The Real Role of β-Blockers in Daily Cardiovascular Therapy

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Published online: 29 March 2017
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Abstract The role of β-adrenoceptor antagonists (β-blockers) in cardiovascular therapy has been subject to diverse trends and changes over the decades. With the advent of a wide variety of excellent drugs for the treatment of antihypertension, β-blockers have been relegated from the first-line treatment of essential hypertension. However, they remain the drugs of first choice in recommendations from the respective medical societies for heart failure, coronary artery disease, and atrial fibrillation as well as in hypertension complicated with heart failure, angina pectoris, or prior myocardial infarction. When indicated, cardioselective β-blockers should be prescribed in patients with diabetes mellitus or chronic obstructive pulmonary disease. We review the available evidence for the use of β-blockers in clinical conditions in which recommendations can be made for everyday practice.

Key Points

β-Adrenoceptor antagonists (β-blockers) are recommended for the first-line treatment of heart failure, coronary artery disease, and atrial fibrillation as well as of hypertension complicated with heart failure, angina pectoris, or prior myocardial infarction.

β-Blockers should not be withheld from patients with diabetes mellitus or chronic obstructive pulmonary disease, although cardioselective agents are preferable.

1 Introduction

Agents that block the adrenergic β-receptors have been used for decades in the treatment of cardiovascular disease (CVD). The development of primary prevention and early-detection strategies as well as the emergence of new and effective therapeutic agents has seen the survival rates and life expectancy of patients with CVD increase considerably, with a consequent increase in the prevalence of these conditions [1]. Patients who develop a chronic heart disease usually need lifelong treatment, and finding the optimal personalized treatment for every patient is crucial.

According to new hypertension guidelines [2], β-blockers have been forced into the second line of therapeutic recommendations for essential hypertension, behind angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs). These recommendations were based on meta-analyses reporting that β-blockers may be less
favorable than some other drug classes for total mortality, cardiovascular (CV) events, and stroke outcomes. However, most of the analyzed data came from studies using atenolol and propranolol and may not apply to other agents [2, 3].

Treatment choices for patients with CVD should be based on the presence and magnitude of all risk factors and comorbid conditions as well as on the individual characteristics of the drugs in question (the primary characteristics of commonly used β-blockers are presented in Table 1). Compared with traditional β-blockers, newer agents with β1 selectivity or vasodilating properties (such as carvedilol or nebivolol) reduce central pulse pressure and aortic stiffness more effectively than atenolol or metoprolol and tend to have fewer metabolic side effects [2].

We present the available evidence for the use of β-blockers in relation to CVD. A comprehensive PubMed search was performed to identify relevant articles for discussion.

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### Table 1 Characteristics of commonly used β-blockers

| Drug       | Indications in CVD (other than hypertension*)   | Daily dose (mg/day) | Half-life (h) | Route of excretion | β1-Selectivity | ISA | α1-Antagonist activity | Membrane stabilizing property | Vasodilatory action |
|------------|-----------------------------------------------|---------------------|--------------|--------------------|----------------|-----|------------------------|-----------------------------|---------------------|
| Acebutolol | Chronic stable angina; tachyarrhythmia       | 200–1200            | 3–4          | Renal 30–40%; non-renal 50–60% | +              | +   | –                      | –                           | –                   |
| Atenolol   | Chronic stable angina; following MI; cardiac arrhythmia | 50–100             | 6–7          | Mainly renal       | +              | –   | –                      | –                           | –                   |
| Bisoprolol | HF with reduced EF                            | 1.25–10             | 9–12         | Renal 50%; non-renal 50% | +              | –   | –                      | –                           | –                   |
| Carvedilol | Mild to severe HF; chronic stable angina; following MI | 3.125–100           | 6–10         | Mainly non-renal   | –              | –   | +                      | +                           | +                   |
| Metoprolol | HF; chronic stable angina; following MI; tachyarrhythmia; thyrotoxicosis | 50–450             | 3–9          | Mainly renal       | +              | –   | –                      | +                           | –                   |
| Nadolol    | Chronic stable angina; tachyarrhythmia; thyrotoxicosis | 20–240             | 20–24        | Mainly renal       | –              | –   | –                      | –                           | –                   |
| Nebivolol  | Mild to moderate HF                           | 2.5–20              | 12–19        | 38–67%; 13–48% renal; 10% renal; 90% non-renal | +              | –   | –                      | –                           | +                   |
| Propranolol| Chronic stable angina; following MI; cardiac arrhythmias; thyrotoxicosis | 10–320             | 3–6          | 10% renal; 90% non-renal | –              | –   | –                      | +                           | –                   |

* CVD cardiovascular disease, EF ejection fraction, HF heart failure, ISA intrinsic sympathomimetic activity, MI myocardial infarction

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2 β-Blockers in Heart Failure

Heart failure (HF) is strongly correlated with hypertension: 75% of incident HF cases are preceded by elevated blood pressure [4]. β-Blockers reduce heart rate and blood pressure and have anti-arrhythmic and anti-ischemic effects [5]. Besides directly blocking sympathetic activity in the heart, they also inhibit ACE release from the juxtaglomerular apparatus [6]. In patients with HF, the action of β-blockers against the harmful effects of increased adrenergic activity (resulting from myocardial dysfunction) facilitates improvements in ventricular structure and function [5]. Long-term use of β-blockers in patients with HF has been shown to significantly improve hemodynamic parameters; β-blockade results in increased left ventricular stroke volume index and left ventricular ejection fraction (EF), reduced cardiac index, and decreased pulmonary artery and wedge pressure [7–11].

The use of a β-blocker along with an ACE inhibitor is recommended by the European Society of Cardiology...
(ESC) and American Heart Association (AHA) guidelines for all patients with systolic HF with reduced EF to prevent symptomatic HF, improve left ventricular remodeling, and reduce the risk of hospitalization and premature death (level I A evidence). Treatment should be started as soon as possible after diagnosis. In coexisting atrial fibrillation (AF), a β-blocker should be the first-line treatment to control the ventricular rate (level I A evidence); in all patients with a recent or remote history of myocardial infarction (MI) or acute coronary syndrome (ACS) and reduced EF, a β-blocker should be used to reduce mortality (level I B evidence) [12, 13]. According to the ESC guideline on peripheral artery disease, β-blockers are not contraindicated in patients with lower extremity artery disease (LEAD) and should be considered in concomitant HF (level IIa B evidence) [14].

### 2.1 Heart Failure with Reduced Ejection Fraction

Recommendations for the use of β-blockers in HF with reduced EF are mainly based on the outcomes of large randomized placebo-controlled trials investigating bisoprolol (CIBIS-II), carvedilol (COPERNICUS), metoprolol (MERIT-HF), and nebivolol (SENIORS) (see Table 2 for the full names of trials mentioned in this article) [12, 13]. These trials have shown the investigated β-blockers to effectively reduce the risk of mortality and admission to hospital (Table 3) [15, 16]. These results verified earlier findings from randomized studies, meta-analyses of which found that the reduction in mortality risk was >30% with the use of β-blockers [9, 19, 20]. A recent network meta-analysis of 21 randomized controlled trials (RCTs) further confirmed approximately the same reduction in all-cause mortality risk. The effect sizes were consistent when comparing trials with shorter and longer (>12 months) follow-up durations. β-Blockers also significantly reduced deaths from CVD as well as sudden deaths. Head-to-head comparisons of individual β-blockers did not show significant differences in the evaluated outcomes, suggesting a strong class effect [7].

There may be individual differences between different β-blockers with regard to clinical outcomes in HF with reduced EF, as suggested by some comparative studies. The COMET investigators found a significant difference in all-cause mortality rate with carvedilol versus bisoprolol [hazard ratio (HR) 0.83; p = 0.0017] [21]. In a retrospective cohort, carvedilol and bisoprolol but not metoprolol significantly reduced the risk of death and hospitalization.

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### Table 2 Acronyms and full names of trials mentioned in this article

| Short name | Full name |
|------------|-----------|
| AF-CHF     | Atrial Fibrillation and Congestive Heart Failure |
| AFFIRM     | The Atrial Fibrillation Follow-up Investigation of Rhythm Management |
| BEST       | Beta-Blocker Evaluation in Survival Trial |
| BHAT       | Beta Blocker Heart Attack Trial |
| BIP        | Bezafibrate Intervention Study |
| CAPRICORN  | Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction |
| CHARISMA   | Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance |
| CIBIS-II   | Cardiac Insufficiency Bisoprolol Study |
| COMET      | Carvedilol Or Metoprolol European Trial |
| COMMIT     | Clopidogrel and Metoprolol in Myocardial Infarction Trial |
| COPERNICUS | Carvedilol Prospective Randomized Cumulative Survival |
| ISIS-I     | First International Study of Infarct Survival |
| J-DHF      | Japanese Diastolic Heart Failure Study |
| MERIT-HF   | Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure |
| MIAMI      | Metoprolol in acute myocardial infarction |
| MOCHA      | Multicenter Oral Carvedilol Heart Failure Assessment |
| MUSTT      | Multicenter Unsustained Tachycardia Trial |
| PRECISE    | Percutaneous Robotic Enhanced Coronary Intervention |
| SENIORS    | Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure |
| UKPDS      | UK Prospective Diabetes Study |
| β-PRESERVE | Rationale and design of the β-blocker in heart failure with normal left ventricular ejection fraction |
for HF [22]. Studies of carvedilol also suggested a dose-related benefit for the improvement of EF and cardiovascular hospitalization and mortality rates [23, 24].

Continuation of previous β-blocker therapy after discharge seems to be beneficial after acute decompensated HF: the use of β-blockers both before admission and after discharge was associated with lower 31- and 180-day mortality in patients with acute decompensation receiving β-blockers than in those who did not receive β-blocker therapy (p < 0.0001) [25].

A genetic component also influences responsiveness to pharmacotherapy with β-blockers. For example, evidence indicates that African-American patients with HF with the GRK5 Gln41Gln genotype (and in the case of bucindolol, also with the ADRB1 Arg389Arg genotype) especially benefit from β-blockade [26].

Table 3 Outcomes of major randomized, placebo-controlled trials in patients with heart failure and reduced ejection fraction

| Trial       | β-Blocker | N    | Mean duration | EF                  | Primary endpoints                   | Main outcomes                                                                 |
|-------------|-----------|------|---------------|---------------------|-------------------------------------|------------------------------------------------------------------------------|
| CIBIS-II [15]| Bisoprolol| 2647 | 1.3 years     | ≤35%                | All-cause mortality                 | 11.8 vs. 17.3% (HR 0.66; p < 0.0001)                                          |
|             |           |      |               |                     | Sudden death                        | 3.6 vs. 6.3% (HR 0.56; p = 0.0011)                                           |
| COPERNICUS [16]| Carvedilol | 2289 | 10.4 months   | <25%                | Combined risk of death or hospitalization for CV reasons | Cumulative risk 41.6 vs. 30.2% (p = 0.00002)                                      |
|             |           |      |               |                     | Combined risk of death or hospitalization for HF | Cumulative risk 37.9 vs. 25.5% (p = 0.000004)                                    |
| MERIT-HF [17]| Metoprolol| 3991 | 1 year        | ≤40%                | Combined total mortality or all-cause hospitalization | Risk reduction 19% (p < 0.001)                                               |
| SENIORS [18]| Nebivolol  | 2128 | 21 months     | ≤35% in 65% of pts; >35% in 35% of pts | Death or hospitalization for CV reasons | 31.1 vs. 35.3% (HR 0.86; p = 0.039)                                           |

| Trial       | β-Blocker | N    | Mean duration | EF                  | Primary endpoints                   | Main outcomes                                                                 |
|-------------|-----------|------|---------------|---------------------|-------------------------------------|------------------------------------------------------------------------------|
|             |           |      |               |                     | All-cause mortality                 | 15.8 vs. 18.1% (HR 0.88; p = 0.21)                                           |

CV cardiovascular, EF ejection fraction, HF heart failure, HR hazard ratio, pts patients

2.2 Heart Failure with Preserved Ejection Fraction

The ESC and AHA guidelines primarily recommend the use of β-blockers for the control of ventricular rate in HF with preserved EF [12, 13].

The J-DHF trial found a favorable effect with standard doses of carvedilol >7.5 mg/day on the endpoints of CVD and unplanned hospitalization for any CV causes compared with the control group (p = 0.0356). However, carvedilol did not improve prognosis in smaller doses or in terms of the primary outcome [27]. A predefined sub-analysis of SENIORS also found a beneficial effect from the β1-selective nebivolol in elderly patients with HF and impaired and preserved EF on the primary endpoint of all-cause mortality or CV hospitalization [28].

Meta-analyses of observational studies with follow-up periods ranging mostly from 1 to 5 years have shown an association between β-blockers and a significant (9–19%) reduction in the relative risk (RR) of all-cause mortality in patients with HF and preserved EF. However, the hospitalization rate for HF was not affected [29, 30].

These results also suggest a protective effect from β-blocker use in this population, and the ongoing prospective RCT of metoprolol, β-PRESERVE, will hopefully provide enough information to enable a recommendation on the matter [31].

2.3 Heart Failure and Chronic Kidney Disease

The beneficial effect of β-blockers on mortality and hospitalization risk can also be seen in patients with HF with reduced EF and co-existent chronic kidney disease (CKD). A meta-analysis of six trials comparing bisoprolol, carvedilol, metoprolol, nebivolol, and acebutolol versus placebo found a significant reduction of all-cause and cardiovascular mortality (by 28 and 34%, respectively) [32]. A post hoc analysis of the CAPRICORN and COPERNICUS trials in patients with systolic left ventricular dysfunction also found that patients with mild to moderate CKD benefited from β-blocker therapy: carvedilol treatment decreased the risks of all-cause, CV, and HF mortality as well as the risk of first hospitalization for HF and the composite of CV mortality or HF hospitalization [33]. The CIBIS-II trial investigated patients with HF and reduced EF and found the beneficial effect of bisoprolol on all-cause mortality and hospitalization due to HF to be consistent irrespective of the stage of CKD, defined by the estimated glomerular
filtration rate (eGFR). The absolute benefit of bisoprolol was greater for patients with HF and deteriorated renal function than for those without [34].

3 β-Blockers in Coronary Artery Disease

The majority of CV-related deaths are associated with coronary artery disease (CAD). The last few decades has seen a decline in CV mortality rates and a parallel increase in prevalence rates, largely because of the increased survival rates and life expectancy of these patients [35].

The anti-anginal effect of β-blockers is mainly based on their negative inotropic and chronotropic properties. The decreased heart rate lessens the myocardial oxygen demand. By prolonging the diastolic filling time and increasing vascular resistance in non-ischemic areas, β-blockers increase coronary perfusion of the ischemic areas and improves the contractility of viable but hibernating myocardial regions. The prevention of myocardial wall stress might also contribute to the prevention of myocardial rupture [5, 36, 37].

In patients with angina pectoris, β-blockers remain the standard of care for the relief of symptoms and secondary prevention of CV events. The AHA and ESC guidelines recommend the first-line use of β-blockers in stable CAD for heart rate and symptom control (level IA evidence) and in patients with hypertension with chronic stable angina and a history of prior MI (level IA evidence). β-Blocker therapy should also be considered in asymptomatic patients with large areas of ischemia (level IIa C evidence) and in microvascular angina to improve effort-related angina symptoms (level I B evidence) [37, 38]. According to the ESC guideline on peripheral artery diseases, β-blockers are not contraindicated in patients with LEAD and should be considered in those with CAD (level IIa B evidence) [14]. The most frequently used agents for the management of CAD are cardioselective β1-blockers without intrinsic sympathomimetic activity (ISA) [37].

3.1 Stable Angina Pectoris

The use of β-blockers in patients with CAD was shown to significantly improve exercise parameters such as time to onset of ST-segment depression and angina, total exercise time, and total workload. They can also reduce symptomatic and asymptomatic ischemic episodes during daily activities [39–41]. In patients with stable angina without prior MI, β-blockers are mainly used for the relief of angina symptoms and reduction of the ischemic burden. No evidence is available from RCTs to support a mortality benefit with β-blockers in patients with stable angina pectoris without MI [42, 43]. A recent meta-analysis of relevant β-blocker trials in patients with stable angina did not find a significant impact of β-blockers on mortality in general but suggested a trend for cardioselective β-blockers to improve survival rates [44].

3.2 Myocardial Infarction

In the early large placebo-controlled RCTs in MI (including the BHAT, the Norwegian Multicenter Study Group Trial, and the Göteborg Trial), administration of β-blockers in patients after a recent MI reduced total mortality by 25–35% [45–47]. In the first week after MI, atenolol significantly reduced mortality by about 15% compared with placebo in the ISIS-1 trial. Overall vascular mortality was also significantly lower (approximately 12%) in the atenolol group after 1 year [48]. The meta-analysis of 22 long-term RCTs in MI confirmed the survival benefits of β-blocker use with a 23% relative reduction in mortality [49]. Meta-analyses of available RCTs found a mortality reduction of about 8–13% with administration of intravenous β-blocker within 24 h of acute MI [36, 50].

β-Blockers seem to have a protective effect for the recurrence of ischemic events. The post hoc analysis of the CHARISMA trial found a lower risk of recurrent infarction (HR 0.62; p = 0.049) in patients with prior MI receiving β-blocker therapy [42]. Early intravenous administration of β-blockers might further protect from recurrent ischemic events. Early compared with delayed administration of metoprolol was associated with decreased incidence of re-infarction (2.7 vs. 5.1%; p = 0.02) and recurrent ischemic events (18.8 vs. 24.1%; p < 0.02), although it did not improve ventricular function or mortality rates [51]. The COMMIT trial, investigating early intravenous and subsequent oral metoprolol therapy in 45,852 patients with MI, showed that early β-blocker use reduced the risk of both re-infarction [odds ratio (OR) 0.82; p = 0.001] and ventricular fibrillation (OR 0.83; p = 0.001) [52]. A recent meta-analysis of 16 RCTs with early intravenous β-blocker use also confirmed a significant risk reduction for myocardial re-infarction (RR 0.73; p = 0.004) [50].

Although the study results from COMMIT confirmed a reduced risk of re-infarction and AF, they also suggested an elevated risk of cardiogenic shock with the use of β-blockers. The excess risk of shock (OR 1.30; p < 0.00001) was mainly observed in the first 24 h and was particularly high in patients aged ≥70 years, in those with systolic blood pressure <120 mmHg, those with a heart rate >110 beats per minute, and those in Killip class III [52]. A meta-analysis of 16 studies with early administration of β-blockers did not confirm the above findings, showing no increase in the risk of cardiogenic shock [RR 1.02, 95% confidence interval (CI) 0.77–1.35, p = 0.91] [50]. Nevertheless, caution in initiating β-blocker therapy is
reasonable when treating high-risk patients after an MI and those at higher risk of developing cardiogenic shock.

3.3 Coronary Artery Disease and Heart Failure

β-Blocker agents have considerable beneficial effects in patients with HF and reduced EF after an acute MI. In the CAPRICORN study, carvedilol significantly reduced the risk of all-cause and cardiovascular mortality (HR 0.77, p = 0.031; HR 0.74, p = 0.024) and the recurrence of non-fatal MI (HR 0.71, p = 0.002) compared with placebo [53]. A sub-analysis of SENIORS found a similar 32% reduction in the risk of ischemic events in those with HF and CAD treated with nebivolol after 2 years of follow-up [54]. The MUSTT investigators also reported a similar reduction in the 5-year mortality risk with β-blocker use in patients with CAD and reduced EF (HR 0.63–0.72, p < 0.0001) [55].

Patients with HF and preserved EF after MI may also benefit from oral β-blockers. A recent meta-analysis of seven observational studies found a reduction in all-cause mortality (HR 0.79, 95% CI 0.65–0.97) in patients receiving oral β-blocker therapy after MI treated with percutaneous coronary intervention [56].

4 β-Blockers in Atrial Fibrillation

The most common risk factors for developing AF are hypertension, valvular disease, ischemic cardiomyopathy, diabetes mellitus, and thyroid disease, with the majority of patients having one or more of these conditions [57].

Agents antagonizing β-adrenergic receptors (also known as class II antiarrhythmic drugs) decrease sympathetic activity on the heart and prolong atrioventricular nodal conduction time and refractoriness. These actions result in a decreased ventricular rate in patients with AF and in the ability to prevent the AF recurrence [58].

The ESC and AHA guidelines recommend patients with AF be treated to achieve acute rate control and to regulate inappropriate ventricular rate or irregular rhythm as they can cause severe hemodynamic distress (level I A evidence). Intravenous β-blocker use is recommended to slow the ventricular heart rate in acute AF in stable patients without pre-excitation (level I A–B evidence). Oral β-blocker therapy is among the recommended measures to slow the ventricular response in patients with paroxysmal, persistent, or permanent AF (level I A–B evidence). β-Blockers are also recommended to prevent recurrent AF in hypertrophic cardiomyopathy and to control ventricular rate in HF, in ACS, and in patients with hyperthyroidism [59, 60].

4.1 Rate Control

Robust data from the AFFIRM trial confirmed β-blockers as the most effective drugs for rate control in patients with AF (p < 0.0001), with overall rate control achieved in 70% of the patients who received a β-blocker compared with treatment initiation with a CCB or digoxin. Rate control was considered achieved when the average resting heart rate was ≤80 beats per minute and either stayed ≤100 for 24 h of monitoring or did not reach 110 beats per minute after 6 min of walking [61].

A non-interventional study of patients with AF found the risk of mortality to be lower for patients receiving rate-control treatment with β-blockers (HR 0.76; 95% CI 0.74–0.78) compared with the control group, who did not receive any rate-control drug [62].

A number of trials have demonstrated benefits such as moderate heart rate and rate control with β-blocker treatment in patients with HF and AF. However, the role of β-blockers has been debated in concomitant HF and AF after a meta-analysis of the Beta-Blockers in Heart Failure Collaborative Group failed to show mortality reduction in this population [63].

The BEST trial, which investigated bucindolol, showed that, in patients with HF and reduced EF and AF, those receiving β-blocker therapy were more likely to achieve a resting heart rate ≤80 beats per minute. In all patients (with or without AF), a resting heart rate ≤80 beats per minute was correlated with a decreased risk of cardiovascular mortality (HR 0.61, p = 0.025) and cardiovascular hospitalization (HR 0.79, p = 0.002) [64]. In the recently published AF-CHF substudy, β-blocker use was also associated with significantly lower all-cause mortality in those with HF and AF (RR 0.72, p = 0.018), although no effect was seen in hospitalization rate [65]. In patients with HF and reduced EF from the Swedish Heart Failure Registry trial, β-blocker use was associated with reduced all-cause mortality in patients with or without AF. A higher resting heart rate was associated with increased mortality in sinus rhythm and also in AF in patients when heart rate exceeded >100 beats per minute [66].

Multivariate analysis of the CIBIS-II data also showed a significant decrease of heart rate with bisoprolol compared with placebo and an increasing mortality benefit in patients with sinus rhythm with both lower baseline heart rates and greater heart rate reductions during follow-up. However, no mortality benefit was found in patients with AF [67]. The meta-analysis of ten RCTs by the Beta-Blockers in Heart Failure Collaborative Group showed similar results, with a significant reduction in all-cause mortality in patients with sinus rhythm (HR 0.73, 95% CI 0.67–0.80, p < 0.001) but not in patients with AF [68].
The prospective RCT RATE-AF trial will evaluate various effects of initial rate control therapy with bisoprolol versus digoxin in permanent AF [69].

### 4.2 Prevention of Recurrent Atrial Fibrillation

The other goal of β-blocker use is to prevent the recurrence of AF. After 6 months of follow-up, metoprolol use was shown to significantly decrease the recurrence of AF compared with placebo in patients enrolled after cardioversion of persistent AF. In those who had a relapse, heart rate was significantly lower in the metoprolol group [70].

In the post hoc analysis of the MERIT-HF study, β-blocker use in patients with HF significantly reduced the risk of new-onset AF compared with placebo (RR 0.53; \(p = 0.0005\)) [71]. A meta-analysis of seven HF trials also found that β-blockers significantly reduced the occurrence of AF, with an RR reduction of 27% (\(p < 0.001\)) [72]. The BEST genetic substudy revealed that only patients with HF with the Arg389Arg genotype experienced a considerable risk reduction for new-onset AF when using bucindolol. The ongoing GENETIC-AF study will investigate the effect of bucindolol versus metoprolol use in ADRB1 Arg389Arg homozygous patients and hopefully shed more light on the pharmacogenomic aspects of β-blockade [26].

In terms of survival, data from the COMET study indicated flutter (HR 0.41; \(p = 0.0005\)) [73]. A meta-analysis of seven HF trials also found that β-blockers significantly reduced the occurrence of AF, with an RR reduction of 27% (\(p < 0.001\)) [72]. The BEST genetic substudy revealed that only patients with HF with the Arg389Arg genotype experienced a considerable risk reduction for new-onset AF when using bucindolol. The ongoing GENETIC-AF study will investigate the effect of bucindolol versus metoprolol use in ADRB1 Arg389Arg homozygous patients and hopefully shed more light on the pharmacogenomic aspects of β-blockade [26].

In patients after MI with left ventricular dysfunction, β-blocker use substantially reduced the incidence of AF or flutter (HR 0.41; \(p = 0.0003\)); the corresponding risk of ventricular tachyarrhythmia was even lower (HR 0.24; \(p < 0.0001\)) [74].

β-Blockers effectively prevent postoperative AF, the most common complication of cardiac surgery. Robust meta-analyses of RCTs found a risk reduction of AF after cardiac surgery of 66–74% with β-blockers [75–78]. Advantages of perioperative use of β-blockers in non-cardiac surgery are less clear. Systematic reviews have shown that, although β-blockers significantly reduced the occurrence of AF, myocardial ischemia, and acute MI, they may also incur a potential increase in all-cause mortality and cerebrovascular events [79, 80].

### 4.3 Atrial Fibrillation and Hyperthyroidism

Atrial fibrillation is a common finding in hyperthyroid states (encountered in 10–15% of the patients) [81]. In those with thyrotoxicosis, treatment with β-blockers not only significantly decreased heart rate and systolic blood pressure but also improved other hyperadrenergic symptoms such as muscle weakness, tremor, degree of irritability, emotional lability, and exercise intolerance [82–85].

### 5 β-Blockers in Diabetes Mellitus and Metabolic Syndrome

Diabetes mellitus (DM) and obesity are highly correlated with CVD and associated with an increased risk of developing major CV events, including CAD, stroke, and HF; the risk is further exacerbated in those with concomitant hypertension. Both metabolic syndrome and DM are associated with high adrenergic drive and cardiac output, resulting in myocardial and vascular damage. Consequently, the risk of mortality due to heart disease and ischemic heart disease is two to four times higher for patients with DM than for those without [86–88].

Despite the supporting facts and guidelines, there is still reluctance to prescribe β-blockers in patients with DM and CVD, especially among patients with the most severe, high-risk disease, who could benefit the most from appropriate therapy [89, 90].

Concerns have been raised regarding the use of β-blockers in the diabetic population or in those at increased risk of DM due to a possible deteriorating metabolic influence of some of these agents. Furthermore, the risk of prolonged hypoglycemia was hypothesized to be higher with non-selective β-blockade in patients using insulin or sulfonylureas. However, no significant difference could be seen in the risk of hypoglycemia with β-blockers in a cohort of 13,559 elderly patients with DM compared with non-users. Only a non-significant trend favoring cardioselective over non-selective β-blockers was registered [86, 91].

Metabolic changes attributable to β-blockers may include elevation of blood sugar and glycated hemoglobin (HbA1c) levels, worsening of insulin sensitivity, and changes in triglyceride and lipoprotein levels and seem to be mainly associated with \(\beta_2\) and \(\beta_3\) receptor blockade [86, 92]. Consequently, while non-selective agents may cause deterioration of metabolic parameters, these disturbances are observed to a much lesser extent with \(\beta_1\)-selective agents (e.g., atenolol or bisoprolol) and cannot be observed with vasodilator agents, including those with intrinsic \(\beta_2\) sympathomimetic activity (e.g., nebivolol) or triggering z-blockade (e.g., carvedilol) [86, 91, 93–99].

According to the ESH/ESC guidelines, all classes of antihypertensive agents are recommended and can be used in patients with hypertension and DM (level I A evidence). In those with metabolic syndrome, antihypertensive agents that potentially improve or at least do not worsen insulin sensitivity (including vasodilating β-blockers) should be considered (level IIa C evidence) [2]. The ESC guidelines...
do not contraindicate β-blocker use for hypertension in patients with LEAD and DM, based on the finding that β-blockers do not adversely affect walking capacity or symptoms of intermittent claudication in patients with mild-to-moderate LEAD [2, 14]. Evidence on the use of various anti-hypertensive drugs in peripheral artery disease is generally poor. Therefore, careful consideration of individual patient therapy should be made on a case-by-case basis.

The American Association of Clinical Endocrinologists (AACE) guidelines find β-blockers to be less appealing for first-line treatment of hypertension in patients with DM (grade A recommendation). The use of third-generation β-blockers that cause vasodilatation and an increase in insulin sensitivity (such as nebivolol or carvedilol) seem to be particularly beneficial (grade A recommendation) [100]. In DM with systolic HF, a β-blocker is recommended to reduce mortality and hospitalization according to the joint ESC/EASD guidelines (level I A evidence). In DM with an ACS, β-blockers should be considered to reduce mortality and morbidity (level IIa B evidence). β-Blockers are also recommended in both HF and after acute MI to prevent sudden cardiac death in patients with DM (level I A evidence) [101].

5.1 Diabetes Mellitus and Hypertension

Although the use of β-blockers has been associated with an increased risk of developing type 2 DM, the influence of adverse metabolic effects seems to be much smaller in those with established and adequately treated DM compared with the several benefits of blood pressure control in those with concomitant hypertension [101–103]. A sub-study of the UKPDS evaluated the long-term impact of blood pressure control in hypertension and with DM. The use of atenolol or captopril significantly reduced the risk of fatal (32%) and non-fatal (24%) macrovascular and microvascular complications over 9 years of follow-up in the tight blood pressure control group (aiming for a blood pressure of <150/85 mmHg), with equal efficacy between the agents studied. The trial not only found mortality and morbidity benefits of a β₁-selective blocker to be similar to those of an ACE inhibitor in patients with DM but also found that tight blood pressure control may be more important than glycemic control in protecting these patients against macrovascular and microvascular disease as well as possibly considerably improving their survival [103, 104].

5.2 Diabetes Mellitus and Heart Failure

Meta-analyses of major HF trials (Australia/New Zealand Heart Failure Research Collaborative Group, BEST, CAPRICORN, CIBIS-II, COPERNICUS, MERIT-HF, MOCHA, PRECISE, US Carvedilol Trials) indicate a similar and significant survival benefit with β-blockers compared with placebo in diabetic and non-diabetic populations (ranging from 16 to 28% and from 28 to 37%, respectively), with consistently overlapping 95% CIs of risk ratios through the analyses. The relative reduction in mortality shows a less favorable trend for patients with diabetes compared with those without. However, as the absolute risk of mortality is considerably greater in patients with DM, the absolute mortality benefit should be equal or even greater for those with DM [87, 105–107]. Subgroup analyses of individual major HF trials also show a similar reduction in hospitalization and improvement of symptoms in those with and without DM [15, 108–110].

5.3 Diabetes Mellitus and Myocardial Infarction

In post-MI patients with DM, β-blockers were shown to reduce the risk of late infarction, sudden death, and arrhythmias and to improve mortality according to retrospective analyses of the MIAMI study and the Göteborg Metoprolol Trial [111]. Data from a multicenter cohort of 2024 patients indicated that β-blocker use is an independent predictor of 1-year cardiac survival following hospital discharge for post-MI patients with DM. Patients with DM receiving β-blocker therapy had a mortality of 10% compared with 23% for those who did not receive a β-blocker [112]. In a retrospective analysis of patients with CAD and non-insulin-dependent DM from the BIP study, those receiving β-blocker therapy had a reduced mortality risk (RR 0.58; p = 0.0001) after 3 years of follow-up than those without β-blocker medication [113].

A large observational study including 59,445 patients with DM showed a 36% mortality reduction 2 years after MI in those treated with a β-blocker. The mortality reduction in patients with no complications was 40%. Again, though the relative benefit compared with patients without DM seems to be somewhat smaller, due to the high mortality rate among patients with DM after MI, the absolute survival benefit is expected to be much larger in patients with DM [87, 89].

6 β-Blockers in Chronic Obstructive Pulmonary Disease and Bronchial Asthma

Cardiovascular disease frequently coexist with chronic obstructive pulmonary disease (COPD). However, β-blockers are substantially underused in patients with both COPD and CVD for fear of adverse pulmonary effects, especially in advanced COPD [114, 115]. β-Blockers are
generally considered to be contraindicated in patients with bronchial asthma [116].

Because of the very sensitive feedback mechanism of the adrenergic system, chronic use of β-blockers sensitizes the β₂ receptors to further stimulation by increasing receptor density in target tissues. Consequently, β-blockers may even improve the effectiveness of β₂ agonists during an exacerbation of reactive airway disease by potentiating their bronchodilator effects. This is a counterintuitive therapeutic approach and has not yet been widely investigated. The β₂-blocking effect of cardioselective β-blockers is negligible in therapeutic doses; therefore, there should be no increase in the risk of bronchoconstriction with their use [117].

According to recommendations from the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD), hypertension, HF, CAD, and AF should be treated according to usual guidelines even in patients with severe COPD. If β-blockers are indicated, a selective β₁-blocker (i.e., bisoprolol, metoprolol, or nebivolol) should be chosen and non-selective blockers avoided, especially in higher doses [118]. The ESC guidelines for HF also encourage the use of selective β₁-blockers in HF with COPD [12]. The Global Initiative for Asthma (GINA) recommendations do not encourage the use of β-blockers in patients with bronchial asthma; if necessary, treatment should be started under close medical supervision and decisions made on a case-by-case basis (level D evidence). Asthma is not an absolute contraindication for cardioselective β-blockers for acute coronary events, but a careful risk–benefit assessment should be undertaken (level D evidence) [119].

A Cochrane review of 29 RCTs of cardioselective β₁-blockers found no adverse respiratory effects in the short term in mild-moderate reversible airway disease or COPD. β₁-Blockers without ISA even showed a nonsignificant trend for increase in respiratory function after β₂-agonist administration compared with placebo [116].

A Cochrane review of 22 RCTs of β₁-selective β-blockers found no adverse effect on lung function or respiratory symptoms compared with placebo in COPD, even in severe chronic airway obstruction or disease with a reversible obstructive component [114].

A prospective multicenter observational study of current and former smokers found β-blockers to be associated with a significant reduction in COPD exacerbations regardless of the severity of airflow obstruction [incidence risk ratio (IRR) 0.73, p = 0.003]. The use of other medications for CVD such as CCBs and ACE inhibitors or ARBs was not associated with a reduction in exacerbation risk [120].

Another study found β-blockers to reduce all-cause mortality and COPD exacerbations when added to established COPD therapy. The additive benefits of β-blockers were independent of other CV drugs and history of overt CVD [121].

A number of observational studies found a survival benefit with β-blocker use in patients with HF and/or after MI [122–125]. In patients with HF and COPD, the use of the β₁-selective bisoprolol reduced mortality (especially at higher doses) as well as the incidence of congestive HF and COPD exacerbations [122, 123].

Although the observational studies even suggest some benefit with β-blockers in COPD, RCTs to confirm these findings are lacking. Patients with COPD should not be denied β-blocker treatment, but careful titration and the use of agents with β₁-selectivity is advised. In bronchial asthma, a benefit-to-risk ratio should be evaluated on an individual basis and β-blockers avoided if possible.

7 Conclusions

The efficacy of β-blockers has been well demonstrated in several CVDs. These agents were found to considerably reduce mortality in HF with reduced EF, in CAD after a MI, and in complicated CVDs, for example with CKD or DM. β-Blockers may also be beneficial in HF with preserved EF. Furthermore, β-blockers improve several symptoms of stable angina pectoris and thyrotoxicosis, provide rate control, and prevent new-onset or recurrent AF in HF, after MI, and following cardiac surgery.

High-risk CV with several comorbidities may also benefit from therapy with β-blockers. In some cases, such as CAD or hypertension complicated with DM, the choice of cardioselective β-blockers or agents with vasodilator activity may be preferable. In CVD complicated with COPD, a β₁-blocker should be the drug of choice when indicated.

Clinical guidelines based on solid evidence give clear recommendations in all the conditions discussed herein. Therapeutic decisions should be evidence based, and patients should not be denied treatment based on personal preconceptions.

The final chapter of the history of β-blockers has not yet been written. Robust prospective studies are ongoing that will hopefully resolve some of the still divisive issues regarding β-blockers. Personalized pharmacogenomic approaches might be the way of optimizing CV therapy in future.

Compliance with Ethical Standards

The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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**Funding** No external funding was used in the preparation of this manuscript.

**Conflict of interest** Csaba András Dézsi and Veronika Szentes have no conflicts of interest that are directly relevant to the contents of this manuscript.

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The Real Role of β-Blockers in Daily Cardiovascular Therapy

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The Real Role of β-Blockers in Daily Cardiovascular Therapy 373