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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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Summary

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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Introduction

Despite recommended treatment including renin–angiotensin system inhibitors, people with type 2 diabetes and chronic kidney disease remain at high risk of developing end-stage kidney disease and cardiovascular complications, particularly when high concentrations of albuminuria persist.[1,2] Endothelin receptor antagonists reduce albuminuria and blood pressure, but can also cause sodium retention. A previous trial using high doses of avosentan, a non-selective endothelin receptor antagonist, in patients with diabetes and chronic kidney disease, was stopped prematurely because of an increased incidence of heart failure.[3] By contrast, short-term treatment with low doses of the more selective endothelin A receptor antagonist atrasentan reduced albuminuria without causing significant fluid retention.[4,5]

The Study of Diabetic Nephropathy with Atrasentan (SONAR) was designed to assess the efficacy and

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for all English-language publications published between Jan 1, 1990, and Feb 15, 2018, with the search terms "endothelin-1", "endothelin receptor antagonist", "albuminuria", "kidney disease", "diabetes", "nephropathy", and "randomised controlled trial". Since the introduction of blood pressure control and renin–angiotensin–aldosterone blockade with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, no additional therapy that lowers albuminuria has been shown to improve long-term renal outcomes. Endothelin receptor antagonists reduce albuminuria in experimental models of diabetes and in clinical studies of patients with chronic kidney disease with or without diabetes. A large randomised controlled trial in patients with type 2 diabetes and chronic kidney disease using the fairly unselective endothelin receptor antagonist avosentan was terminated early because of an increased frequency of heart failure with avosentan. Atrasentan is a more selective endothelin receptor antagonist which, in short-term studies, reduced albuminuria with minimal sodium retention in patients with type 2 diabetes and chronic kidney disease. These preliminary findings justify conducting a phase 3 clinical trial to establish whether atrasentan can delay progression to end-stage kidney disease.

Added value of this study

We describe the results of a randomised, double-blind, placebo-controlled, phase 3 trial designed to study the efficacy and safety of the endothelin receptor antagonist atrasentan as an adjunct to angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy for reducing the frequency of renal disease progression in patients with type 2 diabetes and chronic kidney disease. To enhance the likelihood of detecting a treatment benefit while minimising the risk of heart failure, the trial used an enrichment design. Atrasentan responders were selected on the basis of the degree of albuminuria reduction during a 6-week atrasentan treatment period, while excluding patients who had fluid retention during this period to minimise the risk of heart failure. To our knowledge, this is the first clinical trial in patients with type 2 diabetes to use an enrichment-responder design. During a median follow-up of 2·2 years, atrasentan reduced the rate of the primary renal endpoint compared with placebo (n=79 [6·0%] *vs* 105 [7·9%]; hazard ratio [HR] 0·65; 95% CI 0·49–0·88; p=0·0047). Hospital admission for heart failure occurred in 47 (3·5%) patients in the atrasentan group and 34 (2·6%) patients in the placebo group (HR 1·33 [95% CI 0·85–2·07]; p=0·208).

Implications of all the available evidence

Patients identified as showing substantial albuminuria reduction and minimal signs of sodium retention during short-term treatment with low-dose atrasentan had a significantly reduced risk of a renal event during long-term treatment with atrasentan compared with placebo. These data support a role for atrasentan in modifying renal risk in selected patients with type 2 diabetes and chronic kidney disease.

safety of atrasentan in patients with type 2 diabetes and chronic kidney disease. To enhance the potential benefit–risk profile of atrasentan, we selected responders to treatment, who were identified by the extent of reduction in albuminuria concentration during an initial open-label period of treatment with atrasentan. In this enrichment period, patients who developed evidence of fluid retention were excluded, in an attempt to minimise the risk of heart failure.[6,7] The SONAR study therefore tested whether treatment of atrasentan would improve renal outcomes in carefully selected high-risk patients with diabetes and chronic kidney disease.

Methods

Study design

We did a double-blind, randomised, placebo-controlled event-driven trial at 689 sites in 41 countries. The trial protocol,[6] which was approved by a central or local ethics committees at all study sites, and the statistical analysis plan are available in the appendix. The trial was designed and conducted in accordance with the Declaration of Helsinki (version amended October, 2000) and in compliance with the ethical principles of Good Clinical Practice.

Participants

Adults aged 18–85 years with type 2 diabetes and an estimated glomerular filtration rate (eGFR) of 25–75 mL/min per 1·73 m² of body surface area, a urine albumin-to-creatinine ratio (UACR) of 300–5000 mg/g, serum albumin of at least 25 g/L, brain natriuretic peptide (BNP) concentration of no more than 200 pg/mL, serum potassium of at least 3·5 mmol/L, and systolic blood pressure of 110–180 mm Hg were eligible for participation. Treatment with a stable, recommended (or maximally tolerated) dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker was required for at least 4 weeks before entry into the enrichment period. Key exclusion criteria were a diagnosis of or previous hospital admission for heart failure, a history of severe peripheral or facial oedema, diagnosis of type 1 diabetes, history of pulmonary hypertension, pulmonary fibrosis, or any lung diseases requiring oxygen therapy, and known non-diabetic kidney disease. Inclusion and exclusion criteria are in the appendix.

Randomisation and masking

Randomisation of patients to the atrasentan or placebo group (1:1) was done centrally through an interactive

voice response system using a computer-generated randomisation schedule and was stratified for geographic region, baseline UACR (≤1000 mg/g or >1000 mg/g), and UACR reduction achieved during the enrichment period (30% to <45%, 45% to <60%, and ≥60%). Randomisation gating for enrolment into the non-responder cohort was implemented to ensure equal geographic and temporal distribution of non-responders and responders. Patients and all study personnel (except the independent data monitoring committee) were masked to treatment allocation and the study drug (atrasentan) and placebo were packaged identically with uniform capsule appearance, labelling, administration schedule, appearance, and odour.

Procedures

Following a screening and run-in period to optimise therapy with a diuretic and either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, eligible patients entered a 6-week enrichment period, during which they received open-label treatment with atrasentan 0·75 mg once daily orally. The enrichment period was used to identify atrasentan responders, defined as patients with at least a 30% reduction in UACR, who did not have substantial fluid retention (defined as an increase in bodyweight of 3 kg or more and a BNP increase to 300 pg/mL or more), and who did not have an increase in serum creatinine of more than 0·5 mg/dL and 20% from baseline. We intended to enrich the study population for patients who are likely to exhibit a renal benefit and unlikely to develop heart failure.

After 6 weeks, all responders who continued to meet eligibility criteria were randomly assigned to continue atrasentan 0·75 mg daily or switch to placebo. These responders comprised the primary analysis population used to establish the efficacy and safety of atrasentan. Additionally, a subset of non-responders (UACR reduction of <30% during the enrichment period and no evidence of significant fluid retention) were also randomly assigned to atrasentan or placebo to establish whether renal benefit was observed in this population.

After randomisation, in-person study visits were done after 1 month and 3 months and every 3 months thereafter. A follow-up visit was scheduled 45 days after the last dose of study drug to assess off-drug effects on clinical laboratory or physical parameters as well as adverse events. Participants were followed up to the point of withdrawal of consent or study closure.

During follow-up, study visits occurred every 3 months. At each follow-up visit, blood samples were taken for assessment of biochemical laboratory parameters and vital signs were recorded. Urine was collected at two separate visits 2 weeks apart at the beginning and end of the enrichment period, and at a single visit 1 month and 12 months after randomisation, and then at yearly intervals for assessment of UACR. At specified visits, patients were instructed to collect three consecutive first-morning voids to establish the geometric mean UACR. Results were blinded during the run-in, enrichment, and double-blind periods of the study to prevent unmasking. Study endpoints were recorded throughout follow-up when they occurred. The number of study visits depended on the duration of involvement in the study. Protocol-specific reasons for discontinuation of study medication included commencement of chronic dialysis, receipt of a kidney transplantation, or safety reasons.

Outcomes

The primary outcome was the efficacy of atrasentan in delaying the progression of chronic kidney disease, defined as the time from randomisation to the first occurrence of any of the following components of a composite endpoint: doubling of serum creatinine (confirmed by a second serum creatinine measurement ≥30 days later), onset of end-stage kidney disease (defined as chronic dialysis for >90 days, kidney transplantation, eGFR <15 mL/min per 1·73 m² confirmed by a second measurement ≥90 days later, or death from kidney failure). Secondary endpoints were, in hierarchal order, time to at least a 50% eGFR reduction; a cardiorenal composite endpoint defined as doubling serum creatinine, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke; the primary composite renal endpoint in all randomly assigned patients (responders and non-responders combined); and a cardiovascular composite endpoint defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Time to hospital admission for heart failure in responders and time to the primary renal outcome in non-responders were additional prespecified outcomes. A masked independent committee adjudicated the primary, secondary (except 50% eGFR reduction), and heart failure outcomes (appendix). We reported risk marker values over time to help understand the effects on clinical outcomes. Because endothelin receptor antagonists might cause sodium and fluid retention, adverse events of special interest included hypervolaemia, oedema, anaemia, and heart failure using prespecified standardised queries (appendix). Oedema was assessed at each study visit. Heart failure-related adverse events were collected on a specific case-report form.

Statistical analysis

The analytical approach and power calculation have been published previously,[6] and the prespecified statistical analysis plan is available with the protocol. We originally estimated that 425 events were needed to detect a 27% risk reduction (hazard ratio [HR] 0·73), with 90% power using a two-sided α level of 0·05, assuming an annual rate for the primary renal outcome of 6% in the placebo group. However, after all patients were randomly assigned, it became apparent that the rate of the primary composite outcome was much lower

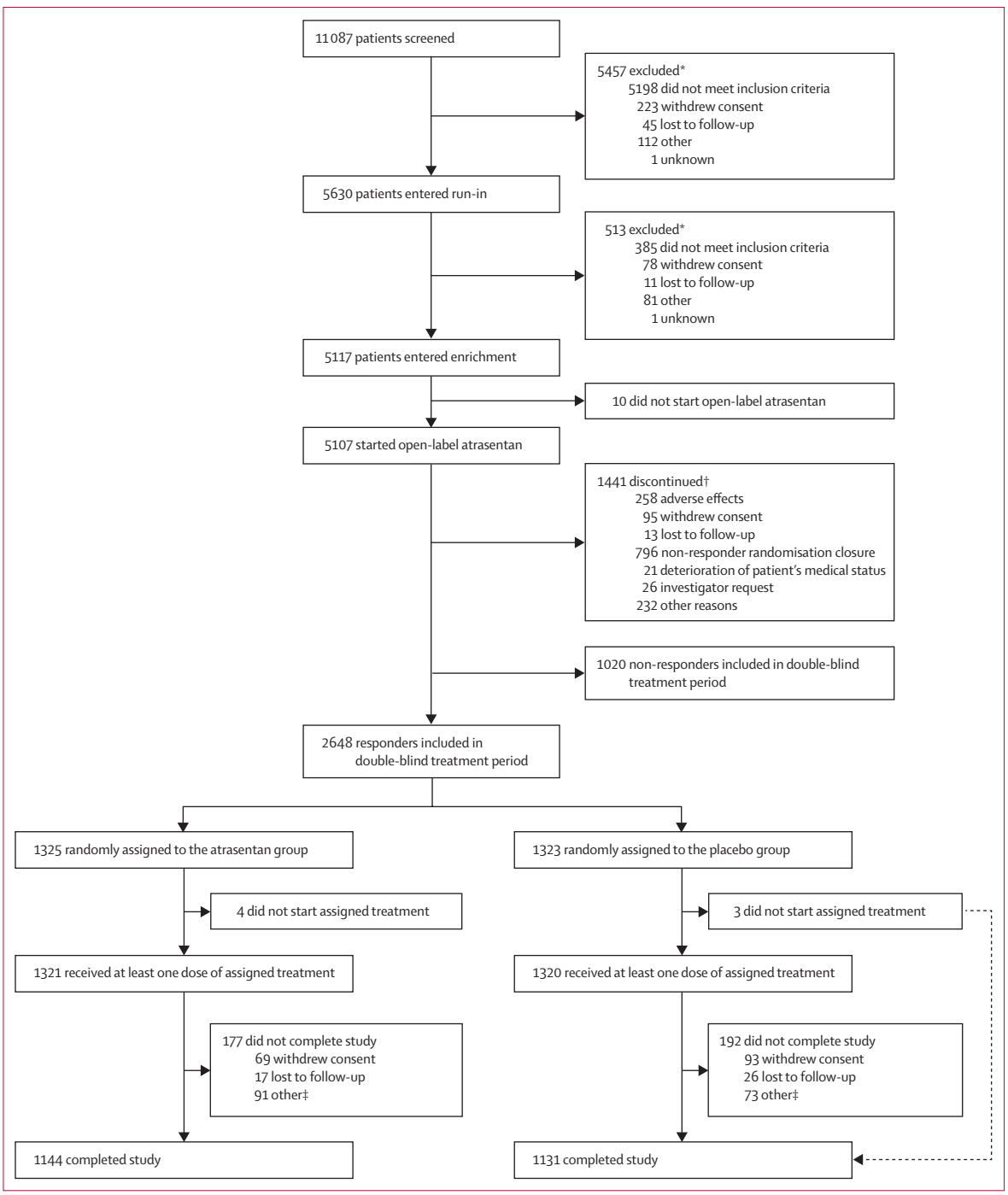

Figure 1: **Trial profile**
During the double-blind treatment period, 260 patients discontinued in the atrasentan group (111 adverse event, 37 withdrew consent, 14 were lost to follow-up, and 98 other) and 251 discontinued in the placebo group (94 adverse event, 58 withdrew consent, 21 lost to follow-up, and 78 other); some of these patients completed the study. *Reasons are not mutually exclusive. †Two patients who discontinued were later randomly assigned and included in the double-blind treatment period. ‡Adverse event, deterioration of the clinical status of the patient, investigator request, and other.

than expected and that the time needed to accrue 425 events would be much longer than expected. Accordingly, the sponsor decided in November, 2017, to stop the trial prematurely. The decision to stop the trial occurred before the planned interim analysis was done. Investigators were subsequently asked to perform the trial close-out procedures as described in the protocol.[6,8] At completion of the trial, 184 primary renal events had

occurred providing more than 90% power to detect an HR of 0·62 and 80% power to detect an HR of 0·66 with a two-sided α level of 0·05 (appendix).

Primary efficacy and safety analyses were done in the responder population; the primary efficacy analysis included all patients, analysed by intention to treat and the safety analysis included all patients who received at least one dose of study drug during the double-blind treatment period. Cox proportional hazard regression was used to estimate the HR and the 95% CI for atrasentan compared with placebo for the primary, secondary, and heart failure outcomes. For patients who had more than one event during follow-up, survival time to the first relevant endpoint was used in each analysis. The treatment effect in the model was adjusted for log-transformed UACR values, serum albumin, age, and eGFR at randomisation. These covariates were prespecified on the basis of previous studies showing that they are strong predictors of renal outcomes in patients with type 2 diabetes and chronic kidney disease.[9,10] The Cox proportional hazard assumptions were verified by visual inspection of the log(–log[survival]) curve and by adding a time-by-treatment interaction to the Cox model. These analyses showed no violations of the model assumptions. Treatment effects for the secondary and heart failure outcomes were analysed using a similar model. p values from the Cox model and from a stratified log-rank test, adjusting for the stratification factors at randomisation, are reported. If superiority of atrasentan over placebo was demonstrated for the primary endpoint at a two-sided significance level of 0·05, secondary endpoints were tested hierarchically using the same significance level in a prespecified order, until superiority over placebo could no longer be shown. The effect of atrasentan on the primary endpoint was analysed in prespecified subgroups using the same Cox model as described for the primary renal endpoint. The effects of atrasentan on continuous outcomes such as UACR and blood pressure were analysed using a mixed model with repeated measurements with an unstructured covariance matrix used to estimate within-subject correlations, and a Satterthwaite method to estimate degrees of freedom. Change in eGFR per year was calculated by a random coefficient model with treatment as a fixed effect, and baseline eGFR, time, and interaction of treatment by time as linear covariates, with intercept and time as random effects. Analyses were done with SAS, version 9.4. An independent data safety monitoring committee oversaw the study (appendix). The study was registered at ClinicalTrials.gov (NCT01858532).

Role of the funding source

The funder participated in study design, data collection, data analysis, data interpretation, and reviewing and approving the manuscript, but was not involved in the writing of the report. Employees of the funder reviewed the manuscript and gave suggestions for important intellectual content and approved the manuscript for

	Atrasentan (n=1325)	Placebo (n=1323)
Characteristics		
Age, years	64·9 (8·6)	64·7 (8·7)
Sex		
Women	331 (25·0%)	352 (26·6%)
Men	994 (75·0%)	971 (73·3%)
Race		
White	753 (56·8%)	744 (56·2%)
Black	73 (5·5%)	76 (5·7%)
Asian	446 (33·7%)	455 (34·4%)
Other	53 (4·0%)	48 (3·6%)
Weight, kg	84·6 (19·9)	84·6 (18·8)
Body-mass index, kg/m²	30·3 (5·8)	30·4 (5·5)
Duration of diabetes, years	16·8 (9·0)	16·7 (9·1)
Current smoker	205 (15·5%)	178 (13·5%)
Retinopathy	459 (34·6%)	453 (34·2%)
Blood pressure		
Systolic, mm Hg	136·5 (15·2)	136·2 (14·8)
Diastolic, mm Hg	75·0 (9·9)	74·8 (10·0)
Serum creatinine, μmol/L	147·5 (43·2)	147·4 (40·9)
Estimated glomerular filtration rate, mL/min per 1·73 m²	44·0 (13·7)	43·7 (13·7)
Cholesterol, mmol/L		
Total	4·6 (1·2)	4·6 (1·2)
Low-density lipoprotein	2·7 (1·0)	2·7 (1·0)
High-density lipoprotein	1·1 (0·4)	1·2 (0·4)
Glycated haemoglobin, %	7·8% (1·5)	7·8% (1·5)
Serum albumin, g/L	39·4 (3·5)	39·3 (3·4)
Haemoglobin, g/L	129·9 (16·9)	128·8 (16·9)
Brain natriuretic peptide, pg/mL	48·0 (26·0–87·0)	49·0 (25·6–89·0)
Serum potassium, mmol/L	4·5 (0·6)	4·5 (0·6)
Urinary albumin-to-creatinine ratio, mg/g	797 (462–1480)	805 (444–1451)
Previous medication		
Angiotensin-converting enzyme inhibitor	474 (35·8%)	487 (36·8%)
Angiotensin receptor blocker	861 (65·0%)	850 (64·2%)
β blocker	556 (42·0%)	541 (40·9%)
Calcium channel blocker	800 (60·4%)	775 (58·6%)
Diuretic		
Loop	595 (44·9%)	599 (45·3%)
Thiazide	409 (30·9%)	409 (30·9%)
Other*	127 (9·6%)	150 (11·3%)
Statin	965 (72·8%)	994 (75·1%)
Glucose-lowering therapies		
Insulin	838 (63·2%)	820 (62·0%)
Metformin	508 (38·3%)	534 (40·4%)
Sulphonylurea derivatives	374 (28·2%)	381 (28·8%)
Dipeptidyl peptidase 4 inhibitor	250 (18·9%)	295 (22·3%)
Glucagon-like peptide-1 receptor agonist	52 (3·9%)	56 (4·2%)
Sodium-glucose cotransporter 2 inhibitor	12 (0·9%)	24 (1·8%)
Antithrombotic drug†	753 (56·8%)	776 (58·7%)

Data are n (%), mean (SD), or median (IQR). *Chlorthalidone, indapamide, mefruside, metolazone, tripamide, and xipamide. †Anticoagulants and antiplatelets.

Table 1: **Baseline characteristics at start of the enrichment period**

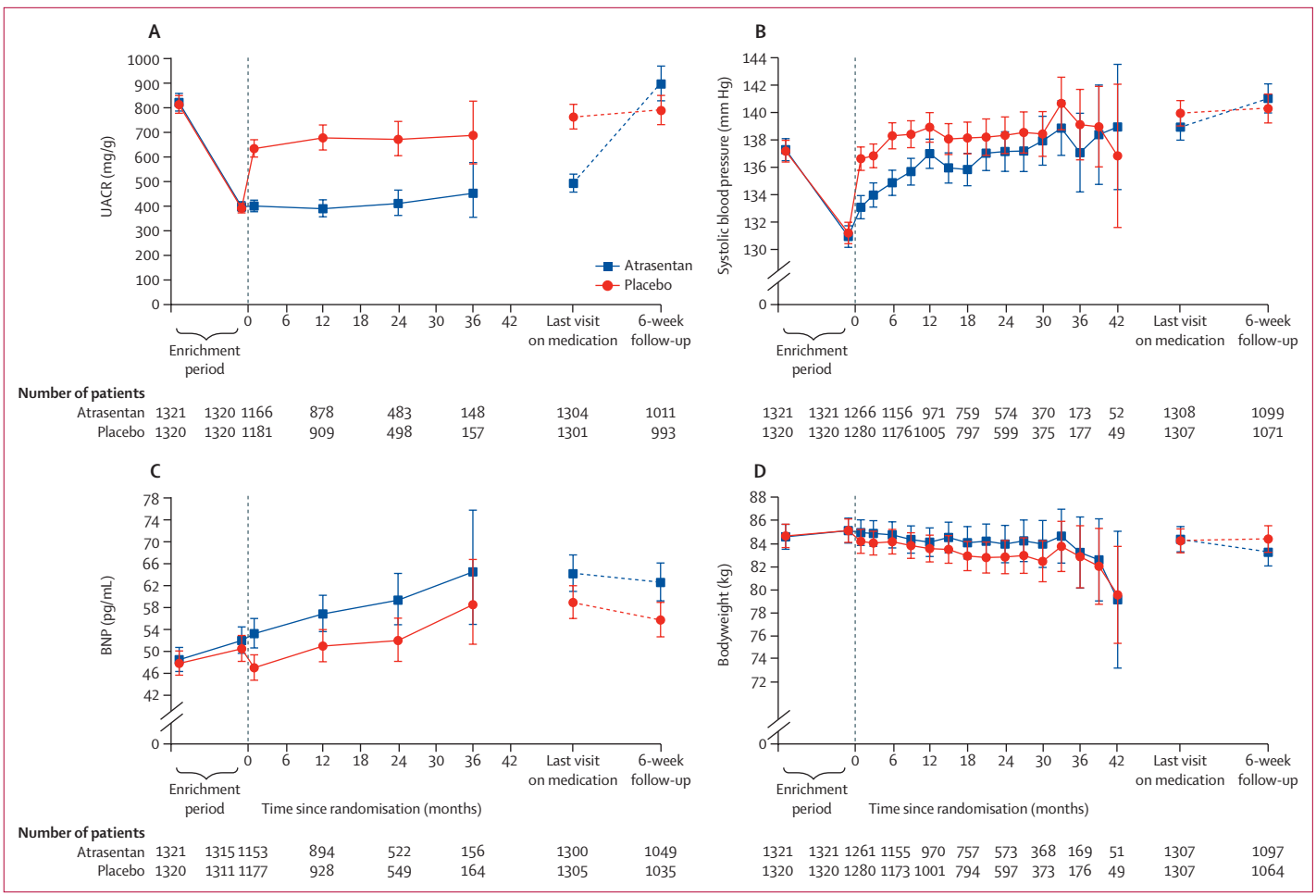

Figure 2: **UACR, systolic blood pressure, BNP, and bodyweight during the study**
Geometric mean UACR (A), mean systolic blood pressure (B), geometric mean BNP (C), and mean bodyweight (D). Error bars are 95% CIs. Vertical dotted lines denote the start of the randomised treatment period. Patients who discontinued medication are included in figures but their data collected after 6-week post-treatment follow-up visit are excluded. BNP=brain natriuretic peptide. UACR=urine albumin-to-creatinine ratio.

submission. Employees of the funder did not have critical comments on the interpretation or conclusions. The corresponding author had full access to all the data in the study. All authors had final responsibility for the decision to submit the manuscript for publication.

Results

Between May 17, 2013, and July 13, 2017, 11087 patients were screened, of whom 5457 were excluded because they did not meet exclusion criteria; 5630 entered the run-in period, of whom 513 were excluded; and 5117 entered the enrichment period (figure 1). 4711 patients completed the enrichment period, of whom 2648 were responders and were randomly assigned to atrasentan (n=1325) or placebo (n=1323). A selection of 1020 of the non-responders were randomly assigned to atrasentan (n=509) or placebo (n=511). Thus, not all non-responders were included in the double-blind treatment period.

Responders who entered the double-blind treatment period were followed up for a median of 2·2 years (IQR 1·4–2·9). During follow-up, 260 (19·6%) of 1325 patients in the atrasentan group and 251 (19·0%) of 1323 in the placebo group discontinued treatment prematurely. At the end of the study, vital status was unknown for 119 (9·0%) patients in the atrasentan group and 141 (10·7%) patients in the placebo group; 1148 (86·6%) patients in the atrasentan group and 1130 (85·4%) in the placebo group were followed up until a timepoint between completion of the study and study completion end date and 58 and 52 were known to have died before study completion.

Baseline characteristics, including medications for diabetes and kidney disease, were balanced between the groups (table 1). Mean age was 64·8 years (SD 8·7), 683 (25·8%) were women, mean eGFR was 43·8 mL/min per 1·73 m² (SD 14), and median UACR was 803 mg/g (450–1469; table 1).

Among the 2648 responders, UACR decreased from baseline by 51·8% (95% CI 51·4–52·4) during the enrichment period. Systolic blood pressure decreased

	Atrasentan (n=1325)		Placebo (n=1323)		Hazard ratio (95% CI)	p value*
	Number	Annual rate	Number	Annual rate		
Primary outcome						
Composite renal outcome	79 (6·0%)	2·8%	105 (7·9%)	3·7%	0·65 (0·49–0·88)	0·0047
Doubling of serum creatinine	56 (4·2%)	2·0%	78 (5·9%)	2·7%	0·61 (0·43–0·87)	0·0055
End-stage kidney disease	67 (5·1%)	2·4%	81 (6·1%)	2·9%	0·73 (0·53–1·01)	0·060
Secondary outcomes†						
50% eGFR reduction	84 (6·3%)	3·0%	99 (7·5%)	3·5%	0·73 (0·55–0·98)	0·038
Cardiorenal composite endpoint‡	147 (11·1%)	5·2%	172 (13·0%)	6·1%	0·80 (0·64–0·999)	0·049
Cardiovascular death	31 (2·3%)	1·1%	28 (2·1%)	1·0%	1·10 (0·66–1·83)	0·720
Non-fatal myocardial infarction	36 (2·7%)	1·3%	33 (2·5%)	1·2%	1·11 (0·69–1·78)	0·675
Non-fatal stroke	8 (0·6%)	0·3%	27 (2·0%)	1·0%	0·29 (0·13–0·64)	0·0021
Primary outcome in all randomly assigned patients§	152 (8·3%)	3·8%	192 (10·5%)	4·8%	0·72 (0·58–0·89)	0·0023
Cardiovascular composite endpoint¶	72 (5·4%)	2·5%	81 (6·1%)	2·9%	0·88 (0·64–1·22)	0·448
Other outcome						
Hospital admission for heart failure	47 (3·5%)	1·7%	34 (2·6%)	1·2%	1·33 (0·85–2·07)	0·208

Data are n (%) unless otherwise specified. eGFR=estimated glomerular filtration rate. Annual rates are numbers of events over total person-years of follow-up. *Cox model for the primary and secondary efficacy outcomes; the log-rank p value was 0·029 for the primary outcome; 0·163 for the time to a 50% eGFR reduction; 0·011 for primary outcome in the total population; and 0·446 for cardiovascular composite endpoint. †Secondary outcomes are ranked according to prespecified hierarchy. ‡Comprises doubling of serum creatinine, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. §Primary renal outcome in combined responders and non-responders (n=1834 atrasentan and n=1834 placebo). ¶Comprises cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.

Table 2: **Effects of atrasentan on renal and cardiovascular outcomes**

by 6·1 mm Hg (5·6–6·7), BNP increased by 6·1% (3·5–8·7), and bodyweight increased by 0·5 kg (0·4–0·6; figure 2). These changes were similar between patients subsequently randomly assigned to atrasentan and those assigned to placebo in the double-blind treatment phase.

After randomisation, during the double-blind treatment period, UACR increased more in the placebo group than in the atrasentan group (difference 33·6% [95% CI 29·1 to 38·2]; p<0·0001), and the mean between-group difference in change in systolic blood pressure from randomisation was –1·6 mm Hg (95% CI –2·5 to –0·7; p=0·00054). Conversely, the increase in BNP from randomisation was 10·5% (95% CI 5·1 to 15·4; p<0·0001) higher with atrasentan than with placebo, and the mean difference in bodyweight change was 0·2 kg (95% CI –0·1 to 0·5; p=0·12; figure 2).

The composite primary outcome occurred in 79 (6·0%) of 1325 patients in the atrasentan group compared with 105 (7·9%) of 1323 patients in the placebo group (HR 0·65 [95% CI 0·49–0·88]; p=0·0047; table 2, figure 3A). The HR was 0·61 (95% CI 0·43–0·87; p=0·0055; figure 3B) for doubling of serum creatinine and 0·73 (0·53–1·01; p=0·060; figure 3C) for end-stage kidney disease. The effects were broadly consistent across a wide range of prespecified subgroups (appendix).

The HR for the first secondary endpoint of at least 50% eGFR decline was 0·73 (95% CI 0·55 to 0·98; p=0·038; table 2). The HR for the cardiorenal composite outcome was 0·80 (0·64 to 0·999; p=0·049). There was no effect of atrasentan on the composite cardiovascular outcome (HR 0·88 [0·64 to 1·22]; p=0·448). The mean rate of change in eGFR during the trial was –2·4 mL/min per 1·73 m² per year (95% CI –2·7 to –2·1) in the atrasentan group compared with –3·1 mL/min per 1·73 m² (–3·4 to –2·8) in the placebo group (p=0·00049).

Baseline characteristics of the 1020 non-responders were balanced between the treatment groups (appendix). Compared with responders, non-responders were younger, and had a slightly higher baseline UACR, and lower eGFR. Among non-responders, the primary renal outcome occurred in 73 (14·3%) patients in the atrasentan group compared with 87 (17·0%) in the placebo group (HR 0·75 [95% CI 0·55–1·03]; p=0·079; figure 4). The effect of atrasentan on the primary renal outcome was consistent in responders and non-responders ($p_{interaction}$=0·41). The incidence of secondary endpoints and rate of eGFR change did not differ between treatment groups in non-responders (appendix).

In the responder and non-responder groups combined (n=3668), the primary renal outcome occurred in 152 (8·3%) of 1834 patients in the atrasentan group and 192 (10·5%) of 1834 patients in the placebo group (HR 0·72 [95% CI 0·58–0·89]; p=0·0023; figure 4, table 2).

The most frequent adverse events that were more commonly reported in the atrasentan than placebo group were fluid retention and anaemia. Serious adverse events occurred more frequently in the atrasentan group (1042 events in 479 [36·3%] of 1321 patients), than in the placebo group (903 events in 430 [32·6%] of 1320 patients). Fluid retention and anaemia, which are adverse events of special interest because they have been previously

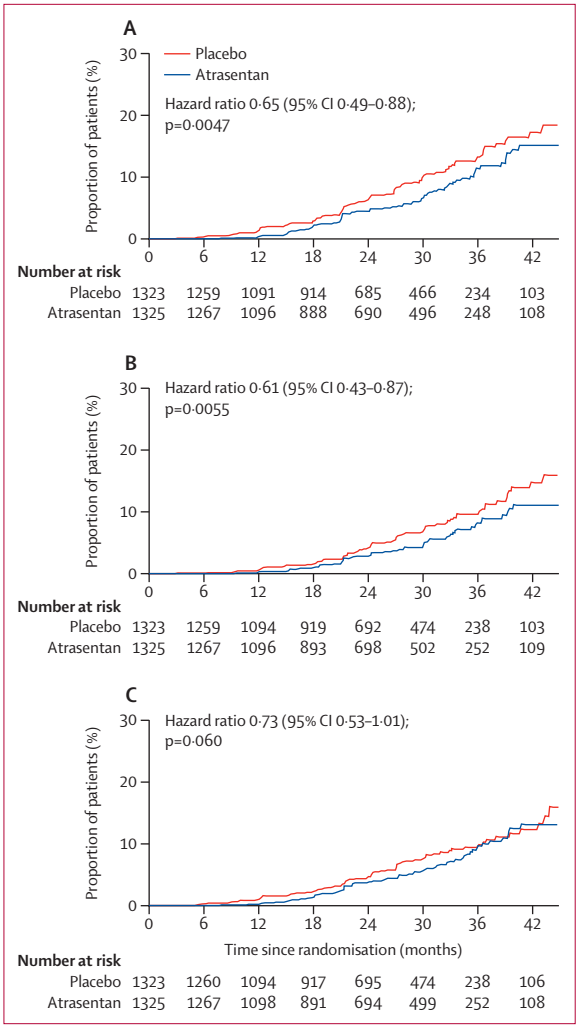

Figure 3: **Effects of atrasentan on the primary composite renal outcome and its components in responders**
Composite primary renal outcome (A), doubling of serum creatinine (B), and end-stage kidney disease (C) in the intention-to-treat population of responders. Calculated by Cox proportional hazard regression models.

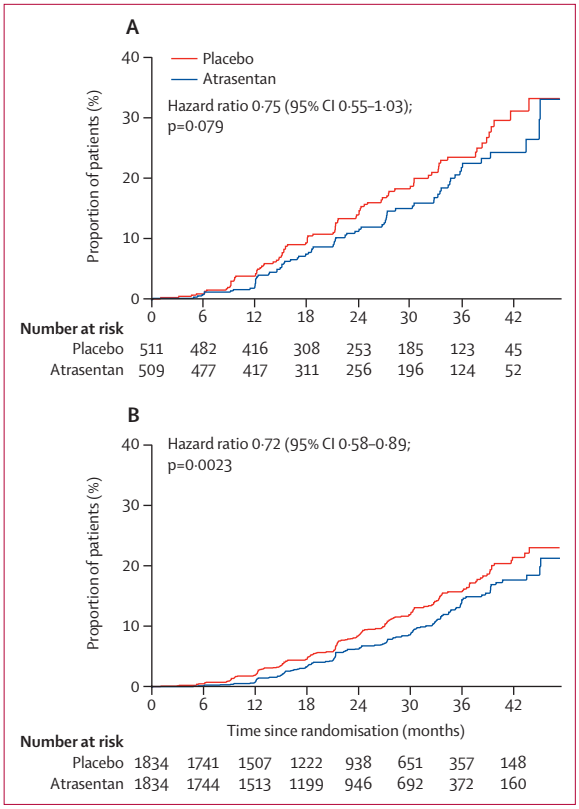

Figure 4: **Effects of atrasentan on the primary composite renal outcome in non-responders and all responders and non-responders combined**
Non-responders (A) and combined responders and non-responders (B). Primary composite renal outcome comprised doubling of serum creatinine and end-stage kidney disease. Calculated by Cox proportional hazard regression models.

reported to be attributable to endothelin receptor antagonists, were more frequent in the atrasentan group than in the placebo group (table 3). Adjudicated hospital admission for heart failure occurred in 47 (3·5%) of 1325 patients in the atrasentan group compared with 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 [Cox model]).

Among non-responders, fluid retention and anaemia were also more frequent in the atrasentan group than the placebo group (appendix). As with responders, some adverse events of special interest, including fluid retention and anaemia, occurred more frequently with atrasentan than with placebo (appendix). Adjudicated hospital admission for heart failure occurred in 26 (5·1%) of 508 patients in the atrasentan group compared with 17 (3·3%) of 510 patients in the placebo group (HR 1·54 [95% CI 0·83–2·86]; p=0·175). 26 (5·1%) patients in the atrasentan group and 27 (5·3%) patients in the placebo group died (HR 0·97 [95% CI 0·56–1·67]; p=0·909). Combining the responder and non-responder groups in a post-hoc analysis, the HR for adjudicated hospital admission for heart failure was 1·39 (95% CI 0·97–1·99; p=0·072).

Discussion

In patients with type 2 diabetes and chronic kidney disease, selected on the basis of having at least a 30% reduction in UACR and no clinical signs of sodium retention during short-term, low-dose treatment with atrasentan, subsequent long-term treatment with this endothelin receptor antagonist significantly reduced the risk of the primary composite renal outcome of doubling of serum creatinine or end-stage kidney disease compared with placebo.

Guidelines recommend use of an angiotensin receptor blocker or angiotensin-converting enzyme inhibitor as well as optimised blood pressure and glycaemic control to minimise renal risk in patients with type 2 diabetes and albuminuria. Increased expression of endothelin-1 has

also been implicated in progressive loss of renal function in patients with diabetic nephropathy.[11] This increase in renal endothelin-1 is stimulated by multiple factors associated with diabetic kidney disease, including acidaemia, angiotensin-II, dyslipidaemia, hypoxia, growth factors, inflammatory cytokines, oxidative stress, insulin, and hyperglycaemia. In turn, endothelin-1 exerts multiple pathophysiological effects, including injury to the vasculature (enhanced vasoreactivity and procoagulation), podocytes (nephron shedding, cytoskeletal disruption, and proteinuria), tubulointerstitium (fibrosis), and mesangium (proliferation and extracellular matrix accumulation) as well as promoting inflammatory cell infiltration.[11] In experimental studies, endothelin receptor antagonists improved renal morphology and function and reduced albuminuria through multiple mechanisms, including attenuated damage to mesangial cells, podocytes, renal tubules, and the glycocalyx.[12–15] In clinical studies, endothelin receptor antagonists reduced albuminuria and blood pressure.[5,16,17] We therefore did this large, international, long-term trial examining the effects of adding atrasentan to the standard of care on clinically meaningful renal endpoints. The findings from SONAR support the value of atrasentan in protecting kidney function in carefully selected patients with type 2 diabetes and chronic kidney disease who show an initial reduction in albuminuria with short-term endothelin receptor blockade.

SONAR is, to our knowledge, the first trial in patients with diabetes and chronic kidney disease to use a design intended to select patients most likely to benefit from treatment, in accord with the concept of personalised medicine.[18] We selected patients with at least a 30% reduction in UACR, because previous observational studies and meta-analyses of randomised controlled trials indicated that this population is at substantially lower risk of progression of renal disease than patients with smaller reductions in albuminuria, regardless of the type of intervention.[10,19–21] The difference in UACR between placebo and atrasentan treatment during the double-blind treatment period in our study was smaller than the difference observed during the enrichment period, because the post-randomisation UACR in the placebo group did not completely return to baseline values. The incomplete reversal of UACR reduction in the placebo group could reflect a legacy effect, although the complete reversal in the atrasentan treatment group during the 6-week washout phase at the end of the trial makes this possibility seem unlikely.

Patients who were more likely to tolerate an endothelin receptor antagonist were also selected by excluding those showing clinical signs of sodium retention. Previous studies in individuals with chronic kidney disease and heart failure have shown that endothelin receptor antagonists can precipitate or worsen heart failure, leading to premature termination of at least one trial.[3] By contrast, two previous short-term studies (8 weeks and 12 weeks duration) of atrasentan showed marked reduction in albuminuria even at low doses that did not cause clinically significant fluid retention.[4,5] These short-term results are important because patients who developed fluid retention on higher doses of atrasentan did so within the first 2–4 weeks of treatment. However, even with the precautionary approach taken in our study, including the use of diuretics, hospital admission for heart failure was higher with atrasentan (47 [3·6%] of 1321) than placebo (34 [2·6%] of 1320) in responders, indicating the necessity for continued vigilant monitoring of these adverse effects if treatment with endothelin receptor antagonists were to be used in clinical practice. Early termination of the trial and the low number of cardiovascular events precluded any definitive assessment of further cardiovascular risk.

Although our trial design was not traditional, it mimics clinical practice in which physicians frequently discontinue therapy in patients who do not respond or tolerate the drug—eg, in the treatment of hypertension. We can only be confident about our findings in the responder population because the study was not powered to assess the effect of atrasentan in the non-responders (or the difference in effect between responders and non-responders) and the effect of atrasentan in the non-responder population was not statistically significant. Therefore, in a clinical setting, a strict interpretation of our results would hold that monitoring of UACR response after atrasentan initiation is required and atrasentan should be discontinued if patients do not show a good response or have side-effects. However, the consistent

	Atrasentan (n=1321)	Placebo (n=1320)	p value*
Any serious adverse event	479 (36·3%)	430 (32·6%)	0·049
Adverse events leading to discontinuation	137 (10·4%)	122 (9·2%)	0·360
Deaths	58 (4·4%)	52 (3·9%)	0·630
Treatment-emergent adverse events of interest			
Hypervolaemia or fluid retention	483 (36·6%)	426 (32·3%)	0·022
Cardiac failure†	72 (5·5%)	51 (3·9%)	0·064
Anaemia	244 (18·5%)	136 (10·3%)	<0·0001
Vasodilation	126 (9·5%)	118 (8·9%)	0·638
Cardiac toxicity	147 (11·1%)	130 (9·8%)	0·310
Serious adverse events (>1% in either group)			
Acute kidney injury	32 (2·4%)	28 (2·1%)	0·696
Pneumonia	32 (2·4%)	22 (1·7%)	0·216
Congestive cardiac failure	23 (1·7%)	15 (1·1%)	0·252
Acute myocardial infarction	21 (1·6%)	21 (1·6%)	1·0
Coronary artery disease	18 (1·4%)	17 (1·3%)	1·0
Anaemia	16 (1·2%)	10 (0·8%)	0·325
Hypoglycaemia	14 (1·1%)	8 (0·6%)	0·284
Urinary tract infection	16 (1·2%)	7 (0·5%)	0·092
Cardiac failure	13 (1·0%)	8 (0·6%)	0·381
Cataract	16 (1·2%)	8 (0·6%)	0·150
Hyperkalaemia	13 (1·0%)	13 (1·0%)	1·0

Data are n (%). *Fisher's exact test. †Cardiac failure events included all investigator-reported treatment-emergent adverse events.

Table 3: **Adverse events during double-blind treatment period**

effect of atrasentan in the combined analysis of responders and non-responders suggests that this type of therapy might have a broader indication. Moreover, the explanation for any potential benefit in non-responders is unknown and requires further study, along with a proper assessment of the usefulness of the enrichment design. It is possible that responders are insufficiently separated from non-responders because of random fluctuations in albuminuria, but it is also possible that atrasentan slows renal disease progression through pathways unrelated to albuminuria change.[22,23] Finally, the threshold of 30% UACR reduction to define responders was arbitrary and might not be the optimal threshold to distinguish atrasentan responders from non-responders in terms of clinical outcomes.

The trial has limitations, the most important of which is its early termination because of a lower-than-planned event rate. The reason for the low event rate is unknown and requires further analysis. Nevertheless, the large treatment effect size observed and an adequate number of endpoints provided sufficient power to draw robust conclusions about the primary renal outcome. Further, vital status of some patients lost to follow-up remained unknown despite the trial close-out procedures being performed according to the protocol.[6] Although these patients were similarly distributed across the placebo and atrasentan groups, this potential bias has to be taken into account in the trial interpretation. Additionally, during the trial, 19% of patients discontinued their assigned treatment. Although this proportion is similar to other trials in patients with diabetes and chronic kidney disease,[24,25] this might have affected the benefit–risk estimation.

In summary, SONAR showed that patients with type 2 diabetes and chronic kidney disease who were selected for a substantial UACR reduction and minimal clinical signs of sodium retention during short-term treatment with atrasentan had a significantly lower risk of doubling of serum creatinine or end-stage kidney disease during long-term treatment with this endothelin receptor antagonist compared with placebo. Data from this study and other trials with endothelin receptor antagonists could define the position of this class in the future treatment armamentarium of the diabetes population with high renal and cardiovascular risk.

For more on **data requests or to submit a request** see https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html

Contributors

HJLH, H-HP, DLA, GB, RC-R, F-FH, DWK, DK, HM, JJVM, VP, ST, and DdZ were involved in the design of the study. All authors were involved in the collection of data. TY and HJLH analysed the data. HJLH and DdZ wrote the first draft of the article. All authors were involved in data interpretation, and in drafting and critically revising the article. All authors had access to study results, and the lead author takes responsibility for the integrity of the data and accuracy of the data reported. All authors reviewed and approved the final version of the article for submission.

Declaration of interests

HJLH, DLA, GB, RC-R, F-FH, DWK, DK, HM, JJVM, VP, and ST were members of the SONAR study steering committee. HJLH serves as a consultant for AbbVie, Astellas, AstraZeneca, Boehringer Ingelheim, Fresenius, Gilead, Janssen, Merck, Mundi Pharma, and Mitsubishi Tanabe. H-HP was the co-chair of the SONAR study steering committee and serves as a consultant for AbbVie. DLA is a former employee of AbbVie and currently provides independent nephrology consulting services. GB was a study investigator for the SONAR study; he is on the steering committees of CREDENCE, CALM-2, and FIDELIO and is principal investigator of FIDELIO; he is a consultant for Bayer, Relypsa, Janssen, Merck, and Vascular Dynamics. RC-R serves on advisory boards for Boehringer and AstraZeneca and has been a speaker for AstraZeneca, Boehringer Ingelheim, AbbVie, Takeda, Amgen, and Janssen. F-FH was a study investigator, and a consultant for and received honoraria from AbbVie and AstraZeneca. DWK was chair of the Event Adjudication Committee for SONAR; has received grant funding from Bayer, Novartis, and the National Institutes of Health, and has been a consultant for AbbVie, Bayer, Merck, Boehringer Ingelheim, Corvia, CinRx, GlaxoSmithKline (GSK), Duke Clinical Research Institute, St Luke's Medical Center, and AstraZeneca. HM is a consultant for Teijin and Boehringer Ingelheim and receives speaker honoraria from Boehringer Ingelheim. VP has served on Steering Committees for trials funded by AbbVie, Boehringer Ingelheim, GSK, Janssen, Novo Nordisk, Retrophin and Tricida; and has participated in scientific presentations or advisory boards with AbbVie, Astellas, AstraZeneca, Bayer, Baxter, Brisol-Myers Squibb, Boehringer Ingelheim, Dimerix, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Mitsubishi Tanabe, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Retrophin, Sanofi, Servier, and Tricida. ST was a study investigator in SONAR; and participates on a steering committee for Bayer Fidelio/Figaro studies, and speaker's bureaux with Servier and Pfizer. DdZ was a co-chair of the SONAR study steering committee; serves on advisory boards or is a speaker for Bayer, Boehringer Ingelheim, Fresenius, Mundipharma, and Mitsubishi Tanabe; participates in steering committees or is a speaker for AbbVie and Janssen; and is on the data safety and monitoring committees for Bayer. JZM, MGM, TY, and MW are employees of AbbVie, receiving stock or stock options. PEP was a SONAR study investigator; has been a consultant for and received personal fees from AbbVie, Akebia, AstraZeneca, Keryx, Reata, ExThera, and Vifor; and has served on advisory boards for Akebia, Keryx, and Vifor; his institution and employer, Renal Associates PA, has received research support from many pharmaceutical companies for his work as a principal investigator.

Data sharing

This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided after review and approval of a research proposal and Statistical Analysis Plan and execution of a Data Sharing Agreement by AbbVie and the corresponding author. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered.

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