# Drug Class Review
# on
# Beta Adrenergic Blockers

**Final Report**

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**http://www.ohsu.edu/drugeffectiveness/reports/documents/Beta Blocker Supplement.pdf**



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## INTRODUCTION

Beta blockers inhibit the chronotropic, inotropic and vasoconstrictor responses to the catecholamines, epinephrine and norepinephrine. Most beta blockers have half-lives of over six hours (Table 1). The shortest acting are pindolol (3-4 hours) and propranolol (3-5 hours). Most beta blockers are metabolized in combination by the liver and kidneys. On the other hand, atenolol is metabolized primarily by the kidneys while the liver has little to no involvement.

The beta blockers listed in Table 1 are approved for the treatment of hypertension. Other Food and Drug Administration (FDA) approved uses are specific to each beta blocker and include stable and unstable angina, arrhythmias, bleeding esophageal varices, coronary artery disease, asymptomatic and symptomatic heart failure, hypertension migraine and secondary prevention post-myocardial infarction (Table 2).

Beta blockers differ in their effects on the 3 adrenergic receptors ($\beta_1$, $\beta_2$, and $\alpha$) and in their duration of effect (Table 1). Cardioselective beta blockers preferentially inhibit $\beta_1$ receptors that are principally found in the myocardium. Non-cardioselective beta blockers also inhibit $\beta_2$ receptor sites, which are found in smooth muscle in the lungs, blood vessels, and other organs. Beta blockers with intrinsic sympathomimetic activity (ISA) act as partial adrenergic agonists and would be expected to have less bradycardic and bronchoconstriction effects than other beta blockers. Finally, carvedilol and labetalol block $\alpha$-adrenergic receptors and would be expected to reduce peripheral vascular resistance more than other beta blockers.

**Table 1. Beta blockers included in the review**

| Drug | Usual Hypertension Dosage (TDD) | Daily dosage frequency | Half-life (hours) | Cardioselective | Partial agonist activity (ISA) | Alpha antagonist effect |
|---|---|---|---|---|---|---|
| Acebutolol | 200-1200 mg | Twice | 3-4 | Yes | Yes | No |
| Atenolol | 50-100 mg | Once | 6-9 | Yes | No | No |
| Betaxolol | 5-40 mg | Once | 14-22 | Yes | No | No |
| Bisoprolol | 5-20 mg | Once | 9-12 | Yes | No | No |
| Carteolol | 2.5-10 mg | Once | 6 | No | Yes | No |
| Carvedilol | 12.5-50 mg | Twice | 7-10 | No | No | Yes |
| Labetalol | 200-1200 mg | Twice | 3-6 | No | No | Yes |
| Metoprolol tartrate | 50-200 mg | Twice | 3-4 | Yes | No | No |
| Metoprolol succinate (extended release) | 50-400 mg | Once | 3-4 | Yes | No | No |
| Nadolol | 20-240 mg | Once | 10-20 | No | No | No |
| Penbutolol | 20 mg | Once | 5 | No | Yes | No |
| Pindolol | 10-60 mg | Twice | 3-4 | No | Yes | No |
| Propranolol | 40-240 mg | Twice | 3-4 | No | No | No |
| Propranolol long-acting | 60-240 mg | Once | 8-11 | No | No | No |
| Timolol | 10-40 mg | Twice | 4-5 | No | No | No |

**Table 2. Approved indications**

| Drug | Hypertension | Chronic stable angina | Atrial arrhythmia | Migraine | Bleeding esophageal varices | Heart failure | Post Myocardial Infarction | Decreased LV function after recent MI |
|---|---|---|---|---|---|---|---|---|
| Acebutolol | Yes | Yes | | | | | | |
| Atenolol | Yes | Yes | | | | | Yes | |
| Betaxolol | Yes | | | | | | | |
| Bisoprolol | Yes | | | | | | | |
| Carteolol | Yes | | | | | | | |
| Carvedilol | Yes | | | | | Mild to severe | | Yes |
| Labetalol | Yes | | | | | | | |
| Metoprolol tartrate | Yes | Yes | | | | | Yes | |
| Metoprolol succinate (extended release) | Yes | Yes | | | | Stable, symptomatic Class II-III | Yes | |
| Nadolol | Yes | Yes | | | | | | |
| Penbutolol | Yes | | | | | | | |
| Pindolol | Yes | | | | | | | |
| Propranolol | Yes | Yes | Yes | Yes | | | | |
| Propranolol long-acting | Yes | Yes | Yes | Yes | | | | |
| Timolol | Yes | | | Yes | | | Yes | |

Adapted from Drug Facts and Comparisons®
†=ISA

## Scope and Key Questions

The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to their constituencies. Initially, the Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed, revised, and approved by representatives of organizations participating in the Drug Effectiveness Review Project. It is the representatives' responsibility to ensure that the questions reflect public input or input from their members. The participating organizations approved the following key questions to guide this review.

**Key Question 1.** For adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine or bleeding esophageal varices, do beta blocker drugs differ in effectiveness?

**Key Question 2.** For adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine or bleeding esophageal varices, do beta blocker drugs differ in safety or adverse events?

**Key Question 3.** Are there subgroups of patients based on demographics (age, racial groups, gender), other medications (drug-drug interactions), or co-morbidities (drug-disease interactions) for which one beta blocker is more effective or associated with fewer adverse effects?

This review includes beta blockers that are available in the U.S. in an oral form and are indicated for hypertension. We excluded esmolol, an ultra-short acting beta blocker available only in intravenous form. Esmolol is used primarily as an antiarrhythmic drug for intraoperative and other acute arrhythmias. We also excluded sotalol, a nonselective beta blocker with Class III antiarrhythmic activity that is used exclusively for arrhythmias. Beta blockers that are unavailable in the U.S. are bopindolol, bucindolol, medroxalol, and oxprenolol.

## METHODS

We searched (in this order): the Cochrane Central Register of Controlled Trials (CCRCT) (1st quarter 2004), Medline (1966- March Week 5 2004), Premedline (April 9, 2004), Embase (1980-April 14, 2004), and reference lists of review articles. In electronic searches we used broad searches, combining terms for included beta blockers with terms for patient populations. Appendix A contains complete CCRCT and Medline search strategies. A similar search strategy was repeated in Embase. In addition, pharmaceutical manufacturers were invited to submit dossiers, including citations, using a protocol issued by the Center for Evidence-based Policy (http://www.ohsu.edu/drugeffectiveness/pharma/Final_Submission_Protocol_Ver1_1.pdf). All citations were imported into an electronic database (EndNote 6.0).

### Study Selection

One reviewer assessed all citations and selected full articles for inclusion, with consultation from a second reviewer where necessary. All disagreements were resolved by consensus.

We included English-language reports of studies of the patient populations and efficacy outcomes listed in Table 3. For studies of hypertension, we excluded studies in which blood pressure lowering was the only endpoint; most of these studies seek to identify equivalent doses of beta blockers rather than differences in clinical effectiveness. Instead, we sought evidence of long-term effects on mortality, cardiovascular events, and quality of life. We only included studies in stable angina patients with duration of 2 months or longer. We only included studies of long-term treatment in post-CABG patients; excluding studies of the short-term use of beta blockers to suppress atrial arrhythmias. We only included studies of recent myocardial infarction with sample sizes of 100 patients or more.

**Table 3. Included outcome measures**

| | |
|---|---|
| Hypertension | 1. All-cause and cardiovascular mortality<br>2. Cardiovascular events (stroke, myocardial infarction, or development of heart failure)<br>3. End-stage renal disease (including dialysis or need for transplantation) or clinically significant and permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance)<br>4. Quality-of-life |
| Stable angina (treatment ≥ 2 months' duration) | 1. Exercise tolerance<br>2. Attack frequency<br>3. Nitrate use |
| Post-coronary artery bypass graft (long-term treatment) | 1. All-cause mortality<br>2. Ischemic events (MI, unstable angina, need for repeat CABG and PTCA) |
| Recent myocardial infarction (with and without LV dysfunction) | 1. All-cause and cardiovascular mortality<br>2. Cardiovascular events (usually, development of heart failure) |
| Symptomatic chronic heart failure | 1. All-cause or cardiovascular mortality<br>2. Symptomatic improvement (heart failure class, functional status, visual analogue scores)<br>3. Hospitalizations for heart failure |
| Asymptomatic LV dysfunction | 1. All-cause and cardiovascular mortality<br>2. Cardiovascular events (usually, development of heart failure) |
| Atrial fibrillation/flutter | 1. Rate control<br>2. Relapse into atrial fibrillation |
| Migraine | 1. Attack frequency<br>2. Attack intensity/severity<br>3. Attack duration<br>4. Use of abortive treatment |
| Bleeding esophageal varices | 1. All-cause mortality<br>2. Fatal/non-fatal rebleeding |

We included the following safety outcomes: overall adverse event incidence, withdrawals due to adverse events, and frequency of important adverse events associated with beta blockers including bradycardia, heart failure, and hypotension. In some studies, only 'serious' or 'clinically significant' adverse events are reported. Some studies do not define these terms, and in other studies, the definitions vary between studies.

To evaluate efficacy, we included randomized controlled trials and good-quality systematic reviews. To evaluate effectiveness and safety, we included trials as well as good-quality observational studies.

## Data Abstraction

From included trials we abstracted information about the study design, setting, population characteristics (including sex, age, race, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome.

## Quality Assessment

We assessed the internal validity (quality) of included studies based on the predefined criteria listed in Appendix B. Overall quality ratings for the individual study were based on ratings of its internal validity, suitability to answer the question, and applicability to current practice.

A particular randomized trial might receive different ratings for efficacy and adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

### Data Synthesis

The comparative efficacy and safety of beta blockers in the specified patient populations are synthesized through a narrative review as well as in tabular form. We analyzed continuous efficacy data by calculating percent change scores when possible. Forest plots of relative risks (RR) or odds ratios (OR) are presented, where applicable, to display data comparatively. Forest plots were created using StatsDirect (CamCode, UK) software. StatsDirect was also used to calculate number needed to treat (NNT) statistics.

## RESULTS

### Overview

Searches identified 5,144 citations: 2,425 from the Cochrane Library, 1,237 from Medline, 1,351 from EMBASE, 120 from reference lists, and 11 from pharmaceutical company submissions, peer reviewers, or public comment. 104 (11 from update search) reports of trials met the inclusion criteria for the systematic review. Included trials are listed in Appendix C.

### Key Question 1: Do beta blocker drugs differ in efficacy?

### 1a. For adult patients with hypertension, do beta blockers differ in efficacy or effectiveness?

### Summary

Beta blockers are equally efficacious in controlling blood pressure in patients with hypertension. No beta blocker has been demonstrated to be more efficacious or to result in better quality of life than other beta blockers, either as initial therapy or when added to a diuretic, ACE inhibitor, or ARB. Evidence from long-term trials is mixed; overall, beta blockers are generally less effective than diuretics, and usually no better than placebo, in reducing cardiovascular events. There was one exception: in one large trial, treatment with metoprolol resulted in lower all-cause mortality than treatment with a thiazide diuretic.

### Detailed Assessment

*Primary or initial therapy.* Beta blockers have been used as initial therapy in patients with hypertension and as additional therapy in patients whose blood pressure is not well-controlled with a diuretic. In several head-to-head trials, beta blockers have similar effects on blood pressure control,[1-9] No trials have examined whether beta blockers have different effects on all cause mortality, cardiovascular mortality, or cardiovascular events among patients with hypertension.

By the time beta blockers became available, diuretics had already been shown to prevent cardiovascular events, primarily strokes. It was considered unethical to compare a beta blocker to placebo in patients who were likely to benefit from a diuretic. For this reason, most large, long-term trials of beta blocker therapy for hypertension use a comparison group taking a diuretic rather than a placebo. Unlike diuretics, then, beta blockers have not been clearly demonstrated to be more effective than placebo in reducing cardiovascular events when used as initial therapy in the general population of patients with hypertension.

The Medical Research Council (MRC) trials, the International Prospective Primary Prevention Study in Hypertension (IPPPSH), the Heart Attack Primary Prevention in Hypertension (HAPPHY) study and the Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) study compared a beta blocker to a thiazide diuretic. Of these trials, only the two MRC trials compared a beta blocker to placebo. In one MRC trial, atenolol 50 mg daily was no better than placebo, and less effective than a diuretic, in adults ages 65-74 who had baseline blood pressures of 160/115 or higher.[10] In the other MRC trial, which recruited 17, 361 patients with mild diastolic hypertension (90-109 mm Hg), beta-blocker therapy (atenolol) reduced the odds for stroke, but only in nonsmokers, and to a smaller degree than a low dose of a thiazide diuretic (bendrofluazide).[11]

Of the trials that compared a beta blocker with a diuretic, only one (MAPHY) had any suggestion that the beta blocker was more effective. In that trial, deaths from heart attacks and strokes as well as total mortality were lower in the metoprolol treated group than in those treated with a diuretic (hydrochlorothiazide or bendroflumethiazide).[12] The trial continues has been cited as strong evidence that beta blockers reduce mortality when used as primary treatment for hypertension. However, it must be weighed against the mixed results of the MRC trials and other trials of beta blockers versus diuretics. A good-quality meta-analysis of 10 trials published in 1998 or earlier, beta blockers were ineffective, or less effective than comparator drugs, in preventing coronary heart disease, cardiovascular mortality, and all-cause mortality (ORs, 1.01, 0.98, and 1.05, respectively).[13]

*Secondary treatment.* The SHEP trial examined a stepped approach for treating isolated systolic hypertension.[14] Chlorthalidone was the first step. Atenolol was prescribed if the blood pressure goal could not be achieved with chlorthalidone 25 mg daily. Compared to placebo, stepped treatment prevented 55 cardiovascular events per 1000 patients over 5 years. The contribution of beta blocker therapy with atenolol to the overall benefit is not clear; most of the benefit was attributed to chlorthalidone.

The ALLHAT study (2002) did not include a beta blocker arm.[15] Based on the results of ALLHAT, the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) recommends a diuretic as the first-line treatment for most patients who have Stage 1 hypertension without compelling indications.[16]

*Quality of life.* There is no definitive evidence that one beta blocker yields a better quality of life than another for patients who have hypertension. Two placebo-controlled trials reported the effect of long-term beta blocker therapy on quality of life in otherwise healthy patients who have hypertension (Evidence Tables 1 and 1a). The Trial of Antihypertensive Interventions and

Management (TAIM) [17-19] had a serious flaw: only patients who were available for the 6-month blood pressure readings (79.4%) were included in the quality-of-life analysis. After 6 months, atenolol and placebo were similar on several dimensions from the *Life Satisfaction Scale, Physical Complaints Inventory, and Symptoms Checklist*, including *summary* ('Total physical problems', 'Overall psychological functioning', 'Overall life satisfaction'), *distress* ('Sexual physical problems', 'Depression', 'Anxiety', 'Sleep disturbances', 'Fatigue') and *well-being* ('Satisfaction with physical health', 'Sexual satisfaction'). In the second trial[20], there were no differences between propranolol and placebo in cognitive or psychological measures after one year of treatment.

### 1b. For adult patients with angina, do beta blockers differ in efficacy?

### Summary

There were no differences in exercise tolerance or attack frequency in head to head trials of carvedilol vs metoprolol, pindolol vs propranolol, and betaxolol vs propranolol in patients with chronic stable angina. Atenolol and bisoprolol were equivalent in angina patients with COPD. Atenolol and labetalol (when combined with chlorthalidone) were equivalent in angina patients with hypertension.

Beta blockers that have intrinsic sympathomimetic activity reduce the resting heart rate less than other beta blockers, a potential disadvantage in patients suffering from angina pectoris. For this reason, experts recommend against using beta blockers with ISA in patients with angina.

### Detailed Assessment

In 1966 the first beta blocker, propranolol, was shown in a multicenter controlled trial to improve symptoms in patients with angina pectoris.[21] Several other beta blockers (acebutolol, atenolol, metoprolol tartrate, metoprolol succinate, nadolol, propranolol, propranolol long-acting) have been demonstrated to reduce symptoms of angina in placebo-controlled trials.

Most head-to-head trials of beta blockers in patients with angina pectoris observe patients for only two to four weeks of treatment.[22-29] In these trials, exercise tolerance, attack frequency, or nitroglycerin use were generally similar at comparable doses.

Five fair-quality head-to-head trials evaluated angina symptoms after two or more months of treatment with beta blockers (Table 4, Evidence Tables 2 and 2a). Mean ages ranged from 55 to 61.5 years and most subjects were men (71.5 percent to 100 percent). Exercise parameters were measured using bicycle ergometric testing in all but two trials[30, 31], which used a treadmill. There were no significant differences in exercise tolerance or attack frequency.

**Table 4. Results of head-to-head trials in patients with angina**

| Trial | Interventions | Results | |
|---|---|---|---|
| | | Exercise parameters | Attack frequency and/or NTG use (% reduction) |
| van der Does, 1999 *n=368* | carvedilol 100 mg metoprolol 200 mg | No difference | Not reported |
| Frishman, 1979 *n=40* | Pindolol 10-40 mg Propranolol 40-240 mg | No difference | No difference |
| Narahara, 1990 *N=112* | Betaxolol 20 and 40 mg Propranolol 160 and 320 mg | No difference | No difference |
| Dorow, 1990 *n=40 (comorbid chronic obstructive pulmonary disease patients)* | Atenolol 50 mg Bisoprolol 5 mg | Not reported | 82.8% vs 64.3% (not significant) |
| Chieffo, 1986 *n=10 (comorbid hypertension)* | Labetolol 200 mg+chlorthalidone 20 mg Atenolol 100 mg+chlorthalidone 25 mg | Not reported | 60% vs 80% (not significant) |

sl ntg=sublingual nitroglycerin

Over the long-term, beta blockers may differ in their ability to prevent or reduce the severity of anginal attacks. In one fair quality 2-year multicenter European trial, propranolol was better than placebo after 8 weeks but not after 24 weeks of treatment.[32] Specifically, after 8 weeks propranolol 60-240 mg reduced the proportion of patients using nitroglycerin (57% vs. 73% in the placebo group; p=0.04) and increased the mean total work time by 48% vs 13% (p=0.04). These effects were transient, however, and propranolol was equivalent to placebo on those parameters after 24 weeks of treatment. Propranolol and placebo had similar effects on the number of weekly angina attacks, the number of attack free days, maximum workload and exercise duration at eight- and 24-week endpoints. The relevance of this trial is limited, because, since the time it was conducted, the rate of progression of angina may have been altered by advances in treatment of atherosclerosis (e.g., statin therapy.)

A good-quality meta-analysis identified 72 randomized controlled trials of a beta blocker vs. a calcium channel blocker and 6 trials comparing a beta blocker to a nitrate.[33] This meta-analysis found that, in general, beta blockers had similar efficacy but fewer discontinuations due to adverse events than calcium channel blockers, but the authors did not report results for each beta blocker separately.

## 1c. For adult patients who have undergone coronary artery bypass grafting, do beta blockers differ in efficacy?

We did not examine the short-term (4-10 days) use of beta blockers to prevent or control atrial tachyarrhythmias after CABG.[34-38] In addition to the beta blockers included in our review, esmolol, a very short-acting, intravenous beta blocker, is used postoperatively to control tachyarrhythmias.

In 7 trials, long-term use of a beta blocker after CABG did not improve mortality or other outcomes (Evidence Tables 3 and 3a). For example, the MACB Study Group conducted a fair quality trial[39] that randomized 967 patients (85.5% male, median age 64 years) to metoprolol 200 mg once daily or placebo within 5-21 days following CABG and measured the effects of treatment on death and cardiac events.. No differences between metoprolol and placebo were found in mortality (3.3% vs 1.8%; p=0.16) or in ischemic events (e.g., MI, unstable angina, need for additional CABG or PTCA).

## 1d. For adult patients with recent myocardial infarction, do beta blockers differ in efficacy?

### Summary

Table 5 summarizes evidence from meta-analyses and major trials of beta blockers in patients with recent myocardial infarction. Timolol was the first beta blocker shown to reduce total mortality, sudden death, and reinfarction outcomes, all in the Norwegian Multicenter Study.[40] Subsequently, similar total mortality reductions were reported across trials of acebutolol[41], metoprolol tartrate (Goteborg), and propranolol (BHAT) in comparable populations. Also, similar benefits in sudden death were reported for propranolol[42] and metoprolol tartrate[43, 44] and in reinfarction for metoprolol tartrate.[44]

Carvedilol reduced reinfarction rates in the CAPRICORN trial, which recruited stable inpatients with recent myocardial infarction and a left ventricular ejection fraction less than 40%. Carvedilol is the only beta blocker shown to reduce mortality in post-MI patients who are already taking an ACE inhibitor.

Indirect comparisons of beta blockers across these trials must be done with caution because the study populations differed in duration, the presence or absence of left ventricular dysfunction, the dose and timing of therapy; and the use of other medications.

**Table 5. Comparison of outcomes of mortality-reducing beta blockers in patients following myocardial infarction**

| Trial | Mortality Reduction in General Population of Post-MI patients | Mortality Reduction in Post-MI patients with LV dysfunction | Sudden death reduction | Reinfarction reduction |
|---|---|---|---|---|
| Acebutolol | Effective | Uncertain | Insignificant effect | Insignificant effect |
| Carvedilol | Not established | Effective | Uncertain (trend) | Uncertain (trend) |
| Metoprolol tartrate | Effective | Probable | Effective | Effective |
| Propranolol | Effective | Probable | Effective | Insignificant effect (BHAT, Hansteen 1982) |
| Timolol | Effective | Uncertain | Effective | Effective |

## Detailed Assessment (Full details in evidence tables 4 & 4a)

Early, routine use of beta blockers after myocardial infarction reduces mortality and rates of hospital admission. We identified only one, fair-quality head-to-head trial of different beta blockers after MI,[45] a 6-week trial comparing atenolol 100 mg to propranolol 120mg which had inconclusive results.

Because of the lack of comparative trials, inferences about the comparative effectiveness of beta blockers in post-MI patients must be made on other grounds. The criteria for making these comparisons might include:

1) demonstration of reduced mortality in large, multicenter placebo-controlled trials
2) the degree of mortality reduction compared with other beta blockers
3) improvements in other outcomes
4) tolerability
5) effectiveness studies, and applicability of efficacy studies to current practice.

### Mortality

Three systematic reviews have analyzed over 60 trials of beta blockers after MI.[46-48] The first (Yusuf, 1985) analyzed 22 long-term trials of beta blockers in acute myocardial infarction. Overall beta blockers reduced mortality by 23%, from an average of 10% to 8%. The second (Hjalmarson, 1997) found an average 20% mortality reduction in 24 trials of a total of 25,000 patients.

A more recent review (Freemantle, 1999) used meta-regression to examine the relationship of characteristics of different beta blockers with the outcome of treatment.[48] In their analysis of 24 long-term trials, cardioselectivity had no effect, but there was a near significant trend towards decreased benefit in drugs with intrinsic sympathomimetic activity. Individually, acebutolol (0.49; 0.25-0.93), metoprolol tartrate (0.80; 0.66-0.96), propranolol (0.71; 0.59-0.85), timolol (0.59; 0.46-0.77) significantly reduced mortality, but there was insufficient data to distinguish among them. The analysis included just one trial of carvedilol, a pilot study in 151 post-MI patients (Basu et al, 1997).[49]

Table 6 below summarizes placebo controlled trials that enrolled > 100 patients, had long-term follow-up (> 6 weeks) and met our other inclusion criteria.

All of the trials in Table 6 were analyzed in the 1999 systematic review except for CAPRICORN, which was conducted from 1997 to 2000 at 163 sites in 17 countries and published in 2001.[50] Unlike the other trials, CAPRICORN included only patients who had reduced left ventricular function (<40%) after acute myocardial infarction as determined by echocardiography or cardiac catheterization. Patients with uncontrolled heart failure, such as those requiring intravenous diuretics, were excluded. Of 1959 subjects randomized to either carvedilol or placebo at an average of 10 days following a confirmed MI, 1289 had no clinical signs of heart failure (Killip Class I), 593 had Killip Class II heart failure, and 65 had Killip Class III failure. The mean ejection fraction was 32.8%.

The original primary endpoint was all-cause mortality. This was revised to include all-cause mortality *plus* cardiovascular hospital admissions as a co-primary endpoint when a blinded interim analysis suggested that overall mortality rates were lower than predicted. There was no difference between carvedilol and placebo for the primary endpoint of mortality plus cardiovascular admissions (35% vs. 37% for placebo over 1.3 years, p=0.299). However, carvedilol reduced the *original* primary endpoint of total mortality (12% vs. 15% for placebo over 1.3 years; NNT=30 or NNT for 1 year=43). The p value was 0.03, which, although nominally significant, did not meet the higher level of significance specified when the combined primary outcome measure was adopted.

CAPRICORN is the only trial to demonstrate the added benefit of a beta blocker in post-MI patients taking ACE inhibitors or having undergone thrombolytic therapy or angioplasty. It is also the only trial specifically designed to evaluate a beta blocker in post-MI patients who have asymptomatic LV dysfunction. Based on CAPRICORN, the FDA gave carvedilol an indication to reduce mortality in "left ventricular failure after a myocardial infarction."

The use of ACE inhibitors, thrombolytics, and angioplasty support the relevance of CAPRICORN to current care in the U.S. and Canada. However, the case for relevance could be strengthened if data were available to compare other practices, and the quality of care, between sites that recruited successfully and those that did not. Additional information about the recruitment of patients and the centers at which the CAPRICORN was conducted might provide additional insight into its relevance to current practice in the U.S. and Canada. Of the 1949 subjects in the trial, 83 were enrolled in the U.S. and 5 were from Canada. Five of the 6 top recruiting sites were in Russia, which enrolled the most subjects of any country (600). Of the 163 study sites, 24 enrolled only 1 subject. In their *Lancet* paper, the authors of CAPRICORN noted that "recruitment was slow in some countries where it was widely perceived that the case for beta-blockers in all patients with myocardial infarction was proven." The statement leaves open the possibility that, in North America, the subjects in CAPRICORN would already have been taking beta blockers.

Is the mortality reduction in CAPRICORN different from what would be expected from older trials of beta blockers in post-MI patients or in patients with heart failure? The authors of the

*Lancet* paper raised this question, noting that the 23% mortality reduction in CAPRICORN is identical to that found in meta-analyses of the older beta blocker trials.

Mortality was higher in CAPRICORN than in previous trials of beta blockers in post-MI patients. The likeliest explanation is that many earlier trials included a broader mix of patients, including many who had normal LV function and a better prognosis. Unlike many major trials, the CAPRICORN publication did not say how many patients with MI were seen at the participating centers during the period of recruitment. It is also not clear what proportion of potentially eligible patients were excluded because they had an ejection fraction greater than 40%. These statistics would be useful in comparing the CAPRICORN subjects to the subjects of previous trials of beta blockers in post-MI patients.

There is no direct evidence that other beta blockers shown to reduce mortality in post-MI patients or in patients with heart failure work as well as carvedilol in post-MI patients with decreased LV function and few or no symptoms of heart failure. While the older trials undoubtedly included some subjects with LV dysfunction, it is difficult to determine how many, or how this subset did compared with post-MI patients with normal LV function. Indirect evidence comes from a good-quality meta-analysis.[51] This analysis examined the relationship between the mortality reduction reported in each trials and the proportion of patients in the trial who had heart failure. There were few data on the effects of beta-blockers after myocardial infarction in patients with documented left ventricular systolic dysfunction, but some studies included subjects with clinical findings of heart failure and reported the proportion of subjects that had these findings. As expected, studies that included patients with heart failure had higher mortality rates. The relative benefit of beta-blockers on mortality after a myocardial infarction was similar in the presence or absence of heart failure.

Two retrospective subgroup analyses in heart failure patients from individual trials included in this meta analysis provide additional details supporting this hypothesis. One is from the BHAT trial (β Blocker Heart Attack Trial), a large, 3-month trial of propranolol published in 1980. In BHAT, 710 of 1916 subjects had a history of congestive heart failure prior to randomization. Propranolol lowered total mortality from 18.4% to 13.3% (a 27% reduction) in patients with a history of heart failure and from 7.8% to 5.9% (25% reduction) in patients who did not have a history of heart failure.[52]

The other retrospective subgroup analysis is from a 1980 placebo-controlled trial of metoprolol. At the time of randomization, 262 (19%) of the 1,395 subjects had signs or symptoms of mild heart failure.[53] Metoprolol or placebo was administered intravenously once, followed by oral metoprolol or placebo for 3 months, followed by open treatment with metoprolol for up to 2 years in all patients who had signs of ischemia. For patients with heart failure, mortality during the first year of the study was 28%, versus 10% in subjects without signs of heart failure ($p<0.0001$). Among the subjects with heart failure at the time of randomization, metoprolol reduced mortality during the 3-month double-blind phase of the trial (14% vs. 27%, $p<0.0009$, NNT=8).

## Sudden death

Significant reductions in sudden death were reported in two of three trials of metoprolol tartrate,[43, 44] one trial of propranolol,[42] and one trial of timolol.[40]

## Reinfarction

Significant reductions in reinfarction rates were reported in one of two trials of metoprolol tartrate[44] and one trial of timolol.[40] Carvedilol reduced reinfarction rates in the CAPRICORN trial.

## Withdrawals

Among the major trials, rates of withdrawal ranged from 9.3% to 36.6%, probably indicating differences in patients' characteristics. Within studies, rates of withdrawal were generally similar for the beta blocker and placebo groups, with three exceptions. Rates of withdrawal were greater for metoprolol tartrate in one[54] of five trials, pindolol in one trial[55], and propranolol in one trial.[56]

**Table 6. Summary of results from placebo-controlled trials of beta blocker therapy following myocardial infarction**

| Study, year | Interventions | Duration | Number enrolled | Total mortality | Sudden Death | Reinfarction | Withdrawals |
|---|---|---|---|---|---|---|---|
| ***Acebutolol*** | | | | | | | |
| Boissel 1990 | A: Acebutolol<br>B: Placebo | 271 days | 607 | A: 5.7% (17/298)<br>B: 11% (34/309)<br>p=0.019; NNT=19 | nr | A: 3%<br>B: 3.6%<br>NS | A: 33%<br>B: 36.6%<br>NS |
| ***Carvedilol*** | | | | | | | |
| Basu 1997 | A: Carvedilol<br>B: Placebo | 6 months | 151 (146 analyzed) | A: 2.7% (2/75)<br>B: 4.2% (3/71<br>p=NS | nr | A: 5.3%<br>B: 11.3%<br>NS | nr |
| CAPRICORN 2001 | A: Carvedilol<br>B: Placebo | 1.3 years (mean) | 1959 | A: 12% (116/975)<br>B: 15% (151/984)<br>p=0.031; NNT=30 | A: 5%<br>B: 7%<br>NS | A: 14%<br>B: 20%<br>p=0.002 | A: 20%<br>B: 18%<br>NS |
| ***Metoprolol*** | | | | | | | |
| Stockholm 1983 | A: Metoprolol<br>B: Placebo | 3 years | 301 | A: 16.2% (25/154)<br>B: 21% (31/147)<br>p=NS | A: 5.9%<br>B: 14.3%<br>p<0.05 | A: 11.7%<br>B: 21.1%<br>p<0.05 | A: 24.7%<br>B: 23.8%<br>NS |
| Amsterdam 1985 | A: Metoprolol<br>B: Placebo | 1 year | 553 | A: 3.3% (9/273)<br>B: 5.7% (16/280)<br>p=NS | A: 0.3%<br>B: 2.5%<br>NS | A: 5.9%<br>B: 7.1%<br>NS | A: 32%<br>B: 24%<br>p=0.02 |
| Belfast 1985 | A: Metoprolol<br>B: Placebo | 1 year | 764 | A: 11.8% (49/416)<br>B: 14.9% (52/348)<br>p=NS | A: 1.9%<br>B: 4.7%<br>p<0.05 | nr | A: 22.8%<br>B: 19%<br>NS |
| Lopressor 1987 | A: Metoprolol<br>B: Placebo | 1.5 years | 2395 | A: 7.2% (86/1195)<br>B: 7.7% (93/1200)<br>p=NS | nr | nr | A: 31.9%<br>B: 29.6%<br>NS |

**Table 6. Summary of results from placebo-controlled trials of beta blocker therapy following myocardial infarction continued**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Goteborg 1981 | A: Metoprolol<br>B: Placebo | 2 years | 1395 | A: 5.7% (40/698)<br>B: 8.9% (62/697)<br>p=0.024; NNT=32 | nr | A: 5%<br>B: 7.7%<br>NS | A: 19.1%<br>B: 19.1%<br>NS |
| ***Pindolol*** | | | | | | | |
| Australian & Swedish Study 1983 | A: Pindolol<br>B: Placebo | 2 years | 529 | A: 17.1% (45/263)<br>B: 17.7% (47/266)<br>p=NS | A: 10.6%<br>B: 11.7%<br>NS | nr | A: 28.8%<br>B: 18.8%<br>p=0.0078 |
| ***Propranolol*** | | | | | | | |
| Baber 1980 | A: Propranolol<br>B: Placebo | 9 months | 720 | A: 7.9% (28/355)<br>B: 7.4% (27/365)<br>p=NS | nr | A: 4.8%<br>B: 7.4%<br>NS | A: 23%<br>B: 24.1%<br>NS |
| Hansteen 1982 | A: Propranolol<br>B: Placebo | 1 year | 560 | A: 8.9% (25/278)<br>B: 13.1% (37/282)<br>p=NS | | | |
| BHAT 1982 | A: Propranolol<br>B: Placebo | 25 months | 3837 | A: 7.2% (138/1916)<br>B: 9.8% (188/1921)<br>p=0.0045; NNT=39 | nr | A: 5.4%<br>B: 6.3%<br>NS | A: 12.7%<br>B: 9.3%<br>p=0.0009 |
| Hansteen 1982 | A: Propranolol<br>B: Placebo | 12 months | 560 | A: 9% (25/278)<br>B: 13.1% (37/282)<br>p=NS | A: 3.9%<br>B: 8.1%<br>p=0.038 | A: 3.9%<br>B: 7.4%<br>NS | A: 25.2%<br>B: 25.5%<br>NS |
| ***Timolol*** | | | | | | | |
| Roque 1987 | A: Timolol<br>B: Placebo | 24 months | 200 | A: 6.7% (7/102)<br>B: 12.2% (12/98)<br>p=NS | nr | nr | nr |
| Norwegian Multicenter Study 1981 | A: Timolol<br>B: Placebo | 17 months | 1884 | A: 10.4% (98/945)<br>B: 16.2% (152/939)<br>p=0.0002; NNT=18 | A: 5%<br>B: 10.1%<br>p<0.0001 | A: 9.3%<br>B: 15%<br>p=0.0002 | A: 24%<br>B: 23.3%<br>NS |

## 1e. For adult patients with heart failure, do beta blockers differ in efficacy?

## Summary

The main findings from placebo-controlled trials in patients with mild to moderate heart failure are summarized in Table 7. Reductions in mortality, sudden death, cardiovascular deaths, and death due to heart failure were similar for bisoprolol, metoprolol succinate, and carvedilol. Because several carvedilol trials performed in the U.S. had significant mortality reductions, the evidence for carvedilol may be more relevant to a U.S. population. When titrated gradually in stable patients, there is no difference in tolerability among these drugs.

In patients with severe heart failure, carvedilol clearly reduced mortality and the combined endpoint of mortality and hospitalizations. Carvedilol has the most direct, strongest evidence. In a large, post-hoc subgroup analysis of MERIT-HF, a good-quality trial, metoprolol succinate demonstrated a mortality reduction similar to that for carvedilol in patients who had a similar mortality risk. This is a weaker level of evidence than that for carvedilol, but the lack of a direct comparator and the difficulty of comparing subjects from the different trials makes it uncertain whether one of these drugs is superior in patients with the various degrees of heart failure.

**Table 7. Main findings in placebo-controlled trials of patients with mild-moderate heart failure**

| Beta Blocker | Mortality reduction | Reduction in sudden death | Reduction in progressive heart failure | Improvement in NYHA Class | Improvement in exercise parameters | Improvement in QOL |
|---|---|---|---|---|---|---|
| Bisoprolol | Yes | Yes | Not proven | Yes | Not significant | Not significant |
| Carvedilol | Yes | Yes | Mixed results | Not proven | Not significant | Not significant |
| Metoprolol succinate | Yes | Yes | Yes | Not proven | Not significant | yes |

In COMET, a head-to-head trial conducted in patients with mild to moderate failure, carvedilol reduced mortality compared with metoprolol tartrate, the immediate-release form of metoprolol. In previous trials, however, metoprolol tartrate had not been proven to reduce mortality. COMET does not resolve the question of whether carvedilol is superior to metoprolol succinate or bisoprolol, the preparations that have been shown to reduce mortality.

## Detailed Assessment

### Placebo-controlled trials (Full details in Evidence Tables 5 and 5a.)

Eight meta-analyses of placebo-controlled trials of various beta blockers in heart failure were published in the mid-1990's through 2000.[57-64] In general, these meta-analyses found that beta blockers reduce mortality by about 30%, preventing 3.8 deaths per 100 patients in the first year of treatment. Nevertheless, the authors of the meta-analyses agreed that larger trials were needed before beta blockers could be recommended routinely for patients with heart failure.

Four beta blockers—bisoprolol, bucindolol, carvedilol, and metoprolol succinate—have been evaluated in such trials (Table 7a). Bisoprolol, in the Cardiac Insufficiency Bisoprolol Study II trial (CIBIS-II); carvedilol, in the Carvedilol Prospective Randomized Cumulative Survival trial COPERNICUS; and metoprolol succinate, in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure trial (MERIT-HF) each reduced total mortality by approximately 35%. Bucindolol, in the BEST trial, was ineffective. The poor result for bucindolol suggests that individual beta blockers may differ in their effectiveness to reduce mortality in heart failure patients. (Bucindolol is not available in the U.S., but is included in Table 7a for comparison.)

**Table 7a. Comparison of major beta blocker trials in heart failure**

| Trial | Drug and target dose | Ejection Fraction Criteria (Mean) | NYHA Class | Number of Subjects | Annual Placebo Mortality | Mortality Reduction | Withdrawal rate for active drug group¥ |
|---|---|---|---|---|---|---|---|
| CIBIS-II | Bisoprolol 10mg qd | <35% (0.27) | III (81%)<br>IV (19%) | 2,647 | 13% | 34% | 15% |
| MERIT-HF | Metoprolol CR 240mg qd | <40% (0.28) | II (41%)<br>III (56%)<br>IV (3.6%) | 3,991 | 11% | 34% | 14% |
| BEST | Bucindolol 100mg bid | <35% | III-IV | 2,708 | 17% | 10%*** | 23% |
| COPERNICUS | Carvedilol 25mg bid | <25% (0.20) | ?? | 2,289 | 19% | 35% | 12.6% |
| US Carvedilol* | Carvedilol 25mg bid** | <35% | II-IV | 1,094 | 12% | 65%§ | § |

¥ All values were not different from the placebo group except for COPERNICUS (placebo withdrawal rate 15.9%, p=0.0026)
*Planned analysis of pooled results of 4 independent, double-blind placebo-controlled trials.
**Dosage target was 50 mg bid in patients whose weight was 85 kg or more.
*** Not significant.
§ Mortality was not the primary endpoint, and the estimated mortality reduction was inflated because of the use of an active-drug run-in period before randomization. Withdrawal rates are also affected by use of an active-drug run-in phase. See Table 7b.

Table 7b summarizes 15 placebo controlled trials (including those in Table 7a) that enrolled > 100 patients and met our other inclusion criteria (Evidence Tables 5 and 5a). These trials evaluated atenolol 50-100 mg[65], bisoprolol 5-10 mg;[66, 67] carvedilol 50-100 mg;[68-75] metoprolol tartrate 100-150 mg;[76, 77] and metoprolol succinate (CR) 12.5-25 mg.[78, 79]

The FDA approval of metoprolol succinate for mild to moderate heart failure (NYHA Class II or III) is based on MERIT-HF. FDA approval of carvedilol for severe heart failure is based on COPERNICUS. Its approval for mild-moderate heart failure is based on 5 other trials, 4 of which constitute the "US Carvedilol study," plus the Australian New-Zealand Heart failure study (see Table 7b). Heart failure is not an FDA-approved indication for bisoprolol, which is a generic drug.

## Relation of Mortality Reduction to Severity of Heart Failure

The trials in Table 7a leave no doubt that, in certain patients, bisoprolol, carvedilol, and metoprolol succinate reduce mortality. The main unresolved questions are 1) whether any of these agents is superior to the others in patients with mild to moderate failure, and 2) whether, in patients with severe failure, bisoprolol or metoprolol succinate are equivalent to carvedilol, which is the only drug that has an FDA indication in this group.

Many authors have used the placebo group mortality rates to make inferences about the baseline severity of patients in the various trials. However several factors, including NYHA Class, ejection fraction, blood pressure, lifestyle, and the quality of medical care influence mortality in patients with heart failure. For this reason it has proven difficult to judge the relative severity of illness among the major trials listed in Table 7a.

**MERIT-HF provides interesting data about the relationship of NYHA class and ejection fraction:**

| *MERIT-HF Subgroups* | EF<25% | EF>25% |
|---|---|---|
| NYHA Class II | 707 ("A") | 928 |
| NYHA Class III-IV | 795 | 1561 ("D") |

The large number of Class II patients with "severe" LV dysfunction (EF<25%) illustrates the hazards of inferring functional class from ejection fraction. Conversely, a significant proportion of patients with "moderate to severe" heart failure (Class III and IV) had an EF>25%. As one would expect, the subgroup with NYHA Class III-IV and EF<25% had the highest mortality. It would be impossible to distinguish between patients in cells "A" and "D" based on mortality rates and entry criteria.

The 4 U.S. Carvedilol trials and the Australian-New Zealand trial demonstrated that in patients with NYHA Class II to IV heart failure, carvedilol reduced mortality. As shown in Table 7b the severity of heart failure of patients in these trials varied substantially, suggesting that carvedilol was effective across a broad spectrum of heart failure patients. These trials used an active drug run-in period during which patients who could not tolerate a small dose of carvedilol, were noncompliant, or died. These patients were excluded prior to randomization. For this reason, the mortality reductions and rates of withdrawal and adverse events are not comparable to those of other trials. In Table 7b we summarize mortality results of these and other trials after adjusting the number of deaths in the carvedilol group by adding in deaths that occurred during the run-in period.

**COPERNICUS** was a well-designed, well-conducted placebo-controlled trial of carvedilol conducted in 334 Centers. Of 2,289 subjects randomized, 627 were recruited from the U.S. and Canada; the rest were recruited in Europe (including Russia), the U.S., Canada, Israel, Australia, South Africa, Argentina, and Mexico.

It is difficult to compare the COPERNICUS subjects to those of other trials because COPERNICUS did not report NYHA Class or exercise capacity, which were inclusion criteria in the other trials. COPERNICUS was intended to recruit a more severely ill population than the U.S. carvedilol trials. COPERNICUS subjects had higher mortality than 3 of the 4 trials that make up the U.S. Carvedilol Trial.

The mortality effect in COPERNICUS was consistent for sex, age, and other subgroups. The effect was lower, but not significantly so, for patients who had an EF<20% vs. those who had EF>20% and for those recruited in Europe, Australia, and the Middle East vs. North and South America.

**MERIT-HF,** conducted in the U.S. and Europe, recruited stable subjects with mild to severe heart failure. Although it had a significant proportion of subjects with NYHA Class II symptoms, the mean ejection fraction was similar to that of CIBIS-II. MERIT-HF was well-designed and well-conducted and had clear-cut overall reductions in overall mortality, death from cardiac causes, sudden death, and heart transplantation, as well as a reduction in all cause hospitalization (RR 0.84, CI 0.76-0.95).

The MERIT-HF investigators defined a "high risk" group consisting of the 795 patients who had NYHA class III-IV and EF<25%. This subgroup had a mean ejection fraction (19%) and placebo group mortality (18.2%) close to that of COPERNICUS.

The applicability of the results of any trial to a U.S. population is a major issue in all of these trials, because heart failure survival depends on other aspects of care. The FDA review of the MERIT-HF trial found "a strong suggestion of a treatment-by-region (U.S. vs. Europe) interaction with respect to mortality". MERIT-HF had 1,071 U.S. subjects and 2,920 European subjects. The placebo group mortality was higher in Europe (168/1462, 11.5%) than in the U.S. (49/539, 9.1%). Metoprolol succinate reduced all-cause mortality in Europe (hazard ratio 0.55, p=0.0001) but not in the U.S. subgroup (hazard ratio 1.05, p=.7961). The lack of any trend toward reduced mortality in the U.S. subgroup is of concern..

For carvedilol, relevance to the U.S. population is not a concern, because the U.S. Carvedilol Trials were performed in the U.S. Rather, the concern is what COPERNICUS adds to what was already known from the U.S. Carvedilol Trials. About 1 in 5 patients in COPERNICUS were from the U.S.; the hazard ratio was 0.80 in the U.S. patients and 0.60 in the rest of the world. Statistically, this difference is not meaningful, but that is not the whole story, for two reasons. First, the "rest of the world" is not homogeneous. Second, the proportion of U.S. patients in COPERNICUS was much lower than in MERIT-HF, so it is not surprising that the U.S. subgroup (n=482) was not a statistical outlier in COPERNICUS. Next to the U.S., Russia (n=309) and Poland (n=299) recruited the most patients in COPERNICUS, and carvedilol had larger mortality reductions in these 2 countries than in 9 of 13 others.

**CIBIS-II** was a well-conducted multicenter European study designed to recruit stable subjects with moderate to severe heart failure (NYHA Class III-IV).[67] Most patients were NYHA Class III. The annual placebo mortality rate was 13%, which is higher than the rate projected by the CIBIS-II investigators based on the results of CIBIS-I. Nevertheless, this mortality rate, and the average ejection fraction of 27%, are closer to those of MERIT-HF, which recruited mostly Class II and III patients, than to those of COPERNICUS, which is thought to have recruited NYHA Class III and IV patients.

In CIBIS-II, 752 subjects were NYHA Class III or IV and had an ejection fraction less than 25%, but the results in this subgroup have not been reported completely.[1] For the Class III patients, annual placebo group mortality was about 13%; over the entire study (averaging 1.3 years of followup), the NNT to prevent one death was about 19. For the Class IV patients, the annual placebo mortality was about 18%, and the NNT to prevent 1 death over 1.3 years was about 15. The mortality reduction for Class IV patients was of borderline statistical significance; when measured as a difference of probabilities, the confidence interval was 0.0005 to 0.127 (from that is, from 0 to 12.7 lives saved for every 100 patients.)

[1] The hazard ratio was said to be 0.78 (0.56 to 1.07).[145]

**Table 7b. Patient characteristics and annualized mortality rates adjusted for active drug run-in periods in trials of beta blockers for heart failure.**

| Trial | Drug | Primary Endpoint | NYHA Class | Entry criterion for EF (average) | Mortality in Placebo Group (per year) | Mortality in Treatment Group (per year) | Sample Size |
|---|---|---|---|---|---|---|---|
| Sturm 2000 | Atenolol | Combined worsening heart failure or death | II-III | ≤ 25% (17%) | 5.0% | 8.0% | 100 |
| CIBIS | Bisoprolol | Mortality | III-IV | <40% (0.25) | 10.4% | 8.3% | 641 |
| CIBIS-II | Bisoprolol | Mortality | III-IV | <35% (0.275) | **13.2%** | **9.0%** | 2647 |
| Bristow* | Carvedilol | Exercise tolerance | II-IV | <35% (0.23) | 33.8% | 10.9% | 345 |
| Packer* | Carvedilol | Exercise tolerance | II-IV | <35% (0.23) | 14.0% | 15.3% | 278 |
| Colucci* | Carvedilol | Morbidity+ mortality | II-III | <35% (0.23) | 6.4% | 2.2% | 366 |
| Cohn* | Carvedilol | Quality of life | III-IV | <35% (0.23) | 8.6% | 4.3% | 105 |
| ANZ * | Carvedilol | Exercise tolerance, morbidity+ mortality | I-III | <35% (0.16) | 7.9% | 7.0% | 415 |
| Christmas | Carvedilol | LVEF | I-III | <39% (0.29) | 4.9% | 6.9% | 387 |
| Copernicus | Carvedilol | Mortality | Not reported** | < 25% (0.20) | **20.9%** | **14.0%** | 2289 |
| MUCHA (Japanese) | Carvedilol | CHF global assessment | II-III | < 40% (30%) | Nr | nr | 190 |
| MDC | Metoprolol | Mortality+ morbidity | I-IV | <40% (0.22) | 11.0% | 12.0% | 383 |
| Waagstein, 2003 | Metoprolol | Nr | II-III | <40% (28.5) | 9.1% | 7.6% | 165 |
| MERIT | Metoprolol CR | Mortality | II-IV | <40% (0.28) | 10.8% | 7.3% | 3991 |
| MERIT high-risk subgroup | Metoprolol CR | Mortality | III-IV | <25% (0.19) | 18.2% | 11.3% | 795 |
| RESOLVD* | Metoprolol-CR | Exercise tolerance, neurohumeral parameters | I-IV | <40% (0.28) | 16.0% | 8.4% | 768 |

*Studies which has an active drug run-in phase are marked with an asterisk. We added deaths during the run-in period to the total for the active drug.

**NYHA Class not reported, but all patients had symptoms on minimal exertion or at rest.

In addition to all-cause mortality, sudden death, and cardiovascular mortality, endpoints in beta blocker trials include symptoms, progression of disease, need for hospitalization, and need for (or time to) transplantation. The major placebo-controlled trials and many smaller trials, described, evaluated these outcomes (Table 8).

### NYHA class

The effect on NYHA class rating was inconsistently reported. The CIBIS trial found that significantly more patients taking bisoprolol improved by at least one NYHA class (21% vs 15%; p=0.03) but there was no differences in patients that deteriorated by at least one class (13% vs 11%). Results were mixed for carvedilol. Two trials[69, 70] showed carvedilol to be superior to placebo in improving the overall NYHA class distribution, but in two other trials[68, 72] carvedilol had no effect. Significant improvement in NYHA class was reported in the MUCHA trial of Japanese patients with heart failure.[75] Metoprolol tartrate did not significantly improve NYHA class in either of two trials. In the MERIT-HF trial, metoprolol CR increased the proportion of patients that improved by at least one NYHA class overall (28.6% vs 25.8%; p=0.003). A post-hoc analysis found the same effect in a subgroup of patients with baseline NYHA class III-IV and LVEF < 25% (46.2% vs 36.7%; p=0.0031).[80] By contrast, carvedilol did not reduce progression of heart failure in COPERNICUS.

### Exercise Capacity

The carvedilol trials[68-70, 72] were consistent in showing equivalency to placebo in exercise capacity improvement as measured by both the 6-minute walk and 9-minute treadmill tests. Results of treadmill testing (modified Naughton protocol) were mixed in two placebo controlled trials of metoprolol.

### Quality of Life

In three trials[68-70] carvedilol had no effect on quality of life as measured using the Minnesota Living With Heart Failure Questionnaire. The MDC trial reported that patients taking immediate release metoprolol experienced significant greater improvements in quality of life than those taking placebo. No data were provided and it is unclear as to which measurement instrument was used.

In the MERIT-HF trial, controlled-release metoprolol reduced the need for hospitalizations and the number of hospital days and improved the patient's self-assessment of treatment as measured by the McMaster Overall Treatment Evaluation. Controlled release metoprolol had no effect on Minnesota Living with Heart Failure Questionnaire scores in a smaller group of MERIT-HF patients (n=741) participating in a quality of life substudy.[81]

CIBIS-II conducted a preplanned economic analysis which provided good-quality data on hospitalizations. Bisoprolol decreased hospitalization rates and hospitalizations for worsening heart failure, but there were more hospitalizations for stroke in the bisoprolol group than in the placebo group.

## Table 8. Outcomes in placebo controlled trials of beta blockers for heart failure

| Study, year | Beta blocker | All-cause mortality rates p-value NNT | Sudden death rates p value NNT | Death due to heart failure p value NNT | NYHA Class | Exercise capacity | Quality of life |
|---|---|---|---|---|---|---|---|
| Sturm 2002 | atenolol | 10% vs 16% NS | NR | 16% vs 39% NS | NR | NR | NR |
| Anonymous 1994<br><br>*CIBIS* | bisoprolol | 16.6% vs 20.9% NS | 4.7% vs 5.3% NS | NR | Improvement (>/= 1 class) 21% vs 15% p=0.03 | NR | NR |
| Anonymous 1999<br><br>*CIBIS-II* | bisoprolol | **12% vs 17% p<0.0001 NNT=19** | **4% vs 6% p=0.0011 NNT=38** | NR | NR | NR | NR |
| Bristow 1996<br><br>*US Carvedilol Heart Failure Study Group: MOCHA* | carvedilol | **4.6% vs 15.5% p<0.001 NNT=9** | **2.3% vs 7.1% p=0.035 NNT=21** | **1.1% vs 7.1% p=0.003 NNT=17** | No effect (data nr) | 6-minute walk test/9-minute self-activated treadmill testing: no effect (data nr) | Mean change in MLHFQ: no effect |
| Packer 1996<br><br>*US Carvedilol Heart Failure Study Group: PRECISE* | carvedilol | 4.5% vs 7.6% NS | NR | NR | Deterioration 3% 15% p=0.001 | Mean increase in 6-minute walk test distance (m): 17 vs 6 (NS)<br><br>9-minute treadmill test distance: no effect | MLHFQ: no effect (original data NR) |
| Colucci 1996<br>*US Carvedilol Heart Failure Study Group: Mild* | carvedilol | 0.9% vs 4% NS | NR | Heart failure progression(deaths+hospitalizations+ need for more medications): 25/232(11%) 28/134(20.9%) p=0.008 NNT=10 | Improved: 9% vs 12% NS | 9-minute self-minute treadmill test: car=pla (data NR) | Mean change in MLHFQ: (-4.9) vs (-2.4) NS |
| Cohn 1997<br><br>US Carvedilol Heart Failure Study Group | carvedilol | 2.8% vs 5.7% NS | NR | NR | % decrease in Class III/IV patients: 20% vs. 9.5% NS | Mean increase in 6-minute walk test distance (m): 19.0 vs 28.4 (NS) | Mean improvement in MLHFQ: 11.6 vs 8.8 (NS) |

*Odds ratios (95% CI) adopted from previously published bayesian meta-analysis (Brophy, 2001)
MLHFQ=Minnesota Living With Heart Failure Questionnaire

## Table 8. Outcomes in placebo controlled trials of beta blockers for heart failure continued

| Study, year | Beta blocker | All-cause mortality rates p-value NNT | Sudden death rates p value NNT | Death due to heart failure p value NNT | NYHA Class | Exercise capacity | Quality of life |
|---|---|---|---|---|---|---|---|
| Anonymous 1997<br>*Australia/New Zealand Heart Failure Research Collaborative Group* | carvedilol | 9.6% vs 12.6%<br>NS | 4.8% vs 5.3%<br>NS | 6.7% vs 7.2%<br>NS | Improved:<br>26% vs 28%<br>NS | Treadmill exercise duration/6-minute walk distance:<br>car=pla<br>(data nr) | NR |
| Packer 2001<br>*COPERNICUS* | carvedilol | **11.2% vs 16.8%<br>p=0.00013<br>NNT=19** | **6.1% vs 3.9%<br>p=0.016<br>NNT=46** | NR | NR | NR | NR |
| Cleland 2003<br>*CHRISTMAS* | carvedilol | 4.3% vs 3.2%<br>NS | NR | NR | NR | Exercise time (method nr) (seconds):<br>405 vs 427<br>NS | NR |
| Hori 2004<br>*MUCHA (Japanese patients)* | carvedilol | NR | NR | NR | Improved<br>5 mg=<br>80.9% vs 48.9%, p<0.001<br>20 mg=<br>70.8% vs 48.9%, p<0.05 | NR | NR |
| Waagstein 1993<br>*MDC* | metoprolol tartrate | 11.8% vs 11.1%<br>NS | 9.3% vs 6.3%<br>NS | 2.6% vs 2.6%<br>NS | Improvement: effective<br>(data NR) | Mean increase in exercise capacity (sec): 76 vs 15<br>p=0.046 | met>pla<br>p=0.01<br>(original data NR) |
| Waagstein 2003 | metoprolol tartrate | 4.6% vs 3.8%<br>NS | NR | NR | Improved:<br>42% vs 33%<br>NS | Bicycle test:<br>met=pla (data nr) | NR |
| Anonymous 1999<br>*MERIT-HF* | metoprolol succinate | **7.3% vs 10.8%<br>p=0.00009<br>NNT=29** | **3.9% vs 6.5%<br>p=0.0002<br>NNT=39** | **1.5% vs 2.9%<br>p=0.0023<br>NNT=72** | NR | NR | McMaster Overall Treatment Evaluation:<br>met>pla<br>(data nr) |
| Anonymous 2000<br>*RESOLVD* | metoprolol succinate | 3.7% vs 8.1%<br>NS | NR | 0.5% vs 1.4%<br>NS | met CR=pla (data nr) | 6-minute walk test change (meters)<br>-1 vs -3 | met CR=pla<br>(data nr) |

*Odds ratios (95% CI) adopted from previously published bayesian meta-analysis (Brophy, 2001)

MLHFQ=Minnesota Living With Heart Failure Questionnaire

## Head-to-head trials

There are no direct comparator trials comparing two or more of the drugs proven to reduce mortality (bisoprolol, carvedilol, and sustained release metoprolol succinate.) Six fair-quality, head to head trials compared the effects of immediate-release metoprolol tartrate with carvedilol in patients with heart failure (see Evidence Tables 5b and 5c (characteristics) and Evidence Table 6 (outcomes).[82-87] These trials recruited stable patients with Class II-IV (mainly II and III) heart failure, most of whom took ACE inhibitors and diuretics.

The most recent trial, the Carvedilol Or Metoprolol European Trial (COMET), was the only one powered to evaluate mortality and cardiovascular events (n=3029). The target dose of carvedilol was 25 mg twice a day; the target for metoprolol tartrate was 50 mg twice a day. The patients were mostly (79.8%) men, with a mean age of 62 years and a mean EF of 26% on optimal treatment with ACE inhibitors and diuretics for NYHA class II-IV heart failure.

When COMET was designed, extended-release metoprolol was not yet available, and immediate-release metoprolol was a logical comparator because, in the MDC trial, metoprolol tartrate was clearly effective, even though it did not change mortality. Specifically, metoprolol tartrate improved ejection fraction, LVEDP, and exercise time and prevented clinical deterioration, reducing the need for transplantation by almost 90% during the followup period. [76]

## Mortality

In COMET, after a mean followup of 58 months (nearly 5 years), the intention-to-treat analysis showed an all-cause mortality reduction in favor of carvedilol (34% vs 40%; NNT 18; $p<0.0017$). The annual mortality rate was 10% for metoprolol tartrate and 8.3% for carvedilol; for comparison, the rates were for metoprolol succinate in MERIT-HF (7.2%) and bisoprolol in CIBIS-II (8.8%). There was no difference between carvedilol and metoprolol in the combined endpoint of deaths plus all-cause admissions (74% vs 76%).

COMET demonstrates unequivocally that carvedilol 25 mg twice a day was better than immediate-release metoprolol (metoprolol tartrate) twice a day. There is disagreement, however, about the relevance of the result, because immediate-release metoprolol had not been shown to reduce mortality in previous trials. Several years ago, after metoprolol tartrate failed to reduce mortality in the Metoprolol in Dilated Cardiomyopathy (MDC) trial, it was hypothesized that the patients who received it were subjected to daily variations in the degree of beta blockade. In COMET, the mean dose of metoprolol tartrate was less than that used in the MDC (85 mg/d vs. 108 mg/d), and the mean decrease in heart rate was also less (11.7 vs. 15 beats per minute.) Subsequently, extended-release metoprolol (metoprolol succinate) was proven to reduce mortality in heart failure patients in the MERIT-HF trial. In MERIT-HF, the mean dose of metoprolol succinate was 159 mg/d and the mean reduction in heart rate was 14 beats per minute.

## Other Outcomes

In COMET, rates of withdrawal of medication (32% vs. 32%) and non-cardiovascular deaths (5% vs 4%) were similar. Worsening heart failure was a prespecified secondary endpoint in COMET, but the result was not reported; in the older trials, there was a nonsignificant trend favoring carvedilol over immediate-release metoprolol. Carvedilol and immediate release

metoprolol (124+/-55 mg/d) had similar effects on quality of life, but metoprolol improved exercise capacity more. There were no differences between the carvedilol and metoprolol groups in quality of life.

### 1f. For adult patients with atrial arrhythmia, do beta blockers differ in efficacy?

Several beta blockers have been used to reduce the heart rate in patients with atrial tachyarrhythmias and to prevent relapse into atrial fibrillation or flutter. A recent good quality systematic review examined 12 studies of rate control in patients with chronic atrial fibrillation.[88] Atenolol, nadolol and pindolol were effective in controlling the ventricular rate, while labetalol was no more efficacious than placebo.

We found one head-to-head trial comparing bisoprolol 10 mg and carvedilol 50 mg in patients subjected to cardioversion of persistent atrial fibrillation (> 7 days).[89] This fair-quality, 12-month trial enrolled 90 patients (mean age=65.5; 82% male) (Evidence Tables 7 and 7a). Similar proportions of patients relapsed into atrial fibrillation during follow-up in the bisoprolol and carvedilol groups (53.4% vs 43.6%; p=NS).

Two placebo-controlled trials evaluated beta blockers in patients with persistent atrial fibrillation.[90-92] One placebo-controlled trial found that metoprolol CR/XL 100-200 mg was effective in preventing relapse of atrial fibrillation/flutter after cardioversion. (Evidence Table 7).[90, 91] This fair quality trial was conducted in Germany and enrolled 433 patients after cardioversion of persistent atrial fibrillation that were 70% male, with a mean age of 60. Over 6 months, atrial fibrillation or flutter relapse rates were significantly lower in patients taking metoprolol CR/XL (48.7% vs 59.9%; p=0.005). This trial was not powered to detect differences in rates of mortality as a primary endpoint. Death was reported as an adverse event and rates were not significantly different for the metoprolol CR/XL and placebo groups (3.1% vs 0.)

The other study examined the effects of carvedilol in managing patients with concomitant atrial fibrillation and heart failure.[92] We only analyzed results from the first phase (4 months) of this two-phase study, in which carvedilol 50-100 mg was compared to placebo; both in combination with background digoxin therapy. Forty-seven patients (mean age=68.5; 61.7% male) with atrial fibrillation (mean duration 131.5 weeks) and heart failure (predominantly NYHA class II-III; mean LVEF=24.1%) were enrolled in this fair-quality study. Carvedilol significantly lowered the 24-hour ventricular rate (data nr; p=0.0001) and improved mean LVEF scores (30.6% vs 26%; p=0.048) and severity of symptoms/functional capacity on a 33-point scale (6 vs 8; p=0.039).

### 1g. For adult patients with migraine, do beta blockers differ in efficacy?

### Summary

Five head to head trials show no difference in efficacy in reduction of attack frequency, severity, headache days or acute tablet consumption or in improvement in any subjective or composite index in any of the comparisons made (atenolol or metoprolol durules or metoprolol or timolol vs propranolol). Results from placebo controlled trials on similar outcome measures generally

supports those for atenolol, metoprolol durules and propranolol seen in head to head trials. Placebo controlled trial results also show that bisoprolol had a significant effect on attack frequency reduction and that pindolol had no appreciable effects.

## Detailed Assessment

### Head to Head trials

We found five fair quality[93-98] head to head trials of beta blockers for the treatment of migraine (Table 9). One study comparing bisoprolol and metoprolol appears to have been published twice.[99, 100] This trial was rated poor quality due to inadequate descriptions of methods of randomization and allocation concealment, lack of use of an intention to treat principle and a high rate of attrition (37.6%).

The five included trials compared propranolol 160 mg to atenolol 100 mg,[96] slow release metoprolol (durules) 200 mg daily[94] , immediate release metoprolol 200 mg daily[93] and timolol 20 mg[97, 98], and propranolol 80 mg to metoprolol 100 mg daily.[95] All four trials were conducted outside of the US, were relatively short-term in duration (12-20 weeks), and were small (35-96 patients). Most patients had common migraine per Ad Hoc Committee and World Federation of Neurology Research Group guidelines (83-93%) and migraine without aura per International Headache Society (92.8%). These patients have mean ages of 33.8-42.3, are 68.6-88.9% female, and have a history of migraine frequency of >3 attacks per month. Use of concomitant analgesics and ergotamines was allowed for abortive migraine treatment. Headache frequency, intensity, severity, duration and abortive treatment tablet usage efficacy parameters were analyzed using patient diary data.

The methods used to assess treatment effects differed across studies. Some of the common outcome results are summarized in Table 10 below. Analysis of variance was used to assess comparative efficacy of metoprolol 200 mg and propranolol 160 mg in one trial.[93]

### Attack Frequency

Metoprolol durules 200 mg, metoprolol tartrate 200 mg, and timolol 20 mg all were similar to propranolol 160 mg in decreasing 4-week attack frequency rates. [93-95, 97, 98]

### Migraine Days

There were differences across trials in methods of assessment of this parameter. When the total number of headache days recorded over 42 days across all 28 patients analyzed was considered in the Stensrud trial, no difference between atenolol and propranolol treatment was found. Metoprolol durules and metoprolol tartrate reduced number of migraine days at rates similar to propranolol across three trials.[93-95]

### Severity

Severity rating methods differed across trials. Metoprolol durules, metoprolol tartrate, and timolol all were similar to propranolol at comparable doses in decreasing attack severity.[94, 95, 97, 98]

## Tablet Consumption

There were no differences in reduction of acute medication (analgesics, ergots) for metoprolol durules or metoprolol tartrate and propranolol.[94, 95, 97, 98]

## Subjective Assessment

Patients in two trials[94, 95] were asked to make a subjective assessment of therapeutic improvement using descriptors of marked, moderate, slight, and unchanged or worse. There were no differences found between slow release metoprolol (durules) and propranolol (76% vs 63%) or between low doses of immediate release metoprolol or propranolol (63% vs 64%) in rates of decreased frequency of mean or median attacks per month.

## Miscellaneous

Two trials[96-98] measured treatment efficacy using a composite score (attack frequency x severity x duration) and found no differences between atenolol or timolol and propranolol. The Gerber et al trial included an analysis of duration of migraine in hours and didn't find any difference between metoprolol and propranolol in percent of patients qualifying as responder type A or B for decrease on this variable.

**Table 9. Outcomes in head-to-head trials of migraine patients**

| Outcomes | Attack frequency /4 wks (% decrease) | Headache days | Severity (% reduction) | Tablet consumption | Subjective (% patients regarding effect as "marked" or "moderate") | Misc. |
|---|---|---|---|---|---|---|
| **Stensrud, 1980** Ate 100 mg vs pro 160 mg n=28 | Nr | 247 vs 257 | nr | nr | nr | Headache Index1 (mean): 410 vs 437 |
| **Kangasniemi, 1984** Met-d 200 mg vs pro 160 mg n=35 | 43.4% vs 43.4% | 45.6% vs 43.8% | 21.8% vs 29.8% | 45.3% vs 45.3% | 76% vs 63% | nr |
| **Olsson, 1984** Met 100 mg vs pro 80 mg n=53 | Nr | 25.4% vs 32.8% | 21.8% vs 29.8% | Ergotamine: 47% vs 43.1% Analgesic: 16.5% vs 37.4% | 63% vs 64% | nr |
| **Gerber, 1991** Met 200 mg vs pro 160 mg Met=22; pro=19 | No differences (ANOVA) | No differences (ANOVA) | No differences (ANOVA) | Ergotamine: No differences (ANOVA) | nr | % reduction in duration (hours): No differences (ANOVA) |
| **Tfelt-Hansen, 1984; Standnes, 1982** Tim 20 mg vs pro 160 mg n=80 | 44% vs 38%; p=NS | nr | 10% vs 6%; p=NS | nr | nr | % reduction in Headache Index1: 49% vs 41%; p=NS Headache Index2: 53% vs 43%; p=NS |

Headache Index1: attack frequency x severity x duration
Headache Index2: attack frequency x severity

## Placebo-controlled Trials

We found 18 fair quality, placebo controlled trials (see Evidence Tables 8 and 8a) of atenolol 100 mg,[101] bisoprolol 5 or 10 mg,[102] metoprolol slow release (Durules) 200 mg,[103, 104] pindolol 7.5-15 mg,[105, 106] propranolol immediate release 80-240 mg[107-115] and long acting propranolol 160 mg.[116, 117] One trial[118] did not report propranolol dosage and will be discussed separately.

All but two[109, 118] of these trials were conducted outside of the US. A crossover design was used in 12 trials, while the other five compared parallel groups. All but two trials reported allowing the use of various concomitant medication to abort migraine pain including common analgesics, ergotamines, and narcotics. These trials ranged in duration from 8-52 weeks, generally enrolling patients with a 1-2 year history of common or classic migraine (Ad Hoc Committee), generally occurring at an average frequency of three per week. One trial included only patients with classic migraine.[104] Patient characteristics reflected the target migraine population, with mean ages in the range of 37-39 and predominantly female (> 75%). Sample sizes ranged from 24-259 patients enrolled. Assessment of attack frequency, duration, severity, and use of acute medication variables was made using patient diary card data.

Placebo controlled trial data is consistent with head to head trial data for atenolol 100 mg, slow release metoprolol (durules) 200 mg and propranolol 80 and 160 mg as discussed above and adds information regarding efficacy of bisoprolol and pindolol. An exception was found in one of the ten fair quality trials of propranolol[110] where a dosage of 120 mg was not significantly superior to placebo in increasing the proportion of patients that had at least a 50 % reduction of migraine attacks in the last four weeks of treatment (42.3% vs 30.9%) or in reducing the mean duration of migraine in hours per month (34.4 vs 13.7).

## Bisoprolol

The results of one placebo controlled trial of 12 week's duration and involving 226 patients[102] indicate that both bisoprolol 5 and 10 mg daily had a significant ($p<0.05$) effect in reducing attack frequency (39% for both bisoprolol doses vs 22% for placebo). Neither dose of bisoprolol showed any obvious influence on reducing attack duration or severity.

## Pindolol

The results of two placebo controlled trials of pindolol 7.5-15 mg daily[105, 106] in a total of 58 patients with predominantly common migraine show no obvious advantage of this nonselective beta blocker in reducing averages per four weeks in headache frequency, headache index, or duration of attacks.

Twelve other placebo controlled trials of beta blockers were found.[97, 98, 119-128] These were rated poor quality due to insufficient detail in reporting randomization and allocation concealment methods, failure to perform efficacy analyses using an intention to treat principle, and rates of attrition ranging from 24% to 48.1% and were not discussed here.

We found a one meta-analysis[129] that evaluated the effects of propranolol in 2403 migraine patients across a combination of 53 head to head, active- and placebo-controlled trials published through 1991. This review was rated poor quality due to failure to report critical assessment of

internal validity and will not be discussed here. We independently assessed and included three head to head and 12 placebo controlled trials from this meta-analysis in our report.

## 1h. For adult patients with bleeding esophageal varices, do beta blockers differ in efficacy?

### Head-to-head Trials

We found one head to head trial of beta blockers for the treatment of bleeding esophageal varices.[130] This trial compared the efficacy of propranolol 40-160 mg daily, a nonselective beta blocker, atenolol 100 mg daily, a selective beta blocker, and placebo in cirrhotic patients. The results of this trial are summarized in Evidence Tables 9 and 9a. This trial was rated fair quality. This trial, conducted in Italy, was designed to measure rebleeding and death and had a mean follow-up of 357 days. The patient population enrolled was typical for esophageal variceal bleeding, with a mean age of 53, 80.8% male and 81.9% alcoholic patients. This study also enrolled a small proportion of patients in which the prior hemorrhage was of a gastric erosion (12.8%) or unknown (inconclusive endoscopy) (6.4%) origin. Concomitant use of ranitidine, oral antacids, spironolactone, saluretics, lactulose, and nonabsorbable antibiotics was allowed.

No significant differences were found between propranolol and atenolol at one year for percentage of patients with fatal/nonfatal rebleeding episodes (2.4% vs 3.1%) or total deaths (12% vs 10%) or deaths due to rebleeding (3.1% vs 3.1%), liver failure (6.2% vs 3.1%) or other unrelated causes (3.1% vs 3.1). Results of a multivariate analysis of parameters hypothesized to have had an influence on rebleeding were also reported. Drinking habits after enrollment was found to have significant effect on rebleeding, in that patients continuing to drink had higher incidences of rebleeding in both the propranolol (drinkers 50% vs abstainers 0%) and atenolol (drinkers 43% vs abstainers 27%) groups. Results of the analyses of the other parameters(severity of prior bleed, randomization time, number of bleeds prior to enrollment, treatment center, interval between index bleed and endoscopy) were insignificant.

### Placebo-controlled trials

We found fair quality, placebo controlled trials of nadolol[131] and propranolol[132-139] for the secondary prevention of bleeding esophageal varices secondary to cirrhosis and schistosomiasis[140]. Results are summarized in Evidence Tables 9 and 9a. These trials were all conducted outside of the US, enrolled samples of 12-82 patients and ranged from 3 months to 2 years in duration. Mean ages ranged from 43-58 for the cirrhotic and 35.8 for non-cirrhotic patients. Populations were predominantly male with alcoholism as the most common etiology for cirrhosis. Treatment was initiated earlier, within 72 hours of the index bleeding episode, in only three of the trials.[132, 135, 139]

### Variceal Rebleeding Rates

As shown in Table 10 below and in 9, compared to placebo, no differences in effect on variceal rebleeding rates were shown for immediate release propranolol in two early treatment trials. [132, 139] A significant difference between the effects of slow release propranolol and placebo was

found in a third early treatment trial (20% vs 75%; p<0.05).[135] For trials of later (≥ 14 days)[134, 136, 137, 141] and unspecified[133, 142] treatment initiation, atenolol was equivalent to placebo (31% vs 24%); nadolol was superior (25% vs 71%; p<0.05); results of immediate release propranolol trials were mixed; and long-acting propranolol was superior (2% vs 20%; p<0.02).

**Table 10. Variceal rebleeding rates**

| Trial | Interventions | Sample size | Treatment initiation Interval | Rebleeding rates |
|---|---|---|---|---|
| ***Early intervention*** | | | | |
| Burroughs, 1983 | pro vs pla | n=48 | 48 hrs | 46.1% vs 50% |
| Villeneuve, 1986 | pro vs pla | n=79 | 6-72 hrs | 76.2% vs 81.2% |
| **Jensen, 1989** | **pro SR vs pla** | **n=31** | **24 hrs** | **20% vs 75%;p<0.05** |
| ***Late intervention*** | | | | |
| Colombo, 1989 | ate vs pla | n=94 | ≥ 15 days | 31% vs 51% |
| **Gatta, 1987** | **nad vs pla** | **n=24** | **15-40 days** | **25% vs 71%; p<0.05** |
| **Colombo, 1989** | **pro vs pla** | **n=94** | **≥ 15 days** | **24% vs 51%; p<0.01** |
| **Lebrec, 1981a** | **pro vs pla** | **n=24** | **10-15 days** | **0 vs 41.7%; p=0.037** |
| **Lebrec, 1981b** | **pro vs pla** | **n=74** | **2 weeks** | **15.8% vs 63.9%; p<0.0001** |
| Lo, 1993 | pro vs pla | n=59 | unspecified | 19.2% vs 11.1% |
| Sheen, 1989 | pro vs pla | n=18 | 10-14 days | 27.8% vs 55.5% |
| **El Tourabi, 1994** | **LA pro vs pla** | **n=82** | **unspecified** | **2% vs 20%; p<0.02** |

Deaths due to variceal rebleeding were reported by seven comparisons to placebo across six trials[132-134, 136, 139, 141]. Results are summarized in Table 11 below and in Evidence Tables 9 and 9a. In one trial of atenolol and five trials of propranolol, no differences from placebo in effect on death due to variceal rebleeding were established regardless of treatment initiation interval. In one trial of patients with portal hypertension secondary to schistosomiasis[142], however, significantly more patients (17%) experienced death due to variceal rebleeding on placebo than after late intervention (2 weeks) with propranolol (0%).

**Table 11. Death due to variceal rebleeding**

| Trial | Interventions | Sample size | Treatment initiation Interval | Rates of death due to rebleeding |
|---|---|---|---|---|
| ***Early intervention*** | | | | |
| Burroughs, 1983 | pro vs pla | n=48 | 48 hrs | 15% vs 9% |
| Villeneuve, 1986 | pro vs pla | n=79 | 6-72 hrs | 12% vs 19% |
| ***Late intervention*** | | | | |
| Colombo, 1989 | ate vs pla | n=94 | ≥ 15 days | 3% vs 10% |
| Colombo, 1989 | pro vs pla | n=94 | ≥ 15 days | 3% vs 10% |
| **Lebrec, 1981b** | **pro vs pla** | **n=74** | **2 weeks** | **0% vs 17%; p<0.05** |
| Lo, 1993 | pro vs pla | n=59 | unspecified | 12% vs 7% |
| Sheen, 1989 | pro vs pla | n=18 | 10-14 days | 0% vs 11% |

## All-cause Mortality

No trial of patients with bleeding esophageal varices involved large enough sample sizes to measure all-cause mortality with sufficient power. Although crude trends suggest numerically smaller numbers of patients taking atenolol, nadolol and propranolol experienced deaths due to any cause in all but one trial of propranolol[132], no significant differences between beta blockers and placebo were found. (Table 12)

**Table 12. All cause mortality in patients with bleeding esophageal varices**

| Trial | Interventions | Sample size | Treatment initiation Interval | All cause mortality |
|---|---|---|---|---|
| ***Early intervention*** | | | | |
| Burroughs, 1983 | pro vs pla | n=48 | 48 hrs | 15% vs 23% |
| Villeneuve, 1986 | pro vs pla | n=79 | 6-72 hrs | 45% vs 38% |
| ***Late intervention*** | | | | |
| Colombo, 1989 | ate vs pla | n=94 | ≥ 15 days | 9% vs 23% |
| Gatta, 1987 | nad vs pla | n=24 | 15-40 days | 8% vs 27% |
| Colombo, 1989 | pro vs pla | n=94 | ≥ 15 days | 13% vs 23% |
| Lo, 1993 | pro vs pla | n=59 | unspecified | 31% vs 33% |
| El Tourabi, 1994 | LA pro vs pla | n=82 | unspecified | 7% vs 18% |

## Summary

In summary one small head to head trial showed no difference between atenolol and propranolol in rates of non-fatal/fatal rebleeding and all-cause mortality. Results of one trial of nadolol and eight small placebo controlled trials of immediate release and two formulations of extended release propranolol do not provide any additional indirect evidence of the comparative efficacy across beta blockers in these clinical outcomes. The somewhat mixed results across the placebo-controlled trials of propranolol suggest that treatment initiation interval may have an effect on rebleeding rates.

## Key Question 2: Do beta blocker drugs differ in safety or adverse effects?

## Summary

Side effects are common among patients taking beta blockers. Longer-term trials (12-58 months) directly comparing beta blockers in patients with hypertension (atenolol vs bisoprolol vs propranolol), heart failure (carvedilol vs metoprolol), bleeding esophageal varices (atenolol vs propranolol), and atrial fibrillation (bisoprolol vs carvedilol) showed no differences in any of the safety parameters measured, with one exception. Carvedilol caused more dizziness than metoprolol (14.7% vs 1.3%; p=0.0046) in a fair quality trial of 122 patients with heart failure.[83] Propranolol caused higher rates of overall adverse event incidence than pindolol in patients with stable angina in one short-term trial (8 weeks) that used potentially flawed randomization methods.[30]

In everyday practice, weight gain, fatigue, dizziness, dyspnea are the most common side effects in patients with heart failure. About 1 in 5 patients require discontinuation of the initial beta blocker choice. In one series of 268 patients seen in a U.S. heart failure clinic, 54% were started on carvedilol and 46% on metoprolol succinate or metoprolol tartrate.143 Overall, about 1 in 5 patients (51 total) could not tolerate the initial choice of treatment. Forty of the 51 patients who could not tolerate the initial choice were switched to another beta blocker. Twenty two of these 40 patients tolerated the 2nd choice, with equal proportions tolerating a switch to carvedilol from metoprolol and to metoprolol from carvedilol.

## Detailed Assessment

Adverse events of beta blockers most commonly reported in randomized controlled trials include cardiovascular symptoms of bradycardia and hypotension and central nervous system symptoms of dizziness. Relatively low rates of withdrawal due to these adverse events suggest that they were mild-moderate in severity. Other adverse events associated with beta blockers that were less commonly reported include sexual dysfunction and various dermatologic and gastrointestinal symptoms.

Head-to-head safety analyses were provided by 3 trials in patients with hypertension[7-9] (Evidence Table 1), 3 trials of patients with angina[30, 31, 144] (Evidence Table 2), 3 trials in patients with heart failure[77, 83, 86] (Evidence Table 5b), 6 trials in migraine patients[93-96, 98, 145] (Evidence table 8) 1 trial in patients with bleeding esophageal varices[130] (Evidence Table 9), 1 trial of patients post-myocardial infarction[45] (Evidence Table 4), and 1 trial of patients with atrial fibrillation (Evidence table 7).[89] Trial characteristics have been described in detail previously and can also be found in the cited evidence tables. In general trials ranged in duration from 6 weeks to 58 months. Sample sizes ranged from 28-3029 patients. All but one[93] of the head to head trials in patients with migraine used crossover designs, only reporting results of the combined intervention periods.

Only one trial[7] of atenolol 100 mg and pindolol SR 20 mg in 107 essential hypertensive patients was designed specifically for adverse event assessment and was rated good quality. Safety assessment in the remaining 17 head to head trials was fair-poor quality due to a lack of descriptive information regarding evaluation techniques. Events analyzed were generally not specified or defined. There was much heterogeneity across the trials in specific adverse events reported. All safety data reported can be found in the evidence tables cited above. The safety data that was most consistently reported (overall adverse event rate; incidence of bradycardia, dizziness, and hypotension; and withdrawals due to adverse events) across a more limited number of trials are summarized in Evidence Table 11.

*Overall adverse event incidence* was reported in nine head to head trials.[8, 30, 31, 86, 94, 95, 98, 99, 144] Rates varied across the trials. For example, rates for carvedilol and metoprolol in a three-month trial of 368 angina patients were 30% and 25%, respectively, as compared to 96% and 94% in a 58 month trial of 3029 patients with heart failure. No significant differences between the beta blocker comparisons were found, with one exception. In one 8-week trial of 40 angina patients[30] adverse events were more frequent in the propranolol group (94.4%) than in the pindolol group (17.4%; $p<0.0001$). Specific adverse events seen more frequently in the propranolol group include fatigue (44.4% vs 0; $p<0.0005$) and mild hypotension (27.8% vs 0; $p=0.0114$). The difference in safety favoring pindolol should be interpreted with caution due to variation between groups in illness severity at baseline. The mean two-week angina attack rate (95% confidence interval) was higher in the propranolol group during run-in [28.5(26.4-30.6) vs 18.4(17.4-19.4)]. This suggests problems with the randomization methods.

*Bradycardia incidence* was reported by one 44-month head to head trial of 122 patients with heart failure and no difference in the effects of carvedilol and metoprolol were found.

*Dizziness incidence* was reported by five head to head trials.[83, 96, 98, 99, 144] A significant difference between beta blockers was found in one 44-month trial of 122 patients with heart failure[83] in that

higher rates of dizziness were seen in the carvedilol group (14.7%) than in the metoprolol group (1.3%; p=0.0046). This significant difference was not seen in another shorter trial (3 months in 368 patients with angina (4.8% vs 5.0%).[144] Reasons for this inconsistency may include differences in definition of dizziness and evaluation techniques between the two trials. This assumption cannot be verified, however, as the methods were not provided. Indirect comparison of the inconsistent head-to-head trial results to available fair-good quality placebo-controlled trials safety data does not offer any additional information as dizziness rates in metoprolol trials were not reported. No differences were reported in comparisons of beta blockers in three trials of migraine patients.

*Hypotension incidence* was reported in one 44-month trial of 122 patients with heart failure[83]. No difference between rates of hypotension for carvedilol (2.7%) and metoprolol (2.7%) were found.

*Withdrawals due to adverse events* were reported by six head to head trials.[9, 77, 89, 98, 99, 130] No significant differences were found in any of the comparisons.

## Key Question 3: Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one beta blocker is more effective or associated with fewer adverse effects?

None of the 14 fair quality head to head trials included in our efficacy analyses across all indications provided any subgroup analyses that differentiated one beta blocker from another in any demographic or comorbidity subgroups.

The Beta-Blocker Pooling Project (BBPP)[146] analyzed mortality in post-infarction patients relative to subgroup risk factors from trials of propranolol[42, 56, 147], pindolol[56], and other beta blockers not available in the United States. This analysis found that none of the age, gender, heart failure and prior diabetes mellitus baseline characteristics interacted significantly with the effect on mortality. This analysis also does not offer any meaningful information about the comparative efficacy of beta blockers in these subgroups.

A 2003 meta-analysis[148] analyzed the effects of bisoprolol (CIBIS-II), carvedilol (US Carvedilol, COPERNICUS), and controlled release metoprolol (MERIT-HF) on mortality in heart failure patients stratified by gender, race and diabetics. Results are summarized in Table 14 below.

**Table 13 Results of Shekelle (2003) meta-analysis by gender, race and diabetics**

| Group of Interest | Number of Studies (Patients in group of interest) | RR for Mortality for Group of Interest (95% CI) | RR for Mortality for Other Subjects (95% CI) |
|---|---|---|---|
| Women | 4 (2134) | 0.63 (0.44-0.91) | 0.66 (0.59-0.75) |
| Blacks | 3 (545) | 0.67 (0.39-1.16) | 0.63 (0.52-0.77) |
| Diabetics | 3 (1883) | 0.77 (0.61-0.96) | 0.65 (0.57-0.74) |

The Shekelle meta-analysis found that beta blockers are equally effective in reducing mortality in subpopulations stratified by gender and race.

## Age/Gender/Race

### Carvedilol

Prescribing information for carvedilol (http://us.gsk.com/products/assets/us_coreg.pdf) reports that effects on efficacy and adverse events were equivalent regardless of age (48% were ≥ 65 years; 11% were ≥ 75 years) in patients with left ventricular dysfunction following myocardial infarction in the CAPRICORN trial.[50] We found no other source of publication of results from this subgroup analysis. The U.S. Carvedilol Heart Failure Study Group published an analysis[149] of the pooled results from a stratified set of three fair-quality and one poor-quality concurrently conducted protocols,[68-71] discussed in detail above, that showed no significant interaction between race and carvedilol treatment in patients with mild-moderate heart failure. More recent analyses from the COPERNICUS trial[73] show that carvedilol had similar effects regardless of age and gender in patients with *severe* heart failure.

### Labetalol

Product information for labetalol (http://www.prometheuslabs.com/pi/TrandateTab.pdf) suggests that required maintenance doses may be lower in geriatric patients due to a reduced rate of elimination. However, we did not find any evidence of differential efficacy of labetalol relative to age.

### Metoprolol

A fair quality review[150] that pooled results from five placebo controlled trials of metoprolol (Amsterdam, Belfast, Goteborg, LIT, Stockholm) found that neither age nor gender had a significant influence on mortality. When considered individually, results from the Goteborg Metoprolol Trial[151] show a nonsignificant trend that patients aged 65-74 years had a more marked reduction in mortality at 3 months post-myocardial infarction (45%) than did all patients aged 40-74 (36%). Results from the MERIT-HF trial also reported that age nor gender had any influence on the effects of metoprolol CR in patients with mild-moderate heart failure.

### Propranolol

The fair quality, placebo controlled Beta Blocker Heart Attack Trial (BHAT)[56] comprised of 3,837 patients found that the protective of propranolol on mortality 25 months (average follow-up) following myocardial infarction was equivalent regardless of age or gender.

No evidence of differential efficacy relative to age, gender or race was found for atenolol, bisoprolol or pindolol in any product labels or included randomized controlled trials. There is no data that suggests that any beta blocker is superior in any demographic subgroup.

## SUMMARY

Results of this review are summarized below in Table 14 by key question and in Table 15 by beta blocker.

**Table 14. Strength of the evidence**

| Key Question 1: Comparative Efficacy | Grade of Evidence* | Conclusion |
|---|---|---|
| a. Hypertension | Overall grade: Poor | No head to head trials of long-term (≥ 6 months) heath or QOL outcomes. Reliable indirect comparisons cannot be made by evidence from 3 long-term placebo-controlled trials of propranolol and atenolol |
| b. Angina | Overall grade: Fair | No significant differences in 5 head to head trials of carvedilol vs metoprolol, pindolol vs propranolol and betaxolol and propranolol in patients with stable angina<br><br>Atenolol=bisoprolol in patients with chronic stable angina and COPD<br><br>Atenolol=labetalol when added to chlorthalidone in patients with chronic stable angina<br><br>One short-term, placebo-controlled trial of propranolol did not add any meaningful evidence of comparative efficacy in the above parameters |
| c. Status-post coronary artery bypass graft (CABG) | Overall grade: Poor | Metoprolol did not benefit mortality or ischemic events in a longer-term (> 7 days), placebo-controlled trial (MACB) |
| e. Recent MI | Overall grade: Fair-good | 1 fair-quality head to head trial found no differences in mortality after one year between atenolol and propranolol, but this was a relatively small trial<br><br>Similar mortality reductions reported for acebutolol, metoprolol tartrate, propranolol and timolol in placebo controlled trials of patients following myocardial infarction without other complications. Similar reductions in sudden death and reinfarction were reported for metoprolol tartrate and timolol and in sudden death for propranolol<br><br>Carvedilol reduced mortality and reinfarction in 1 placebo controlled trial of patients with a mean LVEF of < 32.7% (CAPRICORN)<br><br>4 systematic reviews were not designed to assess comparative efficacy |
| f. Heart failure | Health outcomes in HTH trials: Fair<br><br>Symptoms in HTH trials: Good | Carvedilol > metoprolol tartrate in reducing total mortality in COMET in patients with mild-moderate heart failure<br><br>Carvedilol=metoprolol tartrate in improving symptoms (quality of life; NYHA) and exercise capacity in 4 head to head trials |

**Table 14. Strength of the evidence continued**

| | | |
|---|---|---|
| | Placebo-controlled trials in mild-moderate HF: Good<br><br>Placebo-controlled trials in severe HF: Fair+ for carvedilol and Fair- for metoprolol succinate | Metoprolol succinate reduced total mortality, sudden death, and death due to progressive heart failure and improved quality of life (MERIT-HF)<br>Carvedilol reduced total mortality, sudden death and death due to pump failure (MOCHA)<br>Bisoprolol reduced total mortality and sudden death<br>Carvedilol reduced mortality and the combined endpoint of mortality and hospitalizations in a prospective trial<br>A post-hoc, subgroup analysis of MERIT-HF suggests that metoprolol succinate is similarly effective in comparable patients |
| g. Atrial arrhythmia | Overall grade: Fair | Bisoprolol=carvedilol in preventing relapse of atrial fibrillation in a head-to-head trial<br><br>Metoprolol succinate reduced incidence of atrial arrhythmia/fibrillation in a placebo-controlled trial<br>Carvedilol reduced 24-hour ventricular rate in patients with atrial fibrillation and heart failure in one placebo-controlled trial<br>These placebo-controlled trials do not offer comparative data |
| h. Migraine | Overall grade: Fair | Atenolol, slow release metoprolol, immediate release metoprolol, and timolol were all similar to propranolol in their effects on pain outcomes and acute medication use in 5 head to head trials |
| i. Bleeding esophageal varices | Overall grade: Poor | Results of 1 head to head trial of atenolol and propranolol, 1 placebo controlled trial of nadolol and 6 placebo controlled trials of immediate release and two formulations of extended release propranolol, all fair quality, don't clearly differentiate one beta blocker from another. |
| **Key Question 2: Adverse Effects** | **Quality of Evidence*** | **Conclusion** |
| Hypertension, stable angina, heart failure, atrial arrhythmia, migraine, bleeding esophageal varices, previous myocardial infarction | Overall grade: Fair | Head-to-head trials don't clearly differentiate one beta blocker from another in overall AE incidence, dizziness, hypotension and withdrawal due to adverse events with two exceptions. Carvedilol was associated with a higher rate of dizziness than metoprolol in one long-term trial in heart failure patients. Propranolol was associated with a higher overall rate of adverse events than pindolol in one short-term trial in patients with stable angina. This trial had potentially confounding baseline differences that favored the pindolol group. |
| **Key Question 3: Subgroups** | **Quality of Evidence*** | **Conclusion** |
| a. Demographics (age, gender, race) | Overall grade: Fair | Evidence showed that age, gender and race did not impact the effectiveness of carvedilol, immediate and controlled release metoprolol and propranolol |

**Table 14. Strength of the evidence continued**

| | | |
|---|---|---|
| b. High risk populations | Overall grade: Fair | *Heart failure.* Subgroup analyses of placebo controlled trials showed that a history of MI may reduce the protective effect of bisoprolol on mortality (CIBIS). No risk factor was found to confound the protective effect of carvedilol (COPERNICUS) or controlled release metoprolol (MERIT-HF) on mortality.<br>*Post-myocardial infarction.* The MIAMI trial found that metoprolol had the greatest protective effect on mortality in patients with numerous risk factors. The BHAT trial found no variation in propranolol's protective effect on total mortality based on history of heart failure |

*Quality of evidence ratings based on criteria developed by the Third US Preventive Services Task Force

**Table 15. Summary of comparative efficacy**

| Drug | Hypertension | Angina | Status-post CABG | Heart failure | Atrial arrhythmias | Migraine | Bleeding esophageal varices | Myocardial infarction |
|---|---|---|---|---|---|---|---|---|
| acebutolol | | | | | | | | Effective in reducing all-cause mortality |
| atenolol | | =bisoprolol in patients with comorbid COPD in reducing attack frequency; =labetolol in reducing nitrate use when both combined with chlorthalidone | | | | =propranolol in decreasing migraine days | =propranolol for reducing all-cause mortality and deaths due to rebleeding | |
| betaxolol | | =propranolol | | | | | | |
| bisoprolol | | =atenolol in patients with comorbid COPD | | >placebo in all-cause mortality and sudden death | =carvedilol in preventing relapse of atrial fibrillation | | | |
| carteolol | | | | | | | | |
| carvedilol | | =metoprolol in increasing exercise tolerance | | >metoprolol tartrate in all-cause mortality in mild-moderate HF (COMET)<br>=metoprolol tartrate in improving symptoms and exercise parameters<br>>placebo in total mortality, sudden death, death due to pump failure (MOCHA)<br>>placebo in all-cause mortality in patients with *severe* heart failure (COPERNICUS) | =bisoprolol in preventing relapse of atrial fibrillation<br>>placebo in reducing 24-hour ventricular rate in patients with atrial fibrillation and heart failure | | | Effective in reducing all-cause mortality in patients with LV dysfunction post-MI |
| labetolol | | =atenolol in reducing nitrate use when both combined with chlorthalidone | | | | | | |

**Table 15. Summary of comparative efficacy continued**

| Drug | Hypertension | Angina | Status-post CABG | Heart failure | Atrial arrhythmias | Migraine | Bleeding esophageal varices | Myocardial infarction |
|---|---|---|---|---|---|---|---|---|
| metoprolol tartrate | | =carvedilol in increasing exercise tolerance | =placebo for mortality | < carvedilol in reducing total mortality (COMET)<br>=carvedilol in improving symptoms/exercise parameters | | =propranolol in all parameters measured | | Effective in reducing total mortality, sudden death, and reinfarction |
| metoprolol succinate | | | | > placebo in reducing total mortality, sudden death, death due to progressive heart failure and improved quality of life in mild-moderate HF (MERIT-HF)<br>> placebo in reducing mortality in severe HF (post-hoc, subgroup analysis of MERIT-HF) | CR/XL formulation>placebo in lowering atrial fibrillation/flutter relapse rates | slow release formulation (durules), | | |
| nadolol | | | | | | | > placebo in effect on rebleeding rates | |
| penbutolol | | | | | | | | |
| pindolol | | =propranolol in increasing exercise tolerance, decreasing attack frequency | | | | | | =placebo in all-cause mortality |
| propranolol | =placebo in mortality, CV events, QOL | =betaxolol, pindolol | | | | =atenolol, metoprolol tartrate, metoprolol succinate and timolol | see above | Effective in reducing total mortality and sudden death |
| timolol | | | | | | =propranolol | | Effective in reducing total mortality, sudden death, and reinfarction |

## REFERENCES


1. Potempa, K, Babich, K, Fruh, S, et al. Blood pressure and mood responses in hypertensive patients on antihypertensive medications. Journal of the American Academy of Nurse Practitioners 1993;5(5):211-8.

2. Paran, E, Anson, O, Neumann, L. The effects of replacing beta-blockers with an angiotensin converting enzyme inhibitor on the quality of life of hypertensive patients. Am J Hypertens 1996;9(12 Pt 1):1206-13.

3. Walle, PO, Westergren, G, Dimenas, E, et al. Effects of 100 mg of controlled-release metoprolol and 100 mg of atenolol on blood pressure, central nervous system-related symptoms, and general well being. J Clin Pharmacol 1994;34(7):742-7.

4. Omvik, P, Lund-Johansen, P, Haugland, H. Modest antihypertensive effect of epanolol, a beta 1-selective receptor blocker with beta 1 agonist activity: an acute and long-term hemodynamic study at rest and during exercise and double crossover comparison with atenolol on ambulatory blood pressure. Cardiovasc Drugs Ther 1993;7(1):125-32.

5. Sundar, S, Rajan, AG, Somani, PN, et al. The effects of antihypertensive agents on the quality of life in Indian hypertensives. Acta Cardiol 1991;46(2):227-35.

6. Steiner, SS, Friedhoff, AJ, Wilson, BL, et al. Antihypertensive therapy and quality of life: a comparison of atenolol, captopril, enalapril and propranolol. J Hum Hypertens 1990;4(3):217-25.

7. Foerster, EC, Greminger, P, Siegenthaler, W, et al. Atenolol versus pindolol: side-effects in hypertension. Eur J Clin Pharmacol 1985;28(Suppl):89-91.

8. Fogari, R, Zoppi, A, Corradi, L, et al. Beta-blocker effects on plasma lipids during prolonged treatment of hypertensive patients with hypercholesterolemia. J Cardiovasc Pharmacol 1999;33(4):534-9.

9. Lithell, H, Selinus, I, Hosie, J, et al. Efficacy and safety of bisoprolol and atenolol in patients with mild to moderate hypertension: a double-blind, parallel group international multicentre study. Eur Heart J 1987;8(Suppl M):55-64.

10. Anonymous. Medical Research Council trial of treatment of hypertension in older adults: principal results. MRC Working Party. BMJ 1992;304(6824):405-12.

11. Anonymous. MRC trial of treatment of mild hypertension: principal results. Medical Research Council Working Party. Br Med J (Clin Res Ed) 1985;291(6488):97-104.

12. Wikstrand, J, Warnold, I, Olsson, G, et al. Primary prevention with metoprolol in patients with hypertension. JAMA 1988;259(13):1976-82.

13. Messerli, FH, Grossman, E, Goldbourt, U. Are beta-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. JAMA 1998;279(23):1903-7.

14. Anonymous. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA 1991;265(24):3255-64.

15. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002;288(23):2981-97.

16. Chobanian, AV, Bakris, GL, Black, HR, et al. The seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. JAMA 2003;289(19):2560-2572.

17. Oberman, A, Wassertheil-Smoller, S, Langford, HG, et al. Pharmacologic and nutritional treatment of mild hypertension: changes in cardiovascular risk status. Ann Intern Med 1990;112(2):89-95.

18. Wassertheil-Smoller, S, Blaufox, MD, Oberman, A, et al. Effect of antihypertensives on sexual function and quality of life: the TAIM Study. Ann Intern Med 1991;114(8):613-20.

19. Wassertheil-Smoller, S, Oberman, A, Blaufox, MD, et al. The Trial of Antihypertensive Interventions and Management (TAIM) Study. Final results with regard to blood pressure, cardiovascular risk, and quality of life. Am J Hypertens 1992;5(1):37-44.

20. Perez-Stable, EJ, Halliday, R, Gardiner, PS, et al. The effects of propranolol on cognitive function and quality of life: a randomized trial among patients with diastolic hypertension. Am J Med 2000;108(5):359-65.

21. Grant, RH, Keelan, P, Kernohan, RJ, et al. Multicenter trial of propranolol in angina pectoris. Am J Cardiol 1966;18:361.

22. Bongers, V, Sabin, GV. Comparison of the effect of two metoprolol formulations on total ischaemic burden. Clin Drug Invest 1999;17(2):103-110.

23. Choong, CY, Roubin, GS, Harris, PJ, et al. A comparison of the effects of beta-blockers with and without intrinsic sympathomimetic activity on hemodynamics and left ventricular function at rest and during exercise in patients with coronary artery disease. J Cardiovasc Pharmacol 1986;8(3):441-8.

24. Comerford, MB, Besterman, EM. An eighteen months' study of the clinical response to metoprolol, a selective beta1-receptor blocking agent, in patients with angina pectoris. Postgrad Med J 1976;52(610):481-6.

25. Comerford, MB, Besterman, EM. A comparison of the effects of the slow release formulations of metoprolol and oxprenolol in hypertension. Ann Clin Res 1982;14(1):27-31.

26. Dorow, P, Bethge, H, Tonnesmann, U. Effects of single oral doses of bisoprolol and atenolol on airway function in nonasthmatic chronic obstructive lung disease and angina pectoris. Eur J Clin Pharmacol 1986;31(2):143-7.

27. Koch, G, Fransson, L. Hemodynamic effects at rest and during exercise of combined alpha/beta-receptor blockade and of beta-receptor blockade alone in patients with ischemic heart disease. J Cardiovasc Pharmacol 1987;10(4):474-8.

28. Koch, G, Fransson, L. Hemodynamic and adrenergic effects of combined alpha/beta-receptor blockade versus combined beta-receptor and slow channel calcium blockade in patients with ischemic heart disease. Int J Cardiol 1989;25(1):73-9.

29. Nyberg, G, Bjuro, T, Hagman, M, et al. Relation between ST-depression and chest pain in patients with coronary heart disease receiving no treatment and after beta-blockade and combined alpha-beta-blockade. Acta Medica Scandinavica Supplementum 1981;644:30-3.

30. Frishman, W, Kostis, J, Strom, J, et al. Clinical pharmacology of the new beta-adrenergic blocking drugs. Part 6. A comparison of pindolol and propranolol in treatment of patients with angina pectoris. The role of intrinsic sympathomimetic activity. Am Heart J 1979;98(4):526-35.

31. Narahara, KA. Double-blind comparison of once daily betaxolol versus propranolol four times daily in stable angina pectoris. Am J Cardiol 1990;65(9):577-82.

32. Destors, JM, Boissel, JP, Philippon, AM, et al. Controlled clinical trial of bepridil, propranolol and placebo in the treatment of exercise induced angina pectoris. B.I.S. Fundam Clin Pharmacol 1989;3(6):597-611.

33. Heidenreich, PA, McDonald, KM, Hastie, T, et al. Meta-analysis of trials comparing beta-blockers, calcium antagonists, and nitrates for stable angina. JAMA 1999;281(20):1927-36.

34. Stephenson, LW, MacVaugh, HI, Tomasello, DN, et al. Propranolol for prevention of postoperative cardiac arrhythmias: A randomized study. Ann Thorac Surg 1980;29(2):113-116.

35. Connolly, SJ, Cybulsky, I, Lamy, A, et al. Double-blind, placebo-controlled, randomized trial of prophylactic metoprolol for reduction of hospital length of stay after heart surgery: The β-Blocker Length Of Stay (BLOS) study. American Heart Journal. 2003;145(2):226-232.

36. Jakobsen, CJ, Bille, S, Ahlburg, P, et al. Perioperative metoprolol reduces the frequency of atrial fibrillation after thoracotomy for lung resection. Journal of Cardiothoracic & Vascular Anesthesia 1997;11(6):746-51.

37. Matangi, MF, Strickland, J, Garbe, GJ, et al. Atenolol for the prevention of arrhythmias following coronary artery bypass grafting. Can J Cardiol 1989;5(4):229-34.

38. Lamb, RK, Prabhakar, G, Thorpe, JA, et al. The use of atenolol in the prevention of supraventricular arrhythmias following coronary artery surgery. Eur Heart J 1988;9(1):32-6.

39. Anonymous. Effect of metoprolol on death and cardiac events during a 2-year period after coronary artery bypass grafting. The MACB Study Group. Eur Heart J 1995;16(12):1825-32.

40. Anonymous. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981;304(14):801-7.

41. Boissel, JP, Leizorovicz, A, Picolet, H, et al. Efficacy of acebutolol after acute myocardial infarction (the APSI trial). The APSI Investigators. Am J Cardiol 1990;66(9):24C-31C.

42. Hansteen, V, Moinichen, E, Lorentsen, E, et al. One year's treatment with propranolol after myocardial infarction: preliminary report of Norwegian multicentre trial. British Medical Journal Clinical Research Ed 1982;284(6310):155-60.

43. Salathia, KS, Barber, JM, McIlmoyle, EL, et al. Very early intervention with metoprolol in suspected acute myocardial infarction. Eur Heart J 1985;6(3):190-8.

44. Rehnqvist, N, Olsson, G. Influence of ventricular arrhythmias by chronic post infarction treatment with metoprolol [abstract]. Circulation 1983;68(Suppl 3):69.

45. Wilcox, RG, Roland, JM, Banks, DC, et al. Randomized trial comparing propranolol with atenolol in immediate treatment of suspected myocardial infarction. BMJ 1980;280(6218):885-8.

46. Yusuf, S, Peto, R, Lewis, J, et al. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 1985;27(5):335-71.

47. Hjalmarson, A. Effects of beta blockade on sudden cardiac death during acute myocardial infarction and the postinfarction period. Am J Cardiol 1997;80(9B):35J-39J.

48. Freemantle, N, Cleland, J, Young, P, et al. beta Blockade after myocardial infarction: systematic review and meta regression analysis. BMJ 1999;318(7200):1730-7.

49. Basu, S, Senior, R, Raval, U, et al. Beneficial effects of intravenous and oral carvedilol treatment in acute myocardial infarction: A placebo-controlled, randomized trial. Circulation 1997;96(1):183-191.

50. Anonymous. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet 2001;357(9266):1385-1390.

51. Houghton, T, Freemantle, N, Cleland, JG. Are beta-blockers effective in patients who develop heart failure soon after myocardial infarction? A meta-regression analysis of randomised trials. Eur J Heart Fail 2000;2(3):333-40.

52. Chadda, K, Goldstein, S, Byington, R, et al. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. Circulation 1986;73(3):503-10.

53. Herlitz, J, Waagstein, F, Lindqvist, J, et al. Effect of metoprolol on the prognosis for patients with suspected acute myocardial infarction and indirect signs of congestive heart failure (a subgroup analysis of the Goteborg Metoprolol Trial). Am J Cardiol 1997;80(9B):40J-44J.

54. Manger Cats, V, van Capelle, FLJ, Lie, KJ, et al. The Amsterdam metoprolol trial. Effect of treatment with metoprolol on first year mortality in a single center study with low placebo mortality rate after myocardial infarction. [abstract]. Drugs 1985;29(Suppl. 1):8.

55. Anonymous. The effect of pindolol on the two years mortality after complicated myocardial infarction. Eur Heart J 1983;4(6):367-75HH.

56. Anonymous. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. JAMA 1982;247(12):1707-14.

57. Doughty, RN, Sharpe, N. Beta-adrenergic blocking agents in the treatment of congestive heart failure: mechanisms and clinical results. Annu Rev Med 1997;48:103-14.

58. Avezum, A, Tsuyuki, RT, Pogue, J, et al. Beta-blocker therapy for congestive heart failure: a systemic overview and critical appraisal of the published trials.[comment]. Can J Cardiol 1998;14(8):1045-53.

59. Zarembski, DG, Nolan, PE, Jr., Slack, MK, et al. Meta-analysis of the use of low-dose beta-adrenergic blocking therapy in idiopathic or ischemic dilated cardiomyopathy. Am J Cardiol 1996;77(14):1247-50.

60. Heidenreich, PA, Lee, TT, Massie, BM. Effect of beta-blockade on mortality in patients with heart failure: a meta-analysis of randomized clinical trials. J Am Coll Cardiol 1997;30(1):27-34.

61. Lechat, P, Packer, M, Chalon, S, et al. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. Circulation 1998;98(12):1184-91.

62. Brophy, JM, Joseph, L, Rouleau, JL. Beta-blockers in congestive heart failure. Ann Intern Med 2001;134(7):550-60.

63. Lee, S, Spencer, A. Beta-blockers to reduce mortality in patients with systolic dysfunction: a meta-analysis. J Fam Pract 2001;50(6):499-504.

64. Bouzamondo, A, Hulot, JS, Sanchez, P, et al. Beta-blocker treatment in heart failure. Fundam Clin Pharmacol 2001;15(2):95-109.

65. Sturm, B, Pacher, R, Strametz-Juranek, J, et al. Effect of beta 1 blockade with atenolol on progression of heart failure in patients pretreated with high-dose enalapril. Eur J Heart Fail 2000;2(4):407-12.

66. Anonymous. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS Investigators and Committees. Circulation 1994;90(4):1765-73.

67. Anonymous. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353(9146):9-13.

68. Bristow, MR, Gilbert, EM, Abraham, WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. Circulation 1996;94(11):2807-2816.

69. Packer, M, Bristow, MR, Cohn, JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med 1996;334(21):1349-55.

70. Colucci, WS, Packer, M, Bristow, MR, et al. Carvedilol inhibits clinical pregression in patients with mild symptoms of heart failure. Circulation 1996;94(11):2800-2806.

71. Cohn, JN, Fowler, MB, Bristow, MR, et al. Safety and efficacy of carvedilol in severe heart failure. The U.S. J Card Fail 1997;3(3):173-9.

72. Anonymous. Randomized, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. Australia/New Zealand Heart Failure Research Collaborative Group. Lancet 1997;349(9049):375-80.

73. Packer, M, Coats, AJ, Fowler, MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344(22):1651-8.

74. Cleland, JGF, Pennell, DJ, Ray, SG, et al. Myocardial viability as a determinant of the ejection fraction response to carvedilol in patients with heart failure (CHRISTMAS trial): randomised controlled trial. Lancet 2003;362:14-21.

75. Hori, M, Sasayama, S, Kitabatake, A, et al. Low-dose carvedilol improves left ventricular function and reduces cardiovascular hospitalization in Japanese patients with chronic heart failure: The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) trial. Am Heart J 2004;147(2):324-330.

76. Waagstein, F, Bristow, MR, Swedberg, K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. Lancet 1993;342(8885):1441-6.

77. Waagstein, F, Stromblad, O, Andersson, B, et al. Increased exercise ejection fraction and reversed remodeling after long-term treatment with metoprolol in congestive heart failure: A randomized, stratified, double-blind, placebo-controlled trial in mild to moderate heart failure due to ischemic or idiopathic dilated cardiomyopathy. Eur J Heart Fail 2003;5(5):679-691.

78. Anonymous. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). [see comments.]. Lancet 2001;353(9169):2001-7.

79. Anonymous. Effects of metoprolol CR in patients with ischemic and dilated cardiomyopathy : the randomized evaluation of strategies for left ventricular dysfunction pilot study. Circulation 2000;101(4):378-84.

80. Goldstein, S, Fagerberg, B, Hjalmarson, A, et al. Metoprolol controlled release/extended release in patients with severe heart failure: analysis of the experience in the MERIT-HF study. J Am Coll Cardiol 2001;38(4):932-8.

81. Hjalmarson, A, Goldstein, S, Fagerberg, B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. JAMA 2000;283(10):1295-302.

82. Kukin, ML, Kalman, J, Charney, RH, et al. Prospective, randomized comparison of effect of long-term treatment with metoprolol or carvedilol on symptoms, exercise, ejection fraction, and oxidative stress in heart failure. [see comments.]. Circulation 1999;99(20):2645-51.

83. Metra, M, Giubbini, R, Nodari, S, et al. Differential effects of beta-blockers in patients with heart failure: A prospective, randomized, double-blind comparison of the long-term effects of metoprolol versus carvedilol. Circulation 2000;102(5):546-51.

84. Metra, M, Nodari, S, D'Aloia, A, et al. Beta-blocker therapy influences the hemodynamic response to inotropic agents in patients with heart failure: a randomized comparison of dobutamine and enoximone before and after chronic treatment with metoprolol or carvedilol. J Am Coll Cardiol 2002;40(7):1248-58.

85. Sanderson, JE, Chan, SK, Yip, G, et al. Beta-blockade in heart failure: a comparison of carvedilol with metoprolol. J Am Coll Cardiol 1999;34(5):1522-8.

86. Poole-Wilson, P, Swedberg, K, Cleland, J, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol EUropean Trial (COMET): randomised controlled trial. Lancet 2003;362:7-13.

87. Poole-Wilson, PA, Cleland, JG, Di Lenarda, A, et al. Rationale and design of the carvedilol or metoprolol European trial in patients with chronic heart failure: COMET. Eur J Heart Fail 2002;4(3):321-9.

88. Pitt, B, Poole-Wilson, PA, Segal, R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial--the Losartan Heart Failure Survival Study ELITE II. Lancet 2000;355(9215):1582-7.

89. Katritsis, DG, Panagiotakos, DB, Karvouni, E, et al. Comparison of effectiveness of carvedilol versus bisoprolol for maintenance of sinus rhythm after cardioversion of persistent atrial fibrillation. Am J Cardiol 2003;92(9):1116-1119.

90. Kuhlkamp, V, Schirdewan, A, Stangl, K, et al. Use of metoprolol CR/XL to maintain sinus rhythm after conversion from persistent atrial fibrillation. J Am Coll Cardiol 2000;36(1):139-146.

91. Kuhlkamp, V. Metoprolol verses Placebo in the recidive prophylaxis after cardioversion of atrial fibrillation. Z Kardiol 1998;87(Suppl. 1).

92. Khand, AU, Rankin, AC, Martin, W, et al. Carvedilol Alone or in Combination with Digoxin for the Management of Atrial Fibrillation in Patients with Heart Failure? J Am Coll Cardiol 2003;42(11):1944-1951.

93. Gerber, WD, Diener, HC, Scholz, E, et al. Responders and non-responders to metoprolol, propranolol and nifedipine treatment in migraine prophylaxis: a dose-range study based on time-series analysis. Cephalalgia 1991;11(1):37-45.

94. Kangasniemi, P, Hedman, C. Metoprolol and propranolol in the prophylactic treatment of classical and common migraine. A double-blind study. Cephalalgia 1984;4(2):91-6.

95. Olsson, JE, Behring, HC, Forssman, B, et al. Metoprolol and propranolol in migraine prophylaxis: a double-blind multicentre study. Acta Neurol Scand 1984;70(3):160-8.

96. Stensrud, P, Sjaastad, O. Comparative trial of Tenormin (atenolol) and Inderal (propranolol) in migraine. Upsala Journal of Medical Sciences - Supplement 1980;31:37-40.

97. Standnes, B. The prophylactic effect of timolol versus propranolol and placebo in common migraine: beta-blockers in migraine. Cephalalgia 1982;2(3):165-70.

98. Tfelt-Hansen, P, Standnes, B, Kangasneimi, P, et al. Timolol vs propranolol vs placebo in common migraine prophylaxis: a double-blind multicenter trial. Acta Neurol Scand 1984;69(1):1-8.

99. Worz, R, Reinhardt-Benmalek, B, Grotemeyer, KH, et al. Bisoprolol and metoprolol in the prophylactic treatment of migraine with and without aura - A randomized double-blind cross-over multicenter study. Cephalalgia 1991;11(SUPPL. 11):152-153.

100. Worz, R, Reinhardt-Benmalek, B, Foeh, M, et al. Migraine prophylaxis with bisoprolol. Headache Q 1992;3(1):64-72.

101. Forssman, B, Lindblad, GJ, Zborkinova, V. Atenolol for migraine prophylaxis. Headache 1983;23:188-190.

102. van de Ven, LL, Franke, CL, Koehler, PJ. Prophylactic treatment of migraine with bisoprolol: a placebo-controlled study. Cephalalgia 1997;17(5):596-9.

103. Andersson, P-G, Dahl, S, Hansen, JH, et al. Prophylactic treatment of classical and non-classical migraine with metropolol - a comparison with placebo. Cephalalgia 1983;3:207-212.

104. Kangasniemi, P, Andersen, AR, Andersson, PG, et al. Classic migraine: effective prophylaxis with metoprolol. Cephalalgia 1987;7(4):231-8.

105. Ekbom, K, Lundberg, PO. Clinical trial of LB-46 (d, 1-4-(2-hydroxy-3-isopropylaminopropoxy)indol. An adrenergic beta-receptor blocking agent in migraine prophylaxis. Headache 1972;12(1):15-7.

106. Sjaastad, O, Stensrud, P. Clinical trial of a beta-receptor blocking agent (LB 46) in migraine prophylaxis. Acta Neurol Scand 1972;48:124-128.

107. Borgesen, SE, Nielsen, JL, Moller, CE. Prophylactic treatment of migraine with propranolol. A clinical trial. Acta Neurol Scand 1974;50(5):651-6.

108. Dahlof, C. No clearcut long-term prophylactic effect of one month treatment of propranolol with migraineurs. Cephalalgia 1987;7(Suppl 6):459-460.

109. Diamond, S, Kudrow, L, Stevens, J, et al. Long-term study of propranolol in the treatment of migraine. Headache 1982;22(6):268-271.

110. Diener, HC, Foh, M, Iaccarino, C, et al. Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. Cephalalgia 1996;16(6):441-7.

111. Forssman, B, Henriksson, KG, Johannsson, V, et al. Propranolol for migraine prophylaxis. Headache 1976;16(5):238-45.

112. Mikkelsen, B, Pedersen, KK, Christiansen, LV. Prophylactic treatment of migraine with tolfenamic acid, propranolol and placebo. Acta Neurol Scand 1986;73(4):423-7.

113. Rao, BS, Das, DG, Taraknath, VR, et al. A double blind controlled study of propranolol and cyproheptadine in migraine prophylaxis. Neurology India 2000;48(3):223-6.

114. Wideroe, TE, Vigander, T. Propranolol in the treatment of migraine. BMJ 1974;2(921):699-701.

115. Pita, E, Higueras, A, Bolanos, J, et al. Propranolol and migraine. A clinical trial. Archivos de Farmacologia y Toxicologia 1977;3(3):273-8.

116. Kuritzky, A, Hering, et al. Prophylactic treatment of migraine with long acting propranolol - a comparison with placebo. Cephalalgia 1987;7(Suppl 6):457-8.

117. Pradalier, A, Serratrice, G, Collard, M, et al. Long-acting propranolol in migraine prophylaxis: results of a double-blind, placebo-controlled study. Cephalalgia 1989;9(4):247-53.

118. Malvea, BP, Gwon, N, Graham, JR. Propranolol prophylaxis of migraine. Headache 1973;12(4):163-7.

119. Ahuja, GK, Verma, AK. Propranolol in prophylaxis of migraine. Indian J Med Res 1985;82:263-5.

120. Borgesen, SE. Treatment of migraine with propranolol. Postgrad Med J 1976;52 SUPPL 4(0):163-5.

121. Diamond, S, Medina, J. Double-blind study of propranolol for migraine prophylaxis. Headache 1976;16:24-7.

122. Fuller, GN, Guiloff, RJ. Propranolol in acute migraine: a controlled study. Cephalalgia 1990;10(5):229-33.

123. Johnson, RH, Hornabrook, RW, Lambie, DG. Comparison of mefenamic acid and propranolol with placebo in migraine prophylaxis. Acta Neurol Scand 1986;73(5):490-2.

124. Kaniecki, RG. A comparison of divalproex with propranolol and placebo for the prophylaxis of migraine without aura. Arch Neurol 1997;54(9):1141-5.

125. Nadelmann, JW, Stevens, J, Saper, JR. Propranolol in the prophylaxis of migraine. Headache 1986;26(4):175-182.

126. Nair, KG. A pilot study of the value of propranolol in migraine. J Postgrad Med 1975;21(3):111-3.

127. Palferman, TG, Gibberd, FB, Simmonds, JP. Prophylactic propranolol in the treatment of headache. Br J Clin Pract 1983;37(1):28-9.

128. Weber, RB, Reinmuth, OM. The treatment of migraine with propranolol. Neurology 1972;22(4):366-9.

129. Holroyd, KA, Penzien, DB, Cordingley, GE. Propranolol in the management of recurrent migraine: a meta-analytic review. Headache 1991;31(5):333-40.

130. Colombo, M, de Franchis, R, Tommasini, M, et al. Beta-blockade prevents recurrent gastrointestinal bleeding in well-compensated patients with alcoholic cirrhosis: a multicenter randomized controlled trial. Hepatology 1989;9(3):433-8.

131. Gatta, A, Merkel, C, Sacerdoti, D, et al. Nadolol for prevention of variceal rebleeding in cirrhosis: a controlled clinical trial. Digestion 1987;37(1):22-8.

132. Villeneuve, JP, Pomier-Layrargues, G, Infante-Rivard, C, et al. Propranolol for the prevention of recurrent variceal hemorrhage: a controlled trial. Hepatology 1986;6(6):1239-43.

133. Lo, GH, Lai, KH, Lee, SD, et al. Does propranolol maintain post-sclerotherapy variceal obliteration? A prospective randomized study. J Gastroenterol Hepatol 1993;8(4):358-62.

134. Sheen, IS, Chen, TY, Liaw, YF. Randomized controlled study of propranolol for prevention of recurrent esophageal varices bleeding in patients with cirrhosis. Liver 1989;9(1):1-5.

135. Jensen, LS, Krarup, N. Propranolol in prevention of rebleeding from oesophageal varices during the course of endoscopic sclerotherapy. Scand J Gastroenterol 1989;24(3):339-45.

136. Lebrec, D, Nouel, O, Bernuau, J, et al. Propranolol in prevention of recurrent gastrointestinal bleeding in cirrhotic patients. Lancet 1981;1(8226):920-1.

137. Lebrec, D, Poynard, T, Hillon, P, et al. Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: a controlled study. N Engl J Med 1981;305(23):1371-4.

138. Lebrec, D, Poynard, T, Bernuau, J, et al. A randomized controlled study of propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: a final report. Hepatology 1984;4(3):355-8.

139. Burroughs, AK, Jenkins, WJ, Sherlock, S, et al. Controlled trial of propranolol for the prevention of recurrent variceal hemorrhage in patients with cirrhosis. N Engl J Med 1983;309(25):1539-42.

140. el Tourabi, H, el Amin, AA, Shaheen, M, et al. Propranolol reduces mortality in patients with portal hypertension secondary to schistosomiasis. Ann Trop Med Parasitol 1994;88(5):493-500.

141. Colombo, M, Sangiovanni, A, Tommasini, MA, et al. [Beta-blockers in the prophylaxis of recurrent hemorrhage in cirrhotic patients. Random multicentric study]. Argomenti Gastroenterol Clin 1990;3(2):93-100.

142. El Tourabi, H, El Amin, AA, Shaheen, M, et al. Portal hypertension secondary to schistosomiasis: reduced mortality and rebleeding with propranolol. Medecine et Chirurgie Digestives 1993;22(5):309-310.

143. Butler, J, Khadim, G, Belue, R, et al. Tolerability to B-blocker therapy among heart failure patients in clinical practice. J Cardiac Failure 2003;9(3):203-9.

144. van der Does, R, Hauf-Zachariou, U, Pfarr, E, et al. Comparison of safety and efficacy of carvedilol and metoprolol in stable angina pectoris. Am J Cardiol 1999;83(5):643-9.

145. Worz, R, Reinhardt-Benmalek, B, Foh, M, et al. [Prevention of migraine using bisoprolol. Results of a double-blind study versus metoprolol]. Fortschr Med 1992;110(14):268-72.

146. Anonymous. The Beta-Blocker Pooling Project (BBPP): subgroup findings from randomised trials in post-infarction patients. Eur Heart J 1988;9:8-16.

147. Baber, NS, Evans, DW, Howitt, G, et al. Multicentre post-infarction trial of propranolol in 49 hospitals in the United Kingdom, Italy, and Yugoslavia. Br Heart J 1980;44(1):96-100.

148. Shekelle, P, Morton, S, Atkinson, S. Pharmacologic Management of Heart Failure and Left Ventricular Systolic Dysfunction: Effect in Female, Black, and Diabetic Patients, and Cost-Effectiveness, Evidence Report Number 82. Rockville, MD: Agency for Healthcare Research and Quality; 2003.

149. Yancy, CW, Fowler, MB, Colucci, WS, et al. Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. N Engl J Med 2001;344(18):1358-65.

150. Olsson, G, Wikstrand, J, Warnold, I, et al. Metoprolol-induced reduction in postinfarction mortality: pooled results from five double-blind randomized trials. Eur Heart J 1992;13(1):28-32.

151. Hjalmarson, A, Elmfeldt, D, Herlitz, J, et al. Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial. Lancet 1981;2(8251):823-7.