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

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

Evidence Table 1a. Qu**Evidence Table 1a. Quality assessments of placebo controlled trials of beta blockers for hyperte**

Author, Year Country	Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)*	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
Perez-Stable, 2000	Perez-Stable, 2000	Concomitant use of insulin, bronchodilators, antidepressants or antihypertensive medications within 1 month of screening; coronary artery disease, valcular heart disease, renal insufficiency, cerebrovascular disease, and secondary causes of hypertension	Yes	NR	Yes
Anonymous, 1977 Greenberg, 1984 Anonymous, 1985 Miall, 1987 Anonymous, 1988a Anonymous, 1988b Anonymous, 1992 Lever, 1993 Medical Research Council (MRC) UK	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

Evidence Table 1a. Quansion (continued)

Author, Year Country	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)*	Yes	No
Perez-Stable, 2000	Yes	No
Anonymous, 1977 Greenberg, 1984 Anonymous, 1985 Miall, 1987 Anonymous, 1988a Anonymous, 1988b Anonymous, 1992 Lever, 1993 Medical Research Council (MRC) UK	Yes	Yes

Evidence Table 1a. Quality assessments of placebo controll

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination
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
Perez-Stable, 2000	NR	45% attrition; others NR
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

Evidence Table 1a. Quided trials of beta blockers for hypertension (continued)

Author, Year Country	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)*	None	Fair	ICI Pharmaceuticals; A.H Robins; National Heart, Lung and Blood Institute	Yes	6 months
Perez-Stable, 2000	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	Fair	Duncan, Flockhart and Co Ltd; Imperial Chemical Industries Ltd; CIBA Laboratories; Merck Sharp and Dohme Ltd	Yes	5 years

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

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

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

Author, Year Country	Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Frishman 1989 United States	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
van der Does 1999 Europe	van der Does 1999 Europe	Contraindications to study drugs or exercise testing; other forms of angina pectoris (vasospastic, unstable); myocardial infarction or cardiac surgery within 3 months; main stem steNosis; ventricular aneurysm; marked left ventricular hypertrophy; hypertrophic subaortic steNosis; hemodynamically relevant valcular defects; decompensated cardiac failure; orthostasis; phlebothrombosis; disorders of impulse formation/conduction (e.g., resting heart rate <45 beats/min, bundle brach block, pacemaker); obstructive airways disease; insulin-dependent diabetes mellitus; relevant hepatic impairment; gross obesity; alcohol or drug abuse; epilepsy; concomitant drugs interfering with the study objectives (e.g., other antianginal agents); participation in another clinical study within 30 days	Yes	Yes	Yes	Yes
Dorow 1990	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

Evidence Table

Author, Year Country	Intention-to-treat (ITT) analysis
Frishman 1989 United States	No
van der Does 1999 Europe	No
Dorow 1990	Yes

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

Author, Year Country	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
Frishman 1989 United States	Frishman 1989 United States	NR	Attrition reported; other nr	No	Poor	In part by Schering-Plough	Yes
van der Does 1999 Europe	van der Does 1999 Europe	NR	Attrition reported; other nr	NR	Fair	Boehringer Mannheim	Yes
Dorow 1990	Dorow 1990	N/A	Attrition and compliance reported; others nr	None	Fair	NR	Yes

Evidence Table 1d)

Author, Year Country	Length of follow-up
Frishman 1989 United States	4 months
van der Does 1999 Europe	3 months
Dorow 1990	1 year

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

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

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

Author, Year Country	Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Frishman 1979 United States	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
Chieffo 1986 Italy	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
Placebo controlle	***Placebo controlled trials***					
Destors 1989 Europe	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

Evidence Table
Evidence Table

Author, Year Country	Intention-to-treat (ITT) analysis
Frishman 1979 United States	Yes
Chieffo 1986 Italy	Yes
Placebo controlled	
Destors 1989 Europe	Yes

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

Author, Year Country	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
Frishman 1979 United States	Frishman 1979 United States	NR	NR	NR	Fair	Sandoz, Inc.	Yes
Chieffo 1986 Italy	Chieffo 1986 Italy	NR	NR	NR	Fair	NR	Yes
Placebo controlle	***Placebo controlled trials***						
Destors 1989 Europe	Destors 1989 Europe	NR	Attrition and compliance reported; others nr	7.8% at week 24	Fair	NR	Yes

Evidence Table d)
Evidence Table d)

Author, Year Country	Length of follow-up
Frishman 1979 United States	8 weeks
Chieffo 1986 Italy	8 weeks
Placebo controlle	
Destors 1989 Europe	24 weeks

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

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

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

Author Year Country	Author Year Country	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Placebo control	***Placebo controlled trials of metoprolol in patients with severe angina post-CABG***				
Anonymous (MACB Study Group) 1995 Sweden *Fair quality*	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	<u>*Previous history of(%):*</u> 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*	Sjoland 1995 Sweden *Poor quality*	Calcium antagonixts, long-acting nitrates, diuretics for heart failure, digitalis, other treatment for heart failure, antihypertensives, antiarrhythmics, acetylsalicylic acid, anticoagulation	Exercise test after 2 years	Mean age <u>></u> 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. Placebo controlled trials of beta blockers for coronary artery bypass graft (conti

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

Evidence Tanued)

Author Year Country	Withdrawals due to adverse events (%, adverse n/enrolled n)
Placebo control	
Anonymous (MACB Study Group) 1995 Sweden *Fair quality*	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*	NR

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

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

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

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

Evidence Tal **Evidence Table 4. Placebo controlled trials of beta blockers for coronary artery dis**

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Author, Year Country	Outcomes	Method of adverse effects assessment?
Pepine 1994 USA *Good quality*	NR/NR/306	Pepine 1994 USA *Good quality*	(1) any events: ate = 17/152 (11%) pla = 39/154 (25%) - ate/pla RR 0.44, CI 0.26-0.75, p = 0.001 (2) serious events (death, VT/VF, MI or hospitalization): ate = 7/152 (4.6%) pla = 13/154 (8.4%) - ate/pla RR 0.55, CI 0.22-1.33 (NS) (2a) death or resuscitated VT/VF: ate = 1/152 (0.65%) pla = 4/154 (2.6%) (NS) (3) Aggravation of angina: ate = 9/152 (5.9%) pla = 26/154 (16.9%) - ate/pla RR 0.35, CI 0.17-0.72, p=.003 (4) Revascularization: ate = 1/152 pla = 0/154 (NS)	NR

Evidence Talease (continued)

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Pepine 1994 USA *Good quality*	Titrated to 50 mg:ate = 36/152 (23.7%) pla = 19/154 (12.3%) bradycardia: ate = 10/152 (6.6%) pla = 0, p=0.001	NR

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

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

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

Author, Year Country	Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Head to head trials of beta b	***Head to head trials of beta blockers***				
Wilcox 1980 UK	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
Placebo- and "no treatment'	***Placebo- and "no treatment" controlled trials of atenolol***				
Anonymous, 1986 Sleight, 1987 Anonymous, 1988	Anonymous, 1986 Sleight, 1987 Anonymous, 1988		Yes	unclear	No
First International Study of Infarct Survival (ISIS-1)	*First International Study of Infarct Survival (ISIS-1)*				
Placebo controlled trials of c	***Placebo controlled trials of carvedilol***				
Basu 1997 UK	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

Evidence Table 5a. Qu

Author, Year Country	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Head to head trials of beta b		
Wilcox 1980 UK	Yes	Yes
Placebo- and "no treatment'		
Anonymous, 1986 Sleight, 1987 Anonymous, 1988 *First International Study of Infarct Survival (ISIS-1)*	NO	Yes
Placebo controlled trials of c		
Basu 1997 UK	Yes	Yes

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

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score
Head to head trials of beta blockers				
Wilcox 1980 UK	NR	Attrition=44.1%; others NR	NR	Fair
Placebo- and "no treatment" controlled trials of atenolol				
Anonymous, 1986 Sleight, 1987 Anonymous, 1988 *First International Study of Infarct Survival (ISIS-1)*	NR	Attrition=0.7%; others NR	NR	Fair
Placebo controlled trials of carvedilol				
Basu 1997 UK	NR	NR	None	Fair

Evidence Table 5a. Qu r post myocardial

Author, Year Country	Funding	Control group standard of care	Length of follow-up
Head to head trials of beta b			
Wilcox 1980 UK	Imperial Chemical Industries Ltd.	Yes	1 year
Placebo- and "no treatment'			
Anonymous, 1986 Sleight, 1987 Anonymous, 1988	ICI Pharmaceuticals	Yes	7-day treatment period, with 1-year follow-up
First International Study of Infarct Survival (ISIS-1)			
Placebo controlled trials of c			
Basu 1997 UK	NPH Cardiac Research Fund; Boehringer Mannheim GmbH	Yes	6 months

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

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

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

Author, Year Country	Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Anonymous, 2001 *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)*	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
Placebo controlled trials of i	***Placebo controlled trials of metoprolol***				
Anonymous, 1985 Herlitz, 1990 Hjalmarson, 1997 International *MIAMI* Fair quality	Anonymous, 1985 Herlitz, 1990 Hjalmarson, 1997 International *MIAMI* Fair quality	Current treatment with beta blockers or calcium channel blockres (within 48 hours); heart rate ≤65 beats/minute; Systolic BP ≤105 mm Hg; left ventricular failure; poor peripheral circulation; AV-conduction disturbance; severe chronic obstructive pulmonary disease; implanted pacemaker; resuscitation outside hospital; other serious disease; previous MIAMI participation; participation in other randomized trials; unwilling or unable to give informed consent	Yes	Yes	Yes
Anonymous 1987 USA *Lopressor Intervention Trial*	Anonymous 1987 USA *Lopressor Intervention Trial*		Yes	Yes	Yes

Evidence Table 5a. Qu

Evidence Table 5a. Qu

Evidence Table 5a. Quality assessments of controlled trials of beta blockers fo

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

Author, Year Country	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Anonymous, 2001	Yes	Yes
Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)		
Placebo controlled trials of		
Anonymous, 1985 Herlitz, 1990 Hjalmarson, 1997 International	Yes	Yes
MIAMI		
Fair quality		
Anonymous 1987 USA	Yes	Yes
Lopressor Intervention Trial		

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score
Anonymous, 2001	NR	NR	NR	Fair
Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)				
Placebo controlled trials of metoprolol				
Anonymous, 1985 Herlitz, 1990 Hjalmarson, 1997 International	NR			Fair
MIAMI				
Fair quality				
Anonymous 1987 USA	NR	Attrition=30.7%; others NR	NR	Fair
Lopressor Intervention Trial				

Evidence Table 5a. Qu»r post myocardial
Evidence Table 5a. Qu»r post myocardial

Author, Year Country	Funding	Control group standard of care	Length of follow-up
Anonymous, 2001	GSK	Yes	mean of 1.3 years
Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)			
Placebo controlled trials of i			
Anonymous, 1985 Herlitz, 1990 Hjalmarson, 1997 International	AB Hassle, a subsidiary of Astra Pharmaceutical	Yes	1 year
MIAMI			
Fair quality			
Anonymous 1987 USA	CIBA-GEIGY	Yes	1.5 years
Lopressor Intervention Trial			

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

Herlitz, 1984 Herlitz, 1997 Sweden	Adequate; computer-generated randomization lists in blocks of 10	NR	Yes	Mean age=60 75.5% male	1395 randomized

Goteborg Metoprolol Trial

Fair quality

Evidence Table 5a. Qu	Evidence Table 5a. Quality assessments of controlled trials of beta blockers for post myocardial				
Herlitz, 1984 Herlitz, 1997 Sweden	Herlitz, 1984 Herlitz, 1997 Sweden	Contraindications to beta blockade; need for beta blockade; administrative considerations	Yes	Yes	Yes
Goteborg Metoprolol Trial	*Goteborg Metoprolol Trial*				
Fair quality	Fair quality				

Evidence Table 5a. Qu

Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* Fair quality	Yes	Yes

Evidence Table 5a. Quality assessments of controlled trials of beta blockers fo

Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* Fair quality	NR	Good

Evidence Table 5a. Qu»r post myocardial

Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* Fair quality	NR	Yes	1 year

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

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

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

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

infarction (continued)

Author, Year Country	Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Olsson, 1985 *Stockholm Metoprolol Trial*	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
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* Fair quality	Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* Fair quality		Yes	Yes	Yes
Placebo controlled pindolol	***Placebo controlled pindolol studies***				
Australian & Swedish Study 1983 Australia, Sweden	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

Evidence Table 5a. Qu

Evidence Table 5a. Qu

Evidence Table 5a. Quality assessments of controlled trials of beta blockers fo

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

Author, Year Country	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score
Olsson, 1985	Yes	Yes	Olsson, 1985	NR	Attrition=24.2%; others NR	NR	Fair
Stockholm Metoprolol Trial			*Stockholm Metoprolol Trial*				
Salathia 1985 Northern Ireland	Yes	Yes	Salathia 1985 Northern Ireland	NR	NR	NR	Fair
Belfast Metoprolol Trial			*Belfast Metoprolol Trial*				
Fair quality			Fair quality				
Placebo controlled pindolol			***Placebo controlled pindolol studies***				
Australian & Swedish Study 1983 Australia, Sweden	Yes	Yes	Australian & Swedish Study 1983 Australia, Sweden	NR	Attrition=23.8%; Compliance=54% took 90% or more	NR	Fair

Evidence Table 5a. Qur post myocardial
Evidence Table 5a. Qur post myocardial

Author, Year Country	Funding	Control group standard of care	Length of follow-up
Olsson, 1985	AB Hassle	Yes	3 years
Stockholm Metoprolol Trial			
Salathia 1985 Northern Ireland	Astra Pharmaceuticals	Yes	1 year
Belfast Metoprolol Trial			
Fair quality			
Placebo controlled pindolol			
Australian & Swedish Study 1983 Australia, Sweden	Sandoz Ltd.	Yes	24 months

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

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

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

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

infarction (continued)

Author, Year Country	Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Placebo controlled propranc	***Placebo controlled propranolol studies***				
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States	Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States	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
Beta-blocker Heart Attack Trial (BHAT)	*Beta-blocker Heart Attack Trial (BHAT)*				
Robert, 1984 Rude, 1986 Roberts, 1988 United States	Robert, 1984 Rude, 1986 Roberts, 1988 United States	Cardiogenic shock; advanced cardiac or other disease that would interfere with prognosis; participation in conflicting protocol; inability to particpate because of geographical or psychological reasons; recent major surgery or MI; permanent cardian pacemaker; previous participation in the protocol; failure or inability to give informed consent	Yes	NR	Yes
Multicenter Investigation of the Limitation of Infarct Size (MILIS)	*Multicenter Investigation of the Limitation of Infarct Size (MILIS)*				
Fair quality	Fair quality				
Balcon, 1966	Balcon, 1966	Complete heart block complicating an acute myocardial infarction; unconscious	Yes	NR	Yes

Evidence Table 5a. Qu

Evidence Table 5a. Qu

Evidence Table 5a. Quality assessments of controlled trials of beta blockers fo

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

Author, Year Country	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score
Placebo controlled propranc			***Placebo controlled propranolol studies***				
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States	Yes	Yes	Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States	NR	NR	Lost to fu: pro=4(0.2%); pla=8(0.4%)	Fair
Beta-blocker Heart Attack Trial (BHAT)			*Beta-blocker Heart Attack Trial (BHAT)*				
Robert, 1984 Rude, 1986 Roberts, 1988 United States	Yes	Yes	Robert, 1984 Rude, 1986 Roberts, 1988 United States	NR	NR	1(0.4%) lost to fu (treatment group NR)	Fair-Poor
Multicenter Investigation of the Limitation of Infarct Size (MILIS)			*Multicenter Investigation of the Limitation of Infarct Size (MILIS)*				
Fair quality			Fair quality				
Balcon, 1966	Yes	Yes	Balcon, 1966	NR	Attrition=4.4%	NR	Fair

Evidence Table 5a. Qu»r post myocardial
Evidence Table 5a. Qu»r post myocardial

Author, Year Country	Funding	Control group standard of care	Length of follow-up
Placebo controlled propranc			
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States	National Heart, Lung, and Blood Institute	Yes	mean of 25 months
Beta-blocker Heart Attack Trial (BHAT)			
Robert, 1984 Rude, 1986 Roberts, 1988 United States	Ayerst Laboratories donated propranolol	Yes	36 months
Multicenter Investigation of the Limitation of Infarct Size (MILIS)			
Fair quality			
Balcon, 1966	ICI Pharmaceuticals	Yes	28 days

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

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

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

Author, Year Country	Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Bath, 1966	Bath, 1966	Diagnostic criteria not fulfilled; there was evidence of bronchospasm or a clinical history of bronchial asthma; the heart-rate was less than 60 per minute persisting throughout a 24-hour period; systolic blood-pressure was less than 80 mm Hg after admission	Yes	NR	Yes
Norris, 1968	Norris, 1968	Shock, heart failure, heart block, sinus bradycardia; acute pulmonary edema; systolic blood pressure below 80 mm Hg	Yes	NR	Yes
Hansteen 1982 Norway	Hansteen 1982 Norway	Cotraindications to beta blockade; uncontrolled heart failure	Yes	NR	Yes
Baber 1980 Multinational	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

Evidence Table 5a. Qu

Evidence Table 5a. Qu

Author, Year Country	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Bath, 1966	Yes	No
Norris, 1968	Yes	Yes
Hansteen 1982 Norway	Yes	Yes
Baber 1980 Multinational	Yes	Yes

Evidence Table 5a. Quality assessments of controlled trials of beta blockers fo

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

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score
Bath, 1966	NR	Attrition=13.7%	NR	Fair
Norris, 1968	NR	Attrition=7.9%	NR	Fair
Hansteen 1982 Norway	NR	Attrition=25.3%; Compliance(% taken > 95%): 80	NR	Fair
Baber 1980 Multinational	NR	Attrition=23.5%; others NR	NR	Fair

Evidence Table 5a. Qur post myocardial
Evidence Table 5a. Qur post myocardial

Author, Year Country	Funding	Control group standard of care	Length of follow-up
Bath, 1966	ICI Pharmaceuticals	Yes	28 days
Norris, 1968	ICI Pharmaceuticals	Yes	3 weeks
Hansteen 1982 Norway	Imperial Chemical Industries Ltd.	Yes	12 months
Baber 1980 Multinational	ICI Pharmaceuticals	Yes	9 months

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

Trials included in our evidence tables are in bold.

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

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

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

Trials included in our evidence tables are in bold.

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

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

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

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

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

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

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

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

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

Author, Year Country	Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Anonymous 1994 The Cardiac Insufficiency Bisoprolol Study (CIBIS I) Fair quality	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
Anonymous 1999 The Cardiac Insufficiency Bisoprolol Study (CIBIS II)	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

Evidence Table 8ɑd) **Evidence Table 8a. Quality assessments of placebo controlled trials of beta blc**

Author, Year Country	Intention-to-treat (ITT) analysis	Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score
Anonymous 1994 The Cardiac Insufficiency Bisoprolol Study (CIBIS I) Fair quality	Yes	Anonymous 1994 The Cardiac Insufficiency Bisoprolol Study (CIBIS I) Fair quality	Yes	Attrition=157/641 (24.5%); others NR	No	Fair
Anonymous 1999 The Cardiac Insufficiency Bisoprolol Study (CIBIS II)	Yes	Anonymous 1999 The Cardiac Insufficiency Bisoprolol Study (CIBIS II)	Yes	Attrition=69/2647 (2.6%); others NR	No	Good

Evidence Table 8. Beta-blockers for heart failure (continued)

Author, Year Country	Funding	Control group standard of care	Length of follow-up
Anonymous 1994 The Cardiac Insufficiency Bisoprolol Study (CIBIS I) Fair quality	NR	Yes	Mean 1.9 years
Anonymous 1999 The Cardiac Insufficiency Bisoprolol Study (CIBIS II)	NR	Yes	Mean 1.3 years

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

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

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

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

Evidence Table 8ad) **Evidence Table 8a. Quality assessments of placebo controlled trials of beta blc**

Evidence Table 8ad) **Evidence Table 8a. Quality assessments of placebo controlled trials of beta blc**

Author, Year Country	Intention-to-treat (ITT) analysis	Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score
MOCHA	Unclear	MOCHA	NR	Attrition=52/345 (15%); others NR	No	Fair
Bristow1996 Lindenfeld2001		Bristow1996 Lindenfeld2001				
Multicenter Oral Carvedilol Heart Failure Assessment		Multicenter Oral Carvedilol Heart Failure Assessment				

Evidence Table 8›ckers for heart failure (continued)

Evidence Table 8›ckers for heart failure (continued)

Author, Year Country	Funding	Control group standard of care	Length of follow-up
MOCHA Bristow1996 Lindenfeld2001 Multicenter Oral Carvedilol Heart Failure Assessment	SmithKline Beecham Pharmaceuticals	NR	6 months

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

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
PRECISE Packer1996	NR	NR	Yes	Mean age: 60.3 years Male: 73% Ethnicity: NR	Screened: NR Eligible for run-in: 301 Enrolled: 278

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

Author, Year Country	Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
PRECISE	PRECISE	Uncorrected primary valvular disease, active myocarditis or obstructive or restrictive cardiomyopathy; MI, stroke,	Yes	NR	NR	NR
Packer1996	Packer1996	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 8ad) **Evidence Table 8a. Quality assessments of placebo controlled trials of beta blo**

Evidence Table 8ad) **Evidence Table 8a. Quality assessments of placebo controlled trials of beta blo**

Author, Year Country	Intention-to-treat (ITT) analysis	Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score
PRECISE Packer1996	Unclear	PRECISE Packer1996	NR	Attrition=49/278 (18%); others NR	No	Fair

Evidence Table 8›ckers for heart failure (continued)

Evidence Table 8›ckers for heart failure (continued)

Author, Year Country	Funding	Control group standard of care	Length of follow-up
PRECISE Packer1996	SmithKline Beecham Pharmaceuticals & Boehringer Mannheim Therapeutics	NR	6 months

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

Colucci 1996 U.S. Carvedilol Heart Failure Study Group	NR	NR	Yes	Mean age: 55 Male: 85% Ethnicity: NR	Screened: NR Eligible for run-in: 389 Enrolled: 366

Evidence Table 8

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

Colucci 1996 U.S. Carvedilol Heart Failure Study Group	Colucci 1996 U.S. Carvedilol Heart Failure Study Group	Uncorrected primary valvular disease, nondilated or hypertrophic cardiomyopathy; MI, stroke, unstable angina or CABG within 3 months; symptomatic or sustained ventricular tachycardia not controlled by antiarrhythmic drugs or implantable defibrillator within 3 months; likelihood of revascularization or transplantation within 12 months; sick sinus syndrome or advanced heart block (without pacemaker); any condition other than heart failure that could limit exercise; systolic blood pressure >160 or <85 mm Hg or diastolic blood pressure >100 mm Hg; clinically significant hepatic or renal disease, or any condition that could limit survival. Patients receiving amiodarone within 3 months before screening.	Yes	NR	NR	NR

Evidence Table 8ad)

Colucci 1996 U.S. Carvedilol Heart Failure Study Group	Yes	Colucci 1996 U.S. Carvedilol Heart Failure Study Group	NR	Attrition=31(8.5%); others NR	NR	Fair

Evidence Table 8a. Quality assessments of placebo controlled trials of beta blc

Evidence Table 8. Beta-blockers for heart failure (continued)

Colucci 1996 U.S. Carvedilol Heart Failure Study Group	SmithKline Beecham Pharmaceuticals & Boehringer Mannheim Therapeutics	NR	Mean 7 months

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

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

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

Author, Year Country	Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group*	Cohn 1997 *U.S. Carvedilol Heart Failure Study Group*	Uncorrected primary valvular disease, nondilated or hypertrophic cardiomyopathy; MI, stroke, unstable angina or CABG within 3 months; symptomatic or sustained ventricular tachycardia not controlled by antiarrhythmic drugs or implantable defibrillator within 3 months; likelihood heart transplantation within 6 months; sick sinus syndrome or advanced heart block without pacemaker; any condition other than heart failure that could limit exercise; systolic blood pressure >160 or <85 mm Hg or diastolic blood pressure >100 mm Hg; clinically significant hepatic or renal disease, or any condition that could limit survival.	Yes	NR	NR	NR
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group*	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

Evidence Table 8ad) **Evidence Table 8a. Quality assessments of placebo controlled trials of beta blo**

Evidence Table 8ad) **Evidence Table 8a. Quality assessments of placebo controlled trials of beta blo**

Author, Year Country	Intention-to-treat (ITT) analysis	Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group*	No	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
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group*	Yes	Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group*	NR	Attrition=14.9%; others NR	NR	Good

Evidence Table 8›ckers for heart failure (continued)
Evidence Table 8›ckers for heart failure (continued)

Author, Year Country	Funding	Control group standard of care	Length of follow-up
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group*	SmithKline Beecham Pharmaceuticals & Boehringer Mannheim Therapeutics	NR	Mean 3 months
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group*	SmithKline Beecham - independently initiated conducted, analyzed by ANZ Heart Failure Research Collaborative	Yes	Mean 19 months

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

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

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

Author, Year Country	Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Cleland, 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)*	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
COPERNICUS Eichhorn, 2001 Packer, 2001 Packer, 2002 Krum, 2003	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

Evidence Table 8ød) **Evidence Table 8a. Quality assessments of placebo controlled trials of beta blo**

Evidence Table 8ød) **Evidence Table 8a. Quality assessments of placebo controlled trials of beta blo**

Author, Year Country	Intention-to-treat (ITT) analysis	Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score
Cleland, 2003	No	Cleland, 2003	Unclear	Attrition=21.2%; others nr	nr	Fair
Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)		*Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)*				
COPERNICUS Eichhorn, 2001 Packer, 2001 Packer, 2002 Krum, 2003	Yes	COPERNICUS Eichhorn, 2001 Packer, 2001 Packer, 2002 Krum, 2003	NR	attrition reported; others NR	None	Fair

Evidence Table 8›ckers for heart failure (continued)

Evidence Table 8›ckers for heart failure (continued)

Author, Year Country	Funding	Control group standard of care	Length of follow-up
Cleland, 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)*	Hoffman-La Roche	Yes	189 days (mean)
COPERNICUS Eichhorn, 2001 Packer, 2001 Packer, 2002 Krum, 2003	Roche; GlaxoSmithKline	Yes	Mean 10.4 months

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

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

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

Author, Year Country	Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Packer, 1996 Colucci, 1996 Yancy, 2001 *U.S. Carvedilol Heart Failure Study Group*	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
Anderson 1985	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
Waagstein 1993	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

Evidence Table 8ad) **Evidence Table 8a. Quality assessments of placebo controlled trials of beta blo**

Evidence Table 8ad) **Evidence Table 8a. Quality assessments of placebo controlled trials of beta blo**

Author, Year Country	Intention-to-treat (ITT) analysis	Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score
Packer, 1996 Colucci, 1996 Yancy, 2001 *U.S. Carvedilol Heart Failure Study Group*	Yes	Packer, 1996 Colucci, 1996 Yancy, 2001 *U.S. Carvedilol Heart Failure Study Group*	NR	AE withdrawals reported; others NR	none	fair
Anderson 1985	Yes	Anderson 1985	NR	Attrition=5/50(10%); others NR	No	Fair
Waagstein 1993	Yes for primary endpoint Nor for other	Waagstein 1993	NR	Attrition=14.1%; others NR	High loss for secondary endpoints except hospitalization.	Fair

Evidence Table 8›ckers for heart failure (continued)
Evidence Table 8›ckers for heart failure (continued)

Author, Year Country	Funding	Control group standard of care	Length of follow-up
Packer, 1996 Colucci, 1996 Yancy, 2001 *U.S. Carvedilol Heart Failure Study Group*	SmithKline Beecham Pharmaceuticals and Roche Laboratories Two investigators/authors are employees and stock holders of SKB	Yes	12 months
Anderson 1985	Univ. of Utah SOM and LDS Hospital, Salt Lake City	NR	Mean 19 months
Waagstein 1993	Astra Pharmaceutical divisions and Ciba-Geigy Corp., Swedish Heart & Lung Foundation & Swedish Medical Research Council	NR	12 months and 18 months (n=211/383)

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

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

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

Author, Year Country	Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
MERIT-HF	MERIT-HF	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
Anonymous, 1999 Goldstein, 1999 Hjalmarson, 2000 Goldstein, 2001 Ghali, 2002 Gottlieb, 2002 Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure	Anonymous, 1999 Goldstein, 1999 Hjalmarson, 2000 Goldstein, 2001 Ghali, 2002 Gottlieb, 2002 Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure					
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)*	Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)*	nr	yes	yes	yes	yes

Evidence Table 8ad) **Evidence Table 8a. Quality assessments of placebo controlled trials of beta blo**

Evidence Table 8ad) **Evidence Table 8a. Quality assessments of placebo controlled trials of beta blo**

Author, Year Country	Intention-to-treat (ITT) analysis	Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score
MERIT-HF Anonymous, 1999 Goldstein, 1999 Hjalmarson, 2000 Goldstein, 2001 Ghali, 2002 Gottlieb, 2002 Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure	Yes	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
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)*	yes	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

Evidence Table 8›ckers for heart failure (continued)

Evidence Table 8›ckers for heart failure (continued)

Author, Year Country	Funding	Control group standard of care	Length of follow-up
MERIT-HF Anonymous, 1999 Goldstein, 1999 Hjalmarson, 2000 Goldstein, 2001 Ghali, 2002 Gottlieb, 2002 Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure	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	yes	24 weeks

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

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

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

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

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

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

Evidence Tab

Study, year	Overall quality
Trials of bisopro	
Anonymous 1994 *CIBIS*	Fair
Anonymous 1999 *CIBIS-II*	Good
Trials of bucindo	
Anonymous 2001 *BEST*	
Trials of carvedi	
Bristow 1996 *US Carvedilol Heart Failure Study Group: MOCHA*	Fair

*Odds ratios (95% CI

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

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

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

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

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

Evidence Tab
Evidence Tab

Study, year	Overall quality
Packer 1996 *US Carvedilol Heart Failure Study Group: PRECISE*	Fair
Colucci 1996 *US Carvedilol Heart Failure Study Group: Mild*	Fair
Cohn 1997 US Carvedilol Heart Failure Study Group	Poor
Anonymous 1997 *Australia/New Zealand Heart Failure Research Collaborative Group*	Good

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

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

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

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

Evidence Tab

*Odds ratios (95% CI

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

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

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

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

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

Evidence Tab
Evidence Tab

Study, year	Overall quality
Packer 2001	Fair
COPERNICUS	
Cleland 2003	Fair
CHRISTMAS	
Trials of metopr	
Anderson 1985	Fair
Waagstein 1993	Fair
MDC	

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

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

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

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

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

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

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

Evidence Tab
Evidence Tab

Study, year	Overall quality
Anonymous 1999 *MERIT-HF*	Good
Anonymous 2000 *RESOLVD*	Fair

*Odds ratios (95% CI

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

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

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

Author, Year Country	Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Sanderson 1999 China	Sanderson 1999 China	Valvular heart disease as the etiology of LV dysfunction, active myocarditis, unstable angina, a documented history of sustained ventricular tachycardia or symptomatic nonsustained ventricular tachycardia or second- or third degree atrioventricular block; chronic obstructive lung diseases, asthma, long-term alcohol or drug abuse or chronic renal failure (serum creatine >200 μmol/liter), hepatic hematological, neurological or collagen vascular disease	Yes	Yes	Yes	Yes
Kukin 1999	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
Metra 2000	Metra 2000	Unstable angina,acute myoardial infarction, or a coronary revascularization procedure within 3 months; history of alcohol abuse; primary valve disease; congenital heart disease; systolic blood pressure <90 mm Hg; concomitant disease that might adversely influence prognosis or impair exercise capacity; contraindications to b-blocker therapy; concomitant treatment with other β-blockers, α-antagonists, calcium antagonists or antiarrhythmic agents (except amiodarone)	Yes	Yes	Yes	Yes

Evidence Table **Evidence Table 10a. Quality assessments of head to head trials of beta**

Author, Year Country	Intention-to-treat (ITT) analysis	Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score
Sanderson 1999 China	Unclear	Sanderson 1999 China	Unclear	Attrition reported; Others NR	NR	Fair
Kukin 1999	No	Kukin 1999	NR	Attrition reported; Others NR	None	Fair
Metra 2000	No	Metra 2000	NR	Attrition reported; Others NR	None	Fair

Evidence Table blockers for heart failure (continued)

Author, Year Country	Funding	Control group standard of care	Length of follow-up
Sanderson 1999 China	NR	Yes	12 weeks
Kukin 1999	SKB	Yes	6 months
Metra 2000	CARIPLO funds University of Brescia	Yes	44 months

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

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

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

Author, Year Country	Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Metra 2000 US, Italy	Metra 2000 US, Italy	Patients with an acute ischemic event or a coronary revascularization procedure within 3 months; a history of alcohol abuse; primary valve disease or congenital heart disease; frequent ventricular premature beats and/or runs of ventricular tachycardia; contraindications to beta-blocker therapy; concomitant treatment with other beta-blockers, α-antagonists, calcium antagonists or antiarrhythmic agents (except amiodarone)	Yes	Yes	Yes	Yes
Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	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

Evidence Table **Evidence Table 10a. Quality assessments of head to head trials of beta**
Evidence Table **Evidence Table 10a. Quality assessments of head to head trials of beta**

Author, Year Country	Intention-to-treat (ITT) analysis	Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score
Metra 2000 US, Italy	No	Metra 2000 US, Italy	NR	Attrition reported; Others NR	None	Fair
Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	Yes	Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	NR	31.8% attrition; others NR	None	Fair

Evidence Table blockers for heart failure (continued)
Evidence Table blockers for heart failure (continued)

Author, Year Country	Funding	Control group standard of care	Length of follow-up
Metra 2000 US, Italy	NR	Yes	9-12 months
Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	F Hoffman La Roche and GlaxoSmithKline; first author has served as a consultant to or received travel expenses, payment for speaking at meetings or funding for research from one or more of the major pharmaceutical companies	Yes	58 months

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

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

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

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

Trial	Trial	Exercise capacity	Change in EF following treatment	Quality of Life
Sanderson 1999 *Fair*	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*	Kukin 1999 *Fair*	Improvement in 6-min walk(feet) car=63(5.5%); met=81(6.6%)(NS)	Mean EF(% improvement) car=25(+31.6%); met=23(+27.8%)	Minnesota LWHFQ mean reduction in symptom score(%) car=11(21.1%); met=10(19.6%)
Metra 2000a *Fair*	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*	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)	Poole Wilson, 2003 Carvedilol or Metoprolol European Trial (COMET)	NR	NR	NR

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

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

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

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

Author, Year Country	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
Kuhldamp 2000	Kuhldamp 2000	NR	Yes	Yes	No	Yes	Attrition=6.8%; others NR	No	Fair	AstraZeneca, Sweden	Yes

Evidence

Author, Year Country	Length of follow-up
Kuhldamp 2000	6 months

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

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

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

Author, Year Country	Author, Year Country	Method of Outcome Assessment and Timing of Assessment	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Stensrud 1980 *Fair quality*	Stensrud 1980 *Fair quality*	Charts filled in by patients	Classic migraine=6(17.1%) Common migraine=29(82.8%)	NR/NR/35 included	7(20%) withdrawn/lost to fu nr/28 analyzed
Kangasniemi 1984 Scandinavia *Fair quality*	Kangasniemi 1984 Scandinavia *Fair quality*	*Diary cards:* (a) frequency of migraine attacks; (b) intensity of migraine attacks on 3-point scale (1=light, bothersome migraine which permits daily activities with minimal or no difficulty; 2=moderate, annoying migraine causing difficulty in carrying out daily activities; 3=severe, incapacitation; patient unable to perform daily activities); (3) duration of migraine attacks (in hours); and (d) consumption of acute migraine-relieving medication assessed after each active treatment period	Classical migraine(# patients/%): 6/16.7% Common migraine(# patients/%): 30/83.3% % heredity: 94% Mean duration of migraine(years): 15.6 % earlier prophylactic treatment: 28%	NR/NR/36 entered	3(8.3%) withdrawn/0 lost to fu/35 analyzed

Author, Year Country	Outcomes	Author, Year Country	Method of adverse effects assessment?	Adverse Effects Reported
Stensrud 1980 *Fair quality*	n=28 Total headache days: pro=257; ate=247; pla=287 Total headache index: pro=437; ate=410; pla=498	Stensrud 1980 *Fair quality*	NR	Dizziness: ate=0; pro=1 Reduced physical capacity: ate=1; pro=6 Coldness hand/feet: ate=0; pro=1 Nausea: ate=0; pro=3 Sleep difficulties: ate=0; pro=1
Kangasniemi 1984 Scandinavia *Fair quality*	*Attack frequency* (decrease in mean attacks per 4 weeks/% change): pro=(-2.3)/(-43.4%); met-d=(-2.3)/(-43.4%) *Migraine days* (decrease in mean migraine days per 4 weeks/%change): pro=(-2.5)/(-43.8%); met-d=(-2.6)/(-45.6%) *Severity* (decrease in mean sum of severity score per 4 weeks/%change): pro=(-4.3)/(-44.3%); met-d=(-4.8)/(-49.5%) *Tablet consumption* (decrease in mean acute anti-migraine tablet consumption per 4 weeks/% change): pro=(-3.9)/(-45.3%); met-d=(3.9)/(-45.3%) *Reduction in sum of severity score(# pts/%)* >/= 50%: pro=15/42.8%; met-d=14/48.6% 1-50%: pro=10/28.6%; met-d=10/28.6% Negative: pro=6/17.1%; met-d=5/14.3% *Patients subjective evaluation of improvement(# pts/%)* Marked: pro=7/20%; met-d=6/20% Moderate: pro=15/42.8%; met-d=19/54.3% Slight: pro=9/25.7%; met-d=6/17.1% Unchanged/worse: pro=4/11.4%; met-d=2/5.7%	Kangasniemi 1984 Scandinavia *Fair quality*	NR	Overall incidence[# pts(%) in weeks 1-4/5-8]: pro=24(68.6%)/17(48.6%); met-d=20(57.1%)/16(45.7%) Most common adverse events(# mild/moderate/severe complaints for weeks 1-4; 5-8) CV+resp. Pro=2/1/0; 1/1/0 Met-d=0/0/1; 1/0/0 Gastrointest. Pro=4/0/2; 2/1/0 Met-d=2/2/0; 2/2/0 Sleep disturb. Pro=4/1/1; 2/1/1 Met-d=1/1/0; 0/1/0 CNS Pro=6/3/1; 2/2/0 Met-d=6/1/0; 3/1/0 Fatigue Pro=4/1/1; 4/1/0 Met-d=4/3/0; 4/2/1 Others Pro=3/4/0; 5/4/0 Met-d=10/0/1; 3/1/1

Evidence Taıine (continued)

Author, Year Country	Withdrawals due to adverse events (%, adverse n/ enrolled n)	Comments
Stensrud 1980 *Fair quality*	NR	
Kangasniemi 1984 Scandinavia *Fair quality*	pro=2/36(5.6%) met-d=0	

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

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

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

Author, Year Country	Author, Year Country	Method of Outcome Assessment and Timing of Assessment	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Olsson 1984 Sweden *Fair quality*	Olsson 1984 Sweden *Fair quality*	*Diary cards:* (a) frequency of migraine attacks; (b) intensity of migraine attacks on 3-point scale (1=light, bothersome migraine which permits daily activities with minimal or no difficulty; 2=moderate, annoying migraine causing difficulty in carrying out daily activities); (c) consumption of ergotamine preparations; and (d) consumption of analgesics	Classical migraine(# pts/%): 22/39.3% Common migraine(# pts/%): 34/60.7% % heredity=80% Duration of migraine(years): 20.7 % earlier prophylactic treatment=16% % earlier acute treatment=93%	NR/NR/56 entered	3(5.3%) withdrawn/lost to fu nr/53 analyzed

Evidence Ta **Evidence Table 13. Head to head trials of beta blockers for migra**

Author, Year Country	Outcomes
Olsson 1984 Sweden *Fair quality*	*Outcomes reported per weeks in median/% change format* Attack frequency: pro=(-1.2)/(-22.2%); met=(-1.2)/(-22.2%) Migraine days: pro=(-2.2)/(-32.8%); met=(-1.7)/(-25.4%) Sum of severity: pro=(-3.7)/(-29.8%); met=(-2.7)/(-21.8%) Ergotamine consumption: pro=(-2.2)/(-43.1%); met=(-2.4)/(-47.0%) Analgesic consumption: pro=(-3.4)/(-37.4%); met=(-1.5)/(-16.5%) *Subjective therapeutic evaluation(% patients rating effect of treatment as 'marked' or 'moderate'):* pro=63%; met=64%

Author, Year Country	Method of adverse effects assessment?	Adverse Effects Reported
Olsson 1984 Sweden *Fair quality*	Recorded according to a standardized questionnaire for direct, active questioning Unwanted symptoms were rated as 1=mild; 2=moderate; and 3=severe	Overall incidence(# pts(%) during 1st month/2nd month of treatment): pro=31(58.5%)/31(58.5%); met=31(58.5%)/30(56.6%) Most commonly reported "unwanted symptoms"(# complaints per 1st month/2nd month): Cardiovascular: pro=6/6; met=7/5 Gastrointestinal: pro=7/9; met=10/14 Sleep disturbance: pro=15/7; met=10/7 CNS: pro=13/11; met=19/17 Fatigue: pro=8/9; met=6/8 Others: pro=30/20; met=30/25

Evidence Taıine (continued)
Evidence Taıine (continued)

Author, Year Country	Withdrawals due to adverse events (%, adverse n/ enrolled n)	Comments
Olsson 1984 Sweden	None	

Fair quality

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

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

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

Author, Year Country	Author, Year Country	Method of Outcome Assessment and Timing of Assessment	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Gerber 1991 Germany *Fair quality*	Gerber 1991 Germany *Fair quality*	*Patient headache diary:* 1) Days on which a migraine attack occurred; 2) Duration of migraine attack in hours; 3) Duration of additional, non-migrainous, headaches in hours; 4) Intensity of headache (three assessment times per day using a visual analogue scale); 5) Site of pain; 6) Dose of *all* medication taken; 7) Duration of sleep in hours; 8) Daily mood (visual analogue scale); 9) Weekly evaluation of medication and listing of side effects	Mean migraine duration(yrs): met=21.9; pro=22.9; nif=17.6 Mean migraine frequency/month: met=3.8; pro=3.3; nif=3.5 Diagnosis: Without aura(% pts): met=95.4; pro=94.7; nif=88.2 With aura(% pts): met=4.5; proo=5.2; nif=11.8 Localization: Hemicrania: met=54.5; pro=36.8; nif=58.8 Holocrania: met=45.4; pro=63.1; nif=35.3	NR/NR/58 enrolled(met= 22; pro=19; nif=17)	
Worz 1991, 1992 Germany *Poor quality*	Worz 1991, 1992 Germany *Poor quality*	Headache diary	Without aura: 55/78(70.5%) With aura: 23/78(29.5%) Mean history of migraine(yrs): 19.5	NR/NR/125 enrolled	47(37.6%) withdrawn/ lost to fu nr/78 analyzed

Evidence Ta **Evidence Table 13. Head to head trials of beta blockers for migra**

Author, Year Country	Outcomes	Author, Year Country	Method of adverse effects assessment?	Adverse Effects Reported
Gerber 1991 Germany *Fair quality*	Percentages of responders (ARIMA)-see comments for definition High Dosage Phase (3 months) *Migraine days:* met=54.4%; pro=32.0%; nif=7.7% *Migraine duration:* met=60.0%; pro=27.8%; 30.8% *Severity of headache:* met=55.0%; pro=33.3%; nif=0.0% *Reduction of ergotamine intake:* met=30.0%; pro=38.9%; nif=38.5% Differential efficacy(% change by responder classification A/B/C/D) *Reduction in number of days/month with migraine:* met=54.4/5.0/35.6/0.0; pro=32.0/0.0/62.4/5.6(NS) *Reduction in duration of migraine attacks(hours):* met=60.0/5.0/35.0/0.0; pro=27.8/5.6;61.1/5.6(NS) *Improvement in severity:* met=55.0/5.0/40.0/0.0; pro=33.3/5.6/61.1/0.0(p<0.05) *Reduction in intake of abortive medication:* met=30.0/0.0/65.0/5.0; pro=38.9/0.0/55.6/5.6(NS)	Gerber 1991 Germany *Fair quality*	NR	Most commonly reported side effects(data nr; % patients approximated from Figure 6) Fatigue: met=60; pro=33 Vertigo: met=21; pro=22 Sleep disorders: met=10; pro=11 Body weight increase: met=5; pro=11 Circulatory disturbances: met=4; pro=28 Swelled legs: met=0; pro=4
Worz 1991, 1992 Germany *Poor quality*	Mean attacks/28 days(during last 8 weeks of treatment): bis=2.05; met=1.99	Worz 1991, 1992 Germany *Poor quality*	NR	Overall adverse events reported(# patients): bis=23; met=18 Most frequently reported symptoms: Dizziness: bis=8; met=4 Tiredness/fatigue: bis=3; met=7 Sleep disturbance: bis=2; met=6 Cardiovascular/hypotensive reactions: bis=6; met=1 Gastrointestinal disturbance: bis=5; met=2

Evidence Taıine (continued)
Evidence Taıine (continued)

Author, Year Country	Withdrawals due to adverse events (%, adverse n/ enrolled n)	Comments
Gerber 1991 Germany *Fair quality*	Drop out rate due to side effects or lack of therapeutic effect(# pts): met=2; pro=2	Investigation of comparison of responders versus nonresponders as defined: *Responder type A:* Significant z-values (z >/= -1.65 to 1.96) in parameters: a) reduction in number of days with migraine; b) reduction of duration of migraines; c) reduction of severity of headaches; d) reduced use of analgesics and ergots *Responder type B:* A tendency to improvement (NS) (z </= -1.65 to 1.96) in four parameters above *Non-responder type C:* No improvement in the parameters (z = 0 to -1.65) *Non-responder type D:* Tendency to deterioration, or statistically significant deterioration (positive z-values)
Worz 1991, 1992 Germany *Poor quality*	Withdrawals due to AE's(# patients): bis=8; met=5	

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

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

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

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

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

Author Year Country Study Design	Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Fair Quality **Atenolol**	***Fair Quality*** **Atenolol**				
Forssman 1982 Sweden *Fair quality* RCT Crossover	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 Tab

Author Year Country Study Design	Comments
Fair Quality	
Atenolol	
Forssman 1982 Sweden *Fair quality* RCT Crossover	

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

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

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

Author Year Country Study Design	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	**Bisoprolol**					
van de Ven 1997 The Netherlands Fair quality RCT	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 Tab **Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)**
Evidence Tab **Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)**

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
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 Tab
Evidence Tab

Author	
Year	
Country	
Study Design	**Comments**
Bisoprolol	
van de Ven	
1997	
The Netherlands	
Fair quality	
RCT	

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

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

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

Author Year Country Study Design	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	**Metoprolol**					
Andersson 1983 Denmark *Fair quality* RCT	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 Tab **Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)**

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

Author Year Country Study Design	Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Metoprolol	**Metoprolol**				
Andersson 1983 Denmark *Fair quality* RCT	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 Tab
Evidence Tab

Author Year Country Study Design	Comments
Metoprolol	
Andersson 1983 Denmark *Fair quality* RCT	

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

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

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

Author Year Country Study Design	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	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 Tab **Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)**
Evidence Tab **Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)**

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
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

Evidence Tab
Evidence Tab

Author Year Country Study Design	Comments
Kangasniemi 1987 Scandinavia *Fair quality* RCT	Classic migraine only

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

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Pindolol				
Ekbom 1971 Sweden *Fair quality* RCT	Aged 19-56, with classic or common migraine (Ad Hoc Committee, 1962) at a frequency of at least 4 attacks per 4-week period	Bronchial asthma, severe infectious diseases, diabetes mellitus, pregnancy, pathological ECG findings	Group 1: Pindolol (pin1) 7.5 mg daily *(n=7)* Group 2: Pindolol (pin2) 15 mg daily *(n=9)* Group 3: Placebo (pla) x 4 weeks *(n=10)*	Ergotamines

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

Author Year Country Study Design	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	**Pindolol**					
Ekbom 1971 Sweden *Fair quality* RCT	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

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

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

Author Year Country Study Design	Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Pindolol	**Pindolol**				
Ekbom 1971 Sweden *Fair quality* RCT	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

Evidence Tab
Evidence Tab

Author Year Country Study Design	Comments
Pindolol	
Ekbom 1971 Sweden *Fair quality* RCT	

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

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

Sjaastad 1972 Norway *Fair quality* RCT Crossover	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 Tab Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Sjaastad 1972 Norway *Fair quality* RCT Crossover	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: pin=3/28(10.7%) pla=0 Initial lethargy: pin=3; pla=0 Dizziness/faintness: pin=6; pla=0 Chest discomfort: pin=1; pla=1	

Evidence Tab
Sjaastad
1972
Norway

Fair quality
RCT Crossover

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

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Propranolol				
Borgesen 1974 Denmark *Fair quality* RCT Crossover	Diagnosis of migraine (Ad Hoc Committee on Classification of Headache, 1962); suffered more than one attack per week; did not respond to known prophylactics	Cardiac disease; asthma or diabetes mellitus; physical or neurological abnormalities	Propranolol (pro) 120 mg daily Placebo (pla) x 12 weeks, then crossover	Symptomatic treatments allowed (e.g., salicylates, ergotamines and narcotics)

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

Author Year Country Study Design	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	**Propranolol**					
Borgesen 1974 Denmark *Fair quality* RCT Crossover	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

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

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

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
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

Evidence Tab
Evidence Tab

Author Year Country Study Design	Comments
Propranolol	
Borgesen 1974 Denmark *Fair quality* RCT Crossover	

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

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

Dahlof 1987 Sweden *Fair quality* RCT Crossover	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 Tab **Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)**

Dahlof 1987 Sweden	Dahlof 1987 Sweden	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
Fair quality RCT Crossover	*Fair quality* RCT Crossover				

Evidence Tab

Dahlof	Looked at
1987	longlasting
Sweden	prophylactic effect following
Fair quality	discontinuance
RCT Crossover	

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

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

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

Author Year Country Study Design	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	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 Tab Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)
Evidence Tab Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Diamond 1982 United States *Fair quality* RCT	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 Tab
Evidence Tab

Author	
Year	
Country	
Study Design	**Comments**
Diamond 1982 United States	
Fair quality RCT	

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

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

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

Author Year Country Study Design	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	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 Tab Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Diener 1996 Germany *Fair quality* RCT	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 Tab
Evidence Tab

Author	
Year	
Country	
Study Design	**Comments**
Diener 1996 Germany	
Fair quality RCT	

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

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Forssman 1976 Sweden *Fair quality* RCT Crossover	Diagnosis of migraine; age between 16 and 55 years; at least three attacks per month	Pregnancy or suspicion of pregnancy; indication of renal or heart disease, hypertension, diabetes or asthma; history of earlier treatment of migraine with propranolol	Propranolol (pro) 240 mg daily Placebo (pla) x 12 weeks, then crossover	Previously prescribed acute medication allowed (not specified); oral contraceptives

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

Author Year Country Study Design	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	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

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

Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
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

Evidence Tab
Evidence Tab

Author	
Year	
Country	
Study Design	**Comments**
Forssman 1976 Sweden	
Fair quality RCT Crossover	

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

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

Kuritzky 1987 Israel *Fair quality* RCT Crossover	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 Tab **Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)**

Kuritzky 1987 Israel	Kuritzky 1987 Israel	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
Fair quality RCT Crossover	*Fair quality* RCT Crossover				

Evidence Tab
Kuritzky
1987
Israel

Fair quality
RCT Crossover

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

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

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

Author Year Country Study Design	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	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	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 Tab Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)
Evidence Tab Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Author Year Country Study Design	Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Malvea 1973 United States *Fair quality* RCT Crossover	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	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 Tab
Evidence Tab

Author		
Year		
Country		
Study Design	Comments	
Malvea		
1973		
United States		
Fair quality		
RCT Crossover		
Mikkelsen		
1986		
Denmark		
Fair quality		
RCT Crossover		

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

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Pita 1977 Spain *Fair quality* RCT Crossover	Migraine (Ad Hoc Committee) at a frequency of at least 3-4 attacks monthly and have a history of not responding to prophylactic therapy	Concomitant neurological or psychiatric disorders as well as diabetes mellitus, asthma or cardiac disease	Propranolol (pro) 160 mg daily Placebo (pla) x 2 months; then crossover	Symptomatic analgesic treatment (unspecified)

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

Author Year Country Study Design	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	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

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

Author Year Country Study Design	Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Pita 1977 Spain *Fair quality* RCT Crossover	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

Evidence Tab
Evidence Tab

Author		
Year		
Country		
Study Design	Comments	
Pita		
1977		
Spain		
Fair quality		
RCT Crossover		

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

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

Pradalier 1989 *Fair - Poor* RCT	Pradalier 1989 *Fair - Poor* RCT	Patient form documenting frequency and details of the headache (method nr)	Mean age: LA pro=37.1; pla=37.7 Gender(% female): LA pro=77.5%; pla=73.5% Race nr	Familial history of migraine: LA pro=65%; pla=52.9% Mean age at onset: LA pro=20.8; pla=19.1 Migraine frequency/week: LA pro=1.66; pla=1.40 Type of migraine Aura: LA pro=15%; pro=5.9% No Aura: LA pro=80%; pla=85.3% Aura+No Aura: LA pro=5%; pla=8.8% Severity of crisis(# pts. with severe crisis): LA pro=52.5%; pla=;47.0%	nr/nr/74 entered	33 withdrawn(19 prior to randomization)/9(16.3%) lost to fu/analyzed nr

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

Pradalier 1989 *Fair - Poor* RCT	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 Tab

Pradalier
1989
Fair - Poor
RCT

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

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

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

Author Year Country Study Design	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	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	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 Tab **Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)**
Evidence Tab **Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)**

Author Year Country Study Design	Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Rao 2000 India *Fair quality* RCT	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	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 Tab
Evidence Tab

Author Year Country Study Design	Comments
Rao 2000 India *Fair quality* RCT	
Wideroe 1974 Norway *Fair quality* RCT Crossover	

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

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Poor Quality				
Propranolol				
Ahuja 1985 India *Poor quality* RCT Crossover	Suffering from migraine (Ad Hoc Committee on Headache) at a frequency of > 2 attacks per month in the previous 3 months	Intercurrent illness	Propranolol (pro) 120 mg daily Placebo (pla) x 8 weeks, then crossover	NR

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

Author Year Country Study Design	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**	***Poor Quality*** **Propranolol**					
Ahuja 1985 India	Ahuja 1985 India	*Severity:* rated on 3-point scale (3=severe; 2=moderate, incapacitating; 1=inconvenient, mild)	Age range of 17-55 46.1% female	nr	nr/nr/26 enrolled	nr/nr/nr
Poor quality RCT Crossover	*Poor quality* RCT Crossover	*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				

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

Author Year Country Study Design	Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Poor Quality **Propranolol**	***Poor Quality*** **Propranolol**				
Ahuja 1985 India *Poor quality* RCT Crossover	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

Evidence Tab
Evidence Tab

Author
Year
Country
Study Design **Comments**

Poor Quality

Propranolol

Ahuja
1985
India

Poor quality
RCT Crossover

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

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

Borgensen 1976 Denmark *Poor quality* RCT Crossover	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 Tab **Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)**

Borgensen 1976 Denmark *Poor quality* RCT Crossover	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 Tab

Borgensen
1976
Denmark

Poor quality
RCT Crossover

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

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

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

Author Year Country Study Design	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	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 Tab **Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)**
Evidence Tab **Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)**

Author Year Country Study Design	Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Diamond 1976 United States *Poor quality* RCT Crossover	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 Tab
Evidence Tab

Author	
Year	
Country	
Study Design	**Comments**
Diamond	
1976	
United States	
Poor quality	
RCT Crossover	

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

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

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

Author Year Country Study Design	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	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	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 Tab **Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)**
Evidence Tab **Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)**

Author Year Country Study Design	Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Fuller 1990 London *Poor quality* RCT	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
Johnson 1986 New Zealand RCT Crossover	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 Tab
Evidence Tab

Author Year Country Study Design	Comments
Fuller 1990 London *Poor quality* RCT	*Study of abortive treatment of migraine*
Johnson 1986 New Zealand RCT Crossover	

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

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

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

Author Year Country Study Design	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	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 Tab **Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)**
Evidence Tab **Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)**

Author Year Country Study Design	Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Kaniecki 1997 United States *Poor quality* RCT Crossover Single blind	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 Tab
Evidence Tab

Author	
Year	
Country	
Study Design	**Comments**
Kaniecki 1997 United States	
Poor quality RCT Crossover Single blind	

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

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Nadelmann 1986 *Poor quality* RCT Crossover	Fulfilled diagnostic criteria for classic and/or common migraine headaches (Ad Hoc Committee on the Classification of Headache); had at least four headaches per month during a one-month observation period	Migraine other than classic or common, or other headaches known to be associated with migraine, or if they had known contraindications to beta blockers	Propranolol (pro) 80-320 mg daily Placebo (pla) x 30 weeks (6-week dose-finding, 24-week double-blind)	Analgesics Tranquilizers Ergot Narcotics

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

Author Year Country Study Design	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	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/

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

Author Year Country Study Design	Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Nadelmann 1986 *Poor quality* RCT Crossover	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

Evidence Tab
Evidence Tab

Author	
Year	
Country	
Study Design	**Comments**
Nadelmann 1986	
Poor quality RCT Crossover	

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

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

Nair 1974 India *Poor quality* RCT Crossover	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 Tab **Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)**

Nair 1974 India *Poor quality* RCT Crossover	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 Tab
Nair
1974
India

Poor quality
RCT Crossover

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

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Palferman 1983 London *Poor quality* RCT Crossover	Outpatients with migraine, defined as episodic headache with other accepted disorders of cerebral function including visual disturbances and vomiting, and those with "non-migraine", defined as recurrent 'simple' or 'tension' headaches without the disorders of cerebral function	Patients under 16 or over 65 years; use of beta blockers contraindicated; patients with the possibility of other pathology, disclosed by history, examination or investigations, which might lead to headaches	Propranolol (pro) 120 mg daily Placebo (pla) x 8 weeks, then crossover	nr

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

Author Year Country Study Design	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	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

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

Author Year Country Study Design	Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Palferman 1983 London	Palferman 1983 London	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)	nr	nr	nr
Poor quality RCT Crossover	*Poor quality* RCT Crossover	Average headache score All patients: pro=55; pla=47(p=0.26) Migraine patients only: pro=52; pla=47(NS)			

Evidence Tab
Evidence Tab

Author	
Year	
Country	
Study Design	**Comments**
Palferman 1983 London	
Poor quality RCT Crossover	

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

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

Standes 1982 Norway *Poor quality* RCT Crossover	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 Tab Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)

Standes 1982 Norway *Poor quality* RCT Crossover	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 Tab
Standes
1982
Norway

Poor quality
RCT Crossover

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

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Tfelt-Hansen 1984 Scandinavia *Poor quality* RCT Crossover	Outpatients of both sexes between ages of 18 and 65 years with a history of between 2 and 6 common migraine attacks per month (Ad Hoc Committee)	Other types of headache (including classical migraine) and major head injuries; contraindications to beta blockers; oral contraceptive use; heart rate < 54 after 3 min of rest and with supine DBP >/= 100 mmHg	Timolol (tim) 20 mg daily Propranolol (pro) 160 mg daily Placebo (pla)	NR

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

Author Year Country Study Design	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	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

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

Author Year Country Study Design	Author Year Country Study Design	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Tfelt-Hansen 1984 Scandinavia *Poor quality* RCT Crossover	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%)

Evidence Tab
Evidence Tab

Author	
Year	
Country	
Study Design	**Comments**
Tfelt-Hansen	
1984	
Scandinavia	
Poor quality	
RCT Crossover	

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

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

Weber 1972 United States *Poor quality* RCT Crossover	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 Tab **Evidence Table 14. Placebo controlled trials of beta blockers for migraine (continued)**

Weber 1972 United States *Poor quality* RCT Crossover	Weber 1972 United States *Poor quality* RCT Crossover	<u>Symptomatic response(# pts/%)</u> *First 3 months(pro n=8; pla n=11)* Good/Excellent: pro=5(63%); pla=0 Fair: pro=2(25%); pla=1(9.1%) No effect: pro=1(12.5%); pla=11(91%) *Second 3 months(pro n=11 who received placebo first; pla n=8 who received pro first)* Good/Excellent: pro=10(91%); pla=2(25%) Fair: pro=0; pla=0 No effect: pro=1(9.1%); pla=6(75%) *Irrespective of sequence* pro>pla(#/% pts): 15/79% pro=pla(#/% pts): 4/21%	nr	Abdominal cramps/diarrhea:1 patient	nr

Evidence Tab
Weber
1972
United States

Poor quality
RCT Crossover

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices

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

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Author Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Head-to-Head Tria	***Head-to-Head Trials***				
Colombo, 1989 Italy *Fair quality*	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
Placebo-controlle	***Placebo-controlled trials***				
Gatta, 1987 *Fair quality*	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)

Evidence Table

Author Year Country	Number withdrawn/ lost to fu/ analyzed
Head-to-Head Tria	
Colombo, 1989 Italy *Fair quality*	*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-controlle	
Gatta, 1987 *Fair quality*	Lost to fu: 5/24(21%)

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported
Head-to-Head Tria	***Head-to-Head Trials***			
Colombo, 1989 Italy *Fair quality*	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
Placebo-controlle	***Placebo-controlled trials***			
Gatta, 1987 *Fair quality*	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

Evidence Table

Author Year Country	Withdrawals due to adverse events (%, adverse n/enrolled n)
Head-to-Head Tria	
Colombo, 1989 Italy	pla=0 ate=4(12.5%) pro=0
Fair quality	
Placebo-controlle	
Gatta, 1987	Withdrawals due to asthma: nad=1; pla=0
Fair quality	

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

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

Evidence Table Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)
Evidence Table Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Author Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Burroughs 1983 Hampstead, England *Fair quality*	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

Evidence Table

Evidence Table

Author Year Country	Number withdrawn/ lost to fu/ analyzed
Burroughs 1983 Hampstead, England	Withdrawn=4(8.3%)/0 lost to fu/48 analyzed

Fair quality

Evidence Table Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported
Burroughs 1983 Hampstead, England *Fair quality*	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

Evidence Table
Evidence Table

Author Year Country	Withdrawals due to adverse events (%, adverse n/enrolled n)
Burroughs 1983 Hampstead, England	Withdrawals: pro=4/26(15.4%); pla=0

Fair quality

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
El Tourabi 1994 Sudan *Fair quality*	RCT	Portal hypertension ***secondary to schistosomiasis*** ; age 18-65; past history of schistomiasis (demonstrated by ultrasound); esophageal varices; recent variceal hemorrhage	Evidence or history of heart failure; significant airway obstruction; heart block greater than first degree; insulin dependent diabetes mellitus; bradycardia; severe peripheral vaascular disease; pregnant or lactating; severe depression; MI within previous 3 months	Long-acting propranolol (LA pro) 160 mg daily Placebo (pla)	NR

Evidence Table Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Author Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
El Tourabi 1994 Sudan *Fair quality*	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

Evidence Table

Evidence Table

Author Year Country	Number withdrawn/ lost to fu/ analyzed
El Tourabi 1994 Sudan	33(40%) withdrawn due to "other" reasons/lost to fu=2(2.4%)/analyzed 82
Fair quality	

Evidence Table Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported
El Tourabi 1994 Sudan *Fair quality*	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%)

Evidence Table
Evidence Table

Author Year Country	Withdrawals due to adverse events (%, adverse n/enrolled n)
El Tourabi 1994 Sudan	NR

Fair quality

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Jensen 1989 Denmark *Fair quality*	RCT	Liver disease; age <70; bleeding esophageal varices; no previous bleeding; absence of bleeding for 24 hours after sclerotherapy	Known contraindications to beta blockade	Propranolol slow release (pro SR) 160 mg daily Placebo (pla) x six months	NR
Lebrec 1981a France *Fair quality*	RCT	Histologically proven cirrhosis; gastrointestenal bleeding due to ruptured esophageal or gastric varices; diameter of esophageal varices >5mm at x-ray exam; GI bleeding spontaneously stopped or did not relapse after cessation of esophageal tamponade; hepatic encephalopathy, ascites and jaundice absent or appeared only transiently after bleeding	NR	Propranolol (pro) 80-360 mg daily with goal of 25% heart rate reduction Placebo (pla) x 3 months Treatment initiated **10-15** days following bleeding cessation	NR
Lebrec 1981b Lebrec 1984 France *Fair quality*	RCT	Histologically proven cirrhosis; gastrointestinal bleeding; source of hemorrhage was ruptured esophageal or gastric varices (as determined by endoscopy); volume of blood transfused within first 24 hours was 0.5 liter or more; jaundice was absent or mild; size of esophageal varices was large; gradient between the wedge and free hepatic venous pressures >10mm Hg; GI bleeding stopped and hemodynamic conditions were normal	Heart failure; asthma; chronic disease other than cirrhosis	Propranolol (pro) 40-360 mg daily with goal of 25% heart rate reduction Placebo (pla) Treatment initiated **2 weeks** following bleeding cessation	NR

Evidence Table Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Author Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Jensen 1989 Denmark *Fair quality*	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
Lebrec 1981a France *Fair quality*	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
Lebrec 1981b Lebrec 1984 France *Fair quality*	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

Evidence Table

Evidence Table

Author Year Country	Number withdrawn/ lost to fu/ analyzed
Jensen 1989 Denmark *Fair quality*	NR/NR/31 analyzed
Lebrec 1981a France *Fair quality*	NR/NR/24 analyzed
Lebrec 1981b Lebrec 1984 France *Fair quality*	NR/lost to fu: pro=3/28(7.9%); pla=3/36(5.5%)/analyzed 74

Evidence Table Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)
Evidence Table Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported
Jensen 1989 Denmark *Fair quality*	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
Lebrec 1981a France *Fair quality*	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
Lebrec 1981b Lebrec 1984 France *Fair quality*	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

Evidence Table
Evidence Table

Author Year Country	Withdrawals due to adverse events (%, adverse n/enrolled n)
Jensen 1989 Denmark *Fair quality*	None
Lebrec 1981a France *Fair quality*	None
Lebrec 1981b Lebrec 1984 France *Fair quality*	NR

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

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

Evidence Table Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Author Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Lo 1993 Taiwan *Fair quality*	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
Sheen 1989 Taiwan *Fair quality*	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)

Evidence Table
Evidence Table

Author Year Country	Number withdrawn/ lost to fu/ analyzed
Lo 1993 Taiwan	6(10.2%) withdrawn/lost to fu: pro=1(3.3%); pla=2(6.9%)/53 analyzed
Fair quality	
Sheen 1989 Taiwan	NR/NR/18 analyzed
Fair quality	

Evidence Table Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported
Lo 1993 Taiwan *Fair quality*	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
Sheen 1989 Taiwan *Fair quality*	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

Evidence Table
Evidence Table

Author Year Country	Withdrawals due to adverse events (%, adverse n/enrolled n)
Lo 1993 Taiwan *Fair quality*	*Propranolol(# patients/%):* 3/26(11.%) due to "intolerable general malaise *Placebo:* NR
Sheen 1989 Taiwan *Fair quality*	NR

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices

Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

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

Evidence Table Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Author Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Villeneuve 1986 Montreal, Canada *Fair quality*	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

Evidence Table
Evidence Table

Author Year Country	Number withdrawn/ lost to fu/ analyzed
Villeneuve 1986 Montreal, Canada	0 withdrawn/0 lost to fu/79 analyzed

Fair quality

Evidence Table Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)
Evidence Table Evidence Table 15. Randomized controlled trials of beta blockers for bleeding esophageal varices (continued)

Author Year Country	Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported
Villeneuve 1986 Montreal, Canada	Villeneuve 1986 Montreal, Canada	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/%):*	NR	NR
Fair quality	Fair quality	Rebleeding: pro=5/42(11.9%); pla=7/37(18.9%) Liver failure: pro=8/42(19.0%);pla=3/37(8.1%)		

Evidence Table
Evidence Table

Author Year Country	Withdrawals due to adverse events (%, adverse n/enrolled n)
Villeneuve 1986 Montreal, Canada	Withdrawals: pro=5/42(11.9%); pla=0
Fair quality	Propranolol AE withdrawals due to: Shortness of breath: 3 patients Cardiac failure: 1 patient Septic shock with hypotension: 1 patient

Evidence Table 16. Head to head trials of beta blockers for hypertension

Trial	Interventions	Sample Size	Trial duration	Population Characteristics	Quality	Results
Foerster 1985	Atenolol (ate) 100 mg Pindolol SR (pin-SR) 20 mg	107	24 weeks	Mean age=41.4 65.4% male	Good • Designed specifically for AE assessment • Changes of >1 cm on VAS interpreted as AE	Data for weeks 13-24(% patients): *n: ate=53; pin=54* Sleep disturbance: ate=18; pin=44(p=0.01) Dreams: ate=16; pin=15 Fatigue: ate=28; pin=22 Raynaud's phenomenon: ate=14; pin=26 Muscle cramps: ate=12; pin=20 Sexual disturbance: ate=14; pin=8 GI disturbances: ate=21; pin=20
Fogari 1999	Atenolol (ate) 100 mg Bisprolol (bis) 10 mg Celiprolol (cel) 400 mg Propranolol (pro) 160 mg	152	18 months	100% male Mean age=52	Fair	Overall AE incidence(# pts; %): pro=6/37(16.2%); ate=5/38(13.1%); bis=4/39(10.2%)
Lithell 1987	Atenolol (ate) 50 mg Bisoprolol (bis1) 5 mg Bisoprolol (bis2) 10 mg	292	6 months	59.9% male Mean age=52.6	Fair	Withdrawals due to adverse events (# patients/%): ate=2/97(2.1%); bis1=4/97(4.1%); bis2=4/98(4.1%)

Evidence Table 17. Safety of all head to head trials of beta blockers

Trial	Indication	Sample size	Duration	p-value	*Selective beta blockers*			*Non-selective beta blockers*						
					ate	**bis**	**met**	**cart**	**carv**	**lab**	**nad**	**pen**	**pin**	**pro**
OVERALL ADVERSE EVENT INCIDENCE														
Fogari, 1999	Hypertension	152	18 mos	NS	13.1%	10.2%								16.2%
Frishman, 1979	Angina	40	8 wks	<0.0001									17.4%	94.4%
van der Does, 1999	Angina	368	3 mos	NS			30.0%		25.0%					
Poole-Wilson, 2003 *COMET*	Heart Failure	3029	58 mos	NS			96.0%		94.0%					
Worz, 1991	Migraine	78	12 wks	NS		29.5%	23.1%							
*Kangasniemi, 1984	Migraine	35	8 wks	NS			57.1%							68.6%
							45.7%							48.6%
*Olsson, 1984	Migraine	53	8 wks	NS			58.5%							58.5%
							56.6%							58.5%
BRADYCARDIA INCIDENCE														
Metra, 2000	Heart failure	122	44 mos	NS			2.7%		4.0%					
DIZZINESS INCIDENCE														
van der Does, 1999	Angina	368	3 mos	NS			5.0%		4.8%					
Metra, 2000	Heart failure	122	44 mos	0.0046			1.3%		14.7%					
Stensrud, 1980	Migraine	28	6 wks	NS	0.0%									3.6%
Worz, 1991	Migraine	78	12 wks	NS		10.2%	5.1%							
HYPOTENSION INCIDENCE														
Metra, 2000	Heart failure	122	44 mos	NS			2.7%		2.7%					
WITHDRAWALS DUE TO ADVERSE EVENTS														
Lithell, 1987	Hypertension	292	6 mos	NS	2.1%	4.1%								
Colombo, 1989	Bleeding esophageal varices	94	357 days	NS	12.5%									0.0%
Worz, 1991	Migraine	78	12 wks	NS		10.20%	6.40%							

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