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EDITORIAL COMMENT

Treating Heart Failure on Dialysis

Finally Getting Some Evidence*

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Failing of the heart and kidneys concurrently is a common clinical situation. Heart failure (HF) causing renal failure through various mechanisms has been labeled as the "cardiorenal syndrome," and the opposite (i.e., kidney failure causing HF) has been recently referred to as the "renocardiac syndrome" (1). Among chronic renal failure patients starting dialysis therapy, 36% have HF, and an additional 7% develop HF while receiving dialysis (2). Given that approximately 355,000 patients undergo long-term dialysis in the U.S. (93% in the form of hemodialysis), it can be estimated that in this country alone there are currently more than 140,000 patients receiving hemodialysis with concurrent HF (3).

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The risk of death while receiving hemodialysis is roughly doubled in patients with concomitant HF. In such patients the mean survival while receiving dialysis falls from 5.4 to 3.0 years (4). Unfortunately, the treatment of this dual organ failure syndrome is a very challenging task. Most HF therapies are used at low rates in HF patients receiving dialysis. Importantly, there is little evidence from clinical trials to support the use of proven treatment strategies (beta-blockers, renin-angiotensin-aldosterone inhibitors, device therapies) in hemodialysis patients, because all major HF trials have systematically excluded patients with end-stage renal disease. Expert opinion calls for the treatment of HF in the hemodialysis setting with conventional therapies (5), despite different pathophysiologic aspects of the disease, altered drug and electrolyte metabolism, and lack of clinical trial data (6).

In this issue of the *Journal,* Cice et al. (7)—who have previously conducted 2 clinical trials of beta-blockers in hemodialysis patients with HF (8,9)—report a randomized clinical trial of angiotensin-receptor blocker (ARB) treatment added on top of background angiotensin-converting enzyme (ACE) inhibitor therapy in a similar patient population. Between 1999 and 2003, they randomized 332 hemodialysis patients with New York Heart Association functional class II to III (65% class II) HF with ejection fraction ≤40% to double-blind telmisartan or placebo for 3 years. A "run-in" phase was used to assess tolerability of low-dose telmisartan, and after the run-in phase the agent was titrated to the target dose of 80 mg/day every 2 weeks. The average age was 63 years, and nearly all of them (90%) were men. Slightly more than one-half (57%) had a history of myocardial infarction. All patients were taking an ACE inhibitor at baseline, approximately 60% of them were taking beta-blockers, two-thirds were taking statins, and approximately one-half were receiving digitalis. None of the patients had cardiac resynchronization therapy or an implantable cardioverter-defibrillator. Predictably, there was a high background rate of all-cause mortality (1 of the 3 primary end points) in the placebo group (i.e., 54% at 3 years). The hazard ratio (HR) for all-cause death in the telmisartan group was a striking 0.51 (95% confidence interval: 0.32 to 0.82, $p < 0.01$). The hazard for the other primary end points of cardiovascular death (HR: 0.42, $p < 0.0001$) and HF hospital stay (HR: 0.38, $p < 0.0001$) were also greatly reduced. These benefits were seen early (<3 months), and the decrease in mortality was driven by reductions in pump failure, sudden deaths, and "non-cardiovascular" causes of death; there were few myocardial infarctions or strokes overall. Serial echocardiographic data also paralleled the clinical outcomes in that there was more left ventricular (LV) reverse remodeling (e.g., improved ejection fraction and decreased end-diastolic dimension) in the telmisartan group, which was noted by 6 months and continued up to 2 years.

Telmisartan was well-tolerated for the most part, even though full-dose telmisartan was force titrated in addition to full-dose ACE inhibitor (and in most cases, a vasodilating beta-blocker) with a baseline pre-dialytic blood pressure of 125/84 mm Hg. Only 19 patients (5.4%) were excluded after the run-in phase, of which only 7 were due to hypotension. However, there were more permanent treatment withdrawals (26 vs. 16) in the telmisartan group. Adverse events leading to study drug discontinuation were surprisingly uncommon for a clinical drug trial (16.3% vs. 10.7%). As anticipated, the most common adverse event was hypotension (as is observed frequently in hemodialysis patients with HF), which was significantly more common with telmisartan (67% vs. 40%), particularly in those who were taking both ACE inhibitors and beta-blockers. Hyperkalemia, although

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rare overall, was also more common with telmisartan (3% vs. 1%).

The striking benefits of this apparently well-tolerated therapy in a nonhypertensive patient cohort certainly make one wonder as to the mechanism. In systolic HF without advanced renal insufficiency, early studies using surrogate end points such as blood pressure and LV remodeling provided a strong rationale as well as safety data for the addition of an ARB to an ACE inhibitor. However, the clinical benefits were quite modest in the subsequent large-scale clinical trials. Although the mechanisms of benefit with telmisartan observed in this study are not entirely clear, it could include the effects of neurohormonal antagonism resulting in reverse remodeling as shown in the echocardiographic analysis of this trial. Angiotensin-receptor blockers such as telmisartan might be more effective renin-angiotensin system (RAS) antagonists in this patient population, because ACE inhibitors are in large part removed by dialysis, their dosing is derived from non-dialysis populations, and their effectiveness in decreasing LV mass in this group of patients is unclear (10). In fact, there are no large-scale clinical trials of ACE inhibitors in dialysis patients that demonstrate clinical benefit. A hemodynamic effect could also be relevant in that the clinical benefits seem to accrue early and before LV remodeling would be expected to be seen. The hemodynamic effect might be primarily due to improvements in vascular stiffness rather than blood pressure lowering alone. Aortic pulse wave velocity is an independent predictor of survival in dialysis-dependent renal failure, and blood pressure lowering might only be of benefit if pulse wave velocity is concomitantly lowered (11). Finally, effective RAS antagonism might also decrease arrhythmic risk and has been noted in trials of both ARBs and ACE inhibitors.

Or are these results too good to be true? The positive predictive value of clinical trials (i.e., whether a positive clinical trial is truly positive) depends on: 1) the pre-test probability of the null hypothesis being wrong; 2) the power of the study; and 3) bias (12). Effect size and the level of significance are also important parameters in evaluating a study. For estimating the pre-test probability for this study, there is little information from previous trials in hemodialysis patients with HF. However, data from HF patients not receiving hemodialysis are available, which is probably the most relevant information in this context (Table 1). Two large-scale, double-blind, placebo-randomized trials of 2 different ARBs, valsartan (VaL-HeFT [Valsartan Heart Failure Trial]) (13) and candesartan (CHARM [Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity]-Added trial) (14), have been published. Neither of these trials showed a statistically significant effect on mortality. The pre-test probability of angiotensin-receptor blockade to reduce mortality in this context (i.e. added to an ACE inhibitor) would not be expected to be very high in a repeat trial, albeit in a nondialysis patient population. Ioannidis (12) has shown, with regard to the issue of power, that insufficient power not only inflates the type II error rate (failing to reject null hypothesis when it is wrong) but also reduces the positive predictive value of clinical trials. Although the power calculations in the present study showed 90% power, this was to detect a 50% hazard reduction in death, not a commonly seen magnitude of benefit with most agents in any clinical trial setting. Given this aggressive target of event-reduction benefit and a modest total number of patients (which is comparable to a "pilot" trial), it is not clear whether this trial provides enough power to be definitive. Although it is difficult to judge the level of bias in this communication, the delay in the publication of this trial (approximately 5 years between study completion and full-text publication) is unusual. Conversely, the remarkable effect size, the robust levels of significance, and the similarity of these results to 2 other ARB trials in hemodialysis patients (not necessarily with concomitant HF) (15,16) are important strengths of the trial. Notably, the effect size of mortality reduction was much greater than the modestly increased risk of cancer with ARBs reported in the recent meta-analysis of randomized controlled trials (17).

All things considered, the findings of Cice et al. (7) are important and, like all important studies, should lead to further investigation. Given the grim prognosis of hemodialyzed patients with HF and the premise for improved

Table 1 Major Randomized Placebo-Controlled Trials of ARBs Added to Background ACE Inhibitor Therapy in Patients With HF

Trial/First Author (Ref. #)	Inclusion Criteria	Study Regimen	Average Duration, yrs	All-Cause Mortality			Hospitalization for HF		
				ARB	Placebo	HR (95% CI)	ARB	Placebo	HR (95% CI)
Val-HeFT (13)	NYHA II–IV HF, LVEF <40% (n = 5,010)	Valsartan up to 160 mg twice a day	1.9	19.7%	19.4%	1.02 (0.88–1.18)	13.8%	18.2%	NA
CHARM-Added (14)	NYHA II–IV HF, LVEF ≤40% (n = 2,548)	Candesartan up to 32 mg/day	3.4	29.5%	32.4%	0.89 (0.77–1.02)	24.2%	28.0%	0.83 (0.71–0.96)
Cice et al. (7)	Hemodialysis patients with NYHA II or III HF, LVEF ≤40% (n = 332)	Telmisartan up to 80 mg/day	3.0	35.1%	54.4%	0.51 (0.32–0.82)	33.9%	55.1%	0.38 (0.19–0.51)

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CHARM = Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; CI = confidence interval; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction; NA = not available; NYHA = New York Heart Association functional class; Val-HeFT = Valsartan Heart Failure Trial.

longevity with aggressive RAS inhibition in the current study, it would be reassuring to see another larger trial of add-on angiotensin-receptor blockade in this patient population with similar findings. These investigators should be given credit for paving the way to providing the clinician an evidence base from which to make relevant therapeutic decisions in this complex and mortal disease state. For now, clinicians should carefully evaluate the choice of agents in the treatment of HF when it complicates dialysis and make sure that drugs that antagonize both the RAS and adrenergic axes are considered.

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