Complete Summary

GUIDELINE TITLE

Expert consensus document on beta-adrenergic receptor blockers.

BIBLIOGRAPHIC SOURCE(S)

Lopez-Sendon J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, Tendera M, Waagstein F, Kjekshus J, Lechat P, Torp-Pedersen C. Expert consensus document on beta-adrenergic receptor blockers. Eur Heart J 2004 Aug;25(15):1341-62. [229 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Cardiovascular disease including:

- Acute myocardial infarction (AMI)
- Non-ST-segment elevation acute coronary syndromes
- Chronic, stable ischaemic heart disease
- Heart failure
- Arrhythmias
- Hypertension
- Dilated cardiomyopathy
- Hypertrophic cardiomyopathy
- Mitral valve prolapse

- Myocardial bridging
- Long QT syndrome
- Sudden cardiac death
- Aortic dissection
- Vasovagal syncope

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Prevention
Treatment

CLINICAL SPECIALTY

Cardiology
Emergency Medicine
Family Practice
Internal Medicine
Preventive Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To review the rationale and clinical evidence for the use of beta-adrenergic blockers in patients with cardiovascular disease

TARGET POPULATION

Patients with cardiovascular disease (see diseases/conditions for detailed list), including pregnant women and patients undergoing noncardiac surgery

INTERVENTIONS AND PRACTICES CONSIDERED

Treatment/Prevention

Beta-blocker therapy

1. Nonselective (+ $beta_2$) adrenergic antagonists, including carteolol, nadolol, penbutolol, pindolol, propranolol, sotalol, and timolol
2. Selective $beta_1$-adrenergic antagonists, including acebutolol, atenolol, betaxolol, bisoprolol, celiprolol, esmolol, metoprolol, and nevibolol
3. $Alpha_1$- and beta-adrenergic antagonists, including bucindolol, carvedilol, and labetalol

MAJOR OUTCOMES CONSIDERED

- Morbidity and mortality

- Control of heart rate
- Incidence of stroke
- Prevention of arrhythmias or conversion of arrhythmias to sinus rhythm
- Recurrent ischaemia and reinfarction rate
- Control of hypertension
- Limitation of infarct size in acute myocardial infarction
- Exercise capacity/control of exercise-induced angina
- Symptomatic and asymptomatic ischaemic episodes in patients with angina
- Prevention of myocardial infarction in patients with angina
- Hospitalization rate
- New symptoms of heart failure
- Ventricular function
- Reduction of perioperative ischaemia, hypertension, and arrhythmias
- Control of atrial flutter and fibrillation

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A specific literature search was carried out for original articles in peer review journals included in Medline. In addition, the European Society of Cardiology (ESC) as well as the American Heart Association/American College of Cardiology guidelines with reference to the use of beta-blockers were carefully reviewed.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

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

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Subgroups of the task force formulated drafts in specific areas, then presented the drafts to the entire task force to reach consensus.

Most of the recommendations made in previous European Society of Cardiology guidelines and in American Heart Association/American College of Cardiology guidelines on beta-blockers were maintained; some were updated, and a few are new according to recent evidence in the literature.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Class 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 and/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 European Society of Cardiology.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The document prepared by the task force was circulated among a review board appointed by the European Society of Cardiology (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.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The class of recommendations (I-III) and level of evidence (A-C) are defined at the end of the "Major Recommendations" field.

Clinical Efficacy and Use

The benefit and clinical indications of beta-blockers have been clearly defined in many cardiovascular conditions, and agreement about their potential usefulness has been clearly established in many clinical settings. Beta-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 beta-blockers treatment has been well documented in the following conditions:

Acute Myocardial Infarction (AMI)

During the acute phase of myocardial infarction, oral beta-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 or recurrent ischaemia and for the control of hypertension, tachycardia, and arrhythmias (please refer to the table below entitled "Use of Beta-blockers in AMI").

Beta-blockers limit infarct size, reduce life-threatening arrhythmias, relieve pain, and reduce mortality including sudden cardiac death. Two large trials were particularly relevant to guide the use of beta-blockers during the first hours of AMI. In the First International Study of Infarct Survival (ISIS-1) trial, patients within 12 h of evolution were randomised to receive intravenous (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 1,000 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), i.v. metoprolol followed by oral administration did not significantly reduce 15-day mortality as compared to placebo (4.3 to 4.9% [not significant (ns)]). A meta-analysis of 28 early trials of i.v. beta-blockers revealed an absolute reduction of short-term mortality from 4.3% to 3.7% (7 lives saved/1,000 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.

Two trials of randomised i.v. beta-blockade were conducted after the widespread use of reperfusion therapy in AMI, but the number of events was too small to establish clear conclusions. In the second Thrombolysis in Myocardial Infarction (TIMI-II) trial, 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 beta-blocker group and when treatment was administered 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 showed that immediate beta-blocker administration in patients with AMI treated with tissue plasminogen activator (t-PA) reduces the occurrence of intracranial haemorrhage, although this benefit is small (0.7% and 1.0%; 3 patients/1,000 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 beta-blockers, 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 beta-blockers are used before primary percutaneous interventions.

Use of Beta-blockers in AMI: Guidelines

Setting/indication	Class	Level	References
i.v. administration			
For relief of ischaemic pain	I	B	Van de Werf et al., 2003; ACC/AHA Guidelines for the management of patients with acute myocardial infarction, 1999
To control hypertension, sinus tachycardia	I	B	Van de Werf et al., 2003
Primary prevention of sudden cardiac death	I	B	Priori et al., 2001
Sustained ventricular tachycardia	I	C	Van de Werf et al., 2003
Supraventricular tachyarrhythmias	I	C	Van de Werf et al., 2003; ACC/AHA Guidelines for the management of patients with acute myocardial infarction, 1999
To limit infarct size	IIa	A	Van de Werf et al., 2003
All patients without contraindications	IIb	A	Van de Werf et al., 2003
Oral administration			
All patients without contraindications	I	A	Van de Werf et al., 2003; ACC/AHA Guidelines for the management of patients with acute myocardial infarction, 1999

Secondary Prevention after Myocardial Infarction

Oral beta-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) (please refer to the table below entitled "Use of Beta-blockers in Secondary Prevention after Infarction"). Beta-blockers are underused for this indication.

Several large, long-term trials involving more than 35,000 survivors of myocardial infarction have demonstrated that the use of beta-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. 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.

A meta-analysis of 82 randomised trials (31 with long-term follow-up) provides strong evidence for the long-term use of beta-blockers to reduce morbidity and mortality after acute MI even if aspirin, fibrinolytics, or angiotensin converting enzyme inhibitors (ACE-I) were coadministered. An annual reduction of 1.2 deaths in 100 patients treated with beta-blockers after myocardial infarction was observed; that is, about 84 patients will require treatment for 1 year to avoid one death. 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 nonfatal reinfarction. In the retrospective analysis of the Cooperative Cardiovascular Project, including over 200,000 patients with myocardial infarction, beta-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.

In the Beta-blocker Heart Attack Trial (BHAT), patients were randomised 5 to 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/1,000 treated). In the Norwegian trial, patients were randomly assigned 7 to 28 days after AMI to receive timolol or placebo; mortality was reduced from 9.8% to 7.2%, (26 lives/1,000 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. In the study of Hjalmarson et al., metoprolol given first intravenously and then orally, mortality at 90 days was reduced by 26%. In the Boissel et al. trial Acebutolol et Prevention Secondarie de l'Infartus (APSI) trial, including high-risk patients 2 to 22 days after AMI, there was also a significant 48% reduction in mortality associated with the beta-blocker treatment. In the Carvedilol Post Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial including patients 2 to 21 days after AMI with reduced left ventricular ejection fraction (LVEF) and receiving ACE-I, all-cause mortality was lower in the carvedilol group than in the placebo group (12% vs. 15%). The significant mortality reductions in heart failure observed with beta-blockers and the result of the CAPRICORN trial further supports the use of these agents in high-risk patients with impaired ventricular function or failure after infarction and demonstrate that the benefit of beta-blockers is observed also in patients receiving treatment according to current standards, including reperfusion therapy and ACE-I.

Although the benefit of beta-blockers is observed in a broad population after infarction, 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 beta-blockers because their long-term prognosis is favourable. Chronic stable ischaemic heart disease patients and patients with atherosclerosis (carotid plaque) may benefit from a combined treatment with statins and beta-blockers. Treatment with beta-blockers in diabetic patients seems to be more effective than in nondiabetics and the risk of complications is negligible. Other subgroups at high risk, including late ventricular arrhythmias and post infarction ischaemia, Q wave and non-Q wave infarctions, and elderly patients, also benefit from beta-blockers. Although relative contraindications once may have been thought to preclude the use of beta-blockers in some patients, new evidence suggests that the benefits of beta-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. It is also emphasized that the use of beta-blockers in such patients requires careful monitoring of the patient to be certain that adverse events do not occur.

Use of Beta-blockers in Secondary Prevention after Infarction: Guidelines

Setting/indication	Class	Level	References
All patients without contraindications, indefinitely	I	A	Van de Werf et al., 2003; ACC/AHA guidelines for the management of patients with acute myocardial infarction, 1999; Prevention of coronary heart disease, 1998; Gibbons et al., 1999; Eagle et al., 2002; ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult, 2002; Grundy et al., 1999; Smith et al., 2001
To improve survival	I	A	Van de Werf et al., 2003; Prevention of coronary heart disease, 1998; Gibbons et al., 1999
To prevent reinfarction	I	A	Van de Werf et al, 2003; Prevention of coronary heart disease, 1998; Gibbons et al., 1999
Primary prevention of sudden cardiac death	I	A	Priori et al., 2001
To prevent/treat late ventricular arrhythmias	IIa	B	Van de Werf et al., 2003; Priori et al., 2001

Non-ST-Segment Elevation Acute Coronary Syndromes

Patients with Acute Coronary Syndromes (ACS) without ST-segment elevation should be treated with beta-blockers as soon as possible, to control ischaemia and prevent AMI/reinfarction (class I, level of evidence B). After the acute phase, all

patients should receive beta-blockers during long term for secondary prevention (class I, level of evidence A) (please refer to the table below entitled "Use of Beta-blockers in Non-ST-Segment Elevation ACS").

There are few randomised studies with beta-blockers in patients with unstable angina and non-Q wave myocardial infarction, 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 beta-blockers with placebo A meta-analysis suggested that beta-blocker treatment was associated with a 13% relative reduction in risk of progression to AMI. Although no significant effect on mortality has been demonstrated in unstable angina in these relatively small trials, larger randomised trials of beta-blockers in patients with acute or recent MI have shown a significant effect on mortality. In addition, a retrospective analysis from the Cooperative Cardiovascular Project indicates that the relative risk of death was lower in patients with non-Q wave myocardial infarction receiving beta-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 beta-blockers. There is no evidence that any specific beta-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). Beta-blockers can increase coronary artery tone and are contraindicated in vasospastic angina without obstructive lesions.

Use of Beta-blockers in Non-ST-Segment Elevation ACS: Guidelines

Setting/indication	Class	Level	References
Early benefit, reduction of ischaemia	I	B	Bertrand et al., 2000; Bertrand et al., 2002; Braunwald et al., 2002
Early benefit, prevention MI	I	B	Bertrand et al., 2000; Bertrand et al., 2002
Long-term secondary prevention	I	B	Bertrand et al., 2000; Bertrand et al., 2002

Chronic, Stable Ischaemic Heart Disease

All patients with chronic, stable ischaemic heart disease should receive long-term treatment with beta-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 (please refer to the table below entitled "Use of Beta-blockers in Chronic, Stable Ischaemic Heart Disease"). Beta-blockers should be considered as the first choice in patients with chronic angina or ischaemia, and hypertension, previous

infarction, or poor ventricular function. They appear to be underused for this indication.

Beta-blockers are highly effective to control exercise-induced angina, improve exercise capacity, and reduce or suppress both symptomatic and asymptomatic ischaemic episodes. No clear clinical differences have been demonstrated between different beta-blockers. Also, no clinical relevant differences were found when comparing beta-blockers with calcium channel blockers for the control of ischaemia. Combination therapy with nitrates and beta-blockers may be more effective than nitrates or beta-blockers alone. Beta-blockers may also be combined with dihydropyridines, but the combination with verapamil and diltiazem increases the risk of bradycardia or atrioventricular (AV) block.

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

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 prethrombolytic 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 beta-blockers. The beta-blockers pooling project reported a highly significant reduction in mortality in this subgroup, and it seems reasonable to assume that beta-blockers have the potential to prevent death, especially sudden cardiac death, and myocardial infarction even when there has been no prior infarction.

The effects of beta-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), no difference was found between atenolol and nifedipine, and in the Angina Prognosis Study in Stockholm (APSIS) the clinical outcome was similar in the groups treated with metoprolol and verapamil. In the Atenolol Silent Ischaemia Study (ASIST), 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) 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, metoprolol was more effective than nifedipine in controlling exercise induced ischaemia.

Use of Beta-Blockers in Chronic, Stable Ischaemic Heart Disease: Guidelines

Setting/indication	Class	Level	References
Previous infarction			
To improve survival	I	A	Van de Werf et al., 2003; ACC/AHA Guidelines for the management of patients with acute myocardial infarction, 1999; Priori et al., 2001; Prevention of coronary heart disease, 1998;

Setting/indication	Class	Level	References
			Gibbons et al., 1999
To reduce reinfarction	I	A	Van de Werf et al., 2003; Braunwald et al., 2002
To prevent/control ischaemia	I	A	Van de Werf et al., 2003; ACC/AHA Guidelines for the management of patients with acute myocardial infarction, 1999; Priori et al., 2001; Prevention of coronary heart disease, 1998; Gibbons et al., 1999
No previous infarction			
To improve survival	I	C	Van de Werf et al., 2003; ACC/AHA Guidelines for the management of patients with acute myocardial infarction, 1999; Priori et al., 2001; Prevention of coronary heart disease, 1998; Gibbons et al., 1999
To reduce reinfarction	I	B	Van de Werf et al., 2003; Management of stable angina pectoris,1997
To prevent/control ischaemia	I	A	Van de Werf et al., 2003, Prevention of coronary heart disease, 1998; Gibbons et al., 1999

Heart Failure

All patients with stable, mild, moderate, and severe chronic heart failure from ischaemic or nonischaemic cardiomyopathies and reduced LVEF, in New York Heart Association (NYHA) class II-IV, should be treated with beta-blockers, unless there is a contraindication (class I, level of evidence A). In patients with left ventricular systolic dysfunction (LVSD), with or without symptomatic heart failure following an AMI, long-term beta-blockade is recommended in addition to ACE inhibition to reduce mortality (class I, level of evidence A). Finally, beta-blockers are also recommended in patients with chronic heart failure and preserved left ventricular function (class IIa, level of evidence C) (please refer to the table below entitled "Use of Beta-blockers in Chronic Heart Failure"). Beta-blockers are underused in patients with heart failure.

The evidence of clinical benefit on beta-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. Placebo-controlled mortality trials with carvedilol, bisoprolol and metoprolol 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, beta-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, LVEF, and ischaemic or nonischaemic aetiology, diabetics, and nondiabetics. Black patients may be an exception, since in the BEST trial this ethnic group lacked the benefit from beta-blockers therapy in heart failure. In smaller, controlled studies beta-blockade has been shown to improve ventricular function. Exercise capacity

may also improve as well as symptoms and quality of life, but these effects usually are marginal and have not been consistently demonstrated in all trials comparing beta-blockers with placebo.

In the second Cardiac Insufficiency Bisoprolol Study (CIBIS-2) symptomatic patients in NYHA class III or IV, with LVEF 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/1,000 treated; Number Needed to Treat [NNT] for 1.3 years 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) patients with chronic heart failure in NYHA functional class II-IV and ejection fraction $\leq$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/1,000 treated; 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, 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/1,000 treated; NNT for 10.4 months to save 1 life = 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.

In the CAPRICORN trial patients with LVEF 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 beta-blocker group (12% vs. 15%), although no differences were observed in rehospitalisation rate.

In the Beta-blocker Evaluation of Survival (BEST) Trial patients with chronic heart failure and reduced LVEF 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 beta-blocker in mainly NYHA class II/III (mild-moderate) chronic heart failure (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 beta-blockers in chronic heart failure, a class-effect has not been established. No benefit on survival was observed with bucindolol (BEST), although bucindolol was associated with a reduction in cardiovascular mortality and myocardial infarction. A direct comparison of two different beta-blockers (metoprolol vs. carvedilol) has been assessed in the Carvedilol Or Metoprolol European Trial (COMET). In this study patients with chronic heart failure and reduced LVEF were treated with carvedilol (targed 25 mg twice a day [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 rehospitalisation 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 beta-blockers 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 beta-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 beta-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 beta-blocker action may be biphasic with long-term improvement, possibly preceded by initial worsening, beta-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. Beta-blockers may reduce blood pressure and heart rate excessively, may temporarily induce myocardial depression, and may precipitate heart failure. In addition, beta-blockers may initiate or exacerbate asthma and induce peripheral vasoconstriction. The table below entitled "Practical Guidance on Using Beta-Adrenergic Blockers in Heart Failure" indicates the recommended procedure for the use of beta-blockers in clinical practice and lists the contraindications. Detailed practical guidance on the use of beta-blockers in heart failure can be found elsewhere.

Use of Beta-Blockers in Chronic Heart Failure: Guidelines

Setting/indication	Class	Level	References
All stable patients, with symptomatic heart failure and	I	A	ACC/AHA Guidelines for the Evaluation and Management of

Setting/indication	Class	Level	References
reduced LVEF, functional class II-IV (to prolong survival)			Chronic Heart Failure in the Adult, 2002; Remme et al., 2001
LVSD without symptoms after AMI	I	A	ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult, 2002; Remme et al., 2001
LVSD without symptoms, no previous MI	I	B	ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult, 2002
Chronic HF with preserved systolic function (to reduce heart rate)	IIa	C	Remme et al., 2001
Acute, compensated heart failure after AMI	IIa	B	Nieminen et al., 2004
Patient stable after acutely decompensated chronic heart failure	I	A	Nieminen et al., 2004

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

Heart Failure and Preserved Systolic Function

There is a paucity of data regarding the possible benefit of beta-blockers in patients with heart failure and preserved systolic left ventricular function. Accordingly, the recommended use of beta-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 beta-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. In the COPERNICUS trial, beta-blocker therapy started early after acute decompensation of CHF was associated with a long-term reduction in mortality. In the CAPRICORN trial patients with heart failure or left ventricular dysfunction randomised early after AMI also received benefit from beta-blocker therapy. 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, beta-blockers should be initiated early (class IIa, level of evidence B). In patients with chronic heart failure, beta-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. Uptitration should be adapted to individual response. Patients on beta-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).

Practical Guidance on Using Beta-Adrenergic Blockers in Heart Failure

Who should receive beta-blocker therapy
• All patients with chronic, stable heart failure
• Without contraindications (symptomatic hypotension or bradycardia, 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, nonsteroidal anti-inflammatory 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 beta-blocker only if other actions were ineffective to control symptoms/secondary effects

- Always consider the reintroduction and/or uptitration of the beta-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 beta-blockers if increasing diuretic dose does not work
• Review patient in 12 weeks; if not improved seek specialist advice
• If serious deterioration, halve dose of beta-blocker
• Stop beta-blocker (rarely necessary; seek specialist advice)
Bradycardia
• Electrocardiogram (ECG) to exclude heart block
• Consider pacemaker support if severe bradycardia or AV block or sick sinus node early after starting beta-blockers
• Review need, reduce or discontinue other heart rate slowing drugs (e.g., digoxin, amiodarone, diltiazem)
• Reduce dose of beta-blocker. Discontinuation rarely necessary
Severe decompensated heart failure, pulmonary oedema, shock
• Admit patient to hospital
• Discontinue beta-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; NYHA: New York Heart Association.

Arrhythmias (please refer to the table below entitled "Use of Beta-Blockers in Arrhythmias")

Sinus Tachycardia

Sinus tachycardia is not a primary disorder and treatment should be directed to the underlying cause. In selected individuals beta-blockers can be used to slow heart rate (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 beta-adrenergic state. In patients with pheochromocytoma, beta-blockers are also effective to control sinus tachycardia, but if given alone hypertensive crisis can occur secondary to unopposed alpha-receptor mediated constriction.

Supraventricular Tachycardias

Beta-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 such as after surgery (class I, level of evidence C) (please refer to the table below entitled "Use of Beta-Blockers in Arrhythmias"). On the contrary, multifocal atrial tachycardia is frequently associated with severe obstructive lung disease, in which case beta-blockers are ineffective and contraindicated. AV nodal reciprocating tachycardias, the most common form of paroxismal supraventricular tachycardia, also respond 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 (class I, level of evidence C). Beta-blockers are also useful for the prevention of recurrent episodes. Oral administration of beta-blockers is very effective to prevent paroxysmal tachycardias precipitated by emotion or exercise. Oral propranolol, atenolol, nadolol, and sotalol were found to be effective in the long-term prophylactic treatment of patients with paroxysmal supraventricular tachycardias (class I, level of evidence C). Beta-blockers are also recommended for the treatment of other forms of supraventricular tachycardias, including focal junctional tachycardia and non-paroxysmal junctional tachycardia (please refer to the table below entitled "Use of Beta-Blockers in Arrhythmias").

Tachycardias in Wolff-Parkinson-White (WPW) Syndrome

Beta-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 electrophysiological studies. However, beta-blockers may cause very serious adverse events. Beta-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. For thess reasons, beta-blockers are contraindicated in arrhythmias associated with WPW syndrome. Beta-blockers are also contraindicated in patients with sick sinus or bradycardia/tachycardia syndrome, as sinus arrest with syncope may occur.

Atrial flutter

Beta-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).

Atrial Fibrillation

Beta-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 (please refer to the table below entitled "Use of Beta-Blockers in Arrhythmias").

Prevention. The incidence of atrial fibrillation is lower in patients receiving beta-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 noncardiac surgery.

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. Beta-blockers have also proved to be effective in patients with AF complicating thyrotoxicosis, AMI, chronic stable coronary artery disease, and during pregnancy. For acute control of heart rate, i.v. esmolol is the recommended agent.

For long-term use, beta-blocker 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, beta-blockers were effective in controlling resting heart rate. The effect was drug specific, with sotalol, nadolol, and atenolol being the most efficacious. Atenolol provided better control of exercise-induced tachycardia than digoxin alone. 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 beta-blockers appears to be more effective than either digoxin or beta-blocker alone and better than the combination of digoxin and calcium channel blockers.

Conversion to sinus rhythm. There are few randomised studies exploring the efficacy of beta-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 and reducing their duration and associated symptoms. In AF after noncardiac surgery, intravenous esmolol produced a more rapid conversion to sinus rhythm than did intravenous diltiazem, but other antiarrhythmic drugs are preferred for cardioversion of AF to sinus rhythm. Beta-blockers may also reduce subacute recurrences after conversion to sinus rhythm, bisoprolol being as effective as sotalol and carvedilol to maintain sinus rhythm after AF.

Ventricular Arrhythmias

Beta-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) (please refer to the table below entitled Use of Beta-Blockers in Arrhythmias). Most beta-blockers have proved effective to reduce the number of ventricular premature beats. In sustained ventricular tachycardia, beta-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 beta-blocker to treat ventricular fibrillation (VF) is anecdotal. On the contrary, beta-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.

Use of Beta-Blockers in Arrhythmias: Guidelines

Setting/indication	Class	Level	References
Supraventricular arrhythmias			
Sinus tachycardia	I	C	Blomstrom-Lundqvist et al., 2003
Focal atrial tachycardia, for cardioversion	IIa	C	Blomstrom-Lundqvist et al., 2003
Focal atrial tachycardia, for prevention of recurrence	I	B	Blomstrom-Lundqvist et al., 2003
Atrioventricular nodal reciprocating tachycardia	I	C	Blomstrom-Lundqvist et al., 2003
Focal junctional tachycardia	IIa	C	Blomstrom-Lundqvist et al., 2003
Non-paroxysmal junctional tachycardia	IIa	C	Blomstrom-Lundqvist et al., 2003
WPW with symptomatic arrhythmias	IIa	C	Blomstrom-Lundqvist et al., 2003
Atrial flutter			
Rate control of atrial flutter, poorly tolerated	IIa	C	Blomstrom-Lundqvist et al., 2003
Rate control of atrial flutter, well tolerated	I	C	Blomstrom-Lundqvist et al., 2003
Atrial fibrillation (ESC/AHA/ACC)			
Prevention (post AMI, heart failure, HTA, post surgery, post conversion to sinus rhythm)	I	A	Fuster et al., 2001
Chronic control of heart rate	I	B	Fuster et al., 2001
Acute control of heart rate	I	A	Fuster et al., 2001
Conversion to sinus rhythm	IIa	B	Fuster et al., 2001
Combination with digoxin, for heart rate control	IIa	A	Fuster et al., 2001
Acute control of HR in heart failure	IIb	C	Fuster et al., 2001
Ventricular arrhythmias			

Setting/indication	Class	Level	References
Control of arrhythmias early after AMI (i.v.)	I	A	Van de Werf et al., 2003
Control of arrhythmias late after AMI	I	A	Van de Werf et al., 2003; Priori et al., 2001; Prevention of coronary heart disease, 1998; Grundy et al., 1999; Smith et al., 2001
Prevention of sudden cardiac death in heart failure and after MI	I	A	Blomstrom-Lundqvist et al., 2003

Prevention of Sudden Cardiac Death

There is clear evidence demonstrating that the benefit derived from beta-blocker treatment in part is the consequence of a reduction in sudden cardiac death (SCD). Accordingly, beta-blockers are clearly indicated in the primary and secondary prevention of SCD in different clinical settings, and guidelines have been established (please refer to the table below entitled "Use of Beta-Blockers in the Prevention of Sudden Cardiac Death"). 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 beta-blockers does not preclude the identification and appropriate treatment of ischaemia and the use of implantable defibrillators.

Acute Myocardial Infarction

The use of beta-blockers in AMI has been already discussed. For the prevention of VF, i.v. beta-blockers are indicated in patients with ventricular arrhythmias (class I, level of evidence A) (please refer to the table below entitled "Use of Beta-Blockers in the Prevention of Sudden Cardiac Death"). SCD secondary to VF is very frequent after an acute coronary occlusion. Beta-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. 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 beta-blocker group and in 14 of the control group (p <0:06). Also, i.v. metoprolol in patients with AMI significantly reduced the number of VF episodes. However, in other large studies, including the ISIS-2 and MIAMI 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 beta-blocker administration on the incidence of VF, and the benefit of early i.v. administration of beta-blockers to prevent VF is questionable in patients treated with reperfusion therapy.

After acute myocardial infarction, the efficacy of beta-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) (please refer to the table below entitled "Use of Beta-Blockers in the Prevention of Sudden Cardiac Death"). A recent analysis of beta-blockers trials 170 showed that 13 trials reported data on reduction of SCD, which was reduced from 51% to 43% in patients treated with beta-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.

Heart Failure

Patients with a history of congestive heart failure or depressed left ventricular function show the greatest benefit from beta-blockers in mortality reduction, including SCD, and are indicated in all patients for the prevention of SCD (Class I, level of evidence A) (please refer to the table below entitled "Use of Beta-Blockers in the Prevention of Sudden Cardiac Death"). A consistent contribution to the improved outcome by these drugs is related to a substantial reduction (between 40% and 55%) in SCD rates. 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 beta-blockers, as suggested by the evidence of risk reductions between 30% and 50%.

Dilated Cardiomyopathy

There are no specific studies demonstrating the benefit of beta-blockers for the prevention of sudden cardiac death in dilated cardiomyopathy, but the reduction in mortality was similar in patients with ischaemic or nonischaemic heart failure; accordingly, beta-blockers are recommended for the prevention of sudden cardiac death in this population (class I, level of evidence B) (please refer to the table below entitled "Use of Beta-Blockers in the Prevention of Sudden Cardiac Death").

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. Though beta-blockers may improve symptoms, the currently available data do not support the routine use of beta-blockers in the prevention of sudden cardiac death in these patients.

Mitral Valve Prolapse

Mitral valve prolapse is usually benign; its link with SCD has been suggested but never conclusively demonstrated. No prospective studies have ever been conducted with beta-blockers or antiarrhythmic drugs in this condition. Accordingly, no data are available to define prophylactic interventions that may reduce the risk of SCD. However, beta-blocking agents are generally considered as first choice therapy in symptomatic patients. Yet, the routine or selective use of beta-blockers to prevent sudden cardiac death in patients with mitral valve prolapse is not recommended.

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. Symptoms usually improve with beta-blockers. This

information is based on a limited number of small observational studies (class IIa, level of evidence C).

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. Beta-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 (beta-blockers and/or left cardiac sympathetic denervation) and close to 60% in the group not treated or treated with miscellaneous therapies. These data support the benefit of beta-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 beta-blockers is considered a class I with a level of evidence B, in asymptomatic patients a class IIa, level of evidence C (please refer to the table below entitled "Use of Beta-Blockers in the Prevention of Sudden Cardiac Death").

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. The arrhythmias are reproducible during exercise stress test or during isoproterenol infusion. At the present time beta-blockers seem to be the only therapy that may be effective. Retrospective analysis of the few published cases, shows SCD in 10.5% and 48% of patients with and without beta-blocker therapy, respectively. Although this finding is not conclusive given the lack of controlled studies, beta-blockers are recommended for the primary and secondary prevention of SCD (class IIa, level of evidence C).

SCD in the Normal Heart

Idiopathic VF occurs in up to 8% of victims of SCD. According to the UCARE European registry, prevention of recurrence with antiarrhythmic agents and beta-blockers failed. The Brugada syndrome 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 beta-blockers in this condition has not been investigated. Accordingly, beta-blockers are not currently recommended in this condition.

Other Situations

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

Use of Beta-Blockers in the Prevention of Sudden Cardiac Death: Guidelines

Disease/setting	Indication	Class	Level	References
AMI	Primary prevention	I	A	Van de Werf et al., 2003
Post-MI	Primary prevention, in presence of HF or LV dysfunction	I	A	Priori et al., 2001; Priori et al., 2003
Post-MI	Primary prevention, during and post-MI	I	A	Priori et al., 2001; Priori et al., 2003
Post-MI	Resuscitated VT/VF, spontaneous sustained VT	IIa	C	Van de Werf et al, 2003; Priori et al., 2001; Priori et al., 2003
Heart failure	Primary or secondary prevention	I	A	Priori et al., 2001
Dilated cardiomyopathy	Primary or secondary prevention	I	B	Priori et al., 2001; Priori et al., 2003
Myocardial bridging	Primary prevention	IIa	C	Priori et al., 2001
Long QT syndrome	Primary prevention symptomatic	I	B	Priori et al., 2001
Long QT syndrome	Secondary prevention beta -blockers + ICD	I	C	Priori et al., 2001
Long QT syndrome	Primary prevention asymptomatic	IIa	C	Priori et al., 2001
Catecholaminergic VT	Primary or secondary prevention	IIa	C	Priori et al., 2001
RV cardiomyopathy	Primary prevention	IIb	C	Priori et al., 2001
Patients with implantable defibrillators	Secondary prevention	IIa	C	Priori et al., 2001; Priori et al., 2003

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

Hypertension

Beta-blockers are indicated in the treatment of hypertension (class I, level of evidence A) (please refer to the table below entitled Use of Beta-Blockers in the Treatment of Hypertension). Intravenous beta-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), 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. Thus, beta-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).

In early studies, treatment of hypertension with beta-blockers was associated with an improvement in long-term outcomes, including a reduction in mortality, stroke, and heart failure. In the Swedish Trial in Old Patients with hypertension (STOP-Hypertension trial), all cause mortality and sudden cardiac death was lower in the beta-blocker (metoprolol, pindolol, or atenolol) than in the placebo group. In the MAPHY study comparing metoprolol with thiazide, blood pressure reduction was similar in both groups, but mortality was lower in the metoprolol group. This benefit of beta-blockers compared with diuretics was not observed in other studies. In the Medical Research Council (MRC) trial, 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, beta-blockers (metoprolol, atenolol, or propranolol) did not improve the clinical outcome as compared with diuretics. In a meta-analysis beta-blockers were effective in preventing stroke and heart failure when compared with placebo but not with diuretics.

In more recent trials, beta-blockers were equally efficacious to reduce blood pressure and cardiovascular risk when compared with calcium channel blockers and ACE-inhibitors. In a meta-analysis, including the UK Prospective Diabetes Study (UKPDS) (atenolol vs. captopril), STOP-Hypertension-2 (diuretics or beta-blockers vs. ACE-inhibitors vs. dihydropyridine calcium channel blockers), CAPP (diuretics or beta-blockers vs. captopril) and NORDIL (thiazide or beta-blocker vs. diltizem), ACE-inhibitors offered a similar cardiovascular protection as compared with diuretics or beta-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 beta-blockers or diuretics.

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 beta-blockers, and heart failure or left ventricular ejection fraction of $\leq$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.

Use of Beta-Blockers in the Treatment of Hypertension: Guidelines

Setting/indication	Class	Level	References
To control BP	I	A	Prevention of coronary heart disease, 1998; Grundy et al., 1999; Smith et al., 2001
After MI, in ischaemia, tachyarrythmias, heart failure	I	A	Prevention of coronary heart disease, 1998; Smith et al., 2001, Chobanian et al., 2003

MI: Myocardial Infarction; BP: Blood Pressure.

Aortic Dissection

Beta-blockers are indicated to lower blood pressure in patients with suspected or diagnosed aortic dissection (class I, level of evidence C) (please refer to the table below entitled Use of Beta-Blockers in Aortic Dissection).

Beta-blockers reduce blood pressure and pulse pressure (systolic/diastolic pressure difference), which reflect the force in the aortic wall. For this purpose beta-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 beta-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 of the original document but have to be individually adjusted according to the obtained response. While beta-blocking agents are usually adequate in most patients, combination with intravenous sodium nitroprusside may be required for severe hypertension.

Use of Beta-Blockers in Aortic Dissection: Guidelines

Setting/indication	Class	Level	References
To lower blood pressure	I	C	Erbel et al., 2001

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is a complex disease with a broad spectrum of manifestations and risk profile. Although beta-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.

Prophylactic Use in Noncardiac Surgery

Beta-blockers are indicated in high cardiac risk patients with present or past history of ischaemia, arrhythmias, or hypertension controlled by beta-blockers and in patients with ischaemia in perioperative testing submitted to elective noncardiac surgery (specially vascular surgery), to prevent ischaemic events and arrhythmias (class I, level of evidence A). Also, beta-blockers are indicated for the treatment of perioperative hypertension, ischaemia, and arrhythmias identified preoperatively and previously untreated (class IIa, level of evidence (B) (please refer to the table below entitled Use of Beta-Blockers in Noncardiac Surgery). Perioperative beta-blocker therapy in high-risk patients is underutilized.

In several studies, the preoperative administration of beta-blockers was associated with better control of blood pressure and a reduction in perioperative ischaemia and arrhythmias. There is also evidence that patients with high risk for coronary heart disease have a better outcome if treated with beta-blockers during hospitalisation for noncardiac surgery, including a reduction in mortality and cardiovascular complications during and up to 2 years after surgery. 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. Cardiac mortality (3.4% vs. 17%) and nonfatal infarction (0% vs. 17%) were lower in the bisoprolol group. Boersma et al. reanalysed the cohort of 1,351 consecutive patients enrolled in this study. Patients receiving beta-blockers had a lower risk of cardiac complications than those not receiving beta-blockers. In another trial, atenolol given before general surgery reduced the episodes of ischaemia during electrocardiogram (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.

Use of Beta-Blockers in Noncardiac Surgery: Guidelines

Setting/indication	Class	Level	References
High cardiac risk (history of ischaemia, arrhythmias, hypertension, or stress induced ischaemia, to reduce ischaemic events and arrhythmias	I	A	Eagle et al., 2002
Preoperative use to control ischaemia, hypertension, arrhythmias	I	A	Eagle et al., 2002
Treatment of peroperative ischaemia, hypertension and arrhythmias	IIa	B	Eagle et al., 2002

Vasovagal Syncope

In vasovagal syncope beta-blockers have been thought to lessen the degree of mechanoreceptor activation associated with an abrupt fall in venous return and to block the effects of elevated circulating adrenaline, but this effect could not be demonstrated in five long-term follow-up controlled clinical studies and contradictory results have been reported in short term controlled clinical studies. A rationale for use of beta-blockers is lacking in other forms of neurally mediated syncope, and they may be detrimental in dysautonomic syndromes. Beta-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 beta-blockers in vasovagal syncope (level of evidence A).

Beta-Blockers During Pregnancy

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

Definitions

Class 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

Level of Evidence

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

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see Major Recommendations).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate therapeutic use of beta-blockers in patients with cardiovascular disease

POTENTIAL HARMS

Adverse Effects

- Beta-blockers may cause extreme bradycardia and atrioventricular (AV) block. These effects are seen mainly in patients with impaired sinus node function and AV-node conduction and are rare when beta-blockers are given intravenously to patients with acute myocardial infarction or orally in patients with chronic heart failure.

- Beta-blockers decrease tissue blood flow due to blockade of vascular $beta_2$-receptors and unopposed stimulation of vascular alpha-adrenoceptors and can produce cold extremities and Raynaud's phenomenon and worsen the symptoms in patients with severe peripheral vascular disease.
- Beta-blockers can also increase the coronary vasomotor tone.
- In patients with insulin-dependent type I diabetes, nonselective beta-blockers mask some of the warning symptoms of hypoglycaemia (tremor, tachycardia).
- Beta-blockers can lead to a life-threatening increase in airway resistance.
- Central effects (fatigue, headache, sleep disturbances, insomnia and vivid dreams, depression) may occur but are less common with hydrophilic drugs.
- In some patients fatigue may be related to a decrease in blood flow to skeletal muscles; in other cases, it may be secondary to a central effect.
- In some patients beta-blockers may cause or aggravate impotence and loss of libido.
- Abrupt discontinuation of beta-blockers after chronic treatment can lead to rebound symptoms (i.e., hypertension, arrhythmias, exacerbated angina).

Drug Interactions

Beta-blockers may show pharmacokinetic and pharmacodynamic interactions with other drugs. Aluminium salts, cholestyramine, and colestipol may decrease the absorption of beta-blockers. Alcohol, phenytoin, rifampicin, and phenobarbital, as well as smoking, induce hepatic biotransformation enzymes and decrease plasma concentrations and elimination half-lives of lipophilic beta-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 beta-blocker antagonists and other antihypertensive agents are often observed. Indomethacin and other non-steroidal anti-inflammatory drugs antagonize the antihypertensive effects of beta-blockers.

CONTRAINDICATIONS

CONTRAINDICATIONS

- The contraindications to initiate beta-blocker treatment include asthma, symptomatic hypotension or bradycardia, and severe decompensated heart failure.
- 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. Patients with heart failure and bradycardia due to sick sinus node or second or third degree atrioventricular (AV)-block may benefit from pre-treatment with pacemaker in order to tolerate beta -blockers, although this approach has, however, not been formally tested. Diabetes or intermittent lower limb claudication are not absolute contraindications for beta-blockers use.

QUALIFYING STATEMENTS

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- This consensus document represents the views of the European Society of Cardiology (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.
- 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.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Lopez-Sendon J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, Tendera M, Waagstein F, Kjekshus J, Lechat P, Torp-Pedersen C. Expert

consensus document on beta-adrenergic receptor blockers. Eur Heart J 2004 Aug;25(15):1341-62. [229 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

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 European Society of Cardiology.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the European Society of Cardiology (ESC) Web site.

Print copies: Available from Elsevier Science Ltd. European Heart Journal, ESC Guidelines - Reprints, 32 Jamestown Road, London, NW1 7BY, United Kingdom. Tel: +44.207.424.4422; Fax: +44 207 424 4515; Web site: http://www.eurheartj.org

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

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