and evidence-based practice guidelines, anticoagulation for stroke prevention in AF is under-prescribed [8, 9]. This low adherence rate underscores a critical gap in implementation of best clinical practice among providers, said Dr Gregory Piazza (Brigham and Women's Hospital, USA). ALERT-AF investigated whether alert-based computerised CDSS would increase anticoagulation prescription in hospitalised AF patients at high risk for stroke.

The ALERT-AF trial was a single-centre, unblinded trial including 457 patients (CHA2DS2-VASc score≥1) ≥21 years old with AF or atrial flutter who were not prescribed anticoagulant therapy for stroke prevention. The CDSS tool randomised 247 patients to the alert group and 210 patients to control. Baseline characteristics, comorbidities, stroke risk (CHA2DS2-VASc score), and bleeding risk (HAS-BLED score) were similar between the 2 groups. The primary efficacy endpoint was the rate of anticoagulation prescription during hospitalisation, at discharge and at 90 days. The primary safety endpoint was major bleeding or clinically relevant non-major bleeding, defined by ISTH bleeding classification system, at 90 days from enrolment. The secondary efficacy endpoint was a composite of major adverse cardiovascular events. This was defined as stroke/TIA, systemic embolism, myocardial infarction (MI), or all-cause mortality at 90 days.

Table 3 ALERT-AF: Primary efficacy endpoint [8]

Characteristic, n (%)	Alert n=248	Control n=210	P-value
Clinical response to alert		-	-
Open stroke prevention order set	88 (35.4)		
Read AF guidelines	2 (0.8)		
Exit and provide rationale	158 (63.7)		
Rationale for not prescribing anticoagulation*			-
Bleeding risk	122 (50.0)		
Fall risk	31 (12.0)		
Other	95 (38.0)		
Anticoagulation prescribed during hospitalisation	64 (25.8)	20 (9.5)	<0.0001
Anticoagulation prescribed at discharge	59 (23.8)	27 (12.9)	0.003
Anticoagulation prescribed at 90 days	69 (27.8)	36 (17.1)	0.007
Anticoagulation prescribed during hospitalisation, at discharge, and at 90 days	**48 (19.4)**	**15 (7.1)**	**<0.001**

*More than one reason could have been provided

Results show that the alert group was more likely to be prescribed anticoagulation during the hospitalisation (25.8% vs 9.5%, P<0.0001), at discharge (23.8% vs 12.9%, P=0.003), and at 90 days (27.7% vs 17.1%, P=0.007) compared with the control group (Table 3).

The alert was associated with a lower rate of death, MI, cerebrovascular event, or systemic embolic event at 90 days (11.3% vs 21.9%; P=0.002; adjusted OR 0.45; 95% CI 0.27-0.76 Death at 90 days occurred in 10.1% of patients in the alert group and 14.8% of those in the control group (P=0.13).

The results of this single-centre study are promising and suggest that alerts in electronic medical records may be one mechanism to change provider behaviour. The associated reduction in CV events exceeds that expected based on the mechanism of the drug and must be confirmed in larger multicentre studies.

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Acute Care Cardiology – Preserving Brain and Heart

Preserving brain and heart function after a coronary event is essential to survival and improved quality of life after discharge. Clinical trials advance the safety and efficacy of acute cardiovascular disease (CVD) treatment. They continue to influence the focus of research and drive progress toward optimal care.

Safety and efficacy of early goal-directed haemodynamic optimisation strategy after cardiac arrest

Post-cardiac arrest (CA) patients admitted to the ICU have a poor prognosis, with estimated survival rates of approximately 30%-50% [1]. Cerebral oxygenation, which can cause further damage, drops profoundly in those treated to a mean arterial blood pressure (MAP) target of 65 mmHg during their first 6-12 hours in the ICU. The Neuroprotect Trial investigated optimal cerebral oxygenation and haemodynamic strategies in post-CA ICU patients. Prof. Koen Ameloot (UZ Leuven, Belgium) presented results of the trial.

Neuroprotect examined whether targeting a MAP of 85-100 mmHg optimises cerebral oxygenation, and examined the safety and efficacy of an early goal-directed haemodynamic optimisation strategy (EGDHO) (MAP 85-100 mmHg, SVO_2 65-75%). The aim of the study was to determine if EDGHO improved cerebral oxygenation, reduced anoxic brain damage, and improved functional outcome compared with a MAP 65mmHg strategy.

Neuroprotect was a multicentre, assessor-blind, randomised clinical trial. A total of 112 out-of-hospital CA patients were randomly assigned to EGDHO or MAP 65mmHg strategies during the first 36 hours of their ICU stay. The primary outcome was the extent of anoxic brain damage. It was quantified by the percentage of voxels below an ADC score of 650.10^{-6} mm^2/s on diffusion-weighted MRI performed 4-5 days post-CA. Secondary outcomes were favourable neurological outcomes (CPC scores of 1-2) at ICU discharge and at 180 days. Safety outcomes included life threatening arrhythmias requiring life support.

For patients assigned to EGDHO, MAP had higher cerebral oxygenation during the first 12 hours of their ICU stay (P=0.04) and improved cerebral perfusion. However, the percentage of voxels below an ADC score of 650.10^{-6} mm^2/s did not differ between the groups (16% vs 12%; OR 1.37; P=0.09). The number of patients with favourable neurological outcomes at 180 days was also similar (40% vs 38%; OR 0.98, P=0.96). However, there were fewer adverse events in patients assigned to EGDHO (13% vs 33%; OR 0.32; P=0.02). Patients assigned to EGDHO underwent fewer tracheostomies (4% vs 18%; OR 0.18; P=0.02) and tended to recover earlier (43% vs 27% with CPC scores of 1-2 at ICU discharge; OR 1.91; P=0.15).

Outcomes showed that targeting a higher MAP in post-CA patients is safe and results in improved cerebral perfusion and oxygenation. However, the approach did not reduce the extent of anoxic brain damage shown on diffusion-weighted MRI or improve functional outcome.

Mechanically unloading the left ventricle and delaying reperfusion reduces infarct size in acute myocardial infarction

Data suggest that efforts to reduce infarct size may decrease incidence of heart failure (HF) and improve survival after acute myocardial infarction (MI). Testing in various preclinical models indicates that compared with reperfusion alone, mechanically unloading the left ventricle (LV) before reperfusion limits infarct size after acute MI.

The Door-to-Unload pilot trail in ST-segment elevation myocardial infarction (STEMI), presented by Dr Navin Kapur (Tufts Medical Center, USA), was a multicentre safety and feasibility study, and the first-in-human trial to mechanically unload the LV and delay reperfusion (primary unloading) in acute MI. The prospective, randomised trial included 50 patients with anterior STEMI. All were referred for primary percutaneous coronary intervention (PCI) within 1-6 hours of symptom onset for primary unloading of the LV with an Impella CP. Reperfusion was either immediate (U-IR) or delayed by 30 minutes (U-DR).

The primary safety outcome was a composite of major adverse cardiovascular and cerebrovascular events (MACCE). These included cardiovascular mortality, reinfarction, stroke, and major vascular events at 30 days. Additional safety parameters included myocardial salvage index (MSI) at 3-5 days and infarct size at 30 days using cardiac MRI. Images were assessed in a central blinded core lab. All patients completed the U-IR (n=25) or U-DR (n=25) protocols. Those assigned to the U-DR group underwent 30 minutes of LV unloading prior to PCI. Mean door-to-balloon time (DTB) was 72 minutes in the U-IR group and 97 minutes in the U-DR group.

The overall MACCE rate was 10%. No significant difference was observed between the U-RI and U-DR groups (8% vs 12%). The longer DTB time in the U-DR group did not significantly increase the 30-day mean infarct size (15% U-IR vs 13% U-DR). The overall MSI was similar between the groups (48% U-IR vs 52% U-DR; P=NS). ST-elevation sum≥7mm (n=29/50) reflects a larger area at risk for patients. In this group (n=29), MSI was significantly higher in the U-DR arm compared with the U-RI arm (56% vs 39%; P=0.04).

Unloading the LV with an Impella CP first and delaying reperfusion was feasible in patients with anterior STEMI referred for PCI and associated with a low 30-day MACCE rate. This approach did not increase infarct size. Myocardial salvage in patients with a larger area of myocardium at risk was significantly higher with 30 minutes of LV unloading prior to reperfusion compared with LV unloading and immediate reperfusion. These findings warrant a randomised controlled trial to further assess whether a Door-to-Unload strategy improves infarct size in anterior STEMI.

Low-dose adjunctive alteplase safe but not effective during primary PCI

Microvascular obstruction (MVO) affects half of all patients with acute STEMI. It is more likely in those who present with a major MI and is independently associated with adverse outcomes. The T-TIME trial investigated the effect of low-dose adjunctive alteplase on MVO mass when administered during primary PCI. Prof. Colin Berry (University of Glasgow, UK) presented outcomes from this multicentre, randomised, dose-ranging, phase 2b clinical study at the AHA 2018 Scientific Sessions.

The trial included 440 patients with acute STEMI due to a proximal-mid vessel occlusion of a major coronary artery. All presented ≤6 hours from symptom onset and were randomly assigned (1:1:1) to adjunctive treatment with placebo (n=151), alteplase 10 mg (n=144), or alteplase 20 mg (n=145). CMR imaging was performed in 400 (90.9%) patients at 2-7 days and 367 (83.4%) at 3 months. The study drug (20 mL) was manually infused during 5-10 minutes after reperfusion, before stent implantation during primary PCI. Patients underwent late (10-15 minutes) MRI enhanced with gadolinium contrast at 2-7 days.

The primary outcome was the amount of MVO (percentage of LV mass) volume at 2-7 days and at 30 days. Conditional power for the primary outcome was <30% in both treatment arms (futility criteria), based on a prespecified analysis.

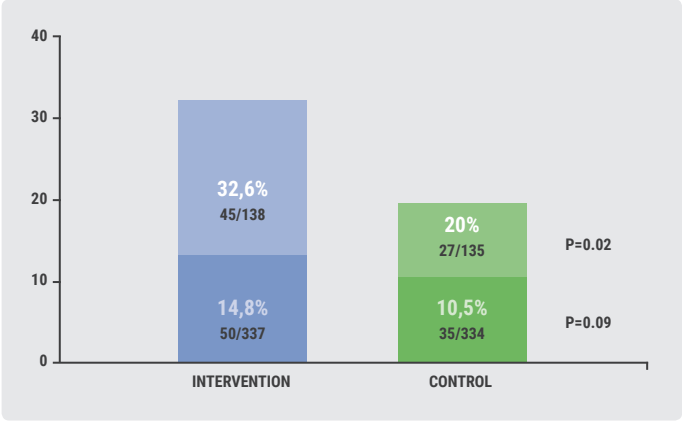
No significant difference was observed in mean MVO mass between the groups (P=0.43 with the van Elteren test). Troponin T was measured in 317 (72%) of patients. The AUC for troponin T increased in both treatment groups compared to placebo (P=0.002). Adjunctive, low-dose intracoronary alteplase during primary PCI was feasible and safe but not effective; troponin T increased with both doses.

Pre-hospital resuscitation intra-arrest cooling effectiveness survival study

Sudden cardiac death is one of the major health issues of the industrialised world [2]. Yet, the prognosis for survival after CA remains grim. Less than 50% of CA patients achieve a return of spontaneous circulation (ROSC); this rate drops to 20% for those who live in rural areas or lack an initial rhythm that can be defibrillated [3,4]. Even fewer are alive on hospital admission, and most of them eventually die from extended post-anoxic brain injury [4,5]. Animal studies of ischaemic cardiac death and clinical studies of reperfusion and delayed injury suggest that hypothermia in CA protects the brain. Most studies, however, are based on hospital cooling. While prehospital cooling with cold fluids is not haemodynamically safe, transnasal evaporative cooling may be a viable option.

The aim of the PRINCESS trial was to study the effect of intra-arrest, transnasal evaporative cooling on neurologically intact survival in out-of-hospital CA patients [6]. Dr Per Nordberg (Karolinska Institute, Sweden) presented the results of this multicentre, randomised, controlled trial. The primary outcome was survival with Cerebral Performance Category Scale (CPC) of 1 (good cerebral performance) or 2 (moderate cerebral disability) at 90 days.

Figure 7 Complete neurologic recovery (CPC 1) in all patients with ventricular fibrillation [6]



Between 2010 and 2018, 667 bystander-witnessed CA patients from 7 European countries were randomised to intra-arrest cooling or control (hospital cooling). Their median age was 65 years, 75% were male, 60% received bystander CPR, and 40% had ventricular fibrillation (VF). In 40% of patients, cooling was started within 19 minutes. The minimum in time to target (<34GR) was 101 minutes for the intervention patients vs 182 minutes for standard care (P<0.001).

The study failed to meet its primary outcome (CPC 1-2), with no significant difference between the groups. Nonetheless, CA patients with VF had the best effect from early cooling, with a significantly improved complete neurologic recovery (32.6% vs 20%) (Figure 7). The earlier the cooling was initiated, the better the neurologic outcome. Transnasal evaporative cooling was haemodynamically safe and significantly shortened time to target temperature.

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2018 AHA/ACC Cholesterol Clinical Practice Guidelines

High cholesterol at any age can increase a person's lifetime risk of heart disease or stroke. The 2018 cholesterol guidelines from the American Heart Association (AHA) and the American College of Cardiology (ACC) [1,2] update the 2013 guidelines based on the latest science in prevention, diagnosis, and treatment.

"The updated guidelines reinforce the importance of healthy living, lifestyle modification, and prevention. They build on the major shift we made in our 2013 cholesterol recommendations to focus on identifying and addressing lifetime risks for cardiovascular disease," said Prof. Ivor Benjamin, president of the AHA.

Guideline summaries

While lifestyle intervention remains the cornerstone of treatment, the new guidelines focus on cardiovascular disease (CVD) prevention across the lifespan, risk assessment, patient-clinician decision-making, and treatment recommendations for specific populations, including women and children.

Primary and secondary prevention

For healthy adults aged 20 years or older, measurement of a fasting or nonfasting plasma lipid profile should be used when estimating ASCVD risk and documenting baseline LDL-C. If an initial nonfasting lipid profile finds triglycerides of ≥400 mg/dL, a repeat lipid profile with fasting should be used to determine baseline LDL-C and triglyceride levels.

Most patients, children and adults, can reduce their lifetime ASCVD risk with a healthy lifestyle. The 2018 guidelines recommend encouraging reduction of caloric intake,

saturated fat, and dietary cholesterol; patients should eliminate all trans fats. An average of 40 minutes of moderate to vigorous physical activity 3-4 times per week, or even moderate amounts of activity, can reduce risk. Patients with metabolic syndrome may also benefit from physical activity. When lifestyle interventions alone are not enough to lower LDL-C, start statin therapy. High-, moderate-, and low-intensity treatments typically lower LDL-C by ≥50%, 30%-49%, or ≤30%, respectively. A stepwise approach is advised. If statins are not well-tolerated, add a bile acid sequestrant, ezetimibe, or PCSK9 inhibitor to statin therapy to further reduce LDL-C levels.

Secondary prevention can reduce the risk of another cardiovascular event or prevent it in patients who have already had them. Use an ideal LDL-C threshold of ≤70 mg/dL when considering the addition of ezetimibe and PCSK9 inhibitors to an existing statin therapy.

Severe (LDL-C ≥190 mg/dL) and familial hypercholesterolemia

Patients with severe hypercholesterolemia do not need ASCVD risk scoring, according to the 2018 guidelines. Statin therapy is recommended. Ezetimibe plus a moderate-intensity statin reduces LDL-C more than statin monotherapy in patients with heterozygous familial hypercholesterolemia. The combination also reduces ASCVD risk more than moderate-intensity statin monotherapy in patients with recent acute coronary syndrome. In select patients whose LDL-C is inadequately controlled with drug therapy, LDL apheresis is an option. Referral to a lipid specialist may be indicated.

Issues specific to women

When discussing lifestyle intervention and the potential benefit of statins, clinicians should consider issues specific to women (e.g. menopause at <40 years of age, history of pregnancy-related disorders). Sexually active women of childbearing age who are treated with statins should be counselled to use reliable contraception. Patients with hypercholesterolemia who plan to become pregnant should stop the statin 1-2 months before attempts to conceive. If a woman on statins becomes pregnant, therapy should be stopped as soon as this is discovered.

Paediatric guideline

The 2018 cholesterol guideline includes recommendations for lifestyle therapy, familial history of early CVD or hypercholesterolemia, and screening for children or adolescents with obesity or other metabolic risk factors.

Intensified lifestyle therapy, including moderate caloric restriction and regular aerobic physical activity, is recommended for children with lipid disorders related to obesity. Lifestyle counselling can help lower LDL-C in this population. The guideline calls for 3-6 months of lifestyle therapy for children or adolescents ≥10 years of age with a persistently high HDL-C level (≥190 mg/dL or ≥4.9 mmol/L) or ≥160 mg/dL (≥4.1 mmol/L) and a clinical presentation consistent with familial hypercholesterolemia. If there is no adequate response, initiation of statin therapy is recommended.

Children or adolescents with a familial history of early CVD or significant hypercholesterolemia are at heightened risk of CVD. In such cases, the recommendation is to measure a fasting or nonfasting lipoprotein profile as early as 2 years of age to detect familial hypercholesterolemia or rare forms of hypercholesterolemia. Reverse-cascade screening of family members is recommended when moderate or severe hypercholesterolemia is found in children or adolescents. Screening should include cholesterol testing of first, second, and if possible, third degree biological relatives to detect familial forms of hypercholesterolemia.

The updated guideline further recommends a fasting lipid profile in children or adolescents with obesity or other metabolic risk factors to detect lipid disorders that might be components of metabolic syndrome. It is reasonable to measure a fasting lipid profile or nonfasting non-HDL-C once between the ages of 9-11 and again between the ages of 17-21 in paediatric patients with no cardiovascular risk factors or family history of CVD. Such testing can detect moderate to severe lipid abnormalities.

Statin safety

Statin therapy is usually well-tolerated and safe. However, like other classes of drugs, it can cause side effects. The most common are statin-associated muscle symptoms, usually subjective myalgia. Though rare in clinical trials, these can be difficult to manage and result in nonadherence, with adverse effects on ASCVD outcomes. Statins can also cause a modest increase in the risk of incident diabetes mellitus in susceptible patients. However, statin-associated side effects should not prompt discontinuation of treatment. Most patients tolerate statin rechallenge with an alternative statin

or a different regimen (e.g. a reduced dose or a combination of a statin and nonstatin). The new guideline recommends a comprehensive approach to statin-associated symptoms. Unless side effects are severe, clinicians should reassess, discuss, and encourage rechallenge as the first approach.

Top 10 take-home messages of the 2018 AHA/ACC cholesterol guidelines

1. High cholesterol at any age increases the risk for cardiovascular disease significantly. In all patients, promote a heart-healthy lifestyle throughout the life course.
2. In patients with clinical atherosclerotic cardiovascular disease (ASCVD), reduce LDL-C with high intensity or maximally tolerated statin therapy.
3. In very high-risk ASCVD, consider adding non-statins to statin therapy at an LDL-C threshold of 70 mg/dL (1.8 mmol/L). When LDL-C levels remain at 70 mg/dL (1.8 mmol/L), stepwise titration is recommended by adding ezetimibe to statin therapy, and subsequently a PCSK9 inhibitor (although long-term safety [>3 years] is uncertain).
4. In patients with severe primary hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L]), start high-intensity statin therapy without calculating their 10-year ASCVD risk.
5. In patients 40-75 years of age with diabetes mellitus and an LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk.
6. In adults 40-75 years of age evaluated for primary ASCVD prevention, have a clinician-patient risk discussion before starting statin therapy.
7. In patients 40-75 years of age with diabetes mellitus and an LDL-C ≥70 mg/dL (≥1.8 mmol/L) at a 10-year ASCVD risk ≥7.5%, start a moderate-intensity statin therapy if a discussion of treatment options favours that option.
8. In adults 40-75 years of age without diabetes mellitus and a 10-year risk of 7.5%-19.9%, additional risk factors favour the initiation of statin therapy.
9. Consider measurement of coronary artery calcium (CAC) if a decision about statin therapy is uncertain in adults 40-75 years of age without diabetes, but with LDL-C levels ≥70 mg/dL – 189 mg/dL (≥1.8-4.9 mmol/L) and a 10-year ASCVD risk ≥7.5% - 19.9%.
10. Assess adherence and LDL-C response to medication and lifestyle changes with repeat lipid measurement 4-12 weeks after statin initiation; repeat every 3-12 months as needed.

Conclusion

The new cholesterol guidelines recommend more personalised risk assessment and active patient involvement in treatment decisions. It emphasises the importance of a personalised lifespan approach to prevent, diagnose, and treat high cholesterol. A healthy diet and lifestyle remain critical for maintaining health and slowing the onset or progression of CVD. When intervention is needed, statins are the cornerstone of effective care. With all patients, ongoing communication is critical. Recommendations call for regular monitoring to check adherence, adequacy of response, and new associated symptoms. Reaffirmation of benefits can help more patients continue treatment and reduce their lifetime risk of CVD.

The AHA/ACC 2018 cholesterol guidelines were simultaneously published in the American Heart Association journal, *Circulation* [1], and *the Journal of the American College of Cardiology* [2]. A special report [3] published as a companion to the cholesterol guidelines provides more details into the use of quantitative risk assessment in primary prevention for CVD.

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