

Drug Class Review on Beta Adrenergic Blockers

Final Report

September 2007



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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INTRODUCTION

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

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

Beta blockers differ in their effects on the 3 adrenergic receptors (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 (ISA) act as partial adrenergic agonists and would be expected to have less bradycardic and bronchoconstriction effects than other beta blockers. Finally, carvedilol and labetalol block 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 Dosage (TDD) | Daily dosage frequency | Half-life (hours) | Cardioselective | Partial agonist activity (ISA) | Alpha antagonist effect |
|---|---------------------------------|------------------------|-------------------|-----------------|--------------------------------|-------------------------|
| Acebutolol | 200-1200 mg | Twice | 3-4 | Yes | Yes | No |
| Atenolol | 50-100 mg | Once | 6-9 | Yes | No | No |
| Betaxolol | 5-40 mg | Once | 14-22 | Yes | No | No |
| Bisoprolol | 5-20 mg | Once | 9-12 | Yes | No | No |
| Carteolol | 2.5-10 mg | Once | 6 | No | Yes | No |
| Carvedilol | 12.5-50 mg | Twice | 7-10 | No | No | Yes |
| Carvedilol phosphate (extended release) | 10-80 mg | Once | 10-11 | No | No | Yes |
| Labetalol | 200-1200 mg | Twice | 3-6 | No | No | Yes |
| Metoprolol tartrate | 50-200 mg | Twice | 3-7 | Yes | No | No |
| Metoprolol succinate (extended release) | 50-400 mg | Once | 3-7 | Yes | No | No |
| Nadolol | 20-240 mg | Once | 10-20 | No | No | No |
| Penbutolol | 20 mg | Once | 5 | No | Yes | No |
| Pindolol | 10-60 mg | Twice | 3-4 | No | Yes | No |
| Propranolol | 40-240 mg | Twice | 3-4 | No | No | No |
| Propranolol long-acting | 60-240 mg | Once | 8-11 | No | No | No |
| Timolol | 10-40 mg | Twice | 4-5 | No | No | No |

Table 2. Approved indications

| Drug | Hypertension | Chronic stable angina | Atrial arrhythmia | Migraine | Bleeding esophageal varices | Heart failure | Post Myocardial Infarction | Decreased LV function after recent MI |
|---|--------------|-----------------------|-------------------|----------|-----------------------------|----------------------------------|----------------------------|---------------------------------------|
| Acebutolol | Yes | Yes | | | | | | |
| Atenolol | Yes | Yes | | | | | Yes | |
| Betaxolol | Yes | | | | | | | |
| Bisoprolol | Yes | | | | | | | |
| Carteolol | Yes | | | | | | | |
| Carvedilol (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 | | | | | | |
| Penbutolol | Yes | | | | | | | |
| Pindolol | Yes | | | | | | | |
| Propranolol | Yes | Yes | Yes | Yes | | | | |
| Propranolol long-acting | Yes | Yes | Yes | Yes | | | | |
| Timolol | Yes | | | Yes | | | Yes | |

Adapted from Drug Facts and Comparisons[®]

†=ISA

Scope and Key Questions

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

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

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

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

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

METHODS

We searched the Cochrane Central Register of Controlled Trials (CCRCT) (4th quarter 2004), MEDLINE (1966 - January Week 3 2005), Premedline (January 27, 2005), Embase (1980 - January 27, 2005), and reference lists of review articles. For this update, we extended the CCRCT search through the 1st quarter 2007 and MEDLINE through the 1st week of March 2007. For this update we also added searches of Cochrane Database of Systematic Reviews (CDSR) (1st quarter 2007) and the Database of Abstracts of Reviews of Effects (DARE) (1st quarter 2007) and repeated MEDLINE In-Process (March 14, 2007) and Daily Update (March 14, 2007) databases. In electronic searches we used broad searches, combining terms for included beta blockers with terms for patient populations. Appendix A contains complete CCRCT and Medline search strategies. A similar search strategy was repeated in Embase. Appendix B contains search strategies used for this update. 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[®] 9.0).

Study Selection

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

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

| | |
|--|--|
| Hypertension | <ol style="list-style-type: none"> 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 \geq 2 month's duration) | <ol style="list-style-type: none"> 1. Exercise tolerance 2. Attack frequency 3. Nitrate use |
| Post-coronary artery bypass graft (long-term treatment) | <ol style="list-style-type: none"> 1. All-cause mortality 2. Ischemic events (MI, unstable angina, need for repeat CABG, and PTCA) |
| Recent myocardial infarction (with and without LV dysfunction) | <ol style="list-style-type: none"> 1. All-cause and cardiovascular mortality 2. Cardiovascular events (usually development of heart failure) |
| Symptomatic chronic heart failure | <ol style="list-style-type: none"> 1. All-cause or cardiovascular mortality 2. Symptomatic improvement (heart failure class, functional status, visual analogue scores) 3. Hospitalizations for heart failure |
| Asymptomatic LV dysfunction | <ol style="list-style-type: none"> 1. All-cause and cardiovascular mortality 2. Cardiovascular events (usually development of heart failure) |
| Atrial fibrillation/flutter | <ol style="list-style-type: none"> 1. Rate control 2. Relapse into atrial fibrillation |
| Migraine | <ol style="list-style-type: none"> 1. Attack frequency 2. Attack intensity/severity 3. Attack duration 4. Use of abortive treatment |
| Bleeding esophageal varices | <ol style="list-style-type: none"> 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-quality observational studies.

Data Abstraction

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

Quality Assessment

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

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

Data Synthesis

The comparative efficacy and safety of beta blockers in the specified patient populations are synthesized through a narrative review as well as in tabular form. We analyzed continuous efficacy data by calculating percent change scores when possible. Forest plots of relative risks (RR) or odds ratios (OR) are presented, where applicable, to display data comparatively. Forest plots were created using StatsDirect (CamCode, UK) software. StatsDirect was also used to calculate Fisher's exact tests when p-values were not reported, as well as number needed to treat (NNT) statistics.

RESULTS

Overview

Searches identified 5,453 citations: 2,536 from the Cochrane Library, 1,274 from Medline, 1,512 from EMBASE, 120 from reference lists, and 11 from pharmaceutical company submissions, peer reviewers, or public comment. 114 (7 new from update #3 search) publications met the inclusion criteria for the systematic review. Included trials are listed in Appendix C.

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

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 ARB. Evidence from long-term trials is mixed; overall, beta blockers are generally less effective than diuretics, and usually no better than placebo, in reducing cardiovascular events. There was one exception: in one large trial, treatment with metoprolol resulted in lower all-cause mortality than treatment with a thiazide diuretic.

Detailed Assessment

Primary or initial therapy

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

By the time beta blockers became available, diuretics had already been shown to prevent cardiovascular events, primarily strokes. It was considered unethical to compare a beta blocker to placebo in patients who were likely to benefit from a diuretic. For this reason, most large,

long-term trials of beta blocker therapy for hypertension use a comparison group taking a diuretic rather than a placebo. Unlike diuretics, then, beta blockers have not been clearly demonstrated to be more effective than placebo in reducing cardiovascular events when used as initial therapy in the general population of patients with hypertension.

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

Of the trials that compared a beta blocker with a diuretic, only one (MAPHY) had any suggestion that the beta blocker was more effective. In that trial, deaths from heart attacks and strokes as well as total mortality were lower in the metoprolol treated group than in those treated with a diuretic (hydrochlorothiazide or bendroflumethiazide).¹² The trial continues 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 MRC trials and other trials of beta blockers versus 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 (ORs, 1.01, 0.98, and 1.05, respectively).¹³

Secondary treatment

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

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

Quality of life

There is no definitive evidence that one beta blocker yields a better quality of life than another for patients who have hypertension. Six trials directly compared atenolol and bisoprolol,¹⁷ metoprolol CR,^{3, 18} or propranolol^{5, 6, 19} and assessed changes in quality of life. We excluded two trials of atenolol versus propranolol based on poor quality ratings.^{5, 19} 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 remaining 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.⁶ This is 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 (PGWB)-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 as to whether these short-term results in men can be generalized to a broader population over a longer period of time, however.

The magnitude of the evidence from the remaining crossover trials is limited by smaller sample sizes and results that were averaged across treatment periods.^{3, 17, 18} Improvement in self-rated sexual interest (Minor Symptom Evaluation (MSE) profile) was greater for atenolol than propranolol in one trial of 16 patients (mean age=58 years; 43.3% male).³ No other differences were found in this trial or in either of the remaining trials.^{3, 17, 18}

Table 4. Quality of Life outcomes in HTH trials of hypertensives

| Trial (quality) | Comparison design sample size | Duration (weeks) | Washout (weeks) | Results |
|-------------------------------------|---|-------------------------|------------------------|---|
| Steiner 1990 ⁶ (Fair) | Atenolol vs. propranolol Parallel N=360 | 4 | n/a | Atenolol>propranolol on <i>some</i> PGWB, SCL-90-R, and Life Satisfaction indices and no differences on Insomnia Symptom Questionnaire or Sexual Function Questionnaire |
| Walle 1994 ³ (Fair) | Atenolol vs. metoprolol CR Crossover N=16 | 6 | NR | Atenolol>propranolol on 1 MSE item; no differences in all other MSE and PGWB scores |
| Buhler 1986 ¹⁷ (Fair) | Atenolol vs. bisoprolol Crossover N=104 | 8 | 2-6 | No differences on unspecified self-assessment questionnaire |
| Dahlof 1988 ¹⁸ (Fair) | Atenolol vs. metoprolol CR Crossover N=74 | 6 | NR | No differences on MSE or Jern's quality of life questionnaires |

Two placebo-controlled trials reported the effect of long-term beta blocker therapy on quality of life in otherwise healthy patients who have hypertension (Evidence Tables 1 and 1a). The Trial of Antihypertensive Interventions and Management (TAIM)²⁰⁻²² had a serious flaw: only patients who were available for the 6-month blood pressure readings (79.4%) were included in the quality-of-life analysis. After 6 months, atenolol and placebo were similar on several dimensions from the *Life Satisfaction Scale, Physical Complaints Inventory, and Symptoms Checklist*, including *summary* (‘Total physical problems’, ‘Overall psychological functioning’, ‘Overall life satisfaction’), *distress* (‘Sexual physical problems’, ‘Depression’, ‘Anxiety’, ‘Sleep disturbances’, ‘Fatigue’), and *well-being* (‘Satisfaction with physical health’, ‘Sexual satisfaction’). In the second trial,²³ there were no differences between propranolol and placebo in cognitive or psychological measures after one year of treatment.

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

Summary

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

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

Detailed Assessment

In 1966 the first beta blocker, propranolol, was shown in a multicenter controlled trial to improve symptoms in patients with angina pectoris.²⁴ Several other beta blockers (acebutolol, atenolol, metoprolol tartrate, metoprolol succinate, nadolol, propranolol, propranolol long-acting) have been demonstrated to reduce symptoms of angina in placebo-controlled trials.

Most head-to-head trials of beta blockers in patients with angina pectoris observe patients for only two to four weeks of treatment.²⁵⁻³² In these trials, exercise tolerance, attack frequency, or nitroglycerin use were generally similar at comparable doses.

Five fair-quality head-to-head trials evaluated angina symptoms after two or more months of treatment with beta blockers (Table 5, Evidence Tables 2 and 2a). Mean ages ranged from 55 to 61.5 years and most subjects were men (71.5 percent to 100 percent). Exercise parameters were measured using bicycle ergometric testing in all but two trials,^{33,34} which used a treadmill. There were no significant differences in exercise tolerance or attack frequency.

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

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

sl ntg=sublingual nitroglycerin

Over the long-term, beta blockers may differ in their ability to prevent or reduce the severity of anginal attacks. In one fair quality 2-year multicenter European trial, propranolol was better than placebo after 8 weeks but not after 24 weeks of treatment.³⁵ Specifically, after 8 weeks propranolol 60-240 mg reduced the proportion of patients using nitroglycerin (57% vs. 73% in the placebo group; $p=0.04$) and increased the mean total work time by 48% vs. 13% ($p=0.04$). These effects were transient, however, and propranolol was equivalent to placebo on those parameters after 24 weeks of treatment. Propranolol and placebo had similar effects on the number of weekly angina attacks, the number of attack free days, maximum workload, and exercise duration at eight- and 24-week endpoints. The relevance of this trial is limited, because, since the time it was conducted, the rate of progression of angina may have been altered by advances in treatment of atherosclerosis (e.g., statin therapy).

A good-quality meta-analysis identified 72 randomized controlled trials of a beta blocker vs. a calcium channel blocker and 6 trials comparing a beta blocker to a nitrate.³⁶ 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?

We did not examine the short-term (4-10 days) use of beta blockers to prevent or control atrial tachyarrhythmias after CABG.³⁷⁻⁴¹ In addition to the beta blockers included in our review, esmolol, a very short-acting, intravenous beta blocker, is used postoperatively to control tachyarrhythmias.

In 7 trials, long-term use of a beta blocker after CABG did not improve mortality or other outcomes (Evidence Tables 3 and 3a). For example, the MACB Study Group conducted a fair quality trial⁴² that randomized 967 patients (85.5% male, median age 64 years) to metoprolol 200 mg once daily or placebo within 5-21 days following CABG and measured the effects of treatment on death and cardiac events. No differences between metoprolol and placebo were found in mortality (3.3% vs. 1.8%; $p=0.16$) or in ischemic events (e.g., MI, unstable angina, need for additional CABG or PTCA).

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

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, all in the Norwegian Multicenter Study.⁴³ Subsequently, similar total mortality reductions were reported across trials of acebutolol,⁴⁴ metoprolol tartrate (Goteborg), and propranolol (BHAT) in comparable populations. In addition, similar benefits in sudden death were reported for propranolol⁴⁵ and metoprolol tartrate^{46, 47} and in reinfarction for metoprolol tartrate.⁴⁷

Carvedilol reduced reinfarction rates in the 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-MI patients who are already taking an ACE inhibitor. An extended-release form of carvedilol (carvedilol phosphate)

was approved by the U.S. FDA 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

| Trial | Mortality reduction in general population of post-MI patients | Mortality reduction in post-MI patients with LV dysfunction | Sudden death reduction | Reinfarction reduction |
|----------------------|--|--|-------------------------------|--|
| Acebutolol | Effective | Uncertain | Insignificant effect | Insignificant effect |
| Carvedilol | Not established | Effective | Uncertain (trend) | 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 |

Detailed Assessment

Early, routine use of beta blockers after myocardial infarction reduces mortality and rates of hospital admission. We identified two head-to-head trials of different beta blockers after MI.^{48, 49} A 6-week trial comparing atenolol 100 mg to propranolol 120mg had inconclusive results.⁴⁸ 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 LVEF 53.9% at baseline. The primary outcome of the study was the change in LVEF at 1 year; time to first serious cardiovascular event was a secondary endpoint. No significant difference was found between the two interventions in either change in LVEF (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).⁴⁹ 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.

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

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

Mortality

Three systematic reviews have analyzed over 60 trials of beta blockers after MI.⁵⁰⁻⁵² The first (Yusuf, 1985) analyzed 22 long-term trials of beta blockers in acute myocardial infarction. Overall beta blockers reduced mortality by 23%, from an average of 10% to 8%. The second (Hjalmarson, 1997) found an average 20% mortality reduction in 24 trials of a total of 25,000 patients.

A more recent review (Freemantle, 1999) used meta-regression to examine the relationship of characteristics of different beta blockers with the outcome of treatment.⁵² 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 one trial of carvedilol, a pilot study in 151 post-MI patients (Basu et al., 1997).⁵³

Table 7 summarizes placebo-controlled trials that enrolled > 100 patients, had long-term follow-up (> 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 2001.⁵⁴ Unlike the other trials, CAPRICORN included only patients who had reduced left ventricular function ($\leq 40\%$) after acute myocardial infarction as determined by echocardiography or cardiac catheterization. Patients with uncontrolled heart failure, such as those requiring intravenous diuretics, were excluded. Of 1959 subjects randomized to either carvedilol or placebo at an average of 10 days following a confirmed MI, 1289 had no clinical signs of heart failure (Killip Class I), 593 had Killip Class II heart failure, and 65 had Killip Class III failure. The mean ejection fraction was 32.8%.

The original primary endpoint was all-cause mortality. 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% vs. 37% for placebo over 1.3 years, $p=0.299$). However, carvedilol reduced the *original* primary endpoint of total mortality (12% vs. 15% for placebo over 1.3 years; NNT=30 or NNT for 1 year=43). The p value was 0.03, which, although nominally significant, did not meet the higher level of significance specified when the combined primary outcome measure was adopted.

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

The use of ACE inhibitors, thrombolytics, and angioplasty support the relevance of CAPRICORN to current care in the U.S. and Canada. However, the case for relevance could be strengthened if data were available to compare other practices and the quality of care between sites that recruited successfully and those that did not. Additional information about the recruitment of patients and the centers at which the CAPRICORN was conducted might provide additional insight into its relevance to current practice in the U.S. and Canada. Of the 1949 subjects in the trial, 83 were enrolled in the U.S. and 5 were from Canada. Five of the 6 top

recruiting sites were in Russia, which enrolled the most subjects of any country (600). Of the 163 study sites, 24 enrolled only 1 subject. In their *Lancet* paper, the authors of CAPRICORN noted that “recruitment was slow in some countries where it was widely perceived that the case for beta-blockers in all patients with myocardial infarction was proven.” The statement leaves open the possibility that, in North America, the subjects in CAPRICORN would already have been taking beta blockers.

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

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

There is no direct evidence that other beta blockers shown to reduce mortality in post-MI patients or in patients with heart failure work as well as carvedilol in post-MI patients with decreased LV function and few or no symptoms of heart failure. While the older trials undoubtedly included some subjects with LV dysfunction, it is difficult to determine how many, or how this subset did compared with post-MI patients with normal LV function. Indirect evidence comes from a good-quality meta-analysis.⁵⁵ 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 provide additional details supporting this hypothesis. One is from the BHAT trial (β Blocker Heart Attack Trial), a large, 3-month trial of propranolol published in 1980. In BHAT, 710 of 1916 subjects had a history of congestive heart failure prior to randomization. Propranolol lowered total mortality from 18.4% to 13.3% (a 27% reduction) in patients with a history of heart failure and from 7.8% to 5.9% (25% reduction) in patients who did not have a history of heart failure.⁵⁶

The other retrospective subgroup analysis is from a 1980 placebo-controlled trial of metoprolol. At the time of randomization, 262 (19%) of the 1,395 subjects had signs or symptoms of mild heart failure.⁵⁷ Metoprolol or placebo was administered intravenously once, followed by oral metoprolol or placebo for 3 months, followed by open treatment with metoprolol for up to 2 years in all patients who had signs of ischemia. For patients with heart failure, mortality during the first year of the study was 28%, versus 10% in subjects without signs of heart failure ($p < 0.0001$). Among the subjects with heart failure at the time of

randomization, metoprolol reduced mortality during the 3-month double-blind phase of the trial (14% vs. 27%, $p < 0.0009$, NNT=8).

Sudden death

Significant reductions in sudden death were reported in two of three trials of metoprolol tartrate,^{46,47} one trial of propranolol,⁴⁵ and one trial of timolol.⁴³

Reinfarction

Significant reductions in reinfarction rates were reported in one of two trials of metoprolol tartrate⁴⁷ and one trial of timolol.⁴³ 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-MI arrhythmia (defined as cardiac arrhythmia, fibrillation, or tachycardia) was found in placebo-controlled trials of acebutolol (1 trial)⁵⁸ or propranolol (1 trial),⁴⁵ while one 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% propranolol vs. 1.0% placebo; $p < 0.025$.)⁵⁹ One trial of timolol found a significantly higher proportion of patients experiencing ventricular tachycardia with placebo use (20% placebo versus 8.5% timolol; $p = 0.05$) while the number of episodes of ventricular tachycardia (55 placebo versus 10 timolol) was not statistically significant (data not provided).⁶⁰

Two publications comparing carvedilol to placebo presented mixed results. One older trial found no significant difference between the two drugs in the rate of cardiac arrhythmias among all enrolled patients.⁵³ In a subgroup analysis of patients ($n = 49/151$; 32%) with baseline LVEF $< 45\%$, 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.⁶¹ As stated above, patients enrolled in the CAPRICORN trial had baseline LVEF $\leq 40\%$. Atrial and ventricular arrhythmias were found to be less common with carvedilol use relative to placebo: HR 0.48 95% CI 0.30-0.76; $p = 0.0015$ and HR 0.37 95% CI 0.24-0.58; $p < 0.0001$, 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 three exceptions. Rates of withdrawal were greater for metoprolol tartrate in one⁶² of five trials, pindolol in one trial,⁶³ and propranolol in one trial.⁵⁹

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 |
|-----------------------------------|--------------------------------------|------------------|--------------------|--|-------------------------------|--------------------------------|----------------------------------|
| <i>Acebutolol</i> | | | | | | | |
| 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 |
| <i>Carvedilol</i> | | | | | | | |
| Basu* 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 |
| <i>Metoprolol tartrate</i> | | | | | | | |
| 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 |
| <i>Pindolol</i> | | | | | | | |
| 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 |
| <i>Propranolol</i> | | | | | | | |
| 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 |
| 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: .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 |

| Study, year | Interventions | Duration | Number enrolled | Total mortality | Sudden Death | Reinfarction | Withdrawals |
|----------------------------------|------------------------------|-----------|-----------------|---|-------------------------------|-------------------------------|----------------------------|
| Hansteen 1982 | A: Propranolol B: Placebo | 12 months | 560 | A: 9% (25/278) B: 13.1% (37/282) p=NS | A: 3.9% B: 8.1% p=0.038 | A: 3.9% B: 7.4% NS | A: 25.2% B: 25.5% NS |
| 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 |

*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?

Summary

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 U.S. had significant mortality reductions, the evidence for carvedilol may be more relevant to a U.S. population. When titrated gradually in stable patients, there is no difference in tolerability among these drugs.

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 2,289 patients with severe heart failure (COPERNICUS), carvedilol clearly reduced mortality and the combined endpoint of mortality and hospitalizations. Carvedilol has 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 similar to that for carvedilol in patients who had a similar mortality risk. This is a weaker level of evidence than that for carvedilol, but the lack of a direct comparator and the difficulty of comparing subjects from the different trials makes it uncertain whether one of these drugs is superior in patients with the various degrees of heart failure.

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

| Beta Blocker | Mortality reduction | Reduction in sudden death | Reduction in progressive heart failure | Improvement in NYHA class | Improvement in exercise parameters | Improvement in QOL |
|----------------------|----------------------------|----------------------------------|---|----------------------------------|---|---------------------------|
| Bisoprolol | Yes | Yes | Not proven | Yes | Not significant | Not significant |
| Carvedilol | Yes | Yes | Mixed results | Not proven | Not significant | Not significant |
| Carvedilol phosphate | No evidence | No evidence | No evidence | No evidence | No evidence | No evidence |
| Metoprolol Succinate | Yes | Yes | Yes | Not proven | Not significant | yes |

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

Detailed Assessment

Placebo-controlled trials

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 5 and 5a).⁶⁴⁻⁷¹ In general, these meta-analyses found that beta blockers reduce mortality by about 30%, preventing 3.8 deaths per 100 patients in the first year of treatment. Nevertheless, the authors of the meta-analyses agreed that larger trials were needed before beta blockers could be recommended routinely for patients with heart failure.

Four beta blockers (bisoprolol, bucindolol, carvedilol, and metoprolol succinate) have been evaluated in such trials (Table 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) each reduced total mortality (as planned primary endpoint) by approximately 35%. Bucindolol, in the BEST trial, was ineffective. The poor result for bucindolol suggests that individual beta blockers may differ in their effectiveness to reduce mortality in heart failure patients (bucindolol is not available in the U.S., but is included in Table 9 for comparison).

Table 10 summarizes 16 placebo controlled trials (including those in Table 9) that enrolled > 100 patients and met our other inclusion criteria (Evidence Tables 5 and 5a). These trials evaluated atenolol 50-100 mg,⁷² bisoprolol 5-10 mg,^{73, 74} carvedilol 50-100 mg,⁷⁵⁻⁸⁴ metoprolol tartrate 100-150 mg,^{85, 86} and metoprolol succinate (CR) 12.5-25 mg.^{87, 88}

The FDA approval of metoprolol succinate for mild to moderate heart failure (NYHA Class II or III) is based on MERIT-HF. FDA approval of carvedilol for severe heart failure is based on COPERNICUS. Its approval for mild-moderate heart failure is based on 5 other trials, 4 of which constitute the "U.S. Carvedilol Study," plus the Australian New-Zealand Heart failure

study (see Table 10). Heart failure is not an FDA-approved indication for bisoprolol, which is a generic drug.

Relation of mortality reduction to severity of heart failure

The trials in Table 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 an FDA indication in this group.

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

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

| <i>MERIT-HF Subgroups</i> | EF<25% | EF>25% |
|---------------------------|-----------|------------|
| NYHA Class II | 707 (“A”) | 928 |
| NYHA Class III-IV | 795 | 1561 (“D”) |

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

The 4 U.S. Carvedilol trials and the Australian-New Zealand trial demonstrated that in patients with NYHA Class II to IV heart failure, carvedilol reduced mortality. As shown in Table 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 2,289 subjects randomized, 627 were recruited from the U.S. and Canada; the rest were recruited in Europe (including Russia), the U.S., Canada, Israel, Australia, South Africa, Argentina, and Mexico. It is difficult to compare the COPERNICUS subjects to those of other trials because COPERNICUS did not report NYHA Class or exercise capacity, which were inclusion criteria in the other trials. COPERNICUS was intended to recruit a more severely ill population than the U.S. carvedilol trials. COPERNICUS subjects had higher mortality than 3 of the 4 trials that make up the U.S. Carvedilol Trial.

The mortality effect in COPERNICUS was consistent for sex, age, and other subgroups. The effect was lower, but not significantly so, for patients who had an EF<20% vs. those who

had EF>20% and for those recruited in Europe, Australia, and the Middle East vs. North and South America.

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

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

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

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

CIBIS-II was a well-conducted multicenter European study designed to recruit stable subjects with moderate to severe heart failure (NYHA Class III-IV).⁷⁴ Most patients were NYHA Class III. The annual placebo mortality rate was 13%, which is higher than the rate projected by the CIBIS-II investigators based on the results of CIBIS-I. Nevertheless, this mortality rate, and the average ejection fraction of 27%, are closer to those of MERIT-HF, which recruited mostly Class II and III patients, than to those of COPERNICUS, which is thought to have recruited NYHA Class III and IV patients.

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

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

| Trial | Drug and target dose | Ejection fraction criteria (mean) | NYHA class | Number of subjects | Annual placebo mortality | Mortality reduction | Withdrawal rate for active drug group [‡] |
|-----------------|------------------------|-----------------------------------|------------------------------------|--------------------|--------------------------|---------------------|--|
| CIBIS-II | Bisoprolol 10mg qd | <35% (0.27) | III (81%) IV (19%) | 2,647 | 13% | 34% | 15% |
| MERIT-HF | Metoprolol CR 200mg qd | <40% (0.28) | II (41%) III (56%) IV (3.6%) | 3,991 | 11% | 34% | 14% |
| BEST | Bucindolol 100mg bid | <35% | III-IV | 2,708 | 17% | 10%* | 23% |
| COPERNICUS | Carvedilol 25mg bid | <25% (0.20) | NR | 2,289 | 19% | 35% | 12.6% |
| US Carvedilol** | Carvedilol 25mg bid*** | ≤35% | II-IV | 1,094 | 12% | 65%§ | § |

[‡] All values were not different from the placebo group except for COPERNICUS (placebo withdrawal rate 15.9%, p=0.0026).

*Not significant.

**Planned analysis of pooled results of 4 independent, double-blind placebo-controlled trials.

***Dosage target was 50 mg bid in patients whose weight was 85 kg or more.

§ 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.

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 | NYHA class | Entry criterion for EF (average) | Mortality in placebo group (per year) | Mortality in treatment group (per year) | Sample size |
|------------|------------|---|----------------|----------------------------------|---------------------------------------|---|-------------|
| Sturm 2000 | Atenolol | Combined worsening heart failure or death | II-III | ≤ 25% (17%) | 5.0% | 8.0% | 100 |
| CIBIS | Bisoprolol | Mortality | III-IV | <40% (0.25) | 10.4% | 8.3% | 641 |
| CIBIS-II | Bisoprolol | Mortality | III-IV | <35% (0.275) | 13.2% | 9.0% | 2647 |
| Bristow* | Carvedilol | Exercise tolerance | II-IV | ≤35% (0.23) | 33.8% | 10.9% | 345 |
| Packer* | Carvedilol | Exercise tolerance | II-IV | ≤35% (0.22) | 14.0% | 15.3% | 278 |
| Colucci* | Carvedilol | Progression of heart failure | II-III | ≤35% (0.23) | 6.4% | 2.2% | 366 |
| Cohn* | Carvedilol | Quality of life | III-IV | ≤35% (0.22) | 8.6% | 4.3% | 105 |
| ANZ * | 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 | Not reported** | < 25% (0.20) | 20.9% | 14.0% | 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* | Metoprolol-CR | Exercise tolerance, neurohumeral parameters | I-IV | <40% (0.28) | 16.0% | 8.4% | 768 |

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

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

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

NYHA class

The effect on NYHA class rating was inconsistently reported. The CIBIS trial found that significantly more patients taking bisoprolol improved by at least one NYHA class (21% vs. 15%; p=0.03) but there was no differences in patients that deteriorated by at least one class (13% vs. 11%). Results were mixed for carvedilol. Three trials suggest carvedilol is superior to placebo in improving the overall NYHA class distribution.^{76, 77, 82} This includes the MUCHA trial of Japanese patients with heart failure.⁸² In three other trials, including a subset of dialysis patients with heart failure,⁸³ carvedilol had no effect.^{75, 79, 83} Metoprolol tartrate did not significantly improve NYHA class in either of two trials. In the MERIT-HF trial, metoprolol CR increased the proportion of patients that improved by at least one NYHA class overall (28.6% vs. 25.8%; p=0.003). A post-hoc analysis found the same effect in a subgroup of patients with baseline NYHA class III-IV and LVEF < 25% (46.2% vs. 36.7%; p=0.0031).⁸⁹ By contrast, carvedilol did not reduce progression of heart failure in COPERNICUS.

Exercise capacity

The carvedilol trials^{75-77, 79} were consistent in showing equivalency to placebo in exercise capacity improvement as measured by both the 6-minute walk and 9-minute treadmill tests. Results of treadmill testing (modified Naughton protocol) were mixed in two placebo controlled trials of metoprolol.

Quality of life

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 moderate⁷⁵⁻⁷⁷ or severe⁷⁸ 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 two trials.^{88, 90}

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 | NYHA class improvement | Exercise capacity | Quality of life |
|--|--------------|--|---|--|---|--|---|
| Sturm 2002 | atenolol | 10% vs. 16% NS | NR | 16% vs. 39% NS | NR | NR | NR |
| Anonymous 1994 <i>CIBIS</i> | 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 <i>CIBIS-II</i> | bisoprolol | 12% vs. 17% p<0.0001 NNT=19 | 4% vs. 6% p=0.0011 NT=38 | NR | NR | NR | NR |
| Bristow 1996 <i>US Carvedilol Heart Failure Study Group: MOCHA</i> | 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 <i>US Carvedilol Heart Failure Study Group: PRECISE</i> | 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 <i>US Carvedilol Heart Failure Study Group: Mild</i> | carvedilol | 0.9% vs. 4% NS | NR | Heart failure progression (deaths+hospitalizations + need for more medications) 25/232(11%) | Improved: 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) NS |

| Study Year | Beta blocker | All-cause mortality rates p-value NNT | Sudden death rates p value NNT | Death due to heart failure p value NNT | NYHA class improvement | Exercise capacity | Quality of life |
|---|---------------------|--|---|--|---|---|--|
| | | | | 28/134(20.9%) p=0.008 NNT=10 | | | |
| 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 <i>Australia/New Zealand Heart Failure Research Collaborative Group</i> | 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 <i>COPERNICUS</i> | carvedilol | 11.2% vs. 16.8% p=0.0001 3 NNT=19 | 6.1% vs. 3.9% p=0.016 NNT=46 | NR | NR | NR | NR |
| Cleland 2003 <i>CHRISTMAS</i> | carvedilol | 4.3% vs. 3.2% NS | NR | NR | NR | Exercise time (method nr) (seconds): 405 vs. 427 NS | NR |
| Hori 2004 <i>MUCHA (Japanese patients)</i> | 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 <i>MDC</i> | 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) |
| Waagstein 2003 | metoprolol tartrate | 4.6% vs. 3.8% NS | NR | NR | Improved: 42% vs. 33% NS | Bicycle test: met=pla (data nr) | 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 | NYHA class improvement | Exercise capacity | Quality of life |
|--|----------------------|---|--------------------------------------|--|-----------------------------|---|--|
| Anonymous 1999 <i>MERIT-HF</i> | metoprolol succinate | 7.3% vs. 10.8% p=0.0000 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 <i>RESOLVD</i> | 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 <i>Australia/ New Zealand Heart Failure Research Collaborative Group</i> | 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 |

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

Head-to-head trials

There are no direct comparator trials comparing two or more of the drugs proven to reduce mortality (bisoprolol, carvedilol, and sustained release metoprolol succinate). Six fair-quality, head to head trials compared immediate-release metoprolol tartrate to carvedilol in patients with heart failure (see Evidence Tables 5b and 5c for characteristics and quality assessments and Evidence Table 6 for outcomes).⁹¹⁻⁹⁶ These trials recruited stable patients with Class II-IV (mainly II and III) heart failure, most of whom took ACE inhibitors and diuretics.

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

When COMET was designed, extended-release metoprolol was not yet available, and immediate-release metoprolol was a logical comparator because, in the MDC trial, metoprolol tartrate was clearly effective, even though it did not change mortality. Specifically, metoprolol tartrate improved ejection fraction, LVEDP, and exercise time and prevented clinical deterioration, reducing the need for transplantation by almost 90% during the followup period.⁸⁵

Mortality

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

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

Other outcomes

Evidence on numerous secondary outcomes from the COMET trial have been published.^{97,98} Carvedilol was superior to immediate-release metoprolol in reducing rates of cardiovascular death, sudden death, and stroke and similar to immediate-release metoprolol in reducing death due to circulatory failure and other CV deaths, as well as in reducing days lost due to impaired well-being.^{97,98}

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 one exception.^{97,98} Rates of non-cardiovascular death, worsening heart failure, change in NYHA classification, and medication withdrawal were similar for carvedilol and immediate release metoprolol.⁹⁷

With regard to combined endpoints, carvedilol was superior in reducing rates of fatal or nonfatal MI and the combination of cardiovascular death, heart transplantation, hospitalization for nonfatal acute MI, or worsening heart failure and was similar to immediate-release metoprolol in reducing the combined rate of all-cause mortality and cardiovascular hospitalizations.⁹⁷ 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 four years when compared to baseline composite scores ($p=0.0068$).⁹⁸ 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/d) had similar effects on quality of life, but metoprolol improved exercise capacity more. There were no differences between the carvedilol and metoprolol groups in quality of life.

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

Several beta blockers have been used to reduce the heart rate in patients with atrial tachyarrhythmias and to prevent relapse into atrial fibrillation or flutter. A recent good quality systematic review examined 12 studies of rate control in patients with chronic atrial fibrillation.⁹⁹

Atenolol, nadolol, and pindolol were effective in controlling the ventricular rate, while labetalol was no more efficacious than placebo.

We found one head-to-head trial comparing bisoprolol 10 mg and carvedilol 50 mg in patients subjected to cardioversion of persistent atrial fibrillation (> 7 days).¹⁰⁰ This fair-quality, 12-month trial enrolled 90 patients (mean age=65.5; 82% male) (Evidence Tables 7 and 7a). Similar proportions of patients relapsed into atrial fibrillation during follow-up in the bisoprolol and carvedilol groups (53.4% vs. 43.6%; p=NS).

Two placebo-controlled trials evaluated beta blockers in patients with persistent atrial fibrillation.¹⁰¹⁻¹⁰³ One placebo-controlled trial found that metoprolol CR/XL 100-200 mg was effective in preventing relapse of atrial fibrillation/flutter after cardioversion (Evidence Table 7).^{101, 102} This fair quality trial was conducted in Germany and enrolled 433 patients after cardioversion of persistent atrial fibrillation that were 70% male, with a mean age of 60. Over 6 months, atrial fibrillation or flutter relapse rates were significantly lower in patients taking metoprolol CR/XL (48.7% vs. 59.9%; p=0.005). This trial was not powered to detect differences in rates of mortality as a primary endpoint. Death was reported as an adverse event and rates were not significantly different for the metoprolol CR/XL and placebo groups (3.1% vs. 0.)

The other study examined the effects of carvedilol in managing patients with concomitant atrial fibrillation and heart failure.¹⁰³ This study was divided into two 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 NYHA class II-III; mean LVEF=24.1%) were enrolled in this fair-quality study. When added to digoxin, carvedilol significantly lowered the 24-hour ventricular rate (65.2 vs. 74.9bpm; p<0.0001) and improved mean LVEF scores (30.6% vs. 26%; p=0.048) and severity of symptoms/functional capacity on a 33-point scale (6 vs. 8; p=0.039). 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?

Summary

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

Detailed Assessment

Head to head trials

We found five fair quality¹⁰⁴⁻¹⁰⁹ 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.^{110, 111} This trial was rated poor quality due to inadequate descriptions of

methods of randomization and allocation concealment, lack of use of an intention to treat principle, and a high rate of attrition (37.6%).

The five included trials compared propranolol 160 mg to atenolol 100 mg,¹⁰⁷ slow release metoprolol (durules) 200 mg daily,¹⁰⁵ immediate release metoprolol 200 mg daily,¹⁰⁴ timolol 20 mg,^{108, 109} and propranolol 80 mg to metoprolol 100 mg daily.¹⁰⁶ All five trials were conducted outside of the U.S., were relatively short-term in duration (12-20 weeks), and were small (35-96 patients). Most patients had common migraine per Ad Hoc Committee and World Federation of Neurology Research Group guidelines (83-93%) and migraine without aura per International Headache Society (92.8%). These patients have mean ages of 33.8-42.3, are 68.6-88.9% female, and have a history of migraine frequency of >3 attacks per month. Use of concomitant analgesics and ergotamines was allowed for abortive migraine treatment. Headache frequency, intensity, severity, duration, and abortive treatment tablet usage efficacy parameters were analyzed using patient diary data.

The methods used to assess treatment effects differed across studies. Some of the common outcome results are summarized in Table 13 below. Analysis of variance was used to assess comparative efficacy of metoprolol 200 mg and propranolol 160 mg in one trial.¹⁰⁴

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.^{104-106, 108, 109} A recent, well-conducted systematic review comparing propranolol to other beta blockers found that there was little difference between propranolol and the comparators (metoprolol, nadolol, timolol) in reducing attack frequency (SMD -0.01 95% CI -0.24-0.22) based on data from four crossover trials.¹¹²

Migraine days

There were differences across trials in methods of assessment of this parameter. When the total number of headache days recorded over 42 days across all 28 patients analyzed was considered in the Stensrud trial, no difference between atenolol and propranolol treatment was found. Metoprolol durules and metoprolol tartrate reduced number of migraine days at rates similar to propranolol across three trials.¹⁰⁴⁻¹⁰⁶

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.^{105, 106, 108, 109}

Tablet consumption

There were no differences in reduction of acute medication (analgesics, ergots) for metoprolol durules or metoprolol tartrate and propranolol.^{105, 106, 108, 109}

Subjective assessment

Patients in two trials^{105, 106} were asked to make a subjective assessment of therapeutic improvement using descriptors of marked, moderate, slight, and unchanged or worse. There were no differences found between slow release metoprolol (durules) and propranolol (76% vs.

63%) or between low doses of immediate release metoprolol or propranolol (63% vs. 64%) in rates of decreased frequency of mean or median attacks per month.

Miscellaneous

Two trials¹⁰⁷⁻¹⁰⁹ 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 wks (% decrease) | Headache days | Severity (% reduction) | Tablet consumption | Subjective (% patients regarding effect as "marked" or "moderate") | Misc. |
|--|--------------------------------------|------------------------|------------------------|---|--|---|
| Stensrud, 1980 Ate 100 mg vs pro 160 mg n=28 | NR | 247 vs. 257 | NR | NR | NR | Headache Index1 (mean): 410 vs. 437 |
| Kangasniemi, 1984 Met-d 200 mg vs pro 160 mg n=35 | 43.4% vs. 43.4% | 45.6% vs. 43.8% | 21.8% vs. 29.8% | 45.3% vs. 45.3% | 76% vs. 63% | NR |
| Olsson, 1984 Met 100 mg vs. pro 80 mg n=53 | NR | 25.4% vs. 32.8% | 21.8% vs. 29.8% | Ergotamine: 47% vs. 43.1% Analgesic: 16.5% vs. 37.4% | 63% vs. 64% | NR |
| Gerber, 1991 Met 200 mg vs pro 160 mg Met=22; pro=19 | No differences (ANOVA) | No differences (ANOVA) | No differences (ANOVA) | Ergotamine: No differences (ANOVA) | NR | % reduction in duration (hours): No differences (ANOVA) |
| Tfelt-Hansen, 1984; Standnes, 1982 Tim 20 mg vs pro 160 mg n=80 | 44% vs. 38%; p=NS | NR | 10% vs. 6%; p=NS | NR | NR | % reduction in Headache Index1: 49% vs. 41%; p=NS Headache Index2: 53% vs. 43%; p=NS |

Headache Index1: attack frequency x severity x duration

Headache Index2: attack frequency x severity

Placebo-controlled trials

We found 18 fair quality, placebo controlled trials (see Evidence Tables 8 and 8a) of atenolol 100 mg,¹¹³ bisoprolol 5 or 10 mg,¹¹⁴ metoprolol slow release (durules) 200 mg,^{115, 116} pindolol 7.5-15 mg,^{117, 118} propranolol immediate release 80-240 mg,¹¹⁹⁻¹²⁷ and long acting propranolol 160 mg.^{128, 129} One trial¹³⁰ did not report propranolol dosage and will be discussed separately.

All but two^{121, 130} of these trials were conducted outside of the U.S. A crossover design was used in 12 trials, while the other five compared parallel groups. All but two trials reported allowing the use of various concomitant medications to abort migraine pain including common analgesics, ergotamines, and narcotics. These trials ranged in duration from 8-52 weeks,

generally enrolling patients with a 1-2 year history of common or classic migraine (Ad Hoc Committee), generally occurring at an average frequency of three per week. One trial included only patients with classic migraine.¹¹⁶ Patient characteristics reflected the target migraine population, with mean ages in the range of 37-39 and gender predominantly female (> 75%). Sample sizes ranged from 24-259 patients enrolled. Assessment of attack frequency, duration, severity, and use of acute medication variables was made using patient diary card data.

Placebo controlled trial data is consistent with head to head trial data for atenolol 100 mg, slow release metoprolol (durules) 200 mg, and propranolol 80 and 160 mg as discussed above and adds information regarding efficacy of bisoprolol and pindolol. An exception was found in one of the ten fair quality trials of propranolol¹²² where a dosage of 120 mg was not significantly superior to placebo in increasing the proportion of patients that had at least a 50% reduction of migraine attacks in the last four weeks of treatment (42.3% vs. 30.9%) or in reducing the mean duration of migraine in hours per month (34.4 vs. 13.7).

Bisoprolol

The results of one placebo controlled trial of 12 week's duration and involving 226 patients¹¹⁴ indicate that both bisoprolol 5 and 10 mg daily had a significant ($p < 0.05$) effect in reducing attack frequency (39% for both bisoprolol doses vs. 22% for placebo). Neither dose of bisoprolol showed any obvious influence on reducing attack duration or severity.

Pindolol

The results of two placebo controlled trials of pindolol 7.5-15 mg daily^{117, 118} in a total of 58 patients with predominantly common migraine show no obvious advantage of this nonselective beta blocker in reducing averages per four weeks in headache frequency, headache index, or duration of attacks.

Twelve other placebo controlled trials of beta blockers were found.^{108, 109, 131-140} 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 a one meta-analysis¹⁴¹ that evaluated the effects of propranolol in 2403 migraine patients across a combination of 53 head to head, active- and placebo-controlled trials published through 1991. This review was rated poor quality due to failure to report critical assessment of internal validity and will not be discussed here. We independently assessed and included three head to head and 12 placebo controlled trials from this meta-analysis in our report.

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

Summary

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

Detailed Assessment

Head-to-head trials

We found one head to head trial of beta blockers for the treatment of bleeding esophageal varices.¹⁴² This trial compared the efficacy of propranolol 40-160 mg daily, a nonselective beta blocker, atenolol 100 mg daily, a selective beta blocker, and placebo in cirrhotic patients. The results of this trial are summarized in Evidence Tables 9 and 9a. This trial was rated fair quality. This trial, conducted in Italy, was designed to measure rebleeding and death and had a mean follow-up of 357 days. The patient population enrolled was typical for esophageal variceal bleeding, with a mean age of 53, 80.8% male and 81.9% alcoholic patients. This study also enrolled a small proportion of patients in which the prior hemorrhage was of a gastric erosion (12.8%) or unknown (inconclusive endoscopy) (6.4%) origin. Concomitant use of ranitidine, oral antacids, spironolactone, saluretics, lactulose, and nonabsorbable antibiotics was allowed.

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

Other-controlled trials

We found numerous fair-quality, placebo-controlled trials of nadolol¹⁴³ and propranolol¹⁴⁴⁻¹⁵¹ for the secondary prevention of bleeding esophageal varices secondary to cirrhosis and schistosomiasis.¹⁵² Results are summarized in Evidence Tables 9 and 9a. These trials were all conducted outside of the U.S., enrolled samples of 12-84 patients, and ranged from 3 months to 2 years in duration. Mean ages ranged from 43-60 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 three of the trials.^{144, 147, 151}

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 two early treatment trials.^{144, 151} A significant difference between the effects of slow release propranolol and placebo was found in a third early treatment trial (20% vs. 75%; $p < 0.05$).¹⁴⁷ For trials of later (≥ 14 days)^{146, 148, 149, 153} and unspecified^{145, 154} treatment initiation, atenolol was equivalent to placebo (31% vs. 24%), nadolol was superior (25% vs. 71%; $p < 0.05$), results of immediate release propranolol trials were mixed, and long-acting propranolol was superior (2% vs. 20%; $p < 0.02$).

Table 13. Variceal rebleeding rates

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

*p-value based on log-rank test

Deaths due to variceal rebleeding were reported by seven comparisons to placebo across six trials.^{144-146, 148, 151, 153} Results are summarized in Table 14 below and in Evidence Tables 9 and 9a. In one trial of atenolol and five trials of propranolol, no differences from placebo in effect on death due to variceal rebleeding were established regardless of treatment initiation interval. In one trial of patients with portal hypertension secondary to schistosomiasis,¹⁵⁴ 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 | pro vs. pla | n=48 | 48 hrs | 15% vs. 9% |
| Villeneuve, 1986 | pro vs. pla | n=79 | 6-72 hrs | 12% vs. 19% |
| Late intervention | | | | |
| Colombo, 1989 | ate vs. pla | n=94 | ≥ 15 days | 3% vs. 10% |
| Colombo, 1989 | pro vs. pla | n=94 | ≥ 15 days | 3% vs. 10% |
| Lebrec, 1981b | pro vs. pla | n=74 | 2 weeks | 0% vs. 17%; p<0.05 |
| Lo, 1993 | pro vs. pla | n=59 | unspecified | 12% vs. 7% |
| Sheen, 1989 | pro vs. pla | n=18 | 10-14 days | 0% vs. 11% |

All-cause mortality

No trial of patients with bleeding esophageal varices involved large enough sample sizes to measure all-cause mortality with sufficient power. Although crude trends suggest numerically smaller numbers of patients taking atenolol, nadolol and propranolol experienced deaths due to any cause in all but one trial of propranolol,¹⁴⁴ 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 | pro vs. pla | n=48 | 48 hrs | 15% vs. 23% |
| Villeneuve, 1986 | pro vs. pla | n=79 | 6-72 hrs | 45% vs. 38% |
| Late intervention | | | | |
| Colombo, 1989 | ate vs. pla | n=94 | ≥ 15 days | 9% vs. 23% |
| Gatta, 1987 | nad vs. pla | n=24 | 15-40 days | 8% vs. 27% |
| Colombo, 1989 | pro vs. pla | n=94 | ≥ 15 days | 13% vs. 23% |
| Lo, 1993 | pro vs. pla | n=59 | unspecified | 31% vs. 33% |
| El Tourabi, 1994 | LA pro vs. pla | n=82 | unspecified | 7% vs. 18% |

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 (12-58 months) directly comparing beta blockers in patients with hypertension (atenolol vs. bisoprolol vs. propranolol), heart failure (carvedilol vs. metoprolol), bleeding esophageal varices (atenolol vs. propranolol), or atrial fibrillation (bisoprolol vs. 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 one series of 268 patients seen in a U.S. heart failure clinic, 54% were started on carvedilol and 46% on metoprolol succinate or metoprolol tartrate.¹⁵⁵ 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.¹⁵⁶ 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% vs. 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% vs. 17%) and a numerically lower proportion of patients with an LVEF < 25% (27% vs. 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 7 trials of patients with hypertension (Evidence Table 1),^{3, 6-9, 17, 18} 3 trials of patients with angina (Evidence Table 2),^{33, 34, 157} 3 trials of patients with heart failure (Evidence Table 5b),^{86, 92, 95, 158} 6 trials of migraine patients (Evidence table 8),^{104-107, 109, 159} 1 trial of patients with bleeding esophageal varices (Evidence Table 9),¹⁴² 2 trials of patients post-myocardial infarction (Evidence Table 4),^{48, 49} and 1 trial of patients with atrial fibrillation (Evidence table 7).¹⁰⁰ 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 28-3029 patients. All but one¹⁰⁴ of the head to head trials in patients with migraine used crossover designs, only reporting results of the combined intervention periods.

Only one trial⁷ 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-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 13 head to head trials.^{3, 6, 8, 17, 18, 33, 34, 95, 105, 106, 109, 110, 157} Rates varied across the trials. For example, rates for carvedilol and metoprolol in a three-month trial of 368 angina patients were 30% and 25%, respectively, as compared to 96% and 94% in a 58 month trial of 3029 patients with heart failure. No significant differences between the beta blocker comparisons were found, with one exception. In one 8-week trial of 40 angina patients,³³ adverse events were more frequent in the propranolol group (94.4%) than in the pindolol group (17.4%; $p < 0.0001$). Specific adverse events seen more frequently in the propranolol group include fatigue (44.4% vs. 0; $p < 0.0005$) and mild hypotension (27.8% vs. 0; $p = 0.0114$). The difference in safety favoring pindolol should be interpreted with caution due to variation between groups in illness severity at baseline. The mean two-week angina attack rate (95% confidence interval) was higher in the propranolol group during run-in [28.5(26.4-30.6) vs. 18.4(17.4-19.4)]. This suggests problems with the randomization methods.

Withdrawals due to adverse events were reported by ten head to head trials.^{3, 6, 9, 17, 18, 86, 100, 109, 110, 142} No significant differences were found in any of the comparisons.

Specific adverse events

Bradycardia

Rates of bradycardia were reported in short-term hypertension trials and in longer-term heart failure trials.^{3, 6, 17, 18, 995} Overall, no significant differences between beta blockers were reported.

Dizziness

Seven head to head trials reported dizziness incidence.^{17, 49, 92, 107, 109, 110, 157} All but one reported no significant differences between beta blockers.⁹² Carvedilol was associated with higher rates of dizziness than metoprolol in a 44-month trial of 122 patients with heart failure (14.7% vs. 1.3%; p=0.0046).⁹² This significant difference was not seen in another shorter trial [3 months in 368 patients with angina (4.8% vs. 5.0%)],¹⁵⁷ nor was there a significant difference in rates of dizziness in a head to head trial of carvedilol versus atenolol in patients with recent myocardial infarction (36.4% vs. 27.2%; p=0.131).⁴⁹ Reasons for this inconsistency may include differences in definition of dizziness and evaluation techniques between the two trials. This assumption cannot be verified, however, as the methods were not provided. Indirect comparison of the inconsistent head-to-head trial results to available fair-good quality placebo-controlled trials safety data does not offer any additional information as dizziness rates in metoprolol trials were not reported.

Hypotension

Rates of hypotension were similar for carvedilol and metoprolol across two longer-term trials of patients with heart failure.^{92, 95} 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.

New-onset diabetes

Retrospective analysis of data from the COMET trial was used to study the development of new-onset diabetes in heart failure patients treated with metoprolol tartrate or carvedilol.¹⁵⁸ New-onset diabetes was identified post-hoc among a cohort of 2,298 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 two 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% vs. 8.7%; HR 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.

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 co-morbidities.

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.

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.¹⁶⁰ 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 (BBPP)¹⁶¹ analyzed mortality in post-infarction patients relative to subgroup risk factors from trials of propranolol,^{45, 59, 162} pindolol,⁵⁹ 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-analysis¹⁶³ 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.

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 Systolic Hypertension in the Elderly Program (SHEP) trial assessed the use of chlorthalidone versus 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.¹⁶⁴

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.⁵⁴ 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 U.S. Carvedilol Heart Failure Study Group published an analysis¹⁶⁵ of the pooled results from a stratified set of three fair-quality and one poor-quality concurrently conducted protocols,⁷⁵⁻⁷⁸ 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 trial⁸⁰ 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.¹⁶⁶ 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 3-46%) and was 37% (95% CI 22-48%) 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 review¹⁶⁷ that pooled results from five placebo controlled trials of metoprolol (Amsterdam, Belfast, Goteborg, LIT, Stockholm) found that neither age nor gender had a significant influence on mortality. When considered individually, results from the Goteborg Metoprolol Trial¹⁶⁸ show a nonsignificant trend that patients aged 65-74 years had a more marked reduction in mortality at 3 months post-myocardial infarction (45%) than did all patients aged 40-74 (36%). Results from the MERIT-HF trial also reported that 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.¹⁶⁹ This analysis found higher rates of all-cause mortality in the placebo group when compared to metoprolol (12.7% vs. 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 (BHAT)⁵⁹ comprised of 3,837 patients found that the protective of propranolol on mortality 25 months (average follow-up) following myocardial infarction was equivalent regardless of age or gender.

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

| Key Question 1: Comparative Efficacy | Grade of Evidence* | Conclusion |
|--|--|--|
| a. Hypertension | Overall grade: Poor | No head to head trials of long-term (≥ 6 months) health or QOL outcomes. Reliable indirect comparisons cannot be made by evidence from 3 long-term placebo-controlled trials of propranolol and atenolol. |
| b. Angina | Overall grade: Fair | No significant differences in 5 head to head trials of carvedilol vs. metoprolol, pindolol vs. propranolol and betaxolol and propranolol in patients with stable angina. Atenolol=bisoprolol in patients with chronic stable angina and COPD. Atenolol=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 (CABG) | Overall grade: Poor | Metoprolol did not benefit mortality or ischemic events in a longer-term (> 7 days), placebo-controlled trial (MACB). |
| d. Recent MI | Overall grade: Fair-good | 1 fair-quality head to head trial found no differences in mortality after one year between atenolol and propranolol, but this was a relatively small trial; 1 fair-quality head-to-head trial found no differences in time to serious cardiovascular events between carvedilol and atenolol. Similar mortality reductions reported for acebutolol, metoprolol tartrate, propranolol and timolol in placebo controlled trials of patients following myocardial infarction without other complications. Similar reductions in sudden death and reinfarction were reported for metoprolol tartrate and timolol and in sudden death for propranolol. No studies of carvedilol phosphate (extended-release carvedilol) in patients with recent MI were identified. Carvedilol reduced mortality and reinfarction in 1 placebo controlled trial of patients with a mean LVEF of $< 32.7\%$ (CAPRICORN). 4 systematic reviews were not designed to assess comparative efficacy. |
| e. Heart failure | Health outcomes in HTH trials: Fair Symptoms in HTH trials: | Carvedilol > metoprolol tartrate in reducing total mortality in COMET in patients with mild-moderate heart failure. Carvedilol=metoprolol tartrate in improving symptoms |

| | | |
|--|---|--|
| | <p>Good</p> <p>Placebo-controlled trials in mild-moderate HF: Good</p> <p>Placebo-controlled trials in severe HF: Fair+ for carvedilol and Fair- for metoprolol succinate</p> | <p>(quality of life; NYHA) and exercise capacity in 4 head to head trials.</p> <p>Metoprolol succinate reduced total mortality, sudden death, and death due to progressive heart failure and improved quality of life (MERIT-HF).</p> <p>Carvedilol reduced total mortality, sudden death, and death due to pump failure (MOCHA).</p> <p>Bisoprolol reduced total mortality and sudden death</p> <p>No studies of carvedilol phosphate (extended-release carvedilol) in patients with mild-moderate heart failure were identified.</p> <p>Carvedilol reduced mortality and the combined endpoint of mortality and hospitalizations in a prospective trial.</p> <p>A post-hoc, subgroup analysis of MERIT-HF suggests that metoprolol succinate is similarly effective in comparable patients.</p> <p>No studies of carvedilol phosphate (extended-release carvedilol) in patients with severe heart failure were identified.</p> |
| f. Atrial arrhythmia | Overall grade: Fair | <p>Bisoprolol=carvedilol in preventing relapse of atrial fibrillation in a head-to-head trial.</p> <p>Metoprolol succinate reduced incidence of atrial arrhythmia/fibrillation in a placebo-controlled trial</p> <p>Carvedilol reduced 24-hour ventricular rate in patients with atrial fibrillation and heart failure in one placebo-controlled trial.</p> <p>These placebo-controlled trials do not offer comparative data</p> |
| g. Migraine | Overall grade: Fair | <p>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.</p> |
| h. Bleeding esophageal varices | Overall grade: Poor | <p>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, don't clearly differentiate one beta blocker from another.</p> |
| Key Question 2: Adverse Effects | Quality of Evidence* | Conclusion |
| Hypertension, stable angina, heart failure, atrial arrhythmia, migraine, bleeding esophageal varices, previous myocardial infarction | Overall grade: Fair | <p>A few differences in specific adverse event rates were noted across longer-term trials directly comparing one beta blocker to another. But, overall, no particular beta blocker(s) stood out from the others as being consistently associated with a less favorable adverse effect profile.</p> |
| Key Question 3: Subgroups | Quality of Evidence* | Conclusion |
| a. Demographics (age, gender, race) | Overall grade: Fair | <p>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 one systematic review.</p> |

| | | |
|---------------------------------|----------------------------|---|
| <p>b. High risk populations</p> | <p>Overall grade: Fair</p> | <p><i>Heart failure.</i> Subgroup analyses of placebo controlled trials showed that a history of MI may reduce the protective effect of bisoprolol on mortality (CIBIS). No risk factor was found to confound the protective effect of carvedilol (COPERNICUS) or controlled release metoprolol (MERIT-HF) on mortality.</p> <p><i>Post-myocardial infarction.</i> 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.</p> <p><i>Diabetes:</i> Subgroup analysis of the SHEP trial found that the addition of atenolol to chlorthalidone did not significantly affect mortality relative to placebo. Metopronol use reduced all-cause mortality and hospitalizations relative to placebo in a subgroup analysis of the MERIT-HF trial.</p> |
|---------------------------------|----------------------------|---|

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

Table 18. Summary of comparative efficacy

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

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

| | | | | | | | | |
|---------|--|--|--|--|--|--------------|--|---|
| Timolol | | | | | | =propranolol | | Effective in reducing total mortality, sudden death, and reinfarction |
|---------|--|--|--|--|--|--------------|--|---|

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Appendix A. Search strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2004>
Search Strategy:

-
- 1 acebutolol.mp. or exp ACEBUTOLOL
 - 2 betaxolol.mp. or exp BETAXOLOL
 - 3 timolol.mp. or exp TIMOLOL
 - 4 1 or 2 or 3 (1436)
 - 5 hypertension.mp. or exp HYPERTENSION
 - 6 angina.mp. or exp ANGINA PECTORIS
 - 7 exp Coronary Artery Bypass/ or coronary artery bypass graft.mp
 - 8 myocardial infarction.mp. or exp Myocardial Infarction
 - 9 exp Heart Failure, Congestive/ or heart failure.mp
 - 10 Left ventricular dysfunction.mp. or exp Ventricular Dysfunction, Left
 - 11 Arrhythmia.mp. or exp Arrhythmia
 - 12 migraine.mp. or exp MIGRAINE
 - 13 exp "Esophageal and Gastric Varices"/ or bleeding esophageal varices.mp
 - 14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
 - 15 4 and 14
 - 16 randomized controlled trial\$.mp. or exp Randomized Controlled Trials/
 - 17 16 and 17
 - 18 from 18 keep 1-8
 - 19 from 19 keep 1-8
 - 20 from 20 keep 1-8
 - 21 atenolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 - 22 bisoprolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 - 23 carteolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 - 24 carvedilol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 - 25 labetalol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 - 26 metoprolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 - 27 nadolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 - 28 pindolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 - 29 penbutolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 - 30 propranolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
 - 31 4 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
 - 32 14 and 32
 - 33 limit 33 to (human and english language) [Limit not valid; records were retained]
 - 34 randomized controlled trial\$.mp. or exp Randomized Controlled Trials
 - 35 34 and 35
-

Database: Ovid MEDLINE(R) <1966- January Week 3 2005>
Search Strategy:

-
- 1 acebutolol.mp. or exp ACEBUTOLOL

2 betaxolol.mp. or exp BETAXOLOL
 3 timolol.mp. or exp TIMOLOL
 4 1 or 2 or 3 (1099)
 5 hypertension.mp. or exp HYPERTENSION
 6 angina.mp. or exp ANGINA PECTORIS
 7 exp Coronary Artery Bypass/ or coronary artery bypass graft.mp
 8 myocardial infarction.mp. or exp Myocardial Infarction
 9 exp Heart Failure, Congestive/ or heart failure.mp
 10 Left ventricular dysfunction.mp. or exp Ventricular Dysfunction, Left
 11 Arrhythmia.mp. or exp Arrhythmia
 12 migraine.mp. or exp MIGRAINE
 13 exp "Esophageal and Gastric Varices"/ or bleeding esophageal varices.mp
 14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
 15 4 and 14
 16 limit 15 to (human and english language)
 17 randomized controlled trial\$.mp. or exp Randomized Controlled Trials
 18 16 and 17
 19 from 18 keep 1-8
 20 from 19 keep 1-8
 21 from 20 keep 1-8
 22 atenolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
 23 bisoprolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
 24 carteolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
 25 carvedilol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
 26 labetalol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
 27 metoprolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
 28 nadolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
 29 pindolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
 30 penbutolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
 31 propranolol.mp. [mp=title, original title, abstract, name of substance, mesh subject
 heading]
 32 4 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
 33 14 and 32
 34 limit 33 to (human and english language)
 35 randomized controlled trial\$.mp. or exp Randomized Controlled Trials/
 36 34 and 35 (226)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations < January 27, 2005 >
 Search Strategy:

1 acebutolol.mp. or exp ACEBUTOLOL
 2 betaxolol.mp. or exp BETAXOLOL
 3 timolol.mp. or exp TIMOLOL
 4 1 or 2 or 3
 5 hypertension.mp. or exp HYPERTENSION

6 angina.mp. or exp ANGINA PECTORIS
7 exp Coronary Artery Bypass/ or coronary artery bypass graft.mp.
8 myocardial infarction.mp. or exp Myocardial Infarction
9 exp Heart Failure, Congestive/ or heart failure.mp
10 Left ventricular dysfunction.mp. or exp Ventricular Dysfunction, Left
11 Arrhythmia.mp. or exp Arrhythmia
12 migraine.mp. or exp MIGRAINE
13 exp "Esophageal and Gastric Varices"/ or bleeding esophageal varices.mp
14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15 4 and 14
16 limit 15 to (human and english language) [Limit not valid; records were retained]
17 randomized controlled trial\$.mp. or exp Randomized Controlled Trials
18 16 and 17
19 [from 18 keep 1-8]
20 [from 19 keep 1-8]
21 [from 20 keep 1-8]
22 atenolol.mp. [mp=title, abstract]
23 bisoprolol.mp. [mp=title, abstract]
24 carteolol.mp. [mp=title, abstract]
25 carvedilol.mp. [mp=title, abstract]
26 labetalol.mp. [mp=title, abstract]
27 metoprolol.mp. [mp=title, abstract]
28 nadolol.mp. [mp=title, abstract]
29 pindolol.mp. [mp=title, abstract]
30 penbutolol.mp. [mp=title, abstract]
31 propranolol.mp. [mp=title, abstract]
32 4 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33 14 and 32
34 randomized controlled trial\$.mp. or exp Randomized Controlled Trials

Database: Embase <1980-January 27, 2005>

Search Strategy: Not available

Appendix B. Search strategies for Update 3

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2007>

Search Strategy:

-
- 1 acebutolol.mp. or exp Acebutolol/ (336)
 - 2 atenolol.mp. or exp Atenolol/ (2387)
 - 3 betaxolol.mp. or exp Betaxolol/ (295)
 - 4 bisoprolol.mp. or exp Bisoprolol/ (339)
 - 5 carteolol.mp. or exp Carteolol/ (129)
 - 6 carvedilol.mp. (432)
 - 7 labetalol.mp. or exp Labetalol/ (325)
 - 8 metoprolol.mp. or exp Metoprolol/ (1982)
 - 9 nadolol.mp. or exp Nadolol/ (284)
 - 10 exp Penbutolol/ or penbutolol.mp. (107)
 - 11 pindolol.mp. or exp Pindolol/ (785)
 - 12 propranolol.mp. or exp Propranolol/ (3896)
 - 13 timolol.mp. or exp Timolol/ (1127)
 - 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 (10076)
 - 15 angina.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (6262)
 - 16 hypertension.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (18895)
 - 17 myocardial infarction.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (9213)
 - 18 CABG.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1125)
 - 19 coronary artery bypass graft.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (941)
 - 20 heart failure.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (5757)
 - 21 atrial arrhythmia.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (39)
 - 22 migraine.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1917)
 - 23 bleeding esophageal varices.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (164)
 - 24 varices.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1104)
 - 25 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (39766)
 - 26 14 and 25 (6011)
 - 27 limit 26 to yr="2005 - 2006" (185)
 - 28 limit 27 to ((clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or randomized controlled trial) and yr="2005 - 2006") (169)
 - 29 from 28 keep 1-169 (169)
-

Database: EBM Reviews - Cochrane Database of Systematic Reviews <1st Quarter 2007>
Search Strategy:

-
- 1 acebutolol.mp. or exp Acebutolol/ (11)
 - 2 atenolol.mp. or exp Atenolol/ (32)
 - 3 betaxolol.mp. or exp Betaxolol/ (9)
 - 4 bisoprolol.mp. or exp Bisoprolol/ (12)
 - 5 carteolol.mp. or exp Carteolol/ (5)
 - 6 carvedilol.mp. (8)
 - 7 labetalol.mp. or exp Labetalol/ (2)
 - 8 metoprolol.mp. or exp Metoprolol/ (28)
 - 9 nadolol.mp. or exp Nadolol/ (14)
 - 10 exp Penbutolol/ or penbutolol.mp. (5)
 - 11 pindolol.mp. or exp Pindolol/ (20)
 - 12 propranolol.mp. or exp Propranolol/ (50)
 - 13 timolol.mp. or exp Timolol/ (15)
 - 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 (71)
 - 15 angina.mp. [mp=title, abstract, full text, keywords, caption text] (149)
 - 16 hypertension.mp. [mp=title, abstract, full text, keywords, caption text] (620)
 - 17 myocardial infarction.mp. [mp=title, abstract, full text, keywords, caption text] (333)
 - 18 CABG.mp. [mp=title, abstract, full text, keywords, caption text] (36)
 - 19 coronary artery bypass graft.mp. [mp=title, abstract, full text, keywords, caption text] (24)
 - 20 heart failure.mp. [mp=title, abstract, full text, keywords, caption text] (247)
 - 21 atrial arrhythmia.mp. [mp=title, abstract, full text, keywords, caption text] (2)
 - 22 migraine.mp. [mp=title, abstract, full text, keywords, caption text] (69)
 - 23 bleeding esophageal varices.mp. [mp=title, abstract, full text, keywords, caption text] (3)
 - 24 varices.mp. [mp=title, abstract, full text, keywords, caption text] (32)
 - 25 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (973)
 - 26 14 and 25 (50)
 - 27 from 26 keep 1-50 (50)
-

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2007>
Search Strategy:

-
- 1 acebutolol.mp. or exp Acebutolol/ (13)
 - 2 atenolol.mp. or exp Atenolol/ (39)
 - 3 betaxolol.mp. or exp Betaxolol/ (6)
 - 4 bisoprolol.mp. or exp Bisoprolol/ (20)
 - 5 carteolol.mp. or exp Carteolol/ (0)
 - 6 carvedilol.mp. (23)
 - 7 labetalol.mp. or exp Labetalol/ (4)
 - 8 metoprolol.mp. or exp Metoprolol/ (42)
 - 9 nadolol.mp. or exp Nadolol/ (6)
 - 10 exp Penbutolol/ or penbutolol.mp. (2)

- 11 pindolol.mp. or exp Pindolol/ (20)
- 12 propranolol.mp. or exp Propranolol/ (36)
- 13 timolol.mp. or exp Timolol/ (14)
- 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 (92)
- 15 angina.mp. [mp=title, full text, keywords] (123)
- 16 hypertension.mp. [mp=title, full text, keywords] (294)
- 17 myocardial infarction.mp. [mp=title, full text, keywords] (317)
- 18 CABG.mp. [mp=title, full text, keywords] (44)
- 19 coronary artery bypass graft.mp. [mp=title, full text, keywords] (52)
- 20 heart failure.mp. [mp=title, full text, keywords] (157)
- 21 atrial arrhythmia.mp. [mp=title, full text, keywords] (0)
- 22 migraine.mp. [mp=title, full text, keywords] (45)
- 23 bleeding esophageal varices.mp. [mp=title, full text, keywords] (1)
- 24 varices.mp. [mp=title, full text, keywords] (16)
- 25 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (691)
- 26 14 and 25 (71)
- 27 (2005\$ or 2006\$ or 2007\$).do. (816)
- 28 26 and 27 (7)
- 29 from 28 keep 1-7 (7)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <March 14, 2007>
 Search Strategy:

- 1 acebutolol.mp. or exp Acebutolol/ (5)
- 2 atenolol.mp. or exp Atenolol/ (84)
- 3 betaxolol.mp. or exp Betaxolol/ (4)
- 4 bisoprolol.mp. or exp Bisoprolol/ (16)
- 5 carteolol.mp. or exp Carteolol/ (0)
- 6 carvedilol.mp. (66)
- 7 labetalol.mp. or exp Labetalol/ (1)
- 8 metoprolol.mp. or exp Metoprolol/ (68)
- 9 nadolol.mp. or exp Nadolol/ (6)
- 10 exp Penbutolol/ or penbutolol.mp. (0)
- 11 pindolol.mp. or exp Pindolol/ (13)
- 12 propranolol.mp. or exp Propranolol/ (120)
- 13 timolol.mp. or exp Timolol/ (22)
- 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 (345)
- 15 limit 14 to yr="2005 - 2007" (282)
- 16 limit 15 to (english language and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or randomized controlled trial)) (8)
- 17 from 16 keep 1-8 (8)

Database: Ovid MEDLINE(R) <1996 to March Week 1 2007>

Search Strategy:

-
- 1 acebutolol.mp. or exp Acebutolol/ (129)
 - 2 atenolol.mp. or exp Atenolol/ (2070)
 - 3 betaxolol.mp. or exp Betaxolol/ (352)
 - 4 bisoprolol.mp. or exp Bisoprolol/ (489)
 - 5 carteolol.mp. or exp Carteolol/ (132)
 - 6 carvedilol.mp. (1336)
 - 7 labetalol.mp. or exp Labetalol/ (195)
 - 8 metoprolol.mp. or exp Metoprolol/ (1809)
 - 9 nadolol.mp. or exp Nadolol/ (298)
 - 10 exp Penbutolol/ or penbutolol.mp. (35)
 - 11 pindolol.mp. or exp Pindolol/ (777)
 - 12 propranolol.mp. or exp Propranolol/ (5616)
 - 13 timolol.mp. or exp Timolol/ (1149)
 - 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 (12127)
 - 15 limit 14 to (humans and english language and yr="2005 - 2007" and clinical trial) (158)
 - 16 from 15 keep 1-151 (151)
 - 17 (20061\$ or 2007\$).ed. (281559)
 - 18 15 and 17 (11)
 - 19 from 18 keep 1-11 (11)
-

Database: Ovid MEDLINE(R) Daily Update <March 14, 2007>

Search Strategy:

-
- 1 acebutolol.mp. or exp Acebutolol/ (0)
 - 2 atenolol.mp. or exp Atenolol/ (1)
 - 3 betaxolol.mp. or exp Betaxolol/ (0)
 - 4 bisoprolol.mp. or exp Bisoprolol/ (1)
 - 5 carteolol.mp. or exp Carteolol/ (0)
 - 6 carvedilol.mp. (4)
 - 7 labetalol.mp. or exp Labetalol/ (1)
 - 8 metoprolol.mp. or exp Metoprolol/ (4)
 - 9 nadolol.mp. or exp Nadolol/ (0)
 - 10 exp Penbutolol/ or penbutolol.mp. (0)
 - 11 pindolol.mp. or exp Pindolol/ (0)
 - 12 propranolol.mp. or exp Propranolol/ (6)
 - 13 timolol.mp. or exp Timolol/ (2)
 - 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 (19)
 - 15 limit 14 to (humans and english language and yr="2005 - 2007" and clinical trial) (1)
 - 16 [from 15 keep 1-151] (0)
 - 17 (20061\$ or 2007\$).ed. (8172)
 - 18 15 and 17 (1)
 - 19 [from 18 keep 1-11] (0)
 - 20 from 15 keep 1 (1)

Appendix C. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and “The Database of Abstracts of Reviews of Effects (DARE)” in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of “good”, “fair” or “poor”. Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are 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 the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?

Adequate approaches to sequence generation:

Computer-generated random numbers

Random numbers tables

Inferior approaches to sequence generation:

Use of alternation, case record numbers, birth dates or week days

Not reported

2. Was the treatment allocation concealed?

Adequate approaches to concealment of randomization:

Centralized or pharmacy-controlled randomization

Serially-numbered identical containers

On-site computer based system with a randomization sequence that is not readable until allocation

Other approaches sequence to clinicians and patients

Inferior approaches to concealment of randomization:

Use of alternation, case record numbers, birth dates or week days
 Open random numbers lists
 Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient kept unaware of the treatment received?
8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?
9. Did the study maintain comparable groups?
10. Did the article report attrition, crossovers, adherence, and contamination?
11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?
2. How many patients were recruited?
3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)
4. What was the funding source and role of funder in the study?
5. Did the control group receive the standard of care?
6. What was the length of followup? (Give numbers at each stage of attrition.)

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?
2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)
3. Were the events investigated specified and defined?
4. Was there a clear description of the techniques used to identify the events?
5. Was there non-biased and accurate ascertainment of events (independent ascertainment; validation of ascertainment technique)?
6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?
7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?
2. How similar is the population to the population to whom the intervention would be applied?
3. How many patients were recruited?
4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)
5. What was the funding source and role of funder in the study?

Systematic Reviews:

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four 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, i.e., 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?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date 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, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been 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 (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either 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 (i.e. how many reviewers 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 judgement 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 size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (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 use 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 evaluations should be weighted in some way (e.g., 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.

Appendix D. List of included studies

Hypertension

Head-to-head trials: 6

Blumenthal JA, Madden DJ, Krantz DS, et al. Short-term behavioral effects of beta-adrenergic medications in men with mild hypertension. *Clin Pharmacol Ther.* 1988;43(4):429-435.

Buhler FR, Berglund G, Anderson OK, et al. Double-blind comparison of the cardioselective beta-blockers bisoprolol and atenolol in hypertension: the Bisoprolol International Multicenter Study (BIMS). *J Cardiovasc Pharmacol.* 1986;8(Suppl 11):S122-127.

Dahlof C, Almkvist G, Dimenas E, et al. No difference in general well-being during antihypertensive treatment with atenolol or metoprolol CR. *Ann Clin Res.* 1988;20(Suppl 48):42-50.

Steiner SS, Friedhoff AJ, Wilson BL, Wecker JR, Santo JP. Antihypertensive therapy and quality of life: a comparison of atenolol, captopril, enalapril and propranolol. *J Hum Hypertens.* 1990;4(3):217-225.

Sundar S, Rajan AG, Somani PN, Kumar K. The effects of antihypertensive agents on the quality of life in Indian hypertensives. *Acta Cardiol.* 1991;46(2):227-235.

Walle PO, Westergren G, Dimenas E, Olofsson B, Albrektsen T. Effects of 100 mg of controlled-release metoprolol and 100 mg of atenolol on blood pressure, central nervous system-related symptoms, and general well being. *J Clin Pharmacol.* 1994;34(7):742-747.

Placebo-controlled trials=3

Perez-Stable, Halliday, Gardiner, Baron, Hauck, Acree and Coates. The effects of propranolol on cognitive function and quality of life: a randomized trial among patients with diastolic hypertension. *American Journal of Medicine.* 2000;108(5):359-65.

TAIM

Oberman, Wassertheil-Smoller, Langford, Blaufox, Davis, Blaszkowski, Zimbaldi and Hawkins. Pharmacologic and nutritional treatment of mild hypertension: changes in cardiovascular risk status. *Annals of Internal Medicine.* 1990;112(2):89-95.

Wassertheil-Smoller, Oberman, Blaufox, Davis and Langford. The Trial of Antihypertensive Interventions and Management (TAIM) Study. Final results with regard to blood pressure, cardiovascular risk, and quality of life. *American Journal of Hypertension.* 1992;5(1):37-44.

Wassertheil-Smoller, Blaufox, Oberman, Davis, Swencionis, Knerr, Hawkins and Langford. Effect of antihypertensives on sexual function and quality of life: the TAIM Study. *Annals of Internal Medicine.* 1991;114(8):613-20.

MRC

Anonymous. Randomised controlled trial of treatment for mild hypertension: design and pilot trial. *British Medical Journal*. 1977;1(6074):1437-40.

Greenberg, Brennan and Miall. Effects of diuretic and beta-blocker therapy in the Medical Research Council trial. *American Journal of Medicine*. 1984;76(2A):45-51.

Anonymous. MRC trial of treatment of mild hypertension: principal results. Medical Research Council Working Party. *British Medical Journal Clinical Research Edition*. 1985;291(6488):97-104.

Miall, Greenberg and Brennan. Further results of the MRC treatment trial for mild hypertension. *Nephron*. 1987;47(Suppl 1):111-4.

Anonymous. Stroke and coronary heart disease in mild hypertension: risk factors and the value of treatment. *British Medical Journal Clinical Research Ed*. 1988;296(6636):1565-70.

Anonymous. Coronary heart disease in the Medical Research Council trial of treatment of mild hypertension. *British Heart Journal*. 1988;59(3):364-78.

Lever and Brennan. MRC trial of treatment in elderly hypertensives. *Clinical & Experimental Hypertension (New York)*. 1993;15(6):941-52.

Angina

Head-to-head trials

van der Does, Hauf-Zachariou, Pfarr, Holtbrugge, Konig, Griffiths and Lahiri. Comparison of safety and efficacy of carvedilol and metoprolol in stable angina pectoris. *American Journal of Cardiology*. 1999;83(5):643-9.

Frishman, Kostis, Strom, Hossler, Elkayam, Goldner, Silverman, Davis, Weinstein and Sonnenblick. Clinical pharmacology of the new beta-adrenergic blocking drugs. Part 6. A comparison of pindolol and propranolol in treatment of patients with angina pectoris. The role of intrinsic sympathomimetic activity. *American Heart Journal*. 1979;98(4):526-35.

Dorow, Thalhofer, Bethge, Disselhoff and Wagner. Long-term treatment of angina pectoris with bisoprolol or atenolol in patients with chronic obstructive bronchitis: a randomized, double-blind crossover study. *Journal of Cardiovascular Pharmacology*. 1990;16(Suppl 5):S36-44.

Chieffo, Palermo, Natale and et al. Labetalol-plus-chlorthalidone (Trandiur(Reg.trademark)) and atenolol- plus-chlorthalidone (Tenoretic(Reg.trademark)) in the treatment of essential hypertension with angina pectoris. *Clinical Trials Journal*. 1986;23(5):323-331.

Narahara. Double-blind comparison of once daily betaxolol versus propranolol four times daily in stable angina pectoris. *American Journal of Cardiology*. 1990;65(9):577-82.

Placebo-controlled trials

Destors, Boissel, Philippon and Schbath. Controlled clinical trial of bepridil, propranolol and placebo in the treatment of exercise induced angina pectoris. B.I.S. *Fundamental & Clinical Pharmacology*. 1989;3(6):597-611.

Meta-analysis of active-controlled studies

Heidenreich, McDonald, Hastie, Fadel, Hagan, Lee and Hlatky. Meta-analysis of trials comparing beta-blockers, calcium antagonists, and nitrates for stable angina. *Jama*. 1999;281(20):1927-36.

CABG

Placebo-controlled trials

(MACB)

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

Sjoland, Caidahl, Lurje, Hjalmarson and Herlitz. Metoprolol treatment for two years after coronary bypass grafting: effects on exercise capacity and signs of myocardial ischaemia. *British Heart Journal*. 1995;74(3):235-41.

Recent MI

Head-to-head trials

Wilcox, Roland, Banks, Hampton and Mitchell. Randomised trial comparing propranolol with atenolol in immediate treatment of suspected myocardial infarction. *British Medical Journal*. 1980;280(6218):885-8.

Jonsson G, Abdelnoor M, Muller C, Kjeldsen SE, Os I, Westheim A. A comparison of the two beta-blockers carvedilol and atenolol on left ventricular ejection fraction and clinical endpoints after myocardial infarction. a single-centre, randomized study of 232 patients. *Cardiology*. 2005;103(3):148-155.

Placebo-controlled trials

Acebutolol

Boissel, 1990Boissel, Leizorovicz, Picolet and Ducruet. Efficacy of acebutolol after acute myocardial infarction (the APSI trial). The APSI Investigators. *American Journal of Cardiology*. 1990;66(9):24C-31C.

Carvedilol

Basu 1997Basu, Senior, Raval, Van der Does, Bruckner and Lahiri. Beneficial effects of intravenous and oral carvedilol treatment in acute myocardial infarction: A placebo-controlled, randomized trial. *Circulation*. 1997;96(1):183-191.

CAPRICORN:

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

Coats. CAPRICORN: a story of alpha allocation and beta-blockers in left ventricular dysfunction post-MI. *International Journal of Cardiology*. 2001;78(2):109-13.

Dargie. Design and methodology of the CAPRICORN trial - a randomised double blind placebo controlled study of the impact of carvedilol on morbidity and mortality in patients with left ventricular dysfunction after myocardial infarction. *European Journal of Heart Failure*. 2000;2(3):325-32.

Metoprolol

Stockholm:

Olsson, Rehnqvist, Sjogren, Erhardt and Lundman. Long-term treatment with metoprolol after myocardial infarction: effect on 3 year mortality and morbidity. *Journal of the American College of Cardiology*. 1985;5(6):1428-37.

Amsterdam:

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

Belfast:

Salathia, Barber, McIlmoyle, Nicholas, Evans, Elwood, Cran, Shanks and Boyle. Very early intervention with metoprolol in suspected acute myocardial infarction. *European Heart Journal*. 1985;6(3):190-8.

LIT:

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

Goteborg:

Hjalmarson, Elmfeldt, Herlitz, Holmberg, Malek, Nyberg, Ryden, Swedberg, Vedin, Waagstein, Waldenstrom, Waldenstrom, Wedel, Wilhelmsen and Wilhelmsson. Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial. *Lancet*. 1981;2(8251):823-7.

Herlitz, Holmberg, Pennert, Swedberg, Vedin, Waagstein, Waldenstrom, Waldenstrom, Wedel, Wilhelmsen and et al. Goteborg Metoprolol Trial: design, patient characteristics and conduct. *American Journal of Cardiology*. 1984;53(13):3D-8D.

Herlitz, Waagstein, Lindqvist, Swedberg and Hjalmarson. Effect of metoprolol on the prognosis for patients with suspected acute myocardial infarction and indirect signs of

congestive heart failure (a subgroup analysis of the Goteborg Metoprolol Trial). *American Journal of Cardiology*. 1997;80(9B):40J-44J.

Pindolol

Australian & Swedish Study

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

Propranolol

MILIS:

Roberts, Braunwald, Muller, Croft, Gold, Hartwell, Jaffe, Mullin, Parker and Passamani. Effect of hyaluronidase on mortality and morbidity in patients with early peaking of plasma creatine kinase MB and non-transmural ischaemia. Multicentre investigation for the limitation of infarct size (MILIS). *British Heart Journal*. 1988;60(4):290-8.

Roberts, Croft, Gold, Hartwell, Jaffe, Muller, Mullin, Parker, Passamani, Poole and et al. Effect of propranolol on myocardial-infarct size in a randomized blinded multicenter trial. *New England Journal of Medicine*. 1984;311(4):218-25.

Rude, Buja and Willerson. Propranolol in acute myocardial infarction: the MILIS experience. *American Journal of Cardiology*. 1986;57(12):38F-42F.

BHAT:

Lichstein, Morganroth, Harrist and Hubble. Effect of propranolol on ventricular arrhythmia. *Circulation*. 1983;67(6 Pt 2):I5-10.

Goldstein. Propranolol therapy in patients with acute myocardial infarction: the Beta-Blocker Heart Attack Trial. *Circulation*. 1983;67(6 Pt 2):I53-7.

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

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

Jafri, Khaja, McFarland, Capone, Dahdah, Haywood, Edmiston, Tilley, Schultz and Goldstein. Efficacy of propranolol therapy after acute myocardial infarction related to coronary arterial anatomy and left ventricular function. *American Journal of Cardiology*. 1987;60(13):976-80.

Furberg, Hawkins and Lichstein. Effect of propranolol in postinfarction patients with mechanical or electrical complications. *Circulation*. 1984;69(4):761-5.

Other:

Baber, Evans, Howitt, Thomas, Wilson, Lewis, Dawes, Handler and Tuson. Multicentre post-infarction trial of propranolol in 49 hospitals in the United Kingdom, Italy, and Yugoslavia. *British Heart Journal*. 1980;44(1):96-100.

Hansteen, Moinichen, Lorentsen, Andersen, Strom, Soiland, Dyrbekk, Refsum, Tromsdal, Knudsen, Eika, Bakken, Smith and Hoff. One year's treatment with propranolol after myocardial infarction: preliminary report of Norwegian multicentre trial. *British Medical Journal Clinical Research Ed*. 1982;284(6310):155-60.

Timolol

Roque, Amuchastegui, Lopez Morillos, Mon, Girotti, Drajer, Fortunato, Moreyra, Tuero, Solchaga and et al. Beneficial effects of timolol on infarct size and late ventricular tachycardia in patients with acute myocardial infarction. *Circulation*. 1987;76(3):610-7.

Norwegian study:

Anonymous. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *New England Journal of Medicine*. 1981;304(14):801-7.

Heart Failure

Head-to-head trials

Kukin, Kalman, Charney, Levy, Buchholz-Varley, Ocampo and Eng. Prospective, randomized comparison of effect of long-term treatment with metoprolol or carvedilol on symptoms, exercise, ejection fraction, and oxidative stress in heart failure. [see comments.]. *Circulation*. 1999;99(20):2645-51.

Metra, Giubbini, Nodari, Boldi, Modena and Dei Cas. Differential effects of beta-blockers in patients with heart failure: A prospective, randomized, double-blind comparison of the long-term effects of metoprolol versus carvedilol. *Circulation*. 2000;102(5):546-51.

Metra, Nodari, D'Aloia, Muneretto, Robertson, Bristow and Dei Cas. Beta-blocker therapy influences the hemodynamic response to inotropic agents in patients with heart failure: a randomized comparison of dobutamine and enoximone before and after chronic treatment with metoprolol or carvedilol. *Journal of the American College of Cardiology*. 2002;40(7):1248-58.

Poole-Wilson, Swedberg, Cleland, Di Lenarda, Hanrath, Komajda, Lubsen, Lutiger, Metra, Remme, Torp-Pedersen, Scherhag and Skene. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet*. 2003;362:7-13.

Sanderson, Chan, Yip, Yeung, Chan, Raymond and Woo. Beta-blockade in heart failure: a comparison of carvedilol with metoprolol. *Journal of the American College of Cardiology*. 1999;34(5):1522-8.

Galatius S, Gustafsson F, Atar D, Hildebrandt PR. Tolerability of (beta)-blocker initiation and titration with bisoprolol and carvedilol in congestive heart failure - A randomized comparison. *Cardiology*. 2004;102(3):160-165.

Placebo-controlled trials

Atenolol

Sturm, Pacher, Strametz-Juranek, Berger, Frey and Stanek. Effect of beta 1 blockade with atenolol on progression of heart failure in patients pretreated with high-dose enalapril. *European Journal of Heart Failure*. 2000;2(4):407-12.

Bisoprolol

CIBIS:

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

CIBIS-II:

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

Carvedilol

Cice G, Ferrara L, D'Andrea A, et al. Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. *J Am Coll Cardiol*. 2003;41(9):1438-1444.

MOCHA:

Bristow, Gilbert, Abraham, Adams, Fowler, Hershberger, Kubo, Narahara, Ingersoll, Krueger, Young and Shusterman. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. *Circulation*. 1996;94(11):2807-2816.

PRECISE:

Packer, Colucci, Sackner-Bernstein, Liang, Goldscher, Freeman, Kukin, Kinhal, Udelson, Klapholz, Gottlieb, Pearle, Cody, Gregory, Kantrowitz, LeJemtel, Young, Lukas and Shusterman. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. *Circulation*. 1996;94(11):2793-2799.

Colucci 1996

Colucci, Packer, Bristow, Gilbert, Cohn, Bowers, Sackner-Bernstein, Young, Holcslaw and Lukas. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. *Circulation*. 1996;94(11):2800-2806.

Cohn 1997

Cohn, Fowler, Bristow, Colucci, Gilbert, Kinhal, Krueger, Lejemtel, Narahara, Packer, Young, Holcslaw and Lukas. Safety and efficacy of carvedilol in severe heart failure. The U.S. *Journal of Cardiac Failure*. 1997;3(3):173-9.

Australia/New Zealand:

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

COPERNICUS:

Packer, Coats, Fowler, Katus, Krum, Mohacsi, Rouleau, Tendera, Castaigne, Roecker, Schultz, DeMets and Carvedilol Prospective Randomized Cumulative Survival Study. Effect of carvedilol on survival in severe chronic heart failure. *New England Journal of Medicine*. 2001;344(22):1651-8.

Fowler MB. Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial: Carvedilol in severe heart failure. *Am J Cardiol*. 2004;93(9 SUPPL. 1):35B-39B.

CHRISTMAS:

Cleland, Pennell, Ray, Coats, Macfarlane, Murray, Dalle Mule, Vered and Lahiri. Myocardial viability as a determinant of the ejection fraction response to carvedilol in patients with heart failure (CHRISTMAS trial): randomised controlled trial. *Lancet*. 2003;362:14-21.

MUCHA:

Hori, Sasayama, Kitabatake, Toyo-Oka, Handa, Yokoyama, Matsuzaki, Takeshita, Origasa, Matsui and Hosoda. Low-dose carvedilol improves left ventricular function and reduces cardiovascular hospitalization in Japanese patients with chronic heart failure: The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) trial. *American Heart Journal*. 2004;147(2):324-330.

Metoprolol tartrate

Waagstein, Stromblad, Andersson, Bohm, Darius, Delius, Goss, Osterziel, Sigmund, Trenkwalder and Wahlqvist. Increased exercise ejection fraction and reversed remodeling after long-term treatment with metoprolol in congestive heart failure: A randomized, stratified, double-blind, placebo-controlled trial in mild to moderate heart failure due to ischemic or idiopathic dilated cardiomyopathy. *European Journal of Heart Failure*. 2003;5(5):679-691.

MDC:

Waagstein, Bristow, Swedberg, Camerini, Fowler, Silver, Gilbert, Johnson, Goss and Hjalmarson. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. *Lancet*. 1993;342(8885):1441-6.

Metoprolol succinate**MERIT-HF**

Anonymous. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)[comment]. *Lancet*. 1999;353(9169):2001-7.

Goldstein, Fagerberg, Hjalmarson, Kjekshus, Waagstein, Wedel, Wikstrand and The. Metoprolol controlled release/extended release in patients with severe heart failure: analysis of the experience in the MERIT-HF study. *Journal of the American College of Cardiology*. 2001;38(4):932-8.

Hjalmarson and Fagerberg. MERIT-HF mortality and morbidity data. *Basic Research in Cardiology*. 2000;95(Suppl 1):198-103.

Goldstein and Hjalmarson. The mortality effect of metoprolol CR/XL in patients with heart failure: results of the MERIT-HF Trial. *Clinical Cardiology*. 1999;22(Suppl 5):V30-5.

Ghali, Pina, Gottlieb, Deedwania, Wikstrand and The. Metoprolol CR/XL in female patients with heart failure: analysis of the experience in Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF). *Circulation*. 2002;105(13):1585-91.

Gottlieb, Fisher, Kjekshus, Deedwania, Gullestad, Vitovec, Wikstrand and The. Tolerability of beta-blocker initiation and titration in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). *Circulation*. 2002;105(10):1182-8.

RESOLVD:

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

Atrial arrhythmia

Head-to-head trials

Katrtsis, Panagiotakos, Karvouni, Giazitzoglou, Korovesis, Paxinos, Anagnostopoulos and Camm. Comparison of effectiveness of carvedilol versus bisoprolol for maintenance of sinus rhythm after cardioversion of persistent atrial fibrillation. *American Journal of Cardiology*. 2003;92(9):1116-1119.

Placebo-controlled trials

Metoprolol succinate

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

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

Khand AU, Rankin AC, Kaye GC, Cleland JG. Systematic review of the management of atrial fibrillation in patients with heart failure. *Eur Heart J.* 2000;21(8):614-632.

Carvedilol

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

Migraine

Head-to-head trials

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

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

Olsson, Behring, Forssman, Hedman, Hedman, Johansson, Kinnman, Palhagen, Samuelsson and Strandman. Metoprolol and propranolol in migraine prophylaxis: a double-blind multicentre study. *Acta Neurologica Scandinavica.* 1984;70(3):160-8.

Stensrud and Sjaastad. Comparative trial of Tenormin (atenolol) and Inderal (propranolol) in migraine. *Uppsala Journal of Medical Sciences - Supplement.* 1980;31:37-40.

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

Tfelt-Hansen, Standnes, Kangasneimi, Hakkarainen and Olesen. Timolol vs propranolol vs placebo in common migraine prophylaxis: a double-blind multicenter trial. *Acta Neurologica Scandinavica.* 1984;69(1):1-8.

Placebo-controlled trials

Atenolol

Forssman, Lindblad and Zborckinova. Atenolol for migraine prophylaxis. *Headache.* 1983;23:188-190.

Bisoprolol

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

Metoprolol succinate

Andersson, Dahl, Hansen, Hansen, Hedman and al. Prophylactic treatment of classical and non-classical migraine with metoprolol - a comparison with placebo. *Cephalalgia*. 1983;3:207-212.

Kangasniemi, Andersen, Andersson, Gilhus, Hedman, Hultgren, Vilming and Olesen. Classic migraine: effective prophylaxis with metoprolol. *Cephalalgia*. 1987;7(4):231-8.

Pindolol

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

Sjaastad and Stensrud. Clinical trial of a beta-receptor blocking agent (LB 46) in migraine prophylaxis. *Acta Neurologica Scandinavica*. 1972;48:124-128.

Propranolol immediate release

Borgesen, Nielsen and Moller. Prophylactic treatment of migraine with propranolol. A clinical trial. *Acta Neurologica Scandinavica*. 1974;50(5):651-6.

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

Diamond, Kudrow, Stevens and Shapiro. Long-term study of propranolol in the treatment of migraine. *Headache*. 1982;22(6):268-271.

Diener, Foh, Iaccarino, Wessely, Isler, Streng, Fischer, Wedekind and Taneri. Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. *Cephalalgia*. 1996;16(6):441-7.

Forssman, Henriksson, Johannsson, Lindvall and Lundin. Propranolol for migraine prophylaxis. *Headache*. 1976;16(5):238-45.

Mikkelsen, Pedersen and Christiansen. Prophylactic treatment of migraine with tolfenamic acid, propranolol and placebo. *Acta Neurologica Scandinavica*. 1986;73(4):423-7.

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