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COMMENTARY

Dec 06, 2024 This Week in Cardiology Podcast

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In This Week's Podcast

For the week ending December 6, 2024, John Mandrola, MD, comments on the following news and features stories: Tirzepatide beats semaglutide in obesity but GLP-1 agonist use is complicated, heart failure (HF) outcomes, the misuse of meta-analyses in HF, and a potential breakthrough in HF care.

SURMOUNT-5

The SURMOUNT 5 trial was phase 3b trial comparing semaglutide and tirzepatide in patients with obesity and one co-morbidity. Lilly announced in a press release this week that tirzepatide provided a 47% greater relative weight loss compared with semaglutide.

- On average, tirzepatide led to a superior weight loss of 20.2% compared with 13.7% loss with semaglutide.
- At 72 weeks, tirzepatide beat semaglutide on both the primary endpoint and all five key secondary endpoints in this trial.
- One particular secondary endpoint of patients who achieved at least a 25% body weight loss occurred in 31.6% in the tirzepatide group vs 16% in the semaglutide group.

Results will be published and presented at an upcoming meeting.

This made big news on the business channels, but I am not sure it's a surprise because, in trials thus far, tirzepatide did seem to induce more weight loss than smaglutide.

Two comments: While tirzepatide induces more weight loss, semaglutide has outcomes data, such asthe SELECT trial of patients with established heart disease. The question is whether this is a semaglutide-specific effect or class effect. I suspect it is a class effect, but it would be nice to have trial evidence.

Second comment is that that when I query Perplexity, it tells me that there are 39 GLP-1 agonists in development. So this is perhaps the tip of the iceberg when it comes to comparing agents in this drug class.

Access to GLP-1 Agonist Drugs

I've long said on this podcast that obesity is a medical illness, one with severe complications. That distinction garnered some controversy, because obesity also has a behavioral and cultural component. Now, though, it is clear that GLP-1 agonist drugs are highly effective anti-obesity drugs, and in some conditions, such as diabetes and heart disease, are clearly disease-modifying outcome-reducing drugs.

But there are many-fold more patients with obesity who have yet to have a complication. For these patients, a drug that induces weight loss is likely to prevent complications.

One problem is obviously philosophical because weight loss could theoretically be achieved through lifestyle interventions. But in patients who have tried but failed this approach, GLP-1 agonists stand a good chance of working. Yet there are cost barriers.

Last week, the major payer in the United States, the Centers for Medicare and Medicaid Services (CMS), put out a proposal in which they recognize obesity as a disease and suggest re-interpreting the statute that excluded coverage of anti-obesity drugs for patients covered by Medicare, Medicaid, and Medicare Advantage.

I did not know there was such a statute, and I am no policy person, but clearly the discovery of this drug class and its use is probably the most important medical question for the next decade.

I have long worried that far too much of American healthcare is a simple wealth transfer from working people to the investor class and medical industry.

But GLP-1 agonists are different. At least over the short-term, they treat one of the Western world's greatest health destroyers — obesity. That weight loss from these drugs reduces outcomes in patients with diabetes and heart disease, offers a clue to their potential benefits in patients without these complications.

Yet the question is how to pay for these drugs. I don't know, but there is a sign in our outpatient pharmacy that our plan does not cover these drugs. The explanation goes something like this: "We can't; we would be bankrupt if we did." It's the same problem for any healthcare payer.

I would also draw a distinction between giving GLP-1 agonist for obesity in a Medicare-aged adult vs a child. How they should be used in people who will take them for more than 2 decades is a much different question than using them in older adult on the brink of a complication.

I may be wrong, but I hope that the incoming health leadership will find a way to make these drugs more available to the people most likely to benefit. I would not even dare to opine on policy solutions. All I can do as a clinician is use healthcare as wisely and as congruently with evidence as possible, and encourage others to be as parsimonious as possible.

Sadly, GLP-1 agonist drugs won't make for walkable neighborhoods, or affordable nutritious food, or bike lanes, or bring physical education back to schools, for these are the big changes that may improve things for the next generation, but GLP-1 agonist drugs are clearly the next big advance in modern medicine.

My Final GLP-1 Agonist Comment

- **Has Tirzepatide Scaled the HFpEF/Obesity SUMMIT?**

I wrote a formal critical appraisal of the SUMMIT trial on theHeart.org | Medscape Cardiology. To briefly review from my previous podcast, SUMMIT delivered positive results for tirzepatide in patients with HF with preserved ejection fraction (HFpEF) and a baseline body mass index of 38.

More than 50 news outlets covered it with glowing headlines. But in my column, I list the six problems with it.

One is the small number of outcome events, and the irony here is that this is what principal investigator Dr Milton Packer has used to shred atrial fibrillation (AF) ablation trials. I remember him saying once that if CASTLE AF was an HF trial, it would be laughed at because of the small numbers of outcome events.

Well, go read my piece. There are shockingly few HF events in the SUMMIT trial. And only 8 vs 5 cardiovascular (CV) deaths (more in the terzepatide arm).

In summary, if we are to extend GLP-1 agonists to HF, we should have a properly powered trial, like DELIVER, or EMPEROR, or SELECT. I am afraid SUMMIT looks more like marketing than science.

Blank Spot in HF Evidence – All Cause Hospitalizations

I will report on a paper in which I was a co-author. First author is Ahmed Sayed, senior author is Andrew Foy.

Our question was how to measure success of new therapies for HF. This is a modern question. In days of old, HF trials measured one bias-free endpoint — alive or dead.

The foundational therapies of HF — ACE inhibitors, ARBs, beta-blockers, and mineralocorticoid receptor antagonists — extended survival. Period. These drugs were so good and patients were so sick, that mortality curves separated quickly and robustly. In addition, nearly all of these therapies also worked in post-myocardial infarction (MI) patients who had left ventricular (LV) dysfunction.

Our success has made it harder to show further incremental gains. Newer therapies cannot extend life any further, primarily because humans have an expiration date. If you stabilize HF, patients live long enough to die of something else.

But this is okay, because many things in medicine improve life without extending life. Think AF ablation, and percutaneous coronary intervention over medical therapy in chronic coronary artery disease.

HF experts have designed another endpoint in an attempt to measure incremental benefit of new treatments.

Their choice: Cardiovascular (CV) death and hospitalizations for HF (HHF). CV death is a fine endpoint. There is an issue of adjudicating death, but it is still a hard endpoint with little bias. HHF, on the other hand, is quite a surrogate measure.

The EMPEROR-Preserved trial of empagliflozin vs placebo in patients with HFpEF illustrates the biggest problem with using HHF as a surrogate measure. That is, empagliflozin reduced HHF over placebo, but the total or all-cause hospitalizations (ACH)

were nearly 10 times more common, and unchanged.

In other words, in patients with HFpEF, HHF represents only a small fraction of total hospitalizations. In the empagliflozin arm, first hospitalizations were 259, total ACH were 2500.

The other reason we should care about total hospitalizations is not just competing causes of the primary outcome, but also because ACH is a way to capture benefit and harm. Let's say a new drug causes hospitalization because of low blood pressure, or acute kidney injury, or aspiration pneumonia; this would be seen in ACH.

With that as background, let me tell you about the study. Ahmed Sayed and colleagues put together a long list of HF trials that were published in *NEJM*, *JAMA*, and *Lancet*. This was to answer three questions:

- To determine the ratio of HHF to ACH;
- To ascertain whether reported treatment effects on HHF are associated with treatment effects on ACH;
- To learn how often ACH is reported alongside HHF.
- We found 113 trials with 261,000 patients.
- Only about half of trials (53%) even reported ACH, and the rate of reporting did not improve over the many-decade span of the study.
- The ratio of HHF to ACH was 46%. That is low but better than the example I just told you about in EMPEROR-Preserved, where it was about 10%.
- The ratio of HHF/ACH increased (ie, HHF became a better surrogate of efficacy) with trials that included more patients with class 3 to 4 HF.
- The ratio decreased (ie HHF became a worse surrogate) with trials that included patients with better EF. Think HFpEF.

The third finding involved some pretty cool Bayesian analyses. We first described the association of the effect size on HHF and ACH. It turns out that to be strong, like an R-squared of 90%. That sounds good but let me tell you more.

The average odds ratio for ACH was way less than it was for HHF. It was about half. So if HHF were reduced by 25%, then ACH would be expected to be reduced by 12.5%,

Here is where the Bayesian statistics come in. We were interested in how much of a reduction in HHF would be needed to affect ACH. You can do this with Bayesian analysis.

For a large trial with minimal uncertainty in estimating HHF:

- To show any (more than zero) effect on ACH, HHF would have to be reduced by 16%.
- To show a (moderate) 10% reduction in ACH, HHF would have to be reduced by 36%.
- To show a (major) 20% reduction in ACH, HHF would have to be massive at 56%.

Comments. We believe these findings on HHF and ACH are probably the best-case scenario because trials are enriched with patients who experience high rates of HHF. We cited an observational study from the US real-world experience wherein only 12.6% of all hospitalizations 2 years after a HF diagnosis were HF related.

While the correlation between HHF and ACH is high, we believe this data argues strongly for the consistent reporting of ACH, because without it, you can't assess how strong HHF is as a surrogate outcome.

Sanjay Kaul wrote the editorial and concluded that yes, it is ok to use cause-specific endpoints like HHF to estimate sample size, but all-cause endpoints should be prespecified in trial protocols and reported. If you don't report all-cause effects, clinicians cannot know a) the degree to which the surrogate of HHF represents total health, and b) ACH captures treatment-related-harm. For instance, one of the reasons that HHF could have a large reduction and ACH not so much is that the treatment causes off-target negative effects.

We used the DIG trial as an example. In the digoxin vs placebo trial in patients with HF with reduced EF, digoxin reduced HHF by a sizable 28%. But ACH were reduced by only 8%, largely because of an doubling in hospital admissions for digoxin toxicity.

In sum, when looking at HF trials that show no reduction in CV death and the only positive endpoint is HHF, it is crucial to study ACH. Based on this analysis of over 100 HF trials, it will take a robust HHF to have any effect on ACH, and that is if the trial is large and has less uncertainty.

A trial like SUMMIT has almost no chance of having a significant effect on ACH, and perhaps that is why they did not report it.

Tell your friends that we want to know how new-treatment XYZ affects ACH. Tell us trialists.

Misuse of Meta-analysis by the HF Community

I am going to pick on HF people in this next segment, but to be sure, electrophysiology docs are no strangers to misuse of the meta-analysis.

Exhibit A: Take a look at a study from Desai and colleagues in *JAMA* in 2004. Their problem was that no trial had shown that a primary prevention implanted defibrillator (ICD) reduced death in nonischemic cardiomyopathy (NICM).

So they put the trials together — CAT, AMIOVERT, DEFINITE, SCD-HeFT — and then added COMPANION. The problem was that COMPANION, the main driver of the benefit, was a cardiac resynchronization therapy trial — not a primary prevention ICD trial. Boom. ICDs were approved for NICM.

It was wildly inappropriate to add COMPANION.

But the HF community has this bad habit, in my opinion, of combining negative studies with positive studies to drive a claim that a drug is beneficial across all EFs.

JAMA Cardiology has published the latest example and it pertains to ACH with sacubitril/valsartan. This is a post-hoc analysis of the PARADIGM HF and PARAGON HF trials.

Right off the bat, this is not appropriate because not only are the patients different, but the comparators were also different.

PARADIGM-HF was sacubitril/valsartan vs enalapril in patients with HFrEF (LVEF mean 29%).

PARAGON HF was sacubitril/valsartan vs valsartan in patients with HFpEF (LVEF mean 57%).

Extremely different.

Here is that they did. Combined trials. And they looked at ACH.

- Sacubitril/valsartan significantly reduced the risk of ACH compared with RAS inhibition (hazard ratio [HR], 0.92; 95% confidence interval [CI], 0.88 to 0.97; *P* = .002). Noticed that they had to use the term “RAS inhibitor” because the comparators were different.
- The difference in first ACH was 2% so they claim a number-needed-to-treat of 48.
- They did note that there was a heterogeneous treatment effect with the main reductions in ACH of sacubitril/valsartan in those with less than a 60% EF and no reduction in those with an EF above 60%.
- They then make these nifty colored figures with cause specific hospitalizations across the LVEF spectrum. These pictures and this mixture let the authors conclude that “sacubitril/valsartan significantly reduced hospitalization for any reason, with benefits most apparent in patients with an LVEF below normal.”

This combination business is dubious. It’s a way of taking the nonsignificant HFpEF trials and mixing them with positive HFrEF trials and getting a statistically significant albeit small relative and absolute risk reduction.

Then the drug (which is costly) can be marketed to nearly every HF patient. But I would argue that the PARADIGM-HF male patient with his age of 64 years and LVEF of 29% is totally different from the 73 year old female patient with her EF of 58%.

PARAGON HF did not reach significance because a) HFpEF patients are different, and b) valsartan is a better comparator.

The HF experts have also done this with the SGLT2 inhibitors, which were positive in HFrEF and nonsignificant in HFpEF and boom, the meta-analysis is positive “across the spectrum of EF.” I don’t like it. You shouldn’t either.

Meta-analyses can be good. But not when you mix totally different patients.

Integration of Palliative Care Into HF Care

This is not a study but a review paper in the *Journal of Cardiac Failure*, first author Dr. Sarah Chuzi. The paper reviews, explains, and emphasizes the integration of palliative care into HF care.

It’s a well-written and open access review. I applaud all the authors, the journal editors, and the leadership of the HF Society of America.

I don’t know about you all but, in my neighborhood, HF care can be extremely heartless. Whether it’s quality measures or oversimplification of guidelines, but what happens instead of the relief of suffering is the mis-application of evidence that was acquired in ambulatory male outpatients to elderly frail patients with multiple diseases.

Instead of integrating palliative care for an 80-year-old patient who has little help at home, walks with a walker because of pain, and has chronic kidney disease and poor health literacy, this patient is put on multiple meds including sacubitril/valsartan and dapagliflozin, which a) could never be paid for, and b) cause hypotension and even more frailty.

Instead of asking these patients what’s most important to them, and focusing on care that relieves their suffering, these patients are treated as if they are wealthy ambulatory patients who can drive themselves to HF clinic.

Here’s another a case that drives me bananas. An older patient who is limited but hanging in there develops AF. Then presents with AF and tachycardia-mediated LV dysfunction. Boom. Diagnosed with HFrEF. Instead of treating the AF, this patient is slammed with guideline directed medical therapy.

In 2014, Dipak Kotecha from the United Kingdom published a meta-analysis of beta blocker trials in HFrEF. All of the benefit of beta blockers occurred in patients in sinus rhythm. For those in AF, there was no benefit. But no, the patient with AF, soft blood pressure, gets a long-acting beta-blocker and sacubitril and dapagliflozin, instead of digoxin and a short acting beta blocker for rate control.

What I see as the benefit of early palliative care is that we increase the chance that someone looks at the whole patient and stops the algorithm-induced torture.

I bet the vast majority of cardiology clinicians don’t know there is a vast difference between palliative care and hospice, and that palliative care should be started early, and can be performed by the primary HF care team or a specialty team.

I also bet many of the listeners of this podcast don’t even have access to a proper palliative care service. Based on what I’ve seen I doubt many trainees get training in palliative care. Perhaps they are too busy learning about LV strain imaging.

I plan to stop this plea before someone says I am ranting, but I see the next big gain in HF care as a major emphasis on palliative care.

I realize this is a problem of incentive. Palliative care doesn’t bring attention on social media. It’s not easy to become a key opinion leader as an advocate for palliative care. Drugs and devices are the drivers of HF stardom. But in the care of many (if not most) patients with HF, nothing could be more beneficial than for someone to think about how best to relieve their suffering.

If I were a healthcare czar, I would outlaw quality measures that incentivize clinicians to mis-apply evidence. Guideline directed medical therapy can be transformative, rendering HF into a chronic condition rather than a death sentence.

But guideline directed medical therapy can also be a source of suffering for those who would never have been in a clinical trial, because of frailty or co-morbidity.

Do read the paper. I have linked to it. Do think about patient characteristics in the seminal trials. And please, someone sit-down and have a serious illness discussion with the patient in HF.

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