**Conflict of interest:** G.L. reports grants from the Italian National Health Service and from the Italian Minister of Education University and Research, outside the submitted work. C.P. reports personal fees from Acticor Biotech, Amgen, Bayer, GlaxoSmithKline, Tremeau, Zambon, and grants from AIFA (Italian Drug Agency), grants from AIFA (Italian Drug Agency), Bayer, Cancer Research UK and European Commission; he chairs the Scientific Advisory Board of the International Aspirin Foundation, outside the submitted work.

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doi:10.1093/eurheartj/ehaa891

## *Weekly Journal Scan*

# Do VERTIS-CV trial results question a class-effect of cardiovascular protection with sodium-glucose cotransporter 2 inhibitors?

The results of 'Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes' have been published in the New England Journal of Medicine (doi: 10.1056/NEJMoa2004967).

### Key points

- VERTIS-CV, a company-sponsored, multicentre, double-blind, event-driven, non-inferiority trial, investigated the cardiovascular (CV) safety and potential efficacy of ertugliflozin, a sodium-glucose cotransporter 2 inhibitor (SGLT2i) in 8246 patients with type 2 diabetes and atherosclerotic CV disease randomized to receive ertugliflozin 5 mg or 15 mg or placebo once daily.
- When added to standard-of-care treatments, ertugliflozin was shown to be non-inferior to placebo with respect to the primary composite outcome of death from CV causes, non-fatal myocardial infarction, or non-fatal stroke [hazard ratio (HR), 0.97; 95.6% confidence interval (CI), 0.85–1.11; $P < 0.001$ for non-inferiority] during a median duration of follow-up of 3 years. The first key secondary outcome of death from CV causes or heart failure hospitalization did not differ significantly between ertugliflozin and placebo (HR, 0.88; 95.8% CI, 0.75–1.03; $P = 0.11$ for superiority); therefore, further statistical testing of other secondary outcomes was not performed.
- The incidence of serious adverse events did not differ significantly between ertugliflozin and placebo. As with other SGLT2i, genital mycotic infections occurred significantly more frequently with either ertugliflozin dose than placebo. Moreover, the percentages of patients who underwent amputation or had diabetic ketoacidosis were numerically higher with either ertugliflozin dose than placebo.

## Comment

VERTIS-CV was planned according to the Food and Drug Administration (FDA) former guidelines to assess the CV safety of new glucose-lowering drugs (recently updated to evaluate safety more broadly). Therefore, this study was originally designed and powered to show non-inferiority of ertugliflozin compared to placebo with respect to CV outcomes in high-risk patients with type 2 diabetes. From this point of view, the 'mission' was accomplished since VERTIS-CV results showed non-inferiority of ertugliflozin compared to placebo. However, based on previous studies showing positive effects of other SGLT2i on CV and renal outcomes, the VERTIS-CV protocol had been amended to reflect a doubling of the original sample size and inclusion of efficacy objectives for superiority.[1-4] Therefore, the largely negative results of VERTIS-CV are surprising and call into question the concept of a class effect of SGLT2i. In trying to explain this apparent discrepancy, the following facts should be considered: (i) the patient populations, study design, rates of the primary endpoint, and use of secondary preventive treatments in the four different SGLT2i CV trials were broadly similar; (ii) the two doses of ertugliflozin appeared equally effective in achieving the expected changes in HbA1c, body weight and systolic blood pressure, suggesting that both were at the top of the dose–response relationship for SGLT2 inhibition; (iii) hospitalization for heart failure, a pre-specified secondary endpoint, showed an HR of 0.70 (95% CI, 0.54–0.90)[4], consistent with the effects of other SGLT2i (ranging between 0.65 of empagliflozin and 0.73 of dapagliflozin)[1-4]; (iv) the statistical uncertainty of the effects of ertugliflozin on the primary endpoint is compatible with the modest reduction (7–14%) in major CV events suggested by previous trials of empagliflozin, canagliflozin, and dapagliflozin.[1-3]

In conclusion, the present results are reassuring in terms of CV safety for those patients already taking ertugliflozin. However, the uncertain results of VERTIS-CV do not provide an additional option within the class to physicians prescribing SGLT2i to high-risk patients with diabetes with the intent of reducing their CV complications. Further studies of ertugliflozin in special populations (e.g. heart failure) should probably revisit the dose requirement for the relevant pharmacodynamic effects.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

**Conflict of interest:** M.V. reports personal fees for speaker bureau and/or consulting in Advisory Board from Amgen, Astra Zeneca, Daiichi-Sankyo, Menarini Int, MSD, Novartis Pharma, Novo Nordisk outside the submitted work. C.P. reports personal fees from Acticor Biotech, personal fees from Amgen, personal fees from Bayer, personal fees from GlaxoSmithKline, personal fees from Tremeau, personal fees from Zambon, grants from AIFA (Italian Drug Agency), grants from European Commission, other from Scientific Advisory Board of the International Aspirin Foundation, outside the submitted work.

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