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See related article, “Rituximab Versus Cyclophosphamide for ANCA-Associated Vasculitis with Renal Involvement,” on pages 976–985.

## $\beta$ -Blockers in Dialysis Patients: A Nephrocardiology Perspective

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$\beta$ -Blockers are the most commonly prescribed cardiovascular medications among dialysis patients, constituting 64% of all prescriptions.<sup>1</sup> However, the evidence supporting their utility in improving cardiovascular outcomes in this population is conflicting. Data from the US Renal Data System (USRDS) identified  $\beta$ -blockers as the only antihypertensive agents independently associated with a reduced hazard of adjusted all-cause mortality in a large sample of dialysis patients in the United States,<sup>2</sup> but observational data from Ontario, Canada, demonstrated no beneficial effects on cardiovascular outcomes among older dialysis patients.<sup>3</sup> Agarwal and colleagues performed a randomized analysis of lisinopril versus atenolol (each administered three times a week) among a predominantly black hemodialysis population,

not only overcoming the limitations of prior observational studies but also comparing two commonly used agents.<sup>4</sup> Although not powered for mortality outcomes, the study was stopped prematurely because of important safety concerns about cardiovascular outcomes in the lisinopril group.

In this context, the study by Weir and colleagues in this issue of *JASN*<sup>5</sup> represents an “a-ha” moment, promising an intriguing pivot from the existing literature. The observational design means that any conclusions must be considered strictly hypothesis generating. Yet the study underscores the fact that not all  $\beta$ -blockers can be considered equal and that it would be a mistake to lump them together as one class for future analysis in the dialysis population. Despite the several caveats and limitations, this study brings into the limelight the glimmer of a possible association with a survival advantage of certain  $\beta$ -blockers simply based on their pharmacokinetic behavior during dialysis. There is an inherent inclusion/survival bias because only dialysis patients older than 65 years of age were studied (to ensure consistent identification of all patients with prescription drug coverage in Ontario), thus excluding patients with premature cardiovascular mortality who presumably have the highest prevalence of vasculopathy.

The low-dialyzability  $\beta$ -blocker of great interest that unfortunately could not be studied by Weir *et al.* is carvedilol. This, admittedly, is due to the existing prescription characteristics of  $\beta$ -blockers in Ontario (“carvedilol use limited to patients with echocardiographic/symptomatic evidence of advanced heart failure”<sup>5</sup>). Carvedilol has shown substantial promise in this population on the basis of translational as well as clinical evidence. Among patients with intradialytic hypertension, carvedilol in high doses is associated with improved endothelial function (flow-mediated vasodilation) and better intradialytic and interdialytic BP control.<sup>6</sup> Carvedilol is also the only  $\beta$ -blocker with a demonstrated survival advantage in a randomized controlled trial (RCT) among dialysis patients with dilated cardiomyopathy.<sup>7</sup> Critics may argue that a single RCT is insufficient to derive generalizable conclusions; regrettably, the academic community has yet to produce another RCT to investigate benefits in this high-risk population. Therefore, it is with the highest enthusiasm that we look forward to the Beta-blocker to LOwer Cardiovascular Dialysis Events (BLOCADE) trial, a randomized placebo-controlled trial that has been planned to assess the role of carvedilol in reducing cardiovascular morbidity and mortality in high-risk patients receiving dialysis (Australian and New Zealand Clinical Trials Registry number: ACTRN12609000174280). On the basis of the study design, we anticipate that high-risk patients for whom  $\beta$ -blocker therapy should already be recommended under existing practice guidelines (*e.g.*, symptomatic systolic heart failure, uncontrolled hypertension) may not be included in the trial (making enrollment particularly challenging); however, safety and tolerability are the primary objectives of this ambitious feasibility trial.

Given the marked heterogeneity of  $\beta$ -blockers, it would be rather naive to assume that dialyzability is the sole factor responsible for benefits noted or should be clinicians’ sole consideration

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in attempting to choose the appropriate  $\beta$ -blocker for an individual patient. It bears emphasis that 96% of patients in the low-dialyzability group in Weir and colleagues' study received bisoprolol, whereas 70% in the high-dialyzability group received metoprolol tartrate (and 27% received atenolol). Hence, this study could simply be about the comparison of bisoprolol versus metoprolol tartrate. As the authors point out, the selectivity of these agents for  $\beta_1$  receptors is also a consideration regarding the differences noted. The lipid solubility of  $\beta$ -blockers is another factor; hydrophilic agents are easily removable during dialysis compared with lipophilic agents. The latter, in turn, are more likely to cross the blood-brain barrier and have the potential to affect central vagal tone, which yields regulatory influence over ventricular arrhythmias.<sup>8</sup> In that regard, although bisoprolol is categorized as hydrophilic,<sup>9</sup> just as atenolol is, it was classified in the low-dialyzability category in the study.

Additional considerations regarding  $\beta$ -blockers include the concern for hyperkalemia; in particular, the phenomenon of fasting hyperkalemia (resulting from insulopenia) is relevant to the use of nonselective  $\beta$ -blockers (because of the role of  $\beta_2$  receptors in facilitating potassium entry intracellularly). Hyperkalemia has been described for nadolol and labetalol, but curiously not for carvedilol.<sup>9</sup> Finally, unintended metabolic and cardiovascular consequences of  $\beta$ -blockers (*i.e.*, association with the development of diabetes mellitus and stroke<sup>10</sup>) are important factors that cannot be definitively discerned using observational data alone. Thus, clinicians must give considerable thought to the choice of a  $\beta$ -blocker for any individual patient; the study by Weir *et al.* identifies one dimension, albeit an important one, among the panorama of the heterogeneous effects of  $\beta$ -blockers.

Perhaps the most provocative question that this study disinters is whether  $\beta$ -blockers with high dialyzability potentially exacerbate or perpetuate the milieu contributing to sudden death. Sudden cardiac death accounts for 27% of deaths among dialysis patients.<sup>11</sup> Existing literature on the role of  $\beta$ -blockers in preventing sudden death are contradictory. In a *post hoc* analysis from the Hemodialysis (HEMO) study, Tangri and colleagues reported no association between  $\beta$ -blocker use and sudden cardiac death<sup>12</sup>; Matsue *et al.* used a more contemporary cohort from a single center in Japan and reported a significant association between  $\beta$ -blocker use and reduction in sudden cardiac death.<sup>13</sup> Interestingly, 85% of patients in the study by Matsue *et al.* received carvedilol (Tangri *et al.* did not comment on the specific  $\beta$ -blockers studied). Dialysis patients have a preexistent milieu conducive to the development of ventricular dysrhythmias by virtue of several factors, including high sympathetic tone, compounded by high prevalence of obstructive sleep apnea, presence of concentric left ventricular hypertrophy and myocardial fibrosis, large hemodynamic and electrolyte fluxes, reduced coronary flow reserve, and high prevalence of ischemic heart disease. In this milieu that predisposes to a high incidence of sudden cardiac death, is it possible that a high-dialyzability  $\beta$ -blocker could actually provoke ventricular dysrhythmias due to rapid removal on dialysis?

An interesting future subanalysis that Weir *et al.* might consider is to compare the occurrence of sudden cardiac death in the two  $\beta$ -blocker groups.

Although cause-specific mortality is extremely difficult to ascertain using observational data, a definition of sudden cardiac death analogous to that described by the former USRDS Cardiovascular Special Studies Center (CVSSC) could be considered (*i.e.*, the CVSSC "complex method"). This definition could incorporate some of the CVSSC's algorithm for identifying presumed sudden cardiac death using administrative data: location of death (outpatient setting/emergency department) and exclusion of patients with terminal illnesses (*e.g.*, malignancy or hospice care), dialysis nonadherence or withdrawal from dialysis, or other conditions (ascertainable from administrative data) that would refute the diagnosis of presumed sudden cardiac death.<sup>11</sup>

Current societal guidelines do not make special mention of the dialysis population in their recommendations for management of patients with systolic heart failure.<sup>14</sup> Are the factors discussed above sufficient to warrant a specific mention, urging clinicians to preferentially consider low-dialyzability  $\beta$ -blockers in this exceedingly high-risk population? We will leave this matter to individual societies to debate and consider. However, we firmly believe sufficient impetus is now present within the academic community for creation of a well-designed RCT to compare specific  $\beta$ -blockers and their effects on all-cause mortality among dialysis patients, with sudden cardiac death as a prespecified adjudicated end point. In the meantime, we are hopeful that the use of  $\beta$ -blockers with the highest strength of evidence (particularly carvedilol) becomes more liberal in Ontario, Canada, and elsewhere in the world.

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## DISCLOSURES

None.

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