SGLT2 inhibitors – the gift that keeps on giving

Gout is common in people with heart failure. In this *post hoc* analysis of the DAPA-HF and DELIVER randomised controlled trials, Butt and colleagues evaluated the association between gout and clinical outcomes in people with heart failure, and the effect of the SGLT2 inhibitor dapagliflozin on the initiation of gout therapy. The prevalence of gout at baseline was around 10% in both those with reduced and preserved ejection fraction, and the primary cardiovascular outcome was more likely to occur in those with a background of gout. Notably, dapagliflozin appeared to significantly reduce the initiation of medication to reduce urate levels (e.g. allopurinol, febuxostat) by 57%, and to significantly reduce the initiation of colchicine by 46%. These results highlight a clinically meaningful additional benefit of SGLT2 inhibitors in people living with heart failure, and they may help reduce polypharmacy and avoid adverse effects of anti-gout medication.

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Gout is one of the earliest clinical conditions to be documented; the Egyptians first described it in 2640 BC and Hippocrates later chronicled "the unwalkable disease" during the 5th century BC. There is also evidence that colchicine (derived from the autumn crocus) was used as a specific treatment for gout by the Byzantine Christian physician Alexander of Tralles during the 6th century AD, and even then its use was limited by adverse gastrointestinal side effects.

Modern treatments for gout include allopurinol and febuxostat. Interestingly, both fenofibrate and losartan have demonstrated uricosuric effects, although neither of these drugs is licensed for the treatment of gout. My own clinical practice is to use losartan as an alternative antihypertensive to diuretics such as indapamide in those with established gout.

SGLT2 inhibitors (derived from phlorizin, found in the root bark of apple) have previously been demonstrated to increase uric acid excretion, and this has been postulated to contribute towards their cardiorenal benefits; it is well recognised that hyperuricaemia is associated with an increased risk of hypertension, cardiovascular disease and chronic kidney disease.

In the present *post hoc* analysis, Butt and colleagues used data from the seminal DAPA-HF and DELIVER randomised controlled trials, which explored the benefits of the SGLT2 inhibitor dapagliflozin in heart failure (both reduced and preserved ejection fractions) in people living with and without type 2 diabetes. These studies found significant reductions in a composite of worsening heart failure or cardiovascular death with dapagliflozin.

Gout is common in people with heart failure, and this analysis aimed to quantify the prevalence of gout at baseline in the two studies, the association between gout and clinical outcomes, and the effect of dapagliflozin on the initiation of gout therapy.

The prevalence of gout at baseline was around 10% in both those with HFrEF and HFpEF. This corroborates that gout frequently occurs in those with heart failure. Predictably, gout was more commonly observed in older individuals (mean observed age of gout, 69.6 years); in males; in those with a higher BMI; in those with multimorbidity, especially chronic kidney disease; and in those treated with a loop diuretic.

The primary outcome of the DAPA-HF and DELIVER studies, a composite of worsening heart failure or cardiovascular death, occurred more frequently in those with a background of gout. The benefits of dapagliflozin were observed irrespective of history of gout.

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In conclusion, these results highlight a clinically meaningful additional benefit of SGLT2 inhibitors in people living with heart failure, and they may help reduce polypharmacy and avoid adverse effects of anti-gout medication such as gastrointestinal side effects (colchicine) and rashes (allopurinol). Furthermore, whilst these results are only hypothesis-generating, they raise the prospect that SGLT2 inhibitors may be a promising independent treatment for gout in the future. ■

Research

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Association of Dapagliflozin Use With Clinical Outcomes and the Introduction of Uric Acid–Lowering Therapy and Colchicine in Patients With Heart Failure With and Without Gout
A Patient-Level Pooled Meta-analysis of DAPA-HF and DELIVER

The full study can be read here