Drug Class Review on Beta Adrenergic Blockers

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TABLE OF CONTENTS

Introduction 4
Scope and Key Questions 6
Methods 6
Data Abstraction 8
Quality Assessment 8
Data Synthesis 9
Results 9
Key Question 1. For adult patients with various indications, do beta blockers differ in efficacy? 9
1a. Hypertension
1b. Angina
1c. CABG
1d. Silent Ischemia
1e. Recent Myocardial Infarction
1f. Heart Failure
1g. Atrial arrhythmias
1h. Migraine Headache
1i. Bleeding esophageal varices

Key Question 2. For adult patients with various indications, do beta blockers differ in adverse effects? 28
Key Question 3. Are there subgroups for which one beta blocker is more effective or associated with fewer adverse events? 30
1a. Blacks
1b. Elderly
1c. Gender differences
Summary 31

In-text Tables
1 – Characteristics of beta blockers
1a- FDA indications
2 - Included outcomes
3 - Results of head to head trials in patients with angina
4 - Mortality reductions in heart failure patients
5- Comparison of major trials of heart failure
6 - Outcomes in head to head trials in migraine headache
7 - Variceal rebleeding rates
8 - Death due to variceal rebleeding
9 - All cause mortality in patients with bleeding esophageal varices
10 - Results of Shekelle (2003) meta-analysis by gender, race and diabetics
11 - Summary of evidence by Key Question
12 - Summary of evidence by beta blocker

Evidence Tables (1-17)
1 and 1a. Placebo controlled trials in hypertension

2 and 2a. Head to head and placebo controlled trials in angina
3 and 3a. Placebo controlled trials in patients post-CABG
4 and 4a. Placebo controlled trials in silent ischemia
5 and 5a. Controlled trials in myocardial infarction (characteristics)
6. Summary of results of systematic reviews of placebo controlled trials of myocardial infarction
7. All-cause mortality in myocardial infarction
8 and 8a. Placebo controlled trials in heart failure (characteristics)
9. Outcomes of placebo controlled trials in heart failure
10 and 10 a. Head to head trials in heart failure (characteristics)
11. Outcomes of head to head trials in heart failure
12 and 12a. Placebo controlled trials in atrial arrhythmia
13 and 13 a. Head to head trials in migraine
14 and 14a. Placebo controlled trials in migraine
15 and 15 a. Head to head and placebo controlled trials of bleeding esophageal varices
16. Head to head trials in hypertensive patients (adverse events)
17. Safety of all head to head trials

Figures

1. Mortality in patients post-MI
2. All cause mortality in placebo controlled trials in heart failure

Appendices

Appendix A: Search Strategy
Appendix B: Methods for drug class reviews

INTRODUCTION

Beta-adrenergic blockers inhibit the chronotropic, inotropic and vasodilator responses to adrenaline by blocking β_1 and β_2 receptor sites throughout the body. Effects on receptors found in the myocardial, kidney, smooth and skeletal muscles and vasomotor centers and pial vessels of the brain generally involve reductions in the oxygen requirements of the heart renin release and sympathetic outflow to the periphery.

Several characteristics of beta blockers may be related to their clinical effectiveness. Beta blockers can be classified by cardioselectivity and intrinsic sympathomimetic activity (ISA) (Table 1). Cardioselective beta blockers (atenolol, bisoprolol and metoprolol) preferentially inhibit only β_1 receptors that are principally found in the myocardium. Non-cardioselective beta blockers inhibit both β_1 and β_2 receptor sites. Pindolol is further distinguished as the only beta blocker marketed in the United States with intrinsic sympathomimetic activity (ISA), which involves simultaneous weak stimulation of the receptors and catecholamine blockage. Carvedilol and labetalol block β_1 and β_2 receptor sites as well as α receptors.

Ten beta blockers that are currently marketed in the United States were considered in this review: atenolol, bisoprolol, carteolol, carvedilol, labetalol, metoprolol, nadolol, penbutolol, pindolol and propranolol. 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. Food and Drug Administration (FDA) indications are relative to each beta blocker and include angina, both stable and severe requiring coronary artery bypass grafting, arrhythmias, bleeding esophageal varices, coronary artery disease, heart failure, hypertension migraine and secondary prevention post-myocardial infarction.

Table 1. Characteristics of beta blockers

Drug	Characteristics	Usual dosage for hypertension, mg/d	Daily Frequency	Half-Life (hours)
Acebutolol	ISA	200-800 mg	2	
Atenolol		25-100 mg	1	6-7
Bisoprolol		2.5-10 mg	1	9-12
Carteolol				6
Carvedilol		12.5-50 mg	2	7-10
Labetalol		200-800 mg	2	6-8
Metoprolol tartrate		50-100 mg		2-7
Metoprolol succinate (extended release)		50-100 mg	1	
Nadolol		40-120 mg	1	20-24
Penbutolol	ISA	10-40 mg	1	5
Pindolol	ISA	10-40 mg	2	3-4
Propranolol		40-160 mg	2	3-5
Propranolol long-acting		60-180 mg	1	
Timolol		20-40 mg	2	

Table 1a. FDA Indications

Drug	Hypertension	Chronic stable angina	HF	Atrial arrhythmia	Migraine	Bleeding esophageal varices	Post MI (with HF or asymptomatic LV dysfunction)
Atenolol	Yes	Yes					Yes
Bisoprolol	Yes						
Carteolol	Yes						
Carvedilol	Yes		Yes				Yes
Labetalol	Yes						
Metoprolol	Yes	Yes	Yes				Yes
Nadolol	Yes	Yes					
Penbutolol	Yes						
Pindolol	Yes						
Propranolol	Yes	Yes		Yes	Yes		

Scope and Key Questions

The scope of the review and key questions were developed and refined with input from experts including pharmacists, primary care clinicians, neurologists, cardiologists, and representatives of the public. In consultation with the subcommittee, we selected the following key questions to guide the review:

1. For adult patients with appropriate indications, do beta blocker drugs differ in efficacy?
2. Do beta blocker drugs differ in safety or adverse effects?
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?

METHODS

We searched (in this order): the Cochrane Central Register of Controlled Trials (CCTR-1st quarter, 2003), MEDLINE (1966-April 2003), EMBASE (1980-1st Quarter 2003), and reference lists of review articles. In electronic searches we used broad searches, combining terms for included beta blockers with terms for relevant clinical outcomes and patient populations (see Appendix A for complete search strategy). Searches on the electronic databases were carried out through April 2003, using updates on electronic databases after the initial searches. In addition, a protocol for submitting dossiers, including citations, to the Evidence-Based Practice Center was disseminated to pharmaceutical manufacturers (http://www.ohppr.state.or.us/index.htm). All electronic and dossier citations were imported into an electronic database (EndNote 6.0).

Study Selection

All English-language titles and abstracts and suggested additional citations were reviewed for inclusion, using criteria developed by the research team with input from the subcommittee. The citations were divided between two reviewers and assessed for inclusion. One reviewer then assessed for inclusion full articles, with consultation from a second reviewer where necessary.

We included studies of patients with the conditions listed in Table 2. The table also lists important outcomes of treatment for each condition. We used this list to determine whether a clinical trial was eligible for inclusion in the review. 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. For studies of the treatment of angina, we included only studies with duration of 2 months or longer. For post-CABG patients, we excluded studies of the short-term use of beta blockers to suppress atrial arrhythmias, but included studies of long-term treatment.

Table 2. Summary of included outcomes

Hypertension	1. All-cause and cardiovascular mortality 2. Cardiovascular events (stroke, myocardial infarction, or development of heart failure) 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) 4. Quality-of-life
Stable angina (short-term treatment)	1. Exercise tolerance 2. Attack frequency 3. Nitrate use
Post-coronary artery bypass graft (long-term treatment)	1. All-cause mortality 2. Ischemic events (MI, unstable angina, need for repeat CABG and PTCA)
Silent ischemia	1. All cause mortality 2. Ischemic events (ventricular tachycardia/fibrillation, MI, unstable angina, need for revascularization)
Recent myocardial infarction (with and without LV dysfunction)	1. All-cause and cardiovascular mortality 2. Cardiovascular events (usually, development of heart failure)
Symptomatic chronic heart failure	1. All-cause or cardiovascular mortality 2. Symptomatic improvement (heart failure class, functional status, visual analogue scores) 3. Hospitalizations for heart failure
Asymptomatic LV dysfunction	1. All-cause and cardiovascular mortality 2. Cardiovascular events (usually, development of heart failure)
Atrial fibrillation/flutter	1. Rate control 2. Relapse into atrial fibrillation
Migraine	1. Attack frequency 2. Attack intensity/severity 3. Attack duration 4. Use of abortive treatment
Bleeding esophageal varices	1. All-cause mortality 2. Fatal/non-fatal rebleeding

To assess safety, we assessed 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. We obtained full-text articles if the title and abstract review met the following criteria:

1. Systematic reviews of the clinical efficacy or adverse event rates of beta blockers for included clinical conditions that reported an included outcome OR
2. Randomized controlled trials that compared one of the included beta blockers to another included beta blocker or placebo-controlled trials for included clinical conditions that reported an included outcome OR
3. Randomized controlled trials and large, good-quality observational studies that evaluated adverse event rates for one or more of the included beta blockers.

We then applied the same criteria to the full-text articles, ensuring that the clinical efficacy or adverse event rates from specific beta blockers were reported or could be calculated. While we preferred studies of longer duration, we generally had no lower limit on the length of

follow-up, but excluded "single-dose studies" examining the effects of a single dose of medication rather than a course of treatment or studies that only evaluated a course of inpatient treatment. Trials that evaluated one beta blocker against another provided direct evidence of comparative efficacy and adverse event rates, and are the primary focus of this report. In theory, trials that compare beta blockers to active controls (non-beta blocker drugs) can provide evidence about comparative efficacy by indirect comparisons. However, the evidence from these studies is difficult to interpret for a number of reasons, primarily involving issues of heterogeneity between trial populations, interventions, and assessment and definition of outcomes and were not analyzed in this review.

Data Abstraction

The following data was abstracted from included trials: 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. We recorded intention-to-treat results if available and the trial did not report loss to follow-up that exceeded 20%.

Quality Assessment

We assessed quality of trials based on the predefined criteria listed in Appendix B, which were submitted to the Health Resources Commission in December 2001 and updated in February 2003. We rated the internal validity of each trial based on methods used for randomization; allocation concealment and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. External validity of trials was assessed based on: adequate description of the study population; similarity of patients to other populations to whom the intervention would be applied; control group receiving comparable treatment; funding source; and role of the funder.

Overall quality was assigned based on criteria developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).[1, 2] Trials with a fatal flaw in one or more categories were rated poor-quality. Trials that met all criteria were rated good-quality. The remainder were rated fair-quality. As the "fair-quality" category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are *unlikely* to be valid, while others are *probably* or *likely* to be valid. A "poor-quality" trial is not valid. The results are at least as likely to reflect flaws in the study design as they are true differences between the compared drugs.

Appendix B shows the criteria we used to rate studies reporting adverse events. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated studies as good-quality for adverse event assessment if they adequately met six or more of the seven pre-defined criteria, fair if they met three to five criteria, and poor if they met two or fewer criteria.

Overall quality ratings for the individual study were based on ratings of the internal and external validity of the trial. A particular randomized trial might receive two different ratings: one for efficacy and another for 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

We constructed evidence tables showing study characteristics, quality ratings and results for all included studies. Poor-quality studies would usually be excluded from evidence tables, but we included them to ensure that the subcommittee is familiar with their limitations.

To assess the overall strength of evidence for a body of literature about a particular key question, we examined the consistency of study designs, patient populations, interventions, and results. Consistent results from good-quality studies across a broad range of populations suggest a high degree of certainty that the results of the studies were true (that is, the entire body of evidence would be considered "good-quality.") For a body of fair-quality studies, however, consistent results may indicate that similar biases are operating in all the studies. Unvalidated assessment techniques or heterogeneous reporting methods for important outcomes may weaken the overall body of evidence for that particular outcome or make it difficult to accurately estimate the true magnitude of benefit or harm.

RESULTS

Overview

Searches identified 4,198 citations: 2,361 from the Cochrane Library, 1,219 from MEDLINE, 487 from EMBASE, 120 from reference lists, and 11 from pharmaceutical company submissions. Ninety-four trials met the inclusion criteria for the systematic review.

The characteristics, results and quality ratings of included trials are summarized in evidence tables and in the text below. Most of the included randomized trials had fair internal validity, but their applicability to community practice was difficult to determine. The treatment and control groups generally received other standard therapies for the condition evaluated, but current therapies varied depending on the date of publication and local practices. Most studies did not report numbers of patients screened or eligible for treatment. Most trials excluded patients with significant co-morbid medical conditions or contraindications for beta blocker therapy. Some studies did not state the source of funding, but almost all that reported funding sources were funded at least in part by the pharmaceutical industry. Some of the larger studies also reported other sources of funding.

Key Question 1: For adult patients with hypertension, coronary artery disease, congestive heart failure, atrial arrhythmias, migraines, or bleeding esophageal varices, do beta blocker drugs differ in efficacy?

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

Head to head Trials

All ten beta blockers reduce blood pressure and are indicated for hypertension. We identified several trials comparing two different beta blockers,[3-11] but none of these trials reported all cause mortality, cardiovascular mortality, or cardiovascular events.

Placebo-controlled Trials

Mortality and cardiovascular events. 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[12]. 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.[13] (Stage 1 hypertension is defined as systolic blood pressure 140-159 and diastolic blood pressure 90-99.) It recommends a beta blocker (usually with a diuretic and an ACE inhibitor or ARB) in patients with Stage 1 or 2 hypertension who also have heart failure, recent myocardial infarction, high coronary disease risk, or diabetes.

No beta blocker has been shown to reduce mortality or cardiovascular events in patients who have essential hypertension but do not have one of these other conditions. For this reason, there is no evidence to suggest that any particular beta blocker is more effective in reducing mortality or cardiovascular events than others.

Systematic reviews performed prior to the publication of ALLHAT found insufficient evidence to conclude that beta blockers reduce the risk of death or cardiovascular events in otherwise healthy patients with hypertension.[14, 15] The largest single trial, the single-blind Medical Research Council (MRC) trial, found that propranolol had no effect on all-cause mortality or coronary events in patients with DBP 90-109 mm Hg (Evidence Table 1). There was a nonsignificant trend toward a reduced risk of stroke. In the MRC as well as ALLHAT, a diuretic was the most effective initial therapy to reduce mortality.

Quality of Life. We found two trials that reported the effect of long-term beta blocker therapy on quality of life in otherwise healthy patients who have hypertension (Evidence Table 1). The Trial of Antihypertensive Interventions and Management (TAIM) [16-18], conducted in the United States, studied 878 randomized patients (56% men, mean age 49). This trial used a factorial design that included three drug interventions (atenolol, chlorthalidone, placebo) and three diet interventions (usual diet, low sodium, weight loss). We only considered results from the atenolol-usual diet and placebo-usual diet groups. The TAIM trial 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').

The second trial[19], also conducted in the US, studied the effects of propranolol versus placebo in 312 patients (66.5% male, mean age of 45.5 years) with diastolic hypertension. Cognitive and psychological functioning dimensions of quality of life were measured using four

standardized neuropsychological tests (Stimulus Evaluation/Response Selection; Continuous Performance Task; Digit Symbol Substitution Task; California Verbal Learning Test) and two self-administered questionnaires designed to measure mood and sexual function (Center for Epidemiological Studies Depression Scale; Beck Depression Inventory). After twelve months of treatment, no differences between propranolol and placebo in change (positive or negative) in cognitive or psychological measures were found.

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

Head-to-head Trials

Atenolol, metoprolol, nadolol, and propranolol are indicated for symptomatic treatment of stable angina pectoris. Most head-to-head and placebo-controlled trials in angina patients assess their short-term effects on exercise tolerance, attack frequency, or nitroglycerin use.[20-27] Four fair-quality head to head trials evaluated angina symptoms after two or more months of treatment with beta blockers (Table 3, Evidence Table 2). Three of the four eligible trials were conducted outside of the United States. 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 one trial[28], which used a treadmill. There were no significant differences in exercise tolerance or attack frequency.

Table 3. Results of head-to-head trials in patients with angina

Trial	Interventions	RESULTS	
		Exercise parameters	*Attack frequency*
van der Does, 1999 *n=368*	carvedilol 100 mg metoprolol 200 mg	% increase in mean total exercise time (sec): 16.7% vs 16.6% (NS) % increase in mean time to angina (sec): 25.7% vs 23.7% (NS)	nr
Frishman, 1979 *n=40*	Pindolol 10-40 mg Propranolol 40-240 mg	% increase in exercise capacity (mets): 21.2% vs 18.5% (NS)	% reduction in attack frequency: 41.8% vs 47.% (NS)
Dorow, 1990 *n=40 (comorbid chronic obstructive pulmonary disease patients)*	Atenolol 50 mg Bisoprolol 5 mg	nr	% reduction in attack frequency: 82.8% vs 64.3% (NS)
Chieffo, 1986 *n=10 (comorbid hypertension)*	Labetolol 200 mg+chlorthalidone 20 mg Atenolol 100 mg+chlorthalidone 25 mg	nr	% patients with reduced angina attacks+reduced sl ntg use: 60% vs 80% (NS)

sl ntg=sublingual nitroglycerin

Placebo-controlled Trials

Short-term, placebo-controlled trials, although numerous, provided insufficient information to assess the comparative efficacy of different beta blockers.

Over the long-term, beta blockers may differ in their ability to prevent or reduce the severity of anginal attacks. We identified one trial that reported changes in the efficacy of a beta blocker over time. This was a fair quality, placebo-controlled, 2-year multicenter European trial of propranolol 60-240 mg and bepridil 100-400 mg in 191 patients with angina. (Evidence Table 2).[29] We are not considering the bepridil treatment results in this discussion. Propranolol reduced the proportion of patients using nitroglycerin (57% vs. 73% in the placebo group) and increased the mean total work time by 48% vs 13% for placebo) after 8 weeks of treatment. 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.

A large number of trials compare a beta blocker to a calcium channel blocker or other antianginal drug. It is possible that two or more studies comparing different beta blockers to the same calcium channel blocker could provide some insight into how the beta blockers compare with one another. We consider this to be unlikely because of the difficulty of determining the equivalency of baseline angina severity, comorbidity, other therapies, and beta blocker doses across these studies.

In summary, head to head trials show no differences in efficacy in several comparisons made for patients with stable angina (carvedilol vs metoprolol and pindolol vs propranolol). Additionally, equivalent effects were seen for atenolol and bisoprolol in angina patients with COPD and for atenolol and labetalol (when combined with chlorthalidone) in angina patients with hypertension.

Active Control Trials

A good-quality meta-analysis identified 72 randomized controlled trials of a beta blocker vs. a calcium channel blocker and 6 RCTs comparing a beta blocker to a nitrate.[30] 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?

Short-term

We did not examine short-term (4-7 days) inpatient trials of beta blockers to prevent atrial arrhythmias after CABG. [31-35]

Long-term

The long-term use of a beta blocker after CABG has not been shown to improve mortality or other outcomes. In 7 placebo controlled trials, long-term treatment with a beta blocker after CABG did not improve mortality or reduce cardiovascular events. For example, the MACB Study Group conducted a fair quality trial[36] that randomized patients to metoprolol 200 mg or placebo within 5-21 days following CABG and measured the effects of treatment on death and cardiac events (Evidence Table 3). This trial was conducted in Sweden and involved a sample of 967 patients that were 85.5% male and had a median age of approximately 64 years. Use of aspirin 250 mg and dipyridamole were allowed. No differences between metoprolol and placebo were found in mortality (3.3% vs 1.8%; p=0.16) or in any of the other ischemic events (e.g., MI, unstable angina, need for additional CABG or PTCA). Early withdrawal was seen in 34.4% of metoprolol patients and 43.5% of those taking placebo due to reasons including need for beta blockers, angina, tachycardia and hypertension.

1d. For adult patients with silent ischemia do beta blockers differ in efficacy?

Head-to-head trials

There are no head to head trials comparing the effect of different beta blockers in patients with silent ischemia.

Placebo-controlled trials

The Atenolol Silent Ischemia Study (ASIST)[37] is a good quality trial that evaluated the effects of atenolol 100 mg and placebo on the primary endpoint of event-free survival in 306 patients with documented coronary artery disease. Results of this trial are summarized in Evidence Table 4. This trial was conducted in the United States with 52 weeks of follow-up. Patients were 86.9% male with a mean age of 64. Concomitant use of nitrates and aspirin were allowed. Atenolol had a protective effect on the occurrence of any fatal/non-fatal ischemic related events (11.2% vs 25.3%; NNT=8; p=0.001). Total mortality was not reported.

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

Head-to-head trials

One fair quality[38] head to head trial compared atenolol 100 mg to propranolol 120 mg, and to placebo in patients with recent myocardial infarction. Patients (n=388) were randomized within 4-12 hours of symptom onset and were followed for one year. Baseline heart failure characteristics (defined as breathlessness, elevated jugular venous pressure and basal crepitations) were not provided. Patients with severe heart failure were excluded. Concomitant use of other typical medications was allowed both during hospitalization and in the follow-up period. Results of this trial are summarized in Evidence Table 5. No differences in rates of mortality between atenolol, propranolol and placebo were found at 6 weeks (8.6% vs 7.5% vs

11.6%) or after one year (12.9% vs 14.9% vs 14.7%). Rates of overall attrition were equivalently high across the atenolol, propranolol and placebo treatment groups (46.2% vs 47.2% vs 38.7%).

Systematic Reviews

One good quality[39] and three fair quality[40-42] reviews have examined the effects of beta blockers on mortality following acute myocardial infarction. The three fair quality reviews did not provide literature search strategy details or account for assessment of internal validity. Together, these reviews summarized the results of 66 randomized controlled trials.[38, 43-107] Thirty-seven trials of included beta blockers that were evaluated in these reviews are listed in Evidence Table 6.

The oldest review[40] provided an overview of total mortality, sudden death, non-fatal reinfarction and adverse event results of 65 randomized controlled trials (n=50,000). This review focused on examining the combined roles of intervention timing (early vs late), drug delivery (purely intravenous; intravenous loading, followed by oral delivery; or purely oral dosing) and trial duration (short-term vs long-term). The second fair quality review[41] pooled mortality results of five randomized controlled trials of metoprolol[50-52, 108, 109] (n=5474) dosed at 200 mg daily. The third fair quality review [42] pooled total mortality results of 28 *early intervention* (n=27,536) and 24 *long-term* (n=26,246) trials of various beta blockers. Pooled results of sudden death in 16 trials (n=19,328) of various beta blockers were also reported.

The most recent, good quality review[39] published in 1999 used stricter inclusion criteria (no crossover designs, duration > 1 day.) The included trials observed 54 234 patients. In a metaregression of the long-term trials, beta blockers without intrinsic sympatheticomimetic activity (ISA) reduced mortality; those with ISA were less effective and the pooled effect for increased mortality approached statistical significance (Odds Ratio=1.19; 95% CI: 0.96-1.47.) Cardioselectivity was unrelated to mortality reduction (Odds Ratio=1.10; 95% CI: 0.89-1.39.) [39] For all-cause mortality reduction, pooled odds ratios for acebutolol (Odds Ratio=0.49; 95% CI: 0.25-0.93), metoprolol (Odds Ratio=0.80; 95% CI: 0.66-0.96), propranolol (Odds Ratio=0.71; 95% CI=0.59-0.85) and timolol (Odds Ratio=0.59; 95% CI: 0.46-0.77) were statistically significant.

Placebo-controlled trials

In addition to the trials examined in the previous reviews, we identified one fair quality, placebo controlled trial of carvedilol in patients with reduced left ventricular function after acute myocardial infarction (CAPRICORN).[110] Evidence Tables 5 (characteristics) and 7 (all-cause mortality) and Figure 1 summarize the placebo controlled trials that enrolled > 100 patients and evaluated one of the drugs included in our review. These trials evaluated atenolol (2 trials), carvedilol (2), metoprolol (7), pindolol (2) and propranolol (7).

Among these trials, differences in mortality rates between beta blockers and placebo were statistically significant in three: CAPRICORN (carvedilol), the Goteborg Metoprolol Trial, and BHAT (propranolol.)

Atenolol. Two large trials compared intravenous followed by oral atenolol to standard care: [48, 73, 111] Both trials were unblinded. The Yusuf trial[73] (n=477) found that atenolol was associated with a significant reduction in total mortality versus standard care after 10 days of

treatment (2% vs 6%; p=0.02). Shortly thereafter, the larger ISIS-1 trial (n=16,027)[112] confirmed these findings with data from 7 days of treatment with atenolol and standard care (3.9% vs 4.6%; p<0.05).

Carvedilol. One fair quality, placebo controlled trial of carvedilol in 146 post-MI patients with a mean LVEF of 48% found no effect on mortality (2.7% vs 4.2%; NNT=65; NS) after six months.[47] Carvedilol decreased the frequency of the primary endpoint (*serious cardiac events* including cardiac death, reinfarction, unstable angina, heart failure, emergency revascularization, ventricular arrhythmia requiring intervention, stroke and additional cardiovascular therapy) in the sample as a whole (24% vs 43.7%; p<0.02) and in the subgroup of patients with LVEF < 45% (20.8% vs 52%; p=0.04).[47, 113]

The CAPRICORN trial[110] randomized 1959 patients with a mean left-ventricular ejection fraction of 32.8% to either carvedilol or placebo as an add-on to ACE inhibitor therapy at an average of 10 days following a confirmed MI. 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. Results of this trial showed significantly lower rates of all-cause mortality for the carvedilol group (12% vs 15%; NNT=30; p=0.03) and equivalent rates for all-cause mortality *plus* cardiovascular hospital admissions (35% vs 37%; Hazard ratio=0.92[0.80-1.07]; p=0.296). No differences between carvedilol and placebo were found for sudden death (5% vs 7%; Hazard ratio=0.74[0.51-1.06]; p=0.098) and hospital admission for heart failure (12% vs 14%; Hazard ratio=0.86[0.67-1.09]; p=0.215).

Metoprolol. Metoprolol 200 mg daily reduced all-cause mortality within 3 month of an MI in the good-quality Goteborg Metoprolol Trial[114, 115], (n=1,395 subjects; mortality 5.7% vs 8.9%; NNT=32; odds ratio=0.62[95% CI=0.40-0.96].) Mortality was also reduced in the subset of 262 patients who had mild-moderate heart failure after MI (10% vs 19%; NNT=11; odds ratio=0.46[95% CI: 0.21-1.0]). Metoprolol reduced reinfarction rates in the overall sample (5% vs 7.7%; NNT=37; odds ratio=0.63[95% CI=0.39-0.99]) but not in the subgroup of patients with heart failure.

Individually, mortality reductions in the 3-year Stockholm Metoprolol Trial[107] (n=301; mortality 16.2% vs 21.1%; NNT=21; NS), the 1-year Belfast Metoprolol Trial[52] (n=800; 11.8% vs 14.9%; NNT=32; NS) and the 1-year Lopressor Intervention Trial[51] (n=2395; 5.8% vs 6.3%; NNT=181; NS) did not reach Results from two other trials available only in abstract form[76, 102] also found no mortality difference between metoprolol and placebo. As noted earlier, however, when results from the metoprolol trials are combined,[41], metoprolol significantly reduced all-cause mortality (6.8% vs 8.2%; NNT=74; p=0.036).

Pindolol had no effect on the mortality of patients post-MI in the fair quality, placebo controlled Australian and Swedish study.[53] In this trial, the mortality of patients (n=529) entered 1-21 days following an MI was 17.1% in the pindolol group and 17.7% in the placebo group. This study also found no differences between pindolol and placebo in rates of sudden death (10.6% vs 11.7%) and reinfarction (4.6% vs 4.9%). A significantly (p<0.05) higher proportion of patients withdrew from pindolol treatment (28.9%) compared with those given placebo (18.8%). An insignificant difference in the proportion of patients withdrawing from pindolol and placebo treatments due to heart failure was reported (7.6% vs 4.1%). Another trial, published in abstract form only[75] supported the finding of equivalency between pindolol and placebo in mortality rates when administered sooner (median=4 hours post-MI), but over a shorter period of time (3 days).

Propranolol. Results of the single blind, fair-poor quality, propranolol 20-600 mg vs placebo limb (n=269) of the Multicenter Investigation of the Limitation of Infarct Size (MILIS),[68] in which the interventions were administered 8.5 hours (mean) post-MI, showed no difference in mortality rates after 36 months of follow-up (17.9% vs 14.8%). Contamination was a significant problem in this study; at six months of followup, 40% of placebo patients and 54% of propranolol patients were receiving beta blockade. Three short-term (21-28 days), fair quality placebo controlled trials[44, 56, 66] showed that lower doses of propranolol (80 mg daily) also had no effect on mortality. Rates of mortality for propranolol and placebo were 23.2% and 24.1%, respectively, in the trial of 114 patients[56], 13.7% and 10.5% in the trial of 454 patients.[66], and 15% and 12.6% in the trial of 226 patients.[44]

The fair quality Beta-Blocker Heart Attack Trial (BHAT)[46, 116-118] is the largest (n=3,837), longest (25 months) trial of propranolol 180-240 mg or placebo administered to patients (mean age=54.8; 84.4% male; 14.6% mild-moderate heart failure) within 5-21 days following myocardial infarction. The BHAT trial found that propranolol had a significant effect on total mortality (7.2% vs 9.8%; NNT=39; p=0.0045) and sudden death (3.3% vs 4.6%; NNT=78; p<0.05) and no effect on rate of reinfarction (5.4% vs 6.3%; NS). A significantly higher proportion of patients withdrew from propranolol treatment as compared to placebo (12.7% vs 9.3%; p=0.0009).

Two smaller trials conducted prior to BHAT had negative findings. When initiated 2-14 days post-MI (n=720), no mortality difference between propranolol and placebo (7.9% vs 7.4%) was found in one 9-month trial.[55] Propranolol and placebo also had equivalent effects on 12-month mortality (8.9% vs 13.1%) in another trial[59] when initiated 4-6 days post-MI in 560 patients.

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

Placebo-controlled trials

Seven previous meta-analyses have examined the use of beta-blockers in patients with heart failure.[119-125] Only the most recent meta-analysis[125] included the results of RESOLVD—Phase 2 and COPERNICUS, published in 2000 and 2001, respectively. Most meta-analyses included small trials of metoprolol[126-128] or carvedilol[129-131] and trials of agents not available in the U.S. (bucindolol and nebivolol.)

In general, these meta-analyses found that beta blockers reduce mortality, preventing 3.8 deaths per 100 patients in the first year of treatment.[123] They also found that, for carvedilol, the pooled mortality reduction was statistically significant even before the publication of COPERNICUS. The pooled results for immediate-release metoprolol were not statistically significant.

Trials of drugs included in our review are summarized in Evidence Tables 8 and 9 and in Table 4 below. We excluded trials with fewer than 100 patients. The remaining trials ranged from 6 months to 2 years in duration.

Mortality was a primary endpoint in four of these trials; in the others, exercise tolerance, morbidity and mortality combined, or quality of life was the primary endpoint. Two evaluated bisoprolol 5-10 mg;[132, 133] seven, carvedilol 50-100 mg;[134-140] two, immediate release metoprolol 100-150 mg;[141, 142] and two, controlled release metoprolol (CR) 12.5-25 mg.[143, 144]

Table 4. Mortality reductions in beta blocker trials with >100 patients (adjusted for run-in phase deaths.)

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
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
MDC	Metoprolol	Mortality+ morbidity	I-IV	<40% (0.22)	11.0%	12.0%	383
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.

Mortality. Table 4 above shows that the annualized placebo and treatment group mortality varied among the trials. In general, the risk of death in the treated group was proportional to the risk in the placebo group.

Sudden Death. Six of the placebo-controlled trials reported sudden death rates. Standard-dose bisoprolol reduced rates of sudden death (4% vs 6%; NNT=38; p=0.0011) but low-dose bucindolol did not (4.7% vs 5.3%). No differences between carvedilol and placebo in sudden death rates were seen in the MOCHA (2.3% vs 7.1%) or Australia/New Zealand (4.8% vs 5.3%) trials. While the controlled release formulation of metoprolol significantly reduced sudden death rates in the MERIT-HF trial (3.9% vs 6.5%; NNT=39; p=0.0002), rates for the immediate release formulation did not differ from placebo in the MDC trial (9.3% vs 6.3%).

Death from Progressive Heart Failure. The method of measuring/reporting incidence of fatal/non-fatal heart failure progression varied among the trials. In the CIBIS-II trial, bisoprolol was shown to significantly reduce hospital admissions for worsening heart failure (12% vs 18%; p=0.001). Carvedilol was found to be superior in reducing heart failure progression (11% vs 20.9%; p=0.008), as measured by a composite of deaths, hospitalizations and need for more medication in the USCHFSG mild heart failure trial. Carvedilol showed no benefit for deaths due to progressive heart failure (6.7% vs 7.2%) in the Australia/New Zealand trial; nor did immediate release metoprolol (2.6% vs 2.6%) in the MDC trial. A significantly lower number of deaths due to progressive heart failure were seen for the metoprolol CR group in the MERIT-HF trial (1.5% vs 2.9%; p=0.0023).

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[135, 136] showed carvedilol to be superior to placebo in improving the overall NYHA class distribution, but in two other trials[134, 138] carvedilol had no effect. Results for the immediate release metoprolol trials were also mixed. The MDC trial noted that metoprolol improved NYHA class compared to placebo but this finding was reported in graphic format only. 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).[145]

Exercise Capacity. The carvedilol trials[134-136, 138] 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[134-136] 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.[146]

Comparison of Major Trials. CIBIS-II (bisoprolol), COPERNICUS (carvedilol) and MERIT-HF (controlled release metoprolol) were all large trials showing similar protective effects on all-cause mortality, the primary endpoint. Relative risks (95% confidence intervals) for all-cause mortality for these and other trials are summarized in Evidence Table 8 and presented in a forest plot in Figure 2. As shown in Figure 2, the relative risk estimates for the three major trials were similar, and the 95% confidence intervals across all trials overlap. In addition, all three drugs reduced hospital admissions for worsening heart failure.

How do the three drugs compare in patients who have severe heart failure? COPERNICUS recruited the largest number of patients. COPERNICUS did not report the NYHA Class of subjects, but all subjects had symptoms on minimal exertion or at rest, that is, CLASS III or IV and had an ejection fraction less than 25%.

A post-hoc analysis in MERIT-HF examined a subgroup of patients similar to that of COPERNICUS. A total of 795 patients had NYHA Class III or IV and had an ejection fraction less than 25%. As shown in Table 4, the placebo group mortality of this subgroup (18.2% vs. 20.9%) and the reduction in mortality (NNT 14.485 vs. 14.492) were similar to that of COPERNICUS. Mortality reduction was numerically higher for metoprolol CR versus placebo in Class III heart failure patients (-39%) than in those with Class II (-25%) and Class IV (-30%); however, this interaction is not considered to be significant as reflected by overlapping confidence intervals. In other subgroup analysis from the MERIT-HF trial, heart failure etiology, history of MI, diabetes mellitus and/or hypertension did not significantly influence the effect of metoprolol CR on patients with heart failure.

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]

Only patients who were hemodynamically stable were eligible for the COPERNICUS trial. Eichhorn and Bristow have pointed out that "The COPERNICUS trial represents a euvolemic set of patients with a low ejection fraction, and symptoms that would conventionally be classified as NYHA class III or IV." They go on to speculate that COPERNICUS included a subgroup of patients with advanced heart failure who had relatively good contractile reserve. They state that the COPERNICUS subjects had a higher mean systolic blood pressure (124 mm Hg) than other major trials. However, while MERIT-HF subjects had an average systolic blood pressure (117 mm Hg), mean systolic blood pressure in the high-risk subgroup of MERIT-HF was the same as that of the COPERNICUS subjects.

The COPERNICUS investigators have partly addressed this criticism by describing a subgroup of subjects who had recent or recurrent cardiac decompensation. They did not state the number of subjects in this group, but they reported the annualized placebo-group mortality rate (24%) and the mortality reduction (relative risk reduction was 39%, CI 11%-59%, p=0.0009).

Head-to-head Trials

Five fair quality, head to head trials compared the effects of metoprolol with carvedilol in patients with heart failure receiving standard care (e.g., angiotensin-converting-enzyme-inhibitors (ACEIs) and diuretics).[130, 147-151] These trials are summarized in Evidence Table 10 (characteristics) and Evidence Table 11 (outcomes). All of the trials compared carvedilol to the immediate-release form of metoprolol. The four earlier trials had several important flaws: most did not use intention to treat analyses or describe randomization and allocation concealment methods.

Mortality. The Carvedilol Or Metoprolol European Trial (COMET) is the most recent, largest (n=3029) and longest (mean duration 58 months) of these trials. 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. The intention-to-treat analysis showed an overall mortality benefit in favor of carvedilol (34% vs 40%; NNT 18; p<0.0017).

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

There were fewer cardiovascular deaths in the carvedilol group (29% vs 35%; NNT=17; p<0.0004). No differences were seen between carvedilol and metoprolol in non-cardiovascular deaths (5% vs 4%) or all deaths and all-cause admission (74% vs 76%).

COMET does not resolve the question of whether carvedilol is superior to long-acting metoprolol or bisoprolol, the other two preparations that have been shown to reduce mortality. The main concern is whether the dose of immediate release metoprolol used in COMET was adequate to provide constant beta blockade. Several years ago, the failure of metoprolol to reduce mortality in the Metoprolol in Dilated Cardiomyopathy (MDC) trial raised the same concern: it was hypothesized that metoprolol failed to reduce mortality because 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.) 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.

Worsening Heart Failure. In one open trial[147] immediate-release metoprolol and carvedilol dosed at 50 mg for patients weighing at or below 85 kg and 100 mg for patients weighing above 85 kg. Patients (n=67) in this trial were 68.6% male, with a mean age of 57.8 years and a mean ejection fraction (EF) of 18-19%. A trend favoring carvedilol over immediate release metoprolol in incidence of worsening heart failure after 6 months was reported in this open trial (8.1% vs 16.7%.)[147] A double-blind trial[130] of 150 patients (90.7% men, mean age 56.5 years, mean EF 20.5%) had similar findings (9.8% and 21.3%).[130] In this trial, patients were prescribed 100 or 200 mg of carvedilol, or 50 or 100 mg of metoprolol, based on a cut-off weight of 75 kg.

Exercise capacity. Equivalent improvements in six-minute walk tests were reported for patients in carvedilol and metoprolol groups after 12 weeks (6.4% vs 8.5%)[149], six months (5.5% vs 6.6%)[147] and 12 months (11.2% ad 15.1%).[130]

Quality of life. There were no differences between the carvedilol and metoprolol groups in mean reductions in the Minnesota Living with Heart Failure Questionnaire symptom scores after 12 weeks (52.9% and 63.3%)[149], 6 months (21.1% and 19.6%)[147] and 12 months (25% and 17.9%).[130]

Summary

In summary, there is good evidence that carvedilol, bisoprolol, and controlled-release metoprolol have similar effects on symptoms and all-cause mortality when compared to placebo in patients with mild to moderate heart failure. There is evidence that controlled-release metoprolol also improves patients' NYHA functional class and well-being. There is also good-quality evidence from a head-to-head trial that carvedilol is superior to immediate-release metoprolol in patients with mild-moderate chronic heart failure (mean LVEF=26%; 48.4% NYHA Class II; 47.8% NYHA Class III). However, immediate-release metoprolol has been ineffective in placebo-controlled trials. For these classes of heart failure, there is no direct evidence that carvedilol is superior to the other formulations that have been shown to reduce mortality: bisoprolol and controlled release metoprolol.

In higher-risk patients, there is good evidence that carvedilol reduces mortality and the combined endpoint of mortality and hospitalizations. There is also fair-to-good evidence from a large, post-hoc subgroup analysis of a good-quality trial that metoprolol CR was equally effective in comparable patients.

Table 5 compares other outcomes reported in the major trials. There is fair-quality evidence that metoprolol-CR improves well-being in a broad spectrum of heart failure patients. This does not mean that metoprolol-CR would improve well-being in the population examined in COPERNICUS. The effect of metoprolol on well-being in the high-risk subgroup of subjects was not reported.

Table 5. Comparison of outcomes of major trials in heart failure.

Trial	Mortality reduction	Improvement by ≥ 1 NYHA Class	Well-Being
CIBIS-II (bisoprolol)	Effective	NR	NR
COPERNICUS (carvedilol)	Effective	NR	NR
MERIT-HF (metoprolol CR)	Effective	Effective	Effective

1g. 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. We did not find any trials that could provide evidence of comparative efficacy. A recent good quality systematic review examined 12 studies of rate control in patients with chronic atrial fibrillation.[152] Atenolol, nadolol and pindolol were effective in controlling the ventricular rate, while labetalol was no more efficacious than placebo.

We found no head-to-head trials of different beta blockers to maintain sinus rhythm after cardioversion for atrial fibrillation or flutter. A large number of studies have compared a beta blocker to sotalol or to other antiarrhythmic drugs after cardioversion, but these trials do not provide comparative information about different beta blockers.

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 12).[153, 154] 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.)

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

Head-to-head Trials

We found four fair quality[155-158] head to head trials of beta blockers for the treatment of migraine (Evidence Table 13). One study comparing bisoprolol and metoprolol appears to have

been published twice.[159, 160] 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 four included trials compared propranolol 160 mg to atenolol 100 mg,[158] slow release metoprolol (durules) 200 mg daily[156] to immediate release metoprolol 200 mg daily[155], and propranolol 80 mg to metoprolol 100 mg daily.[157] All four trials were conducted outside of the US, were relatively short-term in duration (12-20 weeks), and were small (35-58 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 6 below.

Attack Frequency. Two trials reported mean[156] and median[157] attacks per four weeks which allows for comparison of effectiveness of these treatments in decreasing migraine frequency. There were no differences found between slow release metoprolol (durules) and propranolol (43.4% vs 43.4%) or between low doses of immediate release metoprolol or propranolol (22.2% vs 22.2%) in rates of decreased frequency of mean or median attacks per month.

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. There were also no differences found between slow release metoprolol (durules) and propranolol (45.6% vs 43.8%) or between low doses of immediate release metoprolol or propranolol (25.4% vs 32.8%) in rates of decreased frequency of mean or median migraine days per month. In disagreement with the use of response rates defined as percentage of patients responding on the basis of a 50% criterion, Gerber et al set out to use single case analysis and time-series analysis to try to better illustrate the data. Comparison of responders versus nonresponders was investigated as defined: *Responder type A:* Significant z-values (z >/= -1.65 to 1.96) in a) reduction in number of days with migraine, b) reduction of duration of migraines, c) reduction of severity of headaches, d) reduced use of analgesics and ergots; *Responder type B:* A tendency to improvement (NS) (z </= -1.65 to 1.96) in the four parameters above; *Non-responder type C:* No improvement in the parameters (z = 0 to -1.65); *Non-responder type D:* Tendency to deterioration, or statistically significant deterioration (positive z-values). Using ARIMA analysis, Gerber also found no difference between metoprolol and propranolol in percent of patients qualifying as responder type A or B for decrease in migraine days (54.4% vs 32.0%) during the three month "high dosage" phase.

Severity. Severity scores were calculated by multiplying *intensity* and *migraine days* in both the Kangasmiemi and Gerber trials, where intensity was rated using a 3-point scale (1=light, bothersome migraine which permits daily activities with minimal or no difficulty; 2=moderate, annoying migraine causing difficulty in carrying out daily activities; 3=severe, incapacitating,

patient unable to perform daily activities). Using this scoring system, there were no differences found between slow release metoprolol (durules) and propranolol (49.5% vs 44.3%) or between low doses of immediate release metoprolol or propranolol (21.8% vs 29.8%) in rates of decreased frequency of mean or median severity per month. While it is not clear how Gerber et al calculated severity scores, no difference between metoprolol and propranolol in percent of patients qualifying as responder type A or B for decrease in this parameter (55.0% vs 33.3%) during the three month "high dosage" phase

Tablet Consumption. There were no differences in rates of reduction of mean consumption of unspecified acute medication found between slow release metoprolol (durules) and propranolol (45.3% vs 45.3%) or between low doses of immediate release metoprolol or propranolol in rates of decreased median ergotamine (47% vs. 43.1%) or analgesic (16.5% vs 37.4%) use per month. Gerber et al didn't find any difference between metoprolol and propranolol in percent of patients qualifying as responder type A or B for decrease in ergotamine table use either (30% vs 38.9%) during the three month "high dosage" phase.

Subjective Assessment. Patients in two trials[156, 157] 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. One trial[158] measured treatment efficacy using a composite score (Headache Index) denoting severity per headache day and found no differences between atenolol and propranolol in the sums of the mean index scores per 42 days for all 28 patients. 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 6. Outcomes in head to head trials in migraine

Outcome	**Stensrud, 1980** Ate 100 mg vs pro 160 mg N=35	**Kangasniemi, 1984** Met-d 200 mg vs pro 160 mg N=35 *Outcome reporting:* % decrease in mean/4 wks	**Olsson, 1984** Met 100 mg vs pro 80 mg N=53 *Outcome reporting:* % decrease in median/4 weeks	**Gerber, 1991** Met 200 mg vs pro 160 mg Met=22; pro=19 *Outcome reporting:* (% of "responders" per ARIMA analysis)
Attack frequency/4 wks(% decrease)	nr	Met-d=43.4 Pro=43.4	nr	Met=22.2 Pro=22.2
Headache days	pro=257 ate=247 *(Totals for all 28 patients)*	met-d=45.6% pro=43.8%	Met=25.4% Pro=32.8%	Met=54.4% Pro=32.0%
Severity	nr	Met-d=49.5% Pro=44.3%	Met=21.8% Pro=29.8%	Met=55.0% Pro=33.3%
Tablet consumption	nr	*Overall:* met-d=45.3%; pro=45.3%	*Ergotamine:* met=47%; pro=43.1% *Analgesic:* met=16.5%; pro=37.4%	*Ergotamine:* met=30%; pro=38.9%
Subjective (% patients regarding effect as "marked" or "moderate")	Nr	Met-d=76% pro=63%	Met=63% Pro=64%	Nr
Misc.	Headache Index: pro=437; ate=410	Nr	Nr	Duration:

ate=atenolol; met=immediate release metoprolol; met-d: slow release metoprolol(durules); pro=propranolol

Placebo-controlled Trials

We found 18 fair quality, placebo controlled trials (see Evidence Table 14) of atenolol 100 mg,[161] bisoprolol 5 or 10 mg,[162] metoprolol slow release (Durules) 200 mg,[163, 164] pindolol 7.5-15 mg,[165, 166] propranolol immediate release 80-240 mg[167-175] and long acting propranolol 160 mg.[176, 177] One trial[178] did not report propranolol dosage and will be discussed separately.

All but two[169, 178] 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.[164] 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[170] 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[162] 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[165, 166] 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.[179-190] 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[191] 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.

Summary

In summary, four 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 vs propranolol, metoprolol durules vs propranolol, metoprolol 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.

1i. 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.[192] 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 Table 15. 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[193] and propranolol[194-201] for the secondary prevention of bleeding esophageal varices secondary to cirrhosis and schistosomiasis[202]. Results are summarized in Evidence Table 17. 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.[194, 197, 201]

Variceal Rebleeding Rates. As shown in Table 3 below and in Evidence Table 12, compared to placebo, no differences in effect on variceal rebleeding rates were shown for immediate release propranolol in two early treatment trials. [194, 201] A significant difference between the effects of slow release propranolol and placebo was found in a third early treatment trial (20% vs 75%; $p<0.05$).[197] For trials of later (≥ 14 days)[196, 198, 199, 203] and unspecified[195, 204] 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 7. 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[194-196, 198, 201, 203]. Results are summarized in Table 4 below and in Evidence Table 12. 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[204], however, significantly more patients (17%) experienced death due to variceal rebleeding on placebo than after late intervention (2 weeks) with propranolol (0%).

Table 8. 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[194], no significant differences between beta blockers and placebo were found.

Table 9. 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?

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[9-11] (Evidence Table 16), 2 trials of patients with angina[28, 205] (Evidence Table 2), 2 trials in patients with heart failure[130, 150] (Evidence Table 10), 5 trials in migraine patients[155-158, 206] (Evidence Table 13), 1 trial in patients with bleeding esophageal varices[192] (Evidence Table 15), and in 1 trial of patients post-myocardial infarction[38] (Evidence Table 5). 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[155] of the head to head trials in patients with migraine used crossover designs, only reporting results of the combined intervention periods.

Only one trial[9] 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 13 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 17.

Overall adverse event incidence was reported in seven head to head trials.[10, 28, 150, 156, 157, 159, 205] 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[28] 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 only 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 four head to head trials.[130, 158, 159, 205] A significant difference between beta blockers was found in one 44-month trial of 122 patients with heart failure[130] 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%).[205] 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.

Hypotension incidence was reported in one 44-month trial of 122 patients with heart failure[130]. No difference between rates of hypotension for carvedilol (2.7%) and metoprolol (2.7%) were found.

Withdrawals due to adverse events were reported by three head to head trials.[11, 159, 192] No significant differences were found between atenolol and bisoprolol in patients with hypertension; between atenolol and propranolol in patients with bleeding esophageal varices; or between bisoprolol and metoprolol in patients with migraine.

In summary, longer-term trials (12-58 months) directly comparing beta blockers in patients with hypertension (atenolol vs bisoprolol vs propranolol), heart failure (carvedilol vs metoprolol) and bleeding esophageal varices (atenolol vs propranolol) 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.[130] 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.[28]

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)[207] analyzed mortality in post-infarction patients relative to subgroup risk factors from trials of propranolol[46, 55, 59], pindolol[46], 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[208] 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 10 below.

Table 10. 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.[110] We found no other source of publication of results from this subgroup analysis. The U.S. Carvedilol Heart Failure Study Group published an analysis[209] of the pooled results from a stratified set of three fair-quality and one poor-quality concurrently conducted protocols,[134-137] 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[139] 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[41] 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[50] 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)[46] 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 11 by key question and in Table 12 by beta blocker.

Table 11. 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: Poor	No significant differences in any exercise, attack frequency or nitrate use parameters were found in the evidence from 4 head to head trials of patients with stable angina (carvedilol vs metoprolol; pindolol vs propranolol) and those comorbid for COPD (atenolol vs bisoprolol) and in combination with chlorthalidone (atenolol vs labetalol) 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: Fair	In one head to head trial atenolol and propranolol had equivalent effects on rates of non-fatal/fatal rebleeding and all-cause mortality.

d. Silent ischemia	Overall grade: Poor	No head to head trials One good quality, large (n=306), long-term (52 weeks), placebo controlled trial showed atenolol to have a protective effect on incidence of any fatal/non-fatal ischemic events. Evidence of comparative efficacy of beta blockers is not provided by this trial
e. Recent MI	Overall grade: Fair	**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** Carvedilol reduced mortality in 1 placebo controlled trial of patients with a mean LVEF of < 32.7% (CAPRICORN) (fair quality) Metoprolol (Goteborg) and propranolol (BHAT) reduced mortality in two fair quality, placebo controlled trials 4 systematic reviews were not designed to assess comparative efficacy
f. Heart failure	Overall grade: Fair-Good	**Bisoprolol (CIBIS-II), carvedilol (COPERNICUS), and controlled-release metoprolol (MERIT-HF) have similar effects on symptoms and all-cause mortality when compared to placebo (Good quality). Metoprolol-CR also improves well-being and NYHA class (Fair quality)** **1 recent (2003), fair quality head to head trial (COMET) significantly favored carvedilol over immediate release metoprolol for effect on the primary endpoint of all cause mortality (34% vs 40%; NNT=18; p<0.0017) in patients with mild-moderate heart failure (Good quality)** **Another 4 head to head trials were powered to assess symptoms (quality of life; NYHA) and exercise capacity and consistently found no differences between carvedilol and metoprolol (Good quality)** *Higher risk patients (Class III or IV; LVEF < 25%):* Carvedilol (good quality) and metoprolol-CR (fair-good quality) reduce mortality
g. Atrial arrhythmia	Overall grade: Poor	No head to head trials Results from one fair quality trial showing that incidence of atrial arrhythmia/fibrillation relapse was lower in the metoprolol CR/XL group does not offer evidence of comparative efficacy of beta blockers

h. Migraine	Overall grade: Poor	Results from 4 fair quality head to head trials of atenolol, slow release metoprolol and immediate release metoprolol, each respectively compared to propranolol, don't clearly differentiate one beta blocker from another due to variation in measurement methods, dose levels and treatment durations.
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, migraine, bleeding esophageal varices, previous myocardial infarction	Overall grade: Fair	1 good quality head to head trial; 13 fair-poor quality head to head trials. 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. Equivalency was suggested for other safety parameters measured across the direct comparisons made in long- and short-term trials
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
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. *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 12. Summary of comparative efficacy

Drug	Hypertension	Angina	Status-post CABG	Silent ischemia	Heart failure	Atrial arrhythmias	Migraine	Bleeding esophageal varices	Myocardial infarction
atenolol		=bisoprolol in patients with comorbid COPD in reducing attack frequency; =labetolol in reducing nitrate use when both combined with chlorthalidone		>placebo in reducing fatal/non fatal ischemic events			=propranolol in decreasing migraine days	=propranolol for reducing all-cause mortality and deaths due to rebleeding	='standard care' in 7-day mortality (n=16,027)
bisoprolol		see above			>placebo in all-cause mortality and sudden death				
carteolol									
carvedilol		=metoprolol in increasing exercise tolerance			> immediate-release metoprolol in all-cause mortality in mild-moderate HF (COMET) >placebo in all-cause mortality in patients with *severe* heart failure (COPERNICUS)				>placebo in all-cause mortality in patients with LV dysfunction post-MI (n=1,959)
labetolol		see above							

Table 12. Summary of comparative efficacy (continued)

Drug	Hypertension	Angina	Status-post CABG	Silent ischemia	Heart failure	Atrial arrhythmias	Migraine	Bleeding esophageal varices	Myocardial infarction
metoprolol		see above	=placebo for mortality		see above > placebo in controlled release formulation in all-cause mortality, sudden death and death due to worsening heart failure (MERIT-HF) in moderate and high-risk patients	CR/XL formulation>placebo in lowering atrial fibrillation/flutter relapse rates	slow release formulation (durules), low and standard doses of IR formulation=propranolol in all parameters measured		>placebo in 3-month all-cause mortality (n=1,395)
nadolol								> placebo in effect on rebleeding rates	
penbutolol									
pindolol		=propranolol in increasing exercise tolerance and decreasing attack frequency							=placebo in all-cause mortality
propranolol	=placebo in mortality, CV events, QOL	see above					see above (atenolol and metoprolol)	see above	>placebo in all-cause mortality after 25 months (n=3,837)

REFERENCES

1. Harris RP, Helfand M, Woolf SH, et al. Current methods of the third U.S. Preventive Services Task Force. Am J Prev Med 2001; 20:(3S):21-35.

2. Anonymous. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews CRD Report Number 4 (2nd edition). York, UK: NHS Centre for Reviews and Dissemination; 2001. Report No.: 4 (2nd edition).

3. 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.

4. 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.

5. 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.

6. 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.

7. 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.

8. 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.

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

10. 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.

11. 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.

12. 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.

13. 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.

14. 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.

15. Wright JM, Lee CH, Chambers CK. Systematic review of antihypertensive therapies: Does the evidence assist in choosing a first-line drug? Can Med Assoc J 1999; 161:(1):25-32.

16. 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.

17. 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.

18. 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.

19. 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.

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

21. 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.

22. 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.

23. 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.

24. 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.

25. 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.

26. 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.

27. 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.

28. 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.

29. 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.

30. 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.

31. 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.

32. 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.

33. 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.

34. 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.

35. 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.

36. 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.

37. Pepine CJ, Cohn PF, Deedwania PC, et al. Effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life. Circulation 1994; 90:(2):762-8.

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

39. 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.

40. 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.

41. 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.

42. 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.

43. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction > or = 40% treated with diuretics plus angiotensin-converting enzyme inhibitors. Am J Cardiol 1997; 80:(2):207-9.

44. Anonymous. Propranolol in acute myocardial infarction. Lancet 1966; 2:(7479):1435-8.

45. Clausen J, Felsby M, Jorgensen FS, et al. Absence of prophylactic effect of propranolol in myocardial infarction. Lancet 1966; 2:(7470):920-4.

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

47. 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.

48. Anonymous. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative Group. Lancet 1986; 2:(8498):57-66.

49. Anonymous. Metoprolol in acute myocardial infarction (MIAMI). A randomised placebo-controlled international trial. The MIAMI Trial Research Group. Eur Heart J 1985; 6:(3):199-226.

50. 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.

51. Anonymous. The Lopressor Intervention Trial: multicentre study of metoprolol in survivors of acute myocardial infarction. Lopressor Intervention Trial Research Group. Eur Heart J 1987; 8:(10):1056-64.

52. 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.

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

54. Anonymous. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) phase II trial. The TIMI Study Group.[comment]. N Engl J Med 1989; 320:(10):618-27.

55. 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.

56. Balcon R, Jewitt DE, Davies JP, et al. A controlled trial of propranolol in acute myocardial infarction. Lancet 1966; 2:(7470):918-20.

57. Barber JM, Boyle DM, Chaturvedi NC, et al. Practolol in acute myocardial infarction. Acta Med Scand Suppl 1976; 587:213-9.

58. Dotremont G, De Geest H. The use of propranolol (inderal) in acute myocardial infarction. Acta Clin Belg 1968; 23:(3):163-76.

59. 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.

60. Heber ME, Rosenthal E, Thomas N, et al. Effect of labetalol on indices of myocardial necrosis in patients with suspected acute infarction. Eur Heart J 1987; 8:(1):11-8.

61. Kahler RL, Brill SJ, Perkins WE. The role of propranolol in the management of acute myocardial infarction. In: Kattus, AA, Ross G, Hall YE, editors. Cardiovascular beta adrenergic responses. Los Angeles, CA: California Press; 1968. p. 213-222.

62. Kaul UA, Verma R, Garg KC. Early intervention with propranolol after acute myocardial infarction: serial left ventricular function determined by M-mode and cross-sectional echocardiography. Int J Cardiol 1988; 21:(3):301-10.

63. Ledwich JR. A trial of propranolol in myocardial infarction. Can Med Assoc J 1968; 98:(21):988-94.

64. Mazur NA, Kulginskaya IV, Ivanova LA, et al. Results of long-term propranolol treatment in myocardial infarction survivors with advanced grades of ventricular extrasystoles. Cor et Vasa 1984; 26:(4):241-7.

65. Mueller HS, Ayres SM. Propranolol decreases sympathetic nervous activity reflected by plasma catecholamines during evolution of myocardial infarction in man. J Clin Invest 1980; 65:(2):338-46.

66. Norris RM, Caughey DE, Scott PJ. Trial of propranolol in acute myocardial infarction. BMJ 1968; 2:(602):398-400.

67. Norris RM, Barnaby PF, Brown MA, et al. Prevention of ventricular fibrillation during acute myocardial infarction by intravenous propranolol. Lancet 1984; 2:(8408):883-6.

68. Roberts R, Croft C, Gold HK, et al. Effect of propranolol on myocardial-infarct size in a randomized blinded multicenter trial. N Engl J Med 1984; 311:(4):218-25.

69. Sloman G, Stannard M. Beta-adrenergic blockade and cardiac arrhythmias. BMJ 1967; 4:(578):508-12.

70. Van de Werf F, Janssens L, Brzostek T, et al. Short-term effects of early intravenous treatment with a beta-adrenergic blocking agent or a specific bradycardiac agent in patients with acute myocardial infarction receiving thrombolytic therapy. J Am Coll Cardiol 1993; 22:(2):407-16.

71. Von Essen R, Merx W, Neis W, et al. [Wirkung von Metoprolol auf die Infartrobe beim Akuten Myokardinfarkt: Doppelbindstudie]. Deutsches Medizin Wochenschr 1982; 107:1267-1273.

72. Yusuf S, Lopez R, Sleight P. Effect of atenolol on recovery of the electrocardiographic signs of myocardial infarction. Lancet 1979; 2:(8148):868-9.

73. Yusuf S, Ramsdale D, Peto R, et al. Early intravenous atenolol treatment in suspected acute myocardial infarction. Preliminary report of a randomised trial. Lancet 1980; 2:(8189):273-6.

74. Peter T, Norris RM, Clarke ED, et al. Reduction of enzyme levels by propranolol after acute myocardial infarction. Circulation 1978; 57:1091-1095.

75. Owensby D, O'Rourke ME. Failure of pindolol to alter determinants of myocardial oxygen requirements, enzyme release or clinical course in acute myocardial infarction [abstract]. Circulation 1984; 70:(Suppl. II):156.

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

77. 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.

78. Ranganathan N, Rautaharju PM, Jablonsky GG, et al. Prophylaxis of post-myocardial infarction dysrhythmias by long-term timolol therapy. Am Heart J 1988; 115:(2):340-50.

79. Anonymous. Reduction of infarct size with the early use of timolol in acute myocardial infarction. N Engl J Med 1984; 310:(1):9-15.

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

81. Tonkin AM, Joel SE, Reynolds JL, et al. beta-Blockade in acute myocardial infarction. Inability of relatively late administration to influence infarct size and arrhythmias. Med J Aust 1981; 2:(3):145-6.

82. Wilcox RG, Rowley JM, Hampton JR, et al. Randomised placebo-controlled trial comparing oxprenolol with disopyramide phosphate in immediate treatment of suspected myocardial infarction. Lancet 1980; 2:(8198):765-9.

83. Johansson SR, McCall M, Wilhelmsson C, et al. Duration of action of beta blockers. Clin Pharmacol Ther 1980; 27:(5):593-601.

84. Andersen MP, Bechsgaard P, Frederiksen J, et al. Effect of alprenolol on mortality among patients with definite or suspected acute myocardial infarction. Preliminary results. Lancet 1979; 2:(8148):865-8.

85. Evemy KL, Pentecost BL. Intravenous and oral practolol in the acute stages of myocardial infarction. Eur J Cardiol 1978; 7:(5-6):391-8.

86. Ahlmark G, Saetre H, Korsgren M. Letter: Reduction of sudden Deaths after myocardial infarction. Lancet 1974; 2:(7896):1563.

87. Darasz KH, Bayliss J, Underwood SR, et al. Left ventricular volume in thrombolysed patients with acute anterior myocardial infarction: the effect of captopril and xamoterol. Int J Cardiol 1995; 51:(2):137-42.

88. Roque F, Amuchastegui LM, Lopez Morillos MA, et al. Beneficial effects of timolol on infarct size and late ventricular tachycardia in patients with acute myocardial infarction. Circulation 1987; 76:(3):610-7.

89. Julian DG, Prescott RJ, Jackson FS, et al. Controlled trial of sotalol for one year after myocardial infarction. Lancet 1982; 1:(8282):1142-7.

90. Anonymous. An early intervention secondary prevention study with oxprenolol following myocardial infarction. Eur Heart J 1981; 2:(5):389-93.

91. Wilhelmsson C, Vedin JA, Wilhelmsen L, et al. Reduction of sudden deaths after myocardial infarction by treatment with alprenolol. Preliminary results. Lancet 1974; 2:(7890):1157-60.

92. Reynolds JL, Whitlock RM. Effects of a beta-adrenergic receptor blocker in myocardial infarction treated for one year from onset. Br Heart J 1972; 34:(3):252-9.

93. Schwartz PJ, Motolese M, Pollavini G, et al. Prevention of sudden cardiac death after a first myocardial infarction by pharmacologic or surgical antiadrenergic interventions. J Cardiovasc Electrophysiol 1992; 3:(1):2-16.

94. Campbell RC. Beta-bloackade during and after myocardial infarction. Prog Cardiovasc Dis 1985; 27:225-271.

95. Fuccella LM. Report on the double blind trial with compound CIBA 39089 (trascior) in myocardial infarction. Prog Cardiovasc Dis 1968; 10:561-574.

96. Gupta RC. Effect of oral proporanolol on the extent of acute anterior myocardial infarction [abstract]. Presented at: Ninth World Congress on Cardiology; Moscow; 1982.

97. Lombardo M, Selvini A, Belli C, et al. Beta blocking therapy in 440 cases of acute myocardial infarction: a double-blind trial with oxprenolol [abstract]. Presented at: Florence International Meeting on Myocardial Infarction; Florence, Italy; 1979.

98. Snow NJ. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 1980; 27:335-371.

99. Thompson PL, Jones AS, Noon D, et al. A randomised trial of oral beta blockade during myocardial infarction lack of effect on enzymatic indices of myocardial necrosis. Aust N Z J Med 1979; 9:757.

100. Anonymous. Mortality results from the timolol trials in various British hospitals. Beta blockade during and after myocardial infarction: an overview of the randomised trials. Prog Cardiovasc Dis 1985; 27:335-371.

101. Barber JM, Murphy FM, Merrett JD. Clinical trial of propranolol in acute myocardial infarction. Ulster Med J 1967; 36:127-130.

102. Manger Cats V, van Capelle FJL, Lie KI, et al. Effect of treatment with 2 x 100 mg metoprolol on mortality in a single-center study with low placebo mortality rate after infarction. Circulation 1983; 68:(Suppl 3):181.

103. Anonymous. Improvement in prognosis of myocardial infarction by long term beta-adrenoceptor-blockade using practolol. BMJ 1975; 3:735.

104. Anonymous. Comparison of the effects of amiodarone versus metoprolol on the frequency of ventricular arrythmias and on mortality after acute myocardial infarction. Am J Cardiol 1993; 72:1234-1238.

105. Taylor SH, Silke B, Ebbutt A, et al. A long term prevention study with oxprenolol in coronary heart disease. N Engl J Med 1982; 307:1293-1301.

106. Anonymous. A secondary prevention study with slow release oxprenolol after myocardial infarction: morbidity and mortality. Eur Heart J 1984; 5:189-202.

107. Rehnqvist N, Ahnve S, Erhardt L, et al. Effect of metoprolol after acute myocardial infarction [abstract]. Presented at: European Congress of Cardiology; 1980.

108. Olsson G, Rehnqvist N, Sjogren A, et al. Long-term treatment with metoprolol after myocardial infarction: effect on 3 year mortality and morbidity. J Am Coll Cardiol 1985; 5:(6):1428-37.

109. 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.

110. 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.

111. Sleight P. Beta blockade early in acute myocardial infarction. Am J Cardiol 1987; 60:(2):6A-10A.

112. Anonymous. Mechanisms for the early mortality reduction produced by beta-blockade started early in acute myocardial infarction: ISIS-1. ISIS-1 (First International Study of Infarct Survival) Collaborative Group.[erratum appears in Lancet 1988 Jul 30;2(8605):292]. Lancet 1988; 1:(8591):921-3.

113. Senior R, Basu S, Kinsey C, et al. Carvedilol prevents remodeling in patients with left ventricular dysfunction after acute myocardial infarction. Am Heart J 1999; 137:(4 I):646-652.

114. Herlitz J, Holmberg S, Pennert K, et al. Goteborg Metoprolol Trial: design, patient characteristics and conduct. Am J Cardiol 1984; 53:(13):3D-8D.

115. 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.

116. Anonymous. A randomized trial of propranolol in patients with acute myocardial infarction. II. Morbidity results. JAMA 1983; 250:(20):2814-9.

117. Lichstein E, Morganroth J, Harrist R, et al. Effect of propranolol on ventricular arrhythmia. Circulation 1983; 67:(6 Pt 2):I5-10.

118. Jafri SM, Khaja F, McFarland T, et al. Efficacy of propranolol therapy after acute myocardial infarction related to coronary arterial anatomy and left ventricular function. Am J Cardiol 1987; 60:(13):976-80.

119. Doughty RN, Rodgers A, Sharpe N, et al. Effects of beta-blocker therapy on mortality in patients with heart failure. A systematic overview of randomized controlled trials. Eur Heart J 1997; 18:(4):560-5.

120. 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.

121. 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.

122. 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.

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

124. 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.

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

126. Eichhorn EJ, Heesch CM, Barnett JH, et al. Effect of metoprolol on myocardial function and energetics in patients with nonischemic dilated cardiomyopathy: a randomized, double-blind, placebo-controlled study. J Am Coll Cardiol 1994; 24:(5):1310-20.

127. Engelmeier RS, O'Connell JB, Walsh R, et al. Improvement in symptoms and exercise tolerance by metoprolol in patients with dilated cardiomyopathy: a double-blind, randomized, placebo-controlled trial. Circulation 1985; 72:(3):536-46.

128. Fisher ML, Gottlieb SS, Plotnick GD, et al. Beneficial effects of metoprolol in heart failure associated with coronary artery disease: a randomized trial. J Am Coll Cardiol 1994; 23:(4):943-50.

129. Olsen SL, Gilbert EM, Renlund DG, et al. Carvedilol improves left ventricular function and symptoms in chronic heart failure: a double blind randomised study. J Am Coll Cardiol 1995; 25:1225-1231.

130. 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.

131. Krum H, Sackner-Bernstein J, Goldsmith RL, et al. Double-blind, placebo controlled study of the long-term efficacy of carvedilol in patients with sever chronic heart failure. Circulation 1995; 92:1499-1506.

132. 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.

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

134. 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.

135. 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.

136. 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.

137. 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.

138. Anonymous. Randomised, 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.

139. 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.

140. 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.

141. Anderson JL, Lutz JR, Gilbert EM, et al. A randomized trial of low-dose beta-blockade therapy for idiopathic dilated cardiomyopathy. Am J Cardiol 1985; 55:(4):471-5.

142. 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.

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

144. 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.

145. 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.

146. 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.

147. 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.

148. 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.

149. 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.

150. 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.

151. 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.

152. Segal JB, McNamara RL, Miller MR, et al. The evidence regarding the drugs used for ventricular rate control. J Fam Pract 2000; 49:(1):47-59.

153. 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.

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

155. 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.

156. 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.

157. 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.

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

159. 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.

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

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

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

163. 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.

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

165. 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.

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

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

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

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

170. 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.

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

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

173. 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.

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

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

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

177. 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.

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

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

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

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

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

183. 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.

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

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

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

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

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

189. 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.

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

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

192. 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.

193. 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.

194. 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.

195. 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.

196. 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.

197. 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.

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

199. 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.

200. 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.

201. 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.

202. 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.

203. 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.

204. 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.

205. 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.

206. 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.

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

208. 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.

209. 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.

Figure 1. Total mortality in patients following myocardial infarction

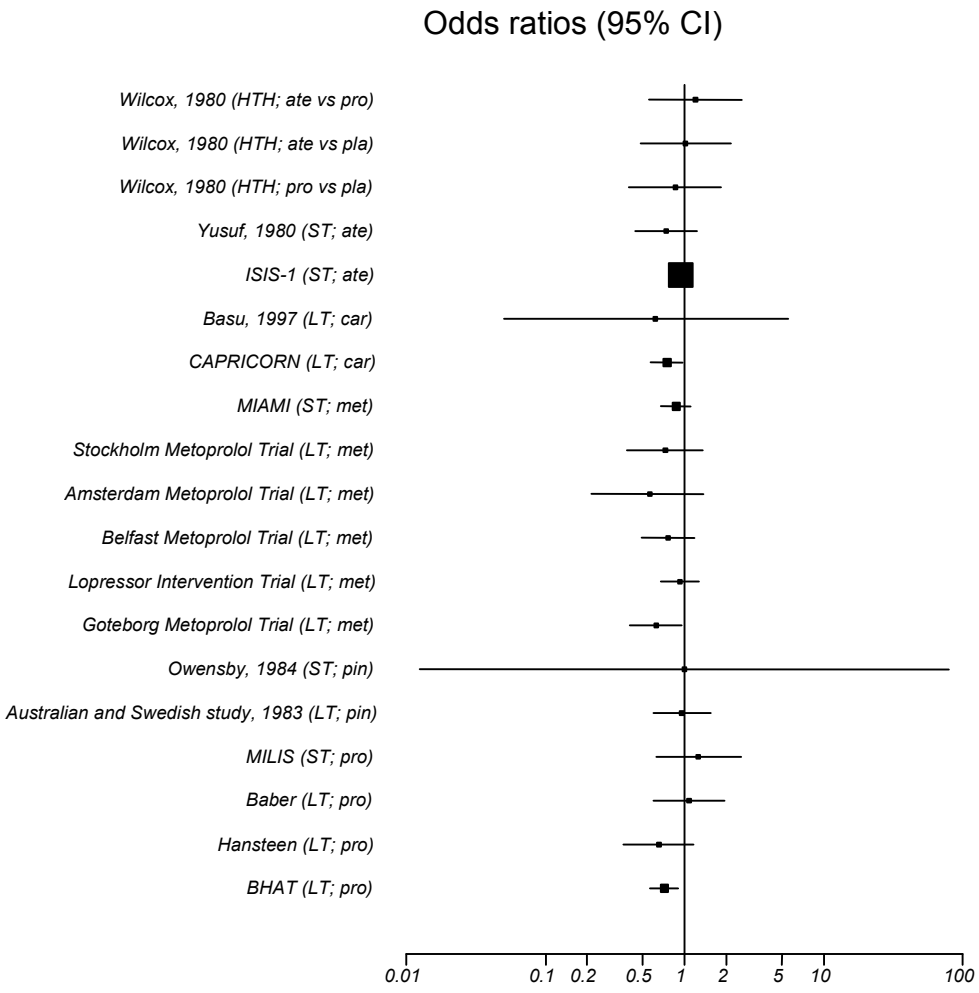
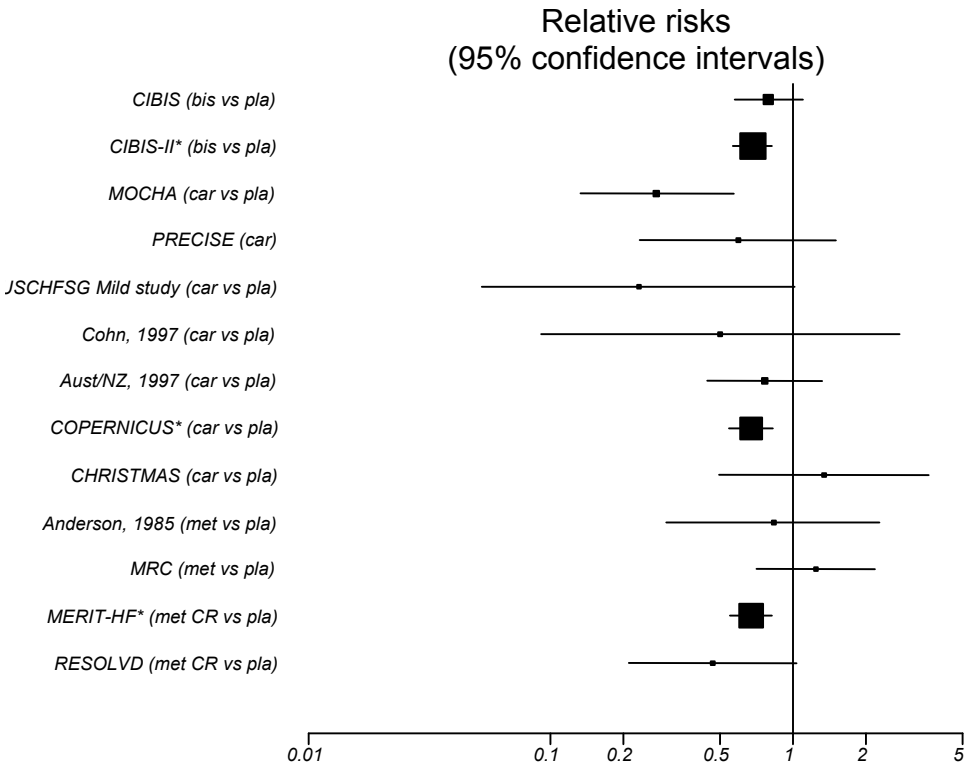


Figure 2. Effect of beta blockers on all-cause mortality in patients with heart failure (placebo-controlled trials)



** Trials with significant findings that analyzed all-cause mortality as primary endpoint*

Evidence Table 1. Placebo controlled trials of beta blockers for hypertension

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Placebo controlled trials measuring Quality of Life outcomes						
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)* Fair quality	RCT	21-65 years old; between 110 and 160% ideal weight (Metropolitan Life Insurance Height-Weight Tables); diastolic BP at baseline of 90-100 mm Hg	History of myocardial infarction, stroke, or asthma, or a serum creatinine level of 177 mmol/d or greater, insulin-dependent diabetes, allergy to thiazides or beta-blockers, pregnancy, or likelihood of difficulty in complying with the interventions	Atenolol (ate) 50 mg Chlorthalidone (chl) 25 mg Placebo (pla)	*Dietary interventions* 1) Usual Diet 2) Low sodium (goal of 52 mmol/d for participants weighing 50 kg or less to 100 mmol/d for those weighing 92 kg) + high potassium (goal: 62 mmol/d to 115 mmol/d) 3) Weight loss group (goal: 4.5 kg or 10% of baseline weight, whichever was greater)	Life Satisfaction Scale Physical Complaints Inventory Symptoms Checklist

Evidence Table 1. Placebo controlled trials of beta blockers for hypertension (continued)

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Placebo controlled trials measuring Quality of Life outcomes				
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)* Fair quality	*Per protocol analysis (n=697)* Mean age=49 56% male 68% white	Previous dug treatment = 66.2% Smokers = 14% Alcohol use (at least once a week) = 39.7%	10, 148 screened/878 eligible/878 randomized	181(20.6%) withdrawn/0 lost to fu/697 analyzed

Evidence Table 1. Placebo controlled trials of beta blockers for hypertension (continued)

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Placebo controlled trials measuring Quality of Life outcomes				
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)* Fair quality	*Per protocol analysis (pla n=232; ate n=238)* *(*negative score indicates improvement)* *Total physical problems: pla=(-0.15); ate=(-0.14) *Overall psychological functioning: pla=(-0.14); ate=(-0.14) Overall life satisfaction: pla=(-0.04); ate=0.02 *Sexual physical problems: pla=(-0.12); ate=(-0.09) *Depression: pla=(-0.15); ate=(-0.14) *Anxiety: pla=(-0.14); ate=(-0.15) *Sleep disturbances: (-0.29); ate=(-0.26) *Fatigue: (-0.20); ate=(-0.15) Satisfaction with physical health: pla=0.21; ate=0.19 Sexual satisfaction: pla=(-0.14); ate=0.04	NR	NR	NR

Evidence Table 1. Placebo controlled trials of beta blockers for hypertension (continued)

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Perez-Stable, 2000 Fair quality	RCT	Patients with mild hypertension, defined as an average diastolic blood pressure between 90 and 104 mm Hg on three readings taken during each of two screening visits 2 weeks apart; aged 18-59	Concomitant use of insulin, bronchodilators, antidepressants or antihypertensive medications within 1 month of screening; coronary artery disease, valcular heart disease, renal insufficiency, cerebrovascular disease, and secondary causes of hypertension	Propranolol (pro) 80-400 mg daily *(n=156)* Placebo (pla) *(n=156)*	NR	*Cognitive Function Test Battery* Stimulus Evaluation/Response Selection Continuous Performance Task(CPT) Digit Symbol Substitution Task(DSST) California Veral Learning Test(CVLT) *Psychological Measures* Center for Epidemiological Studies Depression Scale(CES-D) Beck Depression Inventory(BDI)

Evidence Table 1. Placebo controlled trials of beta blockers for hypertension (continued)

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Perez-Stable, 2000 Fair quality	Age: Pro=4; Pla=45 % male: Pro=67; Pla=66 % White: Pro=76; Pla=71	Current smokers: Pro=10%; Pla=11% Current daily drinkers of alcohol: Pro=11%; Pla=12% Mean DBP: Pro=96; Pla=96 Mean SBP: Pro=140=Pla=141	nr/nr/312	NR/NR/203

Evidence Table 1. Placebo controlled trials of beta blockers for hypertension (continued)

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Perez-Stable, 2000 Fair quality	**Mean changes in:** Selection reaction time(ms): pro=(-3); pla=(-10) ***CPT*** Reaction time(ms): pro=12; pla=6 Correct responses: pro=0; pla=0 Commission errors: pro=(-1); pla=(-1) Omission errors: pro=0.1; pla=0.1 **DSST** correct responses: pro=3; pla=5 ***CVLT*** Monday total: pro=3; pla=1 Tuesday list: pro=2; pla=0 Short-delay free recall: pro=3; pla=2 Short-delay cued recall: pro=4; pla=3 Long-delay free recall: pro=5; pla=4 Long-delay cued recall: pro=5; pla=2 Recognition: pro=3; pla=3 **CES-D:** pro=0; pla=0 **BDI:** pro=(-1); pla=baseline value nr	NR	NR	NR

Evidence Table 1. Placebo controlled trials of beta blockers for hypertension (continued)

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Placebo controlled trials measuring health outcomes						
Anonymous, 1977 Greenberg, 1984 Anonymous, 1985 Miall, 1987 Anonymous, 1988a Anonymous, 1988b Anonymous, 1992 Lever, 1993 UK *Medical Research Council (MRC)* *Fair quality*	RCT Single blind	***Mild hypertension*** Men and women; aged 35-64; with mild hypertension (diastolic BP 90-109 mm Hg, together with systolic pressure below 200 mm Hg)	Secondary hypertension; already on antihypertensive treatment; cardiac failure; MI or stroke within previous 3 months, angina; intermittent claudication; diabetes; gout; asthma; other serious disease; pregnancy	Propranolol (pro) up to 320 mg daily *(n=4403)* Bendrofluazide (ben) 10 mg daily *(n=4297)* Placebo (pla) *(n=8654)* with goal of maintaining DBP below 90 mm Hg x 5 years	Methydopa	Data for terminating events (e.g., strokes, coronary events, all cardiovascular events, and all cause mortality) were analyzed every six months

Evidence Table 1. Placebo controlled trials of beta blockers for hypertension (continued)

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Placebo controlled trials measuring health outcomes				
Anonymous, 1977 Greenberg, 1984 Anonymous, 1985 Miall, 1987 Anonymous, 1988a Anonymous, 1988b Anonymous, 1992 Lever, 1993 UK *Medical Research Council (MRC)* *Fair quality*	Mean age: pro=52; ben=52; pla=52 %male: pro=51.9; ben=52.1; pla=52.3 Race nr	*(Mean values for men/women)* Body weight(kg): pro=81/70; pla=81/70 SBP(mm Hg): pro=158/165; pla=158/165 DBP(mm Hg): pro=98/98; pla=98/98 % cigarette smokers: pro=30/25; pla=32/27 % with LV hypertrophy on ECG: pro=0.3/0.2; pla=0.4/0.4 % with Q-wave abnormalities: pro=1.2/1.7; pla=1.5/1.4 % with history of stroke: pro=0.7/0.7; pla=0.7/0.7	515,000 screened/46,350 eligible/17,354 enrolled	nr/nr/17,354 analyzed

Evidence Table 1. Placebo controlled trials of beta blockers for hypertension (continued)

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Placebo controlled trials measuring health outcomes				
Anonymous, 1977 Greenberg, 1984 Anonymous, 1985 Miall, 1987 Anonymous, 1988a Anonymous, 1988b Anonymous, 1992 Lever, 1993 UK *Medical Research Council (MRC)* *Fair quality*	*# events/rate per 1000 patient years* Strokes: pro=42/1.9; pla=109/2.6 Coronary events: pro=103/4.8; pla=234/5.5 All cardiovascular events: pro=146/6.7; pla=352/8.2 Non-cardiovascular deaths: pro=55/2.5; pla=114/2.7 All deaths: pro=120/5.5; pla=253/5.9	NR	NR	# patients/% Impaired glucose tolerance: pro=43/0.98%; pla=82/0.95% Gout: pro=12/0.27%; pla=14/0.16% Impotence: pro=50/1.14%; pla=20/0.23% Raynaud's phenomenon: pro=75/1.70%; pla=7/0.08% Skin disorder: pro=21/0.48%; pla=7/0.08% Dyspnoea: pro=110/2.5%; pla=10/0.12% Lethargy: pro=104/2.36%; 13/0.15% Nausea/dizziness/headache: pro=103/2.34%; pla=49/0.57% Overall: pro=518/11.76%; pla=202/2.33%

Evidence Table 1a. Quality assessments of placebo controlled trials of beta blockers for hypertension

Author, Year Country	Randomization described	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)*	NR	NR	NR	Mean age=49 56% male	878 randomized 697 analyzed
Perez-Stable, 2000	Adequate: computer-generated list of random numbers	NR	No; statistically significant differences between the two groups on two tests of cognitive function	Fair Mean age=45.5; 66.5% male	312
Anonymous, 1977 Greenberg, 1984 Anonymous, 1985 Miall, 1987 Anonymous, 1988a Anonymous, 1988b Anonymous, 1992 Lever, 1993 Medical Research Council (MRC) UK	NR	NR	Yes	Mean age 52 52.1% male	515,000 screened 46,350 eligible 17,354 enrolled

Evidence Table 1a. Quality assessments of placebo controlled trials of beta blockers for hypertension (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)*	History of myocardial infarction, stroke, or asthma, or a serum creatinine level of 177 mmol/d or greater, insulin-dependent diabetes, allergy to thiazides or beta-blockers, pregnancy, or likelihood of difficulty in complying with the interventions	Yes	NR	Yes	Yes	No
Perez-Stable, 2000	Concomitant use of insulin, bronchodilators, antidepressants or antihypertensive medications within 1 month of screening; coronary artery disease, valcular heart disease, renal insufficiency, cerebrovascular disease, and secondary causes of hypertension	Yes	NR	Yes	Yes	No
Anonymous, 1977 Greenberg, 1984 Anonymous, 1985 Miall, 1987 Anonymous, 1988a Anonymous, 1988b Anonymous, 1992 Lever, 1993 Medical Research Council (MRC) UK	Secondary hypertension; already on antihypertensive treatment; cardiac failure; MI or stroke within previous 3 months, angina; intermittent claudication; diabetes; gout; asthma; other serious disease; pregnancy	Yes	Yes; assessed by an arbitrator igNorant of the treatment regimen	Yes	Yes	Yes

Evidence Table 1a. Quality assessments of placebo controlled trials of beta blockers for hypertension (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)*	NR	Attrition: 181(20.6%); compliance(% of patients taking > 80% of the pills): 92%; others NR	None	Fair	ICI Pharmaceuticals; A.H Robins; National Heart, Lung and Blood Institute	Yes	6 months
Perez-Stable, 2000	NR	45% attrition; others NR	NR	Fair	Public Health Services Grants	Yes	12 months
Anonymous, 1977 Greenberg, 1984 Anonymous, 1985 Miall, 1987 Anonymous, 1988a Anonymous, 1988b Anonymous, 1992 Lever, 1993 Medical Research Council (MRC) UK	NR	Attrition due to primary and adverse events reported; others NR	NR	Fair	Duncan, Flockhart and Co Ltd; Imperial Chemical Industries Ltd; CIBA Laboratories; Merck Sharp and Dohme Ltd	Yes	5 years

Evidence Table 2. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Head to Head trials				
Fair Quality				
Chieffo 1986 Italy Fair quality RCT	Patients with ***comorbid essential hypertension*** (WHO Classes I-II) and stable angina pectoris	Severe bradycardia (< 50 beats per minute); congestive heart failure; myocardial infarction less than three months before the start of the trial; asthma and renal insufficiency	Labetalol 200 mg + chlorthalidone 20 mg (lab+chl) daily *(n=5)* Atenolol 100 mg + chlorthalidone 25 mg (ate+chl) *(n=5)* x 8 weeks	sl ntg
Dorow 1990 Fair quality RCT Crossover	Outpatients aged between 41 and 67 years, suffering from angina pectoris due to coronary artery disease and concomitant reversible, chronic obstructive bronchitis; three angina attacks per week over the last three months (with or without therapy)	Unstable angina or angina at rest; myocardial infarction within the last 6 months; heart failure with or without digitalis treatment; arterial hypertension with supine diastolic blood pressure values under a thiazide diuretic of >/= 105 mm Hg; cardiac arrhythmias requiring treatment; bronchial asthma; restrictive airway disease; pulmonary hypertension; diseases that could impair the implementations of bicycle ergometry	Atenolol (ate) 50 mg daily Bisoprolol (bis) 5 mg daily x 6 months	Diuretics Short-acting and other nitrates Bronchodilators Inhalatory corticoids Antibiotics Mucolytics Expectorants

Evidence Table 2. Randomized controlled trials of beta blockers for angina (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Head to Head trials					
Fair Quality					
Chieffo 1986 Italy Fair quality RCT	Patient daily record	Mean age=56.8 100% male Race nr	NR	NR/NR/10	NR/NR/10 analyzed
Dorow 1990 Fair quality RCT Crossover	Method of measurement of 'Frequency of angina pectoris attacks' nr	Mean age: 55 % Male: 82.5 Race nr	% Smokers: 17.6 % Coronary artery disease: 100 % angina pectoris pretreatment: 80 % MI in case history: 20 % pathological exercise ECG: 100	NR/NR/40	0 withdrawn/1 lost/40 analyzed

Evidence Table 2. Randomized controlled trials of beta blockers for angina (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Head to Head trials					
Fair Quality					
Chieffo 1986 Italy Fair quality RCT	*Effect on angina(# patients with reduced frequency on both 'daily incidence of angina attacks' and 'dosage of sublingual nitroglycerin'):* lab+chl=4/5(80%); ate+chl=3/5(60%)	NR	NR	NR	Comorbid HTN
Dorow 1990 Fair quality RCT Crossover	Angina attacks/week(% decrease in mean): ate=(-82.8%); bis=(-64.3%)	NR	NR	NR	

Evidence Table 2. Randomized controlled trials of beta blockers for angina (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Frishman 1979 United States Fair quality RCT	Patients with angina pectoris due to ischemic coronary artery disease as documented by coronary angiography or previous MI; positive treadmill exercise test showing at least a 1 mm ECG ST segment depression of the ischemic type in association with typical angina pectoris pain; at least 5 attacks of angina pectoris/2 weeks for three months with no evidence for an accelerated course	Co-existent valvular heart disease, congestive heart failure, hypertension, bronchial asthma requiring continued treatment with bronchodilators, severe bradycardia, intermittent claudication, and either myocardial infarction or a coronary artery bypass within 3 months	Pindolol (pin) 10-40 mg daily *(n=23)* Propranolol (pro) 40-240 mg daily *(n=18)* x 8 weeks	Nitroglycerin
van der Does 1999 Europe Fair quality RCT	Male or female (postmenopausal or using reliable contraceptive methods) treated or untreated patients (</=80 years) with chronic angina pectoris, stable for at least preceding 2 months (symptomatic upon exertion and responsive to ntg and/or rest); documented coronary heart disease either by previous angiography (>70% narrowing of a major coronary vessel) or MI (electrocardiogram or cardiac enzymes), or a previous positive exercise test with occurrence of angina and ST-segment depression; capable of performing upright bicycle ergometric exercise tests; not to be at risk while temporarily receiving placebo	Contraindications to study drugs/exercise testing; other forms of angina pectoris (vasospastic, unstable); MI/cardiac surgery within 3 months; main stem stenosis; ventricular aneurysm; marked left ventricular hypertrophy; hypertrophic subaortic stenosis; hemodynamically relevant valcular defects; decompensated cardiac failure; orthostasis; phlebothrombosis; disorders of impulse formation/conduction (resting heart rate <45 beats/min, bundle brach block, pacemaker); obstructive airways disease; insulin-dependent DM; relevant hepatic impairment; gross obesity; alcohol/drug abuse; epilepsy; concomitant drugs interfering with study objectives (e.g., other antianginal agents); other clinical study participation within 30 days	Carvedilol (car) 100 mg daily *(n=247)* Metoprolol (met) 200 mg daily *(n=120)* x 3 months	Nitrates

Evidence Table 2. Randomized controlled trials of beta blockers for angina (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Frishman 1979 United States Fair quality RCT	Patient daily record Treadmill (protocol nr)	Mean age: 55 85.4% male Race nr	*Diagnosis of coronary artery disease* Coronary angiography: 80.5%	NR/NR/40	NR/NR/40 analyzed
van der Does 1999 Europe Fair quality RCT	Erect bicycle ergometric exercise	Mean age: car=62; met=61 %male: car=72; met=71 Race nr	%smokers: car=14; met=19 %systemic hypertension: car=38; met=33 %diabetes mellitus: car=15; met=13 %dyslipidemia: car=32; met=31 %anterior MI: car=9; met=11 %posterior MI: car=18; met=17 %positive angiography: car=23; met=22 %1-vessel disease: car=13; met=10 %2-vessel disease: car=5; met=8 %3-vessel disease: car=5; met=3	nr/393 enrolled/368 randomized	36 withdrawn/lost nr/344 analyzed for efficacy

Evidence Table 2. Randomized controlled trials of beta blockers for angina (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Frishman 1979 United States Fair quality RCT	*Angina attacks/2 weeks(% reduction):* pin=(-41.8%); pro=(-47.0%) *Exercise tolerance(% increase in mets):* pin=(+21.2%); pro=(+18.5%)	NR	Overall incidence: pin=4/23(17.4%); pro=17/18(94.4%) *Pindolol* Nasal stuffiness=1/23(4.3%) Nocturia=1/23(4.3%) Impotence=1/23(4.3%) Palpitations=1/23(4.3%) *Propranolol* Rash=1/18(5.5%) Blurred vision=2/18(11.1%) Fatigue=8/18(44.4%) Dyspnea on exertion=1/18(5.5%) Mild hypotension=5/18(27.8%)	NR	
van der Does 1999 Europe Fair quality RCT	*Per protocol analysis: car=231; met=113* Mean change in total exercise time(s): car=(+60); met=(+60) Mean change in time to angina(s): car=(+77); met=(+76)	Volunteered by subjects or observed by investigator were recorded regardless of their nature and regardless of whether a causal relation to study medication was assumed	*car n=248; met n=120* Any adverse event: car=25%; met=30% <u>Most common AE's, n(%)</u> Dizziness: car=12(4.8), met=6(5.0) Bronchitis: car=9(3.6); met=3(2.5) Asthenia: car=8(3.2); met=3(2.5) Headache: car=8(3.2); met=4(3.3) Back pain: car=6(2.4); met=2(1.7)	AE withdrawals: car=18; met=6	

Evidence Table 2. Randomized controlled trials of beta blockers for angina (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Poor Quality				
Frishman 1989 United States Poor quality RCT	Patients with documented stable angina pectoris and mild to moderate hypertension	Patients with coexistent valvular heart disease, congestive heart failure, bronchial asthma, severe bradycardia (resting heart rate less than 50 beats/min), intermittent claudication, myocardial infarction within 3 months, and age above 70 years or under 18 years	Labetalol (lab) 200-1600 mg daily Propranolol (pro) 80-640 mg daily x 4 months	HCTZ 50 mg daily (if standing DBP > 100 mm Hg)
Placebo controlled trials				
Destors 1989 Europe Fair Quality RCT	Male and female patients who were less than 70 years of age were considered for the study if they had coronary heart disease with chronic angina stabilized for at least 3 months. Women could be included if menopausal for at least 2 years or exhibiting coronary lesions at angiography. Demonstration of at least 8 attacks of angina during the last 14 days or 5 attacks of angina during the last 7 days of the 2-8 week washout period.	Suffering exclusively at rest or had nocturnal attacks; angina pectoris not secondary to atherosclerosis; unstable angina pectoris; so called Prinzmetal's angina or myocardial infarction within the past 6 months; inability to assess pain and fill in diary cards; any contraindication to either active treatment; liver or kidney conditions likely to modify drug metabolism or all reasons preventing close compliance to study protocol	Bepridil (bep) 100-400 mg daily Propranolol (pro) 60-240 mg daily Placebo (pla) x 24 weeks	sl short-acting trinitrine

Evidence Table 2. Randomized controlled trials of beta blockers for angina (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Poor Quality					

Frishman
1989
United States
 	
Poor quality
RCT
	Treadmill ergometer exercise tests (Bruce protocol)
	Patient diary
		Center 1
		Mean age:
		lab=58; pro=57
		Gender (%male):
		lab=66.7;
		pro=100
		Race nr
		Center 2
		Mean age:
		lab=51; pro=58
		Gender(%male):
		lab=100;
		pro=100%
		Race nr
			NR	NR/NR/41	12 withdrawn/1 lost to fu/34 analyzed for efficacy

Placebo controlled trials					

Destors
1989
Europe
 	
Fair Quality
RCT
	Bicycle ergometer x wks 2, 4, 6, 8, 12, 16, 20 & 24
	Patient diary cards x wks 8, 24
		Mean age:
		pla=54.3;
		pro=56.1
		% Male:
		pla=57.1;
		pro=73.1
		Race nr
			History of MI: pla=31.4%; pro=37.2%
			Positive ECG for exercise: pla=77.1%; pro=76.9%
			Positive ECG for attacks: pla=57.1%; pro=56.4%
			Angina duration(mos): pla=69.6; pro=66.6
			Mean weekly attacks: pla=10.3; pro=12.4
			Mean curative ntg tablets/wk: pla=10.6; pro=12.6
			Mean preventive ntg tablets/wk: pla=2.6; pro=3.0
			Mean attack-free days/wk: pla=1.2; pro=1.5
			Mean exercise test duration(min): pla=9.3; pro=9.7
				NR/NR/191	38 withdrawals/15 lost to fu/analyzed 191

Evidence Table 2. Randomized controlled trials of beta blockers for angina (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Poor Quality					
Frishman 1989 United States Poor quality RCT	Total exercise time (%Δ in sec) Center 1: lab=(+7); pro=(+12) Center 2: lab=(+23); pro=(+40) Time to angina onset(%Δ in sec) Center 1: lab=(+29); pro=(+38) Center 2: lab=(+58); pro=(+66) Number of patients with angina endpoint(Δ%) Center 1: lab=(-67); pro=(-63) Center 2: lab=(-38); pro=(-50)	Questioned generally about occurrence of adverse events specifically regarding occurrence of dyspnea, palpitations, sexual dysfunction, GI disturbances and dizziness	NR	NR	Center 1 measured exercise parameters at or close to *peak* drug effect Center 2 measured exercise parameters at or close to *trough* drug effect
Placebo controlled trials					
Destors 1989 Europe Fair Quality RCT	*Angina attacks/week(% reduction)* Week 8: pla=(-49%); pro=(-65%) Week 24: pla=(-77%); pro=(-71%) *Ntg consumption(% reduction)* Week 8: pla=(-57%); pro=(-73%) Week 24: pla=(-79%); pro=(-74%) *Number of attack-free days* Week 8: pla=190; pro=193 Week 24: pla=270; pro=204 Total work(mean % increase): Week 8: pla=13%; pro=48% Week 24: pla=20%; pro=50% Maximum workload(mean % increase): Week 8: pla=6%; pro=27% Week 24: pla=14%; pro=30% Exercise duration(mean % increase): Week 8: pla=7%; pro=22% Week 24: pla=8%; pro=24%	NR	*Number of patients with:* Hypotension: pla=1; pro=4 Bronchospasm: pla=1; pro=1 Allergic reaction: pla=0; pro=1 Raynaud phenomenon: pla=0; pro=1 Fatigue: pla=2; pro=14 Psychiatric problems: pla=1; pro=2 Gastrointestinal problems: pla=2; pro=10 Other: pla=1; pro=6 Any: pla=6; pro=23 Severe coronary events(cardiac death, MI, angina deterioration): pla=2(5.7%); pro=8(10.2%) Development of heart failure/AV block/rhythm disturbances: pla=0; pro=5	Death due to MI(# pts): pla=0; pro=1 CVA(# pts): pla=1; pro=1 Severe clinic events(# pts): pla=1; pro=2 Adverse reaction(# pts): pla=0; pro=1	

Evidence Table 2a. Quality assessments of randomized controlled trials of beta blockers for angina

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Frishman 1989 United States	NR	NR	Not clear	Good mean age=56 91.2% male	34
van der Does 1999 Europe	Block randomization (sets of 6); method of sequence generation nr	NR	Yes	Good mean age >55 higher %male	393 enrolled 368 randomized
Dorow 1990	NR	NR	N/A-crossover	Sample of patients cormorbid with chronic obstructive bronchitis	40

Evidence Table 2a. Quality assessments of randomized controlled trials of beta blockers for angina (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Frishman 1989 United States	Coexistent valvular heart disease, congestive heart failure, bronchial asthma, severe bradycardia (resting heart rate less than 50 beats/min), intermittent claudication, myocardial infarction within 3 months, and age above 70 years or under 18 years	Yes	NR	Yes	Yes	No
van der Does 1999 Europe	Contraindications to study drugs or exercise testing; other forms of angina pectoris (vasospastic, unstable); myocardial infarction or cardiac surgery within 3 months; main stem steNosis; ventricular aneurysm; marked left ventricular hypertrophy; hypertrophic subaortic steNosis; hemodynamically relevant valcular defects; decompensated cardiac failure; orthostasis; phlebothrombosis; disorders of impulse formation/conduction (e.g., resting heart rate <45 beats/min, bundle brach block, pacemaker); obstructive airways disease; insulin-dependent diabetes mellitus; relevant hepatic impairment; gross obesity; alcohol or drug abuse; epilepsy; concomitant drugs interfering with the study objectives (e.g., other antianginal agents); participation in another clinical study within 30 days	Yes	Yes	Yes	Yes	No
Dorow 1990	Unstable angina or angina at rest; myocardial infarction within the last 6 months; heart failure with or without digitalis treatment; arterial hypertension with supine diastolic blood pressure values under a thiazide diuretic of >/= 105 mm Hg; cardiac arrhythmias requiring treatment; bronchial asthma; restrictive airway disease; pulmonary hypertension; diseases that could impair the implementations of bicycle ergometry	Yes	nr	Yes	Yes	Yes

Evidence Table 2a. Quality assessments of randomized controlled trials of beta blockers for angina (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: Differential/high	Score	Funding	Control group standard of care	Length of follow-up
Frishman 1989 United States	NR	Attrition reported; other nr	No	Poor	In part by Schering-Plough	Yes	4 months
van der Does 1999 Europe	NR	Attrition reported; other nr	NR	Fair	Boehringer Mannheim	Yes	3 months
Dorow 1990	N/A	Attrition and compliance reported; others nr	None	Fair	NR	Yes	1 year

Evidence Table 2a. Quality assessments of randomized controlled trials of beta blockers for angina (continued)

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Frishman 1979 United States	NR	NR	Baseline comparisons nr. Run-in mean attack frequencies (95% CI): pin=18.4(17.4-19.4); pro=28.5(26.4-30.6)	Good mean age=55 85.4% male	40 enrolled
Chieffo 1986 Italy	NR	NR	NR	Cormorbid hypertension and angina Good mean age=56.8 100% male	10 enrolled
Placebo controlled trials					
Destors 1989 Europe	NR	NR	Yes	Good mean age=55.3 66.5% male	191 enrolled

Evidence Table 2a. Quality assessments of randomized controlled trials of beta blockers for angina (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Frishman 1979 United States	Co-existent valvular heart disease, congestive heart failure, hypertension, bronchial asthma requiring continued treatment with bronchodilators, severe bradycardia, intermittent claudication, and either myocardial infarction or a coronary artery bypass within 3 months	Yes	NR	Yes	Yes	Yes
Chieffo 1986 Italy	Severe bradycardia (< 50 beats per minute); congestive heart failure; myocardial infarction less than three months before the start of the trial; asthma and renal insufficiency	Yes	NR	Yes	Yes	Yes
Placebo controlled trials						
Destors 1989 Europe	Suffering exclusively at rest or had Nocturnal attacks; angina pectoris Not secondary to atherosclerosis; unstable angina pectoris; so called Prinzmetal's angina or myocardial infarction within the past 6 months; inability to assess pain and fill in diary cards; any contraindication to either active treatment; liver or kidney conditions likely to modify drug metabolism or all reasons preventing close compliance to study protocol	Yes	Yes	Yes	Yes	Yes

Evidence Table 2a. Quality assessments of randomized controlled trials of beta blockers for angina (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: Differential/high	Score	Funding	Control group standard of care	Length of follow-up
Frishman 1979 United States	NR	NR	NR	Fair	Sandoz, Inc.	Yes	8 weeks
Chieffo 1986 Italy	NR	NR	NR	Fair	NR	Yes	8 weeks
Placebo controlled trials							
Destors 1989 Europe	NR	Attrition and compliance reported; others nr	7.8% at week 24	Fair	NR	Yes	24 weeks

Evidence Table 3. Placebo controlled trials of beta blockers for coronary artery bypass graft

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Placebo controlled trials of metoprolol in patients with severe angina post-CABG				
Anonymous (MACB Study Group) 1995 Sweden *Fair quality*	RCT	Patients refered for CABG	Simultaneous valve surgery	Metoprolol (met) 200 mg daily *(n=480)* Placebo *(n=487)* x 2 years Treatment interval: 5-21 days post-CABG
Sjoland 1995 Sweden *Poor quality*	RCT	All CABG patients at 15 regional hospitals in 3 year period	n = 1398 excluded Simultaneous valve surgery = 261(19%) No informed consent = 254 (18%) Need beta blockade = 194 (14%) Age over 75 = 170 (12%) Systolic blood pressure<100 mm Hg = 57 (4%) Severe obstructive pulmonary disease = 62 (4%) In other randomized trials = 61 (4%) Death = 42 (3%) Heart rate < 45 beats/min, severe heart failure, poor peripheral circulation, advanced atrioventricular block or previous participation in study = 87 (6%) Other = 387 (28%)	n= 967 metoprolol (met): 100 mg/day x 2 wks, then 200 mg/day x 2 yrs vs. placebo (pla) x 2 yrs

Evidence Table 3. Placebo controlled trials of beta blockers for coronary artery bypass graft (continued)

Author Year Country	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Placebo controlled trials of metoprolol in patients with severe angina post-CABG					
Anonymous (MACB Study Group) 1995 Sweden *Fair quality*	Aspirin 250 mg daily Dipyridamole TID *Angina* : Long-acting nitrates, Calcium channel blockers *Hypertension:* thiazide diuretic, calcium channel blocker, ACE inhibitor *Supraventricular arrhythmias:* digitalis, disopyramide, calcium antagonist *Ventricular arrhythmias:* class I anti-arrhythmic drug	Endpoints: Ischemic events including death, myocardial infarction, development of unstable angina pectoris, need for coronary artery bypass grafting or percutaneous transluminal coronary angioplasty	Median age: met=64; pla=64 %male: met=84; pla=87 Race: NR	*Previous history of(%):* Angina: met=20.4; pla=20.1 Functional class I: met=0.4; pla=0.4 Functional class II: met=2.5; pla=2.5 Functional class III: met=11.9; pla=12.1 Functional class IV: met=6.0; pla=5.5 Duration of angina (median months): met=36; pla=39 MI: met=11.5; pla=12.5 Hypertension: met=6.9; pla=6.2 Diabetes: met=2.7; pla=2.3 CHF: met=2.9; pla=2.7 CABG: met=0.8; pla=1.0 PTCA: met=1.5; pla=1.0 Smokers: met=2.3; pla=2.5 Ex-smokers: met=12.7; pla=12.5	2365/2365/967
Sjoland 1995 Sweden *Poor quality*	Calcium antagonixts, long-acting nitrates, diuretics for heart failure, digitalis, other treatment for heart failure, antihypertensives, antiarrhythmics, acetylsalicylic acid, anticoagulation	Exercise test after 2 years	Mean age ≥ 65 = (46%) Mean age < 65 =(54%) % male = 85 Race: NR	History: angina pectoris = 949/967 (98%) myocardial infarction = 558/967 (58%) CHF = 129/967 (13%) Hypertension = 334/967 (35%) Diabetes mellitus = 115/967 (12%) Claudication = 105/967 (11%) Cerebrovascular disease = 68/967 (7%) Smoking = 113/967 (12%) Previous smoking = 592/967 (61%) Angina functional class (lo-hi): 1 = 18/967 (2%) 2 = 118/967 (12%) 3 = 554/967 (57%) 4 = 263/967 (27%)	2291 (74 died before screen) 2365 eligible CABG 967 enrolled

Evidence Table 3. Placebo controlled trials of beta blockers for coronary artery bypass graft (continued)

Author Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Placebo controlled trials of metoprolol in patients with severe angina post-CABG					
Anonymous (MACB Study Group) 1995 Sweden *Fair quality*	Total withdrawn: met=165(34%); pla=212(44%) Lost nr Analyzed: met=480; pla=487	Mortality: met=16(3.3%); pla=9(1.8%) Infarct development: met=9(1.9%); pla=10(2.1%) Development of unstable angina pectoris: met=14(2.9%); pla=17(3.5%) Need for CABG: met=2(0.4%); pla=1(0.2%) Need for PTCA=1(0.2%); pla=2(0.4%) Total endpoints: met=42(8.8%); pla=39(8.0%)	NR	NR	Bradycardia: met=12(2%); pla=4(0.8%) (p=0.05) Hypotension: met=6(1%); pla=11(2%) (NS) Congestive heart failure: met=13(3%); pla=6(1%) (NS) Poor peripheral circulation: met=8(2%); pla=13(3%) Atrioventricular block II/III: met=1(0.2%); pla=1(0.2%) Severe obstructive pulmonary disease: met=6(1%); pla=4(0.8%)
Sjoland 1995 Sweden *Poor quality*	Withdrawn = 193/967 (20%) Lost (admin) = 148/967 (15%) Lost (nr) = 8/967 (1%) Analyzed = 618/967 (64%)	Exsercise capacity (median): met = 130W pla = 140W (p=0.02) Angina pectoris at exercise: met = 48/306 (16%) pla = 33/311 (11%) Terminated exercise due to chest pain: met =18/307 (6%) pla = 10/311 (3%) Subjective symptom means: Effort (1-10) : met = 7.6; pla = 7.4 Dyspnoea (0-10): met = 6.6; pla = 6.5 Chest pain (0-10): met = 1.1; pla = 0.6 (p=0.001)	NR	Cardiac events (total): met = 19/307 (6%) pla = 19/311 (6%) Hypotension: met = 6/307 (2%) pla = 4/311 (1%) Bradycardia: met = 7/307 (2%) pla = 1/311 (0.3%)	NR

Evidence Table 3a. Quality assessments of placebo controlled trials of beta blockers for coronary artery bypass graft

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Anonymous (MACB Study Group) 1995	NR	NR	Yes	Median age=64 85.5%male	967
Sjoland 1995	**NR**	NR	No; patients in met group significantly older than those in pla group (p=0.02)	Mean age NR 86.6% male	618

Evidence Table 3a. Quality assessments of placebo controlled trials of beta blockers for coronary artery bypass graft (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Anonymous (MACB Study Group) 1995	Simultaneous valve surgery	Minimal	NR	Yes	Yes	Yes
Sjoland 1995	Simultaneous valve surgery = 261(19%) No informed consent = 254 (18%) Need beta blockade = 194 (14%) Age over 75 = 170 (12%) Systolic blood pressure<100 mm Hg = 57 (4%) Severe obstructive pulmonary disease = 62 (4%) In other randomized trials = 61 (4%) Death = 42 (3%) Heart rate < 45 beats/min, severe heart failure, poor peripheral circulation, advanced atrioventricular block or previous participation in study = 87 (6%) Other = 387 (28%)	Yes	NR	Yes	Yes	No

Evidence Table 3a. Quality assessments of placebo controlled trials of beta blockers for coronary artery bypass graft (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Anonymous (MACB Study Group) 1995	NR	Attrition=38.9%; others NR	NR	Fair	NR	Yes	2 years
Sjoland 1995	NR	Attrition=36.1%; others NR	NR	Poor	NR	Yes	2 years

Evidence Table 4. Placebo controlled trials of beta blockers for silent ischemia

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Pepine 1994 USA *Good quality*	RCT multicenter	Daily life ischemia: asymptomatic and minimally symptomatic (1) documented CAD evidenced by either coronary angiography (>50% diameter stenosis of a major coronary artery) or a previously documented myocardial infarction, and (2) transient ischemia evidenced by abnormalities during an exercise ECG (standard Bruce protocol), thallium-201 uptake, or stress regional wall motion study done within 6 months of study entry.	(1) Unstable angina pectoris, myocardial infarction or coronary revascularization within 3 months (2) ECG abnormality interfering with exercise or AECG ST-segment interpretation (3) Inability to undergo exercise testing (4) Uncontrolled hypertension or other serious condition (medical, psychiatric, cognitive or social) (5) Symptoms requiring antianginal medication other than nitrates (6) Anticipated need for beta blocker or calcium antagonist treatment (7) Heart failure greater than first-degree atrioventricular block, asthma or other contraindications to beta blockade therapy	Atenolol (ate) 100 mg daily titratable to 50 mg vs. placebo (pla) x 52 weeks or until event occurs

Evidence Table 4. Placebo controlled trials of beta blockers for coronary artery disease (continued)

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Pepine 1994 USA *Good quality*	Nitrates, aspirin reported Subset analysis shows no diff in results for nitrate and aspirin use	Exercise ECG + AECG at 4, 15, 26, 39, 52 weeks or whenever interim evaluations were required for symptoms, events or side effects. AECG monitoring done at 4, 26, 52 weeks. Endpoint events = death, VT/TVF, nonfatal myocardial infarction, hospitalization for unstable angina, aggravation of angina requiring antianginal therapy, revascularization.	Ate/pla Age = 64/64 Gender = 90/84% male Ethnic = 92/92% caucasian	Ate/pla % symptomatic = 50/49 nitrates use = 38/32 aspirin use = 62/72 prior MI = 34/40 prior CABG = 25/36 hypertension = 34/26 diabetes = 22/25 active smoking = 7/10 hypercholosterolemia = 23/27 coronary angiography = 76/75	2037/325/306 ate = 152; pla = 154	NR/NR/306

Evidence Table 4. Placebo controlled trials of beta blockers for coronary artery disease (continued)

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Pepine 1994 USA *Good quality*	(1) any events: ate = 17/152 (11%) pla = 39/154 (25%) - ate/pla RR 0.44, CI 0.26-0.75, p = 0.001 (2) serious events (death, VT/VF, MI or hospitalization): ate = 7/152 (4.6%) pla = 13/154 (8.4%) - ate/pla RR 0.55, CI 0.22-1.33 (NS) (2a) death or resuscitated VT/VF: ate = 1/152 (0.65%) pla = 4/154 (2.6%) (NS) (3) Aggravation of angina: ate = 9/152 (5.9%) pla = 26/154 (16.9%) - ate/pla RR 0.35, CI 0.17-0.72, p=.003 (4) Revascularization: ate = 1/152 pla = 0/154 (NS)	NR	Titrated to 50 mg:ate = 36/152 (23.7%) pla = 19/154 (12.3%) bradycardia: ate = 10/152 (6.6%) pla = 0, p=0.001	NR

Evidence Table 4a. Quality assessment of placebo controlled trials of beta blockers for coronary artery disease

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Pepine 1994 USA	Adequate; computer-generated random code	NR	Yes	ate/pla Age = 64/64 Gender = 90/84% male Ethnic = 92/92% caucasian	2037/325/306 ate = 152; pla = 154

Evidence Table 4a. Quality assessment of placebo controlled trials of beta blockers for coronary artery disease (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Pepine 1994 USA	(1) Unstable angina pectoris, myocardial infarction or coronary revascularization within 3 months (2) ECG abnormality interfering with exercise or AECG ST-segment interpretation (3) Inability to undergo exercise testing (4) Uncontrolled hypertension or other serious condition (medical, psychiatric, cognitive or social) (5) Symptoms requiring antianginal medication other than nitrates (6) Anticipated need for beta blocker or calcium antagonist treatment (7) Heart failure greater than first-degree atrioventricular block, asthma or other contraindications to beta blockade therapy	Yes	Yes	Yes	Yes	Yes

Evidence Table 4a. Quality assessment of placebo controlled trials of beta blockers for coronary artery disease (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Pepine 1994 USA	Unclear	NR	NR	Good	ICI/Zeneca	Yes	Avg 10.4 months

Evidence Table 5. Controlled trials in myocardial infarction

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Head to head trials ot beta blockers				
Wilcox 1980 UK *Fair quality*	RCT	Clinical diagnosis of suspected MI within the previous 24 hours	Already taking a beta blocker; severe heart failure; sinus bradycardia of under 40 beats per minute; in second or third degree heart block; systolic BP of >90 mm Hg; history of asthma or diabetes; residence too far away.	Propranolol (pro) 120-160 mg daily Atenolol (ate) 100 mg daily Placebo x one year Treatment initiated within 24 hours post-MI
Trial of atenolol controlled with "standard care"				
Anonymous, 1986 Sleight, 1987 Anonymous, 1988 *First International Study of Infarct Survival (ISIS-1)* *Fair quality*	RCT	Suspected MI thought to be within 12 hours of onset of symptoms.	Already on beta blockers; contraindications to beta blockade; second or third degree heart block; severe heart failure; bronchospasm.	Atenolol (ate) 10 mg iv, followed by 100 mg daily Standard care (con) x 7 days Initial dose loaded intravenously Treatment initiated within 12 hours post-MI

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Head to head trials ot beta blockers				
Wilcox 1980 UK *Fair quality*	NR	Clinic visits at 3-month intervals Cause of death was established from hospital and general practitioners' records and from postmortem reports	Mean age(% patients) <35 yrs: pro=3.8; ate=3.9; pla=2.3 -45 yrs: pro=12.9; ate=10.2; pla=16.3 -55 yrs: pro=33.3; ate=35.4; pla=31.0 -65 yrs: pro=32.6; ate=27.6; pla=31.0 > 65 yrs: pro=17.4; ate=22.8; pla=19.4 % male: Pro=84%; Ate=89%; Pla=81% Race: NR	*Hypertension:* Pro=11%; Ate=10%; Pla=15% *Angina:* Pro=27%; Ate=31%; Pla=24% *Infarction:* Pro=21%; Ate=16%; Pla=19% Drugs being taken for cardiovascular system: Pro=14%; Ate=14%; Pla=20% Drugs taken for other purposes: Pro=14%; Ate=14%; Pla=11%
Placebo controlled trials of atenolol				
Anonymous, 1986 Sleight, 1987 Anonymous, 1988 *First International Study of Infarct Survival (ISIS-1)* *Fair quality*	Diuretic: ate=38%; con=37% iv nitrates: ate=7%; con=8% Calcium antagonists: ate=9%; con=17% Digitalis: ate=11%; con=14% Antiarrhythmics: ate=15%; con=17% Inotropic agents: ate=5%; con=3%	Principal endpoint: vascular death	Mean age = 58.8 % Male = 77 Race: NR	Previous MI = 16.5% Previous diabetes = 6% From pre-randomization ECG: First degree heart block = 2.45% Bundle brach block = 4.41% "Definite" infarction = 44.5%

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Head to head trials ot beta blockers				
Wilcox 1980 UK *Fair quality*	662 screened/388 eligible/388 randomized	Withdrawn=171(44.1%)/lost to fu nr/analyzed=388	Mortality *At 6 weeks:* pro=10(7.5%); ate=11(8,6%); pla=15(11.6%) *At 1 year:* pro=17(12.9%); ate=19(14.9%); pla=19(14.7%)	Side effects separately recorded as either volunteered or elicited
Placebo controlled trials of atenolol				
Anonymous, 1986 Sleight, 1987 Anonymous, 1988 *First International Study of Infarct Survival (ISIS-1)* *Fair quality*	NR/NR/16,027 randomized	112(0.7%) withdrawn/lost to fu nr/16,027 analyzed	Vascular mortality *(original data)* : ate=313/8037(3.89%); con=365/7990(4.57%) (p<0.04) Total mortality *(from Freemantle, 1999 review):* ate=1071/8037(13.3%); con=1120/7990(14.0%) (NS)	NR

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Head to head trials ot beta blockers			
Wilcox 1980 UK *Fair quality*	NR	Withdrawals due to(# pts/%): *Hypotension:* pro=14(10.6%); ate=18(14.2%); pla=2(1.6%) Bradycardia: pro=8(6.1%); ate=9(7.1%); pla=3(2.3%) 2nd degree heart block: pro=3(2.3%); ate=1(0.8%); pla=2(1.6%) 3rd degree heart block: pro=1(0.7%); ate=4(3.1%); pla=2(1.6%) Heart failure: pro=7(5.3%); ate=3(2.4%); pla=8(6.2%) Asthma: pro=1(0.7%); ate=0; pla=0 Other: pro=10(7.5%); ate=16(12.6%); pla=23(17.8%)	
Placebo controlled trials of atenolol			
Anonymous, 1986 Sleight, 1987 Anonymous, 1988 *First International Study of Infarct Survival (ISIS-1)* *Fair quality*	NR	NR	

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Carvedilol				
Basu 1997 UK *Fair quality*	RCT	Chest pain; ECG changes; serum concentration of creatine kinase; MB isoform consistent with diagnosis	Already on ACE or beta blockers; contraindications to ACE or beta blockers; Killip class IV heart failure; cardiogenic shock; severe bradycardia; hypotension; second to third degree heart block; left bundle branch block; severe valvular disease; insulin-dependent DM; renal failure; known malignancy; other severe disease; pregnancy	Carvedilol (car) 2.5-50 mg daily Placebo (pla) x 6 months Initial dose loaded intravenously

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Carvedilol				
Basu 1997 UK *Fair quality*	Aspirin - 100% Heparin - 97% Oral/iv nitrates - 97%	Patients were reviewed at 3-month intervals Exercise test (Bruce protocol) Endpoints: cardiac death, reinfarction, unstable angina, heart failure, emergency coronary revascularization, ventricular arrhythmias requiring intervention, cerebra-vascular accident and initiation of additional cardiovascular drug therapy other than sublingual nitrates for angina	Mean age: car=60; pla=60 % male: car=84; pal=84.5 Race: NR	*Site of MI:* Anterior - Car=51%; Pla=49% Inferior - Car=49%; Pla=51% *Type of MI:* Q-wave - Car=80%; Pla=80% Non-Q-wave - Car=20%; Pla=20% *Heart failure at entry (Killip II/III):* Car=45%; Pla=28% *Thrombolysed:* Car=99%; Pla=96% *Median time to thrombolysis:* Car=3.8 hours; Pla=3.9 hours *Smoker:* Car=67%; Pla=53.5% *Non-smoker:* Car=33%; Pla=46% *Previous IHD:* Car=20%; Pla=25% *NIDDM:* Car=12%; Pla=18% *Median time to infusion:* Car=16.8 hours; Pla=16.7 hours

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Carvedilol				
Basu 1997 UK	416 screened/NR/151 enrolled	146 analyzed (car=75; pla=71)	Serious cardiac events: car=18(24%); pla=31(43.7%) Deaths/reinfarctions: car=11(14.7%); pla=6(8.4%)	NR

Fair quality

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Carvedilol			
Basu 1997 UK	Dizziness(% patients): car=6.5%; pla=1.4%	Withdrawals due to non-cardiac adverse events(# pts): car=4(5.3%); pla=3(4.2%)	
Fair quality			

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Anonymous, 2001 International RCT *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)* Fair quality	RCT	>18 years; stable, definite MI occurring3-21 days prior to randomisation; left-ventricular ejection fraction of 40% or less; receipt of concurrent treatment with ACE inhibitors for at least 48 hours and stable dose for 24+ hours unless proven intolerance to ACE inhibitors; heart failure appropriately treated with diuretics and ACE inhibitorsduring acute phase	Required continued diuretics or inotropes; uncontrollable heart failure; unstable angina; uncontrolled hypertension; bradycardia; unstable insulin-dependent DM; continuing indication for beta blockers for any condition other than heart failure; requiring ongoing therapy with inhaled beta agonists or steroids	Carvedilol (car) up to 50 mg daily Placebo (pla) x 1.3 years (mean) of follow-up

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Anonymous, 2001 International RCT *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)* Fair quality	ACE inhibitors(% patients)=98 Reperfusion therapy(% patients)=46	Patients were reviewed every 3 months during the first year, and every 4 months thereafter	*Carvedilol:* Mean age 63 73% male *Placebo:* Mean age 63 74% male	*Smoking history:* Current - Car=33%; Pla=32% Previous - Car=27%; Pla=25% Never - Car=39%; Pla=43% *Medical history:* Previous MI - Car=31%; Pla=29% Previous angina - Car=57%; Pla=54% Previous hypertension - Car=55%; Pla=52% Previous DM - Car=21%; Pla=23% Other vascular disease - Car=17%; Pla=16% Previous revascularization - Car=12%; Pla=11% Hyperlipidemia - Car=32%; Pla=33% SIte of MI: Anterior - Car=59%; Pla=54% Inferior - Car=21%; Pla=21% Other - Car=20%; Pla=25% Medications at time of randomization: ACE inhibitor - Car=98%; Pla=97% Aspirin - Car=86%; Pla=86%

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Anonymous, 2001 International RCT *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)* Fair quality	NR/NR/1959 randomized	Permanent withdrawals(excluding death): car=192(20%); pla=175(18%)/lost to fu nr/1959 analyzed	*Co-primary endpoints(# patients/%)* All-cause mortality: car=116(12%); pla=151(15%) *(p=0.031)* All-cause mortality or cardiovascular-cause hospital admission: car=340(35%); pla=367(37%) *(NS)* *Secondary endpoints(# patients/%)* Sudden death: car=51(5%); pla=69(7%) *(NS)* Hospital admission for heart failure: car=118(12%); pla=138(14%) *(NS)* *Other endpoints(# patients/%)* Cardiovascular-cause mortality: car=104(11%); pla=139(14%) *(p=0.024)* Death due to heart failure: car=18(2%); pla=30(3%) *(NS)* Non-fatal MI: car=34(3%); pla=57(6%) *(NS)* All-cause mortality or non-fatal MI: car=139(14%); pla=192(20%) *(p=0.002)*	NR

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Anonymous, 2001 International RCT *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)* Fair quality	NR	NR	Original primary endpoint (all-cause mortality) amended during the trial to co-primary endpoints of all-cause mortality (alpha=0.005) and all-cause mortality+cardiovascular hospitalization(alpha=0.045) apparently due to advice by Data Safety Monitoring Board (DSMB) that a blinded interim analysis had shown that power to detect pre-specified total mortality effect size was under threat

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Metoprolol				
Anonymous, 1985 Herlitz, 1990 Hjalmarson, 1997 International *MIAMI* *Fair quality*	RCT	Chest pain of ≥15 minutes duration and/or ECG changes indicating acute MI with estimated onset of 24 hours; age <75	Current treatment with beta blockers or calcium channel blockres (within 48 hours); heart rate ≤65 beats/minute; Systolic BP ≤105 mm Hg; left ventricular failure; poor peripheral circulation; AV-conduction disturbance; severe chronic obstructive pulmonary disease; implanted pacemaker; resuscitation outside hospital; other serious disease; previous MIAMI participation; participation in other randomized trials; unwilling or unable to give informed consent	Metoprolol (met) 15 mg intravenously; 200 mg orally Placebo (pla) Initial dose loaded intravenously (3 injections); then administered orally x 15 days

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Metoprolol				
Anonymous, 1985 Herlitz, 1990 Hjalmarson, 1997 International *MIAMI* *Fair quality*	Cardiac glycosides Diuretics (oral and injections) Antiarrhythmics Nitrates Anticoagulants Atropine Sympathomimetic agents Calcium Channel Blockers Vasodilators Furosemide Narcotic analgesic injections	Mortality: all deaths within the trial period (days 0-15) were recorded and classified	Mean age: met=60; pla=60 % male: met=78; pla=77.2 Race: NR	*Clinical history:* Previous infarction (1)* - Met=16%; Pla=16.1% Angina pectoris (1) - Met=27.7%; Pla=29.5% CHF (1) - Met=3.9%; Pla=3.6% Hypertension (1) - Met=13.6%; Pla=14.1% Diabetes (1) - Met=6.7%; Pla=7.6% Smokers (2) - Met=50.6%; Pla=52.1% *Chronic therapy before admission:* Glycosides (2) - Met=5.3%; pla=6.3% Dluretics (2) - Met=14.1%; Pla=14.8% Antihypertensives (2) - Met=5%; Pla=5.3% Antiarrhythmics (2) - Met=1%; Pla=1.5%

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Metoprolol				
Anonymous, 1985 Herlitz, 1990 Hjalmarson, 1997 International *MIAMI* *Fair quality*	NR/26,439 eligible/5778 randomized	Treatment permanently withdrawn=842(14.6%)/lost to fu=0.04%/5778 analyzed	*Mortality* : met=123/2877(4.3%); pla=142/2901(4.9%); Odds ratio=0.87(95% CI: 0.67-1.12); NS	NR

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Metoprolol			
Anonymous, 1985 Herlitz, 1990 Hjalmarson, 1997 International *MIAMI* *Fair quality*	*Adverse cardiac events(# patients; %)* VT, electrically converted: pla=40(1.4%); met=37(1.3%)(NS) Asystole: pla=64(2.2%); met=74(2.6%)(NS) Bradycardia: pla=138(4.8%); met=372(12.9%)(p<0.001) AV-block I: pla=72(2.5%); met=95(3.3%)(NS) AV-block II-III: pla=153(5.3%); met=160(5.6%)(NS) Atrial fibrillation/flutter: pla=298(10.3%); met=238(8.3%)(p<0.01) Other SVT: pla=265(9.1%); met=125(4.4%) Hypotension: pla=284(9.8%); met=530(18.4%) Congestive heart failure: pla=660(22.8%); met=699(24.3%) Cardiogenic shock: pla=93(3.2%); met=86(3.0%)	Withdrawals due to: *(# patients/%)* Hypotension: pla=76(2.6%); met=136(4.7%)(p<0.001) AV-block: pla=40(1.4%); met=59(2.0%)(NS) Heart failure: pla=64(2.2%); met=93(3.2%)(p=0.02) Bradycardia: pla=34(1.2%); met=85(2.9%)(p<0.001)	

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Anonymous 1987 USA *Lopressor Intervention Trial* *Fair quality*	RCT	Ages 45-74; hospitalized for acute MI	History of CABG; permanent pacemaker; contraindication to beta blocker therapy; conditions likely to require beta blocker therapy; administration of any beta blocker within 3 days before the start of pre-entry evaluation; planned therapy with aspirin, sulfinpyrazone clofibrate;=, or dipyridamole; life threatening conditions other than CHF; conditions likely to affect protocol compliance; history of adverse reaction to metoprolol or its analogues.	Metoprolol (met) 200 mg daily Placebo (pla) x 1 year Treatment interval: 5-15 days post-MI
Hjalmarson, 1981 Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* *Good quality*	RCT	Geographic location; chest pain of acute onset and 30 minutes' duration or ECG signs of acute MI with estimated onset of infarction within previous 48 hours; age 40-74;	Contraindications to beta blockade; need for beta blockade; administrative considerations	Metoprolol (met) 15 mg intravenously; 200 mg orally Placebo (pla) Treatment interval(mean): 11.3 hours Initial dose loaded intravenously (3 injections); then administered orally x 3 months

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Anonymous 1987 USA *Lopressor Intervention Trial*		Interim visits conducted at 1, 3, 7 and 12 months	Mean age = 58 % Male = 83% % White = 90.5%	*Previous medical history:* MI = 14.5% Angina = 25% CHF = 2% Hypertension = 36% Diabetes = 7.5% Location of infarct: Anterior = 50.3% Inferior = 56% Anterior & inferior = 2% High lateral = 2.5% True subendocardial = 2.5%
Hjalmarson, 1981 Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* *Good quality*	*Arrhythmias:* iv lidocaine or procainamide *CHF:* furosemide 40-80 mg iv, then oral *Chest pain:* iv morphine; sl ntg; oral anticoagulants	Physician examination at 1-week and 3 months after inclusion	*Entire sample:* Mean age: met=60; pla=60 % male: met=75.6; pla=76.2 Race nr *Subgroup of patients with indirect signs of mild-to-moderate CHF (met n=131; pla n=131)* Mean age: met=63; pla=63 % male: met=75; pla=76 Race nr	*Clinical history:* Previous infarction - Met=21.2%; Pla=22.7% Angina pectoris - Met=35.7%; Pla=34.7% Hypertension - Met=29.1%; Pla=29.7% Smoking - Met=49.7%; Pla=50.3% *Clinical status at entry:* Pulmonary rales (24) - Met=11.6%; Pla=9% ECG signs of infarction (1) - Met=49.9%; Pla=47.8% Heart rate >100 beats/minute (1) - Met=4.7%; Pla=6.2% Systolic BP <100 mm Hg (2) - Met=3.3%; Pla=4.4% *Dyspnea at onset of pain (29) - Met=28.8%; Pla=30.8%*

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Anonymous 1987 USA *Lopressor Intervention Trial*	NR/NR/2395 enrolled	Withdrawn: met=381(31.9%); pla=355(29.6%)/lost to fu NR/anayzed=2395	Total mortality (# patients/%) *</= 90 days:* met=23(1.9%); pla=37(3.1%) *</= 210 days:* met=42(3.5%); pla=54(4.5%) *</= 365 days:* met=65(5.4%); pla=62(5.2%) *</= 540 days:* met=86(7.2%); pla=93(9.8%)	NR
Hjalmarson, 1981 Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* *Good quality*	2802 screened/2619 eligible/1395 randomized (met n=698; pla n=697)	Withdrawn: met=131(19.1%); pla=131(19.1%)/lost to fu nr/1395 analyzed	*Entire sample:* Mortality: met=40/698(5.7%); pla=62/697(8.9%); Odds ratio=0.62(95% CI=0.40-0.96) Reinfarction: met=35/698(5%); pla=54/697(7.7%); Odds ratio=0.63(95% CI=0.39=0.99) *Subgroup with mild-to-moderate CHF:* Mortality: met=13/131(10%); pla=25/131(19%); Odds ratio=0.47(95% CI=0.21=1.0); p=0.036 Reinfarction: met=9/131(7%); pla=10/131(8%); NS	NR

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Anonymous 1987 USA *Lopressor Intervention Trial*	*Overall incidence:* met=34.6%; pla=23.8% Incidence of (%): Body as a whole: met=9.1; pla=6.2 Cardiovascular: met=17.2; pla=9.6 Digestive: met=4.3; pla=3.3 Endocrine: met=0; pla=0 Haemic/lymphatic: met=0.2; pla=0.2 Metabolic/nutritional: met=1.2; pla=0.5 Musculoskeletal: met=0.3; pla=0.4 Nervous system: met=8.7; pla=7.7 Respiratory: met=4.1; pla=2.7 Skin/appendages: met=1.3; pla=1.5 Special senses: met=2.8; pla=1.3 Urogenital system: met=1.6; pla=1.0	*Overall withdrawal due to adverse events(%):* met=13.1; pla=5.8	
Hjalmarson, 1981 Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* *Good quality*	NR	Withdrawals due to overall adverse events: met=22(3.2%); pla=22(3.2%) *Withdrawals due to(# pts/%):* Hypotension: met=29(4.2%); pla=13(1.9%) (p=0.018) Bradycardia: met=18(2.6%); pla=5(0.7%) (p=0.011) Heart failure: met=4(0.6%); pla=7(1.0%) (NS)	

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Olsson, 1985 *Stockholm Metoprolol Trial* *Fair quality*	RCT	Residence within catchment area; admission to coronary care unit within 48 hours from onset of symptoms and development of acute MI; sinus rhythm without complete bundle branch block.	Systolic BP <100 mm Hg; sever cardiac failure not responding to digitalis or diuretics; severe intermittent claudication; obstructive pulmonary disease; need for beta-adrenoceptor blockade; other major disease; unwillingness to participate.	Metoprolol (met) 200 mg daily Placebo (pla) x 36 months Treatment interval: 48 hours post-MI
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* *Fair quality*	RCT	Admission to CCU at Ulster Hospital	Delay from onset of pain exceeded 6 hours; initial rhythm VF; initial rhythm agonal; systolic BP >90 mm Hg associated with heart rate <100 beats min-1; clinical pulmonary edema or CHF; sinus or junctional bradycardia (<60 min-1), with systolic BP >90 mmHg and not responding to patient's legs elevated; received a beta-adrenergic blocking drug or a type I antiarrhythmic drug during previous 48 hours; atrio-ventricular block greater than first degree; previous admission to the study.	Metoprolol (met) 15 mg iv, followed by 200 mg oral daily dosage Placebo (pla) x 1 year Treatment interval: 48 hours post-mi

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Olsson, 1985 *Stockholm Metoprolol Trial* *Fair quality*	*Angina:* non-beta-andrenergic blocking antianginal agents	Interim visits conducted every 3 months	Mean age: met=60; pla=59 % male: met=78; pla=83 Race = NR	Smokers: Met=53%; pla=60% Ex-smokers: Met=19%; Pla= 18% Previous MI: Met=24.5%; Pla=26.5% DM before MI: Met=10%; Pla=6% Cerebrovascular incidence before MI: Met=5%; Pla=3% Site of infarction: Anterior: Met=44%; Pla=51% Inferior: Met=38%; Pla=31% Unknown: Met=18%; Pla=18%
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* *Fair quality*	NR	NR	Age ≤65 = 548 >65 = 252 % Male 71.5% Race: NR	Previous MI = 26.75% Hypertension = 11.5 % Smoking habit = 47% Previous history of angina = 46.25% Previous history of dyspnoea = 28.38% Initial ventricular ectopic activity = 22.88% Initial supraventricular ectopic activity = 5%

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Olsson, 1985 *Stockholm Metoprolol Trial* *Fair quality*	nr/nr/301	73(24.2%) withdrawn/lost to fu nr/301 analyzed	*Sample size: met n=154; pla n=147* *Total mortality (# patients/%):* pla=31(21.1%); met=25(16.2%) (NS) *Cardiac mortality (# patients/%):* pla=29(19.7%); met=20(13.0%) (NS) *Sudden death (# patients/%):* pla=21(14.3%0; met=9(5.9%) (p<0.05) Reinfarction (# patients/%): pla=31(21.1%); met=18(11.7%) (p<0.05)	NR
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* *Fair quality*	1556 screened/800 eligible/800 enrolled	Withdrawn nr/lost to fu nr/800 analyzed	Total mortality (# patients/%) *At 3 months:* met=37/416(8.9%); pla=35/384(9.1%)(NS) *At one year:* met=52/416(12.5%); pla=53/384(13.8%)(NS) Sudden death (# patients/%) *At 3 months:* met=4/416(1.0%); pla=3/384(2.1%)(NS) *At one year:* met=8/416(1.9%); pla=18/384(4.7%) (p<0.05)	NR

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Olsson, 1985 *Stockholm Metoprolol Trial* *Fair quality*	NR	Withdrawals due to (# patients/%): *Uncontrolled angina:* pla=16(10.9%); met=6(3.9%) (p<0.05) *Heart failure:* pla=1(0.7%); met=7(4.5%) (p<0.05) *Symptomatic bradycardia:* pla=1(0.7%); met=1(0.6%) (NS) *Hypotension:* pla=0; met=2(1.3%)	
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* *Fair quality*	# patients (%) Hypotension: met=20/416(4.8%); pla=14/384(3.6%) (NS) Heart failure: met=47/414(11.4%); 35/378(9.3%) (NS)	NR	

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Pindolol				
Australian & Swedish Study 1983 Australia, Sweden *Fair quality*	RCT	Clinical diagnosis of acute MI within previous 21 days; had to meet 2 of the following criteria: retrosternal severe chest pain of 20+ minutes duration, resistant to nitroglycerine and startinh in previous 48 hours; pulmonary edema without previously known valvular disease; shock without suspicion of acute hypovolaemia or intoxication; transient elevation of glutamine oxaloaecetic acid transminase or asptarate amino transferase in serum to values exceeding the normal limits for the laboratory on at least 2 readings with a maximum approximately 24 hours after the estimated onset of infarction, coupled with absent or less pronounced elevation of glutamine pyruvic acid transaminase or alinine amino transferase in serum; ECG series with presence of Q waves and/or presence of the disappearance of localized ST-elevation combined with development of T-inversion in at least 2 of the routine 12 leads; clinical course complicated by electrical and/or mechanical complications.	Uncontrolled heart failure; unrelated heart disease; persistent heart block of second or third degree; persistent bradycardia <50 beats/minute; obstructive airways disease; uncontrollable inslulin dependent diabetes; known hypersensitivity to beta blocking drugs; other diseases serious enough to worsen the short-term prognosis irrespectively of the MI; pregnancy; necessity to use beta blocking druga or calcium antagonists; unable to return for regular control.	Pindolol (pin) 15-20 mg daily Placebo (pla) x 24 months Treatment interval: up to 21 days post-MI

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Pindolol				
Australian & Swedish Study 1983 Australia, Sweden *Fair quality*	NR	Follow-up visits: months 1, 3, 6, 12, 18 and 24 Primary endpoint: death	*Mean Age:* Pin=58; Pla=58 % male: Pin=83; Pla=83 Australian: Pin=48%; Pla=48% Swedish: Pin=52%; Pla=51.5%	*History:* Smoking: Pin=48%; Pla=43% Hypertension: Pin=24%; Pla=28% (values indicated are those with a 10% or greater variation between patients randomized to pin. or pla.) Angina pectoris: Pin=36%; Pla=32% Functional limitation: Pin=30%; Pla=30% Prior MI: Pin=18%; Pla=16% Diabetes: Pin=5%; Pla=8% (values indicated are those with a 10% or greater variation between patients randomized to pin. or pla.) *Anterior or lateral infarction:* Pin=47%; Pla=46% *Other site of infarction:* Pin=53%; Pla=54% *Medication used at time of randomization:* Digitalis: Pin=31%; Pla=34% Diuretics: 74%; Pla=75% Vasodilators (nitrates): Pin=23%; Pla=22% Antiarrhythmics: Pin=54%; Pla=51% Anticoagulants: Pin=72%; Pla=71% *Medication used at time of discharge:* Digitalis: Pin=31%; Pla=32% Diuretics: Pi46%; Pla=42% Nitrates: Pin=39%; Pla=35%

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Pindolol				
Australian & Swedish Study 1983 Australia, Sweden	2500 screened/529 eligible/529 enrolled	126(23.8%) withdrawn/lost to fu nr/529 analyzed (pin n=263; pla n=266)	*(# patients/%)* *Total mortality:* pla=47(17.7%); pin=45(17.1%) (NS) *Cardiac death:* pla=43(16.2%); pin=40(15.2%) (NS) *Cardiac sudden death:* pla=31(11.7%); pin=28(10.6%) (NS) *Non-cardiac death:* pla=4(1.5%); pin=5(1.9%)	NR
Fair quality				

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Pindolol			
Australian & Swedish Study 1983 Australia, Sweden *Fair quality*	Overall incidence: pin=89(33.8%); pla=45(16.8%) (p=0.0001)	Withdrawals due to adverse events (# patients/%): pin=50(19%); pin=22(8.3%) (p=0.0003) Withdrawals due to: *Cardiac failure:* pin=20(7.6%); pla=11(4.1%) Hypotension: pin=3(1.1%); pla=1(0.4%) Reinfarction: pin=1(0.4%); pla=3(1.1%)	

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Propranolol				
Roberts, 1984 Rude, 1986 Roberts, 1988 United States *Multicenter Investigation of the Limitation of Infarct Size (MILIS)* *Fair-poor quality*	RCT Single-blind	Age <76; history of at least 30 minutes of ischemic pain within 18 hours of potential therapy; new or presumably new ECG changes	Cardiogenic shock; advanced cardiac or other disease that would interfere with prognosis; participation in conflicting protocol; inability to particpate because of geographical or psychological reasons; recent major surgery or MI; permanent cardian pacemaker; previous participation in the protocol; failure or inability to give informed consent	Propranolol (pro): initial dose infused intravenously (0.1 mg per kg of body weight); subsequent oral dosing initiated at 20 mg and increased with an HR target of 45-60 BPM Placebo (pla) x 7 days

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Propranolol				
Roberts, 1984 Rude, 1986 Roberts, 1988 United States *Multicenter Investigation of the Limitation of Infarct Size (MILIS)* *Fair-poor quality*	NR	Follow-up visits: months 3 and 6 Telephone vital status interview: 6-month intervals thereafter	Mean age: pro=54.9; pla=54.6 % male: pro=72.4; pla=74.1 % white: pro=82.1; pla=83.7	Mean age = 54.7 Male = 73.2% White = 83% Current smokers = 50% White collar workers = 39% High school or higher education = 61.3% Regular drinkers = 22% Medical history before recent infarction: Hypertension requiring medication = 44% Documented previous infarction = 14.5% Angina >3 weeks before recent infarction = 39% CHF in previous 3 weeks = 5% Diabetes = 19% Previous cardiac arrest = 0.7% Previous cardiac surgery = 5% Previous cardiac arrythmias = 7%

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Propranolol				
Roberts, 1984 Rude, 1986 Roberts, 1988 United States *Multicenter Investigation of the Limitation of Infarct Size (MILIS)* *Fair-poor quality*	Screened=7597/ Eligible=2408/Eligible after application of exclusion criteria=1589/Eligible for Group A (no contraindications to beta blocker therapy)=879 (pro n=134; pla n=135; hyaluronidase=131)	Overall patient withdrawals nr/lost to fu=1(treatment group nr)/analyzed=269	Mortality(after 36-months of follow-up): pro=24/134(17.9%); pla=20/135(14.8%) Treatment period=10 days Beta blockade at 3 months(% pts): pla=37%; pro=53% Beta blockade at 6 months(% pts): pla=40; pro=54	NR

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Propranolol			
Roberts, 1984 Rude, 1986 Roberts, 1988 United States *Multicenter Investigation of the Limitation of Infarct Size (MILIS)* *Fair-poor quality*	Cardiac failure (%): pla=23; pro=19	NR	

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Balcon, 1966 *Fair quality*	RCT	Symptoms suggestive of acute MI	Complete heart block complicating an acute myocardial infarction; unconscious	Propranolol (pro) 80 mg daily Placebo (pla) x 28 days Treatment interval: 24 hours

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Balcon, 1966 *Fair quality*	Anticoagulants Analgesics Digitalis Diuretics Vasopressors	Follow-up visit schedule nr	Mean age=59.8 69.2% male Race nr	NR

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Balcon, 1966 *Fair quality*	nr/155 eligible/114 enrolled	Overall withdrawals nr/lost to fu nr/114 analyzed	pro n=56; pla n=58 *Outcomes (# patients/%):* Total death: pro=13(23.2%); pla=14(24.1%) Sudden death: pro=7(12.5%); pla=6(10.3%) Heart failure: pro=2(3.6%); pla=2(3.4%)	*Heart failure:* presence of an elevated jugular-venous pressure, triple rhythm, edema of the ankles, persistent basal rales, or radiological evidence of pulmonary edema *Hypotension:* presence of a systolic blood-pressure below 90 mm Hg with or without other features of the shock syndrome *Hypotension with sinus bradycardia:* presence of a systolic blood-pressure below 90 mm Hg and sinus bradycardia with a heart rate of less than 60 per minute with or without other features of the shock syndrome

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Balcon, 1966 *Fair quality*	*Incidence(# patients/%)* Heart failure: pro=30(53.6%); pla=33(56.9%) Hypotension: pro=29(51.8%); pla=22(37.9%) Hypotension with sinus bradycardia: pro=17(30.4%); pla=8(13.8%)	NR	

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Bath, 1966 *Fair quality*	RCT	Presence of any two of the following criteria: 1) characteristic clinical presentation; 2) electrocardiogram changes of recent infarction (pathological Q waves and ST/T chages) or evidence of acute ischemia (ST/T wave only; 3) elevation of serum-glutamic-oxaloacetic-trans-aminase(SGOT), serum-lactate-dehydrogenase(SLDH), or serum-hydroxybutyric-dehydrogenase (SHBD) above the normal for the hospital	Diagnostic criteria not fulfilled; there was evidence of bronchospasm or a clinical history of bronchial asthma; the heart-rate was less than 60 per minute persisting throughout a 24-hour period; systolic blood-pressure was less than 80 mm Hg after admission	Propranolol (pro) 80 mg daily Placebo (pla) x 28 days Treatment interval: 24-48 hours
Norris, 1968 *Fair quality*	RCT	Clinical and electrocardiographic evidence of myocardial infarct	Shock, heart failure, heart block, sinus bradycardia; acute pulmonary edema; systolic blood pressure below 80 mm Hg	Propranolol (pro) 80 mg daily Placebo (pla) x 3 weeks Treatment interval: up to 3 days

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Bath, 1966 *Fair quality*	Anticoagulants Digitalis Diuretics Quinidine Procainamide Pain relieving drugs	Follow-up visit schedule: Weekly intervals	Mean age=58 79.5% male Race nr	nr
Norris, 1968 *Fair quality*	nr	Progress recorded three times weekly on ward rounds	NR	NR

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Bath, 1966 *Fair quality*	nr/nr/226 enrolled	31(13.7%) withdrawn/lost to fu nr/195 analyzed	Death: pro=15/100(15%); pla=12/95(12.6%) Sudden death: pro=7/100(7%); pla=9/95(9.5%) Death due to heart failure: pro=3/100(3%); pla=3/95(3.2%)	nr
Norris, 1968 *Fair quality*	839 screened/536 admitted/454 randomized	36(7.9%) withdrawn/lost to fu nr/454 analyzed	pro n=226; pla n=228 *Outcomes(# patients/%)* Total death: pro=31(13.7%); pla=24(10.5%) Arrhythmia or sudden death: pro=20(8.8%); pla=17(7.4%) Heart failure: pro=3(1.3%); pla=3(1.3%)	NR

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Bath, 1966 *Fair quality*	*Incidence(# patients/%)* Heart failure: pro=31/100(31%); pla=14/95(14.7%0 Hypotension: pro=19/100(19%); pla=10/95(10.5%)	*Withdrawals due to(# patients/%):* Hypotension: 3/100(3%); pla=2/95(2.1%) Bradycardia: pro=0; pla=2/95(2.1%)	
Norris, 1968 *Fair quality*	*Incidence(# patients/%)* Heart failure: pro=17(7.5%); pla=19(8.3%) Hypotension: pro=11(4.9%); pla=8(3.5%)	*Incidence of withdrawals (# patients/%)* Heart failure: pro=3(1.3%); pla=5(2.2%) Hypotension: pro=7(3.1%); pla=4(1.7%) Heart block: pro=2(0.9%); pla=1(1.3%) Bradycardia: pro=6(2.6%); pla=0	

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)* *Fair quality*	RCT	Men and women aged 30-69; hospitalized with symptoms and ECG and enzymatic changes compatible with acute MI	Chronic obstructive lung disease; severe CHF; bradycardia; life-threatening illness other than CHF; need for beta blocking drugs	Propranolol (pro) 180 mg (82% of patients) or 240 mg (18% of patients) *(n=1916)* Placebo (pla) *(n=1921)* Treatment initiated 5-21 days post-MI

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)* *Fair quality*	*% patients* Vasodilator: pro=47.8; pla=47.1 Diuretic: pro=40.8; pla=42.3 Tranquilizer: pro=28.0; pla=30.4 Digitalis: pro=26.9; pla=26.3 Aspirin: pro=21.5; pla=21.6 Antiarrhythmic: pro=20.7; pla=25.6 Potassium: pro=16.3; pla=17.7 Antihypertensive, excluding diuretic: pro=11.8; pla=13.4 Anticoagulant: pro=9.8; pla=8.5 Dipyridamole: pro=6.2; pla=5.5 Insulin: pro=4.8; pla=4.2 Hormonal: pro=4.5; pla=4.4 Oral hypoglycemic: pro=5.5; pla=3.2 Sulfinpyrazone: pro=4.3; pla=5.0	Clinic visits at 3-month intervals Deaths classified by blinded mortality classification subcommittee (relative/witness report; death certificates; attending physician; hospital records; autopsy)	*Propranolol:* Mean age: 54.7 84% male *Placebo:* Mean age: 54.9 85.1% male	*Mean systolic BP mm Hg:* Pro=112.3; Pla=111.7 *Mean diastolic BP mm Hg:* Pro=72.5; Pla=72.3 *Mean heart rate, beats per minute:* Pro=76.2; Pla=75.7 *Mean cholesterol, mg/dL:* Pro=212.7; Pla=213.6 *Mean weight, kg:* Men - Pro=80.2; Pla=79.8 Women - Pro=67.4; Pla=66.5 *Current smoker* : Pro=57.4%; Pla=56.9% *Medical history:* Prior MI - Pro=13.9%; Pla=13.2% Hypertension - Pro=41.1%; Pla=40.1% Angina pectoris - Pro=35.8%; Pla=36.5% CHF - Pro=9%; Pla=9.4% DM - Pro=11.7%; Pla=11.3% *Taking propranolol or other beta blocker:* Pro=7.2%; Pla=6.8% *In-hospital events occurring before randomization:* Atrial fibrillation - Pro=6.8%; Pla=5.7% CHF - Pro=14.3%; Pla=14.9% Vetricular tachycardia - Pro=23%;

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)* *Fair quality*	Screened: 16,400 Eligible/enrolled (total=3,837): pro=1916; pla=1921	Overall number withdrawn nr/12(0.3%) lost to fu/3837 analyzed (pro n=1916; pla n=1921)	*NNT; RR (95% CI)* ***Total mortality:*** NNT=39; RR=0.73(0.59-0.91) ***Deaths due to:*** ***Cardiovascular disease:*** NNT=44; RR=0.74(0.59-0.93) ***Sudden arteriosclerotic heart disease:*** NNT=78; RR=0.72(0.53-0.99) ***Non-sudden arteriosclerotic heart disease:*** NNT=97; RR=0.73(0.52-1.03) ***Other cardiovascular disease:*** NNT=1882(harm); RR=1.14(0.43-3.03) ***Noncardiovascular disease:*** NNT=322; RR=0.65(0.31-1.36)	NR

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Anonymous, 1982	*% patients with complaints:*	*% patient wihdrawals due to:*	
Goldstein, 1983	Shortness of breath: pro=66.8; pla=65.5	CHF: pro=4; pla=3.5 (NS)	
Anonymous, 1983	Bronchospasm: pro=31.3; pla=27.0	Hypotension: pro=1.2; pla=0.3 (p<0.005)	
Lichstein, 1983	(p<0.005)	Pulmonary problems: pro=0.9; pla=0.7 (NS)	
Furberg, 1984	Rapid heartbeat: pro=10.8; pla=15.1	Sinus bradycardia: pro=0.7; pla=0.3 (NS)	
Jafri, 1987	(p<0.001)	New or extended MI: pro=0.4; pla=0.4 (NS)	
United States	Cold hands, feet: pro=10.0; pla=7.7	Serious ventricular arrhythmia: pro=0.3; pla=1.0 (p<0.025)	
	(p<0.025)	Heart block: pro=0.1; pla=0.1 (NS)	
Beta-blocker	Tiredness: pro=66.8; pla=62.1	Syncope: pro=0.1; pla=0.1 (NS)	
Heart Attack Trial	(p<0.005)	Tiredness: pro=1.5; pla=1.0 (NS)	
(BHAT)	Reduced sexual activity: pro=43.2;	Disorientation: pro=0.6; pla=0.6(NS)	
	pla=42	Depression: pro=0.4; pla=0.4 (NS)	
Fair quality	Depression: pro=40.7; pla=39.8	Faintness: pro=0.5; pla=0.2 (NS)	
	Nightmares: pro=39.7; pla=36.9	Nightmares: pro=0.1; pla=0.2 (NS)	
	Faintness: pro=28.7; pla=26.6	Insomnia: pro=0.2; pla=0.0 (NS)	
	Insomnia: pro=21.1; pla=18.8	Reduced sexual activity: pro=0.2; pla=0.0 (p<0.05)	
	Blacking out: pro=9.1; pla=10.3	GI problems: pro=1.0; pla=0.3 (p<0.01)	
	Hallucinations: pro=5.9; pla=4.5	Dermatologic problems: pro=0.3; pla=0.1 (NS)	
	Diarrhea: pro=5.5; pla=3.6 (p<0.01)	Cancer: pro=0.2; pla=0.1 (NS)	

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Hansteen 1982 Norway *Fair quality*	RCT	MI according to WHO criteria, screened on fourth day after MI, only those with increased risk of death were included.	Cotraindications to beta blockade; uncontrolled heart failure	Propranolol (pro) 160 mg daily Placebo (pla) x 12 months Treatment interval: 4-6 days post-MI
Baber 1980 Multinational *Fair quality*	RCT	Diagnosis of anterior MI based on ECG abnorm,alities od an anterior infarction described as "very probable" on WHO ECG criteria; either a typical history or serum enzyme levels (AST and LDH) at least twice the accepted upper limit of normal or three times if CK was used.	Bronchospasm; atriovenyricular block greater than first degree; sinus bradycardia; persistent heart failure; beta blockade at the time of infarction.	Propranolol (pro) 120 mg daily Placebo (pla) x 9 months Treatment interval: 2-14 days post-MI

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Hansteen 1982 Norway *Fair quality*	NR	Follow-up visits: months 2, 6 and 12	Mean age: Pro= 58; Pla=58.8 % male: Pro=84.5%; Pla=85.5%	*No previous CHD:* Pro=51.4%; Pla=48.6% *Angina pectoris:* Pro=30.6%; Pla=31.9% *Previous MI:* Pro=18%; Pla=19.5% *Hypertension (treated):* Pro=22.3%; Pla=18.15 *Intermittent claudication: Pro=8.6%; Pla=5.7%* *CVD:* Pro=3.2%; Pla=2.5% *Drug treatment before admission:* *Digitalis:* Pro=6.1%; Pla=5.7% *Diuretics:* Pro=19.1%; Pla=16% *Other antihy* pertensives: Pro=7.9%; Pla=6.4% Daily smoker: Pro=58.3%; Pla=64.9% *Ex-smoker:* Pro=28.1%; Pla=24.2%
Baber 1980 Multinational *Fair quality*	NR	Follow-up visits: months 1, 3, 6 and 9	*Mean age:* Pro=55; Pla=54.8 *% male:* Pro=86%; Pla=83% *Previous angina:* Positive: Pro=35%; Pla=40% *Concurrent disease:* Hypertension: Pro=13%; Pla=15% Peripheral artery disease: Pro=1%; Pla=2% Diabetes: Pro=3%; Pla=4% *Smokers:* Pro=64%; Pla=65%	*Previous angina:* Positive: Pro=35%; Pla=40% Angina more than 3 months: Pro=15%; Pla=19% *Previous infarct:* *History of cardiac failure:* *Concurrent disease:* Hypertension: Pro=13%; Pla=15% Peripheral artery disease: Pro=1%; Pla=2% Diabetes: Pro=3%; Pla=4% *Smokers:* Pro=64%; Pla=65%

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Hansteen 1982 Norway *Fair quality*	4929 screened/eligible nr/560 enrolled	Withdrawals: pro=70(25.2%); pla=72(25.5%)/lost to fu nr/560 analyzed	pro n=278; pla n=282 *# patients/%* Sudden death: pro=11(3.9%); pla=23(8.1%) (p=0.038) Type 1: pro=9(3.2%); pla=17(6.0%) (NS) Type 2: pro=1(0.3%); pla=3(1.1%)(NS) Type 3: pro=1(0.3%); pla=3(1.1%)(NS) Fatal reinfarction: pro=11(3.9%); pla=10(3.5%) (NS) Other cardiac deaths: pro=0; pla=2(0.7%)(NS) Other deaths: pro=3(1.1%); pla=2(0.7%)(NS) Total deaths: pro=25(8.9%); pla=37(13.1%) (NS) Total cardiac deaths: pro=22(7.9%); pla=35(12.4%) (NS) Non-fatal reinfarctions: pro=16(5.7%); pla=21(7.4%) (NS) Total no of cardiac events: pro=38(13.7%); pla=56(19.8%) (NS)	NR
Baber 1980 Multinational *Fair quality*	nr/nr/720	Total withdrawals: pla=88(24%); pro=82(23%)/lost to fu nr/720 analyzed	pla n=365; pro n=355 # pts/% Cardiac deaths: pla=18(4.9%); pro=19(5.4%) Non-cardiac deaths: pla=2(0.5%); pro=3(0.8%) Cardiac deaths after withdrawal: pla=7(1.9%); pro=6(1.7%) Total deaths: pla=27(7.4%); pro=28(7.9%) Non-fatal reinfarctions: pla=14(3.8%); pro=15(4.2%)	NR

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5. Controlled trials in myocardial infarction (continued)

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Hansteen 1982 Norway *Fair quality*	Overall incidence(% pts): pro=57; pla=51 Most common adverse events(# pts/%): Bradycardia: pro=88(31.6%); pla=13(4.6%) (p<0.05) Heart failure: pro=18(6.5%); pla=25(8.9%) Hypotension: pla=23(8.2%); pla=9(3.2%) (p<0.05) Bronchospasm: pro=10(3.6%); pla=10(3.5%) Cold hands/feet: pro=31(11.1%); pla=30(10.6%) Dizziness/asthenia: pro=38(13.7%); pla=19(6.7%)	*# patients/%* *Withdrawals due to:* Atrioventricular or sinoatrial block: pro=3(1.1%); pla=3(1.1%) Sinus bradycardia: pro=7(2.5%); pla=1(0.3%) Heart failure: pro=22(7.9%); pla=16(5.7%) Hypotension: pro=1(0.3%); pla=1(0.3%) Bronchospasm: pro=1(0.3%); pla=1(0.3%) Intermittent claudication: pro=2(0.7%); pla=0 Cold hands/feet: pro=1(0.3%); pla=0 Nightmares: pro=3(1.1%); pla=3(1.1%) Dizziness/asthenia: pro=2(0.7%); pla=1(0.3%) Other symptoms: pro=3(1.1%); pla=2(0.7%) Reinfarction: pro=6(2.2%); pla=4(1.4%)	
Baber 1980 Multinational *Fair quality*	NR	Reinfarction: pla=9(2.5%); pro=10(2.8%) Cardiac failure: pla=22(6.0%); pro=22(6.2%) Cardiac failure alone: pla=17(4.6%); pla=10(2.8%) Angina: pla=13(3.6%); pro=7(1.9%) Arrhythmias: pla=11(3.0%); pro=7(1.9%) Adverse reaction: pla=5(1.4%); pro=12(3.4%) Other: pla=38(10.4%); pro=42(11.8%)	

* Numbers in parentheses indicate number of patients with missing data

Evidence Table 5a. Quality assessments of controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Head to head trials of beta blockers					
Wilcox 1980 UK	NR	adequate; numbered packs	Yes	Mean age NR 84.7% male	388 randomized
Placebo- and "no treatment" controlled trials of atenolol					
Anonymous, 1986 Sleight, 1987 Anonymous, 1988 *First International Study of Infarct Survival (ISIS-1)*	Adequate; computer-generated randomization lists assigned by telephone	n/a-unblinded	Yes	Mean age NR 77% male	16,027 randomized
Placebo controlled trials of carvedilol					
Basu 1997 UK	NR	NR	Yes	84% male Mean age=60	151 randomized

Evidence Table 5a. Quality assessments of controlled trials of beta blockers for post myocardial infarction (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Head to head trials of beta blockers						
Wilcox 1980 UK	Already taking a beta blocker; severe heart failure; sinus bradycardia of under 40 beats per minute; in second or third degree heart block; systolic BP of >90 mm Hg; history of asthma or diabetes; residence too far away.	Yes	Yes	Yes	Yes	Yes
Placebo- and "no treatment" controlled trials of atenolol						
Anonymous, 1986 Sleight, 1987 Anonymous, 1988 *First International Study of Infarct Survival (ISIS-1)*		Yes	unclear	No	NO	Yes
Placebo controlled trials of carvedilol						
Basu 1997 UK	Already on ACE or beta blockers; contraindications to ACE or beta blockers; Killip class IV heart failure; cardiogenic shock; severe bradycardia; hypotension; second to third degree heart block; left bundle branch block; severe valvular disease; insulin-dependent DM; renal failure; known malignancy; other severe disease; pregnancy	Yes	Yes	Yes	Yes	Yes

Evidence Table 5a. Quality assessments of controlled trials of beta blockers for post myocardial infarction (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Head to head trials of beta blockers							
Wilcox 1980 UK	NR	Attrition=44.1%; others NR	NR	Fair	Imperial Chemical Industries Ltd.	Yes	1 year
Placebo- and "no treatment" controlled trials of atenolol							
Anonymous, 1986 Sleight, 1987 Anonymous, 1988 *First International Study of Infarct Survival (ISIS-1)*	NR	Attrition=0.7%; others NR	NR	Fair	ICI Pharmaceuticals	Yes	7-day treatment period, with 1-year follow-up
Placebo controlled trials of carvedilol							
Basu 1997 UK	NR	NR	None	Fair	NPH Cardiac Research Fund; Boehringer Mannheim GmbH	Yes	6 months

Evidence Table 5a. Quality assessments of controlled trials of beta blockers for post myocardial infarction (continued)

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Anonymous, 2001 *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)*	Adequate; Permuted blocks with stratification by center	NR	Yes	73.5% male Mean age=63 mean LVEF=32.9%	1959 recruited
Placebo controlled trials of metoprolol					
Anonymous, 1985 Herlitz, 1990 Hjalmarson, 1997 International *MIAMI* Fair quality	Adequate; randomization code prepared by the Safety Monitoring Committee in blocks of 50	NR	Yes	Mean age=60 77.5% male	5778 randomized
Anonymous 1987 USA *Lopressor Intervention Trial*	NR	NR	Yes	Mean age=58 83% male	2395 randomized
Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* Fair quality	Adequate; computer-generated randomization lists in blocks of 10	NR	Yes	Mean age=60 75.5% male	1395 randomized

Evidence Table 5a. Quality assessments of controlled trials of beta blockers for post myocardial infarction (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Anonymous, 2001 *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)*	Required continued diuretics or inotropes; uncontrollable heart failure; unstable angina; uncontrolled hypertension; bradycardia; unstable insulin-dependent DM; continuing indication for beta blockers for any condition other than heart failure; requiring ongoing therapy with inhaled beta agonists or steroids	Yes	Yes	Yes	Yes	Yes
Placebo controlled trials of metoprolol						
Anonymous, 1985 Herlitz, 1990 Hjalmarson, 1997 International *MIAMI* Fair quality	Current treatment with beta blockers or calcium channel blockres (within 48 hours); heart rate ≤65 beats/minute; Systolic BP ≤105 mm Hg; left ventricular failure; poor peripheral circulation; AV-conduction disturbance; severe chronic obstructive pulmonary disease; implanted pacemaker; resuscitation outside hospital; other serious disease; previous MIAMI participation; participation in other randomized trials; unwilling or unable to give informed consent	Yes	Yes	Yes	Yes	Yes
Anonymous 1987 USA *Lopressor Intervention Trial*		Yes	Yes	Yes	Yes	Yes
Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* Fair quality	Contraindications to beta blockade; need for beta blockade; administrative considerations	Yes	Yes	Yes	Yes	Yes

Evidence Table 5a. Quality assessments of controlled trials of beta blockers for post myocardial infarction (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Anonymous, 2001	NR	NR	NR	Fair	GSK	Yes	mean of 1.3 years
Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)							
Placebo controlled trials of metoprolol							
Anonymous, 1985 Herlitz, 1990 Hjalmarson, 1997 International	NR			Fair	AB Hassle, a subsidiary of Astra Pharmaceutical	Yes	1 year
MIAMI							
Fair quality							
Anonymous 1987 USA	NR	Attrition=30.7%; others NR	NR	Fair	CIBA-GEIGY	Yes	1.5 years
Lopressor Intervention Trial							
Herlitz, 1984 Herlitz, 1997 Sweden	NR			Good	NR	Yes	1 year
Goteborg Metoprolol Trial							
Fair quality							

Evidence Table 5a. Quality assessments of controlled trials of beta blockers for post myocardial infarction (continued)

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Olsson, 1985 *Stockholm Metoprolol Trial*	NR	NR	Yes	Mean age=59.5 80.5% male	301 randomized
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* Fair quality	Adequate; block randomization	NR	Yes	Mean age NR 71.5% male	800 randomized
Placebo controlled pindolol studies					
Australian & Swedish Study 1983 Australia, Sweden	NR	NR	Yes	Mean age=58 83% male	529 randomized

Evidence Table 5a. Quality assessments of controlled trials of beta blockers for post myocardial infarction (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Olsson, 1985 *Stockholm Metoprolol Trial*	Systolic BP <100 mm Hg; sever cardiac failure not responding to digitalis or diuretics; severe intermittent claudication; obstructive pulmonary disease; need for beta-adrenoceptor blockade; other major disease; unwillingness to participate.	Yes	Yes	Yes	Yes	Yes
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* Fair quality		Yes	Yes	Yes	Yes	Yes
Placebo controlled pindolol studies						
Australian & Swedish Study 1983 Australia, Sweden	Uncontrolled heart failure; uNRelated heart disease; persistent heart block of second or third degree; persistent bradycardia <50 beats/minute; obstructive airways disease; uncontrollable inslulin dependent diabetes; known hypersensitivity to beta blocking drugs; other diseases serious enough to worsen the short-term prognosis irrespectively of the MI; pregnancy; necessity to use beta blocking druga or calcium antagonists; unable to return for regular control.	Yes	Yes	Yes	Yes	Yes

Evidence Table 5a. Quality assessments of controlled trials of beta blockers for post myocardial infarction (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Olsson, 1985 *Stockholm Metoprolol Trial*	NR	Attrition=24.2%; others NR	NR	Fair	AB Hassle	Yes	3 years
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* Fair quality	NR	NR	NR	Fair	Astra Pharmaceuticals	Yes	1 year
Placebo controlled pindolol studies							
Australian & Swedish Study 1983 Australia, Sweden	NR	Attrition=23.8%; Compliance=54% took 90% or more	NR	Fair	Sandoz Ltd.	Yes	24 months

Evidence Table 5a. Quality assessments of controlled trials of beta blockers for post myocardial infarction (continued)

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Placebo controlled propranolol studies					
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)*	NR	NR	Yes	Mean age=54.8 84.4% male 88.8% white	3837 randomized
Robert, 1984 Rude, 1986 Roberts, 1988 United States *Multicenter Investigation of the Limitation of Infarct Size (MILIS)* Fair quality	NR	NR	No; Incidence of hypertension 37.3% higher in pro group	Mean age=54.75 73.2% male	269 randomized
Balcon, 1966	NR	NR	Yes	Mean age=59.8 69.2% male	114 randomized

Evidence Table 5a. Quality assessments of controlled trials of beta blockers for post myocardial infarction (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Placebo controlled propranolol studies						
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)*	Chronic obstructive lung disease; severe CHF; bradycardia; life-threatening illness other than CHF; need for beta blocking drugs	Yes	Deaths classified by blinded mortality classification subcommittee	Yes	Yes	Yes
Robert, 1984 Rude, 1986 Roberts, 1988 United States *Multicenter Investigation of the Limitation of Infarct Size (MILIS)* Fair quality	Cardiogenic shock; advanced cardiac or other disease that would interfere with prognosis; participation in conflicting protocol; inability to particpate because of geographical or psychological reasons; recent major surgery or MI; permanent cardian pacemaker; previous participation in the protocol; failure or inability to give informed consent	Yes	NR	Yes	Yes	Yes
Balcon, 1966	Complete heart block complicating an acute myocardial infarction; unconscious	Yes	NR	Yes	Yes	Yes

Evidence Table 5a. Quality assessments of controlled trials of beta blockers for post myocardial infarction (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Placebo controlled propranolol studies							
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States	NR	NR	Lost to fu: pro=4(0.2%); pla=8(0.4%)	Fair	National Heart, Lung, and Blood Institute	Yes	mean of 25 months
Beta-blocker Heart Attack Trial (BHAT)							
Robert, 1984 Rude, 1986 Roberts, 1988 United States	NR	NR	1(0.4%) lost to fu (treatment group NR)	Fair-Poor	Ayerst Laboratories donated propranolol	Yes	36 months
Multicenter Investigation of the Limitation of Infarct Size (MILIS)							
Fair quality							
Balcon, 1966	NR	Attrition=4.4%	NR	Fair	ICI Pharmaceuticals	Yes	28 days

Evidence Table 5a. Quality assessments of controlled trials of beta blockers for post myocardial infarction (continued)

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Bath, 1966	NR	NR	NR	Mean age=58 79.5% male	226 randomized
Norris, 1968	NR	NR	Yes	unclear; data NR	454 randomized
Hansteen 1982 Norway	Adequate; blocks of 10	NR	No; Mean heart size higher in pro group	Mean age NR 85% male	560 randomized
Baber 1980 Multinational	NR	NR	Yes	Mean age=54.9 84.5% male	720 randomized

Evidence Table 5a. Quality assessments of controlled trials of beta blockers for post myocardial infarction (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Bath, 1966	Diagnostic criteria not fulfilled; there was evidence of bronchospasm or a clinical history of bronchial asthma; the heart-rate was less than 60 per minute persisting throughout a 24-hour period; systolic blood-pressure was less than 80 mm Hg after admission	Yes	NR	Yes	Yes	No
Norris, 1968	Shock, heart failure, heart block, sinus bradycardia; acute pulmonary edema; systolic blood pressure below 80 mm Hg	Yes	NR	Yes	Yes	Yes
Hansteen 1982 Norway	Cotraindications to beta blockade; uncontrolled heart failure	Yes	NR	Yes	Yes	Yes
Baber 1980 Multinational	Bronchospasm; atriovenyricular block greater than first degree; sinus bradycardia; persistent heart failure; beta blockade at the time of infarction.	Yes	NR	Yes	Yes	Yes

Evidence Table 5a. Quality assessments of controlled trials of beta blockers for post myocardial infarction (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Bath, 1966	NR	Attrition=13.7%	NR	Fair	ICI Pharmaceuticals	Yes	28 days
Norris, 1968	NR	Attrition=7.9%	NR	Fair	ICI Pharmaceuticals	Yes	3 weeks
Hansteen 1982 Norway	NR	Attrition=25.3%; Compliance(% taken > 95%): 80	NR	Fair	Imperial Chemical Industries Ltd.	Yes	12 months
Baber 1980 Multinational	NR	Attrition=23.5%; others NR	NR	Fair	ICI Pharmaceuticals	Yes	9 months

Evidence Table 6. Summary of results from systematic reviews of patients post-MI

Trials included in our evidence tables are in bold.

Study	Intervention	Mortality (odds ratio for ACE-I vs. placebo)	95% confidence interval
Trials of short-term beta blocker post-myocardial infarction (Freemantle 1999)			
ISIS-1 Study, 1986	**Atenolol**	**0.94**	**0.86 - 1.03**
Van de Werf, 1993	Atenolol	0.23	0.00 - 2.37
Yusuf, 1980	**Atenolol**	**0.74**	**0.44 - 1.24**
Heber, 1987	**Labetalol**	**1.84**	**0.62 - 5.81**
TIMI IIB Study, 1989	Metoprolol (15 mg)	1.00	0.47 - 2.10
Amsterdam Study, 1983	**Metoprolol**	**0.55**	**0.21 - 1.36**
Salathia, 1985	**Metoprolol**	**0.76**	**0.49 - 1.18**
Goteborg, 1981	**Metoprolol**	**0.62**	**0.40 - 0.96**
MIAMI Study, 1985	**Metoprolol**	**0.87**	**0.67 - 1.12**
Rehnqvist, 1983	**Metoprolol**	**0.73**	**0.39 - 1.35**
Von Essen, 1982	Metoprolol	1.04	0.01 - 85.00
Owensby, 1984	**Pindolol**	**1.00**	**0.01 - 80.8**
Balcon, 1966	**Propranolol**	**0.96**	**0.38 - 2.42**
Barber, 1976	Propranolol	0.69	0.24 - 2.00
Bath, 1966	Propranolol	1.22	0.50 - 3.04
BHAT, 1982	**Propranolol**	**0.72**	**0.56 - 0.91**
Clausen, 1966	Propranolol	0.89	0.39 - 2.04
Dotremont, a987	Propranolol	0.78	0.14 - 3.99
Gupta, 1982	Propranolol	Not estimable	
Kahler, 1968	Propranolol	0.36	0.05 - 1.89
Ledwich, 1968	Propranolol	0.65	0.05 - 6.04
Mueller, 1980	Propranolol	2.06	0.10 - 125.09
Norris, 1968	**Propranolol**	**1.35**	**0.75 - 2.50**
Norris, 1984	Propranolol	1.10	0.49 - 2.49
Peter, 1978	Propranolol	0.50	0.01 - 9.99
Roberts, 1984	**Propranolol**	**1.25**	**0.62 - 2.54**
Sloman, 1967	Propranolol	0.62	0.08 - 4.21
Trials of long-term beta blocker post-myocardial infarction (Freemantle 1999)			
Wilcox, 1980	**Atenolol**	**1.02**	**0.48 - 2.16**
Yusuf, 1979	Atenolol	1.00	0.01 - 86.25
Basu, 1997	**Carvedilol**	**0.62**	**0.05 - 5.61**

Evidence Table 6. Summary of results from systematic reviews (continued)

Trials included in our evidence tables are in bold.

Study	Intervention	Mortality (odds ratio for ACE-I vs. placebo)	95% confidence interval
Lopez, 1993	Metoprolol	1.91	0.76 - 5.05
Australian & Swedish, 1983	**Pindolol**	**0.96**	**0.60 - 1.55**
Aronow, 1997	Propranolol	0.40	0.19 - 0.83
Baber, 1980	**Propranolol**	**1.07**	**0.59 - 1.83**
Hansteen, 1982	**Propranolol**	**0.65**	**0.37 - 1.15**
Kaul, 1988	Propranolol (iv)	1.00	0.12 - 8.31
Mazur, 1984	Propranolol	0.44	0.11 - 1.43
Wilcox, 1980	**Propranolol**	**0.88**	**0.40 - 1.84**

Evidence Table 7. Randomized controlled trials of beta blockers for post-myocardial infarction

Study, year	Interventions	Duration of intervention	Number enrolled	Mortality at end of intervention	Overall quality
Head-to-head trials of one beta blocker vs. another beta blocker					
Wilcox 1980	A: Propranolol B: Atenolol C: Placebo	1 year	388	A: 13% (17/132) B: 14.9% (19/127) C: 14.7% (19/129) (p=NS)	Fair
Trials of atenolol vs. placebo					
Yusuf 1980	A: Atenolol B: Placebo	10 days for infarction, 1-4 years for mortality	477	A: 14.7% (36/244) B: 18.8 (44/233) (p=NS)	Fair
ISIS-1 1986	A: Atenolol B: Placebo	1 year	16,027	A: 13.3% (1071/8037) B: 14% (1120/7990) (p=NS)	Fair
Trials of carvedilol vs. placebo					
Basu 1997	A: Carvedilol B: Placebo	6 months	146	A: 2.7% (2/75) B: 4.2% (3/71 (p=NS)	Fair
CAPRICORN 1999	A: Carvedilol B: Placebo	1.3 years (mean)	1959	A: 12% (116/975) B: 15% (151/984) (p=0.031)	Fair
Trials of metoprolol vs. placebo					
MIAMI 1985	A: Metoprolol B: Placebo	15 days	5778	A: 4.3% (123/2877) B: 4.9% (142/2901) (p=NS)	Fair
Stockholm 1983	A: Metoprolol B: Placebo	3 years	301	A: 16.2% (25/154) B: 21% (31/147) (p=NS)	Fair
Amsterdam 1983	A: Metoprolol B: Placebo	1 year	553	A: 3.3% (9/273) B: 5.7% (16/280) (P=NS)	Abstract only
Belfast 1985	A: Metoprolol B: Placebo	1 year	764	A: 11.8% (49/416) B: 14.9% (52/348) (p=NS)	Fair
Lopressor 1987	A: Metoprolol B: Placebo	1.5 years	2395	A: 7.2% (86/1195) B: 7.7% (93/1200) (p=NS)	Fair
Goteborg 1981	A: Metoprolol B: Placebo	2 years	1395	A: 5.7% (40/698) B: 8.9% (62/697) (p=0.024)	Fair
Trials of pindolol vs. placebo					
Owensby 1984	A: Pindolol B: Placebo	3 days	100	A: 2% (1/50) B: 2% (1/50) (p=NS)	Fair
Australian & Swedish Study 1983	A: Pindolol B: Placebo	2 years	529	A: 17.1% (45/263) B: 17.7% (47/266) (p=NS)	Fair

Evidence Table 7. Randomized controlled trials of beta blockers for post-myocardial infarction (continued)

Study, year	Interventions	Duration of intervention	Number enrolled	Mortality at end of intervention	Overall quality
Trials of propranolol vs. placebo					
MILIS 1984	A: Propranolol B: Placebo	3 years	269	A: 17.9% (24/134) B: 14.8% (20/135) (p=NS)	Fair
Baber 1980	A: Propranolol B: Placebo	9 months	720	A: 7.9% (28/355) B: 7.4% (27/365) (p=NS)	Fair
Hansteen 1982	A: Propranolol B: Placebo	1 year	560	A: 8.9% (25/278) B: 13.1% (37/282) (p=NS)	Fair
BHAT 1982	A: Propranolol B: Placebo	25 months	3837	A: 7.2% (138/1916) B: 9.8% (188/1921) (p=NS)	Fair

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria	Exclusion criteria
Bisoprolol			
Anonymous 1994 *The Cardiac Insufficiency Bisoprolol Study (CIBIS I)* 70 centers in 9 European countries Fair quality	25.4% NYHA Class III: 95% IV: 5%	Age 18-75, CHF, dyspnea or fatigue corresponding to NYHA III or IV, ambulatory, clinically stable past 3 weeks and no heart failure past 6 weeks. Mandatory background medication diuretic and vasodilator therapy. Ejection fraction <40%. Etiology of heart failure: (1) idiopathic dilated cardiomyopathy with no known cause, (2) ischemia with documented history, (3) hypertension with history of therapy, (4) valvular heart disease repaired >6 months and nonischemic dilated cardiomyopathy with significant mitral valve insufficiency.	CHF due to hypertrophic or restrictive cardiomyopathy with predominant left ventricular diastolic dysfunction; or secondary to mitral or aortic valve disease surgically repaired <6 months, or not repaired. MI <3 months. Awaiting bypass surgery or transplantation. Disabling permanent dyspnea at rest, insulin-dependent diabetes, asthma, renal insufficiency, hypothyroidism or hyperthyroidism, short life expectancy due to severe illness or malignancy. Resting heart rate <65 bpm; systolic blood pressure <100 or >160 mm Hg. No digitalis or amiodarone treatment <6 weeks before or 2 months after inclusion. Beta-adrenergic agonist or antagonist drugs and phosphodiesterase inhibitors prohibited.

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Bisoprolol					
Anonymous 1994 *The Cardiac Insufficiency Bisoprolol Study (CIBIS I)* 70 centers in 9 European countries Fair quality	Bisoprolol (bis) 5 mg vs. placebo (pla) for 1+ years Initial dose 1.25 mg/day titrated over 1 month. Clinician choice for dose levels at 1.25 mg (17%), 2.5 mg (30%) , 3.75 mg (2%) or 5 mg (51%) per day.	Diuretic: 100% Vasodilator: ACEIs: 90% Calcium antagonists: 6% Other: 40% Digitalis: 57% Antiarrhythmic: Amiodarone: 20% Other: 6% Anticoagulant: 39% Antiplatelet: 26%	*Primary:* Total mortality. *Secondary* : Bisoprolol tolerability (premature withdrawals, NYHA functional status, number of nonlethal critical events. Followup every 3 months, mean duration 1.9 years.	Mean age 59.6 82.5% Male Race NR	CHF etiology: IDC: 36% Ischemia: 55% Hypertension: 5% Valvular disease: 4% History of acute episodes of heart failure: 56% History of MI: 47% Mean LVEF: 25.4%

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Bisoprolol				
Anonymous 1994 *The Cardiac Insufficiency Bisoprolol Study (CIBIS I)* 70 centers in 9 European countries Fair quality	Total screened & eligible: NR Enrolled: 641 bis (n= 320) pla (n= 321)	Total withdrawn: 157/641 (24.5%) Bis 75/320 (23.4%) Pla 82/321 (25.5%) 1 patient lost to follow-up. Analyzed=641	*Primary (All Deaths):* Bis: 53/320 (16.6%) Pla: 67/321 (20.9%) (NS) Sudden death: Bis: 15/320 (4.7%) Pla: 17/321 (5.3%) (NS) *Secondary:* NYHA class improvement: Bis: 68/320 (21%) Pla: 48/321 (15%) (p<.03) NYHA class deterioration: Bis: 41/320 (13%) Pla: 35/321 (11%) (NS) Heart failure: Bis: 11/320 (3.4%) Pla: 22/321 (6.9%)(NS) *Subgroup deaths, no MI history:* Bis: 18/151 (12%) Pla: 42/187 (22.5%) (p=0.01)	NR

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Bisoprolol			
Anonymous 1994 *The Cardiac Insufficiency Bisoprolol Study (CIBIS I)* 70 centers in 9 European countries Fair quality	NR, except Bis: 2 sinus bradycardia, 2 atrioventricular blockade	NR Non CV events: Bis: 44/320 (13.7%) Pla: 54/321 (16.8%)	

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Mean EF NYHA Class	Eligibility criteria	Exclusion criteria
Anonymous 1999 *The Cardiac Insufficiency Bisoprolol Study (CIBIS II)* Good quality	27.5% NYHA Class III: 83% IV: 17%	Age 18-80, CHF diagnosis >3 months previous, dyspnea on exertion, orthopnea or paroxysmal nocturnal dyspnoea, and fatigue, corresponding to NYHA III or IV; ambulatory, clinically stable past 6 weeks or 3 months for acute MI. CV therapy unchanged past 2 weeks. Mandatory medication diuretic and ACE inhibitor or other vasodilator if ACEI intolerant. Ejection fraction <35%.	Uncontrolled hypertension, MI or unstoppable angina pectoris in past 3 months, revascularization in past 6 months, previous or scheduled heart transplant, atrioventricular block > first degree without pacemaker, resting heart rate < 60 bpm, systolic blood pressure <100, renal failure, reversible obstructive lung disease or planned therapy with beta-adrenoreceptor blockers. No treatment with beta blockers (also eye drops), calcium antagonists, inotropic agents except digitalis, and antiarrhythmic drugs except amiodarone during trial.

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Anonymous 1999 *The Cardiac Insufficiency Bisoprolol Study (CIBIS II)* Good quality	Bisoprolol (bis) 10 mg. vs. placebo (pla) for 1+ years Initial dose 1.25 mg/day titrated weekly for 3 weeks to 5 mg (13%), then 4-week intervals to 7.5 mg (11%) and 10 mg/day (43%). No run-in period.	Diuretic: 99% Vasodilator: -ACE inhibitors: 96% -Calcium antagonists: 2% - Nitrates: 58% Digoxin: 52% Antiarrhythmic: - Amiodarone: 15% Anticoagulant: 31% Antiplatelet: 41%	*Primary:* Total mortality. *Secondary:* All-cause hospital admission, all CV deaths, combined endpoint, permanent treatment withdrawals. Followup every 3 months, mean duration 1.3 years. Study stopped early with significant results.	Mean age 61 80.5% Male Race NR	CHF etiology: - Primary dilated cardiomyopathy: 12% - Ischemia: 50% - Other heart failure: 39%

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Anonymous 1999 *The Cardiac Insufficiency Bisoprolol Study (CIBIS II)* Good quality	Total screened & eligible: NR Enrolled: 2647 Bisoprolol (n= 1327) Placebo (n= 1320)	Total: 69/2647 (2.6%) Bis: 41/1327 (3.1%) Pla: 28/2647 (2.1%) 6 patients lost to follow-up. Analyzed=2.647	*Primary - Total mortality:* Bis: 156/1327 (12%) Pla: 228/1320 (17%) (p<.0001) - Sudden death: Bis: 48/1327 (3.6%) Pla: 83//1320 (6.3%) (p=0.0011) *Subgroup analysis of mortality:* - Ischemic etiology Bis: 75/662 (11.3%) Pla: 121/654 (18.5%) (p<.001) *Secondary:* - All CV deaths Bis: 119/1327 (9.0%) Pla: 161/1320 (12.2%)(p=0.0049) - All-cause hospital admission Bis: 440/1327 (33.2%) Pla: 513/1320 (38.9%)(p=0.0006) *Subgroup analysis of hospital admission:* - for worsening heart failure Bis: 159/1327 (12.0%) Pla: 232/1320 (17.6%)(p=0.0001) - for stroke Bis: 31/1327 (2.3%) Pla: 16/1320 (1.2%) (p=0.04) - for ventricular tachycardia and fibrillation Bis: 6/1327 (0.5%) Pla: 20/1320 (1.5%) (p=0.006) - for hypotension: Bis: 3/1327 (0.2%) Pla: 11/1320 (0.8%) (p=0.03) - for bradycardia: Bis: 14/1327 (1.1%) Pla: 2/1320 (0.2%) (p<.004)	NR

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Anonymous 1999 *The Cardiac Insufficiency Bisoprolol Study (CIBIS II)* Good quality	NR	NR	

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Mean EF NYHA Class	Eligibility criteria	Exclusion criteria
Carvedilol			
Bristow 1996 Lindenfeld 2001 *Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA)* Fair quality	23% NYHA class II: 46% II: 52% IV: 2%	Age 18-85, ejection fraction ≤ 35%, symptomatic ischemic or dilated cardiomyopathy heart failure, symptoms present ≥ 3 months, walk test 150-450 m, stability (no change in NYHA class and absence of hospitalization) ≥ past 1 month, any digoxin use started ≥ 2 months prior and stable dose ≥ past 1 month, resting heart rate ≥ 68 bpm.	Uncorrected valvular disease, hypertrophic or postpartum cardiomyopathy, uncontrolled symptomatic or sustained ventricular tachycardia, acute MI within 3 months, planned or likely revascularization or transplantation within 6 months after screening. Also, sick sinus syndrome, 2nd- or 3rd-degree heart block not treated with pacemaker, symptomatic peripheral vascular disease limiting exercise testing, sitting systolic blood pressure <85 mm Hg or >160 mm Hg, CV accident within last 3 months, cor pulmonale, obstructive pulmonary disease requiring oral bronchodilator or steroid therapy, and other selected disorders and sensitivities. Excluded drugs: alcohol intake >100 g/day, use of investigational drug within 30 days, CCBs, amiodarone within 3 months, and others.

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Carvedilol					
Bristow 1996 Lindenfeld 2001 *Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA)* Fair quality	Carvedilol (car) 12.5 mg, 25 mg, 50 mg daily Placebo (pla) x 6 months 3-week screening phase. 2-week run-in with open-label car. to establish tolerability prior to randomization. 2-week titration phase.	ACE inhibitors: 94% Digitalis: 92% Loop-activity diuretics: 95% Thiazide diuretics: 18% Vasodilators: 35%	*Primary:* Improvement in submaximal exercise, using 6-minute walk test and 9-minute self-powered treadmill test. *Secondary:* Changes in quality of life, NYHA class, EF, need for hospitalization due to heart failure and other CV causes, and signs and symptoms of heart failure.	Mean age 59.5 76% Male 78% White	Ischemic cause: 52%

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Carvedilol				
Bristow 1996 Lindenfeld 2001 *Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA)* Fair quality	Screened: NR Eligible for run-in: 376 Enrolled: 345 car. 50 mg (n=89) car. 25 mg (n=89) car.12.5 mg (n=83) placebo (n=84)	Total: 52/345 (15%) Lost to QOL assessment: 38/345 (11%) Lost to hospitalization assessment: 23/345 (6.7%) Lost to exercise result: NR Analyzed=345	No effect on exercise duration. No effect on NYHA class. Crude mortality at 6 months: car 25 bid: 1/89 (1.3%)(p=0.001) car 12.5 bid: 6/89 (6.7%) (p=0.07) car 6.25 bid: 5/83 (6.0%) (p=<.05) Pla: 13/84 (15.5%) (p-values vs. placebo) Sudden death Car (all)=6/261(2.3%); pla=6/84(7.1%) CV Hospitalizations Total: car 25 bid: 9/82 (11.0%) car 12.5 bid: 11/82 (13.4%) car 6.25 bid: 9/80 (11.3%) Pla: 17/78 (21.8%) (no linear trend) (all car. vs. pl, p=0.03) QOL mean score change: car 25 bid: -5.5 car 12.5 bid: -7.3 car 6.25 bid: -7.9 Pla: -7.3 (NS)	NR

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Carvedilol			
Bristow 1996 Lindenfeld 2001 *Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA)* Fair quality	Dizziness: All car: 83/261 (31.8%) car 25 bid: 34/89 (38.2%) car 12.5 bid: 29/89 (32.6%) car 6.25 bid: 20/83 (24.1%) pla: 19/84 (22.6%) (linear trend, p=0.01) (all car vs. pla, p=0.11) Cardiac failure: All car: 56/261 (21.4%) car 25 bid: 22/89 (24.7%) car 12.5 bid: 23/89 (25.8%) car 6.25 bid: 11/83 (13.3%) pla: 19/84 (22.6%) (linear trend, p=0.34) (all car vs. pla, p=0.82) Edema or weight gain: All car: 30/261 (11.5%) car 25 bid: 9/89 (10.1%) car 12.5 bid: 10/89 (11.2%) car 6.25 bid: 11/83 (13.3%) pla: 5/84 (6.0%) (linear trend, p=0.60) (all car vs. pla, p=0.14) Bradycardia: All car: 21/261 (8.0%) car 25 bid: 10/89 (11.2%) car 12.5 bid: 10/89 (11.2%) car 6.25 bid: 1/83 (1.2%) pla: 1/84 (1.2%) (linear trend, p=0.001) (all car vs. pla, p=.03)	Withdrawals due to any adverse events: car(all)=18%; pla=11%	

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Mean EF NYHA Class	Eligibility criteria	Exclusion criteria
Packer 1996 *PRECISE* Fair quality	22% NYHA class II: 40% III: 56% IV: 4%	Chronic heart failure (dyspnea or fatigue ≥3 months), LVEF ≤35% despite ≥2 months treatment with diuretics and ACEI.	Uncorrected primary valvular disease, active myocarditis or obstructive or restrictive cardiomyopathy; MI, stroke, unstable angina or CABG within 3 months; symptomatic or sustained ventricular tachycardia not controlled by antiarrhythmic drugs or implantable defibrillator; sick sinus syndrome or advanced heart block (without pacemaker); any condition other than heart failure that could limit exercise; systolic blood pressure >160 or <85 mm Hg or diastolic blood pressure >100 mm Hg; heart rate <68 bpm; significant hepatic, renal or endocrine disease; drug or alcohol abuse; or any condition that could limit survival. Patients receiving CCBs, alpha- or beta-adrenergic agonist or antagonists or specific antiarrhythmic drugs.

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Packer 1996 *PRECISE* Fair quality	Carvedilol (car) 50 mg daily vs. placebo (pla) for 6 months Begin 6.25 mg bid titrated over 2-6 weeks (50 mg bid for weight ≥85 kg) - 87% reached target, avg 28 mg/day.	Digitalis: 90% Loop-active diuretic: 99% ACEI: 97% Direct-acting vasodilator: 29%	*Primary:* Exercise tolerance on 6-minute corridor walk and 9-minute treadmill. Secondary: global assessment, NYHA class, LVEF, quality of life	Mean age 60.3 73% Male Race NR	Cause of heart failure - CAD : 52% - Nonischemic dilated cardiomyopathy: 48%

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Packer 1996 *PRECISE* Fair quality	Screened: NR Eligible for run-in: 301 Enrolled: 278 car (n= 133) pla (n= 145)	49/278 (18%) withdrawn Lost to follow-up for NYHA class and global assessment: 9% Lost to follow-up for AE report: 10/278 (4%) Analyzed: 278	*Primary:* 6-minute exercise test increase: car: 17 m pla: 6 m (NS) No difference in 9-minute treadmill test. *Secondary:* NYHA class III/IV improvement: car: 28/130 (21.5%) pla: 9/130 (6.9%) (p=0.014) NYHA class deterioration: car: 3% vs. pla: 15% (p=0.001) No difference in QOL scores. LVEF change: car: +8% pla: +3% (p<.001) Deaths (ITT): car: 6/133 (4.5%) pla: 11/145 (7.6%) (NS) CV hospitalization (ITT): car: 22/133 (16.5%) pla: 37/145 (25.5%) (NS)	NR

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Packer 1996 *PRECISE* Fair quality	Dizziness: car: 31/129 (24.0%) pla: 16/139 (11.5%) (p<.01) Heart failure: car: 15/129 (11.6%) pla: 31/139 (22.3%) (p<.025) Weight gain: NR Bradycardia: car: 7/129 (5.4%) pla: 1/139 (0.7%) (p<.025) Hypotension: car: 8/129 (6.2%) pla: 3/139 (2.2%) (NS)	Withdrawals due to any adverse event: car=7(5.3%); pla=11(8.3%)	

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Mean EF NYHA Class	Eligibility criteria	Exclusion criteria
Colucci 1996 *U.S. Carvedilol Heart Failure Study Group (Mild)* Fair quality	Mild 23% NYHA class II: 85% III: 15%	Age 18-85 with chronic symptomatic heart failure (dyspnea or fatigue) ≥3 months), LVEF ≤35% despite ≥2 months treatment with diuretics and ACEI.	Uncorrected primary valvular disease, nondilated or hypertrophic cardiomyopathy; MI, stroke, unstable angina or CABG within 3 months; symptomatic or sustained ventricular tachycardia not controlled by antiarrhythmic drugs or implantable defibrillator within 3 months; likelihood of revascularization or transplantation within 12 months; sick sinus syndrome or advanced heart block (without pacemaker); any condition other than heart failure that could limit exercise; systolic blood pressure >160 or <85 mm Hg or diastolic blood pressure >100 mm Hg; clinically significant hepatic or renal disease, or any condition that could limit survival. Patients receiving amiodarone within 3 months before screening.

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Colucci 1996 *U.S. Carvedilol Heart Failure Study Group (Mild)* Fair quality	Carvedilol (car) 50 mg daily vs. placebo (pla) for 12 months (mean 7 months) Begin 12.5 mg bid titrated (50 mg bid for weight ≥85 kg) - 85% achieved max dose. Terminated early with significant results.	Background therapy held constant if possible, adjusted for AE	*Primary:* progression of heart failure. *Secondary:* LVEF, NYHA class, heart failure score, global assessments, quality of life, 9-minute self-powered treadmill test, and heart size	Mean age 55 85% Male Race NR	Cause of heart failure: Ischemic: 42% Nonischemic: 58%

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Number screened/ eligible/ enrolled	withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Colucci 1996 *U.S. Carvedilol Heart Failure Study Group (Mild)* Fair quality	Screened: NR Eligible for run-in: 389 Enrolled: 366 car (n=232) pla (n=134)	Withdrawals=8.5%; Lost to fu nr; Analyzed=366	*Primary:* Clinical progression of heart failure: car: 25/232 (10.8%) pla: 28/134 (20.9%) (p=0.008) All deaths: car: 2/232 (0.9%) pla: 5/134 (3.7%) (p=0.048) CV deaths: car: 0 pla: 4/134 (3.0%) (p<.01) Hospitalization for heart failure: car: 9/232 (3.9%) pla: 8/134 (6.0%) (NS) *Secondary:* NYHA class improved: car: 12% vs. pla: 9% NYHA class worsened: car: 4% vs. pla: 15% (overall change favors car, p=0.003) QOL score mean change: car: -4.9 vs. pla: -2.4 (NS) No difference in exercise test.	NR

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Colucci 1996 *U.S. Carvedilol Heart Failure Study Group (Mild)* Fair quality	dizziness: car: 81/232 (34.9%) pla: 27/134 (20.1%) (p<.01) cardiac failure: car: 26/232 (11.2%) pla: 22/134 (16.4%) (NS) weight increase: car: 29/232 (12.5%) pla: 10/134 (7.5%) (NS) bradycardia: car: 30/232 (12.9%) pla: 1/134 (0.7%) (p<.001) hypotension: car: 21/232 (9.1%) pla: 4/134 (3.0%) (p<.05)	nr	

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Mean EF NYHA Class	Eligibility criteria	Exclusion criteria
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group* Poor quality	22% NYHA class II: 1% III: 86% IV: 14%	Age 22-85; symptoms of heart failure (dyspnea or fatigue) ≥3 months); LVEF ≤35% despite ≥2 months treatment with diuretics and ACEI; able to walk less than 150 m on 6-minute corridor walk test assigned to severe protocol (relaxed to <350 m due to slow enrollment).	Uncorrected primary valvular disease, nondilated or hypertrophic cardiomyopathy; MI, stroke, unstable angina or CABG within 3 months; symptomatic or sustained ventricular tachycardia not controlled by antiarrhythmic drugs or implantable defibrillator within 3 months; likelihood heart transplantation within 6 months; sick sinus syndrome or advanced heart block without pacemaker; any condition other than heart failure that could limit exercise; systolic blood pressure >160 or <85 mm Hg or diastolic blood pressure >100 mm Hg; clinically significant hepatic or renal disease, or any condition that could limit survival.

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group* Poor quality	Carvedilol (car) 50 mg daily Placebo (pla) x 6 months, mean 3 months.	Diuretic: 98% ACEI: 93% Digoxin: 90%	*Primary:* quality of life *Secondary:* mortality, CV hospitalizations, global assessments, NYHA class, LVEF, 6-minute walk exercise test	Mean age 60 58% Male Race: 71% White 21% Black 8% Other	Cause of heart failure: Ischemic: 45% Nonischemic: 55%

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Number screened/ eligible/ enrolled	withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group* Poor quality	Screened: NR Eligible for run-in: 131 Enrolled: 105 car (n= 70) pla (n= 35)	Reported withdrawn: 12/105 (11%) (4 deaths, 2 transplants. 5 AE) Reports 1 lost to follow-up. Final sample sizes often NR. Lost to LVEF test: 50/105 (52%). Lost to follow-up in 2 months: 35/105 (33%) Lost to follow-up in 6 months: 92/105 (88%)	[carry-forward analysis] Primary: QOL score improvement: car=11.6; pla=8.8 Secondary: No difference in NYHA class. No difference in CV hospitalization. No difference in deaths. 6-minute exercise test increase: car: 19.0 m pla: 28.4 m (NS)	NR

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group* Poor quality	[sample size NR - unreliable] dizziness: car: 24.3% pla: 31.4% worsening heart failure: car: 10.0% pla: 22.9% weight gain: car: 10.0% pla: 5.7%	*Withdrawals due to:* Bradycardia/heart block: car=3(1.4%); pla=0 Dizziness/hypotension: car=3(1.4%); pla=0 Worsening heart failure: car=5(2.4%); pla=2(0.9%)	

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Mean EF NYHA Class	Eligibility criteria	Exclusion criteria
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group Study* Good quality	29% NYHA class II: 30% III: 54% IV: 16%	Chronic stable heart failure due to ischemic heart disease; LVEF <45%; NYHA functional class II or III or previous NYHA class II-IV	Current NYHA class IV; heart rate below 50 beats per minute; sick sinus syndrome; second or third degree heart block; systolic BP <90 mm Hg or >160/100 mm Hg; treadmill exercise duration <2 minutes or >18 minutes; coronary event or procedure within previous 4 weeks; primary myocardial or valvular disease; current treatment with beta-blocker, beta-agonist or verapamil; insulin-dependent DM; obstructive airways disease; hepatic disease; any other life-threatening non-cardiac disease.

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group Study* Good quality	Carvedilol (car) 50 mg daily Placebo (pla) x 12 months Begin 6.25 mg bid titrated over2-5 weeks. At 6 months, avg. 46 mg daily.	ACEI: 85% Diuretic: 76% Digoxin: 79%	*Primary:* Change in LVEF and treadmill exercise duration (Naughton protocol 2-min. stages) *Secondary:* Change in LV dimension, 6-minute walk distance, symptoms of heart failure, frequency of death, hospital admission, and worsening heart failure Clinical assessment at 5 weeks and 3 months, then every 3 months.	Mean age 67 80% male Race NR	Previous MI: 88.6% Previous hospital admission for CHF: 42% Previous highest NYHA class: II: 26.5% III: 30% IV: 43% Current NYHA class: I: 30% II: 54% III: 16% Current treatment for heart failure: ACEI: 85.5% Diuretic: 75.6% Digoxin: 38%

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group Study* Good quality	Screened: NR Eligible for run-in: 442 Enrolled: 415 car (n= 207) pla (n= 208)	Total withdrawn at 6 months: 43/415 (10%)/lost to fu nr/analyzed=415	*Primary:* Improvement in treadmill duration: data nr *Secondary:* 6-min. walk distance: data nr NYHA class (12 months) improved: car 26%; pla 28% no change: car=58%; pla=58% worse: car 16%; pla 13% Total mortality: car: 20/208 (9.6%) pla: 26/207 (12.6%) (NS) Sudden death: car: 10/208 (4.8%) pla: 11/207 (5.3%) (NS) All hospital admissions: car: 20/208 (9.6%) pla: 26/207 (12.6%) (NS) All CV hospitalizations: car: 99/208 (47.6%) pla: 120/207 (58.0%) (NS)	NR

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group Study* Good quality	nr	*Withdrawals due to:* Dizziness/Hypotension: car: 3/207 (1.4%) pla: 0 (NS) Worsening heart failure: car: 5/207 (2.4%) pla: 2/208 (0.9%) (NS) Bradycardia/Heart block: car: 3/207 (1.4%) pla: 0 (NS)	

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Mean EF NYHA Class	Eligibility criteria	Exclusion criteria
Cleland, 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)* Fair quality	29.5% NYHA Class I: 11.1% II: 60.3% III: 28.5%	Stable chronic heart failure (defined as freedom from an acute cardiovascular event for 3 months; freedom from all-cause admission for 1 month; stable treatment for heart failure for at least 2 weeks) with objective evidence of left ventricular systolic dysfunction (ECG wall motion index cutoff of 1.3 or less; corresponding to an LVEF of <40%) due to coronary artery disease (defined as history of myocardial infarction, coronary revascularisation, or coronary artery disease on arteriography); NYHA Class I-III	Patients younger than 40 years and women of child-bearing age; resting heart rate less than 60 beats per minute; sitting systolic blood pressure less than 85 mm Hg; unstable angina; arrhythmias; uncontrolled hypertension; obstructive pulmonary disease; poorly controlled diabetes; or clinically relevant renal or hepatic disease; those receiving non-dihydropiridine calcium-channel blockers; beta blockers, or antiarrhythmic agents other than amiodarone

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Cleland, 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)* Fair quality	Carvedilol (car) 6.25-50 mg daily Placebo (pla) x 4 months maintenance	Angiotensin-converting enzyme inhibitors treatment compulsory	*Primary:* Change in LVEF in hibernators versus non-hibernators *Secondary:* (1) LVEF change in carvedilol versus placebo, irrespective of hibernation status; (2)relation between volume of hibernating myocardium and change in LVEF; (3) change in contractile dysfunction in hibernators versus non-hibernators; (4) change in number of segments with reversible exercise-induced myocardial perfusion defects on carvedilol versus placebo; (5) *composite of death or worsening of heart failure in carvedilol vs placebo*	Age: 62.5 % male: 90 % white: 91.1	Current smokers: 16.7% Diabetes: 22.3% Previous MI: 90.2% Previous CABG: 45.2% NYHA Class I: 11.1% II: 60.3% III: 28.5% LVEF (mean): 29.5%

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Number screened/ eligible/ enrolled	withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Cleland, 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)* Fair quality	489 screened/440 eligible/387 enrolled	82(21.2%) withdrawn/lost to fu nr/305 analyzed	Exercise time (seconds): car=405; pla=427 (NS) Death: car=6/188(3.2%); pla=6/188=3.2%(NS) Composite of all-cause mortality and worsening heart failure: car=44/187(23.5%); pla=37/188(19.7%) (NS)	nr

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Cleland, 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)* Fair quality	Overall adverse events: frequent in both groups (rates nr) Dizziness, fatigue, syncope and bradycardia were more typical with carvedilol than with placebo (rates nr)	nr	

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Mean EF NYHA Class	Eligibility criteria	Exclusion criteria
Eichhorn 2001 Packer, 2001, 2002 Krum 2003 *The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial* Fair quality	19.8% NYHA Class nr	Patients with severe chronic heart failure as a result of ischemic or nonischemic cardiomyopathy	Heart failure that was caused by uncorrected primary valvular disease or a reversible form of cardiomyopathy; had received or were likely to receive a cardiac transplant; had severe primary pulmonary, renal, or hepatic disease; or had a contraindication to beta-blocker therapy; coronary revascularization, acute myocardial or cerebral ischemic event, sustained or hemodynamically destabilizing ventricular tachycardia or fibrillation within the previous two months; use of an alpha-adrenergic blocker, a calcium-channel blocker, or a class I antiarrhythmic drug within the previous four weeks or a beta-blocker within the previous two months; systolic blood pressure lower than 85 mm Hg; heart rate lower than 68 beats per minute; serum creatinine concentration higher than 2.8 mg per deciliter; serum potassium concentration lower than 3.5 mmol per liter or higher than 5.2 mmol per liter; increase of more than 0.5 mg per deciliter in the serum creatinine concentration or a change in body weight of more than 1.5 kg during the screening period
Metoprolol			
Anderson 1985 USA Fair quality	28% NYHA class avg: 2.8	Idiopathic dilated cardiomyopathy confirmed by ECG	Unstabilized overt cardiac failure; alcohol abuse; secondary cardiomyopathies; firm exclusions to beta blocker treatment (asthma, advanced heart block, allergy)

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Eichhorn 2001 Packer, 2001, 2002 Krum 2003 *The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial* Fair quality	Carvedilol (car) 50 mg daily *(n=1156)* Placebo (pla) *(n=1133)*	Usual medications for heart failure	*Primary: A* ll-cause mortality *Secondary:* (1) Combined risk of death/hospitalization for any reason; (2) combined risk of death or hospitalization for CV reason; (3) combined risk of death/hospitalization for HF; (4) patient global assessment	Age: pla=63.4; car=63.2 %male: pla=80; car=79 Race NR	% ischemic cause: pla=67; car=67 % left ventricular ejection fraction: pla=19.8; car=19.9 % heart failure hospitalization within past year: pla=65; car=66
Metoprolol					
Anderson 1985 USA Fair quality	Metoprolol (met) 100 mg daily Placebo (pla) x 19 months Begin 12.5 mg bid titrated over 2 weeks to target - median dose 25 mg bid.	Digitalis: 87% Diuretic: 80% Vasodilators: 40% Antiarrhythmics: 35% Anticoagulant (warfarin): 12%	*Primary:* Survival *Secondary:* Exercise duration (Naughton protocol)	Mean age 51 66% male Race NR	NR

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Eichhorn 2001 Packer, 2001, 2002 Krum 2003 *The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial* Fair quality	3106 screened/eligible nr/2289 randomized	withdrawn: pla=84; car=70/0 lost/analyzed(ITT): pla=1133; car=1156	*n (hazard ratio; 95%CI)* All-cause mortality: pla=190; car=130 (0.65; 0.52-0.81) Death/hospitalization for any reason: pla=507; car=425 (0.76; 0.67-0.87) Death/hospitalization for CV reason: pla=395; car=314 (0.73; 0.84-0.63) Death/hospitalization for HF: pla=357; pla=271 (0.69; 0.81-0.59) Hospitalizations, n(%) Worsening HF: pla=268(23.7); car=198(17.1) CV reason: pla=314(27.7); car=246(21.3) For any reason: pla=432(38.1); car=372(32.2) More than once: pla=188(16.6); car=152(13.1)	NR
Metoprolol				
Anderson 1985 USA Fair quality	Screened: NR Eligible: 50 Enrolled: 50 met (n=25) pla (n=25)	Dropout from treatment group: 5/25 (20%) Overall, 2 patients lost to follow-up Analyzed=50	*Primary* Deaths: met: 5/25 (20%) pla: 6/25 (24%) (NS) *Secondary* Exercise duration: met: 9.4 min pla: 8.2 min (NS)	NR

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Eichhorn 2001 Packer, 2001, 2002 Krum 2003 *The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial* Fair quality	Serious adverse events: pla=516(45.5%); car=451(39.0%)	One-year withdrawal rates: pla=18.5%; car=14.8%	Study stopped early based on the finding of a significant beneficial effect of carvedilol on survival that exceeded the prespecified interim monitoring boundaries Mortality reduction equivalent for age, gender, LVEF, cause of HF subgroups
Metoprolol			
Anderson 1985 USA Fair quality	NR	NR	

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Mean EF NYHA Class	Eligibility criteria	Exclusion criteria
Waagstein 1993 *Metoprolol in Dilated Cardiomyopathy (MDC) Trial* Fair quality	22% NYHA class I: 3% II: 45% III: 49% IV: 4%	16-75 years; symptomatic dilated cardiomyopathy; state of compensated heart failure by means of conventional treatment; systolic BP ≥90 mm Hg; heart rate ≥45 beats per minute	Treatment with beta blockers, calcium channel blockers, inotropic agents or high doses of tricyclic antidepressant drugs; significant CAD shown by angiography; clinical or histological signs of ongoing myocarditis; other life-threatening diseases; obstructive lung disease; excessive alcohol consumption; drug abuse; insulin-dependent diabetes; pheochromocytoma; thyroid disease

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Waagstein 1993 *Metoprolol in Dilated Cardiomyopathy (MDC) Trial* Fair quality	Metoprolol (met) 100-150 mg daily (higher target for higher weight) vs. placebo for 18 months and 12 months Run-in period 2-7 days. Begin 10 mg titrated over 6+ weeks to target - mean dose 108 mg/day.	Digitalis: 78% ACEI: 79% Nitrates: 14% Antiarrhythmics: 16% Frusemide: 75%	*Primary* Combined - total deaths and need for transplantation. *Secondary* Exercise duration (Naughton protocol in North America, bicycle exercise protocol in Europe begin 20W +10W increments); also LVEF, QOL, and NYHA change; and hospital readmissions. At 45 days, 3, 6, 12 and 18 months.	Mean age 49 73% male Race NR	Current smokers: 18%

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Waagstein 1993 *Metoprolol in Dilated Cardiomyopathy (MDC) Trial* Fair quality	Screened: NR Eligible: 417 Enrolled: 383 met (n=194) pla (n=189)	Withdrawn from study medication at 12 months: 54/383 (14%) Lost to LVEF measure: 44% Lost to QOL measure: 71% Lost to hospital followup: 6% Analyzed=383	*Primary* Total deaths or need for transplantation: met: 25/194 (12.9%) pla: 38/189 (20.1%) (NS) All-cause mortality: met=23(11.8%); pla=21(11.1%) Sudden death: met: 18/194 (9,3%) pla: 12/189 (6.3%) (NS) *Secondary* Exercise capacity at 6 and 12 months: met: +80s and +76s pla: +47s and +15s (Difference at 12 months, p=0.046) NYHA class improvement: data nr Quality of life: data nr Hospitalization patients: met: 37/184 (20.1%) pla: 49/177 (27.7%) (NS) Hospitalization episodes: met: 51/184 (27.7%) pla: 83/177 (46.9%) ($p \leq 0.05$)	NR

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Waagstein 1993 *Metoprolol in Dilated Cardiomyopathy (MDC) Trial* Fair quality	nr	*Withdrawals due to:* Progressive heart failure: met: 7/194 (3.6%) pla: 13/189 (6.9%) (NS) All "related" adverse events: met=1(0.5%); pla=3(1.6%)	

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Mean EF NYHA Class	Eligibility criteria	Exclusion criteria
Anonymous 1999 Goldstein 1999 Hjalmarson 2000 Goldstein 2001 Ghali 2002 Gottlieb 2002 *Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)* Fair quality	28% NYHA class II: 41% III: 55% IV: 4%	Age 40-80; symptomatic heart failure (NYHA class II-IV) for 3 months or more and receiving optimum standard therapy; stable clinical condition during 2 week run-in phase; LVEF of <40%	Acute MI or unstable angina within 28 days; indication or contraindication for treatment with beta-blockade or drugs with beta-blocking properties; heart failure secondary to systemic disease or alcohol abuse; scheduled or performed heart transplantation or cardiomyoplasty; implanted cardioversion defibrillator (expected or performed); CABG or percutaneous transluminal coronary angioplasty planned or performed in the past 4 months; atrioventricular block of the second or third degree; unstable decompensated heart failure; supine systolic BP >100 mm Hg; any serious disease that might complicate management and follow-up according to protocol; use of calcium antagonists; use of amiodarone within 6 months; poor compliance.

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Anonymous 1999 Goldstein 1999 Hjalmarson 2000 Goldstein 2001 Ghali 2002 Gottlieb 2002 *Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)* Fair quality	Metoprolol (met) 200 mg/day vs. placebo for 1 year 2-week placebo run-in. Begin 12.5 mg (NYHA class III/IV) or 25 mg daily, titrated over 6 weeks to target.	Diuretics: 90% ACEI: 89% Angiotensin I: 7% ACEI or Angiotensin II: 96% Digitalis: 64% Aspirin:46% Lipid-lowering agents: 26%	*Primary:* Total mortality, and combined total mortality and all-cause hospitalization (time to first event) *Secondary:* Worsening heart-failure mortality or hospitalization (time to first event), other CV events, NYHA class change, and QOL substudy.	Mean ages: <60: 34% 60-69: 35% ≥70: 31% 77% male 94% White 5% Black 1% Other	Current daily smoker: 14.4% Heart failure: Ischemic: 65% Nonischemic: 35% Previous MI: 48% Atrial fibrillation: 16.6% Hypertension: 44% DM: 24.6%

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Anonymous 1999 Goldstein 1999 Hjalmarson 2000 Goldstein 2001 Ghali 2002 Gottlieb 2002 *Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)* Fair quality	Screened: NR Eligible (recruited): 4427 Enrolled: 3991 met (n=1990) pla (n=2001)	Total withdrawn: 589/3991 (15%) 0 lost to follow-up of vital status. Analyzed=3991	*Primary* All cause mortality: met=145(7.3%); pla=217(10.8%)(p=0.0009) Total mortality or All-cause hospitalization: met: 641/1990 (32.2%) pla: 767/2001 (38.3%)(p<0.001) Sudden death: met=3.9%; pla=6.5%(p=0.0002) Death or heart transplantation: met: 150/1990 (7.5%) pla: 218/2001 (10.9%) (p<0.001) Cardiac death or nonfatal MI: met: 139/1990 (7.0%) pla: 225/2001 (11.2%) (p<0.001) *Secondary* All hospitalization (patients): met: 1021/1990 (51.3%) pla: 1149/2001 (57.4%) (p=0.005) CV hospitalization (patients): met: 394/1990 (19.8%) pla: 494/2001 (24.7%) (p<0.001) NYHA class improvement favors met group (p=0.003).	NR

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Anonymous 1999 Goldstein 1999 Hjalmarson 2000 Goldstein 2001 Ghali 2002 Gottlieb 2002 *Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)* Fair quality		*Withdrawals due to:* Dizziness: met: 12/1990 (0.6%) pla: 6/2001 (0.3%) (NS) Heart failure: met: 78/1990 (3.9%) pla: 117/2001 (5.8%) (p<0.01) Weight increase: NR Bradycardia: met: 16/1990 (0.8%) pla: 5/2001 (0.2%) (p<0.025) Hypotension: met: 12/1990 (0.6%) pla: 5/2001 (0.2%) (NS) Any adverse event: met=9.8%; pla=11.7%	

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Mean EF NYHA Class	Eligibility criteria	Exclusion criteria
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)* Fair quality	28.5% NYHA Class: I: 6.8% II: 69.2% III: 23.5% IV: 0.5%	Symptomatic heart failure (Class II-IV); 6-minute walk distance of <500 m; LVEF<40%	nr

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)* Fair quality	*Stage 1:* Candesartan: 4-16 mg daily Enalapril: 20 mg daily Candesartan 48 mg and enalapril 20 mg *Stage 2:* Addition of Metoprolol CR (met CR) 25-200 mg daily or placebo	Stage I medications	*Primary:* 1) 6-minute walk distance 2) neurohumoral parameters *Secondary:* 1) NYHA functional class 2) Quality of life (Minnesota Living With Heart Failure questionnaire)	Mean age=61.5 82.1% male 87.1% white	Heart failure duration: 7-12 mo: 12.4% >12 mo: 87.6% Previous MI: 63.6% Diabetes: 25.3% Smoker Current: 15% Former: 61% Never: 23.9% NYHA Class: I: 6.8% II: 69.2% III: 23.5% IV: 0.5% LVEF(mean): 28.5%

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)* Fair quality	nr/468/426	nr/nr/426	6-minute walk distance change (meters): met CR=(-1); pla=(-3) Quality of life: met CR=pla (data nr) NYHA functional class: met CR=pla (data nr) All-cause deaths: met CR=8(3.7%); pla=17(8%) (NS) Sudden death due to worsening heart failure: met CR=0.5%; pla=3(1.4%) Hospitalizations due to heart failure: met CR=15(7%); pla=5(2.3%)	nr

Evidence Table 8. Placebo controlled trials of beta blockers for heart failure (continued)

Author Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)* Fair quality	nr	Overall discontinuation due to intolerability: met CR=11%; pla=12% Permanent discontinuation due to: Symptomatic hypotension: met CR=4(1.9%); pla=2(0.9%) Worsening heart failure: met CR=7(3.3%); pla=5(2.4%) Symptomatic bradycardia: met CR=0; pla=0	

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Anonymous 1994 The Cardiac Insufficiency Bisoprolol Study (CIBIS I) Fair quality	Adequate; computer generated	NR	Differences in: - history of MI Bis: 169 (53%) pla: 134 (42%) (p<.005) - diastolic blood pressure Bis: 79.5 mm Hg Pla: 77.9 mm Hg (p=.03)	Mean Age: 59.6 Male: 82.5% Ethnicity: NR	Screened NR 641 randomized
Anonymous 1999 The Cardiac Insufficiency Bisoprolol Study (CIBIS II)	Adequate; computer generated random numbers	Adequate; centralized	Yes	Mean age: 61 Male: 80.5% Ethnicity: NR	Screened NR 2647 randomized

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Anonymous 1994 The Cardiac Insufficiency Bisoprolol Study (CIBIS I) Fair quality	CHF due to hypertrophic or restrictvie cardiomyopathy with predominant left ventricular diastolic dysfunction; or secondary to mitral or aortic valve disease surgically repaired <6 months, or not repaired. MI <3 months. Awaiting bypass surgery or transplantation. Disabling permanent dyspnea at rest, insulin-dependent diabetes, asthma, renal insufficiency, hypothyroidism or hyperthyroidism, short life expectancy due to severe illness or malignancy. Resting heart rate <65 bpm; systolic blood pressure <100 or >160 mm Hg. No digitalis or amiodarone treatment <6 weeks before or 2 months after inclusion. Beta-adrenergic agonist or antagonist drugs and phosphodiesterase inhibitors prohibited.	Yes	Yes, blinded independent committee	Yes, allocation centrally controlled; titration blinded	Yes	Yes
Anonymous 1999 The Cardiac Insufficiency Bisoprolol Study (CIBIS II)	Uncontrolled hypertension, MI or unstoppable angina pectoris in past 3 months, revascularization in past 6 months, previous or scheduled heart transplant, atrioventricular block > first degree without pacemaker, resting heart rate < 60 bpm, systolic blood pressure <100, renal failure, reversible obstructive lung disease or planned therapy with beta-adrenoreceptor blockers. No treatment with beta blockers (also eye drops), calcium antagonists, inotropic agents except digitalis, and antiarrhythmic drugs except amiodarone during trial.	Yes	Yes, blinded independent committee	Yes	Yes	Yes

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Anonymous 1994 The Cardiac Insufficiency Bisoprolol Study (CIBIS I) Fair quality	Yes	Attrition=157/641 (24.5%); others NR	No	Fair	NR	Yes	Mean 1.9 years
Anonymous 1999 The Cardiac Insufficiency Bisoprolol Study (CIBIS II)	Yes	Attrition=69/2647 (2.6%); others NR	No	Good	NR	Yes	Mean 1.3 years

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
MOCHA Bristow1996 Lindenfeld2001 Multicenter Oral Carvedilol Heart Failure Assessment	NR	NR	Yes	Mean age: 59.5 Male: 76% Caucasian: 78%	Screened: NR Eligible for run-in: 376 Enrolled: 345

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
MOCHA Bristow1996 Lindenfeld2001 Multicenter Oral Carvedilol Heart Failure Assessment	Uncorrected valvular disease, hypertrophic or postpartum cardiomyopathy, uncontrolled symptomatic or sustained ventricular tachycardia, acute MI within 3 months, planned or likely revascularization or transplantation within 6 months after screening. Also, sick sinus syndrome, 2nd- or 3rd-degree heart block not treated with pacemaker, symptomatic peripheral vascular disease limiting exercise testing, sitting systolic blood pressure <85 mm Hg or >160 mm Hg, CV accident within last 3 months, cor pulmonale, obstructive pulmonary disease requiring oral bronchodilator or steroid therapy, and other selected disorders and sensitivities. Excluded drugs: alcohol intake >100 g/day, use of investigational drug within 30 days, CCBs, amiodarone within 3 months, and others.	Yes	NR	NR	NR	Unclear

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
MOCHA Bristow1996 Lindenfeld2001 Multicenter Oral Carvedilol Heart Failure Assessment	NR	Attrition=52/345 (15%); others NR	No	Fair	SmithKline Beecham Pharmaceuticals	NR	6 months

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
PRECISE Packer1996	NR	NR	Yes	Mean age: 60.3 years Male: 73% Ethnicity: NR	Screened: NR Eligible for run-in: 301 Enrolled: 278
Colucci 1996 U.S. Carvedilol Heart Failure Study Group	NR	NR	Yes	Mean age: 55 Male: 85% Ethnicity: NR	Screened: NR Eligible for run-in: 389 Enrolled: 366

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
PRECISE Packer1996	Uncorrected primary valvular disease, active myocarditis or obstructive or restrictive cardiomyopathy; MI, stroke, unstable angina or CABG within 3 months; symptomatic or sustained ventricular tachycardia not controlled by antiarrhythmic drugs or implantable defibrillator; sick sinus syndrome or advanced heart block (without pacemaker); any condition other than heart failure that could limit exercise; systolic blood pressure >160 or <85 mm Hg or diastolic blood pressure >100 mm Hg; heart rate <68 bpm; significant hepatic, renal or endocrine disease; drug or alcohol abuse; or any condition that could limit survival. Patients receiving CCBs, alpha- or beta-adrenergic agonist or antagonists or specific antiarrhythmic drugs.	Yes	NR	NR	NR	Unclear
Colucci 1996 U.S. Carvedilol Heart Failure Study Group	Uncorrected primary valvular disease, nondilated or hypertrophic cardiomyopathy; MI, stroke, unstable angina or CABG within 3 months; symptomatic or sustained ventricular tachycardia not controlled by antiarrhythmic drugs or implantable defibrillator within 3 months; likelihood of revascularization or transplantation within 12 months; sick sinus syndrome or advanced heart block (without pacemaker); any condition other than heart failure that could limit exercise; systolic blood pressure >160 or <85 mm Hg or diastolic blood pressure >100 mm Hg; clinically significant hepatic or renal disease, or any condition that could limit survival. Patients receiving amiodarone within 3 months before screening.	Yes	NR	NR	NR	Yes

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
PRECISE Packer1996	NR	Attrition=49/278 (18%); others NR	No	Fair	SmithKline Beecham Pharmaceuticals & Boehringer Mannheim Therapeutics	NR	6 months
Colucci 1996 U.S. Carvedilol Heart Failure Study Group	NR	Attrition=31(8.5%); others NR	NR	Fair	SmithKline Beecham Pharmaceuticals & Boehringer Mannheim Therapeutics	NR	Mean 7 months

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group*	NR	NR	Yes	Mean age: 60 years (range 22-85) Male: 58% Ethnicity: - Caucasian: 71% - Black: 21% - Other: 8%	Screened: NR Eligible for run-in: 131 Enrolled: 105
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group*	Adequate; computer generated	Adequate; centralized	Yes	Mean age 67 80% male Race NR	Screened: NR Eligible for run-in: 301 Enrolled: 278

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group*	Uncorrected primary valvular disease, nondilated or hypertrophic cardiomyopathy; MI, stroke, unstable angina or CABG within 3 months; symptomatic or sustained ventricular tachycardia not controlled by antiarrhythmic drugs or implantable defibrillator within 3 months; likelihood heart transplantation within 6 months; sick sinus syndrome or advanced heart block without pacemaker; any condition other than heart failure that could limit exercise; systolic blood pressure >160 or <85 mm Hg or diastolic blood pressure >100 mm Hg; clinically significant hepatic or renal disease, or any condition that could limit survival.	Yes	NR	NR	NR	No
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group*	Current NYHA class IV; heart rate below 50 beats per minute; sick sinus syndrome; second or third degree heart block; systolic BP <90 mm Hg or >160/100 mm Hg; treadmill exercise duration <2 minutes or >18 minutes; coronary event or procedure within previous 4 weeks; primary myocardial or valvular disease; current treatment with beta-blocker, beta-agonist or verapamil; insulin-dependent DM; obstructive airways disease; hepatic disease; any other life-threatening non-cardiac disease.	Yes	Yes	Yes	Yes	Yes

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group*	NR	Attrition=12(11.4%); others NR	Unclear; 87.6% of patients did not complete final QOL assessment	Poor	SmithKline Beecham Pharmaceuticals & Boehringer Mannheim Therapeutics	NR	Mean 3 months
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group*	NR	Attrition=14.9%; others NR	NR	Good	SmithKline Beecham - independently initiated conducted, analyzed by ANZ Heart Failure Research Collaborative	Yes	Mean 19 months

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Cleland, 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)*	Adequate; random numbers table	Adequate; centralized	Unclear; baseline characteristics provided for only 78.8% of all randomized patients	Good mean age=62.5 90% male	489 screened 387 randomized
COPERNICUS Eichhorn, 2001 Packer, 2001 Packer, 2002 Krum, 2003	NR	NR	Yes	Good mean age >55 higher proportion male	3106 screened 2289 randomized

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Cleland, 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)*	Patients younger than 40 years and women of child-bearing age; resting heart rate less than 60 beats per minute; sitting systolic blood pressure less than 85 mm Hg; unstable angina; arrhythmias; uncontrolled hypertension; obstructive pulmonary disease; poorly controlled diabetes; or clinically relevant renal or hepatic disease; those receiving non-dihydropiridine calcium-channel blockers; beta blockers, or antiarrhythmic agents other than amiodarone	Yes	Yes	Yes	Yes	No
COPERNICUS Eichhorn, 2001 Packer, 2001 Packer, 2002 Krum, 2003	Heart failure that was caused by uncorrected primary valvular disease or a reversible form of cardiomyopathy; had received or were likely to receive a cardiac transplant; had severe primary pulmonary, renal, or hepatic disease; or had a contraindication to beta-blocker therapy; coronary revascularization, acute myocardial or cerebral ischemic event, sustained or hemodynamically destabilizing ventricular tachycardia or fibrillation within the previous two months; use of an alpha-adrenergic blocker, a calcium-channel blocker, or a class I antiarrhythmic drug within the previous four weeks or a beta-blocker within the previous two months; systolic blood pressure lower than 85 mm Hg; heart rate lower than 68 beats per minute; serum creatinine concentration higher than 2.8 mg per deciliter; serum potassium concentration lower than 3.5 mmol per liter or higher than 5.2 mmol per liter; increase of more than 0.5 mg per deciliter in the serum creatinine concentration or a change in body weight of more than 1.5 kg during the screening period	Yes	Yes	Yes	Yes	Yes

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Cleland, 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)*	Unclear	Attrition=21.2%; others nr	nr	Fair	Hoffman-La Roche	Yes	189 days (mean)
COPERNICUS Eichhorn, 2001 Packer, 2001 Packer, 2002 Krum, 2003	NR	attrition reported; others NR	None	Fair	Roche; GlaxoSmithKline	Yes	Mean 10.4 months

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Packer, 1996 Colucci, 1996 Yancy, 2001 *U.S. Carvedilol Heart Failure Study Group*	NR	NR	Yes	Good mean age >55 higher proportion male	Screened NR 1094 randomized
Anderson 1985	Inferior; pairs	NR	Yes	Mean age 51 66% male Race NR	Screened: NR Eligible: 50 Enrolled: 50
Waagstein 1993	Computer-generated with "block size of 4," stratified	NR	Yes	Mean age 49 73% male Race NR	Screened: NR Eligible: 417 Enrolled: 383

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Packer, 1996 Colucci, 1996 Yancy, 2001 *U.S. Carvedilol Heart Failure Study Group*	Major CV event or surgical procedure within 3 months of study entry; uncorrected, primary valvular disease; active myocarditis; sustained ventricular tachycardia or advanced heart block not controlled by antiarrhythmic intervention or a pacemaker; systolic blood pressure of more than 160 or less than 85 mm Hg or diastolic blood pressure of more than 100 mm Hg; a heart rate of less than 68 beats per minute; clinically important hepatic or renal disease; or any condition other than heart failure that could limit exercise or survival; concomitant use of calcium-channel blockers α- or β-adrenergic agonists or antagonists or class IC or III antiarrhythmic agents	Yes	Yes	Yes	Yes	Yes
Anderson 1985	Unstabilized overt cardiac failure; alcohol abuse; secondary cardiomyopathies; firm exclusions to beta blocker treatment (asthma, advanced heart block, allergy)	Yes	NR	NR	NR	Yes
Waagstein 1993	Treatment with beta blockers, calcium channel blockers, inotropic agents or high doses of tricyclic antidepressant drugs; significant CAD shown by angiography; clinical or histological signs of ongoing myocarditis; other life-threatening diseases; obstructive lung disease; excessive alcohol consumption; drug abuse; insulin-dependent diabetes; pheochromocytoma; thyroid disease	Yes	Yes	NR	NR	Yes for primary endpoint Nor for other

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Packer, 1996 Colucci, 1996 Yancy, 2001 *U.S. Carvedilol Heart Failure Study Group*	NR	AE withdrawals reported; others NR	none	fair	SmithKline Beecham Pharmaceuticals and Roche Laboratories Two investigators/authors are employees and stock holders of SKB	Yes	12 months
Anderson 1985	NR	Attrition=5/50(10%); others NR	No	Fair	Univ. of Utah SOM and LDS Hospital, Salt Lake City	NR	Mean 19 months
Waagstein 1993	NR	Attrition=14.1%; others NR	High loss for secondary endpoints except hospitalization.	Fair	Astra Pharmaceutical divisions and Ciba-Geigy Corp., Swedish Heart & Lung Foundation & Swedish Medical Research Council	NR	12 months and 18 months (n=211/383)

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
MERIT-HF Anonymous, 1999 Goldstein, 1999 Hjalmarson, 2000 Goldstein, 2001 Ghali, 2002 Gottlieb, 2002 Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure	Adequate; computer generated	Adequate; centralized	Yes	Mean ages: <60: 34% 60-69: 35% ≥70: 31% 77% male White: 94% Black: 5% Other: 1%	Screened: NR Eligible (recruited): 4427 Enrolled: 3991
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)*	nr	nr	yes	Mean age=61.5 82.1% male 87.1% white	Screened: NR Eligible: 468 Enrolled: 426

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
MERIT-HF Anonymous, 1999 Goldstein, 1999 Hjalmarson, 2000 Goldstein, 2001 Ghali, 2002 Gottlieb, 2002 Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure	Acute MI or unstable angina within 28 days; indication or contraindication for treatment with beta-blockade or drugs with beta-blocking properties; heart failure secondary to systemic disease or alcohol abuse; scheduled or performed heart transplantation or cardiomyoplasty; implanted cardioversion defibrillator (expected or performed); CABG or percutaneous transluminal coronary angioplasty planned or performed in the past 4 months; atrioventricular block of the second or third degree; unstable decompensated heart failure; supine systolic BP >100 mm Hg; any serious disease that might complicate management and follow-up according to protocol; use of calcium antagonists; use of amiodarone within 6 months; poor compliance.	Yes	Yes	NR	NR	Yes
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)*	nr	yes	yes	yes	yes	yes

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blockers for heart failure (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
MERIT-HF Anonymous, 1999 Goldstein, 1999 Hjalmarson, 2000 Goldstein, 2001 Ghali, 2002 Gottlieb, 2002 Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure	NR	Attrition=589/3991 (15%); others NR	No	Fair	Project leader, coordinator, medical advisor, and acknowledgement to Astra Hassle, Sweden	Yes	1 year (mean)
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)*	nr	Compliance (>80% of study medication): met CR=93%; pla=92%; others nr	nr	Fair	nr	yes	24 weeks

Evidence Table 9. Outcomes in placebo controlled trials of beta blockers for heart failure

Study, year	Interventions	Trial Duration	Number enrolled	Mean Ejection Fraction NYHA class	Primary Endpoint	All-cause mortality rates NNT (p-value) Relative Risk (95% CI)	Sudden death rates NNT (p value) Relative Risk (95% CI)
Trials of bisoprolol (selective) vs placebo							
Anonymous 1994 *CIBIS*	A: bis 5 mg B: placebo	1.9 years (mean)	641	25.4% NYHA Class III: 95% IV: 5%	Total mortality	53/320(16.6%) 67/321(20.9%)	15/320(4.7%) 17/321(5.3%)
Anonymous 1999 *CIBIS-II*	A: bis 10 mg B: placebo	1.3 years (mean)	2,647	27.5% NYHA Class III: 83% IV: 17%	All-cause mortality	**156/1327(12%)** **228/1320(17%)** **NNT=19; p<0.0001** **RR(95%CI): 0.68(0.56-0.82)**	**48/1327(4%)** **83/1320(6%)** **NNT=38; p=0.0011** **RR(95%CI): 0.57(0.41-0.81)**
Trials of bucindolol (nonselective) vs placebo							
Anonymous 2001 *BEST*	A: buc 100-200 mg B: placebo	2.0 years (mean)	2,708	23% NYHA Class III: 91.7% IV: 8.3%		411/1354(30%) 449/1354(33%) (NS)	182/1354(13%) 203/1354(15%) (NS)
Trials of carvedilol (nonselective) vs. placebo							
Bristow 1996 *US Carvedilol Heart Failure Study Group: MOCHA*	A: car 12.5 mg B: car 25 mg C: car 50 mg D: all car groups E: placebo	6 months	345	23% NYHA Class II: 46% III: 52% IV: 2%	Improvement in submaximal exercise	**5/83(6%)** **6/89(6.7%)** **1/89(1.1%)** **12/261(4.6%)** **13/84(15.5%)** **NNT(D vs E)=9; p<0.001** **RR(95%CI)(D vs E)=0.27(0.13-0.57)**	D(all): 6/261(2.3%) E(pla): 6/84(7.1%)

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

Evidence Table 9. Outcomes in placebo controlled trials of beta blockers for heart failure (continued)

Study, year	Progressive heart failure death NNT (p value) Odds ratio (95% CI)	NYHA Class	Exercise capacity	Quality of life	Overall quality
Trials of bisoprolol (selective) vs placebo					
Anonymous 1994 *CIBIS*	NR	*Improvement (>/= 1 class)* 68/320(21%) 48/321(15%) (p=0.03) *Deterioration (>/= 1 class)* 41/320(13%) 35/321(11%) (NS)	NR	NR	Fair
Anonymous 1999 *CIBIS-II*	***Hospital admission for worsening heart failure*** **159/1327(12%)** **232/1320(18%); p=0.0001**	NR	NR	NR	Good
Trials of bucindolol (nonselective) vs placebo					
Anonymous 2001 *BEST*					
Trials of carvedilol (nonselective) vs. placebo					
Bristow 1996 *US Carvedilol Heart Failure Study Group: MOCHA*	NR	Carvedilol had no effect on NYHA class ranking (original data NR)	Carvedilol had no effect at any dose on either 6-minute walk test results or 9-minute self-activated treadmill testing (original data NR)	Mean change in Minnesota Living With Heart Failure Questionnaire A=(-7.9) B=(-7.3) C=(-5.5) D=NR E=(-7.3)	Fair

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

Evidence Table 9. Outcomes in placebo controlled trials of beta blockers for heart failure

Study, year	Interventions	Trial Duration	Number enrolled	Mean Ejection Fraction NYHA class	Primary Endpoint	All-cause mortality rates NNT (p-value) Relative Risk (95% CI)	Sudden death rates NNT (p value) Relative Risk (95% CI)
Packer 1996 *US Carvedilol Heart Failure Study Group: PRECISE*	A: car 50-100 mg B: placebo	6 months	278	22% NYHA Class II: 40% III: 56% IV: 4%	Exercise tolerance	6/133(4.5%) 11/145(7.6%) (NS)	NR
Colucci 1996 *US Carvedilol Heart Failure Study Group: Mild*	A: car 50-100 mg B: placebo	12 months	366	23% NYHA Class II: 85% III: 14.5% III: 0	Progression of heart failure	2/232(0.9%) 5/134(4%) (NS)	NR
Cohn 1997 US Carvedilol Heart Failure Study Group	A: car 50 mg B: placebo	8 months	105	22% NYHA Class II: 1% III: 85.7% IV: 13.3%	Quality of life	2/70(2.8%) 2/35(5.7%) (NS)	NR
Anonymous 1997 *Australia/New Zealand Heart Failure Research Collaborative Group*	A: car 50 mg B: placebo	12 months	415	29% NYHA Class II: 26.5% III: 54% IV: 16%	Changes in LVEF; treadmill exercise duration	20/208(9.6%) 26/207(12.6%) (NS)	10/208(4.8%) 11/207(5.3%) (NS)

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

Evidence Table 9. Outcomes in placebo controlled trials of beta blockers for heart failure (continued)

Study, year	Progressive heart failure death NNT (p value) Odds ratio (95% CI)	NYHA Class	Exercise capacity	Quality of life	Overall quality
Packer 1996 *US Carvedilol Heart Failure Study Group: PRECISE*	NR	*Decrease in proportion of patients with Class III or IV (before/after treatment):* 64% to 41% 58% to 51%; p=0.014 *Deterioration* 3% 15%; p=0.001	*Mean increase in 6-minute walk test distance (m): 17 vs 6 (NS)* *Carvedilol had no effect on 9-minute treadmill test distance (original data NR)*	Carvedilol had no effect on quality of life as measured by Minnesota Living With Heart Failure Questionnaire (original data NR)	Fair
Colucci 1996 *US Carvedilol Heart Failure Study Group: Mild*	*Heart failure progression(deaths+hospitalizations+need for more medications):* 25/232(11%) 28/134(20.9%)(p=0.008) RR(95% CI): 0.52(0.32-0.85)	*Overall distribution of changes: car > pla (p=0.003)* Improved: 9% vs 12% Unchanged: 76% vs 84% Worsened: 15% vs 4%	*9-minute self-minute treadmill test: car=pla (original data NR)*	Mean change in Minnesota Living With Heart Failure Questionnaire: (-4.9) vs (-2.4) (NS)	Fair
Cohn 1997 US Carvedilol Heart Failure Study Group	NR		*Mean increase in 6-minute walk test distance (m):* 19.0 vs 28.4 (NS)	Mean improvement in Minnesota Living With Heart Failure Questionnaire: 11.6 vs 8.8 (NS)	Poor
Anonymous 1997 *Australia/New Zealand Heart Failure Research Collaborative Group*	14/208(6.7%) 15/207(7.2%) (NS)	Improved: 26% vs 28% No change: 58% vs 58% Worse: 16% vs 13%	*Treadmill exercise duration: car=pla (mean difference -7 seconds) (original data NR)* *6-minute walk distance: car=pla (mean difference -3 m) (original data NR)*	NR	Good

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

Evidence Table 9. Outcomes in placebo controlled trials of beta blockers for heart failure

Study, year	Interventions	Trial Duration	Number enrolled	Mean Ejection Fraction NYHA class	Primary Endpoint	All-cause mortality rates NNT (p-value) Relative Risk (95% CI)	Sudden death rates NNT (p value) Relative Risk (95% CI)
Packer 2001 *COPERNICUS*	A: car 50 mg B: placebo	10.4 months (mean)	2289	19.8% NYHA Class NR	Death from any cause	**130/1156(11.2%)** **190/1133(16.8%)** **NNT=19; p=0.00013** **RR(95%CI): 0.67(0.54-0.82)**	NR
Cleland 2003 *CHRISTMAS*	A: car 50 mg (100 mg for patients >/= 85 kg) B: placebo	4 months (maintenance)	305	29.5% NYHA Class I: 11.1% II: 60.3% III: 28.5%	Change in LVEF in patients designated as hibernators vs nonhibernators on carvedilol compared with placebo	8/187(4.3%) 6/188(3.2%)	NR
Trials of metoprolol (selective) vs. placebo							
Anderson 1985	A: met 100 mg B: placebo	19 months	50	28% Average NYHA class: 2.8	Survival	5/25(20%) 6/25(24%) (NS)	NR
Waagstein 1993 *MDC*	A: met 100-150 mg B: placebo	12-18 months	383	22% NYHA Class I: 3% II: 44% III: 49% IV: 4%	Combined fatal (all-cause mortality) and non-fatal (need for cardiac transplantation)	23/94(11.8%) 21/189(11.1%) (NS) *Combined primary endpoint:* 25/194(12.9%) 38/189(20.1%) (NS)	18/194(9.3%) 12/189(6.3%) (NS)

Evidence Table 9. Outcomes in placebo controlled trials of beta blockers for heart failure (continued)

Study, year	Progressive heart failure death NNT (p value) Odds ratio (95% CI)	NYHA Class	Exercise capacity	Quality of life	Overall quality
Packer 2001 *COPERNICUS*	NR	NR	NR	NR	Fair
Cleland 2003 *CHRISTMAS*	NR	NR	Exercise time (method nr) (seconds): 405 vs 427	NR	Fair
Trials of metoprolol (selective) vs. placebo					
Anderson 1985	NR	Mean NYHA class: 2.2 vs 2.6 (NS)	Exercise time in minutes (Modified Naughton protocol): 9.4 vs 8.2 (NS)	NR	Fair
Waagstein 1993 *MDC*	5/194(2.6%) 5/189(2.6%) (NS)	Improvement in NYHA class: met>pla; p<0.01 (original data NR)	Mean increase in exercise capacity (sec) (Modified Naughton protocol): 76 vs 15 (p=0.046)	met>pla (p=0.01) (original data NR)	Fair

Evidence Table 9. Outcomes in placebo controlled trials of beta blockers for heart failure

Study, year	Interventions	Trial Duration	Number enrolled	Mean Ejection Fraction NYHA class	Primary Endpoint	All-cause mortality rates NNT (p-value) Relative Risk (95% CI)	Sudden death rates NNT (p value) Relative Risk (95% CI)
Anonymous 1999 *MERIT-HF*	A: met CR 12.5-25 mg B: placebo	1 year (mean)	3991	28% NYHA Class II: 41% III: 55.4% IV: 3.6%	All-cause mortality and all-cause mortality+all-cause admission to hospital	**145/1990(7.3%)** **217/2001(10.8%)** **NNT=29; p=0.00009** **RR(95%CI): 0.67(0.55-0.82)**	**79/1990(3.9%)** **132/2001(6.5%)** **NNT=39; p=0.0002** **RR(95%CI): 0.59(0.45-0.78)**
Anonymous 2000 *RESOLVD*	A: met CR 25-200 mg B: placebo	24 weeks	426	28.5% NYHA Class: I: 6.8% II: 69.2% III: 23.5% IV: 0.5%	1) 6-minute walk distance 2) neurohumoral parameters	8/214(3.7%) 17/212(8.1%) (NS)	nr

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

Evidence Table 9. Outcomes in placebo controlled trials of beta blockers for heart failure (continued)

Study, year	Progressive heart failure death NNT (p value) Odds ratio (95% CI)	NYHA Class	Exercise capacity	Quality of life	Overall quality
Anonymous 1999 *MERIT-HF*	**30/1990(1.5%)** **58/2001(2.9%)** **NNT=72; p=0.0023** **RR(95%CI): 0.51(0.33-0.79)**	NR	NR	NR	Good
Anonymous 2000 *RESOLVD*	1/214(0.5%) 3/212(1.4%)	met CR=pla (data nr)	6-minute walk test change (meters) -1 vs -3	met CR=pla (data nr)	Fair

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

Evidence Table 10. Head to head trials of beta blockers for heart failure

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Sanderson 1999 China	RCT	Patients with typical symptoms of heart failure and reduced LV ejection fraction (<0.45)	Valvular heart disease as the etiology of LV dysfunction, active myocarditis, unstable angina, a documented history of sustained ventricular tachycardia or symptomatic nonsustained ventricular tachycardia or second- or third degree atrioventricular block; chronic obstructive lung diseases, asthma, long-term alcohol or drug abuse or chronic renal failure (serum creatine >200 μmol/liter), hepatic hematological, neurological or collagen vascular disease
Kukin 1999	RCT Open	Patients with chronic heart failure secondary to ischemic heart disease, valvular myopathy, or idiopathic cardiomyopathy; symptomatic (NYHA class II, III, or IV) and had documented systolic dysfunction, with a radionuclide gated blood pool scan ejection fraction </= 35%; taking stable outpatient doses of digoxin and ACEIs or angiotensin II receptor antagonists for >/= 6 weeks and a stable dose of diuretics for >/= 2 weeks	Obstructive valvular disease, acute myocardial infarction within 6 weeks, or active angina

Evidence Table 10. Head to head trials of beta blockers for heart failure (continued)

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Sanderson 1999 China	Metoprolol (met) 100 mg daily *(n=26)* Carvedilol (car) 50 mg daily *(n=25)* x 12 weeks	Frusemide ACE inhibitor Angiotensin II receptor antagonist	Minnesota Heart Failure Symptom Questionnaire NYHA Functional Class assessment 6-min corridor walk test at weeks 4, 8 and 12	Mean age: met=60.4; car=58.7 %male: met=88.5; car=68.0 100% Chinese	Mean NYHA class: met=2.7; car=2.6 Mean symptom questionnaire score: met=13.1; car=17.2 Mean ETT (6-min walk, feet): met=1164; car=1122 *Etiology* IDC%: met=38.5; car=52 ICM%: met=19.2; car=24 HTHD%: met=42.3; car=24	NR/NR/51
Kukin 1999	Metoprolol (met) *(n=30)* or Carvedilol (car) *(n=37)* at a target dose of 50 mg daily for patients weighing < 85 kg and 100 mg daily for patients weighing > 85 kg x 6 months	Digoxin ACEIs Angiotensin II receptor antagonists Diuretics	Minnesota Living with Heart Failure questionnaire (Minn LwHFQ) 6-minute corridor walk tests Maximal exercise bicycle tests at 4 and 6 months	Mean age: met=55; car=60 %male: met=66.7; car=70.3 Race nr	*Etiology* Ischemic%: met=33.3; car=48.6 Idiopathic%: met=60; car=43.2 Valvular%: met=6.7; car=8.1 NYHA II%: met=23.3; car=16.2 NYHA III%: met=70; car=72.9 NYHA IV%: met=6.7; car=10.8 Minn LwHFQ mean: met=52; car=52 6-min walk test mean (ft): met=1228; car=1133	NR/NR/67

Evidence Table 10. Head to head trials of beta blockers for heart failure (continued)

Author Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Sanderson 1999 China	met=3; car=5/nr/nr	Symptom questionnaire score mean: met=4.8; car=8.1 NYHA functional class mean: met=2.2; car=2.2 ETT(6-min walk, feet) mean: met=1263; car=1194	NR	NR	NR
Kukin 1999	14 withdrawn/0 lost/53 analyzed	*NYHA class (#pts at baseline/month 6)* I: met=0/1; car=0/0 II: met=5/11; car=5/9; III: met=17/11; car=22/21 IV: met=1/0; car=3/0 *Minn LwHFQ at 6 months (mean change in points):* met=(-15); car=(-15) *6-minute walk (mean change in ft. at 6 months):* met=(+81);	NR	NR	NR

Evidence Table 10. Head to head trials of beta blockers for heart failure (continued)

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Metra 2000	RCT	Patients with chronic heart failure caused by an ischemic or nonischemic cardiomyopathy; NYHA class II, III, or IV symptoms for >/= 6 months; LV ejection fraction </= 0.35 by radionuclide ventriculography, and a peak VO2 </= 25 mL/kg-1/min-1 by cardiopulmonary exercise testing; concomitant treatment with furosemide and an ACEI (or angiotensin-receptor blocker if the ACEI was not tolerated) and had constant doses of background medicaiton as an outpatient for 1 week before the study	Patients with unstable angina, an acute myoardial infarction, or a coronary revascularization procedure within 3 months; history of alcohol abuse; primary valve disease; congenital heart disease; systolic blood pressure <90 mm Hg; concomitant disease that might adversely influence prognosis or impair exercise capacity; contraindications to b-blocker therapy; concomitant treatment with other β-blockers, α-antagonists, calcium antagonists or antiarrhythmic agents (except amiodarone)

Evidence Table 10. Head to head trials of beta blockers for heart failure (continued)

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Metra 2000	*Weight <75 kg/Weight >/= 75 kg* Metoprolol tartrate (met): 100/200 mg daily (n=75) Carvedilol (car): 50/100 mg daily *(n=75)* x 44 months	Frusemide ACE inhibitor Angiotensin II receptor antagonist	Bicycle exercise testing 6-minute walk test Minnesota Living with Heart Failure Questionnaire (Minn LwHFQ) NYHA functional classification administered every 3 months	Age= met=58; car=55 Gender(%male): met=90.7; car=90.7 Race nr	*Etiology* IDC(%): met=46(61.3); car=47(62.7) CAD(%): met=29(38.7); car=28(37.3) *NYHA class n(%)* II: met=23(30.7); car=23(30.7) III: met=44(58.7); car=46(61.3) IV: met=8(10.7); car=6(8)	NR/NR/150

Evidence Table 10. Head to head trials of beta blockers for heart failure (continued)

Author Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Metra 2000	28 withdrawn/0 lost/122 analyzed	*NYHA class (#pts at baseline/month 6)* I: met=0/1; car=0/0 II: met=5/11; car=5/9; III: met=17/11; car=22/21 IV: met=1/0; car=3/0 *Minn LwHFQ at 6 months (mean change in points):* met=(-15); car=(-15) *6-minute walk (mean change in ft. at 12 months):* met=(+81); car=(+63) Minn LwHFQ mean score, baseline/12 months(change): met=39/32(-7); car=32/24(-8) Bicycle exercise testing duration; sec, mean at baseline/12 mo (change): met=593/649(+56); car=531/576(+45) *Death/urgent transplantation:* met=21; car=17	NR	*Most common AE's* <u>met</u> worsening heart failure=13(17.3%) dizziness=1(1.3%) hypotension=2(2.7%) symptomatic bradycardia=2(2.7%) <u>car</u> dizziness=11(14.7%) worsening heart failure=6(8.0%) symptomatic bradycardia=3(4.0%) hypotension=2(2.7%) Raynaud's phenomenon=1(1.3%)	met=3; car=2

Evidence Table 10. Head to head trials of beta blockers for heart failure (continued)

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Metra 2000 USA, Italy	RCT	Patients with chronic HF caused by an ischemic or nonischemic cardiomyopathy who had NYHA function II-IV symptoms, a LVEF </=35% by radionuclide ventriculography, and ongoing treatment with furosemide and an ACEI	Patients with an acute ischemic event or a coronary revascularization procedure within 3 months; a history of alcohol abuse; primary valve disease or congenital heart disease; frequent ventricular premature beats and/or runs of ventricular tachycardia; contraindications to beta-blocker therapy; concomitant treatment with other beta-blockers, α-antagonists, calcium antagonists or antiarrhythmic agents (except amiodarone)
Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	RCT	Men or women with symptomatic chronic heart failure (HYHA class II-IV); at least one cardiovascular admission during the previous 2 years; on stable heart failure treatment with ACE inhibitors for at least 4 weeks unless contraindicated; on treatment diuretics (>40 mg of frusemid or equivalent) for at least 2 weeks; LVEF </= 35% measured within the previous 3 months by echocardiography or radionuclide ventriculography	Recent change in treatment within 2 weeks before randomization; requirement for intravenous inotropic therapy; current treatment with non-dihydropyridine calcium channel blockers (diltiazem, verapamil); amiodarone (>200 mg per day); class-I antiarrhythmic drugs; unstable angina; myocardial infarction; coronary revascularisation or stroke within the previous 2 months; uncontrolled hypertension (SBP >170 mm Hg or DBP >105 mm Hg); hemodynamically significant valvular disease; symptomatic and sustained ventricular arrhythmias within the past 2 months note adequately treatment with antiarrhythmic drugs or implantation of an automatic defibrillator; pregnancy; women with childbrearing potential on inadequate contraception; known drug or alcohol misuse; poor compliance; any other serious systemic disease; contraindication to beta blockers

Evidence Table 10. Head to head trials of beta blockers for heart failure (continued)

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Metra 2000 USA, Italy	*Weight <75 kg/Weight >/= 75 kg* Metoprolol tartrate (met): 100/200 mg daily (n=17) Carvedilol (car): 50/100 mg daily *(n=17)* x 9-12 months	Furosemide ACE inhibitor	NYHA functional classification x 9-12 months	Mean age: met=60; car=56 Gender(%male): met=17.6; car=23.5 Race nr	*Etiology* IDC n(%): met=11(64.7); car=11(64.7) CAD n(%): met=6(35.3); car=6(35.3) *NYHA functional class* II n(%): met=5(29.4); car=3(17.6) III n(%): met=12(70.6); car=13(76.5) IV n(%): met=0; car=1(5.9)	nr/nr/34
Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	Carvedilol (car) 50 mg Metoprolol (met) 100 mg x 58 months (mean)	ACE inhibitor Diuretic Digitalis Angiotensin II inhibitor Other vasodilator	Follow-up visits at 4-month intervals	Mean age: 62 79.8% male 98.9% White	*NYHA class:* II: 48.4% III: 47.8% IV: 3.8% Duration congestive heart failure: 42.4 months *Cause* Ischemic heart disease: 52.5% Hypertension: 17.7% Dilated cardiomyopathy: 43.9% Previous valve surgery: 2.5% Left ventricular ejection fraction (mean): 26%	nr/nr/3029 (car n=1511; met n=1518)

Evidence Table 10. Head to head trials of beta blockers for heart failure (continued)

Author Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Metra 2000 USA, Italy	29 analyzed	*Per protocol analysis met n=14; car n=15* *NYHA class, n at end of study(%)* I: met=3(21.4); car=4(26.7) II: met=10(71.4); car=7(46.7) III: met=1(7.1); car=3(20.0) IV: met=0; car=1(6.7)	NR	NR	NR
Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	964(31.8%) withdrawn/5(0.03%) lost to fu/3029 analyzed	<u>All deaths</u> car=512(34%) met=600(40%) Hazard ratio(95% CI): 0.83(0.74-0.93) NNT: 18 p=0.002 <u>Cardiovascular deaths</u> car=438(29%) met=534(35%) Hazard ratio(95% CI): 0.80(0.70-0.90) NNT=17 p=0.0004 Non-cardiovascular deaths: car=74(5%); met=66(4%) (NS) All deaths and all-cause admission: car=1116(74%); met=1160(76%) (NS)	All reports of adverse events were included irrespective of whether the investigators thought they had been caused by the treatment; adverse events that were fatal or life-threatening, required or extended admission, or resulted in persistent or significant disability or incapacity were labelled serious	Overall adverse event incidence: car=1420(94%); met=1457(96%)	NR

Evidence Table 10a. Quality assessments of head to head trials of beta blockers for heart failure

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Sanderson 1999 China	NR	NR	Yes	Good Mean age: >55 Gender: >%male	51
Kukin 1999	NR	NR	Yes	Good Mean age: >55 Gender: >%male	67
Metra 2000	NR	NR	Yes	Good Mean age: >55 Gender: >%male	150

Evidence Table 10a. Quality assessments of head to head trials of beta blockers for heart failure (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Sanderson 1999 China	Valvular heart disease as the etiology of LV dysfunction, active myocarditis, unstable angina, a documented history of sustained ventricular tachycardia or symptomatic nonsustained ventricular tachycardia or second- or third degree atrioventricular block; chronic obstructive lung diseases, asthma, long-term alcohol or drug abuse or chronic renal failure (serum creatine >200 μmol/liter), hepatic hematological, neurological or collagen vascular disease	Yes	Yes	Yes	Yes	Unclear
Kukin 1999	Obstructive valvular disease, acute myocardial infarction within 6 weeks, or active angina	Yes	N/A - open study	N/A - open study	N/A - open study	No
Metra 2000	Unstable angina,acute myoardial infarction, or a coronary revascularization procedure within 3 months; history of alcohol abuse; primary valve disease; congenital heart disease; systolic blood pressure <90 mm Hg; concomitant disease that might adversely influence prognosis or impair exercise capacity; contraindications to b-blocker therapy; concomitant treatment with other β-blockers, α-antagonists, calcium antagonists or antiarrhythmic agents (except amiodarone)	Yes	Yes	Yes	Yes	No

Evidence Table 10a. Quality assessments of head to head trials of beta blockers for heart failure (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Sanderson 1999 China	Unclear	Attrition reported; Others NR	NR	Fair	NR	Yes	12 weeks
Kukin 1999	NR	Attrition reported; Others NR	None	Fair	SKB	Yes	6 months
Metra 2000	NR	Attrition reported; Others NR	None	Fair	CARIPLO funds University of Brescia	Yes	44 months

Evidence Table 10a. Quality assessments of head to head trials of beta blockers for heart failure (continued)

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Metra 2000 US, Italy	NR	NR	Yes	Fair Mean age >55 Gender: >%female	34
Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	NR	adequate	Yes	Mean age: 62 79.8% male 98.9% White	3029

Evidence Table 10a. Quality assessments of head to head trials of beta blockers for heart failure (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Metra 2000 US, Italy	Patients with an acute ischemic event or a coronary revascularization procedure within 3 months; a history of alcohol abuse; primary valve disease or congenital heart disease; frequent ventricular premature beats and/or runs of ventricular tachycardia; contraindications to beta-blocker therapy; concomitant treatment with other beta-blockers, α-antagonists, calcium antagonists or antiarrhythmic agents (except amiodarone)	Yes	Yes	Yes	Yes	No
Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	Recent change in treatment within 2 weeks before randomization; requirement for intravenous inotropic therapy; current treatment with non-dihydropyridine calcium channel blockers (diltiazem, verapamil); amiodarone (>200 mg per day); class-I antiarrhythmic drugs; unstable angina; myocardial infarction; coronary revascularisation or stroke within the previous 2 months; uncontrolled hypertension (SBP >170 mm Hg or DBP >105 mm Hg); hemodynamically significant valvular disease; symptomatic and sustained ventricular arrhythmias within the past 2 months note adequately treatment with antiarrhythmic drugs or implantation of an automatic defibrillator; pregnancy; women with childbrearing potential on inadequate contraception; known drug or alcohol misuse; poor compliance; any other serious systemic disease; contraindication to beta blockers	Yes	Yes	Yes	Yes	Yes

Evidence Table 10a. Quality assessments of head to head trials of beta blockers for heart failure (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Metra 2000 US, Italy	NR	Attrition reported; Others NR	None	Fair	NR	Yes	9-12 months
Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	NR	31.8% attrition; others NR	None	Fair	F Hoffman La Roche and GlaxoSmithKline; first author has served as a consultant to or received travel expenses, payment for speaking at meetings or funding for research from one or more of the major pharmaceutical companies	Yes	58 months

Evidence Table 11. Outcomes in head to head trials of beta blockers for heart failure

Trial	Interventions*	Sample Size	Duration	Baseline EF	Mortality	Worsening Heart Failure	NYHA Class
Sanderson 1999 *Fair*	Carvedilol Metoprolol	51	12 weeks	26%	NR	NR	# patients at NYHA class I/II/III/IV car baseline: 0/10/14/1 week 12: 1/14/5/0 met baseline: 0/7/19/1 week 12: 1/19/3/0
Kukin 1999 *Fair*	Carvedilol Metoprolol	67	6 months	18-19%	NR	car=3/37(8.1%) met=5/30(16.7%)	# patients at NYHA class I/II/III/IV car baseline: 0/5/22/3 month 6: 0/9/21/0 met baseline: 0/5/17/1 month 6: 1/11/11/0
Metra 2000a *Fair*	Carvedilol metoprolol	150	12 months	20-21%	NR	car=6/61(9.8%) met=13/61(21.3%)	# patients at NYHA class I/II/III/IV car baseline: 0/18/40/3 month 12: 17/32/11/1 met baseline: 0/22/36/3 month 12: 14/32/15/0
Metra 2000b *Fair*	Carvedilol Metoprolol	34	9-12 months	19-17%	NR	2 patients died due to worsening HF (group assignment NR)	# patients at NYHA class I/II/III/IV car baseline: 0/3/11/1 end of study: 4/7/3/1 met baseline: 0/5/9/0 end of study: 3/10/1/0
Poole Wilson, 2003 Carvedilol or Metoprolol European Trial (COMET)	Carvedilol Metoprolol	3029	58 months (mean)	26%	*All deaths* car=512/1511(34%) met=600/1518(40%) NNT=18 p=0.002	NR	NR

*All in addition to standard therapy that included ACEI and diuretic

Evidence Table 11. Outcomes in head to head trials of beta blockers for heart failure (continued)

Trial	Exercise capacity	Change in EF following treatment	Quality of Life
Sanderson 1999 *Fair*	Improvement in 6-min walk(feet) car=72(6.4%); met=99(8.5%)(NS)	Mean EF at Week 12 (% improvement) car=35(+34.6%); met=31(+24%)	Minnesota QOL mean reduction in symptom score (%) car=9.1(52.9%); met=8.3(63.3%)
Kukin 1999 *Fair*	Improvement in 6-min walk(feet) car=63(5.5%); met=81(6.6%)(NS)	Mean EF(% improvement) car=25(+31.6%); met=23(+27.8%)	Minnesota LWHFQ mean reduction in symptom score(%) car=11(21.1%); met=10(19.6%)
Metra 2000a *Fair*	Improvement in 6-min walk(m) car=50(11.2%); met=63(15.1%)	Mean EF(% improvement) car=31.2(52.9%); met=28.8(33.3%)(p=0.038)	Minnesota LWHFQ mean reduction in symptom score(%) car=8(25%); met=7(17.9%)
Metra 2000b *Fair*	NR	Mean EF at EOS (% improvement) car=27.9(64.1%); met=30.0(47.0%)	NR
Poole Wilson, 2003 Carvedilol or Metoprolol European Trial (COMET)	NR	NR	NR

*All in addition to standard therapy that included ACEI and diuretic

Evidence Table 12. Placebo controlled trials of beta blockers for arrhythmia

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Metoprolol				
Kuhlkamp 2000 Germany	RCT multicenter	Patients at 71 centers with persistent atrial fibrillation of 3 days to 1 year. Must be converted to sinus rhythm. Sufficient anticoagulation for 1+ months strongly recommended to providers.	Use of Class 1 or 3 antiarrhythmic drug, beta-blockers or calcium channel blockers; chronic treatment with amiodarone within 6 months; contraindications to beta-adrenergic blocking agents; untreated thyroid dysfunction; paroxysmal atrial fibrillation or history of it; cardiac surgery in the previous two months	n = 403 metoprolol (met): start 100 mg/day vs. identical placebo (pla) x 6 months Maintain 100 mg/day: met = 122/197 (62%) pla = 131/197 (67%) To 200 mg/day: met = 33/197 (17%) pla = 50/197 (25%) To 50 mg/day: met = 36/197 (18%) pla = 12/197 (6%)

Evidence Table 12. Placebo controlled trials of beta blockers for arrhythmia (continued)

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Metoprolol						
Kuhlkamp 2000 Germany	Digoxin/digitoxin, ACE inhibitor, diuretics, nitrates, calcium-channel blockers of dihydropyridine type	Primary endpoint: relapse into atrial fibrillation or flutter. Mean followup time: met = 93 days pla = 73 days	Mean age 60.5 70% male Race: NR	Previous cardioversion: met = 18/197 (9%) pla = 22/197 (11%) Hypertension: met = 96/197 (49%) pla = 91/197 (46%) Coronary artery disease: met = 52/197 (26%) pla = 48/197 (24%) Heart failure: met = 51/197 (26%) pla = 49/197 (25%) Stroke/TIA: met = 15/197 (8%) pla = 12/197 (12%) Diabetes mellitus: met = 23/197 (12%) pla = 17/197 (9%) NYHA 1: met = 125/197 (64%) pla = 137/197 (70%) NYHA2: met = 64/197 (33%) pla = 54/197 (27%) NYHA3: met = 8/197 (4%) pla = 6/197 (3%)	Screened = nr Eligible = nr Enrolled = 403	Lost for efficacy data (no followup ECG) = 9/403 (2%) Lost for safety data = 4/403 (1%) Analyzed = 394/403 (98%) and 399/403 (99%)

Evidence Table 12. Placebo controlled trials of beta blockers for arrhythmia (continued)

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Metoprolol				
Kuhlkamp 2000 Germany	Death: met = 3/200 (2%) pla = 0 Premature discontinuation due to relapse to atrial fibrillation/flutter: met = 96/197 (49%) pla = 118/197 (60%) Total relapse to atrial fibrillation: met = 87/197 (44%) pla = 118/197 (60%)	NR	Dizziness/vertigo: met = 20/200 (10%) pla = 6/199 (3%) Bradycardia: met = 14/200 (7%) pla = 0 Cardiac failure: met = 3/200 (2%) pla = 0 Hypotension: met = 2/200 (1%) pla = 1/199 (1%)	Total: 26/394 (7%) Serious adverse events: met = 4/197 (2%) pla = 2/197(1%) Nonserious adverse events: met = 16/197 (8%) pla = 4/197(2%)

Evidence Table 12a. Quality assessments of placebo controlled trials of beta blockers for arrhythmia

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Similarity to target population	How many recruited	Exclusion criteria for recruitment	Eligibility criteria specified
Kuhldamp 2000	Adequate, computer generated	NR	Yes	No - selection for healthier population - mean age of sample = 60 years; mean age atrial fibrillation patients = 75 years	N = 403	• Use of Class 1 or 3 antiarrhythmic drug, beta-blockers or calcium channel blockers; chronic treatment with amiodarone within 6 months. • Contraindications to beta-adrenergic blocking agents. • Untreated thyroid dysfunction • Paroxysmal atrial fibrillation or history of it • Cardiac surgery in the previous two months	Yes

Evidence Table 12a. Quality assessments of placebo controlled trials of beta blockers for arrhythmia (continued)

Author, Year Country	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score (good/ fair/ poor)	Funding	Control group standard of care	Length of follow-up
Kuhldamp 2000	NR	Yes	Yes	No	Yes	Attrition=6.8%; others NR	No	Fair	AstraZeneca, Sweden	Yes	6 months

Evidence Table 13. Head to head trials of beta blockers for migraine

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Age Gender Ethnicity
Stensrud 1980 *Fair quality*	RCT Crossover	Patients with a diagnosis of migraine (Ad Hoc Committee on Classification of Headache, 1962) at a frequency of at least 3-4 per month	NR	Atenolol (ate) 100 mg daily Propranolol (pro) 160 mg daily Placebo (pla) x 6 weeks for each treatment period	Analgesics Ergotamine preparations	Age range: 25-60 (mean nr) 68.6% female Race nr
Kangasniemi 1984 Scandinavia *Fair quality*	RCT Crossover	Outpatients diagnosed as having classical or common migraine (World Federation of Neurology Research Group on Migraine and Headache, 1969), with well-defined intermittent migraine attacks and fulfilling at least four out of the following criteria: (a) heredity; (b) pulsating headache, (c) prodromas (perceptive visual disturbances); (d) hemicrania; (3) phono- and/or photophobia during the headache phase and (f) gastroinstestinal disturbances during the headache phase; history of migraine of at least three years, an attack duration of at least one hour and anamnestic 3-10 migraine attacks monthly, which had to be documented during the run-in period for inclusion in the double-blind part of the investigation	Other types of vascular headache, chronic daily headache, contraindications for beta-blockers, treatment with neuroleptics and anti-depressives, coronary or peripheral vascular occlusive disease, severe renal or hepatic disease, change in oral contraceptive medication and pregnancy	Metoprolol durules (met-d) 200 mg daily Propranolol (pro) 160 mg daily x 8 weeks; 4-week washout; then crossover	Consumption of acute migraine-relieving medication allowed (unspecified)	Mean age: 33.8 88.9% female Race nr

Evidence Table 13. Head to head trials of beta blockers for migraine (continued)

Author, Year Country	Method of Outcome Assessment and Timing of Assessment	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Stensrud 1980 *Fair quality*	Charts filled in by patients	Classic migraine=6(17.1%) Common migraine=29(82.8%)	NR/NR/35 included	7(20%) withdrawn/lost to fu nr/28 analyzed	n=28 Total headache days: pro=257; ate=247; pla=287 Total headache index: pro=437; ate=410; pla=498
Kangasniemi 1984 Scandinavia *Fair quality*	*Diary cards:* (a) frequency of migraine attacks; (b) intensity of migraine attacks on 3-point scale (1=light, bothersome migraine which permits daily activities with minimal or no difficulty; 2=moderate, annoying migraine causing difficulty in carrying out daily activities; 3=severe, incapacitation; patient unable to perform daily activities); (3) duration of migraine attacks (in hours); and (d) consumption of acute migraine-relieving medication assessed after each active treatment period	Classical migraine(# patients/%): 6/16.7% Common migraine(# patients/%): 30/83.3% % heredity: 94% Mean duration of migraine(years): 15.6 % earlier prophylactic treatment: 28%	NR/NR/36 entered	3(8.3%) withdrawn/0 lost to fu/35 analyzed	*Attack frequency* (decrease in mean attacks per 4 weeks/% change): pro=(-2.3)/(-43.4%); met-d=(-2.3)/(-43.4%) *Migraine days* (decrease in mean migraine days per 4 weeks/%change): pro=(-2.5)/(-43.8%); met-d=(-2.6)/(-45.6%) *Severity* (decrease in mean sum of severity score per 4 weeks/%change): pro=(-4.3)/(-44.3%); met-d=(-4.8)/(-49.5%) *Tablet consumption* (decrease in mean acute anti-migraine tablet consumption per 4 weeks/% change): pro=(-3.9)/(-45.3%); met-d=(3.9)/(-45.3%) *Reduction in sum of severity score(# pts/%)* >/= 50%: pro=15/42.8%; met-d=14/48.6% 1-50%: pro=10/28.6%; met-d=10/28.6% Negative: pro=6/17.1%; met-d=5/14.3% *Patients subjective evaluation of improvement(# pts/%)* Marked: pro=7/20%; met-d=6/20% Moderate: pro=15/42.8%; met-d=19/54.3% Slight: pro=9/25.7%; met-d=6/17.1% Unchanged/worse: pro=4/11.4%; met-d=2/5.7%

Evidence Table 13. Head to head trials of beta blockers for migraine (continued)

Author, Year Country	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/ enrolled n)	Comments
Stensrud 1980 *Fair quality*	NR	Dizziness: ate=0; pro=1 Reduced physical capacity: ate=1; pro=6 Coldness hand/feet: ate=0; pro=1 Nausea: ate=0; pro=3 Sleep difficulties: ate=0; pro=1	NR	
Kangasniemi 1984 Scandinavia *Fair quality*	NR	Overall incidence[# pts(%) in weeks 1-4/5-8]: pro=24(68.6%)/17(48.6%); met-d=20(57.1%)/16(45.7%) Most common adverse events(# mild/moderate/severe complaints for weeks 1-4; 5-8) CV+resp. Pro=2/1/0; 1/1/0 Met-d=0/0/1; 1/0/0 Gastrointest. Pro=4/0/2; 2/1/0 Met-d=2/2/0; 2/2/0 Sleep disturb. Pro=4/1/1; 2/1/1 Met-d=1/1/0; 0/1/0 CNS Pro=6/3/1; 2/2/0 Met-d=6/1/0; 3/1/0 Fatigue Pro=4/1/1; 4/1/0 Met-d=4/3/0; 4/2/1 Others Pro=3/4/0; 5/4/0 Met-d=10/0/1; 3/1/1	pro=2/36(5.6%) met-d=0	

Evidence Table 13. Head to head trials of beta blockers for migraine (continued)

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Age Gender Ethnicity
Olsson 1984 Sweden *Fair quality*	RCT Crossover	Outpatients of both sexes aged between 18 and 60 years, diagnosed as having classical or common migraine (defined by the World Federation of Neurology Research Group on Migraine and Headache, 1969) with well-defined migraine attacks and fulfilling at least 4 out of the following criteria were included: a) heredity (parents/siblings); b) pulsating headache; c) aura (focal neurological symptoms); d) initial unilateral headache; e0 phono- and/or photophobia during the headache phase; and f) gastrointestinal disturbances during the primary headache phase (not caused by pharmaceutical preparations); medical history of 3-10 migraine attacks monthly, which had to be confirmed during the run-in period of one month for inclusion in the double-blind part of the investigation	Other types of vascular headache; chronic daily headache, non-separable tension and migraine headaches, diet as primary triggering-off factor; change of psychopharmaceutical treatment; contraindications for beta-blockers; pregnancy; change in oral contraceptive therapy and severe somatic disease	Metoprolol (met) 100 mg daily Propranolol (pro) 80 mg daily x 8 weeks; 4 week washout; then crossover	Acute use of ergotamine and analgesics allowed	Mean age=39.6 73.2% female Race nr

Evidence Table 13. Head to head trials of beta blockers for migraine (continued)

Author, Year Country	Method of Outcome Assessment and Timing of Assessment	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Olsson 1984 Sweden *Fair quality*	*Diary cards:* (a) frequency of migraine attacks; (b) intensity of migraine attacks on 3-point scale (1=light, bothersome migraine which permits daily activities with minimal or no difficulty; 2=moderate, annoying migraine causing difficulty in carrying out daily activities); (c) consumption of ergotamine preparations; and (d) consumption of analgesics	Classical migraine(# pts/%): 22/39.3% Common migraine(# pts/%): 34/60.7% % heredity=80% Duration of migraine(years): 20.7 % earlier prophylactic treatment=16% % earlier acute treatment=93%	NR/NR/56 entered	3(5.3%) withdrawn/lost to fu nr/53 analyzed	*Outcomes reported per weeks in median/% change format* Attack frequency: pro=(-1.2)/(-22.2%); met=(-1.2)/(-22.2%) Migraine days: pro=(-2.2)/(-32.8%); met=(-1.7)/(-25.4%) Sum of severity: pro=(-3.7)/(-29.8%); met=(-2.7)/(-21.8%) Ergotamine consumption: pro=(-2.2)/(-43.1%); met=(-2.4)/(-47.0%) Analgesic consumption: pro=(-3.4)/(-37.4%); met=(-1.5)/(-16.5%) *Subjective therapeutic evaluation(% patients rating effect of treatment as 'marked' or 'moderate'):* pro=63%; met=64%

Evidence Table 13. Head to head trials of beta blockers for migraine (continued)

Author, Year Country	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/ enrolled n)	Comments
Olsson 1984 Sweden *Fair quality*	Recorded according to a standardized questionnaire for direct, active questioning Unwanted symptoms were rated as 1=mild; 2=moderate; and 3=severe	Overall incidence(# pts(%) during 1st month/2nd month of treatment): pro=31(58.5%)/31(58.5%); met=31(58.5%)/30(56.6%) Most commonly reported "unwanted symptoms"(# complaints per 1st month/2nd month): Cardiovascular: pro=6/6; met=7/5 Gastrointestinal: pro=7/9; met=10/14 Sleep disturbance: pro=15/7; met=10/7 CNS: pro=13/11; met=19/17 Fatigue: pro=8/9; met=6/8 Others: pro=30/20; met=30/25	None	

Evidence Table 13. Head to head trials of beta blockers for migraine (continued)

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Age Gender Ethnicity
Gerber 1991 Germany *Fair quality*	RCT Parallel	Diagnosis of migraine with or without aura (IHS); occurrence of at least 2 attacks per month over the 4 weeks immediately preceding the study; satisfied at least two of the four named headache parameters	Pregnancy; abuse of ergotamine or analgesics; use of other agents for the prophylaxis of migraine attacks; specific contraindications for the individual substances (e.g., lactation, AV block, heart failure, bradycardia, obstructive pulmonary disease)	Metoprolol (met) 200 mg daily Propranolol (pro) 160 mg daily Nifedipine (nif) 40 mg daily x 3 months (preceded by 1 month of low dose; and followed 3 more months of tapering)	Whichever other medication patients found helpful to abort migraines (unspecified)	Mean age: met=42.9; pro=43.2; nif=40.9 % female: met=81.8%; pro=84.2%; nif=76.5% Race nr
Worz 1991, 1992 Germany *Poor quality*	RCT Crossover	Patients of both sexes diagnosed according to International Headache Society (IHS) criteria as having migraine with aura or without aura; migraine history of at least 2 years duration; a minimum of three attacks documented during the run-in	Free of other headaches, other diseases (psychiatric, somatic or requiring regular medication) and of contraindications to beta-blockade	Bisoprolol (bis) 5-10 mg daily Metoprolol (met) 100-200 mg daily x 12 weeks, then crossover	nr	Mean age: 38.5 80.8% female Race nr

Evidence Table 13. Head to head trials of beta blockers for migraine (continued)

Author, Year Country	Method of Outcome Assessment and Timing of Assessment	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Gerber 1991 Germany *Fair quality*	*Patient headache diary:* 1) Days on which a migraine attack occurred; 2) Duration of migraine attack in hours; 3) Duration of additional, non-migrainous, headaches in hours; 4) Intensity of headache (three assessment times per day using a visual analogue scale); 5) Site of pain; 6) Dose of *all* medication taken; 7) Duration of sleep in hours; 8) Daily mood (visual analogue scale); 9) Weekly evaluation of medication and listing of side effects	Mean migraine duration(yrs): met=21.9; pro=22.9; nif=17.6 Mean migraine frequency/month: met=3.8; pro=3.3; nif=3.5 Diagnosis: Without aura(% pts): met=95.4; pro=94.7; nif=88.2 With aura(% pts): met=4.5; proo=5.2; nif=11.8 Localization: Hemicrania: met=54.5; pro=36.8; nif=58.8 Holocrania: met=45.4; pro=63.1; nif=35.3	NR/NR/58 enrolled(met= 22; pro=19; nif=17)		Percentages of responders (ARIMA)-see comments for definition High Dosage Phase (3 months) *Migraine days:* met=54.4%; pro=32.0%; nif=7.7% *Migraine duration:* met=60.0%; pro=27.8%; 30.8% *Severity of headache:* met=55.0%; pro=33.3%; nif=0.0% *Reduction of ergotamine intake:* met=30.0%; pro=38.9%; nif=38.5% Differential efficacy(% change by responder classification A/B/C/D) *Reduction in number of days/month with migraine:* met=54.4/5.0/35.6/0.0; pro=32.0/0.0/62.4/5.6(NS) *Reduction in duration of migraine attacks(hours):* met=60.0/5.0/35.0/0.0; pro=27.8/5.6;61.1/5.6(NS) *Improvement in severity:* met=55.0/5.0/40.0/0.0; pro=33.3/5.6/61.1/0.0(p<0.05) *Reduction in intake of abortive medication:* met=30.0/0.0/65.0/5.0; pro=38.9/0.0/55.6/5.6(NS)
Worz 1991, 1992 Germany *Poor quality*	Headache diary	Without aura: 55/78(70.5%) With aura: 23/78(29.5%) Mean history of migraine(yrs): 19.5	NR/NR/125 enrolled	47(37.6%) withdrawn/ lost to fu nr/78 analyzed	Mean attacks/28 days(during last 8 weeks of treatment): bis=2.05; met=1.99

Evidence Table 13. Head to head trials of beta blockers for migraine (continued)

Author, Year Country	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/ enrolled n)	Comments
Gerber 1991 Germany *Fair quality*	NR	Most commonly reported side effects(data nr; % patients approximated from Figure 6) Fatigue: met=60; pro=33 Vertigo: met=21; pro=22 Sleep disorders: met=10; pro=11 Body weight increase: met=5; pro=11 Circulatory disturbances: met=4; pro=28 Swelled legs: met=0; pro=4	Drop out rate due to side effects or lack of therapeutic effect(# pts): met=2; pro=2	Investigation of comparison of responders versus nonresponders as defined: *Responder type A:* Significant z-values (z >/= -1.65 to 1.96) in parameters: a) reduction in number of days with migraine; b) reduction of duration of migraines; c) reduction of severity of headaches; d) reduced use of analgesics and ergots *Responder type B:* A tendency to improvement (NS) (z </= -1.65 to 1.96) in four parameters above *Non-responder type C:* No improvement in the parameters (z = 0 to -1.65) *Non-responder type D:* Tendency to deterioration, or statistically significant deterioration (positive z-values)
Worz 1991, 1992 Germany *Poor quality*	NR	Overall adverse events reported(# patients): bis=23; met=18 Most frequently reported symptoms: Dizziness: bis=8; met=4 Tiredness/fatigue: bis=3; met=7 Sleep disturbance: bis=2; met=6 Cardiovascular/hypotensive reactions: bis=6; met=1 Gastrointestinal disturbance: bis=5; met=2	Withdrawals due to AE's(# patients): bis=8; met=5	

Evidence Table 13a. Quality assessments of head to head trials of beta blockers for migraine

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Stensrud 1980 Norway	NR	NR	N/A	Fair 68.6% female mean age NR	35
Worz 1991 Germany	NR	NR	N/A	Fair 80.8% female mean age NR	125
Kangasniemi 1984 Scandinavia	NR	NR	N/A-crossover	Good 88.9% female mean age of 33.8	36
Olsson 1984 Sweden	NR	NR	N/A-crossover	Good 73.2% female mean age of 39.6	56
Gerber 1991 Germany	NR	NR	Yes	80.8% female mean age of 42.3	58

Evidence Table 13a. Quality assessments of head to head trials of beta blockers for migraine (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Stensrud 1980 Norway	NR	Yes	NR	Yes	Yes	No
Worz 1991 Germany	Free of other headaches, other diseases (psychiatric, somatic or requiring regular medication) and of contraindications to beta-blockade	Yes	NR	Yes	Yes	No
Kangasniemi 1984 Scandinavia	Other types of vascular headache, chronic daily headache, contraindications for beta-blockers, treatment with neuroleptics and anti-depressives, coronary or peripheral vascular occlusive disease, severe renal or hepatic disease, change in oral contraceptive medication and pregnancy	Yes	NR	Yes	Yes	No
Olsson 1984 Sweden	Other types of vascular headache; chronic daily headache, non-separable tension and migraine headaches, diet as primary triggering-off factor; change of psychopharmaceutical treatment; contraindications for beta-blockers; pregnancy; change in oral contraceptive therapy and severe somatic disease	Yes	NR	Yes	Yes	No
Gerber 1991 Germany	Pregnancy; abuse of ergotamine or analgesics; use of other agents for the prophylaxis of migraine attacks; specific contraindications for the individual substances (e.g., lactation, AV block, heart failure, bradycardia, obstructive pulmonary disease)	Yes	NR	Yes	Yes	Unclear

Evidence Table 13a. Quality assessments of head to head trials of beta blockers for migraine (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Stensrud 1980 Norway	N/A	Attrition reported; others NR	None	Fair	NR	Yes	21 weeks
Worz 1991 Germany	N/A	Attrition reported; others NR	Lost to fu NR	Poor	NR	Yes	24 weeks
Kangasniemi 1984 Scandinavia	N/A	Attrition reported(8.3%); others NR	None	Fair	NR	Yes	24 weeks
Olsson 1984 Sweden	N/A	Attrition reported(5.3%); others NR	None	Fair	NR	Yes	24 weeks
Gerber 1991 Germany	NR	Attrition reported; others NR	None	Fair	NR	Yes	10-11 months

Evidence Table 14. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Fair Quality				
Atenolol				
Forssman 1982 Sweden *Fair quality* RCT Crossover	History of migraine (Ad Hoc Committee)	NR	Atenolol (ate) 100 mg daily Placebo (pla) x 90 days; then crossover	Common analgesics and ergotamine

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Fair Quality					
Atenolol					
Forssman 1982 Sweden *Fair quality* RCT Crossover	*Patient forms:* 1) number; 2) intensity (3-point scale); 3) duration of attacks; 4) incapacity for work; 5) medication *Integrated headache:* score considering combined effect of intensity and duration Follow-up visits were made after 14, 56, 154, and 254 days	Mean age=40 80% female Race nr	NR	NR/NR/24 enrolled	4(16.7%) withdrawn/0 lost to fu/ 20 analyzed

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Fair Quality					
Atenolol					
Forssman 1982 Sweden *Fair quality* RCT Crossover	*Integrated headache* Mean values/day: ate=2.38; pla=4.58 Relative mean value/day(ate:pla mean/% difference): (-2.2)/(-48%) Relative value per patient/day(# pts/%): ate>pla=19/95%; pla>/=ate=1/5% *Number of attacks* Mean values/day: ate=0.17; pla=0.23 Relative mean value/day(ate:pla mean/% difference): (-0.06)/(-26.1%) Relative value per patient/day(# pts/%): ate>pla=15/75%; pla>/=ate=5/25% *Headache intensity* Comparison of effect per patient(# pts/%): ate>pla=17/18(94.4%) *Ergotamine intake* Comparison of change in intake per patient(# pts w/significant reduction/%): ate>pla=14/14(100%) *Common analgesic intake* Comparison of change in intake per patient: data nr; no difference indicated per patient between periods	NR	Dizziness of orthostatic type(# pts): ate=6; pla=1 Diffuse tiredness: ate=2; pla=0 Mood alterations: ate=1; pla=0	ate=1 pla=0	

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Bisoprolol				
van de Ven 1997 The Netherlands Fair quality RCT	Either sex, 18 to 75 years old; suffering from migraine with or without aura; had a migraine history of at least two years' duration; developed at least three documented migraine attacks during the 28-day run-in period	Current use of drugs for the prevention of migrain; treatment with cardiovascular drugs; usual contrindications for beta blocker use or hypersensitivity to these agents	Bisoprolol (bis) 5 mg OR 10 mg daily Placebo (pla) x 16 weeks	NR

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Bisoprolol					
van de Ven 1997 The Netherlands Fair quality RCT	Patient diary assessed at 4-wk intervals	Mean age: bis 5 mg=38.3; bis 10 mg=38.9; pla=38.9 % female: bis 5 mg=78.4%; bis 10 mg=83.1%; pla=83.1% Race nr	Family history of migraine(# patients/%): bis 5 mg=28/37.8%; bis 10 mg=27/35.1%; pla=26/34.7% Age at onset(yrs): bis 5 mg=18.1; bis 10 mg=20.1; pla=22.7 Migraine with aura(# patients/%): bis 5 mg=17/22.9%; bis 10 mg=22/28.6%; pla=12/16% Migraine without aura(# patients/%): bis 5 mg=57(77%); bis 10 mg=55/71.4%; pla=63/84%	nr/nr/226 randomized	31(13.7%) withdrawn/lost to fu nr/analyzed nr

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Bisoprolol					
van de Ven 1997 The Netherlands Fair quality RCT	Migraine frequency(4-week mean/% reduction): bis 5 mg=2.6/39%; bis 10 mg=2.6(39%); pla=3.2/22% Attack duration(mean hours/% reduction): bis 5 mg=9.5/(-53.9%); bis 10 mg=14.3/(-44.6%); pla=13.2/(-43.6%)	NR	Adverse event incidence(# patients/%): bis 5 mg=26/35%; bis 10 mg=33/43%; pla=25/33% Most frequent adverse events(# patients/%): Fatigue: bis 5 mg=7/9.4%; bis 10 mg=9/11.7%; pla=7/9.3% Dizziness: bis 5 mg=6/8.1%; bis 10 mg=5/6.5%; pla=4/5.3%	Adverse event withdrawals(# patients/%): bis 5 mg=4/74(5.4%); bis 10 mg=7/77(9.1%); pla=4/75(5.3%)	

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Metoprolol				
Andersson 1983 Denmark *Fair quality* RCT	Outpatients of both sexes, with an age over 16 and below 65 years diagnosed to have classical or non-classical migraine (World Federation of Neurology Research Group on Migraine and Headache) of a duration of at least 2 years	Other types of vascular headaches, chronic daily headache not separable from migraine; contraindication for beta blockers; other severe vascular diseases; oral contraceptives and pregnancy	Metoprolol durules (met-d) 200 mg daily Placebo (pla) x 12 weeks	Acute migraine medication allowed (e.g., ergotamine and analgesics)

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Metoprolol					
Andersson 1983 Denmark *Fair quality* RCT	*Patient diary card:* 1) frequency; 2) Intensity (1=annoying, but patient not disabled; 2=patient partly disabled (affecting his/her ability to work); 3=patient disabled(unable to work or in bed); 3) consumption of acute migraine-relieving medicine	Mean age: pla=37.3; met-d=42.4 %female: pla=94.6%; met-d=73.5% Race nr	Classical migraine(#pts/%): pla=8/21.6%; met-d=9/26.5% Non-classical migraine(#pts/%): pla=29/78.4%; met-d=25/73.5% % heredity: pla=65; met-d=65 Mean migraine duration(years): pla=14.6; met-d=22.6 % earlier prophylactic treatment: pla=32; met=38 % earlier acute treatment: pla=76; met=74	nr/75 eligible/71 randomized	Withdrawn: 4/75(5.3%) prior to randomization; 9/71(12.7%) after randomization/lost to fu nr/71 analyzed

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Metoprolol					
Andersson 1983 Denmark *Fair quality* RCT	Per protocol assessment (pla n=35; met-d n=30) *Attack frequency/4 wks(mean/% change):* pla=(-0.53)/(-10.3%); met-d=(-1.3)/(-29.5%) *Migraine days/4 wks(mean/% change): pla=(-0.19)/(-2.4%); met-d=(-2.3)/(-28.8%)* *Sum of severity score(migraine days x intensity)/4 wks(mean/% change):* pla=0.18/1.1%; met-d=(-5.68)/(-32.2%) *Acute tablet consumption/4 wks(mean/% change):* pla=(-0.49)/(-2.4%); met-d=(-8.85)/(-45.1%) *Subjective evaluation(# pts/%)* Marked/moderate: pla=6(18%); met-d=15(54%) Slight: pla=10(29%); met-d=7(25%) Unchanged/worse: pla=18(64%); met-d=6(21%)	NR	Incidence(# pts/%): met-d=16(53.3%); pla=10(28.6%) Most common adverse events(# complaints) at visit 4: Sleep disturbances: met-d=4; pla=4 Fatigue: met-d=3; pla=0 Gastrointestinal: met-d=2; pla=2 Bradycardia: met-d=2; pla=0 Paraesthesia: met-d=0; pla=1 Depression: met-d=1; pla=1 Others: met-d=0; pla=4	Withdrawals(# pts/%): met-d=1(3.3%); pla=1(2.8%)	

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Kangasniemi 1987 Scandinavia *Fair quality* RCT	Outpatients aged 16-65 years, diagnosed as having classic migraine (NIH Ad Hoc Committee); 2-8 migraine attacks per month, of which at least 50% had to be accompanied by focal aura symptoms	Daily use of analgesics and/or total consumption exceeding 40 tablets/month; daily use of ergotamine and/or total consumption exceeding 16 mg/month; treatment with anti-depressive or neuroleptic drugs within the past 2 months; use of narcotic analgestics, chronic treatment with calcium antagonists, clonidine, other beta-blockers or NSAIDSs; change in oral contraceptive therapy 3 months before or during the study; contraindications for beta-blockers; insufficienty treated hypertension; transient ischaemic attacks; epilepsy; hypothyroidism and other severe psychiatric or somatic disease; and pregnancy	Metoprolol durules (met-d) 200 mg daily Placebo (pla) x 8 weeks, then crossover	Former acute migraine medication allowed (not specified)

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Kangasniemi 1987 Scandinavia *Fair quality* RCT	*Diary card* measuring following variables: -Frequency of migraine attacks/interval headache -Time of onset and duration of migraine attack -Intensity of headache (1=mild; 2=moderate; 3=severe) - Symptoms before and during the headache phase - Global rating of the attack on a visual analogue scale (1-10) - Conumption of analgesics and ergotamine	*n=74* Mean age=37.5 79.7% female Race nr	Family history: 54(73%) Attacks per month(mean): 4.3 Duration of migraine(mean years): 17.2 Duration/attack(mean hours): 12.6 Relationship migraine/menstrual cycle(# patients/%): 28/47% Previous prophylactic treatment(# patients/%): 5/6.8% Previous acute treatment(# patients/%): 65/87.8%	nr/nr/77 randomized	3 withdrawn(1 due to narcotic abuse and 2 due to being "dark horses")/0 lost to fu/74 analyzed

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Kangasniemi 1987 Scandinavia *Fair quality* RCT	*Outcomes per 4 weeks(mean score/% change)* Attack frequency: met=1.8/-52.6%; pla=2.5/-34.2%(p=0.0004) Days with migraine: met=1.9/-59.6%; pla=2.6/-44.7%(p=0.01) Days with interval headache: met=1.3/-27.8%; pla=1.6/-11.1%(NS) Sum of intensity score: met=3.6/-50.0%; pla=4.5/-37.5%(p=0.001) Sum of global ratings: met=8.6/-53.5%; pla=12.7/-31.4%(p=0.001) Mean intensity score per attack: met=1.86/-7.0%; pla=2/0.0%(p=0.002) Mean global rating per attack: met=3.8/-30.9%; pla=4.8/-12.7%(p=0.003) Mean duration per attack: met=6/-30.2%; pla=8/-7.0%(p=0.027) Consumption of analgesic tablets: met=1.9/-52.5%; pla=4.4/+10%(p<0.001) Consumption of analgesic tablets/attack: met=1/-16.1%; pla=2/+66.7%((p<0.001) Consumption of ergotamine tablets: met=1.5/-68.1%; pla=3/-36.2%(p=0.007)	Recorded at each visit using unspecified stardardized questionnaire on a 3-point scale (1=mild; 2=moderate; 3=severe)	Adverse effects incidence(% patients): met=36%; pla=18% Most frequent adverse effects(# complaints for weeks 1-4/5-8) Gastrointestinal: met=7/9; pla=1/2 Fatigue: met=6/7; pla=3/1 Cardiovascular: met=1/2; pla=0/3 Sleep disturbances: met=3/1; pla=0/0 Others: met=10/6; pla=7/8	NR	Classic migraine only

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Pindolol				
Ekbom 1971 Sweden *Fair quality* RCT	Aged 19-56, with classic or common migraine (Ad Hoc Committee, 1962) at a frequency of at least 4 attacks per 4-week period	Bronchial asthma, severe infectious diseases, diabetes mellitus, pregnancy, pathological ECG findings	Group 1: Pindolol (pin1) 7.5 mg daily *(n=7)* Group 2: Pindolol (pin2) 15 mg daily *(n=9)* Group 3: Placebo (pla) x 4 weeks *(n=10)*	Ergotamines
Sjaastad 1972 Norway *Fair quality* RCT Crossover	Aged 18-62 years, with classical and common migraine; attack frequency of >/= 2/month	NR	Pindolol (pin) 7.5-15 mg daily Placebo (pla) x 4 weeks, then crossover	Ergotamine preparations; salicylates; dextropropoxipheni chloride

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Pindolol					
Ekbom 1971 Sweden *Fair quality* RCT	*Patient record:* 1) frequency, 2) duration; 3) severity (graded on arbitrary 3-point scale); 4) consumption of ergotamine	Mean age=33.7 86.7% female Race nr	Classic migraine=4(13.3%) Common migraine=26(86.7%) Family history=26(86.7%) Unilateral headache pattern=26(86.7%) Associated symptoms: Nausea=28(93.3%) Vomiting=24(80%) Photophobia/ phonophobia=28(93.3%) Urina spastica=9(30%) Diarrhea=9(30%)	nr/nr/30 enrolled	4(13.3%) withdrawn/lost to fu nr/26 analyzed
Sjaastad 1972 Norway *Fair quality* RCT Crossover	*Special form:* 1) Severity on 3-point scale (Grade I=just discernible symptoms, not appreciably influencing working capaity; Grade II=pronounced symptoms not necessitating bedrest, but markedly influencing working capacity; Grade III=severe symptoms, necessitating bedrest; 2) Headache indices=headache days times severity of attacks	Mean age=35.8 78.6% female Race NR	Common headache=14(50%) Classic headache=14(50%)	nr/nr/28 enrolled	4(14.2%) withdrawn/0 lost to fu/24 analyzed

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Pindolol					
Ekbom 1971 Sweden *Fair quality* RCT	*Headache frequency/4 wks(mean/% change from observation period):* pin1=(-2)/(-13.3%); pin2=(-2)/(-18.2%); pla=(-2)/(20%) *Headache index/4 wks(mean/% change from observation period):* pin1=0; pin2=(-4)/(-20%); pla=(-4)/(-22.2%) *Headache duration/4 wks(mean/% change from observation period):* pin1=0; pin2=(-0.1)/(-1.4%); pla=(-0.7)/(-9.2%) *Tablet consumption:* data nr; paper indicates pin=pla	nr	nr	Withdrawals: pin=4; pla=0 Withdrawals due to: Orthostatic hypotension=2 Increased headache=1 Dizziness/cystopyelitis=1	
Sjaastad 1972 Norway *Fair quality* RCT Crossover	*Reduction in headache indices(# pts/%)* pin "definitely" (>50% reduction in headache indices) better than pla=3(12.%) pin "slightly" better than pla=1(4.2%) pin=pla: 12(50%) pin worse than pla=8(33.3%) *Headache days(group total/4 wks):* pla=181; pin=194; increase of 13(7.2%) headache days on pin *Headache indices(group total/4 wks):* pla=318; pin=313; decrease of 5 points(1.6%) on pin	nr	Untoward effects noted: Initial lethargy: pin=3; pla=0 Dizziness/faintness: pin=6; pla=0 Chest discomfort: pin=1; pla=1	pin=3/28(10.7%) pla=0	

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Propranolol				
Borgesen 1974 Denmark *Fair quality* RCT Crossover	Diagnosis of migraine (Ad Hoc Committee on Classification of Headache, 1962); suffered more than one attack per week; did not respond to known prophylactics	Cardiac disease; asthma or diabetes mellitus; physical or neurological abnormalities	Propranolol (pro) 120 mg daily Placebo (pla) x 12 weeks, then crossover	Symptomatic treatments allowed (e.g., salicylates, ergotamines and narcotics)
Dahlof 1987 Sweden *Fair quality* RCT Crossover	Aged 18-60 years; history of at least 2 years classical or common migraine (World Federation of Neurological Research Group on migraine and headache); 2-8 well-defined migraine attacks/month and fulfill at least 4 of the following criteria: 1) heredity; 2) pulsating headache; 3) prodromas and/or aura; 4) hemicrania; 5) phonophobia; 6) photophobia; 7) gastrointestinal disturbances	Previous treatment with a beta blocker	Propranolol (pro) 120 mg daily Placebo (pla) x one month followed by assessment during a 5-month treatment period; then crossover	Use of common acute medication allowed (unspecified)

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Propranolol					
Borgesen 1974 Denmark *Fair quality* RCT Crossover	*Patient forms:* 1) severity on 3-point scale (severe=forcing patient to stay in bed; moderate=patient able to get up, but incapable of working; mild=patient uncomfortable, but able o work); 2) duration; 3) prodromal and accompanying symptoms; 4) medication used Patients seen at four weekly intervals to record 1) severity; 2) frequency; 3) working capacity; 4) subjective evaluation of the treatment	Mean age=37.6 83.3% female Race nr	Classical migraine (# pts/%): 15(50%) Common migraine (# pts/%): 15(50%)	nr/nr/45 entered	15(33.3%) withdrawn/0 lost to fu/30 analyzed
Dahlof 1987 Sweden *Fair quality* RCT Crossover	*Diary cards:* 1) frequency (method nr); 2) intensity (method nr); sent into investigator each month	Mean age nr 92.8% female Race nr	Classical migraine (# pts/%): 20/71.4% Common migraine (# pts/%): 8/28.5%	nr/nr/28 entered	0 withdrawn/0 lost to fu/28 analyzed

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Propranolol					
Borgesen 1974 Denmark *Fair quality* RCT Crossover	*Attack frequency in propranolol period relative to placebo period(# pts/%):* >100%=9/30%; 100%=3/10%; 75-99%=1/3.3%; 50-75%=8/26.7%; 25-50%=2/6.7%; 1-25%=2/6.7%; 0%=5/16.7% *Patient preference(# pts/%):* pro=17/56.7%; pla=6/20%; no difference=7/23.3% *Working capacity:* data nr; pro>pla(p<0.05) *Medication consumption:* data nr; pro=pla	nr	Data nr; pro=pla for #/severity of complaints of fatigue drowsiness and diarrhea	pro=0 pla=2	
Dahlof 1987 Sweden *Fair quality* RCT Crossover	Migraine frequency(4-week mean): pro=3.2; pla=4.3 Integrated headache(mean): pro=7.6; pla=10.9 Tablets consumed(mean): pro=9; pla=15	nr	nr	nr	Looked at longlasting prophylactic effect following discontinuance

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Diamond 1982 United States *Fair quality* RCT	Diagnosis of classical or common migraine(Ad Hoc Committee, 1962); a history of at least four attacks per month just prior to starting this trial	Patients with migraine associated with other types of headaches, migraine other than classic or common; known contraindications to propranolol	Propranolol (pro) 160 mg daily Placebo (pla) *Phase I(single blind): O* ne month of single-blind treatment, then crossover *Phase II(double-blind):* 6-14 months' with at least a single crossover, but with an option for two crossovers	Simple analgesics; narcotics; ergot compounds

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Diamond 1982 United States *Fair quality* RCT	*Patient daily records* Headache Unit Index (HUI): 'Total score of headache severity'(3-point scale: 1=mild/annoying; 2=moderate/interfering; 3=severe/incapacitating)/'total number of days observed' Relief Medication Unit Index (RMUI): 'Total score of relief medication units'(3-point scale: 1=simple analgesic; 2=narcotic; 3=ergot compound)/'Total number of days observed'	Age range of 21-64 78.7% female Race nr	nr	*Phase I:* nr/nr/245 admitted *Phase II:* All 148 patients that responded to propranolol from Phase I	*Phase I:* 41(16.7%) withdrawn/4(1.6%) lost to fu/204 analyzed *Phase II:* 48(32.4%) withdrawn/10(6.7%) lost to fu/100 analyzed

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Diamond 1982 United States *Fair quality* RCT	Phase I Mean HUI: pla=0.791; pro=0.562(p<0.0001) Mean RMUI: pla=2.553; pro=1.728(p<0.0001)	NR	Frequency of most common adverse events(# patients/%) Dizziness: pro=16/6.5%; pla=3/1.2% Significant nausea: pro=23/9.4%; pla=9/3.7% Visual disturbances: pro=7/2.8%; pla=0 Diarrhea: pro=18/7.3%; pla=5/2.0% Epigastric distress: pro=17/6.9%; pla=1/0.4% Weight gain: 9/3.7%; pla=2/0.8% Weakness/fatigue: pro=32/13.1%; pla=8/3.3% Malaise/lethargy: pro=20/8.2%; pla=4/1.6% Insomnia: pro=17/6.9%; pla=2/0.8% Chest pain/heaviness: pro=8/3.3%; pla=0	Phases I & II combined: pla=3/245(1.2%); pro=14/245(5.7%)	

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Diener 1996 Germany *Fair quality* RCT	Between the age of 18 and 60 years; male or female; migraine with and/or without aura according to the IHS criteria; migraine history of at least 12 months' duration; a mean number of 2-10 migraine attacks per month within the last 3 months prior to the study	Pregnant or lactating women; psychiatric disorders; concomitant non-migraine headaches 3 times per month within the last three months; intake of centrally acting drugs or migraine prophylactic drugs during the 4 weeks peceding the trial; specific contraindication to beta-blocker (asthma, diabetes, clinically relevant hypotension, etc.) or cyclandelate (acute stroke, glaucoma, coagulation disorder); intake of drugs to treat migraine attacks > 12 days/month	Propranolol (pro) 120 mg daily Placebo (pla) Cyclandelate (cyc) 1200 mg daily	Acute migraine medication allowed (not specified)

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Diener 1996 Germany *Fair quality* RCT	Headache diary	Mean age: pro=40; pla=39 % female: pro=76.9%; pla=74.5% Race nr	*pro n=78; pla n=55* Mean migraine history(years): pro=21; pla=19 Migraine with aura(#/% patients): pro=18/23.1%; pla=14/25.5% Migraine without aura(#/% patients): pro=59/75.6%; pla=41/74.5% Migraine with+without aura(#/% patients): pro=1(1.3%); pla=0	235/214/214	40 withdrawn/0 lost to fu/214 analyzed per ITT; 174 analyzed per protocol

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Diener 1996 Germany *Fair quality* RCT	*pro n=78; pla n=55* Migraine frequency(#/% patients with >/= 50% reduction of attacks): pro=33/42.3%; pla=17/30.9%(NS) Mean absolute reduction of migraine duration(hrs): pro=(-34.6); pla=(-13.7)(NS)	NR	Overall adverse effects(#/% patients): pro=19/24.4%; pla=5/9.1% Types of adverse effects of propranolol: increased sweating, hypertension, sleep difficulty, depressed modd; drowsiness; gastric pain, respiratory difficulty, kidney pain Types of adverse effects of place nr	Overall withdrawals due to adverse events(#/% patients): pro=4/5.1%; pla=0	

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Forssman 1976 Sweden *Fair quality* RCT Crossover	Diagnosis of migraine; age between 16 and 55 years; at least three attacks per month	Pregnancy or suspicion of pregnancy; indication of renal or heart disease, hypertension, diabetes or asthma; history of earlier treatment of migraine with propranolol	Propranolol (pro) 240 mg daily Placebo (pla) x 12 weeks, then crossover	Previously prescribed acute medication allowed (not specified); oral contraceptives
Kuritzky 1987 Israel *Fair quality* RCT Crossover	Patients aged 17-53, suffering from classical or common migraine for at least 2 years with at least 3 attacks per month	NR	Long acting propranolol (LA pro) 160 mg daily Placebo (pla)	Analgesics

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Forssman 1976 Sweden *Fair quality* RCT Crossover	*Printed record card:* 1) begin/end times; 2) intensity (slight, moderate or severe); 3) note about ability to work; 4) non-attack headaches; 5) amount of analgesics and preparations containing ergotamine or ergotamine derivatives *Integrated headache:* Indicates combined effect of duration and intensity; divided by number of days *Rating of therapeutic effect:* 'Good' = Reduction of attack frequency or of the number of days with headache by at least 50%; 'Appreciable' = reduction of up to 50%	Mean age=37.4 87.5% female Race nr	Classic migraine=5/32(15.6%) Common migraine=27/32(87.3%) Mean migraine duration(years): 18.9 Family history of migraine(# pts): 39/40(97.5%)	nr/nr/40 included	8(20%) withdrawn/0 lost to fu/32 analyzed
Kuritzky 1987 Israel *Fair quality* RCT Crossover	*Diary:* 1) Headache severity on 1-3 scale (unspecified); 2) duration (hours); 3) analgetics use	Mean age nr Gender nr Race nr	Classical migraine (# pts/%): 7/22.6% Common migraine (# pts/%): 24/77.4%	nr/nr/38 began	7(18.4%) withdrawn/0 lost to fu/31 analyzed

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Forssman 1976 Sweden *Fair quality* RCT Crossover	Attack frequency of propranolol relative to placebo (# patients/%): Good effect(>/= 50% improvement)=11/34.4%; Appreciable effect(< 50 % improvement)=11/34.4%; No change/increase=10/31.3% Reduction of headache days of propranolol relative to placebo(# patients/%): Good effect(>/= 50%)=11/34.4%; Appreciable effect(< 50%)=10/31.3%; No change/increase=11/34.4% Integrated headache(mean/% change): pro=(-2.14)/(-41.6%); pla=(-0.37)/(-7.2%) Ergotamine consumption(change in average number/% of doses per patient per day): pro=(-0.17)/(-51.5%); pla=(-0.08)/(-24.2%) Analgesic consumption(change in average number/% of doses per patient per day): pro=(-0.16)/(-47.0%); pla=(-0.04)/(-11.8%)	NR	*Most common side effects reported(# pts/%)* Increase in weight > 2 kg: pro=5(13.1%); pla=0 Insomnia: pro=5(13.1%); pla=1(2.6%) Tiredness: pro=4(10.5%); pla=3(7.9%) Uncharacteristic dizziness: pro=3(7.9%); pla=2(5.3%) Feeling of numbness/parasthesia: pro=2(5.3%); pla=1(2.6%) Nausea: pro=2(5.3%); pla=1(2.6%) Increased appetite: pro=1(2.6%); pla=0 Palpitations: pro=1(2.6%); pla=1(2.6%) Malaise: pro=0; pla=0	pro=2 pla=2	
Kuritzky 1987 Israel *Fair quality* RCT Crossover	Number of migraine attacks(mean): LA-pro=3.23; pla=5.56 Attack severity(mean): LA-pro=15.66; pla=25.66 Attack duration(mean): data nr (p=0.002)	nr	Most common side effects: tiredness, insomnia and dizziness	nr	

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Malvea 1973 United States *Fair quality* RCT Crossover	Age range of 25-57 with common migraine	Pregnancy, bronchial asthma, congestive heart failure, allergic rhinitis, diabetes mellitus and previous use of propranolol for headache	Propranolol (pro) <dose?> mg daily Placebo (pla) x <duration?>, then crossover	Analgesic, ergot and narcotic drugs
Mikkelsen 1986 Denmark *Fair quality* RCT Crossover	Aged between 18 and 65 years, with history of classic or common migraine (Ad Hoc Committee on Classification of Headache) with at least three migraine attacks per month which had been present for more than one year	Allergy to tolfenamic acid; serious heart, kidney, liver or psychiatric diseases, asthma, bronchitis, diabetes, active ulceration, pregnancy, or breast feeding; any administration of another prophylactic treatment for migraine within the month prior to the start of the study; use of tolfenamic acid within 6 months of study entry	Propranolol (pro) 120 mg daily Tolfenamic acid (tol) 300 mg daily Placebo (pla) x 12 weeks, then crossover	Other kinds of abortive treatment allowed but not specified

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Malvea 1973 United States *Fair quality* RCT Crossover	*Patient record* of: 1) headache frequency; 2) headache severity on 3-point scale (1=mild, annoying; 2=moderate or interfering; 3=severe or incapacitating; 3) use of analgesic and ergo drugs Reviewed at each 6-week period	Mean age nr 87.1% female Race nr	nr	nr/nr/31 enrolled	1(3.2%) withdrawn/0 lost to fu/29 analyzed
Mikkelsen 1986 Denmark *Fair quality* RCT Crossover	*Patient record sheet* 1) Number of attacks 2) Duration of attacks 3) Intensity of attacks (scale of 1-10) 4) Working capacity on 3-point scale (1=ability to work; 2=ability to be ambulant but not able to work; 3=bed confinement)	Mean age=38 Gender(% female)=83.9 % Race nr	Classic=10/31(32.2%) Common=21/31(67.7%)	nr/nr/39	8(20.5%) withdrawn/0 lost to fu/31 analyzed

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Malvea 1973 United States *Fair quality* RCT Crossover	Final preference(# patients/%): pro=16/55.2%; pla=8/27.6%; neither=5/17.2% Headache units/day(sum of means for group as a whole/% change): pro=(-6.8)/(-19.2%); pla=(-2.1)/(-8.3%) Symptomatic drug use/day(sum of means for group as a whole/% change): pro=(-27)/(-34.2%); pla=(-24)/(-30.4%)	nr	Overall incidence: nr Side effects possibly related to the use of propranolol(# pts): Mild nausea: 5 Fatigue: 5 Numbness: 1 Heartburn: 1 Heaviness in leg/arm=1 Light-headedness=1 Vomiting=1 Tingling in leg/arm=1 Depressed=1	nr	
Mikkelsen 1986 Denmark *Fair quality* RCT Crossover	*Clinical data recorded over last 11 weeks of each treatment period:* Number of attacks(mean): pla=8.81; pro=6.65 Working capacity(Total attacks where patients were confined to bed): pla=5.48; pro=4.06(NS) Mean attack duration (hours) of attacks: pla=18.68; pro=14.26(NS) Pain intensity(on scale of 1-10): pla=6.97; pro=6.94(NS)	nr	Overall adverse effects(# patients): pla=3; pro=3(NS) Adverse events recorded with: Placebo=slight neurological symptoms, hot flushes, diarrhea Propranolol=fatigue, polyuria, low back pain	nr	

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Pita 1977 Spain *Fair quality* RCT Crossover	Migraine (Ad Hoc Committee) at a frequency of at least 3-4 attacks monthly and have a history of not responding to prophylactic therapy	Concomitant neurological or psychiatric disorders as well as diabetes mellitus, asthma or cardiac disease	Propranolol (pro) 160 mg daily Placebo (pla) x 2 months; then crossover	Symptomatic analgesic treatment (unspecified)
Pradalier 1989 *Fair - Poor* RCT	Suffering from migraine for at least two years with or without aura according to the criteria of the new International Headache Society classification	History of congestive heart failure or asthma; heart block; bradycardia (<50 beats/min); Raynaud phenomenon; hypertension; resistant to two previously well-followed prophylactic treatments	Placebo (pla) Long-acting propranolol (LA pro) 160 mg daily x 12 weeks	Usual medication

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Pita 1977 Spain *Fair quality* RCT Crossover	1) Frequency; 2) duration; 3) severity rated on 3-point scale (e.g., I=uncomfortable but able to work; II=patient unable to work but not needing bedrest; III=patient necessitating bedrest)	Mean age=32 77.8% female Race nr	Common(#/% patients): 5/9(55.6%) Classic(#/% patients): 4/9(44.4%)	nr/nr/9	1(11.1%) withdrawn/0 lost to fu/8 analyzed
Pradalier 1989 *Fair - Poor* RCT	Patient form documenting frequency and details of the headache (method nr)	Mean age: LA pro=37.1; pla=37.7 Gender(% female): LA pro=77.5%; pla=73.5% Race nr	Familial history of migraine: LA pro=65%; pla=52.9% Mean age at onset: LA pro=20.8; pla=19.1 Migraine frequency/week: LA pro=1.66; pla=1.40 Type of migraine Aura: LA pro=15%; pro=5.9% No Aura: LA pro=80%; pla=85.3% Aura+No Aura: LA pro=5%; pla=8.8% Severity of crisis(# pts. with severe crisis): LA pro=52.5%; pla=;47.0%	nr/nr/74 entered	33 withdrawn(19 prior to randomization)/9(16.3%) lost to fu/analyzed nr

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Pita 1977 Spain *Fair quality* RCT Crossover	*Whole frequency/month:* data nr; narrative indicates pro>pla *Mean frequency/month* : data nr; narrative indicates pro=pla *Mean Grade(severity)/month:* data nr; narrative indicated pro>pla for Grade III *Preference(# patients):* pro=7/8; pla=1/8	nr	*nr*	nr	
Pradalier 1989 *Fair - Poor* RCT	Change in mean crises/month: LA pro= (-2.96/-48.4%); pla= (+0.41/+6.8%)	Volunteered information (e.g., "How did you tolerate the treatment?") and a standardized 17-item questionnaire	Answers to adverse event questionnaire at Day 84 *(LA pro n=22; pla n=19)* Cold extremities: LA pro=0; pla=3(15.8%) Tiredness: LA pro=3(13.6%); pla=2(10.5%) Dyspnea: LA pro=3(13.6%); pla=1(5.3%) Dyspepsia: LA pro=1(4.5%); pla=0 Diarrhea: LA pro=1(4.5%); pla=0 Constipation: LA pro=2(9.1%); pla=2(10.5%) Insomnia: LA pro=2(9.1%); pla=2(10.5%) Depression: LA pro=0; pla=1(10.5%)	LA pro=0 pla=1(due to psoriasis)	

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Rao 2000 India *Fair quality* RCT	Patients with two or more migraine attacks per week	nr	Placebo (pla) Cyproheptadine (cyp) 4 mg daily Propranolol (pro) 80 mg daily Cyproheptadine 4 mg daily+Propranolol 80 mg daily (cyp+pro)	nr
Wideroe 1974 Norway *Fair quality* RCT Crossover	Patients diagnosed with cassic or common migraine (Ad Hoc Committee, 1962) in whom the result of open treatment with propranolol 160 mg daily as part of a pilot study was rated as "excellent" (e.g., reduction of attack rate of more than 50%	NR	Propranolol (pro) 160 mg daily Placebo (pla) x 3 months, then crossover	Analgesic and antimigraine drugs

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Rao 2000 India *Fair quality* RCT	Migraine attack frequency, severity and duration rated by patient using 5-point scale 4=100%, "total" relief 3=75% relief 2=50% relief 1=25% relief 0=0% relief, no change	Mean age=28.6 67.2% female Race nr	nr	nr/nr/259 recruited	55 withdrawn/lost to fu nr/204 analyzed
Wideroe 1974 Norway *Fair quality* RCT Crossover	*Patient record* of a) frequency; b) intensity; c) duration; d) change in premonitory symptoms; e) quality of the attack; f) degree of invalidity; g) consumption of analgesic/antimigraine drugs *Treatment rating by physician:* 1) excellent-a reduction in attack rate of more than 50%; 2) moderate-a reduction in attack rate of less than 50%; 3) no effect; 4) an increase in attack rate x monthly	Mean age=38 Gender(% female)=86.7 % Race nr	Classic=6/30(20%) Common=24/30(80%)	nr/nr/30	4 withdrawn/lost to fu nr/analyzed 26

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Rao 2000 India *Fair quality* RCT	*Frequency (mean response):* pla=1.77; pro=2.85 *Duration (mean response):* pla=1.77; pro=2.83 *Severity (mean response):* pla=1.64; pro=2.87	nr	Incidence(# patients): pla=1/69(1.4%); pro=11/62(17.7%)	nr	
Wideroe 1974 Norway *Fair quality* RCT Crossover	Average rate of migraine attacks/month(mean/% change): pro=0.4(-86.7%); pla=1.7(-58.8%)	nr	nr	nr	

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Poor Quality				
Propranolol				
Ahuja 1985 India *Poor quality* RCT Crossover	Suffering from migraine (Ad Hoc Committee on Headache) at a frequency of > 2 attacks per month in the previous 3 months	Intercurrent illness	Propranolol (pro) 120 mg daily Placebo (pla) x 8 weeks, then crossover	NR
Borgensen 1976 Denmark *Poor quality* RCT Crossover	(a) Diagnosis of migraine (Ad Hoc Committee on Headache, 1962) (b) > 1 migraine attack/week (c) Intractability with known prophylactics	Cardiac disease, asthma, diabetes mellitus, physical or neurological abnormalities	Propranolol (pro) 120 mg daily Placebo x three months, then crossover	nr

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Poor Quality					
Propranolol					
Ahuja 1985 India *Poor quality* RCT Crossover	*Severity:* rated on 3-point scale (3=severe; 2=moderate, incapacitating; 1=inconvenient, mild) *Severity index:* calculated by multiplying the number of attacks /8 weeks with severity points *Attack duration:* scored on 5-point scale (5=duration of attack exceeding pretreatment duration; 4=duration equal before and after treatment; 3=duration of attacks was 75 percent of pretreatment; 2=duration of attacks was 50 percent of pretreatment; 1=duration of attacks was 25 percent of pretreatment) *Duration index:* multiplying number of attacks/8 weeks with duration score	Age range of 17-55 46.1% female	nr	nr/nr/26 enrolled	nr/nr/nr
Borgensen 1976 Denmark *Poor quality* RCT Crossover	nr	nr	Migraine Frequency(# patients): 2-5 attack/4 weeks=1	nr/nr/45 patients	15(33.3%) withdrawn/lost to fu nr/30 analyzed

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Poor Quality					
Propranolol					
Ahuja 1985 India *Poor quality* RCT Crossover	Attack frequency/8 weeks(mean): pro=8.58; pla=14.46(p<0.05) Severity Index/8 weeks(mean): pro=20.69; pla=38.00(p<0.05) Duration index/8 weeks(mean): pro=23.58; pla=52.19(p<0.01)	nr	data nr; no significant side effects of propranolol were observed during the trial period	nr	
Borgensen 1976 Denmark *Poor quality* RCT Crossover	Attack frequency in pro period as percentage of that in pla period(number/% patients): > 100%=9/30% 100%=3/10% 75-99%=1/3.3% 50-75%=8/26.7% 25-50%=2/6.7% 1-25%=2/6.7% 0%=5/16.7%	nr	nr	nr	

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Diamond 1976 United States *Poor quality* RCT Crossover	Classic or common migraine	Asthma, cardiac disease, diabetes mellitus or any physical or neurologic abnormalities	Flexible dosing: Propranolol (pro) 80-160 mg daily Placebo (pla) x 4-8 weeks; then crossover x 8 weeks	Common analgesics, narcotics, ergot medications

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Diamond 1976 United States *Poor quality* RCT Crossover	*Severity* rated on 3-point scale (severe/3 headache units(HU)=incapacitation unable to perform their duties; moderate/2 HU=annoying headache with difficulties to carry out activities; mild/1 HU=bothersome headache which permit fulfillment of obligations with minimal or no difficulties) *Relief medication units(RMU):* ergotamine=3 RMU; narcotic=2 RMU; common analgesic=1 RMU *Headache Index(HI):* HU total/# days observed *Headache Index Ratio:* pla HI/pro H(1=no change; >1=better on pro; <1=better on pla) Relief medication index(RMI): total of RMU/# days observed *Relief medication index ratio(RMIR): pla RMI/pro RMI(1=no change; >1=better on pro; <1=better on pla)*	Average age=38.1 80.7% female Race nr	Common migraine: 57 pts.(91.9%) Classic migraine: 5 pts(8.1%)	nr/nr/83	21 pts(25.3%) withdrawn/lost to fu nr/62 analyzed

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Diamond 1976 United States *Poor quality* RCT Crossover	Responders(# pts preferred treatment): pro=34/62(54.8%); pla=17/62(27.4%) Corroboration of HIR/RMIR scores relative to treatment preference(# pts/%): pro=27/34(79.4%); pla=10/17(58.8%) Comparison of HIR:RMIR relative to treatment preference(pro responder=34; pla responder=17) Low ratio value(HIR/RMIR): pro resp=0.70/0.00; pla resp=0.37/0.00 Medium ratio value(HIR/RMIRO: pro resp=2.03/1.95; pla resp=0.75/0.75 High ratio value(HIR/RMIR): pro resp=14/?; pla=1.44/5.91	nr	Incidence(# pts/%): pro=15/83(18.1%); pla=9/83(10.8%) Benign adverse reactions occurring on both pro and pla(data nr): nausea, light-headedness, fatigue, difficulty catching breath, mild depression, heartburn Benign side effects on pro only(data nr): diarrhea, abdominal cramps, irritability, insomnia, sleepiness	pro=6/83(7.2%) pla=1/83(1.2%)	

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Fuller 1990 London *Poor quality* RCT	Common or classical migraine as defined by the Ad Hoc Committee; migraine of one year's duration; with attacks occurring between once a week and once every four months; age between 16 and 65	Contraindications to propranolol or paracetamol; pre-existing migraine prophylaxis or beta-blocker therapy for other indications; non-migrainous headaches that are not clearly distinguishable from migraine	Propranolol 40 mg Placebo	Paracetamol
Johnson 1986 New Zealand RCT Crossover	Aged 22-80, with a history of least one migraine attack during the month preceding the trial; attacks associated with at least two of the following: 1) a strong family history, 2) nausea or vomiting, 3) some response to vasoconstrictors, 4) a classical prodrome	nr	Mefanamic acid (mef) 500 mg daily Propranolol (pro) 80 mg daily Placebo (pla) x 3 months; then crossover	Acute medication allowed (not specified)

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Fuller 1990 London *Poor quality* RCT	Patient record cards	*n=14* Median age=31 78.6% female Race nr	Common migraine=9/14(64.3%) Classical migraine=5/14(35.7%)	nr/nr/27 recruited	14 analyzed
Johnson 1986 New Zealand RCT Crossover	*Patient charts:* 1) frequency; 2) duration; 3) severity (scale 1-10); 4) associated symptoms; 5) acute medication usage; 6) side effects; 7) disability scored on a 5-point scale (1=mild disability; 5=severe, confinement to bed in a darkened room) Patients assessed monthly	Per protocol analysis (n=17) Mean age=42 76.5% female Race nr	Per protocol analysis (n=17) Common migraine=11(64.7%) Classical migraine=6(35.3%)	nr/nr/29 enrolled	12(41.4%) withdrawn/9(31%) lost to fu/17 analyzed

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Fuller 1990 London *Poor quality* RCT	Change in headache severity(2 hours post-dose): *1-3 point deterioration(# patients):* pro=1(7.1%); pla=4(28.6%) *No change(# patients):* pro=7(50%); pla=4(28.6%) *1-6 point improvement(# patients):* pro=6(42.8%); pla=6(42.8%) Patient analysis of response to treatment: *No effect:* pro=3(21.4%); pla=6(42.8%) *Poor:* pro=4(28.6%); pla=3(21.4%) *Fair:* pro=5(35.7%); pla=4(21.4%) Good: pro=2(14.3%); pla=1(7.1%) *Excellent: pro=0; pla=0*	nr	*Propranolol(# patients):* Light-headedness=1 Stomach pains=1 Sleepiness=1 *Placebo(# patients):* Sleepiness=2 Nausea=2 Dizziness=1	nr	*Study of abortive treatment of migraine*
Johnson 1986 New Zealand RCT Crossover	*Number of attacks/3 months(median/mean):* pro=11/13.8 pla=15/20 Median/% change(pro:pla): -4/-26.7% Mean/% change(pro:pla): -6.3/-31.3% *Total duration (hours) of attack(median/mean):* pro=75/115 pla=138/184 Median/% change(pro:pla): -63/-45.6% Mean/% change(pro:pla): -69/-37.5% *Average duration (hours) of attacks(median/mean):* pro=24/40 pla=26/40 Median/% change(pro:pla): -2/-7.7% Mean/% change(pro:pla): 0	Recorded by patients in charts	Incidence: pro=2(8.7%); pla=1(4.2%) Adverse events on: pro=depression, gastrointestinal symptoms pla=dizziness	Withdrawals: pro=1 pla=1	

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Kaniecki 1997 United States *Poor quality* RCT Crossover Single blind	18 to 65 years of age; meeting diagnostic criteria for migraine without aura as defined by the IHS; migraine frequency of 2-8 times/month, with a maximum of 15 headaches days per month, and a migraine history of greater than 1 year	Past trials of valproate or propranolol; failure of greater than 2 adequate trials of migraine prophylactic agents; severe medical or psychiatric illness; analgesic use of more than 15 days per month; presence of alcohol or drug abuse; use of no contraception by women of childbearing potential; unable to complete a headache diary or differentiate various headache types	Sustained release propranolol (SR pro) 180 mg daily Divalproex sodium (div) 1500 mg daily Placebo (pla)	Symptomatic medication allowed (unspecified)

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Kaniecki 1997 United States *Poor quality* RCT Crossover Single blind	Patient diary Assessments performed at weeks 4, 8, 20, 24, and 36	Mean age nr 81.1% female Race nr	nr	nr/nr/37	5(13.5%) withdrawn)/0 lost to fu/32 analyzed

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Kaniecki 1997 United States *Poor quality* RCT Crossover Single blind	Reduction in mean migraine *frequency* /4 weeks(#/% patients): pla=6/19%; pro=20/63% Reduction in mean migraine *days* /4 weeks(#/% patients): pla=7/22%; pro=22/69%	Documented on forms (not specified)	Adverse event profile for SR propranolol (# events): nausea=2 Fatigue=3 Dizziness=3 Weight gain=1 Depression=2 Increased headache=1 Impotence=1 Insomnia=1 Memory loss=1 Adverse event profile for placebo nr	Overall withdrawals due to adverse events=5(15.6%)	

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Nadelmann 1986 *Poor quality* RCT Crossover	Fulfilled diagnostic criteria for classic and/or common migraine headaches (Ad Hoc Committee on the Classification of Headache); had at least four headaches per month during a one-month observation period	Migraine other than classic or common, or other headaches known to be associated with migraine, or if they had known contraindications to beta blockers	Propranolol (pro) 80-320 mg daily Placebo (pla) x 30 weeks (6-week dose-finding, 24-week double-blind)	Analgesics Tranquilizers Ergot Narcotics
Nair 1974 India *Poor quality* RCT Crossover	History typical of migraine; duration of headache of more than one year; attack rate exceeded 5 or more/month	nr	Propranolol (pro) 80 mg daily Placebo (pla)	*All patients used prochlorperazine 15 mgms daily throughout the duration of the study.* Use of metamizole and ergotamine tartrate also allowed as abortive treatment

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Nadelmann 1986 *Poor quality* RCT Crossover	Data recorded at two-week intervals Daily patient diaries *Headache Unit Index (HUI)* A mild headache=Annoying=1unit A moderate headache=Interfering=2 units A severe headche=Incapacitating=3 units for headaches lasting 2 days A very severe headache=Incapacitating=4 units/day for severe attacks lasting 2 or more days *Relief Medication Unit Index(RMUI)* Simple analgesic, tranquilizer=1 unit Narcotic=2 units Ergot compound=3 units	*Age(%)* 18: 1.6 20-29=37.1 30-39=30.6 40-49=24.2 50-59=4.8 60=1.6 *Gender(%)* Female=85.5 Male=14.5 *Race(%)* White=96.8 Black=3.2	*Diagnosis(%)* Common migraine=56.5 Classic/common migraine=43.5 Classic migraine=0 *History of migraine(% yrs duration)* 1-5=22.6 6-10=27.4 11-15=14.5 16-20=9.7 21-25=8.1 26+=17.7	nr/nr/67 registered	26 withdrawn/2 lost to fu/
Nair 1974 India *Poor quality* RCT Crossover	*Patient charts(2):* 1) # of headaches suffered in one month; 2) # of tablets of metamizole and ergotamine tartrate consumed in one month	Mean age=27.2 50% female Race nr	nr	nr/nr/20	0 withdrawn/0 lost to fu/20 analyzed

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Nadelmann 1986 *Poor quality* RCT Crossover	***Sequence 1:*** contrast between mean change in *placebo* and *propranolol* treatment periods ***Sequence 2:*** contrast between mean change in propranolol and placebo treatment periods *HUI* Sequence 1: 0.33 (p=0.03) Sequence 2: (-0.18) (NS) *RMUI* Sequence 1: 0.66 (NS) Sequence 2: (-0.72) (NS)	nr	% Incidence Malaise: pro=14.1; pla=3.6 Fatigue: pro=40.6; pla=5.4 Lethargy: pro=26.6; pla=3.6 Bradycardia: pro=7.8; pla=0 Nausea: pro=15.6; pla=5.4 Diarrhea: pro=10.9; pla=1.8 Epigastric distress: pro=17.2; pla=3.6 Depressed moods: pro=7.8; pla=0 Vivid dreams: pro=10.9; pla=1.8	NR	
Nair 1974 India *Poor quality* RCT Crossover	Headache frequency(mean/month) pla=6.25 pro=3.15 Mean/% change(pro:pla): (-3.1)/(-49.6%)	nr	nr	nr	

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Palferman 1983 London *Poor quality* RCT Crossover	Outpatients with migraine, defined as episodic headache with other accepted disorders of cerebral function including visual disturbances and vomiting, and those with "non-migraine", defined as recurrent 'simple' or 'tension' headaches without the disorders of cerebral function	Patients under 16 or over 65 years; use of beta blockers contraindicated; patients with the possibility of other pathology, disclosed by history, examination or investigations, which might lead to headaches	Propranolol (pro) 120 mg daily Placebo (pla) x 8 weeks, then crossover	nr
Standes 1982 Norway *Poor quality* RCT Crossover	Outpatients of both sexes between the ages of 18 and 65 years with a history of between two and six common migraine attacks (Ad Hoc Committee) per month	Other types of headache (including classical migraine) and major head injuries; contraindications to beta-blocking agents; use of oral contraceptives; pregnant women; use of timolol or propranolol for other reasons than migraine	Propranolol (pro) 160 mg daily Timolol (tim) 20 mg daily Placebo (pla)	Ergotamine and analgesics

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Palferman 1983 London *Poor quality* RCT Crossover	Patient diary card Subjective daily syptoms graded 0-4 (0=no headache, 1=mild, 2=moderate, 3=severe, 4=worst possible) x 4 weekly intervals	*All patients (n=22)* Mean age=37.8 69.4% female Race nr *Migraine patients only (n=10)* Mean age=41.4 80% female Race nr	*All patients* Average symptom duration(yrs): 11.3 *Migraine patients only* Average symptom duration(yrs): 17.5	nr/nr/22 patients (10 migraine patients) enrolled	14(38.8%) withdrawn/10(27.8%) lost to fu/22 analyzed
Standes 1982 Norway *Poor quality* RCT Crossover	*Patient record:* 1) incidence; 2) severity; 3) duration	Age range: Men=20-57; Women=22-57 80% female Race nr	nr	nr/nr/25 recruited	7(28%) withdrawn/0 lost to fu/18 analyzed

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Palferman 1983 London *Poor quality* RCT Crossover	Average number of days with headache in 56 days: *All patients* (n=22): pla=26; pro=23(NS) *Migraine patients only* (n=10): pla=24; pro=21(NS) Average headache score All patients: pro=55; pla=47(p=0.26) Migraine patients only: pro=52; pla=47(NS)	nr	nr	nr	

Standes
1982
Norway
 	
Poor quality
RCT Crossover
	Reduction in mean attacks/month(mean/% change): pro=(-3.43)/(51.6%); pla=(-2)/(-30.1%)
	Ergotamine use(change in % of attacks during which pain relieving tablets were taken): pro=(-18 percentage points); pla=(-13.4 percentage points)
	Other pain relief tablet use(change in % of attacks during which pain relieving tablets were taken): pro=(-29 percentage points); pla=(-35 percentage points)
	Reduction in frequency of attacks:
	Good(>/= 50% reduction): pro=13 pts./72.2%; pla=6 pts./33.3%
	Some(33.3-49% reduction): pro=0 pts.; pla=1 pt./5.5%
	No effect(0=33.2% reduction); pro=3 pts/16.7%; pla=8 pts./44.4%
	Negative effect(increased frequency): pro=2 pts/11.1%; pla=3 pts/16.7%
		Patient report	Incidence(# pts/%):
			pro=6/25(24%);
			pla=5/25(20%)
			
			Most common adverse events:
			Tiredness:
			pro=3/25(12%);
			pla=4/25(16%)
			Nausea: pro=1/25(4%);
			pla=1/25(4%)
			Sunburn feeling:
			pro=1/25(4%); pla=0
			Depression:
			pro=1/25(4%); pla=0
				2/25(8%)
				treatment nr	

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Tfelt-Hansen 1984 Scandinavia *Poor quality* RCT Crossover	Outpatients of both sexes between ages of 18 and 65 years with a history of between 2 and 6 common migraine attacks per month (Ad Hoc Committee)	Other types of headache (including classical migraine) and major head injuries; contraindications to beta blockers; oral contraceptive use; heart rate < 54 after 3 min of rest and with supine DBP >/= 100 mmHg	Timolol (tim) 20 mg daily Propranolol (pro) 160 mg daily Placebo (pla)	NR
Weber 1972 United States *Poor quality* RCT Crossover	Met criteria for diagnosis of migraine and that were recognized as therapeutic management problems	Abnormal neurological examinations; disorders that could be aggravated by beta blockers (namely cariac disease, asthma, diabetes mellitus)	Propranolol (pro) 80 mg daily Placebo (pla)	NR

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Tfelt-Hansen 1984 Scandinavia *Poor quality* RCT Crossover	*Patient diary card:* 1) frequency; 2) duration; 3) severity of attacks; 4) number of responders (e.g., >/= 50% reduction in frequency of attacks compared to baseline; 5) frequency of attacks with associated symptoms; 6) frequency of attacks requiring medication; 7) headache index=frequency x severity x attack duration in hours; 8) second headache index: attack frequency x severity	Mean age=39.5 73.9% female Race nr	Clinical characteristics(mean) Duration of migraine(years): 20.9 Attack frequency/28 days: 5.7 Attack with nausea frequency/28 days: 2.6 Attack with ergotamine therapy frequency/28 days: 2.4 Attack with any therapy frequency/28 days: 5.1 Duration of attacks(hours): 9.8 Severity of attacks: 2.0	nr/nr/96	withdrawn=27(28.1%)/6(6.2%) lost to fu/80 analyzed
Weber 1972 United States *Poor quality* RCT Crossover	1) Frequency and 2) severity assessed at 4-week intervals Definitions of symptomatic responses Excellent: all or nearly all symptoms of migraine absent after first week of study Good: more than 50% reduction in frequency or severity of headaches Fair: minimal symptomatic improvement No effect: unspecified	Mean age=40.6 52% female Race nr	Classic: 13(68.4%) Common: 6(31.6%)	nr/nr/25	withdrawn=6/25(24%)/lost to fu nr/analyzed 19

Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments

Tfelt-Hansen
1984
Scandinavia
 	
Poor quality
RCT Crossover
	Mean frequencies per 28 days/mean(%) change for propranolol relative to placebo
	Frequency of attacks: pro=3.69; pla=4.84/-1.15(-23.8%)
	Frequqency of attacks with nausea: pro=1.37; pla=1.89/-0.52(-27.5%)
	Frequency of attacks with any therapy: pro=3.24; pla=4.20/-0.96(-22.8%)
	Severity of attacks: pro=1.83; pla=1.93/-0.10(-5.2%)(NS)
	Duration of attacks(hours): pro=7.38; pla=7.95/-0.57(-7.2%)(NS)
	Headache index2: pro=6.66; pla=9.03/-2.37(-35.6%)
	Headache index1: pro=50.3; pla=50.7/-19(-27.4%)
	
	Number of responders(# pts with 50% reduction in frequency): pro=48; pla=24/24(+50%)
		Patient report	Incidence[# pts(%)]:
			pro=35(42.2%);
			pla=23(27.7%)
			Most commonly reported side effects:
			Fatigue/tiredness:
			pro=11(13%);
			pla=15(18%)
			Dizziness: pro=4(5%);
			pla=2(2%)
			Nausea: pro=5(6%);
			pla=2(2%)
			Sleep disturbances:
			pro=3(4%); pla=2(2%)
			Depression: pro=3(4%);
			pla=0
			Abnormal dreaming:
			pro=0; pla=0
				pro=6/89(6.7%)
				pla=2/90(2.2%)	

Weber 1972 United States *Poor quality* RCT Crossover	<u>Symptomatic response(# pts/%)</u> *First 3 months(pro n=8; pla n=11)* Good/Excellent: pro=5(63%); pla=0 Fair: pro=2(25%); pla=1(9.1%) No effect: pro=1(12.5%); pla=11(91%) *Second 3 months(pro n=11 who received placebo first; pla n=8 who received pro first)* Good/Excellent: pro=10(91%); pla=2(25%) Fair: pro=0; pla=0 No effect: pro=1(9.1%); pla=6(75%) *Irrespective of sequence* pro>pla(#/% pts): 15/79% pro=pla(#/% pts): 4/21%	nr	Abdominal cramps/diarrhea:1 patient	nr	

Evidence Table 14a. Quality assessments of placebo controlled trials of beta blockers for migraine

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Nadelmann 1986	NR	NR	N/A-crossover	Fair higher female to male ratio	67 enrolled
Borgensen 1976 Denmark	**NR**	NR	N/A-crossover	Unknown; characteristics NR	45 selected
Fuller 1990 London	NR	NR	N/A-crossover	Good Median age=31 78.6% female	27 enrolled/14 analyzed
Rao 2000 India	Inferior; group allottment via latin square design	NR	NR	Good Mean age=28.6 67.2% female	259 recruited
Pradalier 1989	NR	NR	Yes	Good Mean age=37 75.7% female	74 enrolled
Wideroe 1974 Norway	NR	NR	N/A-crossover	Good Mean age=38 86.7% female	30 enrolled
Mikkelsen 1986 Denmark	NR	NR	N/A-crossover	Good Median age=38 83.9% female	39 enrolled

Evidence Table 14a. Quality assessments of placebo controlled trials of beta blockers for migraine (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Nadelmann 1986	Migraine other than classic or common, or other headaches known to be associated with migraine, or if they had known contraindications to beta blockers	Yes	NR	Yes	Yes	No
Borgensen 1976 Denmark	Cardiac disease, asthma, diabetes mellitus, physical or neurological abnormalities	Yes	NR	Yes	Yes	No
Fuller 1990 London	Contraindications to propranolol or paracetamol; pre-existing migraine prophylaxis or beta-blocker therapy for other indications; non-migrainous headaches that are not clearly distinguishable from migraine	Yes	Yes	Yes	Yes	No
Rao 2000 India	NR	Minimal	Yes	Yes	Yes	Yes
Pradalier 1989	History of congestive heart failure or asthma; heart block; bradycardia (<50 beats/min); Raynaud phenomenon; hypertension; resistant to two previously well-followed prophylactic treatments	Yes	Yes	Yes	Yes	Stated Yes, but unclear
Wideroe 1974 Norway	NR	Minimal	NR	Yes	Yes	No
Mikkelsen 1986 Denmark	Allergy to tolfenamic acid; serious heart, kidney, liver or psychiatric diseases, asthma, bronchitis, diabetes, active ulceration, pregnancy, or breast feeding; any administration of another prophylactic treatment for migraine within the month prior to the start of the study; use of tolfenamic acid within 6 months of study entry	Yes	Yes	Yes	Yes	No

Evidence Table 14a. Quality assessments of placebo controlled trials of beta blockers for migraine (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Nadelmann 1986	NR	Overall rate of attrition: 38.8% Others NR	No	Poor	NR; second author affiliated with Ayerst Laboratories	Yes	34 weeks
Borgensen 1976 Denmark	N/A	Attrition reported(33.3%); others NR	NR	Poor	NR	Yes	6 months
Fuller 1990 London	N/A	Attrition reported (48.1%); others NR	No	Poor	NR	Yes	4 attacks
Rao 2000 India	NR	Attrition reported (21.1%); others NR	No	Fair	NR	Yes	1 year
Pradalier 1989	NR	Attrition reported (44.6%); others NR	16.3% lost to fu	Fair-Poor	NR	Yes	12 weeks
Wideroe 1974 Norway	N/A	Attrition reported (13.3%); others NR	NR	Fair	Tablets/randomization provided by Imperial Chemical Industries Ltd.	Yes	6 months
Mikkelsen 1986 Denmark	N/A	Attrition reported(20.5%); others NR	No	Fair	GEA Ltd., Pharmaceutical Manufacturing Company	Yes	24 weeks

Evidence Table 14a. Quality assessments of placebo controlled trials of beta blockers for migraine (continued)

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Palferman 1983 London	NR	NR	N/A-crossover	Good Mean age=41.4 80% female	36 patients in total (16 with migraine)
Kaniecki 1997 United States	NR	NR	N/A-crossover	Unclear Mean age NR 81.1% female	37 recruited
Diener 1996 Germany	NR	NR	Yes	Good mean age=39 78.0% female	235 screened/214 randomized
van de Ven 1997 The Netherlands	NR	NR	Yes	Good mean age=38.7 82.3% female	226 randomized
Diamond 1982 United States	NR	NR	N/A-crossover	Unclear Mean age NR 78.7% female	245 admitted

Evidence Table 14a. Quality assessments of placebo controlled trials of beta blockers for migraine (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Palferman 1983 London	Under 16 or over 65 years; use of beta blockers contraindicated; possibility of other pathology, disclosed by history, examination or investigations, which might lead to headaches	Yes	NR	Yes	Yes	No
Kaniecki 1997 United States	Past trials of valproate or propranolol; failure of greater than 2 adequate trials of migraine prophylactic agents; severe medical or psychiatric illness; analgesic use of more than 15 days per month; presence of alcohol or drug abuse; use of no contraception by women of childbearing potential; unable to complete a headache diary or differentiate various headache types	Yes	no	NR	NR	No
Diener 1996 Germany	Pregnancy or lactation; psychiatric disorders; concomitant non-migraine headaches 3 times per month within the last three months; intake of centrally acting drugs or migraine prophylactic drugs during the 4 weeks peceding the trial; specific contraindication to beta-blocker (asthma, diabetes, clinically relevant hypotension, etc.) or cyclandelate (acute stroke, glaucoma, coagulation disorder); intake of drugs to treat migraine attacks > 12 days/month	Yes	Yes	Yes	Yes	Yes
van de Ven 1997 The Netherlands	Current use of drugs for the prevention of migrain; treatment with cardiovascular drugs; usual contrindications for beta blocker use or hypersensitivity to these agents	Yes	NR	Yes	Yes	Use of ITT analysis is indicated; but unclear in way data is presented
Diamond 1982 United States	Migraine associated with other types of headaches, migraine other than classic or common; known contraindications to propranolol	Yes	Phase I single blind; Phase II double blind	Yes	Yes	No

Evidence Table 14a. Quality assessments of placebo controlled trials of beta blockers for migraine (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Palferman 1983 London	N/A	Attrition reported(38.8%); others NR	27.80%	Poor	ICI Pharmaceuticals	Yes	16 weeks
Kaniecki 1997 United States	N/A	Attrition reported(13.%)	No	Poor	Abbott Laboratories	Yes	36 weeks
Diener 1996 Germany	NR	Attrition(16.8%); others NR	No	Fair	NR	Yes	20 weeks
van de Ven 1997 The Netherlands	NR	Attrition=31(13.7%); others NR	No	Fair	Merck	Yes	12 weeks
Diamond 1982 United States	N/A	Attrition: Phase I=16.7%; Phase II=32.4%; others NR	Phase I=4/1.6% Phase II=10/6.7%	Fair	Statistical evaluation provided by Ayerst Laboratories	Yes	6-12 months

Evidence Table 14a. Quality assessments of placebo controlled trials of beta blockers for migraine (continued)

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Kangasniemi 1987 Scandinavia	NR	NR	N/A-crossover	Good Mean age 37.5 79.7% female	77 randomized
Malvea 1973 United States	NR	NR	N/A-crossover	Fair Mean age NR 87.1% female	31 enrolled
Forssman 1976 Sweden	NR	NR	N/A-crossover	Good Mean age 37.4 87.5% female	40 included
Borgesen 1974 Denmark	NR	NR	N/A-crossover	Good Mean age 37.6 83.3% female	45 included
Ahuja 1985 India	NR	NR	N/A-crossover	Unclear; mean age NR 46.1% female	26 selected
Dahlof 1987 Sweden	NR	NR	N/A-crossover	Unclear mean age NR 92.8% female	28 entered
Kuritzky 1987 Israel	NR	NR	N/A-crossover	Unclear mean age NR gender NR	38 began

Evidence Table 14a. Quality assessments of placebo controlled trials of beta blockers for migraine (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Kangasniemi 1987 Scandinavia	Daily use of analgesics and/or total consumption exceeding 40 tablets/month; daily use of ergotamine and/or total consumption exceeding 16 mg/month; treatment with anti-depressive or neuroleptic drugs within the past 2 months; use of narcotic analgestics, chronic treatment with calcium antagonists, clonidine, other beta-blockers or NSAIDSs; change in oral contraceptive therapy 3 months before or during the study; contraindications for beta-blockers; insufficienty treated hypertension; transient ischaemic attacks; epilepsy; hypothyroidism and other severe psychiatric or somatic disease; and pregnancy	Yes	Yes	Yes	Yes	Unclear
Malvea 1973 United States	Pregnancy, bronchial asthma, congestive heart failure, allergic rhinitis, diabetes mellitus and previous use of propranolol for headache	Minimal	NR	Yes	Yes	No
Forssman 1976 Sweden	Pregnancy or suspicion of pregnancy; indication of renal or heart disease, hypertension, diabetes or asthma; history of earlier treatment of migraine with propranolol	Yes	NR	Yes	Yes	No
Borgesen 1974 Denmark	Cardiac disease; asthma or diabetes mellitus; physical or neurological abnormalities	Yes	Yes	Yes	Yes	No
Ahuja 1985 India	Intercurrent illness	Yes	NR	Yes	Yes	NR
Dahlof 1987 Sweden	NR	Yes	NR	Yes	Yes	Yes
Kuritzky 1987 Israel	NR	Yes	NR	Unclear	Unclear	No

Evidence Table 14a. Quality assessments of placebo controlled trials of beta blockers for migraine (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Kangasniemi 1987 Scandinavia	N/A	Attrition=3/77(3.9%); others NR	None	Fair	NR	Yes	16 weeks
Malvea 1973 United States	N/A	Attrition=1(3.2%); others NR	None	Fair	Ayerst Laboratories	Yes	12 weeks
Forssman 1976 Sweden	N/A	Attrition=8(20%); others NR	None	Fair	NR	Yes	34 weeks
Borgesen 1974 Denmark	N/A	Attrition=15(33.3%); others NR	None	Fair	ICI-Pharma	Yes	24 weeks
Ahuja 1985 India	N/A	NR	NR	Poor	Alkali and Chemical Corp. India Ltd. Provided tablets	Yes	16 weeks
Dahlof 1987 Sweden	N/A	Attrition=0; others NR	None	Fair	NR	Yes	52 weeks
Kuritzky 1987 Israel	N/A	Attrition=7(18.4%); others NR	None	Poor	NR	Yes	NR

Evidence Table 14a. Quality assessments of placebo controlled trials of beta blockers for migraine (continued)

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Standes 1982 Norway	NR	NR	N/A-crossover	Unclear mean age NR 80% female	25 entered
Forssman 1982 Sweden	NR	NR	N/A-crossover	Good mean age=40 80% female	24 included
Tfelt-Hansen 1984 Scandinavia	NR	NR	N/A-crossover	Good mean age=39.5 79.5% female	96 started
Weber 1972 United States	NR	NR	N/A-crossover	Fair mean age 40.6 68.4% female	25 enrolled
Diamond 1976 United States	NR	NR	N/A-crossover	Good mean age 38.1 80.7% female	83 enrolled
Sjaastad 1972 Norway	NR	NR	N/A-crossover	Good mean age 35.8 78.6% female	28 included
Ekbom 1971 Sweden	NR	NR	Yes	Fair mean age 33.7 86.7% female	30 included
Johnson 1986 New Zealand	NR	NR	N/A-crossover	Per protocol: Good mean age 42 76.5% female	29 started
Andersson 1983 Denmark	NR	NR	Yes	Per protocol: Good Mean age: pla=37.3; met-d=42.4 % female: pla=94.6%; met=73.5%	75 recruited

Evidence Table 14a. Quality assessments of placebo controlled trials of beta blockers for migraine (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Standes 1982 Norway	Other types of headache (including classical migraine) and major head injuries; contraindications to beta-blocking agents; use of oral contraceptives; pregnant women; use of timolol or propranolol for other reasons than migraine	Yes	NR	Unclear	Unclear	No
Forssman 1982 Sweden	NR	Minimal	NR	Yes	Yes	No
Tfelt-Hansen 1984 Scandinavia	Other types of headache (including classical migraine) and major head injuries; contraindications to beta blockers; oral contraceptive use; heart rate < 54 after 3 min of rest and with supine DBP >/= 100 mmHg	Yes	NR	Yes	Yes	No
Weber 1972 United States	Abnormal neurological examinations; disorders that could be aggravated by beta blockers (namely cariac disease, asthma, diabetes mellitus)	Yes	NR	Yes	Yes	No
Diamond 1976 United States	Asthma, cardiac disease, diabetes mellitus or any physical or neurologic abnormalities	Minimal	NR	Yes	Yes	No
Sjaastad 1972 Norway	NR	Yes	NR	Yes	Yes	No
Ekbom 1971 Sweden	Bronchial asthma, severe infectious diseases, diabetes mellitus, pregnancy, pathological ECG findings	Yes	NR	Yes	Yes	No
Johnson 1986 New Zealand	NR	Yes	Yes	Yes	Yes	No
Andersson 1983 Denmark	Other types of vascular headaches, chronic daily headache not separable from migraine; contraindication for beta blockers; other severe vascular diseases; oral contraceptives and pregnancy	Yes	NR	Yes	Yes	No

Evidence Table 14a. Quality assessments of placebo controlled trials of beta blockers for migraine (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Standes 1982 Norway	N/A	Attrition=7(28%); others NR	None	Poor	MSD (Norge) A/S	Yes	40 weeks
Forssman 1982 Sweden	N/A	Attrition=4(16.7%); others NR	None	Fair	ICI-Pharma Ltd.	Yes	254 days
Tfelt-Hansen 1984 Scandinavia	N/A	Attrition=27(28.1%); others NR	6(6.2%)	Poor	NR	Yes	40 weeks
Weber 1972 United States	N/A	Attrition: 6(24%); others NR	NR	Poor	Ayerst Laboratories	Yes	6 months
Diamond 1976 United States	N/A	Attrition: 21(25.3%)	NR	Poor	Ayerst Laboratories provided coded medications	Yes	16 weeks
Sjaastad 1972 Norway	N/A	Attrition=4(14.2%)	None	Fair	NR	Yes	14 weeks
Ekbom 1971 Sweden	NR	Attrition=4(13.3%); others NR	NR	Fair	NR	Yes	8 weeks
Johnson 1986 New Zealand	N/A	Attrition: 12(41.4%); others NR	9(31%)	Poor	Parke Davis Ltd.	Yes	9 months
Andersson 1983 Denmark	N/A	Attrition: 4/75(5.3%) prior to randomization; 9/71(12.7%) after randomization; others NR	NR	Fair	NR	Yes	12 wks

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Head-to-Head Trials					
Colombo, 1989 Italy *Fair quality*	RCT	Patients with cirrhosis that (i) bled from varices or acute gastric erosions, or the bleeding was defined as of "unknown origin," but no lesion besides varices was found by endoscopy done within 5 days, (ii) the bleeding stopped on conservative treatment (vasopressin, somatostatin and/or Sengstaken-Blakemore tube), (iii) no rebleeding requiring definitive treatment (endoscopic sclerotherapy or surgery) occurred before assignment, (iv) they had well-compensated cirrhosis (Child's A or B status); (v) they were less than 70 years of age; (vi) they had been given no previous treatments for portal hypertension (including beta blockers, endoscopic sclerotherapy or surgery), and (vii) they were hemodynamically stable	Patients for whom beta-blockade was contraindicated, who had active peptic ulcer, neoplastic disease and/or Child's C liver status	Propranolol (pro) 40-160 mg daily *(n=32)* Atenolol (ate) 100 mg daily *(n=32)* Placebo (pla) *(n=30)*	Ranitinde, oral antacids, spironolactone, saluretics, lactulose, nonabsorbable antibiotics
Placebo-controlled trials					
Gatta, 1987 *Fair quality*	RCT	Biopsy-proven cirrhosis of different etiologies, who survived a vericeal bleeding, defined endoscopically (within 36 hours of bleed) as proven by criteria: 1) visualization of bleeding site; 20 visualization of a fibrin clot on a varix; 3) presence of varices in the absence of gastroduodenal lesions and of any assumption of drugs affecting gastric mucosa; within 15-40 days after bleeding	Child's C grade; massive ascites; renal failure persisting after compensating hemodynamic conditions (serum creatinine > 1.5 mg/dl); age < 18 or > 70 years; tumors; contraindications to beta-blocking agents (asthma, A-V block > 1 degree; heart failure; clinically evident diabetes)	Nadolol (nad) 40-160 mg daily (target heart rate reduction of 25%) Placebo (pla) x 145 weeks	nr

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Head-to-Head Trials					
Colombo, 1989 Italy *Fair quality*	GI hemorrhage and/or death Quality of life	*Mean age:* pla=54; ate=53; pro=52 *%male:* pla=76.7; ate=78.1; pro=87.5 Race NR	*Etiology(%)* Alcohol: pla=80; ate=81.3; pro=84.4 HBsAg: pla=6.7; ate=0; pro=9.4 Other: pla=13.3; ate=18.7; pro=6.3 *Child's class(%)* A: pla=46.7; ate=46.9; pro=43.8 B: pla=3.3; ate=53.1; pro=56.3 *Bleedings before index bleed(%)* 0: pla=20; ate=46.9; pro=31.2 1: pla=53.3; ate=34.4; pro=50 2 or more: pla=26.7; ate=18.8; pro=18.8 *Source of hemorrhage(%)* Varices: pla=70; ate=26; pro=90.6 Erosions: pla=23.3; ate=9.4; pro=6.2 Unknown: pla=6.7; ate=9.4; pro=3.1	176 evaluated/ 94 eligible/ 94 enrolled	*Withdrawn:* pla=4(13%); ate=8(25%); pro=2(6%) *Lost to fu:* *pla=3(10%);* *ate=3(9.4%);* *pro=1(3.1%)* *Analyzed:* pla=30; ate=32; pro=32
Placebo-controlled trials					
Gatta, 1987 *Fair quality*	Event endpoints of the study were considered 1) onset of side effects necessitating withdrawal of treatment; 2) occurrence of digestive hemorrhage from ruptured esophageal varices; 3) death x assessed monthly for first 3 months; then every three months	Mean age: 49 71% male Race nr	*Etiology* Alcoholic cirrhosis: 75% Cryptogenic cirrhosis: 12.5% Posthepatic cirrhosis: 12.5% *Child Class* A: 37.5% B: 62.5% Ascites: 25% >1 previous hemorrhage: 33.3% *Esophageal varices* 2: 29.2% 3: 41.7% 4: 29.2%	nr/54/24 nad (n=12) pla (n=12)	Lost to fu: 5/24(21%)

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Head-to-Head Trials				
Colombo, 1989 Italy *Fair quality*	*Fatal/nonfatal bleeding episodes at 1 year(% patients):* pla=51; ate=31; pro=24 *Total deaths:* pla=7(23%); ate=3(10%); pro=4(12%) *Deaths due to rebleeding:* pla=3(10%); ate=1(3.1%); pro=1(3.1%) *Deaths due to liver failure:* pla=2(6.7%); ate=1(3.1%); pro=2(6.2%) *Deaths due to unrelated causes:* pla=2(6.7%); ate=1(3.1%); pro=1(3.1%)	NR	NR	pla=0 ate=4(12.5%) pro=0
Placebo-controlled trials				
Gatta, 1987 *Fair quality*	*Per protocol analysis:* Esophageal varices hemorrhage: nad=3(25%); pla=8(71%)(p<0.05) Death due to all causes: nad=1(8.3%); pla=3(27.3%)(NS)	nr	nr	Withdrawals due to asthma: nad=1; pla=0

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Burroughs 1983 Hampstead, England *Fair quality*	RCT	Histologically confirmed cirrhosis; bleeding from a varix or varices; no bleeding for 48 hours	NR	Propranolol (pro) 80 to 800 mg daily with a goal of 25% heart rate reduction Placebo (pla) x 21 months Treatment initiated 48 hours after bleeding cessation	NR

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Burroughs 1983 Hampstead, England *Fair quality*	Assessments at monthly intervals for first 3 months; then at three-month intervals	*Mean age:* pro=51; pla=49 *Gender(% male):* pro=46.1; pla=45.4 Race nr	*Causes of cirrhosis:* Alcoholism - Pro=35%; Pla=50% Chronic active hepatitis - Pro=27%; Pla=32% Cryptogenic - Pro=19%; Pla=14% Primary biliary cirrhosis - Pro=19%; Pla=4% *Pugh's grading:* A - Pro=65%; Pla=54% B - Pro=23%; Pla=36% C - Pro=11.5%; Pla=8% *Previous upper GI hemorrhage:* Pro=77%; Pla=77% *Transfusion (units) after index bleeding episode:* Pro=31%; Pla=41%	60 screened/48 eligible/48 enrolled	Withdrawn=4(8.3%)/0 lost to fu/48 analyzed

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Burroughs 1983 Hampstead, England *Fair quality*	Rebleeding(# patients/%): pro=12/26(46.1%); pla=11/22(50%)(NS) Death due to variceal rebleeding(# patients/%): pro=4/26(15.4%); pla=2/22(9.1%) All-cause mortality(# patients/%): pro=4/26(15.4%); pla=5/22(22.7%)	nr	nr	Withdrawals: pro=4/26(15.4%); pla=0

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
El Tourabi 1994 Sudan *Fair quality*	RCT	Portal hypertension ***secondary to schistosomiasis*** ; age 18-65; past history of schistomiasis (demonstrated by ultrasound); esophageal varices; recent variceal hemorrhage	Evidence or history of heart failure; significant airway obstruction; heart block greater than first degree; insulin dependent diabetes mellitus; bradycardia; severe peripheral vaascular disease; pregnant or lactating; severe depression; MI within previous 3 months	Long-acting propranolol (LA pro) 160 mg daily Placebo (pla)	NR

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
El Tourabi 1994 Sudan *Fair quality*	Full clinical examinations at 3-month intervals Endoscopies performed at 12 and 24 months Primary endpoints: 1) time to first rebleed; 2) time to death	Mean age: LA pro=34.6; pla=37.1 % male: LA pro=80; pla=83 Race nr	*On admission, patients with:* Palmar erythema - Pro=2%; Pla=0 Gynaecomastia - Pro=2%; Pla=0 Spider naevi (bormore) - Pro=0; Pla=0 Jaundice - Pro=0; Pla=0 Peripheral edema - Pro=0; Pla=0 Clubbing - Pro=0; Pla=2.5% Loss of body hair - Pro=2%; Pla=2.5% Bruising - Pro=2%; Pla=0 Distended superficial abdominal veins - Pro=9.5%; Pla=15% Ascites - Pro=7%; Pla=15% Venous hump - Pro=2%; Pla=7.5% *Livers:* Studied - Pro=31%; Pla=15% Shrunken - Pro=24%; Pla=35% Not palpable - Pro=45%; Pla=50% Palpable - Pro=31%; Pla=15% *Spleens:* Studied - Pro=93%; Pla=97.5% Shrunken - Pro=0; Pla=2.5% Not palpable - Pro=5%; Pla=0 Palpable - Pro=95%; Pla=97.5%	*Propranolol:* n=42 *Placebo:* n= 40	33(40%) withdrawn due to "other" reasons/lost to fu=2(2.4%)/analyzed 82

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
El Tourabi 1994 Sudan *Fair quality*	LA pro n=42; pla n=40 Rebleeding(# patients/%): LA pro=1(2%); pla=8(20%)(p<0.02) Death(# patients/%): LA pro=3(7%); pla=7(17.5%)(p<0.02) Median time to rebleeding(# days): LA pro=539; pla=252	Occurrence of adverse effects were volunteered by patients and elicited at follow-up visits	Incidence(# patients/%): LA pro=14(33.3%); pla=12(30%) Most common adverse events(# pts/%) Abdominal swelling: LA pro=0; pla=1(2.5%) Blurred vision: LA pro=1(2%); pla=0 Coughing: LA pro=0; pla=1(2.5%) Diarrhea: LA pro=2(5%); pla=3(7.5%) Drowsiness: LA pro=1(2%); pla=1(2.5%) Dry mouth: LA pro=1(2%); pla=0 Epistaxis: LA pro=1(2%); pla=0 Fatigue: LA pro=0; pla=2(5%) Fever/hot sensation: LA pro=2(5%); pla=1(2.5%) Gastric discomfort: LA pro=1(2%); pla=(2.5%) Hematemesis: LA pro=2(5%); pla=2(5%) Heartburn: LA pro=2(5%); pla=1(2.5%) Hiccups: LA pro=1(2%); pla=0 Hypersomnia: LA pro=0; pla=1(2.5%) Indigestion: LA pro=0; pla=1(2.5%) Itching: LA pro=2(5%); pla=0 Melena: LA pro=0; pla=2(5%) Nervousness: LA pro=1(2%); pla=0 Pain in abdomen: LA pro=1(2%); pla=1(2.5%) Tinnitus: LA pro=1(2%); pla=0 Wheezing: LA pro=0; pla=1(2.5%)	NR

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Jensen 1989 Denmark *Fair quality*	RCT	Liver disease; age <70; bleeding esophageal varices; no previous bleeding; absence of bleeding for 24 hours after sclerotherapy	Known contraindications to beta blockade	Propranolol slow release (pro SR) 160 mg daily Placebo (pla) x six months	NR
Lebrec 1981a France *Fair quality*	RCT	Histologically proven cirrhosis; gastrointestenal bleeding due to ruptured esophageal or gastric varices; diameter of esophageal varices >5mm at x-ray exam; GI bleeding spontaneously stopped or did not relapse after cessation of esophageal tamponade; hepatic encephalopathy, ascites and jaundice absent or appeared only transiently after bleeding	NR	Propranolol (pro) 80-360 mg daily with goal of 25% heart rate reduction Placebo (pla) x 3 months Treatment initiated **10-15** days following bleeding cessation	NR
Lebrec 1981b Lebrec 1984 France *Fair quality*	RCT	Histologically proven cirrhosis; gastrointestinal bleeding; source of hemorrhage was ruptured esophageal or gastric varices (as determined by endoscopy); volume of blood transfused within first 24 hours was 0.5 liter or more; jaundice was absent or mild; size of esophageal varices was large; gradient between the wedge and free hepatic venous pressures >10mm Hg; GI bleeding stopped and hemodynamic conditions were normal	Heart failure; asthma; chronic disease other than cirrhosis	Propranolol (pro) 40-360 mg daily with goal of 25% heart rate reduction Placebo (pla) Treatment initiated **2 weeks** following bleeding cessation	NR

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Jensen 1989 Denmark *Fair quality*	Endoscopy at monthly intervals	*Mean age:* pro SR=46; pla=47 *Gender(% male):* pro SR=100; pla=75 Race nr	*Liver disease:* Alcoholic cirrhosis - Pro=80%; Pla=87.5% Primary biliary cirrhosis - Pro=7%; Pla=0 Chronic active hepatitis - Pro=7%; Pla=6% Cryptogenic cirrhosis - Pro=7%; Pla=6% *Child's classification:* A - Pro=27%; Pla=25% B - Pro=47%; Pla=44% C - Pro=27%; Pla=31%	NR/NR/31 randomized	NR/NR/31 analyzed
Lebrec 1981a France *Fair quality*	NR	NR	*Type of cirrhosis(# patients/%):* Alcoholic=24/87.5% Hepatitis-B infection=1/4.2% Unknown=2/8.3%	NR/NR/24 admitted	NR/NR/24 analyzed
Lebrec 1981b Lebrec 1984 France *Fair quality*	Assessments at 2-month intervals through year 1; then at 4-month intervals through year 2	*Mean age:* pro=52.4; pla=49.9 *Gender(% male):* pro=81.6%; pla=72.2% Race NR	*Causes of cirrhosis:* Alcoholism - Pro=87%; Pla=89% Chronic Hepatitis B infection - Pro=8%; Pla= 5% Cryptogenic - Pro=5%; Pla=5% *Source of bleeding:* Ruptured varices - Pro=74%; Pla=78% Acute gastric erosions - Pro=26%; Pla=22% *Previous episodes of bleeding:* No - Pro=42%; Pla=36% Yes - Pro=58&; Pla=64%	NR/NR/74 randomized	NR/lost to fu: pro=3/28(7.9%); pla=3/36(5.5%)/analyzed 74

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Jensen 1989 Denmark *Fair quality*	Rebleeding(# patients/%): pro SR=3/15(20%); pla=12/16(75%)(p<0.05) Median treatments to achieve obliteration: pro SR=5; pla=5 Median time to obliteration(days): pro SR-163; pla=151	NR	Incidence(# patients/%): pro SR=4/15(26.7%); pla=3/16(18.7%) *Types of adverse events* Pro SR(# pts): Tiredness=2; diarrhea=2 Pla(# pts): Cold extremitis=1; skin rash=1	None
Lebrec 1981a France *Fair quality*	Rebleeding(# patients/%): pro=0; pla=5/12(41.7%)(p=0.037)	NR	Undesirable side effect incidence: pro=0; pla=0	None
Lebrec 1981b Lebrec 1984 France *Fair quality*	*Rebleeding(# patients/%):* Year one: pro=1/38(2.6%); pla=16/36(44.4%)(p<0.0001) Year two: pro=6/38(15.8%); pla=23/36(63.9%) *Time to rebleeding(% patients free of rebleeding at years 1/2):* pro=87/79; pla=42/32(p<0.0001) *Death due to(# patients/%):* Liver failure/septicemia: pro=3/38(7.9%); pla=2/36(5.5%) Rebleeding: pro=0; pla=6/36(16.7%) Percentage of surviving patients at years 1/2: pro=94%/90%(NS); pla=84%/57%(p<0.02)	NR	*Incidence:* NR *Types of adverse events(# patients):* Pro: transient asthemia=8; feeling of well-being=10; transietly reduced sexual activity=2; heart failure development=1 Pla: nausea=1; dizziness=1; cutaneous rash=1	NR

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Lo 1993 Taiwan *Fair quality*	RCT	***Cirrhosis*** ; complete obliteration of esophageal varices; esophageal variceal bleeding; received regular endoscopic injection sclerotherapy (EIS)	Visible esophagogastric varices; association with cancer growth; known contraindications to beta-blockade; beta blockers received prior to variceal obliteration	Propranolol (pro) 60-320 mg daily Placebo (pla)	NR
Sheen 1989 Taiwan *Fair quality*	RCT	***Cirrhosis*** ; stabilized after after treatment for esophageal variceal hemorrhage	Previous treatment with endoscopic sclerotherapy; heart or lung disease; hepatocellular carcinoma	Propranolol (pro) 40 mg daily(mean dosage; range 30-60 mg) with goal of a 25% heart rate reduction Placebo (pla)	NR

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Lo 1993 Taiwan *Fair quality*	Study endpoints: 1) esophagogastic variceal rebleeding (defined as presence of hematemesis, melena and when more than two units of blood transfusion were required and the bleedign site was identified from esophagogastic varices by emergency endoscopy); 2) death	*Mean age:* pro=54.3; pla=51.2 *Gender(% male):* pro=88; pro=92	*Etiology of cirrhosis:* Alcoholic - Pro=11.5%; Pla=15% Post-hepatitic - Pro=81%; Pla=74% Cryptogenic - Pro=7%; Pla=7% *Pugh's grading:* A - Pro=69%; Pla=70% B - Pro=23%; Pla=26% C - Pro=7%; Pla=4%	NR/NR/59 enrolled	6(10.2%) withdrawn/lost to fu: pro=1(3.3%); pla=2(6.9%)/53 analyzed
Sheen 1989 Taiwan *Fair quality*	Study endpoints: 1) Rebleeding from esophageal varices (proven by endoscopy); or 2) loss to follow-up Patients were seen every two months	*Mean age:* pro=43.6; pla=45.3 *Gender (% male):* pro=83; pla=88	*Cause of cirrhosis:* Alcoholic - Pro=33.3%; Pla=55.5% HBV - Pro=55.5%; Pla=33.3% Cryptogenic - Pro=22.2%;Pla=22.2% *Previous bleeding:* Pro=55%; Pla=53% *Encephalopathy:* Pro=0; Pla=0 *Ascites:* Pro=22%; Pla=28% *Pugh's grading:* A - Pro=78%; Pla=72% B - Pro=22%; Pla=28% C - Pro=0; Pla=0	230 screened/36 eligible/36 randomized (pro n=18; pla n=18)	NR/NR/18 analyzed

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Lo 1993 Taiwan *Fair quality*	Esophagogastric variceal *recurrence* (# patients/%): pro=15/26(58%); pla=21/27(77%) Esophageal variceal *rebleeding* (# patients/%): pro=5/26(19.2%); pla=3/27(11.1%) Cardiac variceal rebleeding(# patients/%): pro=2/26(7.6%); pla=2/27(7.4%) Total rebleeding(esophageal+cardiac rebleeding)(# patients/%): pro=7/26(26.9%); pla=5/27(18.5%) *Death due to:* *(per protocol analysis: pro n=26; pla n=27)* Hepatic failure: pro=2/7.6%; pla=4/14.8% Variceal bleeding: pro=3/11.5%; pla=2/7.4% Hepatocellular carcinoma: 2/7.6%; pla=3/11.1% Cerebral hemorrhage: pro=1/3.8%; pla=0 All-cause mortality: pro=8/30.8%: pla=9/33.3%	NR	*Propranolol(%)* Dizziness=28% Drowsiness=18% Chest tightness=11% *Placebo:* NR	*Propranolol(# patients/%):* 3/26(11.%) due to "intolerable general malaise *Placebo:* NR
Sheen 1989 Taiwan *Fair quality*	Rebleeding(# patients/%): pro=5/18(27.8%); pla=10/18(55.5%) Death due to rebleeding(# patients/%): pro=0; pla=2/18(11.1%) Freedom from rebleeding(% at 6, 12, 18 and 24 months): pro=94/87/68/57; pla=81/59/30/15	NR	NR	NR

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Villeneuve 1986 Montreal, Canada *Fair quality*	RCT	Adult; within 72 hours of variceal hemorrhage (demonstrated by endoscopy)	Previous treatment with beta blockers or endoscopic sclerotherapy; absence of Placebo of hemorrhage for at least 6 hours before randomization, using a Sengstaken-Blakemore tube or vasopressin infusio if necessary; heart failure or aortic valve disease other than aortic sclerosis; asthma or chronic obstructive lung disease precluding the administration of beta blockers; cancer or other disease reducing life expectancy to <1 year	Propranolol (pro) initial dose of 80 mg daily wih a goal of plasma concentrations between 50-150 ng per ml Placebo (pla) Treatment initiated within 6-72 hours following bleeding cessation	

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Villeneuve 1986 Montreal, Canada Fair quality	Assessments at monthly intervals for first 3 months; then at three-month intervals Primary endpoint=Variceal rebleeding (shown by endoscopy) Secondary endpoint=Survival	*Mean age:* pro=54; pla=58 *Gender(% male):* pro=57.1%; pla=75.7% Race NR	*Etiology of portal hypertension:* Alcoholic cirrhosis - Pro=74%; Pla=70% Posthepatitic cirrhosis - Pro=7%; Pla=8% Cryptogenic cirrhosis - Pro=9%; Pla=16% Biliary cirrhosis - Pro=7%; Pla=2% Portal vein thrombosis - Pro=2%; Pla=0 Idiopathic portal hypertension - Pro=0; Pla=2% *Pugh's grading:* A - Pro=9%; Pla=13.5% B - Pro=50%; Pla=57% C - Pro=43%; Pla=30% *Previous episodes of bleeding:* Pro=33%; Pla=30% *Alcohol consumtion (>60 gm daily) during month prior to admission:* Pro=43%; Pla=46% *Requied balloon tamponade for index bleed:* Pro=43%; Pla=43%	110 screened/79 eligible/79 enrolled	0 withdrawn/0 lost to fu/79 analyzed

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Villeneuve 1986 Montreal, Canada Fair quality	Rebleeding(# patients/%): pro=32/42(76.2%); pla=30/37(81.2%) All cause mortality: pro=19/42(45.2%); pla=14/30(37.8%) *Mortality due to(# patients/%):* Rebleeding: pro=5/42(11.9%); pla=7/37(18.9%) Liver failure: pro=8/42(19.0%);pla=3/37(8.1%)	NR	NR	Withdrawals: pro=5/42(11.9%); pla=0 Propranolol AE withdrawals due to: Shortness of breath: 3 patients Cardiac failure: 1 patient Septic shock with hypotension: 1 patient

Evidence Table 15a. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal varices

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Colombo 1989 Italy	Adequate. Block randomization. Series of triplet packages provided(ate; pro; pla); the contents of which varied at random.	Block number assignment corresponded to a particular package	Yes	Mean age=53 Gender=80.8% male	94
Gatta 1987	NR	NR	Yes	Mean age: 49 71% male	24
Burroughs 1983 Hampstead, England	Inferior method: sealed envelope	NR	Yes	*Mean age:* pro=51; pla=49 *Gender(% male):* pro=46.1; pla=45.4	48
El Tourabi 1994 Sudan	NR	NR	Yes	Mean age: LA pro=34.6; pla=37.1 % male: LA pro=80; pla=83 Race NR	82
Jensen 1989 Denmark	Adequate: Computer generated randomization schedule	NR	Yes	*Mean age: pro SR=46; pla=47* *Gender(% male): pro SR=100; pla=75* *Race NR*	31

Evidence Table 15a. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Colombo 1989 Italy	Patients for whom beta-blockade was contraindicated, who had active peptic ulcer, neoplastic disease and/or Child's C liver status	Yes	NR	Yes	Yes	Yes
Gatta 1987	Child's C grade; massive ascites; renal failure persisting after compensating hemodynamic conditions (serum creatinine > 1.5 mg/dl); age < 18 or > 70 years; tumors; contraindications to beta-blocking agents (asthma, A-V block > 1 degree; heart failure; clinically evident diabetes)	Yes	Yes	Yes	Yes	No
Burroughs 1983 Hampstead, England	NR	Yes	No; single-blind	Yes	Yes	Yes
El Tourabi 1994 Sudan	Evidence or history of heart failure; significant airway obstruction; heart block greater than first degree; insulin dependent diabetes mellitus; bradycardia; severe peripheral vaascular disease; pregnant or lactating; severe depression; MI within previous 3 months	Yes	NR	Yes	Yes	Yes
Jensen 1989 Denmark	Known contraindications to beta blockade	Yes	NR	Yes	Yes	Yes

Evidence Table 15a. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: deifferential/high	Score	Funding	Control group standard of care	Length of follow-up
Colombo 1989 Italy	NR	Attrition reported; others NR	Pla=3(10%) Ate=3(9.4%) Pro=1(3.1%)	Fair	Imperial Chemical Industries (Milan) supplied trial tablets	Yes	Mean=357 days
Gatta 1987	NR	NR	Lost to fu: 5/24(21%)	Fair	NR	Yes	Mean=145 weeks
Burroughs 1983 Hampstead, England	NR	NR	NR	Fair	NR	Yes	21 months
El Tourabi 1994 Sudan	NR	Attrition=33(40%)	Lost to fu: LA pro=1(2.4%) pla=1(2.5%)	Fair	ICI Pharmaceuticals	Yes	2 years
Jensen 1989 Denmark	NR	NR	NR	Fair	ICI Pharmaceuticals	Yes	6 months

Evidence Table 15a. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Lebrec 1981a France	NR	NR	NR	NR	24
Lebrec 1981b Lebrec, 1984 France	NR	NR	Yes	*Mean age:* pro=52.4; pla=49.9 *Gender(% male):* pro=81.6%; pla=72.2%	74
Lo 1993 Taiwan	NR	NR	Yes	*Mean age:* pro=54.3; pla=51.2 *Gender(% male):* pro=88; pro=92	59
Sheen 1989 Taiwan	NR	NR	Yes	*Mean age:* pro=43.6; pla=45.3 *Gender (% male):* pro=83; pla=88	36
Villeneuve 1986 Montreal, Canada	Inferior method; sealed envelopes	NR	No; more patients in the pro group had severe Class C liver disease (43% vs 30%); less patients in the propranolol group were male (57.1% vs 75.7%)	*Mean age:* pro=54; pla=58 *Gender(% male):* pro=57.1%; pla=75.7%	79

Evidence Table 15a. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Lebrec 1981a France	NR	Yes	NR	Yes	Yes	Yes
Lebrec 1981b Lebrec, 1984 France	Heart failure; asthma; chronic disease other than cirrhosis	Yes	NR	Yes	Yes	Yes
Lo 1993 Taiwan	Visible esophagogastric varices; association with cancer growth; kNown contraindications to beta-blockade; beta blockers received prior to variceal obliteration	Yes	Yes	Yes	Yes	No
Sheen 1989 Taiwan	Previous treatment with endoscopic sclerotherapy; heart or lung disease; hepatocellular carciNoma	Yes	NR	Yes	Yes	Yes
Villeneuve 1986 Montreal, Canada	Previous treatment with beta blockers or endoscopic sclerotherapy; absence of Placebo of hemorrhage for at least 6 hours before randomization, using a Sengstaken-Blakemore tube or vasopressin infusio if necessary; heart failure or aortic valve disease other than aortic sclerosis; asthma or chronic obstructive lung disease precluding the administration of beta blockers; cancer or other disease reducing life expectancy to <1 year	Yes	No; single-blind	Yes	Yes	Yes

Evidence Table 15a. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: deifferential/high	Score	Funding	Control group standard of care	Length of follow-up
Lebrec 1981a France	NR	NR	NR	Fair	ICI Pharmaceuticals	Yes	3 months
Lebrec 1981b Lebrec, 1984 France	NR	NR	Lost to fu: pro=3/38(7.9%) pla=2/36(5.5%)	Fair	NR	Yes	24-38 months (mean=29 months)
Lo 1993 Taiwan	NR	Attrition=6(10.2%)	Lost to fu: pro=1(3.3%); pla=2(6.9%)	Fair	NR	Yes	Mean follow-up of 2 years and 4 months
Sheen 1989 Taiwan	NR	NR	NR	Fair	Prosperous Foundation	Yes	Mean follow-up of 12.4 months
Villeneuve 1986 Montreal, Canada	NR	Attrition reported(None); others NR	None	Fair	Ayerst Laboratories	Yes	2 years

Evidence Table 16. Head to head trials of beta blockers for hypertension

Trial	Interventions	Sample Size	Trial duration	Population Characteristics	Quality	Results
Foerster 1985	Atenolol (ate) 100 mg Pindolol SR (pin-SR) 20 mg	107	24 weeks	Mean age=41.4 65.4% male	Good • Designed specifically for AE assessment • Changes of >1 cm on VAS interpreted as AE	Data for weeks 13-24(% patients)*:* *n: ate=53; pin=54* Sleep disturbance: ate=18; pin=44(p=0.01) Dreams: ate=16; pin=15 Fatigue: ate=28; pin=22 Raynaud's phenomenon: ate=14; pin=26 Muscle cramps: ate=12; pin=20 Sexual disturbance: ate=14; pin=8 GI disturbances: ate=21; pin=20
Fogari 1999	Atenolol (ate) 100 mg Bisprolol (bis) 10 mg Celiprolol (cel) 400 mg Propranolol (pro) 160 mg	152	18 months	100% male Mean age=52	Fair	Overall AE incidence(# pts; %): pro=6/37(16.2%); ate=5/38(13.1%); bis=4/39(10.2%)
Lithell 1987	Atenolol (ate) 50 mg Bisoprolol (bis1) 5 mg Bisoprolol (bis2) 10 mg	292	6 months	59.9% male Mean age=52.6	Fair	Withdrawals due to adverse events (# patients/%): ate=2/97(2.1%); bis1=4/97(4.1%); bis2=4/98(4.1%)

Evidence Table 17. Safety of all head to head trials of beta blockers

Trial	Indication	Sample size	Duration	p-value	*Selective beta blockers*			*Non-selective beta blockers*						
					ate	bis	met	cart	carv	lab	nad	pen	pin	pro
OVERALL ADVERSE EVENT INCIDENCE														
Fogari, 1999	Hypertension	152	18 mos	NS	13.1%	10.2%								16.2%
Frishman, 1979	Angina	40	8 wks	<0.0001									17.4%	94.4%
van der Does, 1999	Angina	368	3 mos	NS			30.0%		25.0%					
Poole-Wilson, 2003 *COMET*	Heart Failure	3029	58 mos	NS			96.0%		94.0%					
Worz, 1991	Migraine	78	12 wks	NS		29.5%	23.1%							
*Kangasniemi, 1984	Migraine	35	8 wks	NS			57.1%							68.6%
							45.7%							48.6%
*Olsson, 1984	Migraine	53	8 wks	NS			58.5%							58.5%
							56.6%							58.5%
BRADYCARDIA INCIDENCE														
Metra, 2000	Heart failure	122	44 mos	NS			2.7%		4.0%					
DIZZINESS INCIDENCE														
van der Does, 1999	Angina	368	3 mos	NS			5.0%		4.8%					
Metra, 2000	Heart failure	122	44 mos	0.0046			1.3%		14.7%					
Stensrud, 1980	Migraine	28	6 wks	NS	0.0%									3.6%
Worz, 1991	Migraine	78	12 wks	NS		10.2%	5.1%							
HYPOTENSION INCIDENCE														
Metra, 2000	Heart failure	122	44 mos	NS			2.7%		2.7%					
WITHDRAWALS DUE TO ADVERSE EVENTS														
Lithell, 1987	Hypertension	292	6 mos	NS	2.1%	4.1%								
Colombo, 1989	Bleeding esophageal varices	94	357 days	NS	12.5%									0.0%
Worz, 1991	Migraine	78	12 wks	NS		10.20%	6.40%							

**Values represent rates from first and second months of treatment, separately*

Appendix A: Search Strategies

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2003>
Search Strategy:

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1 atenolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2089)
2 bisoprolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (256)
3 bucindolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (18)
4 carvedilol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (255)
5 labetolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (5)
6 metoprolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1754)
7 pindolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (751)
8 propranolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (3639)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (7369)
10 hypertension.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (15343)
11 coronary disease.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (4284)
12 (coronary and (arteriosclerosis or stenosis or vasospasm or thrombosis)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1581)
13 11 or 12 (5261)
14 congestive heart failure.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1736)
15 chf.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (509)
16 14 or 15 (1885)
17 migraine.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1434)
18 (atria$ and (arrhythmia$ or flutter$ or fibrillation$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1475)
19 (esophag$ and (varice$ or bleed$ or hemorrhag$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (859)
20 10 or 13 or 16 or 17 or 18 or 19 (25151)
21 9 and 20 (3436)
22 randomized controlled trial.pt. (160228)
23 randomized control trial.sd. (72619)
24 22 or 23 (232204)
25 21 and 24 (2508)
26 from 25 keep 1-2508 (2508)

Database: MEDLINE

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1 atenolol.mp. or exp ATENOLOL/ (3727)
2 bisoprolol.mp. or exp BISOPROLOL/ (282)
3 bucindolol.mp. or exp BUCINDOLOL/ (0)
4 carvedilol.mp. or exp CARVEDILOL/ (0)
5 exp Labetalol/ or labetolol.mp. (1370)
6 exp METOPROLOL/ or metoprolol.mp. (3369)
7 pindolol.mp. or exp PINDOLOL/ (3676)
8 propranolol.mp. or exp PROPRANOLOL/ (32291)

9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (40456)
10 congestive heart failure.mp. or exp Congestive Heart Failure/ (34204)
11 exp HYPERTENSION/ or hypertension.mp. (144357)
12 coronary artery disease.mp. or exp Coronary Artery Disease/ (17841)
13 atrial arrhythmia$.mp. or exp Heart Atrium Arrhythmia/ (0)
14 migraine.mp. or exp MIGRAINE/ (8448)
15 exp Esophagus Varices Bleeding/ or bleeding esophageal varices.mp. (0)
16 10 or 11 or 12 or 13 or 14 or 15 (197932)
17 9 and 16 (7988)
18 limit 17 to randomized controlled trial (1629)
19 limit 18 to (human and english language) (1490)
20 18 not 19 (139)
21 limit 20 to abstracts (115)
22 19 or 21 (1605)
23 from 22 keep 1-1605 (1605)
24 from 22 keep 1-1605 (1605)
25 from 22 keep 1-1605 (1605)

Database: EMBASE Drugs & Pharmacology <1991 to 1st Quarter 2003>:
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1 atenolol.mp. or exp ATENOLOL/ (6941)
2 bisoprolol.mp. or exp BISOPROLOL/ (1602)
3 bucindolol.mp. or exp BUCINDOLOL/ (396)
4 carvedilol.mp. or exp CARVEDILOL/ (2321)
5 exp Labetalol/ or labetolol.mp. (2018)
6 exp METOPROLOL/ or metoprolol.mp. (6301)
7 pindolol.mp. or exp PINDOLOL/ (2284)
8 propranolol.mp. or exp PROPRANOLOL/ (15828)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (27794)
10 congestive heart failure.mp. or exp Congestive Heart Failure/ (9962)
11 exp HYPERTENSION/ or hypertension.mp. (68632)
12 coronary artery disease.mp. or exp Coronary Artery Disease/ (23568)
13 atrial arrhythmia$.mp. or exp Heart Atrium Arrhythmia/ (9338)
14 migraine.mp. or exp MIGRAINE/ (6073)
15 exp Esophagus Varices Bleeding/ or bleeding esophageal varices.mp. (950)
16 10 or 11 or 12 or 13 or 14 or 15 (110057)
17 9 and 16 (9446)
18 Randomized Controlled Trial/ (64079)
19 17 and 18 (928)
20 limit 19 to (human and english language) (859)
21 19 not 20 (69)
22 limit 21 to (abstracts and human) (56)
23 20 or 22 (915)
24 from 23 keep 1-915 (915)
25 from 23 keep 1-915 (915)
26 from 23 keep 1-915 (915)
27 from 23 keep 1-915 (915)

Appendix B: Methods for Drug Class Reviews for Oregon Health Plan Practitioner-Managed Prescription Drug Plan

Oregon Evidence-based Practice Center

December 14, 2001
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Overview

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, in developing drug class reviews for the Oregon Health Plan Practitioner-Managed Prescription Drug Plan.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD. To ensure scientific rigor and relevance of the work, the Oregon EPC develops key questions and criteria for admissible evidence, and uses these to create a literature search strategy that best captures the appropriate evidence. To consider papers identified by the searches, the teams use the criteria for admissible evidence (explicit inclusion and exclusion criteria) to select papers that provide information to help answer the key questions. They abstract key data from these selected papers. The teams use established criteria to assess the internal validity of the evidence in each paper, as well as the total internal validity, external validity, and coherence of the evidence for each key question.

Key Questions and Inclusion/Exclusion Criteria

Key questions are essential in focusing the literature review on a manageable and clinically relevant topic. All key questions are reviewed and approved by the topic team in the process of assessing and refining the topic before the detailed literature review. The EPC teams work with the subcommittee members of the Oregon Health Resources Commission assigned to a particular drug class to finalize the key questions for that drug class.

We clearly document the criteria by which the team chooses to admit evidence on a given key question. Such criteria might include, for example, study design (e.g., randomized

controlled trials, cohort studies), setting, sample size, population studied, language(s) of publication, and year(s) of publication.

No generic criteria for admissible evidence have been established. Rather, the criteria are determined on a topic-by-topic and key question-by-key question basis, depending on the questions involved and the amount and quality of evidence available. All inclusion/exclusion criteria are reviewed and approved by the entire topic team.

Databases to Be Searched and Documenting Search Terms

At a minimum, all topics include a review of the English-language literature in MEDLINE and EMBASE bibliographic databases and the Cochrane Controlled Trials Register. Other databases (e.g., nursing or psychology databases) are searched as deemed necessary by the topic team. Evidence reviews document the databases used.

Search terms used for each key question, along with the yield associated with each term, are documented in a table or set of tables; these appear in the final evidence review.

Database of Abstracts

The EPC, for each review, establishes a database of all abstracts (i.e., both those included and those eventually excluded from the final set of full-text articles reviewed). Information captured in the database includes the key question(s) associated with each included abstract and reason for exclusion if the abstract does not meet inclusion criteria.

Abstraction Forms

Although the EPC has no standard or generic abstraction form, the following broad categories are always abstracted from included articles: study design, study participant description, quality information, and outcomes. Each team uses these (and, if indicated, other) general categories to develop an abstraction form specific to the topic at hand.

Double Abstraction of Included Articles

The EPC teams abstract only those articles that, after review of the entire article, meet criteria for both quality and focus on the key question at hand. Key articles are always read and checked by more than one team member. All reviewers are trained in the topic, the analytic framework and key questions, and the use of the abstraction instrument. Initial reliability checks are done for quality control.

Quality Criteria

Assessment of Internal Validity
To assess the internal validity of individual studies, the EPC adopted criteria for assessing the internal validity of individual studies from the US Preventive Services Task Force and the NHS Centre for Reviews and Dissemination.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record numbers, birth dates or week days
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:
        - Use of alternation, case record numbers, birth dates or week days
        - Open random numbers lists
        - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
    - Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

For Reports of Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainer; validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Economic Studies

Assessment of Internal Validity

Framing

1. Was a well-defined question posed in answerable form?

2. Was a comprehensive description of the competing alternatives given?

3. Are the interventions and populations compared appropriate?

4. Is the study conducted from the societal perspective?

5. Is the time horizon clinically appropriate and relevant to the study question?

Effects

1. Are all important drivers of effectiveness included?

2. Are key harms included?

3. Is the best available evidence used to estimate effectiveness?

4. Are long-term outcomes used?

5. Do effect measures capture preferences or utilities?

Costs

1. Are costs and outcomes measured accurately?
2. Are costs and outcomes valued credibly?
3. Are costs and outcomes adjusted for differential timing?
4. Are all appropriate downstream medical costs included?
5. Are charges converted to costs appropriately?
6. Are the best available data used to estimate costs? (like first question)
7. Are all important and relevant costs and outcomes for each alternative identified?

Results

1. Are incremental cost-effectiveness ratios presented?
2. Are appropriate sensitivity analyses performed?
3. How far do study results include all issues of concern to users?

<u>Assessment of External Validity</u>

1. Are the results generalizable to the setting of interest in the review?

Systematic Reviews:

1. Is the systematic review recent and relevant?
2. Is the review comprehensive in considering sources and in searching databases to find all relevant research?
3. Are inclusion/exclusion criteria reported relating to the primary studies that address the review question? If so, are they explicit and relevant?
4. Are the primary studies summarized appropriately?
5. Is sufficient detail of the primary studies presented?
6. Is there standard appraisal of the primary studies?
7. Is the validity of primary studies adequately assessed?

8. Are there valid conclusions in the systematic review?