Drug Class Review
On Beta Adrenergic Blockers

FINAL REPORT

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The Agency for Healthcare Research and Quality has not yet seen or approved this report.

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 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. 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	3-7
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	10
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 tartrate	Yes	Yes	Yes				Yes
Metoprolol succinate extended-release	Yes	Yes	Yes				
Nadolol	Yes	Yes					
Penbutolol	Yes						
Pindolol	Yes						
Propranolol	Yes	Yes		Yes	Yes		Yes
Propranolol long-acting	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 a subcommittee of the Oregon Health Resources Commission, we designated 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-2003 1st quarter), MEDLINE (1966-2003 April), EMBASE (1980-2003 1st Quarter), 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 with 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.

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/nonfatal rebleeding

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 those that lasted 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.

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. We obtained full-text articles if the title and abstract review met any of 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.
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.
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 provide 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. The evidence from these studies is difficult to interpret, however, due to issues of heterogeneity between trial populations, interventions, and assessment and definition of outcomes. Active-control trials are not analyzed in this review.

Data Abstraction

The following data was abstracted from included trials: study design, setting, and population characteristics (including sex, age, race, diagnosis); eligibility and exclusion criteria; interventions (dose and duration), and comparisons; numbers screened, eligible, enrolled, and lost to follow-up; method of outcome assessment, and results for each outcome. We recorded intention-to-treat results, if available, and whether the reported loss to follow-up 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 true differences between the compared drugs.

Appendix B also 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 predefined criteria, fair if they met three to five criteria, and poor if they met two or fewer criteria.

An overall quality rating for an individual study was 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 appended 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, and 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 comorbid 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 scales (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 United States, studied the effects of propranolol versus placebo in 312 patients (66.5% male, mean age 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 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%	nr

		vs. 16.6% (NS) % increase in mean time to angina (sec): 25.7% vs. 23.7% (NS)	
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, a beta blockers may differ in its 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. After 8 weeks of treatment, propranolol reduced the proportion of patients using nitroglycerin (57% vs. 73% for placebo), and increased the mean total work time (48% vs. 13% for placebo). These effects were transient, After 24 weeks of treatment, propranolol was equivalent to placebo on those parameters. At eight- and 24-week endpoints, propranolol and placebo had similar effects on the number of weekly angina attacks, the number of attack free days, maximum workload, and exercise duration.

A large number of trials compare a beta blocker to a calcium channel blocker or other anti-anginal 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. 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?

Long-term Treatment

We did not examine short-term (4-7 days) inpatient trials of beta blockers to prevent atrial arrhythmias after CABG. [31-35] The long-term use of a beta blocker after CABG has not been shown to improve mortality or other outcomes.

In seven 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, for reasons that included a need for beta blockers, or incidence of angina, tachycardia or 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/nonfatal 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 head-to-head trial[38] compared atenolol 100 mg to propranolol 120 mg, and to placebo, in patients with recent myocardial infarction. Patients (n=388) were randomized within 4 to 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, nonfatal 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=5,474), 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 meta-regression of the long-term trials, beta blockers without intrinsic sympatheticomimetic activity (ISA) reduced mortality; those with ISA were less effective. The pooled effect for increased mortality approached statistical significance (Odds Ratio=1.19; 95% CI: 0.96 to1.47.) Cardioselectivity was unrelated to mortality reduction (Odds Ratio=1.10; 95% CI: 0.89 to 1.39.) [39] For all-cause mortality reduction, pooled odds ratios for acebutolol (Odds Ratio=0.49; 95% CI: 0.25 to 0.93), metoprolol (Odds Ratio=0.80; 95% CI: 0.66 to 0.96), propranolol (Odds Ratio=0.71; 95% CI=0.59 to 0.85) and timolol (Odds Ratio=0.59; 95% CI: 0.46 to 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 (propranolol), 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 compared to 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 left-ventricular ejection fraction (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 1,959 patients with a mean LVEF of 32.8% to either carvedilol or placebo as an add-on to angiotensin-converting-enzyme-inhibitor (ACEI) therapy at an average of 10 days following a confirmed myocardial infarction (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 to 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 to 1.06]; p=0.098) and hospital admission for heart failure (12% vs. 14%; hazard ratio=0.86 [0.67 to 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 to 0.96].) Mortality was also reduced in the subset of 262 patients who had mild to moderate heart failure after MI (10% vs. 19%; NNT=11; odds ratio=0.46 [95% CI: 0.21 to 1.0]). Metoprolol reduced reinfarction rates in the overall sample (5% vs. 7.7%; NNT=37; odds ratio=0.63 [95% CI=0.39 to 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 significance. 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. 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%), or 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, 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%). The study was rated fair to poor quality. Contamination was a significant problem. At six months of follow-up, 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% versus 24.1% in the trial of 114 patients[56], 13.7% versus 10.5% in the trial of 454 patients.[66], and 15% versus 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 to 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; $p<0.05$), but 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),[55] no mortality difference between propranolol and placebo (7.9% vs. 7.4%) was found at 9 months. 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 (n=560).

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 other trials of agents not available in the United States (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, for carvedilol, that 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. We excluded trials with fewer than 100 patients. Included trials ranged from 6 months to 2 years in duration.

Mortality was a primary endpoint in four 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 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/nonfatal 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). In the USCHFSG mild heart failure trial, 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. 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 also 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 significantly greater improvements in quality of life than those taking placebo. No data were provided and it is unclear 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 patient 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 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., 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 men (79.8%), with a mean age of 62 years, and a mean ejection fraction (EF) of 26% on optimal

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

treatment with ACEIs 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). 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 noncardiovascular deaths (5% vs. 4%) or all deaths and all-cause hospitalization (74% vs. 76%).

COMET does not resolve the question 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 was 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 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 to 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; 70% were 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 United States, were relatively short term (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 had mean ages of 33.8 to 42.3, were 68.6% to 88.9% female, and had 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.

Attack Frequency. Two trials reported mean[156] and median[157] attacks per four weeks, which allows 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. Disagreeing with the use of response rates defined as the 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 below.

Responder type A. Significant z-values ($z \geq -1.65$ 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) ($z \leq -1.65$ to 1.96) in the four parameters above.

Nonresponder type C. No improvement in the parameters (z=0 to –1.65).

Nonresponder type D. Tendency to deterioration, or statistically significant deterioration (positive z-values).

Using ARIMA analysis, Gerber et al. also found no difference between metoprolol and propranolol in percent of patients qualifying as responder types 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 was found between metoprolol and propranolol in percent of patients qualifying as responder types 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 found in rates of reduction of mean consumption of unspecified acute medication 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. Also, Gerber et al. did not find any difference between metoprolol and propranolol in percent of patients qualifying as responder types A or B for decrease in ergotamine table use (30% vs. 38.9%) during the three-month "high dosage" phase.

Table 6. Outcomes in head to head trials in migraine

	Stensrud, 1980	Kangasniemi, 1984	Olsson, 1984	Gerber, 1991
Outcome	Ate 100 mg vs pro 160 mg N=35	Met-d 200 mg vs pro 160 mg N=35 *Outcome reporting:* % decrease in mean/4 wks	Met 100 mg vs pro 80 mg N=53 *Outcome reporting:* % decrease in median/4 weeks	Met 200 mg vs pro 160 mg N= 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
Miscellaneous	Headache Index: pro=437 ate=410	nr	nr	nr

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

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 found no difference between metoprolol and propranolol in percent of patients qualifying as responder types A or B for decrease on this variable.

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 United States. 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 to 52 weeks, generally enrolling patients with a history of 1-2 years of common or classic migraine (Ad Hoc Committee), occurring on average three times 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 to 259 patients. Assessments of attack frequency, duration, severity, and use of acute medication variables were 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 weeks' duration (n=226)[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 are not discussed here.

We found one meta-analysis[191] that evaluated the effects of propranolol in 2,403 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 is 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 (atenolol vs. propranolol, metoprolol durules vs. propranolol, metoprolol vs. propranolol). Results from placebo-controlled trials on similar outcome measures generally supports results 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. Conducted in Italy, this trial 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 origin (inconclusive endoscopy) (6.4%). 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 were found to have a significant effect on rebleeding, in that patients continuing to drink had a 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 United States, enrolled samples of 12 to 82 patients, and ranged from 3 months to 2 years in duration. Mean ages ranged from 43 to 58 for the cirrhotic patients, and 35.8 for

noncirrhotic 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]

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**

Variceal Rebleeding Rates. As shown in Table 7 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), long-acting propranolol was superior (2% vs. 20%; p<0.02), and results of immediate-release propranolol trials were mixed..

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 8 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 nonfatal/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 to 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 three trials in patients with hypertension[9-11] (Evidence Table 16), two trials of patients with angina[28,205] (Evidence Table 2), two trials in patients with heart failure[130,150] (Evidence Table 10), five trials in migraine patients[155-158,206] (Evidence Table 13), one trial in patients with bleeding esophageal varices[192] (Evidence Table 15), and one trial of patients post-MI[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, of atenolol 100 mg and pindolol SR 20 mg in 107 essential hypertensive patients,[9] was designed specifically for adverse-event assessment and was rated good quality. Safety assessment in the remaining 13 head-to-head trials was fair-to-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 3,029 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 included 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 was higher in the propranolol group during run-in (28.5 [95% CI 26.4 to 30.6] vs. 18.4 [95% CI 17.4 to 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 of 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 safety data in head-to-head trial results, compared to available fair-to-good-quality placebo-controlled trials, offers no 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. The Shekelle meta-analysis found that beta blockers are equally effective in reducing mortality in subpopulations stratified by gender and race.

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 (2,134)	0.63 (0.44 to 0.91)	0.66 (0.59 to 0.75)
Blacks	3 (545)	0.67 (0.39 to 1.16)	0.63 (0.52 to 0.77)
Diabetics	3 (1,883)	0.77 (0.61 to 0.96)	0.65 (0.57 to 0.74)

Age/Gender/Race

Carvedilol. Prescribing information for carvedilol (online at http://us.gsk.com/products/assets/us_coreg.pdf) reports that effects on efficacy and adverse events were equivalent regardless of age (48% were ≥65years; 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 to 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 (online at 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 in patients aged 65-74 years, with a more marked reduction in mortality at 3 months post-MI (45%) than for all patients aged 40-74 (36%). The MERIT-HF trial reported that neither age or gender had any influence on the effects of metoprolol CR in patients with mild to moderate heart failure.

Propranolol. The fair-quality, placebo-controlled Beta Blocker Heart Attack Trial (BHAT),[46] comprised of 3,837 patients, found the protective effect of propranolol on mortality at 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	Metoprolol did not benefit mortality or ischemic events in a longer-term (> 7 days), placebo-controlled trial (MACB)
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/nonfatal 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)

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