AHA 2023 Conference Review™

Making Education Easy | 11 – 13 November, 2023

In this review:

Abbreviations used in this review:

AF = atrial fibrillation; **CRF** = cardiorespiratory fitness; **GLP-1 RA** = glucagon-like peptide-1 receptor agonists; **GDMT** = guideline-directed medical therapy; **HF** = heart failure; **HFmrEF** = heart failure mid-range ejection fraction; **HFrEF** = heart failure reduced ejection fraction; **MACE** = major adverse cardiovascular events.

Welcome to the American Heart Association (AHA) Conference Review for 2023.

The AHA 2023 Scientific Sessions occurred from November 11 to 13, 2023, in Philadelphia, PA, United States. This premier global event showcased advancements in cardiovascular science and medicine. Attendees had the opportunity to experience top-tier scientific discoveries, engage with practice-changing educational content, and focus on their specialties. The conference catered to scientists, clinicians, researchers, and healthcare professionals involved in cardiovascular disease. Participants could explore the latest innovations, benefit from diverse programming, and network with experts, contributing to the broader mission of the AHA to promote longer, healthier lives worldwide. Professor John O'Sullivan from Sydney has provided independent commentary for ten presentations he found particularly interesting and relevant to local practice.

We hope you enjoy this conference review and welcome your feedback and comments.

Kind Regards,

Dr Janette Tenne
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Contemporary guideline-directed medical therapy for heart failure is associated with a reduced incidence of new-onset atrial fibrillation

Authors: Tokutome M et al.

Summary: In this retrospective study spanning from 2015-2022, researchers investigated the long-term incidence of new-onset atrial fibrillation (AF) in patients with heart failure with reduced ejection fraction (HFrEF) and heart failure with mid-range ejection fraction (HFmrEF) who were initially admitted to hospital for decompensated heart failure (HF). Among the 410 patients included in the study without a history of AF, those prescribed three or more HF medications post-discharge had significantly lower rates of new-onset AF when compared to those on two or fewer medications. The multivariate analysis confirmed that using three or more HF drugs independently predicted a reduced risk of new-onset HF. New onset AF was also found to be correlated with higher presentations of HF re-hospitalisation and all-cause mortality in the studied population.

Comment: This work explored the long-term follow-up of (mean 603 ± 410 days, 2015-2022) new-onset atrial fibrillation after initiating guideline-directed medical therapy (GDMT) for patients diagnosed with HFrEF and HFmrEF. Patients with ≥3 HF drugs versus ≤2 HF drugs had a significantly lower incidence of new-onset AF. New-onset AF was also significantly associated with re-hospitalisation for HF. The authors conclude that the reduction in new-onset AF may contribute to the improved outcomes of GDMT in HF.

Reference: 11995
Abstract

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Independent commentary by Professor John O'Sullivan

Professor John O'Sullivan is a Clinical-Academic Cardiologist specialising in CardioMetabolic Medicine, particularly the nexus of metabolic disturbance and heart disease, based in the School of Medical Sciences, Faculty of Medicine and Health, University of Sydney, and Department of Cardiology, Royal Prince Alfred Hospital. He is a Level 2 NHF Future Leader Fellow, and co-Director of the HFpEF ("Stiff Heart Failure") Clinic at RPAH. He is Director of a Heart Failure Alliance across SLHD and WSLHD, incorporating RPAH, Concord, Westmead, and Blacktown Hospitals. John is Lead Principal Investigator on two clinical trials in HFpEF: CardioNAD at RPAH, and pEFNAD across the Heart Failure Alliance, which are extensions of his discoveries in the laboratory. John is an international expert in heart failure bioenergetics, whose expertise is sought internationally by national grant bodies, in addition to medical and cardiac societies. John's clinical practice focusses on Heart Failure, Proactive Intervention for the prevention of atherosclerotic cardiovascular disease, and is commercialising novel diagnostic tools and therapeutics based on discoveries in his lab.

Association of coagulation factor XI levels with cardiac function and cardiovascular events

Authors: Ji Y et al.

Summary: This analysis highlighted the atherosclerosis risk results in a community study that involved over 4,400 participants. The study investigated the association between plasma factor XI levels, cardiac function and the occurrence of HF and AF. The results found significant associations between factor XI levels and various cardiac function measures, including the E/A ratio, left atrial volume index, left atrium reservoir strain, and left atrium contractile strain. Lower factor XI levels were associated with higher odds of prevalent AF but not HF. However, no significant associations were found between factor XI levels and HF or AF incidence over the seven-year follow-up.

Comment: As a coagulation factor, XI is a promising and novel class of anticoagulants, and recent preclinical work has shown that factor XI actually has an anti-fibrotic role that ameliorated diastolic dysfunction and HF; the authors wished to explore the clinical implications of blocking factor XI. Therefore, they undertook an analysis of 4,471 participants (mean age 75, 57% female, 17% black) who attended ARIC Visit 5 (2011-2013) to investigate a relationship between factor XI, cardiac function, and cardiovascular events (HF and AF). At baseline, there were 665 and 419 participants with prevalent HF and AF; over a median follow-up of 7 years, there were 643 and 415 incident HF and AF events. The authors found significant associations between factor XI level and E/A ratio, left atrial volume index, left atrial reservoir strain, and left atrial contractile strain, but not E/e', left atrial conduit strain, left ventricular ejection fraction, or left ventricle global longitudinal strain. Lower factor XI levels were associated with higher odds of prevalent AF but not HF. In conclusion, the authors surmise that lower factor XI levels are associated with worse diastolic function, left atrial function and size, and prevalent AF, but not left ventricle systolic function, prevalent HF, or incident HF or AF. This work warrants consideration of the potential unwanted cardiac effects of this novel class of medication, and further study should focus on the clinical potential of factor XI modulation for improved cardiac function.

Reference: 12360
Abstract

Clinical outcomes with GLP-1 receptor agonists in patients with heart failure

Authors: Liu Y et al.

Summary: In this meta-analysis of nine randomised controlled trials, 8,920 patients with HF and T2DM were investigated for the impact of glucagon-like peptide-1 receptor agonists (GLP-1 RA) on prognosis. GLP-1 RAs significantly reduced the risk of major adverse cardiovascular events (MACE) compared to placebo in the included patient population. However, there was no observed benefit in all-cause death, hospitalisation for HF, cardiovascular death, myocardial infarction, stroke, death or hospitalisation for HF. GLP-1 RAs did not improve left ventricular ejection fraction, left ventricular end-diastolic volume, left ventricular end-systolic volume, or N-terminal pro-B-type natriuretic peptide. The subgroup analyses indicated that human GLP-1 RAs, but not non-human GLP-1 RAs, reduced the risk of MACE. The study also reported that moderate certainty for MACE, all-cause death and hospitalisation for HF according to the grading of recommendations assessment, development and evaluation suggested a potential risk for false positives of MACE.

Comment: As GLP-1 RAs reduce the risk of major adverse cardiovascular events (MACE) in patients with T2DM, the authors wished to explore the efficacy of GLP-1 RAs in HF. Therefore, they undertook a systematic review and meta-analysis of the literature, finding nine relevant randomised controlled trials involving 8920 patients with HF. The authors found that GLP-1 RAs significantly reduced the risk of MACE compared with placebo in patients with HF and T2DM but without effect on all-cause death, hospitalisation for HF, cardiovascular death, myocardial infarction, stroke, and death or hospitalisation for HF. GLP-1 RAs did not improve left ventricular ejection fraction, left ventricular end-diastolic volume, left ventricular end-systolic volume, nor N-terminal pro-B-type natriuretic peptide. However, GLP-1 RAs did significantly increase the 6-minute walk test. In subgroup analyses, human GLP-1 RAs, but not nonhuman GLP-1 RAs, reduced the risk of MACE. In conclusion, the authors state that GLP-1 RAs may lower the risk of MACE in patients with HF and T2DM, with a more significant efficacy of human GLP-1 RAs.

Reference: 13450
Abstract

Heart rate reduction alone produces reverse remodeling in heart failure patients refractory to beta-blockers

Authors: Altman N et al.

Summary: The PROBE-IT Trial involved 22 dilated cardiomyopathy patients with persistent sinus rhythm and a heart rate ≥70 bpm despite beta-blocker therapy; they explored the hypothesis that inadequate HR reduction may contribute to a non-response to beta-blockers. Patients were randomised to receive ivabradine or placebo in addition to beta-blockers for 24 weeks. Among the 17 patients who completed the trial, those with HR reduction had a shorter HF duration than the control group. Gene expression analysis revealed distinct molecular changes in the HR reduction group, including the upregulation of NRG1 and PP1R3C and downregulation of corticotrophin-1 cytokine genes; the study suggested that there may be potential contributions to reverse remodelling beyond those seen with beta-blockers alone.

Comment: In a 2-centre trial, the pulse reduction on beta-blocker and ivabradine therapy (PROBE-IT) trial tested the hypothesis that failure to adequately reduce HR contributes to beta-blocker non-response. Twenty-two dilated cardiomyopathy patients with a sinus rhythm HR ≥70 bpm without reverse remodelling after target doses of beta-blockers 2:1 to 5±2.5mg b.i.d. of ivabradine or matching placebo and treated for 24 weeks with continuation of beta-blockers (i.e. in addition to IVB or placebo). Echocardiography for left ventricular ejection fraction and endomyocardial biopsies for global gene expression by RNA sequencing were performed at baseline and end of the study. There were equal numbers of patients with a HR reduction (HRI) and a control group with no change in HR (HRV). HRV patients had a longer duration of HF. In HF versus HR variability, there were 18 significantly different mRNAs with lower abundance and 34 with higher abundance, $P < 0.0005$. Gene classification revealed distinct molecular changes for reverse remodelling from beta-blockers alone. The authors suggested gene expression changes contributing to reverse remodelling in HF included increases in neuregulin 1, protein phosphatase 1, multiple mitochondrial electron transport genes, and decreases in genes encoding cardiotrophin-1 cytokines (CTF1 and CLCF1). In conclusion, this work showed that HR lowering produces a substantial increase in LVEF accompanied by gene expression changes distinct from those associated with beta-blocker therapy. This suggests that heart rate reduction has independent beneficial effects on improved cardiac function compared to neurohormonal blockade by beta-antagonists.

Reference: 17715
Abstract

Interactive effects of statins, obesity, and cardiorespiratory fitness in type 2 diabetes mellitus incidence

Authors: Kokkinos PF et al.

Summary: This study involved 570,054 patients with a mean age of 60.7 years without T2DM from the ETHOS cohort; researchers investigated the association between BMI statin therapy, cardiorespiratory fitness (CRF), and the risk of developing T2DM. After completing an exercise treadmill test, 56.6% of participants were treated with statins for 9.5 years. In terms of T2DM risk, the risk was higher in those on statins compared to those not on statin therapy; this risk increased with higher BMI levels, reaching almost three times higher in the obese-II category. However, regardless of statin use and BMI, there was a progressive decline in T2DM risk with increased CRF, with the two highest CRF categories showing a 25-40% lower adjusted risk.

Comment: This important work examined the mitigating effects of developing type 2 diabetes mellitus (T2DM) of cardiorespiratory fitness patients exposed to statins in different weight categories. This work has significant public health implications. The authors started by classifying 570,054 patients in the ETHOS cohort (age 60.7±10.1 years) with no T2DM. All completed a standardised exercise treadmill test (ETT) without evidence of ischaemia. Subsequently, 322,804 (56.6%) were treated with statins for at least eight months (mean 9.5±5.9 years), and 247,249 were not. Participants were classified based on body mass index (BMI) as average weight (BMI<25.0 kg/m2), overweight (BMI 25.0-29.9 kg/m2), Obese-I (BMI 30.0-34.9 kg/m2), and Obese-II (BMI≥35.0 kg/m2). The authors established five CRF categories based on age-specific quintiles of peak metabolic equivalents achieved: Least-Fit (n=95,071); Low-Fit (n=133,404); Moderate-Fit (n=110,973); Fit (n=158,004); and High-Fit (n=72,602). During the follow-up period (median 10.3 years), 44,662 developed T2M (7.4 events/1,000 person-years of observation). The risk of developing T2DM was 44% higher in those treated with statins. The risk increased progressively with higher BMI levels and was nearly three times higher for those in the Obese-II category. When T2DM risk was assessed across CRF categories within BMI groups, a progressive decline was noted in T2DM risk with increased CRF regardless of statin therapy or BMI status. The adjusted risk was approximately 25-40% lower for those in the two highest CRF categories. In conclusion, statin therapy and obesity were associated with an increased risk of developing T2DM. This risk was mitigated significantly with increased CRF regardless of BMI status.

Reference: 14518
Abstract

SGLT2 inhibitors versus sulfonylureas as add-on therapy to metformin in type 2 diabetes

Authors: Umer M et al.

Summary: This comprehensive review of studies up to March 2023 compared SGLT2 inhibitors and sulfonylureas as add-on therapy to metformin for poorly controlled T2DM, regardless of comorbid CVD, 11 studies that met this criterion were analysed. The findings revealed that metformin-SGLT2 inhibitors significantly reduced all-cause mortality and myocardial infarction compared to metformin-sulfonylureas, metformin-SGLT2 inhibitors were also associated with greater efficacy in lowering HbA1c, fasting plasma glucose, systolic BP and weight when compared to metformin-sulfonylurea. Additionally, metformin-SGLT2i was associated with a significantly lower risk of hypoglycaemic events.

Comment: This important work investigated the efficacy of SGLT2 inhibitors compared to sulphonylureas as an add-on therapy to metformin in patients with T2DM poorly controlled on metformin alone. The authors conducted a meta-analysis incorporating 11 studies meeting the inclusion criteria and reporting mortality outcomes. Metformin-SGLT2 inhibitors significantly reduced all-cause mortality and myocardial infarction compared to metformin-sulfonylureas. Metformin-SGLT2 inhibitors were also associated with a significantly greater reduction in HbA1c, fasting plasma glucose, systolic blood pressure, and weight than metformin-sulfonylurea. Moreover, metformin-SGLT2 inhibitors were associated with a significantly lower risk of hypoglycaemic events. In conclusion, this review supports the hypothesis that adding SGLT2i to metformin may yield superior outcomes to adding sulfonylureas to metformin monotherapy in T2DM, poorly controlled with metformin alone.

Reference: 14623
Abstract

Synchronous care in cardiovascular disease

Authors: Marques P et al.

Summary: This retrospective analysis included patients from the DECIDE-CV clinic, a specialised metabolic clinic for individuals with T2DM and comorbidities such as atherosclerotic CVD, HF or CKD. This study included 150 patients and compared baseline data to the last available visit data. The analysis revealed a statistically significant increase in the use of GDMT and a reduction in insulin, sulfonylureas and dipeptidyl peptidase-4 inhibitors. Among patients with two sets of laboratory data, there was a significant decrease in the N-terminal pro-B-type natriuretic peptide and albuminuria.

Comment: The care model for T2DM and its main complications is thought to be "asynchronous" and associated with delays in care and low use of GDMT. Therefore, the authors undertook a retrospective analysis of patients attending the DECIDE-CV cardiometabolic clinic for T2DM patients with either atherosclerotic CVD, HF, or CKD. Baseline data was compared to the data obtained in the last available visit. For patients with only one visit, the treatment prescribed at the end of the first visit was considered in the last-visit group. The authors report that of 150 patients (72% male with a mean age of 67±12 years), 115 (78%) had atherosclerotic CVD, 98 (65%) had HF, and 77 (51%) had CKD. In this synchronous care clinic for T2DM patients, comparing baseline to last visit data, there was a statistically significant increase in GDMT and de-escalation of insulin, sulfonylureas, and DPP4i. For patients with two sets of available laboratory data, there was a significant decrease in N-terminal pro-B-type natriuretic peptide and albuminuria. In conclusion, the authors demonstrated the benefits of such a multi-disciplinary clinic, including GDMT, de-escalation of therapy that lacks morbidity/mortality benefit, and improved predictive biomarkers. These results can lead to better outcomes in this population, which needs further study. If outcomes are improved, this synchronous style clinic across cardiology-endocrinology-nephrology should become the standard of care congruent with the huge prevalence of overweight, obesity, prediabetes, and diabetes as modern healthcare challenges.

Reference: 15244
Abstract

A costly mix-up: genotype-phenotype mismatch of hereditary transthyretin cardiac amyloidosis

Authors: Galani J et al.

Summary: This case series presented three young patients, two with new-onset systolic heart failure and one with left ventricular hypertrophy suggestive of cardiac amyloidosis. Genetic testing revealed the Valine 122 Isoleucine mutation was associated with hATTR-CM, though imaging did not support the diagnosis. The study suggested that these individuals may be silent carriers of the mutation with alternative causes for heart failure. This study highlighted that there should be greater emphasis on the importance of comprehensive evaluation, including genetic testing and multiple imaging modalities, in diagnosing and understanding the variability of hATTR-CM penetrance.

Comment: This is an interesting case series of three young patients with either new onset HF or left ventricular hypertrophy suggestive of cardiac amyloidosis. By background, hATTR-CM is an infiltrative process caused by the extracellular deposition of misfolded amyloid fibrils, resulting in restrictive cardiomyopathy. Over 100 pathogenic genetic variants are associated with hATTR-CM; however, the genetic penetrance is unknown. Typical echocardiographic findings include unexplained LV hypertrophy (specifically concentric left ventricular wall thickness greater than 12mm) and relative apical sparing of longitudinal left ventricular strain. Cardiac MRI shows a characteristic diffuse subendocardial or transmural myocardial delayed gadolinium enhancement pattern. Lastly, technetium-99m pyrophosphate scintigraphy reveals grade 2 or greater myocardial uptake. In this work, genetic testing and cardiac imaging with echocardiography, cardiac MRI, and/or PYP were performed. Genetic testing for all patients revealed the autosomal dominant and variably penetrant Valine 122 Isoleucine mutation, commonly associated with tATTR-CM. However, imaging for these patients was not suggestive of ATTR-CM. Therefore, these patients likely represent silent carriers with alternate aetiologies of heart failure. This case series exemplifies the genotype-phenotype mismatch often seen in hATTR-CM and serves as a timely reminder not to let genetic testing dictate diagnosis and management where there is variable penetrance. Further, the costly transthyretin stabiliser, Tafamadis, must be prioritised in cases where imaging confirms the presence of tATTR-CM.

Reference: 16455
Abstract

Amyloid ambush: a shocking encounter with AL cardiac amyloidosis

Authors: Basheer A et al.

Summary: This case study focused on a 44-year-old female patient who initially presented with gastrointestinal and cardiac symptoms, including epigastric pain, nausea, vomiting and chest discomfort, with a pre-existing diagnosis of carpal tunnel syndrome. Despite intensive support with an intra-aortic balloon pump and multiple compressors, she developed cardiogenic shock and sustained ventricular tachycardia, necessitating transfer to a specialised centre. Diagnostic assessments, including echocardiogram, right heart catheterisation, and cardiac MRI, revealed features consistent with cardiac amyloidosis. Endomyocardial biopsy confirmed AL amyloidosis with abnormal light chain ratios and bone marrow involvement. Unfortunately, the patient's deteriorating condition precluded eligibility for chemotherapy, transplantation, or LVAD placement; the case study highlights the challenging clinical course associated with advanced cardiac amyloidosis.

Comment: This report serves as a reminder of the frequently fatal presentation of cardiac AL amyloidosis. A 44-year-old female with multiple comorbidities had a catastrophic course of cardiac AL amyloidosis. The patient presented with non-specific symptoms, including epigastric pain, nausea, vomiting, and chest discomfort. She had a previous diagnosis of carpal tunnel syndrome. Soon after the presentation, she developed cardiogenic shock and sustained ventricular tachycardia. The echocardiogram showed mildly reduced LVEF and moderately depressed RVSF. Initial right heart cath revealed significantly elevated right and left filling pressures and a low cardiac index. Cardia MRI exhibited abnormal gadolinium kinetics and parametric mapping consistent with cardiac amyloidosis. Endomyocardial biopsy with light chain mass spectrometry confirmed the presence of AL amyloidosis. The kappa/lambda ratio was 60, and a bone marrow biopsy showed 30% plasma cells. The patient's cardiogenic shock worsened despite intensive support with an intra-aortic balloon pump and multiple ion-pressors. Unfortunately, her deteriorating condition rendered her ineligible for chemotherapy, transplantation, and a left ventricular assist device. The authors conclude that this case unveils the elusive nature of AL cardiac amyloidosis, where cardiogenic shock can be the initial presentation. Vigilance is important, recognising LV hypertrophy coupled with low-voltage ECG and a preceding history of carpal tunnel syndrome. It is critical to highlight the often frequent progression and limited treatment options.

Reference: 18070
Abstract

Systemic sclerosis masquerading as heart failure

Authors: Prathivadhi-Bhayankaram S and Mansour S

Summary: This case study work-up focused on a 62-year-old male with diastolic dysfunction presented with acute respiratory failure. A diagnostic workup revealed severely reduced systolic function, non-obstructive coronary artery disease, elevated autoimmune markers, and positive RNA polymerase III antibody. Cardiac MRI indicated inflammation and diffuse fibrosis, and positron emission tomography confirmed myocarditis. Diagnosed with rapidly progressive cutaneous systemic sclerosis and non-ischemic cardiomyopathy, the patient received goal-directed therapy and immunosuppression, showing improved pulmonary function and an increased ejection fraction to 62% six months later. This case study highlighted the importance of recognising systemic sclerosis-related cardiac involvement early for optimal management in a disease with variable phenotypes and potentially fatal cardiac complications.

Comment: This work is an important reminder of the cardiac consequences of systemic sclerosis. Cardiac disease occurs in 80% of patients with SS. Patients may present with various symptoms, including dyspnoea, palpitations, chest pain, and heart failure. Of these, systolic heart failure has the rarest prevalence, estimated between 1-5% of patients. The mechanism behind myocardial damage remains unclear, but likely due to fibrosis secondary to ischaemic necrosis and reperfusion damage. This case report highlights the need to recognise it early for prompt intervention. A 62-year-old male with a history of diastolic dysfunction presented with acute hypoxic respiratory failure. An echocardiogram demonstrated a new severely reduced systolic function at 20%. The angiogram demonstrated non-obstructive coronary artery disease. Autoimmune workup revealed a significantly elevated ANA and highly positive RNA polymerase III antibody. Cardiac MRI showed evidence of inflammation with diffuse myocardial fibrosis concerning an infiltration process. Subsequent PET showed increased uptake in the basal portions of the septum and anterior wall. The patient was subsequently diagnosed with rapidly progressive cutaneous systemic sclerosis and associated non-ischaemic cardiomyopathy. The patient was started on losartan, spironolactone, metoprolol, and empagliflozin. Additionally, the patient was started on mycophenolate mofetil for immunosuppression. Approximately six months later, the patient's pulmonary function tests remained stable, and the ejection fraction improved to 62%. It is important to note that 1/3 of systemic sclerosis-related deaths are due to cardiac involvement. Yet, most patients are asymptomatic during the early stages, with a variable phenotype later in disease progression. In this case, the patient's cardiac dysfunction recovered from optimal goal-directed therapy and immunosuppression.

Reference: 19124
Abstract