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Editorial Comment

EDITORIAL COMMENT

β-blockers in hemodialysis: simple questions, complicated answers

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ABSTRACT

In this issue of the *Clinical Kidney Journal*, Wu *et al.* present the results of a nationwide population-based study using Taiwanese administrative data to compare safety and efficacy outcomes with initiation of bisoprolol versus carvedilol among patients receiving maintenance hemodialysis for >90 days. The primary outcomes were all-cause mortality and major adverse cardiovascular events over 2 years of follow-up. The study found that bisoprolol was associated with a lower risk for both major adverse cardiovascular events and all-cause mortality compared with carvedilol. While the bulk of the existing evidence favors a cardioprotective and survival benefit with β-blockers as a medication class among dialysis patients, there is wide heterogeneity among specific β-blockers in regard to pharmacologic properties and dialyzability. While acknowledging the constraints of observational data, these findings may serve to inform clinicians about the preferred β-blocker agent for dialysis patients to help mitigate cardiovascular risk and improve long-term survival for this high-risk population.

Keywords: β-blocker, beta blocker, bisoprolol, cardiovascular disease, carvedilol, dialysis, end-stage kidney disease, end-stage renal disease, epidemiology, hemodialysis

Cardiovascular disease is the preeminent cause of morbidity and mortality among the dialysis population. Among kidney failure patients treated with dialysis, cardiovascular disease contributes to ∼25% of hospitalizations and 50% of deaths [1]. The rates of cardiovascular mortality in the dialysis population are up to 10- to 20-fold higher than that of the general population [2]. Therefore, effective therapies to mitigate cardiovascular risk in the dialysis population are desperately needed.

Through decades of use and study in the general population, the cardioprotective benefits of β-blockers are well established. β-blockers have been proven effective in (and are recommended for) heart failure with reduced ejection fraction, secondary prevention following myocardial infarction, hypertension and arrhythmias [3–8]. However, the clinical trials that provided the basis for these cardioprotective effects of β-blockers largely excluded dialysis patients [9]. Nevertheless, over half of dialysis patients are prescribed β-blockers [10]. This likely relates to the high burden of comorbidities seen commonly in dialysis patients (e.g. hypertension, atrial fibrillation, coronary artery disease and heart failure), with extrapolation of the benefits from β-blocker therapy seen in clinical trials of nondialysis patients. Additionally, hypothesized benefits of β-blocker therapy unique to dialysis patients include physiologic abnormalities such as high sympathetic tone and blunting of heart rate fluctuations related to the dialysis procedure itself [11–13].

To date, few randomized controlled trials have studied β-blocker use in the dialysis population. Cice *et al.* performed a double-blind, randomized trial comparing carvedilol versus

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placebo in 114 dialysis patients with dilated cardiomyopathy and found that carvedilol reduced left ventricular volume, improved left ventricular function and improved patients' functional status [14]. A follow-up study at the 2-year mark for this trial revealed that patients treated with carvedilol also had lower rates of mortality and hospital admissions compared with placebo [15]. Agarwal *et al.* performed an open-label randomized controlled trial comparing atenolol versus lisinopril in 200 hemodialysis patients with hypertension and left ventricular hypertrophy [16]. The study showed no difference in the primary outcome of left ventricular mass index; however, the trial was terminated early due to an >2-fold higher rate of serious cardiovascular events in the group randomized to lisinopril. Notably, this study did show greater blood pressure reduction with atenolol compared with lisinopril.

An obvious question is why has a large randomized controlled trial not yet been performed in this area? The answer—it simply may not be feasible. Roberts *et al.* performed a multicenter pilot randomized controlled trial [the β-Blocker to LOwer CArdiovascular Dialysis Events (BLOCADE) Trial] in Australia and New Zealand to specifically assess feasibility [17]. With an end goal of randomizing 150 dialysis patients to carvedilol or placebo, 1443 dialysis patients were screened, 354 were eligible, 91 were consented, 72 entered the run-in stage and a paltry 49 (14% of all eligible) were eventually randomized. Possibilities for this discouraging outcome were clinicians' concern regarding true equipoise and/or patient resistance to potentially stopping β-blocker therapy (possibly on their cardiologists' recommendations) [18]. This is particularly true for the estimated 50% of dialysis patients with trial-based indications for β-blocker use, where extrapolation of study findings from the general population may be ingrained [18]. Thus, given the challenges and limited feasibility in terms of recruitment, we remain without any large randomized controlled trials to provide a more definitive answer regarding β-blocker use in dialysis patients, with no such trials on the horizon.

We therefore must turn our attention to observational ('real world') data, with its inherent limitations in determining therapeutic efficacy. A number of studies have identified a protective effect from β-blocker use. A large administrative cohort of hemodialysis patients in Taiwan comparing 1700 β-blocker users with 1700 propensity score-matched nonusers reported reduced mortality among patients receiving β-blockers [19]. Similar findings were seen in a study of 11 142 hemodialysis patients captured within the US Renal Data System, which showed that β-blockers were the antihypertensive drug class associated with the highest rates of survival [20]. An administrative cohort study of 1025 Medicare beneficiaries receiving chronic dialysis hospitalized for an acute myocardial infarction demonstrated that β-blocker administration during the hospital admission was associated with a reduced 30-day mortality [21]. Two other observational studies have shown an association between β-blocker use and a reduction in sudden cardiac death among hemodialysis patients [22, 23]. Conversely, a Canadian cohort study using administrative data compared mortality and cardiovascular event rates among 1836 dialysis patients newly prescribed either a β-blocker ($n = 504$), calcium channel blocker ($n = 570$) or a statin ($n = 762$), and found no evidence of a beneficial effect from β-blocker use [24]. Also, a *post hoc* analysis of the Hemodialysis (HEMO) Study showed no association between β-blocker use and sudden cardiac death in hemodialysis patients [25].

Compounding these issues is the question of whether the specific type of β-blocker matters. Here, two major factors are of concern: (i) higher β_1 receptor activity ('cardioselectivity') versus combined β_1/β_2 receptor activity ('non-cardioselectivity') and (ii) dialyzability [26]. For instance, carvedilol, labetalol, propranolol and nadolol are noncardioselective, while atenolol, bisoprolol and metoprolol are cardioselective. Carvedilol and labetalol additionally demonstrate α_1 receptor blocking activity [27]. In regard to dialyzability, atenolol and metoprolol are highly dialyzable, bisoprolol is moderately dialyzable and carvedilol is poorly dialyzable based on pharmacokinetic properties [28].

The clinical consequences of these two factors (β-blocker dialyzability and cardioselectivity) remain largely unclear. Several prior observational studies have investigated whether specific β-blockers associate with improved outcomes in the dialysis population, with mixed and somewhat conflicting results. Weir *et al.* compared 3294 hemodialysis patients initiated on a highly dialyzable β-blocker (defined as acebutolol, atenolol or metoprolol) and 3294 hemodialysis patients initiated on a poorly dialyzable β-blocker (defined as bisoprolol or propanolol) and found that the highly dialyzable β-blocker group had a higher mortality risk [29]. As 96% of the 'poorly dialyzable' group was prescribed bisoprolol, this study is better viewed as a comparison of bisoprolol (now known to be moderately dialyzable [28]) versus metoprolol/atentolol/acebutolol (highly dialyzable), leaving the effects of a poorly dialyzable β-blockers (such as carvedilol) unknown. To this end, Wu *et al.* recently compared 15 699 hemodialysis patients initiated on a moderate-to-highly dialyzable β-blocker (acebutolol, atenolol, metoprolol or bisoprolol) and 20 094 hemodialysis patients initiated on a poorly dialyzable β-blocker (defined as betaxolol, carvedilol or propanolol) and found that the moderate-to-highly dialyzable β-blocker group had lower mortality and cardiovascular event risks [30]. Shireman *et al.* studied approximately 5000 chronic dialysis patients, comparing those prescribed cardioselective β-blockers (atenolol and metoprolol) with those prescribed noncardioselective β-blockers (carvedilol and labetalol), and found that cardioselective β-blocker users had lower risks for both all-cause and cardiovascular mortality [31]. Finally, Assimon *et al.* compared 17 506 hemodialysis patients initiated on metoprolol (cardioselective/highly dialyzable) with 9558 hemodialysis patients initiated on carvedilol (noncardioselective/poorly dialyzable) and found that the carvedilol group had a higher 1-year all-cause and cardiovascular mortality risk [32]. The authors also found that the carvedilol group had higher rates of intradialytic hypotension and hypothesized that this may provide a mechanism by which to explain the increased mortality risk seen with carvedilol.

In this issue of the *Clinical Kidney Journal*, Wu *et al.* present the results of a nationwide population-based study using Taiwanese administrative data to compare outcomes with bisoprolol versus carvedilol use among maintenance hemodialysis patients [33]. The comparison of bisoprolol (cardioselective/moderately dialyzable) versus carvedilol (noncardioselective/poorly dialyzable) in the hemodialysis population is a highly relevant one, as these are two of the most commonly prescribed β-blockers. The main objective of the study was to compare the risk of all-cause mortality and major adverse cardiovascular events between bisoprolol ($n = 9305$) and carvedilol ($n = 11 171$) users over 2 years of follow-up. Major adverse cardiovascular events were defined as a hospital admission for acute myocardial infarction, heart failure or ischemic stroke. The results were confirmed via multivariable Cox models, propensity score-matched models, and a number of sensitivity analyses including censoring upon β-blocker discontinuation or switching to an alternative β-blocker during follow-up.

In the primary analysis, Wu *et al.* found that bisoprolol users had a 34% lower all-cause mortality risk [adjusted hazard ratio

(HR) = 0.66, 95% confidence interval (CI) 0.60–0.73] and a 15% lower risk for major adverse cardiovascular events (adjusted HR = 0.85, 95% CI 0.80–0.91) compared with carvedilol users [33]. Notably, the reduced risk for major adverse cardiovascular events with bisoprolol was driven by lower rates of heart failure (adjusted HR = 0.83, 95% CI 0.77–0.91) and ischemic stroke (adjusted HR = 0.84, 95% CI 0.72–0.97), whereas there was no significant difference seen with acute myocardial infarction (adjusted HR = 1.03, 95% CI 0.93–1.15). These findings were consistent across propensity score-matched models and in a number of other sensitivity analyses.

Several limitations to this study are worth mention. First, patients had to be on hemodialysis for >90 days to be included in the study. Presumably, the purpose of this requirement was to both exclude patients with acute kidney injury and to align with conventional definitions of what constitutes 'chronic hemodialysis'. However, the early phase of dialysis initiation is the time when patients are particularly vulnerable to cardiovascular events, arrhythmias and sudden cardiac death [34], which are precisely the risks providers hope to mitigate by prescribing β-blockers. Second, the study cohort only represents new β-blocker users, whereas many patients enter chronic dialysis already prescribed β-blockers; therefore, we are left without any additional information on how to manage these patients. Third, the study assumes that whatever β-blocker dose a patient was started on was the dose that they remained on. However, β-blocker doses may have been adjusted over time, which may affect the study outcomes and would require a more complicated time-varying exposure model to account for. Fourth, a limitation inherent to this and most other observational studies is the lack of information on blood pressure (aside from Assimon *et al.* [32]), heart rate, dialysis adequacy, intra-dialytic fluid removal, missed dialysis sessions and, perhaps most importantly, left ventricular ejection fraction. In other words, established indications for β-blocker use (heart failure with reduced ejection fraction, arrhythmias, etc.) were largely unknown. This is important as carvedilol is a preferred agent in patients with heart failure with reduced ejection fraction in the general population and, as such, may be preferentially prescribed to those with lower ejection fractions in the dialysis population. Lastly, the disentangling of dialyzability from cardioselectivity remains unclear. A comparison of a moderately-to-highly dialyzable/cardioselective versus poorly dialyzable/cardioselective β-blocker would be valuable.

Where are we left in terms of β-blocker use in the dialysis population? Certainly, the bulk of the existing evidence favors a cardioprotective and survival benefit with β-blocker use among dialysis patients [14–16, 19–23]. Given the heterogeneity within the β-blocker class of medications as a whole, the bigger questions may be: which specific β-blocker(s) are associated with the best outcomes and which specific β-blocker(s) should be avoided in the dialysis population? Realistically, obtaining large robust randomized controlled trial data to address these questions will be a major challenge as evidenced by the difficulty in recruitment seen with the BLOCADE Trial as discussed above [17]. Perhaps, the emerging culture of trial networks across countries in hemodialysis patients and cluster-randomized trials among hemodialysis units will increase the feasibility for such a study to be performed in the future [35–37].

For the time being, robust observational real-world data serve as our best guide into β-blocker choice for dialysis patients. There seems to be a growing body of evidence suggesting that carvedilol may not be the ideal choice for dialysis patients as multiple studies now suggest worse cardiovascular and mortality outcomes compared with alternative β-blockers [30–33]. A couple of theories have been proposed as to why carvedilol may associate with worse outcomes in dialysis patients. First, carvedilol is a noncardioselective β-blocker and therefore may not provide the same protection as cardioselective β-blockers [31]. Second, carvedilol may predispose to intradialytic hypotension more than other β-blockers [32], a factor well known to contribute to increased morbidity and mortality [38–40]. This predisposition to intradialytic hypotension with carvedilol may relate to both its α_1 receptor blocker activity (thereby inhibiting compensatory sympathetic nervous system-driven vasoconstriction) as well as its negligible dialyzability [27, 28]. On the other hand, while there is some disagreement in the literature in regard to which β-blockers may have the greatest benefit in terms of cardiovascular and mortality risk reduction, the bulk of the existing observational data leans toward cardioselective β-blockers with moderate-to-high dialyzability (such as atenolol, bisoprolol and metoprolol) as the preferred agents for dialysis patients [30–33]. Ultimately, as additional robust observational (and hopefully trial) data become available, we may be able to further refine our understanding of which β-blockers provide the greatest benefit for both the dialysis population as a whole and within subpopulations of the dialysis community.

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CONFLICT OF INTEREST STATEMENT

All authors declare that the results presented in this article have not been published previously in whole or part.

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