AHA 2019 scientific sessions highlights: Novel approaches in cardiovascular risk reduction

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The American Heart Association (AHA) has strived for almost a century to promote scientific knowledge and change clinical practice with regards to the management of cardiovascular disease (CVD), which has consistently been the number 1 killer in the United States of America as well as worldwide. The AHA scientific sessions, initiated in 1925, have always been a milestone in cardiology, being the venue where the word's experts in cardiology are gathered and some of the most influential advances are announced for the first time.

The 2019 AHA scientific sessions demonstrated, once more, an impressive number of basic science and clinical studies across all fields of cardiology, from atrial fibrillation and heart failure (HF) to challenges in atherosclerotic CVD (ASCVD) and paediatric CVD, setting the current and future trends in cardiovascular research. The topic of big data analysis, from metabolomics and transcriptomics analyses to deep learning algorithms, was of special interest during this year's sessions, as it has started dynamically invading clinical medicine to maximize the yield of useful clinical information for CVD diagnosis, stratification and management. More importantly, several important clinical trial results were also presented in this year's AHA sessions, with the potential of changing clinical guidelines worldwide.

Randomised clinical trials on risk reduction in HF

During the 2019 AHA sessions, several sub-analyses of the dapagliflozin DAPA-HF trial, examining the effect of dapagliflozin [a sodium-glucose co-transporter 2 (SGLT2) inhibitor initially used in diabetes to enhance renal excretion of glucose] on heart failure with reduced ejection fraction (EF), were presented. These revealed that dapagliflozin was superior to placebo in reducing the primary endpoint of cardiovascular death, heart

failure hospitalizations or urgent heart failure hospital visits, independently of the presence of diabetes and consistently across all age groups above 55 years as well as across all cardiac health status groups (as evaluated by the Kansas City Cardiomyopathy Questionnaire) (https://www.acc.org/latest-in-cardiology/clinical-trials/2019/08/30/21/33/dapa-hf). Several studies have previously identified pleiotropic roles for SGLT2 inhibition in the heart, and this important clinical trial comes to corroborate the clinical relevance of such experimental studies[5,6].

The PARADIGM-HF and PARAGON-HF evaluated the effects of angiotensin receptor-neprilysin inhibitor sacubitril-valsartan versus enalapril and valsartan respectively on cardiovascular death and heart failure hospitalizations in patients with reduced HF and preserved EF respectively. Previous studies have implied direct roles for the class of angiotensin receptor-neprilysin inhibitors in heart failure by dual regulation of the angiotensin axis and natriuretic peptide bioavailability[7,8]. Accordingly, the trials presented during the 2019 AHA scientific sessions put previous findings into clinical context, revealing that sacubitril-valsartan significantly reduced the composite endpoint hazard ratio only in individuals with reduced EF, whilst sex-specific sub-analysis of the PARAGON-HF trial suggested that women may benefit more than men at a higher EF range (i.e., preserved) (https://www.acc.org/latest-in-cardiology/clinical-trials/2019/08/30/21/24/paragon-hf; https://www.acc.org/latest-in-cardiology/clinical-trials/2014/08/30/12/22/paradigm-hf) .

Randomised clinical trials on risk reduction in ASCVD

This year's AHA sessions featured several clinical trials investigating new approaches to ASCVD risk reduction via interventional versus optical medical therapy, focusing

especially on two major aspects of atherosclerosis pathogenesis, namely inflammation and lipid levels. Inflammation as a target in ASVCD has recently come back to the spotlight following the CANTOS trial[9], while residual lipid risk is an ever-challenging topic contributing to vascular complications[10].

The COLCOT trial was a very interesting study evaluating the effects of low-dose colchicine on major adverse cardiovascular effects (MACE) in patients with recent (<30 days prior to enrolment) myocardial infarction (MI) having undergone all appropriate interventional management. In preclinical studies, colchicine has demonstrated antimitotic, immunomodulatory effects as well as the ability to prevent thrombin-induced platelet aggregation whilst stabilizing the vascular endothelium[11–13]. Interestingly, colchicine was superior to placebo with regards to MACE hazard ratio over the follow-up period, however this was driven by reduced incidence of stroke and urgent angina leading to revascularization. This suggests that colchicine may have a role post MI, which may be due to its anti-inflammatory effects, which however warrants further investigation (https://www.acc.org/latest-in-cardiology/clinical-trials/2019/11/15/17/23/colcot).

The ORION-10 trial evaluated the effect of inclisiran, a small interfering RNA inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9), compared with placebo on LDL cholesterol levels in patients with ASCVD on maximally tolerated statin therapy. PCSK9 inhibition is a powerful means of lipid risk reduction, and molecular techniques are continuously improving to allow for more efficient targeting such as that theoretically provided by inclisiran[10,14]. Indeed, inclisiran reduced LDL cholesterol by 56% compared to placebo (https://www.acc.org/latest-in-cardiology/clinical-trials/2019/11/15/17/21/orion-10). Similar results were reported in the ORION-9 trial in statin- and ezetimibe-treated patients with familiar hypercholesterolaemia

(https://www.acc.org/latest-in-cardiology/clinical-trials/2019/11/15/17/47/orion-9). These trials provide a potentially promising pharmacological agent for further reduction of the lipid risk, which however requires event-oriented clinical trials.

Interventional randomised clinical trials

The ISCHEMIA trial evaluated the role of routine invasive therapy, i.e., coronary angiography and percutaneous coronary intervention (PCI), versus optimal medical treatment targeting the traditional risk factors for ASCVD in patients with moderate to severe angina. The primary outcome was a composite of cardiovascular death, MI, resuscitated cardiac arrest or hospitalization for unstable angina or heart failure. No difference was observed between interventional and medical treatment with regards to the composite or the secondary outcomes, suggesting that the decision for interventional treatment in angina pectoris may need to be re-evaluated. On the other hand, this study refers to a small sub-group of angina patients, excluding individuals with ≥50% left main stenosis, recent MI, left ventricular EF <35% and unacceptable angina at baseline. In such patients, interventional therapy could have an important role (https://www.acc.org/latest-in-cardiology/clinical-trials/2019/11/15/17/27/ischemia).

Moving away from ASCVD, the GALILEO trial addressed the role of anticoagulation therapy with rivaroxaban versus antiplatelet therapy with clopidogrel on top of aspirin during the first three months after transcatheter aortic valve replacement (TAVR) in patients without an established indication for anticoagulant treatment. Patients were randomised to rivaroxaban plus aspirin or clopidogrel plus aspirin for the first three months. The risk of death or thromboembolic event as well as the risk of bleeding were increased in the rivaroxaban group. This study supports an antiplatelet strategy over an

anticoagulation strategy in TAVR patients without indication for anticoagulation, whilst underscoring the challenges of antithrombotic treatment.

Summary

During the 2019 AHA scientific sessions, impressive results in all fields of cardiology were demonstrated once again, whilst several randomised clinical trials reported breakthrough results with the potential of changing clinical practice guidelines regarding the management of HF and ASCVD (summarized in Figure 1). Such important clinical messages include the potential recommendation of dapagliflozin and sacubitril-valsartan in HF treatment, the potential recommendation of colchicine post MI and the critical re-evaluation of interventional strategies in angina management.

References

Table 1: Summary of key randomized clinical trials (RCTs) presented during the 2019 American Heart Association (AHA) scientific sessions.

	Trial	Design	Primary endpoint	Results	Conclusion
HF risk reduction	DAPA-HF	Dapagliflozin vs placebo in HFrEF	CV death, HF hospitalizations, HF urgent visits	↓Composite endpoint HR across all age and KCCQ groups	Dapagliflozin improves outcome in HFrEF
	PARADIGM-HF	Sacubitril-valsartan vs enalapril in HFrEF	CV death, HF hospitalizations	↓Composite endpoint HR	ARNI may be superior to ACEi in HFrEF
	PARAGON-HF	Sacubitril-valsartan vs valsartan in HFpEF	CV death, hospitalizations	↔Composite endpoint HR (↓ in women)	ARNI improves HFpEF outcome only in women
ASCVD risk reduction	COLCOT	Colchicine vs placebo after recent (<30d) AMI	MACE	↓ Composite endpoint HR (driven by angina & stroke)	Colchicine reduces MACE risk following AMI
	ORION-9	Inclisiran vs placebo in statin/ezetimibe-treated FH	LDL-cholesterol	↓LDL-cholesterol	Inclisiran may further reduce residual lipid risk in FH
	ORION-10	Inclisiran vs placebo on statin-treated ASCVD	LDL-cholesterol	↓LDL-cholesterol	Inclisiran may further reduce residual lipid risk in ASCVD
Interventional trials	ISCHEMIA	Interventional vs optimal medical therapy in moderate/severe angina	CV death, AMI, resuscitated cardiac arrest, angina, HF	↔Composite endpoint HR	No benefit of interventional treatment on events in patients with stable angina (*excluding patients with ≥50% left main stenosis, recent AMI, left ventricular EF <35% and unacceptable angina at baseline*)
	GALILEO	Rivaroxaban vs clopidogrel in aspirin-treated TAVR for the first 3 months	Death & thromboembolism (efficacy), bleeding (safety)	↑HR of all endpoints	Antiplatelet strategy may be preferential compared to anticoagulation following TAVR (if no anticoagulation indication)

HF: Heart failure; HFrEF: Heart failure with reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction; ASCVD: Atherosclerotic cardiovascular disease; CV: Cardiovascular; HR: Hazard ratio; KCCQ: Kansas City cardiomyopathy questionnaire; ARNI: Angiotensin receptor-neprilysin inhibitor; AMI: Acute myocardial infarction; TAVR: Trans-catheter aortic valve replacement; MACE: Major adverse cardiovascular events; FH: Familiar hypercholesterolaemia

Biographical sketch: Dr Ioannis Akoumianakis is a finishing DPhil (PhD) graduate at the University of Oxford, UK and currently undertaking clinical work at the University Hospital of Heraklion, Crete, Greece for the purposes of his specialty training in Cardiology. After completing his MD at the School of Medicine, University of Crete, Greece in 2014, he joined the Division of Cardiovascular Medicine at the University of Oxford to pursue doctoral level research. There, he studied the crosstalk between metabolism, adipose tissue and vascular biology, particularly the ways in which disease entities such as obesity and insulin resistance promote atherosclerosis via direct vascular effects and via indirect effects mediated through dysfunctional adipose tissue. Ioannis has expertise in biobanking and translational cardiovascular research, using a wide range of molecular biology techniques, *ex vivo* human tissue models and medical statistics to integrate mechanistic hypotheses with clinical implications in real-life patients with cardiovascular disease.