September 2022 Double Issue

Talk of the Town

-A Midtown Journal Club Newsletter

PCSK9 Inhibitors:

Are the World's Most Expensive Lipid Meds Worth It?

Article by Aleksan Kachatryan (PGY2)

The Proprotein Convertase Subtilisin Kexin-9 (PCSK9) proteins were initially discovered in 2003 as a cause of a few rarer forms of familial hypercholesterolemia. The concept of the PCSK9 proteins as a therapeutic target formed after inactivating mutations were found to have a protective effect against hyperlipidemia in animals and humans.

Since 2017, RCTs such as GAUSS-3 and ODYSSEY-Alternative (for statin-intolerant populations), as well as FOURIER, ODYSSEY-Outcomes, and GLAGOV (for secondary prevention), demonstrated significant cardiovascular benefits from PCSK9 inhibitors.

The biggest downside of these medications is the cost—while a patient can obtain a year's supply of statins as cheap as $40 (out-of-pocket) and ezetimibe around $400-600, PCSK-9 inhibitors can cost around $12,000 or more (Weintraub et al., Pharmacoeconomics 2016). Cost-effectiveness analyses of the FOURIER trial showed that it is too expensive at its current price list, ranging from $100k to $489k per quality-adjusted life year, to be effective. Therefore, research is ongoing to find if these medications are justifiable in at least a particular subset of patients.

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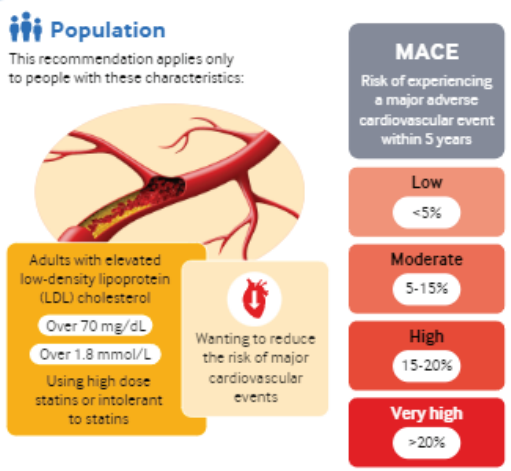
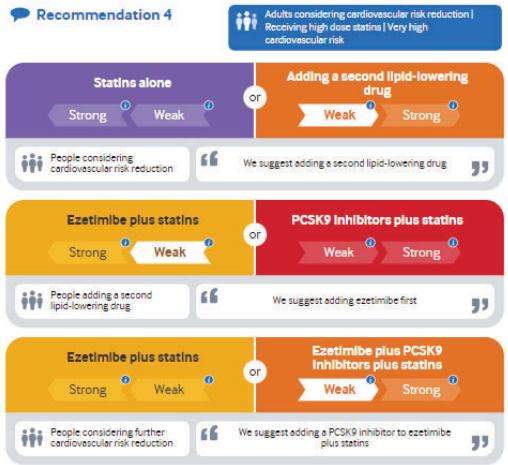


A recent network **meta-analysis** investigated whether PCSK9 inhibitors have an incremental benefit when used on top of statins or ezetimibe. The study included 14 trials with a total of 83,660 adults who were either 1) on **high-dose** statins or 2) **intolerant** to statins. These patients were further categorized into low, moderate, high, or very high 5-year cardiovascular (CV) risk based on a multivariate model developed from the New Zealand PREDICT (Poppe et al., Heart 2020) database. Then within each group, the following four additional treatment options were compared: **control, ezetimibe, PCSK9 inhibitors, and ezetimibe + PCSK9 inhibitors.**

The primary endpoints for this meta-analysis were non-fatal myocardial infarctions (MI), non-fatal stroke, all-cause mortality, and cardiovascular mortality. Overall, for patients on high-dose statins, both ezetimibe and PCSK9-inhibitors reduced MI (RR 0.87 [0.80-0.94] and 0.81 [0.76-0.87], respectively) and stroke (RR 0.82 [0.71-0.96], 0.74 [0.64-0.85]), but not all-cause mortality or cardiovascular mortality. Adding PCSK9 inhibitors to the combination of high-dose statins and ezetimibe further decreased MI and stroke risk in very-high risk patients, but only stroke risk in high-risk patients. Adding either ezetimibe or PCSK9 inhibitors did not benefit low or moderate CV risk patients. For statin-intolerant patients, ezetimibe monotherapy reduced non-fatal MI (16 fewer per 1000) and stroke (17 fewer per 1000), and adding a PCSK9 inhibitor to ezetimibe further reduced non-fatal MI and stroke (20 fewer per 1000).

This study resulted in a new clinical guideline published by the BMJ (with no other association with a specific professional organization), which can be summarized as-- 1) Ezetimibe or PCSK9 inhibitors should only be considered in **high** (15-20%) or **very high** (>20%) CV risk patients, 2) Ezetimibe should be added first before PSCK9 inhibitors (based on expert opinions, despite similar effects on MI and stroke prevention), 3) For patients on **maximal** statins and ezetimibe, PCSK9 inhibitors should be considered only in very **high-risk** patients, 4) For statin-**intolerant** patients on ezetimibe, PCSK9 inhibitors should be considered for high and very high-risk patients, and 5) The main benefit of either medication is for non-fatal **MI and stroke risk** reduction, not mortality.



Limitations of this study include generating data based on indirect comparisons mainly and not including cost-effectiveness. Perhaps, at this time, we should consider recommending better lifestyle interventions rather than adding expensive medications that can be devastating to the wallet.

CLASSICAL TRIAL REVIEW

Where do these *Thresholds* Come From?

Articles by Siham Hussien (PGY2), Mohamed Ethar Mohamed (PGY1), Elvina Yunasan (PGY2)

<1> Blood Pressure Goals of 130/80 (SPRINT)

It has only been 60 years since the concept that one should "treat" high blood pressure was introduced. The multicenter VA co-operative study in the 1970s established the benefit of a diastolic blood pressure (DBP) goal of 90, and the SHEP study in 1991 saw the benefit of a systolic blood pressure (SBP) goal of 160, which is quite generous for modern standards. Subsequent studies, such as the ACCORD-BP and SPS-3 trials, did not show a substantial benefit of strict BP control in patients with diabetes and stroke. Ultimately, the **Systolic Blood Pressure Intervention Trial (SPRINT)** trial (2010-2015) sealed our modern BP goals of 130/80 for the general population.

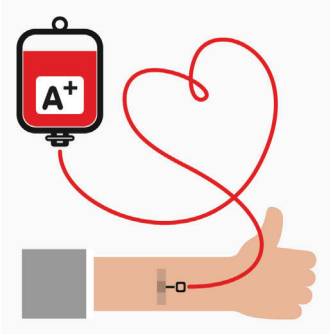
The SPRINT trial was a multi-center clinical trial including 9361 patients with an SBP >=130 and at least 1 of the cardiovascular (CV) risk factors -- prior CV events, coronary arterial disease (CAD), peripheral arterial disease, chronic kidney disease (CKD), Framingham risk score >=15%, and age>=75—but without diabetes or stroke (the very population of ACCORD and SPS-3). Patients were randomly assigned to either a target systolic BP of 140 mmHg (standard treatment) or 120 mm Hg (intensive treatment). The antihypertensives recommended were per the common practice of the time—thiazides as the first-line agent, loop diuretics for CKD, beta-blockers for CAD.

The study was stopped at the median follow-up time of 3.26 years due to **dramatic benefits** in the intensive control group. The primary outcome (a composite of acute coronary syndrome, stroke, heart failure, or death from CV cause) in the intensive treatment group was significantly lower compared to the standard treatment group (5.2% vs. 6.8%, HR 0.75; 95% CI 0.64-0.89; P<0.001; NNT 63). This was mainly driven by a decreased rate of **HF** (38% risk reduction) and **CV mortality** (43% risk reduction). The decrease in ACS or stroke events was not statistically significant. On the other hand, intensive treatment was also associated with 4% higher rates of serious adverse effects from anti-hypertensive medications, including syncope and electrolyte abnormalities. Among patients without CKD, there was also a higher risk of development of new CKD (stage 3 or above)—3.8% vs. 1.1 % (HR 3.49; 95% CI 2.44-5.10; P<0.001).

When the SPRINT study was initially released, a few concerns were raised by reviewers. The median follow-up time of 3.26 years was relatively short, which can overestimate long-term treatment effects. In addition, on average, the intensive treatment group required **one more** antihypertensive medication than the standard treatment group, which warranted a cost-effectiveness analysis of the intensive strategy. A 2017 follow-up analysis showed that intensive BP control improved patients' health by a mean **quality-adjusted life-years** (QALYs) of 0.27 and will cost $47,000 per QALY (if treatment benefits lasted for five years) or $28,000 per QALY (if treatment benefits lasted for the patient's lifetime). This was lower than the standard threshold of $50,000 (5 years) and $100,000 per QALY (lifetime).

Another major concern was that the BP measurements in the SPRINT study were done in a **research setting** (allowing ample time for patients to relax and settle in), which is often unrealistic in a busy real-life clinic. The ACC/AHA guidelines (2017) address this concern by recommending a more relaxed SBP goal of 130 rather than 120, considering real-life BP measurements are likely higher than in research. Other problems, regarding the lack of focus on geriatric patients or long-term cognitive outcomes, were addressed by subsequent studies. SPRINT remains one of the most vital pieces of evidence for intensive BP control.

<2> Transfusion Threshold of Hgb 7g/dL (TRICC/TRISS trials)



The threshold for red blood cell (RBC) transfusions in the critical care setting was somewhat elusive until the early 2000s. The **Transfusion Requirements in Critical Care (TRICC)** trial in 1999 was the first multi-center RCT of its kind to examine a restrictive transfusion (transfusion to maintain hemoglobin ≥7 g/dL) vs. liberal transfusion (transfusion to maintain hemoglobin ≥10 g/dL) strategies. The restrictive transfusion group showed lower in-patient mortality compared to the liberal group, especially amongst less critically ill patients (APACHE II score ≤20, age<55). Despite setting the stage for a paradigm shift for transfusion thresholds worldwide, there remained doubts regarding generalizability as the TRICC trial had only included euvolemic hemodynamically stable patients, excluding septic shock patients.

The **Transfusion Requirements in Septic Shock (TRISS)** trial answered this question 15 years later. This was a multicenter, partially-blinded RCT performed at 30 ICUs in Scandinavia involving 1005 patients. Inclusion criteria were as follows: Age ≥18 years in the ICU, fulfilling full criteria for Septic Shock and with a Hgb ≤ 9 g/dL. Patients were excluded if they had life-threatening bleeding, ongoing MI, or acute burn injury at the time of randomization. Patients were assigned to receive transfusions at the restrictive (≤7 g/dL) threshold or the liberal (≤9 g/dL) threshold.

The primary outcome was mortality on the 90th day of randomization. **No** significant differences were observed between the transfusion strategies; 43% vs. 45% (RR 0.94; 95% CI 0.78-1.09; P=0.44) with both intention-to-treat analysis and per-protocol analyses. There were also no significant differences

in the secondary outcomes—including the use of life support measures on days 5, 14, and 28, the number of patients with ischemic events or severe adverse reactions, and days alive without vasopressor/inotropic therapy, mechanical ventilation, or renal replacement therapy. However, the restrictive strategy nearly **halved** the frequency with which blood transfusions were administered (1,545 vs. 3,088 units; P<0.001).

In summary, a restrictive hemoglobin threshold of 7 g/dL was non-inferior to a more liberal approach in terms of morbidity and mortality while decreasing the overall amount of blood transfusions. Also, it is arguably safer, given the flux of bloodstream inflammatory mediators and microvasculature changes observed in patients with septic shock. The partial blinding of this trial is justified as it would have been virtually impossible to double-blind given the critical nature of septic shock and the questionable morality of blinding the attendings to their patients' intervention assignments. Currently, the **Surviving Sepsis** guideline by the Society of Critical Care Medicine has adopted the restrictive Hgb threshold of 7.

<3> Inpatient Glucose Goal of 140-180 mg/dL (NICE-SUGAR)

Managing glucose in critically ill patients remains a challenge since it requires correcting hyperglycemia while avoiding hypoglycemia. A few major clinical trials helped establish inpatient glycemic goals that we know of today. In the early 2000s, a restrictive glycemic target (80-110 mg/dL) was initially advocated based on the **Leuven Surgical Trial (2001)** which demonstrated improved survival compared to conventional glycemic control (180-200 mg/dL) at the time. However, the **NICE-SUGAR trial (2009)** contradicted these findings 8 years later, showing increased mortality among critically ill patients who received tight sugar control.

NICE-SUGAR was a multicenter, non-blinded, parallel-group, randomized controlled trial. Inclusion criteria were expected ICU stay for ≥3 consecutive days in either a medical or surgical ICU. Patients were recruited regardless of DM status. A total of 6104 subjects were randomly assigned to the intensive group (81-108 mg/dL) or the conventional group (≤180 mg/dL). Glycemic control was achieved with IV insulin infusion. The primary outcome was **90-day mortality,** which was found to be higher in subjects in the intensive group compared to the control group (27.5% vs 24.9% adjusted OR 1.14; 95% CI 1.01-1.29; p=0.04).

Severe hypoglycemia (blood glucose ≤40 mg/dL) was also higher in the intensive group compared to the conventional group (6.8% vs 0.5%; p<0.001). Meanwhile, there were **no** significant differences in the median number of days in the ICU or hospital, median number of days of mechanical ventilation, or renal-replacement therapy.

There were several limitations of this study. First, when recruiting study participants, researchers used subjective judgment to decide if the patient can meet the expected at least 3 consecutive days in the ICU. There was also a lack of blinding for both the patient and staff; however, realistically it would have been difficult to blind the blood glucose target. In addition, all patients were receiving PO nutrition rather than parenteral nutrition, and the amount of carbohydrate intake can vary. Nonetheless, NICE-SUGAR remains one of the largest studies to date regarding glucose targets. A few questions yet remain—do patients with and without a history of diabetes deserve different glucose targets? What should be the target glucose for non-critically ill patients? Although different societies offer divergent recommendations, NICE-SUGAR still stands as a pivotal study that may have protected patients against potential harm from strict glucose control.

MRI of Severe COVID Patients Reveal Brain Damage

Article by Farhad Pishgar (PGY1)

The Internet is full of memes like the above. It has been almost three years since the outbreak of SARS-CoV-2, and apparently, we need more time to process everything we have been through. Not only are there still many questions about the virus itself, but the healthcare systems worldwide are also still struggling with long-term sequels of this virus.

The "SARS-CoV-2 is associated with changes in brain structure in UK Biobank" (Douaud et al. Nature 2022) is a longitudinal investigation on the possible long-term sequels of the SARS-CoV-2 infection on the central nervous system. The authors used clinical data and brain MRI images of 401 cases who tested positive for the infection and 384 healthy matched controls to study the possible effects of this infection on different regions of the brain as well as the overall cognition of participants.

One of the consistent clinical features of the SARS-CoV-2 infection, which can even appear before the onset of respiratory symptoms, is the disturbance in olfaction. Given this, the first finding of this investigation was no surprise; the authors showed a more significant reduction in grey matter thickness in the orbitofrontal cortex and parahippocampal gyrus, as well as more significant changes in markers of tissue damage in regions that are functionally connected to the primary olfactory cortex.

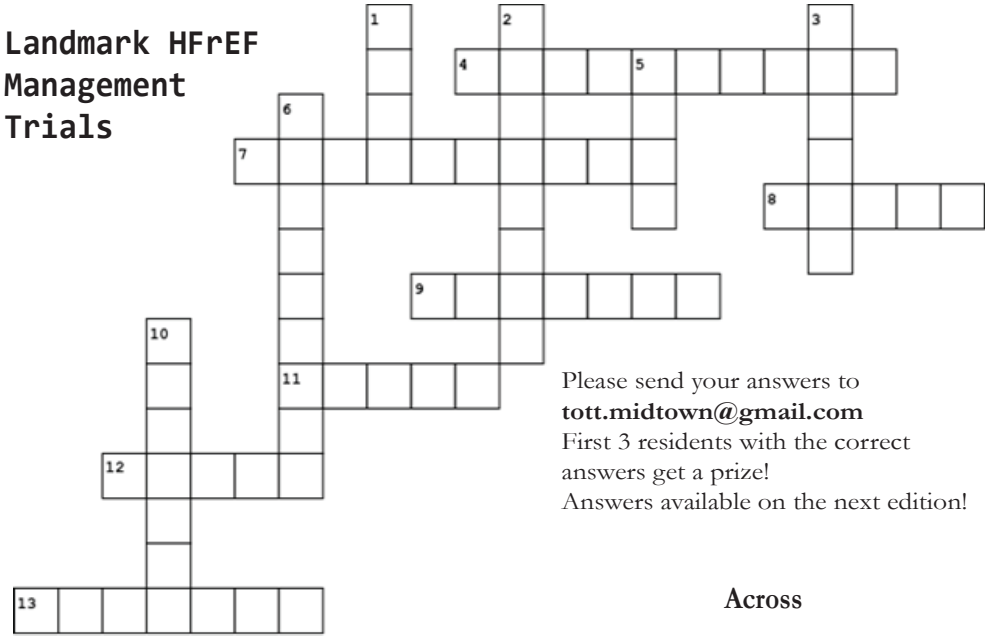
However, this investigation also shed light on the possible effects of the SARS-CoV-2 infection on the other regions of the central nervous system. The authors showed a more significant reduction in global brain size (lower brain volume to total intracranial volume ratio and higher CSF volume) in the cases that tested positive for the infection. Moreover, this investigation showed a more significant cognitive decline after the SARS-CoV-2 infection compared to a similar period in healthy matched controls.

So, suppose you are like me and need more time to process what has happened over the past three years. In that case, you may also be experiencing the long-term effects of this infection on your central nervous system, and you should probably get used to the fact that you might need a little more time to process things these days!

CROSSWORD PUZZLE

Hyphens ("-") are omitted in each answer.

Landmark HFrEF Management Trials



Please send your answers to **tott.midtown@gmail.com**
First 3 residents with the correct answers get a prize!
Answers available on the next edition!

Down

1. This 2000 study demonstrated ramipril reducing CV events in high-risk patients without HFrEF
2. This 2009 study showed that cardiac resynchronization therapy, in addition to ICDs, reduced HF events in pts with HFrEF and QRS>130ms.
3. This 1991 study showed that enalapril was superior to hydralazine+isosorbide for mortality reduction in HF
5. This 2011 study showed that the dosage of loop diuretics had no significant effect on overall effectiveness or safety in acute decompensated HF.
6. This 1987 study showed that enalapril decreased the progression of severe HF and mortality
10. This 2001 study showed that an LV assist device reduced all-cause mortality in patients with severe heart failure on optimal GDMT

Across

4. This 2014 study showed that valsartan-sacubitril reduced the risk of hospitalizations and death from HF
7. This 2002 study showed that the addition of carvedilol to standard severe heart failure (EF<25%) therapy showed risk reduction
8. This 1999 study showed that high-dose ACE inhibitors reduced hospitalizations or death from HF compared to a lower dose.
9. This 1999 study showed that metoprolol reduced mortality in symptomatic HF.
11. This 1994 study showed that ivabradine reduced hospitalization and death from HF in patients with a baseline heart rate > 70.
12. This 1999 study showed that spironolactone reduced all-cause mortality in EF <=35%
13. This 2005 study showed that ICDs decreased mortality in patients with LVEF <=35% and NYHA II-III symptoms

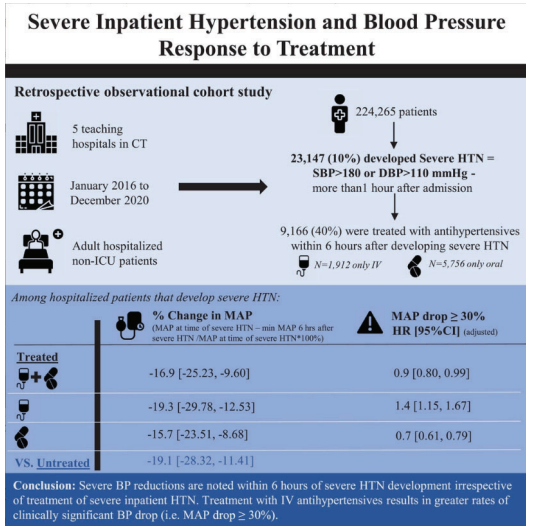
Hospital Medicine

Are We Using Too Much IV Anti-Hypertensives?

Article by Harim Kim (PGY3)

It is very common to have an incident of severe HTN in hospitalized patients occurring during an admission unrelated to HTN. However, compared to severe hypertension in an ambulatory setting, sev-ere HTN that develops during hospitalization is poorly studied and management strategies remain non-standardized. Oftentimes our knee-jerk reflex is to start IV antihypertensives as needed, but this comes with a rapid decrease in BP, which may need to adverse outcomes.

A recent retrospective cohort study at five teaching hospitals associated with the **Yale-New Haven Hospital System** surveyed the current practice of inpatient severe hypertension management. A total of 224,265 patients who were admitted for a reason other than severe hypertension, with a length of stay between 2-30 days, were included. Excluded were patients with a hypertensive emergency at admission or those who were admitted to the maternity ward, intensive care unit, or research unit. For patients with multiple admissions during the study period, this study only included data from their first admission. Severe hypertension itself was defined as the first documented severe BP elevation (SBP > 180 or DBP > 110 mm Hg) reported after admission and did not include BPs captured in the emergency department.



The primary outcome was defined as more than a 30% decrease in MAP within 6 hours of admission. Patients who received IV or PO treatment within 6 hours were compared to those who did not receive any treatment in 6 hours (serving as a control). Results showed that approximately 10% of all patients (23,147) developed severe HTN after admission, and a total of 9166 patients were treated with antihypertensives within 6 hours after the onset of severe HTN. Among these patients who received early treatment, 1912 received IV meds, 5756 received oral meds, and 1498 received both.

Patients who were treated with IV-only medications had a 38% (HR, 95%CI: 1.4 [1.2, 1.7]), 43% (1.4 [1.2, 1.7]), and 32% (1.3 [1.1, 1.6]) greater rate of MAP, SBP and DBP drop ≥30% compared to untreated inpatients, respectively, after adjusting for demographic and clinical characteristics. Severe MAP drop (≥30%) was also greater among patients treated with IV versus oral medications. The following patient characteristics were associated with a greater risk of rapid decrease in MAP: older age, history of congestive heart failure, cardiac arrhythmias, peripheral vascular disease, and receiving crystalloids or sedatives.

The authors concluded that IV anti-hypertensives should be used **judiciously** given their risks. The study however did not investigate whether rapid drops in MAP led to *end-organ damage*—therefore, it is unknown if IV anti-hypertensive are truly "harmful." The study also did not account for the patient's outpatient BP range and the types of medications the patient is taking. The study also included all antihypertensives regardless of type, dose, or if it was a home medication. In sensitivity analysis, loop diuretics and beta blockers were excluded, but IV labetalol is one of the most commonly used IV anti-hypertensives in the hospital. The results of this study were also limited to one hospital system which could hurt its **generalizability**—luckily, another recent study at the Cleveland Clinic system showed similar results. Overall, more studies are needed to guide an evidence-based approach to inpatient hypertension.

Lifestyle Medicine

Low-Fat Diet vs Mediterranean

Article by Priyanka Kumar (PGY1)

A person's diet is often considered a ripe area for intervention in the prevention of cardiovascular disease. Research has investigated dietary intake across the domains of composition, energy consumption, and feeding patterns which may contribute to cardiovascular disease (Bays et al. Am J Prev Cardiol 2022). While regimens such as the Mediterranean diet and low-fat diet are commonly referenced, there is limited research on the long-term cardiovascular outcomes of adhering to these regimens.

The **CORDIOPREV** study was a long-term randomized trial of the Mediterranean diet and low-fat diet to compare the effects of each in the secondary prevention of CV disease (Delgado-Lista et al. Lancet 2022). This 7-year, single-center partially-blinded trial was conducted at the Reina Sofia University Hospital in Cordoba, Spain. The study population consisted of 1002 adults (aged 20-75 years old) with established coronary heart disease including acute myocardial infarction, unstable angina, and chronic high-risk ischemic heart disease. Exclusion criteria consistd of clinical events related to coronary heart disease in the 6 months prior to recruitment, inability to follow a long-term dietary intervention, and comorbid severe chronic disease including those which could modify lipid metabolism (i.e.,chronic renal failure, chronic liver disease).

Study participants were assigned to either (1) a Mediterranean diet, comprising a minimum of 35% of the calories as fat, 15% proteins, and a maximum of 50% carbohydrates, or (2) a low-fat, high complex carbohydrates diet, comprising less than 30% of total fat, 15% protein, and a minimum of 55% carbohydrates. The randomization was blinded to physicians and CORDIO PREV team; only the study participants and dieticians were aware of dietary assignments. During the study period, participants had regularly scheduled face-to-face visits, group sessions, and telephone calls; adherence was captured with the 14-point Mediterranean Diet Adherence Screener (with 14 representing best adherence) and the 9-point low-fat diet scale (with 9 representing best adherence). Of note, participants were not counseled on physical activity in this study.

The primary outcome measure was a composite term for major cardiovascular events, consisting of myocardial infarction, revascularization, peripheral artery disease, and cardiovascular death. At year 7, the study was stopped following 198 primary outcome events, 87 in the Mediterranean diet group and 111 in the low-fat diet group (unadjusted HR 0.745, 95% CI 0.563-0.968). The Mediterranean diet was significantly superior to the low-fat diet in the primary outcome measure across models adjusting for age, sex, hypertension, LDL cholesterol, BMI, smoking, statins, diabetes, and changes in weight/physical activity. Of note, when assessing each of the individual components of the primary outcome, there were no significant differences between the two dietary intervention groups (e.g. non-fatal myocardial infarction (p=0.120), ischemic stroke (p=0.123), cardiovascular death (p=0.12). Lastly, baseline adherence in this study was higher among the participants assigned to the Mediterranean diet (8.78 on the 14-point scale) than in the low-fat diet group (3.81 on the 9-point scale).

In extrapolating these results to the real-world setting, key limitations include (1) unequal adherence between the two diets and (2) generalizability to patient populations with no baseline cardiovascular disease (being a secondary prevention trial) and (3) generalizability to patient populations with co-occurring chronic disease (i.e., hypertension, diabetes). Further, the study lacks a control/non-dietary intervention group, and the effect of patients' diet before trial initiation is not taken into account. Nevertheless, the CORDIOPREV study provides a powerful, long itudinal perspective on the role of specific dietary regimens in the secondary prevention of cardiovascular disease.

SSaSS: The Salt Substitution Study

Replacing Na with K

Article by Mitchell Belkin (PGY1)

Cardiovascular deaths are the leading cause of global deaths. The SSaSS was an open-label, cluster-randomized trial designed to evaluate whether a low-cost salt substitute containing potassium (KCl) would reduce strokes and cardiovascular deaths. The study followed 20,995 persons recruited from 600 villages in 5 provinces in rural China who were randomized at the village level to receive either regular salt (100% NaCl) or a salt substitute (75% NaCl, 25% KCl). Included patients were 60 yrs of age or older with systolic blood pressures ≥140 mm Hg (if they are receiving anti-hypertensives) or ≥160 mm Hg if they are not. Exclusion criteria included contraindications to salt substitution, including use of a potassium-sparing diuretic, use of potassium supplement or known kidney disease, or if they ate most meals outside the home. At baseline, participants' mean age was 65.4 years, 49.5% were female, and 72.6% had a previous stroke. Mean blood pressure was 154/89 mmHg with 79.3% using at least one blood pressure lowering medication (41.8% calcium antagonist, 22.8% ACE-i or ARB, 11.5% a diuretic, 5.7% Beta-blocker, 0.9% alpha-blocker).

Over five years, the participants were followed to track rates of **stroke** (the primary outcome), cardiovascular events and death from any cause (secondary outcomes), and clinical hyperkalemia. The stroke rate was significantly lower in the salt substitute group compared to the regular salt group (29.14 events vs. 33.65 events per 1000 person-years, rate ratio 0.86; 95% CI, 0.77 to 0.96; P = 0.006). The salt substitute group likewise reduced secondary outcomes of major adverse cardiovascular events (49.1 vs. 56.3 events per 1000 person-years, rate ratio, 0.87; 95% CI: 0.80 to 0.94; P<0.001) and death from all causes (39.3 vs 44.6 events per 1000 person-years; rate ratio, 0.88; 95% CI, 0.82 to 0.95; P<0.001).

As for adverse events, only two participants had documented "definite or probable" hyperkalemia (one in each group). An additional 313 participants had possible hyperkalemia (302 died). There was no evidence of a significant difference between the trial groups for definite, probable, or possible hyperkalemia (P=0.76).

The study was limited because potassium was not serially measured. In addition, individuals at the highest risk of hyperkalemia, including CKD patients, were excluded. Furthermore, only one salt substitute was used, so it was impossible to determine a dose-response of stroke/death risk with KCl supplementation. Despite these limitations, KCl supplementation is a practical, low-cost intervention that may lower the risk of stroke, cardiovascular disease, and mortality.

STATS MATTER

The EMPULSE Trial

An Introduction to Win Ratios

Article by Jeayoung Park (PGY3)

Sodium-glucose cotransporter 2 (SGLT2) inhibitors such as empagliflozin and dapagliflozin have become a household name for heart failure (HF) patients, with or without diabetes mellitus (DM). Empagliflozin, specifically, was also shown to be effective in HF with preserved ejection fraction (HFpEF) as well in the recent **EMPEROR-PRESERVED** trial. Determined to continue the win streak for empagliflozin, Eli Lily sponsored **EMPULSE**, a multi-national trial to investigate if the medication can be effective in patients admitted with acute heart failure exacerbation.

The trial was designed as a double-blind trial involving 530 patients with a new diagnosis of heart failure or decompensated chronic HF from 118 centers in 15 countries. Only patients who were medically stable (Sys BP >100mmHg, no inotropic support for 24hrs, and no increase in IV diuretics) were recruited. Patients were also between 24 and 120 hours since admission. Key exclusion criteria included patients with cardiogenic shock, PE, CVA, or acute MI, either currently or within the last 90 days. Patients with an LV assist device and current or expected cardiac transplantation were excluded as well. Patients were randomized to take either once-daily oral empagliflozin 10mg or placebo for 90 days from the start of the trial. All patients were included in the intention-to-treat analysis unless they withdrew consent, did not receive empagliflozin, or were lost to follow-up.

Patients were followed up at days 3, 5, 15, 30, and 90 days after randomization. BNP, eGFR, NHYA grades, and the Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) were measured. The primary outcome was reported in **win ratios**, which is a method of examining composite endpoints that gained popularity in recent clinical trials.

The win ratio is a variant of the **hierarchical** testing method. Think of it as a tournament--person A from the intervention group and person B from the control group are compared in terms of death, HF events, and symptoms scores. Patient A and B are a matched pair in terms of their patient characteristics (age, sex, past history, etc). If patient A "wins" on the death criteria, this round is considered "won" by the intervention group. But if A and B ties, you move towards the next criteria which is the number of HF events. If patient A "wins" here the comparison is over. Alternatively, patients can "tie" when you went through all of the criterias and they tied on everything. After all of these individual "matches" are completed, the final scores are tallied up. The win ratio is defined as the ratio of numbers of group A wins versus group B wins.

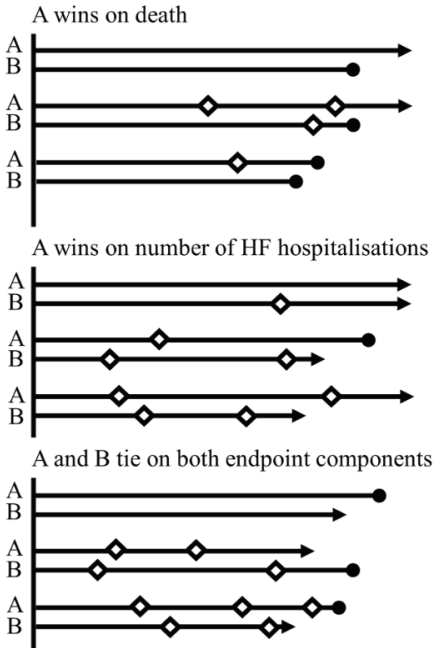


Image: Redfors et al., *Eur Heart J* 2020

The are a few benefits of reporting win ratios over conventional methods to evaluate composite outcomes (such as the Kaplan-Meier estimator and Cox proportional hazard regression). Since win ratios are a hierarchical test, the more clinically severe outcomes (e.g. death) have more weight compared to those with less severity (e.g. improvement in symptoms) in the overall composite. It is also easier to integrate repeat events (e.g. hospitalizations) while being conceptually straightforward.

In the EMPULSE trial, the composite outcome consisted of time to all-cause death, the number of heart failure events (HFEs), time to first HFE, and a 5-point or greater difference from baseline symptom scores, listed in the order of clinical severity Empagliflozin was superior in 53.9% of paired comparisons, while the placebo was superior in 31.7% of paired comparisons (the rest were ties). This gives us a win ratio of 1.36 in favor of empagliflozin (95% CI 1.09-1.68, p=0.0054). Therefore, one could say that if you were to bet on empagliflozin rather than placebo for patients with acute or new HF exacerbations, you are more likely to win.

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The trial showed important and promising results for a patient group that was previously less explored--in previous SGLT-2 inhibitor trials, patients with recent HF exacerbations were typically excluded. Subsequent studies showed its safety in terms of **renal function** as well as improvements in overall quality of life. Perhaps in the near future, we will start HF patients on empagliflozin more routinely in the hospital.