Commentary
The role of β-blockers in the management of hypertension: An Asian perspective

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Abstract
Following publication of the National Institute of Clinical Excellence (NICE) Guidelines in 2006, the use of β-blockers as first-line therapy in hypertension has been somewhat controversial. However, a recent reappraisal of the European Society of Hypertension guidelines highlights that these agents exhibit similar BP lowering efficacy to other classes of agents, prompting a re-examination of the utility of these agents in various patient populations. The authors felt that it is important to address this controversy and provide an Asian perspective on the place of β-blockers in current clinical practice and the benefits of β-blockade in selected patient populations. In addition to their use as a potential first-line therapy in uncomplicated hypertension, β-blockers have a particular role in patients with hypertension and comorbidities such as heart failure or coronary artery disease, including those who had a myocardial infarction. One advantage which β-blockers offer is the additional protective effects in patients with prior cardiovascular events. Some of the disadvantages attributed to β-blockers appear more related to the older drugs in this class and further appraisal of the efficacy and safety profile of newer β-blockers will lend support to the current guideline recommendations in Asian countries and encourage increased appropriate use of β-blockade in current clinical practice within Asia.

Introduction
The Asia Pacific region accounts for approximately half of the worldwide burden of cardiovascular disease. High blood pressure (BP) is an important contributor to this burden, with a population-attributable fraction of hypertension for cardiovascular disease reported to be as high as 66% in Asian countries. It is anticipated that by 2025, the number of hypertensive individuals in China and India alone will increase to >500 million. It is clear that an increased awareness and effective treatment of hypertension will be crucial to reducing the burden of cardiovascular disease within this region.

The use of β-blockers as first-line therapy in hypertension has become somewhat controversial in recent years and, based on some recommendations, physicians may have concerns regarding the prescribing of these agents. The guidelines from the National Institute of Clinical Excellence (NICE) in the United Kingdom recommended that β-blockers should not be used as first-line treatment for hypertension unless there was some additional indication because they appeared to be less effective than some other groups of antihypertensives in reducing cardiovascular events, particularly stroke. However, such cautionary advice may run the risk of overgeneralization and some patients may be deprived of advantageous treatments. Furthermore, a reappraisal of the European Society of Hypertension (ESH) guidelines highlights that β-blockers exhibit not only similar BP lowering efficacy compared with other major antihypertensive drug classes (diuretics, angiotensin converting enzyme inhibitors [ACEIs], angiotensin receptor
blockers [ARBs], calcium channel blockers [CCBs]), but also provide similar protection against coronary heart disease events and stroke. This prompted a re-examination of the utility of these agents in various patient populations.

In Asia, β-blockers are one class of commonly prescribed antihypertensive agents. In light of the reappraisal of the ESH guidelines on hypertension, a group of physicians specializing in the treatment of hypertension in Asia convened to discuss the role of β-blockade in the management of hypertension. The group, who are authors of this paper, felt the need to address the controversy on the role of β-blockers in current clinical practice and provide an Asian perspective on the benefits of β-blockade in selected patient populations.

Epidemiology of hypertension in Asia

Hypertension is a well-established risk factor for cardiovascular disease, and effective BP lowering strategies are an integral component of both primary and secondary prevention strategies. The Asia Pacific Cohort Studies Collaboration (APCSC), which analyzed 44 separate cohorts including approximately 600,000 subjects from China, Hong Kong, Japan, Singapore, South Korea, Taiwan, Thailand, New Zealand and Australia, is the largest meta-analysis to document a link between BP and cardiovascular disease in Asian patients. Data confirmed high BP as a key risk factor for cardiovascular disease in this patient population, and documented a linear relationship between BP and coronary heart disease. A similar relationship has been reported between BP and stroke – although the slope of the relationship was steeper in Asian compared with Caucasian patients.

Within the Asian region there is a moderate-to-high prevalence of hypertension, with estimates ranging from 17 to 53%. While the Hong Kong Cardiovascular Risk Factor Prevalence Study-2 (CRISPS-2; n = 1944) reported a prevalence of 17% in women and 23% in men, prevalence estimates in China, India and Singapore were as high as 42–44% (Table 1). Data from countries such as Indonesia demonstrate the heterogeneity of the Asian hypertensive population, with prevalence estimates varying depending on geographical location (8–53%) and urban (31%) versus rural (32%) distribution. In Malaysia, the prevalence of hypertension among adults aged ≥30 years has shown a gradual increase from 33% in 1996 to 43% in 2006. On the contrary, the prevalence of hypertension in some age groups (≥30 years) may have decreased from 30% in 1998 to 24.9% in 2007 in South Korea.

Despite the clear relationship between high BP and cardiovascular disease, in Asia awareness of hypertension is low, with estimates of <30% in countries such as China, India and the Philippines. In Singapore, National Health Survey data (gathered between 1998 and 2004) suggest a trend towards an increased awareness of hypertension reflected by an increase in the prevalence of hypertensive patients who were aware that they had hypertension (45% in 1998 vs. 60% in 2004). However, in Malaysia rates of awareness have only marginally increased from 33% in 1996 to 36% in 2006. Across the region the low rates of awareness are often coupled with suboptimal treatment rates, particularly in low-income countries. Evidence indicates that the majority of patients receiving treatment for hypertension have uncontrolled BP on monotherapy (up to 80%; Table 1).
Current international and regional guidelines on hypertension

International guidelines

The US Joint National Committee (JNC) seven guidelines from 2003 recommend thiazide diuretics as the preferred initial agent for most patients with uncomplicated hypertension, either alone or combined with drugs from other classes\(^24\). However, the guidelines also state that in hypertensive patients, similar BP reductions and cardiovascular protection can broadly be achieved with the other drug classes, \(\beta\)-blockers, ACEIs, ARBs, and CCBs\(^24\).

A more recent reappraisal of the current European Society of Hypertension (ESH) treatment guidelines confirms the conclusion of the ESH/ESC 2007 guidelines\(^25\) that the main benefits of antihypertensive treatment, i.e. cardiovascular protection, are due to lowering of BP per se. Since all major antihypertensive drug classes, including \(\beta\)-blockers, diuretics, ACEIs, ARBs and CCBs, can adequately lower BP and significantly reduce cardiovascular outcomes, all of these agents are suitable for the initiation and maintenance of antihypertensive treatment either as monotherapy or in combination with each other, according to the reappraisal of the ESH guidelines\(^8\).

These recommendations are based on a number of studies, including the results of a recent meta-analysis that demonstrated that the five main classes of BP lowering drugs (i.e., thiazide diuretics, \(\beta\)-blockers, ACEIs, ARBs, and CCBs) were similarly effective in reducing BP and preventing CHD events and strokes\(^26\). In particular, this meta-analysis demonstrated that \(\beta\)-blockers exert effects beyond BP lowering, in the secondary prevention of coronary artery disease (CAD) and provide a protective effect when administered after myocardial infarction\(^26\). Meanwhile calcium channel blockers appear to have a slightly greater protective effect in primary stroke prevention than the other drug classes.

Regional guidelines

Most Asian countries have their own hypertension management guidelines which are similar to the JNC 7\(^24\) and ESH/ESC guidelines\(^25\) (Table 2)\(^27\)–\(^34\). The majority of these guidelines consider \(\beta\)-blockers to be an appropriate first-line treatment option in the treatment of hypertension.

Atenolol, bisoprolol, carvedilol, metoprolol, and nebivolol were identified as commonly used \(\beta\)-blockers in the representative Asian countries. These \(\beta\)-blockers can be used for the long-term treatment of hypertension indefinitely, within the recommended dosing ranges, unless contraindicated. As a class, \(\beta\)-blockers are used as both first- and second-line agents across a range of additional indications in patients with hypertension (Table 3).

Rationale for an Asian perspective

Within the Asian region current clinical practice in hypertension management varies. However, a number of practical issues with regard to the use of \(\beta\)-blockers have been consistently identified. \(\beta\)-blockers are acceptable as a first-line treatment option for hypertension in most Asian guidelines (Table 2) – largely based on the JNC 7\(^24\) and ESH/ESC 2007 guidelines\(^25\) – but the perception is that they are being used less frequently in clinical practice, and they were cautioned in the 2005 Singapore Ministry of Health Guidelines\(^34\) for patients at risk of developing diabetes. Indonesia recognizes all antihypertensive classes as a first-line treatment option and \(\beta\)-blockers are most commonly prescribed in Malaysia but not necessarily as first-line treatment\(^35\)–\(^37\).

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Table 1. Prevalence awareness and treatment of hypertension in the Asian region.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Prevalence (%)</th>
<th>Awareness (%)</th>
<th>Treated (%)</th>
<th>Controlled (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>China(^16)</td>
<td>16,364</td>
<td>43.8</td>
<td>26.2</td>
<td>22.2</td>
</tr>
<tr>
<td>India(^12)</td>
<td>4711</td>
<td>36</td>
<td>22.1</td>
<td>36.7</td>
</tr>
<tr>
<td>Korea(^23)</td>
<td>6388</td>
<td>43.8</td>
<td>60.1</td>
<td>91.7</td>
</tr>
<tr>
<td>&gt;40 years, rural areas</td>
<td>8485</td>
<td>24.9</td>
<td>63.5</td>
<td>54.8</td>
</tr>
<tr>
<td>Korea(^21)</td>
<td>33,976</td>
<td>32.2</td>
<td>35.8</td>
<td>31.4</td>
</tr>
<tr>
<td>Malaysia(^20)</td>
<td>3415</td>
<td>21</td>
<td>16</td>
<td>65</td>
</tr>
<tr>
<td>Philippines(^13)</td>
<td>5022</td>
<td>41.5</td>
<td>51.8</td>
<td>84.4</td>
</tr>
</tbody>
</table>

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\(\beta\)-blockers in hypertension in Asia Tomlinson et al. 1023
In most Asian countries, issues associated with the use of β-blockers, such as upper airway sensitivity, may have had a negative impact on the class as a whole. This coupled with concerns regarding the risk of developing diabetes, administration in elderly patients (inadequate control of central BP, severe bradycardia) and queries regarding the efficacy of β-blockers on cardiovascular risk reduction, as promulgated by the NICE guidelines, may have contributed to the perceived reduced use of β-blockers in hypertension within the Asian region.

The authors identified a number of common concerns regarding β-blocker use in hypertension including the potential increased risk of (drug-induced new-onset) diabetes and the potential for inadequate efficacy of monotherapy leading to a possible decrease in the popularity of β-blockers as first-line agents despite local guideline recommendations. Concern that, within the region physicians may not be prescribing β-blockers as a first-line treatment in hypertension, and in addition less frequently than indicated in patients with heart failure (HF) or coronary disease, due to several misconceptions has led to formulation of this statement from an Asian perspective. This article is not intended as a systematic review of the literature nor as a formalized guideline but rather provides treatment recommendations based on expert consensus.

### Table 2. Principal regional guidelines and key antihypertensive management recommendations.

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese Expert Consensus 2009</td>
<td>β-Blockers are recommended as first line treatment, for long-term treatment, as monotherapy and in combination</td>
</tr>
<tr>
<td></td>
<td>β-Blockers are recommended for ACS with hypertensive emergencies and severe uncontrolled chest pain</td>
</tr>
<tr>
<td>Indian Society of Hypertension Guidelines</td>
<td>Adapted from JNC 7, ESH/ESC guidelines</td>
</tr>
<tr>
<td></td>
<td>Any of the 5 drug classes are recommended as first-line treatment</td>
</tr>
<tr>
<td></td>
<td>Use of compelling indication</td>
</tr>
<tr>
<td></td>
<td>Target BP &lt;140/90 mmHg or &lt;130/80 mmHg in diabetic patients or those with kidney disease</td>
</tr>
<tr>
<td>Indonesian Society of Hypertension Consensus</td>
<td>Refer to JNC 7</td>
</tr>
<tr>
<td>2007</td>
<td>All antihypertensive drug classes are recognized as a first-line option</td>
</tr>
<tr>
<td></td>
<td>Use of compelling indications</td>
</tr>
<tr>
<td></td>
<td>Combination therapy for BP ≥160/100 mmHg</td>
</tr>
<tr>
<td></td>
<td>Target BP of &lt;140/90 mmHg or &lt;130/80 mmHg in diabetic patients and patients with renal failure</td>
</tr>
<tr>
<td>Korean Society of Hypertension Guidelines 2004</td>
<td>Similar to JNC 7</td>
</tr>
<tr>
<td></td>
<td>β-Blockers are considered as as a first-line option for hypertension</td>
</tr>
<tr>
<td></td>
<td>Four classes of antihypertensive agents except β-blockers are recommended as first-line in newly diagnosed, uncomplicated hypertensives with no compelling indication</td>
</tr>
<tr>
<td></td>
<td>Combination therapy for systolic BP ≥160 and/or diastolic BP ≥100 mmHg</td>
</tr>
<tr>
<td></td>
<td>Target BP on therapy &lt;140/90 mmHg for all and &lt;130/80 mmHg for diabetics</td>
</tr>
<tr>
<td></td>
<td>Drug of choice for compelling indications listed</td>
</tr>
<tr>
<td>Malaysian Clinical Practice Guideline on</td>
<td>Initiate medical treatment if hypertensive (regardless of risk classification)</td>
</tr>
<tr>
<td>Hypertension 2008</td>
<td>Focus on BP control</td>
</tr>
<tr>
<td></td>
<td>All antihypertensive drug classes recognized</td>
</tr>
<tr>
<td>Philippine Society of Hypertension 32,33</td>
<td>All 5 drug classes recognized as first-line option</td>
</tr>
<tr>
<td></td>
<td>Use compelling indications, contraindications</td>
</tr>
<tr>
<td></td>
<td>Combination therapy for BP ≥160/100 mmHg</td>
</tr>
<tr>
<td></td>
<td>Target BP &lt;140/90 mmHg</td>
</tr>
<tr>
<td></td>
<td>Lower BP target of &lt;130/80 mmHg for diabetics and renal failure</td>
</tr>
<tr>
<td></td>
<td>No prehypertension classification</td>
</tr>
<tr>
<td>Singapore MOH Guidelines 2005</td>
<td>All antihypertensive drug classes recognized</td>
</tr>
<tr>
<td></td>
<td>Use compelling indications, contraindications</td>
</tr>
<tr>
<td></td>
<td>Combination therapy for BP ≥160/100 mmHg</td>
</tr>
<tr>
<td></td>
<td>Target BP &lt;140/90 mmHg</td>
</tr>
<tr>
<td></td>
<td>Lower BP target of &lt;130/80 mmHg for diabetics and renal failure</td>
</tr>
<tr>
<td></td>
<td>No prehypertension classification</td>
</tr>
</tbody>
</table>

### Table 3. Recommended indications for β-blocker therapy in Asian countries.

<table>
<thead>
<tr>
<th>Young patients with increased HR</th>
<th>Hypertension with CAD</th>
<th>Hypertension with HF</th>
<th>Tacharrythmias</th>
<th>Post-MI</th>
<th>Hypertension with diabetes</th>
<th>Angina</th>
<th>High risk of CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>India</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Indonesia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Korea</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Malaysia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Philippines</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Singapore</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; CHD, coronary heart disease; MI, myocardial infarction; HF, heart failure; HR, heart rate.
Clinical profile of β-blockers in hypertension

There is a lack of outcome data for newer β-blockers in hypertension, and comparative data evaluating the efficacy and safety of various β-blockers in hypertension is limited. The lack of outcome data for the newer β-blockers necessitates the use of surrogate endpoints in order to support their current use and studies to examine clinical endpoints with these drugs should be pursued.

As a class, β-blockers effectively lower BP – although differences in their pharmacological profiles may translate into diverse clinical benefits. A review of clinical trials involving β-blockers over the past two decades demonstrates that in the majority of trials atenolol has been the most common β-blocker (Table 4). A growing body of evidence indicates that atenolol does not have the best pharmacological profile for treatment of hypertension as a representative of the β-blockers as a class and may not be the best choice for efficacy comparisons with other antihypertensive agents. As a consequence, this class of antihypertensives has often had a less favorable clinical profile than is warranted.

A reanalysis of published data supports the protective cardiovascular effects of β-blockers other than atenolol, indicating that the risk of myocardial infarction is reduced by 13% in patients receiving non-atenolol based β-blockade compared with patients taking atenolol.

A large meta-analysis of 147 randomized trials (including many trials that used atenolol) demonstrated that β-blockers are not only similarly effective in reducing CHD events and strokes compared with the other four main classes of antihypertensive agents (i.e., thiazide diuretics ACEIs, ARBs, CCBs) while β-blockers showed an additional effect in preventing recurrent CHD events (~30% reduction in CHD events), over and above that due to BP reduction, in patients with a history of CHD (i.e., recent myocardial infarction), and CCBs appeared to have a slightly greater protective effect in preventing stroke than the other drug classes, the authors concluded that the BP reduction entirely or largely explains the action of the drugs in preventing CHD events and stroke, thus excluding the possibility that BP lowering drugs in general have material pleiotropic effects.

The beneficial effect of β-blockers becomes even more evident when patients are stratified according to age. A meta-analysis of 21 randomized controlled hypertension trials (n = 145,811), demonstrated that in young to middle-aged patients first-line treatment with β-blockers significantly reduced major cardiovascular outcomes (14% reduction). In this patient population, first-line β-blockers demonstrated similar efficacy to other antihypertensive agents in the reduction of cardiovascular endpoints. While these data indicate that first-line β-blockers are generally not as effective in reducing cardiovascular risk in elderly hypertensive patients, when administered as second-line to low-dose diuretics β-blockers effectively reduce cardiovascular events in elderly hypertensive patients, including those with diabetes.

Data from the UKPDS 39 study further confirm the comparative efficacy of atenolol compared to an ACEI. Similar BP reductions were reported in hypertensive patients with type 2 diabetes receiving treatment based on captopril and atenolol. Both drugs were equally effective in reducing the risk of non-fatal and fatal diabetic complications, diabetes-related mortality, HF, and progression of retinopathy. Although atenolol treatment was associated with slightly greater weight gain and a slightly greater increase in glycated hemoglobin concentrations, this did not affect the reduction in clinical endpoints. Furthermore, this favorable result for the β-blocker was maintained during long-term follow-up, and at 20 years there was a significant reduction in all-cause mortality in the patients allocated to the β-blocker.

As a class, β-blockers demonstrate variable tolerability profiles due to differences in adrenergic receptor selectivity, intrinsic sympathomimetic activity, vasodilatory activity, and pharmacokinetic properties. In clinical practice, common adverse effects associated with β-blockade include bradycardia, hypotension, dizziness, fatigue, depression and sexual dysfunction. However, the conventional wisdom that β-blocker therapy is associated with substantial risks of depressive symptoms, fatigue, and sexual dysfunction is not supported by data from clinical trials.

Older β-blockers, such as propranolol and atenolol, have been associated with metabolic adverse effects concerning glucose and lipid metabolism. These adverse metabolic effects may result from a reduction in cardiac output while peripheral vascular resistance increases or remains unchanged. Highly β1-selective β-blockers (e.g., bisoprolol) and the newer vasodilatory β-blockers (e.g., nebivolol) appear to differ in their tolerability profiles (including metabolic adverse effects) from the older agents. In the case of vasodilatory β-blockers, a reduction in peripheral vascular resistance with little effect on cardiac output may potentially result in less impact on glucose and lipid abnormalities compared with traditional β-blockers.

Recommendations on β-blockade in hypertension management

The authors believe that a major criticism regarding the role of β-blockers in the management of hypertension is due partly to a tendency to view all β-blockers as a homogeneous class. Therefore, unfavorable outcome results
Table 4. Overview of comparative clinical trials conducted between 1982 and 2007 involving β-blockers.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients (n)</th>
<th>β-Blocker</th>
<th>Comparator</th>
<th>Follow-up (years)</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BP endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berglund⁵⁸</td>
<td>106</td>
<td>Propranolol</td>
<td>Bendroflumethiazide</td>
<td>10</td>
<td>Similar reduction in BP between groups</td>
</tr>
<tr>
<td>BISOMET⁵⁹</td>
<td>87</td>
<td>Bisoprolol</td>
<td>Metoprolol</td>
<td>0.1</td>
<td>Greater reduction in exercise BP with bisoprolol vs. metoprolol (p &lt; 0.01)</td>
</tr>
<tr>
<td>Höfler⁴⁰</td>
<td>1597</td>
<td>Bisoprolol</td>
<td>Open control</td>
<td>0.2</td>
<td>Mean SBP/DBP reduction of 26/16 mmHg</td>
</tr>
<tr>
<td>Neutel⁴¹</td>
<td>659</td>
<td>Bisoprolol</td>
<td>Atenolol</td>
<td>0.2</td>
<td>33% greater reduction in 24-hour DBP with bisoprolol (8.7 vs. 11.6 mmHg; p &lt; 0.01)</td>
</tr>
<tr>
<td>Davidov⁴²</td>
<td>276</td>
<td>Bisoprolol</td>
<td>Placebo</td>
<td>0.3</td>
<td>Mean reduction in 24-hour SBP was 8.6, 8.6 and 10.9 (bisoprolol 5, 10 or 20 mg) vs. 3.3 mmHg (placebo; p &lt; 0.01) and DBP 6.3, 8.8 or 10.1 vs. 1.6 mmHg (p &lt; 0.01)</td>
</tr>
<tr>
<td>GENRES⁴³</td>
<td>208</td>
<td>Bisoprolol</td>
<td>Amlodipine</td>
<td>0.1</td>
<td>Median reduction in 24-hour BP: 11/8 (bisoprolol), 9/6 (losartan), 7/5 (amlodipine) and 5/2 mmHg (hydrochlorothiazide)</td>
</tr>
<tr>
<td>Grassi⁴⁴</td>
<td>205</td>
<td>Nebivolol</td>
<td>Atenolol</td>
<td>0.3</td>
<td>Mean BP reduction: 18.2/14.6 (nebivolol) vs. 19.1/14.8 (atenolol) [p &lt; 0.01 vs. baseline]</td>
</tr>
<tr>
<td>INT-CAR-07⁴⁵</td>
<td>99</td>
<td>Carvedilol</td>
<td>Atenolol</td>
<td>0.2</td>
<td>Response rate (DBP &lt; 90 mmHg) 84 vs. 91% for carvedilol vs. atenolol</td>
</tr>
<tr>
<td>Mazza⁴⁶</td>
<td>168</td>
<td>Nebivolol</td>
<td>Amlodipine</td>
<td>0.3</td>
<td>Lower seated (p &lt; 0.05) and standing SBP (p &lt; 0.01) with amlodipine</td>
</tr>
<tr>
<td>NEBIS⁴⁷</td>
<td>273</td>
<td>Nebivolol</td>
<td>Bisoprolol</td>
<td>0.4</td>
<td>Mean reduction in DBP: 15.7 vs. 16.0 for bisoprolol; responders achieving DBP &lt; 90 mmHg: 92 vs. 89.6%</td>
</tr>
<tr>
<td>Ruijlope⁴⁸</td>
<td>325</td>
<td>Carvedilol</td>
<td>Atenolol</td>
<td>0.2</td>
<td>Response rates: 75 vs. 82% for atenolol</td>
</tr>
<tr>
<td>Wiess⁴⁹</td>
<td>909</td>
<td>Nebivolol</td>
<td>Placebo</td>
<td>0.3</td>
<td>Nebivolol reduced trough seated SBP/DBP: 8.0–11.2/4.4–9.5 vs.2.9/þ2.2 (p &lt; 0.002)</td>
</tr>
<tr>
<td><strong>CV endpoint(s)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPPPSH⁵⁰</td>
<td>6357</td>
<td>Oxprenolol</td>
<td>Placebo</td>
<td>4.0</td>
<td>17% reduction in MI with oxprenol</td>
</tr>
<tr>
<td>MRC⁵¹</td>
<td>17,354</td>
<td>Propranolol</td>
<td>Bendroflumethiazide Placebo</td>
<td>5.5</td>
<td>Bendroflumethiazide significantly reduced stroke risk vs. propranolol (p = 0.002); no difference between active treatments for coronary events and all-cause mortality</td>
</tr>
<tr>
<td>HEP⁵²</td>
<td>884</td>
<td>Atenolol</td>
<td>Open control</td>
<td>4.4</td>
<td>Atenolol reduced the stroke rate to 58% (p &lt; 0.03) and fatal stroke rate to 30% of that in the control group (p &lt; 0.025)</td>
</tr>
<tr>
<td>HAPPHY⁵³</td>
<td>6569</td>
<td>Atenolol</td>
<td>Hydrochlorothiazide Bendroflumethiazide</td>
<td>3.8</td>
<td>Lower incidence of fatal stroke with β-blocker vs. diuretic; similar rates of CHD and total mortality</td>
</tr>
<tr>
<td>STOP³⁴</td>
<td>1627</td>
<td>Atenolol</td>
<td>Placebo</td>
<td>2.1</td>
<td>Active treatment significantly reduced the risk of fatal and non fatal stroke, MI and other CV death (p = 0.003) and stroke morbidity and mortality (p = 0.008)</td>
</tr>
<tr>
<td>MRC-old⁵⁵</td>
<td>2138</td>
<td>Atenolol</td>
<td>Diuretic</td>
<td>5.8</td>
<td>Significantly reduced risk of stroke (p = 0.04), coronary events (p = 0.0009), and all CV events (p = 0.0005) with diuretic but not atenolol</td>
</tr>
<tr>
<td>Yurenev⁵⁶</td>
<td>304</td>
<td>Propranolol</td>
<td>Diuretic</td>
<td>4.0</td>
<td>Significantly higher CV mortality with diuretics (p &lt; 0.035)</td>
</tr>
<tr>
<td>DUCTH TIA⁵⁷</td>
<td>1473</td>
<td>Atenolol</td>
<td>Placebo</td>
<td>2.6</td>
<td>No reduction in risk of fatal or nonfatal MI and recurrent stroke with atenolol</td>
</tr>
<tr>
<td>UKPDS³⁸</td>
<td>758</td>
<td>Atenolol</td>
<td>Captopril</td>
<td>9.0</td>
<td>Similar reduction in risk of macrovascular endpoints</td>
</tr>
</tbody>
</table>

(continued)
Table 4. Continued.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients (n)</th>
<th>β-blocker</th>
<th>Comparator</th>
<th>Follow-up (years)</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>STOP259</td>
<td>6614</td>
<td>Atenolol</td>
<td>Enalapril Felodipine</td>
<td>5.0</td>
<td>Reduction in fatal and non fatal stroke, MI and other CV deaths with active treatment vs. placebo (p = 0.003)</td>
</tr>
<tr>
<td>NORDIL60</td>
<td>10,881</td>
<td>Any β-blocker ± Diuretics</td>
<td>Diltiazem</td>
<td>4.5</td>
<td>No difference in the combined incidence of fatal, nonfatal stroke, MI and other CV death; significantly fewer fatal and nonfatal strokes with diltiazem (p = 0.04)</td>
</tr>
<tr>
<td>ELSA61</td>
<td>2334</td>
<td>Atenolol</td>
<td>Lacidipine</td>
<td>3.75</td>
<td>Trend favoring a reduced relative risk of stroke, major CV events and CV and all-cause mortality with lidocaine</td>
</tr>
<tr>
<td>LIFE62</td>
<td>9193</td>
<td>Atenolol</td>
<td>Losartan</td>
<td>4.8</td>
<td>13% greater risk of death and 25% greater risk of fatal or nonfatal stroke with atenolol</td>
</tr>
<tr>
<td>CONVINCE63</td>
<td>16,476</td>
<td>Atenolol</td>
<td>Verapamil</td>
<td>3.0</td>
<td>Similar incidence of CV events between groups (HR 1.02; p = 0.77); non-hemorrhage stroke more common with verapamil (HR 1.54; p = 0.003)</td>
</tr>
<tr>
<td>INVEST64</td>
<td>22,576</td>
<td>Atenolol</td>
<td>Verapamil</td>
<td>2.7</td>
<td>No difference in the first occurrence of death, non fatal MI or nonfatal stroke between groups (10.17 vs. 9.93%)</td>
</tr>
<tr>
<td>ASCOT-BPLA55</td>
<td>19,257</td>
<td>Atenolol</td>
<td>Amlodipine</td>
<td>5.7</td>
<td>Amlodipine reduced the risk of nonfatal MI and fatal CHD (p = 0.105); fatal and nonfatal stroke (p = 0.0003); total CV events and procedures (p &lt; 0.0001)</td>
</tr>
</tbody>
</table>

reported for specific β-blockers, in particular atenolol, often impact on the entire drug class. Importantly there is a gap in transferring knowledge regarding newer β-blockers to practicing doctors. Bridging the gap in disseminating knowledge from reputable clinical guidelines and published studies remains a challenge, particularly with regard to β-blocker use in hypertension. Despite recommendations that β-blockers have a role in hypertension management, many clinicians are influenced by the negative reports associated with β-blockers78. Anecdotal evidence indicates that within Asia, even in hypertensive patients with associated comorbidities (i.e., coronary artery disease (CAD) or HF), there is a reluctance to prescribe a β-blocker. Potential strategies used to address this problem include holding group discussions and providing simplified treatment algorithms. Implementing such strategies is a challenging task, particularly in parts of Asia where there is a need to reach out to more isolated areas to educate and update clinicians.

The authors considered a number of issues regarding the place of β-blockers in current clinical practice which are outlined below:

(1) Is there a role for β-blockade in hypertensive patients? Yes, β-blockade provides effective BP lowering, which is similar on average to all other antihypertensive agents. β-blockers are still an option for the first-line treatment of hypertension.

These statements are supported by the conclusions derived from the reappraisal of the European guidelines on hypertension management8 and the recent meta-analysis comparing antihypertensive drugs in the prevention of cardiovascular disease26. Both publications are consistent in stating that all the five main classes of antihypertensive drugs (i.e., diuretics, BBs, ACEIs, ARBs, and CCBs) have similar BP lowering efficacy. Indeed, trials comparing β-blockers with other antihypertensive agents as first-line treatment showed similar efficacy in terms of lowering BP79,80. While β-blockers should remain a first-line treatment option, in certain conditions or selected patient populations, highly β1-selective β-blockers or those with vasodilating effects may in fact be preferred first-line antihypertensive agents.

(2) Which groups of hypertensive patients would benefit from β-blocker treatment?

- Hypertensive patients with HF
- Hypertensive patients with CAD
- Hypertensive patients with increased sympathetic activity (including many patients with obesity)
- Diabetic patients with hypertension (including patients uncontrolled with other antihypertensives)
• Hypertensive patients with atrial fibrillation with a rapid ventricular rate
• Hypertension in pregnancy (including young women who may become pregnant).

The authors agreed that these patient groups all have compelling indications for \( \beta \)-blocker use. It is worth noting that the ESC guidelines for acute HF recommend continuing \( \beta \)-blockers in patients with acute HF, except in cases of cardiogenic shock and hypotension\(^5\). While there is no clear recommendation regarding \( \beta \)-blocker use in obese patients, the panel agreed that \( \beta \)-blockers are at least not contraindicated in this patient group\(^6^8\). In fact, \( \beta \)-blockers have demonstrated similar efficacy to ACE inhibitors in reducing the risk of micro- and macrovascular events in hypertensive diabetic patients\(^5^8\). However, in the setting of diabetic nephropathy, an ACEI or ARB is preferred; although, \( \beta \)-blockers are not contraindicated in diabetic patients\(^20\).

Due to the lack of conclusive evidence regarding the relationship of \( \beta \)-blockers and the risk of drug-induced new onset diabetes, at this time the authors make no recommendation regarding the use of \( \beta \)-blockers in pre-diabetic patients (e.g., patients with metabolic syndrome and impaired glucose tolerance). However, a recent network meta-analysis of 22 trials involving 143,153 participants showed that there was no significant difference between \( \beta \)-blockers and diuretics in their propensity to be associated with onset of diabetes (\( p=0.30 \))\(^8^1\). Additionally, highly \( \beta_1 \)-selective \( \beta \)-blockers have demonstrated minimal or no effects on metabolic function (e.g., insulin sensitivity) and may therefore have an advantage in this patient population\(^8^2^–8^4\).

Due to the lack of convincing endpoint data comparing the benefits of using highly \( \beta_1 \)-selective \( \beta \)-blockers over other \( \beta \)-blockers no specific recommendations have been made regarding highly \( \beta_1 \)-selective \( \beta \)-blockers. Nonetheless, based on available data for specific BBs, the following can be said: There are positive outcome studies only with metoprolol, bisoprolol, carvedilol and to a limited extent with nebivolol in HF. Meta-analyses have demonstrated the benefit of \( \beta \)-blockers in secondary prevention of CAD, in terms of all-cause mortality, reinfarction, and CAD death\(^8^0,8^5,8^6\), including bisoprolol\(^8^7,8^8\) and carvedilol\(^8^9\). No benefit was demonstrated in trials with alprenolol, atenolol, oxprenolol or xamoterol\(^8^5,8^6\). \( \beta \)-blockers with medium to high intrinsic sympathomimetic activity (ISA) appear to be less effective post-myocardial infarction\(^8^0,8^5\). \( \beta \)-blockers are effective agents in angina pectoris, they reduce anginal symptoms and ischemia\(^8^8,8^5,8^6\). According to the European guidelines on the management of stable angina pectoris\(^9^1\), \( \beta_1 \)-selective agents are preferred due to advantages concerning side-effects and precautions when compared with non-selective \( \beta \)-blockers. The guidelines consider metoprolol, atenolol and bisoprolol as commonly used \( \beta_1 \)-selective \( \beta \)-blockers with good documentation as anti-anginal drugs.

(3) What do you hope to achieve with \( \beta \)-blockade therapy in hypertension?

The authors identified a number of key objectives that can be achieved with \( \beta \)-blockers including: effective BP reduction to \(<140/90 \) mmHg, prevention of ‘new onset’ HF and coronary events and regression of left ventricular hypertrophy. A heart rate (HR) of \(<70 \) bpm is desirable in all hypertensive patients\(^9^2,9^3\), and in patients with established CAD a reduction in HR to \(<65 \) bpm may be preferable\(^9^3\).

The most essential treatment goal in antihypertensive treatment is BP lowering, as inadequately controlled BP is related to the existence or development of other comorbid factors, such as HF.

National guidelines in most Asian countries do not specify HR goals for patients with hypertension\(^2^7–3^4\). However, the panel recognizes the importance of achieving target HR, which may be overlooked when treating hypertension. For instance, clinical experience has shown that while normal BP may be achieved with agents such as dihydropyridine CCBs, increased HR is also often observed\(^8^4\) which may be potentially harmful. Reducing HR may also be beneficial in hypertensive patients with angina pectoris and has recently been shown to be beneficial in a heart failure trial where at least two-thirds of patients were hypertensive (achieved a HR of \(67 \) bpm)\(^9^5\). Higher in-treatment heart rate on serial ECGs was shown to predict greater likelihood of subsequent cardiovascular or all-cause mortality independent of treatment modality, blood pressure lowering, regression of ECG left ventricular hypertrophy (LVH) and changing QRS duration in hypertensive patients with ECG LVH according to a recent report from the LIFE study\(^8^5\).

(4) Dosing considerations for \( \beta \)-blockers in uncomplicated hypertension

\( \beta \)-blockers should be titrated to achieve a target BP of \(<140/90 \) mmHg. The importance of a BP target of \(<140/90 \) mmHg cannot be overstated, particularly in patients with HF in whom an even lower target is desirable. As with the J-curve phenomenon, there have been reports suggesting that aiming for much lower BP levels in hypertensive subjects may no longer be considered beneficial\(^8^6\).

The starting dose in patients with hypertension can be higher than that used in HF and the following doses may be used to initiate treatment in hypertension:

1. Atenolol 50 mg once daily (od)\(^9^7\)
2. Bisoprolol 5 mg od\(^9^8\)
3. Carvedilol 12.5 mg twice daily\(^9^9\)
4. Metoprolol succinate 50 mg od\(^1^0^0\)
5. Nebivolol 5 mg od\(^1^0^1\)

These dosing recommendations reflect common starting \( \beta \)-blocker doses used in Asian patients. These doses are
Table 5. Properties of commonly prescribed β-blockers.²²,²⁵

<table>
<thead>
<tr>
<th>β-blocker</th>
<th>Daily dosage frequency</th>
<th>Half-life (h)</th>
<th>Lipid solubility</th>
<th>Cardioselective</th>
<th>Partial agonist activity (ISA)</th>
<th>Alpha antagonist effect</th>
<th>Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>Once</td>
<td>6–9</td>
<td>Low</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Kidney</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>Once</td>
<td>9–12</td>
<td>Low</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Liver/PTV</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Twice</td>
<td>7–10</td>
<td>Moderate</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Liver</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>Once</td>
<td>3–7</td>
<td>Moderate</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Liver</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>Once</td>
<td>12–19</td>
<td>Low</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Kidney</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Twice</td>
<td>3–4</td>
<td>High</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Liver</td>
</tr>
</tbody>
</table>

ISA, intrinsic sympathomimetic activity.

Table 6. Optimal profile of β-blockade in hypertension.

- Effective lowering of BP to a target of <140/90 mmHg
- Protection over 24 hours
- β₁-selective
- Metabolism does not involve CYP2D6
- Balanced clearance (e.g., half liver/half kidney)
- In patients with established CAD, reduction of HR <65 bpm
- Prevention of ‘new onset’ HF and coronary events

Desirable pharmacological profile of β-blockers in hypertension

Within the β-blocker class, there is wide variation in the structure and pharmacokinetic and pharmacodynamic profiles of individual agents (Table 5)²²,²⁵. The ideal β-blocker for the management of hypertension effectively lowers BP to <140/90 mmHg and HR to ≤70 bpm while providing sustained BP control over 24 hours. Given the complexity of combination treatment for hypertensive patients with comorbidities, it is also desirable to have a β-blocker with a reliable 24-hour action, such as bisoprolol¹⁰⁶ or nebivolol¹⁰⁷, enabling a convenient once-daily dosing to aid patient compliance.

In addition to a relatively long duration of action, the optimal properties of a β-blocker include balanced clearance from the body (Table 6) and greater β₁-selectivity¹⁰⁵.

Certain β-blockers demonstrate altered pharmacokinetics (i.e., extensive metabolism, poor metabolism) based on different cytochrome P450 (CYP) 2D6 genetic polymorphisms.¹⁰⁸ Metoprolol, which is most extensively metabolized by CYP2D6 accounting for 70–80% of its metabolism, exhibits a greater dependency on genetic variation in metabolism compared with agents such as carvedilol or nebivolol leading to large inter-individual variations in plasma concentrations and clinical responses.¹⁰⁸–¹¹²

There is considerable variability in the frequency of individual variants of CYP2D6 between populations. There is not only a marked interethnic difference between the Caucasian and Asian populations but also much variation within the Asian populations. The metabolism of certain β-blockers is particularly dependent on CYP2D6 variants and their effects may vary based on differences in ethnicity.¹⁰⁸,¹¹³,¹¹⁴ A study in healthy subjects demonstrated that Chinese extensive metabolizers appear to have a reduced capacity to metabolize metoprolol compared with Korean or Japanese extensive metabolisers¹¹⁴. This represents a risk of under- or over-dosing in different groups of metabolizers. Propranolol disposition also differs in Chinese subjects with different CYP2D6 genotypes,¹¹⁵ and propranolol was the first β-blocker to be shown to have greater effects in Chinese compared to Caucasian subjects¹¹⁶. Therefore, β-blockers whose metabolic pathways do not involve CYP2D6 may provide a more reliable dose response amongst hypertensive patients.¹¹³,¹¹⁷

In Asia, various ethnic groups may also exhibit different pharmacodynamic responses to β-blockers. Healthy Malay volunteers demonstrated more hypotensive and bradycardic responses compared to those of Indian or Chinese ethnicity.¹¹⁸
Selectivity for $\beta_1$ over $\beta_2$-receptors often improves tolerability since adverse effects mediated by blockade of $\beta_2$-receptors such as bronchoconstriction, vasoconstriction, and changes in lipid and glucose metabolism are less likely to occur compared with non-selective $\beta$-blockers or agents with a lower $\beta_1$-selectivity.$^{105,119}$ $\beta_1$-selectivity of various $\beta$-blockers has been evaluated in different types of in vitro studies using membranes prepared from recombinant cells selectively expressing human $\beta_1$- and $\beta_2$-receptors (Figure 1)$^{120}$ or radioligand binding studies$^{121,122}$. Of the $\beta$-blockers evaluated in one in vitro study, bisoprolol was found to have the highest selectivity for the $\beta_1$-receptor with a $\beta_2/\beta_1$ ratio of 19 (a 19-fold higher affinity for the $\beta_1$-receptor than for the $\beta_2$-receptor)$^{122}$. Atenolol, metoprolol and betaxolol showed lower selectivity for the $\beta_1$-receptor, while propranolol and carvedilol displayed no significant $\beta_1$-selectivity. Some in vitro studies have shown greater $\beta_1$-selectivity with nebivolol compared to bisoprolol$^{123}$ but results vary according to the methods used and other radioligand binding studies in human myocardium revealed greater $\beta_1$-selectivity for bisoprolol compared to nebivolol$^{120}$. Both bisoprolol and nebivolol are highly $\beta_1$-selective; however, based on available data it cannot be definitively determined which of these agents displays the greatest selectivity.

**Conclusion**

Recent meta-analyses support the role of $\beta$-blockers as appropriate first-line treatment of hypertension. $\beta$-blockers have particular clinical utility in specific hypertensive patient subgroups, such as those with comorbidities (e.g., HF or CAD). An effective antihypertensive agent should lower BP to <140/90 mmHg and demonstrate sustained protection over 24 hours. Highly $\beta_1$-selective agents may offer an advantage in terms of efficacy and tolerability especially in patients with prior cardiovascular events. Further appraisal of the efficacy and safety profile of newer $\beta$-blockers will lend support to the current guideline recommendations and encourage increased appropriate use of $\beta$-blockade in current clinical practice within Asia.

**Transparency**

**Funding**
Supported by an educational grant from Merck Serono

**Declaration of financial/other relationships**
B.T. received sponsorship from Abbott Laboratories Ltd, AstraZeneca and Merck Serono. He also received grant/research funding from Abbott Laboratories Ltd, AstraZeneca, Daiichi Sankyo, GlaxoSmithKline, Johnson & Johnson, Merck Serono, Merck Sharp and Dohme, and Roche. He is an advisor to AstraZeneca, Merck Serono, and Merck Sharp and Dohme. He is in the speaker bureau for Abbott Laboratories Ltd, AstraZeneca, Merck Serono, Merck Sharp and Dohme, and Servier. CMRO peer reviewers may have received honoraria for their review work. The peer reviewers on this manuscript have disclosed that they have no relevant financial relationships.

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J.H. is an advisory board member to Merck Serono.

L.P.L. received sponsorship from AstraZeneca and Novartis, and research grant from Servier. He is an advisor to Merck Serono, Merck Sharp and Dohme, AstraZeneca, Eli Lilly, Novo Nordisk, and Novartis. He is in the speaker bureau for AstraZeneca, Merck Sharp and Dohme, and Novartis. He also received honoraria from AstraZeneca, Novartis and PACE.

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F.F. served as a speaker for Merck Serono.

**Acknowledgments**

No assistance in the preparation of this article is to be declared.

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