Nebivolol as a first-line antihypertensive: a justifiable proposal?

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β-Blockers (BBs) have long been used to treat hypertension (HBP). The mechanisms of their antihypertensive effects include negative chronotropy and inotropy, inhibition of β-adrenergic receptor-mediated peripheral vasoconstriction and central adrenergic outflow, as well as renin release.[1] Additionally, newer BBs such as nebivolol have direct peripheral vasodilatory activity and other properties which distinguish them from first-generation and second-generation agents (table 1). In this issue of *Heart Asia*, Kim *et al*[2] commend the use of BBs, and specifically nebivolol, as a first-line agent for HBP.

The potential advantages of nebivolol should be considered in the context of the totality of evidence regarding the net benefits of BBs in HBP. In aggregate, the data from landmark clinical trials, systematic reviews and meta-analyses indicate that BBs are less effective than other major drug classes, in particular calcium ion-channel blockers (CCBs), in preventing stroke or cardiovascular events.[5–9] Among the authoritative guidelines, the 2014 ASH/ISH and JNC 8, as well as the recently updated National Institute for Health and Care Excellence (NICE) guidelines, no longer recommend a BB as initial monotherapy for HBP.[10 11]

In the ASH/ISH guidelines,[11] BBs have been relegated to fourth-line therapy, and are only recommended in the setting of clinical coronary artery disease and heart failure, and even then not as monotherapy.[11] The 2014 JNC 8, which admitted only large and validated randomised controlled trials (RCTs) in its evidence review, excluded only BB among the four major drug classes as initial therapy of HBP in the general non-black population, including diabetics.[10] Likewise, the 2011 NICE guidelines do not recommend a BB as routine initial therapy for uncomplicated HBP.[12] In the 2014 evidence update of these guidelines, a key reference was a 2012 Cochrane review of 13 RCTs in hypertension, comparing BB with placebo, no treatment or active treatment in 91 561 subjects.[6] The main conclusions, which affirmed the existing NICE position, were that patients receiving BBs had significantly higher total mortality compared with those taking CCBs, higher fatal and non-fatal stroke rates than those on CCBs and angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) and, contrary to common belief, did not enjoy a lower risk of coronary heart disease vis-à-vis other drug classes or even placebo.

By contrast, the 2013 European Society of Cardiology (ESC) guidelines state as a class IA recommendation that all drug categories are suited for treating hypertension, either as monotherapy or in combination.[13] These guidelines were less prescriptive, since the authors believed that the benefits of treatment accrue more from BP lowering than specific drug influences.[14] Nevertheless, the ESC recommends a BB only in patients with known cardiovascular disease, that is, manifest ischaemic heart disease, heart failure, atrial fibrillation and aortic aneurysm, and states a preference for non-BB agents in isolated systolic hypertension, diabetes, non-diabetic proteinuria, metabolic syndrome and peripheral vascular disease.[13] The 2014 Canadian Hypertension Education Program recommendations endorse BB use in patients <60 years (grade B), a position supported by meta-analyses which suggest non-inferior cardiovascular outcomes in these younger hypertensives.[15 16] However, methodological concerns have been raised about these studies, and the issue of BB efficacy in relation to age remains contentious.[6 17]

Kim *et al* highlight that a majority of BB trials in HBP mostly used atenolol, and postulate that properties unique to nebivolol could confer improved outcomes. The postulated improvement could be mediated by vasodilation, reduced wave reflection from muscular arteries, lower central aortic pressures and regression of left ventricular mass.[18 19] Whether these effects translate into better outcomes is unknown, since large outcomes-based trials of nebivolol in primary HBP with active comparators are non-existent. It is unrealistic to expect the completion of sufficiently powered RCTs comparing nebivolol against competing antihypertensives, in terms of preventing death or target organ damage. In the absence of hard evidence, the policy of using a more expensive drug is difficult to justify (table 1), especially in a chronic condition like HBP.[11 12]

Notwithstanding the above concerns, the failure to adequately control BP in the community is systemic across most healthcare systems. A key determinant of cardiovascular outcome in HBP is the quality or intensity of BP control.[5 20 21] Furthermore, in clinical practice, two or more agents are required in the majority of patients with hypertension.[10] Therefore, unless there are contraindications or clearly demonstrated evidence for harm, the use of any antihypertensive agent, including a BB, in the pursuit of optimal control of the BP will likely confer benefit.[11 21] However, until hard outcomes evidence emerges from high-quality RCTs favouring the use of nebivolol in HBP, we do not believe that this drug should be a first-line agent, particularly in older persons at the highest risk.

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Table 1 Classification, properties and cost of β-blockers available at National University, Singapore

	Half-life (h)	β-1 Receptor selectivity	Lipophilic/ hydrophilic	Intrinsic sympathomimetic activity	Peripheral vasodilation	Usual dose range (mg/days)	Daily cost at lower and upper end of usual dosing (SGD)
First generation							
Propranolol	3–4	0	High	Yes	No	40–180	0.11–0.66
Second generation							
Atenolol	6–9	+	Low	No	No	25–100	0.06–0.11
Bisoprolol	9–12	++	Moderate	No	No	5–20	0.28–1.12
Metoprolol (tartrate)	3–4	++	High	No	No	100–400	0.36–0.52
Third generation							
Carvedilol	7–10	0	Moderate	No	Yes	12.5–50	0.68–0.92
Labetalol	3–4	+	Low	Yes	Yes	200–800	0.50–2.00
Nebivolol	8–27	+++	Moderate	No	Yes	5–10	0.98–1.96

Adapted from Feldman *et al*[3] and Koda-Kimble and Young's Applied Therapeutics 10th edn, 2012.[4]
SGD, Singapore dollars.

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