Delivering a One-Two Punch in the Treatment of Hypertension With a Vasodilating β-blocker

Introduction

Hypertension (HT) is a known risk factor for cardiovascular disease (CVD), which is the global leading cause of death from non-communicable diseases.[1,2] Patients with CVD and comorbid HT have a poor prognosis owing to increased mortality rates.[2] In recent decades, the prevalence of HT in developing countries has increased owing to economic development and an ageing population.[1] According to the 2019 Malaysian National Health and Morbidity Survey, the prevalence of HT in adults above 18 years of age was 30%, and this increased with age, rising to 81.7% among older adults above 75 years of age.[3] Other established risk factors for HT include gender, body mass index, smoking and alcohol intake.[1] The management of HT typically involves lifestyle modifications and pharmacological treatment with appropriate blood pressure (BP)-lowering medications.[4] Third-generation vasodilating β-blockers are an example of antihypertensives that are increasingly prescribed in recent years.[5]

Pharmacological management of HT

Numerous guidelines have been developed worldwide to assist healthcare professionals in managing patients with HT, including guidelines by the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH), the American College of Cardiology (ACC) and the American Heart Association (AHA), the International Society of Hypertension (ISH) and the Malaysian Ministry of Health.[4–7] Generally, it is recommended that patients with grade 2 or 3 HT be managed with both antihypertensives and lifestyle interventions[5]; depending on the guidelines, pharmacological treatment is also considered in high-normal BP or grade 1 HT cases with high CVD risk or HT-mediated organ damage.[5] There are several classes of antihypertensives, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-blockers, calcium channel blockers (CCBs) and diuretics.[5] These classes of drugs have been shown to reduce BP and cardiovascular (CV) events.[5,8,9] Furthermore, there was evidence of broad equivalence in overall CV morbidity and mortality despite some drugs exhibiting cause-specific differences.[5,8,9] As such, the 2018 ESC/ESH guidelines recommended these five classes of drugs to form the basis of antihypertensive therapy.[5]

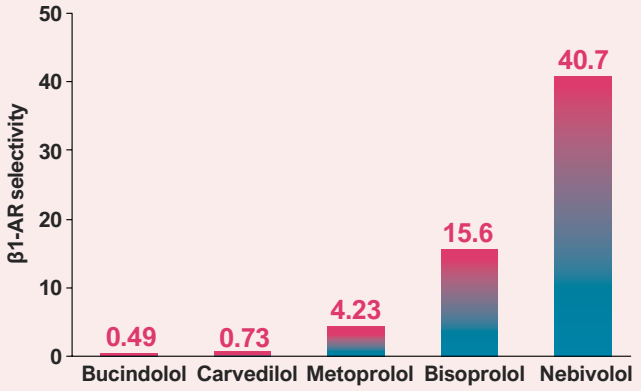
Management of HT with β-blockers

At present, β-blockers can be given as first-line antihypertensives according to some guidelines, including in Europe, Canada, Japan and Taiwan.[5,10–12] Additionally, β-blockers are considered at any step of the treatment algorithm when there is a specific indication (e.g., heart failure, angina, contraindications to ACE inhibitors or ARBs, and in young women with child-bearing potential).[4,5,10] When compared with the placebo, β-blockers have been shown to reduce the risk of stroke, heart failure and major CV events in patients with HT.[5,8] It has been noted, however, that although β-blockers were shown to be equivalent to other antihypertensives in preventing major CV events, they may be comparatively less effective in certain cases (e.g., in stroke prevention).[5,8] Nevertheless, β-blockers are a heterogeneous class of drugs with three generations exhibiting different biochemical and pharmacological properties, mainly deriving from their selectivity for β-adrenoceptors (β-ARs).[13] This heterogeneity contributes to the suitability of different β-blockers in different patient subtypes.[13] The first-generation β-blockers are non-selective to β-ARs, which are expressed in the heart, lungs and adipose tissue.[13,14] This property can result in the occurrence of bronchoconstriction and metabolic disruptions during antihypertensive therapy.[13,14] Conversely, second-generation β-blockers are relatively cardio-selective (i.e., to β1-ARs) and have a more favourable tolerability profile.[15] Finally, the third-generation β-blockers exhibit additional vasodilatory properties with better tolerability and haemodynamic profiles.[15]

Nebivolol: A β-blocker with a dual mechanism of action

Nebivolol is an oral once-daily (5 mg) β-blocker of the third generation that is β1-selective and has vasodilating properties.[13,16] It can be prescribed as a combination therapy, and the treatment algorithms differ in cases of complicated and uncomplicated HT.[13] Nebivolol has been shown to be more effective on central BP, aortic stiffness and endothelial dysfunction[5]; it also exhibited a more favourable side effect profile compared with classical β-blockers and exhibited no adverse effect on the risk of new-onset diabetes.[5] When compared with other β-blockers, nebivolol demonstrated the highest selectivity to β1-ARs (**Figure 1**).[17]

Figure 1. Relative selectivity of β1-ARs in human myocardium.[17]



Adapted from Brixius K, et al. 2001.[17]

Nebivolol is also the only β-blocker that demonstrated nitric oxide (NO)-mediated vasodilation through the activation of β3-ARs and endothelial NO synthase.[13,14] Evidence has shown that NO plays an important role in BP regulation.[18] Reduced concentrations of plasma NO and impaired endothelium-dependent vasodilation have been observed in patients with essential HT.[18]

Nebivolol in the management of HT

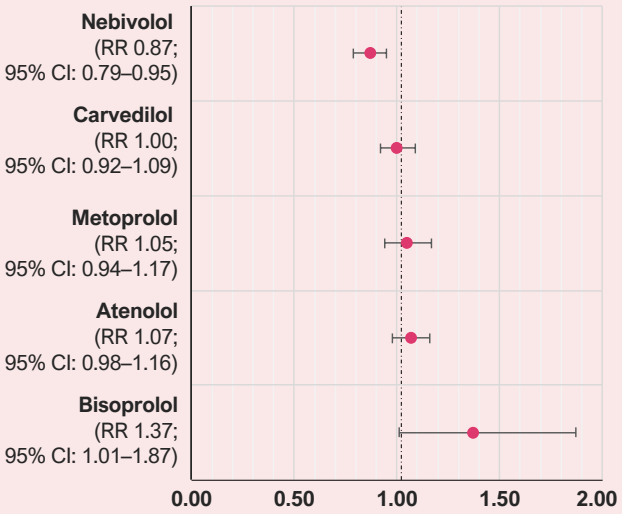
There is no class effect (i.e., no similar benefit) for β-blockers due to their heterogeneous class[14]; however, there is solid documentation on the prevention of CV complications in the treatment of HT with β-blockers.[14] Based on a recent systematic review and meta-analysis, nebivolol demonstrated at least similar control of blood pressure levels in hypertensive individuals when compared with other main classes of antihypertensives.[19] In systolic BP management, nebivolol was more effective than other β-blockers and diuretics, while no comparative differences were observed with ARBs or CCBs.[19] Moreover, nebivolol was more effective than other β-blockers, ARBs, CCBs and diuretics in diastolic BP management.[19] For all doses studied (i.e., 1.25–40 mg daily), nebivolol demonstrated significantly better tolerability versus atenolol or metoprolol (p=0.0001).[19] No significant differences were observed in the incidence of adverse events versus the placebo and other antihypertensives.[19] In another real-world study, nebivolol demonstrated a reduced risk of composite CV–event-related hospitalisation (e.g., angina and stroke) versus atenolol and metoprolol (p<0.001).[20]

Effect of nebivolol on ED and in the management of HT with comorbidities

Erectile dysfunction (ED) is a prevalent adverse event associated with the use of β-blockers.[21] Interestingly, nebivolol has shown improvements in erectile function owing to its unique mode of action through enhanced NO bioavailability.[21] In an observational study of patients with HT, nebivolol was associated with a lower prevalence of ED (odds ratio [OR] 0.27)[22]; this condition was independently and inversely related to the drug in younger patients (OR 0.22).[23] When compared with other β-blockers, nebivolol was also associated with a lower risk of ED (**Figure 2**).[24]

Other than ED, nebivolol was shown to be safe and efficacious in patients with HT with comorbid coronary artery disease and left ventricular ejection fraction ≥40%, whereby 76.5% and 37.7% of patients had achieved their target blood pressure and heart rate, respectively, with no serious adverse events reported.[25] Additionally, 31% and 23.2% of patients in the study demonstrated improvement in at least one category in the Canadian Cardiovascular Society angina severity classification and New York Heart Association Functional Classification, respectively.[25] Diabetes mellitus (DM) often co-exists with HT and share similar risk factors, such as endothelial dysfunction, atherosclerosis and obesity.[26] Both DM and HT are associated with an increased risk of CVD.[26] In one study, both nebivolol and atenolol significantly reduced systolic (p<0.004) and diastolic (p<0.002) BP in patients with HT and comorbid type 2 DM.[27] Although both drugs did not significantly affect glycaemic control and lipid profiles, atenolol was associated with a significant worsening in several parameters, including blood sugar (p=0.002), HbA1c (p=0.0016), cholesterol (p=0.004) and triglycerides (p=0.006), when compared with nebivolol.[27]

Figure 2. The relative risk of ED with β-blockers.[24]



RR, risk ratio; **CI**, confidence interval

Adapted from Sulastri R, et al. 2022.[24]

Summary

- One important risk factor of CVD, which represents the global leading cause of death from non-communicable diseases, is HT.[1,2]
- β-blockers belong to a heterogenous class of drugs and thus do not have a class effect; however, there is solid documentation on the use of β-blockers in the prevention of cardiovascular complications during HT treatment.[14]
- Nebivolol is a third-generation β1-selective β-blocker with vasodilating properties, neutral metabolic effects and good tolerability[13]; it has demonstrated advantages over other β-blockers, making it suitable in managing hypertensive patients with or without comorbidities.[13]
- Nebivolol exerts its vasodilating action through enhanced NO bioavailability[21]; it has been associated with a lower prevalence of ED.[22]

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BB: Beta Blocker; CAD: Coronary Artery Disease; CV: Cardiovascular; DM: Diabetes Mellitus; HT: Hypertension; HFpEF: Heart Failure with Preserved Ejection Fraction.

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