# Renal trials in diabetes need a platform

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# Renal trials in diabetes need a platform: time for a global approach?

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Renal morbidity and mortality in patients with diabetes is high, and although angiotensin-receptor blockers have been successful in reducing morbidity and mortality, the residual risk remains elevated. Patients who do not respond to the prescribed drugs contribute substantially to this unmet need. This variation in therapy response is in part due to heterogeneity in the causes of renal disease progression in patients with diabetes.[1] To increase the therapeutic options available, research has focused on pathways beyond the renin–angiotensin system (RAS). Several drug targets have been tested by evaluating efficacy of drugs to improve surrogate markers such as blood pressure, blood glucose concentration, cholesterol, $HbA_{1c}$, and albuminuria. Many promising drugs were discovered, which appeared to be particularly effective in reducing albuminuria. Unfortunately, only a few have reached the stage of trials assessing hard outcomes. This high attrition rate is not only due to scarce funding for large, expensive, hard outcome trials, but also the fact that each new drug must be tested separately through to phase 4 trials. To date, at least three promising drugs have advanced to the final stage of development: atrasentan (SONAR; NCT01858532), canagliflozin (CREDENCE; NCT02065791), and finerenone (FIDELIO; NCT02540993).

These trials are expected to show that the drug will delay the progression of renal disease on top of current guideline therapy. The outlook is promising for all three drugs; however, no matter how good the outcome, none of these drugs will give protection to all patients. This expected variation in therapy response is supported by the fact that each of these drug classes has shown a variable effect on the important surrogate outcome albuminuria (figure). If this variability translates into variation in hard renal outcomes, it would mean that each trial will have a large group of patients who do not benefit from the drug. A substantial residual risk is, therefore, likely to remain after completion of all three trials.

Far more important than the success of each of these three trials individually is that the results will not answer the question of what to do with the non-responders from each trial. The individual trials will answer whether a non-responder to RAS-intervention has benefited from the new drug, but not whether a non-responder might benefit from one of the other two drugs. Another key question that these trials will not answer is whether the three drugs induce responses only in the same patients, or if each drug provides benefit for a discrete patient population. In the best case scenario of three positive trials resulting in three new protective mechanisms, we could be left with the frustration of having identified three discrete groups of non-responders to single agents, but being deprived of the means to test their response to the other promising alternatives.

The design of studies in this area should be changed to overcome this hurdle, and to get answers about how to deal with responders and non-responders. Directly selecting patients with a positive surrogate marker response to a drug into trials of that drug, as well as de-selecting patients with a negative surrogate marker

response, as suggested in a previous Comment[5] in *The Lancet Diabetes & Endocrinology*, has several advantages over present trial designs. First, the trials could be smaller, shorter, or both, and thus potentially less expensive. Second, non-responders will not be exposed to a drug that is unlikely to benefit them. SONAR is an example of a personalised clinical trial design in diabetic nephropathy, and the results will be an important test of the success of such an approach. This design, however, does not solve the issue of what to do with the non-responders and de-selected patients. The concept of platform or umbrella design could help with this issue.[6]

Such trial designs have been implemented in oncology, Alzheimer's disease, and infectious disease,[7] and should be considered in the diabetes and nephropathy specialties. Such trial designs enable researchers to test multiple drugs in different patients. In existing platform approaches, participants with similar groups of diseases are randomly assigned to different treatment groups, each involving a different intervention or a control. It might be possible to take this concept further—to include a level of study design in which patients are enrolled and randomly assigned according to response on intermediate biomarkers. Instead of running three diabetes nephropathy trial cohorts in parallel with three different drugs, we could start with one large diabetic nephropathy patient cohort (platform). Patients from this worldwide platform would get the first available new drug. The responders would continue with the drug, while the non-responders would be tested with the next available drug, and so on. If the patient did respond, they would be randomly assigned that drug or placebo and followed up until the completion of the relevant trial. Such a design would enable assessment of new drugs, as well as existing drugs or drug combinations. These designs thus offer the advantage of testing the best therapy (personalised or precision medicine) for each patient or group of patients.

A prerequisite of such an approach is that the response of the chosen surrogate marker is a good reflection of the actual hard outcome, in this case renal disease. Unfortunately, no single surrogate meets that requirement in diabetes and renal disease progression; therefore, a multiple response score, such as the Parameter Response Efficacy (PRE)-score,[8] seems to be a much better surrogate to predict treatment effect on hard renal outcomes.

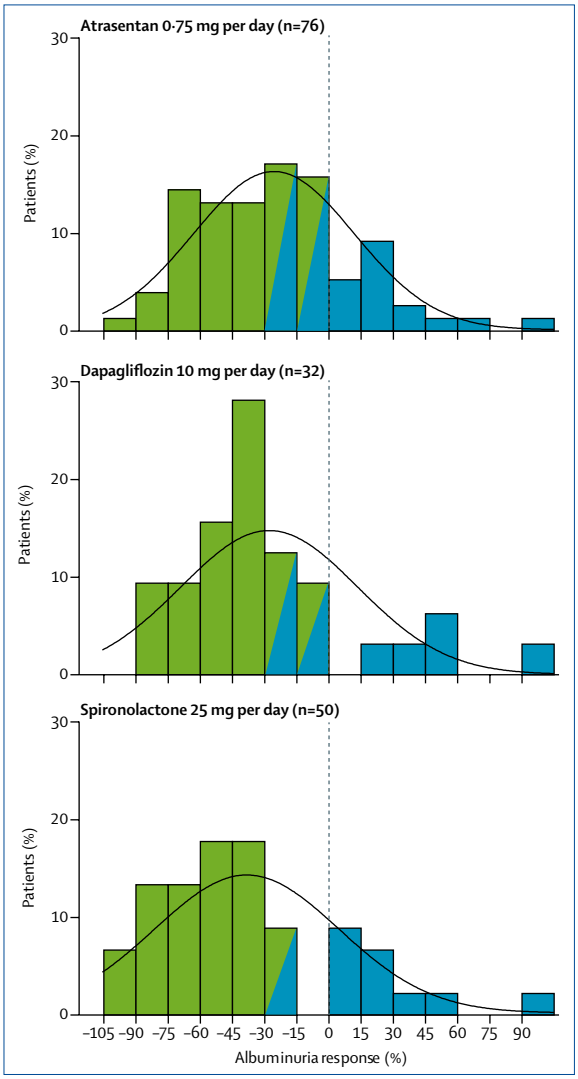


***Figure:*** **Variable response in albuminuria after several weeks of exposure to drugs from three drug classes anticipated to offer renal protection**
Endothelin antagonist atrasentan was given for 12 weeks; sodium-glucose co-transporter-2 inhibitor dapagliflozin was given for 6 weeks, and mineralocorticoid receptor antagonist spironolactone was given for 12 weeks.[2-4] Dotted line denotes no response. Blue bars show patients with increase in albuminuria, blue and green bars show patients with a mild decrease in albuminuria not likely to be associated with protection from renal outcomes, and green bars show patients with albuminuria reduction likely to be associated with improved renal outcome.

Development of this approach to conducting clinical trials will need a coordinated effort and a large international database of patients with diabetes and nephropathy. Organisations in the diabetes and nephrology community, such as the International Society of Nephrology, through its Advancing Clinical Trials group and Clinical Trial Networks, could be instrumental in achieving this aim. The increasing

prevalence of patients with diabetes and nephropathy, their high residual risk, and the many available target options deserve such a new concerted global platform approach.

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