Mohammed Sadiq Azam

Abstract
Cardiology is an everchanging science, and to provide the best of care we need to be updated with the latest in the field. With our busy schedules and with the stress of dealing with a pandemic, we might be hard pressed to review the latest journals and stay up to date. It is with the aim of fulfilling this gap that we present to you this section on journal scan. In this issue, I have focused on articles published from January 2021 to April 2021. The articles I have chosen range from structural heart disease intervention, to heart failure therapeutics, an article on the fast-rising field of cardio-diabetes and of course the quintessential article on COVID-19 cardiology. In my limited capacity, I have made a few comments regarding the utility and impact of these articles on our daily practice. There are a few more articles that I could not incorporate as it fell beyond the scope of this review, and I have mentioned them as suggested reading at the end of the article.

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Introduction
You can’t do today’s job with yesterday’s methods and be in business tomorrow.

Cardiology is an everchanging science, and to provide the best of care we need to be updated with the latest in the field. With our busy schedules and with the stress of dealing with a pandemic, we might be hard pressed to review the latest journals and stay up to date. It is with the aim of fulfilling this gap that we present to you this section on journal scan. In this issue, I have focused on articles published from January 2021 to April 2021. The articles I have chosen range from structural heart disease intervention, to heart failure therapeutics, an article on the fast-rising field of cardio-diabetes and of course the quintessential article on COVID-19 cardiology. In my limited capacity, I have made a few comments regarding the utility and impact of these articles on our practice. There are a few more articles that I could not incorporate as it fell beyond the scope of this review and I have mentioned them as suggested reading at the end of the article.

Hope these few selected articles make for interesting reading!

Article 1: Structural Heart Disease
Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Rheumatic Aortic Stenosis

J Am Coll Cardiol. 2021;77(14):1703-1713.
Amgad Mentias, Marwan Saad, Milind Y Desai, Amar Krishnaswamy, Venu Menon, Phillip A Horwitz, Samir Kapadia, and Mary Vaughan Sarrazin

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Abstract

Background: Patients with rheumatic aortic stenosis (AS) were excluded from transcatheter aortic valve replacement (TAVR) trials.

Objectives: The authors sought to examine outcomes with TAVR versus surgical aortic valve replacement (SAVR) in patients with rheumatic AS, and versus TAVR in nonrheumatic AS.

Methods: The authors identified Medicare beneficiaries who underwent TAVR or SAVR from October 2015 to December 2017, and then identified patients with rheumatic AS using prior validated International Classification of Diseases, Version 10 codes. Overlap propensity score weighting analysis was used to adjust for measured confounders. The primary study outcome was all-cause mortality. Multiple secondary outcomes were also examined.

Results: The final study cohort included 1,159 patients with rheumatic AS who underwent aortic valve replacement (SAVR, n = 554; TAVR, n = 605), and 88,554 patients with nonrheumatic AS who underwent TAVR. Patients in the SAVR group were younger and with lower prevalence of most comorbidities and frailty scores. After median follow-up of 19 months (interquartile range: 13-26 months), there was no difference in all-cause mortality with TAVR versus SAVR (11.2 vs. 7.0 per 100 person-year; adjusted hazard ratio: 1.53; 95% confidence interval: 0.84-2.79; P = .2). Compared with TAVR in nonrheumatic AS, TAVR for rheumatic AS was associated with similar mortality (15.2 vs. 17.7 deaths per 100 person-years (adjusted hazard ratio: 0.87; 95% confidence interval: 0.68-1.09; P = .2) after median follow-up of 17 months (interquartile range: 11-24 months). None of the rheumatic TAVR patients, <11 SAVR patients, and 242 nonrheumatic TAVR patients underwent repeat aortic valve replacement (124 redo-TAVR and 118 SAVR) at follow-up.

Conclusions: Compared with SAVR, TAVR could represent a viable and possibly durable option for patients with rheumatic AS.

Comment

Even though the incidence of rheumatic heart disease (RHD) has seen a steady decline in the West, it is still a cause of significant morbidity in India. With an overall prevalence of about 1.5-2.0/1,000 across all age groups, India comes under a high prevalence zone for RHD. Surgical AVR, though a well-established option, comes with its own challenges. The cost of regular international normalized ratio (INR) monitoring and consequences of not maintaining a therapeutic INR are well documented. In India, patients affected with RHD are often from disadvantaged socio-economic backgrounds, with the associated poor outcome with mechanical valves. The access to cardiac surgery outside of large urban centers is limited. The actual cardiac surgeries performed in 2018 covered only 28% of the population needs in India. This study by Mentias et al. is a major step in raising awareness regarding the feasibility of TAVR as an option for rheumatic aortic valve disease. The authors found comparable outcomes between SAVR and TAVR in patients with rheumatic aortic stenosis. A major limitation continued to be the nonsuitability of TAVR for patients with AR, which is ironically the most predominant type of aortic valve affliction in RHD. While this study cannot be taken as a go ahead to start offering TAVR for all our patients with rheumatic AS (given that most of these patients will be in the fourth to fifth decade in India), it is a unique study in that it opens the door for exploration and further study of this exciting technology as an alternative to SAVR even in the subset of RHD.

Article 2: Percutaneous Coronary Intervention

Ticagrelor Versus Clopidogrel in Elective Percutaneous Coronary Intervention (ALPHEUS): A Randomized, Open-Label, Phase 3b Trial

Lancet. 2020;396(10264):1737-1744. doi:10.1016/S0140-6736(20)32236-4.

Johanne Silvain, Benoît Lattuca, Farzin Beygui, Grégoire Rangé, Zuzana Motovsky, et al, ALPHEUS investigators.

Expert comment: When Less Is More: Dual Antiplatelet Therapy in Elective Percutaneous Coronary Intervention

Giovanna Liuzzo and Carlo Patrono

European Heart J.2021;42(10):965-966. doi:10.1093/eurheartj/ehab006.

Abstract

Background: Percutaneous coronary intervention (PCI)-related myonecrosis is frequent and can affect the long-term prognosis of patients. To our knowledge, ticagrelor has not been evaluated in elective PCI and could reduce periprocedural ischemic complications compared with clopidogrel, the currently recommended treatment. The aim of the ALPHEUS study was to examine if ticagrelor was superior to clopidogrel in reducing periprocedural myocardial necrosis in stable coronary patients undergoing high-risk elective PCI.

Methods: The ALPHEUS study, a phase 3b, randomized, open-label trial, was done at 49 hospitals in France and Czech Republic. Patients with stable coronary artery disease were eligible for the study if they had an indication for PCI and at
least one high-risk characteristic. Eligible patients were randomly assigned (1:1) to either ticagrelor (180 mg loading dose, 90 mg twice daily thereafter for 30 days) or clopidogrel (300-600 mg loading dose, 75 mg daily thereafter for 30 days) by use of an interactive web response system and stratified by center. The primary outcome was a composite of PCI-related type 4 (a or b) myocardial infarction or major myocardial injury, and the primary safety outcome was major bleeding, both of which were evaluated within 48 h of PCI (or at hospital discharge if earlier). The primary analysis was based on all events that occurred in the intention-to-treat population. The trial was registered with ClinicalTrials.gov, NCT02617290.

Findings: Between January 9, 2017 and May 28, 2020, 1,910 patients were randomly assigned at 49 sites, 956 to the ticagrelor group and 954 to the clopidogrel group. A total of 15 patients were excluded from the ticagrelor group and 12 from the clopidogrel group. At 48 h, the primary outcome was observed in 334 (35%) of 941 patients in the ticagrelor group and 341 (36%) of 942 patients in the clopidogrel group (odds ratio [OR]: 0.97, 95% confidence interval [CI]: 0.80-1.17; \( P = .75 \)). The primary safety outcome did not differ between the two groups, but minor bleeding events were more frequently observed with ticagrelor than clopidogrel at 30 days (105 [11%] of 941 patients in the ticagrelor group versus 71 [8%] of 942 patients in the clopidogrel group; OR: 1.54, 95% CI 1.12-2.11; \( P<0.01 \)).

Interpretation: Ticagrelor was not superior to clopidogrel in reducing periprocedural myocardial necrosis after elective PCI and did not cause an increase in major bleeding, but did increase the rate of minor bleeding at 30 days. These results support the use of clopidogrel as the standard of care for elective PCI.

Funding: ACTION Study Group and AstraZeneca.

Comment

The quest to find the perfect dual antiplatelet therapy (DAPT) has been the aim of every cardiologist ever since the advent of the DAPT. The perfect DAPT is one with a fine balance between the benefit of preventing thrombotic events while having the least bleeding risk. Clopidogrel has long been a part of DAPT regimens of choice due to its cost effectiveness and favorable safety profile in terms of lower bleeding risk compared to ticagrelor and prasugrel. However, incidences of clopidogrel resistance and ischemic events arising as a consequence thereof led to the rise of the challengers—ticagrelor and prasugrel. Each with their own pros and cons. Myonecrosis related to PCI is frequent and has an effect on the long-term prognosis of patients. The ALPHEUS study was done with an aim to examine if ticagrelor was superior to clopidogrel in reducing periprocedural myocardial necrosis in stable coronary patients undergoing high-risk elective PCI. The investigators found that at 30 days there was difference in the incidence of the primary outcome (a composite of PCI-related type 4 myocardial ischemia [MI] or major myocardial injury) between ticagrelor and clopidogrel, neither was there a difference with regard to major bleeding events, which was the primary safety outcome, between the two groups. However, there was an increased incidence of minor bleeding events observed with ticagrelor than clopidogrel at 30 days. One of the limitations of this study was that it used periprocedural MI and myocardial damage as a surrogate for hard clinical endpoints, which are rare in elective PCI. ALPHEUS showed that frequency of early ischemic events after elective PCI is unlikely to be reduced with the use of more powerful P2Y12 inhibition as offered by ticagrelor when compared to that offered by clopidogrel. The authors concluded that in stable patients undergoing elective PCI, the humble clopidogrel should remain the standard of care in addition to aspirin as the DAPT of choice.
differences in various survival indicators between patients with chronic obstructive pulmonary disease taking BBs and those not taking BBs. Forty-nine studies were included, with a total sample size of 670, 594. Among these, 12 studies were randomized controlled trials (RCTs; 7 crossover and 5 parallel RCTs) and 37 studies were observational (including 4 post hoc analyses of data from RCTs). The hazard ratios (HRs) of chronic obstructive pulmonary disease exacerbation between patients with chronic obstructive pulmonary disease who were not treated with BBs and those who were treated with BBs, cardioselective BBs, and non cardioselective BBs were 0.77 (95% confidence interval [CI]: 0.67, 0.89), 0.72 (95% CI: 0.56, 0.94), and 0.98 (95% CI: 0.71, 1.34), respectively (HRs <1 indicate favoring BB therapy). The HRs of all-cause mortality between patients with chronic obstructive pulmonary disease who were not treated with BBs and those who were treated with BBs, cardioselective BBs, and non cardioselective BBs were 0.70 (95% CI: 0.59, 0.83), 0.60 (95% CI: 0.48, 0.76), and 0.74 (95% CI: 0.60, 0.90), respectively (HRs <1 indicate favoring BB therapy). Patients with chronic obstructive pulmonary disease treated with cardioselective BBs showed no difference in ventilation effect after the use of an agonist, in comparison with placebo. The difference in mean change in forced expiratory volume in 1 s was 0.06 (95% CI: 0.02, 0.14).

**Conclusion:** The use of BBs in patients with chronic obstructive pulmonary disease is not only safe but also reduces their all-cause and in-hospital mortality. Cardioselective BBs may even reduce chronic obstructive pulmonary disease exacerbations. In addition, cardioselective BBs do not affect the action of bronchodilators. Importantly, BBs reduce the heart rate acceleration caused by bronchodilators. BBs should be prescribed freely when indicated in patients with chronic obstructive pulmonary disease and heart disease.

**Comment**

COPD is one of the commonest respiratory ailments affecting our population. The risk of CVD is 2 to 5 times higher in patients with COPD when compared to the general population—an effect primarily driven by smoking and systemic inflammation. These risk factors also promote atherosclerosis which leads to endothelial dysfunction and plaque formation with subsequent rupture, thrombosis, and risk of acute coronary syndrome. Bronchodilators (β2-agonists) form the mainstay of therapy of COPD, while BBs are the standard of care for most CVDs. The theoretical opposition of the actions of the two form a therapeutic conundrum. However, there is ample evidence to support the use of BBs in patients with COPD and CVD. The 2016 ESC guidelines recommend the use of BBs in patients with COPD and CVD. This study by Yang et al was designed to evaluate the effect of BBs on respiratory function and survival in patients with COPD and CVD. The investigators found that not only did the cardioselective BBs interfere with the action of bronchodilators but they even reduced the COPD exacerbations and controlled the heart rate accelerations due to bronchodilators. The use of BBs in this subset was found to be associated with a lower all-cause and in-hospital mortality as well.

**Article 4: Cardiodiabetes**

**Empagliflozin in Patients With Heart Failure, Reduced Ejection Fraction, and Volume Overload: EMPEROR-Reduced Trial**

Milton Packer, Stefan D Anker, Javed Butler, Gerasimos Filippatos, Joao Pedro Ferreira, et al. *J Am Coll Cardiol.* 2021;77(11):1381-1392.

**Abstract**

**Background:** Investigators have hypothesized that sodium-glucose cotransporter 2 (SGLT2) inhibitors exert diuretic effects that contribute to their ability to reduce serious heart failure events, and this action is particularly important in patients with fluid retention.

**Objectives:** This study sought to evaluate the effects of the SGLT2 inhibitor empagliflozin on symptoms, health status, and major heart failure outcomes in patients with and without recent volume overload.

**Methods:** This double-blind randomized trial compared the effects of empagliflozin and placebo in 3,730 patients with heart failure and a reduced ejection fraction, with or without diabetes. Approximately, 40% of the patients had volume overload in the 4 weeks before study enrollment.

**Results:** Patients with recent volume overload were more likely to have been hospitalized for heart failure and to have received an intravenous diuretic agent in an outpatient setting in the previous 12 months, and to experience a heart failure event following randomization, even though they were more likely to be treated with high doses of a loop diuretic agent as an outpatient (all *P* < .001). When compared with placebo, empagliflozin reduced the composite risk of cardiovascular (CV) death or hospitalization for heart failure, decreased total hospitalizations for heart failure, and improved health status and functional class. Yet despite the predisposition of patients with recent volume overload to fluid retention, the magnitude of these benefits (even after 1 month of treatment) was not more marked in patients with recent volume overload (interaction *P* values > .05). Changes in body weight, hematocrit, and natriuretic peptides (each potentially indicative of a diuretic action of SGLT2 inhibitors) did not track each other closely in their time course or in individual patients.
Conclusions: Taken together, study findings do not support a dominant role of diuresis in mediating the physiological changes or clinical benefits of SGLT2 inhibitors on the course of heart failure in patients with a reduced ejection fraction.

Comment

Cardiodiabetes as a specialty is fast gaining ground. With the increasing numbers of diabetic medications shown to have definite CV benefits, this field is only set to grow. And at the forefront are the SGLT2 inhibitors. Notable among these is empagliflozin which took the cardiac world by storm with its 32% relative risk reduction of all-cause mortality, 38% relative risk reduction of CV mortality, and 35% relative risk reduction in hospitalization for heart failure in the EMPA-REG OUTCOME trial. By virtue of it having a diuretic effect, this article by Packer et al is a secondary analysis of the EMPEROR-Reduced trial to evaluate the effects of empagliflozin on symptoms and major heart failure outcomes in patients with and without recent volume overload. The investigators found that empagliflozin reduced the risk of CV death or hospitalization for heart failure to a similar extent in patients with or without recent volume overload. The symptomatic benefit and improvement in health status was also similar in the two groups. There was no increase in symptomatic hypotension or volume depletion-related events irrespective of the volume status at baseline. This study not only reiterates the place of empagliflozin as a first line therapy in patients with HFrEF but also underscores the point that its benefits are likely mediated by mechanisms unlikely to be linked to its diuretic effect.

Article 5: Hypertension

Systolic Blood Pressure Time in Target Range and Cardiovascular Outcomes in Patients With Hypertension

Nayyra Fatani, Dave L Dixon, Benjamin W Van Tassell, John Fanikos, and Leo F Buckley

J Am Coll Cardiol. 2021;77(10):1290-1299.

Abstract

Background: Standard blood pressure (BP) control metrics may not account for fluctuations in BP over time.

Objectives: This study sought to estimate the independent association between time in systolic BP target range and major adverse cardiovascular (CV) events among adults with hypertension.

Methods: This study was a post hoc analysis of SPRINT (Systolic Blood Pressure Intervention Trial), a randomized clinical trial that compared intensive (<120 mm Hg) and standard (<140 mm Hg) systolic BP treatment interventions in adults with hypertension and high CV risk. Target range was defined as 110 to 130 mm Hg and 120 to 140 mm Hg for the intensive and standard arms, respectively. Time in target range was estimated over the first 3 months of follow-up using linear interpolation. The association between time in target range with major adverse CV events was estimated using adjusted Cox proportional hazards regression models.

Results: Participants with greater time in target range were younger, had lower 10-year CV risk and lower baseline systolic BP, and were more likely women and statin users. Each 1-SD increase in time in target range was significantly associated with a decreased risk of first major adverse CV event in fully adjusted models. Time in target range remained significantly associated with major adverse CV events despite adjustment for mean systolic blood pressure or systolic BP variability. Among participants with mean systolic BP at or below target, time in target range remained associated with major adverse CV events.

Conclusions: Time in systolic BP target range independently predicts major adverse CV event risk.

Comment

Hypertension (HTN) is known as a silent killer, over the last decade we have witnessed tighter targets levels for BP control, which is backed with robust evidence demonstrating a significant mortality benefits with tighter control of BP. The SPRINT trial is the latest of such trials which have significantly impacted our practice. The trial showed that intensive BP lowering to a target of <120 mm Hg versus standard control (<140 mm Hg) had a significantly higher benefit including a reduction of all-cause mortality. But is a single target reading enough? This article by Fatani et al aims to look at the effect of time in systolic BP target range and CV events. The investigators found that there was a significant association between the time in target systolic BP range and CV events—with those having more time in target systolic BP range having lesser events. They concluded that the time in systolic BP target range was an independent predictor of major adverse CV events. This study reiterates the importance of the use of 24h ambulatory BP monitoring for following up patients with HTN to ascertain the duration that the patient is actually at target systolic BP during the day. This will help identify patients at risk for CV events and titrate therapy to increase the time in systolic BP target range.
Article 6: Percutaneous Coronary Intervention

10-Year Follow-Up of Patients With Everolimus-Eluting Versus Bare-Metal Stents After ST-Segment Elevation Myocardial Infarction

Salvatore Brugaletta, Josep Gomez-Lara, Luis Ortega-Paz, Victor Jimenez-Diaz, Marcelo Jimenez, et al.

*J Am Coll Cardiol.* 2021;77(9):1165-1178.

**Abstract**

**Background:** Outcomes data for a durable-polymer everolimus-eluting stent (EES) at extended long-term follow-up in patients with ST-segment elevation myocardial infarction (STEMI) are unknown.

**Objectives:** The aim of this study was to assess the 10-year outcomes of patients enrolled in the EXAMINATION (A Clinical Evaluation of Everolimus Eluting Coronary Stents in the Treatment of Patients With STEMI) trial.

**Methods:** The EXAMINATION-EXTEND (10-Years Follow-Up of the EXAMINATION Trial) study is an investigator-driven 10-year follow-up of the EXAMINATION trial, which randomly assigned 1,498 patients with STEMI in a 1:1 ratio to receive either EES (n = 751) or bare-metal stents (BMS) (n = 747). The primary endpoint was a patient-oriented composite endpoint of all-cause death, any myocardial infarction, or any revascularization. Secondary endpoints included a device-oriented composite endpoint of cardiac death, target vessel myocardial infarction, or target lesion revascularization; the individual components of the combined endpoints; and stent thrombosis.

**Results:** Complete 10-year clinical follow-up was obtained in 94.5% of the EES group and 95.9% of the bare-metal stent group. Rates of the patient-oriented composite endpoint and device-oriented composite endpoint were significantly reduced in the EES group (32.4% vs. 38.0% [hazard ratio: 0.81; 95% confidence interval: 0.68-0.96; *P* = 0.01] and 13.6% vs. 18.4% [hazard ratio: 0.72; 95% confidence interval: 0.55-0.93; *P* = 0.01], respectively), driven mainly by target lesion revascularization (5.7% vs. 8.8%; *P* = 0.02). The rate of definite stent thrombosis was similar in both groups (2.2% vs. 2.5%; *P* = 0.60). No differences were found between the groups in terms of target lesion revascularization (1.4% vs. 1.3%; *P* = 0.96) and definite or probable stent thrombosis (0.6% vs. 0.4%; *P* = 0.70) between 5 and 10 years.

**Conclusions:** At 10-year follow-up, EES demonstrated confirmed superiority in combined patient- and device-oriented composite endpoints compared with BMS in patients with STEMI requiring primary percutaneous coronary intervention. Between 5- and 10-year follow-up, a low incidence of adverse cardiovascular events related to device failure was found in both groups.

**Comment**

The era of the humble BMS is long gone, or so it seems drug-eluting stents (DES) have virtually replaced BMS for coronary use on their merits of a significantly lower rate of restenosis with both first generation as well as the latest generation of DES. A longer duration of dual antiplatelet therapy however is the cost to pay for these superior benefits, a cost that in certain conditions might be a high price to pay. It was thought that BMS may offer improved safety compared to DES in this subset of high bleeding risk patients by virtue of their reduced requirement of DAPT (as low as 30 days). It was at the height of this controversy that the EXAMINATION trial was designed, which compared DES with BMS in STEMI. The DES used was an EES. The EXAMINATION EXTEND study is a 10-year follow-up of the EXAMINATION trial. The investigators completed the extended 10-year follow-up in 95% of the study population, which is a feat worth appreciating. The 10-year results confirmed that EES is superior to BMS with respect to both patient and device-oriented end points. There was a trend toward late stent thrombosis with the EES group, probably due to neoatherosclerosis, but the numbers were too small to analyze meaningfully. This study probably rings the final bell in the battle of DES versus BMS. DES have stood the test of time.

Article 7: Heart Failure

Spironolactone in Patients With Heart Failure, Preserved Ejection Fraction, and Worsening Renal Function

Iris E Beldhuis, Peder L Myhre, Michael Bristow, Brian Claggett, Kevin Damman, et al.

*J Am Coll Cardiol.* 2021;77(9):1211-1221.

**Abstract**

**Background:** Treatment of heart failure with preserved ejection fraction (HFpEF) with spironolactone is associated with lower risk of heart failure hospitalization (HHF) but increased risk of worsening renal function (WRF). The prognostic implications of spironolactone-associated WRF in HFpEF patients are not well understood.

**Objectives:** The purpose of this study was to investigate the association between WRF, spironolactone treatment, and clinical outcomes in patients with HFpEF.

**Methods:** In 1,767 patients randomized to spironolactone or placebo in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial)-Americas study, we examined the incidence of WRF.
(doubling of serum creatinine) by treatment assignment. Associations between incident WRF and subsequent risk for the primary study endpoint of cardiovascular (CV) death, HFH, or aborted cardiac arrest and key secondary outcomes, including CV death, HFH, and all-cause mortality according to treatment assignment, were examined in time-updated Cox proportional hazards models with an interaction term.

**Results:** WRF developed in 260 (14.7%) patients with higher rates in those assigned to spironolactone compared to placebo (17.8% vs. 11.6%; odds ratio: 1.66; 95% confidence interval: 1.27-2.17; \( P < .001 \)). Regardless of treatment, incident WRF was associated with increased risk for the primary endpoint (hazard ratio: 2.04; 95% confidence interval: 1.27-2.17; \( P < .001 \)) after multivariable adjustment. Although there was no statistical interaction between treatment assignment and WRF regarding the primary endpoint (interaction \( P = .11 \)), spironolactone-associated WRF was associated with lower risk of CV death (interaction \( P = .003 \)) and all-cause mortality (interaction \( P = .001 \)) compared with placebo-associated WRF.

**Conclusions:** Among HFpEF patients enrolled in TOPCAT-Americas, spironolactone increased risk of WRF compared with placebo. Rates of CV death were lower with spironolactone in both patients with and without WRF.

**Comment**

HFpEF constitutes a unique therapeutic subset amongst patients with heart failure. While great strides have been made in the last 30 years in the management of heart failure, many of which have led to a significant reduction in HFrEF-related mortality and morbidity, there is yet to be found a molecule that definitively reduces mortality in the HFpEF subset. At the center of our armamentarium against HF is renin-angiotensin-aldosterone system (RAAS) blockade. While there is robust data supporting the use in HFrEF, the benefit-to-risk profile of RAAS blockers in patients with HFpEF is still controversial. The TOPCAT study showed a significant reduction in hospitalization for heart failure in the spironolactone group while the primary composite end point was not significantly different compared to placebo. In this study, Beldhuis et al. used data from the TOPCAT-Americas trial to assess the prognostic implications of ambulatory WRF in patients with HFpEF using spironolactone. The results confirmed previous findings with respect to the deleterious effect of WRF on subsequent adverse cardiac events and demonstrated that spironolactone may increase the rate of WRF by as much as 66%. However, patients on spironolactone had a reduced rate of CV death and all-cause mortality in both those with and without WRF. The most interesting observation was that the greatest benefit of spironolactone in terms of CV death and all-cause mortality was more prominent in patients with WRF. The authors conclude that the development of WRF or azotemia in patients with HFpEF on RAAS blockade should not be a call to withdraw the drugs but rather be a signal to intensify follow-up with an aim of reducing hospitalization and death.

**Article 8: Pulmonary Arterial Hypertension**

**Sotatercept for the Treatment of Pulmonary Arterial Hypertension**

Marc Humbert, Valerrie McLaughlin, J Simon R Gibbs, Mardi Gomberg-Maitland, Marius M Hoeper, et al., for the PULSAR Trial Investigators

*N Engl J Med.* 2021;384:1204-1215. doi:10.1056/NEJMoa2024277.

**Abstract**

**Background:** Pulmonary arterial hypertension (PAH) is characterized by pulmonary vascular remodeling, cellular proliferation, and poor long-term outcomes. Dysfunctional bone morphogenetic protein pathway signaling is associated with both hereditary and idiopathic subtypes. Sotatercept, a novel fusion protein, binds activins and growth differentiation factors in the attempt to restore balance between growth-promoting and growth-inhibiting signaling pathways.

**Methods:** In this 24-week multicenter trial, we randomly assigned 106 adults who were receiving background therapy for PAH to receive subcutaneous sotatercept at a dose of 0.3 mg per kilogram of body weight every 3 weeks or 0.7 mg per kilogram every 3 weeks or placebo. The primary end point was the change from baseline to week 24 in pulmonary vascular resistance.

**Results:** Baseline characteristics were similar among the three groups. The least-squares mean difference between the sotatercept 0.3-mg group and the placebo group in the change from baseline to week 24 in pulmonary vascular resistance was 145.8 dyn·sec·cm⁻³ (95% confidence interval [CI]: −241.0 to −50.6; \( P = .003 \)). The least-squares mean difference between the sotatercept 0.7-mg group and the placebo group was −239.5 dyn·sec·cm⁻³ (95% CI: −329.3 to −149.7; \( P < .001 \)). At 24 weeks, the least-squares mean difference between the sotatercept 0.3-mg group and the placebo group in the change from baseline in 6-min walk distance was 29.4 m (95% CI: 3.8 to 55.0). The least-squares mean difference between the sotatercept 0.7-mg group and the placebo group was 21.4 m (95% CI: −2.8 to 45.7). Sotatercept was also associated with a decrease in N-terminal pro-B-type natriuretic peptide levels. Thrombocytopenia and an increased hemoglobin level were the most common hematologic adverse events. One patient in the sotatercept 0.7-mg group died from cardiac arrest.
**Conclusions:** Treatment with sotatercept resulted in a reduction in pulmonary vascular resistance in patients receiving background therapy for PAH.

**Comment**

The treatment of PAH has grown with leaps and bounds over the last decades. However, the therapeutic agents leave much to be desired with regard to attenuating the progression of PAH. Studies on pathogenesis have found that, disruptions in transforming growth-factor-β and bone morphogenetic protein signaling are associated with the development of PAH. Sotatercept is a novel first in class fusion protein that targets this mechanism. The PULSAR trial investigators found a significant reduction in pulmonary vascular resistance with a concomitant increase in functional capacity (evidenced by an increase in 6-min walk distance) at the end of 24 weeks in the group treated with sotatercept compared to those receiving placebo. This is a promising molecule; however, long-term outcomes and the probability of thrombotic complications need further follow-up. As with all novel PAH agents, the cost burden of this molecule versus its potential benefits needs to be weighed especially in our cost-sensitive populace.

**Article 9: Atrial Fibrillation**

**Relationship Between Device-Detected Burden and Duration of Atrial Fibrillation and Risk of Ischemic Stroke**

Mounir Al-Gibbawi, Hakeem O Ayinde, Neal K Bhatia, Michael S Lloyd, Faisal M Merchant, Soroosh Kiani, et al.

*Heart Rhythm.* 2021;18:338-346. doi:10.1016/j.hrthm.2020.10.017.

**Abstract**

**Background:** Wider availability of continuous rhythm monitoring has made feasible the incorporation of metrics of atrial fibrillation (AF) burden and duration into the decision to initiate anticoagulation. However, the relationship between thresholds of burden and duration and underlying risk factors at which anticoagulation should be considered remains unclear.

**Objective:** The purpose of this study was to evaluate the relationships of these metrics with each other and the outcome of stroke/transient ischemic attack (TIA).

**Methods:** We identified patients with cardiovascular implantable electronic devices (CIEDs) with atrial leads who had at least 1 interrogation in 2016 demonstrating non permanent AF and were not receiving oral anticoagulation (OAC). We evaluated the relationship between burden (ie, percentage of time spent in AF), the longest single episode of AF, and risk factors (ie, CHA₂DS₂-VASc score) in predicting risk of stroke/TIA.

**Results:** The study included 384 patients with mean follow-up of 3.2 ± 0.8 years and incidence of stroke/TIA of 14.8% during follow-up (~4.6% per year). The burden of AF and the duration of longest episode demonstrated a significant positive correlation to each other but not CHA₂DS₂-VASc score. Importantly, although the CHA₂DS₂-VASc score was predictive of stroke/TIA, neither burden nor duration was associated with stroke/TIA.

**Conclusion:** Among patients with CIED-detected AF not receiving OAC, the amount of AF (measured by either burden or duration) does not seem to significantly impact stroke risk, whereas CHA₂DS₂-VASc score does. These data suggest that among patients with CIED-detected AF, once AF occurs, stroke risk seems to be predominantly driven by underlying risk factors.

**Comment**

AF is a precursor of stroke, the risk of which is determined by the CHADS-2 and CHA₂DS₂-VASc scores. However, these scores do not give any importance to the burden or nature of AF (paroxysmal/persistent/permanent). As the use of CIEDs have increased, the incidence of incidentally detected paroxysmal runs of AF has also increased. But do these runs of paroxysmal AF which are asymptomatic constitute an increased risk for stroke? Is anticoagulation indicated in all such cases? This poses a unique therapeutic dilemma to the treating physician. The study by Al-Gibbawi et al attempts to answer these questions. The authors found that in their study cohort the burden and duration of AF did not correlate with the risk of stroke/TIA, whereas the CHA₂DS₂-VASc score was highly predictive of the risk of developing a new stroke/TIA. It is important to remember this, as just the mere presence of paroxysmal AF on device interrogation does not warrant anticoagulation unless it is associated with a high CHA₂DS₂-VASc score.

**Article 10: COVID-19 Cardiology**

**Atrial Fibrillation Is an Independent Predictor for In-Hospital Mortality in Patients Admitted With SARS-CoV-2 infection**

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Abstract

Background: Atrial fibrillation (AF) is the most encountered arrhythmia and has been associated with worse in-hospital outcomes. 

Objective: This study was to determine the incidence of AF in patients hospitalized with coronavirus disease 2019 (COVID-19) as well as its impact on in-hospital mortality.

Methods: Patients hospitalized with a positive COVID-19 polymerase chain reaction test between March 1, 2020 and April 27, 2020 were identified from the common medical record system of 13 Northwell Health hospitals. Natural language processing search algorithms were used to identify and classify AF. Patients were classified as having AF or not. AF was further classified as new-onset AF vs. history of AF.

Results: AF occurred in 1,687 of 9,564 patients (17.6%). Of those, 1,109 patients (65.7%) had new-onset AF. Propensity score matching of 1,238 pairs of patients with AF and without AF showed higher in-hospital mortality in the AF group (54.3% vs. 37.2%; P < .0001). Within the AF group, propensity score matching of 500 pairs showed higher in-hospital mortality in patients with new-onset AF as compared with those with a history of AF (55.2% vs. 46.8%; P = 0.01). The risk ratio of in-hospital mortality for new-onset AF in patients with sinus rhythm was 1.56 (95% confidence interval 1.42-1.71; P < .0001). The presence of cardiac disease was not associated with a higher risk of in-hospital mortality in patients with AF (P = .1).

Conclusion: In patients hospitalized with COVID-19, 17.6% experienced AF. AF, particularly new-onset, was an independent predictor of in-hospital mortality.

Comment

AF is the most common arrhythmia seen in hospitalized patients and is often a harbinger of poor outcomes and clinical deterioration. In patients with severe systemic inflammatory states and critical illness, it is often found to occur both with and as a cause of worsening clinical status. The novel corona virus disease (COVID-19) has been found to be characterized with a systemic inflammatory response, especially in patients needing hospitalization and critical care. AF when it occurs, deranges the hemodynamic status of the patient often compounding the underlying hemodynamic instability due to the systemic effects of COVID-19. A hypercoagulable state that is often found to occur in patients with COVID-19 might also lead to an increased in cadence of thromboembolic events related to AF. This study by Mountantonakis et al has shown that in patients hospitalized with COVID-19, the onset of AF (particularly new-onset AF) is an independent marker of in-hospital mortality irrespective of the presence of underlying cardiac disease. This is an important prognostic marker as we come to terms with newer facets of COVID-19 disease.

Further Reading

- 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction. J Am Coll Cardiol. 2021;77(6):772-810.
- Team-Based Care of Women With Cardiovascular Disease From Pre-Conception Through Pregnancy and Postpartum: JACC Focus Seminar. J Am Coll Cardiol. 2021;77(14):1763-1777.
- 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). European Heart J. 2021;42(14):1289-1367.