REVIEW

β-Blockade for Patients with Hypertension, Ischemic Heart Disease or Heart Failure: Where are We Now?

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Abstract: β-blockers are a heterogeneous class of drugs, with varying selectivity/specificity for β_1 vs β_2 receptors, intrinsic sympathomimetic activity (ISA), and vasodilatory properties (through β_2 stimulation, α receptor blockade or nitric oxide release). These drugs are indicated for the management of arterial hypertension, heart failure or ischemic heart disease (IHD; eg angina pectoris or prior myocardial infarction). Most of the benefit of β-blockade in these conditions arises from blockade of the β_1 receptor, and, in practice, the addition of ISA appears to reduce the potential for improved clinical outcomes in people with heart failure or IHD. Aspects of the benefit/risk balance of β-blockers remain controversial, and recent meta-analyses have shed new light on this issue. We have reviewed the current place of cardioselective β-blockade in hypertension, IHD and heart failure, with special reference to the therapeutic profile of a highly selective β_1-adrenoceptor blocker, bisoprolol.

Keywords: beta blockade, hypertension, congestive heart failure, ischemic heart disease, bisoprolol

Introduction

The β-blockers are a heterogeneous class of therapeutic agents. Individual drugs have differing selectivity for β_1 or β_2 receptors, some display limited activation of β receptors (intrinsic sympathomimetic activity), and some additional effects on α adrenoceptors, or promote release of nitric oxide (NO).[1] This review sets out to provide a pragmatic approach to understanding the therapeutic benefits and limitations of β-blockers in people with hypertension, ischemic heart disease (IHD; with or without prior myocardial infarction) or congestive heart failure (CHF) often associated in the same patient.

Hypertension is managed largely in the primary care setting, while treatment for IHD or CHF is often initiated by a cardiologist. Nevertheless, the need for long-term treatment of IHD or CHF means that the primary care physician will have an important role in managing these therapies. It is important, therefore, that physicians are familiar with the initiation and maintenance of β-blocker therapy, whoever initiated it.

Clinical Relevance of Pharmacologic Differences Between β-Blockers
Interactions with β Receptors and Selectivity for β Receptor Subtypes

Most widely-used β-blockers (metoprolol, carvedilol, propranolol, nebivolol, bisoprolol) are inverse agonists at the β_1-adrenoceptor, meaning that a prevailing (but low)

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level of basal, constitutive downstream signal transduction from the receptor is reduced by exposure to the drug, even in the absence of a β receptor agonist.[2] Differences in the level of inverse agonism between β-blockers may affect their pharmacodynamic properties, for example observation more pronounced negative inotropism for metoprolol vs carvedilol.[3] Biased agonism (where a drug may activate part of a post-receptor signalling cascade) represents another way in which β-blockers may differ. For example, such a mechanism involving activation of the β-arrestin pathway has been proposed as a potentially cardioprotective pathway for carvedilol, especially in the setting of CHF.[3]

Individual β-blockers can also be distinguished from one another on the basis of their selectivity for β_1 vs β_2 receptors, and whether or not they have intrinsic sympathomimetic activity (ISA) directed against β_1 or β_2 receptors (Table 1). Table 2 summarizes briefly the typical clinical impact of these mechanisms. The β_1 blockade component induces changes in cardiac function consistent with reduced oxygen demand (particularly reduced heart rate and contractility). ISA directed against the β_1 receptor tends to limit falls in contractility and heart rate, while agents with additional vasodilatory properties tend to reduce blood pressure without increasing heart rate (although carvedilol reduces heart rate[4]) and have less adverse metabolic consequences, compared with selective β_1 receptor blockade.

A pharmacologic study using cloned human β receptors showed that bisoprolol was 14-fold selective for β_1 vs β_2 receptors (similar to xamoterol), compared with 4.7-fold for atenolol, 2.4-fold for acebutolol and 2.3-fold for metoprolol.[5] Non-selective agents may induce some vasoconstriction,

with potentially adverse consequences for the peripheral circulation and risk of bronchospasm in at-risk subjects. The presence of β_2 or β_3 receptors in muscle and the pancreas imply possible effects on glucose or lipid metabolism;[6] unsurprisingly, cardioselective β-blockers have a smaller effect on glycemia.[7] Another systematic review and meta-analysis of studies in patients with heart failure treated with a β-blocker concluded that there was a small excess of hyperglycemia for β-blocker vs placebo (effect size 1.3), but that 83% of presentations with hyperglycemia were not due to β-blockade.[8] There was no difference in general for side-effects in this analysis for selective (bisoprolol, metoprolol, nebivolol) vs non-selective agents (bucindolol, carvedilol). β-blockade was not associated with risk of new-onset diabetes in the randomized NAVIGATOR diabetes prevention trial, during which 16% of patients started new β-blocker therapy.[9]

Selectivity and Metabolic Effects

β-blockers may modestly increase triglycerides and decrease HDL-cholesterol, with little effect on LDL-cholesterol, although the presence of high β_1-selectivity has been shown to ameliorate such effects.[1,10,11] These potential side effects should not present a barrier to the treatment of most patients, especially with a cardioselective drug.

Selectivity and Effects on the Respiratory System

Use of a β_1-selective agent also reduces the risk of bronchospasm in a patient predisposed to this problem by chronic obstructive pulmonary disease (COPD) or asthma.[12,13] This class of drugs has been shown to reduce mortality post-myocardial infarction in patients with COPD (this registry study did not tell us which β-blockers were used, however).[14] Recent randomized[15] and observational[16] studies have suggested that a highly β_1-selective agent (bisoprolol) was better tolerated (fewer side-effects, or CHF and/or COPD exacerbations) than carvedilol in patients with comorbid CHF and COPD. These observations stress the need for individualization of therapy for these complex patients, and highlight the pharmacologic diversity available within the β-blocker class.

Other Mechanisms of β-Blockers

Some β-blockers demonstrate additional mechanistic properties that may influence their pharmacodynamic properties. For example, labetalol and carvedilol are non-selective β-blockers that additionally block α adrenoceptors,

Table 1 Subclasses of β-Blockers

		β_1 Receptor Selectivity?	
		Yes	**No**
Intrinsic sympathomimetic activity?	**Yes**	Xamoterol Acebutolol[a] Celiprolol[a,b] Nevibolol[c]	Pindolol[a] Oxprenolol Labetolol[b] Bucindolol[b]
	No	Bisoprolol Metoprolol Atenolol Esmolol	Propranolol Sotalol Timolol Carvedilol[b]

Notes: Additional vasodilation: [a]Stimulates β_2 adrenoceptors; [b]blocks α adrenoceptors; [c]activates β_3 receptors. See text for references.

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Table 2 Consequences of β-Adrenoceptor Selectivity and Presence or Absence of ISA

Property	Typical Clinical Consequence
Selective blockade of β_1 receptors	Slowed heart rate (chronotropic effect), reduced cardiac contractility, reduced myocardial oxygen consumption; disturbed glucose metabolism may precipitate hyperglycaemia or new-onset type 2 diabetes
Additional blockade of β_2 receptors	Smooth muscle contraction (vasculature and airways) can cause cold extremities and bronchospasm in at-risk patients; potential for metabolic disturbance, as above
Additional stimulation of β_1 receptors (ISA)	Less resting bradycardia, less reduction in cardiac output, less potentially adverse metabolic effects during long-term treatment vs β_1-selective agents
Additional stimulation of β_2 receptors (ISA)	Additional vasodilation: can reduce blood pressure with limited effect on heart rate vs β_1-selective agents
Additional vasodilatory properties	Additional stimulation of α_1 receptors or enhanced nitric oxide release can reduce blood pressure with limited effect on heart rate vs β_1-selective agents; less potentially adverse metabolic effects during long-term treatment vs β_1-selective agents

Note: See text for references. **Abbreviations**: ISA, intrinsic sympathomimetic activity.

theoretically with potential for greater suppression of sympathetic activation and greater vasodilation.[17] Nebivolol activates β^3-adrenoceptors in addition to its selective β_1- vs β_2 blockade, which increases production of nitric oxide, another vasodilatory mechanism.[18] The degree of lipophilicity of a β-blocker may also influence its pharmacologic properties, in terms of penetration of the central nervous system, metabolism/excretion and pharmacokinetics (in general, lipophilic agents tend to have greater pharmacokinetic variability and a greater tendency to drug interactions).[19] Pindolol, propranolol, timolol, and metoprolol are highly lipophilic; bisoprolol, acebutolol, carvedilol and nebivolol are moderately lipophilic; and atenolol, labetalol and nadolol demonstrate low lipophilicity.[19]

Under use of β-Blockers in Patients with Comorbidities

Clinical experience shows that prescription of a β-blocker improves prognosis in patients with comorbid COPD and cardiovascular conditions.[19] Studies have suggested under-prescribing of β-blockers in patients with comorbid conditions, such as COPD or diabetes, however.[20,21]

β-Blockade in the Management of Chronic Congestive Heart Failure
Overview of the Evidence Base

Randomized, controlled trials have evaluated the potential for β-blockade to improve outcomes in people with CHF,[22,23] and principal outcome trials in this area are summarized in Table 3.[24–31] The initial, underpowered Cardiac Insufficiency Bisoprolol Study (CIBIS) trial demonstrated some symptomatic improvements, but not significant outcome benefits.[24] The larger CIBIS II trial demonstrated a significant outcomes benefit for bisoprolol vs placebo.[25] CIBIS III demonstrated similar outcomes following initiation of therapy with bisoprolol or ACE inhibitor, with both used in combination later.[26] Significant improvements in mortality were also seen in placebo-controlled outcome trials with metoprolol (selective β_1-blocker),[27] nebivolol (selective β_1-blocker with additional vasodilating properties),[28] and carvedilol (non-selective β-blocker with additional α blockade).[30,31] A non-selective β-blocker with ISA did not influence cardiovascular outcomes significantly, compared with placebo).[29]

Meta-analyses provide insight into the overall effects of β-blockers in populations with CHF. One recent meta-analysis of 21 randomized trials in a total of 5849 patients with CHF demonstrated relative risk reductions for β-blockade vs placebo of –29% for overall mortality, –29% for cardiovascular mortality, –34% for death from pump failure, and –30% for sudden death.[32] All of these risk reductions were statistically significant. Other meta-analyses support comparable outcome benefits from the use of β-blockers in CHF.[23,33]

The analyses discussed above relate almost exclusively to patients with reduced left ventricular ejection fraction (HFrEF). Importantly, the outcome benefits from β-blockade in HFrEF are seen in all age groups and in both genders.[34] An editorial accompanying this publication notes that older patients and women have been under-

Table 3 Principal Randomized Outcome Trials of β-Blockers with Varying Selectivity Profiles in Patients with CHF or Ischaemic Heart Disease

Trial	Patients	Randomized Treatments	Main Findings
Selective β₁ adrenoceptor blockers			
CIBIS[24] (bisoprolol)	641 patients with CHF of various etiology and NYHA class III–IV; all had LVEF <40%	Bisoprolol vs placebo added to usual care (diuretic and vasodilator, 90% received ACE inhibitor)	Fewer hospitalizations for CHF decompensation on bisoprolol, but no significant differences between groups for mortality outcomes
CIBIS II[25] (bisoprolol)	2647 patients with NHYA class III–IV CHF and LVEF ≤35	Bisoprolol vs placebo added to background therapy of diuretics and ACE inhibitor	Stopped early due to significant mortality benefit on bisoprolol on interim analysis (HR 0.66 [95% CI 0.54 to 0.81], p<0.0001); also benefit for fewer sudden deaths on bisoprolol (HR 0.56 [0.39 to 0.80], p=0.0011)
CIBIS III[26] (bisoprolol)	1010 patients with mild-to moderate CHF and LVEF ≤35; naïve to β-blockers or RAS blocker treatment	Bisoprolol or ACE inhibitor for 6 months followed by both in combination for 6–24 months	Clinical outcomes were similar for the bisoprolol-first and enalapril-first groups
MERIT-HF[27] (metoprolol)	3991 patients with mild-to-moderate CHF	QD Metoprolol CR/XL 12.5 mg (NYHA III–IV) or 25.0 mg (NYHA II) for 1 year	34% relative risk reduction in all-cause death in favour of metoprolol; also reductions in sudden death (by 41%) and death from worsening CHF (by 49%)
Selective β₁-adrenoceptor blockers with additional vasodilator properties			
SENIORS[28] (nebivolol)	2128 patients with LVEF ≤35%	Nebivolol or placebo for 21 months.	Reduced risk of primary composite (CV death or hospitalization) in favour of nebivolol (−14%)
Non-selective β-blocker with intrinsic sympathomimetic activity			
BEST[29] (bucindolol)	2708 patients with HYHA III–IV CHF	Bucindolol or placebo for 2 years	No significant effect on mortality (primary endpoint); modest reductions with bucindolol in secondary endpoints, eg CV death (−14%) or transplantation or CV death (−14%)
Non-selective β-blocker with additional α-blockade			
US Carvedilol Heart Failure Study Group[30] (carvedilol)	1094 patients with mild, moderate or severe CHF	Carvedilol 6.25–50 mg BID (depending on CHF severity) or placebo, for 6 mo (12 mo for patients with mild CHF)	65% relative risk reduction in mortality in favour of carvedilol in the overall population; also 27% reduction in risk of CV hospitalization and 38% reduction in hospitalization or CV death
COPERNICUS[31] (carvedilol)	2289 patients with severe CHF	Carvedilol (target dose 25 mg BID) or placebo for 10.4 mo	35% relative risk reduction for death in favour of carvedilol; also 24% reduction in risk of hospitalization or death

Notes: All risk reductions shown were statistically significant. Follow-up times are averages.
Abbreviations: CHF, congestive heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

represented in randomized CHF trials, leading to suggestions of reduced benefit in these groups.[35] Meta-analyses support the use of β-blockers where indicated, irrespective of age and gender.

There is no randomized outcomes trial of β-blockade in patients with CHF with preserved left ventricular ejection fraction (HFpEF). A study from the OPTIMIZE-HF registry demonstrated reduced mortality with high-dose β-blockade (vs no β-blockade) in patients with HFpEF and heart rate ≥70 bpm.[36] A meta-analysis demonstrated reduced mortality with β-blockade in patients with HFpEF (relative risk 0.78 [95% CI 0.65 to 0.94], p=0.008), with no significant effect of other treatments, including ACE inhibitors, mineralocorticoid antagonists and aldosterone antagonists.[37] Another patient-level meta-analysis found reduced mortality with β-blockers for patients with LVEF <40% or 40–49%, but with no effect

for patients with LVEF ≥50%.[38] Other data suggest adverse effects of β-blockers in this population, however.[39] Further research will be needed before these studies translate into guideline recommendations for the management of HFpEF (see below).

Are There Clinically Relevant Differences Between Individual β-Blockers or Subtypes of β-Blockers with Regard to Management of CHF?

Interestingly, one meta-analysis described above included a comparison between individual agents (and placebo, each added to standard care), as well as for all trials combined.[33] Randomization to placebo was associated with higher risk of the main outcome of mortality, while there were no clear or significant differences between bisoprolol and other agents. The magnitude of the effect of bisoprolol on secondary cardiovascular outcomes was comparable to that seen in the overall pooled analysis; however, it was not statistically significant, presumably due to the reduced number of patients in the analysis.

Six available large evaluations of β-blockers were used in another meta-analysis to investigate the contribution of ISA to effects on outcomes in patient populations treated with β-blockers plus an ACE inhibitor.[1] For β-blockers without ISA, reductions in all-cause mortality vs placebo were –34% for bisoprolol, –34% for metoprolol and –35% for carvedilol. In contrast, among β-blockers with ISA, bucindolol did not reduce mortality significantly while xamoterol more than doubled the mortality rate in people with severe disease. Also, this analysis is complicated somewhat by the inclusion of β-blockers with additional vasodilatory mechanisms (bucindolol, nebivolol and carvedilol; see Table 1).[32] One randomized comparison of the β_1-selective agents xamoterol (ISA) and metoprolol (no ISA) revealed no significant extra benefits associated with ISA for endpoints such as exercise time, quality of life and NYHA classification, casting further doubt on additional benefits from ISA in patients with heart failure.[40]

What the Guidelines Say

The place of β-blockade (alongside ACE inhibition) in the management of CHF is well-established and supported by influential guidelines (Table 4).[41,42] The US guideline stresses the use of "evidence-based" β-blockers, identified

as bisoprolol, metoprolol and carvedilol. European guidelines emphasize the utility of co-prescribing a β-blocker and a RAS blocker at the diagnosis of stable symptomatic CHF.

Take-Home Messages: β-Blockers in CHF Management

The use of β-blockers in patients with stable, symptomatic CHF is supported by randomized, placebo-controlled outcome trials and by major international guidelines, as described above. The use of a highly cardioselective agent may help to reduce the incidence of side-effects due to blockade of other β receptor subtypes during titration to the optimal (ie maximally tolerated) dose within the drug's labelling. The addition of ISA does not add additional outcome benefits to cardioselective β-blockade in CHF. No large, randomized trial has demonstrated superiority on mortality or other outcomes for β-blockers with additional vasodilatory mechanisms, compared with cardioselective β-blockade alone. β-blockers remain underprescribed, especially in patients with comorbidities such as COPD or diabetes.

β-Blockade in the Management of Ischemic Heart Disease: Overview of the Evidence Base

β-blocker therapy reduces mortality post-MI, with larger effects observed in longer-term trials compared with shorter-term trials.[43] Most of the pivotal evaluations of β-blockers were conducted more than two decades ago, however, and usual-care treatment for myocardial ischemia has changed since that time.[44]

A large meta-analysis of observational studies (26 trials, N=863,335) was conducted in patients with IHD who also received the more modern intervention of percutaneous revascularization.[45] This analysis found a reduction in the risk of mortality for patients taking vs not taking β-blocker therapy (OR 0.69 [0.66 to 0.72]). Importantly, subgroup analyses from this large dataset found benefit irrespective of the nature of the IHD (acute coronary syndrome [ACS] or chronic stable angina), or LVEF. The magnitude of benefit increased as the duration of treatment increased. More randomized evaluations of β-blockade, added to the current standard of care for CHF, are needed.[44]

Other clinical trials and meta-analyses have demonstrated the benefit of starting β-blocker therapy early after acute MI.[45,46] One such study showed that starting

Table 4 Summary of Principal International Guideline Recommendations for the Use of β-Blockers in the USA and Europe

	USA (AHA and Other Expert Societies)	Europe (ESC)
Heart failure[41,42]	Use "evidence-based β-blocker" (bisoprolol, metoprolol, carvedilol) with RAS inhibitor (+diuretic as needed) for CHF with reduced ejection fraction	Start together with ACE inhibitor as soon as CHF is diagnosed Initiate at low dose when CHF with reduced ejection fraction is stable; then titrate the dosage slowly Consider use to control heart rate in patients with AF and high heart rate
IHD or ACS[53–56]	Recommended first-line for post-MI with sustained LV systolic function, required (if not contraindicated) for reduced LV systolic function Intravenous treatment on presentation post-MI with refractory hypertension or continuing ischemia Initiate long-term oral treatment with β-blocker within the first 24 hours after onset of ACS (specifically use evidence-based β-blocker [bisoprolol, carvedilol, metoprolol) for NSTEMI Continue during and after hospitalization Where stablilized heart failure is present, use an evidence-based agent (carvedilol, metoprolol or bisoprolol)	Recommended for use in patients with prior MI and asymptomatic LV dysfunction Included in first-line options for patients with chronic IHD, except for patients with low heart rate Intravenous treatment at presentation with STEMI Initiate long-term oral treatment within the first 24 hours after STEMI Initiate early for NSTEMI with continuing symptoms of ischemia
Hypertension[12,13]	Not included among preferred agents for initiation of antihypertensive therapy unless IHD of CHF is present Bisoprolol and metoprolol are preferred cardioselective β-blockers for hypertensive patients with HFrEF Cardediliol preferred over labetalol for β-blockers with α₁-adrenoceptor agonist activity Cardioselective agents preferred for patients with bronchospastic airway disease	Included among preferred agents for initiation of antihypertensive therapy, based on similar outcome benefits in recent meta-analyses β-blockers are among preferred agents for IHD or CHF, or for pregnant women Contraindicated in asthma, high grade sinoatrial or atrioventricular block or bradycardia (<60 bpm) Caution in metabolic syndrome, glucose intolerance, athletes/physically active Include with RAS blocker in regimens for hypertensive patients with prior MI (see above)

Note: All recommendations are for patients without contraindications to β-blockade.
Abbreviations: ACS, acute coronary syndrome; AHA, American Heart Association; CHF, congestive heart failure; ESC, European Society of Cardiology; HFrEF, heart failure with reduced left ventricular ejection fraction; IHD, ischemic heart disease; LV, left ventricular; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction; RAS, renin-angiotensin system.

a β-blocker within one year of MI reduced mortality significantly, with no significant effect on mortality from starting treatment at later time points.[47] The same analysis found that prescription of a calcium channel blocker at any time point did not reduce mortality risk. A small (but randomized) study in 330 patients with coronary artery disease suggested a reduced 1-year incidence of a composite cardiovascular outcome for patients receiving selective β₁-blockade (bisoprolol) vs a short-active calcium channel blocker (nifedipine).[48,49] Outcome benefits with β-blockade are additive to those from an ACE inhibitor in patients with cardiovascular disease, according to a pooled analysis of three outcome trials.[50]

Are There Clinically Relevant Differences Between Individual β-Blockers or Subtypes of β-Blockers with Regard to Management of IHD?

A retrospective study of >200,000 patients with prior MI found little difference in mortality between β₁-selective (atenolol, metoprolol) or non-selective (propranolol) β-blockers.[43] A meta-analysis supported these findings, and also demonstrated less mortality benefit post-MI for β-blockers with vs without ISA, consistent with experience in heart failure, as described above.[43] Indeed, the US guideline for the management of non-ST elevation MI recommends the use of one of three β-blockers without ISA (carvedilol, metoprolol or biso-

prolol). In addition, a large registry study found no difference in 8-month mortality between carvedilol and pooled data from three β$_1$-selective agents (bisoprolol, metoprolol, nebivolol) among patients who underwent coronary revascularization for acute MI.[51] These data suggest limited benefit for additional vasodilator properties.

What the Guidelines Say

Once again, outcome benefits with β-blockade for patients with prior MI are proven beyond doubt, and major guidelines recommend that this treatment is given early in the absence of contraindications such as acute heart failure or risk of cardiogenic shock, etc. (Table 4).[12,13,41,42,52–57] Influential guidelines recommend β-blockade as first-line therapy for stable coronary artery disease (Table 4).[32,33] All guidelines recommend appropriate anti-ischemic treatment, or treatment to reduce the risk of subsequent MI, such as RAS blockers, antiplatelet agents, statins, anticoagulants, etc., for defined subtypes of patients.

It has been assumed that the dose of a β-blocker should be titrated to the levels used in randomized outcome trials to ensure effective secondary prevention of MI. For example, an expert review from the UK recommended that

> a cardioselective beta-blocker (for example, bisoprolol) should be commenced in all patients once hemodynamically stable and up-titrated to a maximum tolerated dose.[58]

However, recent registry data suggested that the dose level achieved for β-blocker therapy had only limited impact on mortality post-acute MI, with all β-blocker doses associated with improved survival relative to no β-blockade.[59] Reduced heart rate is associated with improved prognosis in patients with heart failure.[60] ESC guidelines for the management of chronic IHD include a target for resting heart rate of 55–60 bpm,[57] and US guidelines have recommended a target for heart rate of 50–60 bpm in these patients.[61] The ESC guideline recommends use of low-dose β-blockade (or a non-dihydropyridine calcium channel blocker) in patients with low blood pressure.[57]

Take-Home Messages: β-Blockers in IHD Management

The benefits of β-blockade post-acute MI are clear, as for the management of CHF, described above. Clinical evidence and guideline recommendations favour early application of β-blockers after MI, where patients are hemodynamically stable, as this approach appears to have

greater long-term outcome benefits. How long to continue β-blocker therapy, and what dose to aim for, remain areas of controversy. The registry study that found outcome benefits for any dose of β-blocker compared with no β-blocker in a post-MI population is especially interesting. These data suggest that any tolerated β-blocker dose is likely to be of benefit for this population, within individualized care for a patient with prior MI with the use of higher doses limited by side-effects, especially if a clinically significant reduction in heart rate is achieved.[56,58,60]

β-Blockade in the Management of Hypertension
Rationale and Overview of the Evidence Base

Meta-analyses show that treatment with a β-blocker reduces the risk of adverse cardiovascular outcomes relative to placebo in people with hypertension.[62,63] Some meta-analyses suggested that the effect on cardiovascular outcomes was modest considering the reductions of blood pressure achieved, and inferior to that seen with other antihypertensive classes (particularly stroke), although the heterogeneity of β-blockers as a therapeutic class may have hindered effective meta-analysis.[62–66]

A more recent and very large meta-analysis (147 trials incorporating 464,000 patients with hypertension) found that β-blockade reduced CHD events by 11% and stroke events by 19%, vs placebo (trials of β-blockade for reduction of IHD events in patients with a history of this condition were excluded from this analysis).[67] These risk reductions were similar to those achieved by use of other classes of antihypertensive agents. The efficacy of β-blockers for preventing CHD events in patients with hypertension (with or without cardiovascular disease) depended largely on the blood pressure reduction achieved (apart from a minor benefit for calcium channel blockers on stroke reduction that may arise from greater lowering of central blood pressure). The authors suggested that previous demonstrations of lack of efficacy of β-blockers on outcomes in previous analyses was due to lack of statistical power or to the use of atenolol. Other meta-analytic evidence suggested that the efficacy on outcomes was similar for different antihypertensive classes for equivalent decreases in blood pressure.[68]

The effects of the major antihypertensive classes on blood pressure and reductions in the risk of adverse cardiovascular outcomes appear to be similar in people with and without diabetes.[69]

Are There Clinically Relevant Differences Between Individual β-Blockers or Subtypes of β-Blockers with Regard to Management of Hypertension?

The phenomenon of sympathetic overdrive has received attention recently, with observations that the elevated sympathetic nervous activation can influence outcomes, particularly in younger, obese subjects or in smokers.[70,71] Moreover, different antihypertensive drug classes may reduce sympathetic activation (β-blockers, RAS blockers), have no effect (long-acting calcium channel blockers) or increase it (diuretics, short-acting calcium channel blockers).[70] The use of β-blockade has been shown to be at least as effective as other antihypertensive agents for improving outcomes in younger hypertensive subjects.[64] Smoking increases catecholamine levels markedly; in one study conducted four decades ago, administration of a non-selective β-blocker (propranolol) to healthy volunteers increased blood pressure during smoking, while a β_1-selective agent (atenolol) did not.[72] The inclusion of non-smokers and smokers together in hypertension trials will potentially mask a greater effect of β-blockade on blood pressure in non-smokers.[73]

A β-blocker with additional α-adrenoceptor blockade may provide additional suppression of sympathetically-mediated vasoconstriction, relative to a β-blocker without this property.[74] Carvedilol represents the most well-known β-blocker with this property, but lacks β_1 selectivity (see above). High inter-individual variations in the pharmacokinetics of carvedilol (along with metoprolol, nebivolol and propranolol) have been observed, however, when compared with other β-blockers (bisoprolol, atenolol, sotalol, labetalol, nadolol, pindolol).[75] It would be interesting to compare the clinical effects in hypertension of β-blockers with and without additional α-blockade, where neither agent was potentially limited by complex pharmacokinetics.

What the Guidelines Say

There is divergence of recommendations for the management of uncomplicated hypertension among major guidelines.[12,13] European guidance noted the results of recent meta-analyses that have, to a large extent, refuted earlier findings of a lack of efficacy with β-blockers compared with other therapies (see above), and has retained β-blockers among the five antihypertensive classes suitable for initiation of pharmacotherapy for the management of uncomplicated primary hypertension. The current US hypertension guideline does not include β-blockers

among preferred first-line antihypertensive agents, citing less effect on damage to target organs vs renin-angiotensin system (RAS) blockers, tolerability issues, and smaller effect on stroke prevention, in particular.[12]

Take-Home Messages: β-Blockers in Hypertension Management

Recent large and well-designed meta-analyses, described above, have largely allayed concerns that β-blockers are less effective than other antihypertensive classes: these analyses have shown that blood pressure reduction per se is the main determinant of outcome in this population, with similar effects on outcomes between different antihypertensive drug classes. Nevertheless, the place of β-blockade in the management of primary hypertension has remained controversial, with important differences in recommendations for their use between major international guidelines. Guidelines agree on the place of β-blockers in the management of hypertension complicated by comorbid IHD or CHF.

Potential for β-Blockade in the Management of Atrial Fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia in Western countries, with a prevalence of about 1–4%, and a somewhat lower prevalence of about 0.5–2% in Asia.[76] The prevalence of AF is increasing in all age groups and in both genders.[77] Population risk factors for AF include male gender, hypertension, valvular disease, diabetes, MI and CHF.[78] Perioperative AF is also a common complication of cardiac surgery.[79] Even transient AF associated with a hospital procedure is a risk factor for subsequent stroke.[80]

Recent US guidelines support the use of β-blockade to slow the ventricular rate in patients with ACS who develop AF, in the absence of contraindications to this treatment.[81] The European Society of Cardiology supports the use of a β-blocker (preferably a cardioselective agent) as first-line pharmacologic therapy for people with stable HFrEF and AF.[82] Finally, influential guidelines also support use of a β-blocker (not sotalol) as initial therapy for a patient indicated for pharmacological control of the ventricular rate in AF.[82,83]

Conclusions

Selective β_1-adrenoceptor blockade remains an important cardiovascular therapy, with a strong evidence base for reducing the risk of adverse cardiovascular outcomes.

Guidelines continue to disagree on the place of β-blockade within the first-line treatment of hypertension, although more recent meta-analyses suggest that the efficacy of antihypertensive treatments for preventing future cardiovascular events depends mostly on the magnitude of blood pressure reduction achieved rather than on the properties of individual classes of antihypertensive agents. The guidelines do agree that there continues to be a strong evidence base for the use of selective β1 receptor blockers, especially without ISA, for the management of hypertension complicated by IHD or heart failure. There is no compelling evidence for a clinically relevant influence of differences in other properties of β-blockers, such as the degree of inverse agonism, lipophilicity etc., although this is hampered by a lack of head-to-head outcome trials between members of the β-blocker class.

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Disclosure

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