SGLT-2 Inhibitors for ALL Heart Failure: A Clinical Game Changer

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are strongly recommended for patients with heart failure with reduced ejection fraction. A new meta-analysis (Lancet 2022 Sep 3;400:757) looked at studies including the large DELIVER and EMPEROR trials asking whether SGLT-2 inhibitors are effective in heart failure patients with preserved ejection fractions. Almost 22,000 patients were randomized in five studies looking at CV-related hospitalization or death and all-cause mortality in various subgroups. Patients were excluded if they had glomerular filtration rates (GFRs) less than 20-30ml/minute/1.73 m². The mean age of participants was 66-72 years with 55% to 77% men. Diabetes was present in 45% to 50% of participants.

Results:
- In patients with preserved ejection fraction (EF), SGLT-2 inhibitors lowered the incidence of CV-related death or hospitalization compared with placebo (14.5% vs 17.8%: NNT=30) and in patients with EF of 50%-59% (NNT=30) and EF/>= 60% (NNT=40).
- Among all patients with heart failure, SGLT-2 inhibitors lowered the incidence of CV-related death or hospitalization (15.8% vs 19.7%: NNT=25).
- Risk reductions were similar in the sub-groups defined by different heart failure phenotypes (e.g., ejection fraction, New York Heart Association functional class, other heart failure therapies and atrial fibrillation) and concurrent conditions (e.g., diabetes, low kidney function and obesity).
• A Game Changer clinically, but probably not for the uninsured and underinsured. Farxiga and Jardiance sell for $536 and $557/month (GoodRx November 2022), respectively. Zach Kareus, Pharm D (UnitedHealthcare) indicates Jardiance will not go generic for its diabetic indication until 2027 and the other SGLT-2s push into the 2030s. Jardiance is one of the drugs on the short list eligible for negotiated Medicare pricing in 2026. Dr. Zach Kareus further comments that SGLT-2s are becoming more readily covered by insurance companies for heart failure.

• Clearly, SGLT-2 inhibitors in general and specifically empagliflozin’s absolute benefit is less for patients with preserved ejection fraction than for heart failure patients with reduced ejection fractions. In a study in JAMA Internal Med 2022 November 7, researchers used EMPEROR data to determine the cost effectiveness of empagliflozin with patients with left ventricular ejection fractions greater than 40%. At a price of $327/month, empagliflozin use resulted in an additional 0.06 quality adjusted life years (QALYS) (~3 weeks) which translates to $437,000 per QALY gained.

• Although they claim no external funding for this study, BE AWARE that eight of the 14 authors of this paper have had financial relationships (advisory boards, clinical trial work, speaker fees, grant support) from Boehringer-Ingelheim and Astra-Zeneca the makers of empagliflozin (Jardiance) and dapagliflozin (Farxiga), respectively.

Short & Sweet: A Series of Synopses

• **Mirena**, the 52 mg levonorgestrel intrauterine system now has FDA approval for eight years of use after original approval for five years. In a study published in the American Journal of Obstetrics and Gynecology (2022 September 9), 362 women completing five years of Mirena use were followed prospectively for three additional years. During those three years, two pregnancies occurred resulting in a cumulative contraception failure rate of 0.68%. Over eight years, Mirena had a contraceptive failure rate (Pearl index) of 0.28 pregnancies per 100 women-years of contraceptive use compared to 0.8 for the copper IUD. More than 90% of the Mirena users were satisfied with the bleeding patterns. About half were completely or nearly amenorrheic.

• **For Pete’s Sake**, QUIT doing or recommending viscosupplementation for knee osteoarthritis. In a meta-analysis of 9000 patients with knee osteoarthritis who were randomized to viscosupplementation or to placebo or no treatment, patients randomized to viscosupplementation had small, statistically significant, but not clinically important pain reductions (2 mm on a 100 mm scale) compared with controls. (Journal Bone Joint Surgery American 2022; 104:43) Make your patients aware that we’ve had good evidence for more than a decade that viscosupplementation doesn’t work for knee osteoarthritis.
- **Doxycycline**, an oldie, but goodie? As rates of drug resistance increase with macrolides and fluoroquinolones for Community Acquired Pneumonia (CAP), a study comparing regimens of IV or oral doxycycline is instructive. (Clinical Infectious Disease 2022 July 29). In a meta-analysis of 834 adult outpatients and inpatients (none of which required intensive care), IV or oral doxycycline was compared with three different macrolides and three different fluoroquinolones. Clinical cures accrued in a little less than 90% of the doxycycline group and were similar to the comparator drugs in terms of length of stay, treatment costs and adverse events.

- **Vivjoa** (otesaconazole) is the first FDA drug approved for managing recurrent vulvovaginal candidiasis. Patients eligible for this drug must have experienced three or more yeast infections per year, be post-menopausal or permanently infertile (contraception does not create eligibility) and affluent. Otesaconazole is teratogenic (fetal ocular abnormalities) in animals and has a half-life of 138 days - sticks around for almost two years! In the induction portion of the drug company supported study comparing otesaconazole with fluconazole, the two drugs had comparable success rates after two weeks (94%-98% cures). In the maintenance portion of the study (out 50 weeks), the authors tilted the scales and compared otesaconazole and placebo. Not unexpectedly, otesaconazole had a better recurrent candidiasis infection rate of 5% versus 42% for the placebo group. **My Take:** So, it’s not clear to me that otesaconazole is any more effective than existing oral fluconazole or vaginal azoles. At $2500-$2700 per course of treatment, there are less expensive, safer products with known track records.

**Treatment of the Common Cold circa 1892**

Sir William Osler is my historical medical hero. He was truly a Renaissance man. In 1892, he published his magnum opus, The Principles and Practice of Medicine, the 1069-page tome that became the principal reference for medical students and physicians for three decades. As we have launched into the “cold season,” I thought it appropriate that we look back at how Dr. Osler treated his patients with the common cold. Have we made progress or perhaps not?

> "Many cases are so mild that the patients are able to be about and to attend their work. If there are fever and constitutional disturbance, the patient should be kept in bed and should take a simple fever mixture, and at night a drink of hot lemonade and a full dose of Dover’s powder (ipecac and opium powders plus potassium sulfate). Many persons find great benefit from the Turkish bath. For local treatment, particularly in the early stage, when the mucous membrane is swollen and there is a distressing sense of tightness and pain over the frontal sinuses, cocaine is very useful and sometimes gives immediate relief. The 4% solution may be injected into the nostrils, or a cottonwool soaked in the solution may be inserted into them.”

- Dr. Osler
My Take:

- I did medical school and residency in “flyover country,” so I missed the opium and cocaine treatments for upper respiratory infections. I suspect Sir William’s URI patients got better pain relief than mine did with acetaminophen.
- Sir William practiced antibiotic stewardship faithfully. There is no mention of Z-paks in his compendium.
- Thomas Dover (1660-1742) was sometimes referred to as Dr. Quicksilver for his propensity to prescribe mercury for a variety of illnesses. As an English physician he became rich peddling Dover’s powders, but unlike modern Big Pharma, Dover put greed aside and spent much of his later life caring for the poor in Bristol England.

“The only way to treat the common cold is with contempt.” - Sir William Osler

Paxlovid Update
(My thanks to Dr. Emily Spivak, University of Utah)

- Paxlovid (nirmatrelvir/ritonavir) is indicated within 5 days of onset of documented mild Covid in non-oxygen requiring outpatients who are at risk of progressive illness to prevent hospitalization and death.
- Initial studies of Paxlovid were done on unvaccinated patients during the delta wave. NNT to prevent one hospitalization/death in those studies was ~18.
- New unpublished (EPIC-SR) data from Pfizer:
  - shows that taking Paxlovid had no significant effect on hospitalization or death in immunized healthy people under 65 years. The trial was halted due to “very low risk of death or hospitalization.”
  - Shows that Paxlovid had a modest effect in preventing hospitalization and death in immunized patients 75 years and older. Number needed to treat = 80-100.
- Current criteria for outpatient use of Paxlovid at the University of Utah:
  - Severe immunocompromise
  - Age >75 years
  - Age 65-74 years AND not up to date on vaccination
  - Age<65 years AND not up to date on vaccination and one risk factor for progression to severe disease
- Risk factors for progression to disease:
  - immunocompromise (high-dose steroids, active cancer treatment, other immunosuppressive drugs)
➢ diabetes
➢ pregnancy
➢ BMI > 30
➢ chronic lung disease
➢ hypertension
➢ chronic kidney disease
➢ chronic liver disease
➢ Sickle cell disease
➢ Patients with tracheostomies, gastrostomies, positive pressure ventilation

• According to Lee et al. (BMJ Evid Based Med 2022 Nov16):
  ➢ Conflicting RCT versus observational data in vaccinated patients with respect to Paxlovid efficacy
  ➢ Lack of data or well-designed trials evaluating impact on symptom resolution, disease transmission or lung Covid
  ➢ There is significant political and public demand for use in Paxlovid which has low or unproven value

MY TAKE

• My approach with Paxlovid had been to rather mindlessly recommend it to any legible family or friends that would listen.
• At age 80, I took Paxlovid in early December 2022, experienced some mild metallic taste and diarrhea and had a rebound COVID infection that necessitated 16 days of total isolation.
• The drug manufacture’s own data now suggest that the drug is useless in healthy immunized patients under 75 years of age.
• On the other hand, in patients over 75 and in those immunocompromised, a number needed to treat of 80-100 to prevent one hospitalization/death with a free, innocuous drug still looks pretty good to me. But stay tuned. The government’s purchased supply of Paxlovid will be exhausted by mid-2023 and Pfizer will undoubtedly market it the public at a bargain basement price.

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