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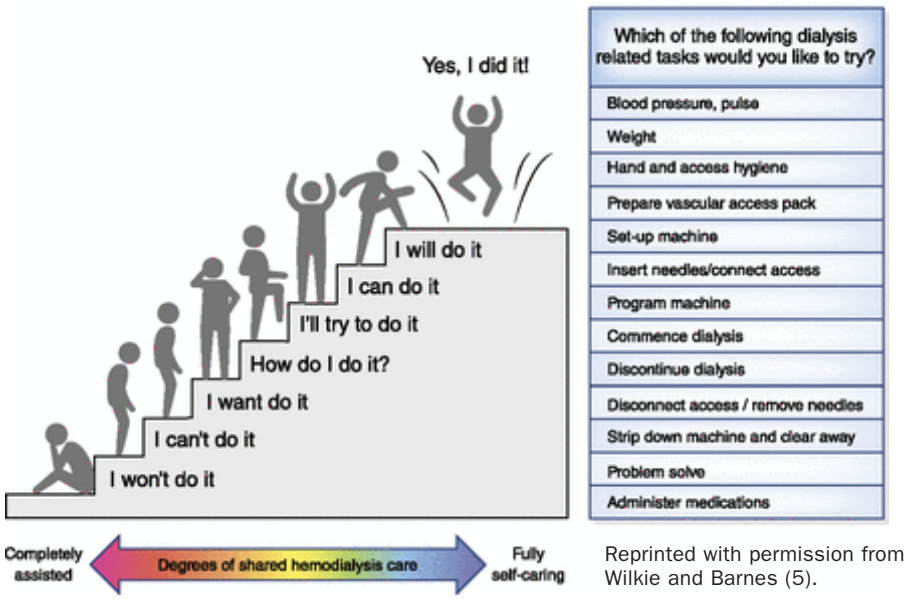
Figure 1. Small steps (tasks) within shared care provides a framework to unlock potential.



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Endothelin Receptor Antagonism in CKD

SONAR and Beyond

By Donald Kohan

On April 15, 2019, the results of the CREDENCE (1) and SONAR (2) trials were published. Both trials showed a 35% reduction in the relative risk of composite renal events in people with type 2 diabetes and kidney disease (DKD). Canagliflozin is now the first drug approved by the US Food and Drug Administration in almost two decades for slowing the progression of chronic kidney disease (CKD) in people with type 2 diabetes. By contrast, the future of endothelin receptor antagonists (ERAs) for treating DKD is uncertain. Various forums within the nephrology community have discussed aspects of atrasentan and SONAR; however, there is apparently no consensus opinion among nephrologists on what SONAR accomplished and the future of ERAs in diabetic or other forms of CKD.

SONAR was the first major DKD trial to incorporate an enrichment period; this involved all study participants receiving atrasentan for 6 weeks to identify individuals who might benefit (proteinuria reduction as a predictor of renoprotection) and in whom minimal side effects might occur (early ERA-induced fluid retention as a predictor of heart failure). Such an approach is highly relevant to the modern era of personalized medicine, whereby the goal is individualized therapy that is effective and safe. In addition, the enrichment period approach will permit correlation of initial drug response with systems biology (e.g., genomics, proteomics, metabolomics). Such analyses for SONAR will be forthcoming and may provide important insights into the biology of DKD.

There was a numerically higher incidence of heart failure events in the atrasentan treatment group in SONAR, although this did not achieve statistical significance and was much lower than in a previous trial of ERAs in DKD patients (3). This obviously indicates the need for continued vigilance for fluid retention, but is it the death knell for ERAs in DKD? Is the future of ERAs in DKD even more dismal, given the sponsor's decision to prematurely stop SONAR? It should be noted that despite the sponsor's actions, a strong renoprotective effect of atrasentan was observed. Further, given that atrasentan conferred renoprotection similar to that of canagliflozin, it begs the question whether combining canagliflozin or another sodium-glucose co-transporter 2 inhibitor (given their unique diuretic properties) and atrasentan (both on top of renin-angiotensin system [RAS] blockade) will yield additive or synergistic renoprotection in DKD while minimizing fluid retention. Hence, it is too soon to say what will happen with atrasentan in DKD; it would indeed be a shame to turn our backs at this point on what appears to be a highly renoprotective drug.

Moving beyond DKD, it is important for the kidney-community to keep in mind that ERAs are being vigorously pursued as a treatment for a variety of kidney diseases, based on an abundance of preclinical data. Relevant kidney and/or hypertension clinical trials include the following:

- Focal segmental glomerulosclerosis (FSGS). The phase 2 DUET trial found that sparsentan, a combined ERA/angiotensin receptor blocker (ARB), reduced proteinuria by ~50% compared with ARB treatment alone in people with primary FSGS (4). On the basis of those studies, the phase 3 DUPLEX trial has been launched involving 300 FSGS patients with a primary endpoint of change in eGFR slope (NCT03541174).
- IgA nephropathy. The phase 3 PROTECT trial is examining the effect of sparsentan versus an ARB on proteinuria in 280 people with IgA nephropathy (NCT03762850).
- Resistant hypertension. The phase 3 PRECISION trial examines the effect of the ERA aprocitentan (vs. placebo) on blood pressure (BP) reduction in 600 people with resistant hypertension (NCT03541174).
- Uncontrolled hypertension and CKD. The phase 3 INSPIRE-CKD trial will examine the effect of the ERA aprocitentan (vs. placebo) on BP reduction in 200 people with stage 3–4 CKD.
- Systemic sclerosis CKD. The phase 2 ZEBRA trial will report shortly on the effect of the ERA zibotentan on renal functional outcomes in people with systemic sclerosis (NCT02047708).
- Sickle cell nephropathy. A recently completed phase I trial examined the effect of the ERA ambrisentan on albuminuria (NCT02712346). The initial findings suggest that in patients using RAS blockade, ambrisentan confers greater albuminuria reduction than does placebo.

To date, fluid retention–related adverse events have not been reported to be an issue in the above-mentioned non-DKD trials. It is notable that most of the patients in these non-DKD studies are less likely to have significant cardiovascular comorbidities than are the patients in SONAR (the latter had a mean eGFR of ~43 mL/min per 1.73 m^2, and fluid retention or hypervolemia was present in 32.3% and 36.6% of the placebo and atrasentan groups, respectively). Thus, it is possible that ERA-induced significant adverse events related to fluid retention may prove to be less of an issue in patients with lower cardiovascular disease involvement.

In summary, I believe that the future holds much promise for the use of ERAs in CKD. Although we remain very mindful of their potential for fluid retention, we as a nephrology community must remain cognizant that this class of drugs has consistently reduced proteinuria, on top of RAS blockade, in the majority of CKD patients in whom they have been tried, and that the renoprotective effect of atrasentan in DKD parallels that of canagliflozin. Looking toward the future, there remain a wide variety of kidney diseases for which ERAs may exert a therapeutic benefit on top of RAS blockade, either as a single add-on agent or together with sodium-glucose co-transporter 2 inhibitors.

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