Supplement to the Drug Class Review on Beta Adrenergic Blockers

September 2004

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Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Placebo controlled trials measuring Quality of Life outcomes					
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)* Fair quality	RCT	21-65 years old; between 110 and 160% ideal weight (Metropolitan Life Insurance Height-Weight Tables); diastolic BP at baseline of 90-100 mm Hg	History of myocardial infarction, stroke, or asthma, or a serum creatinine level of 177 mmol/d or greater, insulin-dependent diabetes, allergy to thiazides or beta-blockers, pregnancy, or likelihood of difficulty in complying with the interventions	Atenolol (ate) 50 mg Chlorthalidone (chl) 25 mg Placebo (pla)	*Dietary interventions* 1) Usual Diet 2) Low sodium (goal of 52 mmol/d for participants weighing 50 kg or less to 100 mmol/d for those weighing 92 kg) + high potassium (goal: 62 mmol/d to 115 mmol/d) 3) Weight loss group (goal: 4.5 kg or 10% of baseline weight, whichever was greater)

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

Author, Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Placebo controlled trials measuring Quality of Life outcomes					
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)* Fair quality	Life Satisfaction Scale Physical Complaints Inventory Symptoms Checklist	*Per protocol analysis (n=697)* Mean age=49 56% male 68% white	Previous dug treatment = 66.2% Smokers = 14% Alcohol use (at least once a week) = 39.7%	10, 148 screened/878 eligible/878 randomized	181(20.6%) withdrawn/0 lost to fu/697 analyzed

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

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Placebo controlled trials measuring Quality of Life outcomes				
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)* Fair quality	*Per protocol analysis (pla n=232; ate n=238)* *(*negative score indicates improvement)* *Total physical problems: pla=(-0.15); ate=(-0.14) *Overall psychological functioning: pla=(-0.14); ate=(-0.14) Overall life satisfaction: pla=(-0.04); ate=0.02 *Sexual physical problems: pla=(-0.12); ate=(-0.09) *Depression: pla=(-0.15); ate=(-0.14) *Anxiety: pla=(-0.14); ate=(-0.15) *Sleep disturbances: (-0.29); ate=(-0.26) *Fatigue: (-0.20); ate=(-0.15) Satisfaction with physical health: pla=0.21; ate=0.19 Sexual satisfaction: pla=(-0.14); ate=0.04	NR	NR	NR

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

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Perez-Stable, 2000 Fair quality	RCT	Patients with mild hypertension, defined as an average diastolic blood pressure between 90 and 104 mm Hg on three readings taken during each of two screening visits 2 weeks apart; aged 18-59	Concomitant use of insulin, bronchodilators, antidepressants or antihypertensive medications within 1 month of screening; coronary artery disease, vascular heart disease, renal insufficiency, cerebrovascular disease, and secondary causes of hypertension	Propranolol (pro) 80-400 mg daily *(n=156)* Placebo (pla) *(n=156)*	NR

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

Author, Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Perez-Stable, 2000 Fair quality	*Cognitive Function Test Battery* Stimulus Evaluation/Response Selection Continuous Performance Task(CPT) Digit Symbol Substitution Task(DSST) California Veral Learning Test(CVLT) *Psychological Measures* Center for Epidemiological Studies Depression Scale(CES-D) Beck Depression Inventory(BDI)	Age: Pro=4; Pla=45 % male: Pro=67; Pla=66 % White: Pro=76; Pla=71	Current smokers: Pro=10%; Pla=11% Current daily drinkers of alcohol: Pro=11%; Pla=12% Mean DBP: Pro=96; Pla=96 Mean SBP: Pro=140=Pla=141	nr/nr/312	NR/NR/203

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

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Perez-Stable, 2000 Fair quality	**Mean changes in:** Selection reaction time(ms): pro=(-3); pla=(-10) ***CPT*** Reaction time(ms): pro=12; pla=6 Correct responses: pro=0; pla=0 Commission errors: pro=(-1); pla=(-1) Omission errors: pro=0.1; pla=0.1 **DSST** correct responses: pro=3; pla=5 ***CVLT*** Monday total: pro=3; pla=1 Tuesday list: pro=2; pla=0 Short-delay free recall: pro=3; pla=2 Short-delay cued recall: pro=4; pla=3 Long-delay free recall: pro=5; pla=4 Long-delay cued recall: pro=5; pla=2 Recognition: pro=3; pla=3 **CES-D:** pro=0; pla=0 **BDI:** pro=(-1); pla=baseline value nr	NR	NR	NR

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

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Placebo controlled trials measuring health outcomes					
Anonymous, 1977 Greenberg, 1984 Anonymous, 1985 Miall, 1987 Anonymous, 1988a Anonymous, 1988b Anonymous, 1992 Lever, 1993 UK *Medical Research Council (MRC)* *Fair quality*	RCT Single blind	***Mild hypertension*** Men and women; aged 35-64; with mild hypertension (diastolic BP 90-109 mm Hg, together with systolic pressure below 200 mm Hg)	Secondary hypertension; already on antihypertensive treatment; cardiac failure; MI or stroke within previous 3 months, angina; intermittent claudication; diabetes; gout; asthma; other serious disease; pregnancy	Propranolol (pro) up to 320 mg daily *(n=4403)* Bendrofluazide (ben) 10 mg daily *(n=4297)* Placebo (pla) *(n=8654)* with goal of maintaining DBP below 90 mm Hg x 5 years	Methydopa

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

Author, Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Placebo controlled trials measuring health outcomes					
Anonymous, 1977 Greenberg, 1984 Anonymous, 1985 Miall, 1987 Anonymous, 1988a Anonymous, 1988b Anonymous, 1992 Lever, 1993 UK *Medical Research Council (MRC)* *Fair quality*	Data for terminating events (e.g., strokes, coronary events, all cardiovascular events, and all cause mortality) were analyzed every six months	Mean age: pro=52; ben=52; pla=52 %male: pro=51.9; ben=52.1; pla=52.3 Race nr	*(Mean values for men/women)* Body weight(kg): pro=81/70; pla=81/70 SBP(mm Hg): pro=158/165; pla=158/165 DBP(mm Hg): pro=98/98; pla=98/98 % cigarette smokers: pro=30/25; pla=32/27 % with LV hypertrophy on ECG: pro=0.3/0.2; pla=0.4/0.4 % with Q-wave abnormalities: pro=1.2/1.7; pla=1.5/1.4 % with history of stroke: pro=0.7/0.7; pla=0.7/0.7	515,000 screened/46,350 eligible/17,354 enrolled	nr/nr/17,354 analyzed

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

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Placebo controlled trials measuring health outcomes				
Anonymous, 1977 Greenberg, 1984 Anonymous, 1985 Miall, 1987 Anonymous, 1988a Anonymous, 1988b Anonymous, 1992 Lever, 1993 UK *Medical Research Council (MRC)* *Fair quality*	*# events/rate per 1000 patient years* Strokes: pro=42/1.9; pla=109/2.6 Coronary events: pro=103/4.8; pla=234/5.5 All cardiovascular events: pro=146/6.7; pla=352/8.2 Non-cardiovascular deaths: pro=55/2.5; pla=114/2.7 All deaths: pro=120/5.5; pla=253/5.9	NR	NR	# patients/% Impaired glucose tolerance: pro=43/0.98%; pla=82/0.95% Gout: pro=12/0.27%; pla=14/0.16% Impotence: pro=50/1.14%; pla=20/0.23% Raynaud's phenomenon: pro=75/1.70%; pla=7/0.08% Skin disorder: pro=21/0.48%; pla=7/0.08% Dyspnoea: pro=110/2.5%; pla=10/0.12% Lethargy: pro=104/2.36%; 13/0.15% Nausea/dizziness/headache: pro=103/2.34%; pla=49/0.57% Overall: pro=518/11.76%; pla=202/2.33%

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

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

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

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

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

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

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

Author Year Country Study Design	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Head to Head trials					
Fair Quality					
Chieffo 1986 Italy Fair quality RCT	sl ntg	Patient daily record	Mean age=56.8 100% male Race nr	NR	NR/NR/10
Dorow 1990 Fair quality RCT Crossover	Diuretics Short-acting and other nitrates Bronchodilators Inhaled corticoids Antibiotics Mucolytics Expectorants	Method of measurement of 'Frequency of angina pectoris attacks' nr	Mean age: 55 % Male: 82.5 Race nr	% Smokers: 17.6 % Coronary artery disease: 100 % angina pectoris pretreatment: 80 % MI in case history: 20 % pathological exercise ECG: 100	NR/NR/40

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

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

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

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

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

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Frishman 1979 United States Fair quality RCT	Patients with angina pectoris due to ischemic coronary artery disease as documented by coronary angiography or previous MI; positive treadmill exercise test showing at least a 1 mm ECG ST segment depression of the ischemic type in association with typical angina pectoris pain; at least 5 attacks of angina pectoris/2 weeks for three months with no evidence for an accelerated course	Co-existent valvular heart disease, congestive heart failure, hypertension, bronchial asthma requiring continued treatment with bronchodilators, severe bradycardia, intermittent claudication, and either myocardial infarction or a coronary artery bypass within 3 months	Pindolol (pin) 10-40 mg daily (n=23) Propranolol (pro) 40-240 mg daily (n=18) x 8 weeks

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

Author Year Country Study Design	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Frishman 1979 United States Fair quality RCT	Nitroglycerin	Patient daily record Treadmill (protocol nr)	Mean age: 55 85.4% male Race nr	Diagnosis of coronary artery disease Coronary angiography: 80.5%	NR/NR/40

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

Author Year Country Study Design	Number withdrawn/lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported
Frishman 1979 United States Fair quality RCT	NR/NR/40 analyzed	Angina attacks/2 weeks(% reduction):pin=(-41.8%); pro=(-47.0%) Exercise tolerance(% increase in mets): pin=(+21.2%); pro=(+18.5%)	NR	Overall incidence: pin=4/23(17.4%); pro=17/18(94.4%) Pindolol Nasal stuffiness=1/23(4.3%) Nocturia=1/23(4.3%) Impotence=1/23(4.3%) Palpitations=1/23(4.3%) Propranolol Rash=1/18(5.5%) Blurred vision=2/18(11.1%) Fatigue=8/18(44.4%) Dyspnea on exertion=1/18(5.5%) Mild hypotension=5/18(27.8%)

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

Author Year Country Study Design	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Frishman 1979 United States Fair quality RCT	NR	

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

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
van der Does 1999 Europe Fair quality RCT	Male or female (postmenopausal or using reliable contraceptive methods) treated or untreated patients (</=80 years) with chronic angina pectoris, stable for at least preceding 2 months (symptomatic upon exertion and responsive to ntg and/or rest); documented coronary heart disease either by previous angiography (>70% narrowing of a major coronary vessel) or MI (electrocardiogram or cardiac enzymes), or a previous positive exercise test with occurrence of angina and ST-segment depression; capable of performing upright bicycle ergometric exercise tests; not to be at risk while temporarily receiving placebo	Contraindications to study drugs/exercise testing; other forms of angina pectoris (vasospastic, unstable); MI/cardiac surgery within 3 months; main stem stenosis; ventricular aneurysm; marked left ventricular hypertrophy; hypertrophic subaortic stenosis; hemodynamically relevant vascular defects; decompensated cardiac failure; orthostasis; phlebothrombosis; disorders of impulse formation/conduction (resting heart rate <45 beats/min, bundle brach block, pacemaker); obstructive airways disease; insulin-dependent DM; relevant hepatic impairment; gross obesity; alcohol/drug abuse; epilepsy; concomitant drugs interfering with study objectives (e.g., other antianginal agents); other clinical study participation within 30 days	Carvedilol (car) 100 mg daily (n=247) Metoprolol (met) 200 mg daily (n=120) x 3 months

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

Author Year Country Study Design	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
van der Does 1999 Europe Fair quality RCT	Nitrates	Erect bicycle ergometric exercise	Mean age: car=62; met=61 %male: car=72; met=71 Race nr	%smokers: car=14; met=19 %systemic hypertension: car=38; met=33 %diabetes mellitus: car=15; met=13 %dyslipidemia: car=32; met=31 %anterior MI: car=9; met=11 %posterior MI: car=18; met=17 %positive angiography: car=23; met=22 %1-vessel disease: car=13; met=10 %2-vessel disease: car=5; met=8 %3-vessel disease: car=5; met=3	nr/393 enrolled/368 randomized

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

Author Year Country Study Design	Number withdrawn/lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported
van der Does 1999 Europe Fair quality RCT	36 withdrawn/lost nr/344 analyzed for efficacy	Per protocol analysis: car=231; met=113 Mean change in total exercise time(s): car=(+60); met=(+60) Mean change in time to angina(s): car=(+77); met=(+76)	Volunteered by subjects or observed by investigator were recorded regardless of their nature and regardless of whether a causal relation to study medication was assumed	car n=248; met n=120 Any adverse event: car=25%; met=30% <u>Most common AE's, n(%)</u> Dizziness: car=12(4.8), met=6(5.0) Bronchitis: car=9(3.6); met=3(2.5) Asthenia: car=8(3.2); met=3(2.5) Headache: car=8(3.2); met=4(3.3) Back pain: car=6(2.4); met=2(1.7)

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

Author Year Country Study Design	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
van der Does 1999 Europe Fair quality RCT	AE withdrawals: car=18; met=6	

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

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

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

Author Year Country Study Design	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Narahara 1990 United States Fair quality	Sublingual nitroglycerin	Patient diary used to measure (1) angina frequency; and (2) nitroglycerin consumption Treadmill exercise testing (modified Naughton protocol) used to measure (1) exercise duration; and (2) time to angina	Mean age=61 21.4% female 92.9% white	History of prior MI = 42% History of coronary angiography = 59% Coronary angiography patients with NYHA functional Class II = 82% Coronary angiography patients with NYHA functional Class III = 17%	nr/nr/112

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

Author Year Country Study Design	Number withdrawn/lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported
Narahara 1990 United States Fair quality	20(17.8%) withdrawn/lost to fu nr/90 analyzed for angina attacks and nitroglycerin tablet use; 82 analyzed for exercise variables	Mean number of angina attacks (% reduction) Betaxolol 20=60 Betaxolol 40=77 Propranolol 160=57 Propranolol 320=70 NS Nitroglycerin tablets/week (% reduction) Betaxolol 20=48 Betaxolol 40=73 Propranolol 160=59 Propranolol 320=55 NS Exercise duration (% increase in minutes) Betaxolol 20=14 Betaxolol 40=15 Propranolol 160=21 Propranolol 320=14 NS	NR	Overall side effects (considered to be due to drug therapy): B20=50%; B40=37%; P160=42%; P320=45% # patients; sample sizes nr Fatigue: B20=1; B40=3; P160=4; P320=3 Increased sweating: B20=0; B40-3; P160=0; P320=0 Headache: B20=2; B40=0; P160=2; P320=0 Parasthesia: B20=0; B40=0; P160=0; P320=0 Diarrhea: B20=2; B40=0; P160=0; P320=0 Dyspepsia: B20=0; B40=2; P160=0; P320=0 Tinnitus: B20=2; B40=0; P160=0; P320=0 Angina: B20=0; B40=0; P16-=2; P320=0 Depression: B20=0; B40=2; P160=0; P320=0 Dyspnea: B20=0; B40=2; P160=0; P320=0 Abnormal vision: B20=0; B40=2; P160=0; P320=0

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

Author Year Country Study Design	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Narahara 1990 United States Fair quality	nr	

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

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Frishman 1989 United States Poor quality RCT	Patients with documented stable angina pectoris and mild to moderate hypertension	Patients with coexistent valvular heart disease, congestive heart failure, bronchial asthma, severe bradycardia (resting heart rate less than 50 beats/min), intermittent claudication, myocardial infarction within 3 months, and age above 70 years or under 18 years	Labetalol (lab) 200-1600 mg daily Propranolol (pro) 80-640 mg daily x 4 months

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

Author Year Country Study Design	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Frishman 1989 United States Poor quality RCT	HCTZ 50 mg daily (if standing DBP > 100 mm Hg)	Treadmill ergometer exercise tests (Bruce protocol) Patient diary	Center 1 Mean age: lab=58; pro=57 Gender (%male): lab=66.7; pro=100 Race nr Center 2 Mean age: lab=51; pro=58 Gender(%male): lab=100; pro=100% Race nr	NR	NR/NR/41

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

Author Year Country Study Design	Number withdrawn/lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported
Frishman 1989 United States Poor quality RCT	12 withdrawn/1 lost to fu/34 analyzed for efficacy	Total exercise time (%D in sec) Center 1: lab=(+7); pro=(+12) Center 2: lab=(+23); pro=(+40) Time to angina onset(%D in sec) Center 1: lab=(+29); pro=(+38) Center 2: lab=(+58); pro=(+66) Number of patients with angina endpoint(D%) Center 1: lab=(-67); pro=(-63) Center 2: lab=(-38); pro=(-50)	Questioned generally about occurrence of adverse events specifically regarding occurrence of dyspnea, palpitations, sexual dysfunction, GI disturbances and dizziness	NR

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

Author Year Country Study Design	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Frishman 1989 United States Poor quality RCT	NR	Center 1 measured exercise parameters at or close to peak drug effect Center 2 measured exercise parameters at or close to trough drug effect

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

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Placebo controlled trials			
Destors 1989 Europe Fair Quality RCT	Male and female patients who were less than 70 years of age were considered for the study if they had coronary heart disease with chronic angina stabilized for at least 3 months. Women could be included if menopausal for at least 2 years or exhibiting coronary lesions at angiography. Demonstration of at least 8 attacks of angina during the last 14 days or 5 attacks of angina during the last 7 days of the 2-8 week washout period.	Suffering exclusively at rest or had nocturnal attacks; angina pectoris not secondary to atherosclerosis; unstable angina pectoris; so called Prinzmetal's angina or myocardial infarction within the past 6 months; inability to assess pain and fill in diary cards; any contraindication to either active treatment; liver or kidney conditions likely to modify drug metabolism or all reasons preventing close compliance to study protocol	Bepridil (bep) 100-400 mg daily Propranolol (pro) 60-240 mg daily Placebo (pla) x 24 weeks

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

Author Year Country Study Design	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Placebo controlled trials					
Destors 1989 Europe Fair Quality RCT	sl short-acting trinitrin	Bicycle ergometer x wks 2, 4, 6, 8, 12, 16, 20 & 24 Patient diary cards x wks 8, 24	Mean age: pla=54.3; pro=56.1 % Male: pla=57.1; pro=73.1 Race nr	History of MI: pla=31.4%; pro=37.2% Positive ECG for exercise: pla=77.1%; pro=76.9% Positive ECG for attacks: pla=57.1%; pro=56.4% Angina duration(mos): pla=69.6; pro=66.6 Mean weekly attacks: pla=10.3; pro=12.4 Mean curative ntg tablets/wk: pla=10.6; pro=12.6 Mean preventive ntg tablets/wk: pla=2.6; pro=3.0 Mean attack-free days/wk: pla=1.2; pro=1.5 Mean exercise test duration(min): pla=9.3; pro=9.7	NR/NR/191

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

Author Year Country Study Design	Number withdrawn/lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported
Placebo controlled trials				
Destors 1989 Europe Fair Quality RCT	38 withdrawals/15 lost to fu/analyzed 191	Angina attacks/week(% reduction) Week 8: pla=(-49%); pro=(-65%) Week 24: pla=(-77%); pro=(-71%) Ntg consumption(% reduction) Week 8: pla=(-57%); pro=(-73%) Week 24: pla=(-79%); pro=(-74%) Number of attack-free days Week 8: pla=190; pro=193 Week 24: pla=270; pro=204 Total work(mean % increase): Week 8: pla=13%; pro=48% Week 24: pla=20%; pro=50% Maximum workload(mean % increase): Week 8: pla=6%; pro=27% Week 24: pla=14%; pro=30% Exercise duration(mean % increase): Week 8: pla=7%; pro=22% Week 24: pla=8%; pro=24%	NR	Number of patients with: Hypotension: pla=1; pro=4 Bronchospasm: pla=1; pro=1 Allergic reaction: pla=0; pro=1 Raynaud phenomenon: pla=0; pro=1 Fatigue: pla=2; pro=14 Psychiatric problems: pla=1; pro=2 Gastrointestinal problems: pla=2; pro=10 Other: pla=1; pro=6 Any: pla=6; pro=23 Severe coronary events(cardiac death, MI, angina deterioration): pla=2(5.7%); pro=8(10.2%) Development of heart failure/AV block/rhythm disturbances: pla=0; pro=5

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

Author Year Country Study Design	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Placebo controlled trials		
Destors 1989 Europe	Death due to MI(# pts): pla=0; pro=1 CVA(# pts): pla=1; pro=1	
Fair Quality RCT	Severe clinic events(# pts): pla=1; pro=2 Adverse reaction(# pts): pla=0; pro=1	

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

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
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

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

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Frishman 1989 United States	Coexistent valvular heart disease, congestive heart failure, bronchial asthma, severe bradycardia (resting heart rate less than 50 beats/min), intermittent claudication, myocardial infarction within 3 months, and age above 70 years or under 18 years	Yes	NR	Yes	Yes	No
van der Does 1999 Europe	Contraindications to study drugs or exercise testing; other forms of angina pectoris (vasospastic, unstable); myocardial infarction or cardiac surgery within 3 months; main stem stenosis; ventricular aneurysm; marked left ventricular hypertrophy; hypertrophic subaortic stenosis; hemodynamically relevant vascular defects; decompensated cardiac failure; orthostasis; phlebothrombosis; disorders of impulse formation/conduction (e.g., resting heart rate <45 beats/min, bundle brach block, pacemaker); obstructive airways disease; insulin-dependent diabetes mellitus; relevant hepatic impairment; gross obesity; alcohol or drug abuse; epilepsy; concomitant drugs interfering with the study objectives (e.g., other antianginal agents); participation in another clinical study within 30 days	Yes	Yes	Yes	Yes	No

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

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: Differential/high	Score	Funding	Control group standard of care	Length of follow-up
Frishman 1989 United States	NR	Attrition reported; other nr	No	Poor	In part by Schering-Plough	Yes	4 months
van der Does 1999 Europe	NR	Attrition reported; other nr	NR	Fair	Boehringer Mannheim	Yes	3 months

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
Narahara 1990 United States	nr	nr	yes	yes	112
Dorow 1990	NR	NR	N/A-crossover	Sample of patients cormorbid with chronic obstructive bronchitis	40
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

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

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Narahara 1990 United States	Contraindications to beta blockade including sinus bradycardia (<50 beats/min), greater than first-degree atrioventricular block, congestive heart failure, asthma, peripheral vascular disease or insulin-dependent diabetes; women of child-bearing potential and patients with unstable angina pectoris or a myocardial infarction within the preceding 3 months	Yes	Yes	Yes	Yes	No
Dorow 1990	Unstable angina or angina at rest; myocardial infarction within the last 6 months; heart failure with or without digitalis treatment; arterial hypertension with supine diastolic blood pressure values under a thiazide diuretic of >/= 105 mm Hg; cardiac arrhythmias requiring treatment; bronchial asthma; restrictive airway disease; pulmonary hypertension; diseases that could impair the implementations of bicycle ergometry	Yes	nr	Yes	Yes	Yes
Frishman 1979 United States	Co-existent valvular heart disease, congestive heart failure, hypertension, bronchial asthma requiring continued treatment with bronchodilators, severe bradycardia, intermittent claudication, and either myocardial infarction or a coronary artery bypass within 3 months	Yes	NR	Yes	Yes	Yes

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

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: Differential/high	Score	Funding	Control group standard of care	Length of follow-up
Narahara 1990 United States	nr	Yes No No No	No No	Fair	Lorex Pharmaceuticals	Yes	10 weeks
Dorow 1990	N/A	Attrition and compliance reported; others nr	None	Fair	NR	Yes	1 year
Frishman 1979 United States	NR	NR	NR	Fair	Sandoz, Inc.	Yes	8 weeks

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
Chieffo 1986 Italy	NR	NR	NR	Cormorbid hypertension and angina Good mean age=56.8 100% male	10 enrolled
Placebo controlled trials					
Destors 1989 Europe	NR	NR	Yes	Good mean age=55.3 66.5% male	191 enrolled

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

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

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

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

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

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

Author Year Country	Allowed other medications/interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
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	2365/2365/967
Sjoland 1995 Sweden *Poor quality*	Calcium antagonists, long-acting nitrates, diuretics for heart failure, digitalis, other treatment for heart failure, antihypertensives, antiarrhythmics, acetylsalicylic acid, anticoagulation	Exercise test after 2 years	Mean age $\geq$ 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%)	2291 (74 died before screen) 2365 eligible CABG 967 enrolled

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

Author Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
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	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*	Withdrawn = 193/967 (20%) Lost (admin) = 148/967 (15%) Lost (nr) = 8/967 (1%) Analyzed = 618/967 (64%)	Exercise capacity (median): met = 130W pla = 140W (p=0.02) Angina pectoris at exercise: met = 48/306 (16%) pla = 33/311 (11%) Terminated exercise due to chest pain: met =18/307 (6%) pla = 10/311 (3%) Subjective symptom means: Effort (1-10) : met = 7.6; pla = 7.4 Dyspnoea (0-10): met = 6.6; pla = 6.5 Chest pain (0-10): met = 1.1; pla = 0.6 (p=0.001)	NR	Cardiac events (total): met = 19/307 (6%) pla = 19/311 (6%) Hypotension: met = 6/307 (2%) pla = 4/311 (1%) Bradycardia: met = 7/307 (2%) pla = 1/311 (0.3%)	NR

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

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

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

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

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

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

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

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Head to head trials ot beta blockers				
Wilcox 1980 UK *Fair quality*	RCT	Clinical diagnosis of suspected MI within the previous 24 hours	Already taking a beta blocker; severe heart failure; sinus bradycardia of under 40 beats per minute; in second or third degree heart block; systolic BP of >90 mm Hg; history of asthma or diabetes; residence too far away.	Propranolol (pro) 120-160 mg daily Atenolol (ate) 100 mg daily Placebo x one year Treatment initiated within 24 hours post-MI
Acebutolol vs placebo				

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Head to head trials ot beta blockers				
Wilcox 1980 UK *Fair quality*	NR	Clinic visits at 3-month intervals Cause of death was established from hospital and general practitioners' records and from postmortem reports	Mean age(% patients) <35 yrs: pro=3.8; ate=3.9; pla=2.3 -45 yrs: pro=12.9; ate=10.2; pla=16.3 -55 yrs: pro=33.3; ate=35.4; pla=31.0 -65 yrs: pro=32.6; ate=27.6; pla=31.0 > 65 yrs: pro=17.4; ate=22.8; pla=19.4 % male: Pro=84%; Ate=89%; Pla=81% Race: NR	*Hypertension:* Pro=11%; Ate=10%; Pla=15% *Angina:* Pro=27%; Ate=31%; Pla=24% *Infarction:* Pro=21%; Ate=16%; Pla=19% Drugs being taken for cardiovascular system: Pro=14%; Ate=14%; Pla=20% Drugs taken for other purposes: Pro=14%; Ate=14%; Pla=11%
Acebutolol vs placebo				

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Head to head trials ot beta blockers				
Wilcox 1980 UK	662 screened/388 eligible/388 randomized	Withdrawn=171(44.1 %)/lost to fu nr/analyzed=388	Mortality *At 6 weeks:* pro=10(7.5%); ate=11(8,6%); pla=15(11.6%) *At 1 year:* pro=17(12.9%); ate=19(14.9%); pla=19(14.7%)	Side effects separately recorded as either volunteered or elicited
Fair quality				
Acebutolol vs placebo				

*** Numbers in parentheses indicate number of patients with missing data**

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

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

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Boissel 1990 France *Fair quality*	RCT	At least 2 of the following risk factors: (1) Typical chest pain of ≥ 1 hour in duration, typical Q waves and significant release of cardiac enzyme(s) (2) admitted for this acute event > 2 and < 22 days before (3) presented ≥ 7 of the secondary risk factors of the selection algorithm, including ≥ 1 "major" secondary risk factor (history of dyspnea when walking on flat ground, documented atrial fibrillation, ventricular fibrillation, ventricular tachycardia, overt heart failure or sinusal tachycardia during the reference event, recurrent AMI or angina pectoris before the eighth day)	Heart rate <45 beats/min; complete auriculoventricular block and acute heart failure that required treatment with ≥ 2 drugs of different classes (e.g., diuretics and vasodilators); contraindication to beta blocking treatment; age > 75 years; death; malignancy; valvular disease; coma; asthma; chronic bronchopneumopathy; Raynaud syndrome; participation in another study; patients enrolled in APSI before	Acebutolol 400 mg daily Placebo x 1 year Treatment initiated within 2-22 days post-MI

Carvedilol

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Boissel 1990 France *Fair quality*	NR	Primary outcome: Total death	Mean age=62.9 years 73% male Ethnicity nr	Angina pectoris=41.5% Unstable angina=28.9% Congestive heart failure=27.1% Renal failure=3.6% Diabetes mellitus=14.6% Cigarette smoker (actual or past)=65.5% Systemic hypertension=32.9% Atrial flutter or fibrillation=13.5% Ventricular flutter or fibrillation=5% Number of secondary risk factors (median)=8

Carvedilol

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Boissel 1990 France *Fair quality*	nr/nr/607	Withdrawn=211 (34.8%)/0 lost to fu/analyzed=607	Acebutolol (n=298) vs placebo (n=309) Total mortality: 17 (5.7%) vs 34 (11%); p=0.019 Vascular death: 12 (4%) vs 30 (9.7%); p=0.006 Reinfarction: 6 (2%) vs 4 (1.3%); p=NS Fatal or nonfatal reinfarction: 9 (3%) vs 11 (3.6%); p=NS Acute pulmonary edema: 20 (6.7%) vs 15 (4.9%); p=NS Fatal or non-fatal cardiac failure: 22 (7.4%) vs 22 (7.1%); p=NS Ventricular flutter or ventricular fibrillation: 1 (0.3%) vs 0; p=NS Ventricular flutter, ventricular fibrillation, or fatal arrhythmia: 0 vs 3 (1%); p=NS Other vascular events: 35 (11.7%) vs 28 (9.1%); p=NS Other nonvascular events: 51 (17.1%) vs 70 (22.7%); p=NS	nr

Carvedilol

*** Numbers in parentheses indicate number of patients with missing data**

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

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

Carvedilol

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Basu 1997 UK *Fair quality*	RCT	Chest pain; ECG changes; serum concentration of creatine kinase; MB isoform consistent with diagnosis	Already on ACE or beta blockers; contraindications to ACE or beta blockers; Killip class IV heart failure; cardiogenic shock; severe bradycardia; hypotension; second to third degree heart block; left bundle branch block; severe valvular disease; insulin-dependent DM; renal failure; known malignancy; other severe disease; pregnancy	Carvedilol (car) 2.5-50 mg daily Placebo (pla) x 6 months Initial dose loaded intravenously
Anonymous, 2001 International RCT *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)* Fair quality	RCT	>18 years; stable, definite MI occurring3-21 days prior to randomization; left-ventricular ejection fraction of 40% or less; receipt of concurrent treatment with ACE inhibitors for at least 48 hours and stable dose for 24+ hours unless proven intolerance to ACE inhibitors; heart failure appropriately treated with diuretics and ACE inhibitors during acute phase	Required continued diuretics or inotropes; uncontrollable heart failure; unstable angina; uncontrolled hypertension; bradycardia; unstable insulin-dependent DM; continuing indication for beta blockers for any condition other than heart failure; requiring ongoing therapy with inhaled beta agonists or steroids	Carvedilol (car) up to 50 mg daily Placebo (pla) x 1.3 years (mean) of follow-up

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Basu 1997 UK *Fair quality*	Aspirin - 100% Heparin - 97% Oral/iv nitrates - 97%	Patients were reviewed at 3-month intervals Exercise test (Bruce protocol) Endpoints: cardiac death, reinfarction, unstable angina, heart failure, emergency coronary revascularization, ventricular arrhythmias requiring intervention, cerebra-vascular accident and initiation of additional cardiovascular drug therapy other than sublingual nitrates for angina	Mean age: car=60; pla=60 % male: car=84; pal=84.5 Race: NR	*Site of MI:* Anterior - Car=51%; Pla=49% Inferior - Car=49%; Pla=51% *Type of MI:* Q-wave - Car=80%; Pla=80% Non-Q-wave - Car=20%; Pla=20% *Heart failure at entry (Killip II/III):* Car=45%; Pla=28% *Thrombolysed:* Car=99%; Pla=96% *Median time to thrombolysis:* Car=3.8 hours; Pla=3.9 hours *Smoker:* Car=67%; Pla=53.5% *Non-smoker:* Car=33%; Pla=46% *Previous IHD:* Car=20%; Pla=25% *NIDDM:* Car=12%; Pla=18% *Median time to infusion:* Car=16.8 hours; Pla=16.7 hours
Anonymous, 2001 International RCT *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)* Fair quality	ACE inhibitors(% patients)=98 Reperfusion therapy(% patients)=46	Patients were reviewed every 3 months during the first year, and every 4 months thereafter	*Carvedilol:* Mean age 63 73% male *Placebo:* Mean age 63 74% male	*Smoking history:* Current - Car=33%; Pla=32% Previous - Car=27%; Pla=25% Never - Car=39%; Pla=43% *Medical history:* Previous MI - Car=31%; Pla=29% Previous angina - Car=57%; Pla=54% Previous hypertension - Car=55%; Pla=52% Previous DM - Car=21%; Pla=23% Other vascular disease - Car=17%; Pla=16% Previous revascularization - Car=12%; Pla=11% Hyperlipidemia - Car=32%; Pla=33% SIte of MI: Anterior - Car=59%; Pla=54% Inferior - Car=21%; Pla=21% Other - Car=20%; Pla=25% Medications at time of randomization: ACE inhibitors Car=98% Pla=97%

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Basu 1997 UK *Fair quality*	416 screened/NR/151 enrolled	146 analyzed (car=75; pla=71)	Serious cardiac events: car=18(24%); pla=31(43.7%) Deaths/reinfarctions: car=11(14.7%); pla=6(8.4%)	NR
Anonymous, 2001 International RCT *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)* Fair quality	NR/NR/1959 randomized	Permanent withdrawals(excluding death): car=192(20%); pla=175(18%)/lost to fu nr/1959 analyzed	*Co-primary endpoints(# patients/%)* All-cause mortality: car=116(12%); pla=151(15%) *(p=0.031)* All-cause mortality or cardiovascular-cause hospital admission: car=340(35%); pla=367(37%) *(NS)* *Secondary endpoints(# patients/%)* Sudden death: car=51(5%); pla=69(7%) *(NS)* Hospital admission for heart failure: car=118(12%); pla=138(14%) *(NS)* *Other endpoints(# patients/%)* Cardiovascular-cause mortality: car=104(11%); pla=139(14%) *(p=0.024)* Death due to heart failure: car=18(2%); pla=30(3%) *(NS)* Non-fatal MI: car=34(3%); pla=57(6%) *(NS)* All-cause mortality or non-fatal MI: car=139(14%); pla=192(20%) *(p=0.002)*	NR

*** Numbers in parentheses indicate number of patients with missing data**

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

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

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Metoprolol				
Anonymous 1987 USA *Lopressor Intervention Trial* *Fair quality*	RCT	Ages 45-74; hospitalized for acute MI	History of CABG; permanent pacemaker; contraindication to beta blocker therapy; conditions likely to require beta blocker therapy; administration of any beta blocker within 3 days before the start of pre-entry evaluation; planned therapy with aspirin, sulfinpyrazone clofibrate;=, or dipyridamole; life threatening conditions other than CHF; conditions likely to affect protocol compliance; history of adverse reaction to metoprolol or its analogues.	Metoprolol (met) 200 mg daily Placebo (pla) x 1 year Treatment interval: 5-15 days post-MI
Hjalmarson, 1981 Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* *Good quality*	RCT	Geographic location; chest pain of acute onset and 30 minutes' duration or ECG signs of acute MI with estimated onset of infarction within previous 48 hours; age 40-74;	Contraindications to beta blockade; need for beta blockade; administrative considerations	Metoprolol (met) 15 mg intravenously; 200 mg orally Placebo (pla) Treatment interval(mean): 11.3 hours Initial dose loaded intravenously (3 injections); then administered orally x 3 months

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Metoprolol				
Anonymous 1987 USA *Lopressor Intervention Trial* *Fair quality*		Interim visits conducted at 1, 3, 7 and 12 months	Mean age = 58 % Male = 83% % White = 90.5%	*Previous medical history:* MI = 14.5% Angina = 25% CHF = 2% Hypertension = 36% Diabetes = 7.5% Location of infarct: Anterior = 50.3% Inferior = 56% Anterior & inferior = 2% High lateral = 2.5% True subendocardial = 2.5%
Hjalmarson, 1981 Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* *Good quality*	*Arrhythmias:* iv lidocaine or procainamide *CHF:* furosemide 40-80 mg iv, then oral *Chest pain:* iv morphine; sl ntg; oral anticoagulants	Physician examination at 1-week and 3 months after inclusion	*Entire sample:* Mean age: met=60; pla=60 % male: met=75.6; pla=76.2 Race nr *Subgroup of patients with indirect signs of mild-to-moderate CHF (met n=131; pla n=131)* Mean age: met=63; pla=63 % male: met=75; pla=76 Race nr	*Clinical history:* Previous infarction - Met=21.2%; Pla=22.7% Angina pectoris - Met=35.7%; Pla=34.7% Hypertension - Met=29.1%; Pla=29.7% Smoking - Met=49.7%; Pla=50.3% *Clinical status at entry:* Pulmonary rales (24) - Met=11.6%; Pla=9% ECG signs of infarction (1) - Met=49.9%; Pla=47.8% Heart rate >100 beats/minute (1) - Met=4.7%; Pla=6.2% Systolic BP <100 mm Hg (2) - Met=3.3%; Pla=4.4% *Dyspnea at onset of pain (29) - Met=28.8%; Pla=30.8%*

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Metoprolol				
Anonymous 1987 USA *Lopressor Intervention Trial* *Fair quality*	NR/NR/2395 enrolled	Withdrawn: met=381(31.9%); pla=355(29.6%)/lost to fu NR/analyzed=2395	Total mortality (# patients/%) *</= 90 days:* met=23(1.9%); pla=37(3.1%) *</= 210 days:* met=42(3.5%); pla=54(4.5%) *</= 365 days:* met=65(5.4%); pla=62(5.2%) *</= 540 days:* met=86(7.2%); pla=93(9.8%)	NR
Hjalmarson, 1981 Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* *Good quality*	2802 screened/2619 eligible/1395 randomized (met n=698; pla n=697)	Withdrawn: met=131(19.1%); pla=131(19.1%)/lost to fu nr/1395 analyzed	*Entire sample:* Mortality: met=40/698(5.7%); pla=62/697(8.9%); Odds ratio=0.62(95% CI=0.40-0.96) Reinfarction: met=35/698(5%); pla=54/697(7.7%); Odds ratio=0.63(95% CI=0.39=0.99) *Subgroup with mild-to-moderate CHF:* Mortality: met=13/131(10%); pla=25/131(19%); Odds ratio=0.47(95% CI=0.21=1.0); p=0.036 Reinfarction: met=9/131(7%); pla=10/131(8%); NS	NR

*** Numbers in parentheses indicate number of patients with missing data**

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

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

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Olsson, 1985 *Stockholm Metoprolol Trial* *Fair quality*	RCT	Residence within catchment area; admission to coronary care unit within 48 hours from onset of symptoms and development of acute MI; sinus rhythm without complete bundle branch block.	Systolic BP <100 mm Hg; sever cardiac failure not responding to digitalis or diuretics; severe intermittent claudication; obstructive pulmonary disease; need for beta-adrenoceptor blockade; other major disease; unwillingness to participate.	Metoprolol (met) 200 mg daily Placebo (pla) x 36 months Treatment interval: 48 hours post-MI
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* *Fair quality*	RCT	Admission to CCU at Ulster Hospital	Delay from onset of pain exceeded 6 hours; initial rhythm VF; initial rhythm agonal; systolic BP >90 mm Hg associated with heart rate <100 beats min-1; clinical pulmonary edema or CHF; sinus or junctional bradycardia (<60 min-1), with systolic BP >90 mmHg and not responding to patient's legs elevated; received a beta-adrenergic blocking drug or a type I antiarrhythmic drug during previous 48 hours; atrio-ventricular block greater than first degree; previous admission to the study.	Metoprolol (met) 15 mg iv, followed by 200 mg oral daily dosage Placebo (pla) x 1 year Treatment interval: 48 hours post-mi

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Olsson, 1985 *Stockholm Metoprolol Trial* *Fair quality*	*Angina:* non-beta-andrenergic blocking antianginal agents	Interim visits conducted every 3 months	Mean age: met=60; pla=59 % male: met=78; pla=83 Race = NR	Smokers: Met=53%; pla=60% Ex-smokers: Met=19%; Pla= 18% Previous MI: Met=24.5%; Pla=26.5% DM before MI: Met=10%; Pla=6% Cerebrovascular incidence before MI: Met=5%; Pla=3% Site of infarction: Anterior: Met=44%; Pla=51% Inferior: Met=38%; Pla=31% Unknown: Met=18%; Pla=18%
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* *Fair quality*	NR	NR	Age ≤65 = 548 >65 = 252 % Male 71.5% Race: NR	Previous MI = 26.75% Hypertension = 11.5 % Smoking habit = 47% Previous history of angina = 46.25% Previous history of dyspnoea = 28.38% Initial ventricular ectopic activity = 22.88% Initial supraventricular ectopic activity = 5%

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Olsson, 1985 *Stockholm Metoprolol Trial* *Fair quality*	nr/nr/301	73(24.2%) withdrawn/lost to fu nr/301 analyzed	*Sample size: met n=154; pla n=147* *Total mortality (# patients/%):* pla=31(21.1%); met=25(16.2%) (NS) *Cardiac mortality (# patients/%):* pla=29(19.7%); met=20(13.0%) (NS) *Sudden death (# patients/%):* pla=21(14.3%0; met=9(5.9%) (p<0.05) Reinfarction (# patients/%): pla=31(21.1%); met=18(11.7%) (p<0.05)	NR
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* *Fair quality*	1556 screened/800 eligible/800 enrolled	Withdrawn nr/lost to fu nr/800 analyzed	<u>Total mortality (# patients/%)</u> *At 3 months:* met=37/416(8.9%); pla=35/384(9.1%)(NS) *At one year:* met=52/416(12.5%); pla=53/384(13.8%)(NS) <u>Sudden death (# patients/%)</u> *At 3 months:* met=4/416(1.0%); pla=3/384(2.1%)(NS) *At one year:* met=8/416(1.9%); pla=18/384(4.7%) (p<0.05)	NR

*** Numbers in parentheses indicate number of patients with missing data**

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

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

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Pindolol				
Australian & Swedish Study 1983 Australia, Sweden *Fair quality*	RCT	Clinical diagnosis of acute MI within previous 21 days; had to meet 2 of the following criteria: retrosternal severe chest pain of 20+ minutes duration, resistant to nitroglycerine and startinh in previous 48 hours; pulmonary edema without previously known valvular disease; shock without suspicion of acute hypovolaemia or intoxication; transient elevation of glutamine oxaloaecetic acid transminase or asptarate amino transferase in serum to values exceeding the normal limits for the laboratory on at least 2 readings with a maximum approximately 24 hours after the estimated onset of infarction, coupled with absent or less pronounced elevation of glutamine pyruvic acid transaminase or alinine amino transferase in serum; ECG series with presence of Q waves and/or presence of the disappearance of localized ST-elevation combined with development of T-inversion in at least 2 of the routine 12 leads; clinical course complicated by electrical and/or mechanical complications.	Uncontrolled heart failure; unrelated heart disease; persistent heart block of second or third degree; persistent bradycardia <50 beats/minute; obstructive airways disease; uncontrollable insulin dependent diabetes; known hypersensitivity to beta blocking drugs; other diseases serious enough to worsen the short-term prognosis irrespectively of the MI; pregnancy; necessity to use beta blocking drug or calcium antagonists; unable to return for regular control.	Pindolol (pin) 15-20 mg daily Placebo (pla) x 24 months Treatment interval: up to 21 days post-MI

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Pindolol				
Australian & Swedish Study 1983 Australia, Sweden *Fair quality*	NR	Follow-up visits: months 1, 3, 6, 12, 18 and 24 Primary endpoint: death	*Mean Age:* Pin=58; Pla=58 % male: Pin=83; Pla=83 Australian: Pin=48%; Pla=48% Swedish: Pin=52%; Pla=51.5%	*History:* Smoking: Pin=48%; Pla=43% Hypertension: Pin=24%; Pla=28% (values indicated are those with a 10% or greater variation between patients randomized to pin. or pla.) Angina pectoris: Pin=36%; Pla=32% Functional limitation: Pin=30%; Pla=30% Prior MI: Pin=18%; Pla=16% Diabetes: Pin=5%; Pla=8% (values indicated are those with a 10% or greater variation between patients randomized to pin. or pla.) *Anterior or lateral infarction:* Pin=47%; Pla=46% *Other site of infarction:* Pin=53%; Pla=54% *Medication used at time of randomization:* Digitalis: Pin=31%; Pla=34% Diuretics: 74%; Pla=75% Vasodilators (nitrates): Pin=23%; Pla=22% Antiarrhythmics: Pin=54%; Pla=51% Anticoagulants: Pin=72%; Pla=71% *Medication used at time of discharge:* Digitalis: Pin=31%; Pla=32% Diuretics: Pi46%; Pla=42% Nitrates: Pin=39%; Pla=35%

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Pindolol				
Australian & Swedish Study 1983 Australia, Sweden *Fair quality*	2500 screened/529 eligible/529 enrolled	126(23.8%) withdrawn/lost to fu nr/529 analyzed (pin n=263; pla n=266)	*(# patients/%)* *Total mortality:* pla=47(17.7%); pin=45(17.1%) (NS) *Cardiac death:* pla=43(16.2%); pin=40(15.2%) (NS) *Cardiac sudden death:* pla=31(11.7%); pin=28(10.6%) (NS) *Non-cardiac death:* pla=4(1.5%); pin=5(1.9%)	NR

*** Numbers in parentheses indicate number of patients with missing data**

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

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

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Propranolol				
Roberts, 1984 Rude, 1986 Roberts, 1988 United States *Multicenter Investigation of the Limitation of Infarct Size (MILIS)* *Fair-poor quality*	RCT Single-blind	Age <76; history of at least 30 minutes of ischemic pain within 18 hours of potential therapy; new or presumably new ECG changes	Cardiogenic shock; advanced cardiac or other disease that would interfere with prognosis; participation in conflicting protocol; inability to participate because of geographical or psychological reasons; recent major surgery or MI; permanent cardiac pacemaker; previous participation in the protocol; failure or inability to give informed consent	Propranolol (pro): initial dose infused intravenously (0.1 mg per kg of body weight); subsequent oral dosing initiated at 20 mg and increased with an HR target of 45-60 BPM Placebo (pla) x 7 days

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Propranolol				
Roberts, 1984 Rude, 1986 Roberts, 1988 United States *Multicenter Investigation of the Limitation of Infarct Size (MILIS)* *Fair-poor quality*	NR	Follow-up visits: months 3 and 6 Telephone vital status interview: 6-month intervals thereafter	Mean age: pro=54.9; pla=54.6 % male: pro=72.4; pla=74.1 % white: pro=82.1; pla=83.7	Mean age = 54.7 Male = 73.2% White = 83% Current smokers = 50% White collar workers = 39% High school or higher education = 61.3% Regular drinkers = 22% Medical history before recent infarction: Hypertension requiring medication = 44% Documented previous infarction = 14.5% Angina >3 weeks before recent infarction = 39% CHF in previous 3 weeks = 5% Diabetes = 19% Previous cardiac arrest = 0.7% Previous cardiac surgery = 5% Previous cardiac arrythmias = 7%

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Propranolol				
Roberts, 1984 Rude, 1986 Roberts, 1988 United States *Multicenter Investigation of the Limitation of Infarct Size (MILIS)* *Fair-poor quality*	Screened=7597/Eligible=2408/Eligible after application of exclusion criteria=1589/Eligible for Group A (no contraindications to beta blocker therapy)=879 (pro n=134; pla n=135; hyaluronidase=131)	Overall patient withdrawals nr/lost to fu=1(treatment group nr)/analyzed=269	Mortality(after 36-months of follow-up): pro=24/134(17.9%); pla=20/135(14.8%) Treatment period=10 days Beta blockade at 3 months(% pts): pla=37%; pro=53% Beta blockade at 6 months(% pts): pla=40; pro=54	NR

*** Numbers in parentheses indicate number of patients with missing data**

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

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

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)* *Fair quality*	RCT	Men and women aged 30-69; hospitalized with symptoms and ECG and enzymatic changes compatible with acute MI	Chronic obstructive lung disease; severe CHF; bradycardia; life-threatening illness other than CHF; need for beta blocking drugs	Propranolol (pro) 180 mg (82% of patients) or 240 mg (18% of patients) *(n=1916)* Placebo (pla) *(n=1921)* Treatment initiated 5-21 days post-MI

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)* *Fair quality*	*% patients* Vasodilator: pro=47.8; pla=47.1 Diuretic: pro=40.8; pla=42.3 Tranquilizer: pro=28.0; pla=30.4 Digitalis: pro=26.9; pla=26.3 Aspirin: pro=21.5; pla=21.6 Antiarrhythmic: pro=20.7; pla=25.6 Potassium: pro=16.3; pla=17.7 Antihypertensive, excluding diuretic: pro=11.8; pla=13.4 Anticoagulant: pro=9.8; pla=8.5 Dipyridamole: pro=6.2; pla=5.5 Insulin: pro=4.8; pla=4.2 Hormonal: pro=4.5; pla=4.4 Oral hypoglycemic: pro=5.5; pla=3.2 Sulfinpyrazone: pro=4.3; pla=5.0	Clinic visits at 3-month intervals Deaths classified by blinded mortality classification subcommittee (relative/witness report; death certificates; attending physician; hospital records; autopsy)	*Propranolol:* Mean age: 54.7 84% male *Placebo:* Mean age: 54.9 85.1% male	*Mean systolic BP mm Hg:* Pro=112.3; Pla=111.7 *Mean diastolic BP mm Hg:* Pro=72.5; Pla=72.3 *Mean heart rate, beats per minute:* Pro=76.2; Pla=75.7 *Mean cholesterol, mg/dL:* Pro=212.7; Pla=213.6 *Mean weight, kg:* Men - Pro=80.2; Pla=79.8 Women - Pro=67.4; Pla=66.5 *Current smoker*: Pro=57.4%; Pla=56.9% *Medical history:* Prior MI - Pro=13.9%; Pla=13.2% Hypertension - Pro=41.1%; Pla=40.1% Angina pectoris - Pro=35.8%; Pla=36.5% CHF - Pro=9%; Pla=9.4% DM - Pro=11.7%; Pla=11.3% *Taking propranolol or other beta blocker:* Pro=7.2%; Pla=6.8% *In-hospital events occurring before randomization:* Atrial fibrillation - Pro=6.8%; Pla=5.7% CHF - Pro=14.3%; Pla=14.9% Vetricular tachycardia - Pro=23%; Pla=23.2% Use of antiarrhythmic drug - Pro=45.8%; Pla=46% *Medications being used at time of randomization:* Antiarrythmic - Pro=16.6%; Pla=17.9% Anticoagulant - Pro=13.9%; Pla=15.1% Antiplatlet - Pro=7.1%; Pla=6.8% Diuretic - Pro=16.1%; Pla=18% Vasodilator - Pro=36%; Pla=36.3% Digitalis - Pro=12.5%; Pla=13% Oral hypoglycemic - Pro=2.2%; Pla=1.8%

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)* *Fair quality*	Screened: 16,400 Eligible/enrolled (total=3,837): pro=1916; pla=1921	Overall number withdrawn nr/12(0.3%) lost to fu/3837 analyzed (pro n=1916; pla n=1921)	*NNT; RR (95% CI)* ***Total mortality:*** NNT=39; RR=0.73(0.59-0.91) ***Deaths due to:*** ***Cardiovascular disease:*** NNT=44; RR=0.74(0.59-0.93) ***Sudden arteriosclerotic heart disease:*** NNT=78; RR=0.72(0.53-0.99) ***Non-sudden arteriosclerotic heart disease:*** NNT=97; RR=0.73(0.52-1.03) ***Other cardiovascular disease:*** NNT=1882(harm); RR=1.14(0.43-3.03) ***Noncardiovascular disease:*** NNT=322; RR=0.65(0.31-1.36)	NR

*** Numbers in parentheses indicate number of patients with missing data**

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

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

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Hansteen 1982 Norway *Fair quality*	RCT	MI according to WHO criteria, screened on fourth day after MI, only those with increased risk of death were included.	Contraindications to beta blockade; uncontrolled heart failure	Propranolol (pro) 160 mg daily Placebo (pla) x 12 months Treatment interval: 4-6 days post-MI
Baber 1980 Multinational *Fair quality*	RCT	Diagnosis of anterior MI based on ECG abnorm,alities od an anterior infarction described as "very probable" on WHO ECG criteria; either a typical history or serum enzyme levels (AST and LDH) at least twice the accepted upper limit of normal or three times if CK was used.	Bronchospasm; atrioventricular block greater than first degree; sinus bradycardia; persistent heart failure; beta blockade at the time of infarction.	Propranolol (pro) 120 mg daily Placebo (pla) x 9 months Treatment interval: 2-14 days post-MI

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Hansteen 1982 Norway *Fair quality*	NR	Follow-up visits: months 2, 6 and 12	Mean age: Pro= 58; Pla=58.8 % male: Pro=84.5%; Pla=85.5%	*No previous CHD:* Pro=51.4%; Pla=48.6% *Angina pectoris:* Pro=30.6%; Pla=31.9% *Previous MI:* Pro=18%; Pla=19.5% *Hypertension (treated):* Pro=22.3%; Pla=18.15 *Intermittent claudication: Pro=8.6%; Pla=5.7%* *CVD:* Pro=3.2%; Pla=2.5% *Drug treatment before admission:* *Digitalis:* Pro=6.1%; Pla=5.7% *Diuretics:* Pro=19.1%; Pla=16% *Other antihy* pertensives: Pro=7.9%; Pla=6.4% Daily smoker: Pro=58.3%; Pla=64.9% *Ex-smoker:* Pro=28.1%; Pla=24.2%
Baber 1980 Multinational *Fair quality*	NR	Follow-up visits: months 1, 3, 6 and 9	*Mean age:* Pro=55; Pla=54.8 *% male:* Pro=86%; Pla=83% *Previous angina:* Positive: Pro=35%; Pla=40% *Concurrent disease:* Hypertension: Pro=13%; Pla=15% Peripheral artery disease: Pro=1%; Pla=2% Diabetes: Pro=3%; Pla=4% *Smokers:* Pro=64%; Pla=65%	*Previous angina:* Positive: Pro=35%; Pla=40% Angina more than 3 months: Pro=15%; Pla=19% *Previous infarct:* *History of cardiac failure:* *Concurrent disease:* Hypertension: Pro=13%; Pla=15% Peripheral artery disease: Pro=1%; Pla=2% Diabetes: Pro=3%; Pla=4% *Smokers:* Pro=64%; Pla=65%

*** Numbers in parentheses indicate number of patients with missing data**

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

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Hansteen 1982 Norway *Fair quality*	4929 screened/eligible nr/560 enrolled	Withdrawals: pro=70(25.2%); pla=72(25.5%)/lost to fu nr/560 analyzed	pro n=278; pla n=282 *# patients/%* Sudden death: pro=11(3.9%); pla=23(8.1%) (p=0.038) Type 1: pro=9(3.2%); pla=17(6.0%) (NS) Type 2: pro=1(0.3%); pla=3(1.1%)(NS) Type 3: pro=1(0.3%); pla=3(1.1%)(NS) Fatal reinfarction: pro=11(3.9%); pla=10(3.5%) (NS) Other cardiac deaths: pro=0; pla=2(0.7%)(NS) Other deaths: pro=3(1.1%); pla=2(0.7%)(NS) Total deaths: pro=25(8.9%); pla=37(13.1%) (NS) Total cardiac deaths: pro=22(7.9%); pla=35(12.4%) (NS) Non-fatal reinfarctions: pro=16(5.7%); pla=21(7.4%) (NS) Total no of cardiac events: pro=38(13.7%); pla=56(19.8%) (NS)	NR
Baber 1980 Multinational *Fair quality*	nr/nr/720	Total withdrawals: pla=88(24%); pro=82(23%)/lost to fu nr/720 analyzed	pla n=365; pro n=355 # pts/% Cardiac deaths: pla=18(4.9%); pro=19(5.4%) Non-cardiac deaths: pla=2(0.5%); pro=3(0.8%) Cardiac deaths after withdrawal: pla=7(1.9%); pro=6(1.7%) Total deaths: pla=27(7.4%); pro=28(7.9%) Non-fatal reinfarctions: pla=14(3.8%); pro=15(4.2%)	NR

*** Numbers in parentheses indicate number of patients with missing data**

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

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

*** Numbers in parentheses indicate number of patients with missing data**

Evidence Table 4a. 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 controlled trial of acebutolol					
Boissel 1990 France	Adequate	Adequate	Significant between-group differences for 7 of >266 baseline variables	Mean age=62.9 years 73% male Ethnicity nr	607 randomized

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

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

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

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

Evidence Table 4a. 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
Placebo controlled trials of carvedilol					
Basu 1997 UK	NR	NR	Yes	84% male Mean age=60	151 randomized
Anonymous, 2001 *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)*	Adequate; Permuted blocks with stratification by center	NR	Yes	73.5% male Mean age=63 mean LVEF=32.9%	1959 recruited

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

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

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

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

Evidence Table 4a. 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
Placebo controlled trials of metoprolol					
Anonymous 1987 USA *Lopressor Intervention Trial*	NR	NR	Yes	Mean age=58 83% male	2395 randomized
Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* Fair quality	Adequate; computer-generated randomization lists in blocks of 10	NR	Yes	Mean age=60 75.5% male	1395 randomized
Olsson, 1985 *Stockholm Metoprolol Trial*	NR	NR	Yes	Mean age=59.5 80.5% male	301 randomized

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

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

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

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

Evidence Table 4a. 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
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* Fair quality	Adequate; block randomization	NR	Yes	Mean age NR 71.5% male	800 randomized

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

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* Fair quality		Yes	Yes	Yes	Yes	Yes	NR

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

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* Fair quality	NR	NR	Fair	Astra Pharmaceuticals	Yes	1 year

Evidence Table 4a. 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
Placebo controlled pindolol studies					
Australian & Swedish Study 1983 Australia, Sweden	NR	NR	Yes	Mean age=58 83% male	529 randomized
Placebo controlled propranolol studies					
Anonymous, 1982, 1983 Goldstein, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)*	NR	NR	Yes	Mean age=54.8 84.4% male 88.8% white	3837 randomized

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

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

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

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Placebo controlled pindolol studies						
Australian & Swedish Study 1983 Australia, Sweden	Attrition=23.8%; Compliance=54% took 90% or more	NR	Fair	Sandoz Ltd.	Yes	24 months
Placebo controlled propranolol studies						
Anonymous, 1982, 1983 Goldstein, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)*	NR	Lost to fu: pro=4(0.2%); pla=8(0.4%)	Fair	National Heart, Lung, and Blood Institute	Yes	mean of 25 months

Evidence Table 4a. 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
Hansteen 1982 Norway	Adequate; blocks of 10	NR	No; Mean heart size higher in pro group	Mean age NR 85% male	560 randomized
Baber 1980 Multinational	NR	NR	Yes	Mean age=54.9 84.5% male	720 randomized

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

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups
Hansteen 1982 Norway	Cotraindications to beta blockade; uncontrolled heart failure	Yes	NR	Yes	Yes	Yes	NR
Baber 1980 Multinational	Bronchospasm; atriovenyricular block greater than first degree; sinus bradycardia; persistent heart failure; beta blockade at the time of infarction.	Yes	NR	Yes	Yes	Yes	NR

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

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Hansteen 1982 Norway	Attrition=25.3%; Compliance(% taken > 95%): 80	NR	Fair	Imperial Chemical Industries Ltd.	Yes	12 months
Baber 1980 Multinational	Attrition=23.5%; others NR	NR	Fair	ICI Pharmaceuticals	Yes	9 months

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Packer, 1996 Colucci, 1996 Yancy, 2001 *U.S. Carvedilol Heart Failure Study Group*	NR	NR	Yes	Good mean age >55 higher proportion male	Screened NR 1094 randomized
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 5a. Quality assessments of placebo controlled trials of beta blockers for heart failure

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Packer, 1996 Colucci, 1996 Yancy, 2001 *U.S. Carvedilol Heart Failure Study Group*	Major CV event or surgical procedure within 3 months of study entry; uncorrected, primary valvular disease; active myocarditis; sustained ventricular tachycardia or advanced heart block not controlled by antiarrhythmic intervention or a pacemaker; systolic blood pressure of more than 160 or less than 85 mm Hg or diastolic blood pressure of more than 100 mm Hg; a heart rate of less than 68 beats per minute; clinically important hepatic or renal disease; or any condition other than heart failure that could limit exercise or survival; concomitant use of calcium-channel blockers α- or β-adrenergic agonists or antagonists or class IC or III antiarrhythmic agents	Yes	Yes	Yes	Yes	Yes
Anderson 1985	Unstabilized overt cardiac failure; alcohol abuse; secondary cardiomyopathies; firm exclusions to beta blocker treatment (asthma, advanced heart block, allergy)	Yes	NR	NR	NR	Yes
Waagstein 1993	Treatment with beta blockers, calcium channel blockers, inotropic agents or high doses of tricyclic antidepressant drugs; significant CAD shown by angiography; clinical or histological signs of ongoing myocarditis; other life-threatening diseases; obstructive lung disease; excessive alcohol consumption; drug abuse; insulin-dependent diabetes; pheochromocytoma; thyroid disease	Yes	Yes	NR	NR	Yes for primary endpoint Nor for other

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

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Packer, 1996 Colucci, 1996 Yancy, 2001 *U.S. Carvedilol Heart Failure Study Group*	NR	AE withdrawals reported; others NR	none	fair	SmithKline Beecham Pharmaceuticals and Roche Laboratories Two investigators/authors are employees and stock holders of SKB	Yes	12 months
Anderson 1985	NR	Attrition=5/50(10%); others NR	No	Fair	Univ. of Utah SOM and LDS Hospital, Salt Lake City	NR	Mean 19 months
Waagstein 1993	NR	Attrition=14.1%; others NR	High loss for secondary endpoints except hospitalization.	Fair	Astra Pharmaceutical divisions and Ciba-Geigy Corp., Swedish Heart & Lung Foundation & Swedish Medical Research Council	NR	12 months and 18 months (n=211/383)

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

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

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

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
MERIT-HF Anonymous, 1999 Goldstein, 1999 Hjalmarson, 2000 Goldstein, 2001 Ghali, 2002 Gottlieb, 2002 Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure	Acute MI or unstable angina within 28 days; indication or contraindication for treatment with beta-blockade or drugs with beta-blocking properties; heart failure secondary to systemic disease or alcohol abuse; scheduled or performed heart transplantation or cardiomyoplasty; implanted cardioversion defibrillator (expected or performed); CABG or percutaneous transluminal coronary angioplasty planned or performed in the past 4 months; atrioventricular block of the second or third degree; unstable decompensated heart failure; supine systolic BP >100 mm Hg; any serious disease that might complicate management and follow-up according to protocol; use of calcium antagonists; use of amiodarone within 6 months; poor compliance.	Yes	Yes	NR	NR	Yes
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)*	nr	yes	yes	yes	yes	yes

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

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
MERIT-HF Anonymous, 1999 Goldstein, 1999 Hjalmarson, 2000 Goldstein, 2001 Ghali, 2002 Gottlieb, 2002 Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure	NR	Attrition=589/3991 (15%); others NR	No	Fair	Project leader, coordinator, medical advisor, and acknowledgement to Astra Hassle, Sweden	Yes	1 year (mean)
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)*	nr	Compliance (>80% of study medication): met CR=93%; pla=92%; others nr	nr	Fair	nr	yes	24 weeks

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	RCT	Men or women with symptomatic chronic heart failure (HYHA class II-IV); at least one cardiovascular admission during the previous 2 years; on stable heart failure treatment with ACE inhibitors for at least 4 weeks unless contraindicated; on treatment diuretics (>40 mg of frusemid or equivalent) for at least 2 weeks; LVEF </= 35% measured within the previous 3 months by echocardiography or radionuclide ventriculography	Recent change in treatment within 2 weeks before randomization; requirement for intravenous inotropic therapy; current treatment with non-dihydropyridine calcium channel blockers (diltiazem, verapamil); amiodarone (>200 mg per day); class-I antiarrhythmic drugs; unstable angina; myocardial infarction; coronary revascularisation or stroke within the previous 2 months; uncontrolled hypertension (SBP >170 mm Hg or DBP >105 mm Hg); hemodynamically significant valvular disease; symptomatic and sustained ventricular arrhythmias within the past 2 months note adequately treatment with antiarrhythmic drugs or implantation of an automatic defibrillator; pregnancy; women with childbrearing potential on inadequate contraception; known drug or alcohol misuse; poor compliance; any other serious systemic disease; contraindication to beta blockers

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

Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	Carvedilol (car) 50 mg Metoprolol (met) 100 mg x 58 months (mean)	ACE inhibitor Diuretic Digitalis Angiotensin II inhibitor Other vasodilator	Follow-up visits at 4-month intervals	Mean age: 62 79.8% male 98.9% White	*NYHA class:* II: 48.4% III: 47.8% IV: 3.8% Duration congestive heart failure: 42.4 months *Cause* Ischemic heart disease: 52.5% Hypertension: 17.7% Dilated cardiomyopathy: 43.9% Previous valve surgery: 2.5% Left ventricular ejection fraction (mean): 26%	nr/nr/3029 (car n=1511; met n=1518)

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

Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	964(31.8%) withdrawn/5(0.03%) lost to fu/3029 analyzed	<u>All deaths</u> car=512(34%) met=600(40%) Hazard ratio(95% CI): 0.83(0.74-0.93) NNT: 18 p=0.002 <u>Cardiovascular deaths</u> car=438(29%) met=534(35%) Hazard ratio(95% CI): 0.80(0.70-0.90) NNT=17 p=0.0004 Non-cardiovascular deaths: car=74(5%); met=66(4%) (NS) All deaths and all-cause admission: car=1116(74%); met=1160(76%) (NS)	All reports of adverse events were included irrespective of whether the investigators thought they had been caused by the treatment; adverse events that were fatal or life-threatening, required or extended admission, or resulted in persistent or significant disability or incapacity were labelled serious	Overall adverse event incidence: car=1420(94%); met=1457(96%)	NR

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Trial	Exercise capacity	Change in EF following treatment	Quality of Life
Sanderson 1999 *Fair*	Improvement in 6-min walk(feet) car=72(6.4%); met=99(8.5%)(NS)	Mean EF at Week 12 (% improvement) car=35(+34.6%); met=31(+24%)	Minnesota QOL mean reduction in symptom score (%) car=9.1(52.9%); met=8.3(63.3%)
Kukin 1999 *Fair*	Improvement in 6-min walk(feet) car=63(5.5%); met=81(6.6%)(NS)	Mean EF(% improvement) car=25(+31.6%); met=23(+27.8%)	Minnesota LWHFQ mean reduction in symptom score(%) car=11(21.1%); met=10(19.6%)
Metra 2000a *Fair*	Improvement in 6-min walk(m) car=50(11.2%); met=63(15.1%)	Mean EF(% improvement) car=31.2(52.9%); met=28.8(33.3%)(p=0.038)	Minnesota LWHFQ mean reduction in symptom score(%) car=8(25%); met=7(17.9%)
Metra 2000b *Fair*	NR	Mean EF at EOS (% improvement) car=27.9(64.1%); met=30.0(47.0%)	NR
Poole Wilson, 2003 Carvedilol or Metoprolol European Trial (COMET)	NR	NR	NR

*All in addition to sta

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

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

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

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Head to head trials						
Katritsis 2003 *Fair quality*	No restrictions, with exception of class I or III antiarrhythmic drugs	Clinic visits at months 1, 3, 6 and 12	Mean age=65.5 82% male Ethnicity nr	Heart rate=71.3 beats per minute Left atrial diameter=4.4 cm Systemic blood pressure > 140/90 mm Hg=60% Coronary artery disease=18.9% Lone atrial fibrillation=11.1% Other conditions (valve disease, hyperthyroidism, dilated cardiomyopathy)=21.1% Diabetes mellitus=14.4%	nr/102/90	8 (8.9%) withdrew/3 (3.3%) lost to fu/82 analyzed for efficacy

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

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

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

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

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

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Placebo-controlled trials						
Metoprolol vs placebo						
Kuhlkamp 2000 Germany	Digoxin/digitoxin, ACE inhibitor, diuretics, nitrates, calcium-channel blockers of dihydropyridine type	Primary endpoint: relapse into atrial fibrillation or flutter. Mean followup time: met = 93 days pla = 73 days	Mean age 60.5 70% male Race: NR	Previous cardioversion: met = 18/197 (9%) pla = 22/197 (11%) Hypertension: met = 96/197 (49%) pla = 91/197 (46%) Coronary artery disease: met = 52/197 (26%) pla = 48/197 (24%) Heart failure: met = 51/197 (26%) pla = 49/197 (25%) Stroke/TIA: met = 15/197 (8%) pla = 12/197 (12%) Diabetes mellitus: met = 23/197 (12%) pla = 17/197 (9%) NYHA 1: met = 125/197 (64%) pla = 137/197 (70%) NYHA2: met = 64/197 (33%) pla = 54/197 (27%) NYHA3: met = 8/197 (4%) pla = 6/197 (3%)	Screened = nr Eligible = nr Enrolled = 403	Lost for efficacy data (no followup ECG) = 9/403 (2%) Lost for safety data = 4/403 (1%) Analyzed = 394/403 (98%) and 399/403 (99%)

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

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Placebo-controlled trials				
Metoprolol vs placebo				
Kuhlkamp 2000 Germany	Death: met = 3/200 (2%) pla = 0 Premature discontinuation due to relapse to atrial fibrillation/flutter: met = 96/197 (49%) pla = 118/197 (60%) Total relapse to atrial fibrillation: met = 87/197 (44%) pla = 118/197 (60%)	NR	Dizziness/vertigo: met = 20/200 (10%) pla = 6/199 (3%) Bradycardia: met = 14/200 (7%) pla = 0 Cardiac failure: met = 3/200 (2%) pla = 0 Hypotension: met = 2/200 (1%) pla = 1/199 (1%)	Total: 26/394 (7%) Serious adverse events: met = 4/197 (2%) pla = 2/197(1%) Nonserious adverse events: met = 16/197 (8%) pla = 4/197(2%)

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

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

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

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Khand 2003 UK *Fair quality*	ACE inhibitors Warfarin	1) LVEF 2) Ventricular rate control by 24-hour ambulatory ECG 3) Symptoms rated using patient self-administered, quantitative questionnaire designed to measure perception of the frequency and severity of symptoms (chest pain/discomfort, fatigue, and shortness of breath at rest, during walking at normal pace, and while climbing stairs and palpitations) and their functional capacity on 4-point scale (0=absent to 3=severe symptoms); responses were summed to produce a symptom score rangingn from 0 (no symptoms to 33 (worst symptoms) 4) Exercise tolerance by 6-minute corridor walk distance	Mean age=68.5 61.7% male Ethnicity nr	IHD etiology=40.4% Mean duration of AF=131.5 weeks Mean previous cardioversion attempts=0.5 Mean resting heart rate of ECG=85.5 beats/minute Mean LVEF=24.1% Mean LVEDD=53.7 mm Mean LA size=48.4 mm <u>NYHA class</u> I=4.2% II=57.4% III=31.9% IV=6.4% Digoxin dose=0.245 mg Digoxin plasma concentration=1.54 mmol/l ACE inhibitors=70.2% Anticoagulated=80.8%	nr/nr/47	<u>Phase I</u> 6 (12.8%)/0/nr <u>Phase II</u> nr/nr/nr

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

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

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

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

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

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

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

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

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

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

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

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

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

Author Year Country Study Design	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Fair Quality					
Atenolol					
Forssman 1982 Sweden *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 Table 8. 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)	Comments
Fair Quality					
Atenolol					
Forssman 1982 Sweden *Fair quality* RCT Crossover	*Integrated headache* Mean values/day: ate=2.38; pla=4.58 Relative mean value/day(ate:pla mean/% difference): (-2.2)/(-48%) Relative value per patient/day(# pts/%): ate>pla=19/95%; pla>/=ate=1/5% *Number of attacks* Mean values/day: ate=0.17; pla=0.23 Relative mean value/day(ate:pla mean/% difference): (-0.06)/(-26.1%) Relative value per patient/day(# pts/%): ate>pla=15/75%; pla>/=ate=5/25% *Headache intensity* Comparison of effect per patient(# pts/%): ate>pla=17/18(94.4%) *Ergotamine intake* Comparison of change in intake per patient(# pts w/significant reduction/%): ate>pla=14/14(100%) *Common analgesic intake* Comparison of change in intake per patient: data nr; no difference indicated per patient between periods	NR	Dizziness of orthostatic type(# pts): ate=6; pla=1 Diffuse tiredness: ate=2; pla=0 Mood alterations: ate=1; pla=0	ate=1 pla=0	

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

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

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

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

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

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

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

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

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

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

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

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine (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
Sjaastad 1972 Norway *Fair quality* RCT Crossover	Aged 18-62 years, with classical and common migraine; attack frequency of >/= 2/month	NR	Pindolol (pin) 7.5-15 mg daily Placebo (pla) x 4 weeks, then crossover	Ergotamine preparations; salicylates; dextropropoxipheni chloride

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

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

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

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine (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)
Dahlof 1987 Sweden *Fair quality* RCT Crossover	Aged 18-60 years; history of at least 2 years classical or common migraine (World Federation of Neurological Research Group on migraine and headache); 2-8 well-defined migraine attacks/month and fulfill at least 4 of the following criteria: 1) heredity; 2) pulsating headache; 3) prodromas and/or aura; 4) hemicrania; 5) phonophobia; 6) photophobia; 7) gastrointestinal disturbances	Previous treatment with a beta blocker	Propranolol (pro) 120 mg daily Placebo (pla) x one month followed by assessment during a 5-month treatment period; then crossover	Use of common acute medication allowed (unspecified)

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

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

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

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

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

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

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

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

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

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

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

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine (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
Kuritzky 1987 Israel *Fair quality* RCT Crossover	Patients aged 17-53, suffering from classical or common migraine for at least 2 years with at least 3 attacks per month	NR	Long acting propranolol (LA pro) 160 mg daily Placebo (pla)	Analgesics

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

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

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

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

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

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

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

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine (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)
Pradalier 1989 *Fair - Poor* RCT	Suffering from migraine for at least two years with or without aura according to the criteria of the new International Headache Society classification	History of congestive heart failure or asthma; heart block; bradycardia (<50 beats/min); Raynaud phenomenon; hypertension; resistant to two previously well-followed prophylactic treatments	Placebo (pla) Long-acting propranolol (LA pro) 160 mg daily x 12 weeks	Usual medication

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

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

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

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

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

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

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

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine (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
Borgensen 1976 Denmark *Poor quality* RCT Crossover	(a) Diagnosis of migraine (Ad Hoc Committee on Headache, 1962) (b) > 1 migraine attack/week (c) Intractability with known prophylactics	Cardiac disease, asthma, diabetes mellitus, physical or neurological abnormalities	Propranolol (pro) 120 mg daily Placebo x three months, then crossover	nr

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine (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
Nair 1974 India *Poor quality* RCT Crossover	History typical of migraine; duration of headache of more than one year; attack rate exceeded 5 or more/month	nr	Propranolol (pro) 80 mg daily Placebo (pla)	*All patients used prochlorperazine 15 mgms daily throughout the duration of the study*. Use of metamizole and ergotamine tartrate also allowed as abortive treatment

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

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

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

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine (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
Standes 1982 Norway *Poor quality* RCT Crossover	Outpatients of both sexes between the ages of 18 and 65 years with a history of between two and six common migraine attacks (Ad Hoc Committee) per month	Other types of headache (including classical migraine) and major head injuries; contraindications to beta-blocking agents; use of oral contraceptives; pregnant women; use of timolol or propranolol for other reasons than migraine	Propranolol (pro) 160 mg daily Timolol (tim) 20 mg daily Placebo (pla)	Ergotamine and analgesics

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

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

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

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

Evidence Table 8. Placebo controlled trials of beta blockers for migraine (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
Weber 1972 United States *Poor quality* RCT Crossover	Met criteria for diagnosis of migraine and that were recognized as therapeutic management problems	Abnormal neurological examinations; disorders that could be aggravated by beta blockers (namely cariac disease, asthma, diabetes mellitus)	Propranolol (pro) 80 mg daily Placebo (pla)	NR

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

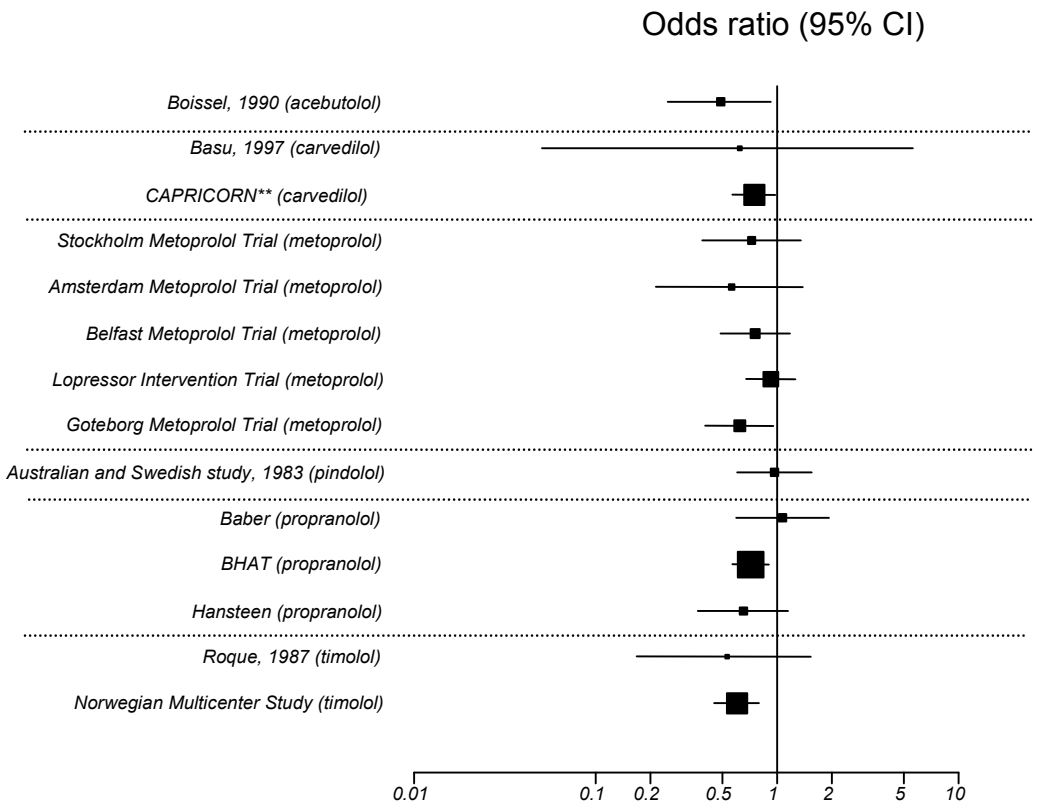
Trial	Indication	Sample size	Duration	p-value	*Selective beta blockers*				*Non-selective beta blockers*								
					ate	bis	met	bet	ace	cart	carv	lab	nad	pen	pin	pro	tim
OVERALL ADVERSE EVENT INCIDENCE																	
Fogari, 1999	Hypertension	152	18 mos	NS	13.1%	10.2%										16.2%	
Frishman, 1979	Angina	40	8 wks	<0.0001											17.4%	94.4%	
van der Does, 1999	Angina	368	3 mos	NS			30.0%				25.0%						
Narahara, 1990	Angina	112	10 wks	nr				50.0%								42%	
								37.0%								45%	
Poole-Wilson, 2003 *COMET*	Heart Failure	3029	58 mos	NS			96.0%				94.0%						
Tfelt-Hansen, 1984	Migraine	96	40 wks	NS												42.0%	46.0%
Worz, 1991	Migraine	78	12 wks	NS		29.5%	23.1%										
*Kangasniemi, 1984	Migraine	35	8 wks	NS			57.1%									68.6%	
							45.7%									48.6%	
*Olsson, 1984	Migraine	53	8 wks	NS			58.5%									58.5%	
							56.6%									58.5%	
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%	
Tfelt-Hansen, 1984	Migraine	96	40 wks	NS												5.0%	6.0%
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%	

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

Trial	Indication	Sample size	Duration	p-value	*Selective beta blockers*				*Non-selective beta blockers*								
					ate	bis	met	bet	ace	cart	carv	lab	nad	pen	pin	pro	tim
Katritsis, 2003	Atrial arrhythmias	90	12 mos	NS		6.4%					4.7%						
Tfelt-Hansen, 1984	Migraine	96	40 wks	NS												5.6%	10.1%
Waagstein, 2003	Heart failure	172	6 mos	NS			11.6%										
Worz, 1991	Migraine	78	12 wks	NS		10.20%	6.40%										

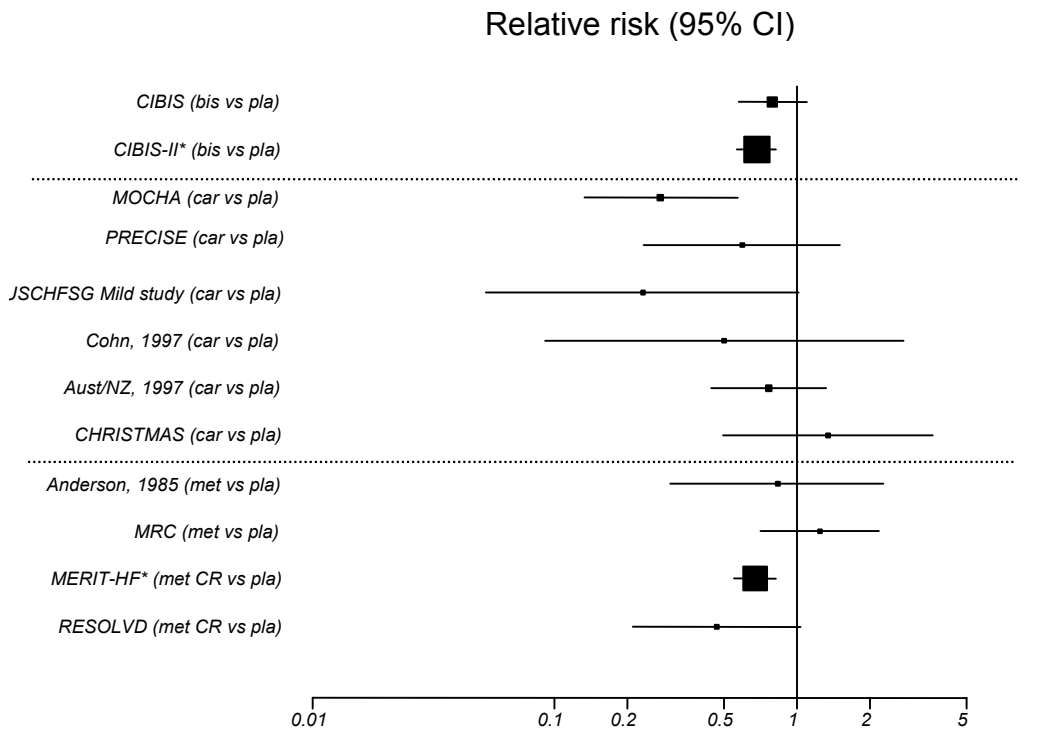
**Values represent rates from first and second months of treatment, separately*

Figure 1. Total mortality in patients following myocardial infarction



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

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



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

Appendix A. Search Strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2004>
Search Strategy:
---
1 acebutolol.mp. or exp ACEBUTOLOL/ (334)
2 betaxolol.mp. or exp BETAXOLOL/ (258)
3 timolol.mp. or exp TIMOLOL/ (967)
4 1 or 2 or 3 (1436)
5 hypertension.mp. or exp HYPERTENSION/ (17107)
6 angina.mp. or exp ANGINA PECTORIS/ (5672)
7 exp Coronary Artery Bypass/ or coronary artery bypass graft.mp. (2838)
8 myocardial infarction.mp. or exp Myocardial Infarction/ (8017)
9 exp Heart Failure, Congestive/ or heart failure.mp. (4826)
10 Left ventricular dysfunction.mp. or exp Ventricular Dysfunction, Left/ (771)
11 Arrythmia.mp. or exp Arrhythmia/ (3161)
12 migraine.mp. or exp MIGRAINE/ (1609)
13 exp "Esophageal and Gastric Varices"/ or bleeding esophageal varices.mp. (608)
14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (37711)
15 4 and 14 (774)
16 limit 15 to (human and english language) [Limit not valid; records were retained] (774)
17 randomized controlled trial$.mp. or exp Randomized Controlled Trials/ (24706)
18 16 and 17 (44)
19 from 18 keep 1-8 (8)
20 from 19 keep 1-8 (8)
21 from 20 keep 1-8 (8)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2004>
Search Strategy:
---
1 acebutolol.mp. or exp ACEBUTOLOL/ (334)
2 betaxolol.mp. or exp BETAXOLOL/ (258)
3 timolol.mp. or exp TIMOLOL/ (967)
4 1 or 2 or 3 (1436)
5 hypertension.mp. or exp HYPERTENSION/ (17107)
6 angina.mp. or exp ANGINA PECTORIS/ (5672)
7 exp Coronary Artery Bypass/ or coronary artery bypass graft.mp. (2838)
8 myocardial infarction.mp. or exp Myocardial Infarction/ (8017)
9 exp Heart Failure, Congestive/ or heart failure.mp. (4826)
10 Left ventricular dysfunction.mp. or exp Ventricular Dysfunction, Left/ (771)
11 Arrythmia.mp. or exp Arrhythmia/ (3161)
12 migraine.mp. or exp MIGRAINE/ (1609)
13 exp "Esophageal and Gastric Varices"/ or bleeding esophageal varices.mp. (608)
14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (37711)
15 4 and 14 (774)

16 limit 15 to (human and english language) [Limit not valid; records were retained] (774)
17 randomized controlled trial$.mp. or exp Randomized Controlled Trials/ (24706)
18 16 and 17 (44)
19 from 18 keep 1-8 (8)
20 from 19 keep 1-8 (8)
21 from 20 keep 1-8 (8)
22 atenolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2226)
23 bisoprolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (295)
24 carteolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (122)
25 carvedilol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (320)
26 labetolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (6)
27 metoprolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1859)
28 nadolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (271)
29 pindolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (770)
30 penbutolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (106)
31 propranolol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (3764)
32 4 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 (9202)
33 14 and 32 (5607)
34 limit 33 to (human and english language) [Limit not valid; records were retained] (5607)
35 randomized controlled trial$.mp. or exp Randomized Controlled Trials/ (24706)
36 34 and 35 (411)
37 (200302$ or 200303$ or 200304$ or 200305$ or 200306$ or 200307$ or 200308$ or 200309$ or 20031$ or 2004$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (26)
38 36 and 37 (0)
39 (2003$ or 2004$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (857)
40 36 and 39 (1)
41 [from 40 keep 1-2] (0)
42 from 36 keep 1-411 (411)

Database: Ovid MEDLINE(R)
Search Strategy:
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1 acebutolol.mp. or exp ACEBUTOLOL/ (834)

2 betaxolol.mp. or exp BETAXOLOL/ (384)
3 timolol.mp. or exp TIMOLOL/ (2070)
4 1 or 2 or 3 (3142)
5 hypertension.mp. or exp HYPERTENSION/ (129907)
6 angina.mp. or exp ANGINA PECTORIS/ (25425)
7 exp Coronary Artery Bypass/ or coronary artery bypass graft.mp. (13419)
8 myocardial infarction.mp. or exp Myocardial Infarction/ (69311)
9 exp Heart Failure, Congestive/ or heart failure.mp. (34823)
10 Left ventricular dysfunction.mp. or exp Ventricular Dysfunction, Left/ (1974)
11 Arrythmia.mp. or exp Arrhythmia/ (71028)
12 migraine.mp. or exp MIGRAINE/ (7412)
13 exp "Esophageal and Gastric Varices"/ or bleeding esophageal varices.mp. (5932)
14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (305334)
15 4 and 14 (1099)
16 limit 15 to (human and english language) (718)
17 randomized controlled trial$.mp. or exp Randomized Controlled Trials/ (6455)
18 16 and 17 (8)
19 from 18 keep 1-8 (8)

Database: Ovid MEDLINE(R) <1996 to March Week 5 2004>
Search Strategy:
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1 acebutolol.mp. or exp ACEBUTOLOL/ (97)
2 betaxolol.mp. or exp BETAXOLOL/ (283)
3 timolol.mp. or exp TIMOLOL/ (844)
4 1 or 2 or 3 (1099)
5 hypertension.mp. or exp HYPERTENSION/ (65072)
6 angina.mp. or exp ANGINA PECTORIS/ (12357)
7 exp Coronary Artery Bypass/ or coronary artery bypass graft.mp. (12313)
8 myocardial infarction.mp. or exp Myocardial Infarction/ (35734)
9 exp Heart Failure, Congestive/ or heart failure.mp. (27464)
10 Left ventricular dysfunction.mp. or exp Ventricular Dysfunction, Left/ (6697)
11 Arrythmia.mp. or exp Arrhythmia/ (26669)
12 migraine.mp. or exp MIGRAINE/ (5560)
13 exp "Esophageal and Gastric Varices"/ or bleeding esophageal varices.mp. (1891)
14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (160408)
15 4 and 14 (289)
16 limit 15 to (human and english language) (226)
17 randomized controlled trial$.mp. or exp Randomized Controlled Trials/ (29378)
18 16 and 17 (22)
19 from 18 keep 1-8 (8)
20 from 19 keep 1-8 (8)
21 from 20 keep 1-8 (8)
22 atenolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] (1421)

23 bisoprolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] (352)
24 carteolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] (108)
25 carvedilol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] (845)
26 labetolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] (20)
27 metoprolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] (1211)
28 nadolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] (213)
29 pindolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] (600)
30 penbutolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] (33)
31 propranolol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] (4326)
32 4 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 (8766)
33 14 and 32 (3121)
34 limit 33 to (human and english language) (2148)
35 randomized controlled trial$.mp. or exp Randomized Controlled Trials/ (29378)
36 34 and 35 (226)
37 (200302$ or 200303$ or 200304$ or 200305$ or 200306$ or 200307$ or 200308$ or 200309$ or 20031$ or 2004$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading] (1520)
38 36 and 37 (0)
39 (2003$ or 2004$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading] (27870)
40 36 and 39 (2)
41 from 40 keep 1-2 (2)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <April 9, 2004>
Search Strategy:
---
1 acebutolol.mp. or exp ACEBUTOLOL/ (8)
2 betaxolol.mp. or exp BETAXOLOL/ (7)
3 timolol.mp. or exp TIMOLOL/ (36)
4 1 or 2 or 3 (48)
5 hypertension.mp. or exp HYPERTENSION/ (3590)
6 angina.mp. or exp ANGINA PECTORIS/ (620)
7 exp Coronary Artery Bypass/ or coronary artery bypass graft.mp. (117)
8 myocardial infarction.mp. or exp Myocardial Infarction/ (2005)
9 exp Heart Failure, Congestive/ or heart failure.mp. (1683)
10 Left ventricular dysfunction.mp. or exp Ventricular Dysfunction, Left/ (147)

11 Arrythmia.mp. or exp Arrhythmia/ (3)
12 migraine.mp. or exp MIGRAINE/ (329)
13 exp "Esophageal and Gastric Varices"/ or bleeding esophageal varices.mp. (7)
14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (7525)
15 4 and 14 (16)
16 limit 15 to (human and english language) [Limit not valid; records were retained] (14)
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19 [from 18 keep 1-8] (0)
20 [from 19 keep 1-8] (0)
21 [from 20 keep 1-8] (0)
22 atenolol.mp. [mp=title, abstract] (80)
23 bisoprolol.mp. [mp=title, abstract] (24)
24 carteolol.mp. [mp=title, abstract] (4)
25 carvedilol.mp. [mp=title, abstract] (53)
26 labetolol.mp. [mp=title, abstract] (2)
27 metoprolol.mp. [mp=title, abstract] (66)
28 nadolol.mp. [mp=title, abstract] (14)
29 pindolol.mp. [mp=title, abstract] (30)
30 penbutolol.mp. [mp=title, abstract] (1)
31 propranolol.mp. [mp=title, abstract] (219)
32 4 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 (445)
33 14 and 32 (132)
34 limit 33 to (human and english language) [Limit not valid; records were retained] (114)
35 randomized controlled trial$.mp. or exp Randomized Controlled Trials/ (563)
36 34 and 35 (1)
37 (200302$ or 200303$ or 200304$ or 200305$ or 200306$ or 200307$ or 200308$ or 200309$ or 20031$ or 2004$).mp. [mp=title, abstract] (5320)
38 36 and 37 (0)
39 (2003$ or 2004$).mp. [mp=title, abstract] (12270)
40 36 and 39 (0)
41 [from 40 keep 1-2] (0)
42 [from 36 keep 1-411] (0)
43 from 36 keep 1 (1)

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

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

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

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record numbers, birth dates or week days
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:
        - Use of alternation, case record numbers, birth dates or week days

Open random numbers lists
Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

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

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

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

3. Were the events investigated specified and defined?

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

5. Was there non-biased and accurate ascertainment of events (independent ascertainer; validation of ascertainment technique)?

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

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

Assessment of External Validity

1. Was the description of the population adequate?

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

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Systematic Reviews:

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

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

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

5. Are the primary studies summarized appropriately?

   The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

   For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Appendix C. List of included studies

Hypertension - 3

Placebo-controlled trials=3

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

TAIM

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

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

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

MRC

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

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

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

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

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

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

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

Angina

Head-to-head trials=5

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

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

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

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

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

Placebo-controlled trials=1

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

Meta-analysis of active-controlled studies=1

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

CABG

Placebo-controlled trials=1

(MACB)

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

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

Recent MI

Head-to-head trials=1

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

Placebo-controlled trials=15

Acebutolol=1

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

Carvedilol=2

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

CAPRICORN

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

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

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

Metoprolol=5

Stockholm

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

Amsterdam

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

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

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

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

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

Herlitz, Waagstein, Lindqvist, Swedberg and Hjalmarson. Effect of metoprolol on the prognosis for patients with suspected acute myocardial infarction and indirect signs of congestive heart failure (a subgroup analysis of the Goteborg Metoprolol Trial). *American Journal of Cardiology.* 1997;80(9B):40J-44J.

Pindolol=1
Australian & Swedish Study
Anonymous. The effect of pindolol on the two years mortality after complicated myocardial infarction. *European Heart Journal.* 1983;4(6):367-75HH.

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

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

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

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

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

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

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

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

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

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

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

Timolol=2
Roque, Amuchastegui, Lopez Morillos, Mon, Girotti, Drajer, Fortunato, Moreyra, Tuero, Solchaga and et al. Beneficial effects of timolol on infarct size and late ventricular tachycardia in patients with acute myocardial infarction. *Circulation.* 1987;76(3):610-7.

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

Heart Failure

Head-to-head trials=5

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

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

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

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

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

Placebo-controlled trials=15

Atenolol=1

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

Bisoprolol=2

CIBIS

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

CIBIS-II

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

Carvedilol=8

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

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

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

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

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

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

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

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

Metoprolol tartrate=2

MDC

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

Waagstein 2003

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

Metoprolol succinate=2

MERIT-HF

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

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

Hjalmarson and Fagerberg. MERIT-HF mortality and morbidity data. *Basic Research in Cardiology.* 2000;95(Suppl 1):I98-103.

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

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

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

RESOLVD

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

Atrial arrhythmia

Head-to-head trials=1

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

Placebo-controlled trials=2

Metoprolol succinate

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

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

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

Carvedilol

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

Migraine

Head-to-head trials=5

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

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

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

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

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

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

Placebo-controlled trials=18
Atenolol=1
Forssman, Lindblad and Zborkinova. Atenolol for migraine prophylaxis. *Headache.* 1983;23:188-190.

Bisoprolol=1
van de Ven, Franke and Koehler. Prophylactic treatment of migraine with bisoprolol: a placebo-controlled study. *Cephalalgia.* 1997;17(5):596-9.

Metoprolol succinate=2
Andersson, Dahl, Hansen, Hansen, Hedman and al. Prophylactic treatment of classical and non-classical migraine with metropolol - a comparison with placebo. *Cephalalgia.* 1983;3:207-212.

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

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

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

Propranolol immediate release=9
Borgesen, Nielsen and Moller. Prophylactic treatment of migraine with propranolol. A clinical trial. *Acta Neurologica Scandinavica.* 1974;50(5):651-6.

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

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

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

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

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

Rao, Das, Taraknath and Sarma. A double blind controlled study of propranolol and cyproheptadine in migraine prophylaxis. *Neurology India.* 2000;48(3):223-6.

Wideroe and Vigander. Propranolol in the treatment of migraine. *British Medical Journal.* 1974;2(921):699-701.

Pita, Higueras, Bolanos, Perez and Mundo. Propranolol and migraine. A clinical trial. *Archivos de Farmacologia y Toxicologia.* 1977;3(3):273-8.

Long acting propranolol=3

Kuritzky, A, Hering and R. Prophylactic treatment of migraine with long acting propranolol - a comparison with placebo. *Cephalalgia.* 1987;7(Suppl 6):457-8.

Pradalier, Serratrice, Collard, Hirsch, Feve, Masson, Masson, Dry, Koulikovsky, Nguyen and et al. Long-acting propranolol in migraine prophylaxis: results of a double-blind, placebo-controlled study. *Cephalalgia.* 1989;9(4):247-53.

Malvea, Gwon and Graham. Propranolol prophylaxis of migraine. *Headache.* 1973;12(4):163-7.

Bleeding Esophageal Varices

Head-to-head trials=1

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Placebo-controlled trials

Nadolol=1

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Propranolol=8

Villeneuve, Pomier-Layrargues, Infante-Rivard, Willems, Huet, Marleau and Viallet. Propranolol for the prevention of recurrent variceal hemorrhage: a controlled trial. *Hepatology.* 1986;6(6):1239-43.

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