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Beta-blockade across the cardiovascular continuum: when and where to use?

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Safety and tolerability of beta-blockers: prejudices and reality

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Beta-blockers substantially improve survival in chronic heart failure and after myocardial infarction. However, concern about side-effects may deter clinicians from prescribing these life-saving drugs. In reality, absolute contraindications are rare. Only 3–5% of patients are intolerant because of hypotension or bradycardia. Data from randomized controlled trials and retrospective studies show that most patients eligible to receive beta-blockers tolerate them well. Beta-blockers are not contraindicated in chronic obstructive pulmonary disease (COPD); in fact, these patients also benefit because of their high cardiovascular risk. In patients with COPD, as in the elderly, beta-blockers should be started at a low dose and uptitrated slowly. Monitoring of lung function during initiation is important, as undiagnosed coexistent asthma could be revealed. When patients are unaware of the drug in use, erectile dysfunction (ED) is reported no more often with beta-blockers than with any other drug prescribed for heart failure or hypertension. However, when patients are aware of the potential side-effects of beta-blockers, the resultant anxiety may cause ED. Patients should be reassured that beta-blockers prolong life and in the great majority are not the cause of ED, which may rather be related to the underlying disease (diabetes, hypertension, and atherosclerosis).

Keywords Adverse effects • Angina pectoris • Anxiety • Impotence • Elderly • Coronary artery disease • Ischaemic heart disease

Introduction

The benefits of beta-blockers across the cardiovascular continuum are clear. They play key roles in the management of hypertension, chronic heart failure (CHF), and myocardial ischaemia—not only in angina pectoris and after myocardial infarction (MI) but also in preventing cardiac complications of non-cardiac surgery. However, many physicians appear to be reluctant to use beta-blockers in line with current recommendations because of concerns about their safety and tolerability. This prejudice applies particularly to the elderly, to patients with concomitant disorders such as chronic obstructive pulmonary disease (COPD), diabetes, and intermittent claudication, and to sexually active men. Of the huge population of eligible patients in whom beta-blockers are indicated because of CHF or previous MI, 30–50% do not receive a beta-blocker.[1–4] Moreover, the SHAPE study reveals that primary care physicians have an exaggerated perception of the risk of adverse events with beta-blockers in CHF.[5]

To ensure that as many patients as possible receive the potentially life-saving benefits of long-term beta-blockade in CHF and after MI, physicians' perceptions need to be examined in light of the clinical evidence. The purpose of this review is to address some of the most common practical issues and, in doing so, separate prejudices from reality.

Absolute contraindications and known side-effects

In practice, only a minority of patients with hypertension, coronary artery disease (CAD), or CHF are ineligible to receive beta-blockers, as absolute contra-indications such as asthma, atrioventricular block, and beta-blocker intolerance are uncommon. Only about 3–5% of patients are genuinely intolerant, mainly because of hypotension or bradycardia, both of which result from the pharmacological action of the drug. Most of the side-effects associated with beta-blockade result from the pharmacological action of the drug—for example, dizziness, fatigue, intermittent claudication, airway obstruction in asthma, heart block, Raynaud's phenomenon, unpleasant dreams, hypoglycaemia, an increase in insulin resistance or new-onset diabetes, and erectile dysfunction (ED). Further side-effects reported for some agents include headache, musculocutaneous reaction, allergy, weight gain, and depression, but these do not appear to be a consequence of beta-blockade itself.

Beta-blockers and chronic obstructive pulmonary disease

Although asthma is a clear contraindication to beta-blockade, COPD, in which airway obstruction is irreversible, is not.[6]

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The option to administer beta-blockers to patients with COPD is important, because COPD and CHF or CAD often coexist. Moreover, cardiovascular mortality among COPD patients is high. About 37% of patients with COPD die from cardiovascular events,[7,8] compared with the 34% who die from COPD itself.[8] Intriguingly, there is evidence that impaired lung function is an independent and powerful predictor of cardiac mortality.[9] Thus, many patients with COPD and concomitant CAD or CHF stand to benefit greatly from beta-blockers.[10] Despite this, physicians are often reluctant to prescribe beta-blockers in COPD.[11] For example, the EuroHeart Failure Survey found that the presence of COPD in patients with CHF decreased the likelihood of receiving a beta-blocker.[2]

Set against this reluctance, there is evidence that beta-blockers save lives in patients with coexistent COPD and CAD, with a mortality reduction of 15–43% in randomized controlled trials.[10] In an analysis of data from more than 200 000 patients in the Cooperative Cardiovascular Project (CCP) database, the post-MI survival benefit of beta-blockade was at least as great in patients with COPD as in those without COPD.[12]

Patients with COPD have been excluded from many CHF trials, and so it is not certain whether beta-blockers reduce mortality as effectively in CHF patients with COPD as in those without. However, current European Society of Cardiology (ESC) guidelines[13] underline the importance of managing CHF effectively in patients with COPD, as coexisting COPD worsens prognosis.[14] The guidelines state that the majority of patients with CHF and COPD can safely tolerate beta-blocker therapy. They also suggest that selective beta-blockade is preferable, as a meta-analysis of studies in COPD patients demonstrated no significant change in FEV_1 vs. placebo when β_1-selective beta-blockers were used.[15]

Lung function in patients with COPD receiving beta-blockers should be carefully monitored, however, as asthma and COPD may coexist. The ESC guidelines recommend starting at a low dose followed by gradual uptitration.[13] Mild deterioration in pulmonary function and symptoms should not lead to prompt discontinuation, but if symptoms worsen, a reduction of the dosage or withdrawal may be necessary. If in doubt, lung function without and with beta-blockers can be measured repeatedly before chronic use.

Beta-blockers and peripheral vascular disease

Raynaud's phenomenon (a common problem in young women with mitral valve prolapse) is rare when β_1-selective beta-blockers are used. Patients with peripheral vascular disease occasionally report intermittent claudication, usually if beta-blockers have been started at high doses. Our own experience in 50 CAD patients before and after slow uptitration of beta-blockers revealed identical stress test results (unpublished data). This agrees with a meta-analysis of 11 studies showing that beta-blockers do not adversely affect walking capacity or symptoms of intermittent claudication in patients with mild to moderate peripheral arterial disease.[16]

Beta-blockers and the central nervous system

Rarely, unpleasant dreams, hallucinations, insomnia, and depression can occur during beta-blocker therapy.[17] Some researchers believe that highly lipid-soluble drugs, such as propranolol may penetrate the central nervous system more than the others. Although headache and depression are listed as possible side-effects of beta-blockers, in some patients beta-blockers have beneficial effects in reducing anxiety, migraine, and depression.

Beta-blockers and diabetes

Increased insulin resistance and a higher incidence of new-onset diabetes mellitus were reported in early trials with beta-blockers. However, more modern agents such as bisoprolol and carvedilol appear to have no detrimental effect on glucose metabolism.[18] Existing diabetes mellitus is no contra-indication to beta-blockade, although β_1-selective agents are preferable in insulin-dependent patients, to avoid masking hypoglycaemia.

In fact, patients with diabetes and concomitant CHF or CAD are among those who can benefit most from beta-blockers. European guidelines recommend beta-blockers for all diabetic patients with acute cardiac syndrome, post-MI, and in CHF.[19] Post-MI beta-blockade reduces mortality by 23% in diabetic patients. In CHF studies, beta-blockers have consistently shown a significant benefit in patients with diabetes. A meta-analysis[20] has been conducted using all-cause mortality data from major randomized placebo-controlled trials reporting outcomes in patients with diabetes mellitus.[21–25] Compared with placebo, beta-blocker therapy for CHF significantly reduced all-cause mortality by 16% (*Figure 1*). This was somewhat less than the 28% reduction for patients without diabetes mellitus, but nevertheless clinically highly worthwhile.

Beta-blockers in elderly patients

Half of the patients with CHF in the general population are in the over-75 age group.[13] Despite this, the likelihood of being prescribed a beta-blocker is halved in patients older than 70 years.[2] Physicians' reluctance to use beta-blockers in the elderly may relate to concerns about comorbidities such as diabetes and COPD, and a belief that elderly patients cannot tolerate beta-blockers. However, the evidence from randomized controlled trials indicates that beta-blockers can be used safely and successfully in most elderly patients with CHF.

As the importance of including beta-blockers in standard therapy for CHF in the elderly has gradually been recognized, the mean age of patients included in major CHF trials has increased. For example, the Cardiac Insufficiency Bisoprolol Study (CIBIS III) was notable for including 'typical' CHF patients with a mean age of 72 years.[26] Prespecified subgroup analysis showed that the bisoprolol-first and enalapril-first strategies were equally effective regardless of age.

Similarly, subgroup analyses of CIBIS II and the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure

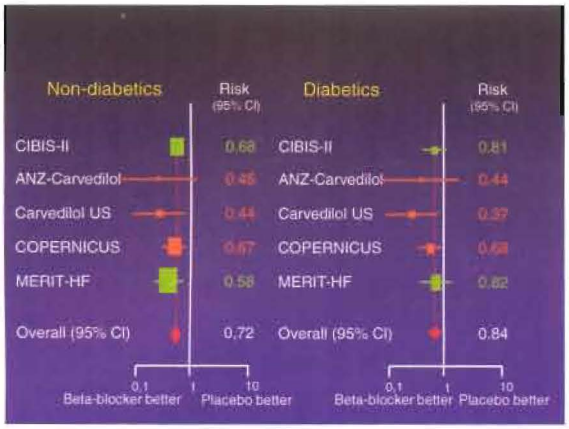

Figure 1 A meta-analysis by Haas *et al.* showed that compared with placebo, beta-blocker therapy for chronic heart failure significantly reduces all-cause mortality by 16% in patients with diabetes. ANZ, Australia/New Zealand Heart Failure Research Collaborative Trial; Carvedilol US, US Carvedilol Heart Failure Study; CIBIS II, Cardiac Insufficiency Bisoprolol Study II; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure. Adapted with permission from: Haas *et al.*[20]

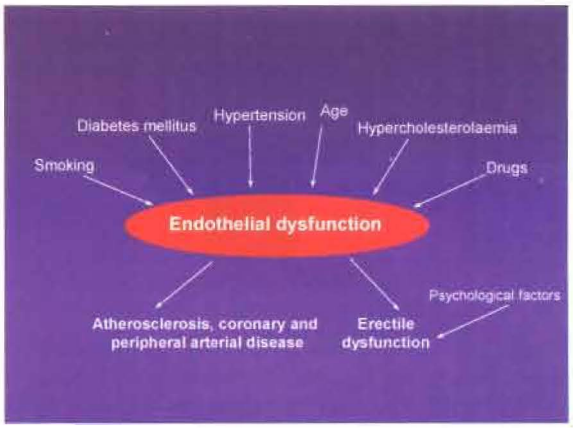

Figure 2 Pathophysiology of erectile dysfunction (ED). Note that, with the exception of psychological factors, the risk factors for ED are the same as for atherosclerosis and coronary and peripheral vascular disease.

(MERIT-HF) showed that beta-blockade reduced mortality as effectively in older patients as in younger patients.[27,28] Further evidence comes from the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS),[29] which was specifically designed to investigate the effects of beta-blockade in elderly CHF patients (mean age 76 years). Nebivolol significantly reduced the primary outcome of all-cause mortality or cardiovascular hospitalization, and was well-tolerated by most patients.[29] More recently, the Carvedilol Open Label Assessment (COLA) II study found that carvedilol was well-tolerated in 1030 CHF patients aged >70 years.[30]

Elderly patients may be more sensitive to the blood pressure-lowering effects of beta-blockers than younger patients, and may therefore require lower doses. As with COPD, 'start low and go slow' should be the rule.

Beta-blockers and erectile dysfunction

Both patients and doctors believe ED to be a common side-effect of beta-blockers, but there is surprisingly little evidence that this is the case. ED is common in patients with cardiovascular disease, regardless of drug treatment. For example, after MI, sexual activity is reduced by 22–75%, because of a combination of physiological and psychological factors.[31] The risk factors for CAD (age, hypertension, hypercholesterolaemia, diabetes, and smoking) are identical to those for ED (*Figure 2*).[32]

Beta-blockers do not seem to be any more closely associated with ED than any other class of antihypertensive. One study in

Table 1 Age-adjusted relative risk of self-reported erectile dysfunction (ED) in 2837 men prescribed various cardiovascular drugs, followed-up for 5 years (incidence 2–13% of users)

Drug class	Age-adjusted relative risk of ED
Angiotensin II antagonists	2.4
Non-selective beta-blockers	2.0
Calcium antagonists	1.8
Diuretics	1.4
ACE-inhibitors	1.2
Selective beta-blockers	1.0
Statins	0.9
Organic nitrates	0.8

The risk of ED appeared to be higher in men using calcium antagonists, angiotensin II antagonists, non-selective beta-blockers, or diuretics, but ED was not associated with organic nitrates, angiotensin converting enzyme (ACE)-inhibitors, selective beta-blockers, or statins. Data from Shiri *et al. Int J Impot Res* 2007;**19**:208–12.

hypertensive men found that the incidence of self-reported ED among those receiving acebutolol, amlodipine, and enalapril was similar to that for placebo.[33] A recent study among 2337 men followed-up for 5 years suggested that ED was more likely to be reported by men taking calcium antagonists, angiotensin II receptor blockers, non-selective beta-blockers, and diuretics (*Table 1*).[34] However, ED was not associated with selective beta-blockers, organic nitrates, ACE-inhibitors, or statins. A prospective trial in 878 overweight hypertensive men found that erection-related problems worsened in 28% with chlortalidone, 11% with atenolol and 3% with placebo.[35] An analysis of self-reported ED in six double-blind prospective trials ($n = 1251$) with drug exposure of 6–14 weeks found a prevalence of sexual dysfunction of 2.1% with placebo, 3.0% with bisoprolol/hydrochlorothiazide, 1.8% with

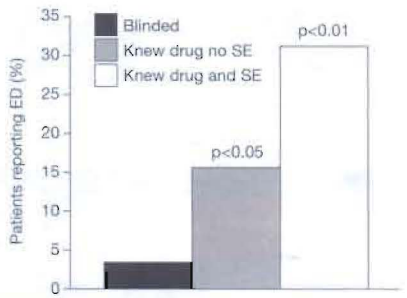

Figure 3 In a study in which all patients were taking atenolol, erectile dysfunction (ED) was commonest among those who knew which drug they were taking and that ED was a possible side-effect. Reproduced with permission from: Silvestri *et al.*[37]

bisoprolol alone, 2.9% with enalapril, 3.9% with amlodipine, and 1.5% with hydrochlorothiazide alone.[36]

Patients may blame their drugs for ED, but much of the problem is likely to be because of their underlying disease, or to anxiety regarding drug side-effects. The importance of psychological factors is exemplified by a recent trial, which entered 96 men with newly diagnosed cardiovascular disease (not suffering from ED) into a two-phase, crossover study.[37] After three months of atenolol treatment (50 mg o.d.), ED was reported by 3.1% of patients blinded with regard to their treatment, 15.6% of those who knew that they were taking atenolol but had not been specifically told that ED was a possible side-effect, and 31.2% of those who had been warned that atenolol might have effects on erectile function (*Figure 3*). All patients who reported ED were then randomized to sildenafil or placebo. Remarkably, both the active treatment and placebo were equally effective in reversing ED. Thus, it seems that the anxiety of knowing that beta-blockers may cause ED may be enough to produce this supposed side-effect.

Conclusions

Overall, in double-blind studies in CHF and post-MI, beta-blockers appear to have a very low rate of drug-related adverse events. Patients with COPD, diabetes, peripheral vascular disease, and the elderly can be prescribed beta-blockers, provided appropriate precautions are taken. Most side-effects are consequences of beta-blockade, and are thus dose-dependent. A policy of 'start low and go slow' can therefore often avoid problems. Although patients and their doctors perceive ED to be a side-effect of beta-blockade, concomitant disease and psychological factors in middle- and old-aged men are probably more important than drug treatment; ED is no more common with beta-blockers than with any other drug prescribed for CHF or hypertension. Thus, physicians may reasonably reassure sexually active men that there is no reason why they should not take a potentially life-saving treatment.

Conflict of interest: none declared.

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