Should nephrologists use beta-blockers? A perspective

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Given the high prevalence of cardiovascular disease in people with chronic kidney disease (CKD) and the clear benefits of mortality reduction observed for most beta-blockers in clinical trials, they are relatively underused in CKD patients [1,2]. The rationale for use of beta-blockers in patients with CKD is reviewed in detail elsewhere [2,3] but is summarized in this editorial.

Alterations in beta- and alpha-receptor responsiveness are associated with sympathetic over-activity in CKD. This increased sympathetic activity is involved in the genesis of hypertension, and contributes to cardiac complications seen in CKD [2,3]. The contribution of the sympathetic nervous system to nephropathy progression is documented in sub-totally nephrectomized rats where non-hypotensive doses of beta-blockers ameliorate development of glomerulosclerosis and cardiac injury [4]. In men, sympathetic over-activity, as assessed by sural nerve microneurography, was present in patients on haemodialysis [5], stage 4 nephropathy [6] and in early stage 2 nephropathy among patients with polycystic kidney disease [7]. The role of the damaged kidney in causing sympathetic over-activity is illustrated by normalization of sympathetic over-activity in haemodialysis patients following bilateral nephrectomy [5] and in renal allograft recipients when their shrunken native kidneys are removed [8].

The most common cause of death in stage 3 and higher CKD results from complications of cardiovascular disease. This may be due, in part, to inadequate treatment of blood pressure, where blood pressure goals were not attained and agents known to reduce mortality secondary to cardiovascular causes, i.e. aspirin, ACE inhibitors and beta-blockers were not used [9]. In a separate study, beta-blockers were used in fewer than 30% of haemodialysis patients [10]. This is surprising, since beta-blockers are well-established, evidence-based therapy for reducing cardiovascular risk in hypertension associated with diabetes and after myocardial infarction [11,12] . Observational studies support definite survival benefits derived from beta-blocker use in patients with advanced CKD [13,14]. Furthermore, a prospective, randomized study of haemodialyzed patients with heart failure demonstrated a decrease in death and hospitalization rates from cardiovascular causes in those on carvedilol [15].

Given the benefits of beta-blockers to reduce cardiovascular risk in CKD, it is paradoxical that they are underutilized. Data indicate that beta-blocker underuse is secondary to fear of adverse haemodynamic and metabolic effects in patients with diabetes. Beta-blockers vary significantly in their pharmacologic properties, and these differences affect tolerability and metabolic effects in patients with CKD [2]. Vasodilating beta-blockers are better tolerated and associated with neutral glycemic and lipids effects. Consequently, knowledge of the vasodilating beta-blockers such as carvedilol and nebivolol [2,3] that have been prospectively tested on these biochemical parameters and found to be neutral would allay these fears [2,16].

A recent meta-analysis has now called into question the use of beta-blockers in patients with hypertension who do not have compelling indications [17]. Unfortunately, this meta-analysis revealed the shortcomings of atenolol, a beta-blocker that has a pharmacology consistent with twice daily use while commonly used once daily [18]. Now we have yet another meta-analysis by Bangalore and colleagues that evaluated the role of heart rate reduction with beta-blockers on the risk of cardiovascular events in patients with hypertension and high cardiovascular risk [19]. Again in this analysis all but one of the studies involved atenolol.

Until this meta-analysis, the literature was replete with studies documenting that a higher resting heart rate was associated with higher cardiovascular risk [20,21]. It is well known that a lower resting heart rate increases diastolic filling and alleviates ischaemia. How is it then that Bangalore et al found a lower heart rate with beta-blockade increased risk of all-cause mortality and cardiovascular mortality for hypertensive patients? What is even more perplexing is the observation that post MI patients or those with heart failure or coronary artery disease had more events with a lower heart rate associated with beta-blocker use. How can this be? Have we been wrong all these years? Are the guidelines wrong to recommend beta-blocker use in these clinical situations?

The answer lies again in looking at the component studies used in Bangalore’s meta-analysis. Remember the results of one or two very large studies will drive the whole result of meta-analyses, so let us look at the studies. Firstly, only 9 of the 22 randomized controlled trials evaluating beta-blockers in hypertensive patients reported heart rate. Thus, these nine studies form the basis of Bangalore group report. Secondly, the majority of patients in the beta-blocker
arms of the studies used received either atenolol (78%) or some variation including atenolol (12%) or hydrochlorothiazide and 9% oxprenolol. Here again we have 90% of the people on atenolol, a drug that has never received an indication by regulatory agencies for cardiovascular risk reduction in anyone who is post MI, has heart failure or coronary artery disease. Moreover, the β-blockers that have received approved indication for use, under such conditions, i.e. carvedilol and metoprolol, were not included in this meta-analysis.

While the focus of this meta-analysis is on heart rate and not β-blocker subclass, two other factors need to be considered, blood pressure and dosing regimen. In all studies reviewed, atenolol was primarily dosed once daily; the shortcomings of this dosing strategy have already been mentioned. Additionally, we already know from data of the CAFE study that even with no cuff blood pressure differences, central pressures could markedly vary and affect outcome [22]. These data, taken together with the lack of 24 h blood pressure control by atenolol, suggest that the assumption of heart rate reduction alone may not be fully responsible for poor cardiovascular outcomes generalizable to the class. Using a drug that lowers heart rate and does not have full 24 h blood pressure control and is not approved for use in post MI or heart failure patients does not necessarily translate into reduced cardiovascular risk because of too low a heart rate. Thus, the Bangalore meta-analysis results are reflective of atenolol and not β—blockers with approved indications for cardiovascular mortality benefit such as metoprolol and carvedilol. It should also be noted that while many people in the studies analysed had CKD, that subgroup was not assessed with regard to mortality benefit. Unfortunately, there are no large-scale prospective trials with atenolol that evaluate CKD progression. Perhaps the best and only long-term data that assessed CKD progression exists with metoprolol tartrate and derived from the African American Study of Kidney Disease (AASK) [23]. In this trial after a 5-year follow-up, metoprolol slowed progression of CKD albeit not by the same magnitude as an ACE inhibitor. Even though the trial was not powered for cardiovascular events (N = 1094) no excess events occurred in the metoprolol group and heart rate was lower than the comparator groups.

In conclusion, sympathetic over-activity is part of CKD and contributes to the maintenance of hypertension and associated cardiac complications. Larger prospective trials are needed to determine whether the properties of the vasodilating β-blockers will translate into improved cardiovascular outcomes in CKD. Until then, given the high prevalence of cardiovascular disease in people with CKD and mortality benefits observed for some β-blockers, there is clearly a need for their use in CKD patients.

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References


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