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ESC Expert consensus document

Expert consensus document on β-adrenergic receptor blockers

The Task Force on Beta-Blockers of the European Society of Cardiology

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Preamble

Guidelines and Expert Consensus documents aim to present all the relevant evidence on a particular issue in order to help physicians to weigh the benefits and risks of a particular diagnostic or therapeutic procedure. They should be helpful in everyday clinical decision-making.

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by the European Society of Cardiology (ESC) and by different organisations and other related societies. This profusion can put at stake the authority and validity of guidelines, which can only be guaranteed if they have been developed by an unquestionable decision-making process. This is one of the reasons why the ESC and others have issued recommendations for formulating and issuing Guidelines and Expert Consensus Documents.

In spite of the fact that standards for issuing good quality Guidelines and Expert Consensus Documents are well defined, recent surveys of Guidelines and Expert Consensus Documents published in peer-reviewed journals between 1985 and 1998 have shown that methodological standards were not complied with in the vast majority of cases. It is therefore of great importance that guidelines and recommendations are presented in formats that are easily interpreted. Subsequently, their implementation programmes must also be well conducted.

The *ESC Committee for Practice Guidelines (CPG)* supervises and coordinates the preparation of new *Guidelines* and *Expert Consensus Documents* produced by Task Forces, expert groups or consensus panels. The chosen experts in these writing panels are asked to provide disclosure statements of all relationships they may have which might be perceived as real or potential conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC. The Committee is also responsible for the endorsement of these Guidelines and Expert Consensus Documents or statements.

The Task Force has classified and ranked the usefulness or efficacy of the recommended procedure and/or treatment and the Level of Evidence as indicated in the tables below:

Classes of Recommendations

Class I:	Evidence and/or general agreement that a given procedure/treatment is beneficial, useful and effective;
Class II:	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the procedure/treatment;
Class IIa:	Weight of evidence/opinion is in favour of usefulness/efficacy;
Class IIb:	Usefulness/efficacy is less well established by evidence/opinion;
Class III*:	Evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful.

*Use of Class III is discouraged by the ESC

Levels of Evidence

Level of Evidence A	Data derived from multiple randomised clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomised clinical trial or non-randomised studies
Level of Evidence C	Consensus of opinion of the experts and/or small studies

Introduction

β-Blocker therapy plays a major role in the treatment of cardiovascular diseases. For many years β-blockers were used for their antiischaemic, antiarryhthmic and antihypertensive properties. More recently, the benefit of adrenoceptor blockade was also established in patients with heart failure. The aim of this document is to review the rationale and clinical evidence for the use of β-adrenergic blockers in patients with cardiovascular disease.

The members for the Beta-blockers in Cardiovascular Disease Task Force were nominated by the Committee for Practice Guidelines (CPG) of the European Society of Cardiology (ESC). A specific literature search was carried out for original articles in peer review journals included in Medline. In addition, the ESC as well as the American Heart Association/American College of Cardiology guidelines with reference to the use of β-blockers were carefully reviewed. Most of the previously made recommendations were maintained; some were updated and a few are new according to recent evidence in the literature.

Using recommendations which are graded provides a simple method for guidance. Levels of recommendation are derived from clinical trials, conducted in selected groups of patients that may not be representative of

broader populations; in fact, patients with contraindications are excluded from clinical trials. Besides, the same strength of evidence may reflect different clinical benefit: mortality, morbidity, clinical symptoms or combined end-points; large or small benefit albeit statistically significant; easily obtained or only observed, or lost, after several years of treatment. Finally, in individual cases the recommended therapy may only be a treatment option and other alternatives may be equally acceptable or even more appropriate. An effort was made to include this information in a relatively short document.

The document prepared by the task force was circulated among a review board appointed by the ESC and approved by the Committee for Practice Guidelines of the ESC. The final document was sent to the European Heart Journal for a formal peer review.

This consensus document represents the views of the ESC and was arrived at after careful consideration of the available evidence. Health professionals are expected to take them fully into account when exercising their clinical judgement. This consensus document does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with that patient, and where appropriate and necessary the patient's guardian or carer.

Pharmacology

Definition

β-Adrenergic antagonists (β-blockers) bind selectively to the β-adrenoceptors producing a competitive and reversible antagonism of the effects of β-adrenergic stimuli on various organs (Table 1). Their pharmacological effects can be explained from the knowledge of the responses elicited by these receptors in the various tissues and the activity of the sympathetic tone.[1,2] Thus, β-blockers have relatively little effect on heart rate and contractility in an individual at rest but slow heart rate and decrease cardiac contractility when the sympathetic nervous system is activated, i.e., during exercise or stress.

Classification of β-blockers

β-Blockers can be broadly classified into (a) non-selective, those producing a competitive blockade of both β_1- and β_2-adrenergic receptors and (b) those with much higher affinity for the β_1 than for the β_2 receptors usually called β_1-selective (Table 2).[1–4] Selectivity is, however, dose-dependent and decreases or disappears when larger doses are used. Paradoxically, some β-blockers can exert a weak agonist response (intrinsic sympathomimetic activity (ISA), and can stimulate and block the β-adrenoceptor. Several β-blockers have peripheral vasodilator activity mediated via α_1-adrenoceptor blockade (carvedilol, labetalol), β_2-adrenergic receptor agonism (celiprolol) or via mechanisms independent of the adrenoceptor blockade (bucindolol, nebivolol). In addition, β-blockers can be classified as lipophilic or hydrophilic.

Pharmacokinetic properties

There are important pharmacokinetic differences among β-blockers[1–4] (Table 1).

Table 1 Effects mediated by β_1- and β_2-adrenoceptors

Tissue	Receptor	Effect
Heart		
SA node	β_1, β_2	Increase in heart rate
AV node	β_1, β_2	Increase in conduction velocity
Atria	β_1, β_2	Increase in contractility
Ventricles	β_1, β_2	Increase in contractility, conduction velocity and automaticity of idioventricular pacemakers
Arteries	β_2	Vasodilation
Veins	β_2	Vasodilation
Skeletal muscle	β_2	Vasodilation, increased contractility Glycogenolysis, K^+ uptake
Liver	β_2	Glycogenolysis and gluconeogenesis
Pancreas (β cells)	β_2	Insulin and glucagon secretion
Fat cells	β_1	Lipolysis
Bronchi	β_2	Bronchodilation
Kidney	β_1	Renin release
Gallbladder and ducts	β_2	Relaxation
Urinary bladder detrusor	β_2	Relaxation
Uterus	β_2	Relaxation
Gastrointestinal	β_2	Relaxation
Nerve terminals	β_2	Promotes noradrenaline release
Parathyroid glands	β_1, β_2	Parathormone secretion
Thyroid gland	β_2	T4 → T3 conversion

SA: Sino-Atrial; AV: Auriculo-Ventricular.

Table 2 Pharmacological classification of commonly used β-adrenergic antagonists (β-blockers)

β-blocker	ISA	Lipid solubility	Peripheral vasodilation	i.v.	Average daily oral dose
I. Non-selective ($\beta_1 + \beta_2$) adrenergic antagonists					
Carteolol	+	Low			2.5—20 mg once/twice daily
Nadolol	0	Low			40—320 mg once daily
Penbutolol	+	Moderate			20—80 mg once/twice daily
Pindolol	++	High			10—40 mg twice daily
Propranolol	0	High		+	40—180 mg twice daily
Sotalol	0	Low		+	
Timolol	0	High			5—40 mg twice daily
II. Selective β_1-adrenergic antagonists					
Acebutolol	+	Moderate			200—800 mg once/twice daily
Atenolol	0	Low		+	25—100 mg once daily
Betaxolol	0	Moderate			5—20 mg once daily
Bisoprolol	0	Moderate			2.5—10 mg once daily
Celiprolol	+	Moderate	+		200—600 mg once daily
Esmolol	0	Low		+	Only i.v.
Metoprolol	0	High		+	50—100 mg once/twice daily
Nevibolol	0		+		2.5—5 mg once daily
III. α_1- and β-adrenergic antagonists					
Bucindolol	+	Moderate	+		25—100 mg twice daily
Carvedilol*	0	Moderate	+		3.125—50 mg twice daily
Labetalol	+	Low	+		200—800 mg twice daily

ISA: Intrinsic Sympathomimetic Activity; i.v.: Intravenous administration possible; AMI: Acute Myocardial Infarction; CHF: Chronic Heart Failure. Included only β-blockers with demonstrated efficacy on clinical outcomes and supporting the guidelines recommendations.

* In some studies there was lack of evidence for peripheral α_1-adrenoceptor blockade during long-term treatment of heart failure with carvedilol.[229]

Lipophilic drugs

Lipophilic drugs (*metoprolol, propranolol, timolol*) are rapidly and completely absorbed from the gastrointestinal tract but are extensively metabolised in the gut wall and in the liver (first pass effect), so that their oral bioavailability is low (10—30%). These drugs may accumulate in patients with reduced hepatic blood flow (i.e., elderly, congestive heart failure, liver cirrhosis). Lipophilic drugs present short elimination half-lives (1-5 h) and they easily enter the central nervous system (CNS), which may account for a greater incidence of central side-effects.

Hydrophilic drugs

Hydrophilic drugs (*atenolol, esmolol*) are absorbed incompletely from the gastrointestinal tract and are excreted unchanged or as active metabolites by the kidney. They have longer half-lives (6—24 h), and do not interact with other liver-metabolised drugs. They barely cross the blood—brain barrier. Elimination half-life is increased when glomerular filtration rate is reduced (i.e., elderly, renal insufficiency).

Balanced clearance drugs

Bisoprolol has a low first-pass metabolism, enters the CNS and is excreted in equal proportion by hepatic and renal routes. *Carvedilol* has a low oral bioavailability due to an extensive first pass effect. It binds to plasma proteins and is eliminated by hepatic metabolism.[4] *Esmolol* is an ultra short-acting drug. It is administered i.v. and rapidly hydrolysed by red cell esterases (half-life 9 min).[5]

Mechanism of action

The mechanisms of action are diverse, not yet completely understood and probably with important differences between agents. The prevention of the cardiotoxic effects of catecholamines plays a central role.[6–8] The following mechanisms are also considered: (a) Antihypertensive action. Associated with a decrease in cardiac output, inhibition of the release of renin and production of angiotensin II, blockade of presynaptic α-adrenoceptors that increase the release of norepinephrine from sympathetic nerve terminals and decrease of central vasomotor activity.[1–9] (b) Anti-ischaemic action β-blockers decrease myocardial oxygen demand by reducing heart rate, cardiac contractility, and systolic blood pressure.[10] In addition, prolongation of diastole caused by a reduction in heart rate may increase myocardial perfusion. (c) Reduction of renin release and angiotensin II and aldosterone production by blocking of β_1-adrenoceptors on renal juxtaglomerular cells. (d) Improvement of left ventricular structure and function, decreasing ventricular size and increasing ejection fraction.[6–8] β-blockers may improve cardiac function because they: (i) reduce heart rate, prolong diastolic filling and coronary diastolic perfusion time, (ii) decrease myocardial oxygen demands, (iii) improve myocardial energetics by inhibiting catecholamine-induced release of free fatty acids from adipose tissue, (iv) upregulate β-adrenergic receptors and (v) reduce myocardial oxidative stress.[1,11,12] (e) The antiarrhythmic effect, the result of direct cardiac electrophysiological effects

(reduced heart rate, decreased spontaneous firing of ectopic pacemakers, slowed conduction and increased refractory period of AV node), reduces the sympathetic drive and myocardial ischaemia, improves baroreflex function and prevents catecholamine-induced hypokalemia.[13] Other mechanisms include: inhibition of cardiac apoptosis mediated via the activation of the β-adrenergic pathway,[14] inhibition of platelet aggregation,[1] reduction of the mechanical stress imposed on the plaque, preventing plaque rupture, resensitization of the β-adrenergic pathway and changes in myocardial gene expression, i.e., an increase in sarcoplasmic reticulum calcium ATPase, mRNA and α-myosin heavy chain mRNA and a decrease in β-myosin heavy chain mRNA levels.[15] Finally, some β-blockers exhibit antioxidant properties and inhibit vascular smooth muscle cell proliferation.[4]

Adverse events

In general, β-adrenergic inhibitors are well tolerated, but serious side-effects may occur, especially when these agents are used in large doses.[1,2]

Cardiovascular

β-blockers reduce heart rate, decrease the firing rate of cardiac ectopic pacemakers and slow conduction and increase the refractory period of the AV node. Thus, they may cause extreme bradycardia and AV block. These effects are seen mainly in patients with impaired sinus node function and AV-node conduction and are rare when β-blockers are given intravenously to patients with acute myocardial infarction[16] or orally in patients with chronic heart failure.[17] β-blockers decrease tissue blood flow due to blockade of vascular β_2-receptors and unopposed stimulation of vascular α-adrenoceptors. As a result, they can produce cold extremities and Raynaud's phenomenon and worsen the symptoms in patients with severe peripheral vascular disease.[4] However, the clinical benefits of β-adrenergic antagonists in patients with peripheral vascular disease and coronary artery disease may be very important.[18,19] These side-effects are less pronounced with drugs exhibiting vasodilator effects and with selective β_1 agents. β-blockers can also increase the coronary vasomotor tone, in part because of unopposed α-adrenergic mediated vasoconstriction.

Metabolic

In patients with insulin-dependent type I diabetes non-selective β-blockers mask some of the warning symptoms of hypoglycaemia (tremor, tachycardia); the other signs of hypoglycaemia (e.g., sweating) are maintained. A selective β-blocker should therefore be preferred at least in insulin dependent patients. In any case, the clinical benefit of treatment with β-blockers outweighs the risk, at least after myocardial infarction.[20,21] In one study carvedilol decreased the new onset diabetes in patients with heart failure.[22]

Pulmonary

β-blockers can lead to a life-threatening increase in airway resistance and are contraindicated in patients with asthma or bronchospastic chronic obstructive pulmonary disease. In some patients with chronic obstructive pulmonary disease, the potential benefit of using β-blockers may outweigh the risk of worsening pulmonary function. A history of asthma, however, should still be considered a contraindication to the use of any β-blocker, but chronic obstructive pulmonary disease is not a contraindication unless there is a significant reactive airway disease.[23]

Central effects

Central effects (fatigue, headache, sleep disturbances, insomnia and vivid dreams, depression) are less common with hydrophilic drugs.[24] In some patients the fatigue may be related to a decrease in blood flow to skeletal muscles; in other cases, it may be secondary to a central effect.

Sexual dysfunction

In some patients β-blockers may cause or aggravate impotence and loss of libido.

Abrupt discontinuation of β-blockers after chronic treatment can lead to *rebound symptoms* (i.e., hypertension, arrhythmias, exacerbated angina).[25,26] This increased risk is related with upregulation of β-adrenoceptors during chronic treatment.

Contraindications

The contraindications to initiate β-blocker treatment include asthma, symptomatic hypotension or bradycardia and severe decompensated heart failure (see later). Contraindications may be relative, in patients in whom the benefit of therapy may outweigh the risk of untoward effects. Chronic obstructive lung disease without bronchospastic activity and peripheral vascular disease are not considered as absolute contraindications and high risk patients may obtain a significant benefit from this therapy.[27,28] Patients with heart failure and bradycardia due to sick sinus node or second or third degree AV-block may benefit from pre-treatment with pacemaker in order to tolerate β-blockers, although this approach has, however, not been formally tested. Diabetes or intermittent lower limb claudication are not absolute contraindications for β-blockers use.[21,29–31]

Drug interactions

β-blockers may show pharmacokinetic and pharmacodynamic interactions with other drugs.[32] Aluminium salts, cholestyramine, and colestipol may decrease the absorption of β-blockers. Alcohol, phenytoin, rifampicin, and phenobarbital, as well as smoking, induce hepatic biotransformation enzymes and decrease plasma concentrations and elimination half-lives of lipophilic β-blockers. Cimetidine and hydralazine may increase the bioavailability of propranolol and metoprolol by reducing hepatic blood flow. Caution should be exercised in patients who are taking verapamil, diltiazem or various antiarrhythmic agents, which may depress sinus-node function or AV conduction. Additive effects on blood

pressure between β-blockers antagonists and other antihypertensive agents are often observed. Indomethacin and other non-steroidal antiinflammatory drugs antagonize the antihypertensive effects of β-blockers.

Dosing of β-blockers

Appropriate dosing of β-blockers varies with the clinical characteristics of the patient and the selected β-blocker. Table 2 shows the average daily oral doses in patients with hypertension and angina. Table 3 indicates the average recommended dose for intravenous use.

Clinical efficacy and use

The benefit and clinical indications of β-blockers have been clearly defined in many cardiovascular conditions and agreement about their potential usefulness has been clearly established in many clinical settings. β-Blockers are safe to use when contraindications have been excluded and the appropriate dosage regimen is used. Abrupt discontinuation should be avoided if possible to prevent withdrawal effects. In case of doubt, specialist advice is recommended.

The benefit of β-blocker treatment has been well documented in the following conditions:

Acute Myocardial Infarction (AMI)

During the acute phase of myocardial infarction, oral β-blockers are indicated in all patients without contraindications (class I, level of evidence A). Intravenous administration should be considered in patients with ischaemic pain resistant to opiates, recurrent ischaemia and for the control of hypertension, tachycardia and arrhythmias (Table 4).[33–35]

β-blockers limit infarct size, reduce life-threatening arrhythmias, relieve pain and reduce mortality including sudden cardiac death.[36–43] Two large trials were particularly relevant to guide the use of β-blockers during the first hours of AMI. In the First International Study of Infarct Survival (ISIS-1) trial[40] patients within 12 h of evolution were randomised to receive i.v. atenolol followed by oral administration for 7 days, or conventional treatment, revealing a significant reduction in mortality at 7 days (3.7% vs. 4.6%; equivalent to 6 lives saved per 1000 treated). The benefit was mainly due to a reduction in heart rupture and was evident by the end of day 1 and sustained at 1 month and 1 year. In the other large study, the Metoprolol in Myocardial Infarction (MIAMI),[41] i.v. metoprolol followed by oral administration did not significantly reduce 15-day mortality as compared to placebo (4.3—4.9% (ns)). A meta-analysis of 28 early trials of i.v. β-blockers[43] revealed an absolute reduction of short-term mortality from 4.3% to 3.7% (7 lives saved/1000 patients treated). This significant albeit small benefit was demonstrated before the reperfusion era. Similar findings were reported in a more recent meta-analysis of 52 trials, most of them including a small number of patients.[44]

Two trials of randomised i.v. β-blockade were conducted after the widespread use of reperfusion therapy in AMI,[45,46] but the number of events was too small to establish clear conclusions. In the second Thrombolysis in Myocardial Infarction (TIMI-II) trial,[45] thrombolysed patients were randomly assigned to early i.v. and oral metoprolol versus oral administration after day 6. Reinfarction and recurrent ischaemia were less frequent in the early β-blocker group and when treatment was ad-

Table 3 Intravenous dosing of β-blockers

Drug	Loading dose	Maintenance dose
Atenolol	5 + 5 mg	Oral, 50—100 mg/day
Esmolol	0.5 mg/kg over 1—5 min	0.05—0.3 mg/kg/min
Labetalol	20 mg in 2 min	2—10 mg/min
Metoprolol	2.5—5 mg i.v. bolus over 2 min; up to three doses	Oral, 25—100 mg/12 h
Propranolol	0.15 mg/kg	0.10—0.20 mg/kg/min oral, 80—240 mg/day

Table 4 Use of β-blockers in AMI: guidelines

Setting/indication	Class	Level	Ref.
i.v. administration			
For relief of ischaemic pain	I	B	33, 34
To control hypertension, sinus tachycardia	I	B	33
Primary prevention of sudden cardiac death	I	B	35
Sustained ventricular tachycardia	I	C	33
Supraventricular tachyarrhythmias	I	C	33, 34
To limit infarct size	IIa	A	33
All patients without contraindications	IIb	A	33
Oral administration			
All patients without contraindications	I	A	33, 34

ministered within 2 h of symptom onset, there was a reduction of the composite endpoint of death or reinfarction. Data from the US National Registry of Myocardial Infarction 2[47] showed that immediate β-blocker administration in patients with AMI treated with *t*-PA reduces the occurrence of intracranial haemorrhage, although this benefit is small (0.7% and 1.0%; 3 patients/1000 treated). However, a post-hoc analysis of the first Global utilization of streptokinase and *t*-PA for occluded coronary arteries (GUSTO-I) trial and a systematic review of the available experience do not support the routine, early, *intravenous* use of β-blockers,[33,44,48] at least when thrombolytic treatment or primary percutaneous intervention is performed. New data from the PAMI (Primary Angioplasty in AMI) Stent-PAMI, Air-PAMI and CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trials seems to demonstrate a reduction in mortality when β-blockers are used before primary percutaneous interventions.[49–51]

Secondary prevention after myocardial infarction

Oral β-blockers are recommended for long-term use (indefinitely) in all patients who recover from AMI and do not present contraindications (class I, level of evidence A) (Table 5).[33–35,52–58] β-blockers are underused for this indication.[59–60]

Several large, long-term trials involving more than 35,000 survivors of myocardial infarction have demonstrated that the use of β-blockers in patients recovering from an episode of AMI improves survival by 20—25% through a reduction of cardiac mortality, sudden cardiac death and reinfarction.[43,44,49,61–66] Positive results have been found in trials comparing propranolol, metoprolol, timolol, acebutolol and carvedilol with placebo; conversely, no benefit was demonstrated in trials with alprenolol, atenolol, oxprenolol or xamoterol.[44] A meta-analysis of 82 randomised trials (31 with long-term follow-up) provides strong evidence for the long-term use of β-blockers to reduce morbidity and mortality after acute MI even if aspirin, fibrinolytics or angiotensin converting enzyme inhibitors (ACE-I) were co-administered.[44] An annual reduction of 1.2 deaths in 100 patients treated with β-blockers after myocardial infarction was observed; that is, about 84 patients will require treatment for 1 year to avoid one death.[44] Similarly, the annual reduction for reinfarction was 0.9 events in 100 treated patients; equivalent to the need to treat 107 patients for 1 year to avoid one non-fatal reinfarction. In the retrospective analysis of the Cooperative Cardiovascular Project, including over 200,000 patients with myocardial infarction, β-blocker use was associated with a reduction in mortality, independent of age, race, presence of pulmonary disease, diabetes, blood pressure, ejection fraction, heart rate, renal function and treatment received during hospitalisation including myocardial revascularisation.[21]

In the Beta-blocker Heart Attack Trial (BHAT)[61] patients were randomised 5—21 days after AMI to receive propranolol or placebo. Mortality after a mean follow-up of 2 years was reduced by 25% (7% vs. 9.5%) (25 lives saved/1000 treated). In the Norwegian trial,[62] patients were randomly assigned 7—28 days after AMI to receive timolol or placebo; mortality was reduced from 9.8% to 7.2%, (26 lives/1000 treated) over a follow-up of 25 months. Sudden cardiac death and reinfarction were also significantly reduced. Interestingly, the beneficial influence of timolol on survival was sustained for at least 6 years.[63] In the study of Hjalmarson et al.,[64] metoprolol given first intravenously and then orally, mortality at 90 days was reduced by 26%. In the Boissel et al. trial Acebutolol et Prévention Secondarie de l'Infartus (APSI) trial,[65] including high risk patients 2—22 days after AMI, there was also a significant 48% reduction in mortality associated with the β-blocker treatment. In the Carvedilol Post Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial including patients 2—21 days after AMI with reduced left ventricular ejection fraction and receiving ACE-I, all-cause mortality was lower in the carvedilol group than in the placebo group (12% vs. 15%).[66] The significant mortality reductions in heart failure observed with β-blockers and the result of the CAPRICORN trial further support the use of these agents in high risk patients with impaired ventricular function or failure after infarction and demonstrate that the benefit of β-blockers is observed also in patients receiving treatment according to current standards, including reperfusion therapy and ACE-I.

Although the benefit of β-blockers is observed in a broad population after infarction,[21,30,67] the benefit of long-term therapy is greatest in high-risk patients (i.e., those with evidence of large or anterior infarction) and there is continued debate about whether low-risk subjects (young, revascularised patients without previous infarction, residual ischaemia or ventricular arrhythmias and normal ventricular function) should be treated with β-blockers because their long-term prognosis is favourable. Chronic stable ischaemic heart disease

Table 5 Use of β-blockers in secondary prevention after infarction: guidelines

Setting/indication	Class	Level	Ref.
All patients without contraindications, indefinitely	I	A	33, 34, 52—57
To improve survival	I	A	33, 52—53
To prevent reinfarction	I	A	33, 52—53
Primary prevention of sudden cardiac death	I	A	35
To prevent/treat late ventricular arrhythmias	IIa	B	33, 35

patients and patients with atherosclerosis (carotid plaque) may benefit from a combined treatment with statins and β-blockers.[68] Treatment with β-blockers in diabetic patients seems to be more effective than in non-diabetics and the risk of complications is negligible.[69] Other subgroups at high risk, include late ventricular arrhythmias and post infarction ischaemia, Q wave and non-Q wave infarctions and elderly patients also benefit from β-blockers.[21,67] Although relative contraindications once may have been thought to preclude the use of β-blockers in some patients, new evidence suggests that the benefits of β-blockers in reducing reinfarction and mortality may actually outweigh its risks, even in patients with (1) insulin dependent diabetes mellitus; (2) chronic obstructive pulmonary disease; (3) severe peripheral vascular disease; (4) PR interval up to 0.24 s; and (5) moderate left ventricular failure.[21] It is also emphasized that the use of β-blockers in such patients requires careful monitoring of the patient to be certain that adverse events do not occur.[34]

Non-ST-segment elevation acute coronary syndromes

Patients with Acute Coronary Syndromes (ACS) without ST-segment elevation should be treated with β-blockers as soon as possible, to control ischaemia and prevent AMI/reinfarction (class I, level of evidence B).[65–67] After the acute phase, all patients should receive β-blockers during long term for secondary prevention (class I, level of evidence A) (Table 6).[70,71]

There are few randomised studies with β-blockers in patients with unstable angina and non-Q wave myocardial infarction,[73–75] and the new non-ST- segment elevation ACS terminology makes the analysis of possible effect even more difficult. Henceforth, the recommendations are based on small studies in unstable angina as well as in the evidence in acute ST-segment elevation myocardial infarction and stable patients with ischaemia and previous myocardial infarction. In fact, there are few studies in patients with unstable angina comparing β-blockers with placebo A meta-analysis suggested that β-blocker treatment was associated with a 13% relative reduction in risk of progression to AMI.[76] Although no significant effect on mortality has been demonstrated in unstable angina in these relatively small trials, larger randomised trials of β-blockers in patients with acute or recent MI have shown a significant effect on mortality.[43,44] In addition, a retrospective analysis from the Cooperative Cardiovascular Project[21] indicates that the relative risk of death was lower in patients with non-Q wave myocardial infarction receiving β-blockers. Pooled data from 2,894 patients with acute coronary syndromes included in five randomised, controlled trials of abciximab during coronary intervention showed a reduction of 30 day and 60 day mortality associated with the use of β-blockers.[77] There is no evidence that any specific β-blocking agent is more effective in producing beneficial effects in unstable angina and oral therapy should be aimed to achieving a target heart rate between 50 and 60 beats per minute. The intravenous route should be preferred in patients at high risk (class II, level of evidence B).[70,71] β-blockers can increase coronary artery tone and are contraindicated in vasospastic angina without obstructive lesions.[78]

Chronic, stable ischaemic heart disease

All patients with chronic, stable ischaemic heart disease should receive long-term treatment with β-blockers to control ischaemia, prevent infarction and improve survival. This is considered as a class I recommendation, level of evidence A in patients with previous myocardial infarction and class I, levels of evidence A, B and C (to control ischaemia, prevent infarction and improve survival, respectively) in the absence of a previous history of infarction (Table 7).[33,34,52,53,57,72,79] β-blockers should

Table 6 Use of β-blockers in non-ST-segment elevation ACS: guidelines

Setting/indication	Class	Level	Ref.
Early benefit, reduction of ischaemia	I	B	70—72
Early benefit, prevention MI	I	B	70, 71
Long-term secondary prevention	I	B	70, 71

Table 7 Use of β-blockers in chronic, stable ischaemic heart disease: guidelines

Setting/indication	Class	Level	Ref.
Previous infarction			
To improve survival	I	A	33—35, 52, 53
To reduce reinfarction	I	A	33, 72
To prevent/control ischaemia	I	A	33—35, 52, 53
No previous infarction			
To improve survival	I	C	33—35, 52, 53
To reduce reinfarction	I	B	33, 79
To prevent/control ischaemia	I	A	33, 52, 53

be considered as the first choice in patients with chronic angina or ischaemia, and hypertension, previous infarction or poor ventricular function.[53,57,58,79] They appear to be underused for this indication.[80]

β-blockers are highly effective to control exercise-induced angina, improve exercise capacity,[81–87] and to reduce or suppress both symptomatic and asymptomatic ischaemic episodes.[85,88–91] No clear clinical differences have been demonstrated between different β-blockers. Also, no clinical relevant differences were found when comparing β-blockers with calcium channel blockers for the control of ischaemia.[92–95] Combination therapy with nitrates and β-blockers may be more effective than nitrates or β-blockers alone.[96] β-blockers may also be combined with dihydropyridines,[97–101] but the combination with verapamil and diltiazem increases the risk of bradycardia or AV block.

If possible, β-blockers (and other anti-ischaemic drugs) should be withheld for four half-lives (usually about 48 h) when a stress test is planned for the diagnosis and risk stratification of patients with suspected coronary artery disease.[102] β-blockers should be withdrawn gradually to avoid withdrawal effects.[26,103]

The effect on prognosis in patients with stable angina has not been specifically studied in large trials, and most of the information comes from studies in the pre-thrombolytic era, when myocardial revascularisation was more restricted. A history of angina has, however, been present in about 1/3 of patients recruited in post infarction studies with β-blockers. The β-blockers pooling project[67] reported a highly significant reduction in mortality in this subgroup, and it seems reasonable to assume that β-blockers have the potential to prevent death, especially sudden cardiac death, and myocardial infarction even when there has been no prior infarction.[53,57,79]

The effects of β-blockers in patients with stable angina without prior MI or hypertension have been investigated in some randomised controlled trials. In the Total Ischaemic Burden European Trial (TIBET)[104], no difference was found between atenolol and nifedipine, and in the Angina Prognosis Study in Stockholm (APSIS)[105] the clinical outcome was similar in the groups treated with metoprolol and verapamil. In the Atenolol Silent Ischaemia Study (ASIST),[91] in patients with mild angina, atenolol decreased ischaemic episodes at 6 weeks as compared with placebo and after 1 year there was an improvement in the cardiovascular combined outcomes. In the Total Ischaemic Burden Bisoprolol Study (TIBBS)[106] bisoprolol was more effective than nifedipine in reducing the number and duration of ischaemic episodes in patients with stable angina. In the International Multicenter Angina Exercise (IMAGE) trial,[107] metoprolol was more effective than nifedipine in controling exercise induced ischaemia.

Heart failure

All patients with stable, mild, moderate and severe chronic heart failure from ischaemic or non-ischaemic cardiomyopathies and reduced left ventricular ejection fraction, in NYHA class II–IV, should be treated with β-blockers, unless there is a contraindication (class I, level of evidence A).[55,108] In patients with left ventricular systolic dysfunction, with or without symptomatic heart failure following an AMI, long-term β-blockade is recommended in addition to ACE inhibition to reduce mortality (class I, level of evidence A).[55,108] Finally, β-blockers are also recommended in patients with chronic heart failure and preserved left ventricular function (class IIa, level of evidence C) [108] (Table 8). β-blockers are underused in patients with heart failure.[109]

The evidence of clinical benefit on β-blockers in patients with chronic heart failure with systolic left ventricular dysfunction was demonstrated in a number of small studies and in several, large, prospective, randomised, placebo controlled trials, including a total of over 15,000 patients.[110–125] Placebo-controlled mortality trials with carvedilol,[66,116,119,124,125] bisoprolol[121] and metoprolol[122,123] have been associated with a long-term reduction in total mortality, cardiovascular mortality, sudden cardiac death and death due to progression of heart failure in patients in functional class II–IV. In these studies, β-blocking therapy also reduced hospitalisations (all, cardiovascular and heart failure-related), improved the functional class and led to less worsening of heart failure than placebo. This beneficial effect has been consistently observed in subgroups of different age, gender, functional class, left ventricular ejection fraction and ischaemic or non-ischaemic aetiology, diabetics and non-diabetics. Black patients may be an exception, since in the BEST trial this ethnic group lacked the benefit from β-blocker therapy in heart failure.[126] In smaller, controlled studies β-blockade has been shown to improve

Table 8 Use of β-blockers in chronic heart failure: guidelines

Setting/indication	Class	Level	Ref.
All stable patients, with symptomatic heart failure and reduced LVEF, functional class II–IV (to prolong survival)	I	A	55, 108
LVSD without symptoms after AMI	I	A	55, 108
LVSD without symptoms, no previous MI	I	B	55
Chronic HF with preserved systolic function (to reduce heart rate)	IIa	C	108
Acute, compensated heart failure after AMI	IIa	B	135
Patient stable after acutely decompensated chronic heart failure	I	A	135

AMI: Acute Myocardial Infarction; LVEF: Left Ventricular Ejection Fraction; LVSD: Left Ventricular Systolic Dysfunction.

ventricular function.[115–127] Exercise capacity may also improve[114] as well as symptoms and quality of life,[17] but these effects usually are marginal and have not been consistently demonstrated in all trials comparing β-blockers with placebo.[128]

In the second Cardiac Insufficiency Bisoprolol Study (CIBIS-2)[121] symptomatic patients in NYHA class III or IV, with left-ventricular ejection fraction of 35% or less, receiving standard therapy with diuretics and ACE-inhibitors, were randomly assigned to receive bisoprolol or placebo during a mean follow of 1.3 years. The study was stopped early because bisoprolol showed a significant mortality benefit (11.8% vs. 17.3%) (55 lives saved/1000 treated; Number Needed to Treat (NNT) for 1.3 year to save 1 life = 18). There were significantly fewer sudden cardiac deaths among patients on bisoprolol than in those on placebo (3.6% vs. 6.3%). Treatment effects were independent of the severity or cause of heart failure.

In the Metoprolol Randomised Intervention Trial (MERIT-HF)[122] patients with chronic heart failure in NYHA functional class II–IV and ejection fraction ≤40% and stabilised with optimum standard therapy, were randomly assigned metoprolol CR/XL or placebo. This study was also stopped early on the recommendation of the independent safety committee after a mean follow-up of 1 year. All-cause mortality was lower in the metoprolol group than in the placebo group (7.2%, per patient-year of follow-up vs. 11.0%) (38 lives saved/1000 treated; number needed to treat (NNT) for 1 year to save 1 life = 28). There was also a 41% reduction in sudden cardiac death and 49% reduction in deaths from worsening heart failure.

In the Carvedilol Prospective Randomised Cumulative Survival (COPERNICUS) study,[124] patients who had symptoms of heart failure at rest or on minimal exertion, clinically euvolemic, and with an ejection fraction of <25% were randomly assigned to placebo or carvedilol for a mean period of 10.4 months. The study also terminated prematurely after observing a significant reduction in mortality: the cumulative risk for death at 1 year was 18.5% in the placebo group and 11.4% in the carvedilol group (71 lives saved/1000 treated; number needed to treat for 10.4 months to save 1 life (NNT) = 18). As in the previous studies, there was a reduction in hospitalisations and sudden cardiac death. In a post hoc analysis from CIBIS II and MERIT-HF including high risk patients with ejection fraction <25% and NYHA class III and IV similar findings were observed.[121,129]

In the CAPRICORN trial[66] patients with left-ventricular ejection fraction of <40% early after an episode of AMI were randomly assigned to carvedilol or placebo. After a mean follow-up of 1.3 years, all-cause mortality alone was lower in the β-blocker group (12% vs. 15%), although no differences were observed in rehospitalisation rate.

In the Beta-blocker Evaluation of Survival (BEST) Trial[130] patients with chronic heart failure and reduced left ventricular ejection fraction were assigned to bucindolol or placebo. The study was stopped prematurely because of lack of differences in total mortality after 2 years of follow-up (33% vs. 30% in the placebo and bucindolol groups, respectively; $p = 0.16$). Nevertheless, the risk of the secondary end-point of death from cardiovascular causes was lower in the bucindolol group (HR, 0.86; 0.74–0.99), as well as rehospitalisation secondary to worsening heart failure. In a subgroup analysis, there was a survival benefit in non-black patients.

Overall, the NNT for approximately 1 year with a β-blocker in mainly NYHA class II/III (mild-moderate) CHF is 28 to prevent 1 death and 16 to prevent 1 death or hospitalisation (based on MERIT-HF) and in moderate to severe CHF (mainly class III/IV) these numbers are 18 and 13, respectively (based on COPERNICUS).

Although a reduction in mortality and hospitalisation has been demonstrated with several β-blockers in chronic heart failure, a class-effect has not been established. No benefit on survival was observed with bucindolol (BEST),[130] although bucindolol was associated with a reduction in cardiovascular mortality and myocardial infarction.[131] A direct comparison of two different β-blockers (metoprolol vs. carvedilol) has been assessed in the Carvedilol Or Metoprolol European Trial (COMET).[132] In this study patients with chronic heart failure and reduced left ventricular ejection fraction were treated with carvedilol (targed 25 mg bid) or metoprolol tartrate (targed 50 mg bid). After a mean follow-up of 58 months all cause mortality was lower in the carvedilol group (34% vs. 40%) (HR 0.83; CI 0.74–0.93), equivalent to an NNT to save one life = 59; and this finding was consistent through predefined groups. No differences in re-hospitalisation were observed between groups. The results of this study suggest that carvedilol is superior to metoprolol to extend life in heart failure patients. However, in this trial the formulation of metoprolol was different from the one used in the MERIT-HF trial (tartrate vs. slow release succinate) and the target dose was lower (50 mg/12 h vs. 100 mg/12 h, equivalent to 130 mg/day of tartrate). In any case, the COMET trial illustrates that selection of a β-blocker and the dose used may have a significant impact on the outcome of patients with heart failure. Accordingly only bisoprolol, metoprolol in the formulation and dose used in MERIT-HF and carvedilol are recommended for the treatment of patients with heart failure.

Further data are needed to establish the effects of β-blocking agents in certain demographic groups, such as elderly subjects (>75 years), certain racial subsets and patients with atrial fibrillation. In SENIORS the effect of β-blockade (nevibolol) in the elderly patient with heart failure is investigated. In another study, CIBIS-3, bisoprolol will be used first, followed by the administration of ACE-inhibitors.

As β-blocker action may be biphasic with long-term improvement, possibly preceded by initial worsening, β-blockers should be initiated under careful control. The initial dose should be small and increased slowly and progressively to the target dose used in the large clinical trials. Uptitration should be adapted to the individual response. β-blockers may reduce blood pressure and heart rate excessively, may temporarily induce myocardial depression and precipitate heart failure. In addition, β-blockers may initiate or exacerbate asthma and induce peripheral vasoconstriction. Table 9 indicates the recommended procedure for the use of β-blockers in clinical

Table 9 Practical guidance on using β-adrenergic blockers in heart failure (modified from Ref. 133)

Who should receive β-blocker therapy
- All patients with chronic, stable heart failure
- Without contraindications (symptomatic hypotension or bradicardia, asthma)

What to promise
Treatment is primarily prophylactic against death and new hospitalisations for cardiovascular reasons. Some patients will experience improvement of symptoms.

When to start
- No physical evidence of fluid retention (use diuretics accordingly)
- Start ACE-I first if not contraindicated
- In stable patients, in the hospital or in outpatient clinics
- NYHA class IV/severe CHF patients should be referred for specialist advice
- Review treatment. Avoid verapamil, diltiazem, antiarrhythmics, non-steroidal anti-inflamatory drugs

Beta-blocker

- Bisoprolol, carvedilol or metoprolol

Dose
- Start with a low dose
- Increase dose slowly. Double dose at not less than 2 weekly intervals
- Aim for target dose (see above) or, if not tolerated, the highest tolerated dose

	Starting dose mg	**Target dose mg**
Bisoprolol	1.25 once daily	10 once daily
Carvedilol	3.125 twice daily	25—50 twice daily
Metoprolol CR/XL	12.5—25 once daily	200 once daily

Monitoring
- Monitor for evidence of heart failure symptoms, fluid retention, hypotension and bradycardia
- Instruct patients to weigh themselves daily and to increase their diuretic dose if weight increases

Problem solving
- Reduce/discontinue β-blocker only if other actions were ineffective to control symptoms/secondary effects
- Always consider the reintroduction and/or uptitration of the β-blocker when the patient becomes stable
- Seek specialist advice if in doubt.

Symptomatic hypotension (dizziness, light headedness and/or confusion)
- Reconsider need for nitrates, calcium channel blockers and other vasodilators
- If no signs/symptoms of congestion consider reducing diuretic dose

Worsening symptoms/signs (increasing dyspnoea, fatigue, oedema, weight gain)
- Double dose of diuretic or/and ACE-I.
- Temporarily reduce the dose of β-blockers if increasing diuretic dose does not work
- Review patient in 1—2 weeks; if not improved seek specialist advice
- If serious deterioration halve dose of β-blocker
- Stop β-blocker (rarely necessary; seek specialist advice)

Bradycardia
- ECG to exclude heart block
- Consider pacemaker support if severe bradycardia or AV block or sick sinus node early after starting β-blockers
- Review need, reduce or discontinue other heart rate slowing drugs, e.g., digoxin, amiodarone, diltiazem
- Reduce dose of β-blocker. Discontinuation rarely necessary

Severe decompensated heart failure, pulmonary oedema, shock
- Admit patient to hospital
- Discontinue β-blocker if inotropic support is needed or symptomatic hypotension/bradycardia is observed
- If inotropic support is needed, levosimendan may be preferred

CHF: Congestive Heart Failure; NYHC: New York Heart Association.

practice and lists the contraindications. Detailed practical guidance on the use of β-blockers in heart failure can be found elsewhere.[133]

Heart failure and preserved systolic function

There is a paucity of data regarding the possible benefit of β-blockers in patients with heart failure and preserved systolic left ventricular function. Accordingly, the recommended use of β-blockers in these patients is empirical, based mainly on the possible benefit of reducing heart rate and improving myocardial ischaemia.

Acute heart failure

There are no randomised clinical trials with β-blockers in acute heart failure targeted to improve the acute condition. In the Gothenburg study i.v. metoprolol or

placebo was initiated early after an AMI and followed by oral therapy for three months. Patients with new symptoms of heart failure were less frequently found in the metoprolol group, and in patients with signs of pulmonary congestion with basal rales and/or i.v. furosemide, metoprolol therapy reduced mortality and morbidity.[134] In the COPERNICUS trial, β-blocker therapy started early after acute decompensation of chronic heart failure was associated with a long-term reduction in mortality.[124] In the CAPRICORN trial patients with heart failure or left ventricular dysfunction randomised early after AMI also received benefit from β-blocker therapy.[66] As recommended in the ESC acute heart failure guidelines.[135] Patients with acute overt heart failure including more than basal pulmonary rales, β-blockers should be used cautiously. In these patients, if ongoing ischaemia and tachycardia are present, intravenous metoprolol can be considered. (class IIb, level of evidence C). However, in patients with AMI who stabilise after acute heart failure, β-blockers should be initiated early (class IIa, level of evidence B). In patients with chronic heart failure β-blockers should be initiated when the patient has stabilised after the acute episode (usually after 4 days) (class I, level of evidence A). The oral initial dose of bisoprolol, carvedilol or metoprolol should be small and increased slowly and progressively to the target dose used in the large clinical trials. Up-titration should be adapted to individual response. Patients on β-blockers admitted due to worsening heart failure, should be continued on this therapy in general unless inotropic support is needed but dose could be reduced if signs of excessive dosages are suspected (low heart rate and hypotension).

Arrhythmias (Table 10)

Sinus tachycardia

Sinus tachycardia is not a primary disorder and treatment should be directed to the underlying cause. In selected individuals β-blockers can be used to slow heart rate[136,137] (class I, level of evidence C) (e.g., if a fast heart rate produces symptoms) and are especially indicated in situations of anxiety, after myocardial infarction, in patients with heart failure, hyperthyroidism and hyperdynamic β-adrenergic state.[137,138] In patients with pheochromocytoma, β-blockers are also effective to control sinus tachycardia, but if given alone hypertensive crisis can occur secondary to unopposed α-receptor mediated constriction.[139]

Supraventricular tachycardias

β-blockers are effective for suppressing atrial premature beats and controlling heart rate and conversion of *focal atrial tachycardia*, as well as preventing its recurrence, in many instances the result of increased sympathetic tone[140] such as after surgery (class I, level of evidence C) (Table 10).[137] On the contrary, *multifocal atrial tachycardia* is frequently associated with severe obstructive lung disease, in which case β-blockers are ineffective and contraindicated. *AV nodal reciprocating tachycardias*, the most common form of paroxismal supraventricular tachycardia, also responds well to i.v. administration of propranolol, metoprolol, atenolol, sotalol or timolol, with a reduction in heart rate, conversion to sinus rhythm or facilitating the success of vagal manoeuvres[137,141–145] (class I, level of evidence C). β-blockers are also useful for the prevention of recurrent episodes. Oral

Table 10 Use of β-blockers in arrhythmias: guidelines

Setting/indication	Class	Level	Ref.
Supraventricular arrhythmias			
Sinus tachycardia	I	C	137
Focal atrial tachycardia, for cardioversion	IIa	C	137
Focal atrial tachycardia, for prevention of recurrence	I	B	137
Atrioventricular nodal reciprocating tachycardia	I	C	137
Focal junctional tachycardia	IIa	C	137
Non-paroxysmal junctional tachycardia	IIa	C	137
WPW with symptomatic arrhythmias	IIa	C	137
Atrial flutter			
Rate control of atrial flutter, poorly tolerated	IIa	C	137
Rate control of atrial flutter, well tolerated	I	C	137
Atrial fibrillation (ESC/AHA/ACC)			
Prevention (post AMI, HF, HTA, post surgery, post conversion to sinus rhythm)	I	A	136
Chronic control of heart rate	I	B	136
Acute control of heart rate	I	A	136
Conversion to sinus rhythm	IIa	B	136
Combination with digoxin, for heart rate control	IIa	A	136
Acute control of HR in heart failure	IIb	C	136
Ventricular arrhythmias			
Control of arrythmias early after AMI (i.v.)	I	A	33
Control of arrythmias late after AMI	I	A	33, 35, 52, 56, 57
Prevention of sudden cardiac death in heart failure and after MI	I	A	137

administration of β-blockers is very effective to prevent paroxysmal tachycardias precipitated by emotion or exercise.[146] Oral propranolol, atenolol, nadolol, and sotalol were found to be effective in the long term prophylactic treatment of patients with paroxysmal supraventricular tachycardias[145] (class I, level of evidence C).[137] β-blockers are also recommended for the treatment of other forms of supraventricular tachycardias, including *focal junctional tachycardia* and *non-paroxysmal junctional tachycardia*[137] (Table 10).

Tachycardias in WPW syndrome

β-blockers may be effective in some patients with supraventricular arrhythmias in the presence of WPW, if the accessory pathway is incapable of rapid anterograde conduction as demonstrated in an electrophysiological studies.[137,145] However, β-blockers may cause very serious adverse events. β-blockers, as well as digitalis and calcium channel blockers, do not block the accessory pathway and may even enhance conduction, resulting in a very rapid ventricular response which may lead to severe hypotension or cardiac arrest.[136,147–149] For this reasons, β-blockers are contraindicated in arrhythmias associated with WPW syndrome. β-blockers are also contraindicated in patients with sick sinus or bradycardia/tachycardia syndrome, as sinus arrest with syncope may occur.[145]

Atrial flutter

β-blockers are not effective for conversion of atrial flutter to sinus rhythm but may be effective for ventricular rate control, for this reason they are indicated in stable patients (class I, level of evidence C).[137]

Atrial fibrillation

β-blockers may be effective to prevent episodes of Atrial Fibrillation (AF), to control heart rate, to revert atrial fibrillation to sinus rhythm and to maintain sinus rhythm after it is restored (Table 10).[136]

Prevention. The incidence of atrial fibrillation is lower in patients receiving β-blockers. This effect has been observed in randomised studies in patients with heart failure, during secondary prevention after acute myocardial infarction, in hypertension and after elective non-cardiac surgery.[136]

Control of heart rate. Propranolol, atenolol, metoprolol, or esmolol may be given i.v. to acutely control the rate of ventricular response to AF in specific settings, especially in states of high adrenergic tone (e.g., postoperatively), but i.v. administration in heart failure is not recommended. β-blockers have also proved to be effective in patients with AF complicating thyrotoxicosis, AMI, chronic stable coronary artery disease[150,151] and during pregnancy.[152] For acute control of heart rate, intravenous esmolol is the recommended agent.[136,153]

For long-term use, β-blockade is a safe therapy to control heart rate in AF patients and antagonises the effects of increased sympathetic tone. In seven of 12 comparisons with placebo, β-blockers were effective in controlling resting heart rate. The effect was drug specific, with sotalol, nadolol and atenolol being the most efficacious.[150] Atenolol provided better control of exercise-induced tachycardia than digoxin alone.[154] Combinations of several agents may often be required to achieve adequate rate control, but care should be taken to avoid excessive slowing. In general, the combination of digoxin and β-blockers appears to be more effective than either digoxin or β-blocker alone and better than the combination of digoxin and calcium channel blockers.[155–158]

Conversion to sinus rhythm. There are few randomised studies exploring the efficacy of β-blockers to revert AF to sinus rhythm or to maintain sinus rhythm. One randomised, open-label, crossover study showed that atenolol was as effective as sotalol and better than placebo at suppressing episodes of AF, reducing their duration and associated symptoms.[150] In AF after non-cardiac surgery, intravenous esmolol produced a more rapid conversion to sinus rhythm than did intravenous diltiazem,[151], but other antiarrhythmic drugs are preferred for cardioversion of AF to sinus rhythm.[136] β-blockers may also reduce subacute recurrences after conversion to sinus rhythm,[151] bisoprolol being as effective as sotalol[159] and carvedilol[160] to maintain sinus rhythm after AF.

Ventricular arrhythmias

β-blockers are effective in the control of ventricular arrhythmias related to sympathetic activation, including stress-induced arrhythmias, AMI, perioperative and heart failure, including the prevention of sudden cardiac death (class I, level of evidence A)[33,35,52,56,57] (Table 10). Most β-blockers have proved effective to reduce the number of ventricular premature beats. In sustained ventricular tachycardia, β-blockers including propanolol, sotalol, metoprolol and oral atenolol have been effective to suppress the tachycardia, but the experience is limited and there is a lack of controlled studies. Success of β-blocker to treat VF is anecdotal.[161] On the contrary, β-blockers have proven to be very efficacious to prevent arrhythmias leading to sudden cardiac death in different conditions, including acute and chronic myocardial ischaemia, heart failure and cardiomyopathies.

Prevention of sudden cardiac death

There is clear evidence demonstrating that the benefit derived from β-blocker treatment in part is the consequence of a reduction in sudden cardiac death (SCD). Accordingly, β-blockers are clearly indicated in the primary and secondary prevention of SCD in different clinical settings and guidelines have been established[33,35,162,163] (Table 11). However, it should be stressed that for secondary prevention of sudden cardiac death and in particular in the presence of severe left ventricular dysfunction, the use of β-blockers does not

Table 11 Use of β-blockers in the prevention of sudden cardiac death: guidelines

Disease/setting	Indication	Class	Level	Ref.
AMI	Primary prevention	I	A	33
Post-MI	Primary prevention, in presence of HF or LV dysfunction	I	A	35, 163
Post-MI	Primary prevention, during and post-MI	I	A	35, 163
Post-MI	Resuscitated VT/VF, spontaneous sustained VT	IIa	C	33, 35, 163
Heart failure	Primary or secondary prevention	I	A	35
Dilated cardiomyopathy	Primary or secondary prevention	I	B	35, 163
Myocardial bridging	Primary prevention	IIa	C	35
Long QT syndrome	Primary prevention − symptomatic	I	B	35
Long QT syndrome	Secondary prevention − β-blockers+ICD	I	C	35
Long QT syndrome	Primary prevention − asymptomatic	IIa	C	35
Catecholaminergic VT	Primary or secondary prevention	IIa	C	35
RV cardiomyopathy	Primary prevention	IIb	C	35
Patients with implantable defibrillators	Secondary prevention	IIa	C	35, 163

HF: Heart Failure; LV: Left Ventricle; MI: Myocardial Infarction; RV: Right Ventricle; VT: Ventricular Tachycardia; BP: Blood Pressure.

preclude the identification and appropriate treatment of ischaemia and the use of implantable defibrillators.[35,163]

Acute myocardial infarction

The use of β-blockers in AMI has been already discussed. For the prevention of VF, i.v. β-blockers are indicated in patients with ventricular arrythmias[33] (class I, level of evidence A) (Table 11). SCD secondary to VF is very frequent after an acute coronary occlusion.[164–167] β-blockers increase the threshold for VF during acute ischaemia and a decrease in VF was demonstrated in some placebo controlled trials with metoprolol, atenolol and propranolol very early after onset of symptoms.[39,168,169] In a randomised study including 735 patients within 4 h after the onset of chest pain, treated with intravenous propranolol followed by oral administration, VF occurred in two patients in the β-blocker group and in 14 of the control group ($p < 0.06$).[39] Also, i.v. metoprolol in patients with AMI significantly reduced the number of VF episodes.[39] However, in other large studies, including the ISIS-2 and MIAMI[40,41] no significant decrease in the incidence of VF was noted. Besides, in the thrombolytic era, there is a lack of controlled studies exploring the effect of early β-blocker administration on the incidence of VF, and the benefit of early intravenous administration of β-blockers to prevent VF is questionable in patients treated with reperfusion therapy.[33]

After acute myocardial infarction, the efficacy of β-blockers is related to a reduction in all-cause mortality and sudden cardiac death and their use is recommended in all patients for the primary prevention of sudden cardiac death (class I, level of evidence A)[33,35,163] (Table 11). A recent analysis of 31 β-blockers trials[170] showed that 13 trials reported data on reduction of SCD, which was reduced from 51% to 43% in patients treated with β-blockers vs. the untreated group. In the CAPRICORN trial in post MI patients with left ventricular dysfunction, there was a trend toward SCD reduction in the carvedilol group.[66]

Heart failure

Patients with a history of congestive heart failure [67] or depressed left ventricular function[171] show the greatest benefit from β-blockers in mortality reduction, including SCD and are indicated in all patients for the prevention of SCD (Class I, level of evidence A)[35] (Table 11). A consistent contribution to the improved outcome by these drugs is related to a substantial reduction (between 40% and 55%) in SCD rates.[115,122,172] The recent introduction of new therapies, such as thrombolytics, ACE-Inhibitors, aldosterone receptor blockers as well as concomitant revascularisation or aspirin does not appear to limit the independent benefit on clinical outcome provided by β-blockers, as suggested by the evidence of risk reductions between 30% and 50%.[21]

Dilated cardiomyopathy

There are no specific studies demonstrating the benefit of β-blockers for the prevention of sudden cardiac death in dilated cardiomyopathy, but the reduction in mortality was similar in patients with ischemic or non-ischaemic heart failure[115]; accordingly, β-blockers are recommended for the prevention of sudden cardiac death in this population (class I, level of evidence B)[35,163] (Table 11).

Hypertrophic cardiomyopathy

Sudden cardiac death secondary to ventricular arrhythmias is frequent in patients with hypertrophic cardiomyopathy, especially during exercise and in the presence of left ventricular outflow obstruction.[163] Though β-blockers may improve symptoms, the currently available data do not support the routine use of β-blockers in the prevention of sudden cardiac death in these patients.[21,35,173–176]

Mitral valve prolapse

Mitral valve prolapse is usually benign; its link with SCD has been suggested but never conclusively demonstrated.[35] No prospective studies have ever been conducted with β-blockers or antiarrhythmic drugs in this condition. Accordingly, no data are available to define prophylactic interventions that may reduce the risk of SCD. However, β-blocking agents are generally considered as first choice therapy in symptomatic patients. Yet, the routine or selective use of β-blockers to prevent

sudden cardiac death in patients with mitral valve prolapse is not recommended.[35]

Myocardial bridging

Although it is considered as a benign condition, patients with myocardial bridging may present with ischaemia and in some cases ventricular arrhythmias and sudden cardiac death.[177] Symptoms usually improve with β-blockers.[178] This information is based on a limited number of small observational studies (class IIa, level of evidence C).[35]

Long QT syndrome (LQTS)

Prolongation of the QT interval not secondary to ischaemia or drugs is associated with life-threatening ventricular arrhythmias, sometimes exercise or stress related.[179,180] β-Blockers are usually considered indicated but there is a lack of prospective, placebo-controlled studies. In the largest of the retrospective analyses, conducted in 233 LQTS patients, all symptomatic for syncope or cardiac arrest, mortality 15 years after the first syncope was 9% for the patients treated by antiadrenergic therapy (β-blockers and/or left cardiac sympathetic denervation) and close to 60% in the group not treated or treated with miscellaneous therapies.[181] These data support the benefit of β-blockers, however, they do not provide total protection and especially for the patients with a history of cardiac arrest the risk of SCD remains unacceptably high. In symptomatic patients the use of β-blockers is considered a class I with a level of evidence B, in asymptomatic patients a class IIa, level of evidence C[35] (Table 11).

Catecholaminergic polymorphic ventricular tachycardia

This clinical entity is characterised by adrenergically induced polymorphic ventricular tachycardia in the absence of structural cardiac abnormalities and a familial history of syncope and SCD occurs in approximately one third of the cases.[182,183] The arrhythmias are reproducible during exercise stress test or during isoproterenol infusion.[183] At the present time β-blockers seem to be the only therapy that may be effective.[183] Retrospective analysis of the few published cases, shows SCD in 10.5% and 48% of patients with and without β-blocker therapy, respectively.[183] Although this finding is not conclusive given the lack of controlled studies, β-blockers are recommended for the primary and secondary prevention of SCD (class IIa, level of evidence C).[35]

SCD in the normal heart

Idiopathic VF occurs in up to 8% of victims of SCD.[184] According to the UCARE European registry, prevention of recurrence with antiarrhythmic agents and β-blockers failed.[185]

The *Brugada syndrome*[186] is an arrhythmogenic disorder associated with high risk of SCD caused by rapid polymorphic ventricular arrhythmias mainly occurring at rest or during sleep in individuals with a structurally normal heart. The occurrence of cardiac arrest at 3 year follow-up may be as high as 30%. The disease is characterised by transient right bundle branch block and ST-segment elevation in leads V1—V3. The efficacy of β-blockers in this condition has not been investigated. Accordingly, β-blockers are not currently recommended in this condition.[35]

Other situations

β-blockers are also indicated in patients with pacemakers and implantable defibrillators for secondary prevention (class IIb and IIa, respectively, level of evidence C).[35]

Hypertension

β-Blockers are indicated in the treatment of hypertension (class I, level of evidence A)[46,52,53] (Table 12). Intravenous β-blockers can be used to treat hypertensive emergencies. Current guidelines strongly recommend reduction of blood pressure to different levels according to the risk profile (the higher the risk the lower the ideal blood pressure)[52,56–58,187–189], and in most patients the appropriate control requires the use of two or more antihypertensive medications. Although the primary objective in hypertensive patients is the control of blood pressure levels, pharmacological treatment should also reduce morbidity and mortality and the selection of a specific drug should be based on the patient profile.[58] Thus, β-blockers may be considered as the first choice therapy, alone or in combination, in patients with previous myocardial infarction, ischaemic heart disease, arrhythmias or heart failure, asymptomatic left ventricular dysfunction, diabetes or high risk of coronary disease, based on the efficacy of these drugs on these patient populations (class I, level of evidence A).[52,56,57,188]

In early studies, treatment of hypertension with β-blockers was associated with an improvement in long-term outcomes, including a reduction in mortality,[190–192] stroke[193–195] and heart failure.[193] In the Swedish Trial in Old Patients with hypertension (STOP-Hypertension trial),[190] all cause mortality and sudden cardiac death was lower in the β-blocker (metoprolol, pindolol or atenolol) than in the placebo group. In the MAPHY study[192], comparing metoprolol with thiazide, blood pressure reduction was similar in both groups, but mor-

Table 12 Use of β-blockers in the treatment of hypertension: guidelines

Setting/indication	Class	Level	Ref.
To control BP	I	A	52, 56, 57
After MI, in ischaemia, tachyarrythmias, heart failure	I	A	52, 57, 188

MI: Myocardial Infarction; BP: Blood Pressure.

tality was lower in the metoprolol group. This benefit of β-blockers compared with diuretics was not observed in other studies. In the Medical Research Council (MRC) trial[191] atenolol failed to reduce cardiovascular events as compared to placebo or diuretics in hypertensive patients without previous myocardial infarction, angina and heart failure. In the HAPPHY study,[194] β-blockers (metoprolol, atenolol or propranolol) did not improve the clinical outcome as compared with diuretics. In a meta-analysis[193] β-blockers were effective in preventing stroke and heart failure when compared with placebo but not with diuretics.

In more recent trials, β-blockers were equally efficacious to reduce blood pressure and cardiovascular risk when compared with calcium channel blockers[196] and ACE-inhibitors.[196–199] In a meta-analysis, including the UK Prospective Diabetes Study (UKPDS) (atenolol vs. captopril), STOP-Hypertension-2 (diuretics or β-blockers vs. ACE-inhibitors vs. dihydropiridine calcium channel blockers), CAPP (diuretics or β-blockers vs. captopril) and NORDIL (thiazide or β-blocker vs. diltizem), ACE-inhibitors offered a similar cardiovascular protection as compared with diuretics or β-blockers and calcium channel blockers provided an extra 13% reduction in the risk of stroke but the risk of infarction was 19% higher than with β-blockers or diuretics.[200]

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study compared the angiotensin II inhibitor losartan with atenolol in hypertensive patients with left ventricular hypertrophy but without myocardial infarction or stroke within the previous 6 months, angina pectoris requiring treatment with β-blockers and heart failure or left ventricular ejection fraction of $\leqslant 40\%$. Losartan was associated with a greater reduction in stroke as compared atenolol (5% vs. 6.7%) over a mean follow up of 8.4 years. Mortality and myocardial infarction was similar in both groups.[201]

Aortic dissection

β-blockers are indicated to lower blood pressure in patients with suspected or diagnosed aortic dissection (class I, level of evidence C) (Table 13).[202]

β-blockers reduce blood pressure and pulse pressure (systolic/diastolic pressure difference), which reflect the force in the aortic wall. For this purpose β-blockers are considered the drug of choice in patients with aortic dissection although this therapeutic approach has not been tested in randomised clinical trials. Intravenous β-blockers (propranolol, metoprolol, atenolol, labetalol and esmolol) should be preferred to achieve rapid control of blood pressure and can be used under careful control of blood pressure, heart rate and end-organ perfusion. The recommended doses are indicated in Table 3 but have to be individually adjusted according to the obtained response.[193,194,203] While β-blocking agents are usually adequate in most patients, combination with intravenous sodium nitroprusside may be required for severe hypertension.

Table 13 Use of β-blockers in aortic dissection: guidelines

Setting/indication	Class	Level	Ref.
To lower blood pressure	I	C	202

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is a complex disease with a broad spectrum of manifestations and risk profile. Although β-blockers, including propranolol, atenolol, metoprolol, sotalol or nadolol have been successfully used to relieve symptoms, improve physical capacity, control heart rate, treat arrhythmias, treat heart failure and prevent sudden cardiac death in patients with and without evidence of left ventricular outflow obstruction, their use has not been clearly standardised.[176] Also, there is no proof that prophylactic drug therapy in asymptomatic patients to prevent or delay progression of congestive symptoms and improve prognosis.

Prophylactic use in non-cardiac surgery

β-Blockers are indicated in high cardiac risk patients, with present or past history of ischaemia, arrhythmias or hypertension controlled by β-blockers and in patients with ischaemia in perioperative testing submitted to elective non-cardiac surgery (specially vascular surgery), to prevent ischaemic events and arrhythmias (class I, level of evidence A). Also, β-blockers are indicated for the treatment of perioperative hypertension, ischaemia and arrhythmias identified preoperatively and previously untreated (class IIa, level of evidence (B) (Table 14).[54] Perioperative β-blocker therapy in high risk patients is underutilized.[205]

In several studies, the preoperative administration of β-blockers was associated with better control of blood pressure[206,207] and a reduction in perioperative ischaemia[204,206–212] and arrhythmias.[213,214] There is also evidence that patients with high risk for coronary heart disease have a better outcome if treated with β-blockers

Table 14 Use of β-blockers in non-cardiac surgery: guidelines

Setting/indication	Class	Level	Ref.
High cardiac risk (history of ischaemia, arrhythmias, hypertension, or stress induced ischaemia, to reduce ischaemic events and arrhythmias	I	A	54
Preoperative use to control ischaemia, hypertension, arrhythmias	I	A	54
Treatment of peroperative ischaemia, hypertension and arrhythmias	IIa	B	54

during hospitalisation for non-cardiac surgery, including a reduction in mortality and cardiovascular complications during and up to 2 years after surgery.[215,216] In one small study, including 112 selected patients with risk factors for ischaemic heart disease and a positive dobutamine stress test, bisoprolol was compared with placebo administered before vascular surgery.[216] Cardiac mortality (3.4% vs. 17%) and non-fatal infarction (0% vs. 17%) were lower in the bisoprolol group. Boersma et al.[217] reanalysed the cohort of 1351 consecutive patients enrolled in this study. Patients receiving β-blockers had a lower risk of cardiac complications than those not receiving β-blockers. In another trial[215,218] atenolol given before general surgery reduced the episodes of ischaemia during ECG monitoring and improved the outcome at six months follow-up as compared to placebo. Although these studies were small and do not provide definite answers, the results suggest an improvement in outcome, especially in high-risk patients.

Vasovagal syncope

In vasovagal syncope β-blockers have been thought to lessen the degree of mechanoreceptor activation associated with an abrupt fall in venous return and block the effects of elevated circulating adrenaline, but this effect could not be demonstrated in five long-term follow-up controlled clinical studies[219–223] and contradictory results have been reported in short term controlled clinical studies.[224,225] A rationale for use of β-blockers is lacking in other forms of neurally mediated syncope and they may be detrimental in dysautonomic syndromes. β-Blockers may enhance bradycardia in the carotid sinus syndrome and in all other cardio-inhibitory forms of neurally-mediated syncope. Therefore, at the moment there is no evidence to support the use of β-blocker in vasovagal syncope (level of evidence A).[226]

β-blockers during pregnancy

β-blockers have been used during pregnancy without evidence of teratogenic effects. Although there is limited experience, β-blockers are considered as indicated in pregnant women with hypertension, mitral stenosis with pulmonary hypertension, coartaction of the aorta, ischaemic heart disease, supraventricular and ventricular arrhythmias, and can be continued during delivery.[152,227,228] Selective agents, without effect on uterine contraction are preferred.

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