November 2021 Issue

Talk of the Town

-A Midtown Journal Club Newsletter

The Rise of Empagliflozin

EMPEROR-Preserved Trial shows morbidity benefit in HFpEF patients as well

SGLT-2 inhibitors have repeatedly shown reduced risk of hospitalizations and adverse cardiovascular outcomes for patients with reduced ejection fraction, but it has not been proven if these medications would benefit patients with preserved ejection fraction.

EMPEROR-Preserved is a multicenter, parallel-group, randomized trial (N=5988) conducted in 622 centers over 23 countries. Included in the study were patients at least of 18 years of age, with NYHA class II-IV symptoms with LVEF >40% while clinically stable.

Study also required patients to have significant proBNP levels (proBNP >300 pg/mL if no Afib or >900 pg/mL if with a history of Afib), hypertensive heart failure or structural heart disease (evidenced by LAE or LVH), and stable diuretic use. Excluded in the study were those with a history of MI, CABG, severe valvular heart disease, acute decompensated HF, rapid Afib/Aflutter, SBP>180 or <10mmHg, ICD placement within the last 3 months, cardiomyopathy including infiltrative disease, muscular dystrophies and HOCM or pericardial constriction, and morbid obesity.

The study's primary outcome was notably a composite of cardiovascular death or hospitalization for heart failure-- 13.8% vs. 17.1% for empagliflozin vs. placebo (hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.69-0.90, $p < 0.001$). This effect was mostly due to decreased rates of hospitalizations (8.6% vs. 11.8%; HR 0.71, 95% CI 0.60-0.83) rather than decrease in death due to

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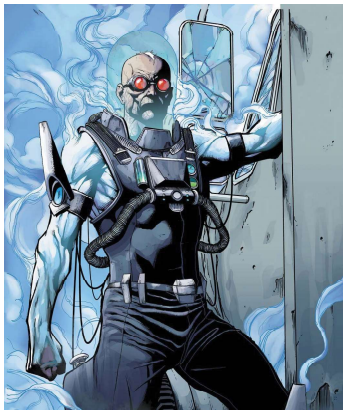
cardiovascular causes (7.3% vs. 8.2%; HR 0.91, 95% CI 0.76-1.09). Among the secondary outcomes, a decrease in total hospitalizations (407 vs. 541; $p < 0.001$) and change in mean eGFR per year (-1.25 vs. -2.62; $p < 0.001$) were significant. Differences in all-cause mortality and composite renal outcomes were not significant.

The benefits of empagliflozin for reduction in HF hospitalizations were similar among patients with or without type 2 diabetes. The benefits were attenuated among patients EF >=60%.

HFpEF is notoriously hard to treat, and most drugs that are currently used such as ACEI/ARBs and spironolactone mostly have benefits for patients with EF between 40-49% rather than true HFpEF. The results of the EMPEROR-Preserved trial is promising in that it has shown some benefits in morbiditiy, not necessarily mortality in HFpEF patients. Currently the mechanism of benefit of SGLT-2 inhibitors in HFpEF is unclear. Both empagliflozin and dapagliflozin are approved by the FDA for treatment of HFrEF, and we may expect to see these SGLT-2 inhibitors to be added to our arsenal for treatment of HFpEF as well. More on 10.1056/NEJMoa2107038.

Article by Siham Hussien, PGY1

No More Mr. Freeze!



Targeted temperature management (TTM) between 32°C to 36°C has been recommended in patients with coma post-cardiac arrest to prevent hypoxic ischemic brain damage. However, supporting evidence is low in certainty. The recent **TTM2** trial did not show benefits of hypothermia on survival and performance of those who suffered out-of-hospital cardiac arrest (OHCA).

Article by Elvina Yunasan, PGY1

Set in 61 centers in 14 countries, 1900 adults with coma after OHCA were randomly assigned in 1:1 ratio to undergo hypothermia (33 °C) or normothermia (≤ 37.5 °C). Excluded were those with unwitnessed cardiac arrest with asystole as the initial rhythm, or interval return from ROSC to screening more than 180 minutes. Primary ourcomes were death from any cause at 6 months, while secondary outcomes were based on the modified Rankin Scale (mRS), with lower numbers (0-3) representing no symptoms through moderate disability and higher numbers (4-6) representing severe disability or death.

The results showed that **TTM was not associated with improved 6-month mortality rate, nor functional outcomes when compared with normothermia.** Rather, TTM showed a significantly higher risk of arrythmias leading to hemodynamic compromise (24% v 16%; RR 1.45, CI 1.21-1.75).

REVIEW: Is Aspirin Worth It?

First extracted from the bark of willow trees, salicylic acid and its modified form acetylsalicylic acid (ASA; aspirin) were one of the oldest analgesics and antipyretics. Medical history was again revolutionized by the discovery of the sustained antiplatlet effects of aspirin. Currently aspirin is the quintessential medication for secondary prevention of cardiovascular events (i.e. MI, CVA).

However, the role of aspirin in **primary prevention** of cardiovascular events is still hotly debated. The preventative benefit of aspirin is complicated by bleeding risk and potential risk reduction of colorectal cancer. Three large multicenter trials (see right side) shed light on this issue. Subsequent metaanlyses (Zheng SL et al, 2019) pooling data from 164,255 patients showed a CV disease risk reduction by 11%, with a number needed to treat (NNT) of 265. Bleeding risk was increased by 43%, with a number needed to harm of 210. Overall there was a non-significant 6% reduction in total mortality.

1) **ARRIVE** trial: in low-moderate risk patients with age >55-60 yrs, no signficant difference in primary composite outcome (CV death, MI, UA, stroke, TIA; 4.3% v 4.5%, p=0.60) after 5 years. Significant increase in GI bleeding (0.97 vs. 0.46%, p = 0.0007) vs. placebo seen.

2) **ASCEND** trial: in diabetic patients, signficant difference in primary CV events (MI, stroke, TIA, all-cause mortality; 8.5% v 9.6%, p=0.01) after 7 years. Major bleeding more common (4.1% vs. 3.2%; p = 0.003) in aspirin vs. placebo mostly GI bleeding.

3) **ASPREE** trial: in older adults (age >65-70) without dementia, no significant difference in primary composite of death, dementia, physical disability. Underpowered for major CV events (HR 0.89, 95% CI 0.77-1.03). Rates of bleeding higher in the aspirin group (8.6 vs. 6.2 events per 1000 person-years; p < 0.001), mostly GI.

Current ACC guidelines suggest that low-dose aspirin can be considered for primary prevention for those with a 10-year ASCVD risk estimate of >=10% **IF** the potential benefit outweighs bleeding risk after clinician-patient risk discussion. It is important to note that the Pooled Cohort Equation is becoming less accurate as populations have changed since its introduction in 2013. Also, the overall population risk of CV disease has been decreasing with more recent developments in preventative strategies. Further evolution of the role of antiplatelet therapy in CV disease is expected in the next forseeable years.

Article by Dena Tran, Jeayoung Park. Article based on 2019 ACC review by Orkaby et al.

No need to "Juice" for Heart Attacks

The recent **REALITY** trial showed that for patients hospitalized for an acute myocardial infarction, a restrictive transfusion threshold (Hgb ≤8) was non-inferior to a liberal threshold (Hgb ≤10) for 30-day major adverse cardiovascular events.

This multicenter, open-label randomized study (N=666) included 35 hospitals in France and Spain. **Notably patients with shock or MI after revascularizations were excluded.** Patient with massive ongoing bleeding or malignant hematolic disease were also excluded.

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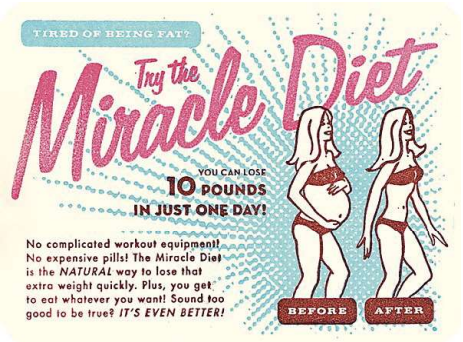
At day 30, MACE (all-cause death, stroke, recurrent MI, emergency revascularization) occureed in 14% vs. 11% in the liberal vs restrictive transfusion group. Group difference was -3% (95% CI -8.4% to 2.4%). This met the non-inferiority criterion.

Although the REALITY trial revealed information in a key population with very little data, sample size was small and a statistical significant for superiority of the restrictive transfusion strategy was not met. Also the outcome was measured at day 30, which was relatively short for post-cardiac arrest followup. A larger trial will be needed for guidance in anemia managment in this population.

Article by Harim Kim, PGY2

GLP-1 agonists: the New Miracle Diet Pill?

Turns out, you still need to exercise and throw away those cakes and muffins.



In 2015, the SCALE trial showed that daily injections of liraglutide plus lifestyle interventions **(500 kcal per day deficit with 150 min/week physical activity)** resulted in a significant number of patients losing at least 5% of body weight compared to placebo plus lifestyle interventions (63.2% vs 27.1% of patients, p<0.001). The study was groundbreaking in that it was effective in patients without diabetes. This lead to the FDA approval of liraglutide for weight loss.

A more recent clinical trial named **STEP 1** demonstrated that weekly injections of semaglutide with lifestyle interventions can achieve similar effects--except that the weight loss effects are even greater. In the intervention group, about 50% of participants lost 15% of body weight after 68 weeks of treatment (-14.9% v. -2.41%; diff -12.4, 95% CI -13.37 to -11.51). Secondary endpoints such as waist circumference, systolic blood pressure, and physical functioning scores also showed very significant difference (p<0.001 for all).

The degree of weight loss seen was almost unprecedented, especially given the benchmark weight loss for improved cardiovascular outcomes is typically 10%. Although the study was limited by a skewed population towards white females and the fact that around half of the study population were pre-diabetic, the study nonetheless gave hope to the general population without a history of diabetes. Further studies with oral regimens and potentially comparative studies against other weight loss agents will be needed.

Article by Jeayoung Park, PGY2

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