Drug Class Review
on
Beta Adrenergic Blockers

Final Report

May 2005

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
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	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 (in this order): 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. In electronic searches we used broad searches, combining terms for included beta blockers with terms for patient populations. Appendix A contains complete CCRCT and Medline search strategies. A similar search strategy was repeated in Embase. In addition, pharmaceutical manufacturers were invited to submit dossiers, including citations, using a protocol issued by the Center for Evidence-based Policy (http://www.ohsu.edu/drugeffectiveness/pharma/Final_Submission_Protocol_Ver1_1.pdf). All citations were imported into an electronic database (EndNote 6.0).

Study Selection

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

We included English-language reports of studies of the patient populations and efficacy outcomes listed in Table 3. For studies of hypertension, we excluded studies in which blood pressure lowering was the only endpoint; most of these studies seek to identify equivalent doses of beta blockers rather than differences in clinical effectiveness. Instead, we sought evidence of long-term effects on mortality, cardiovascular events, and quality of life. We only included studies in stable angina patients with duration of 2 months or longer. We only included studies of long-term treatment in post-CABG patients; excluding studies of the short-term use of beta blockers to suppress atrial arrhythmias. 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	1. All-cause and cardiovascular mortality 2. Cardiovascular events (stroke, myocardial infarction, or development of heart failure) 3. End-stage renal disease (including dialysis or need for transplantation) or clinically significant and permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance) 4. Quality-of-life
Stable angina (treatment ≥ 2 months' duration)	1. Exercise tolerance 2. Attack frequency 3. Nitrate use
Post-coronary artery bypass graft (long-term treatment)	1. All-cause mortality 2. Ischemic events (MI, unstable angina, need for repeat CABG and PTCA)
Recent myocardial infarction (with and without LV dysfunction)	1. All-cause and cardiovascular mortality 2. Cardiovascular events (usually, development of heart failure)
Symptomatic chronic heart failure	1. All-cause or cardiovascular mortality 2. Symptomatic improvement (heart failure class, functional status, visual analogue scores) 3. Hospitalizations for heart failure
Asymptomatic LV dysfunction	1. All-cause and cardiovascular mortality 2. Cardiovascular events (usually, development of heart failure)
Atrial fibrillation/flutter	1. Rate control 2. Relapse into atrial fibrillation
Migraine	1. Attack frequency 2. Attack intensity/severity 3. Attack duration 4. Use of abortive treatment
Bleeding esophageal varices	1. All-cause mortality 2. Fatal/non-fatal rebleeding

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

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

Data Abstraction

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

Quality Assessment

We assessed the internal validity (quality) of included studies based on the predefined criteria listed in Appendix B. Overall quality ratings for the individual study were based on ratings of its internal validity, suitability to answer the question, and applicability to current practice. A particular randomized trial might receive different ratings for efficacy and adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Data Synthesis

The comparative efficacy and safety of beta blockers in the specified patient populations are synthesized through a narrative review as well as in tabular form. We analyzed continuous efficacy data by calculating percent change scores when possible. Forest plots of relative risks (RR) or odds ratios (OR) are presented, where applicable, to display data comparatively. Forest plots were created using StatsDirect (CamCode, UK) software. StatsDirect was also used to calculate 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. 107 (3 new from update #2 search) reports of trials met the inclusion criteria for the systematic review. Included trials are listed in Appendix C.

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

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

Summary

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

Detailed Assessment

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

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

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

Of the trials that compared a beta blocker with a diuretic, only one (MAPHY) had any suggestion that the beta blocker was more effective. In that trial, deaths from heart attacks and strokes as well as total mortality were lower in the metoprolol treated group than in those treated with a diuretic (hydrochlorothiazide or bendroflumethiazide).[12] The trial continues 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. A good-quality meta-analysis of 10 trials published in 1998 or earlier, beta blockers were ineffective, or less effective than comparator drugs, in preventing coronary heart disease, cardiovascular mortality, and all-cause mortality (ORs, 1.01, 0.98, and 1.05, respectively).[13]

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

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

Quality of life. There is no definitive evidence that one beta blocker yields a better quality of life than another for patients who have hypertension. 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). The table 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 *some* 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

Trial (Quality)	Comparison Design Sample size	Duration (weeks)	Washout (weeks)	Results
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.

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

Summary

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

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

Detailed Assessment

In 1966 the first beta blocker, propranolol, was shown in a multicenter controlled trial to improve symptoms in patients with angina pectoris.[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 *n=368*	carvedilol 100 mg metoprolol 200 mg	No difference	Not reported
Frishman, 1979 *n=40*	Pindolol 10-40 mg Propranolol 40-240 mg	No difference	No difference
Narahara, 1990 *N=112*	Betaxolol 20 and 40 mg Propranolol 160 and 320 mg	No difference	No difference
Dorow, 1990 *n=40 (comorbid chronic obstructive pulmonary disease patients)*	Atenolol 50 mg Bisoprolol 5 mg	Not reported	82.8% vs 64.3% (not significant)
Chieffo, 1986 *n=10 (comorbid hypertension)*	Labetolol 200 mg+chlorthalidone 20 mg Atenolol 100 mg+chlorthalidone 25 mg	Not reported	60% vs 80% (not significant)

sl ntg=sublingual nitroglycerin

Over the long-term, beta blockers may differ in their ability to prevent or reduce the severity of anginal attacks. In one fair quality 2-year multicenter European trial, propranolol was better than placebo after 8 weeks but not after 24 weeks of treatment.[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.

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 trial[42] that randomized 967 patients (85.5% male, median age 64 years) to metoprolol 200 mg once daily or placebo within 5-21 days following CABG and measured the effects of treatment on death and cardiac events.. No differences between metoprolol and placebo were found in mortality (3.3% vs 1.8%; p=0.16) or in ischemic events (e.g., MI, unstable angina, need for additional CABG or PTCA).

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

Summary

Table 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. Also, similar benefits in sudden death were reported for propranolol[45] 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.

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
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 only one, fair-quality head-to-head trial of different beta blockers after MI,[48] a 6-week trial comparing atenolol 100 mg to propranolol 120mg which had inconclusive results.

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

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

Mortality

Three systematic reviews have analyzed over 60 trials of beta blockers after MI.[49-51] 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.[51] In their analysis of 24 long-term trials, cardioselectivity had no effect, but there was a near significant trend towards

decreased benefit in drugs with intrinsic sympathomimetic activity. Individually, acebutolol (0.49; 0.25-0.93), metoprolol tartrate (0.80; 0.66-0.96), propranolol (0.71; 0.59-0.85), timolol (0.59; 0.46-0.77) significantly reduced mortality, but there was insufficient data to distinguish among them. The analysis included just one trial of carvedilol, a pilot study in 151 post-MI patients (Basu et al, 1997).[52]

Table 7 below summarizes placebo controlled trials that enrolled > 100 patients, had long-term follow-up (> 6 weeks) and met our other inclusion criteria.

All of the trials in Table 7 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.[53] Unlike the other trials, CAPRICORN included only patients who had reduced left ventricular function (≤ 40%) after acute myocardial infarction as determined by echocardiography or cardiac catheterization. Patients with uncontrolled heart failure, such as those requiring intravenous diuretics, were excluded. Of 1959 subjects randomized to either carvedilol or placebo at an average of 10 days following a confirmed MI, 1289 had no clinical signs of heart failure (Killip Class I), 593 had Killip Class II heart failure, and 65 had Killip Class III failure. The mean ejection fraction was 32.8%.

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

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

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

open the possibility that, in North America, the subjects in CAPRICORN would already have been taking beta blockers.

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

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

There is no direct evidence that other beta blockers shown to reduce mortality in post-MI patients or in patients with heart failure work as well as carvedilol in post-MI patients with decreased LV function and few or no symptoms of heart failure. While the older trials undoubtedly included some subjects with LV dysfunction, it is difficult to determine how many, or how this subset did compared with post-MI patients with normal LV function. Indirect evidence comes from a good-quality meta-analysis.[54] This analysis examined the relationship between the mortality reduction reported in each trials and the proportion of patients in the trial who had heart failure. There were few data on the effects of beta-blockers after myocardial infarction in patients with documented left ventricular systolic dysfunction, but some studies included subjects with clinical findings of heart failure and reported the proportion of subjects that had these findings. As expected, studies that included patients with heart failure had higher mortality rates. The relative benefit of beta-blockers on mortality after a myocardial infarction was similar in the presence or absence of heart failure.

Two retrospective subgroup analyses in heart failure patients from individual trials included in this meta analysis provide additional details supporting this hypothesis. One is from the BHAT trial (β Blocker Heart Attack Trial), a large, 3-month trial of propranolol published in 1980. In BHAT, 710 of 1916 subjects had a history of congestive heart failure prior to randomization. Propranolol lowered total mortality from 18.4% to 13.3% (a 27% reduction) in patients with a history of heart failure and from 7.8% to 5.9% (25% reduction) in patients who did not have a history of heart failure.[55]

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.[56] 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 tartrate[47] and one trial of timolol.[43] Carvedilol was also associated with significantly reduced reinfarction rates in the CAPRICORN trial.

Withdrawals

Among the major trials, rates of withdrawal ranged from 9.3% to 36.6%, probably indicating differences in patients' characteristics. Within studies, rates of withdrawal were generally similar for the beta blocker and placebo groups, with three exceptions. Rates of withdrawal were greater for metoprolol tartrate in one[57] of five trials, pindolol in one trial[58], 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
Acebutolol							
Boissel 1990	A: Acebutolol B: Placebo	271 days	607	A: 5.7% (17/298) B: 11% (34/309) p=0.019; NNT=19	nr	A: 3% B: 3.6% NS	A: 33% B: 36.6% NS
Carvedilol							
Basu* 1997	A: Carvedilol B: Placebo	6 months	151 (146 analyzed)	A: 2.7% (2/75) B: 4.2% (3/71 p=NS	nr	A: 5.3% B: 11.3% NS	nr
CAPRICORN 2001	A: Carvedilol B: Placebo	1.3 years (mean)	1959	A: 12% (116/975) B: 15% (151/984) p=0.031; NNT=30	A: 5% B: 7% NS	A: 3% B: 6% p=0.014	A: 20% B: 18% NS
Metoprolol tartrate							
Stockholm 1983	A: Metoprolol tartrate B: Placebo	3 years	301	A: 16.2% (25/154) B: 21% (31/147) p=NS	A: 5.9% B: 14.3% p<0.05	A: 11.7% B: 21.1% p<0.05	A: 24.7% B: 23.8% NS
Amsterdam 1985	A: Metoprolol tartrate B: Placebo	1 year	553	A: 3.3% (9/273) B: 5.7% (16/280) p=NS	A: 0.3% B: 2.5% NS	A: 5.9% B: 7.1% NS	A: 32% B: 24% p=0.02
Belfast 1985	A: Metoprolol tartrate B: Placebo	1 year	764	A: 11.8% (49/416) B: 14.9% (52/348) p=NS	A: 1.9% B: 4.7% p<0.05	nr	A: 22.8% B: 19% NS

Study, year	Interventions	Duration	Number enrolled	Total mortality	Sudden Death	Reinfarction	Withdrawals
Lopressor 1987	A: Metoprolol tartrate B: Placebo	1.5 years	2395	A: 7.2% (86/1195) B: 7.7% (93/1200) p=NS	nr	nr	A: 31.9% B: 29.6% NS
Goteborg 1981	A: Metoprolol tartrate B: Placebo	2 years	1395	A: 5.7% (40/698) B: 8.9% (62/697) p=0.024; NNT=32	nr	A: 5% B: 7.7% NS	A: 19.1% B: 19.1% NS
Pindolol							
Australian & Swedish Study 1983	A: Pindolol B: Placebo	2 years	529	A: 17.1% (45/263) B: 17.7% (47/266) p=NS	A: 10.6% B: 11.7% NS	nr	A: 28.8% B: 18.8% p=0.0078
Propranolol							
Baber 1980	A: Propranolol B: Placebo	9 months	720	A: 7.9% (28/355) B: 7.4% (27/365) p=NS	nr	A: 4.8% B: 7.4% NS	A: 23% B: 24.1% NS
Hansteen 1982	A: Propranolol B: Placebo	1 year	560	A: 8.9% (25/278) B: 13.1% (37/282) 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
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)

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.

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
Metoprolol succinate	Yes	Yes	Yes	Not proven	Not significant	yes

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

Detailed Assessment

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

Eight meta-analyses of placebo-controlled trials of various beta blockers in heart failure were published in the mid-1990's through 2000.[60-67] 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 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)
*Planned analysis of pooled results of 4 independent, double-blind placebo-controlled trials.
**Dosage target was 50 mg bid in patients whose weight was 85 kg or more.
*** Not significant.
§ Mortality was not the primary endpoint, and the estimated mortality reduction was inflated because of the use of an active-drug run-in period before randomization. Withdrawal rates are also affected by use of an active-drug run-in phase. See Table 10.

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[68], bisoprolol 5-10 mg;[69, 70] carvedilol 50-100 mg;[71-80] metoprolol tartrate 100-150 mg;[81, 82] and metoprolol succinate (CR) 12.5-25 mg.[83, 84]

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

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

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

The 4 U.S. Carvedilol trials and the Australian-New Zealand trial demonstrated that in patients with NYHA Class II to IV heart failure, carvedilol reduced mortality. As shown in Table 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. These patients were excluded prior to randomization. For this reason, the mortality reductions and rates of withdrawal and adverse events are not comparable to those of other trials. In Table 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).[70] Most patients were NYHA Class III. The annual placebo mortality rate was 13%, which is higher than the rate projected by the CIBIS-II investigators based on the results of CIBIS-I. Nevertheless, this mortality rate, and the average ejection fraction of 27%, are closer to those of MERIT-HF, which recruited mostly Class II and III patients, than to those of COPERNICUS, which is thought to have recruited NYHA Class III and IV patients.

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

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

Table 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% (0.23)	14.0%	15.3%	278
Colucci*	Carvedilol	Morbidity+ mortality	II-III	<35% (0.23)	6.4%	2.2%	366
Cohn*	Carvedilol	Quality of life	III-IV	<35% (0.23)	8.6%	4.3%	105
ANZ *	Carvedilol	Exercise tolerance, morbidity+ mortality	I-III	<35% (0.16)	7.9%	7.0%	415
Christmas	Carvedilol	LVEF	I-III	<39% (0.29)	4.9%	6.9%	387
Copernicus	Carvedilol	Mortality	Not reported**	< 25% (0.20)	**20.9%**	**14.0%**	2289
MUCHA (Japanese)	Carvedilol	CHF global assessment	II-III	< 40% (30%)	Nr	nr	190
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.[72, 73, 78] This includes the MUCHA trial of Japanese patients with heart failure.[78] In three other trials, including a subset of dialysis patients with heart failure,[79] carvedilol had no effect.[71, 75, 79] 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).[85] By contrast, carvedilol did not reduce progression of heart failure in COPERNICUS.

Exercise Capacity

The carvedilol trials[71-73, 75] were consistent in showing equivalency to placebo in exercise capacity improvement as measured by both the 6-minute walk and 9-minute treadmill tests. Results of treadmill testing (modified Naughton protocol) were mixed in two placebo controlled trials of metoprolol.

Quality of Life

In three trials[71-73] carvedilol had no effect on quality of life as measured using the Minnesota Living With Heart Failure Questionnaire. The MDC trial reported that patients taking immediate release metoprolol experienced significant greater improvements in quality of life than those taking placebo. No data were provided and it is unclear as to which measurement instrument was used.

In the MERIT-HF trial, controlled-release metoprolol reduced the need for hospitalizations and the number of hospital days and improved the patient's self-assessment of treatment as measured by the McMaster Overall Treatment Evaluation. Controlled release metoprolol had no effect on Minnesota Living with Heart Failure Questionnaire scores in a smaller group of MERIT-HF patients (n=741) participating in a quality of life substudy.[86]

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

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

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

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

Study, year	Beta blocker	All-cause mortality rates p-value NNT	Sudden death rates p value NNT	Death due to heart failure p value NNT	NYHA Class	Exercise capacity	Quality of life
Anonymous 1997 *Australia/New Zealand Heart Failure Research Collaborative Group*	carvedilol	9.6% vs 12.6% NS	4.8% vs 5.3% NS	6.7% vs 7.2% NS	Improved: 26% vs 28% NS	Treadmill exercise duration/6-minute walk distance: car=pla (data nr)	NR
Packer 2001 *COPERNICUS*	carvedilol	**11.2% vs 16.8% p=0.00013 NNT=19**	**6.1% vs 3.9% p=0.016 NNT=46**	NR	NR	NR	NR
Cleland 2003 *CHRISTMAS*	carvedilol	4.3% vs 3.2% NS	NR	NR	NR	Exercise time (method nr) (seconds): 405 vs 427 NS	NR
Hori 2004 *MUCHA (Japanese patients)*	carvedilol	NR	NR	NR	Improved 5 mg= 80.9% vs 48.9%, p<0.001 20 mg= 70.8% vs 48.9%, p<0.05	NR	NR
Cice 2003 (Dialysis patients)	Carvedilol	**51.7% vs 73.2% p<0.01 NNT=5**	3.4% vs 10.6% NS	NR	Class I: 8.3% vs 0% Class II: 66.7% vs 33.4% Class III: 25% vs 44.4% Class IV: 0% vs 22.2% All NS	NR	NR
Waagstein 1993 *MDC*	metoprolol tartrate	11.8% vs 11.1% NS	9.3% vs 6.3% NS	2.6% vs 2.6% NS	Improvement: effective (data NR)	Mean increase in exercise capacity (sec): 76 vs 15 p=0.046	met>pla p=0.01 (original data NR)
Waagstein 2003	metoprolol tartrate	4.6% vs 3.8% NS	NR	NR	Improved: 42% vs 33% NS	Bicycle test: met=pla (data nr)	NR
Anonymous 1999 *MERIT-HF*	metoprolol succinate	**7.3% vs 10.8% p=0.00009 NNT=29**	**3.9% vs 6.5% p=0.0002 NNT=39**	**1.5% vs 2.9% p=0.0023 NNT=72**	NR	NR	McMaster Overall Treatment Evaluation: met>pla (data nr)
Anonymous 2000 *RESOLVD*	metoprolol succinate	3.7% vs 8.1% NS	NR	0.5% vs 1.4% NS	met CR=pla (data nr)	6-minute walk test change (meters) -1 vs -3	met CR=pla (data nr)

*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).[87-92] 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. [81]

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

Numerous secondary outcomes from the COMET trial were recently published.[Torp-Pedersen, 2005 #12065] 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.[Torp-Pedersen, 2005 #12065]

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.[Torp-Pedersen, 2005 #12065] Carvedilol and immediate-release metoprolol had similar effects on rates of overall hospitalization and cause-specific hospitalizations, with one exception. Greater reductions in rates of first hospitalization due to potential complication of heart failure treatment were associated with immediate-release metoprolol than with carvedilol. Non-cardiovascular death, change in NYHA classification, and rates of medication withdrawal were similar for carvedilol and immediate release metoprolol.[Torp-Pedersen, 2005 #12065] Worsening heart failure was reported as a prespecified secondary endpoint in COMET, but the results haven't yet been reported. In the older trials, there was a nonsignificant trend favoring carvedilol over immediate-release metoprolol. Carvedilol and immediate release metoprolol (124+/-55 mg/d) had similar effects on quality of life, but metoprolol improved exercise capacity more. There were no differences between the carvedilol and metoprolol groups in quality of life.

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

Several beta blockers have been used to reduce the heart rate in patients with atrial tachyarrhythmias and to prevent relapse into atrial fibrillation or flutter. A recent good quality systematic review examined 12 studies of rate control in patients with chronic atrial fibrillation.[93] 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).[94] 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.[95-97] 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).[95, 96] 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.[97] 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 (data nr; p=0.0001) and improved mean LVEF scores (30.6% vs 26%; p=0.048) and severity of symptoms/functional capacity on a 33-point scale (6 vs 8; p=0.039). There were no differences between monotherapies with either carvedilol or digoxin in the second phase, however.

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

Summary

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

Detailed Assessment

Head to Head trials

We found five fair quality[98-103] 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.[104, 105] 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,[101] slow release metoprolol (durules) 200 mg daily[99] , immediate release metoprolol 200 mg daily[98] and timolol 20 mg[102, 103], and propranolol 80 mg to metoprolol 100 mg daily.[100] All four trials were conducted outside of the US, were relatively short-term in duration (12-20 weeks), and were small (35-96 patients). Most patients had common migraine per Ad Hoc Committee and World Federation of Neurology Research Group guidelines (83-93%) and migraine without aura per International Headache Society (92.8%). These patients have mean ages of 33.8-42.3, are 68.6-88.9% female, and have a history of migraine frequency of >3 attacks per month. Use of concomitant analgesics and ergotamines was allowed for abortive migraine treatment. Headache frequency, intensity, severity, duration and abortive treatment tablet usage efficacy parameters were analyzed using patient diary data.

The methods used to assess treatment effects differed across studies. Some of the common outcome results are summarized in Table 13 below. Analysis of variance was used to assess comparative efficacy of metoprolol 200 mg and propranolol 160 mg in one trial.[98]

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. [98-100, 102, 103]

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.[98-100]

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.[99, 100, 102, 103]

Tablet Consumption

There were no differences in reduction of acute medication (analgesics, ergots) for metoprolol durules or metoprolol tartrate and propranolol.[99, 100, 102, 103]

Subjective Assessment

Patients in two trials[99, 100] were asked to make a subjective assessment of therapeutic improvement using descriptors of marked, moderate, slight, and unchanged or worse. There were no differences found between slow release metoprolol (durules) and propranolol (76% vs 63%) or between low doses of immediate release metoprolol or propranolol (63% vs 64%) in rates of decreased frequency of mean or median attacks per month.

Miscellaneous

Two trials[101-103] 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)

Outcomes	Attack frequency/ 4 wks (% decrease)	Headache days	Severity (% reduction)	Tablet consumption	Subjective (% patients regarding effect as "marked" or "moderate")	Misc.
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,[106] bisoprolol 5 or 10 mg,[107] metoprolol slow release (Durules) 200 mg,[108, 109] pindolol 7.5-15 mg,[110, 111] propranolol immediate release 80-240 mg[112-120] and long acting propranolol 160 mg.[121, 122] One trial[123] did not report propranolol dosage and will be discussed separately.

All but two[114, 123] of these trials were conducted outside of the US. A crossover design was used in 12 trials, while the other five compared parallel groups. All but two trials reported allowing the use of various concomitant medication to abort migraine pain including common analgesics, ergotamines, and narcotics. These trials ranged in duration from 8-52 weeks, generally enrolling patients with a 1-2 year history of common or classic migraine (Ad Hoc Committee), generally occurring at an average frequency of three per week. One trial included only patients with classic migraine.[109] Patient characteristics reflected the target migraine population, with mean ages in the range of 37-39 and predominantly female (> 75%). Sample sizes ranged from 24-259 patients enrolled. Assessment of attack frequency, duration, severity, and use of acute medication variables was made using patient diary card data.

Placebo controlled trial data is consistent with head to head trial data for atenolol 100 mg, slow release metoprolol (durules) 200 mg and propranolol 80 and 160 mg as discussed above and adds information regarding efficacy of bisoprolol and pindolol. An exception was found in one of the ten fair quality trials of propranolol[115] where a dosage of 120 mg was not significantly superior to placebo in increasing the proportion of patients that had at least a 50 % reduction of migraine attacks in the last four weeks of treatment (42.3% vs 30.9%) or in reducing the mean duration of migraine in hours per month (34.4 vs 13.7).

Bisoprolol

The results of one placebo controlled trial of 12 week's duration and involving 226 patients[107] 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[110, 111] 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.[102, 103, 124-133] These were rated poor quality due to insufficient detail in reporting randomization and allocation concealment methods, failure to perform efficacy analyses using an intention to treat principle, and rates of attrition ranging from 24% to 48.1% and were not discussed here.

We found a one meta-analysis[134] that evaluated the effects of propranolol in 2403 migraine patients across a combination of 53 head to head, active- and placebo-controlled trials published through 1991. This review was rated poor quality due to failure to report critical assessment of internal validity and will not be discussed here. We independently assessed and included three head to head and 12 placebo controlled trials from this meta-analysis in our report.

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

Head-to-head Trials

We found one head to head trial of beta blockers for the treatment of bleeding esophageal varices.[135] This trial compared the efficacy of propranolol 40-160 mg daily, a nonselective beta blocker, atenolol 100 mg daily, a selective beta blocker, and placebo in cirrhotic patients. The results of this trial are summarized in Evidence Tables 9 and 9a. This trial was rated fair quality. This trial, conducted in Italy, was designed to measure rebleeding and death and had a mean follow-up of 357 days. The patient population enrolled was typical for esophageal variceal bleeding, with a mean age of 53, 80.8% male and 81.9% alcoholic patients. This study also enrolled a small proportion of patients in which the prior hemorrhage was of a gastric erosion (12.8%) or unknown (inconclusive endoscopy) (6.4%) origin. Concomitant use of ranitidine, oral antacids, spironolactone, saluretics, lactulose, and nonabsorbable antibiotics was allowed.

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

Placebo-controlled trials

We found fair quality, placebo controlled trials of nadolol[136] and propranolol[137-144] for the secondary prevention of bleeding esophageal varices secondary to cirrhosis and schistosomiasis[145]. Results are summarized in Evidence Tables 9 and 9a. These trials were all conducted outside of the US, enrolled samples of 12-82 patients and ranged from 3 months to 2 years in duration. Mean ages ranged from 43-58 for the cirrhotic and 35.8 for non-cirrhotic patients. Populations were predominantly male with alcoholism as the most common etiology for cirrhosis. Treatment was initiated earlier, within 72 hours of the index bleeding episode, in only three of the trials.[137, 140, 144]

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.[137, 144] 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).[140] For trials of later (≥ 14 days)[139, 141, 142, 146] and unspecified[138, 147] 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%
El Tourabi, 1994	**LA pro vs pla**	**n=82**	**unspecified**	**2% vs 20%; p<0.02**

Deaths due to variceal rebleeding were reported by seven comparisons to placebo across six trials[137-139, 141, 144, 146]. 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[147], 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[137], 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%

Summary

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

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

Summary

Side effects are common among patients taking beta blockers. Longer-term trials (12-58 months) directly comparing beta blockers in patients with hypertension (atenolol vs bisoprolol vs

propranolol), heart failure (carvedilol vs metoprolol), bleeding esophageal varices (atenolol vs propranolol), and atrial fibrillation (bisoprolol vs carvedilol) showed no differences in any of the safety parameters measured, with one exception. Carvedilol caused more dizziness than metoprolol (14.7% vs 1.3%; p=0.0046) in a fair quality trial of 122 patients with heart failure.[88] Propranolol caused higher rates of overall adverse event incidence than pindolol in patients with stable angina in one short-term trial (8 weeks) that used potentially flawed randomization methods.[33]

In everyday practice, weight gain, fatigue, dizziness, dyspnea are the most common side effects in patients with heart failure. About 1 in 5 patients require discontinuation of the initial beta blocker choice. In 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.[148] Overall, about 1 in 5 patients (51 total) could not tolerate the initial choice of treatment. Forty of the 51 patients who could not tolerate the initial choice were switched to another beta blocker. Twenty two of these 40 patients tolerated the 2nd choice, with equal proportions tolerating a switch to carvedilol from metoprolol and to metoprolol from carvedilol.

A higher rate of beta blocker intolerance was reported in another trial that enrolled 90 consecutive patients in a heart failure clinic in Denmark.[149] This trial compared bisoprolol and carvedilol and was designed to measure treatment failure rates under conditions that mimic daily clinical practice. The eligibility criteria was 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.

Detailed Assessment

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

Head-to-head safety analyses were provided by 7 trials in patients with hypertension[3, 6-9, 17, 18] (Evidence Table 1), 3 trials of patients with angina[33, 34, 150] (Evidence Table 2), 3 trials in patients with heart failure[82, 88, 91] (Evidence Table 5b), 6 trials in migraine patients[98-101, 103, 151] (Evidence table 8) 1 trial in patients with bleeding esophageal varices[135] (Evidence Table 9), 1 trial of patients post-myocardial infarction[48] (Evidence Table 4), and 1 trial of patients with atrial fibrillation (Evidence

table 7).[94] 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 one[98] of the head to head trials in patients with migraine used crossover designs, only reporting results of the combined intervention periods.

Only one trial[7] of atenolol 100 mg and pindolol SR 20 mg in 107 essential hypertensive patients was designed specifically for adverse event assessment and was rated good quality. Safety assessment in the remaining 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 event incidence was reported in 13 head to head trials.[3, 6, 8, 17, 18, 33, 34, 91, 99, 100, 103, 104, 150] 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.

Bradycardia. Four trials reported no significant differences between beta blockers in bradycardia incidence.[3, 6, 17, 18, 88] This included a 44-month trial of 122 carvedilol and metoprolol in patients with heart failure[88] and three short-term (4-6 weeks) trials in patients with hypertension that compared atenolol to either metoprolol CR or propranolol.[3, 6, 18]

Dizziness. Six head to head trials reported dizziness incidence.[17, 88, 101, 103, 104, 150] All but one reported no significant differences between beta blockers.[88] 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%; $p=0.0046$).[88] This significant difference was not seen in another shorter trial (3 months in 368 patients with angina (4.8% vs 5.0%).[150] Reasons for this inconsistency may include differences in definition of dizziness and evaluation techniques between the two trials. This assumption cannot be verified, however, as the methods were not provided. Indirect comparison of the inconsistent head-to-head trial results to available fair-good quality placebo-controlled trials safety data does not offer any additional information as dizziness rates in metoprolol trials were not reported.

Hypotension incidence was reported in one 44-month trial of 122 patients with heart failure[88]. No difference between rates of hypotension for carvedilol (2.7%) and metoprolol (2.7%) were found.

Withdrawals due to adverse events were reported by ten head to head trials.[3, 6, 9, 17, 18, 82, 94, 103, 104, 135] No significant differences were found in any of the comparisons.

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

Summary

There is no data that suggests that any beta blocker is superior in any subgroup of patients based on demographic, 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

The Beta-Blocker Pooling Project (BBPP)[152] analyzed mortality in post-infarction patients relative to subgroup risk factors from trials of propranolol[45, 59, 153], pindolol[59], and other beta blockers not available in the United States. This analysis found that none of the age, gender, heart failure and prior diabetes mellitus baseline characteristics interacted significantly with the effect on mortality. This analysis also does not offer any meaningful information about the comparative efficacy of beta blockers in these subgroups.

A 2003 meta-analysis[154] 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 the table 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

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.[53] We found no other source of publication of results from this subgroup analysis. The U.S. Carvedilol Heart Failure Study Group published an analysis[155] of the pooled results from a stratified set of three fair-quality and one poor-quality concurrently conducted protocols,[71-74] discussed in detail above, that showed no significant interaction between race and carvedilol treatment in patients with mild-moderate heart failure. More recent analyses from the COPERNICUS trial[76] show that carvedilol had similar effects regardless of age and gender in patients with *severe* heart failure.

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

Metoprolol. A fair quality review[156] that pooled results from five placebo controlled trials of metoprolol (Amsterdam, Belfast, Goteborg, LIT, Stockholm) found that neither age nor gender had a significant influence on mortality. When considered individually, results from the Goteborg Metoprolol Trial[157] show a nonsignificant trend that patients aged 65-74 years had a more marked reduction in mortality at 3 months post-myocardial infarction (45%) than did all patients aged 40-74 (36%). Results from the MERIT-HF trial also reported that age nor gender had any influence on the effects of metoprolol CR in patients with mild-moderate heart failure.

Propranolol. The fair quality, placebo controlled Beta Blocker Heart Attack Trial (BHAT)[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) heath or QOL outcomes. Reliable indirect comparisons cannot be made by evidence from 3 long-term placebo-controlled trials of propranolol and atenolol

Key Question 1: Comparative Efficacy	Grade of Evidence*	Conclusion
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)
e. Recent MI	Overall grade: Fair-good	1 fair-quality head to head trial found no differences in mortality after one year between atenolol and propranolol, but this was a relatively small trial 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 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
f. Heart failure	Health outcomes in HTH trials: Fair Symptoms in HTH trials: Good Placebo-controlled trials in mild-moderate HF: Good Placebo-controlled trials in severe HF: Fair+ for carvedilol and Fair- for metoprolol succinate	Carvedilol > metoprolol tartrate in reducing total mortality in COMET in patients with mild-moderate heart failure Carvedilol=metoprolol tartrate in improving symptoms (quality of life; NYHA) and exercise capacity in 4 head to head trials Metoprolol succinate reduced total mortality, sudden death, and death due to progressive heart failure and improved quality of life (MERIT-HF) Carvedilol reduced total mortality, sudden death and death due to pump failure (MOCHA) Bisoprolol reduced total mortality and sudden death Carvedilol reduced mortality and the combined endpoint of mortality and hospitalizations in a prospective trial A post-hoc, subgroup analysis of MERIT-HF suggests that metoprolol succinate is similarly effective in comparable patients

Key Question 1: Comparative Efficacy	Grade of Evidence*	Conclusion
g. Atrial arrhythmia	Overall grade: Fair	Bisoprolol=carvedilol in preventing relapse of atrial fibrillation in a head-to-head trial Metoprolol succinate reduced incidence of atrial arrhythmia/fibrillation in a placebo-controlled trial Carvedilol reduced 24-hour ventricular rate in patients with atrial fibrillation and heart failure in one placebo-controlled trial These placebo-controlled trials do not offer comparative data
h. Migraine	Overall grade: Fair	Atenolol, slow release metoprolol, immediate release metoprolol, and timolol were all similar to propranolol in their effects on pain outcomes and acute medication use in 5 head to head trials
i. Bleeding esophageal varices	Overall grade: Poor	Results of 1 head to head trial of atenolol and propranolol, 1 placebo controlled trial of nadolol and 6 placebo controlled trials of immediate release and two formulations of extended release propranolol, all fair quality, don't clearly differentiate one beta blocker from another.
Key Question 2: Adverse Effects	**Quality of Evidence***	**Conclusion**
Hypertension, stable angina, heart failure, atrial arrhythmia, migraine, bleeding esophageal varices, previous myocardial infarction	Overall grade: Fair	Head-to-head trials don't clearly differentiate one beta blocker from another in overall AE incidence, dizziness, hypotension and withdrawal due to adverse events with two exceptions. Carvedilol was associated with a higher rate of dizziness than metoprolol in one long-term trial in heart failure patients. Propranolol was associated with a higher overall rate of adverse events than pindolol in one short-term trial in patients with stable angina. This trial had potentially confounding baseline differences that favored the pindolol group.
Key Question 3: Subgroups	**Quality of Evidence***	**Conclusion**
a. Demographics (age, gender, race)	Overall grade: Fair	Evidence showed that age, gender and race did not impact the effectiveness of carvedilol, immediate and controlled release metoprolol and propranolol
b. High risk populations	Overall grade: Fair	*Heart failure.* Subgroup analyses of placebo controlled trials showed that a history of MI may reduce the protective effect of bisoprolol on mortality (CIBIS). No risk factor was found to confound the protective effect of carvedilol (COPERNICUS) or controlled release metoprolol (MERIT-HF) on mortality. *Post-myocardial infarction.* The MIAMI trial found that metoprolol had the greatest protective effect on mortality in patients with numerous risk factors. The BHAT trial found no variation in propranolol's protective effect on total mortality based on history of heart failure

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

Table 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	
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 *severe* 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
labetolol		=atenolol in reducing nitrate use when both combined with chlorthalidone						

Table 18. Summary of comparative efficacy continued

Drug	Hypertension	Angina	Status-post CABG	Heart failure	Atrial arrhythmias	Migraine	Bleeding esophageal varices	Myocardial infarction
metoprolol tartrate		=carvedilol in increasing exercise tolerance	=placebo for mortality	< carvedilol in reducing total mortality (COMET) =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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Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Head to head controlled trials			
Walle 1994 Fair	HTH Crossover DB	Patients of either sex, more than 21 years of age, with mild to moderate hypertension (diastolic blood pressure in the range of 95 to 110 mmHg) were eligible for the study. The study subjects were either to have received no previous antihypertensive treatment or to have been previously treated	Cardiiovascular diseases, such as angina pectoris, secondary hypertension, grade II or III AV block, heart failure, or a history of myocardial infarction (within 12 months); cerebrovascular ischemia: asthma/ chronic bronchitis; insulin-dependent diabetes; and malignancy or chronic disease requiring treatment
Sundar 1991	HTH Crossover	Patients, who were between the age 35 and 60 years, either never received antihypertensive treatment or had discontinued the drugs for at least 2 weeks prior to entry into trial	Patients with accociated conditions like moderate to severtr congestive infarction within 6 months, accelerated hypertension and those with severe gastrointestinal, renal or hepatie dysfunction were excluded

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

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Head to head controlled trials				
Walle 1994 Fair	Run-in: 4-wk, SB, placebo Treatment periods: Metoprolol CR 100 mg vs Atenolol 100 mg x 6 weeks Washout: NR	No	Psychologic General Well-Being (PGWB) index Minor Symptom Evaluation (MSE) profile	Mean age: 58 y/o, 43.3% male. Ethinicity: NR
Sundar 1991	Wash-out period: 2 weeks between the interventions atenolol (ate): 100mg per day propranolol (pro): 80mg per day duration of treatment: 4 weeks	NR	Quality of life questionnaire (5-point scale) -the sense of well being and satisfaction with life -the physical state -the enotional state -intellectual functions -ability to perform in social roles -sexual life	Age, Ethnicity: NR Gender: 100% male

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

Author, Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Head to head controlled trials				
Walle 1994 Fair	mean weight: 76kg mean height: 171cm mean duration of hypertention: 9 yrs mean BP: 102/178	NR/NR/60	2/0/58	Metoprolol CR vs atenolol PGWB Index (total mean scores): 102.7 vs 102.0; p=NS MSE profile - morning (mean values); all p=NS Contentment: 33.1 vs 32.4 Vitality: 35.2 vs 35.4 Sleep: 31.8 vs 30.0 MSE profile - morning (single items rated using VAS) Sexual interest: favored atenolol (p<0.05) (data NR) Muscular tension, numbness, self-consciousness, sociability, appetite, sweating, physical competance, dreams: p=NS, data NR
Sundar 1991	NR	NR/NR/44	18/0/26	ate vs pro: -the sense of well being and satisfaction with life -the physical state -the enotional state -intellectual functions -ability to perform in social roles -sexual life *all NS

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

Author, Year Country	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Head to head controlled trials			
Walle 1994 Fair	Clinical observation, active questionning	Overall AEs: no differences (data NR) Serious AEs: 0 vs 2 (bradycardia and syncope; both leading to withdrawal)	meto vs ate = 0 vs 2 (3.3%)
Sundar 1991	Reported by patients	ate vs pro (%) headache: 0 vs 0 weakness: 10.5 vs 10.7 warmth: 2.6 vs 0 oedema: 0 vs 0 dyspnoea: 5.3 vs 0 constipation: 0 vs 0	NR

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

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Head to head controlled trials			
Steiner 1990	HTH Parallel	The patients were required to have been diagnosed with mild-to-moderate essential hypertension for at least 1 yea, be at least 21 years of age, emloyed or retired, eucated at high-school level or equivalent, and married or libing with an significant other.	Patients could not have major concomitant medical or mental problems or significant changes in living conditions (e.g., recent death of spouse), or require concomitant therapy that could confound the study results

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

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Head to head controlled trials				
Steiner 1990	placebo run-in for 3-5 weeks titration for 1-4 weeks (lowering of DBP by at least 10 mmHg or to 90mmHg or less) maintenance for 4 weeks Propranolol 80-240mg per day (mean=133.4mg per day) Atenolol 50-100mg per day (mean=56.4mg per day)	No	Four-point scale in the Symptom Check List-90-R (SCL) (by patients) Psychological General Well-Being (PGWB) Index (by patients and spouses or significant others) Insomnia Symptom Questionnaire Sexual Function Questionnaire for male patients (modified) Life satisfaction Index	Age, Ethnicity: NR Gender: 100% male

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

Author, Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Head to head controlled trials				
Steiner 1990	NR	489/360/344 (179 for pro and ate)	27/1/151 pro: 73 ate: 78	Propranolol vs. Atenolol PGWB Index (patients) -Global, anxiety, depressed mood, positive well-being, general health vitality: NS -Self-control: -0.17 vs 0.32, p<0.05 PGWB Index (significant other) -Global, anxiety, depressed mood, self-control, general health vitality: NS -Positive well-being: -0.65 vs 0.33, p<0.05 Symptom Checklist -Global: -0.02 vs -3.46, p<0.05 -Anxiety: -0.35 vs -1.49, p<0.05 -Obsession: 0.03 vs -1.34, p<0.05 -Hostility: 0.38 vs -0.65, p<0.05 Life Satisfaction Index -Global: -1.13 vs 1.19, p<0.05 -Social satisfaction: -0.24 vs 0.71, p<0.05 -Life satisfaction, work satisfaction: NS Sleep function, Sexual function: all NS

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

Author, Year Country	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Head to head controlled trials			
Steiner 1990	Reported by patients	pro(%) vs ate(%), all NS Bradycardia: 4(4.5) vs 9(10) Gastrointestinal distress: 9(10.1) vs 7(7.8) Dry mouth: 5(5.6) vs 4(4.4) Anxiety: 7(7.9) vs 2(2.2) Sleep disturbance: 4(4.5) vs 6(6.7) Libido decreased/impotence: 8(9): 5(5.6) Weakness/fatigue: 15(16.9) vs 8(8.9) Headache: 12(13.5) vs 9(10) Total: 57(64) vs 50(55.6)	pro: 5(6.85) ate: 0(0)

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

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Head to head controlled trials			
Dahlof 1988	HTH Crossover	Patients with either sex with mild to moderate primary hypertension, either newly diagnosed or previously treated with monoterapy	1. The patient had not followed the instructions to fill in and return the questionnaire on 3 occasions during the run-in period 2. The diastolic blood pressure <90mmHg or >105mmHg 3. Previous treatment with metoprolol or atenolol 4. AV-block 2 or 3 5. Non-compensated congestive heart failure 6. Insulin-treated diabetes 7. Bradycardia (heart rate <50 beats/min) 8. Bronchial asthma 9. Any serious concomitant illness or drug abuse which can interfere with the treatment 10. Unwillingness to participate in the study
Blumenthal 1988	HTH exposure design unclear	Participants were eligible for the study if they had resting diastolic blood pressures that were within 90 to 110 mmHg on four separate occassions, using a random zero device, during a 2-week screening interval before testing. Subjects did not take any antihypertensive medication for at least 6 weeks before the screening and were free of any significant disease other than hypertension.	NR

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

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Head to head controlled trials				
Dahlof 1988	placebo run-in: 2 weeks atenolol (ate) 50 mg od metoprolol CR (meto) 100 mg od Duration: 6 weeks	NR	MSE-profile Jern's quality of life questionnaires Beta-blocker questionnaires (subjective symptoms reported) Timing: before, during and after the intervention	mean age: 54.4 ±8.8, 51(66%) male Ethnicity: NR
Blumenthal 1988	Week 1 (b.i.d): Atenolol (ate): 50mg+placebo Propranolol (pro): 40mg+40mg Placebo (pla): placebo+placebo Week 2 (b.I.d): If BP was not reduced by 10mmHg and remained below 90mmHg, increase dosage to: ate 100mg; pro 80mg. Duration: 2 weeks	NR	Psychmetric testing: -The profile of mood states (POMS) -SCL-90 -A side effects measure Timing: before and after drug administration	mean age=42.5, 100% male (22 whites and 4 blacks)

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

Author, Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Head to head controlled trials				
Dahlof 1988	Duration of hypertension: 3.5±5 years WHO I: 75 WHO II: 2 Supine BP: SBP 159±14.9, DBP 97.8±4.8 Heart rate: 74±10.4	NR/NR/77	3/0/74	meto vs ate MSE-profile, contentment, hedonic tone, vitality, activity, sleep, relaxation: NS Subjective symptoms- leg fatigue, constipation, diarrhoea, bradycardia, cold hands and feet, heavy breathing: NS Palpitation: meto> ate, p<0.05 Preference (n): 31 vs 23, NS
Blumenthal 1988	15 (62%) had not taken any antihypertensive medication at any time before participation in the study. 0 (0%) took any sedative medication 23 (80%) had at least some college education 25 (98%) were employed on a full-time basis.	NR/ NR/ 26	0/0/26	POMS (before vs. after): ate: tension- 11.87 vs. 6.12, p<0.002 depression- NS anger- 7.12 vs. 2.00, p<0.03 pro: all NS; pla: all NS SCL-90 (before vs. after): ate: anxiety- NS hostility- 55.00 vs. 48.37, p<0.04 phobic anxiety- NS; depression- NS pro: all NS; pla: all NS

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

Author, Year Country	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Head to head controlled trials			
Dahlof 1988	Beta-blocker questionnaires (subjective symptoms reported)	Subjective symptoms- leg fatigue, constipation, diarrhoea, bradycardia, cold hands and feet, heavy breathing: NS Palpitation: meto> ate, p<0.05	2(2.6%)
Blumenthal 1988	Questionnaire. Reported by patients	sleep items: NS sexual functioning: NS energy: 4 (ate) and 4 (pro) reported being more tired in the morning, while 6 (pla) reported less fatigue.	0

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

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Head to head controlled trials			
Buhler 1986	HTH Crossover DB	Patients with a diastolic blood pressure (DBP) of 100-120 mmHg (Korotkoff V) om the seated position	Patients were on other antihypertensive drugs, had contraindications for beta-blocker therapy, severe disease, or who were known for their poor compliance. Patients with impaired renal function, i.e., serum creatinine>150 umol/l, were also excluded.
Placebo controlled trials			
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)* Fair quality	Placebo-controlled	21-65 years old; between 110 and 160% ideal weight (Metropolitan Life Insurance Height-Weight Tables); diastolic BP at baseline of 90-100 mm Hg	History of myocardial infarction, stroke, or asthma, or a serum creatinine level of 177 mmol/d or greater, insulin-dependent diabetes, allergy to thiazides or beta-blockers, pregnancy, or likelihood of difficulty in complying with the interventions

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

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Head to head controlled trials				
Buhler 1986	Wash-out period: 2 weeks Bisoprolol (bis) 10mg or Atenolol (ate) 50 mg for 2 weeks. Then, if DBP> 95mmHg, increase to: bis 20mg or ate 100mg. Total duraion: 8 weeks Wash-out period: 2 weeks. Then crossover.	NR	self-assessment questionnaire	86 (82.7%) male male: mean age=53.8 female: mean age=50.8 Ethinicity: NR
Placebo controlled trials				
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)* Fair quality	Atenolol (ate) 50 mg Chlorthalidone (chl) 25 mg Placebo (pla)	*Dietary interventions* 1) Usual Diet 2) Low sodium (goal of 52 mmol/d for participants weighing 50 kg or less to 100 mmol/d for those weighing 92 kg) + high potassium (goal: 62 mmol/d to 115 mmol/d) 3) Weight loss group (goal: 4.5 kg or 10% of baseline weight, whichever was greater)	Life Satisfaction Scale Physical Complaints Inventory Symptoms Checklist	*Per protocol analysis (n=697)* Mean age=49 56% male 68% white

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

Author, Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Head to head controlled trials				
Buhler 1986	10 were not available for the crossover comparison because of: intercurrent disease (n=1), BP response deemed unsatisfactory by the investigator (n=3), and unwanted effects (n=6).	138/134/116	12/0/104	Baseline:bis/ baseline:ate (all NS) headache- 20:7/ 19:9 tiredness- 17:20/ 17:13 Nervousness- 17:10/ 10:8 Sleep problems- 18:11/ 15:10 Cold extremities- 14:13/ 16:12 Sweating- 12:9/ 11:11 Tingling sensations- 12:6/ 9:5 Feeling of weakness- 11:6/ 5:7 Dizziness- 11:3/ 8:7 Joint pain- 9:9/ 6:8 Depressed mood- 12:11/ 9:5 Sex problems- 5:7/ 6:4
Placebo controlled trials				
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)* Fair quality	Previous dug treatment = 66.2% Smokers = 14% Alcohol use (at least once a week) = 39.7%	10, 148 screened/878 eligible/878 randomized	181(20.6%) withdrawn/0 lost to fu/697 analyzed	*Per protocol analysis (pla n=232; ate n=238)* *(*negative score indicates improvement)* *Total physical problems: pla=(-0.15); ate=(-0.14) *Overall psychological functioning: pla=(-0.14); ate=(-0.14) Overall life satisfaction: pla=(-0.04); ate=0.02 *Sexual physical problems: pla=(-0.12); ate=(-0.09) *Depression: pla=(-0.15); ate=(-0.14) *Anxiety: pla=(-0.14); ate=(-0.15) *Sleep disturbances: (-0.29); ate=(-0.26) *Fatigue: (-0.20); ate=(-0.15) Satisfaction with physical health: pla=0.21; ate=0.19 Sexual satisfaction: pla=(-0.14); ate=0.04

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

Author, Year Country	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Head to head controlled trials			
Buhler 1986	self-assessment questionnaire	Baseline:bis / baseline:ate (number), all NS headache- 20:7/ 19:9 tiredness- 17:20/ 17:13 Nervousness- 17:10/ 10:8 Sleep problems- 18:11/ 15:10 Cold extremities- 14:13/ 16:12 Sweating- 12:9/ 11:11 Tingling sensations- 12:6/ 9:5 Feeling of weakness- 11:6/ 5:7 Dizziness- 11:3/ 8:7 Joint pain- 9:9/ 6:8 Depressed mood- 12:11/ 9:5 Sex problems- 5:7/ 6:4	bis (1): dizziness ate (5): diarrhea, skin rash, asthmatic bronchitis, vertigo, headache
Placebo controlled trials			
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)* Fair quality	NR	NR	NR

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

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Placebo controlled trials			
Perez-Stable, 2000 Fair quality	Placebo-controlled	Patients with mild hypertension, defined as an average diastolic blood pressure between 90 and 104 mm Hg on three readings taken during each of two screening visits 2 weeks apart; aged 18-59	Concomitant use of insulin, bronchodilators, antidepressants or antihypertensive medications within 1 month of screening; coronary artery disease, vascular heart disease, renal insufficiency, cerebrovascular disease, and secondary causes of hypertension

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

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Placebo controlled trials				
Perez-Stable, 2000 Fair quality	Propranolol (pro) 80-400 mg daily *(n=156)* Placebo (pla) *(n=156)*	NR	*Cognitive Function Test Battery* Stimulus Evaluation/Response Selection Continuous Performance Task(CPT) Digit Symbol Substitution Task(DSST) California Veral Learning Test(CVLT) *Psychological Measures* Center for Epidemiological Studies Depression Scale(CES-D) Beck Depression Inventory(BDI)	Age: Pro=4; Pla=45 % male: Pro=67; Pla=66 % White: Pro=76; Pla=71

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

Author, Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Placebo controlled trials				
Perez-Stable, 2000 Fair quality	Current smokers: Pro=10%; Pla=11% Current daily drinkers of alcohol: Pro=11%; Pla=12% Mean DBP: Pro=96; Pla=96 Mean SBP: Pro=140=Pla=141	nr/nr/312	NR/NR/203	**Mean changes in:** Selection reaction time(ms): pro=(-3); pla=(-10) ***CPT*** Reaction time(ms): pro=12; pla=6 Correct responses: pro=0; pla=0 Commission errors: pro=(-1); pla=(-1) Omission errors: pro=0.1; pla=0.1 **DSST** correct responses: pro=3; pla=5 ***CVLT*** Monday total: pro=3; pla=1 Tuesday list: pro=2; pla=0 Short-delay free recall: pro=3; pla=2 Short-delay cued recall: pro=4; pla=3 Long-delay free recall: pro=5; pla=4 Long-delay cued recall: pro=5; pla=2 Recognition: pro=3; pla=3 **CES-D:** pro=0; pla=0 **BDI:** pro=(-1); pla=baseline value nr

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

Author, Year Country	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Placebo controlled trials			
Perez-Stable, 2000	NR	NR	NR

Fair quality

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

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Placebo controlled trials			
Anonymous, 1977 Greenberg, 1984 Anonymous, 1985 Miall, 1987 Anonymous, 1988a Anonymous, 1988b Anonymous, 1992 Lever, 1993 UK *Medical Research Council (MRC)* *Fair quality*	Placebo-controlled Single blind	***Mild hypertension*** Men and women; aged 35-64; with mild hypertension (diastolic BP 90-109 mm Hg, together with systolic pressure below 200 mm Hg)	Secondary hypertension; already on antihypertensive treatment; cardiac failure; MI or stroke within previous 3 months, angina; intermittent claudication; diabetes; gout; asthma; other serious disease; pregnancy

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

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Placebo controlled trials				
Anonymous, 1977 Greenberg, 1984 Anonymous, 1985 Miall, 1987 Anonymous, 1988a Anonymous, 1988b Anonymous, 1992 Lever, 1993 UK *Medical Research Council (MRC)* *Fair quality*	Propranolol (pro) up to 320 mg daily *(n=4403)* Bendrofluazide (ben) 10 mg daily *(n=4297)* Placebo (pla) *(n=8654)* with goal of maintaining DBP below 90 mm Hg x 5 years	Methydopa	Data for terminating events (e.g., strokes, coronary events, all cardiovascular events, and all cause mortality) were analyzed every six months	Mean age: pro=52; ben=52; pla=52 %male: pro=51.9; ben=52.1; pla=52.3 Race nr

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

Author, Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Placebo controlled trials				
Anonymous, 1977 Greenberg, 1984 Anonymous, 1985 Miall, 1987 Anonymous, 1988a Anonymous, 1988b Anonymous, 1992 Lever, 1993 UK *Medical Research Council (MRC)* *Fair quality*	*(Mean values for men/women)* Body weight(kg): pro=81/70; pla=81/70 SBP(mm Hg): pro=158/165; pla=158/165 DBP(mm Hg): pro=98/98; pla=98/98 % cigarette smokers: pro=30/25; pla=32/27 % with LV hypertrophy on ECG: pro=0.3/0.2; pla=0.4/0.4 % with Q-wave abnormalities: pro=1.2/1.7; pla=1.5/1.4 % with history of stroke: pro=0.7/0.7; pla=0.7/0.7	515,000 screened/46,350 eligible/17,354 enrolled	nr/nr/17,354 analyzed	*# events/rate per 1000 patient years* Strokes: pro=42/1.9; pla=109/2.6 Coronary events: pro=103/4.8; pla=234/5.5 All cardiovascular events: pro=146/6.7; pla=352/8.2 Non-cardiovascular deaths: pro=55/2.5; pla=114/2.7 All deaths: pro=120/5.5; pla=253/5.9

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

Author, Year Country	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Placebo controlled trials			
Anonymous, 1977 Greenberg, 1984 Anonymous, 1985 Miall, 1987 Anonymous, 1988a Anonymous, 1988b Anonymous, 1992 Lever, 1993 UK *Medical Research Council (MRC)* *Fair quality*	NR	NR	# patients/% Impaired glucose tolerance: pro=43/0.98%; pla=82/0.95% Gout: pro=12/0.27%; pla=14/0.16% Impotence: pro=50/1.14%; pla=20/0.23% Raynaud's phenomenon: pro=75/1.70%; pla=7/0.08% Skin disorder: pro=21/0.48%; pla=7/0.08% Dyspnoea: pro=110/2.5%; pla=10/0.12% Lethargy: pro=104/2.36%; 13/0.15% Nausea/dizziness/headache: pro=103/2.34%; pla=49/0.57% Overall: pro=518/11.76%; pla=202/2.33%

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

Author, Year Country	Randomization described	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Head to head controlled trials					
Walle 1994	NR	NR	Unclear	Mean age=58 years 43.3% male Race NR	60
Sundar 1991	NR	NR	n/a-crossover	Mean age=NR 100% male 100% Indian	NR
Steiner 1990	NR	NR	NR	Baseline characteristics NR	489 screened, 360 eligible

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

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Head to head controlled trials						
Walle 1994	Cardiiovascular diseases, such as angina pectoris, secondary hypertension, grade II or III AV block, heart failure, or a history of myocardial infarction (within 12 months); cerebrovascular ischemia: asthma/ chronic bronchitis; insulin-dependent diabetes; and malignancy or chronic disease requiring treatment	Yes	Yes	Yes	Yes	No 13 (21.7%) excluded due to protocol violations
Sundar 1991	Patients with accociated conditions like moderate to severtr congestive infarction within 6 months, accelerated hypertension and those with severe gastrointestinal, renal or hepatie dysfunction were excluded	Yes	Yes	Yes	Yes	Unclear
Steiner 1990	Patients could not have major concomitant medical or mental problems or significant changes in living conditions (e.g., recent death of spouse), or require concomitant therapy that could confound the study results	Yes	Yes	Yes	Yes	No; 16 (4.4%) were excluded due to protocol violations

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

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Head to head controlled trials							
Walle 1994	Unclear	Yes No No No	No No	Fair	NR	Yes	6 weeks
Sundar 1991	Unclear	Yes No No No	Unclear Unclear	Poor	NR	Yes	4 weeks
Steiner 1990	Unclear	Yes No No No	NR	Fair	ICI Pharmaceuticals Group	Yes	4 weeks

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

Author, Year Country	Randomization described	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Head to head controlled trials					
Dahlof 1988	NR	NR	n/a-crossover	Mean age=54.4 66.2% male Race NR	NR
Blumenthal 1988	NR	NR	NR	Mean age=42.5 years 100% male 84.6% white 62% antihypertensive treatment naïve	26
Buhler 1986	NR	NR	n/a - crossover	Mean age=53.3 years 76.1% male Race NR	138

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

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Head to head controlled trials						
Dahlof 1988	1. The patient had not followed the instructions to fill in and return the questionnaire on 3 occasions during the run-in period 2. The diastolic blood pressure <90mmHg or >105mmHg 3. Previous treatment with metoprolol or atenolol 4. AV-block 2 or 3 5. Non-compensated congestive heart failure 6. Insulin-treated diabetes 7. Bradycardia (heart rate <50 beats/min) 8. Bronchial asthma 9. Any serious concomitant illness or drug abuse which can interfere with the treatment 10. Unwillingness to participate in the study	Yes	Yes	Yes	Yes	No; excluded 3 patients (3.9%) due to AE's (1 patient in each group) and noncompliance (group NR)
Blumenthal 1988	NR	Yes	Yes	Yes	Yes	Unclear
Buhler 1986	Patients were on other antihypertensive drugs, had contraindications for beta-blocker therapy, severe disease, or who were known for their poor compliance. Patients with impaired renal function, i.e., serum creatinine>150 umol/l, were also excluded.	Yes	Yes	Yes	Yes	No 30 (22.4%) were excluded due to BP limits or nondrug related problems

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

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Head to head controlled trials							
Dahlof 1988	n/a - crossover	Yes No No No	No No	Fair	NR	Yes	6 weeks
Blumenthal 1988	NR	No No No No	NR NR	Poor	John D. and Catherine T. MacArthur Foundation, National Institutes of Health greants HL30675, HS31514, and AG04238, and a grant (RO7233) from the US Public Health Services	Yes	2 weeks
Buhler 1986	Yes N=104 Mean age=53.3 82.7% male		No No	Fair	NR	Yes	8 weeks

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

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

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

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

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

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

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

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

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

Author Year Country Study Design	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Head to Head trials				
Chieffo 1986 Italy Fair quality RCT	sl ntg	Patient daily record	Mean age=56.8 100% male Race nr	NR
Dorow 1990 Fair quality RCT Crossover	Diuretics Short-acting and other nitrates Bronchodilators Inhaled corticoids Antibiotics Mucolytics Expectorants	Method of measurement of 'Frequency of angina pectoris attacks' nr	Mean age: 55 % Male: 82.5 Race nr	% Smokers: 17.6 % Coronary artery disease: 100 % angina pectoris pretreatment: 80 % MI in case history: 20 % pathological exercise ECG: 100

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

Author Year Country Study Design	Number screened/ eligible/ enrolled	Number withdrawn/lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Head to Head trials				
Chieffo 1986 Italy Fair quality RCT	NR/NR/10	NR/NR/10 analyzed	Effect on angina(# patients with reduced frequency on both 'daily incidence of angina attacks' and 'dosage of sublingual nitroglycerin'): lab+chl=4/5(80%); ate+chl=3/5(60%)	NR
Dorow 1990 Fair quality RCT Crossover	NR/NR/40	0 withdrawn/1 lost/40 analyzed	Angina attacks/week(% decrease in mean): ate=(-82.8%); bis=(-64.3%)	NR

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

Author Year Country Study Design	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Head to Head trials			
Chieffo 1986 Italy Fair quality RCT	NR	NR	Comorbid HTN
Dorow 1990 Fair quality RCT Crossover	NR	NR	

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

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

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

Author Year Country Study Design	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Head to Head trials				
Frishman 1979 United States Fair quality RCT	Nitroglycerin	Patient daily record Treadmill (protocol nr)	Mean age: 55 85.4% male Race nr	Diagnosis of coronary artery disease Coronary angiography: 80.5%
van der Does 1999 Europe Fair quality RCT	Nitrates	Erect bicycle ergometric exercise	Mean age: car=62; met=61 %male: car=72; met=71 Race nr	%smokers: car=14; met=19 %systemic hypertension: car=38; met=33 %diabetes mellitus: car=15; met=13 %dyslipidemia: car=32; met=31 %anterior MI: car=9; met=11 %posterior MI: car=18; met=17 %positive angiography: car=23; met=22 %1-vessel disease: car=13; met=10 %2-vessel disease: car=5; met=8 %3-vessel disease: car=5; met=3

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

Author Year Country Study Design	Number screened/ eligible/ enrolled	Number withdrawn/lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Head to Head trials				
Frishman 1979 United States Fair quality RCT	NR/NR/40	NR/NR/40 analyzed	Angina attacks/2 weeks(% reduction):pin=(-41.8%); pro=(-47.0%) Exercise tolerance(% increase in mets): pin=(+21.2%); pro=(+18.5%)	NR
van der Does 1999 Europe Fair quality RCT	nr/393 enrolled/368 randomized	36 withdrawn/lost nr/344 analyzed for efficacy	Per protocol analysis: car=231; met=113 Mean change in total exercise time(s): car=(+60); met=(+60) Mean change in time to angina(s): car=(+77); met=(+76)	Volunteered by subjects or observed by investigator were recorded regardless of their nature and regardless of whether a causal relation to study medication was assumed

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

Author Year Country Study Design	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Head to Head trials			
Frishman 1979 United States Fair quality RCT	Overall incidence: pin=4/23(17.4%); pro=17/18(94.4%) Pindolol Nasal stuffiness=1/23(4.3%) Nocturia=1/23(4.3%) Impotence=1/23(4.3%) Palpitations=1/23(4.3%) Propranolol Rash=1/18(5.5%) Blurred vision=2/18(11.1%) Fatigue=8/18(44.4%) Dyspnea on exertion=1/18(5.5%) Mild hypotension=5/18(27.8%)	NR	
van der Does 1999 Europe Fair quality RCT	car n=248; met n=120 Any adverse event: car=25%; met=30% <u>Most common AE's, n(%)</u> Dizziness: car=12(4.8), met=6(5.0) Bronchitis: car=9(3.6); met=3(2.5) Asthenia: car=8(3.2); met=3(2.5) Headache: car=8(3.2); met=4(3.3) Back pain: car=6(2.4); met=2(1.7)	AE withdrawals: car=18; met=6	

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

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Head to Head trials			
Narahara 1990 United States Fair quality	Patients of either sex who were > 30 years of age; history of stable angina pectoris of > 3 months' duration; reproducible exercise-induced angina in conjunction with ≥ 1 mm of horizontal or downsloping ST-segment depression measured 0.08 second after the J point	Contraindications to beta blockade including sinus bradycardia (<50 beats/min), greater than first-degree atrioventricular block, congestive heart failure, asthma, peripheral vascular disease or insulin-dependent diabetes; women of child-bearing potential and patients with unstable angina pectoris or a myocardial infarction within the preceding 3 months	Betaxolol 20 mg once daily Betaxolol 40 mg once daily Propranolol 40 mg 4 times daily Propranolol 80 mg 4 times daily x 10 weeks

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

Author Year Country Study Design	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Head to Head trials				
Narahara 1990 United States Fair quality	Sublingual nitroglycerin	Patient diary used to measure (1) angina frequency; and (2) nitroglycerin consumption Treadmill exercise testing (modified Naughton protocol) used to measure (1) exercise duration; and (2) time to angina	Mean age=61 21.4% female 92.9% white	History of prior MI = 42% History of coronary angiography = 59% Coronary angiography patients with NYHA functional Class II = 82% Coronary angiography patients with NYHA functional Class III = 17%

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

Author Year Country Study Design	Number screened/ eligible/ enrolled	Number withdrawn/lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Head to Head trials				
Narahara 1990 United States Fair quality	nr/nr/112	20(17.8%) withdrawn/lost to fu nr/90 analyzed for angina attacks and nitroglycerin tablet use; 82 analyzed for exercise variables	Mean number of angina attacks (% reduction) Betaxolol 20=60 Betaxolol 40=77 Propranolol 160=57 Propranolol 320=70 NS Nitroglycerin tablets/week (% reduction) Betaxolol 20=48 Betaxolol 40=73 Propranolol 160=59 Propranolol 320=55 NS Exercise duration (% increase in minutes) Betaxolol 20=14 Betaxolol 40=15 Propranolol 160=21 Propranolol 320=14 NS	NR

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

Author Year Country Study Design	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Head to Head trials			
Narahara 1990 United States Fair quality	Overall side effects (considered to be due to drug therapy): B20=50%; B40=37%; P160=42%; P320=45% # patients; sample sizes nr Fatigue: B20=1; B40=3; P160=4; P320=3 Increased sweating: B20=0; B40-3; P160=0; P320=0 Headache: B20=2; B40=0; P160=2; P320=0 Parasthesia: B20=0; B40=0; P160=0; P320=0 Diarrhea: B20=2; B40=0; P160=0; P320=0 Dyspepsia: B20=0; B40=2; P160=0; P320=0 Tinnitus: B20=2; B40=0; P160=0; P320=0 Angina: B20=0; B40=0; P16-=2; P320=0 Depression: B20=0; B40=2; P160=0; P320=0 Dyspnea: B20=0; B40=2; P160=0; P320=0 Abnormal vision: B20=0; B40=2; P160=0; P320=0	NR	

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

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

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

Author Year Country Study Design	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Head to Head trials				
Frishman 1989 United States Poor quality RCT	HCTZ 50 mg daily (if standing DBP > 100 mm Hg)	Treadmill ergometer exercise tests (Bruce protocol) Patient diary	Center 1 Mean age: lab=58; pro=57 Gender (%male): lab=66.7; pro=100 Race nr Center 2 Mean age: lab=51; pro=58 Gender(%male): lab=100; pro=100% Race nr	NR
Placebo controlled trials				
Destors 1989 Europe Fair Quality RCT	sl short-acting trinitrin	Bicycle ergometer x wks 2, 4, 6, 8, 12, 16, 20 & 24 Patient diary cards x wks 8, 24	Mean age: pla=54.3; pro=56.1 % Male: pla=57.1; pro=73.1 Race nr	History of MI: pla=31.4%; pro=37.2% Positive ECG for exercise: pla=77.1%; pro=76.9% Positive ECG for attacks: pla=57.1%; pro=56.4% Angina duration(mos): pla=69.6; pro=66.6 Mean weekly attacks: pla=10.3; pro=12.4 Mean curative ntg tablets/wk: pla=10.6; pro=12.6 Mean preventive ntg tablets/wk: pla=2.6; pro=3.0 Mean attack-free days/wk: pla=1.2; pro=1.5 Mean exercise test duration(min): pla=9.3; pro=9.7

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

Author Year Country Study Design	Number screened/ eligible/ enrolled	Number withdrawn/lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Head to Head trials				
Frishman 1989 United States Poor quality RCT	NR/NR/41	12 withdrawn/1 lost to fu/34 analyzed for efficacy	Total exercise time (%D in sec) Center 1: lab=(+7); pro=(+12) Center 2: lab=(+23); pro=(+40) Time to angina onset(%D in sec) Center 1: lab=(+29); pro=(+38) Center 2: lab=(+58); pro=(+66) Number of patients with angina endpoint(D%) Center 1: lab=(-67); pro=(-63) Center 2: lab=(-38); pro=(-50)	Questioned generally about occurrence of adverse events specifically regarding occurrence of dyspnea, palpitations, sexual dysfunction, GI disturbances and dizziness
Placebo controlled trials				
Destors 1989 Europe Fair Quality RCT	NR/NR/191	38 withdrawals/15 lost to fu/analyzed 191	Angina attacks/week(% reduction) Week 8: pla=(-49%); pro=(-65%) Week 24: pla=(-77%); pro=(-71%) Ntg consumption(% reduction) Week 8: pla=(-57%); pro=(-73%) Week 24: pla=(-79%); pro=(-74%) Number of attack-free days Week 8: pla=190; pro=193 Week 24: pla=270; pro=204 Total work(mean % increase): Week 8: pla=13%; pro=48% Week 24: pla=20%; pro=50% Maximum workload(mean % increase): Week 8: pla=6%; pro=27% Week 24: pla=14%; pro=30% Exercise duration(mean % increase): Week 8: pla=7%; pro=22% Week 24: pla=8%; pro=24%	NR

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

Author Year Country Study Design	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Head to Head trials			
Frishman 1989 United States Poor quality RCT	NR	NR	Center 1 measured exercise parameters at or close to peak drug effect Center 2 measured exercise parameters at or close to trough drug effect
Placebo controlled trials			
Destors 1989 Europe Fair Quality RCT	Number of patients with: Hypotension: pla=1; pro=4 Bronchospasm: pla=1; pro=1 Allergic reaction: pla=0; pro=1 Raynaud phenomenon: pla=0; pro=1 Fatigue: pla=2; pro=14 Psychiatric problems: pla=1; pro=2 Gastrointestinal problems: pla=2; pro=10 Other: pla=1; pro=6 Any: pla=6; pro=23 Severe coronary events(cardiac death, MI, angina deterioration): pla=2(5.7%); pro=8(10.2%) Development of heart failure/AV block/rhythm disturbances: pla=0; pro=5	Death due to MI(# pts): pla=0; pro=1 CVA(# pts): pla=1; pro=1 Severe clinic events(# pts): pla=1; pro=2 Adverse reaction(# pts): pla=0; pro=1	

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

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Head to head controlled trials					
Frishman 1989 United States	NR	NR	Not clear	Good mean age=56 91.2% male	34
van der Does 1999 Europe	Block randomization (sets of 6); method of sequence generation nr	NR	Yes	Good mean age >55 higher %male	393 enrolled 368 randomized
Narahara 1990 United States	nr	nr	yes	yes	112
Dorow 1990	NR	NR	N/A-crossover	Sample of patients cormorbid with chronic obstructive bronchitis	40

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

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

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

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: Differential/high	Score	Funding	Control group standard of care	Length of follow-up
Head to head controlled trials							
Frishman 1989 United States	NR	Attrition reported; other nr	No	Poor	In part by Schering-Plough	Yes	4 months
van der Does 1999 Europe	NR	Attrition reported; other nr	NR	Fair	Boehringer Mannheim	Yes	3 months
Narahara 1990 United States	nr	Yes No No No	No No	Fair	Lorex Pharmaceuticals	Yes	10 weeks
Dorow 1990	N/A	Attrition and compliance reported; others nr	None	Fair	NR	Yes	1 year

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

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

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

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

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

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

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

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

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

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

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

Author Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Placebo controlled trials						
Anonymous (MACB Study Group) 1995 Sweden *Fair quality*	2365/2365/967	Total withdrawn: met=165(34%); pla=212(44%) Lost nr Analyzed: met=480; pla=487	Mortality: met=16(3.3%); pla=9(1.8%) Infarct development: met=9(1.9%); pla=10(2.1%) Development of unstable angina pectoris: met=14(2.9%); pla=17(3.5%) Need for CABG: met=2(0.4%); pla=1(0.2%) Need for PTCA=1(0.2%); pla=2(0.4%) Total endpoints: met=42(8.8%); pla=39(8.0%)	NR	NR	Bradycardia: met=12(2%); pla=4(0.8%) (p=0.05) Hypotension: met=6(1%); pla=11(2%) (NS) Congestive heart failure: met=13(3%); pla=6(1%) (NS) Poor peripheral circulation: met=8(2%); pla=13(3%) Atrioventricular block II/III: met=1(0.2%); pla=1(0.2%) Severe obstructive pulmonary disease: met=6(1%); pla=4(0.8%)
Sjoland 1995 Sweden *Poor quality*	2291 (74 died before screen) 2365 eligible CABG 967 enrolled	Withdrawn = 193/967 (20%) Lost (admin) = 148/967 (15%) Lost (nr) = 8/967 (1%) Analyzed = 618/967 (64%)	Exercise capacity (median): met = 130W pla = 140W (p=0.02) Angina pectoris at exercise: met = 48/306 (16%) pla = 33/311 (11%) Terminated exercise due to chest pain: met =18/307 (6%) pla = 10/311 (3%) Subjective symptom means: Effort (1-10) : met = 7.6; pla = 7.4 Dyspnoea (0-10): met = 6.6; pla = 6.5 Chest pain (0-10): met = 1.1; pla = 0.6 (p=0.001)	NR	Cardiac events (total): met = 19/307 (6%) pla = 19/311 (6%) Hypotension: met = 6/307 (2%) pla = 4/311 (1%) Bradycardia: met = 7/307 (2%) pla = 1/311 (0.3%)	NR

Evidence Table 3a. Quality assessments of randomized controlled trials of beta blockers for coronary Artery Bypass Graft

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

Evidence Table 3a. Quality assessments of randomized controlled trials of beta blockers for coronary Artery Bypass Graft

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

Evidence Table 3a. Quality assessments of randomized controlled trials of beta blockers for coronary Artery Bypass Graft

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

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Head to head controlled trials			
Wilcox 1980 UK *Fair quality*	RCT	Clinical diagnosis of suspected MI within the previous 24 hours	Already taking a beta blocker; severe heart failure; sinus bradycardia of under 40 beats per minute; in second or third degree heart block; systolic BP of >90 mm Hg; history of asthma or diabetes; residence too far away.

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Head to head controlled trials			
Wilcox 1980 UK *Fair quality*	Propranolol (pro) 120-160 mg daily Atenolol (ate) 100 mg daily Placebo x one year Treatment initiated within 24 hours post-MI	NR	Clinic visits at 3-month intervals Cause of death was established from hospital and general practitioners' records and from postmortem reports

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Head to head controlled trials				
Wilcox 1980 UK *Fair quality*	Mean age(% patients) <35 yrs: pro=3.8; ate=3.9; pla=2.3 -45 yrs: pro=12.9; ate=10.2; pla=16.3 -55 yrs: pro=33.3; ate=35.4; pla=31.0 -65 yrs: pro=32.6; ate=27.6; pla=31.0 > 65 yrs: pro=17.4; ate=22.8; pla=19.4 % male: Pro=84%; Ate=89%; Pla=81% Race: NR	*Hypertension:* Pro=11%; Ate=10%; Pla=15% *Angina:* Pro=27%; Ate=31%; Pla=24% *Infarction:* Pro=21%; Ate=16%; Pla=19% Drugs being taken for cardiovascular system: Pro=14%; Ate=14%; Pla=20% Drugs taken for other purposes: Pro=14%; Ate=14%; Pla=11%	662 screened/388 eligible/388 randomized	Withdrawn=171(44.1%) /lost to fu NR /analyzed=388

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Outcomes	Method of adverse effects assessment?
Head to head controlled trials		
Wilcox 1980 UK *Fair quality*	Mortality *At 6 weeks:* pro=10(7.5%); ate=11(8,6%); pla=15(11.6%) *At 1 year:* pro=17(12.9%); ate=19(14.9%); pla=19(14.7%)	Side effects separately recorded as either volunteered or elicited

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

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

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Acebutolol vs placebo			
Boissel 1990 France *Fair quality*	RCT	At least 2 of the following risk factors: (1) Typical chest pain of ≥ 1 hour in duration, typical Q waves and significant release of cardiac enzyme(s) (2) admitted for this acute event > 2 and < 22 days before (3) presented ≥ 7 of the secondary risk factors of the selection algorithm, including ≥ 1 "major" secondary risk factor (history of dyspnea when walking on flat ground, documented atrial fibrillation, ventricular fibrillation, ventricular tachycardia, overt heart failure or sinusal tachycardia during the reference event, recurrent AMI or angina pectoris before the eighth day)	Heart rate <45 beats/min; complete auriculoventricular block and acute heart failure that required treatment with ≥ 2 drugs of different classes (e.g., diuretics and vasodilators); contraindication to beta blocking treatment; age > 75 years; death; malignancy; valvular disease; coma; asthma; chronic bronchopneumopathy; Raynaud syndrome; participation in another study; patients enrolled in APSI before

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Acebutolol vs placebo			
Boissel 1990 France *Fair quality*	Acebutolol 400 mg daily Placebo x 1 year Treatment initiated within 2-22 days post-MI	NR	Primary outcome: Total death

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Acebutolol vs placebo				
Boissel 1990 France *Fair quality*	Mean age=62.9 years 73% male Ethnicity nr	Angina pectoris=41.5% Unstable angina=28.9% Congestive heart failure=27.1% Renal failure=3.6% Diabetes mellitus=14.6% Cigarette smoker (actual or past)=65.5% Systemic hypertension=32.9% Atrial flutter or fibrillation=13.5% Ventricular flutter or fibrillation=5% Number of secondary risk factors (median)=8	nr/nr/607	Withdrawn=211 (34.8%) /0 lost to fu /analyzed=607

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Outcomes	Method of adverse effects assessment?
Acebutolol vs placebo		
Boissel 1990 France *Fair quality*	Acebutolol (n=298) vs placebo (n=309) Total mortality: 17 (5.7%) vs 34 (11%); p=0.019 Vascular death: 12 (4%) vs 30 (9.7%); p=0.006 Reinfarction: 6 (2%) vs 4 (1.3%); p=NS Fatal or nonfatal reinfarction: 9 (3%) vs 11 (3.6%); p=NS Acute pulmonary edema: 20 (6.7%) vs 15 (4.9%); p=NS Fatal or non-fatal cardiac failure: 22 (7.4%) vs 22 (7.1%); p=NS Ventricular flutter or ventricular fibrillation: 1 (0.3%) vs 0; p=NS Ventricular flutter, ventricular fibrillation, or fatal arrhythmia: 0 vs 3 (1%); p=NS Other vascular events: 35 (11.7%) vs 28 (9.1%); p=NS Other nonvascular events: 51 (17.1%) vs 70 (22.7%); p=NS	nr

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Acebutolol vs placebo			
Boissel 1990 France *Fair quality*	Acebutolol (n=298) vs placebo (n=309) Angina pectoris: 98 (32.9%) vs 92 (29.8%); p=NS Heart failure: 137 (46%) vs 105 (34%); p=0.003 Conduction or rhythm disturbance: 102 (34.2%) vs 101 (32.7%); p=NS Sinus bradycardia: 48 (16.1%) vs 16 (5.2%); p<0.001 Sinus tachycardia: 8 (2.7%) vs 26 (8.4%); p=0.002 Atrioventricular block: 17 (5.7%) vs 15 (4.9%); p=NS Right bundle branch: 11 (3.7%) vs 16 (5.2%); p=NS Left bundle branch: 4 (1.3%) vs 7 (2.3%); p=NS Flutter or atrial fibrillation: 16 (5.4%) vs 12 (3.9%); p=NS Extrasystola or ventricular tachycardia: 16 (5.4%) vs 26 (8.4%); p=NS Other arrhythmia: 24 (8.1%) vs 29 (9.4%); p=NS	Acebutolol (n=298) vs placebo (n=309) Withdrawals due to adverse events: 12 (4%) vs 11 (3.5%); p=NS	

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Carvedilol vs placebo			
Basu 1997 UK *Fair quality*	RCT	Chest pain; ECG changes; serum concentration of creatine kinase; MB isoform consistent with diagnosis	Already on ACE or beta blockers; contraindications to ACE or beta blockers; Killip class IV heart failure; cardiogenic shock; severe bradycardia; hypotension; second to third degree heart block; left bundle branch block; severe valvular disease; insulin-dependent DM; renal failure; known malignancy; other severe disease; pregnancy
Anonymous, 2001 International RCT *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)* Fair quality	RCT	>18 years; stable, definite MI occurring3-21 days prior to randomization; left-ventricular ejection fraction of 40% or less; receipt of concurrent treatment with ACE inhibitors for at least 48 hours and stable dose for 24+ hours unless proven intolerance to ACE inhibitors; heart failure appropriately treated with diuretics and ACE inhibitors during acute phase	Required continued diuretics or inotropes; uncontrollable heart failure; unstable angina; uncontrolled hypertension; bradycardia; unstable insulin-dependent DM; continuing indication for beta blockers for any condition other than heart failure; requiring ongoing therapy with inhaled beta agonists or steroids

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Carvedilol vs placebo			
Basu 1997 UK *Fair quality*	Carvedilol (car) 2.5-50 mg daily Placebo (pla) x 6 months Initial dose loaded intravenously	Aspirin - 100% Heparin - 97% Oral/iv nitrates - 97%	Patients were reviewed at 3-month intervals Exercise test (Bruce protocol) Endpoints: cardiac death, reinfarction, unstable angina, heart failure, emergency coronary revascularization, ventricular arrhythmias requiring intervention, cerebra-vascular accident and initiation of additional cardiovascular drug therapy other than sublingual nitrates for angina
Anonymous, 2001 International RCT *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)* Fair quality	Carvedilol (car) up to 50 mg daily Placebo (pla) x 1.3 years (mean) of follow-up	ACE inhibitors(% patients)=98 Reperfusion therapy(% patients)=46	Patients were reviewed every 3 months during the first year, and every 4 months thereafter

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Carvedilol vs placebo				
Basu 1997 UK *Fair quality*	Mean age: car=60; pla=60 % male: car=84; pal=84.5 Race: NR	*Site of MI:* Anterior - Car=51%; Pla=49% Inferior - Car=49%; Pla=51% *Type of MI:* Q-wave - Car=80%; Pla=80% Non-Q-wave - Car=20%; Pla=20% *Heart failure at entry (Killip II/III):* Car=45%; Pla=28% *Thrombolysed:* Car=99%; Pla=96% *Median time to thrombolysis:* Car=3.8 hours; Pla=3.9 hours *Smoker:* Car=67%; Pla=53.5% *Non-smoker:* Car=33%; Pla=46% *Previous IHD:* Car=20%; Pla=25% *NIDDM:* Car=12%; Pla=18% *Median time to infusion:* Car=16.8 hours; Pla=16.7 hours	416 screened/NR/15 1 enrolled	146 analyzed (car=75; pla=71)
Anonymous, 2001 International RCT *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)* Fair quality	*Carvedilol:* Mean age 63 73% male *Placebo:* Mean age 63 74% male	*Smoking history:* Current - Car=33%; Pla=32% Previous - Car=27%; Pla=25% Never - Car=39%; Pla=43% *Medical history:* Previous MI - Car=31%; Pla=29% Previous angina - Car=57%; Pla=54% Previous hypertension - Car=55%; Pla=52% Previous DM - Car=21%; Pla=23% Other vascular disease - Car=17%; Pla=16% Previous revascularization - Car=12%; Pla=11% Hyperlipidemia - Car=32%; Pla=33% SIte of MI: Anterior - Car=59%; Pla=54% Inferior - Car=21%; Pla=21% Other - Car=20%; Pla=25% Medications at time of randomization: ACE inhibitor - Car=98%; Pla=97% Aspirin - Car=86%; Pla=86%	NR/NR/1959 randomized	Permanent withdrawals(excluding death): car=192(20%); pla=175(18%)/lost to fu nr/1959 analyzed

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Outcomes	Method of adverse effects assessment?
Carvedilol vs placebo		
Basu 1997 UK *Fair quality*	Serious cardiac events: car=18(24%); pla=31(43.7%) Deaths/reinfarctions: car=11(14.7%); pla=6(8.4%)	NR
Anonymous, 2001 International RCT *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)* Fair quality	*Co-primary endpoints(# patients/%)* All-cause mortality: car=116(12%); pla=151(15%) *(p=0.031)* All-cause mortality or cardiovascular-cause hospital admission: car=340(35%); pla=367(37%) *(NS)* *Secondary endpoints(# patients/%)* Sudden death: car=51(5%); pla=69(7%) *(NS)* Hospital admission for heart failure: car=118(12%); pla=138(14%) *(NS)* *Other endpoints(# patients/%)* Cardiovascular-cause mortality: car=104(11%); pla=139(14%) *(p=0.024)* Death due to heart failure: car=18(2%); pla=30(3%) *(NS)* Non-fatal MI: car=34(3%); pla=57(6%) *(NS)* All-cause mortality or non-fatal MI: car=139(14%); pla=192(20%) *(p=0.002)*	NR

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Carvedilol vs placebo			
Basu 1997 UK *Fair quality*	Dizziness(% patients): car=6.5%; pla=1.4%	Withdrawals due to non-cardiac adverse events(# pts): car=4(5.3%); pla=3(4.2%)	
Anonymous, 2001 International RCT *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)* Fair quality	NR	NR	Original primary endpoint (all-cause mortality) amended during the trial to co-primary endpoints of all-cause mortality (alpha=0.005) and all-cause mortality+cardiovascular hospitalization(alpha=0.045) apparently due to advice by Data Safety Monitoring Board (DSMB) that a blinded interim analysis had shown that power to detect pre-specified total mortality effect size was under threat

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Metoprolol vs placebo			
Anonymous 1987 USA *Lopressor Intervention Trial* *Fair quality*	RCT	Ages 45-74; hospitalized for acute MI	History of CABG; permanent pacemaker; contraindication to beta blocker therapy; conditions likely to require beta blocker therapy; administration of any beta blocker within 3 days before the start of pre-entry evaluation; planned therapy with aspirin, sulfinpyrazone clofibrate;=, or dipyridamole; life threatening conditions other than CHF; conditions likely to affect protocol compliance; history of adverse reaction to metoprolol or its analogues.
Hjalmarson, 1981 Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* *Good quality*	RCT	Geographic location; chest pain of acute onset and 30 minutes' duration or ECG signs of acute MI with estimated onset of infarction within previous 48 hours; age 40-74;	Contraindications to beta blockade; need for beta blockade; administrative considerations

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Metoprolol vs placebo			
Anonymous 1987 USA *Lopressor Intervention Trial* *Fair quality*	Metoprolol (met) 200 mg daily Placebo (pla) x 1 year Treatment interval: 5-15 days post-MI		Interim visits conducted at 1, 3, 7 and 12 months
Hjalmarson, 1981 Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* *Good quality*	Metoprolol (met) 15 mg intravenously; 200 mg orally Placebo (pla) Treatment interval(mean): 11.3 hours Initial dose loaded intravenously (3 injections); then administered orally x 3 months	*Arrhythmias:* iv lidocaine or procainamide *CHF:* furosemide 40-80 mg iv, then oral *Chest pain:* iv morphine; sl ntg; oral anticoagulants	Physician examination at 1-week and 3 months after inclusion

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Metoprolol vs placebo				
Anonymous 1987 USA *Lopressor Intervention Trial* *Fair quality*	Mean age = 58 % Male = 83% % White = 90.5%	*Previous medical history:* MI = 14.5% Angina = 25% CHF = 2% Hypertension = 36% Diabetes = 7.5% Location of infarct: Anterior = 50.3% Inferior = 56% Anterior & inferior = 2% High lateral = 2.5% True subendocardial = 2.5%	NR/NR/2395 enrolled	Withdrawn: met=381(31.9%); pla=355(29.6%)/lost to fu NR/analyzed=2395
Hjalmarson, 1981 Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* *Good quality*	*Entire sample:* Mean age: met=60; pla=60 % male: met=75.6; pla=76.2 Race nr *Subgroup of patients with indirect signs of mild-to-moderate CHF (met n=131; pla n=131)* Mean age: met=63; pla=63 % male: met=75; pla=76 Race nr	*Clinical history:* Previous infarction - Met=21.2%; Pla=22.7% Angina pectoris - Met=35.7%; Pla=34.7% Hypertension - Met=29.1%; Pla=29.7% Smoking - Met=49.7%; Pla=50.3% *Clinical status at entry:* Pulmonary rales (24) - Met=11.6%; Pla=9% ECG signs of infarction (1) - Met=49.9%; Pla=47.8% Heart rate >100 beats/minute (1) - Met=4.7%; Pla=6.2% Systolic BP <100 mm Hg (2) - Met=3.3%; Pla=4.4% *Dyspnea at onset of pain (29) - Met=28.8%; Pla=30.8%*	2802 screened/2619 eligible/1395 randomized (met n=698; pla n=697)	Withdrawn: met=131(19.1%); pla=131(19.1%)/lost to fu NR /1395 analyzed

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

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

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

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

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

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

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Metoprolol vs placebo			
Olsson, 1985 *Stockholm Metoprolol Trial* *Fair quality*	Metoprolol (met) 200 mg daily Placebo (pla) x 36 months Treatment interval: 48 hours post-MI	*Angina:* non-beta-andrenergic blocking antianginal agents	Interim visits conducted every 3 months
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* *Fair quality*	Metoprolol (met) 15 mg iv, followed by 200 mg oral daily dosage Placebo (pla) x 1 year Treatment interval: 48 hours post-mi	NR	NR

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Metoprolol vs placebo				
Olsson, 1985 *Stockholm Metoprolol Trial* *Fair quality*	Mean age: met=60; pla=59 % male: met=78; pla=83 Race = NR	Smokers: Met=53%; pla=60% Ex-smokers: Met=19%; Pla= 18% Previous MI: Met=24.5%; Pla=26.5% DM before MI: Met=10%; Pla=6% Cerebrovascular incidence before MI: Met=5%; Pla=3% Site of infarction: Anterior: Met=44%; Pla=51% Inferior: Met=38%; Pla=31% Unknown: Met=18%; Pla=18%	nr/nr/301	73(24.2%) withdrawn/lost to fu nr/301 analyzed
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* *Fair quality*	Age ≤65 = 548 >65 = 252 % Male 71.5% Race: NR	Previous MI = 26.75% Hypertension = 11.5 % Smoking habit = 47% Previous history of angina = 46.25% Previous history of dyspnoea = 28.38% Initial ventricular ectopic activity = 22.88% Initial supraventricular ectopic activity = 5%	1556 screened/800 eligible/800 enrolled	Withdrawn nr/lost to fu nr/800 analyzed

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

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

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

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

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

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

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Pindolol vs placebo			
Australian & Swedish Study 1983 Australia, Sweden *Fair quality*	Pindolol (pin) 15-20 mg daily Placebo (pla) x 24 months Treatment interval: up to 21 days post-MI	NR	Follow-up visits: months 1, 3, 6, 12, 18 and 24 Primary endpoint: death

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Pindolol vs placebo				
Australian & Swedish Study 1983 Australia, Sweden *Fair quality*	*Mean Age:* Pin=58; Pla=58 % male: Pin=83; Pla=83 Australian: Pin=48%; Pla=48% Swedish: Pin=52%; Pla=51.5%	*History:* Smoking: Pin=48%; Pla=43% Hypertension: Pin=24%; Pla=28% (values indicated are those with a 10% or greater variation between patients randomized to pin. or pla.) Angina pectoris: Pin=36%; Pla=32% Functional limitation: Pin=30%; Pla=30% Prior MI: Pin=18%; Pla=16% Diabetes: Pin=5%; Pla=8% (values indicated are those with a 10% or greater variation between patients randomized to pin. or pla.) *Anterior or lateral infarction:* Pin=47%; Pla=46% *Other site of infarction:* Pin=53%; Pla=54% *Medication used at time of randomization:* Digitalis: Pin=31%; Pla=34% Diuretics: 74%; Pla=75% Vasodilators (nitrates): Pin=23%; Pla=22% Antiarrhythmics: Pin=54%; Pla=51% Anticoagulants: Pin=72%; Pla=71% *Medication used at time of discharge:* Digitalis: Pin=31%; Pla=32% Diuretics: Pi46%; Pla=42% Nitrates: Pin=39%; Pla=35%	2500 screened/529 eligible/529 enrolled	126(23.8%) withdrawn/lost to fu nr/529 analyzed (pin n=263; pla n=266)

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Outcomes	Method of adverse effects assessment?
Pindolol vs placebo		
Australian & Swedish Study 1983 Australia, Sweden *Fair quality*	*(# patients/%)* *Total mortality:* pla=47(17.7%); pin=45(17.1%) (NS) *Cardiac death:* pla=43(16.2%); pin=40(15.2%) (NS) *Cardiac sudden death:* pla=31(11.7%); pin=28(10.6%) (NS) *Non-cardiac death:* pla=4(1.5%); pin=5(1.9%)	NR

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

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

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Propranolol vs placebo			
Roberts, 1984 Rude, 1986 Roberts, 1988 United States *Multicenter Investigation of the Limitation of Infarct Size (MILIS)* *Fair-poor quality*	RCT Single-blind	Age <76; history of at least 30 minutes of ischemic pain within 18 hours of potential therapy; new or presumably new ECG changes	Cardiogenic shock; advanced cardiac or other disease that would interfere with prognosis; participation in conflicting protocol; inability to participate because of geographical or psychological reasons; recent major surgery or MI; permanent cardiac pacemaker; previous participation in the protocol; failure or inability to give informed consent

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Propranolol vs placebo			
Roberts, 1984 Rude, 1986 Roberts, 1988 United States *Multicenter Investigation of the Limitation of Infarct Size (MILIS)* *Fair-poor quality*	Propranolol (pro): initial dose infused intravenously (0.1 mg per kg of body weight); subsequent oral dosing initiated at 20 mg and increased with an HR target of 45-60 BPM Placebo (pla) x 7 days	NR	Follow-up visits: months 3 and 6 Telephone vital status interview: 6-month intervals thereafter

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Propranolol vs placebo				
Roberts, 1984 Rude, 1986 Roberts, 1988 United States *Multicenter Investigation of the Limitation of Infarct Size (MILIS)* *Fair-poor quality*	Mean age: pro=54.9; pla=54.6 % male: pro=72.4; pla=74.1 % white: pro=82.1; pla=83.7	Mean age = 54.7 Male = 73.2% White = 83% Current smokers = 50% White collar workers = 39% High school or higher education = 61.3% Regular drinkers = 22% Medical history before recent infarction: Hypertension requiring medication = 44% Documented previous infarction = 14.5% Angina >3 weeks before recent infarction = 39% CHF in previous 3 weeks = 5% Diabetes = 19% Previous cardiac arrest = 0.7% Previous cardiac surgery = 5% Previous cardiac arrythmias = 7%	Screened=7597/ Eligible=2408/Eligible after application of exclusion criteria=1589/Eligible for Group A (no contraindications to beta blocker therapy)=879 (pro n=134; pla n=135; hyaluronidase=131)	Overall patient withdrawals nr/lost to fu=1(treatment group nr)/analyzed=269

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Outcomes	Method of adverse effects assessment?
Propranolol vs placebo		
Roberts, 1984 Rude, 1986 Roberts, 1988 United States *Multicenter Investigation of the Limitation of Infarct Size (MILIS)* *Fair-poor quality*	Mortality(after 36-months of follow-up): pro=24/134(17.9%); pla=20/135(14.8%) Treatment period=10 days Beta blockade at 3 months(% pts): pla=37%; pro=53% Beta blockade at 6 months(% pts): pla=40; pro=54	NR

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

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

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Propranolol vs placebo			
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)* *Fair quality*	RCT	Men and women aged 30-69; hospitalized with symptoms and ECG and enzymatic changes compatible with acute MI	Chronic obstructive lung disease; severe CHF; bradycardia; life-threatening illness other than CHF; need for beta blocking drugs

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Propranolol vs placebo			
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)* *Fair quality*	Propranolol (pro) 180 mg (82% of patients) or 240 mg (18% of patients) *(n=1916)* Placebo (pla) *(n=1921)* Treatment initiated 5-21 days post-MI	*% patients* Vasodilator: pro=47.8; pla=47.1 Diuretic: pro=40.8; pla=42.3 Tranquilizer: pro=28.0; pla=30.4 Digitalis: pro=26.9; pla=26.3 Aspirin: pro=21.5; pla=21.6 Antiarrhythmic: pro=20.7; pla=25.6 Potassium: pro=16.3; pla=17.7 Antihypertensive, excluding diuretic: pro=11.8; pla=13.4 Anticoagulant: pro=9.8; pla=8.5 Dipyridamole: pro=6.2; pla=5.5 Insulin: pro=4.8; pla=4.2 Hormonal: pro=4.5; pla=4.4 Oral hypoglycemic: pro=5.5; pla=3.2 Sulfinpyrazone: pro=4.3; pla=5.0	Clinic visits at 3-month intervals Deaths classified by blinded mortality classification subcommittee (relative/witness report; death certificates; attending physician; hospital records; autopsy)

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Propranolol vs placebo				
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)* *Fair quality*	*Propranolol:* Mean age: 54.7 84% male *Placebo:* Mean age: 54.9 85.1% male	*Mean systolic BP mm Hg:* Pro=112.3; Pla=111.7 *Mean diastolic BP mm Hg:* Pro=72.5; Pla=72.3 *Mean heart rate, beats per minute:* Pro=76.2; Pla=75.7 *Mean cholesterol, mg/dL:* Pro=212.7; Pla=213.6 *Mean weight, kg:* Men - Pro=80.2; Pla=79.8 Women - Pro=67.4; Pla=66.5 *Current smoker* : Pro=57.4%; Pla=56.9% *Medical history:* Prior MI - Pro=13.9%; Pla=13.2% Hypertension - Pro=41.1%; Pla=40.1% Angina pectoris - Pro=35.8%; Pla=36.5% CHF - Pro=9%; Pla=9.4% DM - Pro=11.7%; Pla=11.3% *Taking propranolol or other beta blocker:* Pro=7.2%; Pla=6.8% *In-hospital events occurring before randomization:* Atrial fibrillation - Pro=6.8%; Pla=5.7% CHF - Pro=14.3%; Pla=14.9% Vetricular tachycardia - Pro=23%; Pla=23.2% Use of antiarrhythmic drug - Pro=45.8%; Pla=46% *Medications being used at time of randomization:* Antiarrythmic - Pro=16.6%; Pla=17.9% Anticoagulant - Pro=13.9%; Pla=15.1% Antiplatlet - Pro=7.1%; Pla=6.8% Diuretic - Pro=16.1%; Pla=18% Vasodilator - Pro=36%; Pla=36.3% Digitalis - Pro=12.5%; Pla=13%	Screened: 16,400 Eligible/enrolled (total=3,837): pro=1916; pla=1921	Overall number withdrawn nr/12(0.3%) lost to fu/3837 analyzed (pro n=1916; pla n=1921)

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Outcomes	Method of adverse effects assessment?
Propranolol vs placebo		
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)* *Fair quality*	*NNT; RR (95% CI)* ***Total mortality:*** NNT=39; RR=0.73(0.59-0.91) ***Deaths due to:*** ***Cardiovascular disease:*** NNT=44; RR=0.74(0.59-0.93) ***Sudden arteriosclerotic heart disease:*** NNT=78; RR=0.72(0.53-0.99) ***Non-sudden arteriosclerotic heart disease:*** NNT=97; RR=0.73(0.52-1.03) ***Other cardiovascular disease:*** NNT=1882(harm); RR=1.14(0.43-3.03) ***Noncardiovascular disease:*** NNT=322; RR=0.65(0.31-1.36)	NR

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

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

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Propranolol vs placebo			
Hansteen 1982 Norway *Fair quality*	RCT	MI according to WHO criteria, screened on fourth day after MI, only those with increased risk of death were included.	Contraindications to beta blockade; uncontrolled heart failure
Baber 1980 Multinational *Fair quality*	RCT	Diagnosis of anterior MI based on ECG abnorm,alities od an anterior infarction described as "very probable" on WHO ECG criteria; either a typical history or serum enzyme levels (AST and LDH) at least twice the accepted upper limit of normal or three times if CK was used.	Bronchospasm; atrioventricular block greater than first degree; sinus bradycardia; persistent heart failure; beta blockade at the time of infarction.

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Propranolol vs placebo			
Hansteen 1982 Norway *Fair quality*	Propranolol (pro) 160 mg daily Placebo (pla) x 12 months Treatment interval: 4-6 days post-MI	NR	Follow-up visits: months 2, 6 and 12
Baber 1980 Multinational *Fair quality*	Propranolol (pro) 120 mg daily Placebo (pla) x 9 months Treatment interval: 2-14 days post-MI	NR	Follow-up visits: months 1, 3, 6 and 9

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Propranolol vs placebo				
Hansteen 1982 Norway *Fair quality*	Mean age: Pro= 58; Pla=58.8 % male: Pro=84.5%; Pla=85.5%	*No previous CHD:* Pro=51.4%; Pla=48.6% *Angina pectoris:* Pro=30.6%; Pla=31.9% *Previous MI:* Pro=18%; Pla=19.5% *Hypertension (treated):* Pro=22.3%; Pla=18.15 *Intermittent claudication: Pro=8.6%; Pla=5.7%* *CVD:* Pro=3.2%; Pla=2.5% *Drug treatment before admission:* *Digitalis:* Pro=6.1%; Pla=5.7% *Diuretics:* Pro=19.1%; Pla=16% *Other antihy* pertensives: Pro=7.9%; Pla=6.4% Daily smoker: Pro=58.3%; Pla=64.9% *Ex-smoker:* Pro=28.1%; Pla=24.2%	4929 screened/eligible nr/560 enrolled	Withdrawals: pro=70(25.2%); pla=72(25.5%)/lo st to fu nr/560 analyzed
Baber 1980 Multinational *Fair quality*	*Mean age:* Pro=55; Pla=54.8 *% male:* Pro=86%; Pla=83% *Previous angina:* Positive: Pro=35%; Pla=40% *Concurrent disease:* Hypertension: Pro=13%; Pla=15% Peripheral artery disease: Pro=1%; Pla=2% Diabetes: Pro=3%; Pla=4% *Smokers:* Pro=64%; Pla=65%	*Previous angina:* Positive: Pro=35%; Pla=40% Angina more than 3 months: Pro=15%; Pla=19% *Previous infarct:* *History of cardiac failure:* *Concurrent disease:* Hypertension: Pro=13%; Pla=15% Peripheral artery disease: Pro=1%; Pla=2% Diabetes: Pro=3%; Pla=4% *Smokers:* Pro=64%; Pla=65%	nr/nr/720	Total withdrawals: pla=88(24%); pro=82(23%)/lost to fu nr/720 analyzed

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

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

Evidence Table 4. Randomized controlled trials of beta blockers for post myocardial infarction

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

Evidence Table 4a. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Head to head controlled trials					
Wilcox 1980 UK	NR	adequate; numbered packs	Yes	Mean age NR 84.7% male	388 randomized
Acebutolol vs placebo					
Boissel 1990 France	Adequate	Adequate	Significant between-group differences for 7 of >266 baseline variables	Mean age=62.9 years 73% male Ethnicity nr	607 randomized

Evidence Table 4a. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups
Head to head controlled trials							
Wilcox 1980 UK	Already taking a beta blocker; severe heart failure; sinus bradycardia of under 40 beats per minute; in second or third degree heart block; systolic BP of >90 mm Hg; history of asthma or diabetes; residence too far away.	Yes	Yes	Yes	Yes	Yes	NR
Acebutolol vs placebo							
Boissel 1990 France	Heart rate <45 beats/min; complete auriculoventricular block and acute heart failure that required treatment with ≥ 2 drugs of different classes (e.g., diuretics and vasodilators); contraindication to beta blocking treatment; age > 75 years; death; malignancy; valvular disease; coma; asthma; chronic bronchopneumopathy; Raynaud syndrome; participation in another study; patients enrolled in APSI before	Yes	Yes	Yes	Yes	Yes	NR

Evidence Table 4a. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Head to head controlled trials						
Wilcox 1980 UK	Attrition=44.1%; others NR	NR	Fair	Imperial Chemical Industries Ltd.	Yes	1 year
Acebutolol vs placebo						
Boissel 1990 France	Yes No Yes No	No No	Fair	NR	Yes	Mean follow-up=271 days

Evidence Table 4a. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Carvedilol vs placebo					
Basu 1997 UK	NR	NR	Yes	84% male Mean age=60	151 randomized
Anonymous, 2001 *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)*	Adequate; Permuted blocks with stratification by center	NR	Yes	73.5% male Mean age=63 mean LVEF=32.9%	1959 recruited

Evidence Table 4a. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups
Carvedilol vs placebo							
Basu 1997 UK	Already on ACE or beta blockers; contraindications to ACE or beta blockers; Killip class IV heart failure; cardiogenic shock; severe bradycardia; hypotension; second to third degree heart block; left bundle branch block; severe valvular disease; insulin-dependent DM; renal failure; known malignancy; other severe disease; pregnancy	Yes	Yes	Yes	Yes	Yes	NR
Anonymous, 2001 *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)*	Required continued diuretics or inotropes; uncontrollable heart failure; unstable angina; uncontrolled hypertension; bradycardia; unstable insulin-dependent DM; continuing indication for beta blockers for any condition other than heart failure; requiring ongoing therapy with inhaled beta agonists or steroids	Yes	Yes	Yes	Yes	Yes	NR

Evidence Table 4a. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Carvedilol vs placebo						
Basu 1997 UK	NR	None	Fair	NPH Cardiac Research Fund; Boehringer Mannheim GmbH	Yes	6 months
Anonymous, 2001	NR	NR	Fair	GSK	Yes	mean of 1.3 years
Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)						

Evidence Table 4a. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Metoprolol vs placebo					
Anonymous 1987 USA *Lopressor Intervention Trial*	NR	NR	Yes	Mean age=58 83% male	2395 randomized
Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* Fair quality	Adequate; computer-generated randomization lists in blocks of 10	NR	Yes	Mean age=60 75.5% male	1395 randomized
Olsson, 1985 *Stockholm Metoprolol Trial*	NR	NR	Yes	Mean age=59.5 80.5% male	301 randomized
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* Fair quality	Adequate; block randomization	NR	Yes	Mean age NR 71.5% male	800 randomized

Evidence Table 4a. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups
Metoprolol vs placebo							
Anonymous 1987 USA *Lopressor Intervention Trial*		Yes	Yes	Yes	Yes	Yes	NR
Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* Fair quality	Contraindications to beta blockade; need for beta blockade; administrative considerations	Yes	Yes	Yes	Yes	Yes	NR
Olsson, 1985 *Stockholm Metoprolol Trial*	Systolic BP <100 mm Hg; sever cardiac failure not responding to digitalis or diuretics; severe intermittent claudication; obstructive pulmonary disease; need for beta-adrenoceptor blockade; other major disease; unwillingness to participate.	Yes	Yes	Yes	Yes	Yes	NR
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* Fair quality		Yes	Yes	Yes	Yes	Yes	NR

Evidence Table 4a. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Metoprolol vs placebo						
Anonymous 1987 USA *Lopressor Intervention Trial*	Attrition=30.7%; others NR	NR	Fair	CIBA-GEIGY	Yes	1.5 years
Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* Fair quality			Good	NR	Yes	1 year
Olsson, 1985 *Stockholm Metoprolol Trial*	Attrition=24.2%; others NR	NR	Fair	AB Hassle	Yes	3 years
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* Fair quality	NR	NR	Fair	Astra Pharmaceuticals	Yes	1 year

Evidence Table 4a. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Pindolol vs placebo					
Australian & Swedish Study 1983 Australia, Sweden	NR	NR	Yes	Mean age=58 83% male	529 randomized
Propranolol vs placebo					
Anonymous, 1982, 1983 Goldstein, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)*	NR	NR	Yes	Mean age=54.8 84.4% male 88.8% white	3837 randomized
Hansteen 1982 Norway	Adequate; blocks of 10	NR	No; Mean heart size higher in pro group	Mean age NR 85% male	560 randomized
Baber 1980 Multinational	NR	NR	Yes	Mean age=54.9 84.5% male	720 randomized

Evidence Table 4a. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups
Pindolol vs placebo							
Australian & Swedish Study 1983 Australia, Sweden	Uncontrolled heart failure; uNRelated heart disease; persistent heart block of second or third degree; persistent bradycardia <50 beats/minute; obstructive airways disease; uncontrollable inslulin dependent diabetes; known hypersensitivity to beta blocking drugs; other diseases serious enough to worsen the short-term prognosis irrespectively of the MI; pregnancy; necessity to use beta blocking druga or calcium antagonists; unable to return for regular control.	Yes	Yes	Yes	Yes	Yes	NR
Propranolol vs placebo							
Anonymous, 1982, 1983 Goldstein, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)*	Chronic obstructive lung disease; severe CHF; bradycardia; life-threatening illness other than CHF; need for beta blocking drugs	Yes	Deaths classified by blinded mortality classification subcommittee	Yes	Yes	Yes	NR
Hansteen 1982 Norway	Cotraindications to beta blockade; uncontrolled heart failure	Yes	NR	Yes	Yes	Yes	NR
Baber 1980 Multinational	Bronchospasm; atriovenyricular block greater than first degree; sinus bradycardia; persistent heart failure; beta blockade at the time of infarction.	Yes	NR	Yes	Yes	Yes	NR

Evidence Table 4a. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Pindolol vs placebo						
Australian & Swedish Study 1983 Australia, Sweden	Attrition=23.8%; Compliance=54% took 90% or more	NR	Fair	Sandoz Ltd.	Yes	24 months
Propranolol vs placebo						
Anonymous, 1982, 1983 Goldstein, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)*	NR	Lost to fu: pro=4(0.2%); pla=8(0.4%)	Fair	National Heart, Lung, and Blood Institute	Yes	mean of 25 months
Hansteen 1982 Norway	Attrition=25.3%; Compliance(% taken > 95%): 80	NR	Fair	Imperial Chemical Industries Ltd.	Yes	12 months
Baber 1980 Multinational	Attrition=23.5%; others NR	NR	Fair	ICI Pharmaceuticals	Yes	9 months

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Eichhorn 2001 Packer, 2001, 2002 Krum 2003 *The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial* Fair quality	Carvedilol (car) 50 mg daily *(n=1156)* Placebo (pla) *(n=1133)*	Usual medications for heart failure	*Primary: A* ll-cause mortality *Secondary:* (1) Combined risk of death/hospitalization for any reason; (2) combined risk of death or hospitalization for CV reason; (3) combined risk of death/hospitalization for HF; (4) patient global assessment	Age: pla=63.4; car=63.2 %male: pla=80; car=79 Race NR	% ischemic cause: pla=67; car=67 % left ventricular ejection fraction: pla=19.8; car=19.9 % heart failure hospitalization within past year: pla=65; car=66

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Eichhorn 2001 Packer, 2001, 2002 Krum 2003 *The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial* Fair quality	3106 screened/eligible nr/2289 randomized	withdrawn: pla=84; car=70/0 lost/analyzed(ITT): pla=1133; car=1156	*n (hazard ratio; 95%CI)* All-cause mortality: pla=190; car=130 (0.65; 0.52-0.81) Death/hospitalization for any reason: pla=507; car=425 (0.76; 0.67-0.87) Death/hospitalization for CV reason: pla=395; car=314 (0.73; 0.84-0.63) Death/hospitalization for HF: pla=357; pla=271 (0.69; 0.81-0.59) Hospitalizations, n(%) Worsening HF: pla=268(23.7); car=198(17.1) CV reason: pla=314(27.7); car=246(21.3) For any reason: pla=432(38.1); car=372(32.2) More than once: pla=188(16.6); car=152(13.1)	NR

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria	Exclusion criteria
Hori 2004 Japan *The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) Trial* *Fair quality*	LVEF=30% NYHA class II/III=78%	Patient who had ischemic or nonischemic cardiomyopathy with stable symptoms (NYHA functional class II or III); LVEF ≤ 40%; age between 20 and 79 years	Valvular heart disease, hypertrophic obstructive cardiomyopathy, cardiogenic shock, systolic blood pressure < 90 mm Hg, bradycardia (<60/min), grade II or III atrioventricular block, life-threatening arrhythmia, unstable angina, resting angina, cor pulmonale, asthma, Raynaud phenomenon, and intermittent claudication; myocardial infarction or coronary artery bypass grafting had occurred within the preceding 3 months

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Hori 2004 Japan *The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) Trial* *Fair quality*	Run-in Open carvedilol 2.5 mg daily x 1-2 weeks; then open carvedilol 5 mg daily x ≥ 2 weeks Treatment Carvedilol 5 mg daily Carvedilol 20 mg daily Placebo x 24-48 weeks	Diuretics, digitalis, ACE inhibitors, calcium channel blockers, vasodilators, anti-arrhythmic agents	*Primary:* Improvement of global assessment of CHF by attending physician (markedly improved, moderately improved, mildly improved, no change, worsened, unassessable) *Secondary:* all-cause death or hospitalization for cardiovascular disease (CVD), CVD hospitalization, hospitalization for worsening CHF, changes of LVEF, and changes of NYHA class	Mean age=60 77% male 100% Japanese	Nonischemic etiology of heart failure=73% NYHA class II/III=78% LVEF=30% Systolic BP (mm HG)=119 Diastolic BP (mm Hg)=72 Heart rate (beats/min)=80 Body weight=61 kg Other medications ACE-inhibitors=76% Diuretics=86% Digitalis=65%

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Hori 2004 Japan *The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) Trial* *Fair quality*	nr/nr/190 enrolled	16 (8.4%) withdrew after run-in (prior to randomization; number withdrawn following randomization nr/lost to fu nr/analyzed=173	Placebo (n=49) vs carvedilol 5 mg (n=47) vs carvedilol 20 mg (n=77); p-value for carvedilol 5 mg vs placebo comparison; p-value for carvedilol 20 mg vs placebo comparison *Primary* Global improvement (proportion of patients with moderate or marked improvement): 36.7% vs 44.7% vs 59.7%; p=NS; p<0.05 *Secondary* Death or CVD hospitalization: 24.5% vs 8.5% vs 5.2%; p=0.024; p=0.002 CVD hospitalization: 24.5% vs 4.3% vs 3.9%; p=0.003; p<0.001 Worsening CHF: 20.4% vs 2.1% vs 2.6%; p=0.004; p<0.001 Other CVD reasons for hospitalizations: 6.1% vs 2.1% vs 1.3%; p=0.229; p=0.116 Change in LVEF units (mean): 6.6 vs 8.7 vs 13.2; p=NS; p<0.05 NYHA class Improved: 48.9% vs 80.9% vs 70.8%; p<0.001; p<0.05 No change: 40.4% vs 17.0% vs 27.8%; p<0.05; p=NS Worsened: 10.6% vs 2.1% vs 1.4%; p=NS; p=NS	nr

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Hori 2004 Japan *The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) Trial* *Fair quality*	Incidence: 63.3% vs 51.1% vs 59.7%; p=NS; p=NS	nr	

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria	Exclusion criteria
Cice 2003 Italy Open	26% NYHA Class II: 33.3% III: 66.7%	Patients with uremia on periodic hemodialysis treatment and dilated cardiomyopathy. All were symptomatics for heart failure (NYHA classes II and III) for 1 year, with a left ventricular ejection fraction (LVEF) <0.35 at echocardiography. All patients had to clinically stable with no change in their usual medications in the lst 2 weeks and should not have required intravenous inotropic drug therapy or experienced weight changes for at least 48 hours before the enrollment.	Patients with current NYHA class IV; heart rate <50 beats/min; sick sinus syndrome; frist degree atrioventricular block (unless controlled by a pacemaker); documented episodes of sustained ventricular tacycardia (>30 s, >120 beats/min); systolic blood pressure (BP, 90mm Hg; stroke; acute myocardial infarction (MI); unstable angina; coronary angioplasty; or aortocoronary bypass surgery in the three previous months; uncorrected valvular heart disease; active myocarditis; obstructive and restrictive cardiomyopathy; curent treatment with verapamil, alpha/beta adrenergic agonists or antagonists; chronic obstructive airways disease; hepatic disease (serum transaminase >3times normal); drug or alcohol abuse; or any other life-threatening non-cardiac disease.

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Cice 2003 Italy Open	Run-in: carvedilol 6.25 mg (bid) x 2 weeks Maintenance: Carvedilol (car) 25 mg bid vs placebo x 24 months	Digitalis: 100% Angiotensin-converting enzyme (ACE) inhibitors: 98.5% Dialysis 4 times per week: 100% Nitrates: 21%	*Primary:* Changes in left ventricular ejection fraction (LVEF) and NYHA classification at 1, 6 and 12 months post-randomization *Secondary:* all-cause mortality, acute non-fatal MI, combined end point (cardiovascular mortality plus acute non-fatal MI), cardiovascular hospital admission, and permanent premature treatment withdrawals	mean age: 55.0 60.5% male Race NR	SBP (mmHg)=134.2

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Cice 2003 Italy Open	Screened: nr Eligible: 132 Enrolled: 114	Total Withdrawn: 11/114 (9.6%) Lost to Follow-up: 0 Analyzed: LVEF=nr; NYHA=103 (car=54, pla=49); all secondary endpoints=114 (car=56, pla=58)	*Primary: Assessment of NYHA Class Over the Treatment Period* Carvedilol vs placebo NYHA Class (% patients, p-value at months 6; 12; and 24) Class I: 5.6% vs 0%, p<0.05; 7.4% vs 0%, p<0.05; 8.3% vs 0%, p=NS. Class II: 63% vs 38.8%, p<0.05; 64.8% vs 38.8%, p<0.05; 66.7% vs 33.4%, p=NS. Class III: 31.4% vs 57.1%, p<0.05; 27.8% vs 55.1%, p<0.05; 25% vs 44.4%, p=NS. Class IV: 0% vs 4.1%, p=NS; 0% vs 6.1%, p=NS; 0% vs 22.2%, p=NS. *LVEF (% change)* *1 month: +3.8% vs 0* *6 months: +35% vs 3.8%, p<0.05* *12 months: +38.5% vs 0, p<0.05* *24 months: +42% vs –7.7%, p<0.05* *Secondary End Points and Exploratory Analyses* Carvedilol vs Placebo; Hazard Ratio (placebo vs carvedilol) (95% CI); pValue <u>Secondary Points</u> All-cause mortality: 30(51.7%) vs 41(73.2%); 0.51(0.32-0.82); p<0.01. All-cause hospital admission: 20(34.5%) vs 33(58.9%); 0.44(0.25-0.77); p<0.005. All cardiovascular deaths: 17(29.3%) vs 38(67.9%); 0.32(0.18-0.57); p<0.0001. Non-fatal m. cardial infarction: 2(3%) vs	NR

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Cice 2003 Italy Open	NR	Carvedilol vs placebo Overall Withdrawal: 4/58 (6.9%) vs 7/56 (12.5%) Specific Adverse Events Withdrawal Rates Hypotension: 1/58 (1.7%) vs 0/56 (0%) Bradycardia: 1/58 (1.7%) vs 0/56 (0%) Second-degree heart block: 1/58 (1.7%) vs 0/56 (0%) Acute MI: 1/58 (1.7%) vs 0/56 (0%) Worsening HF: 0/58 (0%) vs 3/56 (5.4%) Protocol violation:0/58 (0%) vs 2/56 (3.6%) Acute non-fatal MI:0/58 (0%) vs 1/56 (1.8%) Refractory hyperkalemia:0/58 (0%) vs 1/56 (1.8%)	

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria	Exclusion criteria
Metoprolol			
Anderson 1985 USA Fair quality	28% NYHA class avg: 2.8	Idiopathic dilated cardiomyopathy confirmed by ECG	Unstabilized overt cardiac failure; alcohol abuse; secondary cardiomyopathies; firm exclusions to beta blocker treatment (asthma, advanced heart block, allergy)

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Metoprolol					
Anderson 1985 USA Fair quality	Metoprolol (met) 100 mg daily Placebo (pla) x 19 months Begin 12.5 mg bid titrated over 2 weeks to target - median dose 25 mg bid.	Digitalis: 87% Diuretic: 80% Vasodilators: 40% Antiarrhythmics: 35% Anticoagulant (warfarin): 12%	*Primary:* Survival *Secondary:* Exercise duration (Naughton protocol)	Mean age 51 66% male Race NR	NR

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Metoprolol				
Anderson 1985 USA Fair quality	Screened: NR Eligible: 50 Enrolled: 50 met (n=25) pla (n=25)	Dropout from treatment group: 5/25 (20%) Overall, 2 patients lost to follow-up Analyzed=50	*Primary* Deaths: met: 5/25 (20%) pla: 6/25 (24%) (NS) *Secondary* Exercise duration: met: 9.4 min pla: 8.2 min (NS)	NR

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Metoprolol			
Anderson 1985 USA Fair quality	NR	NR	

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria	Exclusion criteria
Waagstein 2003 Europe *Fair quality*	28.5% NYHA Class I=0 IIa=13.3% IIb=49.1% IIIa=29.1% IIIb=8.5%	Symptomatic patients of either sex, 18- to 80-years old, with stable CHF (NYHA class II-III). Patients were prospectively stratified into an ischemic heart disease (IHD) group and a dilated cardiomyopathy (DCM) group. DCM was diagnosed based on the presence of LV dilation and EF ≤ 0.40 without significant coronary artery obstruction; IHD was diagnosed based on LV dilation, EF ≤ 0.40, and the presences or a history of at least one significant coronary obstruction	Coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the previous 6 months or who were scheduled for or expected to require these treatments during the 6-month study; patients who had a major ischemic event (acute MI or unstable angina) within the previous 6 months and those with large anterior aneurysms, acute myocarditis, primary valvular heart disease, exercise-limiting angina pectoris or severe systemic disease; excessive consumption of alcohol (≥ 100 g of pure alcohol/day or ≥ 700 gram/week), resting systolic blood pressure > 190 mmHg or diastolic > 100 mmHg, systolic blood pressure <95 mmHg (unless considered occasional), heart rate < 50 beats/min, second- or third-degree atrioventricular (AV) block, sick sinus syndrome, sinoatrial block or atrial fibrillation (which makes equilibrium radionuclide angiography difficult to perform; pacemaker for third-degree AV block or a ventricular inhibited (VVI) pacemaker programmed with a fixed heart rate above the spontaneous heart rate

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Waagstein 2003 Europe *Fair quality*	Metoprolol 150 mg daily Placebo x 6 months	ACE inhibitors, diuretics and digitalis in patients with overt heart failure ACE inhibitors and digoxin could be used, as long as the dosage remained unchanged for at least 2 weeks before the study period; diuretic doses could be altered as clinically indicated	Maximal exercise capacity (bicycle tests-protocol nr) Self-assessment NYHA classification	Mean age=56.7 80% male Ethnicity nr	Weight=79.1 kg Height=173.1 cm Heart rate=78.1 beats/min Systolic blood pressure=121.5 mmHg Diastolic blood pressure=76.5 mmHg NYHA Class I=0 IIa=13.3% IIb=49.1% IIIa=29.1% IIIb=8.5% Previous MI=48.5% Previous CABG=18.8% Previous PTCA=9.7% ACE inhibitor=91.5% Diuretics=77.6% Digoxin=57% Mean EF=0.285 Mean duration of exercise=515.6 seconds

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Waagstein 2003 Europe *Fair quality*	nr/nr/172 enrolled/169 randomized/165 started double-blind medication	3 (1.7%) withdrew prior to randomization, 31 (18.3%) withdrew following randomization/1(0.6%) lost ot fu/165 analyzed	Metoprolol (n=71) vs placebo (n=65) <u>EF at 6 months (estimates from a graph)</u> EF at rest: 0.36 vs 0.29; p<0.001 EF at exercise: 0.37 vs 0.32; p<0.001 Maximal exercise on bicycle test: data nr; p=NS Death during study or within 3 weeks after discontinuing study medication: 4.6% vs 3.8%; p=NS Hospital/emergency room admission for cardiovascular reasons: data nr; p=NS Improvement in NYHA class: 42% vs 33%; p=NS	nr

Evidence Table 5. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Waagstein 2003 Europe	nr	11.6% vs 12.6%; p=NS	

Fair quality

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

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

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
MOCHA Bristow1996 Lindenfeld2001 Multicenter Oral Carvedilol Heart Failure Assessment	NR	NR	Yes	Mean age: 59.5 Male: 76% Caucasian: 78%	Screened: NR Eligible for run-in: 376 Enrolled: 345
PRECISE Packer1996	NR	NR	Yes	Mean age: 60.3 years Male: 73% Ethnicity: NR	Screened: NR Eligible for run-in: 301 Enrolled: 278

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
MOCHA Bristow1996 Lindenfeld2001 Multicenter Oral Carvedilol Heart Failure Assessment	Uncorrected valvular disease, hypertrophic or postpartum cardiomyopathy, uncontrolled symptomatic or sustained ventricular tachycardia, acute MI within 3 months, planned or likely revascularization or transplantation within 6 months after screening. Also, sick sinus syndrome, 2nd- or 3rd-degree heart block not treated with pacemaker, symptomatic peripheral vascular disease limiting exercise testing, sitting systolic blood pressure <85 mm Hg or >160 mm Hg, CV accident within last 3 months, cor pulmonale, obstructive pulmonary disease requiring oral bronchodilator or steroid therapy, and other selected disorders and sensitivities. Excluded drugs: alcohol intake >100 g/day, use of investigational drug within 30 days, alpha or beta blockers, CCBs, amiodarone within 3 months, and others.	Yes	NR	NR	NR	Unclear
PRECISE Packer1996	Uncorrected primary valvular disease, active myocarditis or obstructive or restrictive cardiomyopathy; MI, stroke, unstable angina or CABG within 3 months; symptomatic or sustained ventricular tachycardia not controlled by antiarrhythmic drugs or implantable defibrillator; sick sinus syndrome or advanced heart block (without pacemaker); any condition other than heart failure that could limit exercise; systolic blood pressure >160 or <85 mm Hg or diastolic blood pressure >100 mm Hg; heart rate <68 bpm; significant hepatic, renal or endocrine disease; drug or alcohol abuse; or any condition that could limit survival. Patients receiving CCBs, alpha- or beta-adrenergic agonist or antagonists or specific antiarrhythmic drugs.	Yes	NR	NR	NR	Unclear

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
MOCHA Bristow1996 Lindenfeld2001 Multicenter Oral Carvedilol Heart Failure Assessment	NR	Attrition=52/345 (15%); others NR	No	Fair	SmithKline Beecham Pharmaceuticals	NR	6 months
PRECISE Packer1996	NR	Attrition=49/278 (18%); others NR	No	Fair	SmithKline Beecham Pharmaceuticals & Boehringer Mannheim Therapeutics	NR	6 months

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Colucci 1996 U.S. Carvedilol Heart Failure Study Group	NR	NR	Yes	Mean age: 55 Male: 85% Ethnicity: NR	Screened: NR Eligible for run-in: 389 Enrolled: 366
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group*	NR	NR	Yes	Mean age: 60 years (range 22-85) Male: 58% Ethnicity: - Caucasian: 71% - Black: 21% - Other: 8%	Screened: NR Eligible for run-in: 131 Enrolled: 105

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Colucci 1996 U.S. Carvedilol Heart Failure Study Group	Uncorrected primary valvular disease, nondilated or hypertrophic cardiomyopathy; MI, stroke, unstable angina or CABG within 3 months; symptomatic or sustained ventricular tachycardia not controlled by antiarrhythmic drugs or implantable defibrillator within 3 months; likelihood of revascularization or transplantation within 12 months; sick sinus syndrome or advanced heart block (without pacemaker); any condition other than heart failure that could limit exercise; systolic blood pressure >160 or <85 mm Hg or diastolic blood pressure >100 mm Hg; clinically significant hepatic or renal disease, or any condition that could limit survival. Patients receiving amiodarone within 3 months before screening. Use of antiarrhythmics, calcium channel blockers, alpha or beta blockers, monoamine oxidase inhibitors, labetalol, or flosequinan.	Yes	NR	NR	NR	Yes
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group*	Uncorrected primary valvular disease, nondilated or hypertrophic cardiomyopathy; MI, stroke, unstable angina or CABG within 3 months; symptomatic or sustained ventricular tachycardia not controlled by antiarrhythmic drugs or implantable defibrillator within 3 months; likelihood heart transplantation within 6 months; sick sinus syndrome or advanced heart block without pacemaker; any condition other than heart failure that could limit exercise; systolic blood pressure >160 or <85 mm Hg or diastolic blood pressure >100 mm Hg; clinically significant hepatic or renal disease, or any condition that could limit survival. Use of antiarrhythmics, calcium channel blockers, alpha or beta blockers, monoamine oxidase inhibitors, labetalol, or flosequinan for the excluded drugs.	Yes	NR	NR	NR	No

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Colucci 1996 U.S. Carvedilol Heart Failure Study Group	NR	Attrition=31(8.5%); others NR	NR	Fair	SmithKline Beecham Pharmaceuticals & Boehringer Mannheim Therapeutics	NR	Mean 7 months
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group*	NR	Attrition=12(11.4%); others NR	Unclear; 87.6% of patients did not complete final QOL assessment	Poor	SmithKline Beecham Pharmaceuticals & Boehringer Mannheim Therapeutics	NR	Mean 3 months

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group*	Adequate; computer generated	Adequate; centralized	Yes	Mean age 67 80% male Race NR	Screened: NR Eligible for run-in: 301 Enrolled: 278
Cleland, 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)*	Adequate; random numbers table	Adequate; centralized	Unclear; baseline characteristics provided for only 78.8% of all randomized patients	Good mean age=62.5 90% male	489 screened 387 randomized

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group*	Current NYHA class IV; heart rate below 50 beats per minute; sick sinus syndrome; second or third degree heart block; systolic BP <90 mm Hg or >160/100 mm Hg; treadmill exercise duration <2 minutes or >18 minutes; coronary event or procedure within previous 4 weeks; primary myocardial or valvular disease; current treatment with beta-blocker, beta-agonist or verapamil; insulin-dependent DM; obstructive airways disease; hepatic disease; any other life-threatening non-cardiac disease.	Yes	Yes	Yes	Yes	Yes
Cleland, 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)*	Patients younger than 40 years and women of child-bearing age; resting heart rate less than 60 beats per minute; sitting systolic blood pressure less than 85 mm Hg; unstable angina; arrhythmias; uncontrolled hypertension; obstructive pulmonary disease; poorly controlled diabetes; or clinically relevant renal or hepatic disease; those receiving non-dihydropiridine calcium-channel blockers; beta blockers, or antiarrhythmic agents other than amiodarone	Yes	Yes	Yes	Yes	No

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group*	NR	Attrition=14.9%; others NR	NR	Good	SmithKline Beecham - independently initiated conducted, analyzed by ANZ Heart Failure Research Collaborative	Yes	Mean 19 months
Cleland, 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)*	Unclear	Attrition=21.2%; others nr	nr	Fair	Hoffman-La Roche	Yes	189 days (mean)

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
COPERNICUS Eichhorn, 2001 Packer, 2001 Packer, 2002 Krum, 2003	NR	NR	Yes	Good mean age >55 higher proportion male	3106 screened 2289 randomized
Hori 2004 Japan *The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) Trial*	nr	nr	yes	100% Japanese	190 enrolled 16 (8.4%) withdrawn following run-in phase 174 randomized

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
COPERNICUS Eichhorn, 2001 Packer, 2001 Packer, 2002 Krum, 2003	Heart failure that was caused by uncorrected primary valvular disease or a reversible form of cardiomyopathy; had received or were likely to receive a cardiac transplant; had severe primary pulmonary, renal, or hepatic disease; or had a contraindication to beta-blocker therapy; coronary revascularization, acute myocardial or cerebral ischemic event, sustained or hemodynamically destabilizing ventricular tachycardia or fibrillation within the previous two months; use of an alpha-adrenergic blocker, a calcium-channel blocker, or a class I antiarrhythmic drug within the previous four weeks or a beta-blocker within the previous two months; systolic blood pressure lower than 85 mm Hg; heart rate lower than 68 beats per minute; serum creatinine concentration higher than 2.8 mg per deciliter; serum potassium concentration lower than 3.5 mmol per liter or higher than 5.2 mmol per liter; increase of more than 0.5 mg per deciliter in the serum creatinine concentration or a change in body weight of more than 1.5 kg during the screening period	Yes	Yes	Yes	Yes	Yes
Hori 2004 Japan *The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) Trial*	Valvular heart disease, hypertrophic obstructive cardiomyopathy, cardiogenic shock, systolic blood pressure < 90 mm Hg, bradycardia (<60/min), grade II or III atrioventricular block, life-threatening arrhythmia, unstable angina, resting angina, cor pulmonale, asthma, Raynaud phenomenon, and intermittent claudication; myocardial infarction or coronary artery bypass grafting had occurred within the preceding 3 months	Yes	nr	nr	nr	No (1 patient that did not received any medication was excluded from ITT)

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
COPERNICUS Eichhorn, 2001 Packer, 2001 Packer, 2002 Krum, 2003	NR	attrition reported; others NR	None	Fair	Roche; GlaxoSmithKline	Yes	Mean 10.4 months
Hori 2004 Japan *The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) Trial*	nr	No No No No	nr	Fair	nr	Yes	mean follow-up nr

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Packer, 1996 Colucci, 1996 Yancy, 2001 *U.S. Carvedilol Heart Failure Study Group*	NR	NR	Yes	Good mean age >55 higher proportion male	Screened NR 1094 randomized
Cice 2003	NR	NR	Yes	mean age: 55.0 60.5% male Race NR	Screened: nr Eligible: 132 Enrolled: 114
Anderson 1985	Inferior; pairs	NR	Yes	Mean age 51 66% male Race NR	Screened: NR Eligible: 50 Enrolled: 50

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Packer, 1996 Colucci, 1996 Yancy, 2001 *U.S. Carvedilol Heart Failure Study Group*	Major CV event or surgical procedure within 3 months of study entry; uncorrected, primary valvular disease; active myocarditis; sustained ventricular tachycardia or advanced heart block not controlled by antiarrhythmic intervention or a pacemaker; systolic blood pressure of more than 160 or less than 85 mm Hg or diastolic blood pressure of more than 100 mm Hg; a heart rate of less than 68 beats per minute; clinically important hepatic or renal disease; or any condition other than heart failure that could limit exercise or survival; concomitant use of calcium-channel blockers α- or β-adrenergic agonists or antagonists or class IC or III antiarrhythmic agents	Yes	Yes	Yes	Yes	Yes
Cice 2003	Patients with current NYHA class IV; heart rate <50 beats/min; sick sinus syndrome; frist degree atrioventricular block (unless controlled by a pacemaker); documented episodes of sustained ventricular tacycardia (>30 s, >120 beats/min); systolic blood pressure (BP, 90mm Hg; stroke; acute myocardial infarction (MI); unstable angina; coronary angioplasty; or aortocoronary bypass surgery in the three previous months; uncorrected valvular heart disease; active myocarditis; obstructive and restrictive cardiomyopathy; curent treatment with verapamil, alpha/beta adrenergic agonists or antagonists; chronic obstructive airways disease; hepatic disease (serum transaminase >3times normal); drug or alcohol abuse; or any other life-threatening non-cardiac disease.	Yes	n/a - open	n/a - open	n/a - open	No
Anderson 1985	Unstabilized overt cardiac failure; alcohol abuse; secondary cardiomyopathies; firm exclusions to beta blocker treatment (asthma, advanced heart block, allergy)	Yes	NR	NR	NR	Yes

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Packer, 1996 Colucci, 1996 Yancy, 2001 *U.S. Carvedilol Heart Failure Study Group*	NR	AE withdrawals reported; others NR	none	fair	SmithKline Beecham Pharmaceuticals and Roche Laboratories Two investigators/authors are employees and stock holders of SKB	Yes	12 months
Cice 2003	NR	Yes No No No	None	Fair	NR	Yes	24 months
Anderson 1985	NR	Attrition=5/50(10%); others NR	No	Fair	Univ. of Utah SOM and LDS Hospital, Salt Lake City	NR	Mean 19 months

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Waagstein 1993	Computer-generated with "block size of 4," stratified	NR	Yes	Mean age 49 73% male Race NR	Screened: NR Eligible: 417 Enrolled: 383
MERIT-HF Anonymous, 1999 Goldstein, 1999 Hjalmarson, 2000 Goldstein, 2001 Ghali, 2002 Gottlieb, 2002 Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure	Adequate; computer generated	Adequate; centralized	Yes	Mean ages: <60: 34% 60-69: 35% ≥70: 31% 77% male White: 94% Black: 5% Other: 1%	Screened: NR Eligible (recruited): 4427 Enrolled: 3991
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)*	nr	nr	yes	Mean age=61.5 82.1% male 87.1% white	Screened: NR Eligible: 468 Enrolled: 426

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Waagstein 1993	Treatment with beta blockers, calcium channel blockers, inotropic agents or high doses of tricyclic antidepressant drugs; significant CAD shown by angiography; clinical or histological signs of ongoing myocarditis; other life-threatening diseases; obstructive lung disease; excessive alcohol consumption; drug abuse; insulin-dependent diabetes; pheochromocytoma; thyroid disease	Yes	Yes	NR	NR	Yes for primary endpoint Nor for other
MERIT-HF Anonymous, 1999 Goldstein, 1999 Hjalmarson, 2000 Goldstein, 2001 Ghali, 2002 Gottlieb, 2002 Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure	Acute MI or unstable angina within 28 days; indication or contraindication for treatment with beta-blockade or drugs with beta-blocking properties; heart failure secondary to systemic disease or alcohol abuse; scheduled or performed heart transplantation or cardiomyoplasty; implanted cardioversion defibrillator (expected or performed); CABG or percutaneous transluminal coronary angioplasty planned or performed in the past 4 months; atrioventricular block of the second or third degree; unstable decompensated heart failure; supine systolic BP >100 mm Hg; any serious disease that might complicate management and follow-up according to protocol; use of calcium antagonists; use of amiodarone within 6 months; poor compliance.	Yes	Yes	NR	NR	Yes
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)*	nr	yes	yes	yes	yes	yes

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Waagstein 1993	NR	Attrition=14.1%; others NR	High loss for secondary endpoints except hospitalization.	Fair	Astra Pharmaceutical divisions and Ciba-Geigy Corp., Swedish Heart & Lung Foundation & Swedish Medical Research Council	NR	12 months and 18 months (n=211/383)
MERIT-HF Anonymous, 1999 Goldstein, 1999 Hjalmarson, 2000 Goldstein, 2001 Ghali, 2002 Gottlieb, 2002 Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure	NR	Attrition=589/3991 (15%); others NR	No	Fair	Project leader, coordinator, medical advisor, and acknowledgement to Astra Hassle, Sweden	Yes	1 year (mean)
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)*	nr	Compliance (>80% of study medication): met CR=93%; pla=92%; others nr	nr	Fair	nr	yes	24 weeks

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Waagstein 2003 Europe	nr	nr	yes	Mean age=56.7 80% male Ethnicity nr	Screened: NR Eligible: NR Enrolled: 172

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Waagstein 2003 Europe	Coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the previous 6 months or who were scheduled for or expected to require these treatments during the 6-month study; patients who had a major ischemic event (acute MI or unstable angina) within the previous 6 months and those with large anterior aneurysms, acute myocarditis, primary valvular heart disease, exercise-limiting angina pectoris or severe systemic disease; excessive consumption of alcohol (≥ 100 g of pure alcohol/day or ≥ 700 gram/week), resting systolic blood pressure > 190 mmHg or diastolic > 100 mmHg, systolic blood pressure <95 mmHg (unless considered occasional), heart rate < 50 beats/min, second- or third-degree atrioventricular (AV) block, sick sinus syndrome, sinoatrial block or atrial fibrillation (which makes equilibrium radionuclide angiography difficult to perform; pacemaker for third-degree AV block or a ventricular inhibited (VVI) pacemaker programmed with a fixed heart rate above the spontaneous heart rate	yes	nr	nr	nr	no (4 patients excluded from ITT due to never taking study medication)

Evidence Table 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Waagstein 2003 Europe	nr	yes no no no	no no	Fair	Medical Research Council (Project 02529), the Swedish Heart-Lung Foundation and AstraZeneca	Yes	6 months

Evidence Table 5b. Head to head trials of beta blockers for heart failure

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

Evidence Table 5b. Head to head trials of beta blockers for heart failure

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

Evidence Table 5b. Head to head trials of beta blockers for heart failure

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

Evidence Table 5b. Head to head trials of beta blockers for heart failure

Metra 2000	RCT	Patients with chronic heart failure caused by an ischemic or nonischemic cardiomyopathy; NYHA class II, III, or IV symptoms for >/= 6 months; LV ejection fraction </= 0.35 by radionuclide ventriculography, and a peak VO2 </= 25 mL/kg-1/min-1 by cardiopulmonary exercise testing; concomitant treatment with furosemide and an ACEI (or angiotensin-receptor blocker if the ACEI was not tolerated) and had constant doses of background medicaiton as an outpatient for 1 week before the study	Patients with unstable angina, an acute myoardial infarction, or a coronary revascularization procedure within 3 months; history of alcohol abuse; primary valve disease; congenital heart disease; systolic blood pressure <90 mm Hg; concomitant disease that might adversely influence prognosis or impair exercise capacity; contraindications to b-blocker therapy; concomitant treatment with other β-blockers, α-antagonists, calcium antagonists or antiarrhythmic agents (except amiodarone)
Metra 2000 USA, Italy	RCT	Patients with chronic HF caused by an ischemic or nonischemic cardiomyopathy who had NYHA function II-IV symptoms, a LVEF </=35% by radionuclide ventriculography, and ongoing treatment with furosemide and an ACEI	Patients with an acute ischemic event or a coronary revascularization procedure within 3 months; a history of alcohol abuse; primary valve disease or congenital heart disease; frequent ventricular premature beats and/or runs of ventricular tachycardia; contraindications to beta-blocker therapy; concomitant treatment with other beta-blockers, α-antagonists, calcium antagonists or antiarrhythmic agents (except amiodarone)

Evidence Table 5b. Head to head trials of beta blockers for heart failure

Metra 2000	*Weight <75 kg/Weight >/= 75 kg* Metoprolol tartrate (met): 100/200 mg daily (n=75) Carvedilol (car): 50/100 mg daily *(n=75)* x 44 months	Frusemide ACE inhibitor Angiotensin II receptor antagonist	Bicycle exercise testing 6-minute walk test Minnesota Living with Heart Failure Questionnaire (Minn LwHFQ) NYHA functional classification administered every 3 months	Age= met=58; car=55 Gender(%male): met=90.7; car=90.7 Race nr	*Etiology* IDC(%): met=46(61.3); car=47(62.7) CAD(%): met=29(38.7); car=28(37.3) *NYHA class n(%)* II: met=23(30.7); car=23(30.7) III: met=44(58.7); car=46(61.3) IV: met=8(10.7); car=6(8)	NR/NR/150
Metra 2000 USA, Italy	*Weight <75 kg/Weight >/= 75 kg* Metoprolol tartrate (met): 100/200 mg daily (n=17) Carvedilol (car): 50/100 mg daily *(n=17)* x 9-12 months	Furosemide ACE inhibitor	NYHA functional classification x 9-12 months	Mean age: met=60; car=56 Gender(%male): met=17.6; car=23.5 Race nr	*Etiology* IDC n(%): met=11(64.7); car=11(64.7) CAD n(%): met=6(35.3); car=6(35.3) *NYHA functional class* II n(%): met=5(29.4); car=3(17.6) III n(%): met=12(70.6); car=13(76.5) IV n(%): met=0; car=1(5.9)	nr/nr/34

Evidence Table 5b. Head to head trials of beta blockers for heart failure

Metra 2000	28 withdrawn/0 lost/122 analyzed	*NYHA class (#pts at baseline/month 6)* I: met=0/1; car=0/0 II: met=5/11; car=5/9; III: met=17/11; car=22/21 IV: met=1/0; car=3/0 *Minn LwHFQ at 6 months (mean change in points):* met=(-15); car=(-15) *6-minute walk (mean change in ft. at 12 months):* met=(+81); car=(+63) Minn LwHFQ mean score, baseline/12 months(change): met=39/32(-7); car=32/24(-8) Bicycle exercise testing duration; sec, mean at baseline/12 mo (change): met=593/649(+56); car=531/576(+45) *Death/urgent transplantation:* met=21; car=17	NR	*Most common AE's* <u>met</u> worsening heart failure=13(17.3%) dizziness=1(1.3%) hypotension=2(2.7%) symptomatic bradycardia=2(2.7%) <u>car</u> dizziness=11(14.7%) worsening heart failure=6(8.0%) symptomatic bradycardia=3(4.0%) hypotension=2(2.7%) Raynaud's phenomenon=1(1.3%)	met=3; car=2
Metra 2000 USA, Italy	29 analyzed	*Per protocol analysis met n=14; car n=15* *NYHA class, n at end of study(%)* I: met=3(21.4); car=4(26.7) II: met=10(71.4); car=7(46.7) III: met=1(7.1); car=3(20.0) IV: met=0; car=1(6.7)	NR	NR	NR

Evidence Table 5b. Head to head trials of beta blockers for heart failure

Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	RCT	Men or women with symptomatic chronic heart failure (HYHA class II-IV); at least one cardiovascular admission during the previous 2 years; on stable heart failure treatment with ACE inhibitors for at least 4 weeks unless contraindicated; on treatment diuretics (>40 mg of frusemid or equivalent) for at least 2 weeks; LVEF </= 35% measured within the previous 3 months by echocardiography or radionuclide ventriculography	Recent change in treatment within 2 weeks before randomization; requirement for intravenous inotropic therapy; current treatment with non-dihydropyridine calcium channel blockers (diltiazem, verapamil); amiodarone (>200 mg per day); class-I antiarrhythmic drugs; unstable angina; myocardial infarction; coronary revascularisation or stroke within the previous 2 months; uncontrolled hypertension (SBP >170 mm Hg or DBP >105 mm Hg); hemodynamically significant valvular disease; symptomatic and sustained ventricular arrhythmias within the past 2 months note adequately treatment with antiarrhythmic drugs or implantation of an automatic defibrillator; pregnancy; women with childbrearing potential on inadequate contraception; known drug or alcohol misuse; poor compliance; any other serious systemic disease; contraindication to beta blockers
Galatius 2004 Denmark Poor Quality	RCT	Patients who fulfilled all standard indications for BB treatment in patients with systolic CHF	Patients who had contraindications for BB treatment; and those who had been admitted, had attended an emergency room, or who had been treated in the heart failure clinic for acute decompensation within 2 weeks prior to randomization. Patients were excluded from data analysis if they died before two months of follow-up.

Evidence Table 5b. Head to head trials of beta blockers for heart failure

Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	Carvedilol (car) 50 mg Metoprolol (met) 100 mg x 58 months (mean)	ACE inhibitor Diuretic Digitalis Angiotensin II inhibitor Other vasodilator	Follow-up visits at 4-month intervals	Mean age: 62 79.8% male 98.9% White	*NYHA class:* II: 48.4% III: 47.8% IV: 3.8% Duration congestive heart failure: 42.4 months *Cause* Ischemic heart disease: 52.5% Hypertension: 17.7% Dilated cardiomyopathy: 43.9% Previous valve surgery: 2.5% Left ventricular ejection fraction (mean): 26%	nr/nr/3029 (car n=1511; met n=1518)
Galatius 2004 Denmark Poor Quality	Bisopolol started at 1.25 mg daily and titrated up (if tolerated) to 10mg/day Carvedilol started at 3.125 mg bid and titrated up (if tolerated) to 25 mg bid	Diruetics = 90.1% ACE Inhibitors or ARB = 90.0% Digoxin = 21.8% Spironolactone = 21.8%	BB tolerance (no BB treatment at discharge or study end) Timing: 2 month of follow-up and at discharge from the clinic	Mean Age=70.15 75.6% male Ethnicity NR	NYHA class III-IV=19.9% Months of CHF=25.2 Ischemic heart disease=52.9% Heart rate, mean bpm=76.3 SBP, mmHg =139.0	NR/90/87

Evidence Table 5b. Head to head trials of beta blockers for heart failure

Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	964(31.8%) withdrawn/5(0.03%) lost to fu/3029 analyzed	<u>All deaths</u> car=512(34%) met=600(40%) Hazard ratio(95% CI): 0.83(0.74-0.93) NNT: 18 p=0.002 <u>Cardiovascular deaths</u> car=438(29%) met=534(35%) Hazard ratio(95% CI): 0.80(0.70-0.90) NNT=17 p=0.0004 Non-cardiovascular deaths: car=74(5%); met=66(4%) (NS) All deaths and all-cause admission: car=1116(74%); met=1160(76%) (NS)	All reports of adverse events were included irrespective of whether the investigators thought they had been caused by the treatment; adverse events that were fatal or life-threatening, required or extended admission, or resulted in persistent or significant disability or incapacity were labelled serious	Overall adverse event incidence: car=1420(94%); met=1457(96%)	NR
Galatius 2004 Denmark Poor Quality	0/3/87	BB tolerance (no BB treatment at discharge or study end): car=19(40%), bis=16(39%); NS 40%(n=35) of the patients didn't tolerate BB treatment. The reasons are dizziness(41%), bradycardia/arrythmia(16%), worsening of claudication/Raybaud's phenomenon(16%), depression/sleep disturbances(9%), asthma(9%), nausea(3%), other(6%)	NR in methods	40%(n=35) of the patients didn't tolerate BB treatment. The reasons are dizziness(41%), bradycardia/arrythmia(16%), worsening of claudication/Raybaud's phenomenon(16%), depression/sleep disturbances(9%), asthma(9%), nausea(3%), other(6%)	0

Evidence Table 5c. Quality assessments of head to head trials of beta blockers for heart failure

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

Evidence Table 5c. Quality assessments of head to head trials of beta blockers for heart failure

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

Evidence Table 5c. Quality assessments of head to head trials of beta blockers for heart failure

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

Evidence Table 5c. Quality assessments of head to head trials of beta blockers for heart failure

Author, Year Country	Control group standard of care	Length of follow-up
Sanderson 1999 China	Yes	12 weeks
Kukin 1999	Yes	6 months
Metra 2000	Yes	44 months

Evidence Table 5c. Quality assessments of head to head trials of beta blockers for heart failure

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

Evidence Table 5c. Quality assessments of head to head trials of beta blockers for heart failure

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

Evidence Table 5c. Quality assessments of head to head trials of beta blockers for heart failure

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

Evidence Table 5c. Quality assessments of head to head trials of beta blockers for heart failure

Author, Year Country	Control group standard of care	Length of follow-up
Metra 2000 US, Italy	Yes	9-12 months
Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	Yes	58 months

Evidence Table 5c. Quality assessments of head to head trials of beta blockers for heart failure

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Galatius 2004	Inadequate; clinical database sequential number	Inadequate; clinical database sequential number	No; patients in carvedilol group were of a potentially greater severity (more males, lower mean LVEF, higher % of pts with LVEF<25%)	Mean Age=70.15 75.6% male Ethnicity NR	87

Evidence Table 5c. Quality assessments of head to head trials of beta blockers for heart failure

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Galatius 2004	Patients who had contraindications for BB treatment; and those who had been admitted, had attended an emergency room, or who had been treated in the heart failure clinic for acute decompensation within 2 weeks prior to randomization. Patients were excluded from data analysis if they died before two months of follow-up.	Yes	No	No	No	No; excluded 3 patients that died prior to completing 2 months of treatment

Evidence Table 5c. Quality assessments of head to head trials of beta blockers for heart failure

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding
Galatius 2004	NR	Yes No No No	NR	Poor	Danish Pharmacy Foundation, Merck Sharp & Dohme A/S (Denmark), Roche A/S (Denmark), and the Quality Assurance Council at Frederiksberg

Evidence Table 5c. Quality assessments of head to head trials of beta blockers for heart failure

Author, Year Country	Control group standard of care	Length of follow-up
Galatius 2004	Yes	10.1 months

Evidence Table 6. Outcomes in head to head trials of beta blockers for heart failure

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

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

Evidence Table 6. Outcomes in head to head trials of beta blockers for heart failure

Trial	Exercise capacity	Change in EF following treatment	Quality of Life
Sanderson 1999 *Fair*	Improvement in 6-min walk(feet) car=72(6.4%); met=99(8.5%)(NS)	Mean EF at Week 12 (% improvement) car=35(+34.6%); met=31(+24%)	Minnesota QOL mean reduction in symptom score (%) car=9.1(52.9%); met=8.3(63.3%)
Kukin 1999 *Fair*	Improvement in 6-min walk(feet) car=63(5.5%); met=81(6.6%)(NS)	Mean EF(% improvement) car=25(+31.6%); met=23(+27.8%)	Minnesota LWHFQ mean reduction in symptom score(% mean change in points) car=15(28.8%); met=15(29.4%)
Metra 2000a *Fair*	Improvement in 6-min walk(m) car=50(11.2%); met=63(15.1%)	Mean EF(% improvement) car=31.2(52.9%); met=28.8(33.3%)(p=0.038)	Minnesota LWHFQ mean reduction in symptom score(%) car=8(25%); met=7(17.9%)
Metra 2000b *Fair*	NR	Mean EF at EOS (% improvement) car=27.9(64.1%); met=30.0(47.0%)	NR
Poole Wilson, 2003 Carvedilol or Metoprolol European Trial (COMET)	NR	NR	NR

*All in addition to sta

Evidence Table 7. Randomized controlled trials of beta blockers for arrhythmia

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Head to head trials				
Katritsis 2003 *Fair quality*	RCT multicenter	Patients subjected to cardioversion of persistent AF (> 7 days)	Terminal illness, age > 80 years, left ventricular ejection fraction <30, concomitant treatment with class I or III antiarrhythmic drugs, amiodarone use within 3 months before randomization, previous treatment with bisoprolol or carvedilol, and contraindications to beta blockade, such as conduction disturbances, asthma, or severe chronic obstructive pulmonary artery disease	Bisoprolol 10 mg daily (or 5 mg daily if LVEF < 40%) carvedilol 50 mg daily (or 25 mg daily if LVEF M 40%) x 12 months

Evidence Table 7. Randomized controlled trials of beta blockers for arrhythmia

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Head to head trials					
Katritsis 2003 *Fair quality*	No restrictions, with exception of class I or III antiarrhythmic drugs	Clinic visits at months 1, 3, 6 and 12	Mean age=65.5 82% male Ethnicity nr	Heart rate=71.3 beats per minute Left atrial diameter=4.4 cm Systemic blood pressure > 140/90 mm Hg=60% Coronary artery disease=18.9% Lone atrial fibrillation=11.1% Other conditions (valve disease, hyperthyroidism, dilated cardiomyopathy)=21.1% Diabetes mellitus=14.4%	nr/102/90

Evidence Table 7. Randomized controlled trials of beta blockers for arrhythmia

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Head to head trials					
Katritsis 2003 *Fair quality*	8 (8.9%) withdrew/3 (3.3%) lost to fu/82 analyzed for efficacy	Bisoprolol (n=43) vs Carvedilol (n=39) Relapse into AF= 23 (53.4%) vs 17 (43.6%); p=NS Median time to relapse (days) 20 vs 14; p=NS	nr	nr	Withdrew due to side effects: 3 (6.4%) vs 2 (4.7%); p=NS

Evidence Table 7. Randomized controlled trials of beta blockers for arrhythmia

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

Evidence Table 7. Randomized controlled trials of beta blockers for arrhythmia

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Placebo-controlled trials					
Metoprolol vs placebo					
Kuhlkamp 2000 Germany	Digoxin/digitoxin, ACE inhibitor, diuretics, nitrates, calcium-channel blockers of dihydropyridine type	Primary endpoint: relapse into atrial fibrillation or flutter. Mean followup time: met = 93 days pla = 73 days	Mean age 60.5 70% male Race: NR	Previous cardioversion: met = 18/197 (9%) pla = 22/197 (11%) Hypertension: met = 96/197 (49%) pla = 91/197 (46%) Coronary artery disease: met = 52/197 (26%) pla = 48/197 (24%) Heart failure: met = 51/197 (26%) pla = 49/197 (25%) Stroke/TIA: met = 15/197 (8%) pla = 12/197 (12%) Diabetes mellitus: met = 23/197 (12%) pla = 17/197 (9%) NYHA 1: met = 125/197 (64%) pla = 137/197 (70%) NYHA2: met = 64/197 (33%) pla = 54/197 (27%) NYHA3: met = 8/197 (4%) pla = 6/197 (3%)	Screened = nr Eligible = nr Enrolled = 403

Evidence Table 7. Randomized controlled trials of beta blockers for arrhythmia

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Placebo-controlled trials					
Metoprolol vs placebo					
Kuhlkamp 2000 Germany	Lost for efficacy data (no followup ECG) = 9/403 (2%) Lost for safety data = 4/403 (1%) Analyzed = 394/403 (98%) and 399/403 (99%)	Death: met = 3/200 (2%) pla = 0 Premature discontinuation due to relapse to atrial fibrillation/flutter: met = 96/197 (49%) pla = 118/197 (60%) Total relapse to atrial fibrillation: met = 87/197 (44%) pla = 118/197 (60%)	NR	Dizziness/vertigo: met = 20/200 (10%) pla = 6/199 (3%) Bradycardia: met = 14/200 (7%) pla = 0 Cardiac failure: met = 3/200 (2%) pla = 0 Hypotension: met = 2/200 (1%) pla = 1/199 (1%)	Total: 26/394 (7%) Serious adverse events: met = 4/197 (2%) pla = 2/197(1%) Nonserious adverse events: met = 16/197 (8%) pla = 4/197(2%)

Evidence Table 7. Randomized controlled trials of beta blockers for arrhythmia

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Metoprolol vs placebo				
Khand 2003 UK *Fair quality*	RCT multicenter	Patients with persistent atrial fibrillation (> 1 month) and heart failure (appropriate symptoms of heart failure for more than two months and echocardiographic evidence of cardiac dysfunction [LVEF < 40% or preserved LV systolic function, together with LV hypertrophy, suggesting diastolic dysfunction in the absence of an alternative potential cause of symptoms]) who were receiving digoxin and diuretics	Heart rate at rest < 60 beats/min, systolic blood pressure < 90 mm Hg, sick sinus synddrome or complete heart block, current treatment with a beta-blocker or HR-lowering calcium channel antagonist or > 200 mg amiodarone, recent major cardiovascular event or procedures, asthma or reversible obstructive airways disease, serum creatinine > 250 µmol/l or significant hepatic disease, uncorrected significant valvular heart disease, or any life-threatening noncardiac disease	Phase I Open digoxin +placebo Open digoxin+carvedilol 50 mg daily (or 100 mg daily for patients > 85 kg) x 4 months Phase II Digoxin Carvedilol 50 mg daily (or 100 mg daily for patients > 85 kg) x 6 months

Evidence Table 7. Randomized controlled trials of beta blockers for arrhythmia

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Metoprolol vs placebo					
Khand 2003 UK *Fair quality*	ACE inhibitors Warfarin	1) LVEF 2) Ventricular rate control by 24-hour ambulatory ECG 3) Symptoms rated using patient self-administered, quantitative questionnaire designed to measure perception of the frequency and severity of symptoms (chest pain/discomfort, fatigue, and shortness of breath at rest, during walking at normal pace, and while climbing stairs and palpitations) and their functional capacity on 4-point scale (0=absent to 3=severe symptoms); responses were summed to produce a symptom score rangingn from 0 (no symptoms to 33 (worst symptoms) 4) Exercise tolerance by 6-minute corridor walk distance	Mean age=68.5 61.7% male Ethnicity nr	IHD etiology=40.4% Mean duration of AF=131.5 weeks Mean previous cardioversion attempts=0.5 Mean resting heart rate of ECG=85.5 beats/minute Mean LVEF=24.1% Mean LVEDD=53.7 mm Mean LA size=48.4 mm NYHA class I=4.2% II=57.4% III=31.9% IV=6.4% Digoxin dose=0.245 mg Digoxin plasma concentration=1.54 mmol/l ACE inhibitors=70.2% Anticoagulated=80.8%	nr/nr/47

Evidence Table 7. Randomized controlled trials of beta blockers for arrhythmia

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Metoprolol vs placebo					
Khand 2003 UK *Fair quality*	Phase I 6 (12.8%)/0/nr Phase II nr/nr/nr	Phase 1 (carvedilol vs placebo) LVEF: 30.6% vs 26%; p=0.048 Symptom score: 7 vs 8; p=0.039 6-min WD (ms): 3904 vs 414; p=NS Mean 24-hour ventricular rate reduction: data nr; p=0.0001 Phase II (carvedilol vs digoxin) LVEF: 21.6% vs 27.2%; p=NS Symptom score: 6 vs 8; p=NS 6-min WD (ms): 374 vs 403; p=NS Mean 24-hour ventricular rate reduction: data nr; p=NS	nr	Deaths Phase I: 4.2% vs 4.3%; p=NS Phase II: 5% vs 4.8%; p=NS	Withdrawals due to adverse events Phase I: 3 (12.5%) vs 1 (4.3%); p=NS Phase II: 3 (15%) vs 1 (4.8%); p=NS Withdrawals due to worsening heart failure Phase I: 0 vs 0 Phase II: 3 (15%) vs 1 (4.8%); p=NS

Evidence Table 7a. Quality assessments of randomized controlled trials of beta blockers for arrhythmia

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Similarity to target population	How many recruited	Exclusion criteria for recruitment	Eligibility criteria specified
Head to head trials							
Katritsis 2003	nr	nr	yes	Selected for patients naïve to study drugs	102	Terminal illness, age > 80 years, left ventricular ejection fraction <30, concomitant treatment with class I or III antiarrhythmic drugs, amiodarone use within 3 months before randomization, previous treatment with bisoprolol or carvedilol, and contraindications to beta blockade, such as conduction disturbances, asthma, or severe chronic obstructive pulmonary artery disease	Yes
Placebo-controlled trials Metoprolol vs placebo							
Kuhlkamp 2000	Adequate, computer generated	NR	Yes	No - selection for healthier population - mean age of sample = 60 years; mean age atrial fibrillation patients = 75 years	N = 403	• Use of Class 1 or 3 antiarrhythmic drug, beta-blockers or calcium channel blockers; chronic treatment with amiodarone within 6 months. • Contraindications to beta-adrenergic blocking agents. • Untreated thyroid dysfunction • Paroxysmal atrial fibrillation or history of it • Cardiac surgery in the previous two months	Yes

Evidence Table 7a. Quality assessments of randomized controlled trials of beta blockers for arrhythmia

Author, Year Country	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score (good/ fair/ poor)	Funding	Control group standard of care	Length of follow-up
Head to head trials											
Katritsis 2003	Yes	nr	nr	No	nr	Yes No No No	No No	Fair	nr	Yes	12 months
Placebo-controlled trials Metoprolol vs placebo											
Kuhlkamp 2000	NR	Yes	Yes	No	Yes	Attrition=6.8%; others NR	No	Fair	AstraZeneca, Sweden	Yes	6 months

Evidence Table 7a. Quality assessments of randomized controlled trials of beta blockers for arrhythmia

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Similarity to target population	How many recruited	Exclusion criteria for recruitment	Eligibility criteria specified
Metoprolol vs placebo							
Khand 2003 UK	nr	nr	yes	Mean age=68.5 61.7% male Ethnicity nr	47	Heart rate at rest < 60 beats/min, systolic blood pressure < 90 mm Hg, sick sinus syndrome or complete heart block, current treatment with a beta-blocker or HR-lowering calcium channel antagonist or > 200 mg amiodarone, recent major cardiovascular event or procedures, asthma or reversible obstructive airways disease, serum creatinine > 250 µmol/l or significant hepatic disease, uncorrected significant valvular heart disease, or any life-threatening noncardiac disease	yes

Evidence Table 7a. Quality assessments of randomized controlled trials of beta blockers for arrhythmia

Author, Year Country	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score (good/ fair/ poor)	Funding	Control group standard of care	Length of follow-up
Metoprolol vs placebo											
Khand 2003 UK	Yes	yes	yes	yes	nr	Yes No No No	No No	Fair	Roche Pharmaceuticals	Yes	Phase I=4 months; Phase II=6 months

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Palferman 1983 London *Poor quality* RCT Crossover	Average number of days with headache in 56 days: *All patients* (n=22): pla=26; pro=23(NS) *Migraine patients only* (n=10): pla=24; pro=21(NS) Average headache score All patients: pro=55; pla=47(p=0.26) Migraine patients only: pro=52; pla=47(NS)	nr	nr	nr	
Standes 1982 Norway *Poor quality* RCT Crossover	Reduction in mean attacks/month(mean/% change): pro=(-3.43)/(51.6%); pla=(-2)/(-30.1%) Ergotamine use(change in % of attacks during which pain relieving tablets were taken): pro=(-18 percentage points); pla=(-13.4 percentage points) Other pain relief tablet use(change in % of attacks during which pain relieving tablets were taken): pro=(-29 percentage points); pla=(-35 percentage points) Reduction in frequency of attacks: Good(>/= 50% reduction): pro=13 pts./72.2%; pla=6 pts./33.3% Some(33.3-49% reduction): pro=0 pts.; pla=1 pt./5.5% No effect(0=33.2% reduction); pro=3 pts/16.7%; pla=8 pts./44.4% Negative effect(increased frequency): pro=2 pts/11.1%; pla=3 pts/16.7%	Patient report	Incidence(# pts/%): pro=6/25(24%); pla=5/25(20%) Most common adverse events: Tiredness: pro=3/25(12%); pla=4/25(16%) Nausea: pro=1/25(4%); pla=1/25(4%) Sunburn feeling: pro=1/25(4%); pla=0 Depression: pro=1/25(4%); pla=0	2/25(8%) treatment nr	

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Tfelt-Hansen 1984 Scandinavia *Poor quality* RCT Crossover	Outpatients of both sexes between ages of 18 and 65 years with a history of between 2 and 6 common migraine attacks per month (Ad Hoc Committee)	Other types of headache (including classical migraine) and major head injuries; contraindications to beta blockers; oral contraceptive use; heart rate < 54 after 3 min of rest and with supine DBP >/= 100 mmHg	Timolol (tim) 20 mg daily Propranolol (pro) 160 mg daily Placebo (pla)	NR
Weber 1972 United States *Poor quality* RCT Crossover	Met criteria for diagnosis of migraine and that were recognized as therapeutic management problems	Abnormal neurological examinations; disorders that could be aggravated by beta blockers (namely cariac disease, asthma, diabetes mellitus)	Propranolol (pro) 80 mg daily Placebo (pla)	NR

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Tfelt-Hansen 1984 Scandinavia *Poor quality* RCT Crossover	*Patient diary card:* 1) frequency; 2) duration; 3) severity of attacks; 4) number of responders (e.g., >/= 50% reduction in frequency of attacks compared to baseline; 5) frequency of attacks with associated symptoms; 6) frequency of attacks requiring medication; 7) headache index=frequency x severity x attack duration in hours; 8) second headache index: attack frequency x severity	Mean age=39.5 73.9% female Race nr	Clinical characteristics(mean) Duration of migraine(years): 20.9 Attack frequency/28 days: 5.7 Attack with nausea frequency/28 days: 2.6 Attack with ergotamine therapy frequency/28 days: 2.4 Attack with any therapy frequency/28 days: 5.1 Duration of attacks(hours): 9.8 Severity of attacks: 2.0	nr/nr/96	withdrawn=27(28.1%)/6(6.2%) lost to fu/80 analyzed
Weber 1972 United States *Poor quality* RCT Crossover	1) Frequency and 2) severity assessed at 4-week intervals Definitions of symptomatic responses Excellent: all or nearly all symptoms of migraine absent after first week of study Good: more than 50% reduction in frequency or severity of headaches Fair: minimal symptomatic improvement No effect: unspecified	Mean age=40.6 52% female Race nr	Classic: 13(68.4%) Common: 6(31.6%)	nr/nr/25	withdrawn=6/25(24%)/lost to fu nr/analyzed 19

Evidence Table 8. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Tfelt-Hansen 1984 Scandinavia *Poor quality* RCT Crossover	*Mean frequencies per 28 days/mean(%) change for propranolol relative to placebo* Frequency of attacks: pro=3.69; pla=4.84/-1.15(-23.8%) Frequqency of attacks with nausea: pro=1.37; pla=1.89/-0.52(-27.5%) Frequency of attacks with any therapy: pro=3.24; pla=4.20/-0.96(-22.8%) Severity of attacks: pro=1.83; pla=1.93/-0.10(-5.2%)(NS) Duration of attacks(hours): pro=7.38; pla=7.95/-0.57(-7.2%)(NS) Headache index2: pro=6.66; pla=9.03/-2.37(-35.6%) Headache index1: pro=50.3; pla=50.7/-19(-27.4%) Number of responders(# pts with 50% reduction in frequency): pro=48; pla=24/24(+50%)	Patient report	Incidence[# pts(%)]: pro=35(42.2%); pla=23(27.7%) Most commonly reported side effects: Fatigue/tiredness: pro=11(13%); pla=15(18%) Dizziness: pro=4(5%); pla=2(2%) Nausea: pro=5(6%); pla=2(2%) Sleep disturbances: pro=3(4%); pla=2(2%) Depression: pro=3(4%); pla=0 Abnormal dreaming: pro=0; pla=0	pro=6/89(6.7%) pla=2/90(2.2%)	
Weber 1972 United States *Poor quality* RCT Crossover	Symptomatic response(# pts/%) *First 3 months(pro n=8; pla n=11)* Good/Excellent: pro=5(63%); pla=0 Fair: pro=2(25%); pla=1(9.1%) No effect: pro=1(12.5%); pla=11(91%) *Second 3 months(pro n=11 who received placebo first; pla n=8 who received pro first)* Good/Excellent: pro=10(91%); pla=2(25%) Fair: pro=0; pla=0 No effect: pro=1(9.1%); pla=6(75%) *Irrespective of sequence* pro>pla(#/% pts): 15/79% pro=pla(#/% pts): 4/21%	nr	Abdominal cramps/diarrhea:1 patient	nr	

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

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Nadelmann 1986	NR	NR	N/A-crossover	Fair higher female to male ratio	67 enrolled
Borgensen 1976 Denmark	**NR**	NR	N/A-crossover	Unknown; characteristics NR	45 selected
Fuller 1990 London	NR	NR	N/A-crossover	Good Median age=31 78.6% female	27 enrolled/14 analyzed
Rao 2000 India	Inferior; group allottment via latin square design	NR	NR	Good Mean age=28.6 67.2% female	259 recruited
Pradalier 1989	NR	NR	Yes	Good Mean age=37 75.7% female	74 enrolled
Wideroe 1974 Norway	NR	NR	N/A-crossover	Good Mean age=38 86.7% female	30 enrolled
Mikkelsen 1986 Denmark	NR	NR	N/A-crossover	Good Median age=38 83.9% female	39 enrolled

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

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Nadelmann 1986	Migraine other than classic or common, or other headaches known to be associated with migraine, or if they had known contraindications to beta blockers	Yes	NR	Yes	Yes	No
Borgensen 1976 Denmark	Cardiac disease, asthma, diabetes mellitus, physical or neurological abnormalities	Yes	NR	Yes	Yes	No
Fuller 1990 London	Contraindications to propranolol or paracetamol; pre-existing migraine prophylaxis or beta-blocker therapy for other indications; non-migrainous headaches that are not clearly distinguishable from migraine	Yes	Yes	Yes	Yes	No
Rao 2000 India	NR	Minimal	Yes	Yes	Yes	Yes
Pradalier 1989	History of congestive heart failure or asthma; heart block; bradycardia (<50 beats/min); Raynaud phenomenon; hypertension; resistant to two previously well-followed prophylactic treatments	Yes	Yes	Yes	Yes	Stated Yes, but unclear
Wideroe 1974 Norway	NR	Minimal	NR	Yes	Yes	No
Mikkelsen 1986 Denmark	Allergy to tolfenamic acid; serious heart, kidney, liver or psychiatric diseases, asthma, bronchitis, diabetes, active ulceration, pregnancy, or breast feeding; any administration of another prophylactic treatment for migraine within the month prior to the start of the study; use of tolfenamic acid within 6 months of study entry	Yes	Yes	Yes	Yes	No

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

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Nadelmann 1986	NR	Overall rate of attrition: 38.8% Others NR	No	Poor	NR; second author affiliated with Ayerst Laboratories	Yes	34 weeks
Borgensen 1976 Denmark	N/A	Attrition reported (33.3%); others NR	NR	Poor	NR	Yes	6 months
Fuller 1990 London	N/A	Attrition reported (48.1%); others NR	No	Poor	NR	Yes	4 attacks
Rao 2000 India	NR	Attrition reported (21.1%); others NR	No	Fair	NR	Yes	1 year
Pradalier 1989	NR	Attrition reported (44.6%); others NR	16.3% lost to fu	Fair-Poor	NR	Yes	12 weeks
Wideroe 1974 Norway	N/A	Attrition reported (13.3%); others NR	NR	Fair	Tablets/randomization provided by Imperial Chemical Industries Ltd.	Yes	6 months
Mikkelsen 1986 Denmark	N/A	Attrition reported(20.5%); others NR	No	Fair	GEA Ltd., Pharmaceutical Manufacturing Company	Yes	24 weeks

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

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Palferman 1983 London	NR	NR	N/A-crossover	Good Mean age=41.4 80% female	36 patients in total (16 with migraine)
Kaniecki 1997 United States	NR	NR	N/A-crossover	Unclear Mean age NR 81.1% female	37 recruited
Diener 1996 Germany	NR	NR	Yes	Good mean age=39 78.0% female	235 screened/214 randomized
van de Ven 1997 The Netherlands	NR	NR	Yes	Good mean age=38.7 82.3% female	226 randomized
Diamond 1982 United States	NR	NR	N/A-crossover	Unclear Mean age NR 78.7% female	245 admitted

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

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Palferman 1983 London	Under 16 or over 65 years; use of beta blockers contraindicated; possibility of other pathology, disclosed by history, examination or investigations, which might lead to headaches	Yes	NR	Yes	Yes	No
Kaniecki 1997 United States	Past trials of valproate or propranolol; failure of greater than 2 adequate trials of migraine prophylactic agents; severe medical or psychiatric illness; analgesic use of more than 15 days per month; presence of alcohol or drug abuse; use of no contraception by women of childbearing potential; unable to complete a headache diary or differentiate various headache types	Yes	no	NR	NR	No
Diener 1996 Germany	Pregnancy or lactation; psychiatric disorders; concomitant non-migraine headaches 3 times per month within the last three months; intake of centrally acting drugs or migraine prophylactic drugs during the 4 weeks peceding the trial; specific contraindication to beta-blocker (asthma, diabetes, clinically relevant hypotension, etc.) or cyclandelate (acute stroke, glaucoma, coagulation disorder); intake of drugs to treat migraine attacks > 12 days/month	Yes	Yes	Yes	Yes	Yes
van de Ven 1997 The Netherlands	Current use of drugs for the prevention of migrain; treatment with cardiovascular drugs; usual contrindications for beta blocker use or hypersensitivity to these agents	Yes	NR	Yes	Yes	Use of ITT analysis is indicated; but unclear in way data is presented
Diamond 1982 United States	Migraine associated with other types of headaches, migraine other than classic or common; known contraindications to propranolol	Yes	Phase I single blind; Phase II double blind	Yes	Yes	No

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

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Palferman 1983 London	N/A	Attrition reported(38.8%); others NR	27.80%	Poor	ICI Pharmaceuticals	Yes	16 weeks
Kaniecki 1997 United States	N/A	Attrition reported(13.%)	No	Poor	Abbott Laboratories	Yes	36 weeks
Diener 1996 Germany	NR	Attrition(16.8%); others NR	No	Fair	NR	Yes	20 weeks
van de Ven 1997 The Netherlands	NR	Attrition=31(13.7%); others NR	No	Fair	Merck	Yes	12 weeks
Diamond 1982 United States	N/A	Attrition: Phase I=16.7%; Phase II=32.4%; others NR	Phase I=4/1.6% Phase II=10/6.7%	Fair	Statistical evaluation provided by Ayerst Laboratories	Yes	6-12 months

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

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Kangasniemi 1987 Scandinavia	NR	NR	N/A-crossover	Good Mean age 37.5 79.7% female	77 randomized
Malvea 1973 United States	NR	NR	N/A-crossover	Fair Mean age NR 87.1% female	31 enrolled
Forssman 1976 Sweden	NR	NR	N/A-crossover	Good Mean age 37.4 87.5% female	40 included
Borgesen 1974 Denmark	NR	NR	N/A-crossover	Good Mean age 37.6 83.3% female	45 included
Ahuja 1985 India	NR	NR	N/A-crossover	Unclear; mean age NR 46.1% female	26 selected
Dahlof 1987 Sweden	NR	NR	N/A-crossover	Unclear mean age NR 92.8% female	28 entered
Kuritzky 1987 Israel	NR	NR	N/A-crossover	Unclear mean age NR gender NR	38 began

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

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Kangasniemi 1987 Scandinavia	Daily use of analgesics and/or total consumption exceeding 40 tablets/month; daily use of ergotamine and/or total consumption exceeding 16 mg/month; treatment with anti-depressive or neuroleptic drugs within the past 2 months; use of narcotic analgestics, chronic treatment with calcium antagonists, clonidine, other beta-blockers or NSAIDSs; change in oral contraceptive therapy 3 months before or during the study; contraindications for beta-blockers; insufficienty treated hypertension; transient ischaemic attacks; epilepsy; hypothyroidism and other severe psychiatric or somatic disease; and pregnancy	Yes	Yes	Yes	Yes	Unclear
Malvea 1973 United States	Pregnancy, bronchial asthma, congestive heart failure, allergic rhinitis, diabetes mellitus and previous use of propranolol for headache	Minimal	NR	Yes	Yes	No
Forssman 1976 Sweden	Pregnancy or suspicion of pregnancy; indication of renal or heart disease, hypertension, diabetes or asthma; history of earlier treatment of migraine with propranolol	Yes	NR	Yes	Yes	No
Borgesen 1974 Denmark	Cardiac disease; asthma or diabetes mellitus; physical or neurological abnormalities	Yes	Yes	Yes	Yes	No
Ahuja 1985 India	Intercurrent illness	Yes	NR	Yes	Yes	NR
Dahlof 1987 Sweden	NR	Yes	NR	Yes	Yes	Yes
Kuritzky 1987 Israel	NR	Yes	NR	Unclear	Unclear	No

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

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Kangasniemi 1987 Scandinavia	N/A	Attrition=3/77(3.9%); others NR	None	Fair	NR	Yes	16 weeks
Malvea 1973 United States	N/A	Attrition=1(3.2%); others NR	None	Fair	Ayerst Laboratories	Yes	12 weeks
Forssman 1976 Sweden	N/A	Attrition=8(20%); others NR	None	Fair	NR	Yes	34 weeks
Borgesen 1974 Denmark	N/A	Attrition=15(33.3%); others NR	None	Fair	ICI-Pharma	Yes	24 weeks
Ahuja 1985 India	N/A	NR	NR	Poor	Alkali and Chemical Corp. India Ltd. Provided tablets	Yes	16 weeks
Dahlof 1987 Sweden	N/A	Attrition=0; others NR	None	Fair	NR	Yes	52 weeks
Kuritzky 1987 Israel	N/A	Attrition=7(18.4%); others NR	None	Poor	NR	Yes	NR

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

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Standes 1982 Norway	NR	NR	N/A-crossover	Unclear mean age NR 80% female	25 entered
Forssman 1982 Sweden	NR	NR	N/A-crossover	Good mean age=40 80% female	24 included
Tfelt-Hansen 1984 Scandinavia	NR	NR	N/A-crossover	Good mean age=39.5 79.5% female	96 started
Weber 1972 United States	NR	NR	N/A-crossover	Fair mean age 40.6 68.4% female	25 enrolled
Diamond 1976 United States	NR	NR	N/A-crossover	Good mean age 38.1 80.7% female	83 enrolled
Sjaastad 1972 Norway	NR	NR	N/A-crossover	Good mean age 35.8 78.6% female	28 included
Ekbom 1971 Sweden	NR	NR	Yes	Fair mean age 33.7 86.7% female	30 included
Johnson 1986 New Zealand	NR	NR	N/A-crossover	Per protocol: Good mean age 42 76.5% female	29 started
Andersson 1983 Denmark	NR	NR	Yes	Per protocol: Good Mean age: pla=37.3; met-d=42.4 % female: pla=94.6%; met=73.5%	75 recruited

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

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Standes 1982 Norway	Other types of headache (including classical migraine) and major head injuries; contraindications to beta-blocking agents; use of oral contraceptives; pregnant women; use of timolol or propranolol for other reasons than migraine	Yes	NR	Unclear	Unclear	No
Forssman 1982 Sweden	NR	Minimal	NR	Yes	Yes	No
Tfelt-Hansen 1984 Scandinavia	Other types of headache (including classical migraine) and major head injuries; contraindications to beta blockers; oral contraceptive use; heart rate < 54 after 3 min of rest and with supine DBP >/= 100 mmHg	Yes	NR	Yes	Yes	No
Weber 1972 United States	Abnormal neurological examinations; disorders that could be aggravated by beta blockers (namely cariac disease, asthma, diabetes mellitus)	Yes	NR	Yes	Yes	No
Diamond 1976 United States	Asthma, cardiac disease, diabetes mellitus or any physical or neurologic abnormalities	Minimal	NR	Yes	Yes	No
Sjaastad 1972 Norway	NR	Yes	NR	Yes	Yes	No
Ekbom 1971 Sweden	Bronchial asthma, severe infectious diseases, diabetes mellitus, pregnancy, pathological ECG findings	Yes	NR	Yes	Yes	No
Johnson 1986 New Zealand	NR	Yes	Yes	Yes	Yes	No
Andersson 1983 Denmark	Other types of vascular headaches, chronic daily headache not separable from migraine; contraindication for beta blockers; other severe vascular diseases; oral contraceptives and pregnancy	Yes	NR	Yes	Yes	No

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

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Standes 1982 Norway	N/A	Attrition=7(28%); others NR	None	Poor	MSD (Norge) A/S	Yes	40 weeks
Forssman 1982 Sweden	N/A	Attrition=4(16.7%); others NR	None	Fair	ICI-Pharma Ltd.	Yes	254 days
Tfelt-Hansen 1984 Scandinavia	N/A	Attrition=27(28.1%); others NR	6(6.2%)	Poor	NR	Yes	40 weeks
Weber 1972 United States	N/A	Attrition: 6(24%); others NR	NR	Poor	Ayerst Laboratories	Yes	6 months
Diamond 1976 United States	N/A	Attrition: 21(25.3%)	NR	Poor	Ayerst Laboratories provided coded medications	Yes	16 weeks
Sjaastad 1972 Norway	N/A	Attrition=4(14.2%)	None	Fair	NR	Yes	14 weeks
Ekbom 1971 Sweden	NR	Attrition=4(13.3%); others NR	NR	Fair	NR	Yes	8 weeks
Johnson 1986 New Zealand	N/A	Attrition: 12(41.4%); others NR	9(31%)	Poor	Parke Davis Ltd.	Yes	9 months
Andersson 1983 Denmark	N/A	Attrition: 4/75(5.3%) prior to randomization; 9/71(12.7%) after randomization; others NR	NR	Fair	NR	Yes	12 wks

Evidence Table 9. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Head-to-Head Trials					
Colombo, 1989 Italy *Fair quality*	RCT	Patients with cirrhosis that (i) bled from varices or acute gastric erosions, or the bleeding was defined as of "unknown origin," but no lesion besides varices was found by endoscopy done within 5 days, (ii) the bleeding stopped on conservative treatment (vasopressin, somatostatin and/or Sengstaken-Blakemore tube), (iii) no rebleeding requiring definitive treatment (endoscopic sclerotherapy or surgery) occurred before assignment, (iv) they had well-compensated cirrhosis (Child's A or B status); (v) they were less than 70 years of age; (vi) they had been given no previous treatments for portal hypertension (including beta blockers, endoscopic sclerotherapy or surgery), and (vii) they were hemodynamically stable	Patients for whom beta-blockade was contraindicated, who had active peptic ulcer, neoplastic disease and/or Child's C liver status	Propranolol (pro) 40-160 mg daily *(n=32)* Atenolol (ate) 100 mg daily *(n=32)* Placebo (pla) *(n=30)*	Ranitinde, oral antacids, spironolactone, saluretics, lactulose, nonabsorbable antibiotics
Placebo-controlled trials					
Gatta, 1987 *Fair quality*	RCT	Biopsy-proven cirrhosis of different etiologies, who survived a vericeal bleeding, defined endoscopically (within 36 hours of bleed) as proven by criteria: 1) visualization of bleeding site; 20 visualization of a fibrin clot on a varix; 3) presence of varices in the absence of gastroduodenal lesions and of any assumption of drugs affecting gastric mucosa; within 15-40 days after bleeding	Child's C grade; massive ascites; renal failure persisting after compensating hemodynamic conditions (serum creatinine > 1.5 mg/dl); age < 18 or > 70 years; tumors; contraindications to beta-blocking agents (asthma, A-V block > 1 degree; heart failure; clinically evident diabetes)	Nadolol (nad) 40-160 mg daily (target heart rate reduction of 25%) Placebo (pla) x 145 weeks	nr

Evidence Table 9. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Head-to-Head Trials					
Colombo, 1989 Italy *Fair quality*	GI hemorrhage and/or death Quality of life	*Mean age:* pla=54; ate=53; pro=52 *%male:* pla=76.7; ate=78.1; pro=87.5 Race NR	*Etiology(%)* Alcohol: pla=80; ate=81.3; pro=84.4 HBsAg: pla=6.7; ate=0; pro=9.4 Other: pla=13.3; ate=18.7; pro=6.3 *Child's class(%)* A: pla=46.7; ate=46.9; pro=43.8 B: pla=3.3; ate=53.1; pro=56.3 *Bleedings before index bleed(%)* 0: pla=20; ate=46.9; pro=31.2 1: pla=53.3; ate=34.4; pro=50 2 or more: pla=26.7; ate=18.8; pro=18.8 *Source of hemorrhage(%)* Varices: pla=70; ate=26; pro=90.6 Erosions: pla=23.3; ate=9.4; pro=6.2 Unknown: pla=6.7; ate=9.4; pro=3.1	176 evaluated/ 94 eligible/ 94 enrolled	*Withdrawn:* pla=4(13%); ate=8(25%); pro=2(6%) *Lost to fu:* *pla=3(10%); ate=3(9.4%); pro=1(3.1%)* *Analyzed:* pla=30; ate=32; pro=32
Placebo-controlled trials					
Gatta, 1987 *Fair quality*	Event endpoints of the study were considered 1) onset of side effects necessitating withdrawal of treatment; 2) occurrence of digestive hemorrhage from ruptured esophageal varices; 3) death x assessed monthly for first 3 months; then every three months	Mean age: 49 71% male Race nr	*Etiology* Alcoholic cirrhosis: 75% Cryptogenic cirrhosis: 12.5% Posthepatic cirrhosis: 12.5% *Child Class* A: 37.5% B: 62.5% Ascites: 25% >1 previous hemorrhage: 33.3% *Esophageal varices* 2: 29.2% 3: 41.7% 4: 29.2%	nr/54/24 nad (n=12) pla (n=12)	Lost to fu: 5/24(21%)

Evidence Table 9. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Head-to-Head Trials				
Colombo, 1989 Italy *Fair quality*	*Fatal/nonfatal bleeding episodes at 1 year(% patients):* pla=51; ate=31; pro=24 *Total deaths:* pla=7(23%); ate=3(10%); pro=4(12%) *Deaths due to rebleeding:* pla=3(10%); ate=1(3.1%); pro=1(3.1%) *Deaths due to liver failure:* pla=2(6.7%); ate=1(3.1%); pro=2(6.2%) *Deaths due to unrelated causes:* pla=2(6.7%); ate=1(3.1%); pro=1(3.1%)	NR	NR	pla=0 ate=4(12.5%) pro=0
Placebo-controlled trials				
Gatta, 1987 *Fair quality*	*Per protocol analysis:* Esophageal varices hemorrhage: nad=3(25%); pla=8(71%)(p<0.05) Death due to all causes: nad=1(8.3%); pla=3(27.3%)(NS)	nr	nr	Withdrawals due to asthma: nad=1; pla=0

Evidence Table 9. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Burroughs 1983 Hampstead, England *Fair quality*	RCT	Histologically confirmed cirrhosis; bleeding from a varix or varices; no bleeding for 48 hours	NR	Propranolol (pro) 80 to 800 mg daily with a goal of 25% heart rate reduction Placebo (pla) x 21 months Treatment initiated 48 hours after bleeding cessation	NR

Evidence Table 9. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Burroughs 1983 Hampstead, England *Fair quality*	Assessments at monthly intervals for first 3 months; then at three-month intervals	*Mean age:* pro=51; pla=49 *Gender(% male):* pro=46.1; pla=45.4 Race nr	*Causes of cirrhosis:* Alcoholism - Pro=35%; Pla=50% Chronic active hepatitis - Pro=27%; Pla=32% Cryptogenic - Pro=19%; Pla=14% Primary biliary cirrhosis - Pro=19%; Pla=4% *Pugh's grading:* A - Pro=65%; Pla=54% B - Pro=23%; Pla=36% C - Pro=11.5%; Pla=8% *Previous upper GI hemorrhage:* Pro=77%; Pla=77% *Transfusion (units) after index bleeding episode:* Pro=31%; Pla=41%	60 screened/48 eligible/48 enrolled	Withdrawn=4(8.3%)/0 lost to fu/48 analyzed

Evidence Table 9. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Burroughs 1983 Hampstead, England *Fair quality*	Rebleeding(# patients/%): pro=12/26(46.1%); pla=11/22(50%)(NS) Death due to variceal rebleeding(# patients/%): pro=4/26(15.4%); pla=2/22(9.1%) All-cause mortality(# patients/%): pro=4/26(15.4%); pla=5/22(22.7%)	nr	nr	Withdrawals: pro=4/26(15.4%); pla=0

Evidence Table 9. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
El Tourabi 1994 Sudan *Fair quality*	RCT	Portal hypertension ***secondary to schistosomiasis*** ; age 18-65; past history of schistomiasis (demonstrated by ultrasound); esophageal varices; recent variceal hemorrhage	Evidence or history of heart failure; significant airway obstruction; heart block greater than first degree; insulin dependent diabetes mellitus; bradycardia; severe peripheral vaascular disease; pregnant or lactating; severe depression; MI within previous 3 months	Long-acting propranolol (LA pro) 160 mg daily Placebo (pla)	NR
Jensen 1989 Denmark *Fair quality*	RCT	Liver disease; age <70; bleeding esophageal varices; no previous bleeding; absence of bleeding for 24 hours after sclerotherapy	Known contraindications to beta blockade	Propranolol slow release (pro SR) 160 mg daily Placebo (pla) x six months	NR

Evidence Table 9. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
El Tourabi 1994 Sudan *Fair quality*	Full clinical examinations at 3-month intervals Endoscopies performed at 12 and 24 months Primary endpoints: 1) time to first rebleed; 2) time to death	Mean age: LA pro=34.6; pla=37.1 % male: LA pro=80; pla=83 Race nr	*On admission, patients with:* Palmar erythema - Pro=2%; Pla=0 Gynaecomastia - Pro=2%; Pla=0 Spider naevi (bormore) - Pro=0; Pla=0 Jaundice - Pro=0; Pla=0 Peripheral edema - Pro=0; Pla=0 Clubbing - Pro=0; Pla=2.5% Loss of body hair - Pro=2%; Pla=2.5% Bruising - Pro=2%; Pla=0 Distended superficial abdominal veins - Pro=9.5%; Pla=15% Ascites - Pro=7%; Pla=15% Venous hump - Pro=2%; Pla=7.5% *Livers:* Studied - Pro=31%; Pla=15% Shrunken - Pro=24%; Pla=35% Not palpable - Pro=45%; Pla=50% Palpable - Pro=31%; Pla=15% *Spleens:* Studied - Pro=93%; Pla=97.5% Shrunken - Pro=0; Pla=2.5% Not palpable - Pro=5%; Pla=0 Palpable - Pro=95%; Pla=97.5%	*Propranolol:* n=42 *Placebo:* n= 40	33(40%) withdrawn due to "other" reasons/lost to fu=2(2.4%)/analyzed 82
Jensen 1989 Denmark *Fair quality*	Endoscopy at monthly intervals	*Mean age:* pro SR=46; pla=47 *Gender(% male):* pro SR=100; pla=75 Race nr	*Liver disease:* Alcoholic cirrhosis - Pro=80%; Pla=87.5% Primary biliary cirrhosis - Pro=7%; Pla=0 Chronic active hepatitis - Pro=7%; Pla=6% Cryptogenic cirrhosis - Pro=7%; Pla=6% *Child's classification:* A - Pro=27%; Pla=25% B - Pro=47%; Pla=44% C - Pro=27%; Pla=31%	NR/NR/31 randomized	NR/NR/31 analyzed

Evidence Table 9. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
El Tourabi 1994 Sudan *Fair quality*	LA pro n=42; pla n=40 Rebleeding(# patients/%): LA pro=1(2%); pla=8(20%)(p<0.02) Death(# patients/%): LA pro=3(7%); pla=7(17.5%)(p<0.02) Median time to rebleeding(# days): LA pro=539; pla=252	Occurrence of adverse effects were volunteered by patients and elicited at follow-up visits	Incidence(# patients/%): LA pro=14(33.3%); pla=12(30%) Most common adverse events(# pts/%) Abdominal swelling: LA pro=0; pla=1(2.5%) Blurred vision: LA pro=1(2%); pla=0 Coughing: LA pro=0; pla=1(2.5%) Diarrhea: LA pro=2(5%); pla=3(7.5%) Drowsiness: LA pro=1(2%); pla=1(2.5%) Dry mouth: LA pro=1(2%); pla=0 Epistaxis: LA pro=1(2%); pla=0 Fatigue: LA pro=0; pla=2(5%) Fever/hot sensation: LA pro=2(5%); pla=1(2.5%) Gastric discomfort: LA pro=1(2%); pla=(2.5%) Hematemesis: LA pro=2(5%); pla=2(5%) Heartburn: LA pro=2(5%); pla=1(2.5%) Hiccups: LA pro=1(2%); pla=0 Hypersomnia: LA pro=0; pla=1(2.5%) Indigestion: LA pro=0; pla=1(2.5%) Itching: LA pro=2(5%); pla=0 Melena: LA pro=0; pla=2(5%) Nervousness: LA pro=1(2%); pla=0 Pain in abdomen: LA pro=1(2%); pla=1(2.5%) Tinnitus: LA pro=1(2%); pla=0 Wheezing: LA pro=0; pla=1(2.5%)	NR
Jensen 1989 Denmark *Fair quality*	Rebleeding(# patients/%): pro SR=3/15(20%); pla=12/16(75%)(p<0.05) Median treatments to achieve obliteration: pro SR=5; pla=5 Median time to obliteration(days): pro SR-163; pla=151	NR	Incidence(# patients/%): pro SR=4/15(26.7%); pla=3/16(18.7%) *Types of adverse events* Pro SR(# pts): Tiredness=2; diarrhea=2 Pla(# pts): Cold extremitis=1; skin rash=1	None

Evidence Table 9. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Lebrec 1981a France *Fair quality*	RCT	Histologically proven cirrhosis; gastrointestenal bleeding due to ruptured esophageal or gastric varices; diameter of esophageal varices >5mm at x-ray exam; GI bleeding spontaneously stopped or did not relapse after cessation of esophageal tamponade; hepatic encephalopathy, ascites and jaundice absent or appeared only transiently after bleeding	NR	Propranolol (pro) 80-360 mg daily with goal of 25% heart rate reduction Placebo (pla) x 3 months Treatment initiated **10-15** days following bleeding cessation	NR
Lebrec 1981b Lebrec 1984 France *Fair quality*	RCT	Histologically proven cirrhosis; gastrointestinal bleeding; source of hemorrhage was ruptured esophageal or gastric varices (as determined by endoscopy); volume of blood transfused within first 24 hours was 0.5 liter or more; jaundice was absent or mild; size of esophageal varices was large; gradient between the wedge and free hepatic venous pressures >10mm Hg; GI bleeding stopped and hemodynamic conditions were normal	Heart failure; asthma; chronic disease other than cirrhosis	Propranolol (pro) 40-360 mg daily with goal of 25% heart rate reduction Placebo (pla) Treatment initiated **2 weeks** following bleeding cessation	NR

Evidence Table 9. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Lebrec 1981a France *Fair quality*	NR	NR	*Type of cirrhosis(# patients/%):* Alcoholic=24/87.5% Hepatitis-B infection=1/4.2% Unknown=2/8.3%	NR/NR/24 admitted	NR/NR/24 analyzed
Lebrec 1981b Lebrec 1984 France *Fair quality*	Assessments at 2-month intervals through year 1; then at 4-month intervals through year 2	*Mean age:* pro=52.4; pla=49.9 *Gender(% male):* pro=81.6%; pla=72.2% Race NR	*Causes of cirrhosis:* Alcoholism - Pro=87%; Pla=89% Chronic Hepatitis B infection - Pro=8%; Pla= 5% Cryptogenic - Pro=5%; Pla=5% *Source of bleeding:* Ruptured varices - Pro=74%; Pla=78% Acute gastric erosions - Pro=26%; Pla=22% *Previous episodes of bleeding:* No - Pro=42%; Pla=36% Yes - Pro=58&; Pla=64%	NR/NR/74 randomized	NR/lost to fu: pro=3/28(7.9%); pla=3/36(5.5%)/analyzed 74

Evidence Table 9. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Lebrec 1981a France *Fair quality*	Rebleeding(# patients/%): pro=0; pla=5/12(41.7%)(p=0.037)	NR	Undesirable side effect incidence: pro=0; pla=0	None
Lebrec 1981b Lebrec 1984 France *Fair quality*	*Rebleeding(# patients/%):* Year one: pro=1/38(2.6%); pla=16/36(44.4%)(p<0.0001) Year two: pro=6/38(15.8%); pla=23/36(63.9%) *Time to rebleeding(% patients free of rebleeding at years 1/2):* pro=87/79; pla=42/32(p<0.0001) *Death due to(# patients/%):* Liver failure/septicemia: pro=3/38(7.9%); pla=2/36(5.5%) Rebleeding: pro=0; pla=6/36(16.7%) Percentage of surviving patients at years 1/2: pro=94%/90%(NS); pla=84%/57%(p<0.02)	NR	*Incidence:* NR *Types of adverse events(# patients):* Pro: transient asthemia=8; feeling of well-being=10; transietly reduced sexual activity=2; heart failure development=1 Pla: nausea=1; dizziness=1; cutaneous rash=1	NR

Evidence Table 9. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Lo 1993 Taiwan *Fair quality*	RCT	***Cirrhosis*** ; complete obliteration of esophageal varices; esophageal variceal bleeding; received regular endoscopic injection sclerotherapy (EIS)	Visible esophagogastric varices; association with cancer growth; known contraindications to beta-blockade; beta blockers received prior to variceal obliteration	Propranolol (pro) 60-320 mg daily Placebo (pla)	NR
Sheen 1989 Taiwan *Fair quality*	RCT	***Cirrhosis*** ; stabilized after after treatment for esophageal variceal hemorrhage	Previous treatment with endoscopic sclerotherapy; heart or lung disease; hepatocellular carcinoma	Propranolol (pro) 40 mg daily(mean dosage; range 30-60 mg) with goal of a 25% heart rate reduction Placebo (pla)	NR

Evidence Table 9. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Lo 1993 Taiwan *Fair quality*	Study endpoints: 1) esophagogastic variceal rebleeding (defined as presence of hematemesis, melena and when more than two units of blood transfusion were required and the bleedign site was identified from esophagogastic varices by emergency endoscopy); 2) death	*Mean age:* pro=54.3; pla=51.2 *Gender(% male):* pro=88; pro=92	*Etiology of cirrhosis:* Alcoholic - Pro=11.5%; Pla=15% Post-hepatitic - Pro=81%; Pla=74% Cryptogenic - Pro=7%; Pla=7% *Pugh's grading:* A - Pro=69%; Pla=70% B - Pro=23%; Pla=26% C - Pro=7%; Pla=4%	NR/NR/59 enrolled	6(10.2%) withdrawn/lost to fu: pro=1(3.3%); pla=2(6.9%)/53 analyzed
Sheen 1989 Taiwan *Fair quality*	Study endpoints: 1) Rebleeding from esophageal varices (proven by endoscopy); or 2) loss to follow-up Patients were seen every two months	*Mean age:* pro=43.6; pla=45.3 *Gender (% male):* pro=83; pla=88	*Cause of cirrhosis:* Alcoholic - Pro=33.3%; Pla=55.5% HBV - Pro=55.5%; Pla=33.3% Cryptogenic - Pro=22.2%;Pla=22.2% *Previous bleeding:* Pro=55%; Pla=53% *Encephalopathy:* Pro=0; Pla=0 *Ascites:* Pro=22%; Pla=28% *Pugh's grading:* A - Pro=78%; Pla=72% B - Pro=22%; Pla=28% C - Pro=0; Pla=0	230 screened/36 eligible/36 randomized (pro n=18; pla n=18)	NR/NR/18 analyzed

Evidence Table 9. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Lo 1993 Taiwan *Fair quality*	Esophagogastric variceal *recurrence* (# patients/%): pro=15/26(58%); pla=21/27(77%) Esophageal variceal *rebleeding* (# patients/%): pro=5/26(19.2%); pla=3/27(11.1%) Cardiac variceal rebleeding(# patients/%): pro=2/26(7.6%); pla=2/27(7.4%) Total rebleeding(esophageal+cardiac rebleeding)(# patients/%): pro=7/26(26.9%); pla=5/27(18.5%) *Death due to:* *(per protocol analysis: pro n=26; pla n=27)* Hepatic failure: pro=2/7.6%; pla=4/14.8% Variceal bleeding: pro=3/11.5%; pla=2/7.4% Hepatocellular carcinoma: 2/7.6%; pla=3/11.1% Cerebral hemorrhage: pro=1/3.8%; pla=0 All-cause mortality: pro=8/30.8%: pla=9/33.3%	NR	*Propranolol(%)* Dizziness=28% Drowsiness=18% Chest tightness=11% *Placebo:* NR	*Propranolol(# patients/%):* 3/26(11.%) due to "intolerable general malaise *Placebo:* NR
Sheen 1989 Taiwan *Fair quality*	Rebleeding(# patients/%): pro=5/18(27.8%); pla=10/18(55.5%) Death due to rebleeding(# patients/%): pro=0; pla=2/18(11.1%) Freedom from rebleeding(% at 6, 12, 18 and 24 months): pro=94/87/68/57; pla=81/59/30/15	NR	NR	NR

Evidence Table 9. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Villeneuve 1986 Montreal, Canada *Fair quality*	RCT	Adult; within 72 hours of variceal hemorrhage (demonstrated by endoscopy)	Previous treatment with beta blockers or endoscopic sclerotherapy; absence of Placebo of hemorrhage for at least 6 hours before randomization, using a Sengstaken-Blakemore tube or vasopressin infusio if necessary; heart failure or aortic valve disease other than aortic sclerosis; asthma or chronic obstructive lung disease precluding the administration of beta blockers; cancer or other disease reducing life expectancy to <1 year	Propranolol (pro) initial dose of 80 mg daily wih a goal of plasma concentrations between 50-150 ng per ml Placebo (pla) Treatment initiated within 6-72 hours following bleeding cessation	

Evidence Table 9. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Villeneuve 1986 Montreal, Canada *Fair quality*	Assessments at monthly intervals for first 3 months; then at three-month intervals Primary endpoint=Variceal rebleeding (shown by endoscopy) Secondary endpoint=Survival	*Mean age:* pro=54; pla=58 *Gender(% male):* pro=57.1%; pla=75.7% Race NR	*Etiology of portal hypertension:* Alcoholic cirrhosis - Pro=74%; Pla=70% Posthepatitic cirrhosis - Pro=7%; Pla=8% Cryptogenic cirrhosis - Pro=9%; Pla=16% Biliary cirrhosis - Pro=7%; Pla=2% Portal vein thrombosis - Pro=2%; Pla=0 Idiopathic portal hypertension - Pro=0; Pla=2% *Pugh's grading:* A - Pro=9%; Pla=13.5% B - Pro=50%; Pla=57% C - Pro=43%; Pla=30% *Previous episodes of bleeding:* Pro=33%; Pla=30% *Alcohol consumtion (>60 gm daily) during month prior to admission:* Pro=43%; Pla=46% *Requied balloon tamponade for index bleed:* Pro=43%; Pla=43%	110 screened/79 eligible/79 enrolled	0 withdrawn/0 lost to fu/79 analyzed

Evidence Table 9. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Villeneuve 1986 Montreal, Canada *Fair quality*	Rebleeding(# patients/%): pro=32/42(76.2%); pla=30/37(81.2%) All cause mortality: pro=19/42(45.2%); pla=14/30(37.8%) *Mortality due to(# patients/%):* Rebleeding: pro=5/42(11.9%); pla=7/37(18.9%) Liver failure: pro=8/42(19.0%);pla=3/37(8.1%)	NR	NR	Withdrawals: pro=5/42(11.9%); pla=0 Propranolol AE withdrawals due to: Shortness of breath: 3 patients Cardiac failure: 1 patient Septic shock with hypotension: 1 patient

Evidence Table 9a. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Colombo 1989 Italy	Adequate. Block randomization. Series of triplet packages provided(ate; pro; pla); the contents of which varied at random.	Block number assignment corresponded to a particular package	Yes	Mean age=53 Gender=80.8% male	94
Gatta 1987	NR	NR	Yes	Mean age: 49 71% male	24
Burroughs 1983 Hampstead, England	Inferior method: sealed envelope	NR	Yes	*Mean age:* pro=51; pla=49 *Gender(% male):* pro=46.1; pla=45.4	48
El Tourabi 1994 Sudan	NR	NR	Yes	Mean age: LA pro=34.6; pla=37.1 % male: LA pro=80; pla=83 Race NR	82
Jensen 1989 Denmark	Adequate: Computer generated randomization schedule	NR	Yes	*Mean age: pro SR=46; pla=47* *Gender(% male): pro SR=100; pla=75* *Race NR*	31

Evidence Table 9a. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Colombo 1989 Italy	Patients for whom beta-blockade was contraindicated, who had active peptic ulcer, neoplastic disease and/or Child's C liver status	Yes	NR	Yes	Yes	Yes
Gatta 1987	Child's C grade; massive ascites; renal failure persisting after compensating hemodynamic conditions (serum creatinine > 1.5 mg/dl); age < 18 or > 70 years; tumors; contraindications to beta-blocking agents (asthma, A-V block > 1 degree; heart failure; clinically evident diabetes)	Yes	Yes	Yes	Yes	No
Burroughs 1983 Hampstead, England	NR	Yes	No; single-blind	Yes	Yes	Yes
El Tourabi 1994 Sudan	Evidence or history of heart failure; significant airway obstruction; heart block greater than first degree; insulin dependent diabetes mellitus; bradycardia; severe peripheral vaascular disease; pregnant or lactating; severe depression; MI within previous 3 months	Yes	NR	Yes	Yes	Yes
Jensen 1989 Denmark	Known contraindications to beta blockade	Yes	NR	Yes	Yes	Yes

Evidence Table 9a. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: deifferential/high	Score	Funding	Control group standard of care	Length of follow-up
Colombo 1989 Italy	NR	Attrition reported; others NR	Pla=3(10%) Ate=3(9.4%) Pro=1(3.1%)	Fair	Imperial Chemical Industries (Milan) supplied trial tablets	Yes	Mean=357 days
Gatta 1987	NR	NR	Lost to fu: 5/24(21%)	Fair	NR	Yes	Mean=145 weeks
Burroughs 1983 Hampstead, England	NR	NR	NR	Fair	NR	Yes	21 months
El Tourabi 1994 Sudan	NR	Attrition=33(40%)	Lost to fu: LA pro=1(2.4%) pla=1(2.5%)	Fair	ICI Pharmaceuticals	Yes	2 years
Jensen 1989 Denmark	NR	NR	NR	Fair	ICI Pharmaceuticals	Yes	6 months

Evidence Table 9a. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Lebrec 1981a France	NR	NR	NR	NR	24
Lebrec 1981b Lebrec, 1984 France	NR	NR	Yes	*Mean age:* pro=52.4; pla=49.9 *Gender(% male):* pro=81.6%; pla=72.2%	74
Lo 1993 Taiwan	NR	NR	Yes	*Mean age:* pro=54.3; pla=51.2 *Gender(% male):* pro=88; pro=92	59
Sheen 1989 Taiwan	NR	NR	Yes	*Mean age:* pro=43.6; pla=45.3 *Gender (% male):* pro=83; pla=88	36
Villeneuve 1986 Montreal, Canada	Inferior method; sealed envelopes	NR	No; more patients in the pro group had severe Class C liver disease (43% vs 30%); less patients in the propranolol group were male (57.1% vs 75.7%)	*Mean age:* pro=54; pla=58 *Gender(% male):* pro=57.1%; pla=75.7%	79

Evidence Table 9a. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Lebrec 1981a France	NR	Yes	NR	Yes	Yes	Yes
Lebrec 1981b Lebrec, 1984 France	Heart failure; asthma; chronic disease other than cirrhosis	Yes	NR	Yes	Yes	Yes
Lo 1993 Taiwan	Visible esophagogastric varices; association with cancer growth; kNown contraindications to beta-blockade; beta blockers received prior to variceal obliteration	Yes	Yes	Yes	Yes	No
Sheen 1989 Taiwan	Previous treatment with endoscopic sclerotherapy; heart or lung disease; hepatocellular carciNoma	Yes	NR	Yes	Yes	Yes
Villeneuve 1986 Montreal, Canada	Previous treatment with beta blockers or endoscopic sclerotherapy; absence of Placebo of hemorrhage for at least 6 hours before randomization, using a Sengstaken-Blakemore tube or vasopressin infusio if necessary; heart failure or aortic valve disease other than aortic sclerosis; asthma or chronic obstructive lung disease precluding the administration of beta blockers; cancer or other disease reducing life expectancy to <1 year	Yes	No; single-blind	Yes	Yes	Yes

Evidence Table 9a. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: deifferential/high	Score	Funding	Control group standard of care	Length of follow-up
Lebrec 1981a France	NR	NR	NR	Fair	ICI Pharmaceuticals	Yes	3 months
Lebrec 1981b Lebrec, 1984 France	NR	NR	Lost to fu: pro=3/38(7.9%) pla=2/36(5.5%)	Fair	NR	Yes	24-38 months (mean=29 months)
Lo 1993 Taiwan	NR	Attrition=6(10.2%)	Lost to fu: pro=1(3.3%); pla=2(6.9%)	Fair	NR	Yes	Mean follow-up of 2 years and 4 months
Sheen 1989 Taiwan	NR	NR	NR	Fair	Prosperous Foundation	Yes	Mean follow-up of 12.4 months
Villeneuve 1986 Montreal, Canada	NR	Attrition reported(None); others NR	None	Fair	Ayerst Laboratories	Yes	2 years

Evidence Table 10. Adverse events in head to head trials of beta blockers for hypertension

Trial	Interventions	Sample Size	Trial duration	Population Characteristics	Quality	Results
Foerster 1985	Atenolol (ate) 100 mg Pindolol SR (pin-SR) 20 mg	107	24 weeks	Mean age=41.4 65.4% male	Good • Designed specifically for AE assessment • Changes of >1 cm on VAS interpreted as AE	Data for weeks 13-24(% patients)*:* *n: ate=53; pin=54* Sleep disturbance: ate=18; pin=44(p=0.01) Dreams: ate=16; pin=15 Fatigue: ate=28; pin=22 Raynaud's phenomenon: ate=14; pin=26 Muscle cramps: ate=12; pin=20 Sexual disturbance: ate=14; pin=8 GI disturbances: ate=21; pin=20
Fogari 1999	Atenolol (ate) 100 mg Bisprolol (bis) 10 mg Celiprolol (cel) 400 mg Propranolol (pro) 160 mg	152	18 months	100% male Mean age=52	Fair	Overall AE incidence(# pts; %): pro=6/37(16.2%); ate=5/38(13.1%); bis=4/39(10.2%)
Lithell 1987	Atenolol (ate) 50 mg Bisoprolol (bis1) 5 mg Bisoprolol (bis2) 10 mg	292	6 months	59.9% male Mean age=52.6	Fair	Withdrawals due to adverse events (# patients/%): ate=2/97(2.1%); bis1=4/97(4.1%); bis2=4/98(4.1%)
Walle 1994	Metoprolol CR 100 mg Atenolol 100 mg	58	6 weeks	43.3% male Mean age=58	Fair	Overall AEs: no differences (data NR) Serious AEs: meto vs ate = 0 vs 2 (3.3%) (bradycardia
Sundar 1991	atenolol: 100mg propranolol: 80mg	26	4 weeks	100% male Mean age=NR	Poor	ate vs pro (%) headache: 0 vs 0 weakness: 10.5 vs 10.7 warmth: 2.6 vs 0 oedema: 0 vs 0 dyspnoea: 5.3 vs 0 constipation: 0 vs 0
Steiner 1990	Propranolol 80-240mg (mean=133.4mg per day) Atenolol 50-100mg (mean=56.4mg per day)	pro: 73 ate: 78	4 weeks	100% male Mean age=NR	Fair	pro(%) vs ate(%), all NS Bradycardia: 4(4.5) vs 9(10) Gastrointestinal distress: 9(10.1) vs 7(7.8) Dry mouth: 5(5.6) vs 4(4.4) Anxiety: 7(7.9) vs 2(2.2) Sleep disturbance: 4(4.5) vs 6(6.7) Libido decreased/impotence: 8(9): 5(5.6) Weakness/fatigue: 15(16.9) vs 8(8.9) Headache: 12(13.5) vs 9(10) Total: 57(64) vs 50(55.6) Withdrawals due to adverse events: pro: 5(6.85); ate: 0(0)

Evidence Table 10. Adverse events in head to head trials of beta blockers for hypertension

Trial	Interventions	Sample Size	Trial duration	Population Characteristics	Quality	Results
Dahlof 1988	atenolol 50 mg metoprolol CR 100 mg	74	6 weeks	51(66%) male Mean age=54.4	Fair	Subjective symptoms- leg fatigue, constipation, diarrhoea, bradycardia, cold hands and feet, heavy breathing: NS Palpitation: meto> ate, p<0.05 Withdrawals due to adverse events: 2(2.6%)
Blumenthal 1988	atenolol 50-100mg propranolol: 40-80mg	26	2 weeks	100% male Mean age=42.5	Poor	sleep items: NS sexual functioning: NS energy: 4 (ate) and 4 (pro) reported being more tired in the morning, while 6 (pla) reported less fatigue.
Buhler 1986	Bisoprolol 10-20mg Atenolol 50-100 mg	104	8 weeks	82.7% male Mean age=53.8	Fair	Baseline:bis / baseline:ate (number), all NS headache- 20:7/ 19:9 tiredness- 17:20/ 17:13 Nervousness- 17:10/ 10:8 Sleep problems- 18:11/ 15:10 Cold extremities- 14:13/ 16:12 Sweating- 12:9/ 11:11 Tingling sensations- 12:6/ 9:5 Feeling of weakness- 11:6/ 5:7 Dizziness- 11:3/ 8:7 Joint pain- 9:9/ 6:8 Depressed mood- 12:11/ 9:5 Sex problems- 5:7/ 6:4 Withdrawals due to adverse events: bis (1): dizziness ate (5): diarrhea, skin rash, asthmatic bronchitis, vertigo, headache

Evidence Table 11. Safety of all head to head trials of beta blockers

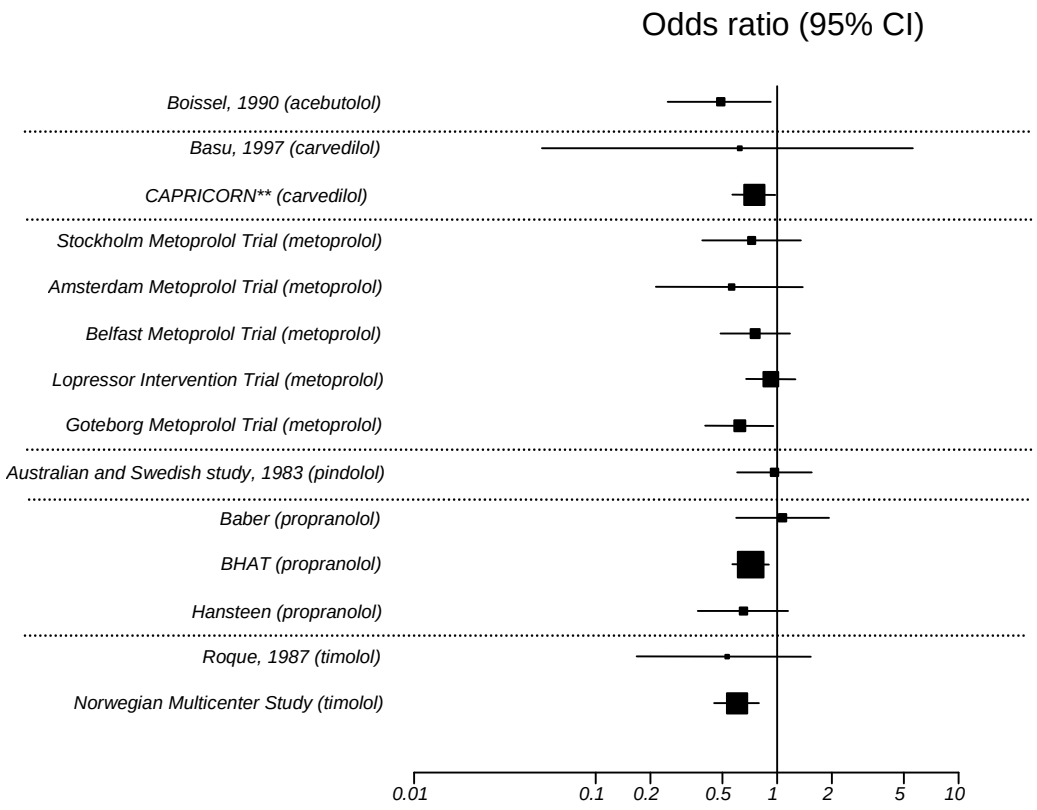
Trial	Indication	Sample size	Duration	p-value	*Selective beta blockers*				*Non-selective beta blockers*								
					ate	bis	met	bet	ace	cart	carv	lab	nad	pen	pin	pro	tim
OVERALL ADVERSE EVENT INCIDENCE																	
Fogari, 1999	Hypertension	152	18 mos	NS	13.1%	10.2%										16.2%	
Frishman, 1979	Angina	40	8 wks	<0.0001											17.4%	94.4%	
van der Does, 1999	Angina	368	3 mos	NS			30.0%				25.0%						
Narahara, 1990	Angina	112	10 wks	nr				50.0%								42%	
								37.0%								45%	
Poole-Wilson, 2003 *COMET*	Heart Failure	3029	58 mos	NS			96.0%				94.0%						
Tfelt-Hansen, 1984	Migraine	96	40 wks	NS												42.0%	46.0%
Worz, 1991	Migraine	78	12 wks	NS		29.5%	23.1%										
*Kangasniemi, 1984	Migraine	35	8 wks	NS			57.1%									68.6%	
							45.7%									48.6%	
*Olsson, 1984	Migraine	53	8 wks	NS			58.5%									58.5%	
							56.6%									58.5%	
Dahlof, 1988	Hypertension	74	6 wks	NS	NR		NR										
Walle, 1994	Hypertension	58	6 wks	NS	NR		NR										
Buhler, 1986	Hypertension	104	8 wks	NS	NR	NR											
Steiner, 1990	Hypertension	151	4 wks	NS	55.6%											64.0%	
BRADYCARDIA INCIDENCE																	
Metra, 2000	Heart failure	122	44 mos	NS			2.7%				4.0%						
Dahlof, 1988	Hypertension	74	6 wks	NS	NR		NR										
Walle, 1994	Hypertension	58	6 wks	NR	3.3%		0.0%										
Steiner, 1990	Hypertension	151	4 wks	NS	10.0%											4.5%	
DIZZINESS INCIDENCE																	
van der Does, 1999	Angina	368	3 mos	NS			5.0%				4.8%						
Metra, 2000	Heart failure	122	44 mos	0.0046			1.3%				14.7%						
Stensrud, 1980	Migraine	28	6 wks	NS	0.0%											3.6%	
Tfelt-Hansen, 1984	Migraine	96	40 wks	NS												5.0%	6.0%
Worz, 1991	Migraine	78	12 wks	NS		10.2%	5.1%										
Buhler, 1986	Hypertension	104	8 wks	NS	2.9%	6.7%											

Evidence Table 11. Safety of all head to head trials of beta blockers

Trial	Indication	Sample size	Duration	p-value	*Selective beta blockers*				*Non-selective beta blockers*								
					ate	bis	met	bet	ace	cart	carv	lab	nad	pen	pin	pro	tim
HYPOTENSION INCIDENCE																	
Metra, 2000	Heart failure	122	44 mos	NS			2.7%				2.7%						
WITHDRAWALS DUE TO ADVERSE EVENTS																	
Lithell, 1987	Hypertension	292	6 mos	NS	2.1%	4.1%											
Colombo, 1989	Bleeding esophageal varices	94	357 days	NS	12.5%											0.0%	
Katritsis, 2003	Atrial arrhythmias	90	12 mos	NS		6.4%					4.7%						
Tfelt-Hansen, 1984	Migraine	96	40 wks	NS												5.6%	10.1%
Waagstein, 2003	Heart failure	172	6 mos	NS			11.6%										
Worz, 1991	Migraine	78	12 wks	NS		10.20%	6.40%										
Dahlof, 1988	Hypertension	74	6 wks	NS	NR		NR										
Walle, 1994	Hypertension	58	6 wks	NR	3.3%		0.0%										
Buhler, 1986	Hypertension	104	8 wks	NS	0.9%	4.8%											
Steiner, 1990	Hypertension	151	4 wks	NS	0.0%											6.9%	

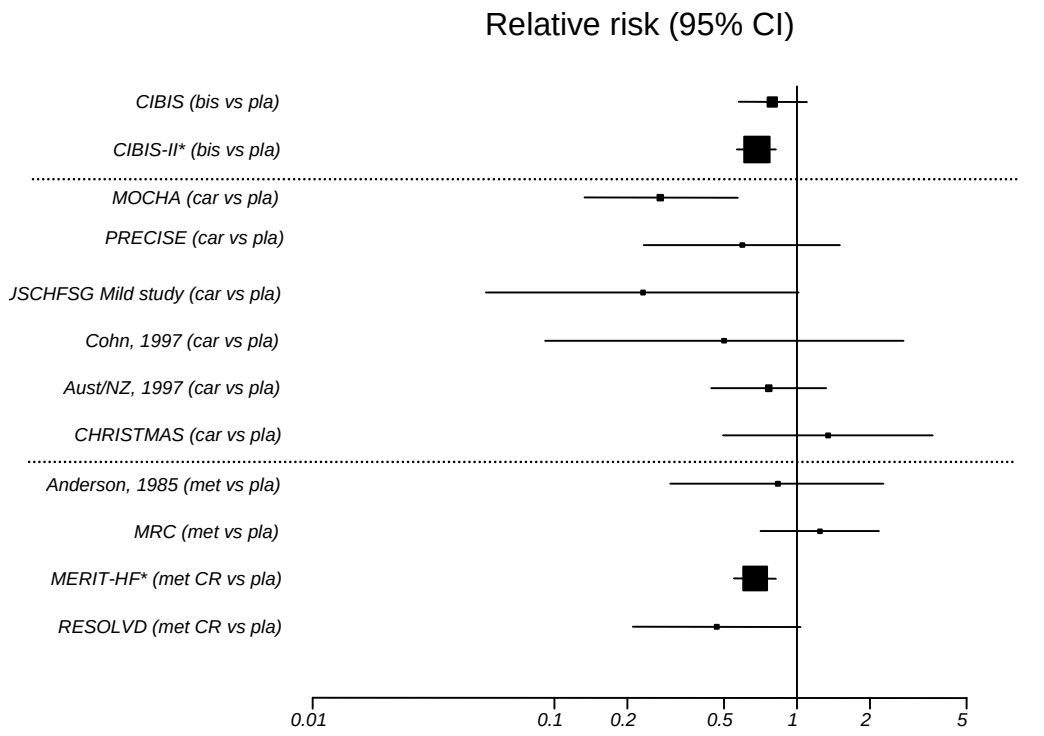
**Values represent rates from first and second months of treatment, separately*

Figure 1. Total mortality in patients following myocardial infarction



** Patients post-myocardial infarction complicated with left ventricular dysfunction, with or without symptoms of heart failure and with adjuvant therapy including ACE-inhibition, anti-platelet therapy, and potential to use a revascularization strategy.

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



*Trials with significant findings that analyzed all-cause mortality as primary endpoint
bis=bisoprolol, car=carvedilol, met=metoprolol tartrate, met CR=metoprolol succinate, pla=placebo

Appendix A. Search Strategy

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

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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 Arrythmia.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$.mp. or exp Randomized Controlled Trials/
17 16 and 17
18 from 18 keep 1-8
19 from 19 keep 1-8
20 from 20 keep 1-8
21 atenolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
22 bisoprolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
23 carteolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
24 carvedilol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
25 labetolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
26 metoprolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
27 nadolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
28 pindolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
29 penbutolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
30 propranolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
31 4 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
32 14 and 32
33 limit 33 to (human and english language) [Limit not valid; records were retained]
34 randomized controlled trial$.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 Arrythmia.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$.mp. or exp Randomized Controlled Trials
18 16 and 17
19 from 18 keep 1-8
20 from 19 keep 1-8
21 from 20 keep 1-8
22 atenolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
23 bisoprolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
24 carteolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
25 carvedilol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
26 labetolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
27 metoprolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
28 nadolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
29 pindolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
30 penbutolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
31 propranolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
32 4 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33 14 and 32
34 limit 33 to (human and english language)
35 randomized controlled trial$.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 Arrythmia.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$.mp. or exp Randomized Controlled Trials
18 16 and 17
19 [from 18 keep 1-8]
20 [from 19 keep 1-8]
21 [from 20 keep 1-8]
22 atenolol.mp. [mp=title, abstract]
23 bisoprolol.mp. [mp=title, abstract]
24 carteolol.mp. [mp=title, abstract]
25 carvedilol.mp. [mp=title, abstract]
26 labetolol.mp. [mp=title, abstract]
27 metoprolol.mp. [mp=title, abstract]
28 nadolol.mp. [mp=title, abstract]
29 pindolol.mp. [mp=title, abstract]
30 penbutolol.mp. [mp=title, abstract]
31 propranolol.mp. [mp=title, abstract]
32 4 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33 14 and 32
34 randomized controlled trial$.mp. or exp Randomized Controlled Trials

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Database: Embase <1980-January 27, 2005>
Search Strategy: Not available

Appendix B. 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 ascertainer; validation of ascertainment technique)?

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

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

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 C. List of included studies

Hypertension - 3

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=5

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=1
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=1
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=1
(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=1
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.

Placebo-controlled trials=15
- Acebutolol=1
  - 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=2
  - 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=5

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=1

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=4

MILIS

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