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# Optimising the Use of β-Adrenoceptor Antagonists in Coronary Artery Disease

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## Abstract

β-Adrenoceptor antagonists (β-blockers) provide multiple benefits to patients with coronary artery disease. The 2001 American Heart Association and American College of Cardiology (AHA/ACC) guidelines for secondary prevention of myocardial infarction (MI) recommend initiating β-adrenoceptor blockade in all post-MI patients and continuing therapy indefinitely. Atenolol and metoprolol have been shown to decrease vascular mortality in the acute-MI period. In the post-MI period timolol provided a 39% reduction in mortality in the Norwegian Multicenter Study group and propranolol was associated with a 26% reduction in mortality in BHAT (Beta-blocker Heart Attack Trial). β-Adrenoceptor antagonist therapy results in reduction of myocardial oxygen demand and is therefore also effective for the treatment of angina pectoris.

In CAST (Cardiac Arrhythmia Suppression Trial) β-adrenoceptor antagonist therapy was associated with a significant reduction in arrhythmic death or cardiac arrest. In the post-MI amiodarone trials EMIAT (European Myocardial Infarct Amiodarone Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) there was a mortality benefit and decreased arrhythmic death in patients who received both amiodarone and β-adrenoceptor antagonist therapy, compared with patients receiving amiodarone therapy alone. In the post-MI defibrillator (implantable cardioverter defibrillator [ICD]) trials, AVID (Antiarrhythmic Versus Implantable Defibrillator) and MUSTT (Multicenter Unsustained Tachycardia

Trial), β-adrenoceptor antagonist therapy was independently associated with improved overall survival. The exception was the ICD patients in MUSTT, and the benefit was attenuated in the amiodarone and ICD patients in AVID.

AHA/ACC guidelines recommend the use of β-adrenoceptor antagonists in all patients with symptomatic left ventricular dysfunction, based on several large, controlled heart failure trials. Extended-release metoprolol succinate reduced all-cause mortality by 34% in MERIT-HF (Metoprolol Controlled-Release/ Extended-Release Randomized Intervention Trial in Heart Failure). Bisoprolol was associated with a 34% mortality benefit in CIBIS-II (Cardiac Insufficiency Bisoprolol Study II) and carvedilol was associated with a 35% mortality reduction in the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) trial.

β-Adrenoceptor antagonists reduce perioperative mortality in patients undergoing cardiac as well as non-cardiac surgery; however, they remain underutilised. Contraindications to β-adrenoceptor antagonist therapy include severe bradycardia, high-grade atrioventricular block, marked sinus node dysfunction and acute exacerbations of heart failure. Many of the perceived adverse effects of β-adrenoceptor antagonists have not been substantiated by large clinical trials.

β-Adrenoceptor antagonists differ with regard to receptor selectivity, receptor affinity, lipophilicity and intrinsic sympathomimetic activity. Beneficial properties of β-adrenoceptor antagonists may not always be extrapolated as a class effect, and patient selection and drug preparations should follow trial guidelines.

The beneficial effects of β-adrenoceptor antagonists are clearly proven in cardiac patients and those at risk for cardiac disease. They are indicated for heart failure and proven beneficial in patients undergoing cardiac and non-cardiac surgery. These benefits appear to be consistent across most patient subgroups. β-Adrenoceptor antagonists are generally well tolerated, yet significant morbidity and mortality result from their continued underutilisation.

β-Adrenoceptor antagonists (β-blockers) have had long-standing use after acute myocardial infarction (MI), and numerous studies have confirmed their benefit in patients with coronary artery disease. There is strong evidence supporting the use of β-adrenoceptor antagonists in the post-MI period. The 2001 American Heart Association and American College of Cardiology (AHA/ACC) guidelines for secondary prevention of MI and death recommend initiating β-adrenoceptor blockade in all post-MI patients and continuing therapy indefinitely. Despite this recommendation, fewer than half of MI patients are prescribed β-adrenoceptor antagonists in the long-term setting.[1] Possible explanations for the reluctance of physicians to use β-adrenoceptor antagonists in the acute-MI setting may be related to concerns regarding blood pressure with concomitant use of ACE inhibitors, a question of their safety in patients with heart failure, concerns of exacerbating chronic obstructive pulmonary disease (COPD), safety of their use in diabetic patients and the elderly, adverse effects, and a lack of perceived benefit in non-ST segment elevation MI. This review of β-adrenoceptor antagonist indications and use was summarised from results of the major randomised clinical trials and OVID database review (table I).

## 1. β-Adrenoceptor Antagonists in Acute Myocardial Infarction (MI)

ISIS-1 (First International Study of Infarct Survival) and MIAMI (Metoprolol in Acute Myocardial Infarction) are the are two major trials that analyse

the use of β-adrenoceptor antagonists in acute MI. The ISIS-1 study randomised the use of atenolol in 16 000 patients with suspected acute MI.[2]Atenolol was given intravenously initially, then orally. Vascular mortality during the treatment period was significantly decreased by 15% in the treatment group. In the MIAMI study 6000 patients with acute MI were randomised to metoprolol or placebo.[3] At 1 month there was a 13% total mortality benefit in the metoprolol group. This was of borderline significance.

## 2. β-Adrenoceptor Antagonists Post MI

The Norwegian Multicenter Study Group in 1981 followed up 1884 post-MI patients for 12–33 months and demonstrated a 39% reduction in mortality and a 28% reduction in reinfarction rate with timolol.[4] BHAT (Beta-Blocker Heart Attack Trial) in 1983 was one of the first large controlled trials to show a significant reduction in overall mortality in post-MI patients treated with propranolol.[5] The study randomised 3837 post-MI patients to propranolol or placebo, with an average follow-up of 27 months. Propranolol was associated with a 26% reduction in mortality. These trials predated the modern thrombolytic era; however, the benefits of β-adrenoceptor antagonists are maintained when fibrinolytics and aspirin (acetylsalicylic acid) are used.

In 1999, Freemantle et al.[6] conducted a meta-analysis of 82 randomised trials that examined the effect of β-adrenoceptor antagonists compared with controls in trials that had data on all-cause mortality in the post-MI period. Many of these studies were not designed to assess mortality endpoints and a variety of different β-adrenoceptor antagonists were used. The analysis included 54 234 patients; 10.1% of patients, randomised to β-adrenoceptor antagonists or control, died. There were 51 short-term trials and 31 long-term trials, reflecting the duration of follow-up and β-adrenoceptor antagonist therapy. β-Adrenoceptor antagonist use was associated with 23% reduction in the odds ratio of death in long-term trials but only a 4% reduction in the odds of death in short-term trials.[6] In the short-term data, the number of deaths was small but there was no difference in mortality between placebo and β-adrenoceptor antagonist groups. However, there was a decrease in the number of subsequent MIs. In the long-term trials, there was an annual reduction of 1.2 deaths for each 100 patients treated with β-adrenoceptor antagonists after MI. Short-term β-adrenoceptor blockade immediately after acute MI was found to be less beneficial unless the treatment was continued long term.

On the basis of available data, it is suggested that β-adrenoceptor antagonists be started as soon as feasible in most patients presenting with acute coro-

**Table I.** Pharmacological properties of β-adrenoceptor antagonists

| Drug | α-Adrenoceptor blocking | Selectivity | ISA | Membrane stabilising | Dose[a] | Half-life |
|---|---|---|---|---|---|---|
| Acebutolol | 0 | + | + | + | 200–800mg | 3–4h |
| Atenolol | 0 | ++ | 0 | 0 | 50–200mg | 6–9h |
| Bisoprolol | 0 | + | 0 | 0 | 2.5–20mg | 9–12h |
| Carvedilol | 0 | 0 | 0 | 0 | 3.125–25mg bid | 7–10h |
| Esmolol | 0 | ++ | 0 | 0 | IV 5–10 mg/kg/min | 9 min |
| Labetalol | + | 0 | + | + | 100–400mg bid | 3–4h |
| Metoprolol | 0 | ++ | 0 | 0 | 25–100mg bid or tid | 3–4h |
| Pindolol | 0 | 0 | ++ | 0 | 5–30mg bid | 3–4h |
| Propranolol | 0 | 0 | 0 | ++ | IV 1–5mg; oral 10–80mg tid or qid | 3–4h |
| Sotalol | + | 0 | 0 | 0 | 80–160mg bid | 12h |
| Timolol | 0 | 0 | 0 | 0 | 10–30mg bid | 4–5h |

a Oral unless otherwise specified.

**bid** = twice daily; **ISA** = intrinsic sympathomimetic activity; **IV** = intravenous; **qid** = four times daily; **tid** = three times daily; **0** = none; **+** indicates moderate; **++** indicates significant.

nary syndromes and continued indefinitely if not contraindicated. Benefits from β-adrenoceptor antagonists are presumed to be a class effect. However, specific β-adrenoceptor antagonists may provide additional benefits in selected patients, though retrospective analysis of post-MI trials has not differentiated the specific types of β-adrenoceptor antagonist therapy utilised. Adherence to clinical trial indications, dosages and specific types of β-adrenoceptor antagonists is preferred. β-Adrenoceptor antagonist therapy is associated with an improvement in survival rate in non-ST segment elevation MI, although not as strong as that for ST segment elevation MI. However, evidence supports the use of β-adrenoceptor antagonists in this group of patients with the same doses that are being used for patients with ST segment elevation MI. These patients may be at higher risk because, as they tend to be older, they have more extensive coronary disease, and a higher rate of residual ischaemia and reinfarction.[1]

## 3. Antiarrhythmic Effects of β-Adrenoceptor Antagonists in Post-MI Patients

The basis for the mortality benefit of β-adrenoceptor antagonists in patients with MI is multifactorial. One potential mechanism is the reduction in proarrhythmic effects of antiarrhythmic agents.[7] In a retrospective nonrandomised analysis of CAST (Cardiac Arrhythmia Suppression Trial), patients receiving optimal β-adrenoceptor antagonist therapy had significantly enhanced survival at 30 days and at 1 and 2 years of follow-up against all-cause mortality, arrhythmic death or nonfatal cardiac arrest.[7] Multivariate adjusted analysis showed β-adrenoceptor antagonist therapy to be independently associated with a significant reduction in arrhythmic death or cardiac arrest. Although only 30% of randomised CAST participants received β-adrenoceptor antagonist therapy, survival from all-cause death was significantly higher in β-adrenoceptor antagonist-treated patients than in those without β-adrenoceptor antagonist therapy. In addition, patients who received antiarrhythmic agents as well as β-adrenoceptor antagonists were found to have significantly better survival from all-cause mortality than patients receiving only the proarrhythmic active agents encainide and flecainide. Similar favourable trends for patients on β-adrenoceptor antagonist therapy with regard to survival from arrhythmic death or cardiac arrest were also found. These findings support the belief that β-adrenoceptor antagonists could prevent the proarrhythmic effect associated with class IC antiarrhythmic therapy. In addition, patients in CAST who fared the best in regards to all-cause mortality and arrhythmic death or cardiac arrest were in the placebo arm of the trial and received β-adrenoceptor antagonist therapy.

Analysis of EMIAT (European Myocardial Infarct Amiodarone Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) supports a beneficial interaction between amiodarone and β-adrenoceptor antagonists.[8,9] A pooled database from the two trials defined four groups of post-MI patients.[10] Analysis done on an intention-to-treat basis found that all-cause mortality risk, cardiac death, arrhythmic cardiac death, non-arrhythmic cardiac death, and arrhythmic death or resuscitated cardiac arrest risks were lower for patients receiving β-adrenoceptor antagonists in combination with amiodarone than for those without β-adrenoceptor antagonists or without amiodarone. The interaction was statistically significant for cardiac death and arrhythmic death or resuscitated cardiac arrest ($p = 0.05$ and 0.03, respectively). These findings were consistent across subgroups. The benefit of the antiarrhythmic effect of amiodarone in this analysis appears similar regardless of the patient's baseline heart rate, but in all groups the relative risk was lower in the group of patients treated with β-adrenoceptor antagonists than in those not so treated. From this analysis the effect of amiodarone was found to be greater in patients recovering from a recent MI already receiving β-adrenoceptor antagonists. Therefore, in patients after MI or any patient with significant arrhythmia in whom treatment with amiodarone is planned, the study demonstrated that amiodarone does not replace a β-adrenoceptor antagonist, and β-adrenoceptor antagonist therapy should be continued if possible.

In the AVID (Antiarrhythmic Versus Implantable Defibrillator) trial, β-adrenoceptor antagonist use was independently associated with improved survival in patients with ventricular fibrillation (VF) or symptomatic ventricular tachycardia (VT) who were not treated with specific antiarrhythmic therapy, but a protective effect was not predominant in patients already receiving amiodarone or a defibrillator.[11] The combination of amiodarone and a β-adrenoceptor antagonist in the AVID trial, however, was not associated with improved survival, in contrast to findings of the EMIAT and CAMIAT. In MUSTT (Multicenter Unsustained Tachycardia Trial), after adjusting for baseline characteristics and hospital course factors, β-adrenoceptor antagonists were associated with improved survival in patients randomised to no therapy and registry patients without inducible VT.[12] In patients receiving an implantable cardioverter defibrillator (ICD), total mortality and arrhythmic deaths were similar regardless of whether they received β-adrenoceptor antagonist therapy or not. β-Adrenoceptor antagonists appear to be useful in this study population and it seems appropriate to prescribe β-adrenoceptor antagonists in patients with prior MI and left ventricular (LV) ejection fraction ≤40%, spontaneous nonsustained VT, and any survivor of cardiac arrest. The above studies did not formally assess β-adrenoceptor antagonist use, but owing to the multiplicity of beneficial effects of β-adrenoceptor antagonist therapy in patients with heart disease, the data support their use in these study populations.

The use of β-adrenoceptor antagonists in heart failure trials is reviewed in section 5. The mortality benefit of β-adrenoceptor antagonists in patients with depressed LV function has not been classified in these trials with regard to reduction of arrhythmic events. However, in the MERIT-HF (Metoprolol Controlled-Release/Extended-Release Randomized Intervention Trial in Heart Failure) trial, β-adrenoceptor antagonist therapy was associated with a 41% reduction in sudden cardiac death.[13] Arrhythmic death can be presumed to be the significant component of sudden cardiac death in these patients.

## 4. β-Adrenoceptor Antagonists in Angina Pectoris

β-Adrenoceptor antagonists have been traditionally used for the treatment of angina pectoris. This condition results from increased myocardial oxygen demands that cannot be met because of limited blood supply resulting from fixed atheromatous coronary narrowing. β-Adrenoceptor antagonists are thought to provide anti-ischaemic benefit for patients with angina pectoris through their negative chronotropic and negative inotropic properties. β-Adrenoceptor antagonist therapy results in reduction in myocardial oxygen demand. In addition, slowing of the heart rate leads to increased diastolic coronary perfusion time. In ASIST (Atenolol Silent Ischemia Study), treatment with atenolol was superior to placebo and reduced the incidence of combined endpoints of death, hospitalisation for unstable angina pectoris and the need for revascularisation.[14] β-Adrenoceptor antagonists are also indicated in patients with chronic stable angina pectoris. Although β-adrenoceptor antagonists have been shown to reduce mortality in survivors of acute MI, mortality benefit is not as clear for patients with stable angina pectoris and preserved LV function.[15] In the AHA/ACC 2002 guidelines for the management of patients with chronic stable angina pectoris, β-adrenoceptor antagonists are indicated as initial therapy in patients with a history of MI. This is a class I indication on the basis of clinical trials. In patients without a history of MI, β-adrenoceptor antagonists are indicated on the basis of expert consensus.

## 5. β-Adrenoceptor Antagonists in Heart Failure

β-Adrenoceptor blockade is now established as a highly effective therapy that reduces morbidity and mortality dramatically in patients with heart failure associated with reduced systolic function. The new AHA/ACC guidelines recommend the use of β-adrenoceptor antagonists in all patients with symptomatic LV systolic dysfunction.[16] Despite clear evidence that sympathetic nervous system activation is associated with increased mortality in patients with congestive heart failure (CHF), antagonism of

central nervous system activation as a therapy for CHF has not been readily embraced, as it appears counterintuitive. Although β-adrenoceptor antagonists can obviously exacerbate CHF episodes in patients with reduced systolic function, multiple trials have now shown that β-adrenoceptor antagonists, when added to ACE inhibitors, reduce morbidity and mortality in CHF associated with systolic dysfunction.

MERIT-HF was a randomised, double-blind, placebo-controlled trial that included 3991 patients with New York Heart Association (NYHA) class II–IV heart failure and LV ejection fraction <40%.[13] Patients were randomised to extended-release (ER) metoprolol succinate versus placebo, and doses were titrated as tolerated. An independent safety committee terminated the trial approximately 18 months after the start of randomisation, because ER metoprolol succinate significantly reduced all-cause mortality by 34%. In addition, there was a 19% relative reduction in the combined endpoint of total mortality or all-cause hospitalisation. The median follow-up at study termination was 12 months. Metoprolol succinate therapy resulted in a 41% relative reduction for sudden death and a 49% relative reduction for death due to worsening heart failure.

CIBIS-II (Cardiac Insufficiency Bisoprolol Study II) was a randomised, double-blind, placebo-controlled study which included 2647 patients with NYHA class III and IV heart failure with a LV ejection fraction of ≤35%.[17] Patients were randomised to receive bisoprolol or placebo in addition to standard heart failure therapies. The trial was discontinued prematurely because of a substantial reduction in mortality, 34% among patients in the bisoprolol group. In addition, there were significantly fewer cardiovascular deaths and all-cause hospitalisations reported in patients treated with bisoprolol.

The COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) trial evaluated carvedilol in 2289 patients with severe heart failure and LV ejection fraction <25%. Patients were randomised to carvedilol or placebo treatment.[18] Patients in the carvedilol treatment group experienced a 35% relative reduction in total mortality. The cumulative risk of death at 1 year was 18.5% in the placebo group versus 11.4% in the carvedilol group. The mortality reduction observed in this study is similar to that observed in the MERIT-HF and CIBIS-II studies and extends the results of the post-MI β-adrenoceptor antagonist trials to patients with very low ejection fraction and clinical CHF, in addition to patients with CHF not due to prior MI.

Despite the overwhelming evidence supporting the use of β-adrenoceptor antagonists in heart failure, implementation of β-adrenoceptor antagonist therapy into medical practice remains limited. At present, only one-third of eligible patients may be actually receiving β-adrenoceptor antagonist therapy for heart failure.[19] The most common barriers to guideline implementations include lack of awareness, difficulty in instituting change to previous practice, lack of agreement and external barriers, including lack of time or staff support. Staff should be encouraged to comply with specified hospital guidelines for pharmacological therapy in post-MI patients and patients with heart failure. This may improve with β-adrenoceptor antagonist utilisation.

The use of β-adrenoceptor antagonists in heart failure is novel and counterintuitive to many physicians. The implementation of β-adrenoceptor antagonist therapy is also viewed as difficult and time consuming because it requires frequent visits for uptitration and careful monitoring of symptoms, physical findings and adverse effects. In a study by Ansari et al.,[19] the use of a nurse facilitator was the most successful approach for implementing a β-adrenoceptor antagonist guideline in heart failure patients. In addition, cardiologists have been shown to have a higher utilisation rate than internists.

## 6. β-Adrenoceptor Antagonists in the Perioperative Period

Surgical patients at high risk for perioperative myocardial ischaemia represent another patient group shown to benefit from β-adrenoceptor antagonist therapy.[20] β-Adrenoceptor antagonists reduce perioperative mortality in patients undergoing cardiac as well as non-cardiac surgery.[21,22] In a large

cohort of patients who underwent coronary artery bypass graft (CABG) after MI, β-adrenoceptor antagonists reduced the 1-year mortality from 12% to 4%.[19] Conversely, investigators in a trial involving patients randomly assigned to receive metoprolol after CABG, where only half of patients had a previous MI, did not observe any decrease in a composite endpoint that included death, cardiovascular events or need for revascularisation. However, 40% of patients were withdrawn from the trial because their physician felt that they required β-adrenoceptor antagonist therapy.[4] The AHA/ACC guidelines recommend that patients with a history of MI undergoing CABG be given a β-adrenoceptor antagonist unless contraindicated. The data are less clear regarding patients without a history of MI. However, use of β-adrenoceptor antagonists is certainly reasonable, given the strong evidence of efficacy of β-adrenoceptor antagonists after MI.

β-Adrenoceptor antagonists have also been shown to decrease perioperative events in noncardiac surgery.[20] The benefits of β-adrenoceptor antagonists are more evident in patients exhibiting increased coronary risk factors. The American College of Physicians (ACP) guidelines endorse the use of a modified index to assess perioperative risk that extends the use of β-adrenoceptor antagonists, not only for patients who have documented coronary artery disease, but also for those who have substantial risk factors for coronary artery disease. This has been supported by several well designed randomised, controlled trials. In spite of these data, β-adrenoceptor antagonists continue to be underutilised perioperatively. As many as 60% of general surgery patients have been identified as appropriate candidates for β-adrenoceptor antagonist therapy, but were not prescribed the drug. More than 30% of patients who were on a β-adrenoceptor antagonist preoperatively did not have them ordered postoperatively.[20]

## 7. Adverse Effects

Common adverse effects of β-adrenoceptor antagonists are fatigue, insomnia and worsening claudication. More severe adverse effects include exacerbation of COPD or asthma and of heart failure, bradycardia or heart block. Contraindications to β-adrenoceptor antagonists include severe bradycardia, pre-existing high grade atrioventricular block, sick sinus syndrome, and severe unstable heart failure. Asthma, COPD, severe depression and severe claudication are relative contraindications. In diabetic patients treated with insulin, β-adrenoceptor antagonists historically have been thought to mask the warning signs of hypoglycaemia, though this has not been a reported problem in the more recent β-adrenoceptor antagonist trials. The frequently discussed complication of erectile dysfunction rarely appeared as an adverse effect in double-blind studies.[15] In BHAT, reduced sexual activity was reported in 43.2% of the propranolol group and 42% in the placebo group. There is a concern that β-adrenoceptor antagonists may also increase claudication in patients with peripheral vascular disease, but, again, clinical studies do not support this concept.[1]

Despite evidence supporting the use of β-adrenoceptor antagonists to prevent ischaemia, MI and sudden cardiac death and to decrease perioperative complications, they continue to be underutilised.[6] This is most evident in selected subgroups, especially elderly patients, diabetic patients, and patients with mild reactive airway disease. In MERIT-HF, several predefined subgroups were analysed to determine any differences in outcome; these included elderly patients, smokers, nonsmokers and those with a history of hypertension, MI or diabetes mellitus.[23] The benefits observed with ER metoprolol succinate in the overall study population were consistent across all predefined subgroups. In the large β-adrenoceptor antagonist meta-analysis, the most common reason for withdrawal from β-adrenoceptor antagonist therapy was decreased heart rate and decreased blood pressure.[6] A recent retrospective analysis of community practice records in Australia confirmed that 88% of patients tolerated β-adrenoceptor antagonist.[16] No single variable predicted intolerance, but rates of drug withdrawal increased with age, worsening NYHA class, elevated blood urea nitrogen and lower diastolic blood

pressure. Although caution is advised when β-adrenoceptor antagonists are being considered in patients with bradyarrhythmia, advanced heart block and asthma or COPD, each patient should be considered individually. Specifically, evidence shows that benefits seen with β-adrenoceptor antagonists may outweigh the risks associated with relative contraindications.

Heart failure is predominantly a disease of the elderly; half of all patients with this condition are aged >75 years. Despite data documenting benefits of β-adrenoceptor antagonist therapy, in one survey, fewer than 51% of elderly patients hospitalised with an acute MI without contraindications to β-adrenoceptor antagonist received early β-adrenoceptor antagonist therapy. However, those who did receive this therapy had a significantly lower rate of in-hospital mortality than those not receiving β-adrenoceptor antagonist.[24] Subgroup analysis of heart failure trials also supports the use of β-adrenoceptor antagonists in the elderly population.[25] However, it is suggested that a less aggressive titration regimen may be more appropriate for older patients, while still attempting to achieve the trial target doses. β-Adrenoceptor antagonists in retrospective analyses in post-MI patients, have also been shown to provide mortality benefit to the elderly (age >75 years). This group of patients has not been enrolled in many of the randomised, controlled trials.[26]

Diabetes markedly increases the risk of MI, stroke, amputation and death. Practitioners have had reservations regarding the use of β-adrenoceptor antagonists in diabetic patients because of the possible risk of masking hypoglycaemia and reduced insulin production. In a prospective study of more than 45 000 patients, β-adrenoceptor antagonists reduced the risk of MI by 23% in patients with type 2 diabetes, without increasing diabetes-related complications. In patients receiving β-adrenoceptor antagonists the risk of reinfarction and cardiac mortality is also decreased compared with age-matched controls.[27] Therefore β-adrenoceptor antagonists are recommended for diabetic patients who have had an MI and for patients with multiple cardiac risk factors.[28]

Women have made up approximately 20% of CHF trial populations. In CIBIS-II, bisoprolol resulted in a similar reduction in mortality for women and men. However, in MERIT-HF, subgroup analysis showed mortality reduction for men, but not for women.[16] Larger meta-analyses are needed to provide more definitive answers.

It has been suggested that African Americans with heart failure may not respond as well to ACE inhibitors or β-adrenoceptor antagonists. Racial differences were evaluated in BEST (Beta-blocker Evaluation of Survival Trial), a trial using bucindolol in patients with NYHA class III and IV heart failure.[29] This analysis found a lack of mortality benefit in African American participants. In contrast, a retrospective review of the US carvedilol trials showed that carvedilol reduced the risk of death from any cause by 56% in Blacks and 68% in non-Blacks. The lack of a race-specific response may be attributed to the pharmacological characteristics of carvedilol, but studies with larger cohorts are needed to support this conclusion as well.[16]

In a study by Chen et al.,[30] patients with asthma or COPD who were not taking bronchodilators and those with mild disease controlled with β-adrenoceptor agonists had a survival benefit with β-adrenoceptor blockade after MI. Asthma is a contraindication for nonselective β-adrenoceptor antagonists, but only a relative contraindication for selective $\beta_1$-adrenoceptor antagonists. COPD is a relative contraindication for nonselective β-adrenoceptor antagonists but not selective $\beta_1$-adrenoceptor antagonists; thus cardioselective agents may be better tolerated in patients with pulmonary disease, and even patients who were prescribed β-adrenoceptor agonists may benefit from the addition of a β-adrenoceptor antagonist.

In a retrospective analysis by Gottlieb et al.,[31] a review of medical records of MI patients who have been typically seen as contraindicated for β-adrenoceptor antagonist therapy (heart failure, pulmonary disease and old age) showed that most received benefit from β-adrenoceptor antagonist therapy.

**Table II.** Major trials involving β-adrenoceptor antagonists

| Condition | Trial | Conclusion |
|---|---|---|
| MI | BHAT[5] | Propranolol decreased total mortality in patients with acute MI |
| MI | Norwegian Multicenter Study Group[4] | Timolol decreased total mortality and reinfarction rate in acute MI |
| Unstable angina pectoris | ASIST[14] | Atenolol reduced the incidence of death and hospitalisation for unstable angina pectoris and the need for revascularisation |
| Post MI | CAST (post-hoc analysis)[7] | β-Adrenoceptor antagonists decreased long-term all-cause mortality and arrhythmic death |
| SCD/secondary prevention | AVID[11] | β-Adrenoceptor antagonist use was independently associated with improved total mortality |
| Post MI/primary prevention | MUSTT[12] | β-Adrenoceptor antagonist use was associated with improved total mortality except in implantable cardioverter-defibrillator subgroup |
| Heart failure | MERIT-HF[13] | Extended-release metoprolol succinate reduced total mortality in patients with NYHA class II–IV CHF |
| Heart failure | CIBIS-II[17] | Bisoprolol reduced mortality in patients with NYHA class III and IV CHF |
| Heart failure | COPERNICUS[18] | Carvedilol reduced mortality in patients with CHF and ejection fraction <25% |
| Heart failure | COMET[33] | Carvedilol was superior to short-acting metoprolol in prevention of all-cause mortality in patients with heart failure |

**ASIST** = Atenolol Silent Ischemia Study; **AVID** = Antiarrhythmic Versus Implantable Defibrillator; **BHAT** = Beta-blocker Heart Attack Trial; **CAST** = Cardiac Arrhythmia Suppression Trial; **CHF** = congestive heart failure; **CIBIS-II** = Cardiac Insufficiency Bisoprolol Study II; **COMET** = Carvedilol Or Metoprolol European Trial; **COPERNICUS** = Carvedilol Prospective Randomized Cumulative Survival; **MERIT-HF** = Metoprolol Controlled-Release/Extended-Release Randomized Intervention Trial in Heart Failure; **MI** = myocardial infarction; **MUSTT** = Multicenter Unsustained Tachycardia Trial; **NYHA** = New York Heart Association; **SCD** = sudden cardiac death.

## 8. Properties of Various β-Adrenoceptor Antagonists

β-Adrenoceptor antagonists differ with regard to receptor selectivity, receptor affinity, lipophilicity and intrinsic sympathomimetic activity. First-generation agents (e.g. propranolol) are nonselective in their blockade of β-adrenoceptors. Second-generation agents (e.g. metoprolol and bisoprolol) are selective $\beta_1$-adrenoceptor antagonists and have no ancillary vasodilatory effects. Third-generation β-adrenoceptor antagonists (e.g. carvedilol, bucindilol) are nonselective β-adrenoceptor antagonists with vasodilatory properties. This is attributed to $\alpha_1$-adrenoceptor blocking properties for carvedilol.[23] Thus, although all β-adrenoceptor antagonists share blockade of the $\beta_1$-adrenoceptor, there is considerable variation in the agents with regard to other properties that they possess (table II). It is not clear whether these pharmacological distinctions translate into meaningful differences in efficacy and safety. $\beta_2$-Adrenoceptor blockade may cause bronchoconstriction and should be used with caution. In patients with mild reactive airway disease, short-acting selective $\beta_1$-adrenoceptor antagonists such as metoprolol or atenolol at low dose may be safer because of limited interaction with $\beta_2$-adrenoceptors. However, their selectivity may be lost at higher dosages. Cardioselectivity was associated with a nonsignificant trend towards reduced benefit of β-adrenoceptor antagonists in the post-MI period in an overview of randomised β-adrenoceptor antagonist trials.[32] Currently, only carvedilol and long-acting metoprolol are approved by the US FDA for treatment of heart failure. COMET (Carvedilol Or Metoprolol European Trial), a randomised, controlled trial, compared the effects of carvedilol and metoprolol on clinical outcomes in 3029 patients with chronic heart failure.[33] The mean study duration was 58 months, and the mean ejection fraction was 26%. The all-cause mortality was 34% for carvedilol-treated patients and 40% for those treated with metoprolol. The reduction in all-cause mortality was consistent across predefined subgroups. These results suggest that carvedilol, a nonselective β-adrenoceptor antagonist, extends survival when compared with short-acting metoprolol. However,

different metoprolol doses and preparations were used in these trials. Alterations in β-receptor regulation in CHF may favour the use of nonselective β-adrenoceptor antagonists. In addition, carvedilol has antioxidant properties that may also provide additional benefits.

Pindolol and acebutolol are β-adrenoceptor antagonists that have intrinsic sympathomimetic qualities. This simultaneous stimulation and blockade of β-adrenoceptors result in less slowing of the heart rate, increased adrenaline (epinephrine) levels and higher peripheral vascular resistance. These effects may be detrimental in heart failure and post-MI patients, but may be helpful in issues related to atrial arrhythmias in patients with sinus node dysfunction.

The specific properties of a particular β-adrenoceptor antagonist may result in a clinical response that is not seen with other β-adrenoceptor antagonists, such as the aforementioned possible benefits of carvedilol in the COMET trial.[32] Many of the heart failure and post-MI trials evaluated the effect of β-adrenoceptor antagonists on total mortality and not arrhythmic mortality. Metoprolol was associated with a 41% reduction in sudden death in MERIT-HF, in which arrhythmia was likely to be a significant component of sudden death.[13] The retrospective analysis of the amiodarone trials EMIAT and CAMIAT combined multiple β-adrenoceptor antagonists and still found a benefit of β-adrenoceptor antagonists on arrhythmic cardiac death.[10] In the SWORD (Survival With ORal D-Sotalol) trial,[34] dexsotalol was associated with increased mortality in patients with prior MI and depressed LV function. The mortality increase has been postulated to be the result of proarrhythmia. The racemic sotalol has β-adrenoceptor blocking properties thought to ameliorate this proarrhythmia.[35] The racemic sotalol is useful for treatment of ventricular as well as atrial arrhythmia, but may result in QT prolongation and potential risk for torsade de pointes. Initiation and dose increases require close monitoring of the QT interval to prevent proarrhythmia, unlike for other β-adrenoceptor antagonists.

## 9. Conclusion

The beneficial effects of β-adrenoceptor antagonists are clearly proven in cardiac patients and those at risk for cardiac disease. They are indicated for heart failure and have proven beneficial in patients undergoing cardiac and non-cardiac surgery. These benefits appear to be consistent across most patient subgroups. However, specific clinical benefits of β-adrenoceptor antagonists may not be generalised to a class effect, and agents should be prescribed in accordance with findings of clinical trials, with efforts to titrate to trial dosages. Each patient should be evaluated individually, and if a specific agent is not tolerated, a different class of agent should be tried. β-Adrenoceptor antagonists are generally well tolerated, yet significant morbidity and mortality result from their continued underutilisation.

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