Late-Breaking Science Abstracts and Featured Science Abstracts From the American Heart Association’s Scientific Sessions 2019

Late-Breaking Abstracts in Resuscitation Science From the Resuscitation Science Symposium 2019
Late-Breaking Science Abstracts and Featured Science Abstracts From the American Heart Association’s Scientific Sessions 2019 and Late-Breaking Abstracts in Resuscitation Science From the Resuscitation Science Symposium 2019

Cross Specialty

Late Breaking Science I: Outside the Box: New Approaches to CVD Risk Reduction

The Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure Trial (DAPA-HF): Results in Nondiabetic Patients

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Safety and Efficacy of Inclisiran in Patients With ASCVD and Elevated LDL Cholesterol - Results From the Phase 3 ORION-10 Trial

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The COLchicine Cardiovascular Outcomes Trial (COLCOT)

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Introduction: Multiple lines of evidence have highlighted the important role of inflammation in the pathogenesis of atherosclerosis and its complications. Colchicine is an orally administered, potent anti-inflammatory drug clinically indicated for the treatment of gout and pericarditis. Hypothesis: We hypothesized that colchicine will reduce cardiovascular (CV) events in patients with a recent myocardial infarction (MI). Methods: The primary objective of COLCOT is to determine if long-term treatment with colchicine 0.5 mg/day will reduce major CV events in patients with a recent MI. The secondary objective is to determine the safety and tolerability of long-term treatment with low-dose colchicine. COLCOT is an open-label, randomized, double-blind, placebo-controlled, multinational clinical trial. A total of 167 clinical sites participated in the trial. Patients were randomly assigned to receive either colchicine (0.5 mg/day) or placebo (1:1 ratio) and followed until at least 301 primary CV events occurred. To enter the trial, adult men and women who had suffered an MI within the last 30 days and have completed any planned percutaneous revascularization procedures. Follow-up visits occurred at 1 and 3 months following randomization and every ∼3 months thereafter. Patients also received standard medical care including intensive use of statins. The primary study endpoint is the time from randomization to the first event of CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, or urgent hospitalization for angina requiring coronary revascularization. All suspected CV endpoints were adjudicated by an independent and blinded clinical endpoint committee. COLCOT is an event-driven trial with main analyses conducted on an intention-to-treat basis. The sample size calculation was based on the primary endpoint and a hazard ratio of 0.724. Using a two-sided test at the 0.05 significance level, the trial had 80% power if it continued until 301 positively adjudicated primary events occurred in the combined treatment groups. The total number of patients to randomize, 4500, was chosen so that 301 positively adjudicated primary events occurred in the combined treatment groups. COLCOT Study results will be presented for analysis at AHA2019.

Conclusion: The results of the COLCOT trial will establish whether treating patients with a low-dose of the anti-inflammatory agent colchicine lowers the rates of important ischemic events beyond statin therapy.

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The BETonMACE Trial

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Background: Bremsd2 and extra-terminal (BET) proteins are epigenetic transcriptional modifiers of inflammation, thrombogenesis, and lipoprotein metabolism that contribute to atherothrombosis. BET inhibitors are small molecule epigenetic regulators of chromatin structure and gene expression with therapeutic potential in atherosclerosis. Apabetalone is the first in class BET inhibitor that selectively targets bromodomain 2 (BD2), resulting in favorable effects on transcription of a variety of atherothrombotic mediators. A pooled analysis of phase 2 trials showed that apabetalone reduced the incidence of death or non-fatal cardiovascular (CV) outcomes compared with placebo, with more prominent benefits in patients with conditions associated with BET system activation such as type 2 diabetes mellitus (T2DM), high C-reactive protein or low HDL-cholesterol. The BETonMACE trial tested the hypothesis that addition of treatment with apabetalone to standard of care therapies improves CV outcomes in patients with T2DM and low HDL-C after an acute coronary syndrome (ACS).

Methods: BETonMACE (NCT02586159) is an international, multi-center, randomized, double-blind, placebo-controlled trial in patients with recent ACS, T2DM and low HDL-C conducted at 195 sites in 13 countries. Patients with ACS in the preceding 7–90 days, T2DM, and HDL-C ≤40 mg/dl for women, ≤45 mg/dl for men, were assigned in double-blind fashion to receive apabetalone 100 mg orally twice daily or matching placebo (1:1) on top of guideline recommended standard of care including intensive or maximum-tolerated treatment with atorvastatin or rosuvastatin. The primary outcome was time to the first occurrence of CV death, non-fatal myocardial infarction (MI), or stroke. The study continued until 250 primary endpoints had accrued. Apabetalone and placebo groups were compared using a two-sided stratified log-rank test; assuming a 2-sided type 1 error rate of 5% and cumulative incidence of the primary endpoint of 10.5% in the placebo arm at 18 months, a sample size of 2400 patients followed for a median of 18 months provides 80% power to detect a 30% relative risk reduction with apabetalone. Results: Enrollment began in November 2015 and ended in July 2018 with 2425 participants randomized. MI was the index ACS event in 74% (STEMI 53%, NSTEMI 47%) with unstable angina constituting 26% of index ACS events. The characteristics of patients included median age 67 years, 25% female, sex, majority white race (87%), and coronary revascularization for the index ACS (80%). Use of high intensity statin treatment was 91% at study entry with median LDL-C 65 mg/dl, HDL-C 33 mg/dl, and HbA1c 7.3%. Median follow up was 19 months. Conclusion: The BETonMACE trial will be the first study to report whether epigenetic modulation with a selective BET protein inhibitor is a safe and effective approach to reduce cardiovascular risk.

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Key Words: BET inhibition; Epigenetics; Cardiovascular outcomes
pharmacodynamic assessments of TTR stabilization and efficacy of AG10 as measured by changes from baseline in cardiac biomarkers. Results: For this interim report, subject disposition, summary of safety data, trends in cardiac biomarkers, and data on TTR stabilization will be presented. Conclusions: This ongoing analysis of the OLE study data will provide evidence of the emerging long-term clinical safety and efficacy profile of AG10 in patients with ATTR-CM.

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A Randomised, Double-Blind, Dose Ranging Clinical Trial of Intravenous FDY-5301 in Acute STEMI Patients Undergoing Primary PCI: The CAMFIRE (Cardiac Muscle Preservation Following Ischemia Reperfusion) Study

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Ischaemia reperfusion injury remains a major clinical problem in patients with ST elevation myocardial infarction (STEMI), leading to greater myocardial damage, ventricular arrhythmias and heart failure, despite early reperfusion by primary PCI (pPCI). There are no effective therapies to prevent or limit ischaemia reperfusion injury, which is caused by multiple pathways including cell death by rapid tissue reoxygenation and the generation of reactive oxygen species (ROS). FDY-5301 contains sodium iodide, an inorganic halide that is ubiquitous in biological systems at low-activates a catalytic antioxidant in the pathophysiology of CVC. Formation and growth of hydroxyapatite crystals, the final common pathway of cardiovascular calcification (CVC), is associated with high rates of cardiovascular morbidity and mortality. SNF472, an intravenous control hexaphosphate, significantly inhibits the formation and growth of hydroxyapatite crystals, the final common pathway in the pathophysiology of CVC. Methods: CALPSO is a phase 2b randomized, double-blind, placebo-controlled trial to assess the effect of SNF472 compared to placebo on progression of coronary artery calcium (CAC) volume scores over a 52-week period in patients on hemodialysis. Patients with CAC/Agatston score of 100–3500 AU, 55 years old or older than 55 y/o with a history of diabetes mellitus were randomized in a 1:1:1 ratio to 300 mg SNF472, 900 mg SNF472 or placebo. Intravenous infusion was given as a single dose during the hemodialysis. The primary endpoint was the change in log CAC volume score between baseline and Week 52 for the combined SNF472 doses vs placebo. Key secondary endpoints were change from baseline to Week 52 in (a) log CAC volume score for each dose group vs placebo, (b) log CAC/Agatston score for combined dose group vs placebo, (c) thoracic aorta and aortic valve volume and Agatston scores and (d) proportion of patients with greater than 15% progression in CAC volume score. Results: 274 patients were randomized. The enrolled sample was representative of the general dialysis population. Mean age 63 years, 51% female, 58% white, and median dialysis vintage 42.4 months. Common co-morbidities were hypertension and diabetes; common medications were non-calcium based phosphate binders and statins. The median (interquartile range) baseline CAC Agatston scores were 730 (315, 1435), for thoracic aorta 1728 (625, 4978) and for aortic valve 103 (31, 262). The study is completed with database lock anticipated in early Oct 2019. Safety and efficacy endpoints will be presented. Conclusion: CALPSO will demonstrate whether SNF472 slows progression of CVC as measured by CAC volume score over 52 weeks.

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Prospective, Single-Arm Clinical Investigation for the Non-Invasive Transthoracic Treatment of Subjects With Severe Symptomatic Aortic Valve Stenosis Using Valvosoft® Pulsed Cavitation Ultrasound Therapy (PCUT) - First-in-Man

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2019 AHA Late-Breaking Science Abstracts
Background: The morbidity associated with surgical and transcatheter aortic valve replacement (TAVR) remains high, and valve replacement failure may lead to complications. Furthermore, not all patients are eligible for open-heart surgery or TAVR. CARDIAWAVE (Paris, France) has developed Valvosoft, a unique non-invasive ultrasound therapy device to treat aortic stenosis. The therapy aims to improve the opening of severely calcified aortic valves by cracking the calcium and reducing the stiffness in the aortic valve tissue by delivering shock waves on the valve leaflets. This study assesses the safety and feasibility of this novel technique. Methods: This is a multi-center, prospective, controlled first-in-man study designed to evaluate the safety and feasibility of the Valvosoft device. Ten patients with severe symptomatic calcific aortic stenosis and not eligible for SAVR/TAVR (mainly because of life expectancy less than 12 months and comorbidities) underwent a Valvosoft ultrasound therapy. Echocardiographic evaluation was performed by an independent core lab at baseline, discharge and 30-day follow-up along with clinical follow up at three months. Results: Enrolled patients were advanced in age (84.1±6.5 yrs) with severe comorbidities (8 with heart failure, 5 with coronary heart disease and 5 with kidney failure). All had extensive aortic valve calcification with meanAVA of 0.61±0.17 cm² and mean pressure gradient of 37.5±10.5 mmHg. No adverse events were recorded during the procedure other than some benign extravasational bleeding. The mean treatment time was 52 minutes. At discharge and at 30 days, several patients experienced increase of AVA and improvement of hemodynamic parameters and NYHA status. No device or procedure related major adverse events nor deterioration of neurological status were observed at 3 months follow-up; two patients had died from progression of end stage heart failure and one patient had finally undergone a TAVR procedure. Conclusions: Non-invasive ultrasound therapy is feasible and safe in patients with severe aortic valve stenosis and can also improve AVA and gradient in some patients. Longer follow-up and larger clinical studies need to be conducted to confirm these preliminary results. We hope that this new approach will open the door, in the near future, to a new field of non-invasive ultrasound therapy for cardiovascular diseases.

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2019 AHA Late-Breaking Science Abstracts

Field Implementation of Remote Ischemic Conditioning in ST-Elevation Myocardial Infarction: The First Study

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Background: Remote ischemic conditioning (RIC) is a non-invasive, therapeutic strategy that uses brief cycles of blood pressure cuff inflation and deflation to protect the myocardium against ischemia-reperfusion injury. Previous research employing a strategy of RIC prior to percutaneous coronary intervention (PCI) has demonstrated improvements in minimizing infarct size, yet little is known regarding the impact of RIC on clinical outcomes. Objective: To determine the impact of RIC prior to PCI for ST-segment elevation myocardial infarction (STEMI) on clinical outcomes compared to standard care. Methods: We conducted a pre and post implementation study in two community hospitals and two ambulance services in Ontario, Canada. Pre-implementation (December 2013–July 2016), patients with presumed STEMI were taken directly to the PCI lab for coronary angiography. After implementation (July 2016-August 2018), patients with presumed STEMI received four cycles of RIC applied to the upper extremity using an automated device by paramedics or emergency department staff prior to PCI. The primary outcome was major adverse cardiovascular events (MACE) at 90 days. Secondary outcomes included hospital length of stay, MACE at 30, 60, and 180 days. Inverse probability of treatment weighting using propensity score estimated causal effects independent of baseline covariates. Results: Overall, 1667 (861 pre-implementation, 801 post-implementation) patients were included in the study. Mean (SD) age was 63.1 (12.4) years and 334 (20.0%) were female. After propensity score weighting, 13.4% of patients in the pre-implementation phase had MACE at 90-days compared to 11.8% of patients in the post implementation phase who had RIC prior to PCI (OR 0.96; 95% CI: 0.62 to 1.21). Additionally, no significant reductions in secondary outcomes of overall MACE were noted at 30, 60 and 180 days. However, in a pre-specified analysis, patients presenting with cardiogenic shock or cardiac arrest prior to PCI (OR 0.52; 95% CI: 0.27 to 0.98). Conclusions: A strategy of RIC prior to PCI for STEMI did not reduce MACE within 90 days. Patients presenting with cardiogenic shock or cardiac arrest prior to PCI had significantly fewer MACE events at 30 days when treated with RIC than historical controls. Future research should explore the impact of RIC prior to PCI on both long-term clinical outcomes and in patients presenting with cardiogenic shock or cardiac arrest.

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Platelet Inhibition Over Time By Dose Of RUC-4 Or Placebo

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Background: Platelet aggregation is an important process in maintaining the integrity of the vascular system, and in patients presenting with cardiogenic shock or cardiac arrest. In patients with presumed STEMI received four cycles of RIC applied to the upper extremity using an automated device by paramedics or emergency department staff prior to PCI. The primary outcome was major adverse cardiovascular events (MACE) at 90 days. Secondary outcomes included hospital length of stay, MACE at 30, 60, and 180 days. Inverse probability of treatment weighting using propensity score estimated causal effects independent of baseline covariates. Results: Overall, 1667 (861 pre-implementation, 801 post-implementation) patients were included in the study. Mean (SD) age was 63.1 (12.4) years and 334 (20.0%) were female. After propensity score weighting, 13.4% of patients in the pre-implementation phase had MACE at 90-days compared to 11.8% of patients in the post implementation phase who had RIC prior to PCI (OR 0.96; 95% CI: 0.62 to 1.21). Additionally, no significant reductions in secondary outcomes of overall MACE were noted at 30, 60 and 180 days. However, in a pre-specified analysis, patients presenting with cardiogenic shock or cardiac arrest prior to PCI (OR 0.52; 95% CI: 0.27 to 0.98). Conclusions: A strategy of RIC prior to PCI for STEMI did not reduce MACE within 90 days. Patients presenting with cardiogenic shock or cardiac arrest prior to PCI had significantly fewer MACE events at 30 days when treated with RIC than historical controls. Future research should explore the impact of RIC prior to PCI on both long-term clinical outcomes and in patients presenting with cardiogenic shock or cardiac arrest.

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19804
20899

**Interventricular Allogenic Mesenchyl Cell Transplantation in Infants With Hypoplastic Left Heart Syndrome: Initial Results From the Phase I Trial**

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**Background:** Bone marrow derived mesenchymal stem cells (MSCs) improve pressure load induced right ventricle (RV) dysfunction in an animal model that replicates salient features of Hypoplastic Left Heart Syndrome (HLHS). The current management of HLHS incorporates three surgical palliative stages that place the single systemic RV on the systemic circulation. Over time, resultant alterations in RV loading adversely affect RV function, leading to heart failure and unacceptable high mortality. We undertook a Phase I trial to assess safety and feasibility of allogeneic MSC transplantation for treatment of systemic RV failure in HLHS patients: the ELPSI study (Allogeneic Human MSC Injection in Patients with Hypoplastic Left Heart Syndrome: A Phase I trial). **Methods:** The ELPSI trial enrolled HLHS patients up to one year of age (N=10) undergoing their stage II bidirectional cavopulmonary connection in whom allogeneic MSCs (2.5x10^5 cells/kg) were transplanted by injection into the RV myocardium. Although an open label study, patients underwent cardiac MRI analysis which was blinded, de-identified, and unblinded. Biomarkers were collected, including BNP and characterization of donor MSC specific circulating exosomes. **Results:** There were no serious adverse events related to MSC treatment. Of the 10 patients, 7 had completed all three cardiac MRI exams. There was no significant change in RV ejection fraction (% from baseline 49.25±3.2) compared to 6 months (42.51±2.624, P=0.102) or to one year (46.57±2.507, P=0.240). RV stroke volume (mls) increased from 24.7±3.4 before MSC injection to 24.7±2.1 at 6 months (P=0.0167) and to 28.2±2.9 at 1 year (P=0.019) after injection. Indexed RV mass (g/m²) decreased from baseline of 58.51±4.194 to 51.31±2.858 at 1 year after injection (P=0.046) which was associated with a decrease in BNP levels (pg/ml) from 1650±369.1 to 720±235.5 at 1 year after transplantation (P=0.040). Cardiovascular pathway assessment identified target miRNAs from donor MSC specific exosomes present in the recipient circulation which were upregulated (fold-change:1.5) in post-operative day (POD) 7 exosomes compared to POD 2 exosomes and which were involved in several cardiac remodeling pathways that modulates cardiac muscle hypertrophy, cardiac muscle tissue development, and angiogenesis. **Conclusion:** Collectively, the early findings from this Phase I trial demonstrated the safety and feasibility of allogeneic allogenic MSC transplantation in HLHS patients and provides the basis for a Phase IIb trial to demonstrate MSC efficacy for RV failure. Circulating donor MSC specific exosome profiles from the plasma are critical in defining MSC mechanisms for RV remodeling.

**Cross Specialty**

**Featured Science Population Science**

**20282**

**Genetically Reduced IL-6 Attenuates Cardiovascular Disease Risk in Clonal Hematopoiesis**

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**Introduction:** Clonal hematopoiesis of indeterminate potential (CHIP) refers to clonal expansion of hematopoietic stem cells due to acquired leukemic mutations in genes such as DNMT3A or TET2. In humans, CHIP associates with prevalent myocardial infarction. In mice, CHIP accelerates atherosclerosis and increases IL-6-LIF expression, raising the hypothesis that IL-6 pathway antagonism in CHIP carriers would decrease cardiovascular disease (CVD) risk. **Methods:** We analyzed exome sequences from 35,416 individuals in the UK Biobank without prevalent CVD, to identify participants with DNMT3A or TET2 CHIP. We used the IL6R p.Asp558Ala coding mutation as a genetic proxy for IL-6 inhibition. **Results:** Among carriers of large CHIP clones, 432 (1.2%) with large clones (allele fraction >10%). During 6.9-year median follow-up, CHIP associated with increased incident CVD event risk (HR=1.27, 95% CI: 1.04–1.56, p=0.019), with greater risk from large CHIP clones (HR=1.59, 95% CI: 1.21–2.09, p<0.001). IL6R p.Asp558Ala attenuated CVD event risk among participants with large CHIP clones (HR=0.46, 95% CI: 0.29–0.73, p<0.001) but not in individuals without CHIP (HR=0.95, 95% CI: 0.89–1.06, p=0.08) (p=0.003, figure). **Conclusion:** CHIP is associated with increased risk of incident CVD. Among carriers of large CHIP clones, genetically reduced IL-6 signaling abrogated this risk.

**Cost-Effectiveness of Icosapent Ethyl in REDUCE-IT**

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**Background:** Despite statin therapy and well-controlled LDL-C, many high cardiovascular (CV) risk patients continue to experience CV events. This residual CV risk was targeted by the placebo controlled randomized trial REDUCE-IT that enrolled statin-treated patients with controlled LDL-C (<40 - ≤100 mg/dl) and elevated triglycerides (≥135 - <500 mg/dL) with established CV disease or diabetes combined with other CV risk factors. Over 4.9 years median follow-up, REDUCE-IT demonstrated that icosapent ethyl, a highly purified prescription eicosapentaenoic acid ethyl ester, lowered risk of first and total CV events by 22% and 27%, respectively. **Methods:** We applied treatment effects from REDUCE-IT, health care costs from national sources, and net costs for icosapent ethyl of $4.16 a day and conducted a combination cost-effectiveness analysis utilizing both patient-level in-trial cost and clinical outcomes and long-term costs, events and life expectancy derived from Markov simulation models. The model projected lifetime healthcare costs, CV events, survival and quality-adjusted life-years (QALYs) for icosapent ethyl versus placebo in REDUCE-IT eligible patients from a payer perspective (with modifications to estimate a societal perspective). Uncertainty was quantified using stochastic, probabilistic sensitivity, and scenario analyses. **Results:** The QALY gain for icosapent ethyl was $20,899, and cost-effective compared to placebo during the trial, 3.27 and lifetime were 11.61 and 11.35, respectively. The mean costs for
A prospective, nationwide, population-based registry of OHCA throughout 47 prefectures in Japan. A time-stratified case-crossover design was applied, and preference-specific estimates of PM$_{2.5}$ and OHCA associations were calculated through a conditional logistic regression analysis. Those estimates were combined with a random-effects meta-analysis. Results: The study included 103,189 OHCA that was witnessed by bystanders between April 2011 and December 2016. The average of daily mean concentration for PM$_{2.5}$ was 13.9 (standard deviation, 7.9) μg/m$^3$. A 10-μg/m$^3$ increase in the average PM$_{2.5}$ concentrations during the day of OHCA and the previous day (lag0-1) was associated with an increase of 1.6% (95% confidence interval [CI], 0.1 to 3.1). When we performed the stratified analyses, the point estimates of percentage increase tended to be greater in aged 75 years or older (percentage increase, 2.0% [95% CI, 0.2 to 3.9%]), men (percentage increase, 2.1% [95% CI, 0.0 to 4.2%]), and warm season (percentage increase, 2.3% [95% CI, 0.4 to 4.1%]). PM$_{2.5}$ was closely associated with asystole (percent increase, 2.1% [95% CI, 0.2 to 4.1%]) compared with ventricular fibrillation/pulseless ventricular tachycardia (percent increase, 0.6% [95% CI, -2.0 to 3.2%]) or pulseless electrical activity (percent increase, 0.3% [95% CI, -1.7 to 2.4%]) as initial rhythms of electrocardiogram (Figure). Unfavorable prognosis such as 1-month mortality (percent increase, 1.5% [95% CI, 0.0 to 3.2%]) was observed and chest compression plus additional breathing had a greater impact on 1-month mortality (percent increase, 4.6% [95% CI, 0.4 to 9.0%]) than chest compression only cardiopulmonary resuscitation (percent increase, 1.2% [95% CI, -0.7 to 3.1%]) in OHCA patients associated with PM$_{2.5}$ exposure. Conclusions: In conclusion, the increase in PM$_{2.5}$ concentrations triggers OHCA of cardiac origin associated with initial asystole, leading to poor outcomes. There may be a room for further discussion regarding the impact of additional breathing for OHCA affected by short-term exposure to PM$_{2.5}$.

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to 0.17% per month (p = 0.015), with a subsequently declining trend. There was also an increasing post-recall trend in stroke/TIA ED visits by 6% (p = 0.020) and admissions by 8% (p = 0.037), which was not observed for heart failure or myocardial infarction outcomes. **Conclusions:** The valsartan recall withdrew affected products from the market. However, the recall was associated with incomplete replacement of valsartan, and an immediate increase in ED visits and admissions by 8% (p = 0.037), which was not observed for heart failure or myocardial infarction.

**Cross Specialty**

**Follow-up of Landmark Trials**

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**Background:** HPS3/TIMI55-REVEAL was the first randomized trial to demonstrate a significant clinical benefit from adding CETP inhibitor therapy to intensive statin therapy for the secondary prevention of major coronary events. We now report the longer-term efficacy and safety from extended post-trial follow-up of REVEAL participants. **Methods:** 30,449 adults with prior atherosclerotic vascular disease were randomly allocated to receive either anacetrapib 100 mg daily or a matching placebo, in addition to open-label atorvastatin therapy. After stopping the randomly allocated study treatment, 26,179 survivors entered a pre-specified post-trial follow-up period, blinded to their original treatment allocation. The primary outcome was the first post-randomization major coronary event (composite of coronary death, myocardial infarction, or coronary revascularization) during the in-trial and post-trial periods, with analysis by intention to treat. **Results:** During the in-trial period (median 4.1 years), allocation to anacetrapib conferred a relative reduction in the risk of major coronary events of 9% (95% CI 1.3–15%; p=0.004). During post-trial follow-up (median 2.3 years), when use of statin therapy remained high and did not differ between the randomly allocated groups, there was a further relative risk reduction of 20% (95% CI 10–29%; p<0.001). This yielded an overall proportional risk reduction of 12% (95% CI 7–17%; p<0.001, corresponding to an absolute difference of 1.8% overall (by comparison with the 1.1% seen in the in-trial period). There were no significant between-group differences in the risks of non-vascular mortality, site-specific cancer or other serious adverse events. **Conclusions:** During the REVEAL trial, the beneficial effects of anacetrapib treatment on major coronary events appeared to increase with increasing duration of treatment. The present results indicate that there are further benefits after prolonged follow-up. No safety concerns emerged for non-vascular mortality or morbidity during the post-trial period. These findings demonstrate the importance of continuing trials of lipid-modifying treatment for as long as possible, and for continuing post-trial follow-up. For the AHA Congress, it is proposed to present more detailed results for occlusive vascular events and other major health outcomes.

| **Table 1: Effect of Anacetrapib on Major Coronary Events During In-Trial, Post-Trial and Combined Follow-Up Periods of the REVEAL Trial** |
| --- |
| **In-trial** (median 4.1 years) | **Post-trial** (median 2.3 years) | **Overall** (median 6.3 years) | **Proportional reduction** |
| **In-trial** | **Post-trial** | **Overall** | **In-trial** | **Post-trial** | **Overall** | **In-trial** | **Post-trial** |
| | | | | | | | |
| **Anacetrapib** | 1043/15255 (10.8%) | 1805/15258 (11.9%) | 3848/30513 (12.4%) | 31.3% (19.3%) | 31.3% (19.3%) | 31.3% (19.3%) | 31.3% (19.3%) |
| **Placebo** | 1043/15255 (10.8%) | 1805/15258 (11.9%) | 3848/30513 (12.4%) | 31.3% (19.3%) | 31.3% (19.3%) | 31.3% (19.3%) | 31.3% (19.3%) |

Author Disclosures: For author disclosure information, please visit the AHA Scientific Sessions 2019 Online Program Planner and search for the abstract title.

**Circulating Levels of Small Dense Low-Density Lipoprotein Cholesterol and Cardiovascular Event Risk in Patients With Stable Coronary Artery Disease Treated With High- versus Low-Dose Pitavastatin in the Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy With Pitavastatin in Coronary Artery Disease Trial**

Junnichi Ishii1, Kosuke Kashivabara2, Hiroshi Takahashi3, Hitoshi Nishimura4, Hideki Kawai5, Takashi Muramatsu6, Masahide Harada7, Akira Yamada8, Mutsumi Hayashi9, Hiroyuki Naruse10, Sadako Motoyama11, Masayoshi Sarai12, Eiichi Watanabe13, Yutaka Matsuayama14, Hideo Izawa15, Yukio Ozaki16, Ryozo Nagai17, 1Dept of Joint Risch Laboratory of Clinical Medicine, Fujita Health Univ Sch of Medicine, 2019 AHA Late-Breaking Science Abstracts
Effects of Bariatric Surgery in Patients With Hypertension: 3-Year Outcomes From the Randomized GATEWAY Trial

Carlos A Schiavoni, Deepak L Bhatt, Eliana V Santucci, Juliana D Oliveira, Renato N Santos, Lucas P Damiani, Raquel H Machado, Patricia M Nogueira, Helio Halpern, Frederico L Monteiro, Marco G Sousa, Celso Amodeo, Luiz Bortolotto, Dimas T Ikeda, Alexandre B Cavalcanti, Otavio Berwanger, Luciano F Drager, *R*ich Institute, Heart Hosp, Sao Paulo, Brazil, 1Heart and Vascular Ctr, Brigham and Women’s Hosp, Boston, MA, 2Surgical Ctr, Heart Hosp, Sao Paulo, Brazil, 3Dept of Hypertension, Dante Paisanese Institute of Cardiology, Sao Paulo, Brazil, 4Clinica Cerravel, Sao Paulo, Brazil, 5Hypertension Unit, Heart Institute, Sao Paulo, Brazil, 6Hypertension Unit, Cardiovascular Institute, Sao Paulo, Brazil, 7HCOR Rsch Institute, Sao Paulo, Brazil, 8ACADEMIC RESEARCH ORGANIZATION, Albert Einstein Hosp, Sao Paulo, Brazil, 9Heart Institute, Sao Paulo, Brazil

Introduction: The GATEWAY short-term follow-up (1 year) showed significant improvements and remission of hypertension after bariatric surgery. However, it is unclear whether these effects are sustained. Methods: We conducted a randomized (concealed), single-center, phase II, parallel design clinical trial, with intention-to-treat analysis. We assessed outcomes 3 years after 100 patients had been randomly allocated to either Roux-en-Y Gastric Bypass (GB) combined with medical therapy (MT) or MT alone. The primary endpoint was evaluated at 3 years (reduction of at least 30% of the total antihypertensive drugs, while maintaining controlled blood pressure (BP) levels ≤140/90mmHg). Key secondary endpoints included various biomarkers. Results: A total of 100 patients were included (76% female, age: 43.6±9.2 years, body mass index, BMI: 36.9±7.2kg/m²) and information for primary and key secondary endpoints were available for 84 patients. At 3 years, BMI was 26.8±3.7kg/m² for GB and 36.3±4.2kg/m² for MT (P<0.001). A total of 32 out of 44 patients from the GB group (72.7%) compared with 5 out of 40 patients (12.5%) in the MT group reduced at least 30% of the total antihypertensive drugs while keeping BP controlled (incidence rate ratio [95% CI]: 5.82 [2.51;13.47]; P<0.001) (Figure 1). Median (IQR) number of drugs in the GB and MT groups was 1 (0 to 2) and 3 (2.8 to 4), respectively (P<0.001). A total of 40.9% of patients randomized to GB compared with one patient randomized to MT (but who had GB at 24 months) had hypertension remission (no drugs with BP<140/90 mmHg) at 3 years (Figure 2). Hypertension improvement occurred early after surgery. The differences between groups (GB-MT) at 3 years for glycated hemoglobin, LDL-cholesterol, triglycerides, and high sensitivity C-reactive protein levels were -0.6% (-0.8 to -0.3; P=0.001), -43.4mg/dL (-57.6 to -29.2, P<0.001), -6.2mg/dL (-9.1 to -3.5, P<0.001), and -6.0mg/L (-9.9 to -2.1, P=0.003), respectively. Conclusion: Bariatric surgery represents an effective strategy for reducing antihypertensive drugs and in improving metabolic and inflammatory profiles in hypertensive patients with grade 1 and 2 obesity during long-term follow-up.

Figure 1 Rate ratio (95% CI): 5.82 (2.51 to 13.47) P-value: <0.001

Figure 2

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Ten-Year Clinical Outcomes From a Randomized Trial of Polymer-Free Sirolimus- and Probucol-Eluting Stents versus Permanent Polymer Zotarolimus-Eluting Stents in Patients With Coronary Artery Disease

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Background: The permanent polymer-based zotarolimus-eluting stent (PP-ZES) is a new-generation drug-eluting stent (DES) that is frequently used in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI). The polymer-free sirolimus- and probucol-eluting stent (PF-SES) is a DES with a unique design that enables effective drug release without the need of a polymer. Very long-term outcomes of patients treated with either of these DES have not been assessed to date. Methods: We assessed the 10-year outcomes of patients enrolled in the ISAR-TEST 5 trial. In this trial, 3002 patients were randomized to treatment with either PF-SES (n=2002) or PP-ZES (n=1000). The primary endpoint was the composite of cardiac death, target vessel-related myocardial infarction or target lesion revascularization (a device-oriented endpoint, DOCE). Additional endpoints of interest were the patient-oriented endpoint (POCE), a composite of all-cause death, any myocardial infarction or any revascularization and individual components of the composite endpoints including definite/probable stent thrombosis. Results: The median age of the patients at randomization was 69 years. At 10-years, there was no difference in the incidence of device- and patient-oriented endpoints between the PF-SES and PP-ZES (DOCE: 43.8% versus 43.0%, hazard ratio = 1.01, 95% CI, 0.89–1.14; P=0.90; Figure). POCE: 65.5% versus 67.5%, hazard ratio = 0.93 95%CI, 0.85–1.03; P=0.90. The rates of the individual components of the composite endpoints were comparable in both groups. The incidence of definite/probable stent thrombosis over 10 years was low in both groups (1.6% vs. 1.9%; hazard ratio = 0.85 [95% CI, 0.46–1.54], P=0.58). Clinical results are displayed in Table Conclusion: In this unique long-term analysis out to 10 years, there were no measurable differences in outcomes between patients treated with a polymer-free sirolimus- and probucol-eluting stent and those treated with a new generation durable polymer-based zotarolimus-eluting stent. Although the incidence of stent thrombosis was low in both groups, high cumulative clinical event rates were observed during 10-year follow-up.

Cross Specialty

How Do (or Don’t) New Therapies Work to Reduce CVD Risk? Latest from Recent Trials

Influence of Ejection Fraction on the Effect of Treatment in the Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure Trial (DAPA-HF)

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Background: DAPA-HF investigated the effect of the sodium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin in patients with heart failure (HF) and reduced ejection fraction (HFrEF), including participants without diabetes. Left ventricular ejection fraction (LVEF) is a powerful predictor of mortality and hospitalisation related to HF. Therefore, the potential absolute benefit of therapy is greatest in patients with the lowest LVEF and it is important to establish whether new treatments are effective across the range of LVEF. We assessed the efficacy (morbidity, mortality and quality of life) and safety of dapagliflozin across the range of LVEF reported in DAPA-HF. Methods: The key inclusion criteria were: 1) NYHA functional class II-IV, 2) LVEF ≤40%, 3) modestly elevated NT-proBNP and 4) standard drug and device therapy for HF. Key exclusion criteria included systolic BP >130 mmHg and eGFR below 30 ml/min/1.73m². The double-blind study treatments were dapagliflozin (10 mg qd) or matching placebo. We hypothesized that dapagliflozin would be superior to placebo for the primary composite outcome of a first episode of worsening HF (hospitalization for HF or an urgent HF visit requiring intravenous therapy) or death from cardiovascular (CV) causes. Other outcomes were assessed, including all-cause and CV death plus recurrent hospitalizations, and a prespecified renal outcome. Symptoms were assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ). Safety/tolerability analyses included: treatment discontinuation, serious adverse events and adverse events of interest such as volume depletion and renal dysfunction. Results: From February 15, 2017, through August 17, 2018, 4774 patients were randomized at 410 centers in 20 countries. The mean age of patients was 66 years and 23% were women. 68% of patients were in NYHA class II, and the median NT-proBNP was 1437pg/ml. 56% of patients had an ischemic etiology and 42% had type 2 diabetes. Mean eGFR was 66 ml/min/1.73m² and 41% had an eGFR below 60. 94% of patients were treated with a renin-angiotensin system blocker, 96% with a beta-blocker and 71% with an MRA. The mean LVEF was 31% and was the same in those with and without diabetes; 24% of patients had a LVEF of ≤25%, 21% of patients LVEF 26–30%, 25% LVEF 31–35%, and 29% LVEF 36–40%. Conclusions: DAPA-HF will determine whether the SGLT2 inhibitor dapagliflozin is superior to placebo in improving outcomes, including quality of life across the spectrum of LVEF in patients with chronic symptomatic HFrEF. (Funded by AstraZeneca; DAPA-HF ClinicalTrials.gov number, NCT03036124.)

Timing of Onset of Clinical Benefit with Dapagliflozin in Patients with Heart Failure: An Analysis from the Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure Trial (DAPA-HF)

Marc S Sabatine, David L DeMets, Silvio E Inzucchi, Lars Kober, Mikhail N Kosiborod, Anna Maria langkilde, Felipe Martinez, Olof Bengtsson, Piotr Poniokowski, Mikaela Sjostrand, Scott J Solomon, John J McMurray, TIMI Study Group, TIMI Study Group, Boston, MA, Dept of Biostatistics and Med Informatics, Univ of Wisconsin, Madison, WI, Section of Endocrinology, Yale Univ Sch of Medicine, New Haven, CT, Cardiology, Rigshospitalet, Copenhagen, Denmark, St. Luke’s Health System, St. Luke’s Health System, Kansas City, MO

Background: DAPA-HF investigated the effect of the sodium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin in patients with heart failure (HF) and reduced ejection fraction (HFrEF), including participants without diabetes. Left ventricular ejection fraction (LVEF) is a powerful predictor of mortality and hospitalisation related to HF. Therefore, the potential absolute benefit of therapy is greatest in patients with the lowest LVEF and it is important to establish whether new treatments are effective across the range of LVEF. We assessed the efficacy (morbidity, mortality and quality of life) and safety of dapagliflozin across the range of LVEF reported in DAPA-HF. Methods: The key inclusion criteria were: 1) NYHA functional class II-IV, 2) LVEF ≤40%, 3) modestly elevated NT-proBNP and 4) standard drug and device therapy for HF. Key exclusion criteria included systolic BP >130 mmHg and eGFR below 30 ml/min/1.73m². The double-blind study treatments were dapagliflozin (10 mg qd) or matching placebo. We hypothesized that dapagliflozin would be superior to placebo for the primary composite outcome of a first episode of worsening HF (hospitalization for HF or an urgent HF visit requiring intravenous therapy) or death from cardiovascular (CV) causes. Other outcomes were assessed, including all-cause and CV death plus recurrent hospitalizations, and a prespecified renal outcome. Symptoms were assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ). Safety/tolerability analyses included: treatment discontinuation, serious adverse events and adverse events of interest such as volume depletion and renal dysfunction. Results: From February 15, 2017, through August 17, 2018, 4774 patients were randomized at 410 centers in 20 countries. The mean age of patients was 66 years and 23% were women. 68% of patients were in NYHA class II, and the median NT-proBNP was 1437pg/ml. 56% of patients had an ischemic etiology and 42% had type 2 diabetes. Mean eGFR was 66 ml/min/1.73m² and 41% had an eGFR below 60. 94% of patients were treated with a renin-angiotensin system blocker, 96% with a beta-blocker and 71% with an MRA. The mean LVEF was 31% and was the same in those with and without diabetes; 24% of patients had a LVEF of ≤25%, 21% of patients LVEF 26–30%, 25% LVEF 31–35%, and 29% LVEF 36–40%. Conclusions: DAPA-HF will determine whether the SGLT2 inhibitor dapagliflozin is superior to placebo in improving outcomes, including quality of life across the spectrum of LVEF in patients with chronic symptomatic HFrEF. (Funded by AstraZeneca; DAPA-HF ClinicalTrials.gov number, NCT03036124.)

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**Background:** DAPA-HF investigated the effect of the sodium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin in patients with heart failure and reduced ejection fraction (HFREF), including participants without diabetes. Clinical inertia often underlies initiation of new beneficial therapy. To further explore the potential lost opportunity due to this inertia, we examined the timing of the onset of the clinical benefit with dapagliflozin after randomization in DAPA-HF: Methods: The key inclusion criteria for DAPA-HF were: 1) New York Heart Association functional class II-IV, 2) LVEF of 40% or less, 3) plasma NT-proBNP of at least 600 pg/ml (400 pg/ml if hospitalized for HF in prior 12 months or at least 900 pg/ml if atrial fibrillation) and 4) standard drug and device therapy for HF. Key exclusion criteria included symptoms of hypotension or systolic blood pressure below 95 mmHg, estimated glomerular filtration rate (eGFR) below 30 ml/min/1.73m2, or type 1 diabetes. The double-blind study treatments were dapagliflozin (10 mg once daily) or matching placebo. We hypothesized that dapagliflozin would be superior to placebo for the primary composite outcome of a first episode of worsening HF (hospitalization for HF or an urgent HF visit requiring intravenous therapy) or death from cardiovascular causes. A range of outcomes were also assessed including all-cause and cardiovascular death as well as recurrent hospitalisations. Quality of life was assessed using the Kansas City Cardiomyopathy Questionnaire. Results: From February 15, 2017, through August 17, 2018, 4744 patients were randomized to 410 centers in 20 countries. The mean age of patients was 66 years. Women accounted for 23% of patients and 68% of patients were in NYHA class II; mean LVEF was 31% and the median NT-proBNP 1437 pg/ml. 56% of patients had an ischemic etiology and 42% had type 2 diabetes. Mean eGFR was 66 ml/min/1.73m2 and 41% had an eGFR below 60. 94% of patients were treated with a renin-angiotensin system blocker, 96% with a beta-blocker and 71% with an MRA. The detailed results of DAPA-HF are currently embargoed and the results of these analyses will be available for the AHA Scientific Sessions. Conclusions: The SGLT2 inhibitor dapagliflozin reduces the risk of worsening HF or death from cardiovascular causes. The timing of the onset of that benefit and other clinical outcomes will be available to be presented at AHA. (Funded by AstraZeneca; DAPA-HF ClinicalTrials.gov number, NCT03036124.)

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**20800 Empagliflozin Leads to a Rapid and Sustained Improvement of Diastolic Function in Patients With Type 2 Diabetes Independent of Hemodynamic Changes**

Michael Lehrke1, Nikolaus Marx2, Michael Böhm3, Ertunc Altiok1, András P Keszi4, Alexander Schul4, Niels U Hartmann, Kirsten Thié4, Matthias Rau1, Carina Schütte1, Univ Hosp, Aachen, Germany, 3Cardiology, Uni Hosp Saarland, Homburg, Germany, 4Univ Hosp, Aachen, Aachen

**Background:** In the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial) treatment with the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin significantly reduced heart failure hospitalization (HHF) in patients with type 2 diabetes mellitus (T2D) and established cardiovascular disease. The early separation of the HHF event curves within the first 3 months of the trial suggest that immediate hemodynamic effects may play a role. However, hitherto no data exist on early effects of SGLT2 inhibitors on hemodynamic parameters and cardiac function. Thus, this study examined early and delayed effects of empagliflozin treatment on hemodynamic parameters including heart rate, systemic vascular resistance index, and stroke volume index, as well as echocardiographic measures of cardiac function. Methods: In this placebo-controlled, randomized, double blind, exploratory study patients with T2D were randomized to empagliflozin 10 mg or placebo for a period of 12 weeks. Hemodynamic and echocardiographic parameters were assessed after 1 day, 3 days and 12 weeks of treatment. Results: Baseline characteristics were comparable in the empagliflozin (n=22) and placebo (n=20) group. Empagliflozin led to a significant increase in urinary glucose excretion (baseline: 7.3 ± 22.7 g/24 hrs; day 1: 48.4 ± 34.7 g/24 hrs; p<0.001) as well as urinary volume (baseline: 1740 ± 201 ml/24 hrs to 2112 ± 218 ml/24 hrs; p<0.011) already after one day compared to placebo. Treatment with empagliflozin had no effect on the primary endpoint of systemic vascular resistance index, nor on cardiac index, stroke volume index or pulse rate at any time point. In addition, echocardiography showed no difference in left ventricular systolic function as assessed by left ventricular ejections fraction and strain analysis. However, empagliflozin significantly improved left ventricular diastolic function as assessed by a reduction of early mitral inflow velocity relative to early diastolic left ventricular relaxation (E/e’) which became significant at day 1 of treatment (baseline: 9.2 ± 2.6; day 1: 8.5 ± 2.2; p=0.005) and remained apparent throughout the study. This was primarily attributable to reduced early mitral inflow velocity E (baseline: 0.8 ± 0.2 m/sec; day 1: 1.07 ± 0.2 m/sec; p=0.003). Conclusions: Empagliflozin treatment of patients with T2D has no significant effect on hemodynamic parameters after 1 or 3 days, nor after 3 months, but leads to rapid and sustained significant improvement of diastolic function.

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**20983 Are the Beneficial Cardiovascular Effects of Glucagon-Like Peptide 1 Receptor Agonists in Diabetic Patients Metabolically Mediated?**

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**Background:** Previous trials have shown that glucagon-like peptide 1 receptor agonists (GLP1 RA) reduce major adverse cardiovascular events (MACE) in high-risk diabetic patients. Aggregate data, including the recently reported trials, gives us greater robustness to analyze individual cardiovascular outcomes, safety and potential mechanisms of action. Hypothesis: GLP1 RA reduce some of the beneficial clinical effects by their metabolic glucose-lowering activity. Methods: We analyzed data from randomized trials that compared the safety and efficacy of GLP1 RA with placebo in patients with type 2 diabetes and had MACE as the primary outcome. We conducted a systematic review, based on a search of MEDLINE, EMBASE and the Cochrane Library up to June 2019; studies with >1000 participants were eligible. We conducted a meta-analysis to calculate overall estimates for each cardiovascular and safety outcome. Prespecified subgroup analyses were performed using a mixed-effects model. A univariate meta-regression analysis was performed to describe the relationship between the on-trial change in HbA1c, systolic blood pressure and body weight (relative difference of the area under the HbA1c curves and weighted average differences) and the risk estimates for MACE. Results: GLP1 RA reduced the risk of MACE by 12% (HR 0.88, 95% CI 0.82–0.94, p<0.001); myocardial infarction by 9% (HR 0.91, 95% CI 0.83–0.99, p=0.04); stroke by 16% (HR 0.84, 95% CI 0.76–0.93, p<0.001); hospital admissions for heart failure by 9% (HR 0.91, 95% CI 0.83–0.99, p=0.028); cardiovascular mortality by 12% (HR 0.88, 95% CI 0.81–0.96, p=0.003) and total mortality by 11% (HR 0.89, 95% CI 0.83–0.95, p=0.001) versus placebo. Rates of severe hypoglycemia, reported pancreatitis and pancreatic cancer were similar between the GLP1 RA and placebo groups. GLP1 RA showed a negative statistically significant association between on-trial HbA1c relative reduction and MACE (slope=−0.31, p<0.01). GLP1 RA reduced the risk of MACE hazard risk reduction for each unit-weighted average HbA1c reduction. No significant association was observed between HbA1c and systolic blood pressure or body weight. Conclusion: Our meta-analysis and meta-regression analysis demonstrated that GLP1 RA show a robust, moderate, and consistent beneficial effect on the combined and individual cardiovascular outcomes, and suggest that their beneficial effects are, at least in part, metabolically mediated.

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**Effect of Eicosapentaenoic Acid/Docosahexaenoic Acid on Coronary High-Intensity Plaques Detected With Non-Contrast T1-Weighted Imaging (The AQUAMARINE EPA/DHA Study)**

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**Background:** Despite the success of statin therapy in reducing atherothrombotic cardiovascular events, a residual risk for cardiovascular events in patients with coronary artery disease (CAD) remains. Recently, the Reduction of Cardiovascular Events with ERA-intervention Trial (REDUCE-IT) demonstrated that a high-dose purified form of the eicosapentaenoic acid (EPA) improve cardiovascular outcome. However, anti-atherogenic effect of high dose EPA/Docosahexaenoic acid (DHA) has not been clarified. We reported that coronary high-intensity plaques (HIPs) detected with non-contrast T1-weighted imaging (T1WI) on cardiac magnetic resonance (CMR) (Figure 1), which can be uniquely quantitative assessed using the plaque-to-myocardium signal intensity ratio (PMR) of ≥1.4, are significantly associated with future coronary events. Moreover, we demonstrated that intensive statin therapy reduces the PMR of coronary HIPs (J Am Coll Cardiol 2015;66:245–256). Hence, the present study was designed as a single-center, double-blind, placebo-controlled, crossover trial of the effect of EPA/DHA evaluating the change in PMR of coronary HIPs after 12 months of EPA/DHA therapy.

**Methods:** This study was designed as a single-center, triple-arm, parallel-group, randomized controlled, open-label, superiority trial examining the effect of 12 months of additional EPA/DHA therapy on coronary HIPs in patients with CAD who receiving statin therapy (Trials. 2018 Jan 8;19(1):12). Eligible subjects are randomly assigned to the 2 g/day EPA/DHA group, the 4 g/day group, or the no-treatment group (Figure 2). The PMR was defined as the signal intensity of the coronary plaque divided by that of nearby left ventricular myocardium. The primary endpoint is the change in PMR after EPA/DHA therapy. **Results:** Among 83 study patients, the prevalence of HIP-positive (PMR ≥1.4) was 40.4% and average of PMR was 1.40. Study patients were assigned to the 2 g/day EPA/DHA group (n=29), the 4 g/day (a high-dose) EPA/DHA group (n=27), or the no-treatment group (n=28). There were 12 (41%) HIP-positive patients in the 2 g/day EPA/DHA group, 12 (44%) patients in the 4 g/day EPA/DHA group, and 10 (36%) patients in the no-treatment group. After randomization, the 3 groups were well matched at baseline, with no statistically significant differences in age, male sex, conventional coronary risk factors, lipid profile, HbAT1C, medications used, and PMR. **Discussion:** The present trial outcomes will provide novel insights into the effect of EPA/DHA on high-risk coronary plaques and may provide additional information of EPA/DHA for lowering the residual risk in patients with CAD on statin therapy.

**Figure 1. Representative images of coronary HIP**

**Figure 2. Study flow of this study**

**Coronary Flow Reserve, Myocardial Mechanics and Inflammation in Patients With Coronary Artery Disease Enrolled in the Cardiovascular Inflammation Reduction Trial**

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**Introduction:** Inflammation is a key determinant of cardiovascular outcomes. Coronary flow reserve (CFR) is a sensitive measure of myocardial ischemia affecting the macro- and microvascular circulation and identifies patients at risk for death, myocardial infarction and heart failure with preserved ejection fraction. We investigated the relationship between CFR, myocardial strain and inflammation in a prospective, multicenter ancillary study of the Cardiovascular Inflammation Reduction Trial (CIRT-CFR). (Funded by the NHLBI; CIRT-CFR ClinicalTrials.gov identifier NCT02786134.) **Methods:** Consecutive subjects enrolled in CIRT-CFR underwent noninvasive imaging with cardiac stress positron emission tomography (PET) and transthoracic echocardiography at baseline (N=50) and following randomization (N=39) to low-dose methotrexate or placebo treatment. All patients had previous myocardial infarction or multivessel CAD and either type 2 diabetes or the metabolic syndrome. Average time between baseline and follow-up studies was 8.5 months. CFR was quantified as stress/rest myocardial blood flow from PET. Global longitudinal strain (GLS) and markers of diastolic dysfunction (E, e') were obtained from echocardiography. Blood samples collected during study visits were analyzed for inflammatory and lipid biomarkers. Data were analyzed by a centralized core laboratory blinded to study details. **Results:** The median age was 65 (IQR 59–71) years, median LVEF at baseline was 53 (0.46–0.60) and 72% of subjects had normal resting myocardial perfusion. The mean CFR was 2.11 (1.64–2.59) at baseline and 2.10 (1.60–2.76) at follow-up. As in the overall CIRT, there were no significant treatment effects in subject randomized to methotrexate (mean % change in CFR +0.05 in methotrexate vs. -0.16 in placebo groups, p=0.29). CFR was directly correlated with favorable GLS (r = -0.39, p=0.005) and inversely correlated with higher E/e' (r = -0.29, p=0.04). CFR was inversely correlated with IL-6 (r = -0.45, p=0.002) and IL-1β (r = -0.32, p=0.03), and was not significantly associated with hsCRP, total cholesterol, LDL, HDL, or triglycerides (p>0.1 for all). Inflammation modified the relationship between CFR and GLS (r = -0.59, p=0.001) for upper median of IL-6, vs. -0.10, p=0.67 for lower median of IL-6, p for interaction 0.03). In multivariable mixed linear regression modeling adjusting for age, sex, race, BMI, LVEF, myocardial perfusion imaging and lipids, CFR remained independently associated with IL-6 and GLS. **Conclusion:** In patients enrolled in CIRT-CFR, impaired CFR was associated with inflammation and myocardial strain, independently of traditional markers of cardiovascular risk such as lipids, LVEF, and regional myocardial perfusion. Inflammation further modified the relationship between coronary vasomotor function and myocardial mechanics.

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**Omega-3 Fatty Acids and Risk of Cardiovascular Disease: Systematic Review and Meta-Analysis of Randomized Controlled Trials With 127,447 Individuals and a Mendelian Randomization Study**

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**INTRODUCTION:** Both randomized and observational studies produced controversial results on the beneficial impact of omega-3 fatty acids on risk of cardiovascular disease (CVD). **HYPOTHESIS:** We undertook a systematic review

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**Omega-3 Fatty Acids and Risk of Cardiovascular Disease: Systematic Review and Meta-Analysis of Randomized Controlled Trials With 127,447 Individuals and a Mendelian Randomization Study**
and meta-analysis of RCTs and performed a Mendelian randomization (MR) to evaluate the link (or possible causality) between omega-3 supplementation and CVD and selected cardiometabolic risk factors. METHODS: Selected databases were searched until June 2019 to identify prospective studies evaluating the impact of omega-3 fatty acids supplementation on CVD events/mortality. Fixed-effects models meta-analysis was used for quantitative data synthesis. MR was performed by using summary-level data from the largest genome-wide association studies and inverse variance weighted method (IVW), weighted median-based method, MR-Egger and MR-Pleiotropy RESidual Sum and Outlier (PRESSO) were applied. Sensitivity analysis was conducted using the leave-one-out method. RESULTS: From 46825 entries identified via searches, 13 studies with 127,447 individuals were finally included to the meta-analysis. We showed a significant reduction in the risk of coronary heart disease (CHD) death (risk ratio (RR) 0.91, 95%CI 0.85–0.97, p=0.010), major vascular event (RR 0.95, 95%CI 0.93–0.98, p=0.001), non-fatal myocardial infarction (MI) (RR 0.89, 95%CI 0.83–0.95, p=0.001) (Figure 1), and all-cause mortality (RR 0.95, 95%CI 0.92–0.99, p=0.025) with omega-3-intervention. With regard to impact of alpha-linolenic acid (ALA) on cardiometabolic risk factors, we found that a genetically determined higher level of serum ALA has a negative impact on the risk of CHD (IVW=Beta: -2.296, p=6.8*e-16) levels, while there was a positive effect on triglyceride (TG) levels (IVW=Beta: 3.146, p=5.4*e-09). For eicosapentaenoic acid (EPA) levels, there was only a positive effect on fasting blood glucose (IVW=Beta: 0.246, p=0.003), TC (IVW=Beta: 0.464, p=6.8*e-16) and LDL-C (IVW=Beta: 0.469, p=6.8*e-16) levels, while there was a negative impact on TG levels (IVW=Beta: -0.463, p=5.2*e-05). CONCLUSIONS: These findings support the current recommendations for routine dietary supplementation with omega-3 fatty acids to prevent vascular events and mortality and improve cardio-metabolic risk factors.

The Pooled Estimate (Risk Ratio) [RR] of The Effect of Omega-3 Fatty Acid Supplementation on Non-Fatal Myocardial Infarction

| Study name | Statistics for each study | Risk ratio limit | p-value |
|------------|---------------------------|-----------------|---------|
| DOIT       |                           |                 |         |
| ARBESD-2   |                           |                 |         |
| SU-PLC1OM3  |                           |                 |         |
| JELIS      |                           |                 |         |
| OMDD       |                           |                 |         |
| RMP        |                           |                 |         |
| GEBB-HF    |                           |                 |         |
| ORIG1      |                           |                 |         |
| GHSS-P      |                           |                 |         |
| ASCEND     |                           |                 |         |
| REDUCE-IT   |                           |                 |         |
| Overall    |                           |                 |         |

| Risk ratio | Lower limit | Upper limit | p-value |
|------------|-------------|-------------|---------|
| 1.99       | 0.607       | 6.543       | 0.256   |
| 0.718       | 0.149       | 1.149       | 0.167   |
| 0.699       | 0.605       | 0.705       | 0.007   |
| 0.746       | 0.538       | 1.036       | 0.080   |
| 1.086       | 0.785       | 1.502       | 0.618   |
| 0.923       | 0.774       | 1.101       | 0.375   |
| 0.930       | 0.764       | 1.131       | 0.471   |
| 0.725       | 0.587       | 0.897       | 0.000   |
| 0.891       | 0.608       | 0.839       | 0.000   |
| 0.894       | 0.838       | 0.934       | 0.001   |

Main effect p<0.001, interaction v=0.231

Conclusion: Omega-3 fatty acids supplementation may exert an independent protective effect on non-fatal myocardial infarction.

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Use of a Genetic Risk Score to Predict Coronary and Vascular Events and Benefit From Evolocumab Therapy in Patients With Atherosclerotic Disease From the FOURIER Trial

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Background: Genetic risk scores have been developed to predict incident coronary artery disease (CAD); however, the ability to predict risk in established cardiovascular (CV) disease and identify individuals who derive greater benefit from PCSK9 inhibition has not been established. Methods: From the FOURIER trial of patients with prior CV events, we studied 14,298 patients of European ancestry who provided a genetic sample. A previously validated 27-SNP GRS associated with CAD was calculated using the genotype dosage for each allele multiplied by its weight, and then summed across all variants. Genetic risk was defined as low (Q1), intermediate (Q2-4), or high risk (Q5). For comparison, we also categorized patients by burden of atherosclerotic clinical risk factors including diabetes, hypertension, LDL-C ≥ 100 mg/dl, and smoking; ≥2 risk factors was considered “high clinical risk”. Outcomes consisted of major coronary events (MCE; coronary heart death, MI, or coronary revascularization) and major vascular events (MVE; MCE + ischemic stroke). Median follow up was 2.3 years. Adjusted Cox proportional hazards regression analyses were performed. Results: In the placebo arm, 774 patients had a MVE, 673 of which were MCE. After adjusting for clinical factors, the GRS was associated with risk for both MVE (P=0.007) and MCE (P<0.0001). Individuals with a high GRS had a 1.65-fold increased hazard for MCE, whereas individuals with intermediate GRS had a 1.23-fold increased hazard compared with those with low GRS (Fig, left). As genetic risk increased, there was a trend towards greater relative risk reduction (p-interaction = 0.07) and significantly greater absolute risk reduction (p-interaction = 0.04) with evolocumab vs. placebo. Elevated genetic risk was additive to clinical risk factors and identified patients who were more likely to benefit from evolocumab (Fig, right), with a 13% relative risk reduction and a 1.4% ARR in MVE in patients with multiple clinical risk factors and low-intermediate genetic risk, and a 21% relative risk reduction and 4.0% absolute risk reduction in patients with high genetic risk (respective of clinical risk factors). High genetic risk patients who received evolocumab had event rates similar to patients with a low burden of both genetic and clinical risk factors. Conclusion: In established CV disease, a GRS identified subsets of patients who had significantly increased risk of recurrent events beyond clinical risk factors and identified individuals who derived greater benefit from evolocumab. Elevated genetic risk was mitigated by treatment with evolocumab.

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Lowlands Saves Lives: A Randomized Controlled Trial to Compare CPR Quality and Long-Term Attitude Towards CPR Performance Between Face-to-Face and Virtual Reality Training With the Lifesaver VR-app

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Introduction: Bystander cardiopulmonary resuscitation (CPR) is crucial for survival after cardiac arrest, but not performed in the majority of cases. New, low cost and easily accessible training methods such as virtual reality (VR) may reach broader target populations, but data on achieved CPR-skills are lacking. Therefore, we compared CPR-quality between VR and face-to-face CPR-training. Methods: Lowlands Saves Lives was a 1:1 randomized controlled noninferiority trial with a prospective randomized open blinded end-point (PROBE) design, conducted on the science section of the Lowlands music festival (August 16-18th, 2019; the Netherlands, 55,000 attendees). Adult participants were randomized to one of the following two standardized CPR protocols on CPR and automated external defibrillator-use: instructor-led face-to-face training, or VR-training using the Resuscitation Council (UK) endorsed Lifesaver VR smartphone application. During a standardized CPR-scenario following the training, we assessed the primary outcome CPR-quality, measured as chest compression depth and rate using CPR-manikins (Laerdal Medical, Stavanger, Norway). Overall CPR-performance was assessed by examiners, blinded for study groups, using a European Resuscitation Council-endorsed checklist (maximum score=33). Additional secondary outcomes were chest compression fraction (CCF), proportions of participants with mean depth (50-60mm) and rate (100-120min⁻¹) within guideline-ranges, and proportions compressions with full release (CPR). Results: We randomized 381 participants: 57% female, median age 26 years (IQR 22–31). Lifesaver VR (n=190) was inferior to face-to-face training (n=191) for chest compression depth (VR: 10mm, face-to-face: 57±5mm; mean difference –8mm, 95% CI [9,6], and noninferior for chest compression rate (Lifesaver VR: 114mm·s⁻¹, face-to-face: 109mm·s⁻¹, 12% mean difference 6mm·s⁻¹, 95% CI [3.8]. The Lifesaver VR-group had lower overall CPR-performance scores (10 [IQR 8–12] vs. 12 [IQR 12–13], p<0.001), and CCF (61% [IQR 52–66] vs. 67% [IQR 62–71], p=0.001) and proportions of participants fulfilling depth (51% vs. 75%, p<0.001) and rate (50% vs. 63%, p=0.01) requirements were also lower in the Lifesaver VR-group. The proportion CPR was higher in the Lifesaver VR-group (98% [52–100] vs. 88% [55–99], p=0.002). Conclusion: Lifesaver VR-training results in comparable chest compression rate, but inferior compression depth compared to face-to-face training. Given its potential to reach a larger target population, further development of VR-training is needed to achieve the overall CPR-skills acquired by face-to-face training. Trial registration: This study is registered on www.clinicaltrials.gov (NCT04013633).

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Integrated Health Systems Strategies for Blood Pressure Reduction in Rural Communities in Bangladesh, Pakistan, and Sri Lanka - A Multi-Country Cluster Randomized Controlled Trial

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Background: Blood pressure (BP) control is important for reducing the high burden of cardiovascular disease in low-resource settings. There is also growing evidence that BP control can be improved by integrated health systems strategies. The Lowlands Saves Lives program, a multi-country randomized controlled trial of CPR training to improve outcomes after cardiac arrest, was linked to a separate BP intervention. Here we report the results of the BP intervention in the Lowlands Saves Lives program. Methods: A total of 4,650 study participants were randomized into one of four study arms: 1) usual care (UC); 2) UC plus integrated health systems strategies (IHS); 3) UC plus CPR training only; and 4) UC plus both IHS and CPR training. The IHS intervention involved integration of the CPR program with routine health services, including integration of CPR training into routine health systems, establishment of a surveillance and feedback mechanism to track implementation of CPR training into routine care, and piloting of mobile phone applications to support implementation of the IHS intervention. The UC intervention involved no additional BP intervention. Mean systolic BP (SBP) and diastolic BP (DBP) at 12 months follow-up were compared between the four study arms. Results: At 12 months follow-up, the mean SBP was 136.6 mm Hg (95% CI 135.2–137.9) in the UC group, 136.9 mm Hg (95% CI 135.6–138.2) in the UC plus CPR training group, 136.6 mm Hg (95% CI 135.2–138.0) in the UC plus IHS group, and 136.9 mm Hg (95% CI 135.6–138.2) in the UC plus both IHS and CPR training group. Mean DBP was 84.7 mm Hg (95% CI 83.4–86.0) in the UC group, 84.7 mm Hg (95% CI 83.4–86.0) in the UC plus CPR training group, 84.7 mm Hg (95% CI 83.4–86.0) in the UC plus IHS group, and 84.7 mm Hg (95% CI 83.4–86.0) in the UC plus both IHS and CPR training group. The differences in SBP and DBP between the UC group and the UC plus both IHS and CPR training group were not statistically significant. Conclusion: The integrated health systems strategy for improving blood pressure control was not effective in this low-resource setting.
Integrating Depression and Acute Coronary Syndrome Care in Low-Resource Hospitals in China (I-CARE Study): A Randomized Clinical Trial

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Background: Depression and acute coronary syndrome (ACS) are significant public health problems in the US and worldwide. ACS often co-occurs with depression, which adversely affects prognosis and is associated with increased medical costs. Low-cost, sustainable, and effective scalable interventions to integrate depression care into the management of ACS are critically needed. Purpose: I-CARE is a multi-center, randomized clinical trial to evaluate the effects of an 11-month integrated care (IC) intervention compared to usual care (UC) in the management of ACS patients after hospital discharge. Methods: A total of 1048 patients with ACS were enrolled between 2014 and 2017 in 16 Chinese hospitals without PCI facilities, and were randomized to IC (n = 520) or UC (n = 518) and followed for up to 4 years through March 2018. The IC intervention was a post-discharge nurse-led program consisting of an optimal ACS secondary prevention program and a depression care including case screening, group-based counseling, individual problem-solving therapy and antidepressant medications as needed. The patients in UC received usual care. The primary outcome was change in depressive symptoms assessed by the Patient Health Questionnaire-9 (PHQ-9) from baseline to 6 and 12 months. Secondary outcomes included incidence of major adverse events (MAEs) after discharge and proportion of patients with evidence-based ACS secondary prevention medication use. Data were analyzed by using a mixed linear model following the intent-to-treat principle. Results: The mean age of the patients was 61±10 years and 68% were men, only 33% of participants obtained a clinically significant PHQ-9 score≥10 at baseline. There were no group differences in demographic and clinical characteristics between IC and UC groups. There were no treatment group differences in change of PHQ-9 scores from baseline to 6- and 12-months (-1.54 in IC group vs -1.46 in UC group; adjusted p=0.313). The intervention effect did not differ by groups in severity of depression at baseline (P for interaction=0.078). There were also no group differences in the risk of MAEs after discharge. However, secondary prevention medication use was significantly higher in IC compared to UC groups after 12 months (45.0% vs 40.7%; adjusted p=0.004). Conclusions: Results from the I-CARE trial showed that a nurse-coordinated ACS and depression IC intervention did not reduce depression or improve clinical outcomes among patients with ACS compared to usual care controls. The low prevalence of depression was unexpected and may have minimized any potential added benefits of the IC intervention compared to UC on depression or clinical outcomes.

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Background: The current trends of unhealthy lifestyle behaviors in underserved communities are disturbing. Thus, effective health promotion strategies constitute an unmet challenge. Objective: To assess the impact of two different lifestyle interventions on parents/caregivers of children attending preschools in a socioeconomically disadvantaged community. Methods: The FAMILIA study is a cluster-randomized trial involving 15 Head Start preschools in Harlem, New York. Schools, and their children’s parents/caregivers, were randomized to receive either an “individual-focused” or “peer-to-peer based” lifestyle intervention program for 12 months or to control. The primary outcome was the change from baseline at 12 months in a composite health score related to Blood pressure, Exercise, Weight, Alimentation and Tobacco (Fuster-BEWAT Score, FBS), ranging from 0 to 15 (ideal health=15). To assess the sustainability of the intervention, we evaluated the change of FBS at 24 months. Main pre-specified secondary outcomes included changes in FBS subcomponents and the impact of the knowledge of presence of atherosclerosis as assessed by bilateral carotid/femoral vascular ultrasound. Mixed-effects models were used to test for intervention effects. Results: We enrolled 635 parents/caregivers with a mean age of 38±11 years, 83% female, 57% Hispanic/Latino and 31% African-American, and a baseline FBS of 9.3±2.4 points. The mean within-group change in FBS from baseline at 12 months was −0.20 points in all groups, with no overall between-group differences. However, high-adherence participants to the intervention exhibited a greater change in FBS than their low-adherence counterparts: 0.30 points (95% CI: 0.03 to 0.57; p-value = 0.025) vs. 0.00 points (95% CI: −0.43 to 0.43; p-value = 1.0), respectively (Figure). Furthermore, the knowledge by the participant of the presence of atherosclerosis significantly boosted the intervention effects. Similar results were sustained at 24 months. Conclusions: Although we did not observe overall significant differences between intervention and control groups, the FAMILIA trial highlights that high adherence rates to lifestyle interventions may improve effectiveness and health outcomes. It also suggests a potential contributory role of the presentation of atherosclerosis pictures, providing helpful information to improve future lifestyle interventions in adults.

Effect of Different Lifestyle Interventions on Adults From Underserved Communities: The FAMILIA Trial

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Figure 1. A) The PDC for statins was improved by nudges compared to control at 12 months (p=0.002), but not at baseline (p=0.88), 3 months (p=0.33), 6 months (p=0.35), or 9 months (p=0.10). B) Similar results were found for the percentage of subjects with ≥80% statin adherence, which was increased at 12 months by nudges (p=0.036) but not different at baseline through 9 months (all p>0.22).

A) Statin Adherence (PDC)

B) Subjects with ≥80% Statin Adherence

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Effect of Different Lifestyle Interventions on Adults From Underserved Communities: The FAMILIA Trial

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SGLT2i Treatment Reduces Cardiorenal Disease Risk in T2D Patients Without Established Cardiovascular and Renal Diseases: A Large Observational Study

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Introduction: Cardiorenal disease has recently been shown to be the most common first T2D CV manifestation in patients with type 2 diabetes (T2D) without a history of established cardiovascular (CV) and renal diseases, herein after defined as CV free. It is also the costliest and associated with high mortality risk. The aim was to examine the effects of sodium-glucose cotransporter-2 inhibitor (SGLT2i) vs other glucose lowering drugs (oGLD) on cardiorenal diseases in CV free T2D patients. Methods: CV free patients were identified in claims health care registry in Japan. Two groups were compared; new users of SGLT2i and new users of oGLD (secondary with dipeptidyl peptidase 4 inhibitor [DPP4i], matched 1:1 by propensity score calculated by using extensive number of variables. Hazard ratios (HRs) were estimated with unadjusted Cox survival regressions. Outcomes recorded in hospital care: heart failure (HF), chronic kidney disease (CKD), cardiorenal disease (HF and/or CKD), stroke, myocardial infarction (MI), and all-cause death (ACD). Results: After propensity score matching, 108,362 CV free patients were new users of SGLT2i (n=54,181) or oGLD (n=54,181). Baseline characteristics were well balanced, and patients were followed-up for a mean of 1.52 years, 164,710 patient-years. SGLT2i was associated with lower risks of cardiorenal disease, HF, CKD, stroke and ACD; HR (95% CI) 0.55 (0.49–0.61); HR 0.73 (0.61–0.87); HR 0.45 (0.39–0.52); HR 0.69 (0.59–0.81) and HR 0.52 (0.46–0.58), respectively (Table). MI showed no associations. In 34,464 new users of SGLT2i vs DPP4i similar results for cardiorenal disease was observed; HR 0.45 (0.37–0.55). Conclusion: In >100,000 CV free T2D patients, initiation of SGLT2i was associated with lower risks of cardiorenal diseases compared with oGLD or DPP4i.

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Validation of the Preoperative Cardiovascular Risk Index in Surgical Subpopulations

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Background: The Cardiovascular Risk Index (CVRI) is a newly derived and validated index for preoperative cardiovascular evaluation. It is based on six easily acquired data elements: Age ≥ 75 years, hemoglobin < 12 mg/dl, male gender, history of diabetes, history of angina or dyspnea, vascular surgery, and emergency surgery. Objective: To study the performance of the CVRI in a broad range of surgical subpopulations. Methods: The study population consisted of 1,167,278 non-cancer surgeries registered in the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database between 2008 and 2012. The performance of the CVRI index was studied in the nine broad surgical specialty groups: General, vascular, orthopedics, gynecology, urology, neurosurgery, otolaryngology, plastics, and thoracic surgery and in eight commonly performed site-specific surgeries: Cholecystectomy, mastectomy, colectomy, hip, hysterectomy, prostatectomy, abdominal aortic aneurysm surgical repair, and spine surgery. The primary outcome measure was death, myocardial infarction, or stroke at 30 days after surgery. Results: The CVRI score (0, 1, 2, 3, >3) was able to stratify risk in all the surgical subgroups (<p=0.0001) (Figure-1). The area under the receiver operator curve (AUC) ranged from 0.71 in vascular and thoracic surgery to more than 0.80 in orthopedic, general, and plastic surgery. For the site-specific surgeries, the AUC ranged from 0.73 in spine surgery to 0.83 in cholecystectomy. In the majority of surgeries, patients with a CVRI of 0 had an event rate of less than 0.5%. Conclusion: This study extends the validation of the CVRI to a broad spectrum of surgical subpopulations with a range of discriminatory power and underscores its ability to identify a large group of low risk patients with a CVRI of 0. These findings have important implications for the efficient triage and management of patients undergoing non-cardiac surgery.

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Contrasting Patterns of Risk Factors, Treatments and Outcomes in Women and Men in Those With and Without Prior Cardiovascular Disease in High (H), Middle (M), and Low-Income Countries (LIC)

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Introduction: Differences in cardiovascular treatments between women and men have been described but these reports have been mainly from HIC. Given that >80% of global CVD occurs in LMIC, we investigated whether such differences were also seen globally and whether they affected outcomes. We studied differences in cardiovascular disease (CVD) risk factors, treatments, incidence, and mortality between women and men in 202,072 individuals from the community from 27 countries and 5 continents. Methods: We compared CVD risk factors, medications, cardiac investigations, interventions and incident CVD and deaths (over 9.5 years) between women and men. Results: Women had a lower CVD risk factors (Framingham risk score) compared to men; this was consistent across all continents. Primary prevention strategies were more frequent in women than men and CVD incidence and mortality were lower in women. These differences between women and men were more marked in LMIC than HIC. By contrast, secondary prevention treatments, cardiac investigations, and coronary revascularization were less frequent in women than in men in all groups of countries. Yet, women had lower risks of recurrent CVD events and mortality after a CVD event. Conclusions: Among those without known CVD, risk factors were lower, primary prevention strategies were more common in women, and CVD incidence and mortality was lower in women than in men worldwide. However, in those with existing CVD, secondary prevention drugs, investigations and interventions were less frequent in women than men (in all groups of countries) but women still had lower mortality. These data do not suggest systematic biases that adversely affect outcomes in women compared to men. Understanding why women have better outcomes than men globally, both among those with and without CVD, may identify new strategies to improve outcomes in both sexes.

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Cross Specialty Observational Studies II

20852

SGLT2i Treatment Reduces Cardiorenal Disease Risk in T2D Patients Without Established Cardiovascular and Renal Diseases: A Large Observational Study

20951

Validation of the Preoperative Cardiovascular Risk Index in Surgical Subpopulations

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Contrasting Patterns of Risk Factors, Treatments and Outcomes in Women and Men in Those With and Without Prior Cardiovascular Disease in High (H), Middle (M), and Low-Income Countries (LIC)
Heart Rate Variability for the Detection of Myocardial Ischemia in Subjects Without Known Coronary Artery Disease: The HRV-DETECT Study

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Background: Detecting significant coronary artery disease (CAD) in the general population is complex and relies on combined assessment of traditional CAD risk factors and noninvasive testing. Exercise stress testing (EST) is commonly used for CAD assessment but is not recommended for screening due to limited sensitivity. Accordingly, additional noninvasive modalities are necessary for CAD screening. Heart rate variability (HRV) values were shown to be low in CAD patients and to predict cardiovascular mortality. Hypothesis: We hypothesized that a CAD-specific HRV algorithm can be used to improve detection of subclinical or early ischemia in subjects without known CAD.

Methods: Between 2015 and 2018 we prospectively enrolled 1043 subjects with low to intermediate pretest probability for CAD were screened for myocardial ischemia in tertiary medical centers in the US and Israel. Subjects underwent one-hour Holter testing, with immediate HRV analysis using the HeartTrends DyDx algorithm, followed by exercise stress echocardiography (eSE: N=612) or exercise myocardial perfusion imaging (eMPI: N=431). Follow-up continued through May 2019. The primary endpoint was the presence of myocardial ischemia detected by eSE or eMPI. The secondary endpoint was the first occurrence of a cardiovascular event during follow-up (comprising coronary intervention, nonfatal myocardial infarction, and cardiovascular mortality).

Results: Mean age was 59 years and 38% were women. Myocardial ischemia was detected in 66 (6.3%) study subjects. After adjustment for CAD risk factors and EST results, low HRV (median) was independently associated with a significant 2-fold increased likelihood for myocardial ischemia (OR=2.11 [95% CI 1.47–2.95]; p<0.001). Furthermore, each single unit reduction in HRV was associated with a significant 52% (p=0.01) increased likelihood for myocardial ischemia. Adding HRV to traditional CAD risk factors improved the pretest probability for myocardial ischemia (Figure). During an average follow-up of 3.5 years 115 (11%) developed a cardiovascular event. Low HRV was independently associated with a significant increase in the risk for the development of cardiovascular events (adjusted HR=1.72 [95% CI 1.32–2.29]; p=0.008). Conclusions: HRV-DETECT is the largest prospective international clinical study to evaluate the association of HRV with the risk of myocardial ischemia and cardiovascular events in individuals without known CAD. We show that short-term HRV testing can be used as a novel digital-health test.

Acute Coronary Syndromes

Late Breaking Science IV: State of the Art Interventional Management for ACS Patients

Colchicine in Percutaneous Coronary Intervention

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Background: Vascular injury and inflammation during percutaneous coronary intervention (PCI) is associated with increased risk of post-PCI adverse outcomes. Colchicine decreases neutrophil recruitment to sites of vascular injury. The...
anti-inflammatory effects of acute colchicine administration prior to PCI on subsequent myocardial injury are unknown. Methods: In this prospective, single-site, double-blind trial, subjects referred for possible PCI (n=714) were randomized to acute pre-procedural oral administration of colchicine 1.8 mg or placebo (Figure 1). The primary outcome was PCI-related myocardial injury. Secondary outcomes were major adverse cardiovascular events (MACE) defined as the composite outcome of death, non-fatal myocardial infarction (MI) and target vessel revascularization at 30 days and PCI-related MI defined by the Society for Cardiovascular Angiography and Interventions. A nested inflammatory biomarker sub-study evaluated the primary biomarker endpoint, change in interleukin (IL)-6 concentrations from pre-procedure baseline to post-PCI. Results: Among the 400 subjects who underwent PCI, PCI-related myocardial injury did not differ between the colchicine (n=206) and placebo (n=194) groups (57.3% vs. 64.2%, p=0.19) (Figure 2). Rates of MACE at 30 days (11.2% vs. 12.9%, p=0.71) and PCI-related MI (2.9% vs. 4.7%, p=0.49) also did not differ between colchicine and placebo. Among the 280 PCI subjects in the sub-study, change in IL-6 concentrations from pre-procedure baseline to one-hour post-PCI did not differ between the colchicine (n=141) and placebo (n=139) groups, but increased less 24 hours post-PCI in the colchicine versus placebo groups (76% [-6, 898] vs. 338% [27, 1264], p=0.02). High sensitivity C-reactive protein (hsCRP) concentration also increased less 24 hours after PCI in the colchicine versus placebo groups (7% [-13, 70] vs. 57% [0, 145], p=0.001). Conclusions: Acute pre-procedural administration of colchicine attenuated the increase in IL-6 and hsCRP concentrations after PCI when compared with placebo but did not lower the risk of PCI-related myocardial injury.

Table 2: Procedure characteristics

| Procedure characteristics | AB (%) | 
|---------------------------|--------|
| Primary PCI               | 83 (89.2) |
| Pharmacovasive PCI        | 2 (2.2)  |
| Rescue PCI                | 8 (9.6)  |
| Radial access - no (%)    | 46 (92.5) |
| Thrombus aspiration - no. (%) | 8 (8.6)  |
| Syntax score (Angiographic core lab) | 8.1±4.8 |
| STEMI culprit lesion specific score | 8.1±4.8 |
| Non-Culprit Lesion Specific score | 8.1±4.8 |
| Baseline (including STEMI culprit) | 16±7.0  |
| Residual (after index PCI) | 8.2±5.0  |
| Post Non-culprit lesion PCI - no. (%) | 82.86 (95.3) |
| 0                          | 46.7 (4.7) |

Culprit lesion location (core lab) - no. (%) | 82.86 (95.3) |

Left main | 0 (0.0)
Left anterior descending (LAD) | 25.86 (29.1)
Proximal LAD | 11.90 (12.1)
Mid LAD | 12.80 (14.0)
Apical LAD | 16.06 (16.2)
Diagonal | 16.06 (16.2)
 circumflex | 16.06 (16.2)
Prox LCX and OM/Ramus | 16.06 (16.2)
Total LCX and PLV | 46.46 (4.7)
RCA | 42.46 (4.8)
RCA before the Crux | 40.46 (4.5)
RCA beyond the Crux | 2.62 (3.3)

Table 3: OCT Imaging findings by lesion

Non-Culprit Lesion Plaque Morphology in Patients With ST-Segment Elevation Myocardial Infarction: Results From the COMPLETE Trial Optical Coherence Tomography (OCT) Substudy

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Background: Complete revascularization with routine percutaneous coronary intervention (PCI) of non-culprit lesions after primary PCI improves outcomes in ST-segment elevation myocardial infarction (STEMI). Whether non-culprit lesions are more commonly associated with vulnerable plaque morphology is unclear. Methods and Results: In a prospective sub-study of the COMPLETE trial, we performed optical coherence tomography (OCT) of at least 2 major epicardial coronary arteries prior to non-culprit lesion percutaneous coronary intervention in 93 patients with STEMI and multi-vessel disease. Non-culprit lesions were categorized as obstructive (≥70% stenosis by visual angiographic assessment) or non-obstructive and as thin cap fibroatheroma (TCFA) or non-TCFA. Overall, 47% of patients had at least 1 non-culprit lesion TCFA. Among 158 obstructive lesions, 39% were TCFAs and 61% were non-TCFAs. The minimal lumen area of obstructive TCFAs and non-TCFAs did not differ (1.9 vs. 1.7, p=0.52). However, compared with obstructive non-TCFAs, obstructive TCFAs contained a greater amount of lipid (78.4% vs. 36.5%, p<0.001), mastophages (94.8% vs. 52.2%, p<0.001) and cholesterol crystals (82.8% vs. 45.7%, p<0.001). Among 275 non-obstructive lesions, 27% were TCFAs and 73% were non-TCFAs. Conclusion: Almost one-half of patients with STEMI and multi-vessel disease harbor obstructive non-culprit lesions containing complex vulnerable plaque morphology. This may explain the benefit of routine PCI of obstructive non-culprit lesions in patients with STEMI and multi-vessel disease.
**Background:** Out-of-hospital cardiac arrest (OHCA) is a leading cause of death in Europe and the United States. Despite advances in the field of resuscitation and intensive care management, the outcome of these patients remains poor. The most frequent cause of cardiac arrest is ischemic heart disease. In patients with myocardial infarction as cause of the arrest, immediate coronary angiography (CAG) and subsequent percutaneous coronary intervention (PCI) potentially improves outcome. The COronary Angiography after Cardiac arrest Rest (COACT) trial was the first randomized controlled study to report the effect of an immediate CAG and PCI if necessary in patients successfully resuscitated after cardiac arrest in the absence of ST segment elevation, compared to a delayed invasive strategy and found no difference on 90 day survival. The effect of an immediate versus delayed invasive strategy on long-term outcome in this patient group is currently lacking. We now present the 1 year clinical outcome of the COACT trial.

**Methods:** The COACT trial was an investigator initiated, randomized, open-label multicenter trial. In this trial 552 OHCA patients without ST segment elevation on the electrocardiogram (ECG) were randomized in a 1:1 ratio to an immediate or a delayed invasive strategy. The aim of our current study was to determine the effect of an immediate versus delayed invasive approach on survival and the occurrence of major cardiac events (MACE) at 1 year. MACE was defined as death, myocardial infarction, coronary bypass grafting and percutaneous coronary intervention. We also reported hospitalization for heart failure.

**Results:** Final results will be presented at the time of the AHA 2019 meeting.

**Conclusion:** The COACT trial is the first randomized study evaluating the effect of an immediate versus a delayed invasive strategy on survival and MACE at 1 year in cardiac arrest patients without ST segment elevation.

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**One Year Outcomes of Coronary Angiography After Cardiac Arrest**

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**Introduction:** Cardiogenic shock (CS) complicates 4-12% of acute myocardial infarctions (AMI) and is associated with substantial morbidity and mortality. Impella® devices provide greater mechanical circulatory support (MCS) than intra-aortic balloon pumps (IABP), but there are limited data on Impella’s real-world safety and effectiveness among AMI-CS patients. We used data from the National Cardiovascular Data Registry (NCDR) to characterize MCS utilization and outcomes among patients with AMI-CS receiving either Impella or IABP. **Methods:** We linked NCDR’s CathPCI and Chest Pain-MI Registries or IABP. utilizations and outcomes among patients with AMI-CS receiving either Impella or IABP.

**Results:** Of the 1,911 patients included in our analysis, 17% received Impella® and 3% received IABP. The median age was 65.0 (IQR 12.6) years, 33.0% were female, 81.3% had an ST-elevation MI, and 43.3% had a concomitant decrease in IABP utilization (32.1% to 27.3%; p<0.001 for both). Among 1,680 propensity-matched AMI-CS patients treated with IABP or Impella, standardized differences for all covariates were <0.10, indicating a robust match. In-hospital death and major bleeding rates were

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Acute Coronary Syndromes

**Acute Myocardial Infarction**

**Effects of Intracoronary Recombinant Human Plasminogen Activator on Coronary Flow and Outcome Among Acute Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Intervention**

| Authors | Background | Methods | Results | Conclusions |
|---------|------------|---------|---------|-------------|
| Dong Huang1, Juying Qian1, Zongjun Liu2, Yawei Xu3, Zengyong Qiao4, Junbo Ge5, 1Cardiology, Zhongshan Hosp, Shanghai, China, 2Cardiology, No. 10 Hosp, Shanghai, China, 3Cardiology, Fengxian District Central Hosp, Shanghai, China, 4Cardiology, Zhongshan hosp, Shanghai, China | BACKGROUND: No randomized trial has been conducted to compare intracoronary thrombolysis therapy versus high-dose bolus intracoronary administration of tirofiban for preventing no-reflow during primary percutaneous coronary intervention (PPCI) for ST-segment elevation acute myocardial infarction. Recombinant human plasminogen activator (rh-PA) is a fibrin-specific plasminogen activator that has structural similarities to t-PA and can be converted into active urokinase and produce thrombolytic effects. METHODS: In this multicenter, randomized trial, we compared intracoronary infusion of rh-PA (20mg, Tasis, China), tirofiban (10ug/kg, Grand Pharma China) or saline (20ml) through selective microcatheter after manual thrombus-aspiration during PPCI in 345 patients with ST-segment elevation admitted to the 11 hospitals in China. The primary end point was coronary flow and myocardial perfusion immediately after PPCI. RESULTS: Compared with that of the saline group, there was a significant improvement of corrected thrombolysis in myocardial infarction frame count (CTFC) after PPCI in the rh-PA group and tirofiban groups (33.0 frames vs 26.5 and 28.8 frames, P<0.001). Compared with the saline group, the rh-PA and tirofiban groups had more complete ST-segment resolution at 2 hours (47.8% vs 69.5% and 66.7%, P=0.012) and lower peak CKMB level (442.5U/L vs 437.2U/L and 527.7U/L, P<0.001). The incidence of MACCEs defined as the composite of cardiac death, myocardial infarction, stroke, and target vessel revascularization at 30 days after PCI was similar among the 3 groups (rh-PA, 2.6% vs 1.7%, P=0.121), but rh-PA and tirofiban were associated with a higher rate of major and minor bleeding (17.1% and 8.6% vs 5.1%, P=0.009), including more instances of minor bleeding. CONCLUSIONS: Intracoronary thrombolysis therapy with rh-PA after thrombus-aspiration is not inferior to tirofiban for PPCI, without an increase in the rate of overall major bleeding. | | | **20874**

**Acute Coronary Syndromes**

**Early Coronary Angiography versus No Early Coronary Angiography for Post-Cardiac Arrest Patients Without ST-Segment Elevation: The PEARL Study**

| Authors | Background | Methods | Results | Conclusions |
|---------|------------|---------|---------|-------------|
| Karl B Kern1, Peter Radice2, David B Seder3, Jacob C Jentzer4, Kwan Lee1, Dion Stub1, Chiu-Hsien Hsu5, Marko Noc2, 1Sarver Heart Ctr, Univ of Arizona, Tucson, AZ, 2Internal Medicine, Univ Med Ctr Ljubljana, Ljubljana, Slovenia, 3NeuroIntensive Care, Maine Med Ctr, Portland, ME, 4Mayo Clinic, Rochester, MN, 5Medicine, Alfred Hosp, Melbourne, Australia, 1College of Public Health, Univ of Arizona, Tucson, AZ, 3Dept of Internal Medicine, Univ Med Ctr Ljubljana, Ljubljana, Slovenia | BACKGROUND: The benefit of emergent coronary angiography for patients without ST-segment elevation post resuscitation from out-of-hospital cardiac arrest is controversial. The aim of this pilot randomized trial was to evaluate the efficacy and safety of early coronary angiography in the absence of ST-segment elevation post arrest, while prospectively determining the incidence of acute coronary occlusion in this population. METHODS: Adults (>18 years) resuscitated from out-of-hospital cardiac arrest were randomized in a 1:1 fashion under Exception to Informed Consent (EFIC) regulations to early coronary angiography (< 120 minutes from arrival at the PCI capable facility) vs no early coronary angiography. The primary endpoint was a composite endpoint of emergent coronary angiography (< 120 minutes from arrival at the PCI capable facility) vs no early coronary angiography. Secondary endpoints included incidence of culprit vessels with acute occlusion, adverse events, survival, and neurological function at follow-up. RESULTS: Ninety-nine resuscitated patients were enrolled (75 shockable and 24 non-shockable rhythms), with 49 patients randomized to early coronary angiography. The efficacy composite endpoint was 55% for early cath vs 50% for no early cath, p=0.69. The safety composite endpoint was 27% vs 26%; p=1.0. The efficacy composite endpoint was 55% for early cath vs 50% for no early cath, p=0.69. The safety composite endpoint was 27% vs 26%; p=1.0. Early coronary angiography revealed a culprit vessel in 41%, with that culprit acutely occluded in 63%. Hence, 26% of those undergoing early coronary angiography had an acutely occluded culprit coronary found without manifesting electrocardiographic ST-segment elevation. CONCLUSIONS: This pilot study did not show a significant difference in outcome, but early coronary angiography demonstrated an acutely occluded culprit coronary in one out of every four resuscitated patients without ST segment elevation after out-of-hospital cardiac arrest. | | | **20950**

**Acute Coronary Syndromes**

**ACS & CAD: From Out of Hospital Arrest to Chronic Management**

| Authors | Background | Methods | Results | Conclusions |
|---------|------------|---------|---------|-------------|
| | | | | |
Dobutamine Stress Echocardiography Ischaemia as a Predictor of the Placebo-Controlled Efficacy of Percutaneous Coronary Intervention in Stable Coronary Artery Disease: The Stress Echo-Stratified Analysis of ORBITA

Rasha K Al-lamee1, Matthew Shun-Shin1, James Howard2, Alexandra Nowbar2, Christopher Rajkumar1, David Thompson1, Sayan Sen3, Sukh Nijjer2, Ricardo King, The Placebo-Controlled Efficacy of Percutaneous Coronary Intervention in Stable Coronary Artery Disease: The Stress Echo-Stratified Analysis of ORBITA

Background: Dobutamine stress echocardiography (DSE) is widely used to test for ischemia in patients with stable coronary artery disease (CAD). In this analysis we study the ability of pre-randomisation stress echocardiography to predict placebo-controlled efficacy of percutaneous coronary intervention (PCI) within the ORBITA trial. Methods: One hundred and eighty-three patients underwent DSE before randomization. Each DSE was reported twice by 6 reporters blinded to treatment allocation, time-point of the test, other reporters’ opinion and their own first opinion. The stress echocardiogram is broadly the number of segments abnormal at peak stress, with akinetic segments counting double and dyskinetic triple. The ability of pre-randomization stress echocardiography to predict the placebo-controlled effect of PCI on response variables was tested using regression modelling. Results: At pre-randomization, the stress echo score was 1.58a±1.77 in the PCI arm (n=88) and 1.61±1.73 in the placebo arm (n=85). There was a detectable interaction between pre-randomization stress echo score and the effect of PCI on angina frequency score with a larger placebo-controlled effect in patients with the highest stress echo score (p=0.031). With our sample size we were unable to detect an interaction between stress echo score and any other patient-reported response variables: freedom from angina (p=0.026), physical limitation (p=0.461), quality of life (p=0.689), EQ-5D-5L quality of life score (p=0.157), EQ-5D-3L quality of life score (p=0.157). Conclusions: The degree of ischaemia assessed by DSE predicts the placebo-controlled efficacy of PCI on patient-reported angina frequency. When the downstream effect of the stenosis is detectable as an increase in regional wall motion on stress echo, there is a detectable reduction in patient symptoms with PCI.

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One-year Outcomes of Angina Management Guided by Invasive Coronary Function Testing (CORMICA)

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Background: The COMPASS trial demonstrated that dual pathway inhibition (DPI) with rivaroxaban 2.5mg twice-daily plus aspirin (ASA) 100mg once-daily vs ASA 100 mg once-daily reduced cardiovascular death, stroke, or myocardial infarction, as well as mortality in patients with chronic coronary artery disease or peripheral artery disease. Methods: We examined the efficacy and safety of DPI vs ASA according to history of percutaneous coronary intervention (PCI). Results: Of 27,395 patients enrolled, 16,560 coronary disease patients were randomized to DPI or ASA, and of these 9,862 (59.6%) had prior PCI (mean age 68.2±7.8, female 19.4%, diabetes 35.7%, prior myocardial infarction [MI] 74.8%, multivessel PCI 38.0%). Average time from PCI to randomization was 5.4 yrs (SD 4.4). Regardless of prior PCI, DPI vs ASA produced consistent reductions in MACE [PCI 4.0% vs. 5.2%, hazard ratio [HR] 0.74, 95% CI: 0.61-0.94; p-interaction 0.882] and mortality [PCI 2.5% vs. 3.5%, HR 0.73, 95% CI: 0.58-0.92; no PCI: 4.1% vs. 5.0%, HR 0.80, 95% CI 0.64-1.00, p-interaction 0.590] and increase in major bleeding [PCI: 3.3% vs 2.0%, HR 1.72, 95% CI 1.34-2.12; no PCI: 2.9% vs 1.8%, HR 1.58, 95% CI 1.15-2.17, p-interaction 0.680]. Among those with prior PCI (Table, DPI vs ASA produced consistent reduction in MACE irrespective of time since prior PCI, or prior MI, with no difference in stent thrombosis (0.6% in both groups). Conclusions: DPI compared with ASA produced consistent reductions in MACE and of certain adverse cardiovascular events (MACE: all-cause mortality, myocardial infarction, unstable angina hospitalization/ revascularization, heart failure hospitalization, cerebrovascular event) adjudicated by a blinded clinical endpoint committee. Results: 391 patients were enrolled between 1/1/2016-12/2017. Coronary angiography revealed obstructive disease in 206 (53%). 153 (39%) patients without obstructive CAD were randomized (n=75 intervention group; n=76 blinded-control group). Overall angiography (SAQ summary score) improved in the intervention group by 27% at one year (difference 13.6 units; 95% CI 7.3 to 19.9, P<0.001). Quality of life (EQ5D index) improved in the intervention group relative to the control group (mean difference 0.11 units [18%]; 0.03 to 0.19; p=0.010). Systolic and diastolic blood pressure (BP) were lower in the intervention group at one year (systolic BP -11.9mmHg [-19.3 to -4.5], p=0.002; diastolic BP -8.5mmHg [-11.1, -5.9]; p=0.010). An objective score at cardiac rehabilitation was higher in the intervention group (40% v 16%; RR 2.53, 95% CI 1.41 to 4.56, p=0.001). There were no significant differences in weight change (mean difference -1.26kg, 95% CI -4.23 to 1.71, p=0.403), or physical activity levels (median MET minutes in intervention group 1386 v 1188, p=0.072). After a median follow-up of 19 (IQR 16, 22) months, 9 (12%) subjects in the intervention group and 8 (11%) in the control group experienced a MACE (p=0.803). Conclusion: Stratified medicine in NOCA leads to marked and sustained improvements in angina and quality of life at one year. Mechanisms involved improvements in risk factors and adherence with cardiac rehabilitation. Novel, disease-modifying therapy is needed to improve prognosis.
time since last PCI or history of MI. Our findings should be considered when contemplating an antithrombotic strategy in patients with prior PCI.

Table: CV death, stroke or MI in patients with prior PCI

| PFI | ASA | HR | P Value |
|-----|-----|----|---------|
| Time since PCI | (N=9463) | (N=8489) | (95% CI) | (Int) |
| ≤1 year | 3.2% | 6.5% | 0.49(0.21-1.15) | 0.65 |
| 1-2 years | 3.1% | 4.8% | 0.64(0.40-1.02) | 0.05 |
| >2 years | 4.4% | 5.6% | 0.76(0.40-1.02) | 0.05 |
| No | 3.5% | 5.5% | 0.68(0.47-0.99) | 0.64 |

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Ticagrelor Monotherapy versus Standard Dual Antiplatelet Therapy After Drug-Eluting Coronary Stent Implantation: A Systematic Review and Individual Patient Data Meta-Analysis From the Single versus Dual Antiplatelet Therapy (SIDNEY) Collaboration

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Dual antiplatelet therapy (DAPT), including aspirin and an oral P2Y12 inhibitor, is recommended after percutaneous coronary intervention (PCI) to mitigate the risks of stent-related and unrelated ischemic events. However, prolonged DAPT carries a heightened risk of major bleeding affecting mortality, morbidity and costs. P2Y12 inhibitor monotherapy might limit bleeding risk while retaining the ischemic benefits associated with prolonged DAPT. Caution has been raised towards the use of clopidogrel monotherapy after PCI due to evidence of poor or even non-responsiveness to this treatment in a sizable proportion of patients. Ticagrelor exerts consistent inhibition of ADP-related platelet activation and has been shown to provide greater ischemic protection, but higher bleeding risk, as compared to clopidogrel on a background treatment with aspirin. Ticagrelor monotherapy may provide lower bleeding but similar or even improved ischemic risks as compared to standard DAPT in patients who underwent PCI for unstable or stable coronary artery disease. We searched for randomized clinical trials of patients undergoing percutaneous coronary revascularization with new-generation drug-eluting stents receiving ticagrelor monotherapy or standard DAPT duration. A search performed on June 5th 2019 identified two randomized trials fitting eligibility criteria (GLASSY and TWILIGHT trials) and both study leadership agreed to provide individual patient data (IPD) for the purpose of the pooled analysis. The protocol of the SIDNEY (Single versus Dual Antiplatelet Therapy for secondary prevention) collaborative study was finalized before the TWILIGHT database lock on July 9th, 2019, and was registered in PROSPERO. The primary outcomes are the composite of BARC 3 or 5, to be tested for superiority, and if met, the non-inferiority analysis in the per-protocol population. The case report forms of both studies were checked for common variables and when needed data recoded for consistency. Outcomes definitions appeared largely consistent between studies for the majority of bleeding and ischemic endpoints. Cross-adjudication of a random sample of 100 events in each study will provide information on consistency in clinical data review and application of standardized definitions by the two independent clinical event committees. The full results of the study will become available in late September and will be disclosed at the time of oral presentation.

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Stent Thrombosis After Percutaneous Coronary Intervention Among Patients With Atrial Fibrillation Treated With Apixaban or Aspirin: Insights From the AUGUSTUS Trial

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Background: In the AUGUSTUS trial, patients with atrial fibrillation (AF) and a recent acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) had less bleeding with apixaban than with vitamin K antagonist (VKA) and placebo compared with aspirin. The current analysis evaluates rates and timing of stent thrombosis, overall and by randomized treatment. Methods: In a 2 x 2 factorial design, 4614 patients with AF and recent ACS or PCI on a P2Y12 inhibitor were randomized to open-label apixaban or VKA and blinded aspirin or placebo for 6 months. Most patients received aspirin prior to randomization, which occurred a median of 6 days after ACS or PCI. Stent thrombosis was classified as definite, definite or probable, or any stent thrombosis (definite/probable). Patients who were medically managed for their qualifying events (n=1097) were excluded from this analysis. Results: At 6-months, definite, definite or probable, and any stent thrombosis occurred in 20 (0.57%), 30 (0.86%), and 57 (1.63%) patients. In most of the patients (n=24 [80%]) the definite or probable stent thrombosis occurred within 30 days of PCI, with the highest incidence in the first 2 weeks. The proportion of patients with definite or probable stent thrombosis was 0.74% with apixaban and 0.97% with VKA and was 0.63% with aspirin and 1.08% with placebo. Definite or probable stent thrombosis occurred in 0.57% of patients treated with apixaban plus aspirin, in 0.91% with apixaban without aspirin, in 0.69% with VKA plus aspirin, and in 1.26% with VKA without aspirin (Figure). Conclusion: Among patients with AF and recent PCI, including current generation of drug-eluting stents, definite or probable stent thrombosis is rare and the vast majority of events occur early after PCI. These data support the use of apixaban and a P2Y12 inhibitor without aspirin during the first 6 months for the majority of patients, considering the almost 2-fold increase in bleeding with aspirin use. In patients with a high risk of stent thrombosis and an acceptable risk of bleeding, using aspirin up to 30 days after PCI should be considered. Further studies to identify patients who might benefit the most from this strategy are warranted.

Cardiometabolic Health and Diabetes

Late Breaking Science VI: New Frontiers in Lipid Therapy

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Effect of Icosapent Ethyl on Progression of Coronary Atherosclerosis in Patients With Elevated Triglycerides (200-499mg/dl) on Statin Therapy (EVAPORATE Study)

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LBS ABSTRACTS

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**Background:** Though statin therapy has reduced cardiovascular events and the slowing of coronary atherosclerosis progression, significant cardiovascular (CV) risk remains. Icosapent ethyl (IPE) added to a statin has been shown to reduce initial CV events by 25% and total CV events by 30% in the REDUCE-IT clinical trial. The slowing of coronary atherosclerosis progression, significant cardiovascular (CV) risk remains. Icosapent ethyl (IPE) added to a statin has been shown to reduce initial CV events by 25% and total CV events by 30% in the REDUCE-IT clinical trial. To be included, patients had to have coronary atherosclerosis as documented by MDCT (1 or more angiographic stenoses with ≥20% narrowing) or diabetes, on stable statin therapy with low-density lipoprotein cholesterol levels 40 to 115 mg/dl, and persistently high triglyceride levels (135-499 mg/dl). Patients underwent an interim scan at 9 months and are currently being followed for an additional 9 months with MDCT at 0, 9 and 18 months. We present the protocol-specified interim efficacy and safety analyses.

**Results:** A total of 80 patients were enrolled, with 67 completing the 9-month visit and having interpretable MDCT at baseline and at 9-months (age=57±6 years, male=36). At the 9-month interim analysis, there was no significant change in low attenuation plaque between active and placebo groups (74% vs 94%, p=0.469). However, there was a significantly lower non-calcified plaque (sum of L, A, P, calci-fatty, and fibrous plaque) (-1% v. 9%, p=0.001), total plaque (non-calcified + calcified plaque) (p=0.0004), fibrous plaque (15 v. 26%, p=0.011) and calcified plaque (-1% v. 9%, p=0.001) after adjustment by baseline plaque, age, sex, diabetes status, baseline triglyceride levels, and randomization status. EVAPORATE is the first study using MDCT to evaluate the effects of IPE as an adjunct to statin therapy on plaque characteristics in a high-risk CV risk population with persistently high TG levels. EVAPORATE provides important mechanistic data with relevance to the reduction in CV events seen in the REDUCE-IT clinical trial.

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**Safety and Efficacy of Inclisiran in Patients With Heterozygous Familial Hypercholesterolemia - Results From the Phase 3 ORION-9 Trial**

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**Background:** Familial hypercholesterolemia (FH), a genetic disorder that affects approximately 1 in 250 persons worldwide, is characterized by elevated low-density lipoprotein cholesterol (LDL-C) levels throughout life and premature atherosclerotic cardiovascular disease (ASCVD). Pharmacological management of FH includes high intensity statins with or without ezetimibe, and more recently monoclonal antibodies directed against circulating proprotein convertase subtilisin/kexin type 9 (PCSK9), which reduce LDL-C by >50% but require 26 injections per year. The ORION-1 Phase 2 dose finding trial showed that inclisiran, a small interfering RNA (siRNA) targeting hepatic PCSK9 synthesis, has the potential to produce reductions in LDL-C of >50% safely, with an infrequent dosing regimen. ORION-9 is the first dedicated global trial to evaluate this approach in heterozygous FH (HeFH). **Methods:** ORION-9 is a Phase 3, placebo-controlled, double-blind, randomized study in subjects with HeFH based on genetic confirmation or established phenotypic criteria conducted in 8 countries across 46 sites. In addition, subjects had to have LDL-C >100 mg/dl despite receiving maximally tolerated statin therapy with or without other lipid-lowering therapy (excluding PCSK9 inhibitors). Subjects were randomized 1:1 to inclisiran sodium 300 mg or matching placebo administered at Day 1, Day 90, Day 270 and Day 450. After randomization, patients underwent 14 days of washout to biochemistry measurements, 14 days to assess stability and tolerability of inclisiran. The co-primary endpoints were the percent change from baseline in LDL-C at Day 510 and the time-adjusted average percentage change from baseline in LDL-C between Day 90 up to Day 540. Key secondary endpoints included the mean absolute change at Day 510, the time averaged absolute reduction from baseline between Day 90 up to Day 540, and changes in other lipids and lipoproteins. Other pre-specified endpoints included the proportion of subjects who attained lipid targets for the on-treatment period and time to dosing. Subjects were randomized 1:1 to inclisiran sodium 300 mg or matching placebo administered at Day 1, Day 90, Day 270 and Day 450. After randomization, patients underwent 14 days of washout to biochemistry measurements, 14 days to assess stability and tolerability of inclisiran. The co-primary endpoints were the percent change from baseline in LDL-C at Day 510 and the time-adjusted average percentage change from baseline in LDL-C between Day 90 up to Day 540. Key secondary endpoints included the mean absolute change at Day 510, the time averaged absolute reduction from baseline between Day 90 up to Day 540, and changes in other lipids and lipoproteins. Other pre-specified endpoints included the proportion of subjects who attained lipid targets for the on-treatment period and time to dosing. According to the ORION-9 Phase 3 trial, inclisiran showed a significant reduction in LDL-C of up to 69% (p<0.001) and 68% (p<0.001), respectively. The figure shows LDL-C, TGs and HDL-C.

**Conclusions:** ARO-APOC3 is a RNAi-based therapy using Arrowhead Pharmaceuticals’ TRIM™ platform to durably reduce apoC3 expression by hepatocytes. Methods: This phase 1 study [ARO/APOC31001, NCT03783377] uses a single-dose escalation design in healthy volunteers (HV) with TGs >80 mg/dl at baseline. HVs were given 10, 25, 50 or 100 mg (cohorts of 10: 6 active, 4 placebo) as a single subcutaneous (SC) dose. All participants are followed for ≥ 4 months post dose, evaluating safety, pharmacokinetics, and changes in circulating APOC3, VLDL-C, LDL-
C, TGs and HDL-C. Results: 24 HVs received ARO-APOC3 and 16 placebo. Single doses of ARO-APOC3 as low as 25 mg reduced mean maximal APOC3 by >80% (p<0.001) from baseline with APOC3 trials, and mean absolute change in LDL-C of up to 69% (p<0.001) was observed. These results indicate dose frequency will likely be every 3 months or longer. Mean changes in placebo HVs were modest. As of August 12, 2019, there were no discontinuations and no serious adverse events (SAEs). Most AEs were reported as mild. Conclusions: ARO-APOC3, given as a single SC dose, stably reduced APOC3, TGs and VLDL-C levels for at least 12 weeks, with favorable safety. Increases in HDL-C were seen. Multi-dose patient cohorts are currently enrolling.
Benefits of a Target LDL Cholesterol Less Than 70 mg/dl After an Ischemic Stroke of Atherosclerotic Origin, the Treat Stroke to Target Trial Results

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INTRODUCTION: The PROVE-IT (PROspective Study of Pravastatin in patients with Recent ISchemic Stroke) Trial with pravastatin in ischemic stroke patients with elevated serum low-density lipoprotein cholesterol achieved a 24% relative reduction in major cardiovascular events. Intensive lipid lowering therapy (LTT) with statins is recommended in patients after ischemic stroke, and several studies have shown that lowering low-density lipoprotein cholesterol (LDL-C) to less than 70 mg/dL reduces cardiovascular events. The ATLAS Study demonstrated that lowering LDL-C to less than 70 mg/dL significantly reduced the risk of recurrent ischemic stroke. These studies suggest that LDL-C values in the very low range may achieve greater benefit in reducing cardiovascular events. However, it remains uncertain whether LDL-C should first descend below 70 mg/dL before achieving a target LDL-C value of less than 40 mg/dL.

METHODS: A post hoc analysis of the PRESTO (PROspective Randomized Study of Pravastatin in Ischemic Stroke with Targeted Lipid Levels) study was conducted to evaluate the time to achieve an LDL-C level of less than 70 mg/dL from baseline and the duration of LDL-C level below 70 mg/dL in the group assigned to the target LDL-C of less than 40 mg/dL (target group) compared to the group assigned to the target LDL-C of less than 70 mg/dL (control group).

RESULTS: Of the 3472 patients enrolled in the PRESOTI study, 1735 patients were assigned to the target LDL-C of less than 40 mg/dL (target group), and 1737 patients were assigned to the target LDL-C of less than 70 mg/dL (control group). No significant differences were observed between the target group and control group with respect to baseline characteristics such as age, gender, race, and history of cardiovascular disease. The mean baseline LDL-C level was 110 mg/dL in the target group and 111 mg/dL in the control group. The time to achieve an LDL-C level of less than 70 mg/dL from baseline was shorter in the target group (8.4 weeks) than in the control group (12.3 weeks). The median duration of LDL-C level below 70 mg/dL was 2.1 years in the target group and 1.5 years in the control group.

CONCLUSION: This post hoc analysis of the PRESTO study supports the use of a target LDL-C level of less than 40 mg/dL for patients with recent ischemic stroke and high-risk features, even after the achievement of an LDL-C level of less than 70 mg/dL. Further research is needed to determine the optimal duration of LDL-C level below 70 mg/dL and to assess the long-term clinical outcomes with intense lipid lowering therapy in this patient population.

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Benefits of a Target LDL Cholesterol Less Than 70 mg/dl After an Ischemic Stroke of Atherosclerotic Origin, the Treat Stroke to Target Trial Results

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Electrophysiology and Arrhythmias

Late Breaking Trials in EP and LV Function

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Apple Watch App Identifies Clinically Important Arrhythmias Other Than Atrial Fibrillation: Results From the Apple Heart Study

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INTRODUCTION: The Apple Watch Series 3 app that notifies participants of an irregular pulse. Those notified wore an Apple Watch Heart Rate app that notified participants of an irregular pulse notification, and 450 completed ECG patches which were adjudicated by clinicians for AF, heart block, supraventricular tachycardia and ventricular tachycardia. Results: Of 419,297 participants enrolled, 2,161 received an irregular pulse notification, and 450 completed ECG patches which were applied a mean of 13 days after notification and worn on average 6 days. ECG patch participants were 23% female, 4.4% Hispanic, 3.6% African American and 40% above the age of 65. Twenty percent of the participants were contacted for findings of AF with rates >200bpm (18), pause > 6 seconds (1) and nonsustained ventricular tachycardia (NSVT) > 6 seconds (1). There were 153 (34%) participants with over 30 seconds of AF. Of the 297 participants without AF, 74 (25%) had a premature atrial contraction (PAC) burden between 1-15%, and 4 (1.3%) had a PAC burden > 15%. Three had episodes of high-grade AV block associated with transient sinus slowing lasting less than 4 seconds. Two had > 15% premature ventricular contractions, and 11 (3.7%) had an episode of NSVT > 8 beats. None had Mobitz II or complete heart block. Additional details on rhythms concurrent with irregular pulse notifications will be presented. Conclusion: ECG patch monitoring after an irregular pulse notification identified several arrhythmias other than AF that may require further medical attention. Clinical assessment, management, and outcomes following detection of these arrhythmias are important for future research.

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Apple Watch App Identifies Clinically Important Arrhythmias Other Than Atrial Fibrillation: Results From the Apple Heart Study

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Apixaban versus Warfarin for Stroke Prevention in Patients With End Stage Renal Disease on Hemodialysis and Atrial Fibrillation: Results of a Randomized Clinical Trial Assessing Safety

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Prevalence of atrial fibrillation (AF) is substantially higher in patients with end-stage renal disease (ESRD) on hemodialysis than in the general population, as are the rates of stroke and major bleeding. There are no published randomized trial data of anticoagulation to reduce stroke risk in patients on hemodialysis with AF. Warfarin reduces risk of stroke by two-thirds among patients with AF in the general population. However, the safety and efficacy of warfarin has never been prospectively studied in patients on hemodialysis. All currently marketed non-vitamin K oral anticoagulants (NOACs) have some component of renal clearance, and there are no high-quality randomized data studying the relative safety and efficacy of NOACs in ESRD. Based on pharmacokinetics and pharmacodynamics, as well as observational data, apixaban may be safe and effective in the ESRD population.

The RENAL-AF (RENeal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation) Trial is a prospective, randomized, open-label, blinded endpoint evaluation (PROBE) study of apixaban versus warfarin for reduction of the composite of major bleeding or clinically relevant non-major bleeding in patients with AF; a CHADS2-VASc ≥ 2, and ESRD on hemodialysis. All patients randomized to apixaban will have a day 1 sample for PK, and a subset of 50 patients randomized to apixaban will have additional PKPD samples collected at day 3 and month 1. Between January 4, 2017 and January 4, 2019, 154 patients were randomized at 42 clinical sites in the United States. Patients were randomly assigned in a 1:1 ratio to receive apixaban 5 mg twice daily (or 2.5 mg twice daily for patients with age ≥ 80 years and/or weight ≤ 60 kg) or dose-adjusted warfarin. Warfarin was monitored and managed at the discretion of the patients’ clinical providers. The mean age of the trial population was 68 years and 26% were ≥ 75 years, while 36% were female and 44% were black. Patients had been on dialysis for a mean of 4.4 years at enrollment, and the trial was curtailed prematurely due to slow enrollment in this complicated patient population and limited resources. Furthermore, such early DOAC use did not increase the incidence of intracranial hemorrhage. Compared with warfarin there was a 40% reduction in the composite of stroke, major bleeding, death, or recurrent stroke. In each arm, brain MRI identified five asymptomatic cerebral microbleeds. Conclusion: Early use of apixaban after ischemic stroke from atrial fibrillation may result in improved outcomes versus warfarin initiated at two weeks. The results of this study support the recent AHA/ASA/ACC guideline document that favors early DOAC use and benefit of anticoagulation following ischemic stroke from atrial fibrillation.

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Carvedilol Does Not Improve Exercise Performance in Fontan Patients: Results of a Cross Over Trial

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Background: Increased circulating catecholamines are associated with worse exercise performance in adult heart failure patients. Single ventricle patients with Fontan physiology have increased circulating catecholamines due to abnormal atrial dilatation and ventricularization which could benefit from beta blockade. We hypothesized that carvedilol would improve exercise performance in Fontan patients. Methods: A double-blind, placebo-controlled, cross over trial of carvedilol was performed. Single ventricle patients with a previous Fontan operation between the ages of 10 to 35 years at screening who were able to complete a maximal exercise test (RER >1.0) were included. Exclusion criteria included: exposure to beta-blocker therapy within 2 months of screening, listing for heart transplantation, uncontrolled protein-losing enteropathy or protein breakdown, serum NT-proBNP >300 pg/ml, or contraindication to receiving carvedilol. Two 12-week treatment arms were separated by a 6-week washout period. Exercise testing was performed at beginning and end of each treatment arm. Study drug was increased to a goal maximum dose (0.2-0.3 mg/kg/dose BID). Primary endpoint was improvement in peak oxygen consumption (kgivO2) from baseline. Results: Of the 26 subjects enrolled, 23 completed the study. 4 subjects did not reach goal maximum carvedilol dose, vs. 1 for placebo (p=0.14). [LM1] The mean change in ivO2 between treatments was not different (carvedilol = -2.1 ml/kg/min v. placebo = -1.42, p=0.28). The peak heart rate (p=0.01) decreased in subjects taking carvedilol leading to an increase in peak oxygen pulse (p<0.01). There was no difference in VE/VCO2 slope, oxygen uptake efficiency or maximal work performed. Serum NT-proBNP increased with carvedilol (mean change of +3.77 pg/ml) compared to placebo (mean change of -5.37 pg/ml, p=0.03). There were no serious adverse events related to study drug. Conclusion: The majority of subjects with Fontan physiology were able to safely tolerate carvedilol. However, carvedilol was not associated with improved exercise performance and was associated with mild increased in NT-proBNP. This should not be used routinely in healthy Fontan patients and its role in Fontan patients with heart failure requires further study.

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Randomized Controlled Trial of Testosterone Treatment on Left Ventricular Mass in Older Men With Low Testosterone

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Background: Left ventricular hypertrophy is an independent predictor of myocardial infarction, heart failure, and sudden cardiac death. Based on animal and observational studies, testosterone has been hypothesized to act as a hypertrophic stimulus on cardiac muscle. There have been no randomized controlled trials measuring the effect of testosterone treatment on left ventricular mass in older men. Methods: The Testosterone Trials (TTrials) are a set of seven, randomized, double-blind, placebo-controlled trials of testosterone gel in older men with low testosterone. The Cardiovascular Trial is a substudy of TTrials in which participants underwent coronary CT angiography at baseline and after one year of treatment to determine the effect of testosterone treatment on coronary artery plaque. The current analysis considers the effect of testosterone on cardiac function in older men.

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chamber size. The primary end-point of this analysis is change in body surface area (BSA)-indexed left ventricular mass (LVM) by randomization status. Secondary endpoints were changes in cardiac chamber volumes indexed by BSA. Results: Baseline characteristics are shown in Table 1. Testosterone treatment significantly increased serum testosterone levels into the mid-normal range for young men (Figure 1); levels in the placebo arm did not change. At month 12, testosterone treatment was associated with a significantly increased LVM compared to placebo treatment; p=0.033. The average magnitude of change was 3.09 ml/m² (95% CI 0.36, 5.92). The differences in change in all other chamber measurements were not significant between groups (Table 2). Conclusion: Testosterone is widely used to treat male hypogonadism, but its effects on the heart have not been fully delineated. In this study, testosterone treatment was associated with a significant increase in left ventricular mass. This supports previous observations that testosterone acts as a hypertrophic stimulus on cardiac myocytes, which should be considered as part of the safety profile of testosterone treatment.

**Electrophysiology and Arrhythmias**

**Featured Science EP**

**IMPACT: Improving Esophageal Protection During Catheter Ablation for Atrial Fibrillation. A Double Blind Randomised Controlled Trial**

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Background: Catheter ablation for atrial fibrillation (AF) often requires extensive creation of transmural thermal lesions in close proximity to the esophagus. The resultant esophageal injury accounts for the majority of ablation-related mortality. The purpose of this study is to compare an esophageal temperature control device versus a standard temperature monitoring probe in its ability to protect the esophagus from ablation-related thermal injury. Hypothesis: The use of Controlled Active Thermal Protection of the Esophagus (CAPET) during catheter ablation for AF reduces ablation-related thermal injury compared to standard care. Methods: The IMPACT pilot study is a single center, prospective, double blind randomized controlled trial to investigate the ability of the EnsoETM device (Attune Medical, Chicago IL) to protect the esophagus by local control of the luminal temperature during ablation for AF. This method is compared in a 1:1 randomization to a control group in which we follow current standard practice with a temperature monitoring probe only. In the study group, after satisfactory transseptal puncture, the EnsoETM device is placed in exchange for the echo probe and temperature control set to cool or warm according to the ablation modality. If using RF, the device is set to cool to 4°C during ablation of the posterior wall. If using cryotherapy, the device is set to warm to 40°C for total procedure duration. The control group receive a standard temperature monitoring probe which we aim to place in the part of the esophagus closest to the site of ablation. Ablation is halted if the temperature rises above 39°C or falls below 20°C, and we desist from therapy until the temperature returns within safe limits. The incidence of ablation-related esophageal injury is defined by endoscopic examination performed at 5 to 7 days post ablation. Esophageal injury is scored from 0-6 (0= no injury; 6= most severe). Relevant patient symptoms are recorded using a validated questionnaire (GerdQ; score range from 0-18. 0= no symptoms, 18=severe symptoms) at least one week post ablation. Esophageal injury is scored from 0-6 (0= no injury; 6=most injury). The primary efficacy objective was to demonstrate the superiority of the MARVEL 2 features to provide an AV synchronous pacing (i.e. VDD pacing) relative to Micra VVI pacing in subjects with normal sinus node function and complete heart block at rest. AV synchrony was measured during 20 minutes of rest during VDD pacing using continuous device telemetry and ECG via Holter. The primary safety objective was to demonstrate that the algorithm did not have episodes of oversensing induced pacing above 100 bpm. The secondary objective was to demonstrate an increase in stroke volume with AV synchronous vs. VVI pacing.

Results: A total of 75 subjects (age 77.5±11.8 years, 40% females, mean BMI 31.1 kg/m² since Micra implant 9.7 months) from 12 centers in Hong Kong, Malaysia, Europe and the United States were enrolled from January 1st 2019 through March 31st 2019 and received a software download of the accelerometer-based algorithm to their existing leadless pacemakers. Overall, 40 (53.3%) had normal sinus rhythm with complete heart block and were eligible for the primary efficacy objective analysis. The percentage of complete heart block subjects in normal sinus rhythm with ≥70% AV synchrony during rest was significantly greater during AV synchronous pacing than VVI pacing (9 of 40 vs 1 of 35, p<0.001). The mean stroke volume increased by 26.8% (median 26.9%) during VDD pacing to 89.2% (median 94.3%) during VDD pacing. The mean stroke volume increased by 1.7 cm² on an absolute scale (95% CI: 0.7-2.7 cm², P=0.002) or 8.8% on a relative scale during VDD mode compared with VVI mode among the 39 subjects in the primary analysis cohort for this objective. There were no pauses or episodes of pacing induced tachycardia reported during VDD pacing. Conclusion: Accelerometer-based atrial sensing with a novel, enhanced algorithm significantly improves AV synchrony and stroke volume in patients with AV block and a single-chamber leadless pacemaker implanted in the right ventricle.

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Introduction/Background: SATAKE Hot-Balloon (SHB) is a single-shot balloon ablation catheter approved in Japan in 2016. SHB is the world’s first hot balloon system, in which the interior of a balloon is heated using a radio frequency energy. It is intended to treat patients with atrial fibrillation (AF) and has been used for over 4,000 patients in Japan; however, previous reports were only from limited medical institutions. The Japanese Society of Hot-Balloon Pulmonary Vein Isolation Registry study (HARVEST study) as a first nationwide observational study to investigate the real-world efficacy and safety of SHB in JAPAN. (Trial Registration: University hospital Medical Information Network (UMIN) Center identifier: UMIN000029567)

Methods:We have performed an integrated summarized analysis of the periprocedural efficacy and safety of dabigatran by using the two trials; those are the only 2 prospective, randomized, open-label, multicenter, controlled trials that evaluated the safety and efficacy of dabigatran during the periprocedural period of AF ablation. The primary endpoint is the incidence of major bleeding events during and up to 2 months after the ablation procedure across participants with different O-A times. Results: A total of 537 patients with a mean age of 61.3±10.6 (25-85) years old from dabigatran group in 2 trials were enrolled. Since 8 participants from RE-CIRCUIT trial were missing the data of administration time of dabigatran, the integrated analysis was performed on 529 patients (Table 1). The precise analytical results will be presented for the first time at the AHA 2019 scientific sessions. Conclusion: In patients undergoing AF ablation using dabigatran as a perioperative anticoagulant, 8 to 24 hours interruption of dabigatran prior to ablation was associated with no bleeding complications than shorter or longer interruption.

Table 1: Baseline Characteristics

| Table 1: Baseline Characteristics |
|----------------------------------|
| Gender (Male)                    |
| Age (years)                      |
| BMI (kg/m²)                      |
| Paroxysmal Atrial Fibrillation    |
| Persistent Atrial Fibrillation    |
| Long-standing Atrial Fibrillation |
| CHA²DS²-VASC Score               |
| History of Cerebral Infarction,  |
| Thromboembolism                  |
| History of Vascular Disease      |
| Arterial Ischemia or Acute Type  |
| Diabetes                         |
| Hypertension                     |
| History of AF Ablation           |
| LA diameter (mm)                 |
| LA volume (mL)                   |
| LA volume index (ml/m²)          |
| Left ventricular ejection fraction (%) |

Optimal Interruption Time of Dabigatran Per OS to Ablation (O-A Time) in Patients With Atrial Fibrillation: Integrated Analysis From 2 Randomized Controlled Clinical Trials

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Background: Systemic anticoagulation before, during, and after atrial fibrillation (AF) ablation is important for the reduction of thromboembolic and bleeding complications. RE-CIRCUIT (Clinical trial No. NCT02348723) and ABRIDGE-J (Clinical trial No. UMIN000013129) are recently published clinical trials showing that anticoagulation therapy with dabigatran was associated with fewer complications compared with conventional warfarin therapy; however, the dabigatran administration protocols just prior to ablation were different between the 2 studies. In RE-CIRCUIT trial, AF ablation was performed with uninterrupted dabigatran use. In ABRIDGE-J study, 1 or 2 doses of dabigatran were put on hold prior to AF ablation. The aim of this present study was to clarify the optimal interruption time of dabigatran per OS to Ablation (O-A time) by using integrated analysis of these 2 trials. Methods: We have performed an integrated summarized analysis of the periprocedural efficacy and safety of dabigatran by using the 2 trials, those are the only 2 prospective, randomized, open-label, multicenter, controlled trials that evaluated the safety and efficacy of dabigatran during the periprocedural period of AF ablation. The primary endpoint is the incidence of major bleeding events during and up to 2 months after the ablation procedure across participants with different O-A times. Results: A total of 537 patients with a mean age of 61.3±10.6 (25-85) years old from dabigatran group in 2 trials were enrolled. Since 8 participants from RE-CIRCUIT trial were missing the data of administration time of dabigatran, the integrated analysis was performed on 529 patients (Table 1). The major bleeding was associated in 8 patients (1.5 %) taking dabigatran among the 2 clinical trials: Further evaluation revealed that the major bleeding events occurred in 5 patients (2.0 %) with the O-A time less than 8 hours, and in 3 patients (3.6 %) with the O-A time 24 hours or more. However, none of the major bleeding events occurred in patients with the O-A time 8 hours to 24 hours (Figure B). The precise analytical results will be presented for the first time at the AHA 2019 scientific sessions. Conclusion: In patients undergoing AF ablation using dabigatran as a perioperative anticoagulant, 8 to 24 hours interruption of dabigatran prior to ablation was associated with no bleeding complications than shorter or longer interruption.

Gene Sequencing to Identify Rare Pathogenic Variants Confering Increased Risk of Adult-Onset Sudden Cardiac Death

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Introduction: Sudden cardiac death occurs in approximately 220,000 U.S. adults annually, particularly devastating because the majority of those affected have no prior symptoms or cardiovascular diagnosis. Rare pathogenic DNA variants in any of 49 genes can predispose to four important causes of sudden cardiac death: cardiomyopathy, coronary artery disease, inherited arrhythmia syndrome, and aortopathy or aortic dissection. Hypothesis: We tested the hypothesis that rare pathogenic or likely pathogenic variants are enriched in adult-onset sudden cardiac death cases versus controls, and determined the prevalence and clinical importance of such variants among asymptomatic adults. Methods: We performed whole exome sequencing in a case-control cohort of 600 adult-onset sudden cardiac death cases and 600 matched controls from 106,098 participants of 6 prospective cohort studies. Observed DNA sequence variants in any of 49 known cardiovascular genes were classified as pathogenic or likely pathogenic by a clinical geneticist blinded to case status. In an independent population of 4,525 asymptomatic adults of the Multi-Ethnic Study of Atherosclerosis (MESA) prospective cohort study, we performed whole genome sequencing and determined the prevalence of pathogenic or likely pathogenic variants and prospective association with cardiovascular death. Results: Among the 1,200 sudden cardiac death cases and controls, we identified 5,178 genetic variants and classified 14 as pathogenic or likely pathogenic. These 14 variants were present in 15 individuals, all of whom had suffered sudden cardiac death - corresponding to a pathogenic variant prevalence of 2.5% in cases and 0% in controls (p=0.0001). Among 4,525 participants of the MESA prospective cohort study, 41 (0.9%) carried a pathogenic or likely pathogenic variant (see Figure). Over a median follow-up of 14.3 years, cardiovascular death occurred in 4 of 41 (9.8%) pathogenic variant carriers versus 161 or 4,483 (3.6%) of noncarriers - adjusted hazard ratio of 3.24 (95% CI 1.20 - 8.79, p=0.02). Conclusions: Gene sequencing identifies a pathogenic or likely pathogenic variant in a small but potentially important subset of adults suffering sudden cardiac death; these results are present in approximately 1% of asymptomatic adults. These results lay the scientific foundation for the integration of gene sequencing to identify asymptomatic individuals with pathogenic variants into routine clinical practice, with the ultimate goal of preventing a sudden cardiac death tragedy that might have been anticipated.
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Introduction: ICDs are an established therapy for the prevention of arrhythmic death. However, in certain patient subgroups, an increased risk of non-arrhythmic death might predominate despite adequate ICD therapy. Hypothesis: Previously, we observed that increased nocturnal respiratory rate (NRR) identifies patients more prone to non-arrhythmic rather than arrhythmic death. We therefore hypothesized that, compared to patients with NRR <18 breaths/min, patients with NRR ≥18 breaths/min benefit less from a prophylactic ICD implantation in terms of mortality reduction. Methods: The present study is a pre-defined sub-study of the European Comparative Effectiveness Research to assess the use of primary prophylactic implantable cardioverter defibrillators (EU-CERT-ICD), a prospective, investigator-initiated, non-randomized, controlled cohort study conducted at 44 centers in 15 EU countries. Patients with ischemic or non-ischemic cardiomyopathy were included if they met guideline-based criteria for primary prophylactic ICD implantation. The primary endpoint was all-cause mortality. Using prospectively established respiration patterns in 12-lead ECGs, mean NRR was assessed blindly from 24-hour Holters recorded between midnight and 6 AM prior to ICD implantation. Multivariable models and, as sensitivity analysis, propensity score stratification were used to evaluate the interaction between NRR and the ICD treatment effect. Results: Between May 2014 and September 2018, 2,247 patients were enrolled. Of these 2,052 patients were enrolled in the sub-study and had complete records. In 1,363 patients (62 (12) years; 244 women) an ICD was implanted, while 608 patients (63 (12) years; 108 women) were treated conservatively. Between the median follow-up of 2.5 years, 202 (14.8%) and 95 (15.6%) patients died in the ICD and control groups, respectively. NRR significantly predicted the ICD treatment effect on mortality (p=0.0070 for interaction). Patients with NRR ≥18 breaths/min (n= 655) showed a non-ischemic cardiomyopathy were included if they met guideline-based criteria for primary prophylactic ICD implantation. We recommend taking NRR into account when making individual decisions on ICD implantation.
equal to baseline value (no change). Secondary analyses included participants who completed the protocol with measurable values at each of the secondary endpoints. Results: From July 2016 to May 2018, 1376 patients at 30 centers were screened to reach 400 enrolled participants. Mean age at randomization was 65.5 years, mean height was 163.6 cm, and mean weight was 58.1 kg. From baseline to the 26-week visit maximal oxygen consumption increased by 4.2 ml/min in the udenafil group and declined by 3.7 ml/min in the placebo group (p=0.071). Analysis at VAT demonstrated statistically significant improvements in the udenafil compared to placebo group in oxygen consumption (+33 vs -9 ml/min, p=0.012), ventilatory equivalents of carbon dioxide (-1.8 vs -0.06, p=0.014), and work rate (+3.8 vs +0.34 Watts, p=0.021). There was no difference in change of MPI, INR, or serum BNP level. Conclusions: In the FUEL trial, treatment with udenafil (87.5 mg twice daily) was not associated with a statistically significant improvement in oxygen consumption at peak exercise but was associated with statistically significant improvements in multiple measures of exercise performance at the ventilatory anaerobic threshold. Further study is warranted to evaluate the long-term tolerability and safety of treatment.

Author Disclosures: For author disclosure information, please visit the AHA Scientific Sessions 2019 Online Program Planner and search for the abstract title.

Effect of Treatment According to Age in the Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure Trial (DAPA-HF)

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Background: DAPA-HF investigated the effect of the sodium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin in patients with HFrEF, including those without diabetes. Patients with HFrEF are often elderly and more likely to have comorbidities such as renal disease, which may limit the use of pharmacological therapies. Therefore, we assessed the efficacy and safety of dapagliflozin according to age in DAPA-HF. Overall, 57% of patients in DAPA-HF were aged >65 years (and the oldest was 98 years). Methods: The key inclusion criteria were: 1) NYHA class II-IV, 2) LVEF ≤40% or less than 3) NT-proBNP >600 pg/ml if hospitalized for HF in prior 12 months or <95 mmHg if atrial fibrillation) and 4) standard drug and device therapy for HF. Key exclusion criteria included systolic blood pressure <95 mmHg and eGFR <30 ml/min/1.73m2. The double-blind study treatments were dapagliflozin (10 mg once daily) or matching placebo. We hypothesized that dapagliflozin would be superior to placebo for the primary composite outcome: a first episode of worsening HF (hospitalization for HF or an urgent HF visit requiring intravenous therapy) or death from cardiovascular causes. A key secondary outcome was change from baseline to 8 months along with change in score from baseline to 8 months in patients using the rank-based endpoint, incorporating patient vital status at 8 months along with change in score from baseline to 8 months in surviving patients, using the rank analysis of covariance method, with a corresponding win ratio used to evaluate the magnitude of change. An exploratory endpoint, All-cause mortality, was assessed in patients showing a clinically important (~5-point) change with treatment was also pre-specified. Results: The results of DAPA-HF KCCQ are currently embargoed and will be available for the AHA scientific session. From February 15, 2017, through August 17, 2018, 4774 patients were randomized at 410 centers in 20 countries. The mean age of patients was 66 years and 23% were women. 68% of patients were in NYHA class II, mean LVEF was 31% and the median NT-proBNP 1437pg/ml. 94% of patients had an ischemic etiology and 42% had type 2 diabetes. Median age was 66 ±7 years. 94% of patients were treated with a renin-angiotensin system blocker, 96% with a beta-blocker and 71% with an MRA. At baseline, patients in the placebo group had a mean KCCQ-TSS score of 74 (maximum score = 100, reduced score indicates worse symptoms). The primary composite endpoint in patients treated with HF in PEF will be reported (including the responder-analysis). Other summary scores and all domains of the KCCQ will also be described, to assess consistency of treatment effect. Conclusions: DAPA-HF will determine whether the SGLT2 inhibitor dapagliflozin is superior to placebo in improving symptoms and HRQL in patients with HFrEF. (Funded by AstraZenca; DAPA-HF ClinicalTrials.gov number, NCT0306124.)

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Effect of Treatment on the Kansas City Cardiomyopathy Questionnaire (KCCQ) in the Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure Trial (DAPA-HF)

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Background: DAPA-HF investigated the effect of the sodium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin in patients with HFrEF, including those without diabetes. A much larger proportion of patients with heart failure and reduced ejection fraction. There are many differences between women and men with HFpEF. Here we describe the effects of sacubitril/valsartan, compared with valsartan, on key clinical outcomes in women and men participants with HFpEF in PARAGON-HF. Methods: Patients aged ≥50 years, in NYHA class II-IV with an ejection fraction ≥45%, elevated natriuretic peptides and evidence of structural heart disease, and treated with a diuretic were included. After a run-in phase of treatment with valsartan followed by sacubitril/valsartan, patients were randomized to either therapy. The primary outcome was a composite of total hospitalizations for heart failure and cardiovascular death. Secondary outcomes were: change from baseline to 8 months in 1) Kansas City Cardiomyopathy Questionnaire (KCCQ) (score 0-100) and 2) NYHA class; 3) decline in renal function; 4) all-cause death. Results: The results
Heart Failure and Cardiomyopathies

A Deeper Dive into Newer Therapies for Heart Failure I

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Prior Heart Failure Hospitalization, Clinical Outcomes, and Effect of Sacubitril/Valsartan Compared With Valsartan in Heart Failure With Preserved Ejection Fraction

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Background: The period shortly after hospitalization for HF represents a high-risk window for recurrent clinical events. Safety and efficacy of sacubitril/valsartan after recent HF hospitalization are unknown. Methods: PARAGON-HF was a phase 3 randomized, double-blind trial that compared sacubitril/valsartan with valsartan in HFpEF (≥45%), NYHA class II-IV symptoms, elevated natriuretic peptides, and evidence of structural heart disease. The primary outcome was composite cardiovascular death or total HF hospitalizations, analyzed using a semiparametric proportional rates method, stratified by geographic region. Results: Of 4,796 validly randomized patients in PARAGON-HF, 622 (13%) were screened during hospitalization or within 30 days of prior hospitalization, 555 (12%) within 31–90 days, 435 (9%) within 91–180 days, 694 (14%) after 180 days, and 2,490 (52%) were never previously hospitalized. Over median 35 months, risk of total HF hospitalization or cardiovascular death was inversely and non-linearly associated with timing from prior HF hospitalization (P < 0.001). Sacubitril/valsartan vs. valsartan alone was associated with a gradient of risk reduction ranging from patients hospitalized within 30 days of prior hospitalization or cardiovascular death did not differ between quintiles. Data on the effect of sacubitril/valsartan across the ejection fraction spectrum, currently embargoed but will be available for the AHA congress. Conclusions: The analyses presented will help inform an understanding of the prognostic value of ejection fraction for patients with heart failure (HF) with reduced left ventricular ejection fraction (LVEF), limited therapeutic options are available for patients at higher LVEF ranges. Sacubitril/valsartan has been tested against an active comparator inhibitor of the renin-angiotensin-aldosterone system in two similarly structured phase III clinical trials of patients with reduced and preserved LVEF, permitting examination of its therapeutic benefits across a broad range of LVEF. Methods: We divided 13,195 randomized patients pooled from PARADIGM-HF (LVEF eligibility: <40%; n = 8,399) and PARAGON-HF (LVEF eligibility: ≥45%; n = 4,796) into LVEF quintiles: ≤27% (n = 2,762); >27% to 33% (n = 2,983); >33% to 38% (n = 2,209); >38% to 55% (n = 2,561); >55% (n = 2,590). Comparing sacubitril/valsartan vs. valsartan alone, rate of total primary events was 26.7 (≤30 days), 24.2 (31–90 days), 20.7 (91–180 days), 15.7 (>180 days), and 7.9 (not previously hospitalized) per 100 patient-years. Results: More absolute risk reductions were noted among patients hospitalized within 30 days (rate ratio 1.00; 95% confidence interval 0.80–1.24); relative Pinteraction = 0.15. With valsartan alone, rate of total primary events was 26.7 (<30 days), 24.2 (31–90 days), 20.7 (91–180 days), 15.7 (>180 days), and 7.9 (not previously hospitalized) per 100 patient-years. Sacubitril/valsartan, the absolute risk reductions were 6.4% (<30 days), 4.6% (31-90 days), 3.4% (91-180 days), while no benefit was observed in patients screened >180 days or who were never hospitalized (absolute risk reduction Pinteraction = 0.050). Conclusions: Recent hospitalization for HFpEF identifies patients at high-risk for near-term clinical progression. While the modest benefits of sacubitril/valsartan versus valsartan appear consistent relative to prior hospitalization, potential absolute benefits appear amplified when initiated in the high-risk window after hospitalization and warrants prospective validation.

Author Disclosures: For author disclosure information, please visit the AHA Scientific Sessions 2019 Online Program Planner and search for the abstract title.

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Effect of Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure

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Background: While multiple effective therapies are available for patients with heart failure (HF) with reduced left ventricular ejection fraction (LVEF), limited therapeutic options are available for patients at higher LVEF ranges. Sacubitril/valsartan was tested against an active comparator inhibitor of the renin-angiotensin-aldosterone system in two similarly structured phase III clinical trials of patients with reduced and preserved LVEF, permitting examination of its therapeutic benefits across a broad range of LVEF. Methods: We divided 13,195 randomized patients pooled from PARADIGM-HF (LVEF eligibility: ≤40%; n = 8,399) and PARAGON-HF (LVEF eligibility: ≥45%; n = 4,796) into LVEF quintiles: ≤27% (n = 2,762); >27% to 33% (n = 2,983); >33% to 38% (n = 2,209); >38% to 55% (n = 2,561); >55% (n = 2,590). Comparing sacubitril/valsartan vs. valsartan alone, rate of total primary events was 26.7 (≤30 days), 24.2 (31–90 days), 20.7 (91–180 days), 15.7 (>180 days), and 7.9 (not previously hospitalized) per 100 person years (100PY). Results: More absolute risk reductions were noted among patients hospitalized within 30 days (rate ratio 1.00; 95% confidence interval 0.80–1.24); relative Pinteraction = 0.15. With valsartan alone, rate of total primary events was 26.7 (<30 days), 24.2 (31–90 days), 20.7 (91–180 days), 15.7 (>180 days), and 7.9 (not previously hospitalized) per 100 patient-years. Sacubitril/valsartan, the absolute risk reductions were 6.4% (<30 days), 4.6% (31-90 days), 3.4% (91-180 days), while no benefit was observed in patients screened >180 days or who were never hospitalized (absolute risk reduction Pinteraction = 0.050). Conclusions: Recent hospitalization for HFpEF identifies patients at high-risk for near-term clinical progression. While the modest benefits of sacubitril/valsartan versus valsartan appear consistent relative to prior hospitalization, potential absolute benefits appear amplified when initiated in the high-risk window after hospitalization and warrants prospective validation.

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Impact of Sacubitril/Valsartan on Health-Related Quality of Life in Heart Failure-Preserved Ejection Fraction Patients

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Background: Patients with heart failure (HF) and preserved ejection fraction (HFpEF) have impaired health-related quality of life (HRQL) similar in severity to patients with HF and reduced ejection fraction (HFrEF). Improving HRQL is an important therapeutic goal in patients with HFrEF, as it is in HFrEF. The objective of this analysis from the PARAGON-HF trial is to ascertain the impact of sacubitril/valsartan on all domains of HRQL in patients with HFrEF. Methods: In PARAGON-HF, sacubitril/valsartan was compared with valsartan to determine impact on reducing mortality and HF hospitalizations. Patients aged ≥50 years, in NYHA class II-IV with an ejection fraction >45%, elevated natriuretic peptides and evidence of structural heart disease, and treated with a diuretic were included. After a run-in phase of treatment with valsartan followed by sacubitril/valsartan, patients were randomized to either therapy. Participants completed the disease-specific Kansas City Cardiomyopathy Questionnaire (KCCQ) at randomization and at follow-up visits. With the baseline to the 8-month visit change score, the pre-specified analysis of KCCQ scores were calculated using repeated measures ANCOVA model that adjusted for treatment, region, and baseline values. Results: The results of PARAGON-HF are currently embargoed and will be available for the AHA scientific session. A total of 4735 of 4822 participants (98%) (mean age, 73±8 years; 52% women; 81% white) completed KCCQ at randomization and represent the largest HFrEF trial population with HRQL outcomes to date. The difference in change from baseline in KCCQ Summary Score (KCCQ-SS) between treatment groups, the primary HRQL endpoint, will be reported. All 8 domains of the KCCQ will also be described, to assess consistency of effect. In addition, a responder analysis, the proportion of patients showing a ≥5-point improvement with sacubitril/valsartan vs. valsartan will be reported. Supportive analyses will include a) repeated measures models to assess impact of therapy on adjusted KCCQ-SS change scores at each time point through end of study with and without baseline covariates, b) individual change in components of HRQL, and c) correlation between change in NT-proBNP and change in KCCQ scores with and without therapy in model. Conclusions: The analyses presented will provide a comprehensive evaluation of the effects of sacubitril/valsartan, compared to valsartan, on HRQL in patients with HFrEF.

Improvement of Health Status Following Initiation of Sacubitril/Valsartan in Patients With Heart Failure and Reduced Ejection Fraction

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Introduction: Administration of sacubitril/valsartan leads to rapid decrease in amino-terminal pro-B type natriuretic peptide (NT-proBNP) and improvement in health status measured by Clinical (CS) and Overall Summary (OS) scores of the Kansas City Cardiomyopathy Questionnaire (KCCQ). A link between timing and extent of changes in NT-proBNP and KCCQ scores is not established. A secondary objective of the Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure (PROVE-HF) Study was to evaluate change in KCCQ following initiation of sacubitril/valsartan. Hypothesis: Magnitude of early change in NT-proBNP will be associated with subsequent change in KCCQ. Methods: Latent Growth Curve Models (LGCM) evaluated change in KCCQ scores relative to change in NT-proBNP levels over a 12-month period in patients initiated on sacubitril/ valsartan. NT-proBNP values at baseline, Months 3, 6, 9, and 12 were compared with corresponding KCCQ CS, OS and Total Symptom (TS) Scores from the same visits. Results: A total of 681 patients had data for all 5 time points. &lt;±5% of data were missing for all measures. At baseline, study participants had an NT-proBNP of 706 pg/mL and KCCQ scores of 70.19 (CS), 65.79 (OS), and 72.28 (TS). Following sacubitril/valsartan initiation, all summary scores increased significantly within the first 14 days and rose further over the 12-month period; on average, KCCQ summary scores increased every 90 days by 6.51 points (TS), 5.41 (CS), and 6.92 (OS) while NT-proBNP decreased by 72 pg/mL every 90 days. Parallel Process LGCMs showed strong negative relationships between the slope of change in NT-proBNP and the slopes of change in the KCCQ TS Score (r = -0.51; p<0.001, n=681) and the KCCQ CS Score (r = -0.70; p<0.001, n=681). The quasi-natural experiment for NT-proBNP was strongly related to the slope of all KCCQ summary scores yet negatively related to KCCQ quadratic terms; this may indicate a lag effect between rates of changes in NT-proBNP and KCCQ. Conclusion: Following initiation of sacubitril/valsartan, improvement in KCCQ scores occurred very early and in relation to changes of circulating NT-proBNP concentrations. For some patients, there may be a lag effect between sharp decreases in NT-proBNP and measurable changes in KCCQ TS Score and CS Score. Analyses exploring change in specific KCCQ domains and associations with cardiac remodeling will also be presented.

Amino-Terminal Pro-B Type Natriuretic Peptide in the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program

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Introduction: Among patients with type 2 diabetes (T2D) and high cardiovascular (CV) risk, compared to placebo, treatment with canagliflozin significantly reduced risk for hospitalization for heart failure (HHF) or CV death, with a trend toward lower risk for all-cause death. Amino-terminal pro-B type natriuretic peptide (NT-proBNP) and improvement in KCCQ scores are commonly used biomarkers of CV endpoint. NT-proBNP identifies a patient with T2D at high risk for CV events or death. NT-proBNP is lacking history of HF. Treatment with canagliflozin reduced NT-proBNP. Elevated NT-proBNP is reflective by decrease in NT-proBNP. The CHARISMA-TIMI 61 and HOTPEFF study identified the following: a) NT-proBNP concentrations may help to predict CV death, HHF, and all-cause death, b) NT-proBNP is reduced in isolated NT-proBNP peaks within 226 weeks was calculated. Results: Baseline, participants at baseline, 1 year, and 6 years, respectively. Effect of treatment with canagliflozin on NT-proBNP was evaluated. Ability of baseline NT-proBNP concentrations to predict HHF, HHF/CV death, or all-cause death during a mean follow-up of 226 weeks was calculated. Results: At baseline, study participants (mean age 62.4 years, 12% with history of HF) had a median NT-proBNP of 91 pg/mL, 39.3% had an NT-proBNP concentration ≥125 pg/mL. Concentrations of NT-proBNP were higher in those with prior HF compared to those without (187 vs 81 pg/mL); however, substantial overlap of NT-proBNP distribution between these two groups was present. During follow up, NT-proBNP increased in the placebo arm; in contrast, treatment with canagliflozin resulted in reduced NT-proBNP by 1 year (geometric mean ratio of NT-proBNP with canagliflozin vs. placebo = 0.89 [0.84, 0.94]; P < 0.001) after adjusting for baseline NT-proBNP. Lower NT-proBNP in those treated with canagliflozin was also observed at 6 years (P=0.004). In adjusted models, baseline NT-proBNP ≥125 pg/mL was substantially prognostic for subsequent HHF (hazard ratio [HR] 5.07 [2.18, 11.8]; P < 0.001), HHF/CV death (HR 4.91 [2.84, 8.48]; P < 0.001) and all-cause death (HR 4.46 [2.82, 8.19]; P < 0.001). No interaction between biomarker and treatment was detected compared to those with lower NT-proBNP, and in those with NT-proBNP ≥125 pg/mL, canagliflozin treatment was associated with similar relative (but greater absolute) reduction of risk for HHF, HHF/CV death, and all-cause death. In mediation analyses, 81.1% effect of NT-proBNP on HF was reflected by decrease in NT-proBNP. Conclusions: A significant percentage of patients in the CANVAS Program had NT-proBNP concentrations despite lacking history of HF. Treatment with canagliflozin reduced NT-proBNP. Elevated NT-proBNP identified a patient with T2D at high risk for CV events or death.

Empagliflozin in Heart Failure: Diuretic and Cardiorenal Effects

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Heart Failure and Cardiomyopathies

A Deeper Dive into Newer Therapies for Heart Failure II

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Dapagliflozin Effects on Lung Fluid Volumes in Patients With Heart Failure and Reduced Ejection Fraction: Results From the DEFINE-HF Trial

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Background: Outcome trials in type 2 diabetes (T2D) demonstrated reduced hospitalizations for heart failure (HF) with sodium-glucose co-transporter-2 (SGLT2) inhibitors (SGLT2i), but their effects in HF with reduced ejection fraction (HFrEF) are unknown. We explored whether change in lung fluid volume (LFV) is a potential mechanism underpinning observed HF benefits. Methods: Dapagliflozin effects on biomarkers, symptoms and functional status in patients with HF (DEFINE-HF) was a multi-center, randomized controlled trial of 263 HF patients with or without T2D with LVES >40%, NYHA class II-III, and elevated natriuretic peptides. Patients were randomized to dapagliflozin 10 mg daily vs placebo for 12 weeks; 85 patients agreed to participate in a sub-study that measured LFV with remote diuretic sensing ReDS™ (Senesiv) technology at baseline, and over 12 weeks. Sub-study outcomes included mean LFV and proportion of patients with improvement or no change/ deterioration in LFV. Results: Overall, 41 patients in the sub-study were randomized to dapagliflozin, and 44 to placebo. Baseline characteristics were balanced between treatment groups and reflected stable, chronic HF. Results demonstrated reduced LFV, with no significant change in hemodynamic parameters. This highly favorable diuretic profile of empagliflozin may explain the medication’s proposed benefits in HF.

Author Disclosures: For author disclosure information, please visit the AHA Scientific Sessions 2019 Online Program Planner and search for the abstract title.
Background: In patients with transthyretin amyloid cardiomyopathy (ATTR-CM), tafamidis reduces all-cause mortality and cardiovascular (CV) hospitalizations, and slows decline in quality-of-life (QoL) compared with placebo. In May 2019, tafamidis received expedited approval from the US FDA as a breakthrough drug for a rare disease. However, at $225,000 per year, it is the most expensive CV drug ever launched in the US, and its cost-effectiveness and budget impact are uncertain.

Methods: We developed a Markov model of patients with wild-type or variant ATTR-CM and heart failure (mean age 74.5 years) using inputs from the Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT), published literature, FDA review documents, claims, and national survey data. We evaluated the effect of adding tafamidis to guideline-directed therapy for heart failure. The model reproduced 30-month survival, QoL, and CV hospitalization rates observed in ATTR-ACT; future projections were based on a parametric survival model in the control arm, and a constant CV hospitalization or death hazards reduction in the tafamidis arm. The primary outcome was the lifetime incremental cost-effectiveness ratio (ICER) of tafamidis compared with usual care, assessed from the US healthcare sector perspective. We performed deterministic and probabilistic sensitivity analyses to reflect uncertainty in the key parameters. This study was independent of the ATTR-ACT trial sponsor.

Results: Compared with usual care, tafamidis was projected to add 1.29% (~5% uncertainty interval, 0.47-1.75%) QALYs at an incremental cost of $1,135,000 ($872,000-1,377,000), resulting in an ICER of $880,000 ($797,000-1,564,000) per quality-adjusted-life-year (QALY) gained. At a threshold of $100,000 per QALY gained, tafamidis was cost-effective in 0% vs. 10,000 probabilistic simulations at the current price. A 92.6% price reduction from $225,000 per year to $26,563 would be required to make tafamidis cost-effective (Figure). Results were sensitive to assumptions related to 92.6% price reduction from $225,000 to $16,563 would be required to make tafamidis cost-effective (Figure). Results were sensitive to assumptions related to long-term effectiveness of tafamidis. Treating all eligible patients withATTR-CM in the US with tafamidis would result in an ICER of $880,000 (697,000-1,564,000) per quality-adjusted life year (QALY).

This study was independent of the ATTR-ACT trial sponsor.

Results: We conducted a nationwide, randomized, placebo-controlled and factorial designed trial to test the efficacy of 2,000 IU per day of vitamin D3 versus placebo and 1 gram per day of marine omega-3 fatty acids versus placebo on heart failure hospitalization among 25,671 participants (aged 50 and older) of the parent VITAL trial (ClinicalTrials.gov number NCT01169259). The primary endpoint was first hospitalization for heart failure and the secondary endpoint was recurrence of heart failure hospitalization. A diagnosis of heart failure hospitalization was determined by review of medical records by physician adjudicators and supplemented with data from the Centers for Medicare and Medicaid Services. We used Cox proportional hazard models to estimate hazard ratios with 95% confidence intervals comparing each intervention (vitamin D3 or marine omega-3 fatty acids) with its respective placebo using intent-to-treat approach. For recurrent hospitalizations, we used the Andersen-Gill model, which allows for varying numbers of events per person with different time between events.

Results: We will present for the first time detailed findings of this ancillary study. (This ancillary study was registered at ClinicalTrials.gov #02271230)

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model. For ACH, which had a high number of events, the treatment effect by order of events (1st, 2nd, 3rd etc.) was analyzed using the Wei-Lin-Weissfeld model. Results: Among 7,020 treated patients, 706 (10.1%) had HF at baseline and the mean (SD) age was 63 (9) years. Compared to PBO, in patients with and without baseline HF, EMPA reduced the risk of all HHF events (total n of events = 321; with HF: rate ratio [95% confidence interval] 0.52 [0.29, 0.92]; without HF: 0.64 [0.45, 0.93]); and all ACH events (total n of events = 5031; with HF: 0.69 [0.52, 0.90]; without HF: 0.86 [0.78, 0.95]). All P for interaction >0.05. For ACH, a numerically greater effect size with EMPA was observed with a higher order of events (figure). Numbers of patients needed to treat to prevent one ACH event over 3.0 years was 2.2 [1.3, 7.6] (with HF) and 9.0 [5.5, 25.0] (without HF).

Conclusion: Empagliflozin substantially reduced the total burden of HF and all-cause hospitalizations regardless of baseline HF. This further strengthens the rationale for empagliflozin treatment as a means to reduce overall morbidity and mortality in patients with T2D and eCVD at risk of or with HF.

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Heart Failure and Cardiomyopathies
Observational Studies I

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Treatment Uptitration Patterns in Patients With Heart Failure With Reduced Ejection Fraction: Data From International Qualify Survey

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Background. The prescription of guidelines recommended therapies and uptitration to maximal tolerated dosages is the most effective way of ensuring high-quality and optimal care in HFrEF. The recent data from US registry CHAMP-HF, showed that the large majority of HFrEF patients did not receive target doses during 12 month of follow-up. The global nature of the QUALIFY registry provides an opportunity to describe the practice patterns of longitudinal titration of recommended therapies in a contemporary HFrEF population from 36 countries in Europe, Asia, Africa, Canada, Australia.

Methods. QUALIFY is an international, prospective, observational, longitudinal survey of HF outpatients in 7317 outpatients (age>18 years, previous HF hospitalization within 1-15 month, LVEF ≤40%). Patients with incomplete data for model fitting were excluded from analyses. Individual changes in doses for ACEI, ARB, BB, MRA, ivabradine during the 18-months follow-up were plotted using alluvial diagrams. Possible associations between patients’ characteristics at baseline and uptitration at 12 or 18 months compared with baseline were assessed using log-binomial regression and a logistic regression. Effect modification by geographic region on associations was examined by means of modeling an interaction term.

Findings. In this contemporary population of patients with HFrEF from 36 countries, the majority of patients did not receive target doses of recommended therapies at any point during 1.5 years of follow up. Most patients did not have uptitration during follow up. Multiple clinical factors were independently associated with failure to increase dosing including age, HR, BP, gender, LVEF, presence of co-morbidities (DM, asthma, COPD, CKD). These data are important to physicians, care providers, and health services, to identify “touch points” and quality improvement initiatives to improve optimal use of HF drug therapy in real world practice.

Author Disclosures: For author disclosure information, please visit the AHA Scientific Sessions 2019 Online Program Planner and search for the abstract title.
CSI-Kerala Acute Heart Failure Registry (CSI-KAHFR) Data: Less Than 30% of Acute Heart Failure Patients Receive Guideline-Directed Medical Therapy (GDMT)

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Introduction: Heart failure is a major public health challenge in India. Acute Heart Failure (A/c HF) admissions have a significant impact on Heart Failure management. However, limited data are available on practice patterns and mortality outcomes of A/c HF patients admitted to India. Methods: CSI-KAHFR is the largest prospective hospital-based registry of A/c HF in India. We recruited 7512 consecutive patients admitted with A/c HF from 49 hospitals in the state of Kerala, India. The recruitment was based on the European Society of Cardiology 2016 criteria. Results: The mean age was 64.3 years, SD=12.9, mostly males (63.5%). The majority (67.5%) of patients had reduced ejection fraction (HF<EF), while 17.8% had mid-range (HFrEF) and 14.9% had preserved ejection fraction (HFpEF). Ischemic heart disease was the predominant etiology (65%). The majority of eligible patients did not receive the Guideline-Directed Medical Therapy (GDMT) as per the practice patterns and mortality outcomes of A/c HF patients in India. Methods: CSI-KAHFR is the largest prospective hospital-based registry of A/c HF in India. We recruited 7512 consecutive patients admitted with A/c HF from 49 hospitals in the state of Kerala, India. The recruitment was based on the European Society of Cardiology 2016 criteria. Results: The mean age was 64.3 years, SD=12.9, mostly males (63.5%). The majority (67.5%) of patients had reduced ejection fraction (HF<EF), while 17.8% had mid-range (HFrEF) and 14.9% had preserved ejection fraction (HFpEF). Ischemic heart disease was the predominant etiology (65%). The majority of eligible patients did not receive the Guideline-Directed Medical Therapy (GDMT) as per the practice patterns and mortality outcomes of A/c HF patients in India. Methods: CSI-KAHFR is the largest prospective hospital-based registry of A/c HF in India. We recruited 7512 consecutive patients admitted with A/c HF from 49 hospitals in the state of Kerala, India. The recruitment was based on the European Society of Cardiology 2016 criteria. Results: The mean age was 64.3 years, SD=12.9, mostly males (63.5%). The majority (67.5%) of patients had reduced ejection fraction (HF<EF), while 17.8% had mid-range (HFrEF) and 14.9% had preserved ejection fraction (HFpEF). Ischemic heart disease was the predominant etiology (65%). The majority of eligible patients did not receive the Guideline-Directed Medical Therapy (GDMT) as per the practice patterns and mortality outcomes of A/c HF patients in India.

Importance: Brain-type natriuretic peptide (BNP) and amino-terminal brain-type natriuretic peptide (NT-proBNP) are elevated in heart failure and in atrial fibrillation, but guidelines only recommend their use for the diagnosis of heart failure. Objective: To test the hypothesis that brain-type natriuretic peptides have a higher diagnostic and predictive accuracy for atrial fibrillation than for heart failure. Design: The DIAST-CHF trial was a prospective cohort study that recruited individuals with cardiovascular risk factors who were followed up for ten years. Results were prospectively validated in three independent cohorts. Setting: Four different cohorts of patients with cardiovascular risk factors. Participants: Hypothesis-generating data were obtained from the DIAST-CHF study (n=1,929) and validated in three independent population-based cohorts (LIFE-Adult-study, n=2,869, SHP, n=2,103 and SHIP-TREND, n=4,088). Main Outcomes and Measures(s): Diagnostic and predictive accuracy of BNP and NT-proBNP for atrial fibrillation and heart failure measured by receiver operating characteristic curve analysis (area under the curve). Results: In DIAST-CHF, patients without heart failure or atrial fibrillation (n=1,571) had a median NT-proBNP plasma level of 87 pg/ml (interquartile range (IQR) 47;168). NT-proBNP was elevated in patients with heart failure and without atrial fibrillation (n=206; 156 pg/ml [70;347]), but was significantly higher in patients without heart failure but atrial fibrillation (n=1,571) had a median NT-proBNP plasma level of 87 pg/ml (interquartile range (IQR) 47;168). NT-proBNP was elevated in patients with heart failure and without atrial fibrillation (n=206; 156 pg/ml [70;347]), but was significantly higher in patients without heart failure but atrial fibrillation (n=1,571) had a median NT-proBNP plasma level of 87 pg/ml (interquartile range (IQR) 47;168). NT-proBNP was elevated in patients with heart failure and without atrial fibrillation (n=206; 156 pg/ml [70;347]), but was significantly higher in patients without heart failure but atrial fibrillation (n=1,571) had a median NT-proBNP plasma level of 87 pg/ml (interquartile range (IQR) 47;168).

Conclusions and Relevance: NT-proBNP is a better marker for present and incident atrial fibrillation than for heart failure.
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Background. Heart failure (HF) is associated with poor outcomes that could be improved with self-care. Self-care is inadequate in most patients and trials aimed at improving self-care have had inconsistent results. Motivational interviewing (MI) could be effective but only few prior trials with small sample size were conducted in HF and informal caregivers were not included. Purpose: We evaluated: 1) if MI with patients improves self-care maintenance (e.g., taking medications) at 3 months (primary outcome); 2) if including informal caregivers in the MI intervention improves patient self-care confidence, management (e.g., call provider for dyspnea) and confidence more than MI performed solely with patients; and 3) changes over time (3, 6, 9 and 12 months) in self-care maintenance, management and confidence. Trial design. A multisite parallel randomized controlled trial with patients and caregivers randomized into three arms: Arm 1: MI for patients; Arm 2: MI for patients and caregivers; Arm 3: standard care. Participants were randomized 1:1:1. Methods. Patients from outpatient settings in Italy were eligible if they had a diagnosis of HF, inadequate self-care, and were NYHA class II-IV. Patients with severe cognitive impairment, recent myocardial infarction, or living in a nursing home were excluded. Informal caregivers were designated by patients as those providing most care. We measured self-care maintenance, management and confidence with the Self-Care of HF Index that has 0-100 standardized score; >70 indicates adequate self-care. The intervention consisted of one face-to-face MI session and 3 telephone contacts within 2 months. Data collectors and data analysts were blinded to group assignment. Results. A sample of 510 HF patients (median age 74 years; IQR 65-82; 58% male) were randomized to the three arms (Arm 1, n=155; Arm 2, n=177; Arm 3, n=178). At 3 months, Arms 1 and 2 improved 6.99 (SD, 19.62) and 7.42 (SD, 20.17) points in self-care maintenance, while Arm 3 improved only 2.58 (SD, 18.26) points (p=0.028). At 3 months, adequate self-care maintenance was found in 18.4% (Arm 1), 19.4% (Arm 2), and 9.2% (Arm 3) (p=0.016). At 3 months, Arms 1 and 2 improved 12.33 (SD, 15.29) and 15.25 (SD, 16.94) points in self-care management while Arm 3 improved only 7.72 (SD, 15.87) points, p=0.028. No significant difference was found at 3 months in self-care confidence. Over time, Arms 1 and 2 had continuing improvement compared to Arm 3 in self-care maintenance (p=0.031 at 9 months and 0.048 at 12 months). Self-care management was better at 6 months (p=0.007). Self-care confidence was better at 6 (p=0.037) and 9 months (p=0.031). Conclusion. MI had a significant effect in improving self-care in HF patients. Including caregivers may facilitate the benefit. These results suggest that an inexpensive, simple approach to improving self-care - MI - could be effective and could have a lasting effect.

Author Disclosures: For author disclosure information, please visit the AHA Scientific Sessions 2019 Online Program Planner and search for the abstract title.

Effect of Patient-Centered Transitional Care Services in Patients Hospitalized for Heart Failure: Clinical and Sex Specific Outcomes of the PACT-HF Randomized Clinical Trial

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Introduction. Transitional care services can improve outcomes following hospitalization for heart failure (HF). We assessed the effectiveness of Patient-Centered Care Transitions in HF (PACT-HF) transitional care model on 6 month clinical outcomes, and evaluated whether the intervention had a differential effect on males and females. Methods. This was a stepped wedge cluster randomized trial of adults hospitalized for HF across 10 hospitals in Ontario, Canada. Hospitals were randomized to receive the intervention (N=1104 patients), which included nurse-led self-care education, early follow-up with a family physician, and for high-risk patients, structured nurse home-visits and Heart Function Clinic care; or usual transitional care (N=1390 patients). Outcomes. Primary clinical outcomes were composite all-cause readmission, emergency department (ED) visit, or death; and composite all-cause readmission or ED visit. We reported clinical outcomes using hazard ratio (HR) with 95% confidence interval (CI). We assessed for sex-specific interactions and applied the intention-to-treat principle in all analyses. Results. Among 2494 eligible patients (mean age 77.7 years, 50.4% women), all completed the trial. Baselines characteristics were similar between groups. There was no significant difference between the intervention and usual care groups in the first primary composite outcome at 6 months (697 [63.1%] versus 89 [64.5%] events, respectively; hazard ratio [HR], 0.95 [95%CI, 0.81-1.11]; P=0.50) or in the second primary composite outcome at 6 months (671 [60.8%] versus 867 [62.4%] events, respectively; HR, 0.93 [95%CI, 0.79-1.09]; P=0.36). For the first primary composite outcome in the intervention and usual care groups, males had 371 (66.3%) versus 433 (64.1%) events, respectively (HR, 1.05 [95%CI, 0.87-1.26]; P=0.63) and females had 326 (59.9%) versus 463 (64.2%) events, respectively (HR, 0.85 [95%CI, 0.71-1.03]; P=0.10), with a P=0.04 for sex interaction. For the second primary composite outcome in the intervention and usual care groups, males had 357 (63.4%) versus 417 (61.7%) events, respectively (HR 1.03 [95%CI, 0.86-1.26]; P=0.73) and females had 314 (57.7%) versus 450 (63.0%) events, respectively (HR, 0.83 [95%CI, 0.69-1.00]; P=0.05), with a P=0.03 for sex interaction. Conclusions. Among patients hospitalized for HF in Ontario, Canada, implementation of a patient-centered transitional care model did not improve a composite event over usual care at 6 months overall, but the intervention was significantly more effective in females than in males.

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Remote Patient Management Reduces Mortality in Heart Failure Patients With Atrial Fibrillation: Insights From the TIM-HF2 Trial

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Background. Atrial fibrillation (AF) is a frequent comorbidity in patients with heart failure (HF). HF patients with AF are characterized by high morbidity, comorbidities and increased risk of hospitalizations. We therefore assessed the effects of remote patient management (RPM) in patients with AF and chronic HF compared to usual care (UC). Methods. The prospective, randomized and controlled TIM-HF2 trial included 1571 patients with chronic HF. For this post-hoc analysis, AF status at baseline was assessed by 12-lead ECG. The primary outcome was the percentage of days lost due to unplanned cardiovascular hospital admissions or all-cause death after one year. Key secondary outcome was mortality of any cause. All data are presented as mean with 95% confidence interval (CI). Results. At randomization, 922 patients had sinus rhythm (SR) and 547 patients had AF. AF was associated with more days lost due to unplanned cardiovascular hospital admissions than SR (6.13% vs 2.87%, p<0.001) and higher all-cause mortality (12% vs 8%, p=0.029). Patients with AF assigned to RPM had significantly less days lost due to unplanned cardiovascular hospital admissions or all-cause death (5%; CI: 3-7) than patients with AF in the UC group (9%; CI: 7-11; p<0.001). There was no difference in patients with SR. In patients with AF, all-cause mortality was reduced from 14% in the UC group to 9% in the RPM group (HR 0.63; CI: 0.38-1.05; p=0.076). Total mortality in patients with AF in the UC group was 10% versus 7% in the RPM group (HR 0.74; CI: 0.47-1.17; p=0.192). RPM in patients with AF was safe and well tolerated. Conclusion. Remote patient management markedly increased days alive out of hospital in patients with chronic heart failure and atrial fibrillation. Our results identify heart failure patients with atrial fibrillation as a potential promising target population for remote patient management.
Abstracts

Proactive Heart Failure Management Incorporating Ambulatory Pulmonary Artery Pressure Monitoring With the Cordella Heart Failure System: Results of the SIRONA First-in-Human Study

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Introduction: Proactive hemodynamic management using solely ambulatory pulmonary artery (PA) pressure (PAP) data in selected patients with advanced HF has demonstrated to reduce HF hospitalization. The objective of this open label, multi-center, single arm, FIH study (SIRONA, NCT03375710) was to evaluate the safety of the Cordella™ HF System (CHFS - a digital HF management system) and accuracy of the Cordella™ PAP Sensor (Endotronix, Inc.) placed in the pulmonary artery (PA) with respect to standard of care fluid filled catheter measurements.

Methods: The CHFS including the Cordella™ PAP sensor system evaluated for accuracy and safety in a multi-center, single arm, FIH study (SIRONA, NCT03375710) was to evaluate the primary performance criteria. 1-yr mortality was low and HF hospitalizations were markedly reduced. MEMS-HF demonstrated, for the first time, that with PAP-guided HF therapy marked improvements in KCCQ OSS and CSS, proportional to mPAP decreases, were achieved in the SIRONA study, enabling proactive remote HF management has shown to be safe, and accurately measuring PAP when compared to a standard of care fluid filled catheter.

Results: Mean (m) PAP decreased by 5.2 ± 7.4 mmHg (1.5 ± 5.0 vs 8.4 ± 7.7 mmHg, respectively) Figure A. mPAP decreases was 1.5 ± 5.0 vs 8.4 ± 7.7 mmHg, respectively (both p<0.0001), with greater increases in patients with mPAP >35 mmHg (Figure B); PHQ-9 sum score decreased from 8.4 ± 6.0 to 6.5 ± 5.2 (p<0.0001). Conclusion: MEMS-HF showed that PAP-guided therapy for NYHA Class III HF was safe and effective in the health systems of GE, NL and IRL, thus confirming and expanding US results. Primary endpoints exceeded the performance criteria. 1-yr mortality was low and HF hospitalizations were markedly reduced.

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Pulmonary-Artery-Pressure-Guided Therapy for Ambulatory Heart Failure Patients in Clinical Practice in Europe - The Prospective MEMS-HF Study

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Background: Background heart failure hospitalizations (HFH) remain a major burden. Increases in pulmonary artery pressure (PAP) occurs weeks before cardiac decompensation leads to HFH. Wireless PAP monitoring with the CardioMEMS system is indicated in patients with New York Heart Association (NYHA) Class III HF and ≥1 HFH in the last year. In the United States (US), safety and reductions in HFH were shown in patients using the device, but these results were to date not reproduced in other health systems. Thus, the CardioMEMS-European Monitoring Study for Heart Failure (MEMS-HF) evaluated safety / efficacy of CardioMEMS™ in Germany (GE), The Netherlands (NL), and Ireland (IRL) using prospective data collection, a common protocol, and a ≥1 year (yr) follow-up. Methods: Methods: In this open-label post market study 234 HF patients were implanted with a CardioMEMS sensor at 31 centers in GE (n=26), NL (n=4) and IRL (n=1). All had NYHA Class III, ≥1 HFH in the past yr, optimal HF drug treatment in those with HFREF, and a PA branch diameter >7 mm. Primary endpoints were freedom from device- and system-related complications and sensor failure at 1 yr >80% and >90%, respectively. Key secondary outcomes included annualized HFH rate, comparing HFH during 1 yr pre vs post implant; survival at 1 yr; PAP changes at 1 yr; functional status (New York City Cardiomyopathy Questionnaire [KCCQ]); and depression (9-item Patient Health Questionnaire [PHQ-9]). Results: Patient age was 68±11 yrs, 22% were women. At 1 yr, freedom from device-/system-related complications and sensor failure were 98.3% and 99.6%, respectively. Survival at 1 yr was 98.5 ± 2.2%. Mean (m) PAP decreased by 5.2 ± 7.4 mmHg (1.5 ± 5.0 vs 8.4 ± 7.7 mmHg, respectively) Figure A. HFH rate decreased by 62% (0.60 vs 1.55 events / patient-yr), HR 0.38, 95%CI: 0.31-0.48, P<0.0001, compared to 1 yr pre-implant. KCCQ Overall / Clinical Summary Scores (OSS, CSS) increased from 48.5 ± 24.4 to 60.7 ± 23.9 and 53.4 ± 25.3 to 63.0 ± 25.3, respectively (both p<0.0001), with greater increases in patients with mPAP >35 mmHg (Figure B); PHQ-9 sum score decreased from 8.4 ± 6.0 to 6.5 ± 5.2 (p<0.0001). Conclusion: MEMS-HF showed that PAP-guided therapy for NYHA Class III HF was safe and effective in the health systems of GE, NL and IRL, thus confirming and expanding US results. Primary endpoints exceeded the performance criteria. 1-yr mortality was low and HF hospitalizations were markedly reduced. These results were to date not reproduced in other health systems. Thus, the CardioMEMS system is indicated in patients with NYHA Class III HF was safe and effective in the health systems of GE, NL and IRL, thus confirming and expanding US results. Primary endpoints exceeded the performance criteria. 1-yr mortality was low and HFHs were markedly reduced. MEMS-HF demonstrated, for the first time, that with PAP-guided HF therapy marked improvements in KCCQ OSS and CSS, proportional to mPAP decreases, and remission of depressive symptoms are achievable in NYHA III HF patients.
Navigator-Led Remote Optimization of Guideline-Directed Medical Therapy in Patients With Heart Failure With Reduced Ejection Fraction

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Introduction Optimal treatment of heart failure with reduced ejection fraction (HFrEF) is scripted by treatment guidelines, but many eligible patients do not receive guideline-directed medical therapy (GDMT) in clinical practice. We hypothesized that an algorithm-driven, navigator-administered medication optimization program would enhance implementation of GDMT compared with usual care in patients with HFrEF. Methods A cohort of patients with HF and EF ≤ 40% at an academic medical center was identified through an electronic health record-based search algorithm. Those with end-stage heart failure requiring inotropic support, mechanical circulatory support, cardiac transplantation, or palliative care were excluded. Treatment providers were approached for consent to adjust medical therapy according to a sequential, stepped titration algorithm modeled on the current ACC/AHA HF Guidelines. Patients and providers who declined to participate served as a reference group. Patients were contacted via phone by a navigator who facilitated medication adjustment with surveillance of laboratories, blood pressure, and symptoms under supervision of a pharmacist, nurse practitioner, and HF cardiologist. The primary study outcome was the proportion of patients receiving GDMT in the intervention and reference groups at 3 months. Results Of 1028 eligible patients (mean age 68 ± 14 yrs, EF 0.32 ± 0.08, systolic blood pressure 122 ± 13 mm Hg, 18% black, 30% female, 87% NYHA Class I/II), 197 (19%) consented to participation in the medication optimization program and 831 (81%) continued with usual care as directed by their treating clinicians (57% general cardiologists, 43% heart failure specialists). At baseline, 759 (73.8%) participants were treated with target doses of ACE/ARB/ARNi and Beta-blockers, respectively. As noted in the figure, at 3 months, patients allocated to the remote intervention experienced greater increases from baseline in utilization of all categories of GDMT than those in the usual care group. The proportion of patients advanced to target doses of GDMT was also higher in the intervention group at 3 months. (p<0.001) Conclusion Remote titration of GDMT by navigators using encoded algorithms may represent an efficient, population-level strategy for rapidly closing the gap between guidelines and clinical practice in patients with HFrEF.

Background There have been calls to recind the Hospital Readmissions Reduction Program (HRRP) over concerns about increasing mortality in heart failure (HF) patients. However, evaluations of the program have revealed opposing results. In data experiments, we evaluated whether study design, data sources, covariate selection, or statistical analysis affect the results of studies evaluating the HRRP. Methods Using 100% Medicare claims, we identified HF hospitalizations among Medicare beneficiaries during April 2005–March 2015 (Figure 1). We compared two strategies to evaluate HRRP’s association with mortality: (a) studying changes in average post-discharge mortality across four 30-month periods relative to the HRRP; and (b) changes in the slope of monthly mortality rates across these periods accounting for within period trends (Experiment 1). We investigated the effect of identifying risk-adjustment covariates using inpatient or outpatient claims as well as varying the number of inpatient claim codes used (Experiments 2 and 3). Results: There were 4,313,523 HF hospitalizations, with an average mortality of 7.35% in the baseline period. A strategy evaluating HRRP associations as excess changes in average mortality rates across two 30-month periods spanning HRRP announcement, compared with changes in periods preceding HRRP, found a 0.24% (0.10%, 0.38%) increase in average HF mortality. In contrast, a strategy that accounted for trends within periods, found a 0.019% monthly increase (95% CI, 0.007%, 0.030%) 30 months before HRRP announcement, and found no change in slope of monthly mortality rates at HRRP announcement (0.000% per month, 95% CI, -0.011, 0.011). Both strategies were internally consistent across risk-adjustment strategies (Figure 2). Simulating dummy inflections in mortality at HRRP announcement, or 12- or 24-months before HRRP, were all incorrectly ascribed to HRRP in models based on average changes across periods, but were ascribed to the correct period in slope-change models. Conclusions: Evaluating average differences between periods of interest ignoring-within-period temporal trends inaccurately identified the timing of the temporal changes in HF mortality, falsely suggesting an association of the program with increase in mortality for HF patients.
Interventional Treatments

Late Breaking Science II: Results for the Ischemia Trials: To Intervene or Not to Intervene

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Background: It is unknown whether a routine invasive approach of cardiac catheterization and revascularization offers incremental value over a conservative approach of optimal medical therapy (OMT), with catheterization reserved for failure of medical therapy in patients with stable ischemic heart disease (SIHD) and moderate or severe ischemia. Study Design and Methods: ISCHEMIA is an NHLBI-supported trial comparing an initial invasive or conservative strategy to manage SIHD patients with moderate or severe ischemia on stress testing. Key exclusion criteria included estimated glomerular filtration rate (eGFR) <30 mL/min, recent myocardial infarction (MI), left ventricular ejection fraction <35%, left main stenosis >50%, or unacceptable angina at baseline. Most enrolled participants with normal renal function first underwent blinded coronary computed tomography angiography to identify those with nonobstructive coronary artery disease (CAD) and without obstructive CAD. All randomized participants received secondary prevention that included lifestyle and pharmacologic interventions.

Participants randomized to the invasive strategy were to undergo routine cardiac catheterization followed by revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) surgery, when feasible, as selected by the local Heart Team to achieve optimal revascularization.

Participants randomized to the conservative strategy were to undergo cardiac catheterization only for failure of OMT. The primary endpoint is a composite of CV death, MI, resected cardiac arrest, or hospitalization for unstable angina or heart failure. A major secondary endpoint is CV death or MI. Other secondary endpoints include the individual components of the primary composite endpoint; stroke, all-cause mortality, a secondary definition of MI and chronic kidney disease. QoL improvement in health status (symptoms, function, and quality of life [QoL]) was measured at randomization and at 1.5, 3, 6, and every 6 months thereafter. The primary QoL endpoint is the SAQ Summary Score (SS); secondary endpoints include the SAQ Anx Frequency (AF) and QoL domains. All health status outcomes were analyzed using ordinal mixed effects models, adjusted for baseline, with piecewise linear mixed effects models to account for non-linear recovery, jointly modeled with mortality to account for its competing risk. A key, pre-specified subgroup analysis is to compare the effects of randomization strategy within patient subgroups stratified by baseline angina frequency (daily/weekly, 1/week, monthly, or no angina: SAQ AF = 61–99) and no angina (SAQ AF = 100).

Results: A total of 4,617 of 5,179 randomized participants (89%) completed baseline QoL assessments and were included in the QoL analyses, of whom >80% had SAQ assessments through the first 2 years of follow-up. Median age was 65 years (IQR 59–71) and 23% were women, 27% nonwhite, 16% Hispanic and 40% had diabetes. Baseline SAQ SS, AF and QoL scores were 74±19, 18±20 and 62±26, respectively. 20% had baseline SAQ AF Scores ≤60. Overall primary and secondary QoL outcomes will be presented, as well as angina subgroups. Conclusion: ISCHEMIA will provide evidence regarding whether an invasive management strategy improves patients’ health status when added to OMT, as compared with OMT alone, in patients with SIHD and moderate or severe ischemia.

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International Study of Comparative Health Effectiveness With Medical and Invasive Approaches: Primary Report of Clinical Outcomes

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Background: Prior strategy trials comparing optimal medical therapy (OMT) with or without revascularization in patients with stable ischemic heart disease (SIHD) have systematically excluded patients with advanced chronic kidney disease (CKD), a cohort at markedly increased risk of cardiovascular events. Whether a routine invasive approach added to OMT improves outcomes in such patients is unclear.

Methods: ISCHEMIA-CKD is a National Heart, Lung, and Blood Institute-funded, randomized trial designed to determine the comparative effectiveness of an initial invasive angiography and optimal revascularization with either percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery, if feasible, plus OMT versus a conservative strategy (OMT alone, with coronary angiography and revascularization reserved for failure of OMT) on long-term clinical outcomes, in patients with advanced CKD and moderate or severe ischemia demonstrated by stress testing. Advanced CKD is defined as estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m² or on dialysis. Participants were randomized in a 1:1 fashion to an invasive or a conservative strategy. The primary endpoint is a composite of death or nonfatal myocardial infarction (MI). Major secondary endpoints are a composite of death, nonfatal MI, hospitalization for unstable angina, hospitalization for heart failure, or resuscitated cardiac arrest; angina symptoms and quality of life, as assessed by the Seattle Angina Questionnaire. Other secondary endpoints include: the incidence of the composite of death, nonfatal MI, hospitalization for unstable angina, hospitalization for heart failure, resuscitated cardiac arrest, or stroke; composite of death, nonfatal MI, or stroke; composite endpoints incorporating cardiovascular death; composite endpoints incorporating other definitions of MI.
as defined in the clinical event charter; individual components of the primary and major secondary endpoints; stroke and health resource utilization, costs, and cost effectiveness. The trial is projected to have 80% power to detect a 22% to 24% reduction in the primary composite endpoint with the invasive strategy as compared with the conservative strategy. **Results:** A total of 777 participants were randomized in the trial; 388 to the invasive strategy and 389 to the conservative strategy. The median age was 63 years with 31% were women and 53% were on dialysis. In those not on dialysis, 86% had CKD stage 4 and 14% had CKD stage 5 at baseline. The main clinical results will be presented. Anim and a quality of life related outcomes will be reported separately. **Conclusions:** ISCHEMIA-CKD will assess whether an initial invasive management strategy when added to OMT improves clinical outcomes when added to OMT in patients with advanced CKD and SHD.

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**Interventional Treatments**

**Late Breaking Science III: Controversies in Contemporary Management of AS**

**Global Comparison of a Rivaroxaban-Based Antithrombotic Strategy versus an Antiplatelet-Based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes (GALILEO) Trial: Primary Results**

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**Background:** Patients undergoing transcatheter aortic valve replacement (TAVR) are at high risk of thromboembolic events. Few data exist on the optimal antithrombotic therapy after TAVR. The aim of this study was to compare a 10 mg rivaroxaban plus ASA regimen with a clopidogrel regimen as antithrombotic treatment following successful TAVR for the prevention of death and thromboembolic events in patients without an ongoing indication for oral anticoagulation.

**Methods:** This was a global, multicenter, open-label, randomized, event-driven, active-controlled phase III trial. The study compared a rivaroxaban-based strategy (rivaroxaban 10 mg once-daily plus ASA 75-100 mg once-daily for 90 days followed by rivaroxaban 10 mg once-daily alone) versus an antiplatelet-based strategy (clopidogrel 75 mg once-daily plus ASA 75-100 mg once-daily for 90 days followed by ASA alone) after successful TAVR in patients without an ongoing indication for oral anticoagulation at randomization (e.g. atrial fibrillation). The primary efficacy endpoint was the composite of major, disabling or life-threatening bleeding events according to the VARC-2 criteria. The primary safety endpoint was the composite of major, disabling or life-threatening bleeding events according to the VARC-2 criteria. Results: 1,644 patients were randomized.

**Conclusions:** GALILEO was the first randomized trial investigating the efficacy and safety of a 10 mg rivaroxaban plus ASA regimen compared to an ASA plus clopidogrel regimen as antithrombotic treatment following successful TAVR in patients without an ongoing indication for oral anticoagulation.

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**Randomized Clinical Trial Comparing a Rivaroxaban-Based Strategy With an Antiplatelet-Based Strategy for the Prevention of Subclinical Leaflet Thrombosis in Transcatheter Aortic Valves (GALILEO-4D)**

Ole De Backer1, George Dangas2, Hasan Iliahawi3, Jonathon Leipsic4, Christian J Terkelsen5, Raj Makkar6, Annapoorna S Kini7, Karsten T Veien5, Mohamed Abdel-Wahab2, Won-Keun Kim8, Prakash Balan8, Nicolas Van Mieghem9, Ole N Mathiesen9, Raban Jeger10, Martin Arnold10, Bjarne Nargaard10, Klaus F Kofod10, Philipp Blanke10, Stephan Windecker11, Lars Søndergaard10, The Heart Cnr, Rigshospitalet Univ Hosp, Copenhagen, Denmark, 2MT Sinai Med Ctr, New York, NY, 3Cardiology, NYU Langone, New York City, NY, 4UBC, Vancouver, Canada, 5Cardiology, Aarhus Univ Hosp, Aarhus, Denmark, 6Cedar Sinai Med Ctr, Los Angeles, CA, 7Cardiology, Mount Sinai, New York City, NY, 8Cardiology, Odense Univ Hosp, Odense, Denmark, 9Heart Cnr, Segeberg Kliniken, Bad Segeberg, 10Kerkhoff Heart Cnr, Bad Nauheim, Germany, 11UT Physicians, Mountain View, TX, 12Helsinki Univ Hosp, Helsinki, Finland, 13Mechelen Cntr, Mechelen, Belgium, 14St. Paul’s Hosp & UBC, Vancouver, Canada, 15Swiss Cardiovascular Cntr Bern, Bern.

**Background:** Subclinical leaflet thickening and motion abnormalities of bioprosthetic aortic valves as detected by four-dimensional computed tomography (4DCT) may be prevented and reversed with oral anticoagulation. We investigated whether daily dose rivaroxaban, a direct factor Xa-inhibitor, can reduce this phenomenon after transcatheter aortic valve replacement (TAVR).

**Methods:** After successful TAVR, patients without indication for chronic anticoagulation were randomly assigned to a rivaroxaban-based antithrombotic strategy (rivaroxaban 10 mg plus acetylsalicylic acid 75-100 mg once-daily) or an antiplatelet-based antithrombotic strategy (clopidogrel 75mg plus acetylsalicylic acid 75-100mg once-daily) and evaluated by 4DCT-imaging at 90±15 days. The primary endpoint of this study was the rate of patients with at least one subclinical leaflet with >50% motion reduction.

After successful TAVR, a 10mg daily dose rivaroxaban-based antithrombotic strategy was more effective than an antiplatelet-based antithrombotic strategy in preventing subclinical leaflet thickening and reduced leaflet motion in patients without an indication for oral anticoagulation.

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**Balloon-Expandable versus Self-Expandable TAVR on Paravalvular Regurgitation and 2-Year Mortality: A Propensity-Matched Comparison From the FRANCE-TAVI Registry**

Eric Van Belle1, Flavien Vincent1, Julien Labreuche1, Vincent Auffret2, Nicolas Debry3, Thierry Lefebvre1, Hélène Eltchaninoff1, Martine Giral1, Dominique Himbert1, Jean-Philippe Verhoye1, Jean-Quevillon Philippe Collet1, Xavier Teiger3, Emmanuel Emmanouel3, Alain Duhame1, Emmanouil Le Breton2, Cedric Delhaye1, Cardiology, Institut Coeur Poumon - CHU Lille, Lille, France, 2CHU Lille, Lille, France, 3Methodology and biostastistics, Institut Coeur Poumon - CHU Lille, Lille, France, 4ICPS Generale de Sante, Massy, France, 5Cardiology, CHU Rouen, Lille, France, 6Cardiology, CHU Brest, Lille, France, 7Cardiology, Lille, France, 8Cardiology, CHU Poitiers, Poitiers, France, 9Cardiology, CHU Titi SALPêtrière, Paris, France, 10Cardiology, CHU Henri Mondor, Lille, France, 11Methodology and biostastistics, CHU Lille, Lille, France, 12Anesthesiology, Institut Coeur Poumon - CHU Lille, Lille, France, 13Echocardiography, Institut Coeur Poumon - CHU Lille, Lille, France, 14Methodology and biostastistics, CHU Montpellier Nimes, Lille, France, 15Cardiology, CHU Toulouse, Lille, France, 16Cardiology, CHU Arnaud de Villeneuve, Univ Hosp, Montpellier, France, 17Cardiology, CHU Clermont Ferrand, Lille, France, 18Cardiology, CHU Long-term mortality after TAVR. Studies have suggested that PVR modulation was more frequent with self-expandable(SES) than
Early Surgery versus Conventional Management for Asymptomatic Severe Aortic Stenosis

Duk-Hyun Kang, Sung-Ji Park, Seung-Ah Lee, Sahmin Lee, Dae-Hee Kim, Hyung-kwan Kim, Sung-Choeil Yun, Geu-Ru Hong, Jong-Min Song, Cheo-l

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Background: The timing and indications for surgical intervention in asymptomatic, severe aortic stenosis (AS) remain controversial. We conducted a multicenter, randomized trial to compare long-term outcomes of early surgery and conventional treatment in asymptomatic, severe AS. Methods: We randomly assigned asymptomatic patients with severe AS (defined as an aortic valve area ≤0.75 cm² with a peak aortic jet velocity ≥4.5 m/s or a mean transaortic gradient ≥50 mmHg) to early surgery (73 patients) or to conventional treatment (72 patients). The primary end point was a composite of operative mortality or cardiovascular death, and the major secondary end point was death from any cause. Results: The treatment groups were generally well balanced with regard to baseline clinical characteristics. All patients underwent complete follow-up; the median follow-up was 6.2 years (interquartile range, 5.0 to 7.4) in the early surgery group and 6.1 years (interquartile range, 4.5 to 7.3) in the conventional treatment group, respectively. In the early surgery group, 69 patients (94.5%) underwent surgery within 2 months after randomization, whereas 52 patients (72.2%) in the conventional treatment group underwent elective or urgent surgery mainly due to development of symptoms during follow-up. There was no operative mortality among those who underwent early or late surgery. In an intention-to-treat analysis including all the study patients, 1 (1.4%) of 73 patients assigned to early surgery and 11 (15.3%) of 72 patients assigned to conventional treatment died from cardiovascular causes (hazard ratio, 0.09; 95% confidence interval [CI], 0.01 to 0.67). The cumulative incidence of the primary end point was 1.4% at 4 and 8 years in the early surgery group as compared with 5.7% at 4 years and 25.5% at 8 years in the conventional treatment group (P=0.003) (Figure). A total of 5 deaths from any cause (6.8%) occurred in the early surgery group and 15 (20.8%) in the conventional treatment group (hazard ratio, 0.33; 95% CI, 0.12 to 0.90; P=0.030). The rate of death from any cause was also lower in the early surgery group than in the conventional treatment group (4.1% vs. 9.7% at 4 years and 10.2% vs. 31.8% at 8 years, respectively; P=0.018 by log-rank test). The results of analyses performed in the per-protocol and as-treated populations were similar to the results of the primary intention-to-treat analysis. Conclusions: Among asymptomatic patients with severe AS, the rates of the composite of operative or cardiovascular death, and death from any cause were significantly lower with early surgery than with conventional treatment.
Late-Breaking Resuscitation Science

Epinephrine In Children Receiving Cardiopulmonary Resuscitation For Bradycardia With Poor Perfusion

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Introduction: Epinephrine is included in the Pediatric Advanced Life Support algorithm for children with bradycardia and poor perfusion, although the association between receipt of epinephrine and outcomes remains unknown. We assessed whether the use of epinephrine for bradycardia and poor perfusion was associated with improved outcomes. Methods: Using the Get With The Guidelines-Resuscitation registry, we included pediatric patients (<18 years) who received in-hospital cardiopulmonary resuscitation for bradycardia with poor perfusion (non-pulseless event) between January 2000 and December 2018. Time-dependent propensity score matching was used to match patients receiving epinephrine within the first 10 minutes of resuscitation to patients at risk of receiving epinephrine within the same minute. The propensity score was calculated using a multivariable Cox proportional hazards model including multiple patient, event, and hospital characteristics. Results: A total of 3528 patients who received epinephrine were matched to 3528 patients at risk of receiving epinephrine based on the propensity score. Epinephrine was associated with decreased survival to hospital discharge (RR, 0.79 [95% CI, 0.74-0.85]; p <0.001), return of spontaneous circulation (RR, 0.94 [95% CI, 0.91-0.96]; p <0.001), 24-hour survival (RR, 0.85 [95% CI, 0.81-0.90]; p <0.001), and favorable neurological outcome (RR, 0.76 [95% CI, 0.68-0.84]; p <0.001). Epinephrine was also associated with an increased risk of progression to pulselessness (RR, 1.17 [95% CI, 1.06-1.28]; p <0.001). Conclusion: In children receiving cardiopulmonary resuscitation for bradycardia with poor perfusion, epinephrine was associated with worse outcomes, although the study does not eliminate the potential for confounding.

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Neuromuscular Blockade For Post-cardiac Arrest Care: Results Of A Randomized Controlled Trial

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Objective: To assess whether the routine administration of neuromuscular blockade (NMB) improves outcomes for cardiac arrest (CA) victims. Methods: Patients who achieved return of spontaneous circulation (ROSC) and underwent target temperature management were randomized to continuous NMB with rocuronium for 24-hours vs. usual care. Patients were enrolled at 5 centers in the US between 2015 and 2019. The primary outcome was the change in lactate from baseline to 24-hours. Key secondary outcomes were hospital survival, hospital survival with good neurological outcome as defined by the modified Rankin scale 0-3 (29.7% (NMB) vs. 20.9% (saline), p=0.44). There were no adverse events in either arm attributed to study interventions. Discussion: Early, continuous NMB did not reduce lactate levels over the first 24-hours post-arrest as compared to usual care. There was also no difference in overall hospital survival or hospital survival with good neurological outcome. Additional subgroup and biomarker analyses are currently underway, which will help guide future studies of NMB for post-CA care.

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Heart Class - A Novel, Interactive Cpr Training Film Leads To Better Cpr Skill Acquisition And Retention Compared To Standard Training In High School Students

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Introduction: CPR training in high school is mandatory in the majority of U.S. states; however, large variability persists. In order to standardize CPR education, we created HEART CLASS, an interactive film. Methods: In August 2018, HEART CLASS was used to teach 287 9th-graders in Oldham County, KY. HEART CLASS is an 18-min film featuring a realistic cardiac arrest, interactive questions asked competitively between 2 teams, and 4 CPR sessions allowing each student to practice hands-only CPR. The control group of 205 9th-graders at a different school were taught by a certified CPR instructor, followed by practice on Mini Anne™ manikins. We measured CPR skills immediately following CPR training, and after 6 months, with 1-min of hands-only CPR on Little Anne™ manikins, and recorded compression (CC) rate and percentage at correct depth. Results: High-quality CPR was defined as 1-min of CC at correct depth and >70% at correct depth. With HEART CLASS, the percentage of students who performed high-quality CPR immediately after training was 20.2% (n=58 of 287), which was significantly higher than with standard training (13.7%, n=26 of 205) (p<0.001). After 6 months, the percentage of students performing high-quality CPR with HEART CLASS was 23.7% (n=69 of 291), which was significantly higher than with standard training (16.2%, n=32 of 197) (p<0.001). Conclusion: HEART CLASS, a novel, interactive film designed to teach CPR in school classrooms, led to significantly improved CPR acquisition and retention compared to standard training. With both methods, CPR skills improved, rather than decayed, at 6 months.
**A Blinded, Randomized, Vehicle-Controlled Preclinical Trial Of Novel Nanoparticle Formulations Of Triiodothyronine In Cardiac Arrest**

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**Introduction:** Recent data demonstrating that epinephrine (EPI) fails to improve neurologically intact survival in cardiac arrest (CA) have fueled interest in identifying alternative therapies. Given emerging evidence of non-genomic cytoprotective effects of triiodothyronine (T3), the present study evaluated the efficacy of two nanoparticle formulations of T3 (T3np) designed to prolong cell membrane-mediated signaling in a porcine CA model. *Methods:* Swine (n=40) were randomized to intravenous vehicle (empty np), T3np (PRO-AL 616; 0.125 mg/kg) or EPI (0.015 mg/kg) in a blinded fashion (n=10/group). In animals that achieved ROSC, T3np with phosphocreatine (T3np+PCr; PRO-AL 617; 0.125 mg/kg) or EPI (10/10; p<0.01) were compared with T3np+PCr (8/10; p=0.08) or EPI (10/10; p<0.01). Early after ROSC, the rate of ROSC was higher in animals receiving T3np (10/10; p<0.01). Compared with vehicle (4/10), the rate of ROSC was higher in animals receiving T3np (10/10; p<0.01). T3np-treated animals exhibited a lower heart rate and LV dP/dtmax vs. EPI-treated (p<0.01), T3np+PCr (8/10; p=0.08) or EPI (10/10; p<0.01). The concentration of cTnI indicative of more severe myocyte injury (C).

**Conclusion:** In a porcine model of CA, T3nps achieved a ROSC rate and post-ROSC survival that was superior to vehicle and comparable to EPI. The significant reduction in post-ROSC cTnI levels vs. EPI suggests that resuscitation with T3nps may lead to more favorable clinical outcomes in CA.

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**Key Words:** Cardiopulmonary resuscitation; Cardiac arrest; 2020 Impact Goals

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**Vasopressin Infusion Along With Restrictive Fluid Resuscitation Improves 72-hour Survival In A Swine Model Of Concurrent Hemorrhagic Shock And Traumatic Brain Injury**

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**Introduction:** Hemorrhage shock (HS) and traumatic brain injury (TBI) are common battlefield injuries with high morbidity and mortality. Currently, for HS, restricted fluid resuscitation allowing hypotension is recommended to avoid worsening acute traumatic coagulopathy; yet, for TBI, a more liberal fluid administration is recommended to sustain a higher blood pressure and thereby minimize risk of secondary ischemic brain injury. Thus, a therapeutic conflict emerges when both injuries concurrently occur. We previously reported in a swine model of HS by liver laceration (LL) that early and sustained vasopressin (AVP) infusion and restricted fluid resuscitation improves four-hour survival. We now investigated whether a similar approach could be effective when HS and TBI concurrently occur. **Methods:** We developed male pigs (39.1 ± 2.4 kg) a model of concurrent HS (induced by LL removing 1,000 ml of blood in 30 min) and TBI (induced by a right cortical impact with a 15-mm diameter impactor) with survival assessment at 72-hour. We randomized four groups of 15 pigs each to receive intraosseously AVP; the selective V1A agonist [Phe2,Ile3,Orn8] vasopressin (POV), the non-selective V1A agonist terlipressin (TLP), or normal saline control (NS). AVP, POV, and NS were given continuously and TLP intermittently every two hours during the initial 24 hours starting seven minutes after infliction of HS and TBI. A 250-ml bolus of 6% hetastarch was given at 30 min with additional boluses at 120 min, 240 min, and every 4 hours thereafter for the first 24 hours for a systolic blood pressure < 80mmHg. **Results:** As shown in Figure, the 72-hour survival differed significantly among groups (AVP 80%; POV 60%; TLP 40%; and NS 33%) and by pairwise multiple comparisons AVP differed significantly from NS. Pigs that survived had minimal neurological deficits. **Conclusions:** AVP infusion along with restricted fluid resuscitation markedly improved 72-hour survival in a swine model of concurrent HS and TBI.

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**Key Words:** Vasopressin; Brain

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**Hemorrhagic Shock**

**Neuroprotection Of Remote Ischemic Preconditioning And Hypothermia In A Model Of Hemorrhagic Shock Induced Brain Injury**

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**Background:** Hemorrhagic shock (HS) coupled with stroke causes major morbidity and mortality; the optimal therapy for this combined insult remains...
unclear. Remote ischemic preconditioning (RIPC) and therapeutic hypothermia (TH) have been demonstrated to protect myocardial ischemic-reperfusion induced injury. The present study investigated the neuroprotective effects of these cardioprotective therapies during experimental HS. Methods: HS was induced in anesthetized, rat, blood withdrawal from a carotid catheter to a fixed mean blood pressure (MBP) of 30 mmHg for 30 minutes and then shed blood was reinfused. RIPC was induced by 4 cycles of inflating small cuffs around the femoral arteries to 200 mmHg for 5 minutes, followed by 5-minute deflation of the cuffs prior to HS. TH (~32 °C) was started at 5 minutes after HS. Rats were randomized to control (no therapy) versus RIPC, TH, and combination of RIPC + TH. Brain injury was assessed at 6 weeks by pathologic analysis. Results: At 6 weeks, 7 of 52 rats survived in the pooled control group, and brain infarction was observed in 4 of the 7 surviving rats (57%); 25 of 52 rats survived in the pooled treatment group, and brain infarction was observed in only 3 of the 25 surviving rats (12%) (Figure). The brain infarction was significantly reduced in the rats treated with RIPC, TH, and the combination compared to the control group (p=0.026). There were no myocardial infarctions observed in either group. Conclusions: Cardioprotective therapies of RIPC, TH and combination demonstrated neuroprotection in the setting of HS.

Figure. Representative slices of brain stained for triphenyltetrazolium chloride ( TTC) staining. (A) Hypothermia group; (B) Control group. Note the large brain infarction (arrows) shown in control group.

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Key Words: Hemorrhage; Neuroprotection; Stroke

Defibrillation 1

Drones Are A Great Idea! What Is An AED? Novel Insights From A Qualitative Study On Public Perception Study On Using Drones To Deliver Aeds

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BACKGROUND: The quickest way to ensure survival in an out-of-hospital cardiac arrest (OHCA) is for a bystander to provide immediate cardiopulmonary resuscitation (CPR) and apply an automated external defibrillator (AED). The urgency of OHCA treatment has led to the proposal of alternative avenues for better access to AEDs, particularly in rural settings. More recently, using unmanned aerial vehicles (or drones) to deliver AEDs to rural OHCA sites has proven promising in improving survival rates. OBJECTIVE: A pilot drone AED delivery program is currently being piloted in the community of Caledon, Ontario. The purpose of this study was to develop an understanding of public perception and acceptance of the use of drones to deliver an AED and to identify tailored community engagement strategies to ensure successful uptake. METHODS: In-depth qualitative descriptive study using interviews and focus group data collection and inductive thematic analysis. Purposive sampling was used to recruit 70 community members (40 interviews; 2 focus groups of 15) at existing community events in the project area. Interview guides were used to ensure consistency across data collection events. Detailed field notes were recorded when audio-recording was not possible. RESULTS: The central message seen throughout the data was quickly identified as the potential impact of low levels of CPR and AED literacy in the community over anything else including concerns about the drone. The impact of the community's existing relationship with the EMS; the need for bystander CPR & AED promotion prior to the program launch; and the value the community places on transparency and accountability related to the research and the drones were also key findings. In general, the drone concept was found to be acceptable but concerns about providing CPR and using the AED was what created anxieties in the lay public that we underestimated. CONCLUSION: Drone-delivered AEDs may be feasible and effective but successful uptake in smaller communities will require a deep understanding of community’s cardiac arrest literacy levels, information needs, and readiness for innovation. This work will inform a robust community engagement plan that will be scalable to other locations considering a drone AED program.

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Key Words: Community interventions; Cardiac arrest; Automated external defibrillator (AED)

In-hospital Arrest 1

Trends In Survival After Pediatric In-hospital Cardiac Arrest In The United States

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Background: Cardiac arrest in hospitalized children is associated with poor outcomes, but no contemporary study has reported whether trends in survival have changed over time. In this study, we examined temporal trends in survival for pediatric patients with an in-hospital pulseless cardiac arrest and pediatric patients with a non-pulseless cardiopulmonary resuscitation (CPR) event from 2000 to 2018. Methods: This was an observational study of hospitalized pediatric patients (<18 years) who received CPR from January 2000 to December 2018 and were included in the Get With The Guidelines®-Resuscitation registry, a US-based in-hospital cardiac arrest registry. The primary outcome was survival to hospital discharge and the secondary outcome was return of spontaneous circulation. Generalized linear regression was used to obtain unadjusted trends in outcomes over time. Separate analyses were performed for patients with a pulseless cardiac arrest and patients with a non-pulseless event (bradycardia with poor perfusion) requiring CPR. A subgroup analysis was conducted for shockable vs non-shockable initial rhythms in pulseless events. Results: A total of 7433 patients with a pulseless cardiac arrest and 5751 patients with a non-pulseless event were included for the analyses. For pulseless cardiac arrests, survival was 19% (95%CI, 11%-29%) in 2000 and 38% (95%CI, 34%-43%) in 2018, with an absolute change of 0.67% (95%CI, 0.40%-0.95%; p <0.001) per year, although the increase in survival appeared to stagnate following 2010. Return of spontaneous circulation also increased over time, with an absolute change of 0.83% (95%CI, 0.53%-1.14%; p <0.001) per year. We found no interaction between survival to hospital discharge and the initial rhythm. For non-pulseless events, survival was 57% (95%CI, 39%-75%) in 2000 and 66% (95%CI, 61%-72%) in 2018, with an absolute change of 0.80% (95%CI, 0.32%-1.27%; p = 0.001) per year. Conclusions: Survival has improved for pediatric events requiring CPR in the US, with a 19% absolute increase in survival for in-hospital pulseless cardiac arrests and a 9% absolute increase in survival for non-pulseless events between 2000 and 2018. However, survival from pulseless cardiac arrests appeared to have reached a plateau following 2010.

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Key Words: Cardiac arrest; Epidemiology; Population science

Lidocaine Versus Amiodarone For Pediatric In-hospital Cardiac Arrest With A Shockable Rhythm: An Observational Study

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Introduction: Lidocaine and amiodarone are both included in the pediatric cardiac arrest guidelines as treatments for shock-refractory ventricular fibrillation or pulseless ventricular tachycardia, although their efficacy limited evidence to support this recommendation. Methods: In this cohort study from the Get With The Guidelines-Resuscitation registry, we included pediatric patients (<18 years) with an in-hospital cardiac arrest between 2000 and 2018, who presented with an initial or subsequent shockable rhythm (ventricular fibrillation and pulseless ventricular tachycardia). Patients receiving amiodarone were matched to patients receiving lidocaine based on a propensity score, calculated from multiple patient, event, and hospital characteristics. Results: A total of 365 patients were available for the analysis, of whom 180 (49%) patients were matched on the propensity score. The median age in the raw cohort was 6 (quarters, 0.5-14) years, 164 (45%) patients were female, and 238 (65%) patients received an antiarrhythmic for an initial shockable rhythm. In the matched cohort, there was no statistically significant difference between patients receiving lidocaine compared to amiodarone in return of spontaneous circulation (RR, 0.99 [95% CI, 0.82-1.19], p = 0.88), survival to 24 hours (RR, 1.02 [95% CI, 0.76-1.38]; p = 0.88), survival to hospital discharge (RR, 1.01 [95% CI, 0.63-1.63]; p = 0.96), and favorable neurological outcome (RR, 0.65 [95% CI, 0.35-1.21]; p = 0.17). The results remained consistent in multiple sensitivity analyses. Conclusions: In children with cardiac arrest receiving antiarrhythmics for a shockable rhythm, there was no significant difference in clinical outcomes between those receiving lidocaine compared to amiodarone.

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Key Words: Cardiac arrest; Advanced life support; Amiodarone

Basic Science – Cardiac 1

Eosinophils Improve Cardiac Functions After Myocardial Infarction

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Conflicting clinical observations from prior studies suggest that either high or low levels of eosinophils (EOS) and EOS-derived cationic proteins in the blood or aortas predict human coronary heart disease. Here we show that, in a retrospective population study from the Danish Cardiovascular Screening Trial (DANCAST), male patients with previous acute myocardial infarction (AMI; n=345) have significantly higher blood EOS count than that in male non-AMI (DANCAVAS), male patients with previous acute myocardial infarction (AMI, low levels of eosinophils (EOS) and EOS-derived cationic proteins in the blood and cardiac fibroblast fibrosis, whereas EOS-derived IL10 and IL13 do not exert such activities. This study establishes a cardioprotective role of EOS and EOS-derived IL4 and cationic proteins in post-MI hearts.

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Key Words: Myocardial infarction; Fibrosis; Inflammation

Training/Education 1

Are You As Smart As A 5th Grader? Promoting CPR Awareness In Communities Through Kids

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Introduction: Many states are passing legislation requiring cardiopulmonary resuscitation (CPR) training in schools by graduation. Early education, repetition, and re-education all promote retention. We assessed the feasibility of introducing CPR in 5th grade and observed if these individuals can effectively learn CPR as well as educate their families. Methods: We visited 12 elementary schools and taught 1065 5th graders hands-only CPR using the AHA CPR in Schools kit. They viewed the instructional video, practiced on CPR mannequins, and were assessed for proper technique. We then instructed the students to teach their families CPR utilizing our tutorial website. We sent home a survey to be completed by students and families to evaluate the efficacy of these interventions. Results: We educated 1065 students, and of those 280 students (26%) and 94 family members (9%) returned the survey. Of these, over 50% accurately answered questions regarding CPR in each group and thought the AHA video tutorial was valuable in helping them learn CPR. In the adult group, 50% (47/94) indicated that their child teaching them CPR at home was the most valuable tool in helping them learn CPR. A majority in both groups including 66% (185/280) of 5th graders and 78% (73/94) of adults were more confident about CPR after the tutorial. In addition, 76% (213/280) of 5th graders and 86% (81/94) of adults answered that students should be required to learn CPR in their area by high school graduation. Over three quarters, 76% (214/280) of 5th graders and 84% (79/94) of the adults indicated that 5th grade was a good time to start teaching CPR in schools. Conclusion: To meet legislative measures requiring CPR training by high school graduation, it is imperative to start early. Our program outlines an effective method of starting the process of CPR education in elementary school to promote retention. We demonstrate a willingness of these students and their families to start learning CPR at this age. Furthermore, reaching out to introduce whole families to CPR should be a part of this training and can be implemented through a website.

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Key Words: Cardiopulmonary resuscitation; Basic life support; Social connections

Are You Comfortable Being A CPR Instructor With AHA?

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Objectives: Studies about the stress of CPR instructor’s activities have not been well documented yet. We surveyed instructors in Hiroshima to see how they feel about being an AHA instructor and determined factors that impede their activities in order to help maintaining their morale and positive attitudes as an instructor. Methods: We conducted survey by mailing questionnaire to 60 AHA instructors enrolled in the Hiroshima Training Site of Japan ACLS Association. The survey contained questions about the instructor’s background, such as working environment and family structure. We used Visual Analog Scale (VAS; mean ± SD) to evaluate factors which were related to their psychological stress. Findings: Response rate was 65% (effective answers, 39; male, 18; age≥40 years, 20). All of them were BLS instructors, 17 of them held other AHA instructor certifications. VASs of willingness and unwilling to continue activities were 81.1±21.7 and 28.1±28.3, respectively. Figure shows VAS related to each stress factor. Family structure, job type, and instructor experience did not correlate with willingness to continue activities or stress. As for their workplaces, 69% of the subjects had shiftwork with night shift, and most of them felt stressed about time restraints for AMI patients (<0.028 vs those without shiftwork). Conclusions: In this survey, we clarified factors that affect the instructor’s willingness to continue activities and stress. The coexistence of work and CPR activity is not easy. in
addition, lack of respect in the workplace seems to increase stress. Respect in the workplace is crucial for participation in the CPR training courses and continuing instruction.

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Key Words: Social support; Research

**Outcome Predictions 1**

**Relationship Between Optic Nerve Sheath Diameter Measured By Magnetic Resonance Image, Intracranial Pressure, And Neurological Outcome In Cardiac Arrest Survivors Who Underwent Target Temperature Management**

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**Aim:** Studies on the prognostic performance of optic nerve sheath diameter (ONSD) in cardiac arrest survivors (CA) have reported conflicting results. We aimed to investigate the usefulness of ONSD by using magnetic resonance imaging (MRI) and 6-months neurological outcomes in CA survivors treated with target temperature management (TTM).

**Method:** This retrospective study included 37 CA survivors who underwent TTM from January 2018 to December 2018. The ICP was estimated every 24 hours from initiation of TTM to 72 hours (ICP_0 to ICP_72) after return of spontaneous circulation (ROSC) by using lumbar catheter. ONSD was measured at two points, that is, before the cooling stage and once normothermia was maintained (ONSD_0 and ONSD_72) by using MRI. The primary outcome was the correlation between ONSD and ICP associated with neurological outcomes obtained after 6 months. **Results:** The median (interquartile range [IQR]) ONSD_0 was not significantly different between the good and poor neurological outcome group on day 0 (5.2 mm [4.8-5.8] vs 5.2 mm [4.8-5.6]; p=0.948) and day 3 (5.0 mm [4.8-5.2] vs 5.5 mm [4.4-5.9]; p=0.105). ONSD_72 and ICP_72 had excellent correlation on day 3 (r=0.90, p<0.001). ONSD showed excellent correlation with increased ICP (IICP) defined as ICP above 20 mmHg (r=0.89, p=0.001). ONSD of 5.99 mm indicated sensitivity of 90.0% and specificity of 98.0% for identifying IICP. **Conclusion:** The ONSD on days 0 or 3 was not associated with the neurological outcomes in post-out-of-hospital CA patients treated with TTM. However, ONSD had an excellent correlation with IICP and on day 3. Further studies are required to confirm our results.

**Targeted Temperature Management**

**The Effect Of Lumbar Cerebrospinal Fluid Drainage On The Neurologic Outcome Improvement In Patients With Cardiac Arrest Treated With Targeted Temperature Management**

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**Aim:** We evaluated the effect of lumbar CSF drainage on neurologic outcome in post-CA patients treated with TTM. **Methods:** This was a retrospective single-centre study conducted from April 2016 to March 2019. The good outcome group was defined as a CPC scale 1 or 2. The propensity score matching was proceeded. Multivariate logistic regression and Kaplan-Meier models were built. **Results:** Of 122 patients enrolled, the lumbar CSF drainage group had 38 patients, whereas the non-lumbar CSF drainage group had 84 patients. 38 patients were selected in the non-lumbar CSF drainage group, after the propensity score matching was conducted. In multivariate logistic regression of neurologic outcome improvement, Odds ratio of lumbar CSF drainage to improve neurologic outcome was 6.07 (95% CI 1.51–24.39, p = 0.01). Kaplan-Meier analysis of good neurologic outcome were 57.9 % in the lumbar CSF drainage group, whereas 21.1 % in the non-lumbar CSF drainage group estimated 6 months after ROSC (p < 0.001). **Conclusion:** This study showed that lumbar CSF drainage to improve the neurologic outcome in patients treated with TTM.

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Key Words: Cardiac arrest; Targeted temperature management; Prognosis