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EDITORIAL

Beta-blockers in heart failure patients with severe chronic kidney disease—time for a randomized controlled trial?

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Cardiovascular disease is a major cause of morbidity and mortality in patients with chronic kidney disease (CKD). Hospitalizations from heart failure are among the most commonly observed cardiovascular morbidity seen in clinical trials among those with Type 2 diabetes and CKD [1, 2]. The heart failure guidelines recommend that among patients with heart failure with reduced ejection fraction (HFrEF), the following drugs be prescribed to reduce cardiovascular morbidity and mortality: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor–neprilysin inhibitor, evidence-based β-blockers and mineralocorticoid receptor antagonists in selected patients [3, 4]. However, the evidence base for this is essentially nonexistent for those with Stage 4 CKD. In part, this is because patients with advanced CKD are almost systematically excluded from trials of heart failure [5, 6]. Thus, to guide therapy in this high-risk population, we are limited to small subgroup analyses of randomized clinical trials or to observational data [7].

In this issue of *Nephrology Dialysis Transplantation*, Molnar *et al.* [8] report a retrospective observational study examining the modifying effect of levels of CKD determined by estimated glomerular filtration rate (eGFR) on the cardiovascular protection afforded by β-blockers. Cardiovascular protection of β-blockers was assessed by examining the relationship between incident congestive heart failure (CHF) and subsequent all-cause mortality among patients aged ≥66 years. In Ontario, Canada, they identified 320 703 such patients who had incident CHF; only 27 777 (8.7%) were not receiving β-blockers. Of these, 5862 (21.1%) started on a β-blocker soon after hospitalization. These patients were matched on age (±2 years), sex, CKD stage and CHF diagnosis date (±2 years) to nonusers of β-blockers. Because patients who may be treated were not selected at random from the total pool of patients, a high-dimensional propensity score (HDPS) was used to match users and nonusers (within 0.2× SD of the logit score of HDPS). This reduces bias of β-blocker prescription at least to the extent controlled by factors specified in HDPS. Although the motivation was to draw causal inference from the analysis, this should be strongly cautioned against as with the use of such a technique, unmeasured biases that could be at least as large as the apparent

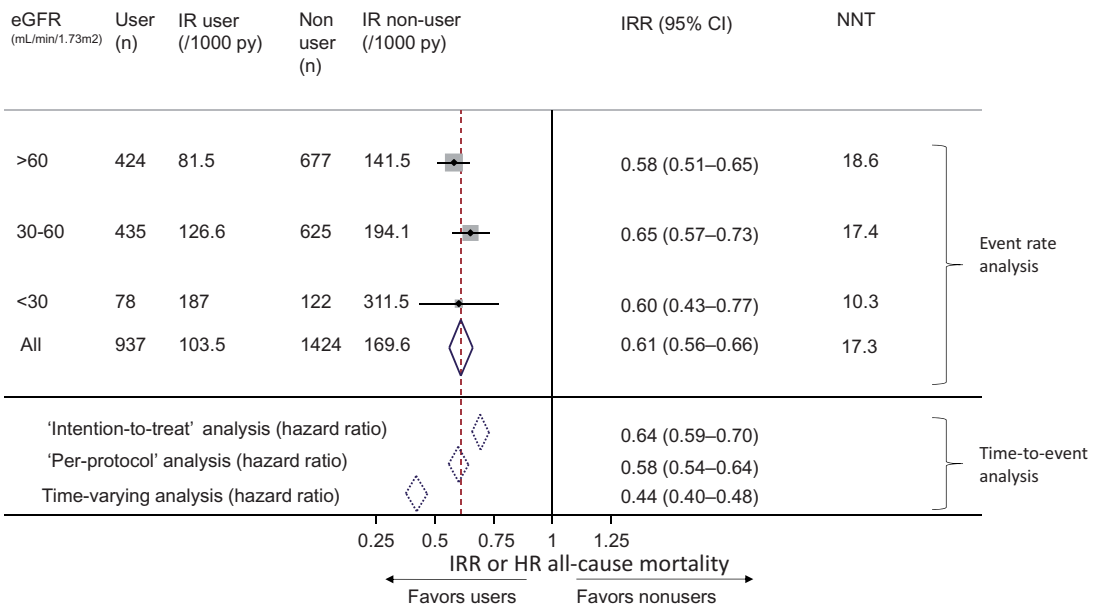

FIGURE 1: Level of CKD as determined by the eGFR does not affect the protective effect of β-blocker in incident heart failure as judged by all-cause mortality. The incidence rate (IR) per 1000 patient-years is higher in those with severe CKD, but the mortality benefit is similar to those with less severe degrees of CKD (top three rows). The absolute risk of all-cause mortality was greater in those with severe CKD. Accordingly, the number needed to treat was lower. The time-to-event analyses were similar to the event rate analyses. IRR, incidence rate ratio.

association with β-blocker and subsequent outcomes cannot be excluded.

In the nonusers group, over a median follow-up of 0.61 years, 1424 (24%) patients died yielding an incident mortality rate of 169.6/1000 patient-years. In contrast, in the β-blocker group, over a median follow-up of 0.72 years, 937 (16%) patients died yielding an incident mortality rate of 103.5/1000 patient-years. The incidence rate ratio was 0.61 [95% confidence interval (CI) 0.56–0.66]. In a time-to-event analysis (Cox proportional hazards model), the hazard ratio (HR) was 0.58 (95% CI 0.54–0.64). Thus, the two analyses were concordant (see Figure 1).

The central question posed in this study was whether the CKD stage modified the relationship between β-blocker use and all-cause mortality. To test this hypothesis, the authors classified the patients as CKD Stages 3 and 4; CKD Stages 1 and 2 served as comparator. The HR for all-cause mortality in CKD Stage 1 or 2 was 0.55, Stage 3 was 0.63 and Stage 4 was 0.55. The interaction effect was not significant ($P = 0.3$), which means that the severity of CKD did not modify the relationship between β-blocker use and all-cause mortality in patients with incident CHF. In the above analysis, the authors censored patients in the nonuser group when β-blocker was started. They also censored patients in the β-blocker group when the drugs were stopped. This is akin to a 'per-protocol' analysis in a randomized controlled trial. In a sensitivity analysis, they relaxed the assumption, making it analogous to an intention-to-treat analysis. In the intention-to-treat analysis, the severity of CKD still did not modify the relationship between β-blocker use and all-cause mortality. However, the HR increased from 0.58 to 0.64. In other words, the apparent protection afforded by beta-blocker use was less.

The authors provide even more evidence for the protective effect of β-blocker use in elderly patients with CHF that emerged from a time-varying analysis of β-blocker use. The HR in the time-varying analysis was 0.44 (95% CI 0.40–0.48). The upper bound of the time-varying HR was lower than the lower bound of the primary analysis. Taken together, this suggests that β-blocker use is associated with reduced all-cause mortality in CHF. This observation is well supported by clinical trials in patients without advanced CKD. More importantly, this study shows that the CKD stage does not modify the protective relationship between β-blockers use in incident CHF and all-cause mortality. Furthermore, this protection extends to Stage 4 CKD.

Overall, we can calculate from the data provided by the authors that only 17.3 elderly patients with CHF need to be treated for 1 year to prevent one death [9]. However, just 10.3 elderly patients with CHF and CKD Stage 4 need to be treated for 1 year to prevent one death. Although recurrent hospitalization from heart failure was not reported, it is quite likely that health-related quality of life, morbidity and costs are also likely to benefit in those with advanced CKD even more so than in those with earlier stages of CKD.

Some limitations of the analyses should be pointed out. First, although the motivation of HDPS matching was to draw causal inference from the analysis, even with the use of such a technique, the unmeasured biases are not eliminated. Second, whether β-blocker should be used on top of renin–angiotensin–aldosterone system (RAAS) inhibitors is unclear from this report. The P-value for interaction was 0.07, suggesting that renal failure may modify the relationship between β-blocker and mortality when RAAS inhibitor is not used. Third, mineralocorticoid receptor antagonists are used minimally in those with

CKD, likely because of their propensity to cause hyperkalemia. Whether their use should be mandated prior to β-blocker use in CKD similarly remains unknown. Fourth, the lack of ejection fraction data, as acknowledged by the authors themselves, which prevented them from determining if the 'observed survival benefit extends to all elderly patients with CHF and CKD or only those with CHF and HFrEF'. Indeed, β-blockers are evidence-based live-saving drugs in HFrEF only, whereas in heart failure with preserved ejection fraction, none of the treatments tested to date has been definitively proven to improve survival [3, 4]. Fifth, the study likely magnified the mortality benefit of β-blocker use. For example, in a *Lancet* meta-analysis, β-blocker use among patients participating in randomized trials and who were in sinus rhythm had an HR for all-cause mortality of 0.73 (95% CI 0.67–0.80) [10]. This is much smaller than the analysis reported by Molnar *et al.* [HR 0.58 (95% CI 0.54–0.64)]. Sixth, the presence of atrial fibrillation modifies the protective effect of β-blocker in patients with HFpEF in which it has no protective effect on all-cause mortality [10]. Although Molnar *et al.* adjusted for the presence or absence of atrial fibrillation, the interaction effect was not reported.

In this study, the severity of CKD did not modify the CHF–mortality relationship even with those β-blockers that have not had the evidence base of cardiovascular protection in clinical trials among patients with CHF. Such β-blockers include metoprolol tartrate and atenolol. In other words, even the 'non-evidence-based β-blockers' afforded all-cause mortality protection in patients with incident CHF. Only 6% of the study population was on atenolol in this study, but among dialysis patients—not a subject of study in this report—atenolol administered three times a week protects from both hard cardiovascular outcomes and hospitalization from heart failure [11]. This therapy is inexpensive and in the USA, an annual supply of atenolol administered 50 mg once daily costs just $20. This drug is not metabolized and is removed by the kidney, and therefore in patients with CKD can be used just once a day and in those on dialysis three times weekly after dialysis. Thus, the benefit of β-blockers may extend to patients on long-term dialysis.

Cardiovascular trialists should take note of these data. From this well-done pharmacoepidemiology study, it is evident that inclusion of patients with Stage 4 CKD may reduce the size of the trials owing to the much higher event rate and provide benefit similar to that seen among those without CKD. Despite its size, observational studies are subject to various biases and confounding and should not be taken as evidence of cause and effect [12]. Whether β-blockers can save lives, alleviate hospitalizations for heart failure and reduce costs appears promising, but whether it is so will require adequately powered and specifically designed randomized trials. Indeed, the limitations of standard endpoint definitions in patients with CKD are well known: they encompass difficulties in determining whether some signs and symptoms commonly used to identify an endpoint event (e.g. heart failure) are attributable to cardiovascular disease or to the underlying kidney disease. Furthermore, some biomarkers (e.g. natriuretic peptides) may be altered in CKD and interpretation can be challenging [13]. Another hurdle may be the potential reluctance of the medical community in some countries to acknowledge the equipoise and challenge some established medical practices despite a poor evidence base. As an example, Bosselmann *et al.* [14] identified patients with systolic heart failure in the Danish Heart Failure database and new-onset end-stage renal disease. In this setting, despite a poor evidence base, 82% of the patients with a baseline Stage 4 CKD were treated with a β-blocker. Thus, there may be reluctance on part of physicians to test the β-blocker hypothesis in a randomized controlled trial among patients with Stage 4 CKD. If so, we will continue to practice despite a poor evidence base.

In our view, however, it is time to perform such a study—the costs of doing nothing are too high.

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CONFLICT OF INTEREST STATEMENT

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(See related article by Molnar *et al.* The association of beta-blocker use with mortality in elderly patients with congestive heart failure and advanced chronic kidney disease. *Nephrol Dial Transplant* 2020; 35: 782–789)

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Dietary protein restriction in chronic kidney disease: one size does not fit all

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Twenty-five years after the publication of the seminal Modification of Diet in Renal Disease (MDRD) Study, which suggested a small benefit of dietary protein restriction on the progression of chronic kidney disease (CKD) [1], there are considerable variations from one centre to another, even from one nephrologist to another, in the prescription of protein restriction for various matters. These are linked to scientific and medical considerations, but also to feasibility, acceptance by patients and the organization of health care. In this context, sharing of expertise by centres that have long-term experience with protein restriction might be useful to share, even in the perspective of reassessment of the effect of protein restriction in CKD in a properly designed randomized clinical trial (RCT) [2]. In this issue of *Nephrology Dialysis Transplantation*, Piccoli *et al.* [3] report the experience of the use of protein restriction in 422 patients with CKD Stages 1–5D in four centres in Italy. The study is focused on quality of life (QoL) and dietary satisfaction of these patients, i.e. objectives different from most studies that have evaluated the impact of protein restriction on CKD progression and other clinical endpoints, including end-stage kidney disease (ESKD).

As a matter of fact, the debate over the effectiveness of protein restriction is far from closed; in a recent Cochrane review, Palmer *et al.* [2] stated that 'dietary interventions may prevent one person in every 3000 treated for one year avoiding ESKD, although the certainty in this effect was very low'. Nevertheless, there were significant beneficial effects of protein restriction on systolic and diastolic blood pressure, estimated glomerular filtration rate (eGFR) and low-density lipoprotein cholesterol. In an even more recent Cochrane review, it was found that very low protein intake compared with a low protein intake probably reduces the number of patients who reach ESKD (165 per 1000 fewer reached ESKD), but the evidence was of moderate certainty [4]. Both reviews conclude that large-scale pragmatic RCTs are needed to test the effects of dietary interventions on patient outcomes [2, 4]. This study contains important information to be taken into account if such RCTs are to be performed, given the experience of our Italian colleagues, with the present cohort being one of the largest reported so far.

The first information is that protein restriction may not be proposed to all patients with CKD, since it is not adapted to patients with high comorbidities, malnutrition or poor life expectancy and since patients may not want to limit their protein intake [3]. This latter aspect may depend on cultural background and habits. Global protein intake is two times higher in industrialized countries, with meat intake being three times higher. In consumers of Mediterranean diets, such as in Italy, an equilibrium exists between plant and animal protein, and it is easier to reduce protein intake than in meat eaters [5]. Protein restriction is therefore a relative concept [6], depending on regional and personal dietary protein consumption. In this respect, the authors are right to highlight the Mediterranean