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REVIEW ARTICLE

Safety and tolerability of β-blockers: importance of cardioselectivity

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ABSTRACT

Cardioselective β-blockade is generally well tolerated in practice and contraindications to this therapy are uncommon. β-blockers are a diverse therapeutic class, and their individual tolerability profiles are influenced strongly by their pharmacodynamic effects across different adrenergic receptors. Bisoprolol, probably the β-blocker with the highest selectivity for blockade of β_1- vs. β_2-adrenoceptors, does not block β_2-adrenoceptors to an appreciable extent at doses in therapeutic use. Side-effects often attributed to β-blockers, such as erectile dysfunction and adverse metabolic effects are uncommon with bisoprolol and other β-blockers used at doses which only block β_1-adrenoceptors. Cautious use of a cardioselective β-blocker is not contraindicated in people with chronic obstructive pulmonary disease or asthma and the outcomes benefits of β-blockers in patients with coronary heart disease or heart failure are also apparent in patients with concurrent COPD. Starting with a low dose and titrating upwards carefully is important for optimising the tolerability of a β-blocker. Most people with hypertension will receive combination antihypertensive therapy in practice, and the low-dose combination therapy approach provides a useful strategy for optimising the efficacy and tolerability of a regimen that includes a β-blocker, compared with up-titrating an existing monotherapy.

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Introduction

β-blockers are recognised as evidence-based care for the control of hypertension, especially in patients with comorbid coronary heart disease (CHD) and heart failure (HF)[1]. These are lifelong conditions, and it is important that patients take their medicines continuously. In addition, for people with CHD and HF, evidence-based therapies should be used whenever possible at the dosages evaluated in cardiovascular outcomes trials. Tolerability and safety are key determinants of the likelihood of a patient adhering well to a cardiovascular therapeutic regimen[2]. This review considers the tolerability and safety of β-blockers, with special reference to β-adrenoceptor selectivity and strategies to optimise tolerability and adherence to therapy.

Principal side-effects of β-blockers

Importance of β-adrenoceptor selectivity

The nature of the side-effects of different β-blockers depends importantly on their selectivity for different β-adrenoceptors. Table 1 provides a brief overview of the physiological consequences of the most common modes of interaction with β-blocker drugs with these receptors: blockade of β_1- and β_2-adrenoceptors and activation of β_3-adrenoceptors. β_1-adrenoceptors are located mainly in the heart and (cardio)selective blockade of β_1-receptors reduces heart rate (by opposing the effects of catecholamines on the conduction of cardiac action potentials through the atrioventricular node[3]) and myocardial contractility, which together reduce myocardial oxygen consumption[4]. Overactivation of the sympathetic nervous system is a key driver of adverse left ventricular remodelling (for example in the settings of hypertension or heart failure) and β_1-adrenoceptor blockade opposes these pathological changes[5]. Bisoprolol, metoprolol and nebivolol demonstrate a high degree of selectivity for β_1- vs. β_2-adrenoceptors; atenolol is often described as "cardioselective" but is less so than bisoprolol and blocks about 25% of β_2-adrenoceptors at its higher recommended dose[6–8].

Non-cardioselective β-blockers also block β_2-adrenoceptors, by definition. In the heart, this implies a loss of cardioprotective mechanisms associated with signalling *via* this receptor[4]. In the periphery, β_2-adrenoceptor blockade induces constriction of smooth muscle in the arteries and bronchial tree (among other locations), resulting in increased peripheral resistance and risk of bronchospasm, respectively[4]. Propranolol was the prototype non-cardioselective β-blocker, a property shared with other agents such as oxprenolol, bucindolol, labetolol and carvedilol[7]. The presence of additional vasodilator mechanisms for some agents complicates

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Table 1. Overview of physiological implications of altered emodelin through different β-adrenoceptors during treatment with cardioselective or non-cardioselective β-blockers.

β_1-adrenoceptor blockade	β_2-adrenoceptor blockade	β_3-adrenoceptor agonism
↓ Heart rate	↑ Vasomotor tone (peripheral vasoconstriction)	↓ Vasomotor tone (peripheral vasodilatation) *via* a mechanism based on increased production of nitric oxide
↓ Myocardial contractility	↑ Peripheral vascular resistance	
↓ Myocardial O_2 consumption	↑ Bronchoconstriction	
↓ Intracardiac conduction	↑ Cardiac contractility and O_2 consumption	
↓ Adverse cardiac remodeling during hypertension and heart failure	↓ Cardioprotective effects of β_2-adrenoceptor stimulation	

See text for references.

Table 2. Contraindications to the use of a cardioselective β-blocker and non-cardioselective agents with or without additional vasodilator properties.

Contraindication	Propranolol	Bisoprolol	Carvedilol
History of bronchospasm or asthma	☒[a]	Caution[b]	☒
Chronic obstructive pulmonary disease	☒[a]	Caution[b]	☒
Bradycardia	☒	☒[c]	☒[g]
Second or third degree heart block	☒	☒[d]	☒[d]
Sick sinus syndrome	☒	☒	☒[h]
Cardiogenic shock	☒	☒	☒
Uncontrolled heart failure	☒	☒	☒[i]
Hypotension	☒	☒[e]	☒
Severe peripheral arterial disease	☒	☒[f]	Caution
Prinzmetal's angina	☒	Caution	☒
Untreated phaeochromocytoma	☒	☒	☒
Prolonged fasting, or prone to hypoglycaemia	☒	Caution	Caution
Metabolic acidosis	☒	☒	☒
Combination with verapamil or diltiazem	☒	Caution	☒[j]

More detail is given for some contraindications with agents approved subsequently to propranolol: [a]Contraindicated where there is history of "wheezing or asthma"; [b]contraindicated in "severe bronchial asthma or chronic obstructive pulmonary disease"; [c]heart rate <60 bpm before therapy initiation; [d]without pacemaker; [e]systolic blood pressure <100 mmHg; [f]and Raynaud's syndrome; [g]<50 bpm; [h]including sinoatrial block; [i]New York heart Association Class IV heart failure with marked fluid retention or overload requiring i.v. inotropic treatment; [j]refers to i.v. treatment, other modes of administration are included under special warnings and precautions for use. Hypersensitivity to the active ingredient or excipients is a contraindication for all three agents and is omitted from the table for brevity. Compiled from Summaries of Product Characteristics available at medicines.org.uk/emc/ (accessed November 2023).

the picture. β-blockers with additional agonism at β_3-adrenoceptors, e.g. nebivolol, exert additional vasodilator properties associated with increased production of nitric oxide[9]. Pindolol activates β_2-adrenoceptors and bucindolol, labetolol and carvedilol also block peripheral vascular α_1-adrenoceptors[7]. An accompanying article in this series describes in detail the differences between individual β-blockers, in terms of selectivity and other properties[10].

The remainder of this review will focus mainly on the implications for tolerability and safety of β_1- vs. β_2-adrenoceptor selectivity.

Contraindications and precautions

Bisoprolol, as a highly cardioselective β-blocker, serves as a useful example of the safety and tolerability profiles of a cardioselective β-blocker. Table 2 summarises contraindications relating to bisoprolol, a non-selective β-blocker (propranolol) and a non-selective β-blocker with additional vasodilator properties (carvedilol). The contraindications relate mainly to situations where the negative chronotropic or negative inotropic properties of a β-blocker would be unwelcome, such as uncontrolled or decompensated HF, intracardiac conduction block, severe bradycardia or severe hypotension.

Cardioselectivity influences the list of contraindications to some extent. The non-selective agents have a formal contraindication in Europe for "history of asthma or wheezing" (in the case of propranolol), while bisoprolol is contraindicated only for severe asthma (please note that precise details of contraindications may vary between countries, however). The non-selective β-blockers are contraindicated in patients with vasospastic angina, consistent with the blockade of β_2-adrenoceptors.

Propranolol is contraindicated in subjects at risk of hypoglycaemia, while this is a caution to the use of bisoprolol: the negative chronotropic action of a β-blocker may mask tachycardia during hypoglycaemia, which is an important warning sign of that condition. α_1-adrenoceptor blockade (e.g. with carvedilol) may be associated with postural hypotension and dizziness. A retrospective study of 23 patients with HF who were unable to up-titrate carvedilol due to dizziness or hypotension showed that a switch to bisoprolol relieved these symptoms in all 7 patients with dizziness and in 9/16 patients with hypotension[11]. Subsequent up-titration of bisoprolol was achieved safely, with an improvement in signs and symptoms of HF.

Overall, the contraindications and precautions relating to the therapeutic use of β-blockers reflect their heterogeneous pharmacologic actions as summarised above. In practice, contraindications to cardioselective β-blockade are uncommon, with 5% or fewer of patients with an indication for this treatment unable to receive it due to hypotension or bradycardia[12]. The clinical evidence relating to the actions of cardioselective and non-selective β-blockers in patients with respiratory disease and other important comorbidities is summarised in more detail in a later section of this review.

Most common side effects of β-blockers

The most common side-effects of bisoprolol from a pooled analysis of clinical trials included in its US labelling are shown in Figure 1. Fatigue was the only side-effect that was clearly more common in the bisoprolol vs. placebo groups, although only about 7% of the bisoprolol group reported fatigue. This is a recognised side-effect of the β-blocker class and probably results from reduced maximal cardiac output due to the reductions in heart rate and cardiac contractility during treatment with a β-blocker. Importantly, there was no bronchospasm during treatment with bisoprolol in the pooled analysis, and no excess of other side-effects relating to the respiratory system were observed. Fatigue can occur during exercise in a β-blocker-treated patient especially if

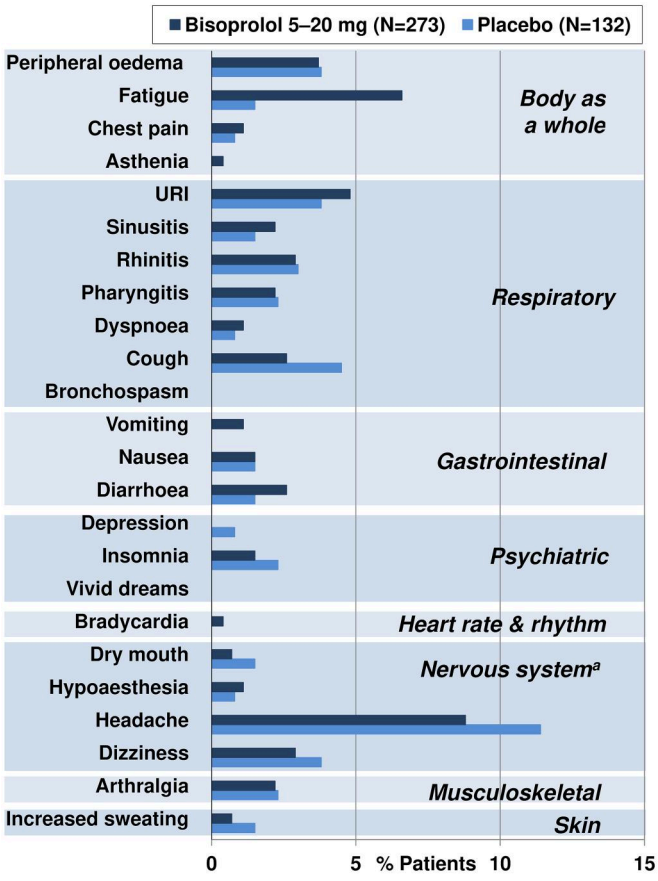

Figure 1. Side-effects of bisoprolol from a pooled analysis of placebo-controlled clinical trials. Shaded areas and associated labels show the standard body system classification for side-effects used in clinical trials ([a]side-effects in the central and autonomic nervous systems have been shown together here). Data for bisoprolol 5–40 mg (shown in the original source) have been omitted here as the maximum labelled dose of bisoprolol is 20 mg/day. URI: upper respiratory infection. Drawn from data presented in the US Prescribing Information for bisoprolol.

they attempt to use a previously determined elevation of heart rate as a marker of exercise intensity, despite the negative chronotropic effects of the drug; patients are counselled not to do this[13]. An observational follow-up to a previous clinical trial enrolled 164 patients with a history of mild-to-moderate hypertension that had been well controlled (DBP $\leq$90 mmHg) during prior treatment with bisoprolol[14]. At the end of three years of treatment, 102 patients were still receiving bisoprolol. BP was well controlled without need for additional therapy, except for an additional diuretic in 4 cases. Most were receiving bisoprolol at a dose of 10 mg (63%) or 5 mg (21%) at study end. Thirty-four adverse events were reported, which were mostly mild and transient. Two patients withdrew for sexual dysfunction. One was considered "possibly" treatment-related but may have been due to atherosclerotic cardiovascular disease and concomitant receipt of benzbromarone for gout/hyperuricaemia, conditions which are themselves associated with sexual dysfunction[15]. The other was also rated as possibly treatment-related and was not investigated further. The most common other side-effects considered "probably" or "very probably" related to treatment were dizziness (7 reports) and headache (2 reports); otherwise, no potentially treatment-related individual side-effect occurred more than once.

Cold extremities is a common side-effect of non-cardioselective β-blockers and is due to peripheral vasoconstriction arising from blockade of β_2-adrenoceptors[16]. Selective β_1-adrenoceptor blockade with bisoprolol 20 mg was not associated with reductions in isoprenaline-induced vasoconstriction in forearms of healthy volunteers, while treatment with atenolol 100 mg reduced this parameter[17]. Propranolol, but not bisoprolol, increased forearm vascular resistance in another experimental study in volunteers[18]. A randomised, crossover study in 14 patients with hypertension showed that treatment with bisoprolol did not affect the diameter, blood flow or vascular resistance of the carotid and brachial circulations vs. placebo[19].

Current management guidelines for hypertension provide strong support for the use of combinations of antihypertensive agents[1]. The therapeutic use of a rational combination of low doses of a cardioselective β-blocker with another agent with a complementary mechanism of action (e.g. a dihydropyridine calcium channel blocker [CCB]) often provides superior efficacy and fewer side-effects than uptitration of an existing insufficiently effective monotherapy[20].

A meta-analysis of 11 clinical trials that incorporated 13,833 patients with HF with reduced ejection fraction (who were in sinus rhythm) showed that the rate of discontinuation for side-effects was similar for patients receiving β-blockers (14.4%) and placebo (15.6%)[21]. Importantly, there was no significant interaction between tolerability and age or gender in this study. While the analysis did not focus on the incidence of individual side-effects that did not prompt discontinuation, these data suggest that β-blockade was generally well tolerated in this population.

Use of β-blockers in special populations

Patients with airways disease

Chronic obstructive airways disease

Blockade of β_2-adrenoceptors in bronchial smooth muscle brings an increased risk of bronchoconstriction and bronchospasm, as described above. A randomised, placebo-controlled study in 12 subjects with COPD compared the effects of bisoprolol 20 mg and atenolol 100 mg (the highest recommended dose in each case) on heart rate (β_1-adrenoceptor-mediated effect) and airway resistance (β_2-adrenoceptor mediated effect)[8]. Atenolol, but not bisoprolol, increased airway resistance at 4 h and 24 h post-dose. Interestingly, atenolol only reduced heart rate at the 4 h period and not the 24 h period, while bisoprolol reduced heart rate at both time points. These data are consistent with higher β_1- vs. β_2-adrenoceptor selectivity for bisoprolol vs. atenolol, as per above, and suggest that the duration of partial β_2-adrenoceptor blockade with atenolol outlasted the duration of β_1-adrenoceptor blockade. Similarly, a randomised, placebo-controlled evaluation of metoprolol in 532 patients with COPD (without a clinical indication for β-blockade) found no difference between groups with respect to time to first COPD exacerbation, but randomisation to metoprolol was associated with an approximate doubling of the risk of hospitalisation for a COPD exacerbation (HR 1.91 [95%CI 1.29–2.83)[22].

Estimates of the prevalence of concurrent HF and COPD range from about 10% to about 50% of the overall population with HF and the risk of adverse outcomes in these patients is high[23]. A randomised comparison of bisoprolol with carvedilol in 63 elderly patients with mild-to-moderate HF showed that more patients in the bisoprolol group achieved the maximum permitted dosage (56% vs. 42% for carvedilol), although changes in heart rate were similar, suggesting comparable β_1-adrenoceptor blockade[24]. There were fewer adverse events in the bisoprolol vs. carvedilol groups (19% vs. 42%, $p = 0.045$), and two patients on carvedilol withdrew for respiratory side-effects (wheezing, dyspnoea) vs. none for bisoprolol. Forced expiratory volume in one second (FEV_1) increased during treatment with bisoprolol (suggesting improved airway function), but there was no significant change during treatment with carvedilol (1561 ± 414 mL to 1698 ± 519 mL, $p = 0.046$, and 1704 ± 484 mL to 1734 ± 548 mL, $p = 0.44$, respectively). Data from a recent (2020) meta-analysis of 49 studies that included data from 670,594 patients with comorbid cardiovascular disease and COPD support the use of cardioselective β-blockade in patients with COPD[25]. The use vs. non-use of a β-blocker in this analysis reduced mortality whether or not the β-blocker was cardioselective (relative risk [RR] 0.60 [95%CI 0.48–0.76]) or non-cardioselective (RR 0.74 [95%CI 0.60–0.90]). However, cardioselective β-blockade also reduced the frequency of COPD exacerbations (RR 0.72 [95%CI 0.56–0.94]), while non-cardioselective β-blockade did not (RR 0.98 [95%CI 0.71–1.34). However, a randomised trial in people with moderate or severe COPD and no indication for β-blockade found no difference between metoprolol and placebo for time to COPD exacerbation, although hospitalisations for COPD exacerbation were increased by almost 2-fold in the metoprolol vs. placebo groups[22].

A 2-year randomised trial is currently evaluating the effects of low-dose bisoprolol in patients with moderate-to-severe COPD[26] and a 1-year trial is evaluating the impact of randomisation to bisoprolol vs. placebo at a dose of up to 5 mg on the frequency of COPD exacerbations in a population with moderate COPD[27]. These data will be important in guiding therapy for the challenging population of patients with cardiovascular diseases and comorbid COPD/asthma, as there is evidence that β-blockers are underused in people with COPD and cardiovascular conditions[28]. Current guidelines for the management of hypertension in Europe support the cautious use of more cardioselective β-blockers in people with COPD, starting from a low dose[1].

Asthma

A 6-week, randomised trial compared of the effects of bisoprolol vs. verapamil (or both together at a low dose) in 120 patients with stable angina and mild or moderate asthma[29]. There were no changes in FEV_1 in any treatment group in patients with mild asthma. However, a significant decrease in FEV_1 occurred in patients with moderate asthma who received bisoprolol 10 mg. There were no changes in FEV_1 in patients receiving bisoprolol 2.5 mg or 5 mg, or in the group randomised to bisoprolol 5 mg + verapamil 5 mg. Another randomised, controlled trial showed that bisoprolol 10 mg did not affect the ability of salbutamol to reverse bronchoconstriction in people with asthma[30]. These data generally support the cautious use of cardioselective β-blockers for patients with asthma, a condition where non-selective β-blockers are generally contraindicated, as described above.

Patients with dyslipidaemia

A 12-month clinical trial in 52 patients with mild-to-moderate hypertension reported no significant differences in levels of lipids or lipoproteins between patients randomised to lisinopril 10–20 mg or bisoprolol 2.5–10 mg[31]. These data are consistent with observations that activation of β_2-adrenoceptors induces favourable changes in the lipid profile, with a reversal of these effects in the setting of non-selective β-blockade[32]. Also, blockade of β_2-adrenoceptors may permit relatively unopposed signalling *via* α_1-adrenoceptors, which exerts deleterious effects on the lipid profile[33]. These observations may account for improvements in lipids with β-blockers that also block α_1-adrenoceptors, such as carvedilol[34]. However, the effects of (especially cardioselective) β-blockers tend to be small and transient[35], and thus may lack overall clinical relevance for a patient receiving treatment to control the lipid profile along with other cardiovascular risk factors.

Patients with (or at risk of) diabetes

A large database study from Taiwan followed a population of 65,686 patients with hypertension, but no diabetes, in order to study the factors associated with an increased risk of new-onset diabetes[36]. Receipt of a β-blocker overall was not associated with a significant risk of developing diabetes during an average of 31 months of follow-up (HR 1.291 [95%CI 0.947–1.760], $p = 0.106$). However, stratifying the population according to the type of β-blocker received revealed a significant risk of developing diabetes associated with non-cardioselective β-blockers (HR 1.508 [95%CI 1.079–2.109], $p = 0.016$), but not with cardioselective β-blockers (HR 0.937 [95%CI 0.596–1.473], $p = 0.780$).

A randomised trial in type 2 diabetes patients showed that bisoprolol 10 mg did not affect blood glucose metabolism[37]. Bisoprolol also did not affect blood glucose in observational studies of patients with cardiovascular disease or hypertension[38] or healthy volunteers[17]. Atenolol, metoprolol or nebivolol did not adversely affect blood glucose regulation in randomised trials in patients with type 2 diabetes or prediabetes[39–41]. In contrast, elsewhere, atenolol decreased insulin sensitivity and/or increased indices of blood glucose vs. an ACEI[42] or calcium channel blocker[43]. Blockade of β_1-adrenoceptors appears to be associated with some improvement in blood glucose regulation, similar to effects on lipid profiles[44].

Overall, these studies suggest that there is little or no adverse effect on glycaemia with highly cardioselective β-blockers, and also for β-blockers with additional α_1-adrenoceptor blockade. Importantly, pooled data from three outcomes trials in populations with HF (CIBIS II, MERIT-HF and

COPERNICUS) confirmed that treatment with a β-blocker improved clinical outcomes in populations with or without diabetes, which underpins the importance of these patients receiving evidence-based treatment with a β-blocker[45].

Patients with chronic kidney disease (CKD)

β-blockers are commonly prescribed in the predialysis CKD patient population, as these patients often have substantial cardiovascular comorbidity[46]. Sympathetic overactivity is common in patients with CKD, and contributes to the increased risk of both cardiovascular events and progression of renal disease[47]. Studies with carvedilol have demonstrated reductions in albuminuria and in cardiovascular event rates in CKD patients with hypertension that were dependent upon lowering of BP[47] Overall, vasodilator β-blockers like carvedilol appeared not to be superior to non-vasodilator agents in reducing proteinuria, however[48]. Accordingly, while β-blockers are not recommended as the primary means of controlling hypertension in predialysis CKD patients, their use should be considered according to the presence of cardiovascular comorbidities and especially for patients with high heart rate and/or resistant hypertension[46]. Dose adjustments of some β-blockers may be needed for use in patients with CKD. Hydrophilic β-blockers (e.g. atenolol, bisoprolol) are eliminated *via* the kidney, so that a dose adjustment is required in patients with acute or CKD with reduced renal function; on the other hand, metoprolol, propranolol and labetalol are metabolised hepatically and such adjustments are mostly not necessary. Bisoprolol demonstrates balanced renal and hepatic clearance, so that accumulation of the drug is much less likely, even in the setting of end-stage renal failure[49].

The role of β-adrenergic blocking agents may be greater in patients with end-stage CKD requiring chronic dialysis[46]. These patients are at especially high cardiovascular risk and a meta-analysis suggested superior improvement in cardiovascular outcomes with cardioselective vs. non-cardioselective β-blockers[50]. As a result of these observations, β-blockers have been proposed as the first-line pharmacologic agent for hypertension in patients on haemodialysis[46].

In addition, drug dialysability may be relevant to the clinical use of β-blockers and these agents, broadly speaking, can be divided into dialyzable and non-dialyzable agents. Atenolol, metoprolol, propranolol, sotalol, and bisoprolol are dialyzable to some degree, while carvedilol, labetalol, and propranolol are considered to be non-dialyzable or poorly dialyzable[51]. However, dialyzability does not seem to reduce the antihypertensive efficacy of these drugs in haemodialysis patients[52]. More research is needed to fully clarify this issue, also due to a lack of randomised, controlled trials and because of some uncertainty regarding the exact degree of dialysability of certain β-blockers, such as bisoprolol. Some authors advocate the use of bisoprolol as first choice in hypertensive haemodialysis patients due to its overall favourable general pharmacokinetic properties[53]. It is important to note that the use of β-blockers should be discouraged in dialysis patients who display intradialytic hypotension with bradycardia[46].

Patients with intermittent claudication (IC)

There is no evidence that treatment with a β-blocker worsens the signs and symptoms or limb outcomes associated with IC[54–58]. One retrospective analysis of propensity score-matched populations with IC who did or did not receive a β-blocker found no differences in the rates of lower limb amputation, limb salvage and major limb-related adverse events[58]. Current European guidelines support the use of β-blockers in this population[59], although severe peripheral arterial disease is a contraindication for most agents (Table 1).

Other adverse events of special interest

Effects on erectile dysfunction (ED)

ED is common among patients with cardiovascular diseases and is frequently cited as a major side-effect of β-blockers[60]. Cardioselective β-blockade with bisoprolol, metoprolol, acebutolol, atenolol or nebivolol was not associated with erectile dysfunction in studies conducted in populations with hypertension or HF[61–65], although a decrease in the International Index of Erectile Function-5 score with metoprolol has been reported[66]. ED has been reported in patients taking propranolol in some but not all studies[67,68]. The additional β_3-adrenoceptor mediated generation of nitric oxide by nebivolol may ameliorate erectile dysfunction[61,64,66].

A nocebo effect may be at play with regard to ED and β-blocker therapy, as physicians routinely warn patients of this possible side-effect. This was investigated in a study where 114 metoprolol-treated patients with hypertension were divided into three groups and given the following information: (a) they were receiving metoprolol and it might cause ED; (b) they were receiving metoprolol with no information on possible ED; (c) no information on metoprolol or ED[69]. The subsequent incidence of ED in each group was 32%, 13%, and 8%, respectively, and placebo was as effective as the phosphodiesterase (PDE)-5 inhibitor, tadalafil, in reversing it. A 3-period crossover study in 96 men with newly diagnosed coronary artery disease but no history of ED involved treatment with atenolol throughout, but patients were informed before each successive treatment period: (a) of the drug name but not its side-effects; (b) of the drug name and its potential side-effects, including ED; and (c) of neither[70]. Again, the subsequent incidence of ED was higher where patients were informed of the possibility of ED (31%), compared with being given the drug name only (16%) or no information (3%); again, a PDE-5 inhibitor (sildenafil) and placebo were similarly effective.

Psychiatric side-effects

Some β-blockers, particularly more lipophilic agents, enter the central nervous system, with the possibility of inducing

psychiatric side-effects, as reported in a number of observational studies (reviewed elsewhere[71]). A large meta-analysis from 2021 (285 studies that included 53,533 patients) found that use vs. non-use of a β-blocker was not associated with an increased risk of depression (odds ratio [OR] odds ratio, 1.02 [95%CI 0.83–1.25]) or withdrawal from a study for depression (OR 0.97 [95%CI, 0.51–1.84])[72]. There were also no differences for this outcome between β-blockers and other pharmacologic treatments for depression. An increased risk of unusual dreams, insomnia, or disturbed sleep associated with β-blockade could not be excluded, however. Another meta-analysis found that depression was more common in the placebo arms of β-blocker trials[73]. Finally, a recent, large observational study in Sweden ($N = 1.4$ million) found no excess of psychiatric side-effects in patients taking vs. not taking β-blockers, with an intriguing suggestion of reduced admission rates for depression and psychosis in the β-blocker group[71].

Conclusions

β-blockers are a diverse therapeutic class, and their individual tolerability profiles are influenced strongly by their pharmacodynamic effects across different adrenergic receptors. Cardioselective β-blockade is well tolerated in practice, although these agents should be used with caution in people with COPD[12]. The reported incidence of erectile dysfunction with β-blockers may reflect a nocebo effect to a large extent, as described above. A systematic review found that 28 of 33 side-effects commonly attributed to β-blockers were not more common during treatment with a β-blocker vs. placebo in double-blind, randomised clinical trials in populations with HF. Starting with a low dose and titrating upwards carefully is important for optimising the tolerability of a β-blocker[12]. Most people with hypertension will receive combination antihypertensive therapy in practice, and the low-dose combination therapy approach provides a useful strategy for optimising the efficacy and tolerability of a regimen that includes a β-blocker, compared with up-titrating an existing monotherapy[1,20].

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References for inclusion in this narrative review were identified using PubMed searches for "beta blockade", "beta blocker" or the names of common agents of this class, together with subjects of interest for different sections, such as "erectile dysfunction" or "chronic obstructive airways disease", etc. Authors' experience and reference collections also provided source material.

Supplement statement

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Artificial intelligence (AI)

No AI-related technology was used in the preparation of this article.

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