Drug Class Review

Beta Adrenergic Blockers

Final Report
Update 4

July 2009

Update 3: September 2007
Update 2: May 2005
Update 1: September 2004
Original Report: September 2003

The literature on this topic is scanned periodically.

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Published in a separate document.

The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

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INTRODUCTION

Beta blockers inhibit the chronotropic, inotropic, and vasoconstrictor responses to the catecholamines, epinephrine, and norepinephrine. Most beta blockers have half-lives of over 6 hours (Table 1). The shortest acting are pindolol (3 to 4 hours) and propranolol (3 to 5 hours). Most of the included beta blockers are metabolized in combination by the liver and kidneys, with the exception of atenolol, which is metabolized primarily by the kidneys while the liver has little to no involvement.

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

Beta blockers differ in their effects on the 3 adrenergic receptors (β_1, β_2, and α) and in their duration of effect (Table 1). Cardioselective beta blockers preferentially inhibit β_1 receptors that are principally found in the myocardium. Non-cardioselective beta blockers also inhibit β_2 receptor sites, which are found in smooth muscle in the lungs, blood vessels, and other organs. Beta blockers with intrinsic sympathomimetic activity act as partial adrenergic agonists and would be expected to have less bradycardic and bronchoconstriction effects than other beta blockers. Finally, carvedilol and labetalol block α-adrenergic receptors and would be expected to reduce peripheral vascular resistance more than other beta blockers.

Table 1. Beta blockers included in the review

Drug	Usual hypertension dose	Daily dosing frequency	Half-life (hours)	Cardio-selective	Partial agonist activity (ISA)	Alpha antagonist effect
Acebutolol	200-1200 mg/d	Twice	3-4	Yes	Yes	No
Atenolol	50-100 mg/d	Once	6-9	Yes	No	No
Betaxolol	5-40 mg/d	Once	14-22	Yes	No	No
Bisoprolol	5-20 mg/d	Once	9-12	Yes	No	No
Carteolol	2.5-10 mg/d	Once	6	No	Yes	No
Carvedilol	12.5-50 mg/d	Twice	7-10	No	No	Yes
Carvedilol phosphate (controlled release)	20-80 mg/d	Once	10.6-11.5	No	No	Yes
Labetalol	200-1200 mg/d	Twice	3-6	No	No	Yes
Metoprolol tartrate	50-200 mg/d	Twice	3-7	Yes	No	No
Metoprolol succinate (extended release)	50-400 mg/d	Once	3-7	Yes	No	No
Nadolol	20-240 mg/d	Once	10-20	No	No	No
Nebivolol	5-40 mg/d	Once	12-19	Yes	No	No
Penbutolol	20 mg/d	Once	5	No	Yes	No
Pindolol	10-60 mg/d	Twice	3-4	No	Yes	No
Propranolol	40-240 mg/d	Twice	3-4	No	No	No
Propranolol long-acting	60-240 mg/d	Once	8-11	No	No	No
Timolol	10-40 mg/d	Twice	4-5	No	No	No

Abbreviations: d, day; ISA, intrinsic sympathomimetic activity.

Table 2. Approved indications

Drug	Hyper-tension	Chronic stable angina	Atrial arrythmia	Migraine	Bleeding esophageal varices	Heart failure	Post-myocardial infarction	Decreased left ventricular function after recent myocardial infarction
Acebutolol	Yes	Yes						
Atenolol	Yes	Yes					Yes	
Betaxolol	Yes							
Bisoprolol	Yes							
Carteolol	Yes							
Carvedilol (immediate release)	Yes					Mild to severe		Yes
Carvedilol phosphate (extended release)	Yes					Mild to severe		Yes
Labetalol	Yes							
Metoprolol tartrate	Yes	Yes					Yes	
Metoprolol succinate (extended release)	Yes	Yes				Stable, symptomatic Class II-III		
Nadolol	Yes	Yes						
Nebivolol	Yes							
Penbutolol	Yes							
Pindolol	Yes							
Propranolol	Yes	Yes	Yes	Yes				
Propranolol long-acting	Yes	Yes	Yes	Yes				
Timolol	Yes			Yes			Yes	

Adapted from Drug Facts and Comparisons®

Purpose and Limitations of Evidence Reports

Systematic reviews, or evidence reports, are the building blocks underlying evidence-based practice. An evidence report focuses attention on the strength and limits of evidence from published studies about the effectiveness of a clinical intervention. The development of an evidence report begins with a careful formulation of the problem. The goal is to select questions that are important to patients and clinicians, then to examine how well the scientific literature answers those questions. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix A and are defined as they apply to reports produced by the Drug Effectiveness Review Project.

An evidence report emphasizes the patient's perspective in the choice of outcome measures. Studies that measure health outcomes (events or conditions that the patient can feel, such as quality of life, functional status, and fractures) are emphasized over studies of

intermediate outcomes (such as changes in bone density). Such a report also emphasizes measures that are easily interpreted in a clinical context. Specifically, measures of absolute risk or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions is dependent on the numbers of events in both groups, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant across groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than the absolute risk reduction. Another measure useful in applying the results of a study is the number needed to treat (or harm), the NNT (or NNH). The NNT represents the number of patients who would have to be treated with an intervention for 1 additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the NNT.

An evidence report also emphasizes the quality of the evidence, giving more weight to studies that meet high methodological standards that reduce the likelihood of biased results. In general, for questions about the relative benefits of a drug, the results of well-done, randomized controlled trials are regarded as better evidence than results of cohort, case-control, or cross-sectional studies. In turn, these studies are considered better evidence than uncontrolled trials or case series. For questions about tolerability and harms, controlled trials typically provide limited information. For these questions, observational study designs may provide important information that is not available from trials. Within this hierarchy, cohort designs are preferred when well conducted and assessing a relatively common outcome. Case control studies are preferred only when the outcome measure is rare, and the study is well conducted.

An evidence report pays particular attention to the generalizability of *efficacy* studies performed in controlled or academic settings. *Efficacy* studies provide the best information about how a drug performs in a controlled setting that allows for better control over potential confounding factors and bias. However, the results of efficacy studies are not always applicable to many, or to most, patients seen in everyday practice. This is because most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, medication compliance, or severity of illness. For many drug classes, including antipsychotics, unstable or severely impaired patients are often excluded from trials. Often, efficacy studies also exclude patients who have comorbid diseases, meaning diseases other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that may be impractical in other practice settings. They often restrict options, such as combining therapies or switching drugs that are of value in actual practice. They often examine the short-term effects of drugs that in practice are used for much longer periods of time. Finally, efficacy studies tend to use objective measures of effects that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

An evidence report also highlights studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. *Effectiveness* studies conducted in primary care or office-based settings use less stringent eligibility criteria, assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the “average” patient than results from highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality of life, hospitalizations, and the ability to work or function in social activities. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it is neither possible nor desirable to exclude evidence based on these characteristics. Labeling each study as an efficacy or effectiveness study, while convenient, is of limited value; it is more useful to consider whether the patient population, interventions, time frame, and outcomes are relevant to one's practice, or, in the clinical setting, how relevant they are to a particular patient.

Studies across the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard to determine whether the characteristics of different drugs are related to their effects on disease. An evidence report reviews the efficacy data thoroughly to ensure that decision-makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how much there is of it, may have limited applicability to practice. Clinicians can judge the relevance of the study results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs, there are few or no effectiveness studies and many efficacy studies. As a result, clinicians must make decisions about treatment for many patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. An evidence report indicates whether or not there is evidence that drugs differ in their effects in various subgroups of patients, but it does not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these are decisions that must be informed by clinical judgment.

In the context of developing recommendations for practice, evidence reports are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. By themselves, they do not tell you what to do. Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is not true. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policies. Additional criteria include acceptability to physicians or patients, the potential for unrecognized harms, the applicability of the evidence to practice, and consideration of equity and justice.

Scope and Key Questions

The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to their constituencies. Initially, the Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest,

and based on these, the eligibility criteria for studies. These were reviewed, revised, and approved by representatives of organizations participating in the Drug Effectiveness Review Project. It is the representatives' responsibility to ensure that the questions reflect public input or input from their members. The participating organizations approved the following key questions to guide this review.

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

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

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

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

METHODS

To identify relevant citations, we searched Ovid MEDLINE (1966 to January Week 4 2009), the Cochrane Database of Systematic Reviews (Second Quarter 2008), Database of Abstracts of Reviews of Effects (Third Quarter 2008) and the Cochrane Central Register of Controlled Trials (Third Quarter 2008), using terms for included drugs, indications, and study designs (see Appendix B for complete search strategies). In addition, pharmaceutical manufacturers were invited to submit dossiers, including citations, using a protocol issued by the Center for Evidence-based Policy (available at: http://www.ohsu.edu/drugeffectiveness/pharma/index.htm). All citations were imported into an electronic database (EndNote® X2).

Study Selection

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

We included English-language reports of studies of the patient populations and efficacy outcomes listed in Table 3. For studies of hypertension, we excluded studies in which blood

pressure lowering was the only endpoint; most of these studies sought to identify equivalent doses of beta blockers rather than differences in clinical effectiveness. Instead, we sought evidence of long-term effects on mortality, cardiovascular events, and quality of life. We only included studies in stable angina patients with duration of 2 months or longer. We only included studies of long-term treatment in post-coronary artery bypass graft patients, excluding studies of the short-term use of beta blockers to suppress atrial arrhythmias. With regard to placebo-controlled trials of recent myocardial infarction or heart failure, we only included studies with sample sizes of 100 patients or more.

Table 3. Included outcome measures

Population	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 (treatment ≥ 2 month's duration)	1. Exercise tolerance 2. Attack frequency 3. Nitrate use
Post-coronary artery bypass graft (long-term treatment)	1. All-cause mortality 2. Ischemic events (myocardial infarction, unstable angina, need for repeat coronary artery bypass graft, and percutaneous transluminal coronary angioplasty)
Recent myocardial infarction (with and without left ventricular 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 left ventricular 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

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

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

Data Abstraction

From included trials we abstracted information about the study design; setting; population characteristics (including sex, age, race, and 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.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix C. These criteria are based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK) criteria.[1, 2] We rated the internal validity of each trial based on the 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 followup; and the use of intention-to-treat analysis. Trials that had a fatal flaw 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 *likely* to be valid, while others are only *possibly* valid. A poor-quality trial is not valid—the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs. A fatal flaw is reflected by failing to meet combinations of items of the quality assessment checklist. A particular randomized trial might receive 2 different ratings, one for effectiveness and another for adverse events.

Appendix C also shows the criteria we used to rate observational studies of adverse events. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met 6 or more of the 7 predefined criteria, fair quality if they met 3 to 5 criteria, and poor quality if they met 2 or fewer criteria.

Included systematic reviews were also rated for quality based on pre-defined criteria (see Appendix C); clear statement of the questions(s), inclusion criteria, adequacy of search strategy, validity assessment, and adequacy of detail provided for included studies; and appropriateness of the methods of synthesis. Again, these studies were categorized as good when all criteria were met.

The overall strength of evidence for a particular key question or outcome reflects the risk of bias of the study (based on quality and study design), consistency, directness, and precision of the set of studies relevant to the question. The overall strength of evidence was graded as good, fair, and poor.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy of evidence approach, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed. Studies that evaluated one beta blocker against another provided direct evidence of comparative effectiveness and adverse event rates. Where possible, these data are the primary focus. As such, direct comparisons were preferred over indirect comparisons. Similarly, effectiveness and long-term safety outcomes were preferred to efficacy and short-term tolerability outcomes.

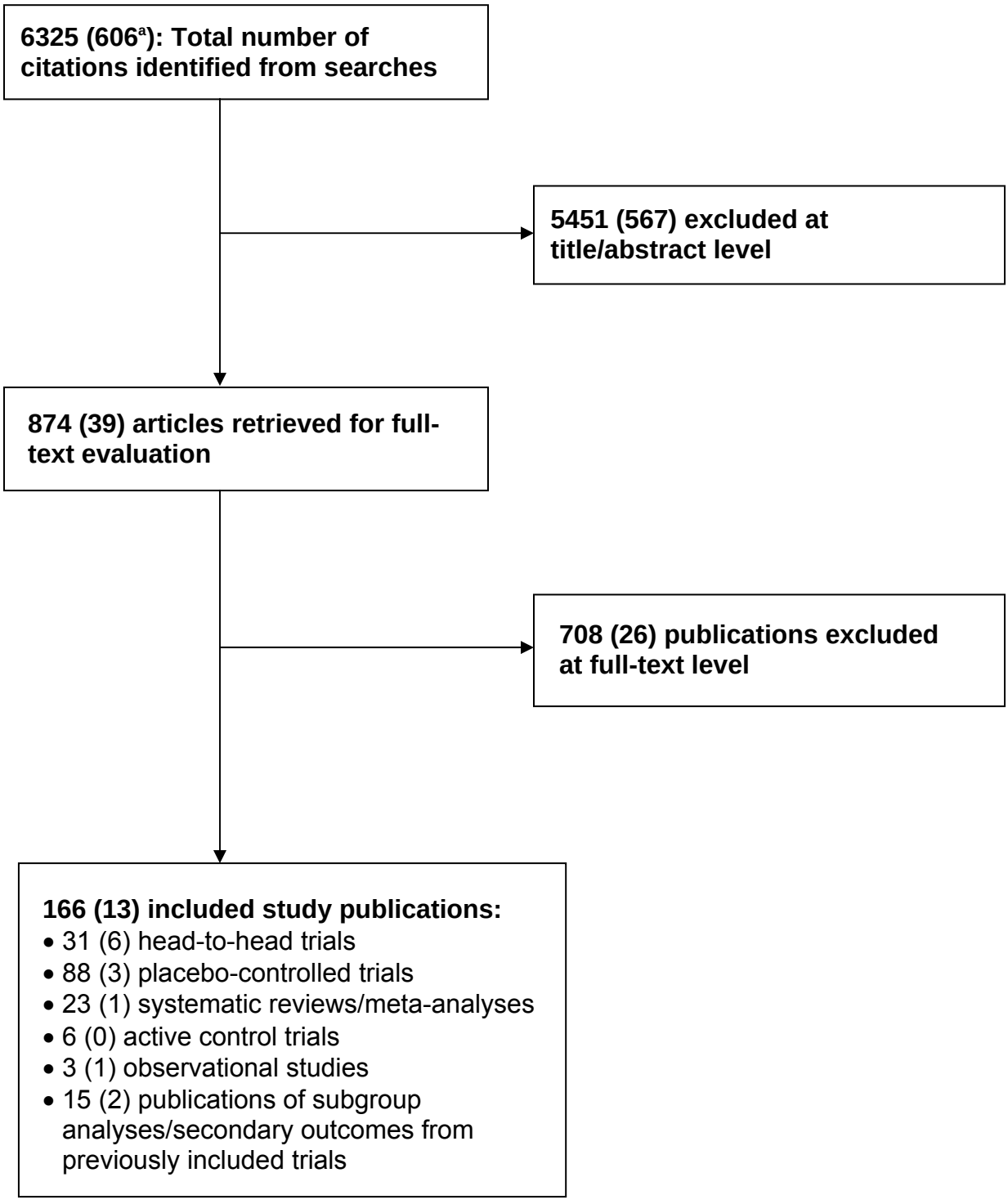
In theory, trials that compared beta blockers to other drug classes or placebos could also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily issues of heterogeneity between trial populations, interventions, and assessment of outcomes. Data from indirect comparisons were used to support direct comparisons, where they exist, and were also used as the primary comparison where no direct comparisons existed. Such indirect comparisons should be interpreted with caution.

RESULTS

Overview

Searches identified 6325 citations, with 606 new in Update 4. The results of study selection are outlined in Figure 1. Dossiers were received for Update 4 from the manufacturers of carvedilol, carvedilol controlled release, and nebivolol. Studies excluded at the full text level are listed in Appendix D.

Figure 1. Results of study selection



[a] Numbers in parentheses are results of the literature search new to Update 4.

Summary of Findings

Efficacy/effectiveness

Hypertension

- Direct comparisons
  - There were no head-to-head trials of different beta blockers on long-term (≥6 months) health or quality-of-life outcomes.
  - No consistent differences between beta blockers in quality-of-life outcomes were found in shorter-term, head-to-head trials of beta blockers.
- Placebo-controlled trials
  - Long-term placebo-controlled trials of propranolol and atenolol were found, however no reliable indirect comparisons can be made from them.
- Gaps: Long-term effectiveness; quality of life

Angina

- Direct comparisons
  - There were no significant differences in exercise tolerance or attack frequency in 6 head-to-head trials of carvedilol compared with metoprolol, pindolol compared with propranolol, betaxolol and propranolol, or betaxolol compared with metoprolol in patients with stable angina.
  - Atenolol and bisoprolol were equivalent in angina patients with chronic obstructive pulmonary disease.
  - Atenolol and labetalol (when combined with chlorthalidone) were equivalent in angina patients with hypertension.
- Placebo-controlled trials
  - One short-term, placebo-controlled trial of propranolol did not add any meaningful evidence of comparative efficacy in attack frequency or exercise parameters.

After coronary artery bypass graft

- Direct comparisons
  - There were no head-to-head trials of beta blockers in adults following coronary artery bypass graft.
- Placebo-controlled trials
  - Two placebo-controlled trials suggested that long-term use of a beta blocker after coronary artery bypass graft does not improve mortality or other outcomes. For example, the MACB Study Group conducted a fair-quality trial that randomized 967 patients (85.5% male, median age 64 years) to metoprolol 200 mg once daily or placebo within 5 to 21 days following coronary artery bypass graft and measured the effects of treatment on death and cardiac events. No differences between metoprolol and placebo were found in mortality (3.3% compared with 1.8%; P=0.16) or in ischemic events (myocardial infarction, unstable angina, need for additional coronary artery bypass graft, or percutaneous transluminal coronary angioplasty).

- Gaps: long-term direct comparisons

Recent myocardial infarction

- Direct comparisons
  - One fair-quality head-to-head trial found no differences in mortality after 1 year between atenolol and propranolol, but this was a relatively small trial.
  - One fair-quality head-to-head trial found no differences in time to serious cardiovascular events between carvedilol and atenolol.
  - One fair-quality head-to-head trial found no differences in time to first cardiac adverse event or all-cause mortality between carvedilol and metoprolol tartrate.
- Placebo-controlled trials
  - In placebo-controlled trials, similar mortality reductions were reported for acebutolol, metoprolol tartrate, propranolol, and timolol for patients following myocardial infarction without other complications. Similar reductions in sudden death and reinfarction were reported for metoprolol tartrate and timolol and in sudden death for propranolol. Carvedilol is the only beta blocker shown to reduce mortality in post-myocardial infarction patients who are already taking an ACE (angiotensin-converting enzyme) inhibitor. No studies of carvedilol phosphate (extended-release carvedilol) in patients with recent myocardial infarction were identified. Carvedilol reduced mortality and reinfarction in 1 placebo-controlled trial of patients with a mean left ventricular ejection fraction of greater than 32.8% (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction [CAPRICORN] trial).

Heart failure

- Direct comparisons
  - There were no direct comparator trials comparing 2 or more of the drugs proven to reduce mortality (bisoprolol, carvedilol, and sustained release metoprolol succinate).
  - In the Carvedilol or Metoprolol European Trial (COMET) trial, carvedilol was superior to metoprolol tartrate reducing all-cause mortality (number needed to treat, 18) after a mean follow-up of 58 months in patients with mild to moderate heart failure.
  - No differences were found between carvedilol and metoprolol tartrate in improving symptoms (quality of life; New York Heart Association classification) or exercise capacity in 4 smaller head-to-head trials.
  - Improvements in New York Heart Association function class and on walking distance (6-minute walk test) were similarly slight for both carvedilol and nebivolol.
- Placebo-controlled trials
  - Bisoprolol, metoprolol succinate, and carvedilol have each reduced total mortality, as a planned primary endpoint, by approximately 35%.
  - Based on findings from the COPERNICUS trial (N=2289), carvedilol is designated as the beta blocker with the most direct, strongest evidence of having a mortality benefit in patients with severe heart failure. In a post-hoc subgroup

analysis of 795 patients from the good-quality MERIT-HF trial, metoprolol succinate has also demonstrated a mortality reduction relative to placebo similar to that for carvedilol in patients who had a similar mortality risk.
    - In the SENIORS trial (N=2128), which involved patients who were, overall, older (mean age of 76 years) and healthier than in the prior major trials (higher mean left ventricular ejection factor, lower annual placebo mortality rate), nebivolol was superior to placebo in reducing the risk of the primary composite outcome of all-cause mortality or cardiovascular hospital admission (31.1% compared with 35.3%; hazard ratio, 0.86; 95% CI, 0.74 to 0.99). When components of the primary outcome were examined individually as secondary outcome measures, differences between nebivolol and placebo were no longer statistically significant.
    - We found no trials that directly evaluated the effects of carvedilol phosphate, the long acting form of carvedilol, on mortality in adults with heart failure. Approval of the heart failure indication for carvedilol phosphate was based on "equivalence of pharmacokinetic and pharmacodynamic parameters between carvedilol phosphate and conventional carvedilol tablets."

Atrial arrhythmia

- Direct comparisons
    - There were no differences between bisoprolol 10 mg and carvedilol 50 mg in preventing relapse of atrial fibrillation in patients subjected to cardioversion of persistent atrial fibrillation (>7 days).
- Placebo-controlled trials
    - Atenolol, nadolol, and pindolol, but not labetalol, were effective in controlling the ventricular rate, while labetalol was no more efficacious than placebo based on findings from a good-quality systematic review examining 12 studies of rate control in patients with chronic atrial fibrillation.
    - One placebo-controlled trial found that metoprolol CR/XL 100 to 200 mg was effective in preventing relapse of atrial fibrillation/flutter after cardioversion. Over 6 months, atrial fibrillation or flutter relapse rates were significantly lower in patients taking metoprolol CR/XL. Death rates were similar. The study was not powered to examine mortality.
    - A study examining the effects of carvedilol in managing patients with concomitant atrial fibrillation and heart failure found that when added to digoxin, carvedilol significantly improved mean left ventricular ejection fraction scores and reduced severity of symptoms/functional capacity when compared to digoxin alone. There were no differences between monotherapies of carvedilol or digoxin.

Migraine

- Direct comparisons
    - Head-to-head trials showed 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, metoprolol durules, metoprolol, or timolol compared with propranolol or nebivolol compared with metoprolol).

- Placebo-controlled trials
    - In placebo-controlled trials atenolol, metoprolol durules, and propranolol had similar results as was observed in head-to-head trials. Placebo-controlled trial results also showed that bisoprolol reduced effect attack frequency significantly and that pindolol had no appreciable effects.

Bleeding esophageal varices

- Direct comparisons
    - One small head-to-head trial showed no difference between atenolol 100 mg and propranolol 40 to 160 mg in rates of non-fatal/fatal rebleeding and all-cause mortality.
- Placebo-controlled trials
    - Results of 1 trial of nadolol and 8 small placebo-controlled trials of immediate-release and 2 formulations of extended-release propranolol for the secondary prevention of bleeding esophageal varices secondary to cirrhosis and schistosomiasis did 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.

Harms

- There were no consistent significant differences between beta blockers in head-to-head trials in overall adverse events, withdrawals due to adverse events, or individual adverse events.

Subgroups

- A meta-analysis (see Table 16) suggested that beta blockers are equally effective in reducing mortality in subpopulations stratified by gender and race.
- There is insufficient evidence to draw conclusions about the effects of beta blockers on perinatal mortality or preterm birth.

Key Question 1. Do beta blocker drugs differ in efficacy or effectiveness?

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

Summary

Beta blockers are equally efficacious in controlling blood pressure in patients with hypertension. No beta blocker has been demonstrated to be more efficacious or to result in better quality of life than other beta blockers, either as initial therapy or when added to a diuretic, ACE inhibitor, or angiotensin receptor blocker. Evidence from long-term trials is mixed; overall, beta blockers are generally less effective than diuretics, and are usually no better than placebo, in reducing cardiovascular events. The exception was 1 large trial in which treatment with metoprolol resulted in lower all-cause mortality than treatment with a thiazide diuretic.

Detailed Assessment

Primary or initial therapy

Beta blockers have been used as initial therapy in patients with hypertension and as additional therapy in patients whose blood pressure is not well controlled with a diuretic. In several head-to-head trials, beta blockers have similar effects on blood pressure control.[3-11] No trials have examined whether beta blockers have different effects on all-cause mortality, cardiovascular mortality, or cardiovascular events among patients with hypertension.

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

The Medical Research Council trials, the International Prospective Primary Prevention Study in Hypertension, the Heart Attack Primary Prevention in Hypertension study, and the Metoprolol Atherosclerosis Prevention in Hypertensives study compared a beta blocker to a thiazide diuretic. Of these trials, only the 2 Medical Research Council trials compared a beta blocker to placebo. In 1 Medical Research Council trial, atenolol 50 mg daily was not better than placebo and less effective than a diuretic in adults ages 65 to 74 who had baseline blood pressures of 160/115 mm Hg or higher.[12] In the other Medical Research Council trial, which recruited 17 361 patients with mild diastolic hypertension (90 to 109 mm Hg), beta blocker therapy (atenolol) reduced the odds for stroke, but only in nonsmokers and to a smaller degree than a low dose of a thiazide diuretic (bendrofluazide).[13]

Of the trials that compared a beta blocker with a diuretic, only 1 (Metoprolol Atherosclerosis Prevention in Hypertensives study) had any suggestion that the beta blocker was more effective. In that trial, deaths from heart attacks and strokes as well as total mortality were lower in the metoprolol treated group than in those treated with a diuretic (hydrochlorothiazide or bendroflumethiazide).[14] The trial continues to be cited as strong evidence that beta blockers reduce mortality when used as primary treatment for hypertension. However, it must be weighed against the mixed results of the Medical Research Council trials and other trials of beta blockers compared with diuretics. In a good-quality meta-analysis of 10 trials published in 1998 or earlier, beta blockers were ineffective, or less effective than comparator drugs, in preventing coronary heart disease, cardiovascular mortality, and all-cause mortality (odds ratios 1.01, 0.98, and 1.05, respectively).[15]

Secondary treatment

The Systolic Hypertension in the Elderly Program (SHEP) trial examined a stepped approach for treating isolated systolic hypertension in the elderly.[16] Chlorthalidone was the first step. Atenolol was prescribed if the blood pressure goal could not be achieved with chlorthalidone 25 mg daily. Compared to placebo, stepped treatment prevented 55 cardiovascular events per 1000 patients over 5 years. The contribution of beta blocker therapy with atenolol to the overall benefit is not clear; most of the benefit was attributed to chlorthalidone.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (2002) did not include a beta blocker arm.[17] Based on the results of this trial, 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.[18]

Quality of life

There was no definitive evidence that 1 beta blocker yields a better quality of life than another for patients who have hypertension. Eight trials directly compared different beta blockers[19] on changes of quality of life-associated measures. We excluded 2 trials of atenolol compared with propranolol based on poor-quality ratings.[7, 20] The methods described in these publications were insufficient to rule out the possibilities that results were biased by inadequate randomization procedures (methods weren't described and baseline characteristics weren't reported) and/or by mishandling of missing data (attrition reasons not described and proportion of patients included in analyses not reported). Table 4 below summarizes the results of the fair-quality trials.

The strongest evidence of any differences between beta blockers came from a 4 week trial of captopril, enalapril, propranolol, and atenolol that used a larger sample size (N=360) and a parallel design.[8] This was the only trial that is clearly industry-funded. Patients were all men that were "at least 21 years of age, employed or retired, educated at high-school level or equivalent, and married or living with a significant other." Self-ratings of improvements were greater for atenolol than propranolol in Psychologic General Well-Being-measured self-control, distress overall and that caused by obsessions and hostility symptoms (Symptom Check List-90-R), and on global and social satisfaction indices from the Life Satisfaction Index. It remains unclear, however, as to whether these short-term results in men can be generalized to a broader population over a longer period of time.

The strength of the evidence from the remaining trials was limited by smaller sample sizes and, in the crossover trials, results that were averaged across treatment periods.[5, 19, 21-23] Improvement in self-rated sexual interest (Minor Symptom Evaluation profile) was greater for atenolol than metoprolol CR in 1 trial of 60 patients (mean age 58 years; 43.3% male).[5]

Two trials of metoprolol succinate compared to nebivolol examined quality of life measures. One trial was conducted in Germany and compared nebivolol 5 mg to metoprolol succinate 95 mg. After 12 weeks of treatment, 48 men (ages 40 to 55) with newly diagnosed hypertension experienced decreased sexual function on metoprolol 95 mg, but not nebivolol 5 mg.[23] However, the article provides insufficient detail to determine how the metoprolol succinate 95 mg product compares to the metoprolol succinate product available in the United States and Canada. In another trial, after 6 weeks of treatment of 46 adults with mild hypertension, sleep quality, as measured by scores on the Pittsburgh Sleep Quality Index, was improved by treatment with nebivolol 5 mg, but declined following treatment with metoprolol CR 100 mg.[19]

Table 4. Quality-of-life outcomes in head-to-head trials of hypertensives

Trial (quality)	Comparison Design Sample size	Duration (weeks)	Washout (weeks)	Results
Steiner 1990[8] (Fair)	Atenolol vs. propranolol Parallel N=360	4	NA	Atenolol superior to propranolol on *some* Psychologic General Well-Being, SCL-90-R, and Life Satisfaction indices and no differences on Insomnia Symptom Questionnaire or Sexual Function Questionnaire
Walle 1994[5] (Fair)	Atenolol vs. metoprolol CR Crossover N=16	6	NR	Atenolol superior to propranolol on 1 Minor Symptom Evaluation item; no differences in all other Minor Symptom Evaluation and Psychologic General Well-Being scores
Buhler 1986[21] (Fair)	Atenolol vs. bisoprolol Crossover N=104	8	2-6	No differences on unspecified self-assessment questionnaire
Dahlof 1988[22] (Fair)	Atenolol vs. metoprolol CR Crossover N=74	6	NR	No differences on Minor Symptom Evaluation or Jern's quality-of-life questionnaires
Yilmaz 2008 (Fair)	Nebivolol vs. Metoprolol ER Parallel N=46	6	NR	Nebivolol superior to metoprolol ER at end of treatment. Nebivolol (32% poor sleepers) compared with metoprolol (76% poor sleepers) (*P*=0.006). Mean global PSQI score decreased (5.77 to 4.55) for nebivolol arm; increased (5.11 to 6.53) for metoprolol arm. Higher score indicated worse sleep.
Brixius 2007 (Fair)	Nebivolol vs. Metoprolol Crossover N=48	28	NR	Metoprolol 95 mg (–0.92 points), but not nebivolol (+0.13 points) decreased erectile function (*P*=0.04).

Abbreviations: NA, not applicable; NR, not reported; PSQI, Pittsburgh Sleep Quality Index.

Two placebo-controlled trials reported the effect of long-term beta blocker therapy on quality of life in otherwise healthy patients who have hypertension (Evidence Tables 1 and 2). The Trial of Antihypertensive Interventions and Management[24-26] 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, the Physical Complaints Inventory, and the Symptoms Checklist, including *summary* ("total physical problems", "overall psychological functioning", "overall life satisfaction"), *distress* ("sexual physical problems", "depression", "anxiety", "sleep disturbances", "fatigue"), and *well-being* ("satisfaction with physical health", "sexual satisfaction"). In the second trial,[27] there were no differences between propranolol and placebo in cognitive or psychological measures after 1 year of treatment.

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

Summary

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

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

Detailed Assessment

In 1966 the first beta blocker, propranolol, was shown in a multicenter controlled trial to improve symptoms in patients with angina pectoris.[28] Several other beta blockers (acebutolol, atenolol, metoprolol tartrate, metoprolol succinate, nadolol, propranolol, and propranolol long-acting) have been demonstrated to reduce symptoms of angina in placebo-controlled trials.

Most head-to-head trials of beta blockers in patients with angina pectoris observe patients for only 2 to 4 weeks of treatment.[29-36] In these trials, exercise tolerance, attack frequency, or nitroglycerin use were generally similar at comparable doses.

Six fair-quality head-to-head trials evaluated angina symptoms after 2 or more months of treatment with beta blockers (Table 5, Evidence Tables 3 and 4). Mean ages ranged from 55 to 61.5 years and most subjects were men (71.5% to 100%), with the exception of 1 study, which included 40% male subjects.[37] Exercise parameters were measured using bicycle ergometric testing in all but 2 trials,[38, 39] which used a treadmill. One study, however, did not include exercise parameters in its study design.[37] There were no significant differences in exercise tolerance or attack frequency. No significant differences were found between betaxolol 20 mg and metoprolol tartrate 100 mg on 5 of 6 health-related quality-of-life parameters. Compared with metoprolol tartrate (15%), however, significantly greater numbers of patients on betaxolol improved on the 'Physical Function' parameter (43%; $P<0.01$).[37]

Table 5. Results of head-to-head trials in patients with angina

Trial Sample size	Interventions	Results	
		Exercise parameters	Attack frequency and/or nitroglycerine use (% reduction)
Van der Does 1999 N=368	Carvedilol 100 mg Metoprolol 200 mg	No difference	Not reported
Frishman 1979 N=40	Pindolol 10-40 mg Propranolol 40-240 mg	No difference	No difference
Narahara 1990 N=112	Betaxolol 20 and 40 mg Propranolol 160 and 320 mg	No difference	No difference
Dorow 1990 N=40 (comorbid chronic obstructive pulmonary disease patients)	Atenolol 50 mg Bisoprolol 5 mg	Not reported	82.8% compared with 64.3% (not significant)
Chieffo 1986 N=10 (comorbid hypertension)	Labetalol 200 mg +chlorthalidone 20 mg Atenolol 100 mg +chlorthalidone 25 mg	Not reported	60% compared with 80% (not significant)
Kardas 2007 N=112	Betaxolol 20 mg once daily Metoprolol tartrate 50 mg twice daily	Not reported	0.42/week compared with 0.46/week[a] (not significant)

[a] Decrease in number of chest pain episodes per week compared with baseline.

Over the long term, beta blockers may differ in their ability to prevent or reduce the severity of anginal attacks. In 1 fair-quality 2-year multicenter European trial, propranolol was better than placebo after 8 weeks but not after 24 weeks of treatment.[40] Specifically, after 8 weeks propranolol 60 to 240 mg reduced the proportion of patients using nitroglycerin (57% compared with 73% in the placebo group; P=0.04) and increased the mean total work time by 48% compared with 13% (P=0.04). These effects were transient, however, and propranolol was equivalent to placebo on those parameters after 24 weeks of treatment. Propranolol and placebo had similar effects on the number of weekly angina attacks, the number of attack-free days, maximum workload, and exercise duration at 8- and 24-week endpoints. The relevance of this trial was limited because since the time it was conducted, the rate of progression of angina may have been altered by advances in treatment of atherosclerosis (for example statin therapy).

A good-quality meta-analysis identified 72 randomized controlled trials of a beta blocker compared with a calcium channel blocker and 6 trials comparing a beta blocker to a nitrate.[41] 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.

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

We did not examine the short-term (4 to 10 days) use of beta blockers to prevent or control atrial tachyarrhythmias after coronary artery bypass graft.[42-46] In addition to the beta blockers included in our review, esmolol, a very short-acting, intravenous beta blocker, is used postoperatively to control tachyarrhythmias.

In 7 trials, long-term use of a beta blocker after coronary artery bypass graft did not improve mortality or other outcomes (Evidence Tables 5 and 6). For example, the MACB Study Group conducted a fair-quality trial[47] that randomized 967 patients (85.5% male, median age 64 years) to metoprolol 200 mg once daily or placebo within 5 to 21 days following coronary artery bypass graft and measured the effects of treatment on death and cardiac events. No differences between metoprolol and placebo were found in mortality (3.3% compared with 1.8%; P=0.16) or in ischemic events (myocardial infarction, unstable angina, need for additional coronary artery bypass graft or percutaneous transluminal coronary angioplasty).

Key Question 1d. For adult patients with recent myocardial infarction, do beta blockers differ in efficacy or effectiveness?

Summary

Table 6 summarizes evidence from meta-analyses and major trials of beta blockers in patients with recent myocardial infarction. Timolol was the first beta blocker shown to reduce total mortality, sudden death, and reinfarction outcomes in the Norwegian Multicenter Study.[48] Subsequently, similar total mortality reductions were reported across trials of acebutolol,[49] metoprolol tartrate (Goteborg), and propranolol (Beta Blocker Heart Attack Trial) in comparable populations. In addition, similar benefits in sudden death were reported for propranolol[50] and metoprolol tartrate[51, 52] and in reinfarction for metoprolol tartrate.[52]

Carvedilol reduced reinfarction rates in the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial, which recruited stable inpatients with recent myocardial infarction and a left ventricular ejection fraction of 40% or less. Carvedilol is the only beta blocker shown to reduce mortality in post-myocardial infarction patients who are already taking an ACE inhibitor. An extended-release form of carvedilol (carvedilol phosphate) was approved by the US Food and Drug Administration in October 2006. No studies of carvedilol phosphate in patients following myocardial infarction were identified through literature searches. Approval of the left ventricular dysfunction following myocardial infarction indication for carvedilol phosphate was based on pharmacokinetic and pharmacodynamic data that demonstrated bioequivalence with carvedilol.

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

Table 6. Comparison of outcomes of mortality-reducing beta blockers in patients following myocardial infarction

Beta blocker	Mortality reduction in general population of post-myocardial infarction patients	Mortality reduction in post-myocardial infarction patients with left ventricular dysfunction	Sudden death reduction	Reinfarction reduction
Acebutolol	Effective	Uncertain	Insignificant effect	Insignificant effect
Carvedilol	Not established	Effective	Uncertain (trend)	Effective
Carvedilol phosphate	No evidence	No evidence	No evidence	No evidence
Metoprolol tartrate	Effective	Probable	Effective	Effective
Propranolol	Effective	Probable	Effective	Insignificant effect (BHAT, Hansteen 1982)
Timolol	Effective	Uncertain	Effective	Effective

Head-to-Head Trials

No consistent differences between beta blockers were found in 3 head-to-head trials in post-myocardial infarction patients.[53-55] A 6-week trial comparing atenolol 100 mg to propranolol 120 mg had inconclusive results.[53] The second trial, an open-label study with a median follow-up of 1.6 years, compared carvedilol to atenolol. Patients in this study had mean left ventricular ejection fraction 53.9% at baseline. The primary outcome of the study was the change in left ventricular ejection fraction at 1 year; time to first serious cardiovascular event was a secondary endpoint. No significant difference was found between the 2 interventions in either change in left ventricular ejection fraction (P=NR) or time to occurrence of a serious cardiovascular event (P=0.524), which remained when controlling for use of diuretics (P=0.990).[56] However, these results are not conclusive, as the study's authors acknowledge that the study was underpowered to detect such a difference for this secondary outcome. A study of 313 patients comparing metoprolol tartrate 100 mg twice daily to carvedilol 25 mg twice daily for a mean of 13.4 months found no differences in time to first composite cardiac adverse event (all-cause death, postinfarction angina, heart failure, rehospitalization, and revascularization) or time to composite hard event (cardiovascular death and nonfatal reinfarction).[55] There were statistically significant differences in 5 of 8 health-related quality-of-life domains measured using the Short Form-36 questionnaire (adjusted for age and baseline differences) favoring the carvedilol group.[55]

Placebo-controlled Trials

Because there are so few comparative trials, inferences about the comparative effectiveness of beta blockers in post-myocardial infarction patients must be made on other grounds. The criteria for making these comparisons might include:

1. Demonstration of reduced mortality in large, multicenter placebo-controlled trials
2. Degree of mortality reduction compared with other beta blockers
3. Improvements in other outcomes

4. Tolerability
5. Effectiveness studies and applicability of efficacy studies to current practice.

Mortality

Three systematic reviews have analyzed over 60 trials of beta blockers after myocardial infarction.[57-59] The first (Yusuf, 1985) analyzed 22 long-term trials of beta blockers in acute myocardial infarction. Overall beta blockers reduced mortality by 23%, from an average of 10% to 8%. The second (Hjalmarson, 1997) found an average 20% mortality reduction in 24 trials of a total of 25000 patients.

A more recent review (Freemantle, 1999) used meta-regression to examine the relationship of characteristics of different beta blockers with the outcome of treatment.[59] In their analysis of 24 long-term trials, cardioselectivity had no effect, but there was a near significant trend towards decreased benefit in drugs with intrinsic sympathomimetic activity. Individually, acebutolol (0.49; 0.25-0.93), metoprolol tartrate (0.80; 0.66-0.96), propranolol (0.71; 0.59-0.85), and timolol (0.59; 0.46-0.77) significantly reduced mortality, but there was insufficient data to distinguish among them. The analysis included just 1 trial of carvedilol, a pilot study in 151 post-myocardial infarction patients.[60]

Table 7 summarizes placebo-controlled trials that enrolled over 100 patients, had long-term follow-up (greater than 6 weeks), and met our other inclusion criteria. All of these trials were analyzed in the 1999 systematic review except for CAPRICORN, which was conducted from 1997 to 2000 at 163 sites in 17 countries and published in 2001.[61] Unlike the other trials, CAPRICORN included only patients who had reduced left ventricular function (≤ 40%) after acute myocardial infarction as determined by echocardiography or cardiac catheterization. Patients with uncontrolled heart failure, such as those requiring intravenous diuretics, were excluded. Of 1959 subjects randomized to either carvedilol or placebo at an average of 10 days following a confirmed myocardial infarction, 1289 had no clinical signs of heart failure (Killip Class I), 593 had Killip Class II heart failure, and 65 had Killip Class III failure. The mean ejection fraction was 32.8%.

The original primary endpoint was all-cause mortality. Subsequently, following a masked interim analysis in which the data and safety monitoring board found that overall mortality rates were lower than predicted, the CAPRICORN steering committee decided to adopt the co-primary endpoints of all-cause mortality together with all-cause mortality *plus* cardiovascular hospital admissions. There was no difference between carvedilol and placebo for the primary endpoint of mortality plus cardiovascular admissions (35% compared with 37% for placebo over 1.3 years, P=0.299). However, carvedilol reduced the *original* primary endpoint of total mortality in the first 30 days (19% compared with 33%; hazard ratio, 0.58; 95% CI, 0.33 to 1.02) [62] and over 1.3 years (12% compared with 15% for placebo over 1.3 years; number needed to treat, 30 or number needed to treat for 1 year, 43). The P value was 0.03, which, although nominally significant, did not meet the higher level of significance specified when the combined primary outcome measure was adopted.

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

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

Is the mortality reduction in CAPRICORN different from what would be expected from older trials of beta blockers in post-myocardial infarction patients or in patients with heart failure? The authors of the *Lancet* paper raised this question, noting that the 23% mortality reduction in CAPRICORN is identical to that found in meta-analyses of the older beta blocker trials.

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

There was no direct evidence that other beta blockers shown to reduce mortality in post-myocardial infarction patients or in patients with heart failure worked as well as carvedilol in post-myocardial infarction patients with decreased left ventricular function and few or no symptoms of heart failure. While the older trials undoubtedly included some subjects with left ventricular dysfunction, it is difficult to determine how many, or how this subset did compared with post-myocardial infarction patients with normal left ventricular function.

Indirect evidence came from a good-quality meta-analysis.[63] This analysis examined the relationship between the mortality reduction reported in each trial and the proportion of patients in the trial who had heart failure. There were few data on the effects of beta blockers after myocardial infarction in patients with documented left ventricular systolic dysfunction, but some studies included subjects with clinical findings of heart failure and reported the proportion of subjects that had these findings. As expected, studies that included patients with heart failure had higher mortality rates. The relative benefit of beta blockers on mortality after a myocardial infarction was similar in the presence or absence of heart failure.

Two retrospective subgroup analyses in heart failure patients from individual trials included in this meta analysis provided additional details supporting this hypothesis. One is from the Beta Blocker Heart Attack Trial (BHAT), a large, 3-month trial of propranolol published in 1980. In BHAT, 710 of 1916 subjects had a history of congestive heart failure prior to randomization. Propranolol lowered total mortality from 18.4% to 13.3% (a 27% reduction) in

patients with a history of heart failure and from 7.8% to 5.9% (25% reduction) in patients who did not have a history of heart failure.[64]

The other retrospective subgroup analysis was from a 1980 placebo-controlled trial of metoprolol. At the time of randomization, 262 (19%) of the 1395 subjects had signs or symptoms of mild heart failure.[65] Metoprolol or placebo was administered intravenously once, followed by oral metoprolol or placebo for 3 months, followed by open treatment with metoprolol for up to 2 years in all patients who had signs of ischemia. For patients with heart failure, mortality during the first year of the study was 28%, compared with 10% in subjects without signs of heart failure ($P<0.0001$). Among the subjects with heart failure at the time of randomization, metoprolol reduced mortality during the 3-month double-blind phase of the trial (14% compared with 27%, $P<0.0009$, number needed to treat=8).

Sudden death

Significant reductions in sudden death were reported in 2 of 3 trials of metoprolol tartrate,[51, 52] 1 trial of propranolol,[50] and in 1 trial of timolol.[48]

Reinfarction

Significant reductions in reinfarction rates were reported in 1 of 2 trials of metoprolol tartrate[52] and in 1 trial of timolol.[48] Carvedilol was also associated with significantly reduced reinfarction rates in the CAPRICORN trial.

Arrhythmias

Evidence on the effect of beta blockers on post-myocardial infarction arrhythmias is unclear based on the available evidence. No significant difference in occurrence of post-myocardial infarction arrhythmia (defined as cardiac arrhythmia, fibrillation, or tachycardia) was found in placebo-controlled trials of acebutolol (1 trial)[66] or propranolol (1 trial),[50] while 1 placebo-controlled trial of propranolol found a small, but significantly higher, percentage of withdrawals due to serious ventricular arrhythmia in the placebo group (0.3% propanolol compared with 1.0% placebo; $P<0.025$).[67] One trial of timolol found a significantly higher proportion of patients experiencing ventricular tachycardia with placebo use (20% placebo compared with 8.5% timolol; $P=0.05$) while the number of episodes of ventricular tachycardia (55 placebo compared with 10 timolol) was not statistically significant (data not provided).[68]

Two publications comparing carvedilol to placebo presented mixed results. One older trial found no significant difference between the 2 drugs in the rate of cardiac arrhythmias among all enrolled patients.[60] In a subgroup analysis of patients (N=49/151; 32%) with baseline left ventricular ejection fraction <45%, carvedilol was associated with a significant decrease in serious cardiac events, a combined endpoint that included death, reinfarction, unstable angina, congestive heart failure, and ventricular tachycardia ($P=0.04$). The second publication, a post-hoc analysis of data from the CAPRICORN trial, compared rates of atrial and ventricular arrhythmias.[69] As stated above, patients enrolled in the CAPRICORN trial had baseline left ventricular ejection fraction ≤40%. Atrial and ventricular arrhythmias were found to be less common with carvedilol use relative to placebo (hazard ratio, 0.48; 95% CI, 0.30 to 0.76; $P=0.0015$ and hazard ratio, 0.37; 95% CI, 0.24 to 0.58; $P<0.0001$, respectively. These values remained significant when controlling for history of arrhythmias. Carvedilol was also found to reduce the risk of all analyzed combinations of death and arrhythmia outcomes.

Withdrawals

Among the major trials, rates of withdrawal ranged from 9.3% to 36.6%, probably indicating differences in patient characteristics. Within studies, rates of withdrawal were generally similar for the beta blocker and placebo groups, with 3 exceptions. Rates of withdrawal were greater for metoprolol tartrate in 1[70] of 5 trials, pindolol in 1 trial,[71] and propranolol in 1 trial.[67]

Table 7. Summary of results from placebo-controlled trials of beta blocker therapy following myocardial infarction

Study Year	Interventions	Duration	Number enrolled	Total mortality	Sudden death	Reinfarction	Withdrawals
Acebutolol							
Boissel 1990	A: Acebutolol B: Placebo	271 days	607	A: 5.7% (17/298) B: 11% (34/309) *P*=0.019; NNT=19	NR	A: 3% B: 3.6% NS	A: 33% B: 36.6% NS
Carvedilol							
Basu[a] 1997	A: Carvedilol B: Placebo	6 months	151 (146 analyzed)	A: 2.7% (2/75) B: 4.2% (3/71) *P*=NS	NR	A: 5.3% B: 11.3% NS	NR
CAPRICORN 2001	A: Carvedilol B: Placebo	1.3 years (mean)	1959	A: 12% (116/975) B: 15% (151/984) *P*=0.031; NNT=30	A: 5% B: 7% NS	A: 3% B: 6% *P*=0.014	A: 20% B: 18% NS
Metoprolol tartrate							
Stockholm 1983	A: Metoprolol tartrate B: Placebo	3 years	301	A: 16.2% (25/154) B: 21% (31/147) *P*=NS	A: 5.9% B: 14.3% *P*<0.05	A: 11.7% B: 21.1% *P*<0.05	A: 24.7% B: 23.8% NS
Amsterdam 1985	A: Metoprolol tartrate B: Placebo	1 year	553	A: 3.3% (9/273) B: 5.7% (16/280) *P*=NS	A: 0.3% B: 2.5% NS	A: 5.9% B: 7.1% NS	A: 32% B: 24% *P*=0.02
Belfast 1985	A: Metoprolol tartrate B: Placebo	1 year	764	A: 11.8% (49/416) B: 14.9% (52/348) *P*=NS	A: 1.9% B: 4.7% *P*<0.05	NR	A: 22.8% B: 19% NS
Lopressor 1987	A: Metoprolol tartrate B: Placebo	1.5 years	2395	A: 7.2% (86/1195) B: 7.7% (93/1200) *P*=NS	NR	NR	A: 31.9% B: 29.6% NS
Goteborg 1981	A: Metoprolol tartrate B: Placebo	2 years	1395	A: 5.7% (40/698) B: 8.9% (62/697) *P*=0.024; NNT=32	NR	A: 5% B: 7.7% NS	A: 19.1% B: 19.1% NS
Pindolol							
Australian & Swedish Study 1983	A: Pindolol B: Placebo	2 years	529	A: 17.1% (45/263) B: 17.7% (47/266) *P*=NS	A: 10.6% B: 11.7% NS	NR	A: 28.8% B: 18.8% *P*=0.0078
Propranolol							
Baber 1980	A: Propranolol B: Placebo	9 months	720	A: 7.9% (28/355) B: 7.4% (27/365) *P*=NS	NR	A: 4.8% B: 7.4% NS	A: 23% B: 24.1% NS

Study Year	Interventions	Duration	Number enrolled	Total mortality	Sudden death	Reinfarction	Withdrawals
Hansteen 1982	A: Propranolol B: Placebo	1 year	560	A: 8.9% (25/278) B: 13.1% (37/282) *P*=NS	A: 3.9% B: 8.1% *P*=0.038	A: 3.9% B: 3.5% *P*=NS	A: 25% B: 25% *P*=NS
BHAT 1982	A: Propranolol B: Placebo	25 months	3837	A: 7.2% (138/1916) B: 9.8% (188/1921) *P*=0.0045; NNT=39	NR	A: 5.4% B: 6.3% NS	A: 12.7% B: 9.3% *P*=0.0009
Timolol							
Roque 1987	A: Timolol B: Placebo	24 months	200	A: 6.7% (7/102) B: 12.2% (12/98) *P*=NS	NR	NR	NR
Norwegian Multicenter Study 1981	A: Timolol B: Placebo	17 months	1884	A: 10.4% (98/945) B: 16.2% (152/939) *P*=0.0002; NNT=18	A: 5% B: 10.1% *P*<0.0001	A: 9.3% B: 15% *P*=0.0002	A: 24% B: 23.3% NS

Abbreviations: NNT, number needed to treat; NR, not reported; NS, not significant.
[a] Primary endpoint was occurrence of combined cardiac events (cardiac death, re-infarction, unstable angina, heart failure, emergency revascularization, ventricular arrhythmia, stroke, or additional cardiovascular therapy).

Key Question 1e. For adult patients with heart failure, do beta blockers differ in efficacy or effectiveness?

Summary

The United States Food and Drug Administration approval of metoprolol succinate for mild to moderate heart failure (New York Heart Association Class II or III) is based on MERIT-HF. United States Food and Drug Administration approval of carvedilol for severe heart failure is based on COPERNICUS. Its approval for mild to moderate heart failure is based on 5 other trials, 4 of which constitute the United States Carvedilol Study plus the Australian-New Zealand Heart failure study (see Table 10). Heart failure is not a United States Food and Drug Administration-approved indication for nebivolol or bisoprolol, which is a generic drug.

The main findings from placebo-controlled trials in patients with mild to moderate heart failure are summarized in Table 8. Reductions in mortality, sudden death, cardiovascular deaths, and death due to heart failure were similar for bisoprolol, metoprolol succinate, and carvedilol. Because several carvedilol trials performed in the United States had significant mortality reductions, the evidence for carvedilol may be more relevant to a United States population. When titrated gradually in stable patients, there is no difference in tolerability among these drugs.

No studies of carvedilol phosphate (extended-release carvedilol) in patients with heart failure were identified through literature searches. Approval of the heart failure indication for carvedilol phosphate was based on pharmacokinetic and pharmacodynamic data that demonstrated bioequivalence with carvedilol.

In 2289 patients with severe heart failure (COPERNICUS), carvedilol clearly reduced mortality and the combined endpoint of mortality and hospitalizations. Carvedilol had the most direct, strongest evidence. In a post-hoc subgroup analysis of 795 patients from the good-quality MERIT-HF trial, metoprolol succinate demonstrated a mortality reduction relative to placebo similar to that for carvedilol in patients who had a similar mortality risk. This was a weaker level

of evidence than that for carvedilol, but the lack of a direct comparator and the difficulty of comparing subjects from the different trials makes it uncertain whether one of these drugs is superior in patients with the various degrees of heart failure.

Table 8. Main findings in placebo-controlled trials of patients with mild to moderate heart failure

Beta blocker	Mortality reduction	Reduction in sudden death	Reduction in progressive heart failure	Improvement in New York Heart Association class	Improvement in exercise parameters	Improvement in quality of life
Bisoprolol	Yes	Yes	Not proven	Yes	Not significant	Not significant
Carvedilol	Yes	Yes	Mixed results	Not proven	Not significant	Not significant
Carvedilol phosphate	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence
Metoprolol Succinate	Yes	Yes	Yes	Not proven	Not significant	Yes
Nebivolol	Not significant	Not significant	No evidence	Not significant	No evidence	No evidence

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

Detailed Assessment

Placebo-controlled trials

Mortality

Eight meta-analyses of placebo-controlled trials of various beta blockers in heart failure were published in the mid-1990's through 2000 (Evidence Tables 9 and 10).[73-80] In general, these meta-analyses found that beta blockers reduce mortality by about 30%, preventing 3.8 deaths per 100 patients in the first year of treatment. Nevertheless, the authors of the meta-analyses agreed that larger trials were needed before beta blockers could be recommended routinely for patients with heart failure.

The mortality benefits of seven beta blockers (atenolol, bisoprolol, bucindolol, carvedilol, metoprolol tartrate, metoprolol succinate, and nebivolol) have been evaluated in placebo-controlled trials in adults with heart failure. Five of these beta blockers (bisoprolol, bucindolol, carvedilol, metoprolol succinate, and nebivolol) have been evaluated in major trials that enrolled 1000 to almost 4000 patients (Table 9). Bisoprolol, in the Cardiac Insufficiency Bisoprolol Study II trial (CIBIS-II); carvedilol, in the Carvedilol Prospective Randomized Cumulative Survival trial COPERNICUS; and metoprolol succinate, in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure trial (MERIT-HF); but not bucindolol, in the

BEST trial, reduced total mortality (as planned primary endpoint) by approximately 35%. The nonsignificant result for bucindolol suggest that individual beta blockers may differ in their effectiveness to reduce mortality in heart failure patients (bucindolol is not available in the United States, but is included in Table 9 for comparison).

Two trials evaluated nebivolol in relation to all-cause mortality or cardiovascular hospitalization, New York Heart Association class reduction, and quality of life.[72, 98] Mortality was included as a secondary outcome measure in both of these trials. The SENIORS study of 2128 elderly patients included patients with a history of heart failure (hospital admission for heart failure during the past 12 months or an ejection fraction of ≤35%). The mean age of patients was 76 and the mean ejection fraction was 36%. SENIORS included some patients who were similar to those included in the other trials, but a majority of patients who were older, had little or no left ventricular dysfunction, and had a lower risk of death. Thirty-five percent had an ejection fraction of >35%, and the annualized placebo mortality rate was 10%. When compared with placebo, nebivolol reduced the composite risk of all-cause mortality or cardiovascular hospital admission (31.1% compared with 35.3%; hazard ratio, 0.86; 95% CI, 0.74 to 0.99)[72] but had nonsignificant effects on the individual variables examined as secondary outcomes. A subgroup analysis demonstrated that the risk of mortality or hospitalization for patients with a left ventricular ejection fraction of either ≤35 or >35% was not significantly different (*P*=0.42). In a post-hoc analysis, researchers identified the subgroup of patients most similar to the other major outcome trials. In this subgroup, defined as patients of less than 75.2 years with an ejection fraction ≤35% (n=342 for nebivolol and n=342 for placebo), findings were similar to that seen with metoprolol-controlled release, bisoprolol, and carvedilol (hazard ratio for the primary composite variable was 0.73; 95% CI, 0.56 to 0.96). For all-cause mortality alone, the hazard ratio was 0.62 (95% CI, 0.43 to 0.89). It should be noted, however, that the older and healthier patients (those with less severe left ventricular distinction) in the SENIORS trial were not evaluated in a subgroup analysis, and therefore it is unknown as to whether nebivolol would be effective in this population.

In the ENECA trial, nebivolol was examined for 8 months as an add on therapy in 260 elderly patients with chronic heart failure.[98] Total mortality, included as a secondary outcome measure, was not significant when compared to placebo (survival rate 67.47% compared with 62.89; *P*=0.696). Results of the ENECA study are discussed below in relation to the study's primary outcome measures of New York Heart Association class reduction and quality of life.

Table 10 summarizes 16 placebo-controlled trials (including those in Table 9) that enrolled over 100 patients and met our other inclusion criteria (Evidence Tables 9 and 10). These trials evaluated atenolol 50 to 100 mg,[81] bisoprolol 5 to 10 mg,[82, 83] carvedilol 50 to 100 mg,[84-93] metoprolol tartrate 100 to 150 mg,[94, 95] metoprolol succinate (CR) 12.5 to 25 mg,[96, 97] and nebivolol 10 mg.[72, 98]

Relation of mortality reduction to severity of heart failure

The trials in Table 9 leave no doubt that, in certain patients, bisoprolol, carvedilol, and metoprolol succinate reduce mortality. The main unresolved questions are 1) whether any of these agents is superior to the others in patients with mild to moderate failure, and 2) whether, in patients with severe failure, bisoprolol or metoprolol succinate are equivalent to carvedilol, which is the only drug that has a United States Food and Drug Administration indication in this group.

Many authors have used the placebo group mortality rates to make inferences about the baseline severity of patients in the various trials. However, several factors, including New York Heart Association Class, ejection fraction, blood pressure, lifestyle, and the quality of medical care influence mortality in patients with heart failure. For this reason it has proven difficult to judge the relative severity of illness among the major trials listed in Table 9.

MERIT-HF provides interesting data about the relationship of New York Heart Association class and ejection fraction:

MERIT-HF Subgroups	EF<25%	EF>25%
New York Heart Association Class II	707 ("A")	928
New York Heart Association Class III-IV	795	1561 ("D")

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

The 4 United States Carvedilol trials and the Australian-New Zealand trial demonstrated that in patients with New York Heart Association Class II to IV heart failure, carvedilol reduced mortality. As shown in Table 10, the severity of heart failure of patients in these trials varied substantially, suggesting that carvedilol was effective across a broad spectrum of heart failure patients. These trials used an active drug run-in period during which patients who could not tolerate a small dose of carvedilol, were noncompliant, or died were excluded prior to randomization. For this reason, the mortality reductions and rates of withdrawal and adverse events are not comparable to those of other trials. In Table 10 we summarize mortality results of these and other trials after adjusting the number of deaths in the carvedilol group by adding in deaths that occurred during the run-in period.

COPERNICUS was a well-designed, well-conducted placebo-controlled trial of carvedilol conducted in 334 Centers. Of 2289 subjects randomized, 627 were recruited from the United States and Canada; the rest were recruited in Europe (including Russia), the United States, Canada, Israel, Australia, South Africa, Argentina, and Mexico. It is difficult to compare the COPERNICUS subjects to those of other trials because COPERNICUS did not report New York Heart Association Class or exercise capacity, which were inclusion criteria in the other trials. COPERNICUS was intended to recruit a more severely ill population than the United States carvedilol trials. COPERNICUS subjects had higher mortality than 3 of the 4 trials that make up the United States Carvedilol Trial.

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

MERIT-HF**,** conducted in the United States and Europe, recruited stable subjects with mild to severe heart failure. Although it had a significant proportion of subjects with New York Heart Association Class II symptoms, the mean ejection fraction was similar to that of CIBIS-II. MERIT-HF was well-designed and well-conducted and had clear-cut overall reductions in

overall mortality, death from cardiac causes, sudden death, and heart transplantation, as well as a reduction in all-cause hospitalization (RR, 0.84; CI, 0.76-0.95).

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

The applicability of the results of any trial to a United States population is a major issue in all of these trials, because heart failure survival depends on other aspects of care. The United States Food and Drug Administration review of the MERIT-HF trial found "a strong suggestion of a treatment-by-region (United States compared with Europe) interaction with respect to mortality." MERIT-HF had 1071 United States subjects and 2920 European subjects. The placebo group mortality was higher in Europe (168/1462; 11.5%) than in the United States (49/539; 9.1%). Metoprolol succinate reduced all-cause mortality in Europe (hazard ratio, 0.55; *P*=0.0001) but not in the United States subgroup (hazard ratio, 1.05; *P*=0.7961). The lack of any trend toward reduced mortality in the United States subgroup is of concern.

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

CIBIS-II was a well-conducted multicenter European study designed to recruit stable subjects with moderate to severe heart failure (New York Heart Association Class III-IV).[83] Most patients were New York Heart Association Class III. The annual placebo mortality rate was 13%, which is higher than the rate projected by the CIBIS-II investigators based on the results of CIBIS-I. Nevertheless, this mortality rate and the average ejection fraction of 27% are closer to those of MERIT-HF, which recruited mostly Class II and III patients, than to those of COPERNICUS, which is thought to have recruited New York Heart Association Class III and IV patients.

In CIBIS-II, 752 subjects were New York Heart Association Class III or IV and had an ejection fraction less than 25%, but the results in this subgroup have not been reported completely, although the hazard ratio was said to be 0.78 (0.56 to 1.07). For the Class III patients, annual placebo group mortality was about 13%; over the entire study (averaging 1.3 years of followup), the number needed to treat to prevent 1 death was about 19. For the Class IV patients, the annual placebo mortality was about 18%, and the number needed to treat to prevent 1 death over 1.3 years was about 15. The mortality reduction for Class IV patients was of borderline statistical significance; when measured as a difference of probabilities, the confidence interval was 0.0005 to 0.127 (from that is, from 0 to 12.7 lives saved for every 100 patients).

Table 9. Comparison of major beta blocker trials in heart failure

Trial	Drug and target dose	Ejection fraction criteria (mean)	New York Heart Association class	Number of subjects	Annual placebo mortality	Mortality reduction	Withdrawal rate for active drug group[a]
CIBIS-II	Bisoprolol 10mg once daily	<35% (0.27)	III (81%) IV (19%)	2647	13%	34%	15%
MERIT-HF	Metoprolol CR 200mg once daily	<40% (0.28)	II (41%) III (56%) IV (3.6%)	3991	11%	34%	14%
BEST	Bucindolol 100mg twice daily	<35%	III-IV	2708	17%	10%[b]	23%
COPERNICUS	Carvedilol 25mg twice daily	<25% (0.20)	NR	2289	19%	35%	12.6%
US Carvedilol[c]	Carvedilol 25mg twice daily[d]	≤35%	II-IV	1094	12%	65%[e]	11%[f]
SENIORS (age ≥ 70 yrs)	Nebivolol 10 mg daily	≤35%[g] (0.36)	I 2.85% II 56.4% III 38.7% IV 2.05%	2128	10%	13%[b,h]	26.7%

[a] All values were not different from the placebo group except for COPERNICUS (placebo withdrawal rate 15.9%, *P*=0.0026).
[b] Not significant.
[c] Planned analysis of pooled results of 4 independent, double-blind placebo-controlled trials.
[d] Dosage target was 50 mg twice daily in patients whose weight was 85 kg or more.
[e] Mortality was not the primary endpoint, and the estimated mortality reduction was inflated because of the use of an active-drug run-in period before randomization. Withdrawal rates are also affected by use of an active-drug run-in phase. See Table 10.
[f] Study stopped early on recommendation of Data and Safety Monitoring Board based on finding of a significant effect of carvedilol on survival. When program was terminated, more patients were receiving or had completed treatment with carvedilol than placebo (89% compared with 83%, *P*=0.002).
[g] The SENIORS trial included patients with at least one of the following: documented hospital admission within previous 12 months with discharge diagnosis of congestive heart failure or documented left ventricular ejection fraction ≤ 35% within the previous 6 months.
[h] The composite of all-cause mortality or cardiovascular hospital admission was the primary endpoint and all-cause mortality was measured as a secondary outcome.

Table 10. Patient characteristics and annualized mortality rates adjusted for active drug run-in periods in trials of beta blockers for heart failure

Trial	Drug	Primary endpoint	New York Heart Association class	Entry criterion for ejection fraction (average)	Mortality in placebo group (per year)	Mortality in treatment group (per year)	Sample size
Sturm 2000	Atenolol	Combined worsening heart failure or death	II-III	≤25% (17%)	5.0%	8.0%	100
CIBIS	Bisoprolol	Mortality	III-IV	<40% (0.25%)	10.4%	8.3%	641
CIBIS-II	Bisoprolol	Mortality	III-IV	<35% (0.275%)	13.2%	9.0%	2647
Bristow[a]	Carvedilol	Exercise tolerance	II-IV	≤35% (0.23%)	33.8%	10.9%	345
Packer[a]	Carvedilol	Exercise tolerance	II-IV	≤35% (0.22%)	14.0%	15.3%	278
Colucci[a]	Carvedilol	Progression of heart failure	II-III	≤35% (0.23%)	6.4%	2.2%	366
Cohn[a]	Carvedilol	Quality of life	III-IV	≤35% (0.22%)	8.6%	4.3%	105
ANZ[a]	Carvedilol	Exercise tolerance, LVEF	I-III	<45% (0.29%)	7.9%	7.0%	415
Christmas	Carvedilol	LVEF	I-III	<40% (0.29%)	4.9%	6.9%	387
Copernicus	Carvedilol	Mortality	NR	< 25% (0.20%)	18.5%	11.4%	2289
MUCHA (Japanese)	Carvedilol	CHF global assessment	II-III	≤40% (30%)	NR	NR	190
Cice 2003 (dialysis)	Carvedilol	LVEF, NYHA	II-III	<35% (0.26%)	36.6%	25.8%	114
MDC	Metoprolol	Mortality+ morbidity	I-IV	<40% (0.22%)	11.0%	12.0%	383
Waagstein 2003	Metoprolol	NR	II-III	<40% (28.5%)	9.1%	7.6%	165
MERIT	Metoprolol CR	Mortality	II-IV	<40% (0.28%)	10.8%	7.3%	3991
MERIT high-risk subgroup	Metoprolol CR	Mortality	III-IV	<25% (0.19%)	18.2%	11.3%	795
RESOLVD[a]	Metoprolol CR	Exercise tolerance, neurohumoral parameters	I-IV	<40% (0.28%)	16.0%	8.4%	768

Trial	Drug	Primary endpoint	New York Heart Association class	Entry criterion for ejection fraction (average)	Mortality in placebo group (per year)	Mortality in treatment group (per year)	Sample size
Edes 2005 ENECA	Nebivolol	LVEF	II-IV	≤35% (0.259%)	5.9%	5.6%	260
Flather 2005 SENIORS	Nebivolol	Mortality and cardiovascular hospital admission	I-IV	≤35% (0.36%)	10.3%	9.0%	2128

Abbreviations: CHF, congestive heart failure; LVEF, left ventricular ejection fraction; NR, not reported; NYHA, New York Heart Association classification.
[a] 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.
[b] New York Heart Association Class not reported, but all patients had symptoms on minimal exertion or at rest.

In addition to all-cause mortality, sudden death, and cardiovascular mortality, endpoints in beta blocker trials include symptoms, progression of disease, need for hospitalization, and need for (or time to) transplantation. The major placebo-controlled trials and many smaller trials evaluated these outcomes in Table 11.

New York Heart Association class

The effect on New York Heart Association class rating was inconsistently reported. The CIBIS trial found that significantly more patients taking bisoprolol improved by at least 1 New York Heart Association class (21% compared with 15%; P=0.03) but there was no differences in patients that deteriorated by at least 1 class (13% compared with 11%). Results were mixed for carvedilol. Three trials suggest carvedilol is superior to placebo in improving the overall New York Heart Association class distribution.[85, 86, 91] This includes the MUCHA trial of Japanese patients with heart failure.[91] In 3 other trials, including a subset of dialysis patients with heart failure,[92] carvedilol had no effect.[84, 88, 92] Metoprolol tartrate did not significantly improve the New York Heart Association class in either of 2 trials. In the MERIT-HF trial, metoprolol CR increased the proportion of patients that improved by at least 1 New York Heart Association class overall (28.6% compared with 25.8%; P=0.003). A post-hoc analysis found the same effect in a subgroup of patients with baseline New York Heart Association class III-IV and left ventricular ejection fraction < 25% (46.2% compared with 36.7%; P=0.0031).[99] By contrast, carvedilol did not reduce progression of heart failure in COPERNICUS. In the ENECA study of 260 patients with chronic heart failure treated with nebivolol as an add on therapy, compared with placebo (27%), slightly fewer elderly patients (≥65 years) with heart failure taking nebivolol at an average dose of 7.4 mg improved by at least 1 New York Heart Association class overall (26%).[98]

Exercise capacity

The carvedilol trials[84-86, 88] 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 2 placebo-controlled trials of metoprolol.

Quality of life

Quality of life in heart failure patients was most commonly assessed using the Minnesota Living with Heart Failure Questionnaire. Overall, placebo-controlled trials provided limited evidence that beta blockers significantly improve quality of life in heart failure patients. Carvedilol was consistently associated with nonsignificant improvements in quality of life in patients with mild to moderate[84-86] or severe[87] heart failure.

In the MDC trial, patients taking immediate release metoprolol experienced significantly greater improvements in quality of life than those taking placebo, however, no data were provided and it is unclear as to which measurement instrument was used. For controlled-release metoprolol, results of quality-of-life assessments were mixed across 2 trials.[97, 100] In the ENECA study, reductions in Minnesota Living with Heart Failure Questionnaire scores were similar for nebivolol compared with placebo.[98]

Table 11. Outcomes in placebo-controlled trials of beta blockers for heart failure

Study Year	Beta blocker	All-cause mortality rates *P* value NNT	Sudden death rates *P* value NNT	Death due to heart failure *P* value NNT	New York Heart Association class improvement	Exercise capacity	Quality of life
Sturm 2002	Atenolol	10% vs. 16% NS	NR	16% vs. 39% NS	NR	NR	NR
Anonymous 1994 CIBIS	Bisoprolol	16.6% vs. 20.9% NS	4.7% vs. 5.3% NS	NR	Improvement (≥1 class) 21% vs. 15%; *P*=0.03	NR	NR
Anonymous 1999 CIBIS-II	Bisoprolol	12% vs. 17% *P*<0.0001 NNT=19	4% vs. 6% *P*=0.0011 NNT=38	NR	NR	NR	NR
Bristow 1996 US Carvedilol Heart Failure Study Group: MOCHA	Carvedilol	4.6% vs. 15.5% *P*<0.001 NNT=9	2.3% vs. 7.1% *P*=0.035 NNT=21	1.1% vs. 7.1% *P*=0.003 NNT=17	No effect (data NR)	6-minute walk test/9-minute self-activated treadmill testing: no effect (data NR)	Mean change in MLHFQ: no effect
Packer 1996 US Carvedilol Heart Failure Study Group: PRECISE	Carvedilol	4.5% vs. 7.6% NS	NR	NR	Improvement: 21.5% vs. 6.9%; *P*=0.014	Mean increase in 6-minute walk test distance (m): 17 vs. 6 (NS) 9-minute treadmill test distance: no effect	MLHFQ: no effect (original data NR)
Colucci 1996 US Carvedilol Heart Failure Study Group:	Carvedilol	0.9% vs. 4% NS	NR	Heart failure progression (deaths+hospitalizations + need for	Improvement: 12% vs. 9%; *P*=0.003	9-minute self-minute treadmill test: car=pla (data NR)	Mean change in MLHFQ: (−4.9) vs. (−2.4)

Study Year	Beta blocker	All-cause mortality rates *P* value NNT	Sudden death rates *P* value NNT	Death due to heart failure *P* value NNT	New York Heart Association class improvement	Exercise capacity	Quality of life
Mild				more medications) 25/232(11%) 28/134(20.9 %) *P*=0.008 NNT=10			NS
Cohn 1997 US Carvedilol Heart Failure Study Group	Carvedilol	2.8% vs. 5.7% NS	NR	NR	% decrease in Class III/IV patients: 20% vs. 9.5%; NS	Mean increase in 6-minute walk test distance (m): 19.0 vs. 28.4 (NS)	Mean improvement in MLHFQ: 11.6 vs. 8.8 (NS)
Anonymous 1997 Australia/New Zealand Heart Failure Research Collaborative Group	Carvedilol	9.6% vs. 12.6% NS	4.8% vs. 5.3% NS	6.7% vs. 7.2% NS	Improved: 26% vs. 28%; NS	Treadmill exercise duration/6-minute walk distance: car=pla (data NR)	NR
Packer 2001 COPERNICUS	Carvedilol	11.2% vs. 16.8% *P*=0.00013 NNT=19	6.1% vs. 3.9% *P*=0.016 NNT=46	NR	NR	NR	NR
Cleland 2003 CHRISTMAS	Carvedilol	4.3% vs. 3.2% NS	NR	NR	NR	Exercise time (method NR) (seconds): 405 vs. 427 NS	NR
Hori 2004 MUCHA (Japanese patients)	Carvedilol	NR	NR	NR	Improved 5 mg= 80.9% vs. 48.9%; *P*<0.001 20 mg= 70.8% vs. 48.9%; *P*<0.05	NR	NR
Cice 2003 (Dialysis patients)	Carvedilol	51.7% vs. 73.2% *P*<0.01 NNT=5	3.4% vs. 10.6% NS	NR	Class I: 8.3% vs. 0% Class II: 66.7% vs. 33.4% Class III: 25% vs. 44.4% Class IV: 0% vs. 22.2% All NS	NR	NR
Waagstein 1993 MDC	Metoprolol tartrate	11.8% vs. 11.1% NS	9.3% vs. 6.3% NS	2.6% vs. 2.6% NS	Improvement: effective (data NR)	Mean increase in exercise capacity (sec): 76 vs. 15; *P*=0.046	met>pla *P*=0.01 (original data NR)

Study Year	Beta blocker	All-cause mortality rates *P* value NNT	Sudden death rates *P* value NNT	Death due to heart failure *P* value NNT	New York Heart Association class improvement	Exercise capacity	Quality of life
Waagstein 2003	Metoprolol tartrate	4.6% vs. 3.8% NS	NR	NR	Improved: 42% vs. 33% NS	Bicycle test: met=pla (data NR)	NR
Anonymous 1999 MERIT-HF	Metoprolol succinate	7.3% vs. 10.8% *P*=0.00009 NNT=29	3.9% vs. 6.5% *P*=0.0002 NNT=39	1.5% vs. 2.9% *P*=0.0023 NNT=72	NR	NR	McMaster Overall Treatment Evaluation: met>pla (data NR)
Anonymous 2000 RESOLVD	Metoprolol succinate	3.7% vs. 8.1% NS	NR	0.5% vs. 1.4% NS	met CR=pla (data NR)	6-minute walk test change (meters) −1 vs. −3	met CR=pla (data NR)
Anonymous 1997 Australia/ New Zealand Heart Failure Research Collaborative Group	Carvedilol	9.6% vs. 12.6% NS	4.8% vs. 5.3% NS	6.7% vs. 7.2% NS	Improvement: 26% vs. 28% NS	Treadmill exercise duration/6-minute walk distance: carvedilol= pla (data NR)	NR
Edes 2005 ENECA	Nebivolol	NR	NR	NR	Improvement: (≥1 class) 26.1% vs. 29.3%; NS	NR	Mean decrease 9.13 vs. 11.01 NS points
Flather 2005 SENIORS	Nebivolol	15.8% vs. 18.1% (NS)	36% vs. 48% (*P*=NR)	NR	NR	NR	NR

Abbreviations: MLHFQ=Minnesota Living with Heart Failure Questionnaire; NNT, number needed to treat; NR, not reported; NS, not significant.
[a] Odds ratios (95% CI) adopted from previously published bayesian meta-analysis (Brophy, 2001).

Head-to-head trials

There are no direct comparator trials comparing 2 or more of the drugs proven to reduce mortality (bisoprolol, carvedilol, and sustained release metoprolol succinate). We are aware of 1 trial in process that compares the tolerance of bisoprolol and carvedilol in elderly patients (≥65 years) with systolic or diastolic chronic heart failure.[101]

Otherwise, we found 6 fair-quality, head-to-head trials comparing immediate-release metoprolol tartrate to carvedilol in patients with heart failure and 1 trial that compared nebivolol to carvedilol (see Evidence Tables 11 and 12 for characteristics and quality assessments and Evidence Table 13 for outcomes).[102-107] These trials recruited stable patients with Class II-IV (mainly II and III) heart failure, most of whom took ACE inhibitors and diuretics.

Only 1 trial (COMET) was adequately powered to evaluate mortality and cardiovascular events (N=3029). The target dose of carvedilol was 25 mg twice a day and the target for metoprolol tartrate was 50 mg twice a day. The patients were mostly (79.8%) men, with a mean age of 62 years and a mean ejection fraction of 26% on optimal treatment with ACE inhibitors and diuretics for New York Heart Association class II-IV heart failure.

When COMET was designed, extended-release metoprolol was not yet available, and immediate-release metoprolol was a logical comparator because in the MDC trial metoprolol tartrate was clearly effective, even though it did not change mortality. Specifically, metoprolol tartrate improved ejection fraction, left ventricular end diastolic pressure, and exercise time and prevented clinical deterioration, reducing the need for transplantation by almost 90% during the followup period.[94]

Mortality

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

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

Other outcomes

Carvedilol compared with metoprolol. Evidence on numerous secondary outcomes from the COMET trial have been published.[108, 109, 110] Carvedilol was superior to immediate-release metoprolol in reducing rates of cardiovascular death, sudden death, stroke, cardiovascular events, and unstable angina, and similar to immediate-release metoprolol in reducing death due to circulatory failure and other cardiovascular deaths, as well as in reducing days lost due to impaired well being.[108, 109]

Greater reductions in rates of first hospitalization due to potential complication of heart failure treatment were more associated with immediate-release metoprolol than with carvedilol. Both interventions had similar effects on rates of overall hospitalization and cause-specific hospitalizations, with 1 exception.[108, 109] Rates of non-cardiovascular death, worsening heart failure, change in New York Heart Association classification, and medication withdrawal were similar for carvedilol and immediate release metoprolol.[108]

With regard to combined endpoints, carvedilol was superior in reducing rates of fatal or nonfatal myocardial infarction and the combination of cardiovascular death, heart transplantation, hospitalization for nonfatal acute myocardial infarction, or worsening heart failure and was similar to immediate-release metoprolol in reducing the combined rate of all-cause mortality and cardiovascular hospitalizations.[108] Another combined endpoint of days of life

lost due to death, hospitalization, impaired well-being, or need to increase diuretic use (deemed the 'patient journey') found carvedilol to be superior to metoprolol over 4 years when compared to baseline composite scores (P=0.0068).[109] It is important to note however, that this combined endpoint considered all factors to be equal; days lost due to death were considered equivalent to days lost due to hospitalization.

In the older trials, there was a nonsignificant trend favoring carvedilol over immediate-release metoprolol. Carvedilol and immediate release metoprolol (124+/–55 mg daily) had similar effects on quality of life, but metoprolol improved exercise capacity more. There were no differences between the carvedilol and metoprolol groups in quality of life.

Nebivolol compared with carvedilol. One trial of 70 patients with heart failure, a left ventricular ejection fraction of 40% or lower, and a New York Heart Association functional class of II or III, compared treatment with mean doses of carvedilol 44 mg and a lower than recommended target dose of nebivolol (4.4 mg) over 6 months. Compared with baseline, carvedilol and nebivolol demonstrated slight improvements in New York Heart Association functional class and the 6-minute walk test.[111]

Key Question 1f. For adult patients with atrial arrhythmia, do beta blockers differ in efficacy or effectiveness?

Several beta blockers have been used to reduce the heart rate in patients with atrial tachyarrhythmias and to prevent relapse into atrial fibrillation or flutter. A recent good-quality systematic review examined 12 studies of rate control in patients with chronic atrial fibrillation.[112] Atenolol, nadolol, and pindolol were effective in controlling the ventricular rate, while labetalol was no more efficacious than placebo.

We found 1 head-to-head trial comparing bisoprolol 10 mg and carvedilol 50 mg in patients subjected to cardioversion of persistent atrial fibrillation (> 7 days).[113] This fair-quality, 12-month trial enrolled 90 patients (mean age, 65.5; 82% male) (Evidence Tables 14 and 15). Similar proportions of patients relapsed into atrial fibrillation during follow-up in the bisoprolol and carvedilol groups (53.4% compared with 43.6%; P=NS).

Two placebo-controlled trials evaluated beta blockers in patients with persistent atrial fibrillation.[114-116] One placebo-controlled trial found that metoprolol CR/XL 100 to 200 mg was effective in preventing relapse of atrial fibrillation/flutter after cardioversion (Evidence Table 14).[114, 115] 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% compared with 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% compared with 0).

The other study examined the effects of carvedilol in managing patients with concomitant atrial fibrillation and heart failure.[116] This study was divided into 2 phases. The first phase involved a 4-month comparison of digoxin alone to the combination of digoxin and carvedilol and the second phase involved a 6-month comparison of digoxin alone to carvedilol alone. Forty-seven patients (mean age, 68.5; 61.7% male) with atrial fibrillation (mean duration, 131.5 weeks) and heart failure (predominantly New York Heart Association class II-III; mean left ventricular ejection fraction, 24.1%) were enrolled in this fair-quality study. When added to digoxin,

carvedilol significantly lowered the 24-hour ventricular rate (65.2 compared with 74.9 bpm; $P \leq 0.0001$) and improved mean left ventricular ejection fraction scores (30.6% compared with 26%; $P=0.048$) and severity of symptoms/functional capacity on a 33-point scale (6 compared with 8; $P=0.039$). There were no differences between monotherapies with either carvedilol or digoxin in the second phase, however.

Key Question 1g. For adult patients with migraine, do beta blockers differ in efficacy or effectiveness?

Summary

Six head-to-head trials show no difference in efficacy in reduction of attack frequency, severity, headache days or acute tablet consumption, or in improvement in any subjective or composite index in any of the comparisons made (atenolol or metoprolol durules or metoprolol or timolol compared with propranolol or nebivolol compared with metoprolol). Results from placebo-controlled trials on similar outcome measures generally supports those for atenolol, metoprolol durules, and propranolol seen in head-to-head trials. Placebo-controlled trial results also show that bisoprolol had a significant effect on attack frequency reduction and that pindolol had no appreciable effects.

Detailed Assessment

Head-to-head trials

We found 6 fair-quality[117-122] head-to-head trials of beta blockers for the treatment of migraine (Table 12). One study comparing bisoprolol and metoprolol appears to have been published twice.[123, 124] 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 6 included trials compared propranolol 160 mg to atenolol 100 mg,[120] slow release metoprolol (durules) 200 mg daily,[118] immediate release metoprolol 200 mg daily,[117] timolol 20 mg,[121, 122] propranolol 80 mg to metoprolol 100 mg daily,[119] and nebivolol 5 mg to metoprolol 142.5 mg.[125] All 6 trials were conducted outside of the United States, were relatively short-term in duration (12 to 20 weeks), and were small (30 to 96 patients). Most patients had common migraine per Ad Hoc Committee and World Federation of Neurology Research Group guidelines (83 to 93%) and migraine without aura per International Headache Society (92.8%). These patients have mean ages of 33.8 to 42.3, are 68.6% to 88.9% female, and have a history of migraine frequency of greater than 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 13 below. Analysis of variance was used to assess comparative efficacy of metoprolol 200 mg and propranolol 160 mg in 1 trial.[117]

Attack frequency

Metoprolol durules 200 mg, metoprolol tartrate 200 mg, and timolol 20 mg all were similar to propranolol 160 mg in decreasing 4-week attack frequency rates.[117-119, 121, 122] A recent, well-conducted systematic review comparing propanol to other beta blockers found that there was little difference between propanol and the comparators (metoprolol, nadolol, timolol) in reducing attack frequency (pooled standard mean difference, −0.01; 95% CI, −0.24 to +0.22) based on data from 4 crossover trials.[126] In a study comparing nebivolol to metoprolol there were no statistically significant differences in attack frequency, although nebivolol fared better with regards to tolerability.[125]

Migraine days

There were differences across trials in methods of assessment of this parameter. When the total number of headache days recorded over 42 days across all 28 patients analyzed was considered in the Stensrud trial, no difference between atenolol and propranolol treatment was found. Metoprolol durules and metoprolol tartrate reduced number of migraine days at rates similar to propranolol across 3 trials.[117-119] In a comparison of nebivolol to metoprolol over an 18-week period, no differences were found.[125]

Severity

Severity rating methods differed across trials. Metoprolol durules, metoprolol tartrate, and timolol all were similar to propranolol at comparable doses in decreasing attack severity.[118, 119, 121, 122] As measured using a 100-mm visual analog scale, headache severity at endpoint was similar for nebivolol and metoprolol (50 compared with 54 points).[125]

Tablet consumption

There were no differences in reduction of acute medication (analgesics, ergots) for metoprolol durules or metoprolol tartrate and propranolol.[118, 119, 121, 122] Moreover, the number of patients using pain medication at endpoint were similar between nebivolol and metoprolol.[125]

Subjective assessment

Patients in 2 trials[118, 119] were asked to make a subjective assessment of therapeutic improvement using descriptions of marked, moderate, slight, and unchanged or worse. There were no differences found between slow release metoprolol (durules) and propranolol (76% compared with 63%) or between low doses of immediate release metoprolol or propranolol (63% compared with 64%) in rates of decreased frequency of mean or median attacks per month.

Miscellaneous

Two trials[120-122] measured treatment efficacy using a composite score (attack frequency x severity x duration) and found no differences between atenolol or timolol and propranolol. The Gerber et al. trial included an analysis of duration of migraine in hours and didn't find any difference between metoprolol and propranolol in percent of patients qualifying as responder type A or B for decrease on this variable.

Table 12. Outcomes in head-to-head trials of migraine patients

Outcomes	Attack frequency/4 weeks (% decrease)	Headache days	Severity (% reduction)	Tablet consumption	Subjective (% patients regarding effect as "marked" or "moderate")	Miscellaneous
Stensrud 1980 Atenolol 100 mg vs. propranolol 160 mg N=28	NR	247 vs. 257	NR	NR	NR	Headache Index1 (mean): 410 vs. 437
Kangasniemi 1984 Metoprolol-d 200 mg vs. propranolol 160 mg N=35	43.4% vs. 43.4%	45.6% vs. 43.8%	21.8% vs. 29.8%	45.3% vs. 45.3%	76% vs. 63%	NR
Olsson 1984 Metoprolol 100 mg vs. propranolol 80 mg N=53	NR	25.4% vs. 32.8%	21.8% vs. 29.8%	Ergotamine: 47% vs. 43.1% Analgesic: 16.5% vs. 37.4%	63% vs. 64%	NR
Gerber 1991 Metoprolol 200 mg vs. propranolol 160 mg Metoprolol=22 Propranolol=19	No differences (ANOVA)	No differences (ANOVA)	No differences (ANOVA)	Ergotamine: No differences (ANOVA)	NR	Percent reduction in duration (hours): No differences (ANOVA)
Schellenberg 2008 Metoprolol 142.5 mg vs. nebivolol 5 mg N=30	61.7% vs. 51.5%	NR	54% vs. 50% Endpoint Means	77% vs. 67%	NR	NR

Abbreviation: NR, not reported.
Headache Index 1: attack frequency x severity x duration
Headache Index 2: attack frequency x severity

Placebo-controlled trials

We found 19 fair-quality, placebo-controlled trials (see Evidence Tables 16 and 17) of atenolol 100 mg,[127] bisoprolol 5 mg or 10 mg,[128] metoprolol slow release (durules) 200 mg,[129, 130 131] pindolol 7.5 mg to 15 mg,[132, 133] propranolol immediate release 80 mg to 240 mg,[134-142] and long-acting propranolol 160 mg.[143, 144] One trial[145] did not report propranolol dosage and will be discussed separately.

All but 2[136, 145] of these trials were conducted outside of the United States A crossover design was used in 12 trials, while the other 6 compared parallel groups. All but 2 trials reported allowing the use of various concomitant medications 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 1 to 2 year history of common or classic migraine (Ad Hoc Committee), generally occurring at an average frequency of 3 per week. One trial included only

patients with classic migraine.[130] Patient characteristics reflected the target migraine population, with mean ages in the range of 37 to 39 and gender predominantly female (>75%). Sample sizes ranged from 24 to 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 was consistent with head-to-head trial data for atenolol 100 mg and slow-release metoprolol (durules) 200 mg, but added no additional evidence that is not reported in the head-to-head trials. Propranolol 80 mg and 160 mg, as discussed above, added information regarding efficacy of bisoprolol and pindolol. An exception was found in 1 of the 10 fair-quality trials of propranolol[137] 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 4 weeks of treatment (42.3% compared with 30.9%) or in reducing the mean duration of migraine in hours per month (34.4% compared with 13.7%).

Bisoprolol

The results of 1 placebo-controlled trial of 12 week's duration and involving 226 patients[128] indicated that both bisoprolol 5 and 10 mg daily had a significant ($P<0.05$) effect in reducing attack frequency (39% for both bisoprolol doses compared with 22% for placebo). Neither dose of bisoprolol showed any obvious influence on reducing attack duration or severity.

Pindolol

The results of 2 placebo-controlled trials of pindolol 7.5 to 15 mg daily[132, 133] in a total of 58 patients with predominantly common migraine showed no obvious advantage of this nonselective beta blocker in reducing averages per 4 weeks in headache frequency, headache index, or duration of attacks.

Twelve other placebo-controlled trials of beta blockers were found.[121, 122, 146-155] 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%, which were not discussed here.

We found 1 meta-analysis[156] 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 3 head-to-head and 12 placebo-controlled trials from this meta-analysis in our report.

Key Question 1h. For adult patients with bleeding esophageal varices, do beta blockers differ in efficacy or effectiveness?

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 1 trial of nadolol and 8 small placebo-controlled trials of immediate release and 2 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.

Detailed Assessment

Head-to-head trials

We found 1 head-to-head trial of beta blockers for the treatment of bleeding esophageal varices.[157] This trial compared the efficacy of propranolol 40 to 160 mg daily, a nonselective beta blocker, atenolol 100 mg daily, a selective beta blocker, and placebo in cirrhotic patients. The results of this trial are summarized in Evidence Tables 18 and 19. 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 1 year for percentage of patients with fatal/nonfatal rebleeding episodes (2.4% compared with 3.1%) or total deaths (12% compared with 10%) or deaths due to rebleeding (3.1% compared with 3.1%), liver failure (6.2% compared with 3.1%) or other unrelated causes (3.1% compared with 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% compared with abstainers 0%) and atenolol (drinkers 43% compared with 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.

Other-controlled trials

We found numerous fair-quality, placebo-controlled trials of nadolol[158] and propranolol[159-166] for the secondary prevention of bleeding esophageal varices secondary to cirrhosis and schistosomiasis.[167] Results are summarized in Evidence Tables 18 and 19. These trials were all conducted outside of the United States, enrolled samples of 12 to 84 patients, and ranged from 3 months to 2 years in duration. Mean ages ranged from 43 to 60 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 3 of the trials.[159, 162, 166]

Variceal rebleeding rates

As shown in Table 13 below, compared to placebo, no differences in effect on variceal rebleeding rates were shown for immediate release propranolol in 2 early treatment trials. [159, 166] A significant difference between the effects of slow release propranolol and placebo was found in a third early treatment trial (20% compared with 75%; $P<0.05$).[162] For trials of later (≥14 days)[161, 163, 164, 168] and unspecified[160, 169] treatment initiation, atenolol was equivalent to placebo (31% compared with 24%), nadolol was superior (25% compared with 71%; $P<0.05$), results of immediate release propranolol trials were mixed, and long-acting propranolol was superior (2% compared with 20%; $P<0.02$).

Table 13. Variceal rebleeding rates

Trial	Interventions	Sample size	Treatment initiation interval	Rebleeding rates
Early intervention				
Burroughs 1983	Propranolol vs. placebo	N=48	48 hours	46.1% vs. 50%
Villeneuve, 1986	Propranolol vs. placebo	N=79	6-72 hours	76.2% vs. 81.2%
Jensen 1989	Propranolol SR vs. placebo	N=31	24 hours	20% vs. 75%; *P*<0.05
Late intervention				
Colombo 1989	Atenolol vs. placebo	N=94	≥ 15 days	31% vs. 51%
Gatta 1987	Nadolol vs. placebo	N=24	15-40 days	25% vs. 71%; *P*<0.05
Colombo 1989	Propranolol vs. placebo	N=94	≥ 15 days	24% vs. 51%; *P*<0.01
Lebrec 1981a	Propranolol vs. placebo	N=24	10-15 days	0 vs. 41.7%; *P*=0.037
Lebrec 1981b	Propranolol vs. placebo	N=74	2 weeks	15.8% vs. 63.9%; *P*<0.0001
Lo 1993	Propranolol vs. placebo	N=59	Unspecified	19.2% vs. 11.1%
Sheen 1989	Propranolol vs. placebo	N=18	10-14 days	27.8% vs. 55.5%
El Tourabi 1994	Propranolol long-acting vs. placebo	N=82	Unspecified	2% vs. 20%; *P*<0.02

P value based on log-rank test

Deaths due to variceal rebleeding were reported by 7 comparisons to placebo across 6 trials.[159-161, 163, 166, 168] Results are summarized in Table 14 below and in Evidence Tables 18 and 19. In 1 trial of atenolol and 5 trials of propranolol, no differences from placebo in effect on death due to variceal rebleeding were established regardless of treatment initiation interval. In 1 trial of patients with portal hypertension secondary to schistosomiasis,[169] however, significantly more patients (17%) experienced death due to variceal rebleeding on placebo than after late intervention (2 weeks) with propranolol (0%).

Table 14. Death due to variceal rebleeding

Trial	Interventions	Sample size	Treatment initiation Interval	Rates of death due to rebleeding
Early intervention				
Burroughs 1983	Propranolol vs. placebo	N=48	48 hours	15% vs. 9%
Villeneuve 1986	Propranolol vs. placebo	N=79	6-72 hours	12% vs. 19%
Late intervention				
Colombo 1989	Atenolol vs. placebo	N=94	≥ 15 days	3% vs. 10%
Colombo 1989	Propranolol vs. placebo	N=94	≥ 15 days	3% vs. 10%
Lebrec 1981b	Propranolol vs. placebo	N=74	2 weeks	0% vs. 17%; *P*<0.05
Lo 1993	Propranolol vs. placebo	N=59	Unspecified	12% vs. 7%
Sheen 1989	Propranolol vs. placebo	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 1 trial of propranolol,[159] no significant differences between beta blockers and placebo were found (Table 15).

Table 15. All-cause mortality in patients with bleeding esophageal varices

Trial	Interventions	Sample size	Treatment initiation Interval	All-cause mortality
Early intervention				
Burroughs 1983	Propranolol vs. placebo	N=48	48 hours	15% vs. 23%
Villeneuve 1986	Propranolol vs. placebo	N=79	6-72 hours	45% vs. 38%
Late intervention				
Colombo 1989	Atenolol vs. placebo	N=94	≥ 15 days	9% vs. 23%
Gatta 1987	Nadolol vs. pla	N=24	15-40 days	8% vs. 27%
Colombo 1989	Propranolol vs. placebo	N=94	≥ 15 days	13% vs. 23%
Lo 1993	Propranolol vs. placebo	N=59	Unspecified	31% vs. 33%
El Tourabi 1994	Propranolol long-acting vs. placebo	N=82	Unspecified	7% vs. 18%

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

Summary

Side effects are common among patients taking beta blockers. In longer-term trials (12 to 58 months) directly comparing beta blockers in patients with hypertension (atenolol compared with bisoprolol compared with propranolol), heart failure (carvedilol compared with metoprolol), bleeding esophageal varices (atenolol compared with propranolol), or atrial fibrillation (bisoprolol compared with carvedilol), a few differences in specific adverse events were noted. But, overall, no particular beta blocker stood out from the others as being consistently associated with a significantly less favorable adverse effect profile.

In everyday practice, weight gain, fatigue, dizziness, and dyspnea are the most common side effects in patients with heart failure. About 1 in 5 patients require discontinuation of the initial beta blocker choice. In a retrospective review of 1 series of 268 patients seen in a United States heart failure clinic, 54% were started on carvedilol and 46% on metoprolol succinate or metoprolol tartrate.[170] Overall, about 1 in 5 patients (51 total) could not tolerate the initial choice of treatment. Forty of the 51 patients who could not tolerate the initial choice were switched to another beta blocker. Twenty-two of these 40 patients tolerated the second choice, with equal proportions tolerating a switch to carvedilol from metoprolol and to metoprolol from carvedilol.

A higher rate of beta blocker intolerance was reported in another trial that enrolled 90 consecutive patients in a heart failure clinic in Denmark.[171] This trial compared bisoprolol and carvedilol and was designed to measure treatment failure rates under conditions that mimic daily

clinical practice. The eligibility criteria were lax and the dosing regimen was flexible. Overall, 40% of patients (35 of 87) did not tolerate beta blocker therapy. Intolerance rates were similar in the bisoprolol and carvedilol groups (39% compared with 40%). This trial had some important methodological flaws, however. The trial used an inadequate method of randomization. Between-group differences at baseline confirm the inadequacy of the randomization method. The bisoprolol group was comprised of a significantly higher proportion of females (31% compared with 17%) and a numerically lower proportion of patients with a left ventricular ejection fraction < 25% (27% compared with 43%). Further, the team that treated and assessed the patients was not blinded to beta blocker assignment and the analysis excluded 3 patients that died prior to completing 2 months of follow-up. Group assignment of the 3 excluded patients was not reported. For these reasons, we rated this trial as poor quality and recommend a cautious interpretation of these potentially unreliable results.

Detailed Assessment

Adverse events of beta blockers most commonly reported in randomized controlled trials include cardiovascular symptoms of bradycardia and hypotension and central nervous system symptoms of dizziness. Relatively low rates of withdrawal due to these adverse events suggest that they were mild 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 9 trials of patients with hypertension (Evidence Table 1),[5, 8-11, 21, 22 19, 23] 4 trials of patients with angina (Evidence Table 3),[37-39, 172] 5 trials of patients with heart failure (Evidence Table 11),[95, 103, 106, 173, 111] 7 trials of migraine patients (Evidence Table 16),[117-120, 122, 174, 125] 1 trial of patients with bleeding esophageal varices (Evidence Table 18),[157] 3 trials of patients post-myocardial infarction (Evidence Table 7),[53, 55, 56] and 1 trial of patients with atrial fibrillation (Evidence Table 14).[113] 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 4 weeks to 58 months. Sample sizes ranged from 28 to 3029 patients. All but 2[117, 125] of the head-to-head trials in patients with migraine used crossover designs, only reporting results of the combined intervention periods. Furthermore, in a hypertension study examining nebivolol and metoprolol,[23] authors reported "no critical" adverse events were found, but did not supply data nor did they define "critical" adverse events.

Only 1 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 21 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 11.

Overall adverse events

Overall adverse event incidence was reported in 17 head-to-head trials.[5, 8, 10, 21, 22, 38, 39, 106, 118, 119, 122, 123, 172 19, 37, 111, 125] Rates varied across the trials. For example, rates for carvedilol and

metoprolol in a 3-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 1 exception. In one 8-week trial of 40 angina patients,[38] 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% compared with 0; $P<0.0005$) and mild hypotension (27.8% compared with 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 2-week angina attack rate was higher in the propranolol group during run-in [28.5 (95% CI, 26.4 to 30.6) compared with 18.4 (95% CI, 17.4 to19.4)]. This suggests problems with the randomization methods.

Withdrawals due to adverse events were reported by 13 head-to-head trials.[5, 8, 11, 21, 22, 95, 113, 122, 123, 157 37, 111, 125] No significant differences were found in any of the comparisons.

Specific adverse events

Bradycardia

Rates of bradycardia were reported in short-term hypertension trials, in longer-term heart failure trials, a 2-month angina trial,[3, 6, 17, 18, 937, 106, 111] and in a long-term trial for treatment of migraine.[125] Overall, no significant differences between beta blockers were reported, with the exception of the 1 trial, which found a difference of bradycardia/electrocardiogram pauses >2.5 seconds for carvedilol 3 (9%) and 1 (3%) for nebivolol.[111]

Dizziness

Eight head-to-head trials reported dizziness incidence.[21, 56, 103, 111, 120, 122, 123, 172] All but 1 reported no significant differences between beta blockers.[103] Carvedilol was associated with higher rates of dizziness than metoprolol in a 44-month trial of 122 patients with heart failure (14.7% compared with 1.3%; $P=0.0046$).[103] This significant difference was not seen in another shorter trial [3 months in 368 patients with angina (4.8% compared with 5.0%)],[172] nor was there a significant difference in rates of dizziness in a head-to-head trial of carvedilol compared with atenolol in patients with recent myocardial infarction (36.4% compared with 27.2%; $P=0.131$).[56] Reasons for this inconsistency may include differences in definition of dizziness and evaluation techniques between the 2 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- to good-quality placebo-controlled trials safety data did not offer any additional information as dizziness rates in metoprolol trials were not reported.

Hypotension

Rates of hypotension were similar for carvedilol and metoprolol across 2 longer-term trials of patients with heart failure.[103, 106] Only 2.7% of patients from either treatment group experienced hypotension in the smaller (N=122), 44-month trial. After 58 months in the COMET trial (N=3029), 14% of patients taking carvedilol and 11% of patients taking metoprolol had hypotensive events. A study of left ventricular dysfunction after acute myocardial infarction (carvedilol compared with metoprolol), reported incidence of hypotension leading to withdrawal, but did not report the incidence for each study arm.[55] In a 6-month heart failure study, no differences were found between nebivolol and carvedilol.[111] A 30-week trial of treatment for migraine found similar rates between metoprolol compared with nebivolol.[125]

New-onset diabetes. Direct comparisons between beta blockers on risk of new-onset diabetes were only available from 1 retrospective analysis of data from the COMET trial, which compared metoprolol tartrate and carvedilol in adults with heart failure.[173] New-onset diabetes was identified post-hoc among a cohort of 2298 patients without diabetes at baseline. The endpoint of new-onset diabetes was based on patient reporting and notes in hospital files and was considered present when there was documentation of a diagnosis of diabetes mellitus or diabetic coma, patients started antidiabetic treatment during the trial, or if patients had 2 or more random blood glucose readings above 11.1 mmol/l. The main finding of this analysis was that more patients receiving metoprolol tartrate developed new-onset diabetes than those receiving carvedilol (10.1% compared with 8.7%; hazard ratio, 0.78; 95% CI, 0.61 to 0.997). Although noteworthy, this finding should be interpreted with caution, keeping in mind that it is based on a post-hoc analysis and relies on a clinical, rather than guideline-based definition of diabetes.

Otherwise the only evidence we found came from a meta-analysis that pooled data from 12 trials (94 492 patients) of beta blockers compared with placebo, diuretics, ACE inhibitors, and calcium channel blockers which generated combined estimates of risk of new-onset of diabetes for each beta blocker.[175] Pooled estimates based on a random effects model found that when compared to other comparators (placebo, diuretics, ACE inhibitors, calcium channel blockers) there is an increased the risk of new-onset DM for atenolol (pooled RR, 1.30; 95% CI, 1.11 to 1.52) and metoprolol (pooled RR, 1.34; 95% CI, 1.04 to 1.73), but not for propranolol (pooled RR, 0.77; 95% CI, 0.37 to 1.60).[175] It should be noted that had a fixed effects model been used, only atenolol would have resulted in a statistically significant finding. The results of this meta-analysis should be interpreted with caution, as it did not evaluate the potential effects of variation among trials in internal validity factors.

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?

Summary

There is no data that suggests that any beta blocker is superior in any subgroup of patients based on demographics, other medications, or comorbidities.

Detailed Assessment

Head-to-head trials

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 based on demographics, concomitant medications, or comorbidities.

Placebo-controlled trials

We are aware of 1 placebo-controlled trial that examined the efficacy and tolerability of nebivolol in hypertensive African American patients.[176] This study, however, did not meet our inclusion criteria as its focus was on blood pressure lowering and it did not report long-term health outcomes.

Meta-analyses

A recent systematic review conducted by the Cochrane Collaboration compared beta blockers to placebo in reducing the risk of severe hypertension and need for additional antihypertensives during pregnancy.[177] Studies of acebutolol, atenolol, metoprolol, pindolol, and propranolol were included in this review, but no evidence of comparative effectiveness is provided. Rather, the focus of the review is on comparing beta blockers as a class to placebo. The review found that there was insufficient evidence to draw conclusions about the effects of beta blockers on perinatal mortality or preterm birth.

The Beta Blocker Pooling Project[178] analyzed mortality in post-infarction patients relative to subgroup risk factors from trials of propranolol,[50, 67, 179] pindolol,[67] and other beta blockers not available in the United States. This analysis found that none of the age, gender, heart failure, or 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[180] 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 16 below and suggest that beta blockers are equally effective in reducing mortality in subpopulations stratified by gender and race.

Observational analyses

A 12-month observational study comparing the tolerability of carvedilol (target dose 25 mg daily) in patients (ages ≥70) with and without diabetes mellitus found the rates of withdrawal due to adverse events (bradycardia, bronchospasm) were low in both the diabetes and nondiabetes subgroups (6% compared with 3%).[181]

Table 16. 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)

Subgroup analyses and prescribing information

Atenolol

The SHEP trial assessed the use of chlorthalidone compared with placebo in controlling hypertension. Once desired blood pressure was reached, participants were further randomized to receive atenolol or reserpine. A subgroup analysis of long-term data (median 14.3 years) found that adding atenolol to chlorthalidone did not significantly affect mortality relative to placebo in diabetic patients, including both patients who were diabetic at baseline and those who developed diabetes during time on trial.[182]

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.[61] We found no other source of publication of results from this subgroup analysis.

A number of additional meta-analyses have been published that evaluate the effects of carvedilol in subgroups of patients based on demographics and/or comorbidities. The United States Carvedilol Heart Failure Study Group published an analysis[183] of the pooled results from a stratified set of 3 fair-quality and 1 poor-quality concurrently conducted protocols,[84-87] 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[89] show that carvedilol had similar effects regardless of age and gender in patients with *severe* heart failure.

The most recent and largest manufacturer-funded meta-analysis (N=5757) of published and unpublished data from 7 clinical trials focused on evaluating the effects of carvedilol in patients with heart failure, with and without comorbid diabetes.[184] Consistent with previous analyses, the main findings confirmed that similar reductions in risk of all-cause mortality were seen in heart failure patients, regardless of diabetes status. The relative risk reduction in the subgroup of patients with diabetes was 28% (95% CI, 3 to 46) and was 37% (95% CI, 22 to 48) in the non-diabetic patients.

Labetolol

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[185] that pooled results from 5 placebo-controlled trials of metoprolol (Amsterdam, Belfast, Goteborg, Stockholm, Lopressor Intervention Trial) found that neither age nor gender had a significant influence on mortality. When considered individually, results from the Goteborg Metoprolol Trial[186] show a nonsignificant trend that patients aged 65 to 74 years had a more marked reduction in mortality at 3 months post-myocardial infarction (45%) than did all patients aged 40 to 74 (36%). Results from the MERIT-HF trial also reported that neither age nor gender had any influence on the effects of metoprolol CR in patients with mild to moderate heart failure.

A subgroup analysis of the MERIT-HF trial evaluated the influence of comorbid diabetes on the effects of metoprolol CR.[187] This analysis found higher rates of all-cause mortality in the placebo group when compared to metoprolol (12.7% compared with 10.1% per patient year; risk reduction, 18%; 95% CI, +44 to −19). Metoprolol CR also significantly reduced risks of hospitalizations for worsening heart failure (including those patients identified as having severe heart failure) regardless of diabetic status.

Propranolol

The fair-quality, placebo-controlled Beta Blocker Heart Attack Trial[67] comprised of 3837 patients found that the protective of propranolol on mortality 25 months (average follow-up) following myocardial infarction was equivalent regardless of age or gender.

Nebivolol

Subgroup analysis of the SENIORS trial found no significant differences in the effect of nebivolol on subpopulations of gender, ejection fraction, age, diabetes, and prior myocardial infarction.[72]

SUMMARY

Results of this review are summarized below in Table 17 by key question and in Table 18 by beta blocker.

Table 17. Strength of the evidence

	Strength of evidence[a]	Conclusion
Key Question 1. Comparative efficacy		
a. Hypertension	Overall grade: Poor	No head-to-head trials of long-term (≥6 months) health or quality-of-life outcomes. Reliable indirect comparisons cannot be made by evidence from 3 long-term placebo-controlled trials of propranolol and atenolol.
b. Angina	Overall grade: Fair	No significant differences in 6 head-to-head trials of carvedilol compared with metoprolol, pindolol compared with propranolol, betaxolol, and propranolol, and betaxolol compared with metoprolol in patients with stable angina. Atenolol equivalent to bisoprolol in patients with chronic stable angina and chronic obstructive pulmonary disease. Atenolol equivalent to labetalol when added to chlorthalidone in patients with chronic stable angina. 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	Overall grade: Poor	Metoprolol did not benefit mortality or ischemic events in a longer-term (>7 days) placebo-controlled trial (MACB).
d. Recent myocardial infarction	Overall grade: Fair-good	One fair-quality head-to-head trial found no differences in mortality after 1 year between atenolol and propranolol, but this was a relatively small trial; 1 fair-quality head-to-head trial found no differences in time to serious cardiovascular events between carvedilol and atenolol. One fair-quality trial of carvedilol and metoprolol tartrate found no differences in time to first cardiac adverse event or all-cause mortality. Similar mortality reductions reported for acebutolol,

	Strength of evidence[a]	Conclusion
		metoprolol tartrate, propranolol, and timolol in placebo-controlled trials of patients following myocardial infarction without other complications. Similar reductions in sudden death and reinfarction were reported for metoprolol tartrate and timolol and in sudden death for propranolol. No studies of carvedilol phosphate (extended-release carvedilol) in patients with recent myocardial infarction were identified. Carvedilol reduced mortality and reinfarction in 1 placebo-controlled trial of patients with a mean left ventricular ejection fraction of <32.7% (CAPRICORN). Four systematic reviews were not designed to assess comparative efficacy.
e. Heart failure	Health outcomes in head-to-head trials: Fair	Carvedilol more effective than metoprolol tartrate in reducing total mortality in COMET in patients with mild to moderate heart failure.
	Symptoms in head-to-head trials: Good	Carvedilol equivalent to metoprolol tartrate in improving symptoms (quality of life; NYHA) and exercise capacity in 4 head-to-head trials. Improvements in NYHA function class and on walking distance (6-minute walk test) were similarly slight for both carvedilol and nebivolol.
	Placebo-controlled trials in mild-moderate heart failure: Good	Metoprolol succinate reduced total mortality, sudden death, and death due to progressive heart failure and improved quality of life (MERIT-HF). Carvedilol reduced total mortality, sudden death, and death due to pump failure (MOCHA). Nebivolol significantly reduced the composite outcome of all-cause mortality or cardiovascular hospital admission, but had nonsignificant effects each component as individual secondary outcomes. Bisoprolol reduced total mortality and sudden death. No studies of carvedilol phosphate (extended-release carvedilol) in patients with mild to moderate heart failure were identified.
	Placebo-controlled trials in severe heart failure: Fair for carvedilol and Fair for metoprolol succinate	Carvedilol reduced mortality and the combined endpoint of mortality and hospitalizations in a prospective trial. A post-hoc subgroup analysis of MERIT-HF suggests that metoprolol succinate is similarly effective in comparable patients. No studies of carvedilol phosphate (extended-release carvedilol) in patients with severe heart failure were identified.
f. Atrial arrhythmia	Overall grade: Fair	Bisoprolol equivalent to carvedilol in preventing relapse of atrial fibrillation in a head-to-head trial. Metoprolol succinate reduced incidence of atrial arrhythmia/fibrillation in a placebo-controlled trial. Carvedilol reduced 24-hour ventricular rate in patients with atrial fibrillation and heart failure in 1 placebo-controlled trial. These placebo-controlled trials did not offer

	Strength of evidence[a]	Conclusion
		comparative data.
g. Migraine	Overall grade: Fair	Atenolol, slow release metoprolol, immediate release metoprolol, and timolol were all similar to propranolol in their effects on pain outcomes and acute medication use in 5 head-to-head trials. No significant differences were found between nebivolol and metoprolol on frequency of migraine attacks and severity.
h. 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 2 formulations of extended release propranolol, all fair quality, didn't clearly differentiate one beta blocker from another.
Key Question 2. Adverse effects		
Hypertension, stable angina, heart failure, atrial arrhythmia, migraine, bleeding esophageal varices, previous myocardial infarction	Overall grade: Fair	A few differences in specific adverse event rates were noted across longer-term trials directly comparing one beta blocker to another. Overall, no particular beta blocker stood out from the others as being consistently associated with a less favorable adverse effect profile.
Key Question 3. Subgroups		
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. There was insufficient evidence on the effect of beta blockers on perinatal mortality or preterm birth based on 1 systematic review.
b. High risk populations	Overall grade: Fair	*Heart failure.* Subgroup analyses of placebo-controlled trials showed that a history of myocardial infarction 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. *Diabetes.* Subgroup analysis of the SHEP trial found that the addition of atenolol to chlorthalidone did not significantly affect mortality relative to placebo. Metoprolol use reduced all-cause mortality and hospitalizations relative to placebo in a subgroup analysis of the MERIT-HF trial.

Abbreviations: NYHA, New York Heart Association classification.
[a] Quality of evidence ratings based on criteria developed by the Third United States Preventive Services Task Force.

Table 18. Summary of comparative efficacy

Drug	Hypertension	Angina	After coronary artery bypass graft	Heart failure	Atrial arrhythmias	Migraine	Bleeding esophageal varices	Myocardial infarction
Acebutolol								Effective in reducing all-cause mortality
Atenolol		Equivalent to bisoprolol in patients with comorbid chronic obstructive pulmonary disease in reducing attack frequency; Equivalent to labetalol in reducing nitrate use when both combined with chlorthalidone				Equivalent to propranolol in decreasing migraine days	Equivalent to propranolol for reducing all-cause mortality and deaths due to rebleeding	Equivalent to carvedilol in time to serious cardiovascular event post-myocardial infarction
Betaxolol		Equivalent to propranolol; Equivalent to metoprolol tartrate in chest pain episodes; Equivalent to metoprolol tartrate in 5 of 6 quality-of-life dimensions						
Bisoprolol		Equivalent to atenolol in patients with comorbid chronic obstructive pulmonary disease		More effective than placebo in all-cause mortality and sudden death	Equivalent to carvedilol in preventing relapse of atrial fibrillation			
Carteolol								

Drug	Hypertension	Angina	After coronary artery bypass graft	Heart failure	Atrial arrhythmias	Migraine	Bleeding esophageal varices	Myocardial infarction
Carvedilol		Equivalent to metoprolol in increasing exercise tolerance		More effective than metoprolol tartrate in all-cause mortality, cardiovascular events, unstable angina in mild-moderate HF (COMET); Equivalent to metoprolol tartrate in improving symptoms and exercise parameters; Improvements in NYHA function class and on walking distance (6-minute walk test) were similarly slight for both carvedilol and nebivolol; More effective than placebo in total mortality, sudden death, death due to pump failure (MOCHA); More effective than placebo in all-cause mortality in patients with *severe* heart failure (COPERNICUS)	Equivalent to bisoprolol in preventing relapse of atrial fibrillation; More effective than placebo in reducing 24-hour ventricular rate in patients with atrial fibrillation and heart failure			Effective in reducing all-cause mortality in patients with left ventricular dysfunction post-myocardial infarction; Equivalent to atenolol in time to serious cardiovascular event post-myocardial infarction; Equivalent to metoprolol tartrate in all-cause mortality, cardiovascular death, nonfatal reinfarction
Carvedilol phosphate								
Labetalol		Equivalent to atenolol in reducing nitrate use when both combined with chlorthalidone						
Metoprolol tartrate		Equivalent to carvedilol in increasing exercise tolerance; Equivalent to betaxolol in chest pain episodes; Equivalent to betaxolol in 5 of 6 quality-of-life	Equivalent to placebo for mortality	Less effective than carvedilol in reducing total mortality, cardiovascular events, unstable angina (COMET); Equivalent to carvedilol in improving symptoms/ exercise parameters		Equivalent to propranolol in all parameters measured; Equivalent to nebivolol in		Effective in reducing total mortality, sudden death, and reinfarction; Equivalent to carvedilol in all-

Drug	Hypertension	Angina	After coronary artery bypass graft	Heart failure	Atrial arrhythmias	Migraine	Bleeding esophageal varices	Myocardial infarction
		dimensions				all parameters measured		cause mortality, cardiovascular death, nonfatal reinfarction
Metoprolol succinate	Less effective than nebivolol in quality of sleep; Less effective than nebivolol in erectile function			More effective than placebo in reducing total mortality, sudden death, death due to progressive heart failure and improved quality of life in mild-moderate heart failure (MERIT-HF); More effective than placebo in reducing mortality in severe heart failure (post-hoc, subgroup analysis of MERIT-HF)	CR/XL formulation more effective than placebo in lowering atrial fibrillation/flutter relapse rates			
Nadolol							More effective than placebo in effect on rebleeding rates	
Penbutolol								
Pindolol		Equivalent to propranolol in increasing exercise tolerance, decreasing attack frequency						Equivalent to placebo in all-cause mortality
Propranolol	Equivalent to placebo in mortality, cardiovascular events, quality of life	Equivalent to betaxolol and pindolol				Equivalent to atenolol, metoprolol tartrate, metoprolol succinate, and timolol	Equivalent to atenolol for reducing all-cause mortality and deaths due to rebleeding	Effective in reducing total mortality and sudden death

Drug	Hypertension	Angina	After coronary artery bypass graft	Heart failure	Atrial arrhythmias	Migraine	Bleeding esophageal varices	Myocardial infarction
Timolol						Equivalent to propranolol		Effective in reducing total mortality, sudden death, and reinfarction
Nebivolol	More effective than metoprolol succinate in quality of sleep More effective than metoprolol succinate in erectile function			Equivalent to placebo in all-cause mortality and cardiovascular hospital admission as individual secondary outcomes; More effective than placebo as composite outcome; Equivalent to placebo in NYHA, time to first hospitalization, quality of life, survival rate; Equivalent to placebo in exercise test; Improvements in NYHA function class and on walking distance (6-minute walk test) were similarly slight for both carvedilol and nebivolol		Equivalent to metoprolol in all parameters measured		

Abbreviations: NYHA, New York Heart Association classification.

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Appendix A. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see *External Validity*

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The US Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers —do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report were hypothetically repeated on a collection of 100 random samples of studies, the resulting 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term

in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity.*

Half- life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as (Q-(n-1))/Q, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intention to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intention to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the interval validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (hear attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See *Blinding*

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the

effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intention-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo-controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo-controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combing data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomization when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term ‘‘safe’’) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug's adverse effects impact the patient's ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete*: taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal*: taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

Appendix B. Search strategies for Update 4

First searches: November 2008

Database: Ovid MEDLINE(R) <1996 to October Week 5 2008>
Search Strategy:
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1 acebutolol.mp. or exp Acebutolol/ (140)
2 atenolol.mp. or exp Atenolol/ (2416)
3 betaxolol.mp. or exp Betaxolol/ (384)
4 bisoprolol.mp. or exp Bisoprolol/ (567)
5 carteolol.mp. or exp Carteolol/ (143)
6 carvedilol.mp. (1594)
7 labetolol.mp. or exp Labetalol/ (224)
8 metoprolol.mp. or exp Metoprolol/ (2138)
9 nadolol.mp. or exp Nadolol/ (329)
10 exp Penbutolol/ or penbutolol.mp. (36)
11 pindolol.mp. or exp Pindolol/ (828)
12 propranolol.mp. or exp Propranolol/ (6273)
13 timolol.mp. or exp Timolol/ (1317)
14 nebivolol.mp. (332)
15 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (14046)
16 limit 15 to (english language and humans and yr="2007 - 2008") (934)
17 limit 16 to (clinical trial, all or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or randomized controlled trial) (369)
18 observational stud$.mp. (16111)
19 exp Cohort Studies/ or cohort$.mp. (461575)
20 exp Retrospective Studies/ or retrospective$.mp. (248093)
21 18 or 19 or 20 (650615)
22 21 and 16 (192)
23 22 or 17 (436)
24 from 23 keep 1-436 (436)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2008>
Search Strategy:
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1 acebutolol.mp. or exp Acebutolol/ (14)
2 atenolol.mp. or exp Atenolol/ (46)
3 betaxolol.mp. or exp Betaxolol/ (6)
4 bisoprolol.mp. or exp Bisoprolol/ (23)
5 carteolol.mp. or exp Carteolol/ (0)
6 carvedilol.mp. (24)
7 labetalol.mp. or exp Labetalol/ (12)
8 metoprolol.mp. or exp Metoprolol/ (45)
9 nadolol.mp. or exp Nadolol/ (6)

10 penbutolol.mp. or exp Penbutolol/ (2)
11 nebivolol.mp. (9)
12 propranolol.mp. or exp propranolol/ (40)
13 pindolol.mp. or exp Pindolol/ (21)
14 timolol.mp. or exp timolol/ (15)
15 6 or 11 or 3 or 7 or 9 or 12 or 2 or 14 or 8 or 1 or 4 or 13 or 10 or 5 (106)
16 hypertension.mp. [mp=title, full text, keywords] (374)
17 angina.mp. [mp=title, full text, keywords] (146)
18 coronary artery bypass graft.mp. [mp=title, full text, keywords] (68)
19 myocardial infarction.mp. [mp=title, full text, keywords] (404)
20 heart failure.mp. [mp=title, full text, keywords] (212)
21 atrial arrhythmia.mp. [mp=title, full text, keywords] (0)
22 bleeding esophageal varices.mp. [mp=title, full text, keywords] (2)
23 varices.mp. [mp=title, full text, keywords] (23)
24 migraine.mp. (57)
25 21 or 17 or 20 or 22 or 18 or 24 or 16 or 19 or 23 (902)
26 25 and 15 (82)
27 (2007$ or 2008$).do. (633)
28 27 and 26 (2)
29 from 28 keep 1-2 (2)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2008>
Search Strategy:
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1 acebutolol.mp. or exp Acebutolol/ (15)
2 atenolol.mp. or exp Atenolol/ (34)
3 betaxolol.mp. or exp Betaxolol/ (13)
4 bisoprolol.mp. or exp Bisoprolol/ (16)
5 carteolol.mp. or exp Carteolol/ (9)
6 carvedilol.mp. (12)
7 labetalol.mp. or exp Labetalol/ (20)
8 metoprolol.mp. or exp Metoprolol/ (34)
9 nadolol.mp. or exp Nadolol/ (20)
10 penbutolol.mp. or exp Penbutolol/ (7)
11 nebivolol.mp. (4)
12 propranolol.mp. or exp propranolol/ (58)
13 pindolol.mp. or exp Pindolol/ (22)
14 timolol.mp. or exp timolol/ (22)
15 6 or 11 or 3 or 7 or 9 or 12 or 2 or 14 or 8 or 1 or 4 or 13 or 10 or 5 (87)
16 hypertension.mp. [mp=title, abstract, full text, keywords, caption text] (728)
17 angina.mp. [mp=title, abstract, full text, keywords, caption text] (182)
18 coronary artery bypass graft.mp. [mp=title, abstract, full text, keywords, caption text] (29)
19 myocardial infarction.mp. [mp=title, abstract, full text, keywords, caption text] (393)
20 heart failure.mp. [mp=title, abstract, full text, keywords, caption text] (283)
21 atrial arrhythmia.mp. [mp=title, abstract, full text, keywords, caption text] (2)

22 bleeding esophageal varices.mp. [mp=title, abstract, full text, keywords, caption text] (3)
23 varices.mp. [mp=title, abstract, full text, keywords, caption text] (35)
24 migraine.mp. (74)
25 21 or 17 or 20 or 22 or 18 or 24 or 16 or 19 or 23 (1125)
26 25 and 15 (59)
27 from 26 keep 1-59 (59)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2008>
Search Strategy:
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1 acebutolol.mp. or exp Acebutolol/ (337)
2 atenolol.mp. or exp Atenolol/ (2468)
3 betaxolol.mp. or exp Betaxolol/ (310)
4 bisoprolol.mp. or exp Bisoprolol/ (368)
5 carteolol.mp. or exp Carteolol/ (136)
6 carvedilol.mp. (502)
7 labetalol.mp. or exp Labetalol/ (503)
8 metoprolol.mp. or exp Metoprolol/ (2060)
9 nadolol.mp. or exp Nadolol/ (288)
10 penbutolol.mp. or exp Penbutolol/ (107)
11 nebivolol.mp. (113)
12 propranolol.mp. or exp propranolol/ (3942)
13 pindolol.mp. or exp Pindolol/ (785)
14 timolol.mp. or exp timolol/ (1240)
15 6 or 11 or 3 or 7 or 9 or 12 or 2 or 14 or 8 or 1 or 4 or 13 or 10 or 5 (10652)
16 hypertension.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (20388)
17 angina.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (6532)
18 coronary artery bypass graft.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1101)
19 myocardial infarction.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (10149)
20 heart failure.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (6445)
21 atrial arrhythmia.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (42)
22 bleeding esophageal varices.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (170)
23 varices.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1166)
24 migraine.mp. (2099)
25 21 or 17 or 20 or 22 or 18 or 24 or 16 or 19 or 23 (42595)
26 25 and 15 (6356)
27 limit 26 to yr="2007 - 2008" (153)

28 from 27 keep 1-153 (153)

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Second searches: March 2009

Database: Ovid MEDLINE(R) <1996 to February Week 1 2009>
Search Strategy:
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1 acebutolol.mp. or exp Acebutolol/ (142)
2 atenolol.mp. or exp Atenolol/ (2451)
3 betaxolol.mp. or exp Betaxolol/ (386)
4 bisoprolol.mp. or exp Bisoprolol/ (581)
5 carvedilol.mp. (1635)
6 labetolol.mp. or exp Labetalol/ (229)
7 metoprolol.mp. or exp Metoprolol/ (2186)
8 nadolol.mp. or exp Nadolol/ (337)
9 exp Penbutolol/ or penbutolol.mp. (36)
10 pindolol.mp. or exp Pindolol/ (831)
11 propranolol.mp. or exp Propranolol/ (6355)
12 timolol.mp. or exp Timolol/ (1347)
13 nebivolol.mp. (347)
14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (14221)
15 limit 14 to (english language and humans) (7080)
16 (20081$ or 2009$).ed. (229157)
17 16 and 15 (178)
18 limit 17 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or randomized controlled trial) (63)
19 observational stud$.mp. (16813)
20 exp Cohort Studies/ or cohort.mp. (469080)
21 exp Retrospective Studies/ or retrospective$.mp. (256019)
22 21 or 19 or 20 (664341)
23 22 and 17 (38)
24 18 or 23 (79)
25 from 24 keep 1-79 (79)

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Appendix C. Quality assessment for the Drug Effectiveness Review Project

Study quality is objectively assessed using predetermined criteria for internal validity, based on the combination of the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination criteria. This appendix lists questions that are posed for each included study in order to assess study quality. These quality-assessment questions differ for systematic reviews, controlled trials, and nonrandomized trials.

Regardless of design, all studies that are included are assessed for quality and assigned a rating of "good," "fair," or "poor." Studies with fatal flaws are rated poor quality. A fatal flaw is failure to meet combinations of criteria that may indicate the presence of bias. An example would be inadequate procedure for randomization or allocation concealment combined with important differences in prognostic factors at baseline. Studies that meet all criteria are rated good quality, and the remainder is 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 likely to be valid, while others are only probably valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs.

Systematic Reviews

1. Does the review report a clear review question and inclusion/exclusion criteria that relate to the primary studies?
   A good-quality review should focus on a well-defined question or set of questions. These questions ideally are reflected in the inclusion/exclusion criteria, which guide the decision of whether to include or exclude specific primary studies. The criteria should relate to the 4 components of study design: indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, such as how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?
   If details of electronic database searches and other identification strategies are given, the answer to this question usually is yes. Ideally, search terms, dates, and language restrictions should be presented. In addition, descriptions of hand searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered. For example, if only Medline was searched for a review looking at proton pump inhibitors then it is unlikely that all relevant studies were located.

3. Is the validity of included studies adequately assessed?
   A systematic assessment of the quality of primary studies should include an explanation of the criteria used (for example, how randomization was done, whether outcome

assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use a published checklist or scale or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (how many reviewers were involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?
   The review should demonstrate that the studies included are suitable to answer the question posed and that a judgment on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample sizes, patient characteristics, interventions, settings, outcome measures, follow-up periods, drop-out rates (withdrawals), effectiveness results, and adverse events.

5. Are the primary studies summarized appropriately?
   The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis). For reviews that provide a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual studies should be weighted in some way (for example, according to sample size or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Controlled Trials

Assessment of internal validity

1. Was the assignment to treatment groups really random?
   Adequate approaches to sequence generation:
   - Computer-generated random numbers
   - Random-numbers table

   Inferior approaches to sequence generation:
   - Use of alternation, case record number, birth date, or day of week

   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

   Inferior approaches to concealment of randomization:
   - Use of alternation, case record number, birth date, or day of week

Open random-numbers list
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 (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 (giving numbers for each group)?

Assessment of external validity (applicability)

1. How similar is the population to the population to which 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 follow-up? (Give numbers at each stage of attrition.

Nonrandomized Studies

Assessment of internal validity

1. Was the selection of patients for inclusion unbiased? In other words, was any group of patients systematically excluded?

2. Is there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group.)

3. Were the investigated events specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there unbiased and accurate ascertainment of events (independent ascertainers and validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of follow-up correlate with 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 which 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?

References:

Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews.* CRD Report Number 4. 2nd ed. University of York, UK; 2001.

Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med.* Apr 2001;20(3 Suppl):21-35.

Appendix D. Excluded studies

The following full-text publications were considered for inclusion but failed to meet the criteria for this report.

Part I. Excluded for Update 4

Publication	Reason for Exclusion
Abalos, Duley, Steyn, et al. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy [Systematic Review]. *Cochrane Database of Systematic Reviews.* 2008;3:3.	Wrong study design
Abraham WT, Massie BM, Lukas MA, et al. Tolerability, safety, and efficacy of beta-blockade in black patients with heart failure in the community setting: insights from a large prospective beta-blocker registry. *Congestive Heart Failure.* Jan-Feb 2007;13(1):16-21.	Wrong outcome
Ahrens W, Hagemeier C, Muhlbauer B, et al. Hospitalization rates of generic metoprolol compared with the original beta-blocker in an epidemiological database study. *Pharmacoepidemiology & Drug Safety.* Dec 2007;16(12):1298-307.	Wrong outcome
Aneja P, Srinivas A and Biswas AD. Comparative clinical study of the efficacy and safety of a S-metoprolol ER tablet versus a racemate metoprolol ER tablet in patients with chronic stable angina. *International Journal of Clinical Pharmacology & Therapeutics.* May 2007;45(5):253-8.	Wrong study design
Aursnes I, Osnes J-B, Tvete IF, et al. Does atenolol differ from other beta-adrenergic blockers? *BMC Clinical Pharmacology.* 2007;7:4.	Wrong publication type
Brehm BR, Wolf SC, Gorner S, et al. Effect of nebivolol on left ventricular function in patients with chronic heart failure: a pilot study. *European Journal of Heart Failure.* Dec 2002;4(6):757-63.	Wrong study design
Capucci A, Botto G, Molon G, et al. The Drug And Pace Health cliNical Evaluation (DAPHNE) study: a randomized trial comparing sotalol versus beta-blockers to treat symptomatic atrial fibrillation in patients with brady-tachycardia syndrome implanted with an antitachycardia pacemaker. *American Heart Journal.* Aug 2008;156(2):373.e1-8.	Wrong study design
Coca A, Messerli FH, Benetos A, et al. Predicting stroke risk in hypertensive patients with coronary artery disease: a report from the INVEST. *Stroke.* Feb 2008;39(2):343-8.	Wrong drug
Dahlof B, Devereux RB, Kjeldsen SE, et al. Atenolol as a comparator in outcome trials in hypertension: a correct choice in the past, but not for the future? *Blood Pressure.* 2007;16(1):6-12.	Wrong publication type
Dart AM, Cameron JD, Gatzka CD, et al. Similar effects of treatment on central and brachial blood pressures in older hypertensive subjects in the Second Australian National Blood Pressure Trial. *Hypertension.* Jun 2007;49(6):1242-7.	Wrong drug
DasGupta P, Jain D, Lahiri A, et al. Long term efficacy and safety of carvedilol, a new beta-blocking agent with vasodilating properties, in patients with chronic ischaemic heart disease. *Drug Invest.* 1992;4(3):263-272.	Wrong study design

Publication	Reason for Exclusion
Delea TE, Taneja C, Moynahan A, et al. Valsartan versus lisinopril or extended-release metoprolol in preventing cardiovascular and renal events in patients with hypertension. *American Journal of Health-System Pharmacy.* Jun 1 2007;64(11):1187-96.	Wrong outcome
Dobre D, Haaijer-Ruskamp FM, Voors AA, et al. beta-Adrenoceptor antagonists in elderly patients with heart failure: a critical review of their efficacy and tolerability. *Drugs & Aging.* 2007;24(12):1031-44.	Wrong publication type
Dungen H-D, Apostolovic S, Inkrot S, et al. Bisoprolol vs. carvedilol in elderly patients with heart failure: rationale and design of the CIBIS-ELD trial. *Clinical Research in Cardiology.* Sep 2008;97(9):578-86.	Wrong publication type
Earl GL, Verbos-Kazanas MA, Fitzpatrick JM, et al. Tolerability of beta-blockers in outpatients with refractory heart failure who were receiving continuous milrinone. *Pharmacotherapy.* May 2007;27(5):697-706.	Wrong outcome
Garcia-Monco JC, Foncea N, Bilbao A, et al. Impact of preventive therapy with nadolol and topiramate on the quality of life of migraine patients. *Cephalalgia.* Aug 2007;27(8):920-8.	Wrong study design
Go AS, Yang J, Gurwitz JH, et al. Comparative effectiveness of beta-adrenergic antagonists (atenolol, metoprolol tartrate, carvedilol) on the risk of rehospitalization in adults with heart failure. *American Journal of Cardiology.* Aug 15 2007;100(4):690-6.	Wrong study design
Kataoka M, Satoh T, Yoshikawa T, et al. Comparison of the effects of carvedilol and metoprolol on exercise ventilatory efficiency in patients with congestive heart failure. *Circulation Journal.* Mar 2008;72(3):358-63.	Wrong outcome
Krum H, Sackner-Bernstein J and al. e. Double-blind, palcebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. *Circulation.* 1995;92(6):1499-1506.	Wrong study design
Rector TS, Anand IS, Nelson DB, et al. Carvedilol versus controlled-release metoprolol for elderly veterans with heart failure. *Journal of the American Geriatrics Society.* Jun 2008;56(6):1021-7.	Wrong outcome
Rinfret S, Abrahamowicz M, Tu J, et al. A population-based analysis of the class effect of beta-blockers after myocardial infarction. *American Heart Journal.* Feb 2007;153(2):224-30.	Wrong outcome
Taylor FR. Weight change associated with the use of migraine-preventive medications. *Clinical Therapeutics.* Jun 2008;30(6):1069-80.	Wrong publication type
Uhlir O, Dvorak I, Gregor P, et al. Nebivolol in the treatment of cardiac failure: a double-blind controlled clinical trial. *Journal of Cardiac Failure.* Dec 1997;3(4):271-6.	Wrong study design
Van Bortel LM, Fici F and Mascagni F. Efficacy and tolerability of nebivolol compared with other antihypertensive drugs: a meta-analysis. *American Journal of Cardiovascular Drugs.* 2008;8(1):35-44.	Wrong publication type

Part II. Previously excluded

1. Agrawal RL. Double-blind comparison of Inderal LA (160 mg), Half-Inderal LA (80 mg), and Half-Inderal LA plus bendrofluazide (2. *Br. J. Clin. Pract.* 1987;41(9):916-920.
2. Agrawal RL, Alliott RJ, George M, et al. The treatment of hypertension with propranolol and bendrofluazide. *Journal of the Royal College of General Practitioners.* 1979;29(207):602-606.
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4. Ajayi AA, Sofowora GG, Adigun AQ, Asiyanbola B. Adjunctive sympathoplegic therapy to ACE inhibition in Blacks with congestive heart failure: a comparison of alpha-1 with beta-1 blockade on exercise tolerance and cardiac sympathovagal reflex activity. *Ethnicity & Disease.* 2003;13(1):71-79.
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17. 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.

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19. Anonymous. New beta blocker reduces heart failure mortality by two-thirds. *Geriatrics.* 1996;51(1):16-19.
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Postoperative Atrial Fibrillation (SPPAF), a randomized, placebo-controlled trial. *Am. Heart J.* 2004;147(4):636-643.
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