CLOSER LOOK

MEMORANDUM

J&J's real-world EASEL study finds CV benefit + amputation risk associated with SGLT-2 inhibitors vs. other glucose-lowering drugs - November 20, 2017

Executive Highlights

- J&J just announced and published data from the real-world EASEL study (n=25,258) comparing SGLT-2 inhibitors (including canagliflozin, empagliflozin, and dapagliflozin) vs. other glucose-lowering drugs. SGLT-2 inhibitors reduced risk for the primary composite endpoint of all-cause death/heart failure hospitalization by 43% (p<0.0001) and reduced risk for three-point MACE by 33% (p<0.0001).
- Below-the-knee amputations were almost twice as common in the SGLT-2 group vs. the "other" group (HR=1.99, p=0.018). The divide between SGLT-2 inhibitors was 58% canagliflozin (which showed an amputation signal in CANVAS), 26% empagliflozin, and 16% dapagliflozin, but the study was not powered to compare between agents. Overall amputation rates were low: 0.17 events per 100 patient-years in the SGLT-2 arm vs. 0.09 in the "other" arm.

J&J just announced results from the real-world, matched-cohort EASEL study (n=25,258 adults with type 2 diabetes and established CV disease), comparing CV outcomes between new users of an SGLT-2 inhibitor (n=12,629) vs. new users of another diabetes drug (n=12,629). Over a median follow-up of 1.6 years, SGLT-2 agents were associated with a 43% relative risk reduction for the primary composite endpoint of all-cause mortality/hospitalization for heart failure (HR=0.57, 95% CI: 0.50-0.65, p<0.0001). SGLT-2 inhibitors also showed a 33% relative risk reduction for three-point MACE (non-fatal MI, non-fatal stroke, or CV death), with a hazard ratio of 0.67 (95% CI: 0.60-0.75, p<0.0001). EASEL results lend further support to the notion that cardioprotection is an SGLT-2 inhibitor class effect: AZ's CVD-REAL (n=154,523) found a 46% risk reduction for the composite of all-cause mortality/heart failure hospitalization with an SGLT-2 inhibitor vs. other diabetes therapies (p<0.001), in a study population that was 87% primary prevention (suggesting that SGLT-2 inhibitors could have CV benefit even in those without prior CV events). EASEL gives similarly positive results in a high-risk population with established CV disease. We're encouraged by the results from both real-world studies, which show that the CV benefits demonstrated in CANVAS (for J&J's Invokana) and EMPA-REG OUTCOME (for Lilly/BI's Jardiance) translate to the real world.

On the other hand, EASEL also continues the story of Invokana's complicated risk/benefit profile, reporting roughly two-fold risk for below-the-knee amputations with SGLT-2 inhibitors vs. other diabetes drugs (HR=1.99, 95% CI: 1.12-3.51, p=0.018). Like in CANVAS, absolute event rates were very low - 0.17 vs. 0.09 events per 100 person-years - even though this was a pretty sick patient population in terms of established CV disease (which elevates risk for other complications as well). Investigators note that Invokana (canagliflozin) was used disproportionately in this participant pool (58%), compared to Jardiance (empagliflozin; 26%) and AZ's Farxiga (dapagliflozin; 16%). EASEL was not powered to compare between these agents. To-date, the amputation signal has only been associated with canagliflozin in CANVAS and not with empagliflozin in EMPA-REG OUTCOME, though it's important to keep in mind that amputations were collected differently across CVOTs and that amputation itself is a soft endpoint (with decision-making left to the patient/provider), which makes cross-trial comparison difficult. We continue to believe, given the low number of events overall, that this risk can be managed in the real world for patients taking Invokana (the glucose-lowering, weight loss, and cardioprotective benefits of canagliflozin should not be undersold) - that said, much work remains in defining and spreading best practice foot care. Moreover, we hope results from DECLARE for dapagliflozin will clarify the issue further.

- **EASEL pulled data from the Military Health System records. These results were published last week in Circulation.**
- **Additional secondary endpoint data:** In EASEL, SGLT-2 inhibitors reduced risk for all-cause death specifically by 43% (HR=0.57, 95% CI: 0.49-0.66, p<0.0001) compared to other diabetes therapies. For context, CVD-REAL found a 51% relative risk reduction for all-cause death (p<0.001), and together, these real-world findings support a robust benefit to SGLT-2 treatments on a very meaningful outcome. The relative risk reduction for heart failure hospitalization specifically was 43% in EASEL (HR=0.57, 95% CI: 0.45-0.73, p<0.0001) and was 39% in CVD-REAL (p<0.001) with SGLT-2 inhibitors, again demonstrating a robust and clinically-meaningful CV benefit.

-- by Ann Carracher, Payal Marathe, and Kelly Close