

Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial.

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Collaborators (692)

Erratum in

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Abstract

BACKGROUND: Short-term treatment for people with type 2 diabetes using a low dose of the selective endothelin A receptor antagonist atrasentan reduces albuminuria without causing significant sodium retention. We report the long-term effects of treatment with atrasentan on major renal outcomes.

METHODS: We did this double-blind, randomised, placebo-controlled trial at 689 sites in 41 countries. We enrolled adults aged 18-85 years with type 2 diabetes, estimated glomerular filtration rate (eGFR) 25-75 mL/min per 1.73 m² of body surface area, and a urine albumin-to-creatinine ratio (UACR) of 300-5000 mg/g who had received maximum labelled or tolerated renin-angiotensin system inhibition for at least 4 weeks. Participants were given atrasentan 0.75 mg orally daily during an enrichment period before random group assignment. Those with a UACR decrease of at least 30% with no substantial fluid retention during the enrichment period (responders) were included in the double-blind treatment period. Responders were randomly assigned to receive either atrasentan 0.75 mg orally daily or placebo. All patients and investigators were masked to treatment assignment. The primary endpoint was a composite of doubling of serum creatinine (sustained for ≥30 days) or end-stage kidney disease (eGFR <15 mL/min per 1.73 m² sustained for ≥90 days, chronic dialysis for ≥90 days, kidney transplantation, or death from kidney failure) in the intention-to-treat population of all responders. Safety was assessed in all patients who received at least one dose of their assigned study treatment. The study is registered with ClinicalTrials.gov, number [NCT01858532](#).

FINDINGS: Between May 17, 2013, and July 13, 2017, 11 087 patients were screened; 5117 entered the enrichment period, and 4711 completed the enrichment period. Of

these, 2648 patients were responders and were randomly assigned to the atrasentan group (n=1325) or placebo group (n=1323). Median follow-up was 2·2 years (IQR 1·4-2·9). 79 (6·0%) of 1325 patients in the atrasentan group and 105 (7·9%) of 1323 in the placebo group had a primary composite renal endpoint event (hazard ratio [HR] 0·65 [95% CI 0·49-0·88]; p=0·0047). Fluid retention and anaemia adverse events, which have been previously attributed to endothelin receptor antagonists, were more frequent in the atrasentan group than in the placebo group. Hospital admission for heart failure occurred in 47 (3·5%) of 1325 patients in the atrasentan group and 34 (2·6%) of 1323 patients in the placebo group (HR 1·33 [95% CI 0·85-2·07]; p=0·208). 58 (4·4%) patients in the atrasentan group and 52 (3·9%) in the placebo group died (HR 1·09 [95% CI 0·75-1·59]; p=0·65).

INTERPRETATION: Atrasentan reduced the risk of renal events in patients with diabetes and chronic kidney disease who were selected to optimise efficacy and safety. These data support a potential role for selective endothelin receptor antagonists in protecting renal function in patients with type 2 diabetes at high risk of developing end-stage kidney disease.

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