

A turning point for chronic kidney disease in diabetes



The worldwide prevalence of chronic kidney disease is one in seven to one in ten adults.^{1,2} This pandemic is closely linked to a global diabetes emergency.³ In 2017, 425 million adults had diabetes, with a projection for a 48% increase to 629 million by 2045.³ About half of those with diabetes develop chronic kidney disease.⁴ Progressive chronic kidney disease eventuates in end-stage kidney disease requiring dialysis or kidney transplantation to sustain life. However, only about 10% of patients survive to end-stage kidney disease because of premature death, predominantly from cardiovascular diseases and infections.^{1,2} Moreover, chronic kidney disease-related deaths have nearly doubled over the past quarter of a century, and less than half of patients globally have access to kidney replacement therapy for end-stage kidney disease.^{1,5,6} There is an urgent unmet need to improve outcomes for chronic kidney disease in patients with diabetes; the last new drugs approved were angiotensin receptor blockers in 2001. In the early 1990s, angiotensin converting enzyme inhibitors were introduced. A series of drugs failed in conventional clinical trials.⁷⁻¹¹ Although there were myriad reasons, a major problem was clinical trial designs that were misaligned with heterogeneous patient features, relevant outcomes, or reasonable timeframes.

The Study Of Diabetic Nephropathy with Atrasentan (SONAR) in *The Lancet* demonstrates a turning point in trial innovation.¹² This double-blind, randomised, placebo-controlled trial tested the endothelin A receptor antagonist atrasentan in patients with chronic kidney disease and type 2 diabetes using an enrichment design to select participants on the basis of drug tolerance for safety and responder status for efficacy. The protocol used typical inclusion criteria, including persistence of macroalbuminuria while using a renin-angiotensin system inhibitor. If candidates had clinical or laboratory evidence of heart failure or increase in serum creatinine during 6 weeks of open-label treatment with atrasentan, they were excluded. Those who subsequently entered the study were divided into responders ($\geq 30\%$ albuminuria reduction) and non-responders and then randomly assigned to either the atrasentan group or placebo group. Of 2648 responders, 1325 were assigned atrasentan and 1323 to placebo. SONAR was

stopped prematurely by the sponsor because of the low numbers of primary outcome events—namely, doubling of serum creatinine (sustained for ≥ 30 days) and end-stage kidney disease (estimated glomerular filtration rate < 15 mL/min per 1.73 m² sustained for ≥ 90 days, chronic dialysis for > 90 days, kidney transplantation, or death from kidney failure). Nevertheless, the atrasentan group had significantly reduced numbers of primary outcome events in both the responder population and in the combined population of responders and non-responders. Among responders, 79 (6.0%) of 1325 participants in the atrasentan group and 105 (7.9%) of 1323 in the placebo group had a primary composite renal endpoint event (hazard ratio 0.65 [95% CI 0.49–0.88]; $p=0.0047$). Interaction between responder and non-responder status was not significant, suggesting that results were similar overall. Effects on the primary outcome were maintained across subgroups, including by sex, age, albuminuria or glycaemia, and kidney function. Serious adverse events, including fluid retention and anaemia, occurred more frequently in the atrasentan group than in the placebo group, but no significant effects of atrasentan were detected on risks of hospital admission for heart failure or all-cause mortality.

SONAR¹² succeeded in shifting trial design to match patients with treatment on the basis of safety and response assessments during a prerandomisation enrichment period. Yet such innovation uncovers new questions and issues. For example, is it feasible to implement a corresponding enrichment strategy into daily clinical practice? Notably, selection of atrasentan-tolerant responders might have biased the study toward lower-risk participants with fewer events, and therefore produced an overestimate of treatment effect. Atrasentan-tolerant non-responders appear to react similarly, although caution is warranted given the underpowered analyses. However, if true, then assessment might not be needed for response, but only for safety. Understanding of the primary outcome results would be enhanced by graphical presentation of longitudinal data for estimated glomerular filtration rate, the causal pathway to events, by treatment group. Additionally, post-randomisation albuminuria concentration did not return to baseline in the placebo



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group, suggesting a legacy effect of atrasentan, and treatment discontinuation occurred in nearly 20% of participants across groups. However, these issues would bias results to the null, making the favourable outcomes with atrasentan perhaps more impactful, especially considering premature study termination.

Along with newer glucose-lowering drugs (sodium-glucose co-transporter-2 inhibitors and glucagon-like-peptide 1 agonists), atrasentan is poised to join the selection of drugs for treatment of patients with diabetes and chronic kidney disease.¹³⁻¹⁶ SONAR took a step forward to target treatment toward patient-specific safety and response parameters. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (NCT02065791) trial testing canagliflozin (a sodium-glucose co-transporter-2 inhibitor) against placebo for patients with diabetes and chronic kidney disease was stopped early for strong evidence of efficacy. Perhaps recommendations for ubiquitous renin-angiotensin system inhibitor use as a standard of care will now be challenged. It will also be essential to understand when, and if, combinations of drugs from different classes should be applied, or whether they can be discontinued or temporarily interrupted if remission occurs versus the customary indefinite treatment. Finally, whether patients with chronic kidney disease who do not have diabetes will receive similar benefits, particularly for conditions thought to share biological mechanisms such as hypertension-related or obesity-related chronic kidney disease, is yet to be established.

This overall direction is crucial for future breakthroughs to arise through even deeper biological profiling by molecular studies of blood, urine, and kidney tissue. The aspirational goal to deliver the right treatment to the right patient at the right time is within sight to tackle the global burden of diabetes and chronic kidney disease.

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