radcliffe cardiology

Title: ACC 24 Late-Breaker Discussion: The EMPACT-MI Trial
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Dr Harriette Van Spall and Prof Javed Butler

"**Dr. Harriette Van Spall:** I'm Harriette Van Spall, Associate Professor of Medicine from McMaster University, and I'm delighted to have Professor Javed Butler, Distinguished Professor of Medicine at the University of Mississippi Medical Center in Jackson, here with us as principal investigator of the EMPACT MI trial. He is presenting his results at the Late-Breaking Clinical Trial Session of ACC 2024. We're here to chat about the trial and its results. Welcome, Javed.

Prof. Javed Butler: Thank you, it's great to be here.

Dr. Harriette Van Spall: I wonder if you could tell our viewers about the hypothesis that you aimed to test with this EMPACT MI trial.

Prof. Javed Butler: Sure. We have seen many advances in the management of patients post-myocardial infarction (MI), such as revascularization strategies, systems of care, and quality metrics like door-to-balloon time. Reducing the risk of recurrent MI with dual antiplatelet therapy, lipid therapy, and other treatments has changed how we treat myocardial infarction. However, a feared complication of MI is the risk of developing heart failure, which is one of the worst prognostic factors post-MI. The idea behind this study was to take a broad group of patients with MI, including STEMI and non-STEMI, with or without diabetes, and test whether giving patients early (within the first 14 days) SGLT2 inhibitor empagliflozin versus placebo, on top of all the revascularization and standard of care, would reduce the risk of developing heart failure or all-cause mortality.

Dr. Harriette Van Spall: Sure. And we've certainly had a broad evidence base to support the use of SGLT2 inhibitors in both the prevention and treatment of heart failure. This adds to that body of work and also to the recent DAPA MI trial, right?

Prof. Javed Butler: Yes, absolutely. In the DAPA MI trial, we learned that the cardiometabolic benefits of SGLT2 inhibitors in patients with ischemic heart disease, chronic kidney disease, and diabetes were significant. However, the number of events in that trial was too few to focus on the cardiovascular outcome, which was one of the reasons we focused on this trial as well.

Dr. Harriette Van Spall: So, you sought to test the efficacy and safety of empagliflozin compared with placebo in people who were either actively hospitalized or recently hospitalized for MI and had characteristics enriched for heart failure. Tell us about those inclusion and exclusion criteria for our viewers.

Prof. Javed Butler: Certainly. But before I tell you about the inclusion and exclusion criteria, it's important to mention that when we do these trials, we test for both efficacy and safety. Safety is crucial—first, do no harm. We have a lot of data and trials documenting the safety of SGLT2 inhibitors, but in this trial, patients with acute MI were getting IV contrast, undergoing procedures, and starting new RAAS inhibitors, MRAs, and SGLT2 inhibitors, all of which come with their own risks. So, safety was a key consideration. Regarding eligibility criteria, patients with a history of heart failure were excluded. However, patients could have congestion requiring treatment, regardless of EF, or a new drop in EF to less than 45%. We included various enrichment factors like age over 65, EF less than 35, peripheral vascular disease, high PA pressures, diabetes, and others. Patients just needed to qualify for one of these factors.

Dr. Harriette Van Spall: Tell us a little more about the study design. This was a randomized controlled trial, correct? What was the protocol like?

Prof. Javed Butler: Yes, it was a randomized controlled trial with a pragmatic and streamlined design to address the high cost of conducting clinical trials. We made it practical and easy for both sites and patients. Inclusion criteria were broad, allowing for various patient types. We had few face-to-face visits—just at enrollment and six months—with most follow-up being remote. Data collection was streamlined, focusing only on essential information. We didn't have any central adjudication of events, relying instead on site-level adjudication with some education for investigators. Our primary

endpoint was all-cause mortality, not cardiovascular mortality, due to the lack of central adjudication. We also focused only on hospitalized heart failure events, excluding outpatient events due to their lower accuracy in site reporting.

Dr. Harriette Van Spall: Tell us about your sample size and baseline characteristics in both groups.

Prof. Javed Butler: We enrolled about 6,500 patients and followed them for about 530 primary events, ending up with 565 primary events. The patient characteristics were as expected—a healthy mix of those with and without diabetes and CKD. However, we still face challenges in enrolling women and minorities, and more work is needed in this area. Additionally, the ratio of STEMI to non-STEMI was almost flipped compared to real-world registries. In our trial, three-quarters of the patients were STEMI, which is higher than in real-world scenarios.

Dr. Harriette Van Spall: Was the uptake of co-interventions the same in both groups? Were there any gaps in evidence-based medical therapy at baseline?

Prof. Javed Butler: Revascularization was done in 90% of the patients. Use of RAAS inhibitors, beta blockers, statins, and aspirin was above 90%, which was satisfying. However, MRA use post-MI is still a problem, traditionally around 35-40%, and in our trial, it was closer to 47%, so there's still a gap.

Dr. Harriette Van Spall: You compared empagliflozin 10 mg daily with a placebo. You included patients who had established diabetes in this trial. Tell us about some considerations there and why you included diabetes patients.

Prof. Javed Butler: Patients with diabetes are at higher risk for adverse outcomes and renal dysfunction, so we need data on these patients. There was tension about randomizing them to placebo, but at the time of the study's design, there were no data on HFpEF patients with SGLT2 inhibitors. We excluded patients with a history of heart failure from the study. The study size was increased to shorten follow-up and mitigate

risk, with only 6% open-label use, avoiding much effect on the trial from ramping up HFpEF and CKD indications in clinical practice.

Dr. Harriette Van Spall: And while trials in diabetes with cardiovascular risk factors or established coronary artery disease preceded this trial, SGLT2 inhibitors are routinely withheld when patients are hospitalized with acute illness. Perhaps that was another factor in including people with diabetes to test the drug's efficacy in an acute setting. Tell us about your primary results.

Prof. Javed Butler: The primary endpoint was all-cause mortality and heart failure hospitalization. We did not meet the primary endpoint, with a 10% relative risk reduction (p=0.21). There was no reduction in all-cause mortality, but a 23% statistically significant reduction in heart failure hospitalization. Combining first and recurrent heart failure hospitalizations showed a 33% relative risk reduction. We had a very interesting twist in the results, which I'll explain shortly.

Dr. Harriette Van Spall: I think your selection of the primary endpoint was very relevant, but there's tension in pivoting from cardiovascular deaths to all-cause deaths. Did you see any change in cardiovascular death, and did you look at it specifically?

Prof. Javed Butler: We did look at cardiovascular death, though without central adjudication. There were a few peculiar aspects: early mortality post-MI due to factors unaffected by SGLT2 inhibitors, COVID-era data affecting heart failure hospitalization patterns, and global conflicts affecting our highest enrolling regions. Our follow-up was a bit short, about one and a half years, with heart failure developing around six months on average. We didn't have enough power to see long-term effects on mortality, but the exciting twist is in the safety data.

Dr. Harriette Van Spall: Go ahead and tell us your exciting twist.

Prof. Javed Butler: The twist is in the collection of outpatient heart failure events as part of the serious adverse events (SAE) data. Including both inpatient and outpatient events, the relative risk reduction for heart failure events was 37%. When combining all

heart failure and all-cause mortality, it became statistically significant. Additionally, there was a statistically significant lower risk of being started on RAAS inhibitors, beta blockers, MRAs, and diuretics in the outpatient setting. These findings support the heart failure results as real and not a chance finding.

Dr. Harriette Van Spall: And were your event rates as expected for the primary analysis?

Prof. Javed Butler: No, the event rates were lower than expected. The placebo arm's primary endpoint event rate was 9.1 per 100 person-years, and EMPA was 8.2. Mortality in the placebo arm was 5.5%, with first heart failure hospitalization around 4.7%. This likely reflects the well-managed patient population with a high rate of revascularization and STEMI predominance, not representative of real-world event rates, which are higher.

Dr. Harriette Van Spall: Thank you so much for being here this morning, for leading this important work, and for sharing your results with us. Javed, always a pleasure to talk to you.

Prof. Javed Butler: Thank you, Harriette.