

Good for your heart and safe for your toes - a patient-level meta-analysis of DAPA-HF and DELIVER

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In this Edition of *European Heart Journal*, Butt and colleagues report the efficacy and safety of the sodium glucose co-transporter (SGLT) 2 inhibitor dapagliflozin in high risk individuals with both heart failure and peripheral artery disease (PAD).¹ They achieve this through an individual patient-level analysis of more than 11 000 patients, 7.4% with a history of PAD, who participated in two large-scale heart failure trials – the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial² and the Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction (DELIVER) trial.³

There are three main findings from the analyses. First, across a broad spectrum of patients with heart failure, those with concurrent PAD compared to those without PAD had an approximate fifty per cent greater risk of the primary outcome of worsening heart failure or cardiovascular death. These increased risks persisted even after controlling for other cardiometabolic risk factors and highlight this patient group as a priority for intensive treatment and monitoring. Second, dapagliflozin reduced the proportional risk of key outcomes irrespective of the presence or absence of PAD. Absolute treatment benefits were consistently greater in those with established PAD. The number needed to treat for the prevention of worsening heart failure or cardiovascular death was 17 in those with PAD compared to 24 in those without PAD. Finally, whilst those with PAD were at a greater background risk of amputation, treatment with dapagliflozin did not increase amputation risk. This was true both for those with and without a history of PAD at entry to the study.

The analysis confirms the high value of dapagliflozin for high-risk heart failure patients, and highlights the potential for significant benefit amongst the subset with PAD. This is an important finding because early SGLT2 inhibitor trial results generated uncertainty about the balance of benefits and risks of SGLT2 inhibitor use in those with PAD, and this uncertainty may still be adversely impacting prescribing behaviours.

Concern about the use of SGLT2 inhibitors amongst patients with PAD first arose following an unexpected signal of increased amputation risk in patients with type 2 diabetes treated with canagliflozin in the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program.⁴ Extensive subsequent research across the SGLT2 inhibitor class, including a further large trial of canagliflozin,⁵ has mostly dispelled the notion that SGLT2 inhibitors cause amputation.^{6,7} At the time, however, the CANVAS finding resulted in a United States Food and Drug Agency 'Black Box' warning for canagliflozin and amputation and significant reluctance to prescribe

any SGLT2 inhibitor to patients with PAD. While the 'Black Box' warning was subsequently removed a degree of uncertainty remained.

The reluctance to prescribe SGLT2 inhibitors to those with PAD extended to include patients perceived to be at increased risk of PAD because of exposure to factors that may modulate PAD risk. For example, diuretics reduce blood volume and increase blood viscosity¹ and haemoconcentration was widely cited as a possible cause of the increased amputation rates observed in the CANVAS Program. Individuals with heart failure are frequently assigned high doses of diuretics and even in the absence of PAD, may be less likely to receive SGLT2 inhibitors because of perceived PAD risk.

To better assess the efficacy and safety of dapagliflozin use in the context of heart failure, the authors expanded analyses of the overall population group to explore effects in subgroups with and without PAD, as well as those with other risks for limb ischemia such as high dose diuretic use, type 2 diabetes and combinations thereof. For none of the analyses was there any evidence that dapagliflozin treatment increased the risk of amputation or that effects on amputation risk differed between groups. The findings of constant effects across patient subgroups are aligned directly with detailed investigations of the effects of canagliflozin in the CANVAS Program and CREDENCE trial datasets. Those analyses of canagliflozin likewise identified no difference in amputation risk amongst patients with type 2 diabetes separated into subgroups defined by history of heart failure, PAD or diuretic use.^{7,8}

There are more than 64 million people living with heart failure globally.⁹ At least one in twenty, but likely closer to one in ten, have concomitant PAD.¹ The findings from this analysis and multiple prior data sets show very clearly that these patients have reduced quality of life and poor functional capacity. They also have elevated rates of morbidity and premature mortality as well as incurring major health care costs.⁹ The great majority are likely to benefit from SGLT2 inhibitor therapy but current prescription rates for SGLT2 inhibitors to indicated patient groups is low. This is a consequence of multiple factors including access, cost and physician behaviour with misconceptions about the likely balance of benefits and risks also likely to contribute to prescribing inertia.

Data from the United States suggest that less than two per cent of patients with type 2 diabetes receive SGLT2 inhibitor therapy.¹⁰ While there are still patient groups with diabetes for which there is no clear indication for treatment, there are very large numbers for which there is compelling evidence of benefit from multiple large-scale clinical outcome trials. Evidence of cardiorenal benefits in patients with type 2 diabetes¹¹ have been followed by a series of similarly compelling heart failure trials. First in heart failure with reduced ejection fraction² and subsequently also for patients with preserved ejection fraction.³ Recent studies of United States prescribing patterns for SGLT2 inhibitors in patients with heart failure show similarly small proportions prescribed treatment. For the period 2021 to 2022 only about three per cent of patients with heart failure with reduced ejection fraction were regular users of SGLT2 inhibitors.¹²

The huge discrepancy between indications for treatments and use of treatments speaks to the broader health system challenge of evidence to implementation gaps. A delay of

seventeen years between evidence generation for novel therapies and corresponding widespread clinical use has been reported.¹³ While it is unlikely that the implementation gap for SGLT2 inhibitors is driven primarily by misunderstanding of likely benefits and risks, it is clear that this has been an issue for the drug class in regard to PAD. The new data reported for dapagliflozin in these most recent analyses should further address that.

The findings reported here also serve to highlight the value of secondary analyses for targeting therapies to those most likely to achieve benefit. Patients with heart failure are already identified as a high-risk group with large potential for the cost-effective prevention of serious adverse health outcomes with the use of SGLT2 inhibitors. However, if there was any question about the value of treatment in those with co-existent PAD, the very high rates of vascular events in this group, and the large absolute benefits reported in these analyses, should address that uncertainty. This is a patient group in need of intensive risk reduction, in whom the benefits of SGLT2 inhibitor therapy are amongst the largest observed in any patient group. To withhold treatment based on perceived but unfounded concerns of increased adverse events would be erroneous and costly.

The current analysis is robust, well-powered and informative, benefiting greatly from the rigour of the clinical trials on which it is based. The likelihood that the findings are importantly biased or at risk from the play of chance is low. The story of SGLT2 inhibitors and amputation is, however, a timely reminder of the need for caution in the interpretation of even the most compelling findings. When first reported it seemed very likely that canagliflozin was a cause of amputation and that amputation would become a recognised harm of the SGLT2 inhibitor class. Now, tens of thousands of patient years of follow up later, it is far more likely that the signal of amputation risk observed in the CANVAS Program was a spurious finding. Large-scale clinical trials are designed specifically to avoid making mistakes and to identify the true effects of an intervention. The CANVAS Program was no exception. But the science behind trials is strong only for the prespecified outcomes, analysis plan and overall population group for which the study is powered.⁶ And even with strong designs chance findings can occur, sometimes with major clinical and commercial implications.

The balance of evidence across diverse populations, including those with type 2 diabetes, heart failure and chronic kidney disease, indicates strong protective effects from the use of SGLT2 inhibitors with serious harms caused infrequently. In regard to amputation risk specifically, the likelihood that SGLT2 inhibitors increase risks is further lowered by this latest report. Collaborative heart failure care, involving clinicians, patients and the breadth of health system stakeholders will optimise care and enhance guideline-directed uptake of heart failure therapy, which will in many cases involve the prescription of an SGLT2 inhibitor. Butt et al have presented a powerful case for the safety and utility of this drug class in the highest risk heart failure patients, those with PAD. This is a welcome and timely addition to the literature with important implications for this patient subset in particular, but also the much wider group of people now eligible for SGLT2 inhibitor therapy.

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