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REVIEW ARTICLE

β-blockers are not all the same: pharmacologic similarities and differences, potential combinations and clinical implications

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ABSTRACT

β-blockers are a heterogeneous class, with individual agents distinguished by selectivity for β_1- vs. β_2- and α-adrenoceptors, presence or absence of partial agonist activity at one of more β-receptor subtype, presence or absence of additional vasodilatory properties, and lipophilicity, which determines the ease of entry the drug into the central nervous system. Cardioselectivity (β_1-adrenoceptor selectivity) helps to reduce the potential for adverse effects mediated by blockade of β_2-adrenoceptors outside the myocardium, such as cold extremities, erectile dysfunction, or exacerbation of asthma or chronic obstructive pulmonary disease. According to recently updated guidelines from the European Society of Hypertension, β-blockers are included within the five major drug classes recommended as the basis of antihypertensive treatment strategies. Adding a β-blocker to another agent with a complementary mechanism may provide a rational antihypertensive combination that minimizes the adverse impact of induced sympathetic overactivity for optimal blood pressure-lowering efficacy and clinical outcomes benefit.

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Introduction

The clinical use of β-adrenergic receptor antagonists (β-blockers) began nearly 60 years ago with the invention of propranolol by Black et al.[1] The initial therapeutic use was for angina pectoris, but soon extended to managing hypertension and other cardiovascular disorders[2]. Propranolol is a non-selective β-blocker that blocks β-adrenoceptors indiscriminately. Following its introduction, different subtypes of β-adrenergic receptors were discovered in the heart, vasculature and elsewhere; and research to develop specific receptor subtype blockers grew apace, along with elucidation of variations in their molecular pharmacology and the clinical applications[2].

Currently available β-blockers are a heterogeneous class of therapeutic agents and significant intra-class differences in individual drug selectivity, lipophilicity, and potential for partial agonism can inform the choice of β-blocker for a patient with one or more of a range of comorbid conditions[3]. This article reviews the clinical pharmacology of β-blockers, with an emphasis on the difference between members of this heterogeneous class. With regard to hypertension treatment, the use of guideline-recommended combinations of two or more antihypertensive agents has been reviewed in an accompanying article and we will also consider the relevance of variations in β-blocker pharmacology for their use within combination regimens. Other accompanying articles in this series explore the implications of the properties of individual β-blockers for tolerability and safety[4], and the management of hypertension[5], coronary heart disease[6], and heart failure[7].

β-adrenergic receptors: where they are and what they do

Table 1 provides an overview of the actions of β_1-, β_2- and β_3-adrenoceptors in the heart, vascular smooth muscle, the bronchial airways and the kidney[8–15]. More detail on the function of each β-receptor subtype is given below. However, this section focuses mainly on those tissues most relevant to the efficacy and tolerability of β-blockers.

The β_1-adrenoceptor is expressed mainly in the heart, kidney and adipocytes. Activation of cardiac β_1-adrenoceptors, mainly by noradrenaline released by sympathetic nerves or adrenaline from the adrenal cortex, activates adenylate cyclase, inducing an increase in cyclic adenosine monophosphate in cardiac myocytes. This, in turn, promotes the influx of extracellular calcium into cardiomyocytes, resulting in increases in contractility (and oxygen consumption) and heart rate (*via* increases in conduction velocities in the sinus node pacemaker and atrioventricular nodal tissues). The intensity of β_1-adrenoceptor stimulation is regulated by the balance between the sympathetic and parasympathetic nervous systems, modulated by baroreceptors located in the carotid sinus[16]. A sudden increase in autonomic and hormonal cardiac β_1-adrenoceptor stimulation constitutes an important part of the "fight or flight" reflex, where additional

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Table 1. Overview of key actions of β_1- and β_2-adrenoceptors.

	β_1-adrenoceptors	β_2-adrenoceptors	β_3-adrenoceptors
Myocardium	↑ Contractility and heart rate ↑ Myocardial necrosis/apoptosis	↓Myocardial necrosis/apoptosis	Variable effects on contractility[a] Limited evidence for positive chronotropy
Bronchial smooth muscle	–	↑ Bronchodilation	↑ Bronchodilation (varies with species, uncertain in humans)
Vascular smooth muscle	–	↑ Vasodilatation	↑ Vasodilatation
Kidney	↑ Renin release	Possible nephroprotective effect	↑ Activity of water-solute transporters
Adipocytes	↑Lipolysis	↑ Lipolysis	↑ Lipolysis

Notes: Possible decrease in contractility mediated *via* a nitric oxide-related mechanism, or increase in contractility associated with increased intracellular cAMP production. Compiled from information presented in references[8–15].

blood flow to muscles from enhanced cardiac performance contributes to heightened ability to escape from an imminent threat[17]. The density of β_1-adrenoceptors in the heart outnumbers that of β_2-adrenoceptors (see below) by about 4:1, although this ratio may reduce to as low as 1:1 in the setting of HFrEF or certain other cardiovascular diseases[11].

The β_2-adrenoceptor is expressed mainly in the vasculature and smooth muscles of the airways, as well as, to some extent, in the heart and a range of other cell types. Activation of β_2-adrenoceptors causes relaxation of smooth muscles through cyclic adenosine monophosphate-dependent mechanisms that involve activation of protein kinase A with reduction of calcium influx, sequestration and storage of intracellular calcium (in contrast to β_1-adrenoceptor effects in cardiomyocytes, as described above)[11]. Accordingly, stimulation of β_2-adrenoceptors may cause vasodilatation, reduction of blood pressure (BP) and reflex tachycardia. Activation of β_2-adrenoceptors also increases energy expenditure and improves glucose homeostasis[18]. On the other hand, blockade of β_2-adrenoceptors causes vasoconstriction (with reduced blood flow to the extremities), bronchoconstriction and disturbances of metabolic function[19,20]. Adrenaline activates β_2-adrenoceptors more effectively than noradrenaline and is the main contributor to β_2-adrenoceptor tone under physiological conditions.

The β_3-adrenoceptor is a relatively new addition to the knowledge base of β-adrenergic function, having been cloned in 1989. Activation of β_3-adrenoceptors increases the production of nitric oxide, which reduces cardiac contractility and induces vasodilatation in the peripheral arteries; these actions may oppose overactivation of either β_1- or β_2-adrenoceptors, which are potentially cardioprotective mechanisms[14,15,19]. Interestingly, the expression of β_3-adrenoceptors is increased in the failing heart[21], and experimental evidence suggest that upregulation of β_3-adrenoceptors in the heart in the setting of chronic heart failure may promote positive inotropism[22]. In addition, they are able to activate brown adipose tissue as well as inducing browning of white adipose tissue, with associated increased thermogenesis and energy expenditure[23]. Consequently, research interest in the potential of β_3-adrenoceptor agonists as anti-obesity agents has burgeoned.

Pharmacologic properties of individual *β*-blockers

Administration and pharmacokinetics

Posology, administration and elimination

Table 3 summarizes key aspects of administration, pharmacokinetics and elimination of commonly used β-blockers, including β_1-adrenoceptor selective agents (bisoprolol, metoprolol and atenolol), agents with additional vasodilatory properties (nebivolol, carvedilol), and the prototype non-selective β-blocker, propranolol, based on information contained in labelling and hypertension management guidelines from three large regions of the world (Europe, the USA and China)[24–27]. The long plasma half-life of bisoprolol allows for once-daily dosing; pharmacodynamic studies confirm its effective β-blockade throughout the 24-h dosing interval[28]. In contrast, a randomized study in patients with angina pectoris found that reductions in maximal heart rate and the double-product of heart rate and BP were more attenuated with atenolol versus nadolol, implying a less than 24-h true duration of action of atenolol[29]. The elimination half-lives of metoprolol, carvedilol and propranolol are all shorter than that of bisoprolol. Nebivolol is metabolized by hepatic cytochrome CYP2D6 enzymes, and is sensitive to genetic polymorphisms that are expressed as "fast/extensive" or "slow/poor" metabolizer phenotypes. Accordingly, the bioavailability and plasma levels of nebivolol can exhibit substantial individual variations[30]. The presence of active metabolites also complicates the pharmacokinetics of nebivolol, carvedilol and propranolol.

Bisoprolol undergoes almost complete absorption *via* the gut, and its balanced renal and hepatic elimination routes limit the impact of functional organ impairment on drug exposure[31,32]. This contrasts with other β-blockers that are either eliminated mainly by the kidney (atenolol) or liver (metoprolol, nebivolol, carvedilol, propranolol), for which dose reductions become obligatory in the setting of significant dysfunction of these organ systems. Finally, while there is little first-pass metabolism with bisoprolol, the extensive hepatic metabolism or excretion of metoprolol, nebivolol, carvedilol and propranolol reduce their bioavailability substantially.

Inter-individual variation in pharmacokinetics

The complexity of the pharmacokinetic profiles of individual β-blocker drugs (Table 2) is directly related to the predilection for inter-individual variability in drug exposure, which has been quantified in a systematic review[33]. Figure 1 shows the proportions of studies with β-blockers that demonstrated high variability in the respective areas under the drug concentration-time curve (a standard measure of drug exposure); high variability being defined as a coefficient of variation that exceeds 40%. Focusing on the β-blockers listed in Table 3, pharmacokinetic variability was substantial for all β-blockers, with the exception of bisoprolol and atenolol.

Drug-drug interactions

β-blockers, in general, are susceptible to important drug-drug interactions. For example, drug concentrations may increase leading to excessive reductions in heart rate and/or myocardial contractility when β-blockers are used in combination with non-dihydropyridine calcium channel blockers (CCB), centrally-acting antihypertensive agents, or amiodarone, which may produce adverse events in patients with pre-existing myocardial dysfunction[34]. Combination with a dihydropyridine CCB or non-steroidal anti-inflammatory enhances the hypotensive effect, which may be the intended effect when prescribing β-blocker-CCB combination antihypertensive therapy[26]. Drug-drug interactions for individual β-blockers depend largely on their metabolism. For example, combination of metoprolol or nebivolol with another agent extensively eliminated *via* the hepatic CYP2D6 pathway is likely to increase exposure to both drugs. Non-selective β-blockers increase blood glucose and are thus likely to oppose the effect of antihyperglycaemic medications, while highly β_1-adrenoceptor selective agents are much less likely to do so[31].

Table 2. Subclasses of β-blockers.

		β_1 receptor antagonist selectivity?	
		Yes	No
Intrinsic sympathomimetic activity?	No	Bisoprolol	Propranolol
		Metoprolol	Sotalol
		Atenolol	Timolol
		Esmolol	Carvedilol[a]
	Yes	Xamoterol	Pindolol[b]
		Acebutolol[b]	Oxprenolol
		Celiprolol[a,b]	Labetolol[a]
		Nebivolol[c]	Bucindolol[a]

Notes: Additional vasodilation: [a]blocks α-adrenoceptors; [b]stimulates β_2-adrenoceptors; [c]activates β_3-adrenoceptors. Reproduced from reference[31] according to Creative Commons Attribution – Non Commercial v3.0 Licence (http://creativecommons.org/licenses/by-nc/3.0/).

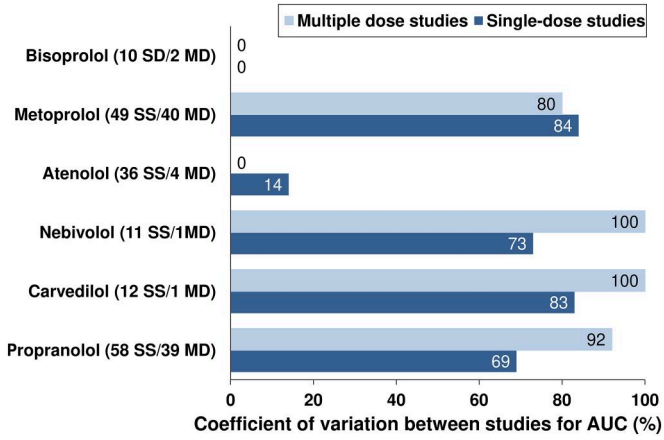

Figure 1. Variability of exposure to different β-blockers from a systematic review of pharmacokinetic studies. Information in parentheses next to drug names is (number of studies involving single dose [SS] administration/number of studies involving multiple dose [MD] administration to pharmacokinetic steady state). AUC, area under the plasma concentration-time curve. Note that the 100% values for nebivolol and carvedilol are based on a single available study. Drawn from data presented in reference[33].

Table 3. Administration, key pharmacokinetic parameters and administration of some commonly used β-blockers.

Drug	Posology	Plasma half-life (h)	Bioavailability	Absorption from the GO tract	Elimination	Active metabolites?
Bisoprolol[a]			90%	Almost complete	Evenly *via* renal excretion and hepatic metabolism	No
Europe	5–20 mg QD	10–12				
China	*2.5–10 mg QD*	*10–12*				
USA	5–20 mg QD	9–12				
Metoprolol[a]			50%	Complete	Primarily *via* hepatic CYP2D6	No
Europe	50–200 mg QD[d]	1–9[e]				
China	*50–100 mg QD*	*3–4*				
USA	25–200 mg QD	3–7				
Atenolol[a]			About 50%	About 50%	Primarily *via* the kidney	No
Europe	50–100 mg QD	6–10				
China	*12.5–50 mg BID*	*6–10*				
USA	50–100 mg QD	6–7				
Nebivolol[a,b]			12–100%[e]	Complete	Extensive hepatic metabolism[f]	Yes
Europe	2.5–5 mg QD	10–50[f]				
China	*5 mg QD*	*12–19*				
USA	5–40 mg QD	12–19				
Carvedilol[c]			25%	Complete	Mainly *via* bile and faeces	Yes
Europe	12.5–50 mg BID[f]	6				
China	*12.5–50 mg BID*	*6–7*				
USA	6.25–25 mg BID	7–10				
Propranolol			25%	Complete	Primarily *via* hepatic metabolism	Yes
Europe	80–160 mg BID	2				
China	*20–90 mg BID*	*2–3*				
USA	40–120 mg BID[g]	3–6				

[a]Selective for β_1-adrenoceptors.
[b]Also stimulated production of nitric oxide.
[c]Also blocks α_1-adrenoceptors.
[d]Dose must not exceed 400 mg.
[e]Average 3.5 h.
[f]According to a "fast metabolizer" or "slow metabolizer" phenotype arising from genetic variation in the hepatic cytochrome CYP2D6 system. BID administration is recommended for patients with angina pectoris.
[g]Dose can be as high as 640 mg/day if required. Administration: BID = twice-daily; QD = once daily. Values for half life and bioavailability are approximate. Abstracted from information provided in European Summaries of Product Characteristics (www.medicines.org.uk), US Prescribing Information (www.fdaaccessdata.gov) and references[24,25]. Recommended dosages may vary between those shown here and documents from other regulatory authorities or expert societies or between different formulations of the same drugs.

Properties influencing interactions with adrenoceptors

Receptor selectivity

Table 2 summarizes the receptor selectivity of common β-blockers used in clinical practice[31]. Propranolol, sotalol, timolol, carvedilol, pindolol, oxprenolol, labetolol, and bucindolol block both β_1- and β_2-adrenoceptors. In contrast, bisoprolol, metoprolol, atenolol, xamoterol, acebutolol, celiprolol, nebivolol and esmolol (an agent with ultra-short duration of action that is used exclusively in specialized care settings) are cardioselective for the β_1- vs. β_2-adrenoceptor. Among the latter, the level of β_1-adrenoceptor selectivity in individual agents differs. In an experiment that used cloned human β-adrenoceptors to measure the β_1- vs. β_2-adrenoceptor selectivity of different β-blockers[35], bisoprolol and xamoterol were shown to be the most selective for β_1-adrenoceptors (14-fold selective), followed by atenolol (4.7-fold selective), acebutolol (2.4-fold selective), and metoprolol (2.3-fold selective). In another study that assessed the clinical pharmacodynamic effects of various β-blockers on terbutaline (a selective β_2-adrenoceptor agonist)-induced tachycardia, nebivolol and bisoprolol were found to be more β_1-selective than atenolol, especially when the higher dose of atenolol (100 mg) was used[36]. The higher recommended dose of atenolol (100 mg) has been described as blocking about 25% of β_2-adrenoceptors, compared with effectively zero for the higher recommended dose of bisoprolol (10 mg)[30]. Comparisons of β_1-selectivity between bisoprolol and nebivolol have been mixed, showing higher β_1-selectivity for nebivolol in studies on human myocardium[37,38], but higher β_1-selectivity for bisoprolol in a study that used cloned β-adrenoceptors[39].

A re-analysis of a published meta-analysis suggested that atenolol may be less effective than other β-blockers in reducing the risk of adverse cardiovascular outcomes in patients with hypertension, although the reasons for this finding remain unclear[40]. A relatively high dose of carvedilol (non-cardioselective β-blocker with additional α_1-adrenoceptor blockade) was found to confer mortality benefit versus a less potent dose of metoprolol (cardioselective β-blocker) in patients with HFrEF in the Carvedilol Or Metoprolol European Trial (COMET)[41]: this finding emphasizes the importance of considering equipotent dosages when comparing drugs with different β-adrenoceptor selectivity.

A recent study applied the concept of kinetic selectivity to investigate ways in which individual β-blockers interact with cloned β_1- and β_2-adrenoceptors expressed in cultured cells[42]. Among cardioselective β-blockers, the rate of association of bisoprolol with the β_1-adrenoceptor was slower compared with either metoprolol or atenolol. However, bisoprolol's rate of dissociation was also much slower than either drug, resulting in a longer overall average time of occupation of the β_1-adrenoceptor. Another part of this study involved incubating cells containing β_1- or β_2-adrenoceptors at concentrations of β-blockers that were 30-fold higher than their individual K_d values (the concentration at which half the target receptors become occupied). At this high relative concentration, all β_1-adrenoceptors were effectively occupied by bisoprolol, metoprolol, atenolol or carvedilol; occupancy rates of β_2-adrenoceptors were 95–100% for all agents except for bisoprolol with about 55% occupancy. When the β-blockers were removed, bisoprolol dissociated completely from β_2-adrenoceptors within seconds, compared with about 40 min for its dissociation from β_1-adrenoceptors. Dissociation rates of metoprolol and atenolol from both β_1- vs. β_2-adrenoceptors were more similar, while carvedilol dissociated from β_1-adrenoceptors more quickly than from β_2-adrenoceptors. These experimental findings underpin the observed clinical differences in β receptor selectivity among individual members of the β-blocker class.

Blockade of β_2-adrenoceptors accounts for important adverse effects of β-blockers, including bronchoconstriction, adverse effects on glycaemia and erectile dysfunction[31]. A highly β_1-selective β-blocker such as bisoprolol has little or no effect on the peripheral vasculature at full β-blocking doses, unlike non-selective or less selective agents[43]. Similarly, cardioselective β-blockade has little effect on airway smooth muscle (these drugs have no absolute contraindication in people with obstructive airways disease)[44], glucose metabolism[45,46], or erectile performance[47] (further details on these issues are available from an accompanying article in this series[4]). A nocebo effect may apply to some reports of erectile dysfunction with β-blockers, likely due to patients being briefed to expect this side-effect[48]. These observations are important, as there is evidence that β-blockers are underused in populations with airway diseases or diabetes, with patients denied the outcome benefits associated with the use of these drugs[49]. Finally, reports of increased blood pressure variability with β-blockers vs. other antihypertensive classes may relate less to cardioselective or vasodilating β-blockers, compared with non-selective β-blockers[50–53]. Most people with hypertension will receive antihypertensive combination therapy[26,27] (see below) and reductions in blood pressure variability induced by calcium channel blockers persist when other antihypertensive agents are added[52].

Lipophilicity

β-blockers differ considerably in their physical chemistry. Lipophilic (oil-soluble) β-blockers are more likely than hydrophilic (water-soluble) β-blockers to enter the central nervous system (CNS) and exert their pharmacological actions there. Pindolol, timolol and propranolol are highly lipophilic; nadolol, atenolol and labetalol are highly hydrophilic; and metoprolol, bisoprolol, nebivolol, acebutolol and carvedilol exhibit moderate lipophilicity/hydrophilicity[54]. Treatment with β-blockers has been reported to induce neuropsychiatric side-effects in some patients, raising the hypothesis that the degree of lipophilicity of a β-blocker might be predictive of the risk of CNS side-effects[54]. However, this hypothesis was refuted by a meta-analysis, which showed that the incidence of side-effects that were possibly related to drug actions in the CNS (depression, fatigue, sexual dysfunction) during treatment with a β-blocker was not related to the degree of lipophilicity of the drugs prescribed[55].

Inverse agonism

β-adrenoceptors, like many G-protein coupled receptors, maintain a low level of intracellular signal transduction without an agonist[56]. An inverse agonist is a molecule that binds to the receptor and stabilizes it in such a way that the level of constitutive activity is reduced, compared with the unbound receptor, i.e. an inverse agonist has the opposite action to an agonist[57]. Most ligands at both β_1- and β_2-adrenoceptors demonstrate at least some inverse agonism. This phenomenon reduces the rate of desensitization of receptors, and increases their density on the heart or vascular cell surface[57]. Some differences in the inverse agonist activity of β-blockers have been described, with higher inverse activity for atenolol, metoprolol, nebivolol and bisoprolol than for carvedilol[39]. However, evidence for a true clinical benefit associated with the presence or absence of inverse agonism at the β_1-adrenoceptor is lacking, and other aspects of β-blocker pharmacology are likely to exercise more importance in defining the therapeutic and clinical profiles of these agents.

Biased signal transduction

Classical receptor theory dictates that a receptor exists in one of two fundamental states: quiescent (inactive) or stimulated (active). Biased signal transduction refers to the observation that two ligands at the same receptor can activate different intracellular transduction pathways[58]. In the case of β_2-adrenoceptors, differential activation by different drugs of the classical G-protein coupled signal cascade and the β-arrestin pathway has instigated much research in recent years[58]. For example, carvedilol acts at the β_2-adrenoceptor as an inverse agonist at the classical G-protein-coupled signal transduction pathway and as a partial agonist at the β-arrestin pathway[59,60]. Nebivolol, usually described as a β_1-adrenoceptor antagonist with additional vasodilator properties, also partially activates the β-arrestin pathway downstream of the β_2-adrenoceptor[59,60]. Biased signal transduction at β-adrenoceptors has also been described for cardioselective β-blockers, including bisoprolol[61] and metoprolol[62].

Variations in the level of biased signal transduction have been cited as an important source of the broad pharmacologic heterogeneity of this class[59,60]. While the impact of the activation of β-arrestins on downstream signalling from G-protein coupled receptors is complex and pleiotropic, potential benefits from exploiting this pathway have been proposed for cardiovascular and numerous other fields of medicine[58]. Further research will be required to translate this potential into proven clinical benefit.

Other sympathoinhibitory mechanisms

β-blockers reduce the activity of the sympathetic nervous system by inhibiting presynaptic β_1-adrenoceptors and thus reducing the release of adrenaline and noradrenaline (epinephrine and norepinephrine), in addition to interacting with postsynaptic β-adrenoceptors in the heart, vasculature and elsewhere[63]. Other mechanisms are at play, however, which vary between individual agents and contribute to the heterogeneity of the β-blocker class[63,64]. For example, non-lipophylic β-blockers are unable to enter the brain and reduce sympathetic nerve traffic there (see the section on lipophilicity, above). Effects of β-blockers on baroreflex function also vary[63]. Polymorphisms in β_1-adrenoceptors can also modulate the clinical response to β-blocker treatment in heart failure[64]. Finally, a study in humans with heart failure treated with carvedilol or metoprolol demonstrated lower levels of coronary sinus noradrenaline (a marker of the intensity of cardiac sympathetic innervation) and density of β_1-adrenoceptors on the myocardium with carvedilol[65].

Dialyzability

Patients on haemodialysis have been largely excluded from clinical trials, despite as many as 80% of this population having comorbid hypertension[66]. One study found that 64% of the United States Medicare population receiving dialysis for end-stage renal dysfunction were receiving a β-blocker[67]. Among β-blockers, atenolol and metoprolol are highly dialysable, i.e. cleared effectively from the circulation by dialysis; bisoprolol is moderately dialysable; and carvedilol, nebivolol and propranolol exposure are little affected by dialysis[68].

β-blockers and peripheral vasodilatation

Intrinsic sympathomimetic activity (ISA) at the β_1-adrenoceptor

Some β-blockers demonstrate ISA, acting as partial agonists at the β_1- or β_2-adrenoceptor (Table 2). Non-selective β-blockers with ISA may activate β_2-adrenoceptors and induce peripheral vasodilatation[69]. For cardioselective β-blockers with ISA, the pharmacodynamic reductions of heart rate and contractility may be attenuated, compared with those without ISA; for non-selective β-blockers, ISA may limit the potential for adverse effects or coldness of the extremities[50]. However, there is no compelling evidence that ISA directed at the β_1-adrenoceptor confers any clinical outcome benefit; in fact, the opposite may be true: in a meta-analysis, the presence of ISA reduced the clinical benefit of β-blockers in patients with stable CHD[70]. In a placebo-controlled study, xamoterol (a β-blocker with pronounced β_1-adrenoceptor-directed ISA) induced modest improvements in dyspnoea severity, with minimal effects on other symptoms, in patients with severe symptomatic HFrEF (New York Heart Association [NYHA] class III–IV)[71]. Importantly, patients randomized to xamoterol had a more than two-fold higher mortality rate within 100 days of randomization compared with the control group (9.1% vs. 3.7%, $p = .02$). Another randomized trial demonstrated no survival benefit for bucindolol (another β-blocker with ISA directed at the β_1-adrenoceptor) versus placebo in patients with NYHA III–IV HFrEF[72]. β-blockers without ISA improve outcomes in heart failure[31]; indeed, expert opinion suggests that the absence of ISA is a key pre-requisite for optimal clinical outcomes with β-blocker therapy[8].

Additional vasodilatory mechanisms of action

Peripheral vasodilation can also be induced by upregulated nitric oxide production, e.g. due to simulation of β_3-

adrenoceptors by nebivolol[73]. BP reduction may ensue in either case. Any resultant reflex tachycardia is likely to be counterbalanced by the effects of β_1-adrenoceptor blockade, which minimizes changes in the heart rate compared with a cardioselective agent. However, there is no clear evidence that partial agonism to β_2- or β_3-adrenoceptor confers additional outcomes benefit over a cardioselective β-blocker. Bisoprolol, a highly cardioselective β_1-blocker without ISA, exhibited equal BP-lowering efficacy vs. nebivolol, a highly cardioselective β_1-blocker with β_3-adrenoceptor agonism, both drugs in a small single-blind trial[74]. While head-to-head randomized outcomes trials between agents with and without vasodilatory properties are lacking, the clinical outcomes of bisoprolol versus nebivolol were reported to be similar for management of patients with heart failure in a meta-analysis[75], and of patients with cardiovascular diseases in a review[76]. No significant differences in clinical outcomes were demonstrated between propensity score-matched patients with hypertension treated with first- versus third-generation β-blockers (with and without additional vasodilatory activity, respectively) in a large observational study[77]. Lastly, carvedilol, labetolol, celiprolol and bucindolol all block α_1-adrenoceptors, which constitutes an additional mechanism that can induce peripheral vasodilation[78]. Of note, carvedilol can effectively reduce heart rate despite the potential for vasodilatation-associated reflex tachycardia[79]. These observations may be important clinically, as reduction of heart rate has been proposed as a mechanism leading to improved outcomes in patients with heart failure[80].

Implications for *β*-blocker-based combination therapy

The recently published (2023) European Society of Hypertension (ESH) clinical practice guideline for diagnosing and managing hypertension includes β-blockers within the five main classes of antihypertensive agents suitable for first-line use[26]. This is largely due to recognizing that risk reduction of adverse cardiovascular events is dependent on the magnitude of BP lowering *per se*, rather than the pharmacologic properties of the different antihypertensive drug classes. As stroke outcomes appear especially sensitive to central BP, the slightly lower efficacy of β-blockade for reducing central BP compared with other drug classes, particularly CCBs, may attenuate its efficacy for lowering stroke risk[26]. However, as most patients with hypertension require combinations of antihypertensive drugs for adequate BP control, the reduced efficacy of β-blockers for central BP lowering need not be a critical limitation. While a combination of an angiotensin converting enzyme inhibitor and CCB is often the first-choice combination treatment[81], selective β-blockade may also fit well mechanistically into rational antihypertensive combinations for selected patients, especially those with established CHD or HFrEF. For example, adding a cardioselective β-blocker to a dihydropyridine CCB, which markedly reduces central blood pressure, will provide complementary and additional peripheral blood pressure lowering *via* β1-adrenoreceptor blockade in the heart[82,83]. Of note, CCBs may also increase the availability of nitric oxide in the vasculature[84] or block α_1-adrenoceptors, both of which would enhance lowering of central blood pressures.

Activation of the sympathetic nervous system increases the activity of the renin-angiotensin-aldosterone system (RAAS), which in turn promotes sympathetic overactivity in a vicious circle, driving the development of hypertensive target organ disease and heart failure[85]. Combining a cardioselective β-blockade with a RAAS blocker (an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker) thus represents a rational strategy for managing hypertension and other cardiovascular diseases. Importantly, β-blockers are as effective as other antihypertensive classes in reducing BP when added to an existing antihypertensive monotherapy[86]. RAAS activation also reduces the response to a diuretic in patients with hypertension or HFrEF, providing further rationale for the efficacy of a β-blocker-diuretic combination in this setting[87]. Finally, delivering antihypertensive combination therapy *via* fixed-dose single-pill combinations helps maintain treatment adherence, which is important for optimal BP goal attainment[88,89].

Current guidelines for managing heart failure recommend using β-blockers (principally bisoprolol, metoprolol, or carvedilol) for patients with HFrEF[90], although up to almost 90% of the populations of recent randomized trials in populations with HFpEF have received a β-blocker as background therapy[91]. Thus, cardiologists who have taken care of patients in randomized trials in populations with HFpEF found that β-blockers were indicated in the majority of the patients for reasons such as tachycardia (including rapid atrial fibrillation) and ischaemia due to left ventricular hypertrophy and/or macrovascular coronary disease. In the management of HFrEF, β-blockers are recommended to be combined with other pillars of therapy that may also have antihypertensive effects, including RAAS blockers or angiotensin receptor-neprilysin inhibitor, mineralocorticoid antagonist and sodium/glucose cotransporter-2 inhibitors[90]. Recent research shows that the benefit of the relatively new class of sodium-glucose co-transporter 2 inhibitors is not diminished by continuing treatment with these other evidence-based background therapies[92].

Conclusions

The updated ESH guidelines have restored β-blockade as one of the five main classes of antihypertensive therapy suitable for initiating pharmacologic antihypertensive therapy, especially in patients with cardiovascular comorbidities such as CHD or heart failure. In this review, we have set out to reinterpret the properties of this diverse therapeutic class in the light of the new evidence that has prompted this change in guidance. Recent management guidelines in this area have also emphasized the need to prescribe combination antihypertensive therapies for most people with hypertension. The mechanism of β-blockade is complementary to most other antihypertensive agents and adding a β-blocker to another agent with a complementary mechanism may provide a rational antihypertensive combination that reduces

the adverse impact of the activated RAAS on the cardiovascular system. Cardioselective β_1-adrenoceptor β-blockers are as effective as other subclasses of β-blockers for BP management; and bisoprolol is one three cardioselective β-blockers (along with carvedilol) that are recommended for improving clinical outcomes in patients with HFrEF in current European guidance[90]. Moreover, β_1-selectivity helps to reduce the potential for adverse effects associated with the contraction of smooth muscle cells due to the blockade of β_2-adrenoceptors, leading to cold extremities, erectile dysfunction, or exacerbation of asthma or chronic obstructive pulmonary disease[31]. At the same time, these agents remain strongly recommended for patients with defined cardiovascular comorbidities such as coronary heart disease or heart failure.

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