Drug Class Review
on
Calcium Channel Blockers

Final Report Update 2 Evidence Tables

March 2005

Original Report Date: September 2003
Update 1 Report Date: June 2004
A literature scan of this topic is done periodically

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

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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). Upon review of the last scan, the Drug Effectiveness Review Project governance group elected not to proceed with another full update of this report. Some portions of the report may not be up to date. Prior versions of this report can be accessed at the DERP website.

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Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Amlodipine comparisons							
TOMHS (Treatment of Mild Hypertension Study) Mascioli, 1990 Treatment of Mild Hypertension Research Group, 1991 Neaton, 1993 Grimm, 1997 United States	Adequate; a block randomization scheme was used with stratification by clinical center and use of antihypertensive drugs at initial screening	NR	No; Neaton reported between-groups differences in: 1) number of VPBs on 24-hour ambulatory ECG (p=0.01) 2) percentage with echocardiographic LVH (p=0.04)	Yes	Yes	Yes	In Neaton, 1993 stated that "all analyses were by treatment allocation (ITT)", but Treatment of Mild Hypertension Research Group, 1991 noted that there are differences in patient # between baseline and QOL data at 1 year
Omvik, 1993 Norway	NR	NR	Yes	Yes	Yes	Yes	No
VALUE Julius 2004 Weber 2004 Multinational (US and Europe)	Adequate, computer-generated.	NR	Yes	Yes	Yes	Yes	Yes
Lewis 2001 International	NR	Adequate	No; slightly lower proportion of the patients in the placebo group were female (p=0.02)	Yes	Yes	Yes	Yes
Nifedipine comparisons							
Metelitsa, 1996	NR	NR	Absolute data NR, but described homogeneity between groups	Yes	Yes	Yes	No
Bulpitt, 2000 Austria, Italy, Germany, Netherlands, Poland, Spain, Switzerland, and the UK	NR	NR	Not clear Described as "very similar"; data NR; may be available in separate paper	Yes	Yes	Yes	No

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population	Number recruited	Exclusion criteria for recruitment
Amlodipine comparisons							
TOMHS (Treatment of Mild Hypertension Study) Mascioli, 1990 Treatment of Mild Hypertension Research Group, 1991 Neaton, 1993 Grimm, 1997 United States	Unclear	Attrition, adherence, contamination clearly reported in Neaton, 1993	No	Fair	Good Average age: 55 years Gender: 62% male Race: 54.6% white	11,914 screened 902 randomized	Patients with evidence of cardiovascular disease or life-threatening illness or who were unable to make nutritional changes; inability to obtain a technically satisfactory baseline echocardiogram
Omvik, 1993 Norway	Unclear	Attrition reported clearly Others NR	No	Fair	Good Mean age: aml=54.1; ena=54.6 SBP(mmHg): aml=162; ena=162 DBP(mmHg): aml=106; ena=106	461	Patients with malignant or secondary HTN; known intolerance to calcium antagonists or ACE inhibitors, or hepatic, hematological or other diseases prohibiting the use of these drugs; women who were pregnant, breastfeeding, using oral contraceptives or intending to become pregnant within the study period; angina pectoris, recent MI (within previous 6 months) or cerebrovascular accident within the previous year; patients who were more than 30% overweight
VALUE Julius 2004 Weber 2004 Multinational (US and Europe)	Yes	Attrition, yes, others no.	No: 0.5% valsartan vs 0.6% amlodipine	Good	High CV risk	15,313	Renal artery stenosis, pregnancy, acute MI, percutaneous transluminal coronary angioplasty or coronary artery bypass graft within the past 3 months, clinically relevant valvular disease, cerebrovascular accident in the past 3 months, severe hepatic disease, severe chronic renal failure, congestive heart failure requiring ACE inhibitor therapy, patients on monotherapy with beta blockers for both coronary artery disease and hypertension.
Lewis 2001 International	Yes	Yes No No No	No No	Fair	NR	1,715	NR
Nifedipine comparisons							
Metelitsa, 1996	Unclear	Attrition reported clearly Others NR	No	Fair-Poor	Not clear Absolute data NR	345 enrolled	NR
Bulpitt, 2000 Austria, Italy, Germany, Netherlands, Poland, Spain, Switzerland, and the UK	Unclear	Attrition clearly reported Others NR	No	Fair	Good for elderly population Mean age: bis=67.9; nifr=68.5	771 enrolled 747 randomized	NR

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Control group standard of care	Length of follow-up	Funding
Amlodipine comparisons			
TOMHS (Treatment of Mild Hypertension Study) Mascioli, 1990 Treatment of Mild Hypertension Research Group, 1991 Neaton, 1993 Grimm, 1997 United States	Yes	At least 4 years	National Heart, Lung and Blood Institute, Merck, Harp and Dohme Research Laboratories and Pfizer, Inc.
Omvik, 1993 Norway	Yes	50 weeks	NR
VALUE Julius 2004 Weber 2004 Multinational (US and Europe)	Yes	Mean 4.2 years	Novartis
Lewis 2001 International	Yes	932 days	BMS
Nifedipine comparisons			
Metelitsa, 1996	Yes	8 months	Bristol-Meyers
Bulpitt, 2000 Austria, Italy, Germany, Netherlands, Poland, Spain, Switzerland, and the UK	Yes	6 months	Merck

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Fletcher, 1992 Europe	NR	NR	Yes	Yes	Yes	Yes	No
JMIC-B Yui, 2004 Japan	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Poole-Wilson 2004 Multi-national	blocked and stratified by centre	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population	Number recruited	Exclusion criteria for recruitment
Fletcher, 1992 Europe	Unclear	Attrition clearly reported Others NR	No	Fair	Good Average age: pin=55.9; nif=56.4 Gender(%male): pin=54; nif=48	281 screened 257 randomized	Pregnant or breastfeeding women; any patients with a history of MI or cerebrovascular event within the previous 3 months; previous history of angina pectoris, congestive heart failure, dizziness, syncope, tachydysrhythmia, vascular headache or edema; impaired renal or hepatic function or any severe chronic disease; contraindication to thiazide treatment including unstable diabetes or uncontrolled hyperuricaemia; laboratory values outside the normal range; tablet compliance outside the range of 80-120% during run-in
JMIC-B Yui, 2004 Japan	Unclear-differential withdrawal rate, but characteristics at folllowup not reported.	Attrition yes, others no.	Differential: higher withdrawal rate in ACE inhibitor group (12.9% nifedipine vs 17.3% ACE inhibitor, p=0.004).	Fair	CAD	1,888 assessed for eligibility 1,650 randomized	Diastolic BP ≥120 mmHg or secondary hypertension; symptomatic cerebrovascular disease, overt heart failure, atrial fibrillation, serious arrhythmias (ventricular tachycardia, ventricular fibrillation), renal dysfunction (serum creatinine concentration of more than 176.8 mmol/l), severe hepatic dysfunction, uncontrollable diabetes mellitus, and familial hypercholesterolemia.
Poole-Wilson 2004 Multi-national	Unclear	Attrition yes others NR	No	Fair	Good Mean age: nif=63.5; pla=63.4 Gender(%male): nif=80%; pla=79%	7797 randomized 7665 intention-to-treat analyses	Overt heart failure; any major cardiovascular event or intervention within the past 3 months; planned coronary angiography or intervention; known intolerance to dihydropyridines; clinically significant valvular or pulmonary disease; unstable insulin-dependent diabetes mellitus; any gastrointestinal disorder that could compromise absorption of nifedipine GITS or passage of the tablet; any condition other than coronary artery disease that limited life expectancy; symptomatic orthostatic hypotension or supine systolic blood pressure 90mmHg or less; systolic blood pressure at least 200mmHg, diastolic blood pressure at least 105mmHg, or both; creatinine more than twice the local upper limit of normal; alanine or aspartate transminase greater than three times the local upper limit of normal. Woman could only participate if pregnancy is not a risk.

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Control group standard of care	Length of follow-up	Funding
Fletcher, 1992 Europe	Yes	6 months	Leo Pharmaceutical Products
JMIC-B Yui, 2004 Japan	Yes	3 years	Preventive Arteriosclerosis Research Association
Poole-Wilson 2004 Multi-national	Yes	4.5-6 years	Bayer Healthcare AG. Wuppertal Germany

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Verapamil comparisons							
Boissel, 1995	Adequate	No; open trial	No; differences in HTN risk factors (e.g., obesity; alcohol consumption; NSAIDS use)	Yes	No, open trial	No, open trial	No
Isradipine comparisons							
LOMIR-MCT-IL trial Amir, 1994 Bar-On, 1993 Yodfat, 1996 Israel	NR	NR	Yes	Yes	Yes	Yes	Unclear; suspected that patients who were lost to follow-up and who refused to continue were not included in analysis
AMSA *(Amlodipine vs slow release Metoprolol in the treatment of Atable exertional Angina)* Midtbo 2000 Norway	NR	NR	Small differences, duration of angina longer and % male higher in met group, % with prior MI higher in aml group	Yes	Yes	Yes	No
APSIS *(The Angina Prognosis Study in Stockholm)* Sweden Rehnqvist, 1994 Rehnqvist, 1996	NR	NR	No. Significantly more women ($p<0.05$) and non-smokers ($p<0.001$) in Ver group, which could reflect a slightly better prognosis.	Yes	Yes	Yes	Yes for fatal and non-fatal CV events No for psychological variables

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population	Number recruited	Exclusion criteria for recruitment
Verapamil comparisons							
Boissel, 1995	Unclear	Adherence clearly reported; others NR	No	Poor	Mean age: diu=52.2; bis=50.5; ver=52.3; ena: 51.4 Gender(%male): diu=42; bis=43; ver=49; ena=52 Race NR Population of "recently discovered HTN that had not been treated	722 enrolled	NR
Isradipine comparisons							
LOMIR-MCT-IL trial Amir, 1994 Bar-On, 1993 Yodfat, 1996 Israel	Unclear	Attrition clearly reported; others NR	No	Fair	100% male	368 enrolled	Patients with secondary hypertension; malignant hypertension; unstable angina; recent myocardial infarction; or any clinical relevant cardiovascular or other chronic disease or abnormal laboratory findings; history of alcohol abuse or mental disorder; insulin-dependent diabetes mellitus
AMSA *(Amlodipine vs slow release Metoprolol in the treatment of Atable exertional Angina)* Midtbo 2000 Norway	Not clear	Yes	No	Fair-Poor	Good	NR/31 randomized	Unstable angina within previous 3 months; MI within previous 6 months; congestive heart failure; serious cardiac valvular disease; significant peripheral vascular disease; paroxysmal or chronic atrial fibrillation; supine or standing SBP <100 mmHg; significant bradycardia (<50 beats/minute); CABG within previous 3 months; stroke within previous 6 months; moderate or severe anemia; hypoxic states (e.g. pulmonary disease); 2nd or 3rd degree AV-block; electrocardiograph patterns not allowing interpretation of ECG exercise data; use of drugs which effect ECG interpretation of ischemia (digitalis); insulin-treated diabetes; Active heaptic or renal disease likely to restrict exercise tests; other major concurrent disease
APSIS *(The Angina Prognosis Study in Stockholm)* Sweden Rehnqvist, 1994 Rehnqvist, 1996	Not clear	Withdrawals due to AEs and other administrative reasons clearly reported. Others not reported.	No	Fair-Poor	Good; older population, greater proportion male	809	Contraindications to the study drugs; myocardial infarction within the last 3 years; unstable angina or anticipated need for revascularization within one month; presence of other severe disorders; alcohol abuse; suspected non-compliance; non-compensated heart failure; significant valvular disease

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Control group standard of care	Length of follow-up	Funding
Verapamil comparisons			
Boissel, 1995	Yes	1 year	Searle France; Merck Sharpe & Dohme Chibret; Merck Clevenot; Loratories Knoll France
Isradipine comparisons			
LOMIR-MCT-IL trial Amir, 1994 Bar-On, 1993 Yodfat, 1996 Israel	Yes	1 year	Sandoz Pharma
AMSA (Amlodipine vs slow release Metoprolol in the treatment of Atable exertional Angina) Midtbo 2000 Norway	Yes	2 months	Pfizer
APSIS (The Angina Prognosis Study in Stockholm) Sweden Rehnqvist, 1994 Rehnqvist, 1996		Median 3.4 years	Swedish Heart Lung Foundation; Swedish Research Medical Council; Knoll AG

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Destors 1989 4 European countries	Inadequate (sealed envelope)	NR	Small difference in duration of angina (months): bep 52, pro 67	Yes	Yes	Yes	Yes
Hall, 2001 UK	NR	NR	Yes	Yes	Yes	Yes	Reported ITT as including all patients that received one dose of drug *and* completed at least one efficacy analysis (e.g., 193 of original 196)
Hauf-Zachariou, 1997 Great Britain	NR	NR	Yes	Yes	Yes	Yes	Reported ITT as including all patients randomized (248); however, outcome results provided for *per protocol* population (212) only
Kawanishi, 1992 United States	NR	NR	Yes	Yes	Yes	Yes	Not clear

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population	Number recruited	Exclusion criteria for recruitment
Destors 1989 4 European countries	Not clear	Unclear	Overall 20% bep 19%, pro 22%, pla 17%	Fair-Good	Good	NR/191 randomized	Suffered exclusively at rest; nocturnal attacks; angina pectoris not secondary to atherosclerosis; unstable angina pectoris; Prinzmetal's angina; MI within past 6 months; unable to assess pain and fill in diary cards and sel-assessment forms; contraindication to proporandol or bepridil treatment; liver or kidney condition likely to modify drug metabolism; all reasons preventing close compliance to study protocol
Hall, 2001 UK	Not clear	Attrition reported. Others NR	No	Fair	Good; older population, greater proportion male	NR/196 enrolled	Unstable angina; MI or cardiac surgery within the preceding 3 months; uncompensated congestive heart failure; uncontrolled atrial fibrillation; gross left ventricular hypertrophy; insulin-dependent diabetes mellitus; gross obesity; severely impaired renal or hepatic function; significant anaemia or electrolyte abnormality or other major diseases; women of child-bearing capacity and pregnant or breast-feeding women; contraindications to treatment with alpha- or beta-adrenoceptor antagonists and CCB's
Hauf-Zachariou, 1997 Great Britain	Not clear	Attrition reported Others NR	No	Fair	Good; older population, greater proportion male	NR/313 enrolled	History of MI or coronary revascularization procedure within previous 3 months; insulin-requiring diabetes; bronchospastic lung disease or other diseases with symptoms that could be confused with angina pectoris; left bundle brach block; left ventricular hypertrophy; digoxin therapy; treatment with antiarrhythmic agents or any condition or medication that would interfere with interpretation of ST segment changes on the exercise ECG
Kawanishi, 1992 United States	Not clear	None reported	NR	Fair	Yes	74	Unstable angina within 2 months of study entry; MI or a revascularization procedure (coronary artery bypass surgery, percutaneous coronary intervention) within 6 months before study entry; any significant valvular disease, cardiomyopathy or CHF (NYHA class II-IV); uncontrolled hypertension (defined as systolic blood pressure (SBP) >/= 180 mmHg or diastolic blood pressure (DBP) >/= 110 mmHg or hypotension (SBP<100 mmHg); coexisting conditions limiting the ability to exercise; repolarization abnormalities rendering ST-segment evaluation not ideal for analysis (e.g., left ventricular hypertrophy with strain, left bundle branch block, paced rhythm); women who were pregnant or lactating; significant renal or hepatic impairment; stroke or transient ischemic attack within 12 months; allergy or hypersensitivity to calcium antagonists

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Control group standard of care	Length of follow-up	Funding
Destors 1989 4 European countries	Yes	6 months	possibly Organon
Hall, 2001 UK	Yes	28 weeks	NR
Hauf-Zachariou, 1997 Great Britain	Yes	12 weeks	Boehringer Mannheim GmbH
Kawanishi, 1992 United States	Yes	3 months	Pfizer

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Lee, 2002 Canada	adequate (block randomization)	NR	Yes	Yes	Yes	Yes	Not clear
Meyer, 1991 Israel	NR	NR	No; differences in 1) angina duration and 2) frequency of previous MI's	Yes	Yes	Yes	No; analysis did not include 3 patients who withdrew due to lack of efficacy
Myers 1988 Canada	NR	NR	No, number on nitrate therapy = nif 17%, pro 36%	Yes	Yes	no	primary outcomes and adverse events yes, secondary outcomes no.
Pandhi, 1991 India	NR	NR	Yes	Yes	Yes	Yes	No; analysis did not include patients who became lost-to-followup or withdrew due to worsening of angina
Pehrsson, 2000 Sweden	NR	NR	Yes	Yes	Yes	Yes	Not clear
Petersen, 2001 Denmark	Method NR	NR	Yes	Yes	Yes	Yes	Results for renal function are given for 48/60 patients (80%); those who withdrew or went on dialysis were excluded from the analysis. However, number who reached end stage renal disease, need for dialysis or doubling of serum creatinine is reported.

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population	Number recruited	Exclusion criteria for recruitment
Lee, 2002 Canada	Not clear	Withdrawals due to AEs and compliance clearly reported. Others NR	Not clear	Fair			Intolerance to the study medication; MI or heart surgery within 3 months prior to the beginning of the trial; contraindications to the performance or ergometry
Meyer, 1991 Israel	Not clear	Withdrawals due to lack of efficacy clearly reported. Others NR	No	Poor	Good; Average age >50; higher proportion male	NR/31 randomized	Beta blocker or calcium channel blocker therapy during previous 2 weeks; MI within previous 3 months; evidence of congestive heart failure (Framingham criteria); heart block (PR interval > 0.24 s); hypotension (supine SBP <100 mmHg); asthma; insulin dependent diabetes mellitus; renal dysfunction (serum creatinine >30 mg/dL; hepatic disease (enzymes <30% above normal); ventricular tachycardia or fibrillation in previous month; rapid atrial fibrillation as cause of unstable angina
Myers 1988 Canada	Not clear	Attrition reported Others NR	loss = 0, withdrawals nif 17%, pro 29%	Poor	Fair, more women than men	NR/27 randomized	Evidence of aortic valve disease; cardiovascular syphilis; hepatic or renal failure; insulin dependent diabetes mellitus; myocardial infarction within the last 3 months; presence of possible cause of angina pectoris other than ischemic heart disease; evidence of left ventricular failure or severe retinopathy
Pandhi, 1991 India	Not clear	Attrition reported Others NR	No	Fair	Good; older population, greater proportion male	NR/40 enrolled	MI; coronary bypass surgery; percutaneous transluminal coronary angioplasty (PTCA) in the preceding 3 months, unstable angina; signs and/or symptoms of CHF; significant arrhythmia; second or third degree atrioventricular block, diastolic blood pressure >115 mmHg or systolic blood pressure >250 mmHg; medication influencing ECG; receiving beta blockers or calcium antagonists that could not be safely withdrawn; in need of supplementary anti-ischemic medication other than ntg during the run-in period; in need of revascularization
Pehrsson, 2000 Sweden	Not clear	Attrition clearly reported. Others NR	No	Fair	Good; Average age >50; higher proportion male	442 screened/351 randomized	Significant hepatic, renal, cardiac, brochospastic disease; major concurrent disease; women of childbearing potential
Petersen, 2001 Denmark	Unclear	Attrition yes, others no.	No	Fair	Chronic renal disease	60	Renal artery stenosis or severe congestive heart failure (NYHA class III-IV).

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Control group standard of care	Length of follow-up	Funding
Lee, 2002 Canada	Yes		
Meyer, 1991 Israel	Yes	8 weeks	NR
Myers 1988 Canada	Yes	stated to be 3 months, but some outcome measures only reported for 2 wks	Miles Labs, Heart and Stroke Foundation of Ontario, Sunnybrook Trust for Medical Research
Pandhi, 1991 India	Yes	8 weeks	NR
Pehrsson, 2000 Sweden	Yes	10 weeks	NR
Petersen, 2001 Denmark	Yes	21 months	Supported by grants from Novartis, Danish Research Academy, Research Foundation of the Danish Society of

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Singh 1993 USA	NR	NR	yes, but very few measured presented	Yes	NR	Yes	Not clear
SWAN study group 1999 Switzerland, Austria	NR	NR	No, number with prior MI aml 41%, nic 25%, also aml group longer duration of angina (6 months)	Yes	nr	Yes	no, stated to be but 3 patients not accounted for
TIBET (Total Ischaemic Burden European Trial) 9 European countries Dargie, 1996 The TIBET Study Group, 1992	NR	All drugs formulated as matching capsules. Information about packaging NR	Yes	Yes	Yes	Yes	Yes

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population	Number recruited	Exclusion criteria for recruitment
Singh 1993 USA	Not clear	Attrition clearly reported. Others NR	Overall 24%; aml 20%, nad 28%	Fair-Poor	Fair	NR/80 randomized	MI; invasive coronary intervention; unstable angina; angina at rest or vasospastic angina within last 3 months; hypertension with supine DBP >105 mmHg; electrocardiogram recordings not allowing evaluation of the ST-segment; manifest congestive heart failure (NYHA class III-IV); peripheral arterial obstructive disease or any exercise test limiting disease; cardiac valvular disease with hemodynamic or clinical consequences; supine SBP <100 mmHg or DBP <70 mmHg; postural hypotension (>20% decrease in SBP 1 minute after standing); severe concomitant disease
SWAN study group 1999 Switzerland, Austria	Not clear	Not clearly reported	No	Poor	Good	143 recruited/121 randomized	Any clinically important concomitant disease: MI within previous 3 months; renal impairment (serum creatinine >200 mmol/l or >2.3 mg/100 ml); hepatic function impairment (aspartate transaminase (AST/SGOT) or alanine transaminase(ALT/SGPT) enzyme results +15% above the upper normal limit and deemed clinically significant); anemia, (hemoglobin concentration of <11 g/dl in females or <12 g/dl in males); hypotension, (standing SBP=100 mgHg; and hypertension, defined as SBP=200 mmHg or DBP>105 mmHg on placebo); contraindications to beta blockade (decompensated heart failure, second- or third-degree heart block, left or right bundle branch block or preexcitations states, reversible obstructive airways disease, IDDM, previous intolerance to beta blockage) or nifedipine: premenopausal women, unless they had a hysterectomy or previous intolerance to the drug; presence of confounding factors for interpretations of ECG (left ventricular hypertrophy and resting ST-T wave abnormalities on electrocardiogram, predominant cardiac rhythm other than sinus rhythm, concurrent treatment with digoxin
TIBET (Total Ischaemic Burden European Trial) 9 European countries Dargie, 1996 The TIBET Study Group, 1992	Not clear	Overall attrition clearly reported. Others NR	No	Fair-Good	Good; Average age >50; higher proportion male	916 screened/682 randomized	Recent myocardial infarction (<3 months); unstable angina; angina at rest; or vasospastic angina; uncontrolled hypertension; ECG tracings disturbing the evaluation of the ST segment; congestive heart failure; history of exercise-induced arrhythmia; concomitant medication with digitalis, antiarrhythmics and antianginal drugs

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Control group standard of care	Length of follow-up	Funding
Singh 1993 USA	Yes	24 weeks	NR
SWAN study group 1999 Switzerland, Austria	Not in US	8 weeks	NR
TIBET (Total Ischaemic Burden European Trial) 9 European countries Dargie, 1996 The TIBET Study Group, 1992	Yes	mean 2 years	ICI Pharmaceuticals

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Ulvenstam; 1992 Europe (Norway, Sweden, Iceland)	NR	NR	No; differences in history of MI and weekly anginal attack rate	Yes	Yes	Yes	Yes for safety(n=58); no for efficacy(n=55); reason for 3-patient discrepancy NR
Vliegen, 1991 The Netherlands	Unspecified randomization schedule with a blocking factor of 6	NR	No - statistically significant differences in age and height were seen	Yes	Yes	Yes	No
Armstrong, 1986 UK	NR	NR	Yes	Yes	Yes	Yes	No; analysis did not include 12 patients that withdrew "early on" due to adverse events
Bernink, 1991 The Netherlands	NR	NR	Some differences; % male higher and angina attack severity lower in Aml group	Yes	Yes	Yes	No

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population	Number recruited	Exclusion criteria for recruitment
Ulvenstam; 1992 Europe (Norway, Sweden, Iceland)	Not clear	only withdrawals due to AEs reported	No	Fair-Poor	Good; older population, greater proportion male	68	Recent myocardial infarction (<3 months); unstable angina; angina at rest; or vasospastic angina; uncontrolled hypertension; ECG tracings disturbing the evaluation of the ST segment; congestive heart failure; history of exercise-induced arrhythmia; concomitant medication with digitalis, antiarrhythmics and antianginal drugs
Vliegen, 1991 The Netherlands	Not clear	Attrition clearly reported; others NR	No	Fair-Poor	Good; older population, greater proportion male	NR/56 enrolled	Unstable angina; MI or bypass surgery within 3 months prior to study; severe valvular disease; congestive heart failure; moderate or severe hypertension; functioning cardiac pacemaker; atrial fibrillation or severe symptomatic arrhythmias; resting ECG abnormalities that render the interpretation of ST-segment changes difficult; bundle branch block at rest of during exercise; any degree of atrioventricular block; contraindication to the use of either study drug; inability to perform an exercise test or adhere to the protocol for whatever reason; the presence of any condition disregulating the pharmacokinetics of the medication during the study; the use of any medication during the study that might interfere with the efficacy or adverse effects of either study drug; pregnancy or lactation in women; or any other serious medical disease
Armstrong, 1986 UK	Not clear	Attrition reported Others NR	No	Fair	Good; older population, greater proportion male	46	Pregnancy, lactation, recent MI, valvular disease, arrhythmias, heart block or other ECG alterations, arterial BP >200/120 mmHg in supine position, postural hypotension, bradycardia, unstable angina, severe concomitant diseases, use of other calcium antagonists, hypersensitivity to dihydropyridine drugs, drug dependence, participation in other studies.
Bernink, 1991 The Netherlands	Not clear	Withdrawals due to adverse events, lack of efficacy and compliance reported clearly. Others NR	*Difference in 35.9% of Aml patients and 70.7% of Dil patients between randomization and efficacy analysis reported to be due to exercise protocol violations or lack of a final visit.	Poor	Good; older population, greater proportion male	80	Unstable or variant (Prinzmetal's) angina; history of myocardial infarction coronary angioplasty or coronary artery bypass surgery within 3 months of enrollment; stroke or transient ischemic attack within this 3-month period; cardiovascular disease other than chronic stable angina; disorders that could cause incomplete absorption of the study medication were excluded; psychiatric conditions that could lead to noncompliance; treatment with transdermal nitrate preparations and other antianginal agents; digoxin and cimetidine use

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Control group standard of care	Length of follow-up	Funding
Ulvenstam; 1992 Europe (Norway, Sweden, Iceland)	Yes	8 weeks	NR
Vliegen, 1991 The Netherlands	Yes	23 patients completed 8 weeks of follow-up; 39 patients completed 32 weeks of follow-up	Supply of Dil CR provided by Lorex Pharmaceutica
Armstrong, 1986 UK	Yes	8 weeks	NR
Bernink, 1991 The Netherlands	Yes	8 weeks	NR

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Canale, 1991 Italy	NR	NR	Yes	Yes	Yes	Yes	Yes
Hall, 1998 UK	NR	NR	Yes	Yes	Yes	Yes	ITT for safety (the 288 patients randomized) "Valid cases analysis" used for: Subjective efficacy analysis(n=234) Exercise test analysis (n=226) Referred to other ITT for subjective and exercise test (n=271) showing results that did not differ from valid-cases-analysis; method of deriving this ITT population NR
Knight, 1998 UK	NR	NR	Yes	Yes	Yes	Yes	Yes

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population	Number recruited	Exclusion criteria for recruitment
Canale, 1991 Italy	Yes	Reported that adverse events did not require discontinuation. Others NR	No	Fair	Good; older population, greater proportion male	40	NR
Hall, 1998 UK	Not clear	Attrition reported Others NR	No	Fair	Good; older population, greater proportion male	320	MI, coronary angioplasty, coronary artery bypass surgery, stroke or transient ischemic attack within previous 3 months, clinical features suggestive of impending MI, unstable angina, variant (Prinzmetal's) angina; congestive heart failure, left ventricular failure, clinically significant valvular disease; clinical evidence of major arrhythmia requiring treatment with anti-arrhythmic medication or with prolongation of conduction time in ECG or known conduction disturbances; uncontrolled HTN (seated systolic or diastolic blood pressure >180 mm Hg or 100 mmHg, respectively); clinically significant renal dysfunction (creatinine >200 μmol/L), hepatic dysfunction (serum transaminases >2 times upper limit of normal), systemic, hematologic, central nervous system, metabolic disease; taking digoxin, amiodarone, theophylline, cimetidine, cyclosporine, lithium, anti-epileptics, barbiturates; ECG changes that prevented accurate analysis of ST-segment changes during exercise; transdermal nitrate preparations, other anti-anginal agents not allowed during study or in preceding 2 weeks.
Knight, 1998 UK	Yes	Not clear	No	Fair	Good; older population, greater proportion male	109	NR

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Control group standard of care	Length of follow-up	Funding
Canale, 1991 Italy	Yes	10 weeks	NR
Hall, 1998 UK	Yes	8 weeks	Bayer AG
Knight, 1998 UK	Yes	8 weeks	Pfizer

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Littler, 1999 UK	NR	NR	Yes	Yes	Yes	Yes	227 patients were randomized; only 219 patients were considered to be valid for the ITT efficacy analysis; reason(s) for difference of 8 patients NR
Pehrsson 1996 Sweden	NR	NR	no, aml group had lower exercise capacity as measured by bicycle test. Aml group had > angina attacks/wk but < NTG tabs/wk at baseline	Yes	NR	Yes	Unclear
Radice 1991 Italy	NR (met and nif randomized, dil added later)	NR	no, but very little data presented	Yes	No	NR	NR
Reicher-Reiss 1992 Israel	NR	NR	Nis group had better exercise tolerance at baseline, but slightly more angina attacks and NTG use per week.	Yes	NR	Yes	Unclear

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population	Number recruited	Exclusion criteria for recruitment
Littler, 1999 UK	Not clear	Attrition reported Others NR	No	Fair	Good; older population, greater proportion male	293	MI, coronary angioplasty, coronary artery bypass surgery, stroke or transient ischemic attack within previous 3 months, clinical features suggestive of impending MI, unstable angina, variant (Prinzmetal's) angina; congestive heart failure, left ventricular failure, clinically significant valvular disease; clinical evidence of major arrhythmia requiring treatment with anti-arrhythmic medication or with prolongation of conduction time in ECG or known conduction disturbances; uncontrolled HTN (seated systolic or diastolic blood pressure >180 mm Hg or 100 mmHg, respectively); clinically significant renal dysfunction (creatinine >200 μmol/L), hepatic dysfunction (serum transaminases >2 times upper limit of normal), systemic, hematologic, central nervous system, metabolic disease; taking digoxin, amiodarone, theophylline, cimetidine, cyclosporine, lithium, anti-epileptics, barbiturates; ECG changes that prevented accurate analysis of ST-segment changes during exercise; transdermal nitrate preparations, other anti-anginal agents not allowed during study or in preceding 2 weeks.
Pehrsson 1996 Sweden	NR	Yes	16% overall, and per group	Poor	Good	NR	MI, CABG and/or PTCA within past 3 months, unstable angina, signs and/or symptoms of CHF, significant arrhythmia, affecting the ECG (e.g. digoxin or antiarrhythmic drugs) and malignant hypertension, hepatic or renal failure or those unable to attend regular follow-up.
Radice 1991 Italy	NR	NR	NR	Poor	Unclear	NR	MI within 6 months, coronary reperfusion procedures, contraindications or calcium and beta blockers or to repeated exercise tests, need for concomitant therapy with antiarrhythmic or inotropic agents, abnormalities on the rest ECG that could interfere with interpretation of ST-segment changes.
Reicher-Reiss 1992 Israel	NR	Yes	no, only 1 drop out in nis group	Poor	Unclear	NR	Unstable angina, a recent AMI (less than 3 months), a definite need for calcium antagonist therapy or known sensitivity to calcium antagonists, presence of advanced AV conduction disturbances or clinical evidence of CHF.

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Control group standard of care	Length of follow-up	Funding
Littler, 1999 UK	Yes	12 weeks	Bayer
Pehrsson 1996 Sweden	Yes	8 weeks	Pfizer
Radice 1991 Italy	Yes	3 months	NR
Reicher-Reiss 1992 Israel	Yes	8 weeks	Bayer

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Singh 1991 USA	NR	NR	Small differences at baseline in % receiving max allowable dose of dil at baseline, taking beta blocker, and with history of MI.	Yes	NR	Yes	No
Van Kesteren	NR	NR	Yes	Yes	Yes	Yes	Stated ITT, but not clear
Johnson, 1981 United States	NR	NR	Crossover	Yes	Yes	NR	No
Johnson, 1981 United States	NR	NR	N/A	Yes	NR	NR	Yes
AASK Agodoa, 2001 Wright, 2002 US	NR	double-masked	Yes	Yes	Yes, double-masked	Yes to study drugs	Yes
ALLHAT Furberg, 2002; Grimm, 2001; Vidt, 2000; HALLHAT Officers, 2002; US	On site computer generated	Yes	Yes	Yes	Yes, double blind	NR for study drugs Open label for additional drugs	Yes

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population	Number recruited	Exclusion criteria for recruitment
Singh 1991 USA	NR	Yes	Overall 16% loss, bep 20%, dil 12%	Poor	Good	NR	MI within 3 months, CHF, or any other cardiac condition that might interfere with data interpretation or put patient at undue risk, bradycardia <50 bpm, QTc prolongation >15% above the upper limit for their age/sex, serum potassium levels <3.5 mEq/L, minor tranquilizers, nonnarcotic analgesic and diuretic drugs, other calcium antagonists, antiarrhythmic drugs, cardiac glycosides, tricyclic antidepressants, and neuroleptics.
Van Kesteren	Not clear	Attrition reported Others NR	No	Fair	Good; older population, greater proportion male	132	Unstable angina; recent MI; heart failure; valvular or congenital heart disease; arrhythmias; bradycardia or tachycardia; hypotension; chronic liver disease; chronic obstructive pulmonary disease; insulin-dependent diabetes mellitus; coronary artery bypass graft or percutaneous transluminal coronary angioplasty performed less than 3 months before randomization; women of child-bearing potential; lactating women
Johnson, 1981 United States	Crossover	Yes	No	Fair	Yes	19	Yes
Johnson, 1981 United States	Crossover	No	No	Fair	Yes	10	
AASK Agodoa, 2001 Wright, 2002 US	Yes	Yes	No Total 8.1%	Fair	Yes	1094	DBP < 95, diabetes, Urinary Protein/Creatine > 2.5, accelerated hypertension in past 6 months, secondary hypertension, non-BP renal disease, serious systemic disease, CHF, contraindication for study drug
ALLHAT Furberg, 2002; Grimm, 2001; Vidt, 2000; HALLHAT Officers, 2002; US	Yes	Yes	No Aml 2.8% Chl 2.7% Lis 3.0%	Good	Yes	42418	Confusing. Furberg stated patients could not be on other clinical trial. Vidt stated that 25% of ALLHAT patients participating in open label clinical trial on lowering LDLs.

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Control group standard of care	Length of follow-up	Funding
Singh 1991 USA	Yes	8 weeks	McNeil, grants from Medical Research Service of Veterans Affairs, American Heart Assoc., 2 members of collaborative study group from McNeil
Van Kesteren	Yes	8 weeks	Pfizer
Johnson, 1981 United States	Yes	9 months	NIH Ischemic Heart Disease Specialized Center of Research grant
Johnson, 1981 United States	Yes	8 months	NIH; Knoll Pharmaceutical Company; Pfizer Pharmaceutical Company supplied tablets
AASK Agodoa, 2001 Wright, 2002 US	Yes	2-5 years	NIH, National Institute of Diabetes and Digestive and Kidney Diseases, Pfizer, Astra-Zeneca King Pharmaceuticals
ALLHAT Furberg, 2002; Grimm, 2001; Vidt, 2000; HALLHAT Officers, 2002; US	Yes	6 years	National Heart, Lung and Blood Institute, AstraZeneca, Bristol-Myers Squibb and Pfizer, Inc.

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
FACET Tatti, 1998 Pahor, 1998 Italy	Computer-generated random number sequence	Yes	Yes	Yes	Yes	N, open-label	Yes
NICS-EH NICS-EH Study Group, 1999;	Controller in central office	NR	Yes	NR	Yes, steering committee	double-dummy	Yes, 'Per protocol"
Marin, 2001 Spain	NR	NR	Yes	Yes	No, open trial	No, open trial	Stated ITT, unclear
Chan, 1992 Chan, 2000 Hong Kong	102 allocation numbers corresponding to similarly numbered drug supplies employed; patients with microalbuminuria or macroalbuminuria assigned allocation numbers in a descending manner; normoalbuminuria assigned ascending numbers	Yes	No; Nif group younger by 4 years (56.1 vs. 60.1), lower SBP (166.5 vs. 172.1) and lower total cholesterol (5.45 vs. 5.97)	Yes	Yes	Yes	Yes
International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment (INSIGHT) Brown, 1996 Brown, 1997 Mancia, 1998 Brown, 2000 Brown, 2001 Brown, 2001 UK, France, Israel, Netherlands, Spain, Italy, Sweden, Denmark, Norway	Treatment allocation by minimization taking account of age, sex, risk factor status, aspirin therapy, and entry to side-arm study	NR	Yes	Yes	Yes	Yes	Nif GITS=3157; Co-ami=3164 patients included in ITT; 132 patients in Nif GITS group and 122 patients in Co-ami group withdrawn for misconduct not included in ITT

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population	Number recruited	Exclusion criteria for recruitment
FACET Tatti, 1998 Pahor, 1998 Italy	Yes, Only diff albuminuria 24 (aml) vs 20 (fos) p<0.05	Yes by self-report, pill count and bp, adherence>80%	No	Good	Yes	380	Stated
NICS-EH NICS-EH Study Group, 1999;	Yes	Yes	No	Fair	Yes	414/429	NR
Marin, 2001 Spain	Yes	Attrition reported Others NR	No	Fair	Good Mean age: Fos=53; Nif GITS=56 Gender(%male): Fos=60.5; Nif GITS: 57.1	241	Diabetes mellitus, with a previous recent history of cardiovascular disease (stroke, MI, or heart failure), taking concomitant medications that could interfere with study results (steroids, immunosuppressant drugs, or NSAIDS), or presenting intolerance to either study drug
Chan, 1992 Chan, 2000 Hong Kong	Yes	Attrition reported Others NR	No	Fair	100% Chinese Mean age: Ena=60.0; Nif=56.2(p=0.047) Gender(%male): Ena=40; Nif=40.4	102 enrolled	Patients receiving insulin or had a history of non-diabetic renal disease; appreciablerenal impairment (plasma creatinine concentration >/= 200 mmol/L); plasma potassium concentration >/= 5 mmol/L; cardiac failure or any concurrent systemic disease; receiving treatment for any concomitant disorder
International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment (INSIGHT) Brown, 1996 Brown, 1997 Mancia, 1998 Brown, 2000 Brown, 2001 Brown, 2001 UK, France, Israel, Netherlands, Spain, Italy, Sweden, Denmark, Norway	Unclear	Attrition reported Others NR	Lost to fu: Nif GITS=2.0%; Co-ami=2.5%	Fair	*Age:* <60: Nif GITS=24.1%; Co-ami=22.3% 60-70: Nif GITS=47.9%; Co-ami=49.2% >70: Nif GITS=28.0%; Co-ami=28.6% *Gender(%male):* Nif GITS=46.1%; Co-ami=46.6%; lower % male than in most trials	7434 enrolled 6575 randomized	History of malignant HTN; congestive heart failure; unstable insulin-dependent diabetes mellitus; subarachnoid hemorrhage; PTCA; CABG or either MI or stroke in the 12 months prior to study entry

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Control group standard of care	Length of follow-up	Funding
FACET Tatti, 1998 Pahor, 1998 Italy	Yes	3 years	Bristol-Myers Squibb, Pfizer
NICS-EH NICS-EH Study Group, 1999;	Yes		NR
Marin, 2001 Spain	Yes	A minimum of 3 years	NR
Chan, 1992 Chan, 2000 Hong Kong	Yes	5+ years	NR
International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment (INSIGHT) Brown, 1996 Brown, 1997 Mancia, 1998 Brown, 2000 Brown, 2001 Brown, 2001 UK, France, Israel, Netherlands, Spain, Italy, Sweden, Denmark, Norway	Yes	48 months	Bayer AG

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
NORDIL (Nordic Diltiazem Study) The NORDIL Group, 1993 Hedner, 1999 Hansson, 2000 Kjeldsen, 2002 Norway/Sweden	Adequate; Call-in system via central randomization center	N/A; open study	yes	Yes	Yes	No, open trial	Data from 35 patients from one center were not included in analysis because of uncertainty about data quality
ABCD (Appropriate Blood Pressure Control in Diabetes) Savage, 1993 Schrier, 1996 Estacio, 1998a Estacio, 1998b United States	Method NR; stratified by baseline DBP, gender, cardiovascular disease history	NR	No; Nis group had higher level of high density lipoprotein (HDL) and lower prevalence of abnormal ankle brachial indices	Yes	Yes	Yes	Yes
MIDAS (Multicenter Isradipine Diuretic Atherosclerosis Study) The MIDAS Research Group, 1989 Borhani, 1990 Borhani, 1991 Borhani, 1992 Furberg, 1993 Borhani, 1996 United States	NR	NR	Yes	Yes	Yes	Yes	Yes

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population	Number recruited	Exclusion criteria for recruitment
NORDIL (Nordic Diltiazem Study) The NORDIL Group, 1993 Hedner, 1999 Hansson, 2000 Kjeldsen, 2002 Norway/Sweden	Unclear	Attrition, crossovers, contamination reported. Adherence NR	Lost to fu: Dil=24(0.4%); Con=28(0.5%)	Fair	Mean age: Dil=60.5; Con=60.3 Gender(%male): Dil=48.5; Con=48.7; lower % male than in most trials	Enrolled NR 10916 randomized	Younger than 50 years or older than 70; clinically relevant bradycardia (< 50 BPM); secondary hypertension (e.g., renal hypertension); atrial fibrillation with WPW-syndrome; contraindications to study medication according to FASS/FELLES KATALOGEN: sick sinus syndrome, AV-block II and II without functioning pacemaker; treatment with beat-blockers, diuretics, calcium channel blockers, or other antihypertensives not included in the study; history of cerebrovascular disease or MI within the previous 6 months; present congestive heart failure
ABCD (Appropriate Blood Pressure Control in Diabetes) Savage, 1993 Schrier, 1996 Estacio, 1998a Estacio, 1998b United States	Unclear	Attrition, contamination reported. Others NR	NR	Fair	Good Mean age: Nis=57.2; Ena=57.7 Gender(%male): Nis=68.1; Ena=66.8	470 enrolled in hypertension arm	Known allergy to dihydropyridine calcium-channel blockers or ACE inhibitors; MI or cerebrovascular accident or unstable angina pectoris within previous 6 months; coronary-artery bypass surgery within previous 3 months; NYHA class III or IV congestive heart failure; absolute need for therapy with ACE inhibitors of calcium-channel blockers; receiving hemodialysis or peritoneal dialysis; serum creatinine concentration >3 mg per deciliter
MIDAS (Multicenter Isradipine Diuretic Atherosclerosis Study) The MIDAS Research Group, 1989 Borhani, 1990 Borhani, 1991 Borhani, 1992 Furberg, 1993 Borhani, 1996 United States	Unclear	Attrition, contamination reported. Others NR	NR	Fair	Good Mean age: Isr=58.2; HCTZ=58.7 Gender(%male): Isr=79.9; HCTZ=75.7	18,800 signed consent 883 met criteria and were randomized	Patients with known allergy to dihydropyridine calcium-channel blockers or ACE inhibitors; MI or cerebrovascular accident within the previous six months; had undergone coronary-artery bypass surgery within the previous 3 months; had unable angina pectoris within the previous six months; had NYHA class III or IV congestive heart failure; had an absolute need for therapy with ACE inhibitors of calcium-channel blockers; were receiving hemodialysis or peritoneal dialysis; had a serum creatinine concentration > 3 mg per deciliter

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Control group standard of care	Length of follow-up	Funding
NORDIL (Nordic Diltiazem Study) The NORDIL Group, 1993 Hedner, 1999 Hansson, 2000 Kjeldsen, 2002 Norway/Sweden	Yes	Mean follow-up 4.5 years	Pharmacia
ABCD (Appropriate Blood Pressure Control in Diabetes) Savage, 1993 Schrier, 1996 Estacio, 1998a Estacio, 1998b United States	Yes	67 months for Nis group, at which time these patients were switched to open enalapril therapy; mean fu NR	Bayer AG
MIDAS (Multicenter Isradipine Diuretic Atherosclerosis Study) The MIDAS Research Group, 1989 Borhani, 1990 Borhani, 1991 Borhani, 1992 Furberg, 1993 Borhani, 1996 United States	Yes	67 months for Nis group, at which time these patients were switched to open enalapril therapy; mean fu NR	Bayer AG

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
CONVINCE Black, 1998, 2001, US	Stratified by site and control drug (ate or HCTZ) in successive permuted blocks 2,4, or 6 selected randomly. Central site randomized with call in protocol	Yes	Yes	Yes	Yes	Yes	Y, although 62 (ver) and 64 (HCTZ and ate) patients excluded due to data integrity concerns at 2 sites.
Testa, 1998 Spain	NR	NR	No; mean age higher in nif group(p=0.023)	Yes	Yes	Yes	Unclear Randomized: nif=178; aml=178 ITT: nif=172; aml=175 Table 4 results: nig=161; aml=174
Black, 2001	NR	NR	Yes	Yes	Yes	Yes	Yes for safety; no for QOL
Yilmaz	NR	NR	Yes	Yes	NR	NR	NR

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population	Number recruited	Exclusion criteria for recruitment
CONVINCE Black, 1998, 2001, US	Yes	Yes	N At 1 year 8% (ver) 7% (HCTZ or ate) At 2 years 14% (ver) 14% (HCTZ or ate) At 3 years 21% (ver) 20% (HCTZ or ate)	Fair	Good	16602	History of heart failure, NYHA class II-IV. Untreated SBP >190 or DBP >220 mmHG; secondary hypertension; cardiac dysrhythmias requiring medication; sick sinus syndrome; symptomatic MI w/in past 12 months or stroke or symptomatic angina w/in past 6 mo; known renal insufficiency; need specific study medication to achieve goal BP or need more than 3 drugs to control BP; contraindications for any of the study medications; low likelihood of compliance; other life threatening diseases; participation in other clinical trial of antihypertensive medications within 30 days of randomization; working evening, night or alternating shifts.
Testa, 1998 Spain	Unclear	Withdrawals due to lack of efficacy, AEs and 'other' clearly reported Others NR Overall withdrawal(%): nif=31; aml=25	No	Fair	Good Mean age: nif=56.3; aml=53.6 BP: nif=158.5/100.1; aml=155.5/100.1	430 screened 356 randomized	NR
Black, 2001	Unclear	Attrition clearly reported; others NR	No	Fair	Good; nearly half age>65 years, which the paper reported as being typical of this population	250 screened 171 enrolled	NR
Yilmaz	NR	NR	NR	Fair	Fair	NR	*Preoperative* Rhythm/conduction disturbances; BB agents; hyperthyroidism; GI diseases causing absorption dysfunction; LV aneurysm; severe LV dysfunction *Operative* Surgical interventions added to coronary artery surgery (e.g., aneurysmectomy, valve procedures) *Postoperative* MI; renal insufficiency; low cardiac output; severe respiratory complications; ventricular arrhythmias; symptomatic sinus bradycardia

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Control group standard of care	Length of follow-up	Funding
CONVINCE Black, 1998, 2001, US	Yes	2 to 4.25 years Note: Sponsor stopped study 2 years early.	Searle, Pharmacia Note: sponsor stopped study 2 years early.
Testa, 1998 Spain	Yes	24 weeks	Quimica Farmaceutics Bayer
Black, 2001	Yes	52 weeks	AstraZeneca, LP
Yilmaz	Yes	Extremely short	NR

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Botto, 1998 Italy	NR	NR	N/A - crossover study	Yes	Yes	no	Yes
Lundstrom, 1990 Sweden	NR	nr	na - crossover study	yes, but extremely vague	Yes	Yes	No
Ochs 1985 Germany	NR	NR	Dil group had more patients with mitral valve disease, had AF longer, mean 4.6 vs 2.4 yrs, and more men (53% vs 27%)	Yes	Yes	Yes	No, but calculated based on numbers presented
Dahlstrom 1992 Sweden	NR	NR	N/A - crossover study	Yes	NR	NR	No
Farshi, 1999 US	NR	NR	N/A - crossover study	Yes	No	No	No

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population	Number recruited	Exclusion criteria for recruitment
Botto, 1998 Italy	Yes	Yes	None	Fair	Good	NR	Renal failure, congestive heart failure, left ventricular ejextion fraction <40%, angina or recent myocardial infarction (< 6 months), preexcitation syndrome, electrolyte imbalance, uncontrolled hypertension (SBP >160 mmHg and DBP >100 mmHg) and concomitant therapy with antiarrhythmic agents. Rate modifying drugs not used as antiarrhythmics also excluded (e.g. bronchodilators), patients requiring digoxin or with contraindications to CCBs were excluded.
Lundstrom, 1990 Sweden	Yes	Yes	Yes, 1 lost during dil, none in ver or placebo. But overall rate is low.	Fair	Fair	NR	NR
Ochs 1985 Germany	NR	Yes	Overall withdrawal rate = 20%, 27% in ver group, 7% in dil group	Fair	Fair	NR	NR
Dahlstrom 1992 Sweden	NA	Yes	Overall withdrawal rate 23% dil 0% pro 8% dil + pro 15%	Fair	Unclear	28/13 due to adverse events from combination therapy	Angina pectoris,decomesnsated heart disease NYHA classes III-IV, severe ventricular arrhythmias, untreated thyureotoxicosis, marked anemia, galucoma, advanced pulmonary disease, systolic blood pressure <95 or >160/95 mmHg (before or during the prestudy period), diabetes mellitus, severe hepatic or renal disease, inability to withdraw a) other antiarrhythmic drugs, other than digoxin; b) vasodilators, including calcium entry blockers, c) beta blockers, d) tricyclic antidepressants, pehnothiazines, and diazepam and MI within preceding 6 months.
Farshi, 1999 US	NA	No	None	Fair	Fair	NR	LVEF <35% by Echo, HR < 55 bpm, Wolff-Parkinson-White syndrome, clinically significant renal thyroid or heparic dysfunction, uncontrolled hypertension, sick sinus syndrome, implanted pacemaker, unstable angina or acute MI or persistent systolic blood pressure <95 mmHg, taking theophylline, clonidine,or inhaled beta-agonists, or with previous exposure to amiodarone.

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Control group standard of care	Length of follow-up	Funding
Botto, 1998 Italy	Yes	Extremely short	NR
Lundstrom, 1990 Sweden	Yes	Extremely short	Swedish Heart and Lung Foundation, and Ferrosan (Swedish medical device and nutritional supplement co.)
Ochs 1985 Germany	Yes	Extremely short	Deutsche Forschungsgemeinschaft (German Research Foundation)
Dahlstrom 1992 Sweden	Yes	Extremely short	KABI-Pharmacia, Swedish Heart Lung Foundation and the Gothenburg Medical Faculty
Farshi, 1999 US	Yes	Extremely short	Friends of Research

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Koh, 1995 Korea	NR	NR	Yes	Yes	No	No	No
Koh, 1995 Korea	NR	NR	Yes	Yes	No	No	No
Hohnloser 2000 Germany	NR	NR	some differences: dil group longer duration AF, more recurrent AF at baseline, higher proportion with hypertension.	Yes	No	No	Stated to be ITT, but data not available for all patients (e.g. not all patients had 24 hour Holter or 6 min walk test data)
Lewis 1988 Scotland	NR	NR	N/A - crossover study	Yes, but extremely vague	NR	Yes	No
Ahuja 1989 India	NR	NR	N/A - crossover study	Yes, but extremely vague	No	No	No
Channer 1987 UK	NR	NR	N/A - crossover study	Yes, but extremely vague	Yes	No	No
Dorian, 1996 multiple countries	NR	NR	Yes	yes	no	No	Yes
James, 1989 UK	NR	NR	N/A - crossover study	Yes, but extremely vague	Yes	No	No
Lewis 1987 Scotland	adequate (random numbers)	NR	N/A - crossover study	Yes, but extremely vague	Yes	No	No

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population	Number recruited	Exclusion criteria for recruitment
Koh, 1995 Korea	NR	Yes	NR	Fair	Fair	NR	HR at rest < 60 bpm, ejection fraction <30%, diabetes mellitus, bronchial asthma, chronic obstructive lung disease, untreated thyrotoxicosis < 2 months after myocardial infarction, and SBP < 90 mmHg
Koh, 1995 Korea	NR	Yes	NR	Fair	Fair	NR	HR at rest <60 bpm, ejection fraction <30%, diabetes mellitus, bronchial asthma, chronic obstructive lung disease, untreated thyrotoxicosis <2 months after MI, and SBP <90 mmHg
Hohnloser 2000 Germany	NR	Yes	Yes - high loss to follow up in ami group	Fair	Good	NR	NYHA class IV heart failure, unstable angina, acute MI within 30 days, AF with an average of fewer than 50 BPM, known sick-sinus syndrome, AF in setting of Wolff-Parkinson-White syndrome, CABG or valve replacement within past 3 months, echo documentation of intracardiac thrombus formation, central or peripheral embolization within the past 3 months, hypertrophic cardiomyopathy, amiodarone therapy within the last 6 months, acute thyroid dysfunction, pacemaker therapy, contraindications for systemic anticoagulation therapy.
Lewis 1988 Scotland	NA	Yes	3 withdrew during treatment with dil	Fair	Unclear	NR	NR
Ahuja 1989 India	NA	Yes	None	Poor	Fair	NR	NR
Channer 1987 UK	NA	Yes	None	Fair	Poor, very high proportion of women, high proportion of valve disease	NR	NR
Dorian, 1996 multiple countries	NR	Yes	NR	Fair	NR	NR	Coexisting paroxysmal atrial fibrillation or flutter, prior history of MI or unstable angina, history of sustained ventricular tachycardia, NYHA class III or IV CHF, second or third degree AV block, or a PR interval >0.28 seconds or QRS interval >0.15 seconds during sinus rhythm
James, 1989 UK	NR	Yes	NR	Fair	Fair	NR	NR
Lewis 1987 Scotland	NR	Yes	NR	Fair	Good	NR	NR

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Control group standard of care	Length of follow-up	Funding
Koh, 1995 Korea	Yes	Moderate	NR
Koh, 1995 Korea	Yes	Moderate	Inha University grants
Hohnloser 2000 Germany	Yes	Good	Sanofil Synthelabo Research, and Parke Davis Research
Lewis 1988 Scotland	Yes	Extremely short	NR
Ahuja 1989 India	Yes	Extremely short	NR
Channer 1987 UK	Yes	Extremely short	NR
Dorian, 1996 multiple countries	Yes	Good	3M Pharmaceuticals
James, 1989 UK	Yes	Extremely short	Wellcome Trust
Lewis 1987 Scotland	Yes	Extremely short	NR

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Lewis, 1989 Scotland	NR	NR	N/A - crossover study	Yes	Yes	No	No
Lundstrom, 1992 Sweden	NR	NR	N/A - crossover study	Yes, but extremely vague	Yes	No	No
Rasmussen	NR	NR	NR	Yes, but extremely vague	NR	No	No
Van Nord	NR	NR	Yes	Yes, but extremely vague	NR	No	Yes
Clair, 1992	NR	NR	NR	Yes	Yes	Yes	Unclear
DAVIT II (Part of the Danish Verapamil Infarction Trial II) Jespersen 1992 Denmark	NR	NR	Yes	Yes	Yes	Yes	Unclear

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population	Number recruited	Exclusion criteria for recruitment
Lewis, 1989 Scotland	NR	Yes	None	Fair	Good	NR	History of uncontrolled cardiac failure, "sick-sinus syndrome", obstructive airways disease, insulin-dependent diabetes mellitus, or angina pectoris of a severity sufficient to limit exercise tolerance
Lundstrom, 1992 Sweden	NR	Yes	None	Fair	Good	NR	Complete AV block, severe ventricular arrhythmias, bronchopulmonary disease, thyrotoxicosis, myocardial infarction that occurred less than 2 months before entry into the study, hepatic or renal disease or any other disease that would be likely to interfere with the evaluation of the drug effects
Rasmussen	NR	Yes	None	Fair	Fair	NR	NR
Van Nord	Yes	Yes	None	Fair	Good	NR	History of 2nd or 3rd degree AV conduction block; known sick sinus syndrome; heart failure according to NYHA functional class III or IV; unstable angina pectoris; current treatment with CCB's, digoxin, Class I or III antiarrhythmic drugs (amiodarone within last 3 months); untreated hyperthyroidism or hypothyroidism; serious pulmonary, hepatic, hematologic, metabolic, renal, gastrointestinal, CNS, or psychiatric disease; pacemaker treatment; contraindications for oral anticoagulant agents; age <18 or >85 years
Clair, 1992	Unclear	Attrition and compliance clearly reported. Others NR	No	Fair	NR	17	Left ventricular failure of NYHA functional class III or IV; medically required beta-blockers, digitalis glycosides, other antiarrhythmic agents; required treatment with other investigational drugs; unstable angina; Wolff-Parkinson-White syndrome with antidromic reciprocating tachycardia; MI within 3 months before study; terminal illness; women able to bear children
DAVIT II (Part of the Danish Verapamil Infarction Trial II) Jespersen 1992 Denmark	Unclear	None reported	Unclear	Fair	Good Mean age: plac=60; ver=59 Gender(%male): plac=76; ver=75	157 recruited	Heart failure requiring more than 160 mg furosemide daily; systolic blood pressure <90 mmHg; second or third degree atrioventricular block; sinoatrial block; heart rate below 45 $b.min^{-1}$; treatment with beta blockers or calcium antagonists; treatment with digoxin or anti-arrhythmics; atrial flutter or fibrillation or an electrocardiogram with ventricular hypertrophy, strain or intraventricular block

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Control group standard of care	Length of follow-up	Funding
Lewis, 1989 Scotland	Yes	Extremely short	Tablets provided by ICI plc
Lundstrom, 1992 Sweden	Yes	Extremely short	Swedish Heart and Lung Foundation, Clinical Research Unit, ICI Pharma
Rasmussen	Yes	Good	NR
Van Nord	Yes	Extremely short	The Netherlands Heart Foundation Grant 98.105
Clair, 1992	Yes	4 months	NR
DAVIT II (Part of the Danish Verapamil Infarction Trial II) Jespersen 1992 Denmark	Yes	1 month	NR

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis
Bertaglia 2001	NR	NR	Yes	NR	Yes	Yes	Stated ITT, but excluded 13 patients having spontaneous conversion to sinus rhythm and 6 patients that refused internal electrical cardioversion following unsuccessful external cardioversion
Stern, 1982 United States	NR	NR	N/A-crossover; characteristics reported for group overall	Yes	Yes	Yes	Efficacy analysis did not include 1 patient for unspecified reason
Tse, 2001 China	NR	NR	N/A-crossover; characteristics reported for group overall	Yes	Yes	Yes	Unclear
Suwa 1996	Inferior: according to month of birth	NR	Yes	Minimal	NR	Yes	No
Schofer 1990	NR	NR	NR	Yes	Yes	Yes	Yes
de Vries 1995	NR	NR	Yes	Yes	Yes	Yes	Yes
Agostoni 1986	NR	NR	Yes, crossover	Yes	NR	Yes	No
Elkayam 1990 USA	Adequate - Latin square design, computer-generated code	NR	NR	Yes	NR - says double blind, No details	Yes	No

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population	Number recruited	Exclusion criteria for recruitment
Bertaglia 2001	Unclear	Attrition clearly reported Others NR	No	Fair	Good Mean age: ver+ami=65.9; ami=65.3 Gender(%male): ver+ami=64; ami=64	189 referred 133 eligible 100 randomized	Treatment with intracellular calcium lowering drugs; mean ventricular rate < 60 beats/min; previous side effects of verapamil; left ventricular ejection fraction <40%
Stern, 1982 United States	N/A-crossover trial	Attrition clearly reported Others NR	No	Fair	Good Mean age: Group 1=53.5; Group 2=49.2; Group 3=54.5 Gender(%male): Group 1=75; Group 2=60; Group 3=50	13 enrolled	*Chronic atrial fibrillation groups (1 and 2):* significant congestive heart failure (any combination of cardiomegaly, hepatomegaly, rales, S_3 gallop, venous hypertension); hypotension (SBP < 90 mmHg); severe hypertension (DBP > 115 mmHg); severe bradycardia at rest (HR < 50/min) *Paroxysmal atrial fibrillation group:* NR
Tse, 2001 China	N/A-crossover trial	None reported	Not suspected	Fair	Good Mean age: 60 Gender(%male): 81.8%	11 enrolled	NR
Suwa 1996	NR	Withdrawals=5/18 (27.8%); others NR	No	Poor	Mean age 53.5 68.2% male	18	NR
Schofer 1990	NR	NR	NR	Fair	Mean age=55.4 75% male	24	Significant hematopoietic, liver and renal dysfunction (serum creatinine >2 mg%.
de Vries 1995	NR	NR	NR	Fair	Mean age=65 84.5% male	52 screened 46 randomized	Active myocarditis; obstructive cardiomyopathy, hemodynamically significant valvular disease; hypotension (systolic BP <100 mm Hg), MI; coronary angioplasty or cardiac surgery <3 months; severe obstructive pulmonary disease; known intolerance to study drugs; treatment with ACEIs or dihydropyridines within previous 6 months.
Agostoni 1986	NR	Attrition Yes others NR	high overall loss (31%), group assignment NR	Fair to poor	Selected for dilated cardiomyopathy	n = 26	Supine systolic BP <100 mm Hg; angina pectoris; history or ECG signs of MI; hepatic or renal impairment.
Elkayam 1990 USA	NR	attrition, NR on crossover details or contamination	No 5/28 (18%) overall	Fair	Unclear	51	Pregnancy; childbearing potential; currently nursing; history of acute MI within first month before study entry; primary valvular disease as a reason of symptoms; angina pectoris; cardiomyopathy other than dilated congestive cardiomyopathy; significant primary pulmonary, hepatic, renal or hematological disease; inability to give informed consent.

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Control group standard of care	Length of follow-up	Funding
Bertaglia 2001	Yes	8 weeks	NR
Stern, 1982 United States	Yes	7-8 months	NR
Tse, 2001 China	Yes	3 months	NR
Suwa 1996	Yes	10.5 months; crossover duration unclear	NR
Schofer 1990	Yes	3 months	NR
de Vries 1995	Yes	16 weeks	ASTRA
Agostoni 1986	Yes, crossover	8 wks (x2)	NR
Elkayam 1990 USA	Yes	24 weeks	NR

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups
INVEST Pepine, 2003 Pepine, 1998 International	Adequate	Adequate	Yes	Yes	Yes	N-open	Yes	Unclear

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population	Number recruited	Exclusion criteria for recruitment	Control group standard of care
INVEST Pepine, 2003 Pepine, 1998 International	Y Y N Y	No	Fair	Yes	23,482	Unstable angina, angioplasty, coronary bypass or stroke within the previous month; beta-blocker use within the previous 2 weeks or previous year for post-MI patients; sinus bradycardia, sick sinus syndrome or atrioventricular block of more than firs degree in the absence of an implanted pacemaker; severe (NYHA class IV) heart failure; severe renal (creatine ≥ 4.0) or hepatic failure; or contraindication to verapamil	Yes

Evidence Table 1. Quality assessment of randomized trials

Author, Year Country	Length of follow-up	Funding
INVEST Pepine, 2003 Pepine, 1998 International	2-3 years	University of Florida, BASF Pharma, and Abbott Laboratories

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Study Design, Setting	Eligibility criteria	Exclusion criteria	Subgroup	Interventions (drug, regimen, duration, n)
Amlodipine					
AASK Agodoa, 2001 Wright, 2002 Douglas, 2003 US Fair	Randomized double-blind 3 (drugs) x2 (BP goals) factorial trial	Self-identified African Americans, hypertensive (DBP > 95), with GFR between 20 to 65 mL/min per 1.73 m^2, aged 18-70	DBP < 95, diabetes, Urinary Protein/Creatine > 2.5, accelerated hypertension in past 6 months, secondary hypertension, non-BP renal disease, serious systemic disease, CHF, contraindication for study drug	Black	aml 5 to 10 mg daily, n=194 ram 2.5 to 10 mg daily, n=400 met 50 to 200 mg daily, n=411

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Allowed other medications/ interventions	Anti-hypertensive Therapy Summary			
		CCB	**Diuretic**	**Beta Blocker**	**ACE Inhibitor**
Amlodipine					
AASK	Addition of in order	During study	NR	During study	During study
Agodoa, 2001	furosemide, doxazosin	Mean no. of drug classes: 2.65		Mean no. of drug classes:	Mean no. of drug classes:
Wright, 2002	mesylate, clonidine	(1.24)		2.66 (se 1.23)	2.66 (se 1.23)
Douglas, 2003	hydrochloride, hydralazine	Level 1 (aml): 83.4%		Level 1 (met): 83.6%	Level 1 (ram):76.8%
US	hydrochloride, minoxidil	Level 2 (fur): 70.8%		Level 2 (fur): 74.0%	Level 2 (fur): 74.0%
	to maximum tolerated dose	Level 3 (dox): 46.3%		Level 3 (dox): 42.0%	Level 3 (dox):42.0%
Fair	before adding next agent	Level 4 (clo): 44.4%		Level 4 (clo): 34.4%	Level 4 (clo):34.4%
		Level 5 (min): 24.1%		Level 5 (min): 27.5%	Level 5 (min):27.5%
		Crossover: 6.4%		Crossover: 7.6%	Crossover: 10.9%

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Additional treatment information	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Amlodipine				
AASK Agodoa, 2001 Wright, 2002 Douglas, 2003 US Fair	NR	Followup visits, glomerular filtration rate was assessed by iothalamate clearance at baseline twice, then at 3, 6 and every 6 months. Serum and urinary levels of creatine and protein assessed by central lab every 6 months.	mean 54 61% male 100% black	n=1094 97% on BP medication 51% ram history of heart disease and 55% aml history of heart disease

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Number screened, eligible, enrolled	Number withdrawn/ lost to fu/ analyzed	Event Rates	
			CCB Outcomes	**Diuretic Outcomes**
Amlodipine				
AASK Agodoa, 2001 Wright, 2002 Douglas, 2003 US Fair	2801 screened 1459 eligible 1094 enrolled	total 0/89/1005 aml 0/23/194 ram 0/36/400 met 0/30/411	Amlodipine, 2 to 5 years per patient year all cause mortality 1.7 cardiovascular mortality 0.9 cardiovascular event or death 1.7 dialysis 36/217 over study Primary and secondary outcomes were unchanged after controlling for follow-up BP and mean number of add-on drugs as covariates.	NR

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Event Rates			Method of adverse effects assessment?
	Beta Blocker Outcomes	Ace Inhibitor	Angiontensin II Receptor Antagonist Outcomes	
Amlodipine				
AASK Agodoa, 2001 Wright, 2002 Douglas, 2003 US Fair	Metoprolol, 3 to 6 years, per patient year all cause mortality 2.0 cardiovascular mortality 0.8 cardiovascular event or death 2.9 dialysis 73/441 (16.6%) over study	Ramipril, 3 to 6 years followup per patient year all cause mortality 1.5 cardiovascular mortality 0.5 cardiovascular event or death 2.5 dialysis 62/436 (14.2%) over study	N/A	NR

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Amlodipine			
AASK Agodoa, 2001 Wright, 2002 Douglas, 2003 US Fair	NR	NR	

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Study Design, Setting	Eligibility criteria	Exclusion criteria	Subgroup	Interventions (drug, regimen, duration, n)
ALLHAT, Furberg, 2002 Grimm, 2001 Vidt, 2000 Vidt, 2003 US Good	Randomized double-blind, active-controlled, 625 clinical sites in US, Canada, Puerto Rico, US Virgin Islands	Hypertensive (SBP ≥140 or DBP ≥90 or taking antihypertensive medications) men and women age 55 with at least 1 CHD risk factor	History of heart failure, left ventricular ejection fraction <35%. Symptomatic MI or stroke w/in past 6 mo, symptomatic angina w/in past 6 months. Known renal insufficiency, requirement of diuretics other than for BP. Need more than 2 medications to achieve goal BP. Low likelihood of compliance. Other life threatening diseases. Participation in other clinical trial.		Amlodipine (aml) 2.5 to 10 mg daily, n=15,255 Lisinopril (lis) 10 to 40 mg daily, n=9048 Chlorthalidone (chl) 12.5 to 25 mg daily, n=9054 Doxazosin (dox) 2 to 8 mg daily, n=8619 No other antihypertensive initially after randomization

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Allowed other medications/ interventions	Anti-hypertensive Therapy Summary			
		CCB	**Diuretic**	**Beta Blocker**	**ACE Inhibitor**
ALLHAT, Furberg, 2002 Grimm, 2001 Vidt, 2000 Vidt, 2003 US Good	Addition of Step 2: ate 25-100 mg/d, Step 2: clo 0.2 to 0.6 mg daily Step 2: res 0.05 to 0.2 mg daily Step 3: hyd 50 to 200 mg daily Other drugs at physician's discretion	At end of 5 years Mean no. of hypertension meds: 1.9 (1.0) Step 1 (aml): 72.1% Step 1+ (aml or other CCB): 80.4% Step 2 or 3 (ate, clo, res, hyd): 39.4% Full crossover: 6.9% Partial crossover: 16.6% Other drugs: 8.0%	At end of 5 years Mean no. of hypertension meds: 1.8 (1.0) Step 1 (chl): 71.2% Step 1+ (chl or other diuretic): 80.5% Step 2 or 3 (ate, clo, res, hyd): 40.7% Full crossover: 9.0% Partial crossover: 13.2% Other drugs: 4.9%	NR	At end of 5 years Mean no. of hypertension meds: 2.0 (1.2) Step 1 (lis): 61.2% Step 1+ (lis or other ace): 72.6% Step 2 or 3 (ate, clo, res, hyd): 43.0% Full crossover: 8.5% Partial crossover: 15.7% Other drugs: 4.9%

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Additional treatment information	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
ALLHAT, Furberg, 2002 Grimm, 2001 Vidt, 2000 Vidt, 2003 US Good	NR	Followup visits, death certificates, clinic investigator reports, hospital discharge summaries, searches of Medicare, Medicaid, VA, National Death Index and Social Security Administration databases, 4-8 years	Mean 67 53% male 36% black 19% Hispanic	90% on BP medication 19% diabetic 22% current smoker 26% history of CHD BMI mean 29.8

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Number screened, eligible, enrolled	Number withdrawn/ lost to fu/ analyzed	Event Rates	
			CCB Outcomes	**Diuretic Outcomes**
ALLHAT, Furberg, 2002 Grimm, 2001 Vidt, 2000 Vidt, 2003 US Good	NR NR 42418	total 196/1118/41976 chl 80/339/15255 aml 58/200/9048 lis 58/218/9054 dox NR/361/8619 (stopped after 3 years)	Amlodipine, 6 year rate per 100 patients(se) all cause mortality 16.8 (0.5) CHD 19.9 (0.5) Stroke 5.4 (0.3) Combined CVD 32.0 (0.6) End-stage renal 2.1 (0.2) Heart failure 10.2 (0.4) Heart failure (hosp or fatal) 8.4 (0.4) Angina 12.6 (0.4) Angina (hosp) 8.4 (0.4) Coronary revascularizations 10.0 (0.4) Peripheral arterial disease 3.7 (0.2) Combined CV disease 32.0 (nr) 4 years (% patients) Incidence of new-onset diabetes=9.8%	Chlorthalidone, 6 year rate per 100 patients(se) all cause mortality 17.3 (0.4) CHD 19.9 (0.4) Stroke 5.6 (0.2) CVD 30.9 (0.5) End-stage renal 1.8 (0.1) Heart failure 7.7 (0.3) Heart failure (hosp or fatal) 6.5 (0.3) Angina 12.1 (0.3) Angina (hosp) 8.6 (0.3) Coronary revascularizations 9.2 (0.3) Peripheral arterial disease 4.1 (0.2) Combined CV disease 30.9 (nr) 4 years (% patients) Incidence of new-onset diabetes=11.6% (p=0.04 compared with amlodipine)

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Event Rates			Method of adverse effects assessment?
	Beta Blocker Outcomes	Ace Inhibitor	Angiontensin II Receptor Antagonist Outcomes	
ALLHAT, Furberg, 2002 Grimm, 2001 Vidt, 2000 Vidt, 2003 US Good	NR	Lisinopril, 6 year rate per 100 patients(se) all cause mortality 17.2 (0.5) CHD 20.8 (0.5) Stroke 6.3 (0.3) CVD 33.3 (0.6) End-stage renal 2.0 (0.2) Heart failure 8.7 (0.4) Heart failure (hosp or fatal) 6.9 (0.4) Angina 13.6 (0.4) Angina (hosp) 9.6 (0.4) Coronary revascularizations 10.2 (0.4) Peripheral arterial disease 4.7 (0.4) Combined CV disease 33.3 (nr) 4 years (% patients) Incidence of new-onset diabetes=8.1%	N/A	Searches of Medicare and Medicaid and VA databases for angioedema and hospitalization for gastrointestinal bleeding.

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
ALLHAT, Furberg, 2002 Grimm, 2001 Vidt, 2000 Vidt, 2003 US Good	6 year rate per 100 patients(se) aml cancer 10.0 (0.4) gastrointestinal bleeds 8.0 (0.4) chl cancer 9.7 (0.3) gastrointestinal bleeds 8.8 (0.3) lis cancer 9.9 (0.4) gastrointestinal bleeds 9.6 (0.4)	aml (27%,2409/9048) chl (27%,4108/15255) lis (36%,3241/9054)	Results are a bit unclear since the authors list compliance as "aml or other CCB". If patients were switched to another CCB it might impact the outcomes.

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Study Design, Setting	Eligibility criteria	Exclusion criteria	Subgroup	Interventions (drug, regimen, duration, n)
FACET Tatti, 1998 Pahor, 1998 Italy Good	Open-label, randomized prospective, outpatient diabetic clinic	Hypertensive (SBP>140 or DBP > 90 mmHG on 3 consecutive visits or SBP >160 or BP > 95 mmHG on 2 consecutive or nonconsecutive visits) patients with NIDDM. Hypertension less tha 1 year. No insulin,fasting glucose > 140 mg/dl	History of heart failure, left ventricular ejection fraction <35%. History of CHD or stroke. Serum creatine level > 1.5 mg/dl; microalbuminuria > 40 ug/min. Use of lipid lowering drugs, aspirin or antihypertensive agents other than diuretics or beta blockers. Low likelihood of compliance. Other life threatening diseases. Participation in other clinical trial.		aml 10 mg daily, n=191 fos 20 mg daily, n=189 If BP not at goal, other study drug at full dose also given.

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Allowed other medications/ interventions	Anti-hypertensive Therapy Summary			
		CCB	**Diuretic**	**Beta Blocker**	**ACE Inhibitor**
FACET Tatti, 1998 Pahor, 1998 Italy Good	None	At end of 3 years 141/191 (73.8%) aml only 50/191 (26.2%) aml + fos	NR	NR	At end of 3 years 131/189 (69.3%) fos only 58/189 (30.7%) fos + aml

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Additional treatment information	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
FACET Tatti, 1998 Pahor, 1998 Italy Good	NR	Clinic visits, hospital and medical records assessed by blinded independent clinicians. Events were assessed by standardized algorithms.	Mean 63 56% (aml) male 64% (fos) male	7% current smoker (aml) 5% current smoker (fos) BMI mean 30.5 (aml) BMI mean 30.7 (fos)

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Number screened, eligible, enrolled	Number withdrawn/ lost to fu/ analyzed	Event Rates	
			CCB Outcomes	**Diuretic Outcomes**
FACET	1172	4	Any major CV event	N/A
Tatti, 1998	380	4	Over 3 years followup	
Pahor, 1998	376	276	Note: not intent to treat	
Italy			Aml 27/141 (19.2%)	
			Aml + Fos 4/108 (3.7%)	
Good				
			Stroke (fatal, nonfatal)	
			Per 100 patient years	
			Aml 1.9	
			Fos 0.7	
			Hazard ratio (95% CI)	
			Fos vs aml 0.39 (0.12 to 1.23)	
			MI (fatal, nonfatal)	
			Per 100 patient years	
			Aml 2.4	
			Fos 1.8	
			Hazard ratio (95% CI)	
			Fos vs aml 0.77 (0.34 to 1.75)	

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Event Rates			Method of adverse effects assessment?
	Beta Blocker Outcomes	Ace Inhibitor	Angiontensin II Receptor Antagonist Outcomes	
FACET Tatti, 1998 Pahor, 1998 Italy Good	N/A	Any major CV event over 3 years followup Note: not intent to treat Fos 10/131 (7.6%) Aml + Fos 4/108 (3.7%) Major CV event, hazard ratio (95% CI) Fos vs aml 0.37 (0.18 to 0.77) p=0.008 Aml + Fos vs Aml 0.17 (0.06 to 0.50) p=0.001 Stroke (fatal, nonfatal) Per 100 patient years Fos 0.7 Hazard ratio (95% CI) Fos vs aml 0.39 (0.12 to 1.23) MI (fatal, nonfatal) Per 100 patient years Fos 1.8 Hazard ratio (95% CI) Fos vs aml 0.77 (0.34 to 1.75)	N/A	NR

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
FACET Tatti, 1998 Pahor, 1998 Italy Good	NR	Withdrawals reasons not stated aml 52/191 fos 36/189	Aml provided better blood pressure control than fos but had more risk of a major CV event.

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Study Design, Setting	Eligibility criteria	Exclusion criteria	Subgroup	Interventions (drug, regimen, duration, n)
VALUE Julius 2004 Multinational (US and Europe) Fair	Prospective, double-blind, randomized, active-controlled, parallel-group trial	Age 50 or older, with treated or untreated hypertension at baseline and predefined combinations of cardiovascular risk factors and cardiovascular disease. Qualifying risk factors were male sex, age older than 50 years, verified diabetes mellitus, current smoking, high total cholesterol, left ventricular hypertrophy by electrocardiogram, proteinuria on dipstick and raised serum creatinine between 150 and 265 mmol/L (if >265 mmol/L patients were judged to have severe renal failure and were excluded). Qualifying diseases were verified coronary disease, cerebrovascular disease or peripheral arterial occlusive disease, or left ventricular hypertrophy with strain pattern.	Renal artery stenosis, pregnancy, acute MI, percutaneous transluminal coronary angioplasty or coronary artery bypass graft within the past 3 months, clinically relevant valvular disease, cerebrovascular accident in the past 3 months, severe hepatic disease, severe chronic renal failure, congestive heart failure requiring ACE inhibitor therapy, patients on monotherapy with beta blockers for both coronary artery disease and hypertension.	High cardiovascular risk	amlodipine 5 mg (n=7596) or valsartan 80 mg (n=7649) 4-6 years followup

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Allowed other medications/ interventions	Anti-hypertensive Therapy Summary			
		CCB	**Diuretic**	**Beta Blocker**	**ACE Inhibitor**
VALUE Julius 2004 Multinational (US and Europe) Fair	None	amlodipine vs valsartan: At primary endpoint: amlodipine 5 mg or valsartan 80 mg: 20.8% vs 15.9% amlodipine 10 mg or valsartan 160 mg: 14.5% vs 11.% amlodpine 5 mg plus HCTZ or valsartan 80 mg: 4.3% vs 2.1% amlodipine 10 mg plus HCTZ or valsartan 160 mg: 19.5% vs 22.5% Other combinations of drugs: 16.8% vs 23%	amlodipine vs valsartan: diuretics as monotherapy: 15.0% vs 13.4% diuretics as part of combination therapy: 4.2% vs 4.2%	18.3% amlodipine, 24.4% valsartan	19.3% amlodipine, 20.7% valsartan

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Additional treatment information	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
VALUE Julius 2004 Multinational (US and Europe) Fair	amlodipine vs valsartan statins: 46.4% vs 46.6% aspirin: 72.7% vs 73.1%	An endpoint committee, blinded to therapy allocation, reviewed the clinical records of all cardiovascular events reported by clinical centers and adjudicated according to theprotocol criteria.	Mean age 67 (SD 8) 58% male 89% White 4% Black 3% Asian 3% Other	amlodipine vs valsartan: coronary heart disease: 46% vs 45.6% peripheral arterial disease: 14% vs 13.8% stroke or TIA: 19.8% vs 19.8% LVH with strain pattern: 6.1% vs 5.9% previously treated for hypertension: 92% vs 92.7%

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Number screened, eligible, enrolled	Number withdrawn/ lost to fu/ analyzed	Event Rates	
			CCB Outcomes	**Diuretic Outcomes**
VALUE Julius 2004 Multinational (US and Europe) Fair	18,124 screened 15,313 eligible 15,245 enrolled	161 withdrawn 90 lost to followup 15,245 analyzed	Amlodipine, N (%); per 1000 patients years Primary composite*: 789 (10.4%); 24.7 Cardiac mortality: 304 (4.0%); 9.2 Cardiac morbidity: 578 (7.6%); 18.1 Myocardial infarction: 313 (4.1%); 9.6 Heart failure: 400 (5.3%);12.4 Stroke: 281 (3.7%); 8.7 All-cause mortality: 818 (10.8%); 24.8 New onset diabetes: 845 (16.4%); 41.1 *Primary composite=sudden cardiac death, fatal MI, death during or after percutaneous coronary intervention or CABG, death due to heart failure, and death associated with recent MI on autopsy, heart failure requiring hospital management, non-fatal MI, or emergency procedures to prevent MI. Hazard ratio, valsartan vs amlodipine: Primary composite (see definition above): 1.04 (0.94-1.15) Cardiac mortality: 1.01 (0.86-1.18) Cardiac morbidity: 1.02 (0.91-1.15) Myocardial infarction: 1.19 (1.02-1.38) Heart failure: 0.89 (0.77-1.03) Stroke: 1.15 (0.98-1.35) All-cause mortality: 1.04 (0.94-1.14) New onset diabetes: 0.77 (0.69-0.86)	N/A

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Event Rates			Method of adverse effects assessment?
	Beta Blocker Outcomes	Ace Inhibitor	Angiontensin II Receptor Antagonist Outcomes	
VALUE Julius 2004 Multinational (US and Europe) Fair	N/A	N/A	N (%); per 1000 patients years Primary composite*: 810 (10.6%); 25.5 Cardiac mortality: 304 (4.0%); 9.2 Cardiac morbidity: 586 (7.7%); 18.4 Myocardial infarction: 369 (4.8%); 11.4 Heart failure: 354 (4.6%);11.0 Stroke: 322 (4.2%); 10.0 All-cause mortality: 841 (11.0%); 25.6 New onset diabetes: 690 (13.1%); 32.1 *Primary composite=sudden cardiac death, fatal MI, death during or after percutaneous coronary intervention or CABG, death due to heart failure, and death associated with recent MI on autopsy, heart failure requiring hospital management, non-fatal MI, or emergency procedures to prevent MI.	Not reported. States adverse experiences and prespecified safety parameters were monitored thoughout the trial.

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
VALUE Julius 2004 Multinational (US and Europe) Fair	amlodipine vs valsartan Prespecified Adverse Events: Peripheral edema: 32.9% vs 14.9% (p<0.0001) Dizziness: 14.3% vs 16.5% (p<0.0001) Headache: 12.5% vs 14.7% (p<0.0001) Fatigue: 8.9% vs 9.7% (p<0.0001) Additional Common Adverse Events: Diarrhea:6.8% vs 8.8% (p<0.0001) Angina: 6.4% vs 9.3% (p<0.0001) Serious angina: 3.1% vs 4.4% (p<0.0001) Edema other: 6.1% vs 3.2% (p<0.0001) Hypokalemia: 6.2% vs 3.5% (p<0.0001) Atrial fibrillation: 2.0% vs 2.4% (p=0.1197) Syncope: 1.0% vs 1.7% (p<0.0001)	12.9% amlodipine, 11.9% valsartan	

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Study Design, Setting	Eligibility criteria	Exclusion criteria	Subgroup	Interventions (drug, regimen, duration, n)
Lewis 2001 Berl 2003 International Irbesartan Diabetic Nephropathy Trial (IDNT) Fair	Prospective, double-blind, randomized, active-controlled, parallel-group trial	Ag between 30 and 70 years, a documented diagnosis of type 2 diabetes mellitus, hypertension (sitting SBP > 135 mm Hg ; sitting DBP > 85 mm Hg; or documented treatment with antihypertensive agents), and proteinuria, with urinary protein excretion of at least 900 mg/24 hours. The serum creatinine concentration was required to be between 1.0 and 3.0 mg/deciliter (88 and 265 µmol/L) in women and 1.2 and 3.0 mg/deciliter (106 and 265 µmol/L) in men	NR	Type 2 diabetes mellitus proteinuria	Amlodipine (aml) 2.5 to 10 mg daily, n=567 Irbesartan (irb) 75 to 300 mg daily, n=579 Placebo (pla), n=569 Mean duration=932 days

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Allowed other medications/ interventions	Anti-hypertensive Therapy Summary			
		CCB	**Diuretic**	**Beta Blocker**	**ACE Inhibitor**
Lewis 2001 Berl 2003 International Irbesartan Diabetic Nephropathy Trial (IDNT) Fair	Antihypertensive agents other than ACE-Is, ARBS, and CCBs were used as needed in each group	irb vs aml vs pla (number pts/%) CCB: 41 (7.1) vs 48 (8.5) vs 47 (8.1), p=NS	Thiazides: 181 (31.3) vs 192 (33.9) vs 198 (34.8), p=NS Loop agents: 388 (67.1) vs 411 (72.5) vs 405 (71.2), p=NS Potassium-sparing: 26 (4.5) vs 44 (7.8), 25 (4.4), p=0.018 Combination: 24 (4.2) vs 46 (8.1) vs 33 (5.8), p=0.018	251 (43.4) vs 227 (40.0) vs 293 (51.5), p=0.001	36 (6.2) vs 48 (8.5) vs 38 (6.7), p>0.2

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Additional treatment information	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Lewis 2001 Berl 2003 International Irbesartan Diabetic Nephropathy Trial (IDNT) Fair	NR	All outcomes were reviewed and classified by an outcome committee Primary end point composite=doubling of the baseline serum creatinine concentration, the onset of end-stage renal disease (as indicated by the initiation of dialysis, renal transplantation, or a serum creatinine concentration of at least 6.0 mg/dl), or death from any cause Secondary cardiovascular end point composite=death from cardiovascular causes, nonfatal myocardial infarction, heart failure resulting in hospitalization, a permanent neurologic deficit caused by a cerebrovascular event, or lower limb amputation above the ankle	Mean age=58.9 years 66.5% male 72.4% white 13.3% black 4.8% hispanic 4.9% asian 4.5% other race	Body mass index: 30.8 SBP: 159 mm Hg DBP: 87 mm Hg Insulin use at entry (% pts): 57.8% History of CV disease (% pts): 28.7% Retinopathy: 66.6% Serum creatinine: 1.67 mg/dl Urinary pretein excretion - g/24 hr (median): 2.9 Urinary albumin excretion - g/24 hr (median): 1.9 Glycosylated hemoglobin: 8.2

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Number screened, eligible, enrolled	Number withdrawn/ lost to fu/ analyzed	Event Rates	
			CCB Outcomes	**Diuretic Outcomes**
Lewis 2001 Berl 2003 International Irbesartan Diabetic Nephropathy Trial (IDNT) Fair	NR/NR/1715	NR/11 (0.6%)/1715	number (%) Primary composite: 233 (41.1) Doubling of serum creatinine concentration: 144 (25.4) End-stage renal disease: 104 (18.3) Death from any cause: 83 (14.6) Secondary composite: 128 (22.6) CV death: 37 (6.5) **Congestive heart failure: 93 (16.4) > irbesartan (p=0.004)** Myocardial infarction: 27 (4.8) Cerebrovascular accident: 15 (2.6) Cardiac revascularization: 28 (4.9)	n/a

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Event Rates			Method of adverse effects assessment?
	Beta Blocker Outcomes	Ace Inhibitor	Angiontensin II Receptor Antagonist Outcomes	
Lewis 2001 Berl 2003 International Irbesartan Diabetic Nephropathy Trial (IDNT) Fair	n/a	n/a	number (%) Primary composite: 189 (32.6) Doubling of serum creatinine concentration: 98 (16.9) End-stage renal disease: 82 (14.2) Death from any cause: 87 (15.0) Secondary composite: 138 (23.8) Cardiovascular death: 52 (9%) Congestive heart failure: 60 (10.4) Myocardial infarction: 44 (7.6) Cerebrovascular accident: 28 (4.8) Cardiac revascularization: 27 (4.7)	Adverse events were recorded at quarterly visits

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Lewis 2001 Berl 2003 International Irbesartan Diabetic Nephropathy Trial (IDNT) Fair	Overall adverse events: NR Specific adverse events: NR	Overall withdrawals due to adverse events: NR Withdrawal due to hyperkalemia: aml=3 (0.5%) vs irb=11 (1.9%) (p=0.01 for both comparisons) vs pla=2 (0.4%)	

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Study Design, Setting	Eligibility criteria	Exclusion criteria	Subgroup	Interventions (drug, regimen, duration, n)
Nicardipine					
NICS-EH NICS-EH Study Group 1999 Kuwajima 2001 Kuramoto 1994 Ogihara 2000, Tokyo Fair	RCT, double-dummy method	Patients aged 60 and older. 160≤SBP≤220 and DBP<115 after 4 weeks of placebo.	Primary aldosteronism		nic 40 mg sustained release daily, n=215 tri 2 mg daily, n=214 Doubling of study medication as needed

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Allowed other medications/ interventions	Anti-hypertensive Therapy Summary			
		CCB	**Diuretic**	**Beta Blocker**	**ACE Inhibitor**
Nicardipine					
NICS-EH NICS-EH Study Group 1999 Kuwajima 2001 Kuramoto 1994 Ogihara 2000, Tokyo Fair	None	NR	NR	NA	NA

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Additional treatment information	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Nicardipine				
NICS-EH NICS-EH Study Group 1999 Kuwajima 2001 Kuramoto 1994 Ogihara 2000, Tokyo Fair	NR	Assessed by independent endpoint committee. Median followup: nic, 4.5 yrs; tri, 4 yrs	Mean 70 33% male	61% on BP medication 10% current smoker 26% history of CHD BMI mean 23.5

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Number screened, eligible, enrolled	Number withdrawn/ lost to fu/ analyzed	Event Rates	
			CCB Outcomes	**Diuretic Outcomes**
Nicardipine				
NICS-EH NICS-EH Study Group 1999 Kuwajima 2001 Kuramoto 1994 Ogihara 2000, Tokyo Fair	NR/426/414	15/NR/414	Nicardipine, 4.5 year followup all cause mortality 3/204 Stroke 1/204 CVD 21/204, (27.8/1000 patient/year) Myocardial infarction 2/204 Heart failure 0/204 Angina 2/204 Aneurysm 0/204	Trichlormethiazide, 4 year followup all cause mortality 2/210 Stroke 0/204 CVD 18/204, (26.8/1000 patient/year) Myocardial infarction 2/210 Heart failure 3/210 Angina 2/210 Aneurysm 1/210

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Event Rates			Method of adverse effects assessment?
	Beta Blocker Outcomes	Ace Inhibitor	Angiontensin II Receptor Antagonist Outcomes	
Nicardipine				
NICS-EH	N/A	N/A	N/A	Judged by attending physician
NICS-EH Study Group 1999 Kuwajima 2001 Kuramoto 1994 Ogihara 2000, Tokyo				
Fair				

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Nicardipine			
NICS-EH NICS-EH Study Group 1999 Kuwajima 2001 Kuramoto 1994 Ogihara 2000, Tokyo Fair	Nic 6/215 (2.8%) Tri 9/214 (4.2%)	5 year followup Nic headache1/204 (0.5%) fatigue 0/204 (0,0%) rash 1/204 (0.5%) joint pain 1/204 (0.5%) gastrointestinal complaint 1/204 (0.5%) Tri headache1/210 (0.5%) fatigue 2/210 (1.0%) rash 2/210 (1.0%) joint pain 0/204 (0.0%) gastrointestinal complaint 1/204 (0.5%)	

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Study Design, Setting	Eligibility criteria	Exclusion criteria	Subgroup	Interventions (drug, regimen, duration, n)
Nifedipine					
Marin, 2001 Spain Fair	RCT Open study	Male or female patients aged 18-75 years, with serum creatinine values between 1.5 and 5 mg/dl. Hypertension was defined by a blood pressure > 140/90 mmHg, or by the use of antihypertensive agent(s). A proven progression of chronic renal failure in the previous 2 years was defined by an increase by more than 25% or >0.5 mg/dl in serum creatinine.	Patients with diabetes mellitus, with a previous recent history of cardiovascular disease (stroke, myocardial infarction, or heart failure), taking concomitant medications that could interfere with study results (steroids, immunosuppressant drugs, or NSAIDS), or presenting intolerance to either study drug	Diabetes	Fos 10-30 mg daily *(n=129)* Nif GITS 30-60 mg daily *(n=112)* *+lifestyle modifications:* moderate sodium restriction (4-8 g/day of salt) protein intake around 0.8-1 g/kg per day

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Allowed other medications/ interventions	Anti-hypertensive Therapy Summary			
		CCB	**Diuretic**	**Beta Blocker**	**ACE Inhibitor**
Nifedipine					
Marin, 2001 Spain Fair	BP goal: <140/90 mmHg Step 2: Furosemide up to 100 mg daily Step 3: Atenolol up to 100 mg daily Step 4: Doxazosin up to 12 mg daily	NR	NR	NA	NA

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Additional treatment information	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Nifedipine				
Marin, 2001 Spain Fair	NR	Time elapsed until serum creatinine values doubled, or the need to enter a dialysis program	Mean age: Fos=53; Nif GITS=56 Gender(%male): Fos=60.5; Nif GITS: 57.1 Race NR	Weight(kg): Fos=75; Nif GITS: 72 SBP(mmHg): Fos=155; Nif GITS=157.5 DBP(mmHg): Fos=96; Nif GITS: 96 Serum Creatinine(mg/dl): Fos=2.8; Nif GITS: 2.9 Creatinine clearance(ml/min per 1.73 m^2): Fos=37; Nif GITS=34 *Underlying disease(%):* Glomerulonephritis: Fos=29; Nif GITS=34 Nephrosclerosis: Fos=25; Nif GITS=27 Polycystic disease: Fos=23; Nif GITS=14 Interstitial nephropathy: Fos=13; Nif GITS=11 Unknown: Fos=10; Nif GITS=14

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Number screened, eligible, enrolled	Number withdrawn/ lost to fu/ analyzed	Event Rates	
			CCB Outcomes	**Diuretic Outcomes**
Nifedipine				
Marin, 2001 Spain Fair	screened NR/enrolled 241	Withdrawn: Fos=37.9%; Nif GITS=39.3% Lost NR Analyzed: unclear	*Nif GITS (n=112)* *Renal events* Doubled serum creatinine or dialysis program entry: 36% *Withdrawals due to:* *Death* Sudden death: 3 (2.7%; RR 3.45; CI 0.50-23.94) MI: 1 (0.9%; RR 0.57; CI 0.07-4.34) Acute stroke: 2 (1.8%; RR 5.75; CI 0.28-118.6) *Non-fatal events* Acute stroke: 0 (RR 0.38; CI 0.01-9.32)	N/A

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Event Rates			Method of adverse effects assessment?
	Beta Blocker Outcomes	Ace Inhibitor	Angiontensin II Receptor Antagonist Outcomes	
Nifedipine				
Marin, 2001 Spain Fair	N/A	*Fos (n=129)* *Renal events* Doubled serum creatinine or dialysis program entry: 21% *Withdrawals due to:* *Death* Sudden death: 1(0.8%) MI: 2(1.5%) Acute stroke: 0 *Non-fatal events* Acute stroke: 1(0.8%)	N/A	NR

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Nifedipine			
Marin, 2001 Spain Fair	Most common AEs and overall incidence NR	Cancer: Fos=1; Nif GITS=1 Edema(%): Fos=0.8; Ni GITS=8.9 Hyperkalemia: Fos=4.6; Nif GITS=0 Impaired renal function: Fos=3.1; Nif GITS=0.9 Cough: Fos=2.3; Nif GITS=0	

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Study Design, Setting	Eligibility criteria	Exclusion criteria	Subgroup	Interventions (drug, regimen, duration, n)
Chan, 1992 Chan, 2000 Hong Kong Fair	RCT	Chinese patients aged over 18 with non-insulin dependent diabetes treated by diet or oral hypoglycemic drugs, or both, who were either hypertensive or receiving antihypertensive drugs and who were attending the outpatient diabetic clinic at the hospital	Patients receiving insulin or had a history of non-diabetic renal disease; appreciable renal impairment (plasma creatinine concentration >/= 200 mmol/L); plasma potassium concentration >/= 5 mmol/L; cardiac failure or any concurrent systemic disease; receiving treatment for any concomitant disorder	Diabetes	ena 10-40 mg daily, n=41 Modified Release Nifedipine (Nif) 40-80 mg daily x one year, n=49

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Allowed other medications/ interventions	Anti-hypertensive Therapy Summary			
		CCB	**Diuretic**	**Beta Blocker**	**ACE Inhibitor**
Chan, 1992 Chan, 2000 Hong Kong Fair	*Target supine SBP:* < 140 mmHg Step 2: Indapamide 2.5 mg daily Step 3: Frusemide up to 120 mg daily *replacing* Indapamide *Additional, unspecified antihypertensive drugs were used as well, with the exception of ACEI in the Nif group*	NR	Initial 12-month diuretic use: Nif=14%(Indapamide=57.1%; Frusemide=42.9%); Ena=76% (Indapamide=64.5%; Frusemide=35.5%) Diuretic use rates after one-year analysis: Nif=17%; Ena=12%	NR	*NR*

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Additional treatment information	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Chan, 1992 Chan, 2000 Hong Kong Fair	Initial 12-month diuretic use: Nif=14%(Indapamide=57.1%; Frusemide=42.9%); Ena=76% (Indapamide=64.5%; Frusemide=35.5%) Diuretic use rates after one-year analysis: Nif=17%; Ena=12% Additional antihypertensive drug use: Nif=46%; Ena=68%	Renal events assessed at 5 years	Mean age: Ena=60.0; Nif=56.2(p=0.047) Gender(%male): Ena=40; Nif=40.4 Race: 100% Chinese	SBP(mmHg): Ena=172.1; Nif=166.5 DBP(mmHg): Ena=92.5; Nif=92.5 Total cholesterol(mmol/L): Ena=5.97; Nif=5.45(p=0.024) Creatinine clearance(mL/min): Ena=73.7; Nif=76.9 Normoalbuminuria(%): Ena=40; Nif=46.1 Microalbuminuria: Ena=42; Nif=28.1 Macroalbuminuria: Ena=18; Nif=25 Duration of diabetes(years): Ena=5.5; Nif=5.6 Duration of HTN(years): Ena=5.6; Nif=5.3

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Number screened, eligible, enrolled	Number withdrawn/ lost to fu/ analyzed	Event Rates	
			CCB Outcomes	**Diuretic Outcomes**
Chan, 1992 Chan, 2000 Hong Kong Fair	NR/102 enrolled	Withdrawals: Nif=3(5.8%); Ena=9(18%)/0 lost/analyzed: Nif=49; Ena=41	*Nif (n=52)* *At 5 years:* Renal events: 5(9.6%)	N/A

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Event Rates			Method of adverse effects assessment?
	Beta Blocker Outcomes	Ace Inhibitor	Angiontensin II Receptor Antagonist Outcomes	
Chan, 1992 Chan, 2000 Hong Kong Fair	N/A	*Ena (n=50)* *At 5 years:* Renal events: 6(12%)	N/A	

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Chan, 1992 Chan, 2000 Hong Kong Fair		*Ena* Overall withdrawals due to AEs: 3/50(6%), all due to cough *Nif* Overall withdrawals due to AEs: 0	

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Study Design, Setting	Eligibility criteria	Exclusion criteria	Subgroup	Interventions (drug, regimen, duration, n)
INSIGHT (International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment) Brown, 1996 Brown, 1997 Mancia, 1998 Brown, 2000 Brown, 2001 Brown, 2001 Mancia, 2003 UK, France, Israel, Netherlands, Spain, Italy, Sweden, Denmark, Norway Fair	RCT	Patients, aged between 55-80 years, with essential hypertension; BP >/= 150/95 mmHg, or systolic value must be >/= 160 mmHg regardless of diastolic pressure; meeting >/= 1 of following risk factors: 1) current cigarette smoker (>/= 10 cigarettes per day) or ex-smoker having stopped within the last year but previously smoking >/= 10 cigarettes daily; 2) hypercholesterolemia, total cholesterol >/= 250 mg/dL; 3) type I or type II diabetes mellitus; 4) stable angina or asymptomatic coronary heart disease confirmed by coronary-angiographic or electrocardiographic evidence (repolarisation changes upon exercise); 5) peripheral vascular disease classified as Fontaine/Leriche stage II-IV; 6)St-T wave alterations indicative of HTN with LV strain, e.g., down-sloping ST depression with inverted or biphasic T waves observed in the lateral chest leads; 7)current evidence of LV hypertrophy confirmed by ECG; 8) family history of CV disease (MI in parent or sibling before the age of 50); 9) previous MI; 10) proteinuria, defined as a positive urine dipstick result obtained at visit 1 and confirmed by a 24 hour urine collection prior to visit 2 demonstrating >/= 0.5 g protein/24 h	History of malignant HTN; congestive heart failure; unstable insulin-dependent diabetes mellitus; subarachnoid hemorrhage; PTCA; CABG or either MI or stroke in the 12 months prior to study entry	Additional cardiovascular risk factors	Nifedipine GITS (Nif GITS) 30-60 mg daily, n=3157 Amiloride/HCTZ 2.5/25 (Co-ami - 5/50 mg daily, n=3164 3-year treatment period

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Allowed other medications/ interventions	Anti-hypertensive Therapy Summary			
		CCB	**Diuretic**	**Beta Blocker**	**ACE Inhibitor**
INSIGHT (International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment) Brown, 1996 Brown, 1997 Mancia, 1998 Brown, 2000 Brown, 2001 Brown, 2001 Mancia, 2003 UK, France, Israel, Netherlands, Spain, Italy, Sweden, Denmark, Norway Fair	Step 2: atenolol 25-50 mg or enalapril 5-10 mg (if beta-blockers are contraindicated) Step 3: unspecified additional antihypertensive drug (chosen by investigator); with the exclusion of diuretics in the Nif GITS group and calcium antagonists in the Ami/HCTZ group	NR	NR	NR	NR

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Additional treatment information	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
INSIGHT (International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment) Brown, 1996 Brown, 1997 Mancia, 1998 Brown, 2000 Brown, 2001 Brown, 2001 Mancia, 2003 UK, France, Israel, Netherlands, Spain, Italy, Sweden, Denmark, Norway Fair	% patients remaining on monotherapy *Month 12*: Nif GITS=66; Co-ami=65 *Month 36*: Nif GITS=63; Co-ami=63 *Month 48*: Nif GITS=69; Co-ami=72	Cardiovascular and cerebrovascular morbidity (stroke, intracerebral and subarachnoid hemorrhage; myocardial infarction; heart failure, sudden death) and mortality	Age: <60: Nif GITS=24.1%; Co-ami=22.3% 60-70: Nif GITS=47.9%; Co-ami=49.2% >70: Nif GITS=28.0%; Co-ami=28.6% Gender: Nif GITS=46.1%; Co-ami=46.6% Race NR	*Risk Factors(%)* Hypercholesterolemia: Nif GITS=52.1; Co-ami=52.0 Smoker: Nif GITS=28.2; Co-ami=28.5 Family history: Nif GITS=20.5; Co-ami=20.9 Diabetes mellitus(types 1 or 2): Nif GITS=20.6; Co-ami=20.6 Left-ventricular hypertrophy: Nif GITS=10.7; Co-ami=10.6 Coronary heart disease: Nif GITS=6.6; Co-ami=6.2 LV strain: Nif GITS=6.4; Co-ami=6.2 Previous MI: Nif GITS=6.2; Co-ami=5.9 Peripheral vascular disease: Nif GITS=5.7; Co-ami=5.5 Proteinuria: Nif GITS=3.1; 2.3

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Number screened, eligible, enrolled	Number withdrawn/ lost to fu/ analyzed	Event Rates	
			CCB Outcomes	**Diuretic Outcomes**
INSIGHT (International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment) Brown, 1996 Brown, 1997 Mancia, 1998 Brown, 2000 Brown, 2001 Brown, 2001 Mancia, 2003 UK, France, Israel, Netherlands, Spain, Italy, Sweden, Denmark, Norway Fair	7434 screened/6575 randomized	Overall withdrawals: Nif GITS=40.3%; Co-ami=33.1% Lost to fu: Nif GITS=2.0%; Co-ami=2.5% Analyzed: Nif GITS=3157; Co-ami=3164	Nif GITS *Primary outcomes(%)* Composite: 6.3 Non-fatal MI: 1.9 Fatal MI: 0.5 Sudden death MI: 0.5 Non-fatal stroke: 1.7 Fatal stroke: 0.3 Non-fatal heart failure: 0.8 Fatal heart failure: 0.1 Other CV death: 0.4 *Secondary outcomes(%)* Composite: 12.1 Deaths All(first event): 4.8 Non-CV: 2.2 Unknown: 0.7 CV: 1.9 Non-fatal CV Primary events: 4.4 Angina (worsening or new): 1.8 TIAs: 0.8 Renal failure: 0.3 Incidence of new diabetes mellitus in nondiabetic subgroup: 136(4.3%)	*Co-ami* *Primary outcomes(%)* Composite: 5.8 Non-fatal MI: 1.8 Fatal MI: 0.2 Sudden death MI: 0.7 Non-fatal stroke: 2.0 Fatal stroke: 0.3 Non-fatal heart failure: 0.3 Fatal heart failure: <0.1 Other CV death: 0.4 *Secondary outcomes(%)* Composite: 12.5 Deaths All(first event): 4.8 Non-CV: 2.1 Unknown: 1.1 CV: 1.6 Non-fatal CV Primary events: 4.1 Angina (worsening or new):0.4 TIAs: 0.8 Renal failure: 0.4 Incidence of new diabetes mellitus in nondiabetic subgroup: 176(5.6%) p=0.023

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Event Rates			Method of adverse effects assessment?
	Beta Blocker Outcomes	Ace Inhibitor	Angiontensin II Receptor Antagonist Outcomes	
INSIGHT (International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment) Brown, 1996 Brown, 1997 Mancia, 1998 Brown, 2000 Brown, 2001 Brown, 2001 Mancia, 2003 UK, France, Israel, Netherlands, Spain, Italy, Sweden, Denmark, Norway Fair	N/A	N/A	N/A	NR

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
INSIGHT (International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment) Brown, 1996 Brown, 1997 Mancia, 1998 Brown, 2000 Brown, 2001 Brown, 2001 Mancia, 2003 UK, France, Israel, Netherlands, Spain, Italy, Sweden, Denmark, Norway	*Serious AEs(%):* Nif GITS=25; Co-ami=28 *Most commonly reported AEs(%)* Edema: Nif GITS=28; Co-ami=4.3 Syncope: Nif GITS=1.5; Co-ami=2.8 Headache: Nif GITS=12; Co-ami=9.2 Palpitation: Nif GITS=2.5; Co-ami=2.7 Peripheral vascular disorder: Nif GITS=3.0; Co-ami=5.3 Impotence: Nif GITS=1.6; Co-ami=1.9 Flushing: Nif GITS=4.3; Co-ami=2.3 Diabetes: Nif GITS=3.0; Co-ami=4.3 Dizziness: Nif GITS=8.0; Co-ami=10.0 Gout: Nif GITS=1.3; Co-ami=2.1 Accidental injury: Nif GITS=1.2; Co-ami=2.2 Depression: Nif GITS=3.9; Co-ami=5.7 Hypokalemia: Nif GITS=1.9; Co-ami=6.2 Hyponatremia: Nif GITS=0.2; Co-ami=1.9 Hyperlipidemia: Nif GITS=4; Co-ami=6.3 Hyperglycemia: Nif GITS=5.6; Co-ami=7.7 Hyperuricemia: Nif GITS=1.3; Co-ami=6.4 Impaired renal function: Nif GITS=1.8; Co-ami=4.6	Per-protocol analysis: Any AE(%): Nif GITS=539/3157(17.1%); Co-ami=304/3164(9.6%) Serious AE(%): Nif GITS=6.3; Co-ami=7.7 Peripheral edema(%): Nif GITS=8.4; Co-ami=0.4 Headache(%): Nif GITS=1.9; Co-ami=1.0 Flushing(%): Nif GITS=1.3; Co-ami=0.6 Dizziness(%): Nif GITS=0.7; Co-ami=0.5	Fair

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Study Design, Setting	Eligibility criteria	Exclusion criteria	Subgroup	Interventions (drug, regimen, duration, n)
JMIC-B Yui, 2004a Japan Fair	Randomized, open, blinded endpoint.	Outpatients under age 75 who had diagnoses of both hypertension and coronary artery disease, enrolled at 354 Japanese hospitals specializing in the management of cardiovascular disease.	Diastolic BP $\geq$120 mmHg or secondary hypertension; symptomatic cerebrovascular disease, overt heart failure, atrial fibrillation, serious arrhythmias (ventricular tachycardia, ventricular fibrillation), renal dysfunction (serum creatinine concentration of more than 176.8 mmol/l), severe hepatic dysfunction, uncontrollable diabetes mellitus, and familial hypercholesterolemia.	Coronary artery disease	nifedipine retard 10mg-20 mg or an ACE inhibitor (enalapril 5-10 mg, imidapril 5-10 mg, or lisinopril 10-20 mg) for 3 years.

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Allowed other medications/ interventions	Anti-hypertensive Therapy Summary			
		CCB	**Diuretic**	**Beta Blocker**	**ACE Inhibitor**
JMIC-B Yui, 2004a Japan Fair	If BP reduction was unsatisfactory, an alpha blocker (doxazosin, bunazosin, or prazosin) was administered concomitantly. If the antianginal effect of the treatment was inadequate, long-acting or short-acting nitrates and/or beta blockers were used concomitantly.	NR	NA	NR	NR

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Additional treatment information	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
JMIC-B Yui, 2004a Japan Fair		Primary endopoint was overall incidence of cardiac events, defined as 1) cardiac death or sudden death, 2) MI (initial and recurrent; detected by clinical symptoms combined with Q waves, ST-segment elevation, or both on the electrocardiogram and elevated levels of cardiac enzymes); 3) angina pectoris requiring hospitalization; 4) heart failure requiring hospitalization (dyspnea or fatigue at rest or on minimal exertion, NYHA class III or IV) and a left ventricular ejection fraction less than 30%; 5) serious arrhythmia (ventricular tachycardia, ventricular fibrillation); or 6) performance of coronary interventions (PTCA, CABG, or stenting)	Mean 64.5 (SD 8.5) 69% male 100% Japanese	42% MI 65% angina 12% asymptomatic myocardial ischemia 23% hyperlipidemia 23% diabetes mellitus 19% other complications 34% history of smoking 62% coronary angiography within past year 29% PTCA within past year

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Number screened, eligible, enrolled	Number withdrawn/ lost to fu/ analyzed	Event Rates	
			CCB Outcomes	**Diuretic Outcomes**
JMIC-B Yui, 2004a Japan Fair	1888 screened 1650 eligible 1650 enrolled	250 withdrawn 100 lost to followup 1650 analyzed	Nifedipine: N (%) with events; rate per 1000 patient-years: Cardiac events: 116 (14.0%); 64.69 Sudden death/cardiac death: 6 (0.7%); 3.11 MI: 16 (1.9%); 8.36 Angina requiring hospitalization: 50 (6%); 26.72 Heart failure requiring hospitalization: 12 (1.4%); 6.23 Serious arrhythmia: 4 (0.5%); 2.07 Coronary intervention: 81 (9.8%); 44.47 Cerebrovascular accidents: 16 (1.9%); 8.34 Worsening of renal dysfunction: 6 (0.7%); 3.11 Non-cardiac death: 6 (0.7%); 3.11 Total mortality: 12 (1.4%); 6.21 Relative risk for nifedipine vs ACE inhibitor: Cardiac events: 1.05 (0.81-1.37) Sudden death/cardiac death: 0.96 (0.31-3.04) MI: 1.31 (0.63-2.74) Angina requiring hospitalization: 0.80 (0.55-1.18) Heart failure requiring hospitalization: 1.25 (0.52-2.98) Serious arrhythmia: 0.98 (0.24-3.98) Coronary intervention: 1.04 (0.76-1.43) Cerebrovascular accidents: 1.00 (0.50-2.02) Worsening of renal dysfunction: 2.70 (0.54-13.49) Non-cardiac death: 0.64 (0.23-1.81) Total mortality: 0.76 (0.35-1.63)	N/A

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Event Rates			Method of adverse effects assessment?
	Beta Blocker Outcomes	Ace Inhibitor	Angiontensin II Receptor Antagonist Outcomes	
JMIC-B Yui, 2004a Japan Fair	N/A	ACE Inhibitors: N (%) with events; rate per 1000 patient-years: Cardiac events: 106 (12.9%); 63.42 Sudden death/cardiac death: 6 (0.7%); 3.36 MI: 13 (1.6%); 7.31 Angina requiring hospitalization: 56 (%); 32.49 Heart failure requiring hospitalization: 9 (%); 5.06 Serious arrhythmia: 4 (%); 2.24 Coronary intervention: 75 (%); 44.37 Cerebrovascular accidents: 16 (%); 9.03 Worsening of renal dysfunction: 2 (%); 1.12 Non-cardiac death: 9 (%); 5.04 Total mortality: 15 (1.8%); 8.40	N/A	New symptoms that had not been observed during the observation period, abnormal laboratory data, and worsening of symptoms or signs that were initially seen during the observation period were classified as adverse events.

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
JMIC-B Yui, 2004a Japan Fair	76 nifedipine, 121 ACE inhibitors. Major adverse events occurring in the nifedipine group were those related to vasodilatory effect, including hypotension, facial erythema, and hot flushes. Dry cough accounted for most of the adverse events occurring in the ACE inhibitor grouop.	nifedipine (n=828) vs amlodipine (n=822), n (%) withdrawn due to AEs: Hypotension: 8 (1.0%) vs 2 (0.2%) (p<0.01) Palpitations, tachycardia: 7 (0.8%) vs 0 (p<0.01) Edema: 7 (0.8%) vs 0 (p<0.01) Facial erythema, hot flushes: 6 (0.7%) vs 0 (p<0.05) Dry cough: 0 vs 60 (7.3%) (p<0.01) Headache, dull headache: 3 (0.4%) vs 3 (0.4%) Gingival hypertrophy: 3 (0.4%) vs 1 (0.1%) Digestive, intestinal disorder: 2 (0.2%) vs 3 (0.4%) Malaise, fatigue: 3 (0.4%) vs 0 Others: 2 (0.2%) vs 3 (0.4%) Total: 41 (5.0%) vs 72 (8.8%) (p<0.01)	

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Study Design, Setting	Eligibility criteria	Exclusion criteria	Subgroup	Interventions (drug, regimen, duration, n)
JMIC-B Yui, 2004b (subgroup analysis of Yui, 2004a) Japan Fair	Randomized, open, blinded endpoint.	Subgroup of JMIC-B (Yui, 2004a) with diabetes	Diastolic BP ≥120 mmHg or secondary hypertension; symptomatic cerebrovascular disease, overt heart failure, atrial fibrillation, serious arrhythmias (ventricular tachycardia, ventricular fibrillation), renal dysfunction (serum creatinine concentration of more than 176.8 mmol/l), severe hepatic dysfunction, uncontrollable diabetes mellitus, and familial hypercholesterolemia.	Coronary artery disease and diabetes	nifedipine retard 10mg-20 mg or an ACE inhibitor (enalapril 5-10 mg, imidapril 5-10 mg, or lisinopril 10-20 mg) for 3 years.

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Allowed other medications/ interventions	Anti-hypertensive Therapy Summary			
		CCB	**Diuretic**	**Beta Blocker**	**ACE Inhibitor**
JMIC-B Yui, 2004b (subgroup analysis of Yui, 2004a) Japan Fair	If BP reduction was unsatisfactory, an alpha blocker (doxazosin, bunazosin, or prazosin) was administered concomitantly. If the antianginal effect of the treatment was inadequate, long-acting or short-acting nitrates and/or beta blockers were used concomitantly.	NR	NA	NR	NR

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Additional treatment information	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
JMIC-B Yui, 2004b (subgroup analysis of Yui, 2004a) Japan Fair		Same as Yui, 2004a (above)	Mean age 64.5 (SD 8.5) 69% male 100% Japanese	All had Diabetes 41% MI 66% angina 12% asymptomatic myocardial ischemia

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Number screened, eligible, enrolled	Number withdrawn/ lost to fu/ analyzed	Event Rates	
			CCB Outcomes	**Diuretic Outcomes**
JMIC-B Yui, 2004b (subgroup analysis of Yui, 2004a) Japan Fair	1278 with diabetes (subgroup analysis)		Nifedipine: N (%) with events; Relative risk vs ACE inhibitors (95% CI); p-value): Sudden death/cardiac death: 1 (0.50%) 0.31 (0.03-3.37) MI: 4 (2.01%) 1.08 (0.25-4.65) Angina requiring hospitalization: 16 (8.04%) 1.03 (0.47-2.27) Heart failure requiring hospitalization: 8 (4.02%) 1.55 (0.47-5.05) Serious arrhythmia: 0 -- Coronary intervention: 19 (9.55%) 1.09 (0.54-2.18) Cerebrovascular accidents: 4 (2.01%) 0.50 (0.13-1.84) Worsening of renal dysfunction: 4 (2.01%) 1.98 (0.34-11.45) Total mortality: 2 (1.01%) 0.33 (0.06-1.77)	

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Event Rates			Method of adverse effects assessment?
	Beta Blocker Outcomes	Ace Inhibitor	Angiontensin II Receptor Antagonist Outcomes	
JMIC-B Yui, 2004b (subgroup analysis of Yui, 2004a) Japan Fair		ACE inhibitors N (%) with events: Sudden death/cardiac death: 3 (1.73%) MI: 4 (2.31%) Angina requiring hospitalization: 12 (6.94%) Heart failure requiring hospitalization: 5 (2.89%) Serious arrhythmia: 0 Coronary intervention: 16 (9.25%) Cerebrovascular accidents: 6 (3.47%) Worsening of renal dysfunction: 2 (1.16%) Total mortality: 5 (2.89%)		

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
JMIC-B Yui, 2004b (subgroup analysis of Yui, 2004a) Japan Fair			

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Study Design, Setting	Eligibility criteria	Exclusion criteria	Subgroup	Interventions (drug, regimen, duration, n)
Diltiazem					
NORDIL (Nordic Diltiazem Study) The NORDIL Group, 1993 Hedner, 1999 Hansson, 2000 Kjeldsen, 2002 Norway/Sweden Fair	RCT Open study	Patients between 50 and 69 years with primary hypertension, previously treated or untreated. Previously treated patients should have a documented resting supine DBP of >/= 100 mmHg on two consecutive visits at least one week apart in the absence of pharmacological antihypertensive treatment. Previously untreated patients with other risk factors such as diabetes mellitus, hypercholesterolemia, smoking and left ventricular hypertrophy should have a documented resting supine DBP >/= 100 mmHg on at least two consecutive visits, at least one week apart. Previously untreated patients without other risk factors should have a documented resting supine DBP of >/= mmHg on at least two consecutive visits at least one week apart. Previously untreated patients without other risk factors should have a documented resting supine DBP of >/= 100 mmHg on at least three consecutive visits over three months involving treatment according to established non-pharmacological clinical practice.	Patients who are younger than 50 years or aged at least 70 years; with clinically relevant bradycardia (< 50 BPM); secondary hypertension (e.g., renal hypertension); atrial fibrillation with WPW-syndrome; contraindications to study medication according to FASS/FELLES KATALOGEN: sick sinus syndrome, AV-block II and II without functioning pacemaker; require treatment with beat-blockers, diuretics, calcium channel blockers, or other antihypertensives not included in the study; history of cerebrovascular disease or MI within the previous 6 months; present congestive heart failure	N/A	Diltiazem (Dil) 180-360 mg daily; short-acting formulation used initially; replace by a longer-acting formulation in 1997, n=5410 Non-calcium antagonist group: Beta-blockers or diuretics used as first-line therapy (Conventional treatment=Con), n=5471

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Allowed other medications/ interventions	Anti-hypertensive Therapy Summary			
		CCB	**Diuretic**	**Beta Blocker**	**ACE Inhibitor**
Diltiazem					
NORDIL (Nordic Diltiazem Study) The NORDIL Group, 1993 Hedner, 1999 Hansson, 2000 Kjeldsen, 2002 Norway/Sweden Fair	*Goal DBP: </= 90 mmHg* <u>Diltiazem group</u> Step 2: Dil dose increment Step 3: Other antihypertensive drug add-on (preferably ACE inhibitors) Step 4: Diuretics <u>Conventional treatment group</u>: Step 2: Combined thiazide diuretic/beta-blocker Step 3: Other antihypertensive drug add-on (preferably beta-blocker and diuretic) Step 4: Other drugs added, with exception of calcium antagonists	*See additional treatment information column*	*See additional treatment information column*	*n/a*	*n/a*

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Additional treatment information	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Diltiazem				
NORDIL (Nordic Diltiazem Study) The NORDIL Group, 1993 Hedner, 1999 Hansson, 2000 Kjeldsen, 2002 Norway/Sweden Fair	*Treatment at final visit:* *Randomized monotherapy: Dil=50%; Con=45%* *Randomized treatment: Dil=77%; Con=93%* Thiazide diuretics: Dil=4.1; Con=13.3 Loop diuretics: Dil=6.8; Con=8.4 Potassium-sparing diuretics: Dil=1.1; Con=2.5 Fixed-ratio thiazides plus potassium-sparing diuretics: Dil=4.9; Con=19.1 Non-selective BB: Dil=1.0; Con=3.2 Beta-selective blockers: Dil=10.9; Con=61.1 Alpha-blockers and BB: Dil=0.7; Con=2.2 Diltiazem: Dil=71.1; Con=1.4 Dihydropyridine calcium antagonists: Dil=4.8; Con=6.8 Verapamil: Dil=0.4; Con=0.3 ACEI: Dil=14.9; Con=11.3 Fixed-ratio ACEI+thiazide: Dil=3.1; Con=4.0 AT_1 antagonists: Dil=7.2; Con=4.0 Fixed-ratio AT_1 antagonist+thiazide: Dil=1.7; Con=4.3 Alpha-blockers: Dil=3.3; Con=4.4 Hydralazine or similar: Dil=4.3; Con=3.0 Alpha-methyldopa or clonidine: Dil=0.03; Con=0.05 No antihypertensive treatment: Dil=5.3; Con=3.6	All endpoints were assessed by an independent endpoint committee according to pre-specified criteria	*Dil n=5410; Con n=5471* Mean age: Dil=60.5; Con=60.3 Gender(%male): Dil=48.5; Con=48.7 Race NR	Mean supine BP(mmHg): Dil=174/106; Con=173/106 Standing BP(mmHg): Dil=169/107; Con=169/107 Mean S-cholesterol(mmol/L): Dil=6.45; Con=6.41 Mean S-triglycerides: Dil=1.78; Con=1.80 Mean B-glucose: Dil=5.26; Con=5.28 Smokers(%): Dil=22.7; Con=21.9 *Previous disease history(%)* MI: Dil=2; Con=2 IHD: Dil=3; Con=3 Stroke: Dil=1; Con=2 Diabetes mellitus: Dil=7; Con=7 Renal impairment: Dil=0; Con=0

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Number screened, eligible, enrolled	Number withdrawn/ lost to fu/ analyzed	Event Rates	
			CCB Outcomes	**Diuretic Outcomes**
Diltiazem				
NORDIL (Nordic Diltiazem Study) The NORDIL Group, 1993 Hedner, 1999 Hansson, 2000 Kjeldsen, 2002 Norway/Sweden Fair	Screened NR/10916 randomized	Overall withdrawals NR Lost to fu: Dil=24(0.4%); Con=28(0.5%) Analyzed: Dil=5410; Con=5471	*Diltiazem* Occurrence of endpoints(%) Primary endpoint: 7.4 All stroke: 2.9 Fatal stroke: 0.4 All stroke+TIA: 3.7 All MI: 3.4 Fatal MI: 0.5 CV death: 2.4 Total mortality: 4.3 All cardiac events: 9.0 Diabetes mellitus: 3.9 Atrial fibrillation: 1.9 CHF: 1.2	*Conventional therapy(beta-blockers/diuretics* Occurrence of endpoints(%) Primary endpoint: 7.3 All stroke: 3.6 Fatal stroke: 0.4 All stroke+TIA: 4.3 All MI: 2.9 Fatal MI: 0.5 CV death: 2.1 Total mortality: 4.2 All cardiac events: 8.6 Diabetes mellitus: 4.6 Atrial fibrillation: 2.3 CHF: 0.9

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Event Rates			Method of adverse effects assessment?
	Beta Blocker Outcomes	Ace Inhibitor	Angiontensin II Receptor Antagonist Outcomes	
Diltiazem				
NORDIL (Nordic Diltiazem Study) The NORDIL Group, 1993 Hedner, 1999 Hansson, 2000 Kjeldsen, 2002 Norway/Sweden Fair	*Conventional therapy(beta-blockers/diuretics* Occurrence of endpoints(%) Primary endpoint: 7.3 All stroke: 3.6 Fatal stroke: 0.4 All stroke+TIA: 4.3 All MI: 2.9 Fatal MI: 0.5 CV death: 2.1 Total mortality: 4.2 All cardiac events: 8.6 Diabetes mellitus: 4.6 Atrial fibrillation: 2.3 CHF: 0.9	N/A	N/A	Reported in answer to open active questioning at every visit and were not restricted to those thought to be associated with the drugs taken

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Diltiazem			
NORDIL (Nordic Diltiazem Study) The NORDIL Group, 1993 Hedner, 1999 Hansson, 2000 Kjeldsen, 2002 Norway/Sweden Fair	Most frequently reported AEs(%) Dizziness: Dil=9.3; Con=8.9 Arthralgia: Dil=7.7; Con=7.1 Headaches: Dil=8.5; Con=5.7 Chest discomfort: Dil=5.7; Con=5.9 Coughing: Dil=5.6; Con=5.4 Fatigue: Dil=4.4; Con=6.5 Back pain: Dil=4.7; Con=5.4 Depression: Dil=3.7; Con=3.4 Abdominal pain: Dil=3.5; Con=3.4 Dyspnea: Dil=2.9; Con=3.9 Myalgia: Dil=3.2; Con=3.4 Impotence: Dil=2.3; Con=3.7 Diabetes mellitus: Dil=3.9; Con=4.6	NR	

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Study Design, Setting	Eligibility criteria	Exclusion criteria	Subgroup	Interventions (drug, regimen, duration, n)
Nisoldipine					
ABCD (Appropriate Blood Pressure Control in Diabetes) Savage, 1993 Schrier, 1996 Estacio, 1998a Estacio, 1998b United States Fair	RCT	Patients between the ages of 40-74 with NIDDM, diagnosed according to World Health Organization criteria (1985) and DBP of 80 mmHg	Patients with known allergy to dihydropyridine calcium-channel blockers or ACE inhibitors; MI or cerebrovascular accident within the previous six months; had undergone coronary-artery bypass surgery within the previous 3 months; had unable angina pectoris within the previous six months; had NYHA class III or IV congestive heart failure; had an absolute need for therapy with ACE inhibitors of calcium-channel blockers; were receiving hemodialysis or peritoneal dialysis; had a serum creatinine concentration > 3 mg per deciliter	NIDDM	Nis 10-60 mg daily, n=235 Ena 5-40 mg daily, n=235

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Allowed other medications/ interventions	Anti-hypertensive Therapy Summary			
		CCB	**Diuretic**	**Beta Blocker**	**ACE Inhibitor**
Nisoldipine					
ABCD (Appropriate Blood Pressure Control in Diabetes) Savage, 1993 Schrier, 1996 Estacio, 1998a Estacio, 1998b United States Fair	*Intensive goal:* DBP=75.0 mmHg *Moderate goal:* DBP=89.0 mmHg *Open-blind medications in stepwise order:* Metoprolol 100-200 mg daily HCTZ 12.5-25 mg daily Clonidine 0.2-0.6 mg daily Doxazosin 1-16 mg daily Minoxidil 5-40 mg daily Additional antihypertensive medications were added at the discretion of the medical director, but these did not include a calcium-channel blocker or ACE inhibitor	NA	Diuretic agent use: Nis=93(39.5%); Ena=119(50.6%)	BB: Nis=89(37.9%); Ena=99(42.1%)	NA

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Additional treatment information	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Nisoldipine				
ABCD (Appropriate Blood Pressure Control in Diabetes) Savage, 1993 Schrier, 1996 Estacio, 1998a Estacio, 1998b United States Fair	BB: Nis=89(37.9%); Ena=99(42.1%) Diuretic agent use: Nis=93(39.5%); Ena=119(50.6%)	CV outcomes as secondary endpoints	*Mean age:* Nis=57.2; Ena=57.7 *Gender(%male):* Nis=68.1; Ena=66.8 *Race(%):* Non-Hispanic White: Nis=66.4; Ena=67.2 African American: Nis=14.0; Ena=13.6 Hispanic White: Nis=16.2; Ena=17.4 Other: Nis=3.4; Ena=1.7	Family history of coronary artery disease(%): Nis=49; Ena=45 Mean duration of diabetes mellitus(yr): Nis=8.7; Ena=8.5 Mean fasting glucose(mg/dl): Nis=189; Ena=191 Mean glycosylated hemoglobin(%): Nis=11.7; Ena=11.5 Mean duration of hypertension(yr): Nis=11.2; Ena=12.2 Mean SBP(mmHg): Nis=155; Ena=156 Mean DBP(mmHg): Nis=98; Ena=98 Current or former smoker(%): Nis=64; Ena=60 Pack-yr of smoking: Nis=21; Ena=17 Mean total cholesterol(mg/dL): Nis=218; Ena=218 Mean HDL: Nis=43; Ena=40 Mean LDL: Nis=128; Ena=130 Mean triglycerides(mg/dL): Nis=294; Ena=288 BMI: Nis=31.3; Ena=31.9 Previous MI: Nis=2.5; Ena=3.4 CAD history: Nis=10.6; Ena=10.2 Angina on Rose questionnaire: Nis=0.8; Ena=2.5 Previous cerebrovascular accident: Nis=1.3; Ena=0.8 Previous congestive heart failure: Nis=0.4; Ena=0.8 Abnormal ankle-brachial index: Nis=2.9; Ena=5.9 Left ventricular hypertrophy on ECG: Nis=12.8; Ena=15.3

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Number screened, eligible, enrolled	Number withdrawn/ lost to fu/ analyzed	Event Rates	
			CCB Outcomes	**Diuretic Outcomes**
Nisoldipine				
ABCD (Appropriate Blood Pressure Control in Diabetes) Savage, 1993 Schrier, 1996 Estacio, 1998a Estacio, 1998b United States Fair	Screened NR/470 enrolled	Overall withdrawals: Nis=142(60.4%); Ena=129(54.9%) Lost NR Analyzed: Nis=235; Ena=235	*Nisoldipine* CV outcomes(%) Fatal or nonfatal MI: 10.6 Nonfatal MI: 9.4 Cerebrovascular accident: 4.7 Congestive heart failure: 2.5 Death from cardiovascular causes: 4.2 Death from any cause: 7.2	N/A

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Event Rates			Method of adverse effects assessment?
	Beta Blocker Outcomes	Ace Inhibitor	Angiontensin II Receptor Antagonist Outcomes	
Nisoldipine				
ABCD (Appropriate Blood Pressure Control in Diabetes) Savage, 1993 Schrier, 1996 Estacio, 1998a Estacio, 1998b United States Fair	N/A	*Enalapril* CV outcomes(%) Fatal or nonfatal MI: 2.1 Nonfatal MI: 2.1 Cerebrovascular accident: 2.9 Congestive heart failure: 2.1 Death from cardiovascular causes: 2.1 Death from any cause: 5.5		NR

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Nisoldipine			
ABCD (Appropriate Blood Pressure Control in Diabetes) Savage, 1993 Schrier, 1996 Estacio, 1998a Estacio, 1998b United States Fair	Incidence NR	Total withdrawals due to AEs: Nis=54(22.9%); Ena=41(17.4%) Edema withdrawals: Nis=20(8.5%); Ena=11(4.7%) Headache withdrawals: Nis=10(4.2%); Ena=1(0.4%)	

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Study Design, Setting	Eligibility criteria	Exclusion criteria	Subgroup	Interventions (drug, regimen, duration, n)
Isradipine					
The MIDAS Research Group, 1989 Borhani, 1990 Borhani, 1991 Borhani, 1992 Furberg, 1993 Borhani, 1996 United States *Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS)* Fair	RCT	Hypertensive (DBP > 90 mmHg) patients aged 40 years or more who have one or more early atherosclerotic lesion(s) in the extracranial carotid arteries as documented by B-mode imaging.	Elevated lipid (cholesterol and triglycerides), blood sugar, creatinine and liver enzyme levels; malignant hypertension or secondary hypertension; insulin-dependent diabetes mellitus; hypo- or hyperthyroidism; history cerebrovascular disease, carotid endarterectomy, heart failure, cardiac arrhythmias, coronary bypass surgery, percutaneous transluminal coronary angioplasty, uncontrolled angina, and recent MI; factors that may interfere with full participation in the study; use of several drugs that may interfere with the evaluation of the trial results; known adverse reaction to any of the study drugs	None	Isr 5-10 mg daily, n=442 HCTZ 25-50 mg dailyn=441

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Allowed other medications/ interventions	Anti-hypertensive Therapy Summary			
		CCB	**Diuretic**	**Beta Blocker**	**ACE Inhibitor**
Isradipine					
The MIDAS Research Group, 1989 Borhani, 1990 Borhani, 1991 Borhani, 1992 Furberg, 1993 Borhani, 1996 United States *Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS)* Fair	*Goal DBP:* For patients with DBP </= 105 at baseline=a reduction of at least 10 mmHg and DBP<90 mmHg; For patients with DBP between 105 and 115 mmHg at baseline=a reduction of at least 10 mmHg and DBP<95 mmHg Open-label Enalapril 5-20 mg daily	*Please see 'Additional treatment information' column*	*Please see 'Additional treatment information' column*	*n/a*	*n/a*

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Additional treatment information	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Isradipine				
The MIDAS Research Group, 1989 Borhani, 1990 Borhani, 1991 Borhani, 1992 Furberg, 1993 Borhani, 1996 United States *Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS)* Fair	*Treatment at 36 months(%)* Monotherapy: Isr=55.5; HCTZ=54.2 Use of add-on Enalapril: Isr=24.7; HCTZ=27.5 Off both medications: Isr=19.8; HCTZ=18.3	Independent panel classification	*Mean age:* Isr=58.2; HCTZ=58.7 *Gender(%male):* Isr=79.9; HCTZ=75.7 *Race(%)* White: Isr=71.0; HCTZ=73.7 African American: Isr=22.4; HCTZ=20.6 Other: Isr=6.3; HCTZ=5.7	*Risk factors(mean)* SBP(mmHg): Isr=150.6; HCTZ=148.9 DBP(mmHg): Isr=96.7; HCTZ=96.2 HTN duration(y): Isr=9.9; HCTZ=10.2 Cigarette smoking(%) Former: Isr=37.6; HCTZ=40.0 Current: Isr=19.0; HCTZ=21.0 Never: Isr=43.4; HCTZ=39.0 Pack/yr: Isr=15.4; HCTZ=17.0 Cholesterol(mg/dL): Isr=217; HCTZ=216 LDL: Isr=147; HCTZ=146 HDL: Isr=47; HCTZ=48 Triglycerides(mg/dL): Isr=331; HCTZ=322 BMI: Isr=27.9; HCTZ=27.6 *Prior history(%)* MI: Isr=1.4; HCTZ=2.5 Angina: Isr=1.1; HCTZ=0.2 Coronary bypass: Isr=0.6; HCTZ=2.3

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Number screened, eligible, enrolled	Number withdrawn/ lost to fu/ analyzed	Event Rates	
			CCB Outcomes	**Diuretic Outcomes**
Isradipine				
The MIDAS Research Group, 1989 Borhani, 1990 Borhani, 1991 Borhani, 1992 Furberg, 1993 Borhani, 1996 United States *Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS)* Fair	18,800 signed consent 883 met inclusion criteria 883 enrolled	nr	*Isradipine(n=442)* Any event(morbid/fatal): 27.1 All-cause mortality: 1.8 *Major vascular events:* Stroke: 1.3 MI: 1.3 Sudden death: 0.4 CHF: 0.4 Angina: 2.5 Other CV disease/death: 0.2 Any major vascular event: 5.6 Major vascular events and procedures: 6.8 Fatal cancer: 0.9 Nonfatal cancer: 2.0 Any cancer: 2.9 *Other types of events and procedures* Fatal: 0.2 Nonfatal: 17.2	*HCTZ (n=441)* Any event(morbid/fatal): 27.2 All-cause mortality: 2.0 *Major vascular events:* Stroke: 0.7 MI: 1.1 Sudden death: 0.4 CHF: 0 Angina: 0.7 Other CV disease/death: 0.2 Any major vascular event: 3.2 *Major vascular events and procedures: 4.3* Fatal cancer:1.1 Nonfatal cancer: 3.4 Any cancer: 4.5 *Other types of events and*

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Event Rates			Method of adverse effects assessment?
	Beta Blocker Outcomes	Ace Inhibitor	Angiontensin II Receptor Antagonist Outcomes	
Isradipine				
The MIDAS Research Group, 1989 Borhani, 1990 Borhani, 1991 Borhani, 1992 Furberg, 1993 Borhani, 1996 United States *Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS)* Fair	N/A	N/A	N/A	NR

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Isradipine			
The MIDAS Research Group, 1989 Borhani, 1990 Borhani, 1991 Borhani, 1992 Furberg, 1993 Borhani, 1996 United States *Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS)* Fair	Severe adverse event incidence: Isr=183(41.1%); HCTZ=172(39.0%) Chest pain: Isr=0.7%; HCTZ=0.8% Other cardiovascular-related adverse reactions: Isr=3.0%; HCTZ=0.9% Central nervous system adverse reactions: Isr=6.2%; HCTZ=4.4% (primarily due to more reports of headaches in the Isr groupx Kidney stones: Isr=0.4%; HCTZ=0.0% Headache: Isr=2.2%; HCTZ=1.1% Faintness: Isr=0.0%; HCTZ=0.4%	*3-year cumulative incidence* Isr=9.3% HCTZ=8.2%	

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Study Design, Setting	Eligibility criteria	Exclusion criteria	Subgroup	Interventions (drug, regimen, duration, n)
Petersen, 2001 Denmark Fair	Single-center, randomized, double-blind comparison of 3 parallel groups.	Patients between ages 18 and 75 with chronic, inactive renal disease and serum creatinine between 150 and 600 mol/l; BP higher than 95 mmHg diastolic or 140 mmHg systolic without treatment.	Renal artery stenosis or severe congestive heart failure (NYHA class III-IV).	Chronic renal disease	isradipine 5 mg or spirapril 6 mg daily, or spirapril 3 mg plus isradipine 2.5 mg

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Allowed other medications/ interventions	Anti-hypertensive Therapy Summary			
		CCB	**Diuretic**	**Beta Blocker**	**ACE Inhibitor**
Petersen, 2001 Denmark Fair	14 patients were on a protein-controlled diet ecause their serum creatinine level increased to more than 500 mol/l; 5 patients received erythropoietin treatment because the hemoglobin level decreased to less than 6 mmol/l. Patients with secondary hyperparathyroidism were treated with -calcidol, and patients with edema were treated with loop diuretics. Loop diuretics and labetolol were the only drugs accepted as additional antihypertensive treatment when the study medication was insufficent in controlling blood pressure.	Patients receiving a CCB before randomization: spirapril group: 40% isradipine group: 45% spirapril plus isradipine group: 40%	Patients receiving a diuretic before randomization: spirapril group: 90% isradipine group: 65% spirapril plus isradipine group: 60%		Patients receiving an ACE inhibitor before randomization: spirapril group: 55% isradipine group: 15% spirapril plus isradipine group: 25%

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Additional treatment information	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Petersen, 2001 Denmark Fair	NR	During the 6 months before randomization, patients were seen at least 3 times in the outpatient clinic and their renal function was estimated 3 times. After randomization, patients seen 4 times during the first 2 months and then every 3.5 months. Progression of renal function was evaluated as the number of patients in each group reaching one of the following endpoints: doubling of serum creatinine or need for dialysis.	isradipine: mean age 54 (SD 14); 65% male spirapril: mean age 62 (SD 9); 70% male isradipine + spirapril: mean age 55 (14); 65% male race/ethnicity not reported	isradipine: spirapril: isradipine + spirapril: isradipine: spirapril: isradipine + spirapril: isradipine: spirapril: isradipine + spirapril:

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Number screened, eligible, enrolled	Number withdrawn/ lost to fu/ analyzed	Event Rates	
			CCB Outcomes	Diuretic Outcomes
Petersen, 2001 Denmark Fair	number screened not reported (74 initially enrolled but not randomized) 60 eligible 60 enrolled	11 withdrawn number lost to followup not reported 48 analyzed	4/20 (20%) isradipine, 4/20 (20%) spirapril, 4/20 (20%) isradipine plus spirapril reached end stage renal failure and started dialysis. Need for dialysis or doubling of serum creatinine: 5/20 (25%) spirapril, 35% isradipine, and 20% isradipine plus spirapril ($p<0.02$). No relative risks are reported	N/A

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Event Rates			Method of adverse effects assessment?
	Beta Blocker Outcomes	Ace Inhibitor	Angiontensin II Receptor Antagonist Outcomes	
Petersen, 2001 Denmark Fair	N/A	4/20 (20%) spirapril, and 4/20 (20%) isradipine plus spirapril reached end stage renal failure and started dialysis. Need for dialysis or doubling of serum creatinine: 5/20 (25%) spirapril, 35% isradipine, and 20% isradipine plus spirapril (p<0.02).	N/A	NR

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Petersen, 2001 Denmark Fair	NR	NR	

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Study Design, Setting	Eligibility criteria	Exclusion criteria	Subgroup	Interventions (drug, regimen, duration, n)
Verapamil					
CONVINCE Black, 1998, Black, 2003 US Fair	RCT	Hypertensive, no medication or medication less than 2 months (and 140 < SBP < 190 or 90 < DBP < 110) or taking antihypertensive medications for at least 2 months (and SBP < 175 mm Hg, DBP < 100 mm Hg) men and women age 55 and older at least one: prior history of MI (> 12 months ago); stroke (> 6 months ago); transiant ischemic attack; diabetes; known vascular disease; or at least one cardiovascular risk factor.	History of heart failure, NYHA class II-IV. Untreated SBP > 190 or DBP > 220 mm HG. Secondary hypertension. Cardiac dysrhythmias requiring medication. Sick sinus syndrome. Symptomatic MI w/in past 12 months or stroke w/in past 6 mo, symptomatic angina w/in past 6 months. Known renal insufficiency. Need specific study medication to achieve goal BP or need more than 3 drugs to control BP. Contraindications for any of the study medications. Low likelihood of compliance. Other life threatening diseases. Participation in other clinical trial of antihypertensive medications within 30 days of randomization. Working evening, night or alternating shifts.	none	COER verapamil daily, n=8241 HCTZ or atenolol, n=8361 Before randomization, investigator assigned each patient to be HCTZ or ate based on suitability. If the patient was selected as control, he/she began the assigned control drug.

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Allowed other medications/ interventions	Anti-hypertensive Therapy Summary			
		CCB	**Diuretic**	**Beta Blocker**	**ACE Inhibitor**
Verapamil					
CONVINCE Black, 1998, Black, 2003 US Fair	Step 1: If study medication is not tolerated or BP not controlled (<140/90), study medication doubled. Step 2: Added up to 25 mg HCTZ daily to Verapimil or Atenolol groups (blinded) Added 50 mg of atenolol to HCTZ group (blinded Step 3: Any other antihypertensive (other than CCB, diuretic or beta blocker) (unblinded)	Median time receiving study drug 2.2 years At end of study Level 1 (ver): 60.6% Level 2 (HCTZ): 15.5%% Level 3 (other): 16.7%	Median time receiving study drug 2.2 years At end of study Level 1 (HCTZ): 60.3% Level 2 (ate): 16.1% Level 3 (other): 18.2%	Median time receiving study drug 2.2 years At end of study Level 1 (ate): 60.3% Level 2 (HCTZ): 16.1% Level 3 (other): 18.2%	n/a

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Additional treatment information	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Verapamil				
CONVINCE Black, 1998, Black, 2003 US Fair	nr	Followup visits, death certificates, clinic investigator reports, hospital discharge summaries, 5 years	Mean 66 44% male 7% black 7% Hispanic 84% white	23% smoker in past 3 years 50% obese 20% diabetic 8% previous MI 5% previous stroke 2% TIAA

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Number screened, eligible, enrolled	Number withdrawn/ lost to fu/ analyzed	Event Rates	
			CCB Outcomes	**Diuretic Outcomes**
Verapamil				
CONVINCE Black, 1998, Black, 2003 US Fair	NR, 16602, 16476	3086 (ver) withdrawn 3164 (HCTZ or ate) withdrawn 570 (ver) lost 563 (HCTZ or ate) lost 8179 (ver) analyzed 8297 (HCTZ or ate) analyzed	*Verapamil, 3 year followup* *all cause mortatity 337/8179 (4.1%)* *Stroke 133/8179 (1.6%)* *Myocardial infarction 133/8179 (1.6%)* *Heart failure 126/8179 (1.5%)* *Renal failure 27/8179 (0.3%)*	HCTZ or ate, 3 year followup all cause mortatity 319/8297 (3.8%) Stroke 118/8297 (1.4%) Myocardial infarction 166/8297 (2.0%) Heart failure 100/8297 (1.2%) Renal failure 34/8297 (0.4%)

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Event Rates			Method of adverse effects assessment?
	Beta Blocker Outcomes	Ace Inhibitor	Angiontensin II Receptor Antagonist Outcomes	
Verapamil				
CONVINCE Black, 1998, Black, 2003 US Fair	HCTZ or ate, 3 year followup all cause mortatity 319/8297 (3.8%) Stroke 118/8297 (1.4%) Myocardial infarction 166/8297 (2.0%) Heart failure 100/8297 (1.2%) Renal failure 34/8297 (0.4%)	n/a	N/A	nr

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Verapamil			
CONVINCE Black, 1998, Black, 2003 US Fair	Death or hospitalization due to adverse effect 1381/8179 (ver) 1363/8297 (HCTZ or ate)	16.5%, 1353/8179 (ver) 15.3%, 1278/8361 (HCTZ or ate)	none

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Study Design, Setting	Eligibility criteria	Exclusion criteria	Subgroup	Interventions (drug, regimen, duration, n)
INVEST Pepine, 2003 Pepine, 1998 International Fair	RCT Open	Age 50 years or older, essential hypertension as defined by the JNC VI requiring drug therapy and documented CAD. Documented CAD is defined as any one of the following: remote confirmed MI, abnormal coronary angiogram (>50% narrowing of at least one major coronary artery), abnormalities on two different types of stress tests of diagnosis of classical angina pectoris	Unstable angina, angioplasty, coronary bypass or stroke within the previous month; beta-blocker use within the previous 2 weeks or previous year for post-MI patients; sinus bradycardia, sick sinus syndrome or atrioventricular block of more than firs degree in the absence of an implanted pacemaker; severe (NYHA class IV) heart failure; severe renal (creatine ≥ 4.0) or hepatic failure; or contraindication to verapamil	CAD	*Step 1* Verapamil SR 240-360 mg, n=11,267 Atenolol 50-100 mg, n=11,309 2-3 years

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Allowed other medications/ interventions	Anti-hypertensive Therapy Summary			
		CCB	**Diuretic**	**Beta Blocker**	**ACE Inhibitor**
INVEST Pepine, 2003 Pepine, 1998 International Fair	*Target: SBP<140 mm Hg and DBP<90 mm Hg or SBP<130 mm Hg and DBP<85 mm Hg when diabetes or renal impairment is present* *Step 2 Add drug* Verapamil SR 240 mg/trandolapril 2 mg combination product (Tarka) Atenolol 50 mg + HCTZ 25 mg *Step 3 Increase dose* Verapamil SR 180 mg/trandolapril 2 mg combination product (Tarka) twice daily Atenolol 100 mg + HCTZ 50 mg *Step 4 Add drug* Verapamil SR 180 mg/trandolapril 2 mg combination product (Tarka) twice daily + HCTZ 25 mg Atenolol 100 mg + HCTZ 50 mg + trandolapril 2 mg *Step 5* *Add nonstudy antihypertensive medication*	Number(%) patients at 24 months <u>Study medication</u> Verapamil SR=6391(81.5%) *Mean dose=288 mg* Trandolapril=4934(62.9%) *Mean dose=4 mg* HCTZ=3430(43.7%) *Mean dose=29 mg* <u>Non-study medication</u> Any non-study=2944(43.3%) ACE Inhibitor=1300(19.1%) Centrally acting=132(1.9%) Calcium antagonist=1133(16.7%) Diuretic=1314(19.3%) Alpha-blocker/other vasodilator=365(5.4%) Beta blocker=373(5.5%) Other class=616(9.1%)	n/a	Number(%) patients at 24 months <u>Study medication</u> Atenolol=6083(77.5%) *Mean dose=76 mg* Trandolapril=4113(52.4%) *Mean dose=4 mg* HCTZ=4733(60.3%) *Mean dose=29 mg* <u>Non-study medication</u> Any non-study=2929(42.9%) ACE Inhibitor=1310(19.2%) Centrally acting=137(2.0%) Calcium antagonist=479(7.0%) Diuretic=1439(21.1%) Alpha-blocker/other vasodilator=365(5.4%) Beta blocker=967(14.2%) Other class=626(9.2%)	n/a

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Additional treatment information	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
INVEST Pepine, 2003 Pepine, 1998 International Fair	nr	*Primary outcome:* first occurrence of all-cause death, nonfatal MI, or nonfatal stroke *Secondary outcomes:* individual primary outcome components; time to most serious event (ranked from death as most serious, to MI, to stroke as least serious), cardiovascular death, angina, cardiovascular hospitalizations, blood pressure control, cancer, Alzheimer disease, Parkinson disease, and gastrointestinal tract bleeding Three members of the events committee, masked to treatment assignment, confirmed all outcome events by reviewing documentations and other pertinent patient records Protocol visits were scheduled every 6 weeks for the first 6 months and then biannually	66.0 52.1% female 48.4% white	MI=32.0% Abnormal angiogram=39.2% Prior MI or abnormal angiogram=53% Concordant stress test abnormalities=21.2% Angina pectoris=66.6% CABG ≥ 1 month ago=15.8% PCI ≥ 1 month ago=15% CABG or PCI=27.3% Stroke=5.1% LV hypertrophy=21.9% Unstable angina ≥ 1 month ago=11.4% Arrhythmia=7.1% Heart failure (class I-III)=5.6% Peripheral vascular disease=11.9% Smoking in the past=46.3% Smoking within last 30 days=12.4% Never smoked=53.6% Diabetes=28.3% Hypercholesterolemia=55.8% Renal impairment=1.9% Cancer=3.4%

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Number screened, eligible, enrolled	Number withdrawn/ lost to fu/ analyzed	Event Rates	
			CCB Outcomes	**Diuretic Outcomes**
INVEST	nr	2662(11.8%) withdrawn	*Number(%)*	n/a
	23,482	568(2.5%) lost to fu	*24-month outcomes*	
Pepine, 2003	22,576	22576 analyzed		
Pepine, 1998			Primary outcome=data nr	
International			First event=1119(9.93%)	
			Death=873(7.75%)	
Fair			Nonfatal MI=151(1.34%)	
			Nonfatal stroke=131(1.16%)	
			CV-related death=431(3.83%)	
			CV-related hospitalization=726(6.44%)	

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Event Rates			Method of adverse effects assessment?
	Beta Blocker Outcomes	Ace Inhibitor	Angiontensin II Receptor Antagonist Outcomes	
INVEST Pepine, 2003 Pepine, 1998 International Fair	*Number(%)* *24-month outcomes* Primary outcome=data nr First event=1150(10.17%) Death=893(7.90%) Nonfatal MI=153(1.35%) Nonfatal stroke=148(1.31%) CV-related death=431(3.81%) CV-related hospitalization=709(6.27%)	n/a	N/A	Adverse experiences were collected from responses to open, active questioning not restricted to those events known to be associated with the drugs taken

Evidence Table 2. Hypertension Active Controlled Trials

Study, Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
INVEST Pepine, 2003 Pepine, 1998 International Fair	Development of diabetes Verapamil SR=569/8098(7.03%) Atenolol=665/8078(8.23%) (RR=0.85; 95% CI 0.77-0.95) Cancer Verapamil SR=192(1.70%) Atenolol=186(1.64%);NS Angina Verapamil SR=261(2.32%) Atenolol=228(2.02%) CABG/PCI Verapamil SR=280(2.49%) Atenolol=275(2.43%) Constipation Verapamil SR=195(1.73%) Atenolol=15(0.13%) Cough Verapamil SR=201(1.78%) Atenolol=152(1.34%) Dizziness Verapamil SR=154(1.37%) Atenolol=151(1.34%) Dyspnea Verapamil SR=82(0.73%) Atenolol=114(1.01%) Heart failure (class I-IV) Verapamil SR=189(1.68%) Atenolol=173(1.53%) Lightheadedness Verapamil SR=48(0.43%) Atenolol=70(0.63%) Symptomatic bradycardia Verapamil SR=74(0.66%) Atenolol=143(1.26%) Unstable angina Verapamil SR=131(1.16%) Atenolol=122(1.08%) Other Verapamil SR=1158(10.28%) Atenolol=1180(10.43%)	Verapamil SR=327(2.9%) Atenolol=267(2.4%)	

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Hypertension				
Amlodipine comparisons				
TOMHS (Treatment of Mild Hypertension Study) Stamler, 1987 Mascioli, 1990 Treatment of Mild Hypertension Research Group, 1991 Neaton, 1993 Grimm, 1997 United States Fair	RCT	Patients aged 45-69 *Stratum 1:* not taking antihypertensive medication at initial screening and DBP of 90-99mmHg at both of the first two eligibility visits and averaged 90-99mmHG over the three eligibility visits *Stratum 2:* taking only one type of antihypertensive drug at the first eligibility visit and, after drug withdrawal, their DBP averaged 85-99 mmHg at 3 subsequent eligibility visits	Patients with evidence of cardiovascular disease or life-threatening illness or who were unable to make nutritional changes; inability to obtain a technically satisfactory baseline echocardiogram	Acebutolol (ace) 400 mg daily; Amlodipine (aml) 5 mg daily; Chlorthalidone (chl) 15 mg daily; Doxazosin (dox) 2 mg daily, following 1 mg daily for one month; Enalapril (ena) 5 mg daily; Placebo

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Hypertension			
Amlodipine comparisons			
TOMHS (Treatment of Mild Hypertension Study) Stamler, 1987 Mascioli, 1990 Treatment of Mild Hypertension Research Group, 1991 Neaton, 1993 Grimm, 1997 United States Fair	All participants received nutritional-hygienic advice to reduce weight and sodium and alcohol intake and to increase physical activity The addition of a step-2 drug (ena 2.5-5 mg daily for the chl group; chl 15-30 mg for all other groups) when mean DBP >/= 95 mmHg on 3 successive visits, or mean DBP >/= 105 mmHg at a single visit	Quality of life measures selected from a larger set used in the Rand Medical Outcomes Study QOL questionnaire administered at 3 months and then annually	*Mean age:* ace=54.6; aml=53.8; chl=55.2; dox=54.8; ena=55.3; plac=54.9 *Gender(%male):* ace=68.9; aml=58.8; chl=64.0; dox=60.4; ena=57.0; plac=61.5 *Race(%black):* ace=20.5; aml=13.7; chl=22.8; dox=18.7; ena=20.0; plac=20.0

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Hypertension			
Amlodipine comparisons			
TOMHS (Treatment of Mild Hypertension Study) Stamler, 1987 Mascioli, 1990 Treatment of Mild Hypertension Research Group, 1991 Neaton, 1993 Grimm, 1997 United States Fair	*Mean age:* ace=54.6; aml=53.8; chl=55.2; dox=54.8; ena=55.3; plac=54.9 *Gender(%male):* ace=68.9; aml=58.8; chl=64.0; dox=60.4; ena=57.0; plac=61.5 *Race(%black):* ace=20.5; aml=13.7; chl=22.8; dox=18.7; ena=20.0; plac=20.0 *Mean characteristics of the 902 randomized patients* Weight(lbs): 187.4 BMI(kg/m^2): 28.9 Overnight urinary sodium excretion (mEq/8h): 53.6 Alcohol use(%): 72.7 Drinks/wk for alcohol drinkers: 5 Plasma cholesterol (mg/dl): 228.3 Cigarette smokers(%): 10.9 Taking medication at initial screen(%): ace=60.6; aml=61.1; chl=60.3; dox=61.2; ena=60.7; plac=61.1 SBP(mmHg): ace=140.2; aml=138.1; chl=140.5; dox=140.8; ena=140.8; plac=141.1 DBP(mmHg): ace=90.7; aml=90.9; chl=90.4; dox=90.6; ena=90.2; plac=90.5 Left ventricular hypertrophy(%): aml=13.4; aml=7.4; chl=22.3; dox=15.6; ena=12.8; plac=16.1(p=0.04) VPB >10/h upon ambulatory ECG(%): ace=6.1; aml=8.5; chl=19.2; dox=17.6; ena=13.8; plac=15.3(p=0.01)	11,914 screened/eligible NR/902 randomized	53(6%) withdrawn prior to 12-month visit/lost NR/

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Outcomes	Method of adverse effects assessment?
Hypertension		
Amlodipine comparisons		
TOMHS (Treatment of Mild Hypertension Study) Stamler, 1987 Mascioli, 1990 Treatment of Mild Hypertension Research Group, 1991 Neaton, 1993 Grimm, 1997 United States Fair	*Quality of life measures (baseline score/change at 12 months/change at 4 years)* *General Health Index* (range 10-50): ace=38.9/2.6/2.2; aml=39.8/0.8/0.6; chl=39.5/1.8/1.5; dox=39.5/1.9/1.2; ena=38.8/1.5/0.8; plac=38.8/1.6/1.0 *Energy/Fatigue* (range 4-24): ace=17.0/1.6/1.4; aml=17.6/0.8/0.7; chl=17.0/1.71.4; dox=17.8/0.6/0.5; ena=17.3/1.0/0.8; plac=17.2/0.9/0.7 *Mental Health Index* (range 13-78): ace=62.0/2.9/3.1; aml=62.5/2.0/2.0; chl=63.4/2.7/2.7; dox=63.6/1.4/1.6; ena=62.8/1.3/1.3; plac=62.2/1.4/1.4 *General Functioning Index* (range 3-15): ace=14.0/0.4/0.1 aml=14.0/0.3/0.1; chl=14.0/0.4/0.1; dox=14.3/(-0.3)/(-0.3); ena=14.1/(-0.1);(-0.1) plac=14.2/(-0.2)/(-0.3) *Satisfaction with physical abilities* (range 1-6): ace=4.4/0.6/0.4; aml=4.3/0.6/0.5; chl=4.5/0.6/0.4; dox=4.5/0.3/0.3; ena=4.5/0.4/0.4; plac=4.5/0.4/0.3 *Social functioning relative to others* (range 1-5): ace=3.6/0.1/0.2; aml=3.7/0.2/0.1; chl=3.6/0.1/0.2; dox=3.7/0.0/0.0; ena=3.7/0.2/0.1; plac=3.8/0.0/(-0.1) *Social contacts* (range 2-12): ace=5.8/0.0/0.1; aml=5.6/0.3/0.4; chl=5.8/(-0.2)/(-0.2); dox=6.1/0.0/0.0; ena=5.8/(-0.1)/0.1; plac=5.7/0.2/0.2	A 55-item checklist was used to elicit possible side effects to treatment. Each item in the checklist was rated on a 4-point scale (e.g., 1=not troubled; 2=mild, bothersome, but does not interfere with usual daily activities; 3=moderate, interferes with usual daily activities; 4=severe, so bad that usual daily activities cannot be performed

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Hypertension			
Amlodipine comparisons			
TOMHS (Treatment of Mild Hypertension Study) Stamler, 1987 Mascioli, 1990 Treatment of Mild Hypertension Research Group, 1991 Neaton, 1993 Grimm, 1997 United States Fair	Acceptibility of treatment(continued to be prescribed initially assigned medication alone at 12 months): 83% % patients taking initially assigned treatment only at 48 months: ace=77.8; aml=82.5; chl=67.5; dox=66.1; ena=68.1; plac=58.5; all drug treatments: 72.4 Adherence: 89% of participants taking study medication took at least 80% of the prescribed dose of capsules *Specific AE incidence(%):* Faintness/dizziness: ace=18.4; *aml=18.6;* chl=19.4; dox=23.0; ena=22.8; plac=20.7 Headaches: ace=22.1; *aml=22.9* ; chl=21.7; dox=31.4; ena=25.2; plac=34.3 Flushed face: ace=8.8; *aml=10.2* ; chl=7.3; dox=3.3; ena=8.9; plac=10.3 Swelling of feet, ankles: ace=11.2; *aml=13.6* ; chl=8.9; dox=10.7; ena=11.4; plac=10.3	Serious adverse events requiring interruption of therapy: Drug treatment groups=14(2.1%); Placebo=9(3.8%)	A block randomization scheme was used with stratification by clinical center and use of antihypertensive drugs at initiatial screening

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Omvik 1993 Norway Fair	RCT	Patients aged 40-70 with mild-moderate HTN (Wold Health Organization stages I or II) and were either formerly untreated or had previous antihypertensive medication withdrawn for 4 weeks before active therapy	Patients with malignant or secondary HTN; known intolerance to calcium antagonists or ACE inhibitors, or hepatic, hematological or other diseases prohibiting the use of these drugs; women who were pregnant, breastfeeding, using oral contraceptives or intending to become pregnant within the study period; angina pectoris, recent MI (within previous 6 months) or cerebrovascular accident within the previous year; patients who were more than 30% overweight	Aml 5-10 mg daily Ena 10-40 mg daily x 12 weeks of 'dose adjustment' and 38 weeks of maintenance

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Omvik 1993 Norway Fair	*HCTZ 25-50 mg daily added at 12 weeks for nonresponders (DBP >/= 95 mmHg)* HCTZ addition: aml=11%; ena=20% (p<0.01)	*Psychological general well-being* -Psychological General Well-Being Index (PGWB) *General health perception* General Health Rating Index (GHRI) *Sexual functioning scale* -modified from previous studies on impotence (Pfizer, unpublished data, 1987) *Social and work relations* -adapted from a scale developed by Croog et al. *Cognitive functioning* -Sickness Impact Profile *Functional impact of symptoms and side effects* -Symptom Side Effect Index developed specifically for this trial and standardized to a 0-10 scale *Assessments completed at 1) study entry; 2) end of placebo period; 3) end of dose titration phase; 4) after 26 weeks; 5) after 50 weeks*	Mean age: aml=54.1; ena=54.6 Gender(%male): aml=52.8; ena=50.9 Race NR

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Omvik 1993 Norway Fair	Mean age: aml=54.1; ena=54.6 Gender(%male): aml=52.8; ena=50.9 Race NR Mean HTN duration(yrs): aml=6.4; ena=6.6 Previously treated(%): aml=68.8; ena=71.3 SBP(mmHg): aml=162; ena=162 DBP(mmHg): aml=106; ena=106 Heart rate(beats/min): aml=74; ena=74	NR/NR/461	Withdrawn: aml=3; ena=7/Lost NR/Analyzed: aml=228; ena=223

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Outcomes	Method of adverse effects assessment?
Omvik 1993 Norway Fair	*Week 50 outcomes (per protocol analyses)* *Change in psychological general well-being* Anxiety: aml=0.63; ena=0.68 Depression: aml=0.10; ena=(-0.04) Well-being: aml=0.35; ena=0.39 Self-control: aml=0.09; ena=0.22 General health: aml=0.38; ena=0.34 Vitality: aml=0.36; ena=0.52 Total index: aml=1.92; ena=2.09 *Change in social and sexual functioning* Family: aml=0.12; ena=0.36 Work: aml=0.31; ena=0.31 Sexual: aml=(-0.40); ena=(-0.33) *Cognitive functioning* Alertness: aml=(-0.39); ena=(-1.18) *Change in health outlook(GHRI)* *Current health: aml=0.31; ena=0.43* *Health outlook: aml=(-0.04); ena=0.06*	Recorded by type, onset, degree of severity and relationship to treatment

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Omvik 1993 Norway Fair	*Overall incidence(related or possibly related):* aml=49%; ena=50% *Dose reduction:* aml=6%; ena=2% *Incidence of most common AE's:* Peripheral edema: aml=22%; ena=NR Coughing: aml=NR; ena=13% *Mean change at week 50* Dizziness: aml=(-0.24); ena=(-0.41) Cardiovascular: aml=(-0.27); ena=(-0.17) Cough: aml=0.19; ena=0.85(p<0.01) Cold extremity: aml=0.01; ena=0.20 Sleep disturbance: aml=(-0.06); ena=0.21 GI: aml=(-0.14); ena=(-0.13) Dermatological: aml=(-0.14); ena=0.01 Cramps: aml=(-0.04); ena=(-0.02) Concentration: aml=(-0.15); ena=(-0.12) Fatigue: aml=(-0.22); ena=(-0.16) Headache: aml=(-0.64); ena=(-0.40) Flushing: aml=(-0.23); ena=(-0.27) Vision: aml=(-0.03); ena=(-0.02) Edema: aml=0.31; ena=(-0.23)(p<0.001)	Withdrawals due to "definitely related" adverse events: aml=4%; ena=4% Death: aml=1(unspecified sudden death) ena=1(accidental head injury)	

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Nifedipine comparisons				
Fletcher 1992 Europe	RCT	patients were aged 35-69 years and were able to read and write	1. Patients had severe hypertension, angina pectoris, a myocardial infarction in the 6 months before study entry, a history of heart failure or of cerebrovascular accident, atrioventricular block on the prestudy electrocardiogram, or a hemodynamically relevant heart rhythm disturbance. 2. Patients had a history of psychiatric illness, alcoholism or drug abuse, or had clinically significant neurological, respiratory, hepatic, gastrointestinal, hematologic, autoimmune, renal, or endocrine disease. 3. Women of childbearing porential	cilazapril 2.5mg qid, for 6 months atenolol 50mg qid, for 6 months nifedipine 20mg bid for 6 months
Metelitsa 1996 Fair-Poor	RCT Open	Patients aged 30-60 years with stable mild-moderate arterial hypertension stages I-II according to WHO criteria; DBP measured in the right arm 95-114 mmHg and no other chronic diseases requiring treatment	NR	Captopril (Cap) 50 or 100 mg daily *(n=86)* Nifedipine (Nif) 60 or 90 mg daily *(n=89)* Hydrochlorothiazide (HCTZ) 25 or 50 mg daily *(n=83)* Propranolol (Pro) 80 or 240 mg daily *(n=87)*

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Nifedipine comparisons			
Fletcher 1992 Europe	1-12 weeks: if the mean sitting diastolic blood pressure(SDBP) is greater than 90mmHg at 2-8 hours after dosage remained, the dosage was double once. After 12 weeks: if the SDBP still greater than 90mmHg, hydrochlorothiazide (HCTZ), was added in from 12.5mg daily increasing to 25mg if necessary.	QOL questionnaires: 1. placebo run-in period: beginning(w1) and end (w4) 2. active therapy period: after 12 and 24 weeks	cilazapril=179 with mean-age 53.6, 64.2% male atenolol=182 with mean-age 54.8, 50% male nifedipine=179 with mean-age 53.1, 55.9% male Race NR
Metelitsa 1996 Fair-Poor	Unspecified additional antihypertensive treatment (combination therapy) allowed after 2 months in the cases of insufficient control with monotherapy 87 of 296 completers on combined therapy (29.4%)	General Well-Being Questionnaire (GWBQ) at month 8	Absolute data NR; data presented in graphical format; stated no differences in age

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Nifedipine comparisons			
Fletcher 1992 Europe	cilazapril=179 with mean age=53.6, 64.2% male atenolol=182 with mean age=54.8, 50% male nifedipine=179 with mean age=53.1, 55.9% male SBP(mmHg): cil=159.5, ate=160.8, nif=160.1 DBP(mmHg): cil=102.5, ate=102.7, nif=102.3	Screen NR/636 eligible/540 enrolled	drop-out number (all reason): nif=38(21.2%), cil=25(14.0%), ate=23(12.6%) drop-out number due to adverse events: nif=31(17%), cil=9(5%), ate=15(8%) /Lost NR
Metelitsa 1996 Fair-Poor	Absolute data NR Data presented in graphical format Stated no differences in height, body weight and HTN duration	Screened NR/Eligible NR/345 enrolled	49 withdrawn Lost NR

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Outcomes	Method of adverse effects assessment?
Nifedipine comparisons		
Fletcher 1992 Europe	mean decrease DBP(SD): cil=14.7(8.7), ate=15.5(8.8), nif=14.7(8.5) number of patients having the addition of HCTZ: cil=65(36.3%), ate=45(24.7%), nif=42(23.5%), p=0.01 drop-out rate: nif>cil, nif>ate (p=0.04), cil=ate total drop-out number (all reason): nif=38(21.2%), cil=25(14.0%), ate=23(12.6%) drop-out number due to adverse events: nif=31(17%), cil=9(5%), ate=15(8%), p=0.001 95% CI of change for comparison: Complaint score: cil vs. ate =(-1.1, 2.4), cil vs. nif=(-3.4, 0.1), ate vs. nif =(-4.0, -0.5) --> nif>cil, nif =ate, cil=ate Fatigue: cil vs. ate =(-0.8, 1.0), cil vs. nif =(0.1, 1.9), ate vs. nif =(0.1,1.8) --> cil=ate, cil>nif , ate>nif 20% or more symptoms comlaints are from nif: heartburn, swollen ankles, itching, cramps in legs, flushing of face, night urine	interview and self-report questionnaires
Metelitsa 1996 Fair-Poor	Absolute data NR	NR

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Nifedipine comparisons			
Fletcher 1992 Europe	number of events: cil=161, ate=194, nif=242 number of patients with one or more events: cil=93(52%), ate=112(62%), nif=115(64%)	nif=31(17%) cil=9(5%) ate=15(8%)	
Metelitsa 1996 Fair-Poor	Adverse event frequency: Nif=38.1% Cap=18.6% HCTZ=16.9% Pro=28.7%	AE withdrawals: Nif=2.2% Cap=1.2% HCTZ=2.4% Pro=6.9%	

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Bulpitt 2000 Austria, Italy, Germany, Netherlands, Poland, Spain, Switzerland, and the UK Fair	RCT	Patients over 60; suffering from essential hypertension (sitting DBP >/= 95 mmHg and </= 115 mmHg	NR	Bisoprolol (bis) 5-10 mg daily Nifedipine retard (nif r) 20-40 mg daily x 24 weeks

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Bulpitt 2000 Austria, Italy, Germany, Netherlands, Poland, Spain, Switzerland, and the UK Fair	HCTZ 25 mg daily added after 4 weeks for nonresponders (> 90 mmHg)	*Sickness Impact Profile (SIP)* *Digit symbol substitution* from the Wechsler Adult Intelligence Scale (WAIS) *Symbol copying* adapted from Digit symbol substitution test *Cognitive Failures Qustionnaire 1* *Cognitive Failures Questionnaire 2* *Profile of Mood States (POMS)* *Symptom assessment* *Health Status Index (HSI)*	Mean age: bis=67.9; nif r=68.5 Gender NR Race NR

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Bulpitt 2000 Austria, Italy, Germany, Netherlands, Poland, Spain, Switzerland, and the UK Fair	Mean age: bis=67.9; nif r=68.5 Gender NR Race NR NR	771 enrolled/eligible NR/ 747 randomized	Overall withdrawals 133/Lost NR/Safety analysis: bis=368, nif r=379; QOL analysis: bis=309; nif r=309

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Outcomes	Method of adverse effects assessment?
Bulpitt 2000 Austria, Italy, Germany, Netherlands, Poland, Spain, Switzerland, and the UK Fair	*Change in scores from baseline to 'last available' questionnaire* Complaint rate(%): bis=(-2.27); nif r=(-1.02) *Sickness Impact Profile Total:* bis=(-4.03); nif r=(-3.96) *Profile of Mood States* Tension/Anxiety: bis=(-2.04); nif r=(-0.69)(p<0.001) Depression/Dejection: bis=(-1.42); nif 4=(-1.68) Anger/hostility: bis=(-1.29); nif r=(-0.52)(p=0.032) Vigour/activity: bis=0.83; nif r=(-0.24)(p=0.002) Fatigue/inertia: bis=(-0.74); nif r=(-0.64) Confusion/bewilderment: bis=(-0.79); nif 4=(-0.35)(p=0.050) *Digit symbol substitution(correct responses):* bis=4.86; nif r=3.81 *Symbol copying(correct responses):* bis=6.55; nif r=6.59 *Cognitive failures 1:* bis=(-0.69); nif r=(-0.38) *Cognitive failures 2:* bis=(-3.03); nif r=(-1.97) *Health status index:* bis=0.039; nif r=0.046	Volunteered by subjects or observed by the investigators; recorded regardless of whether or not a causal relationship was assumed; assessed as to intensity (mild, moderate, or severe)

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Bulpitt 2000 Austria, Italy, Germany, Netherlands, Poland, Spain, Switzerland, and the UK Fair	*ITT:* bis n=368; nif r n=379 *Incidence of most common AE's:* Edema: bis=3(0.8%); nif r=14(3.7%) Flushing: bis=1(0.3%); nif r=10(2.6%) Headache: bis=1(0.3%); nif r=5(1.3%) *Percentage improved/worsened at last available analysis* *Edema:* Improved: bis=17; nif r=16 Worse: bis=16; nif r=34(p<0.001) *Flushing:* Improved: bis=17; nif r=18 Worse: bis=10; nif r=15 *Headache:* Improved: bis=38; nif r=36 Worse: bis=12; nif r=16 *Heart thumps and misses beat* Improved: bis=25; nif r=22 Worse: bis=8; nif r=17 (p=0.039) *Racing heart* Improved: bis=35; nif r=30 Worse: bis=8; nif r=19(p=0.027) *Itching:* Improved: bis=10; nif r=12 Worse: bis=12; nif r=17 *Wheezing:* Improved: bis=10; nif r=17(p=0.039) Worse: bis=8; nif r=12 *Constipation:* Improved: bis=19; nif r=17 Worse: bis=8; nif r=23(p<0.001) *Nocturia:* Improved: bis=29; nif r=25 Worse: bis=16; nif r=29(p=0.002)	bis=23(6.7%) nif 4=51(13.5%)	

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Fletcher 1992 Europe Fair	RCT	Patients aged between 18 and 75 years and with a supine DBP (phase V) of 95 mmHG or more despite current treatment with a diuretic, alone or with another antihypertensive agent	Pregnant or breast-feeding women; any patients with a history of MI or cerebrovascular event within the previous 3 months; previous history of angina pectoris, congestive heart failure, dizziness, syncope, tachydysrhythmia, vascular headache or edema; impaired renal or hepatic function or any severe chronic disease; contraindication to thiazide treatment including unstable diabetes or uncontrolled hyperuricaemia; laboratory values outside the normal range; tablet compliance outside the range of 80-120% during run-in	Pinacidil (pin) 25-100 mg daily Nif 20-80 mg daily x 6 months *Both drugs were sustained-release formulations*

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Fletcher 1992 Europe Fair	Bendrofluazide 5 mg daily or equivalent doses of another thiazide diuretic	*Overall Health Index:* unspecified questionnaires including a checklist of symptoms and side effects, questions on work and leisure; perception of antihypertensive treatment impact; completed by patient and relative *Psychological well-being:* measured by *Symptom Rating Test (SRT)* and completed by patient	Average age: pin=55.9; nif=56.4 Gender(%male): pin=54; nif=48 Race NR

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Fletcher 1992 Europe Fair	Supine SBP(mmHg): pin=168.4; nif=168.8 Supine DBP(mmHg): pin=103.4; nif=103.9 Mean duration of HTN: pin=73.4; nif=67.4 Smoker: pin=30%; nif=24% Exsmoker: pin=17%; nif=19% Nonsmoker: pin=54%; nif=55% History of increased lipids: pin=10%; nif=6% Previous treatment Diuretic alone: pin=37%; nif=27% Diuretic+bis: pin=34%; nif=32% Diuretic+ACEI: pin=10%; nif=15% Diuretic+methyldopa: pin=3%; nif=6% Diuretic+others: pin=16%; nif=20% Salt restriction: pin=25%; nif=27% Weight reduction: pin=17%; nif=21% Exercise: pin=8%; nif=13%	281 screened/eligible NR/257 randomized	Overall withdrawals: pin=23; nif=18

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Outcomes		Method of adverse effects assessment?
Fletcher 1992 Europe Fair	*Mean changes from 0-6 months* Complaint rate: pin=(-2.01); nif=(-3.14) Health index: pin=1.07; nif=2.62 *% net changes in symptoms* Sleepiness: pin=(-5.0); nif=(-15.4) Blurred vision: pin=(-3.8); nif=(-19.2) Slower walking: pin=(-1.2); nif=(-10.4) Poor concentration: pin=0; nif=(-6.3) Bad taste: pin=(-7.7); nif=1.3 Heartburn: pin=(-6.6); nif=11.5 Runny nose: pin=0; nif=(-6.3) Sore throat: pin=(-2.6); nif=3.8 Rash: pin=(-1.3); nif=3.8 Itch: pin=(-4.9); nif=5.1 Extra hair on body: pin=14.3; nif=4.9 Flushing: pin=(-5.0); nif=3.7 White fingers: pin=7.4; nif=(-2.6) Headache: pin=(-10.1); nif=(-17.5) Palpitations: pin=10.7; nif=(-6.2) Sweating: pin=(-6.2); nif=(-11.3) Swollen gums: pin=(-2.4); nif=3.8 Leg cramps: pin=7.2; nif=(-6.5) Nocturia: pin=6.3; nif=(-1.3) Lack of sexual interest: pin=(-10.0); nif=0 Net change(%) in symptoms reported by relatives Sleepiness: pin=(-13.0); nif=(-10.4) Walking slowed down: pin=(-5.6); nif=4.3 Shortness of breath: pin=(-11.3); nif=(-12.8) Concentration worsened: pin=7.3; nif=(-4.2) Memory worsened: pin=5.5; nif=2.1 Overall health deterioration: pin=(-5.8); nif=(-8.5)	*Psychological well-being* Total: pin=(-2.33); nif=0.06 Depression: pin=(-0.52); nif=(-0.15) Anxiety: pin=(-0.37); nif=(-0.06) Somatic: pin=(-0.19); nif=0.06 Cognitive: pin=(-0.44); nif=0.24 Hostility: pin=(-0.81); nif=(-0.08)	Information collected via spontaneous patient report to physician

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Fletcher 1992 Europe Fair	Overall incidence: pin=49%; nif=56% Most common AE's: Edema: pin=22%; nif=17.7 Headache: pin=9.4%; nif=8.5% Dizziness: pin=7.9%; nif=6.9% Flushing: pin=1.6%; nif=8.5%(p<0.03)	pin=18(14.2%) nif=12(9.2%)	

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Outcomes	Method of adverse effects assessment?
	Shortness of breath: pin=(-11.3); nif=(-12.8) Concentration worsened: pin=7.3; nif=(-4.2) Memory worsened: pin=5.5; nif=2.1 Overall health deterioration: pin=(-5.8); nif=(-8.5)	

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Verapamil comparisons				
Boissel 1995 Poor	RCT Open trial	Patients aged > 18; given informed consent; DBP in the range 90-119 mmHg measured on 2 consecutive occasions separated by 1-6 weeks; had not received any hypertensive treatment in the previous 12 months	NR	Altizide or spironolactone (diu) 15-25 mg daily Enalapril (ena) 20 mg daily Bisoprolol (bis) 10 mg daily Verapamil (ver) 250 mg daily x 1 year

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Verapamil comparisons			
Boissel 1995 Poor	NR	All Body Organs and Functions (ABOF) questionnaire SQLP questionnaire (subjective quality of life) Assessments completed at months 1, 3, 6, 9 and 12 Success-Failure criteria: Success defined as positive response to 1) attendance at final visit; 2) having complied with study treatment; 3) >/= 9 BP recordings during study; and 4) median supine DBP < 90 mmHg and at least 10 mmHg lower than baseline	Mean age: diu=52.2; bis=50.5; ver=52.3; ena: 51.4 Gender(%male): diu=42; bis=43; ver=49; ena=52 Race NR

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Verapamil comparisons			
Boissel 1995 Poor	Mean age: diu=52.2; bis=50.5; ver=52.3; ena: 51.4 Gender(%male): diu=42; bis=43; ver=49; ena=52 Race NR Mean DBP(mmHg): diu=101.0; bis=101.1; ver=100.3; ena=100.5 Mean SPB(mmHg): diu=166.8; bis=167.4; ver=165.7; ena=164.5 Mean weight(kg): diu=70.3; bis=74.0; ver=71.8; ena=73.8 *HTN risk factors:* oral contraception(%): diu=2.4; bis=4.3; ver=3.7; ena=3.0 Frequent use of NSAIDS(%): diu=0.6; bis=0; ver=1.2; ena=4.3(p=0.027) High consumption of alcohol(%): diu=3.0; bis=6.2; ver=0; ena=1.2(p=0.004) High sodium chloride content in diet(%): diu=1.8; bis=1.2; ver=1.8; ena=3.6 High calcium chloride content in diet(%): diu=1.2=bis=0; ver=0.6; ena=0 Obesity(%): diu=9.1; bis=22.8; ver=12.3; ena=18.3(p=0.003)	NR/NR/722 enrolled: 653 assigned to "main stratum" due to eligibility for all treatments (no contraindications); the remaining 69 (9.6%) had a contraindication for at least one of the treatments/	109 patients did not attend the final visit(38 withdrew consent; 23 changed practitioners; 25 forgot to attend)

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Outcomes	Method of adverse effects assessment?
Verapamil comparisons		
Boissel 1995 Poor	Last visit with initially allocated treatment being taken(%): diu=68.3; bis=61.7; ver=62.0; ena=66.5 ABOF questionnaire responses at 9 months: data NR; results described as not significantly different between groups	Evaluated using the ABOF questionnaire and spontaneous patient report

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Verapamil comparisons			
Boissel 1995 Poor	Overall incidence: data NR: p=0.914 Total number of major adverse reactions: data NR; p=0.011, with largest number being reported by diu(15) and bis(11) groups Most common AE's: Cough: data NR; higher incidence in ena group(NS) Fatigue: data NR; higher incidence in diu and bis groups(NS)	NR Changing the original treatment assigned or prescribing an additional antihypertensive drug due to poor tolerance or inefficacy, or both: diu=20; bis=26; ver=33; ena=35	Randomization stratified on basis of contraindications for one or more study treatments 9.6% of screened had contraindications; excluded from the reported results; only main stratum results reported here *Compliance:* 158(24.2%) treatment modified at least once; 31(4.7%) permanently withdrawn; 23(3.5%) temporarily stopped;123(18.8%) received another antihypertensive treatment after permanent withdrawal from allocated treatment (n=72;11.0%) or concomitantly (n=51;7.8%) Treatments not administered to patients; prescriptions bought at independent pharmacies

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Isradipine comparisons				
LOMIR-MCT-IL trial Bar-On, 1993 Amir, 1994 Yodfat, 1996 Israel Fair	RCT	Male patients aged 40-65 years with essential hypertension with a sitting diastolic BP of 95-105 mmHg measured on two consecutive visits after a washout period (in patients on antihypertensive treatment) and in a 2-4 week single-blind (to the patients) placebo period. The patients were either newly diagnosed as hypertensives or had been taking antihypertensive treatment with inadequate control	Patients with secondary hypertension; malignant hypertension; unstable angina; recent myocardial infarction; or any clinical relevant cardiovascular or other chronic disease or abnormal laboratory findings; history of alcohol abuse or mental disorder; insulin-dependent diabetes mellitus	Isradipine (isr) (n=124) 2.5-5 mg daily Methyldopa (met) (n=120) 500-1000 mg daily Placebo (pla) (n=124)

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Isradipine comparisons			
LOMIR-MCT-IL trial Bar-On, 1993 Amir, 1994 Yodfat, 1996 Israel Fair	Captopril 25-50 mg daily add-on for 113 patients (30.7%) after second titration of randomized treatment if DBP was not normalized (> 90 mmHg)	Unspecified new QOL measures compared with a battery of previously validated measures: Sleep/physical/sexual dysfunction: compared with Croog et al. questionnaire Hardiness: overall factor identical to Kobasa's original Depression: intercorrelated and based on Lomeranz et al. questionnaire Categorical/episodic/emantic memory: basis of item development and validation information not described Work-related stress: basis of item development and validation information not described	Mean age: Isr=52.1; Met=51.9; Plac=52.0 Gender: 100% male Race NR

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Isradipine comparisons			
LOMIR-MCT-IL trial Bar-On, 1993 Amir, 1994 Yodfat, 1996 Israel Fair	Weight(kg): Isr=82.3; Met=83.6; Plac=84.6 Mean SBP: Isr=154.5; Met=152.0; Plac=150.7 Mean DBP: Isr=99.7; Met=99.3; Plac=99.8 Depression: Isr=8.2; Met=9.6; Plac=7.8 Subjective current QOL: Isr=2.5; Met=2.8; Plac=2.4 Sleep disorders: Isr=0.2; Met=0.2; Plac=0.05 Physical dysfunction: Isr=0.1; Met=0.1; Plac=0.05 Sexual difficulties: Isr=0.2; Met=0.2; Plac=0.03 Tension at workplace: Isr=3.5; Met=3.4; Plac=3.6 *Recent critical life events:* Desirability: Isr=2.2; Met=2.1; Plac=2.1 Control: Isr=3.1; Met=2.7; Plac=2.9 Severity: Isr=5.6; Met=5.5; Plac=5.1 Semantic Memory: Isr=21.4; Met=20.8; Plac=22.3	NR/NR/368 enrolled	Withdrawals(number of patients): Lack of efficacy: Isr=8; Met=4; Plac=22(p<0.001) AE's: Isr=4; Met=16; Plac=9 Life-threatening events: Isr=3; Met=1; Plac=3(p<0.025) Refusal to continue: 21 Lost to follow-up: 10 Analyzed: Unclear, suspect the 337 patients that were reported to have completed the 1-year follow-up

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Outcomes	Method of adverse effects assessment?
Isradipine comparisons		
LOMIR-MCT-IL trial Bar-On, 1993 Amir, 1994 Yodfat, 1996 Israel Fair	Data NR	NR
	Semantic memory: paper described "significant difference" between isr+cap and other study treatments (met=20.16; isr=32.63; pla=24.75; p<0.001) *Evaluation of current functional level:* paper described isr+cap as showing a clear tendency toward a more positive evaluation	

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Isradipine comparisons			
LOMIR-MCT-IL trial	Adverse reactions(%)	Overall: 29(7.9%)	
Bar-On, 1993	Cardiovascular: Isr=14.8; Met=18.5; Plac=14.5		
Amir, 1994	Sleep disorders: Isr=5.0; Met=12.9; Plac=4.8(p<0.01)		
Yodfat, 1996	Sexual disorders: Isr=6.7 Met=13.7; Plac=4.8(p<0.03)		
Israel	Headache: Isr=20.1; Met=13.7; Plac=18.5		
	Fatigue: Isr=12.5; Met=15.3; Plac=12.1		
Fair	GI: Isr=8.3; Met=13.7; Plac=4.8		

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Supraventricular arrhythmia				
PIAF (Pharmacological Intervention in Atrial Fibrillation Trial) Hohnloser 2000 Germany Fair	RCT	Patients aged 18 to 75 years presenting with symptomatic persistent atrial fibrillation of between 7 days and 360 days duration	Congestive heart failure, New York Heart Association(NYHA) class IV; unstable angina pectoris; acute myocardial infarction within 30 days; atrial fibrillation with an average rate of fewer than 50 beats per minute; known sick-sinus syndrome; atrial fibrillation in the setting of Wolff-Parkinson-White syndrome; coronary artery bypass graft surgery or valve replacement within the past 3 months; echocardiographic documentation of intracardiac thrombus formation; central or peripheral embolisation within the past 3 months; hypertrophic cardiomyopathy; amiodarone therapy within the past 6 months; acute thyroid dysfunction; pacemaker therapy; contraindications for systemic anticoagulation therapy; pregnancy	Group A: Rate control*(n=125)* *Goal:* achieve improvement in symptoms by controlling ventricular rate in persistent atrial fibrillation *Intervention:* Diltiazem 180-270 mg daily+additional therapy at discretion of physician Group B: Rhythm control*(n=127)* *Goal:* Following pharmacological and possibly electrical cardioversion, antiarrhythmic therapy aimed at prevention of recurrent atrial fibrillation *Intervention:* Amiodarone 600 mg daily x 3 weeks

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Supraventricular arrhythmia			
PIAF (Pharmacological Intervention in Atrial Fibrillation Trial) Hohnloser 2000 Germany Fair	All patients were anticoagulated throughout the entire study period (international normalised ratio of 2.0-3.0) *Baseline concomitant medication use(%):* Digoxin: dil=70; ami=72 ACEI: dil=46; ami=44 Beta-blockers: dil=9; ami=10	Medical Outcomes Study short-form health survey (SF-36) at baseline and at 12 months	Mean age: dil=61; ami=60 Gender(%male): dil=74; ami=72 Race NR

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Supraventricular arrhythmia			
PIAF (Pharmacological Intervention in Atrial Fibrillation Trial) Hohnloser 2000 Germany Fair	% *Underlying heart disease* HTN: dil=54; ami=46 CAD: dil=26; ami=20 Previous MI: dil=15; ami=9 Valve disease: dil=15; ami=17 Dilated cardiomyopathy: dil=15; ami=18 None: dil=17; ami=14 *Atrial fibrillation-related symptoms* Palpitations: dil=70; ami=69 Dyspnoea: dil=67; ami=66 Dizziness: dil=30; ami=29 *Other* Left ventricular end diastolic diameter mean(mm): dil=53; ami=53 Left atrium mean(mm): dil=46; ami=45 Mean AF duration(days): dil=118; ami=103 Recurrent AF(%): dil=59; ami=51	NR/NR/252	Overall withdrawals NR/Lost NR/Analyzed not clear, but states ITT(252)

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Outcomes	Method of adverse effects assessment?
Supraventricular arrhythmia		
PIAF (Pharmacological Intervention in Atrial Fibrillation Trial) Hohnloser 2000 Germany Fair	*Mean change (+) from baseline at month 12* Physical functioning: dil=7; ami=8 Physical role function: dil=20; ami=17 Bodily pain: dil=10; ami=8 General health: dil=3; ami=3 Vitality: dil=10; ami=7 Social functioning: dil=8; ami=10 Emotional role functioning: dil=3; ami=0 Mental health: dil=5; ami=4	NR

Evidence Table 3. Quality of Life Trial Summary

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Supraventricular arrhythmia			
PIAF (Pharmacological Intervention in Atrial Fibrillation Trial) Hohnloser 2000 Germany Fair	Overall incidence(%): dil=47; ami=64(p=0.011) Most frequently encountered AE's: Dil: peripheral edema(17/125; 13.6%) Ami: corneal dispositions(10/127; 7.9%); thyroid problems(7/127; 5.5%); photosensitivity(7/127;5.5%)	Death: dil=2(intractable heart failure; recurrent pulmonary embolism); ami=2(ventricular fibraillation; sudden death with no other detailed information) Withdrawals due to AE's: dil=14% ami=25%(p=0.036)	

Evidence Table 4. Angina Head to Head Trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Amlodipine vs Diltiazem			
Bernink 1991 The Netherlands Poor	RCT	Patients with typical symptoms of stable exertional angina pectoris precipitated by physical exertion and persisting for 1-10 min duration; experience of at least 6 angina episodes during a 2-week placebo run-in period with a minimum of 2 attacks in 1 week and significant ST-segment deviation when performing standard bicycle ergometric exercise at the end of each week of the placebo run-in phase	Serious cardiovascular disorders, including unstable angina, pervious or impending MI, CHF, serious cardiac valvular disease, moderate or severe anemia, hypoxic states, extremes or rapid fluctuations of heart rate (HR) or blood pressure (BP), supine or standing systolic BP of < 100 or > 250 mmHg, supine or standing diastolic BP >110 mmHg; second- or third-degree atrioventricular block, bundle branch block, atrial fibrillation, other cardiac arrhythmias requiring drug therapy, electrocardiogram (ECG) patterns not allowing interpretation of ECG exercise data or coronary artery surgery within the preceding 3 months, active hepatic or renal disease, or other major concurrent disease.
Canale 1991 Italy Fair	RCT	Typical symptoms of angina pectoris, usually induced by exercise lasting less than 10 min and responsive to treatment with sublingual nitroglycerin.	Pregnancy, lactation, recent myocardial infarction, valvular disease, arrhythmias, heart block or other ECG alterations, arterial BP > 200/120 mm Hg in the supine position, postural hypotension, bradycardia, unstable angina, other severe concomitant diseases, use of other calcium antagonists, hypersensitivity to dihydropyridine drugs, drug dependence, and participation in other studies.
Knight 1998 UK Fair	RCT	Patients with coronary artery narrowing (70% diameter stenosis of a major epicardial artery on angiogram) or documented Q-wave myocardial infarction; stable angina pectoris (>/ 1 attack of angina/week despite beta-blockade) and a positive exercise test result (1.5-mm ST-segment depression measured 80 ms beyond the J point, within 9 minutes of starting the test)	NR

Evidence Table 4. Angina Head to Head Trials

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Amlodipine vs Diltiazem						
Bernink 1991 The Netherlands Poor	aml 2.5-10 mg daily dil 180-360 mg daily x 8 weeks	sl ntg	Bicycle ergometric tests performed on entry to and after each week of single-blind placebo therapy and at completion of the study Daily diary cards	Mean age: aml 59.1; dil 59.2 Gender(%male): aml 71.8; dil 53.6 Race NR	Severity of angina attacks Mild: aml 69.2; dil 46.3 Mod: aml 25.6; dil 53.6 Severe: aml 5.3; dil 0 Mean duration of angina(months): aml 32; dil 33.9	107 entered placebo run-in period/ 89 eligible for double-blind randomization/ 89 randomized (aml 39; dil 41
Canale 1991 Italy Fair	aml 5-10 mg daily dil 90-180 mg daily x 10 weeks	sl ntg	Patient diary Investigator assessment of therapy response	Mean age NR Gender: aml 50% male; dil 60% male Race NR	NR	NR/NR/40
Knight 1998 UK Fair	aml 5-10 mg daily dil 180-360 mg daily x 4-8 weeks Daily dosages doubled at 4 weeks if angina was still present	Atenolol 50 mg daily sl GTN	Patient diary card Ambulatory ST-segment Holter monitoring Exercise testing (Bruce protocol) Nottingham Health Profile questionnaire	Mean age: 58 for both groups Gender(%male): aml 89.4; dil 90 Caucasian/Asian(%): aml 91.5/8.5; dil 98/2	Mean duration of angina(yrs): aml 3.6; dil 4.1 >/ 70% coronary occlusion on angiogram(%): aml 87.2; dil 78 Previous Q-wave MI(%): aml 27.7; dil 36 HTN(%): aml 6.4; dil 10	109 screened/eligible NR/97 randomized

Evidence Table 4. Angina Head to Head Trials

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Method of adverse effects assessment	Adverse Effects Reported	Withdrawals due to adverse events	Comments
Amlodipine vs Diltiazem					
Bernink 1991 The Netherlands Poor	Withdrawals: aml 2(5.1%); dil 5(12.2%)/0 lost/Analyzed: aml 25; dil 12* 35.9% of aml and 70.7% of dil patients originally randomized included in efficacy analysis due to exercise protocol violations or lack of a final visit.	All observed and volunteered adverse events during the study were recorded and classified by the investigator as drug-related, possibly related or not related.	aml n 39; dil n 41 Overall incidence: aml 41.0%; dil 41.5% Side effects affecting the nervous system were the most frequent in both groups and consisted mainly of headache and dizziness. Nausea and peripheral edema also occurred occasionally on both treatments. Data NR	dil 4.9% aml 0%	
Canale 1991 Italy Fair	NR/NR/40	All observed side effects were recorded at each visit, detailing the nature, severity, onset date, duration and outcome.	Overall: aml 55%; dil 55% Headache: aml 40%; dil 25% Flushing: aml 20%; dil 0% Edema: aml 10%; dil 10% Gastric pyrosis: aml 0%; dil 15%	Total: 0	
Knight 1998 UK Fair	Overall withdrawals(%): aml 12.8; dil 20.0/0 lost/97 analyzed	NR	% Total cardiovascular: aml 19.1; dil 20 Syncope: aml 0; dil 2 Atrial fibrillation: aml 0; dil 2 Bradycardia: aml 0; dil 4 Palpitations: aml 0; dil 2 Hypotension: aml 2.1; dil 2 Edema: aml 17.0; dil 8 Nervous system: aml 10.6; dil 14 Gastrointestinal: aml 0; dil 10 Other: aml 6.4; dil 16	aml 4.3% dil 14.0%	

Evidence Table 4. Angina Head to Head Trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Pehrsson 1996 Sweden Poor	RCT	Clinically stable angina pectoris (defined as precordial discomfort, tightness, heaviness, ache with or without radiation and dyspnea, usually provoked by exertion or cold and relieved by rest or nitroglycerin within 10 minutes) for > 3 months and > 5 attacks in last 2 weeks, age 18 to 80, and one positive bicycle exercise test with ST-segment depression horizontal or down-sloping > 1mm within 15 minutes with or without chest pain.	MI, CABG and/or PTCA within past 3 months, unstable angina, signs and/or symptoms of CHF, significant arrhythmia, affecting the ECG (e.g. digoxin or antiarrhythmic drugs) and malignant hypertension, hepatic or renal failure or those unable to attend regular follow-up.
Van Kesteren, 1998 The Netherlands Fair	RCT	History of stable angina pectoris of more than 3 months' duration; positive thallium scan or a positive coronary angiogram and a positive exercise tolerance test	Unstable angina; recent MI; heart failure; valvular or congenital heart disease; arrhythmias; bradycardia or tachycardia; hypotension; chronic liver disease; chronic obstructive pulmonary disease; insulin-dependent diabetes mellitus; coronary artery bypass graft or percutaneous transluminal coronary angioplasty performed less than 3 months before randomization; women of child-bearing potential; lactating women

Evidence Table 4. Angina Head to Head Trials

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Pehrsson 1996 Sweden Poor	aml 5mg daily x 2 wks, then aml 10mg daily x 2 wks dil 180mg daily x 2 wks then 360mg daily x 2 wks dose reduced if higher dose not tolerated after 2 wks Final dose x 8 weeks	NR	Diary cards for angina attacks and NTG use Exercise tests at baseline and 12 weeks Perception of chest pain during exercise assessed by Borg scale (0 no pain, 10 max pain). Exercise was terminated when pain reached 5 to 6. The perception of exertion or tiredness in the legs was also ranked.	Mean age 65 aml, 66 dil 75% male NR	mean duration of angina: 4 yrs mean number of attacks/wk: 9 aml, 7 dil exercise capacity (watts): aml 112, dil 125 NTG tabs/wk: aml 5, dil 6	NR/NR/119
Van Kesteren, 1998 The Netherlands Fair	aml 5-10 mg daily dil CR 90-120 mg daily x 8 weeks x 8 weeks	sl ntg	Electronically braked bicycle ergometer at weeks 0, 4 and 8; 12 hours post dose Patient diary cards	Mean age: aml 61; dil CR 62 88.6% male 98.5% White	MI >3 months prior to study initiation: aml 44%; dil CR 27% Smokers: aml 30%(current)/38%(former); dil CR 23%(current)/47%(former) Hypercholesterolemia/hypertension/peripheral vascular disease: aml 74%; dil CR 62%	NR/NR/132 enrolled

Evidence Table 4. Angina Head to Head Trials

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Method of adverse effects assessment	Adverse Effects Reported	Withdrawals due to adverse events	Comments
Pehrsson 1996 Sweden Poor	18/1/unclear	Diary	Adverse events reported by 36/61 (59%) aml, 29/58 (50%) dil (NS) Reported that total number of events was significantly higher in aml group (p 0.017), data not reported. Most commonly reported events: aml: swollen legs 26/61 (43%) dil dizziness 13/58 (22%)	Overall 7 (6%) aml 4/61 (7%) dil 3/58 (5%)	Overall withdrawal:16% in each group. How data for these handled not reported, Numbers stopping exercise for various reasons appear to overlap (numbers sum > 119). Diary data are means over 8 wks, not reflect final week only.
Van Kesteren, 1998 The Netherlands Fair	Overall withdrawals: aml 8%; dil CR 11%/lost 0/analyzed 132	Recorded at each visit as reported by the patient or observed by the investigator	Overall: aml 15%; dil CR 26% Headache aml 4.5%; dil CR 6.1% Edema: aml 4.5%; dil CR 4.5% GI complaints: aml 0; dil CR 4.5% Dizziness: aml 0; dil CR 3% Flushes: aml 1.5%; dil CR 1.5% Rash: aml 0; dil CR 1.5%	Withdrawals: aml 3%; dil CR 9%	

Evidence Table 4. Angina Head to Head Trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Nisoldipine vs amlodipine			
Hall 1998 UK Fair	RCT	Diagnosis of chronic stable angina pectoris of at least 3 months' duration and with a severity defined as New York Heart Association Class II or III; receiving atenolol (25, 50, 0r 100 mg daily) and glyceryl trinitrate (GTN) (sl or spray) for symptomatic relief of angina for at least 1 month; atenolol dosage to remain stable throughout the study; physically capable of undertaking repeated treadmill tests using the Bruce protocol	Unstable or variant (Prinzmetal's) angina; history of myocardial infarction coronary angioplasty or coronary artery bypass surgery within 3 months of enrollment; stroke or transient ischemic attack within this 3-month period; cardiovascular disease other than chronic stable angina; disorders that could cause incomplete absorption of the study medication were excluded; psychiatric conditions that could lead to noncompliance; treatment with transdermal nitrate preparations and other antianginal agents; digoxin and cimetidine use
Other CCBs vs diltiazem			
Singh 1991 USA Poor	RCT	Chronic stable angina pectoris refractory to a range of antianginal therapy confirmed by history and positive exercise tolerance test if typical angina developed during exercise and was associated with > 1mm horizontal or downsloping ST-segment depression measured 0.08 section from the J point. All patients had received dil +/- a beta blocker at max doses (360mg/day) without adequate control of anginal symptoms.	MI within 3 months, CHF, or any other cardiac condition that might interfere with data interpretation or put patient at undue risk, bradycardia <50 bpm, QTc prolongation >15% above the upper limit for their age/sex, serum potassium levels <3.5 mEq/L, minor tranquilizers, nonnarcotic analgesic and diuretic drugs, other calcium antagonists, antiarrhythmic drugs, cardiac glycosides, tricyclic antidepressants, and neuroleptics.

Evidence Table 4. Angina Head to Head Trials

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Nisoldipine vs amlodipine						
Hall 1998 UK Fair	Nis CC 20 mg daily aml 5 mg daily x 4 weeks Nis CC 40 mg daily aml 10 mg daily x additional 4 weeks Atenolol (25, 50 or 100 mg daily) taken concomitantly at an unaltered dose throughout the duration of the study	GTN	Standard treadmill exercise testing (Bruce protocol) at baseline and weeks 4 and 8 Patient diary	Mean age: Mis CC 59.6; aml 59.1 Gender(% male): Nis CC 80.7; aml 77.0 Race NR	% Diabetes Mellitus: Nis CC 5.7; aml 4.7 HTN: Nis CC 14.3; aml 23.0 Hyperlipidemia: Nis CC 10.0; aml 8.8 MI: Nis CC 35.7; aml 31.1 Angioplasty: Nis CC 0.7; aml 1.4 Coronary artery bypass: Nis CC 10.0; aml 6.8	320 assessed for inclusion/NR/288 randomized
Other CCBs vs diltiazem						
Singh 1991 USA Poor	bep 200mg daily increased at 2 week intervals to 400mg daily as tolerated dil 360mg daily (or max tolerated dose)	Long acting nitrates, beta blockers at previously established doses, SL NTG for symptoms	Diary cards for angina attacks and NTG use at 2, 4, 6, 8 wks Exercise tests (treadmill, modified Bruce protocol) at baseline, 4 and 8 weeks	mean age 62 (range 42 to 79) 81% male 87% white 9% black 3% other	Previous MI bep 61%, dil 50% Previous CABG: bep 37%, dil 40% Received max dil dose prior to rand: bep 50%, dil 60% Taking Beta blocker: bep 72%, dil 58% Taking long acting nitrate: bep 53%, dil 60%	NR/NR/86

Evidence Table 4. Angina Head to Head Trials

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Method of adverse effects assessment	Adverse Effects Reported	Withdrawals due to adverse events	Comments
Nisoldipine vs amlodipine					
Hall 1998 UK Fair	Overall withdrawals: 54(18.7%) Nis CC: 21.4%; aml 16.2% Lost to fu overall: 3 Efficacy analysis of the subjective variables: 234 patients Efficacy analysis of the exercise tests: 226 patients (Nis CC 110; aml 116) ITT: 271 patients (Nis CC 129; aml 142	Adverse events recorded after open questioning every two weeks after randomization	NisCC: n 140 at 20 mg; n 124 at 40 mg aml: n 148 at 5 mg; n 135 at 10 mg First 4-wk dose phase data(%)/Second 4-wk dose phase data(%) Asthenia: NisCC 2.1/5.6; aml 1.4/2.2 Dizziness: NisCC 2.1/4.8; aml 2.7/3.0 Dyspnea: NisCC 1.4/1.6; aml 2.7/3.0 Peripheral edema: NisCC 14.3/30.6; aml 4.7/20.0 Headache: NisCC 6.4/3.2; aml 4.1/5.9 Pain: NisCC 0.0/0.8; aml 2.7/4.4 Somnolence: NisCC 0.7/0.8; aml 2.7/2.2 Vasodilation: NisCC 0.7/1.6; aml 1.4/3.0 Any event: NisCC 28.6/44.4; aml 27.0/42.2	N 288(NisCC 140; aml 148) NisCC 12.8% aml 7.4%	
Other CCBs vs diltiazem					
Singh 1991 USA Poor	14/0/varies	Diary	Patients reporting at least one adverse event: bep 75%, dil 86% Most common: bep nausea, asthenia, dizziness, headache, diarrhea dil : asthenia, nausea, headache, edema, constipation and dizziness	bep: 4 (9%) dil: 1 (3%)	Study population is preselected to favor bep, as all had been on max tolerated doses of dil and still had chest pain

Evidence Table 4. Angina Head to Head Trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Littler 1999 UK Fair	RCT	Men or women 60 to 80 years of age with chronic stable angina pectoris of >/ 3 months' duration, with a severity defined as NYHA Class II or III; patients experiencing >/ 2 anginal attacks per week, who were taking a beta blocker and nitroglycerin (sl or spray) for >/ 1 month; patients physically capable of undertaking repeated treadmill exercise tolerance tests using the Bruce protocol who were limited to between 2 and 9 minutes of exercise by moderate angina or ischemic changes on electrocardiogram (ECG) at the initial visit.	History of MI, coronary angioplasty or coronary artery bypass surgery within the previous 3 months, or had clinical features suggestive of impending MI, unstable angina, or variant (Prinzmetal's) angina; history of stroke or transient ischemic attack within the past 3 months; congestive heart failure, left ventricular failure, or clinically significant valvular disease; had clinical evidence of major arrhythmia requiring treatment with anti-arrhythmic medication or with prolongation of conduction time in the ECG or known conduction disturbances; uncontrolled HTN (seated systolic or diastolic blood pressure >180 mm Hg or 100 mm Hg, respectively); clinically significant renal dysfunction (creatinine >200 mmol/L), hepatic dysfunction (serum transaminases >2 times the upper limit of normal), or systemic, hematologic, central nervous system, or metabolic disease; were taking digoxin, amiodarone, theophylline, cimetidine, cyclosporine, lithium, anti-epileptics, or barbiturates; had ECG changes that did not permit accurate analysis of ST-segment changes during exercise; transdermal nitrate preparations and other anti-anginal agents were not permitted during the study or in the preceding 2 weeks.
Radice 1991 Italy Poor	RCT for nif and met, dil group added later	Stable angina pectoris with chest pain due only or mainly to physical exertion, ischemic heart disease confirmed by angiographic documentation or atherosclerotic obstruction (>75%) of at least ne major coronary vessel or by stress thallium-201 imaging and radionuclide angiography, pathologic response to exercise testing, defined either as angina or > 0.1mV flat or downsloping ST-segment depression 0.08 sec after the J point or both, stability of the ischemic threshold checked during preliminary exercise tests (changes of exercise time to ischemic threshold among the tests of each patient < 1 min).	Recent MI (within 6 months), coronary reperfusion procedures, contraindications or calcium and beta blockers or to repeated exercise tests, need for concomitant therapy with antiarrhythmic or inotropic agents, abnormalities on the rest ECG that could interfere with interpretation of ST-segment changes.

Evidence Table 4. Angina Head to Head Trials

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Littler 1999 UK Fair	Nis CC 10-40 mg daily dil CR 120-240 mg daily x 12 weeks All patients were required to take concomitant beta blocker therapy at a constant dosage throughout the study.	sl ntg	Treadmill testing Daily diary Health Status Questionnaire 2.0 (Health Outcomes Institute) at visits 2 and 6	Mean age: Nis CC 65.8; dil CR 66.7 %male: Nis CC 79.7; dil CR 73.4 Race White: Nis CC 87.3%; dil CR 89.9% Asian: Nis CC 9.3%; dil CR 10.1% Black: Nis CC 2.5%; dil CR 0 Other: Nis CC 0.8%; dil CR 0	Current smoker: Nis CC 5.9; dil CR 6.4	NR/293 eligible/227 enrolled (randomized)
Radice 1991 Italy Poor	nif 40 to 200mg daily dil 180 to 360mg daily met 100 to 200mg daily dose increased weekly to max tolerated. X 3 months	nr	Ambulatory ECG Exercise test (bicycle) until > 0.2mV ST-segment depression, moderate chest pain, or exhaustion	mean age 59 (range 37 to 71) 52% male NR	Ejection fraction: mean nif 0.55, dil 0.53, met 0.59	NR/NR/50

Evidence Table 4. Angina Head to Head Trials

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Method of adverse effects assessment	Adverse Effects Reported	Withdrawals due to adverse events	Comments
Littler 1999 UK Fair	Withdrawn: Nis CC 17.8%; dil CR 13.8% Lost to fu: 0 Analyzed: ITT 219; Valid cases efficacy analysis 212	NR	Any adverse event incidence: Nis CC 49.2%; dil CR 48.6% Angina pectoris: Nis CC 6.8%; dil CR 2.8% Asthenia: Nis CC 5.9%; dil CR 0.9% Dizziness: Nis CC 3.4%; dil CR 5.5% Headache: Nis CC 5.9%; dil CR 4.6% Infection: Nis CC 7.6%; dil CR 0.9% Peripheral edema: Nis CC 17.8%; dil CR 7.3%	(n 227) Nis CC 10.2% dil CR 10.1%	
Radice 1991 Italy Poor	NR/NR/unclear	NR	NR	NR	

Evidence Table 4. Angina Head to Head Trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Other CCBs vs Nifedipine			
Armstrong, 1986 UK Fair	RCT	Patients showing exercise-induced MI diagnosed by a sustained ST segment depression of 1 mm or more in the V5 chest lead	Patients who suffered from other conditions which may have caused a false positive stress test; unstable angina pectoris; congestive cardiac failure; clinically significant valvular heart disease or cardiac septal defects; second or third degree atrioventricular block; myocardial infarction or cerebrovascular accident in the preceding two months; results of a pre-study blood test showed they had clinically significant renal, hepatic or thyroid function abnormalities, anemia or abnormal potassium levels; insulin-treated diabetes mellitus; hypotension; moderate hypertension; mental illness
Reicher-Reiss 1992 Israel Poor	RCT	Chronic stable angina with history of at least 3 anginal attacks per week, a documented ischemic response to exercise, and documentation of coronary artery disease based on angiography or remote MI.	Unstable angina, a recent AMI (less than 3 months), a definite need for calcium antagonist therapy or known sensitivity to calcium antagonists, presence of advanced AV conduction disturbances or clinical evidence of CHF.

Evidence Table 4. Angina Head to Head Trials

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Other CCBs vs Nifedipine						
Armstrong, 1986 UK Fair	NCI 90 mg daily Nif 60 mg daily x 8 weeks	sl GTN	Treadmill exercise tests(modified Bruce protocol) Patient diary Investigator assessment	median age 57 74.2% male race NR	Concomitant disease(diabetes, heart failure, duodenal ulcer, arthritis, asthma, bronchitis): 61.3%	screened NR/eligible NR/enrolled 46
Reicher-Reiss 1992 Israel Poor	nis 10mg daily nif 30mg daily x 8 weeks	sl NTG	Diary cards for angina attacks and NTG use T 2, 4, 6, 8 wks Exercise tests (bicycle ergometer) at baseline, 4 and 8 weeks (stopped with severe angina pain)	mean age 61 (range 45 to 72) 93% male 2 females enrolled, both in nif group NR	Mean angina attacks/wk: nis 7, nif 6 Mean NTG tabs/wk: nis 7, nif 6 History of MI: nis 47%, nif 40% Coronary bypass: nis 7%, nif 13%	NR/NR/30

Evidence Table 4. Angina Head to Head Trials

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Method of adverse effects assessment	Adverse Effects Reported	Withdrawals due to adverse events	Comments
Other CCBs vs Nifedipine					
Armstrong, 1986 UK Fair	withdrawn 18/lost 0/analyzed 31	Patients were questioned indirectly to assess the incidence and severity of adverse experiences	Overall: NCI 58%; Nif 76% Specific adverse event incidence NR	NCI 26.3% Nif 33.3%	
Reicher-Reiss 1992 Israel Poor	1 (nis)/0/ unclear	NR	Adverse events reported by 2/15 (13%) nis, 2/15 nif (13%) sinus tachycardia and increased chest pain, headache, mild leg edema, nausea and palpitations	1/15 (7%) nis, 0 nif	Nis group had better exercise tolerance at baseline, but slightly more angina attacks and NTG use per week.

Evidence Table 5. Angina active controlled trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
AMSA (Amlodipine vs slow release Metoprolol in the treatment of Atable exertional Angina) Midtbo 2000 Norway Fair-Poor	RCT	Male and female (females without childbearing potential) outpatients; aged 18-80 with documented CAD (documented history of MI; coronary angiography showing >70% narrowing of at least one major coronary artery; previous radionuclide test with evidence of reversible profusion defects; previous CABG or PTCA); previous positive exercise test; stable angina pectoris precipitated by exertion, persisting for 1-10 minutes and relieved by rest and/or sublingual nitroglycerine	Unstable angina within previous 3 months; MI within previous 6 months; congestive heart failure; serious cardiac valvular disease; significant peripheral vascular disease; paroxysmal or chronic atrial fibrillation; supine or standing SBP <100 mmHg; significant bradycardia (<50 beats/minute); CABG within previous 3 months; stroke within previous 6 months; moderate or severe anemia; hypoxic states (e.g. pulmonary disease); 2nd or 3rd degree AV-block; electrocardiograph patterns not allowing interpretation of ECG exercise data; use of drugs which effect ECG interpretation of ischemia (digitalis); insulin-treated diabetes; active hepatic or renal disease likely to restrict exercise tests; other major concurrent disease

Evidence Table 5. Angina active controlled trials

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
AMSA (Amlodipine vs slow release Metoprolol in the treatment of Atable exertional Angina) Midtbo 2000 Norway Fair-Poor	aml 5-10mg daily met 100-200mg daily Dose increase after 2 wks if needed x 8 wks total	SL NTG	Patient diary card Ergometer bicycle Patient assessment of disease activity by VAS	Mean age 64 87% male NR	mean duration of angina (months): aml 53, met 62 prior MI: aml 37%, met 30% smokers: 23% (each group)	NR/NR/110

Evidence Table 5. Angina active controlled trials

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events	Comments
AMSA (Amlodipine vs slow release Metoprolol in the treatment of Atable exertional Angina) Midtbo 2000 Norway Fair-Poor	10/0/117 analyzed: aml 57, met 60	Mean change in time to onset of angina during exercise (end therapy - baseline): aml 60.2 sec met 59 sec	Reported and observed events	Major events requiring withdrawal: aml 4 (unstable angina, AMI, additional antianginal drugs requested, nausea and headache) met 5 (2 AMI, sudden death, fatal cerebral thrombosis, severe CHF) Minor events aml 23, met 27	aml 4/62 (6%) met 5/65 (8%)	

Evidence Table 5. Angina active controlled trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
APSIS (The Angina Prognosis Study in Stockholm) Sweden Rehnqvist, 1994 Rehnqvist, 1996 Fair-Poor	RCT	Clinical history of stable angina pectoris	Contraindications to the study drugs; myocardial infarction within the last 3 years; unstable angina or anticipated need for revascularization within one month; presence of other severe disorders; alcohol abuse; suspected non-compliance; non-compensated heart failure; significant valvular disease

Evidence Table 5. Angina active controlled trials

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
APSIS (The Angina Prognosis Study in Stockholm) Sweden Rehnqvist, 1994 Rehnqvist, 1996 Fair-Poor	Metoprolol 200 mg daily Verapamil 480 mg daily x 6-75 months	Acetylsalicylic acid, ACE inhibitors, lipid lowering drugs and long acting nitrates	Psychological interview (Cornell Medical Index, evaluation of sleep disturbances, estimate of overall life satisfaction on a visual analogue scale of 1-120) Exercise test 24h ambulatory ECG recording	Mean age 59 Gender: Met 73% male; Ver 66% male Race NR	*Previous history(%)* AMI: Met 16; Ver 16 CHF: Met 6; Ver 7 HTN: Met 28; Ver 26 Cerebrovascular event: Met 5; Ver 4 CABG/PTCA: Met 5; Ver 7 Intermittent claudication: Met 4; Ver 2 Diabetes mellitus: Met 8; Ver 9 *Smoking habits(%)* Smokers: Met 22; Ver 22 Ex-smokers: Met 50; Ver 36 Non-smokers: Met 28; Ver 42 *Angina class (%)* *I: Met 27; Ver 25* *II: Met 68; Ver 69* *III: Met 5; Ver 6* *Median duration of angina(yrs):* Met 2; Ver 2 *Therapy at baseline(%)* Acetylsalicylic acid: Met 39; Ver 38 Long-acting nitrates: Met 49; Ver 53 Beta-blockers: Met 56; Ver 54 Calcium antagonists: Met 14; Ver 16	NR/NR/809

Evidence Table 5. Angina active controlled trials

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events	Comments
APSIS (The Angina Prognosis Study in Stockholm) Sweden Rehnqvist, 1994 Rehnqvist, 1996 Fair-Poor	Withdrawals Met 20; Ver 17/ Lost NR Analyzed CV events: Met 406; Ver 403 Psychological variables: Met 268; Ver 275	Overall death(%): Met 5.4; Ver 6.2 Cardiovascular(%) Sudden death within 2hrs: Met 1.2; Ver 1.5 AMI: Met 2.9; Ver 2.7 Vascular: Met 0.5; Ver 0.5 Non-fatal cardiovascular events(%): Overall: Met 26.1; Ver 24.3 AMI: Met 4.2; Ver 3.4 CABG: Met 11.3; Ver 9.7 PTCA: Met 2.9; Ver 1.2 Angiography without revascularization: Met 4.2; Ver 5.0 Other unstable angina: Met 0; Ver 1.2 Cerebrovascular disease: Met 2.7; Ver 3.2 Peripheral vascular disease: Met 0.7; Ver 0.5	NR	Gastrointestinal: Met 2.5%; Ver 5.4%(p 0.029) Neurological: Met 5.4%; Ver 6.2% Cardiovascular: Met 3.7%; Ver 4.0% Malignancy: Met 0.7%; Ver 1.5%	Met 11.1% Ver 14.6%	

Evidence Table 5. Angina active controlled trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Destors 1989 4 European countries Fair-Good	RCT	Male and female (women menopausal for at least 2 years or exhibiting coronary lesions at angiography); age <70; CHD with chronic angina stabilized for at least 3 months; characteristic description of attacks of angina pectoris; characteristic ECG during pain or exercise; MI at least 6 months previously From December 1982 on, typical exercise ECG was mandatory Wash-out period of 2 - 8 weeks; patients included if weekly number of attacks during usual activity conditions was 8 during last 14 days or 5 during last 7 days	Suffered exclusively at rest; nocturnal attacks; angina pectoris not secondary to atherosclerosis; unstable angina pectoris; Prinzmetal's angina; MI within past 6 months; unable to assess pain and fill in diary cards and sel-assessment forms; contraindication to proporandol or bepridil treatment; liver or kidney condition likely to modify drug metabolism; all reasons preventing close compliance to study protocol
Hall 2001 UK Fair	RCT	Male or female patients; aged 65 years or older; diagnosed with stable angina; either untreated or maintained (inadequately) on any 2 combinations of short-acting nitrates, short-acting CCBs or a stable dose of a beta-blocker; total exercise time, as limited by angina, was not to exceed 12 min; demonstration of at least a 1-mm S-T segment depression with angina, with the S-T segment extending horizontally, or downsloping for greater than, or equal to 80 mm after the J point	Presence of atrial fibrillation; primary diagnosis of congestive heart failure; acute MI or cerebrovascular accident within 3 months prior to study; significant valvular disease, congenital heart disease, clinically uncontrolled arrhythmias or left bundle block, or uncontrolled hypertension

Evidence Table 5. Angina active controlled trials

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
Destors 1989 4 European countries Fair-Good	bep 100 - 400mg daily pro 60 - 240mg daily placebo daily Dose increase/decrease every 2 wks x 8 wks, then maintained through 24 wks (16 wks on final dose)	glyceryl trinitrate (GTN)	Self evaluation forms at visits and patient diaries (recording critical events, functional status, use of SL NTG, angina attacks) ergonometric bicycle exercise test (not all patients) Primary endpoint: success/failure : failure withdrawal due to lack of efficacy or side effects, AND as assessed by blinded physicians based on angina attacks and critical events)	Mean age: 56 (range 30 to 70) 66% male NR	History of MI: bep 33%, pro 37%, pla 31% Duration of angina (months): bep 52, pro 67, pla 67 Angina attacks/wk: bep 11, pro 12, pla 10 SL NTG/wk: bep 14, pro 16, pla 13	NR/NR/191
Hall 2001 UK Fair	Aml 5-10 mg daily Isosorbide mononitrate (Iso) 25-50 mg daily x 28 weeks	glyceryl trinitrate (GTN)	Exercise test (Bruce protocol) at weeks 2, 4, 12 and 28 Short-form (SF-36) questionnaire	Overall mean age: 72.1 Gender: Aml 75.3% male; Iso 70.7% Race NR	*Abnormalities of(%):* *Musculoskeletal system: Aml 12.4; Iso 21.9* *Eye/ear/nose/throat: Aml 13.4; Iso 20.8* *Heart: Aml 16.5; Iso 19.8* *Gastrointestinal tract: Aml 11.3; Iso 12.5* *ECG: Aml 45.4; Iso 58.3*	NR/NR/196

Evidence Table 5. Angina active controlled trials

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events	Comments
Destors 1989 4 European countries Fair-Good	38/15/191	% Success by withdrawal: bep 81%, pro 78%, pla 83% % Success by Committee: bep 68%, pro 63%, pla 77% Mean change in number of attacks/w (from baseline): bep-69%, pro -71%, pla -77% Change in NTG consumption/wk (from baseline): bep -71%, pro - 74%, pla -79% Change in functional status (from baseline): data not reported Critical events: CV and all cause deaths: bep 1, pro 2, pla 0 CV events (including angina deterioration): bep 8%, pro 10%, pla 6%	Patient diaries, self reported, and by questioning at visits	Any adverse event: bep 12%, pro 29%, pla 17% Heart failure or AV block: bep 0, pro 5, pla 0 Most common: bep: fatigue, GI problems pro: fatigue, GI problems pla: fatigue, GI problems	Overall: 4 (2%) dep 4%, pro 1.3%	
Hall 2001 UK Fair	Withdrawn 3/Lost NR/Analyzed 193	ITT(Aml 78; Iso 79) Median number angina attacks: Aml 0; Iso 0 GTN use: Data NR Quality of life: +5 increase on bodily pains scale across both groups; -11 decrease in reported health transition in both groups, indicating better feeling of health	NR	Overall incidence: Aml 58%; Iso 53% Serious adverse events: Aml 7%; Iso 7% Peripheral edema: Aml 14%; Iso 0 Headache: Aml 2%; Iso 13%	Aml 8% Iso 18%	

Evidence Table 5. Angina active controlled trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Hauf-Zachariou 1997 UK Fair	RCT	Men or women aged 18-75 years with a history of exertional chest pain relieved by rest of glyceryl trinitrate (GTN) for at least 2 months; coronary artery disease confirmed by either coronary angiography showing a luminal narrowing of at least 60% of a major coronary artery or one of its primary branches or a history of myocardial infarction substantiated by either ECG evidence or cardiac enzymes or symptom-limited exercise test evoking anginal pain and ST-segment depression >/ 1 mm	Unstable angina; MI or cardiac surgery within the preceding 3 months; uncompensated congestive heart failure; uncontrolled atrial fibrillation; gross left ventricular hypertrophy; insulin-dependent diabetes mellitus; gross obesity; severely impaired renal or hepatic function; significant anaemia or electrolyte abnormality or other major diseases; women of childbearing capacity and pregnant or breast-feeding women; contraindications to treatment with alpha- or beta-adrenoceptor antagonists and CCBs
Kawanishi 1992 United States Fair	RCT	History of chronic stable angina that was mild enough for them to tolerate a 2-week (control) period with only sl ntg and with no prophylactic antianginal medications; angina defined as the presence of a dull, pressure-like pain or discomfort in the precordium that was reproducibly brought on by exertion or emotional upset; at least 3 episodes of angina/week and <50% variability in the weekly angina frequency over 2 months prior to enrollment; documented coronary artery disease	History of MI or coronary revascularization procedure within previous 3 months; insulin-requiring diabetes; bronchospastic lung disease or other diseases with symptoms that could be confused with angina pectoris; left bundle brach block; left ventricular hypertrophy; digoxin therapy; treatment with antiarrhythmic agents or any condition or medication that would interfere with interpretation of ST segment changes on the exercise ECG

Evidence Table 5. Angina active controlled trials

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
Hauf-Zachariou 1997 UK Fair	Car 50 mg daily Ver 360 mg daily x 12 weeks	sl gtn	Treadmill exercise test (modified Bruce protocol) at weekly intervals Patient diary cards 24-hour holter monitor	Mean age: 60 Gender: Car 78.6%; Ver 76.2% male Race NR	Mean duration of angina(years): Car 3; Ver 4 Smokers(%): Car 16.7%; Ver 17.2% History of: -MI(%): Car 66.7; Ver 70.5 -HTN(%): Car 2.4; Ver 4.9 -Hyperlipidemia(%): Car 38.1; Ver 39.3	NR/NR/313
Kawanishi 1992 United States Fair	Nif 10 mg Pro 20 mg; both titrated to *maximally tolerated dose* x 3 months	sl ntg	Angina diaries Treadmill exercise testing at end of each Phase (I-III) Ambulatory ECG monitoring	Average age 54 years 66% male Ethnicity NR	NYHA angina class: I 4%; II 73%; III 23% Prior MI: 62% CABG: 14% PTCA 1% Hypertension: 39%	NR/NR/74 patients

Evidence Table 5. Angina active controlled trials

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events	Comments
Hauf-Zachariou 1997 UK Fair	5 patients due to worsening angina; 7 patients due to adverse events/Lost 0/ Analyzed 248	Exercise testing at 12 wks Per protocol evaluation (Car n 107; Ver n 105) Total exercise time(s): Car 436; Ver 438 Change in time to angina(s): Car +58; Ver +41 Patient diary card Mean change in number of angina attacks/wk: Car -0.1; Ver -3.2 Mean gtn doses: Car -1.1; Ver -3.2	Adverse events were volunteered by patients or observed by the investigator and were recorded whether or not they were considered drug related.	Overall incidence: Car 48%; Ver 58% Serious AEs: Car 3.2%; Ver 5.7% Most commonly reported AEs Asthenia: Car 10.4%; Ver 6.6% Constipation: Car 0.8%; Ver 27.0%	Overall: 2.8%	65 patients withdrawn prior to randomization due to failure to meet exercise test inclusion criteria
Kawanishi 1992 United States Fair	NR/NR/NR	Phase II (3 months) Angina frequency(episodes/week): Nif 4.3; Pro 3.2 NTG use(tablets/week): Nif 1.7; Pro 1 Time to onset of angina(seconds): Nif increase from 199 to 286; Pro increase from 255 to 342 24-hour ambulatory ECG (available for 52 of 74 patients): Mean painful ischemic episodes/24h: Nif 0.4; Pro 0.3 % with no painful ischemic episodes: Nif 81%; Pro 88% Duration of painful ischemic episodes(min/24h): Nif 7; Pro 3 Phase III (6 months) Angina frequency(episodes/week): Nif 2.7; Pro 2 NTG use(tablets/week): Nif 0.7; Pro 0.7 Time to onset of angina(seconds): Nif increased again to 304; Pro increased to 346	NR	Untoward cardiovascular events (e.g., death, nonfatal myocardial infarction, revascularization procedure): no occurrences in any group	NR	

Evidence Table 5. Angina active controlled trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Lee 2002 Canada Fair	RCT	Patients aged >/ 18 years; with a diagnosis of coronary artery disease (e.g., history of MI or angiographic evidence of >/ 1 artery with a >/ 50 % diameter stenosis or positive stress thallium or cardiolyte study) and a history of chronic stable angina pectoris; 2 reproducible exercise tolerance tests(Bruce protocol) with persistent ST-segment depression of >/ 1 mm that were terminated because of the development of any of the following symptoms or signs: shortness or breath, fatigue, angina or a fall in systolic blood pressure of >/ 10 mmHg compared with pre-exercise measure; initial exercise tolerance test duration was between 3 and 9 minutes with 1 or 2 subsequent exercise tests (all required to be within 15% of the initial exercise time).	Unstable angina within 2 months of study entry; MI or a revascularization procedure (coronary artery bypass surgery, percutaneous coronary intervention) within 6 months before study entry; any significant valvular disease, cardiomyopathy or CHF (NYHA class II-IV); uncontrolled hypertension (defined as systolic blood pressure (SBP) >/ 180 mmHg or diastolic blood pressure (DBP) >/ 110 mmHg or hypotension (SBP<100 mmHg); coexisting conditions limiting the ability to exercise; repolarization abnormalities rendering ST-segment evaluation not ideal for analysis (e.g., left ventricular hypertrophy with strain, left bundle branch block, paced rhythm); women who were pregnant or lactating; significant renal or hepatic impairment; stroke or transient ischemic attack within 12 months; allergy or hypersensitivity to calcium antagonists
Meyer 1991 Israel Poor	RCT	Patients under age 65; suffering from stable angina pectoris; diagnosis of angina was based on a history of typical chest pain, previously sustained acute coronary events, as well as on a positive exercise test	Intolerance to the study medication; MI or heart surgery within 3 months prior to the beginning of the trial; contraindications to the performance or ergometry
Myers 1988 Canada Poor	RCT	Patients at Sunnybrook Medical Centre in Toronto, Canada; age 65 or older; unstable angina	Beta blocker or calcium channel blocker therapy during previous 2 weeks; MI within previous 3 months; evidence of congestive heart failure (Framingham criteria); heart block (PR interval > 0.24 s); hypotension (supine SBP <100 mmHg); asthma; insulin dependent diabetes mellitus; renal dysfunction (serum creatinine >30 mg/dL; hepatic disease (enzymes <30% above normal); ventricular tachycardia or fibrillation in previous month; rapid atrial fibrillation as cause of unstable angina

Evidence Table 5. Angina active controlled trials

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
Lee 2002 Canada Fair	mibefradil (mib) 50-100 mg daily dil 180-360 mg daily x 8 weeks	sl or spray ntg	Exercise tolerance test (Bruce Protocol) at weeks 2, 4, and 8 Patient diary	Age: mib 62; dil 63 Gender(%male): mib 83.5; dil 84.1 Race(%white): mib 96.7; dil 94.6	% Previous MI: mib 38.8; dil 39.8 Previous positive perfusion imaging test: mib 88.0; dil 88.4 Coronary angiography (stenosis >50%): mib 66.1; dil 64.6 Previous beta-adrenergic blocker: mib 45.5; dil 42.5 Previous calcium antagonist: mib 49.6; dil 51.3 Previous nitrates: mib 20.7; dil 19.5	328 screened/eligible NR/234 randomized(mib 121; dil 113)
Meyer 1991 Israel Poor	Bopindolol(bop)1 mg daily Dil 120 mg daily x first 4 weeks Bop 2 mg daily Dil 240 mg daily x last 4 weeks		Exercise tolerance test (Bruce protocol) at week 8 Patient diary	Average age: dil 59.4; bop 58.1 Gender(%male): dil 75; bop 80 Race NR	Average number of months since first anginal episode: dil 36; bop 87.7 % HTN: dil 31.2; bop 46.7 Diabetes mellitus: dil 12.5; bop 13.3 Catheterization prior to trial: dil 0; bop 6.7 >/ 1 MI prior to trial: dil 6.2; bop 20 Coronary surgery prior to trial: dil 0;	NR/NR/31
Myers 1988 Canada Poor	nif 30 to 90mg daily pro 60 to 240mg daily Doses increased every 24 to 72h to max tolerated	SL NTG	Patient diary Treadmill exercise test (modified Naughton protocol) Primary endpoints: unstable angina, MI, sudden death	Mean age: mif 76, pro 75 42% male NR	% on nitrates: nif 17%, pro 36% mean LVEF: nif 58, pro 58	NR/NR/26

Evidence Table 5. Angina active controlled trials

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events	Comments
Lee 2002 Canada Fair	Overall withdrawal NR/Lost NR/Analyzed not clear	Mean time to onset of angina: data NR, but comparison at 8 weeks described as statistically borderline difference Self-reported angina: data NR; but stated that both groups had fewer weekly episodes, difference insignificant Weekly sl ntg consumption: data not shown; paper reported there was no significant between-groups difference	NR	Overall incidence: mib 27.3%; dil CD 31.9 % Asthenia: mib 3.3; dil 2.7 Constipation: mib 0.8; dil 6.2 Dizziness: mib 9.9; dil 3.5 Headache: mib 0.8; dil 2.7 Nausea: mib 3.3; dil 1.8 Peripheral edema: mib 2.5; dil 6.2 Vasodilation: mib 1.7; dil 2.7	mib 4.9 dil CD 2.6	
Meyer 1991 Israel Poor	Overall withdrawals: dil 1; bop 2/lost NR/analyzed 28	Decrease in number of pain episodes/month: dil 1.65; bop 22 Pain time per month(number of pain episodes x duration of each)(min): dil 129.3; bop 256.5 Change in anginal index: dil 11.1; bop 7.6 Average time free of pain(min): dil 0.75; bop 2.2	NR	Overall incidence: NR Most common AEs: dil pedal edema; bop sinus bradycardia, insomnia (data NR)	NR	
Myers 1988 Canada Poor	7/0/varies by outcome and timepoint	Recurrent unstable angina: nif 50%, pro 14% MI nif 8% (1), pro 0 Mean change in NTG use at 2 wks: nif 2 mg/d (based on 6 patients), pro 3.1 mg/d (based on 10 patients)	Patient diaries, self reported, and by questioning at visits	Overall: nif 67%, pro 64% nif: ankle edema (4, 33%), 1(8%) each postural hypotension, pruritus, flushing, lightheadedness pro: CHF (2, 14%), fatigue (2, 14%), 1 (7%) each itching, hallucinations, lightheadedness	nif 2 (17%) postural hypotension, pruritus pro 4 (29%) CHF (2), hallucinations, fatigue	

Evidence Table 5. Angina active controlled trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Pehrsson 2000 Sweden Fair	RCT	History of clinically stable angina, defined as precordial discomfort, tightness, heaviness, pain with or without radiation and dyspnea, usually provoked by exertion or cold and relieved within 10 min by rest or by ntg, for at least 3 months and with at least 3 anginal attacks per week before the start of the run-in period. Also required was one positive bicycle exercise test, defined as ST depression > 1 mm within 7 min (max. 90W) in women and with 13 min (max. 150 W) in men, with or without chest pain.	MI; coronary bypass surgery; percutaneous transluminal coronary angioplasty (PTCA) in the preceding 3 months, unstable angina; signs and/or symptoms of CHF; significant arrhythmia; second or third degree atrioventricular block, diastolic blood pressure > 115 mmHg or systolic blood pressure > 250 mmHg; medication influencing ECG; patients receiving beta blockers or calcium antagonists that could not be safely withdrawn; those in need of supplementary anti-ischemic medication other than ntg during the run-in period; those in need of revascularization

Evidence Table 5. Angina active controlled trials

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
Pehrsson 2000 Sweden Fair	aml 5 mg daily ate 50 mg daily aml 5 mg daily + ate 50 mg daily x 4 weeks, then increase to aml 10 mg daily ate 100 mg daily aml 10 mg daily + ate 100 mg daily x 6 weeks if tolerated	ntg tablets	Patient cards Ambulatory ECG apparatus at weeks 4 and 10 Bicycle ergometer at week 10 Borg scale of 0-10 (0 no pain; 10 maximal pain)	Mean age: aml 63; ate 63 Gender(%male): aml 75.9; ate 79.3 Race NR	Angina duration(yrs): aml 5; ate 5 Attacks/week: aml 5; ate 5 HTN(%): aml 26; ate 28 Smokers(%): aml 10.3; ate 14.6 Mean number cigarettes per day: aml 8; ate 8 Previous MI(%): aml 26; ate 23 Previous PTCA(%): aml 4; ate 6 Previous CABG(%): aml 11; ate 14 Insulin-dependent diabetes(%): aml 4; ate 3 NIDDM(%): aml 5; ate 9 Antianginal therapy in past 3 months(%) ntg: aml 96; ate 94 short-acting: aml 89; ate 88 long-acting: aml 45; ate 46 BB: aml 49; ate 54 Calcium antagonists: aml 25; ate 24	442 entered trial/eligible NR/ 351 randomized(aml 116; ate 116; aml+ate 119)

Evidence Table 5. Angina active controlled trials

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events	Comments
Pehrsson 2000 Sweden Fair	Overall withdrawals: aml 13(11.2%); ate 8(6.9%)/lost NR/analyzed not clear	Number of patients interrupting exercise due to chest pain at entry vs. wk10 (%): aml 50/26(40/25); ate 50/43(47/40) Change from baseline to wk10 Time to onset of angina(min): aml 0.8; ate 1.0 Maximum chest pain(Borg score): aml 0.8; ate 0.4 Patient diary Average anginal attacks/week: aml 3.4; ate 3.7 Average consumption of ntg/week: aml 2.2; ate 2.2	NR	Overall incidence(%): aml 51.7; ate 44.8 Most common AEs: data NR Deaths: 1-during wash-out prior to combo treatment; additional 3 patients who had been screened but not randomized	aml 6.9% ate 5.2%	

Evidence Table 5. Angina active controlled trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Singh 1993 USA Fair-Poor	RCT	Males and females; aged 18-80; chest pain usually precipitated by exertion lasting 1-10 minutes; significant ST-segment deviation (of > 1 mm) after exercise at the end of 2 week single-blind placebo run-in period; at least 3 angina attacks during the 2 week period	Significant hepatic, renal, cardiac, bronchospastic disease; major concurrent disease; women of childbearing potential
SWAN study group 1999 Switzerland, Austria Poor	RCT	Aged 18-80; females postmenopausal or surgically sterile; stable angina pectoris for > 3 months; CHD confirmed by history of MI or positive angiogram (> 50% stenosis of a main coronary artery)	MI; invasive coronary intervention; unstable angina; angina at rest or vasospastic angina within last 3 months; hypertension with supine DBP > 105 mmHg; electrocardiogram recordings not allowing evaluation of the ST-segment; manifest congestive heart failure (NYHA class III-IV); peripheral arterial obstructive disease or any exercise test limiting disease; cardiac valvular disease with hemodynamic or clinical consequences; supine SBP <100 mmHg or DBP <70 mmHg; postural hypotension (>20% decrease in SBP 1 minute after standing); severe concomitant disease

Evidence Table 5. Angina active controlled trials

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
Singh 1993 USA Fair-Poor	aml 2.5 - 10mg daily nad 40 to 160mg daily Increased every 4 wks until max benefit or adverse effects Final dose x 24 weeks	SL NTG	Treadmill exercise test (modified Bruce protocol) Patient diary cards Patient self assessment of angina disease activity Global assessment by Investigator at baseline, 12 and 24 wks	Mean age aml 65, nad 62 89% male 73% white 14% Black 1% Hispanic	Mean duration of angina (months): aml 80, nad 78 Severity of attacks: aml mild 58%, mod 40%, severe 3% nad: mild 55%, mod 43%, severe 3%	NR/NR/80
SWAN study group 1999 Switzerland, Austria Poor	aml 5 to 10mg daily nic 20 to 40mg daily Doses increased after 2 wks if tolerated x 8 weeks total	SL NTG	Patient diary Ergometer Bicycle Exercise Tolerance Test at baseline and every 2 weeks QOL questionnaire (4 questions)	Mean age 62 80% male NR	Mean number anginal attacks/wk: aml 4.4, nic 4.3 (for whole group) aml 3.3, nic 3.4 (for evaluable group) Duration of angina (months): aml 57, nic 51 Prior MI: aml 41%, nic 25% Essential HTN 37% Hypercholesterolemia 21%	143/143/121

Evidence Table 5. Angina active controlled trials

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events	Comments
Singh 1993 USA Fair-Poor	19/0/unclear	Mean change in time to angina onset during exercise: aml +72 sec, nad +31 Median change in number of angina attacks/wk: aml -3.7, nad -2.7 Median change in number of SL NTG tabs used/wk: aml -1.7, nad -1.5 Patient assessment: Change in mod/severe rating: aml -6, nad -5 Investigator rating of mod/markedly improved: aml 74%, nad 54%	Observed or volunteered	Any adverse event: aml 43%, nad 83% Most common: aml: headache, edema, palpitations, hypoesthesia and flushing cc nad: bradycardia, dizziness, headache, fatigue, dyspnea, palpitations	aml 3.40 (8%), nad 4/40 (10%)	
SWAN study group 1999 Switzerland, Austria Poor	6/0/118	Mean change in time to angina pain during exercise: aml 1.4, nic 0.9 Mean change in number of angina attacks/wk: aml -2.4, nic -1.3 Mean change in number of NTG units for immediate pain relief: aml -0.4, nic -0.8 (baseline aml 1.0, nic 2.3 units) QOL ratings improved on all 4 questions for both groups (data not presented)	NR	Any adverse event: aml 31%, nic 35% Most common: aml: edema, flushing nic: headache, vertigo	aml 3%, nic 5%	

Evidence Table 5. Angina active controlled trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
TIBET (Total Ischaemic Burden European Trial) 9 European countries Dargie, 1996 The TIBET Study Group, 1992 Fair-Good	RCT	Patients aged 40-79; history of anginal symptoms of a stable pattern, with or without treatment, for a minimum of 3 months; not currently being evaluated for CABG; patients with a previous diagnosis of angina pectoris who are experiencing few or no episodes of angina on their current medication and are by definition "stable"; objective demonstration of ischemia during exercise testing after the 2-week placebo washout period, defined as ST-segment depression of 1.0 mm or more occurring 80 msec after the J point, persisting for three consecutive beats and occurring before 10 METS, is mandatory; patients who have undergone angioplasty or CABG and suffered a recrudescence of symptoms; patients who have undergone coronary angiography	Presence of any clinically important concomitant disease (in particular, MI within the previous 3 months; renal impairment, described as serum creatinine >200 mmol/l or >2.3 mg/100 ml; hepatic function impairment, defined as aspartate transaminase (AST/SGOT) or alanine transaminase(ALT/SGPT) enzyme results more than 15% above the upper normal limit and deemed to be clinically significant; anemia, defined as a hemoglobin concentration of <11 g/dl in females of <12 g/dl in males; hypotension, defined as standing SBP=100 mgHg; and hypertension, defined as SBP=200 mmHg or DBP>105 mmHg on placebo; contraindications to beta blockade (decompensated heart failure, second- or third-degree heart block, left or right bundle branch block or preexcitations states, reversible obstructive airways disease, IDDM, previous intolerance to beta blockage) or nifedipine (women capable of childbearing, i.e., premenopausal women, unless they have had a hysterectomy or previous intolerance to the drug; presence of confounding factors for the interpretations of the ECG (patients with left ventricular hypertrophy wave abnormalities on the electrocardiogram, predominant cardiac rhythm other than sinus rhythm, concurrent treatment with digoxin
Ulvenstam 1992 3 European countries Fair-Poor	RCT	Patients <76 years old with a history of typical effort-induced angina pectoris relieved by sl ntg or rest; anginal pain had to be induced in 2 successive standardized ETTs during the run-in period	Patients with a recent myocardial infarction (<3 months); unstable angina; angina at rest; or vasospastic angina; uncontrolled hypertension; ECG tracings disturbing the evaluation of the ST segment; congestive heart failure; history of exercise-induced arrhythmia; concomitant medication with digitalis, antiarrhythmics and antianginal drugs

Evidence Table 5. Angina active controlled trials

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
TIBET (Total Ischaemic Burden European Trial) 9 European countries Dargie, 1996 The TIBET Study Group, 1992 Fair-Good	nifSR 40 mg daily ate 100 mg daily ate 100 mg+nifSR 40 mg daily(combo) x at least 1 year	*Inadequate symptom control after 2 weeks:* nifSR: adding additional nifSR 40 mg daily allowed ate: adding placebo allowed combo: adding additional nifSR 50 mg daily allowed	Standard exercise test using *either* a bicycle or a treadmill(Bruce protocol) x weeks 2 and 6 Continuous ambulatory (holter) ECG recordings for 48 hours x week 6 Diary cards x week 6	Mean age: ate 58.8; NifSR 60.0 Gender(%male): ate 86.7; nifSR 82.3 Race NR	% Previous MI: ate=34.1; nifSR=30.6 Previous heart failure: ate=0.9; nifSR=1.7 HTN: ate=23.0; nifSR=23.3 Diabetic: ate=4.4; nifSR=3.0 Current smokers: ate=17.2; nifSR=12.9 Previous angiogram: ate=29.6; nifSR=26.7 Previous PTCA: ate=1.8; nifSR=2.2 Previous CABG: ate=6.2; nifSR=5.2	916 entered/eligible NR/682 randomized
Ulvenstam 1992 3 European countries Fair-Poor	*First 4-wk phase* Nicorandil(Nic) 20 mg daily Nif 40 mg daily *Second 4-wk phase* Nic 40 mg daily Nif 40 mg daily	sl ntg	Patient diary card Ergometer bicycle	Mean age 62.3 for men; 60.3 for women 93.1% male Race NR	Previous history(%) MI: Nic=44.8; Nif=20.7 Cardiac failure: Nic=3.4; Nif=3.4 Bypass surgery: Nic=1.0; Nif=3.4 Cerebrovascular disease: Nic=3.4; Nif=0 Peripheral vascular disease: Nic=1.0; Nif=6.9 HTN: Nic=20.7; Nif=13.8 Smokers/ex-smokers: Nic=69.0; Nif=69.0	Recruited 68/eligible 58/enrolled 58

Evidence Table 5. Angina active controlled trials

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events	Comments
TIBET (Total Ischaemic Burden European Trial) 9 European countries Dargie, 1996 The TIBET Study Group, 1992 Fair-Good	Overall withdrawals: ate 27%; nifSR 40%	Severest endpoints(%) Cardiac death: ate 1.3; nifSR 2.6 Non-fatal MI: ate 6.2; nifSR 6.5 Unstable angina: ate 5.3; nifSR 1.7 CABG: ate 3.1; nifSR 2.6 PTCA: ate 0.4; nifSR 0	NR	NR	NR	Analyses of *''severest endpoints''* reported appear to have included patients no longer on study treatment
Ulvenstam 1992 3 European countries Fair-Poor	overall withdrawals NR/lost NR/55 analyzed for efficacy; 58 analyzed for safety	Weekly anginal attack rate(mean) Baseline: Nic 4.3; Nif 7.2 4 wks: Nic 2.6; Nif 7.0 8 wks: Nic 2.1; Nif 7.4 Number of sl ntg used: data NR; reported to have "usually paralleled the number of anginal attacks" Time to onset of angina pectoris(min) Baseline: Nic 5.9; Nif 6.1 4 wks: Nic 7.4; Nif 7.8 8 wks: Nic 8.7; Nif 7.6	AEs recorded at each visit during the study and an assessment of possible relationship to the drug was made by the investigator.	% Cardiovascular Vasodilation: Nic=13.8; Nif=31.0 Other: Nic=6.9; Nif=17.2 Headache: Nic=44.8; Nif=31.0 Misc.: Nic=20.7; Nif=17.2 No AEs: Nic=37.9; Nif=37.9	Nic 13.8% Nif 10.3%	

Evidence Table 5. Angina active controlled trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Vliegen 1991 The Netherlands Fair-Poor	RCT	Stable effort-induced angina pectoris for at least 3 months, relieved by sl nitrates, with attacks occurring at a frequency of 3/week; positive baseline exercise tests; achievement of a work load of at least 60 W during the exercise tolerance test; between the ages of 21 and 79 years; proof of coronary insufficiency for women	Unstable angina; myocardial infarction or bypass surgery within 3 months prior to study; severe valvular disease; congestive heart failure; moderate or severe hypertension; functioning cardiac pacemaker; atrial fibrillation or severe symptomatic arrhythmias; resting ECG abnormalities that render the interpretation of ST-segment changes difficult; bundle branch block at rest of during exercise; any degree of atrioventricular block; contraindication to the use of either study drug; inability to perform an exercise test or adhere to the protocol for whatever reason; the presence of any condition disregulating the pharmacokinetics of the medication during the study; the use of any medication during the study that might interfere with the efficacy or adverse effects of either study drug; pregnancy or lactation in women; or any other serious medical disease

Evidence Table 5. Angina active controlled trials

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
Vliegen 1991 The Netherlands Fair-Poor	Dil CR 240 daily Met 200 mg daily x 32 weeks	sl ntg	Exercise testing at weeks 8, 20 and 32	Mean age: Dil CR 58; Met 64(p<0.05) Gender NR Race NR	NR	NR/NR/56

Evidence Table 5. Angina active controlled trials

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events	Comments
Vliegen 1991 The Netherlands Fair-Poor	Withdrawn: Dil CR 8; Met 5 Lost NR Analyzed: 8 weeks: Dil CR 28; Met 23; 32 weeks: Dil CR 20; Met 19	8 weeks Mean frequency of anginal attacks/week: Dil CR 3.5; Met 4.7 Mean change in time to angina(min): Dil CR 1.0; Met 1.5 20 weeks Mean frequency of anginal attacks/week: NR Mean change in time to angina(min): Dil CR 1.5; Met 0.7 32 weeks Mean frequency of anginal attacks/week: NR Mean change in time to angina(min): Dil CR 1.1; Met 1.4	NR	Fatigue and sleep disturbances were slightly more often seen in the Met group; Data NR	Dil CR 3.3% Met 0%	

Evidence Table 6. Angina Placebo Controlled Trials

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Variant angina pectoris			
Johnson 1981 United States Fair		Prinzmetal's variant angina	Evidence of myocardial necrosis; congestive heart failure; uncontrolled systemic arterial hypertension; hypotension; associated valvular or congenital cardiac disease; azotemia; clinically important hepatic disease or electrolyte imbalance; inslin-dependent diabetes mellitus; myocardial infarction within 3 months of study; any terminal illness; sick-sinus syndrome; left bundle-branch block; severe bradycardia; second or third-degree atrioventricular block; atrial flutter or fibrillation; pre-excitation syndrome; use of disopyramide, beta-andrenergic blockers or another investigational drug

Evidence Table 6. Angina Placebo Controlled Trials

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)
Variant angina pectoris					
Johnson 1981 United States Fair	One month open Verapamil 240-480 mg daily; then randomized to receive either Ver or Placebo first, to be alternated in 2-month blocks over a total of 8 months	Oral isosorbide dinitrate; procainamide or quinidine; digoxin; methyldopa or hydralazine; sl ntg	Patient diary (recorded daily) Holter monitor for 24 hours during each week of the study	Mean age 52 68% male Race NR	n=19 Fixed arteriosclerotic coronary-artery disease=26.3 Out-of-hospital cardiac arrests=15.8% Three prior MI's: 5.3%

Evidence Table 6. Angina Placebo Controlled Trials

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Variant angina pectoris				
Johnson 1981 United States Fair	NR/NR/19	Withdrawn 2/ Lost 0/ Analyzed 16	n=16 Mean angina episodes(both periods): Pla=12.6; Ver=1.7 Mean sl ntg tablets/week(both periods): Pla=13.8; Ver=2.1	Number of unwanted side effects measured by investigator monthly from patient daily diary recordings

Evidence Table 6. Angina Placebo Controlled Trials

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Variant angina pectoris		
Johnson 1981 United States Fair	Constipation: Plac=0; Ver=12.5%	Plac=0 Ver=0

Evidence Table 6. Angina Placebo Controlled Trials

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Johnson 1981 United States Fair	RCT Double crossover	Prinzmetal's variant angina pectoris after they had one or more episodes of angina at rest associated with reversible S-T segment elevation of at least 0.2 millivolts on electrocardiography	Underlying CHF, uncontrolled systemic arterial hypertension, hypotension, associated valve or congenital cardiac disease, azotemia, clinically important hepatic disease, clinically important electrolyte imbalance, IDDM, MI within 3 months of study, terminal illness of any sort, sick sinus syndrome, left bundle branch block, severe bradycardia, second or third degree atrioventricular block, atrial flutter or fibrillation, preexcitation syndrome; concomitantly administered medications including disopyramide, beta andrenergic blocking agents, another investigations drug

Evidence Table 6. Angina Placebo Controlled Trials

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)
Johnson 1981 United States Fair	Ver 240-480 mg daily Placebo x 8 months (consisting of four 2-month periods; double crossover)	Oral isosorbide dinitrate	Daily patient diary Ambulatory electrocardiographic monitoring(calibrated two channel) for 24 hours during each week	Average age 52 NR 60% male Race NR	

Evidence Table 6. Angina Placebo Controlled Trials

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Johnson 1981 United States Fair	NR/NR/10	NR/NR/analyzed 10	Drug compliance: Plac=87%; Ver=89% Mean anginal episodes/week: Plac=15.9; Ver=2.2 Mean ntg tablets/week: Plac=18.3; Ver=3.2 Hospitalization for clinical instability: Plac=20%; Ver=0	NR

Evidence Table 6. Angina Placebo Controlled Trials

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Johnson 1981 United States Fair	*n=10* Placebo: no AEs Vernumber of patients): Palpitations: 1; asymptomatic sinus nodal pauses of 2 seconds' duration during sleep=1; mild constipation=2;	No withdrawals due to adverse events in either group

Evidence Table 6. Angina Placebo Controlled Trials

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Poole-Wilson 2004 Multi-national Fair	RCT Double blind	patients with a history of myocardial infarction, angiographic coronary artery disease, or a positive exercise test or perfusion defect were aged 35 years or older, and had angina pectoris that had been stable for at least 1 month and needed oral or transdermal treatment either to treat or prevent anginal attacks.	overt heart failure; any major cardiovascular event or intervention within the past 3 months; planned coronary angiography or intervention; known intolerance to dihydropyridines; clinically significant valvular or pulmonary disease; unstable insulin-dependent diabetes mellitus; any gastrointestinal disorder that could compromise absorption of nifedipine GITS or passage of the tablet; any condition other than coronary artery disease that limited life expectancy; symptomatic orthostatic hypotension or supine systolic blood pressure 90mmHg or less; systolic blood pressure at least 200mmHg, diastolic blood pressure at least 105mmHg, or both; creatinine more than twice the local upper limit of normal; alanine or aspartate transminase greater than three times the local upper limit of normal. Woman could only participate if pregnancy is not a risk.

Evidence Table 6. Angina Placebo Controlled Trials

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)
Poole-Wilson 2004 Multi-national Fair	nifedipine 30mg/d, increasing to 60mg/d within 6 weeks if no evidence of intolerence was seen.	NR	Echocardiography, NYHA class, vital signs, and adverse events, were recorded at least every 6 months. Events classifed by critical events committee according to predefined criteria.	Average age 63.5 80% male Race NR	NR

Evidence Table 6. Angina Placebo Controlled Trials

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Poole-Wilson 2004 Multi-national Fair	NR/7797/7665	Withdrawn 360/ Lost 601/ Analyzed 6704 (87.4%): nif 3334, pla 3370	Nifedipine vs placebo number of patients with events (incidence per 100 patient-years) All-cause mortality: 310 (1.64) vs 291 (1.53) Noncardiovascular: 132 (0.70) vs 114 (0.60) Cardiovascular or unknown: 178 (0.94) vs 177 (0.93) Myocardial infarction: 267 (1.46) vs 257 (1.39) Refractory angina: 150 (0.81) vs 174 (0.94) New overt heart failure: 86 (0.46) vs 121 (0.65) Debilitating stroke: 77 (0.41) vs 99 (0.53) Peripheral revascularization: 146 (0.79) vs 118 (0.63) Coronary angiography: 895 (5.46) vs 1068 (6.69) Percutaneous coronary intervention: 385 (2.15) vs 417 (2.34) Coronary bypass surgery: 294 (1.62) vs 371 (2.06) Hazard ratio (95% CI); p-value (includes 24 nifedipine, 28 placebo unknown) All-cause mortality: 1.07 (0.91-1.25); p=0.41 Noncardiovascular: 1.16 (0.90-1.49); p=0.24 Cardiovascular or unknown: 1.01 (0.82-1.24); p=0.93 Myocardial infarction: 1.04 (0.88-1.24); p=0.62 Refractory angina: 0.86 (0.69-1.07); p=0.18 New overt heart failure: 0.71 (0.54-0.94); p=0.015 Debilitating stroke: 0.78 (0.58-1.05); p=0.10 Peripheral revascularization: 1.25 (0.98-1.59); p=0.073 Coronary angiography: 0.82 (0.75-0.90); p<0.0001 Percutaneous coronary intervention: 0.92 (0.80-1.06); p= Coronary bypass surgery: 0.79 (0.68-0.92); p=0.0021	The critical events committee classified serious adverse events that suggested a possible major cardiovascualr event with predefined criteria, irrespective of the investigators' diagnosis. Cause of death was categorized as unknown, cardiovascular, or non-cardiovascular.

Evidence Table 6. Angina Placebo Controlled Trials

Author, Year Country	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Poole-Wilson 2004 Multi-national Fair	Not reported	Not reported

Evidence Table 7. Supraventricular Arrhythmia Head to Head Trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Diltiazem vs Verapamil					
Botto, 1998 Italy	RCT, crossover	Documented history of stable permanent atrial fibrillation (> 6mos), resting heart rate > 100bpm (without HR modifying drugs), and good exercise tolerance (NYHA functional class I).	Renal failure, congestive heart failure, left ventricular ejection fraction <40%, angina or recent myocardial infarction (< 6 months), preexcitation syndrome, electrolyte imbalance, uncontrolled hypertension (SBP >160 mmHg and DBP >100 mmHg) and concomitant therapy with antiarrhythmic agents. Rate modifying drugs not used as antiarrhythmics also excluded (e.g. bronchodilators), patients requiring digoxin or with contraindications to CCBs were excluded.	dil ER 240mg daily ver ER 240 mg daily gal ER 200 mg daily dig to achieve serum concentration 0.8 - 1.4 mcg/ml (mean dose 0.25mg daily) x 7 days each then crossed over	None
Lundstrom, 1990 Sweden	RCT, crossover	AF > 1month duration	NR	dil 270mg daily ver 240mg daily placebo x 3 weeks each then crossover	digoxin all antiarrhythmic drugs discontinued prior to study

Evidence Table 7. Supraventricular Arrhythmia Head to Head Trials

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	Outcomes
Diltiazem vs Verapamil						
Botto, 1998 Italy	24 hour Holter monitor on day 7 of each 7 day course. A 6 minute walking test was administered during this time. Outcomes recorded: mean ventricular rate (VR) minimum VR at night peak VR during walking test impairment of VR calculated as % of age adjusted theoretical peak during walking test	Mean age 66 (range 54 to 72) 83% male NR	0% structural heart disease 44% hypertension 56% lone AF	NR/NR/18	0/0/18	Mean VR (bpm) dil SR 240mg: 82 ver SR 240mg: 80 gal SR 200mg: 91 dig 0.25mg: 90 Peak VR during walking test: dil SR 240mg: 142 ver SR 240mg: 137 gal SR 200mg: 149 dig 0.25mg: 167 % of theoretical maximum during walking test dil SR 240mg: 65% ver SR 240mg: 62% gal SR 200mg: 68% dig 0.25mg: 106% NS for dil vs ver on all outcomes
Lundstrom, 1990 Sweden	VR by: 24 hour Holter monitor (timing of test not stated) Bicycle ergonometry exercise test (timing of test not stated) Patient evaluation of exertion on exercise test (Borg scale 6-20 points)	mean age 65 (range 55 to 74) 68% male NR	lone AF 61% 28% underlying cardiac disorders All were NYHA Functional Class I or II 94% also on digoxin	NR/19/19	1/0/18	mean VR during 24 hour Holter monitoring: dil 76 (mean change from placebo 12) ver 80 (mean change from placebo 8) pla 88 VR at max exercise: dil 159 (mean change from placebo 20) ver 158 (mean change from placebo 21) pla 179 Patient perception of exertion: dil 19.3 ver 19.2 pla 19.1

Evidence Table 7. Supraventricular Arrhythmia Head to Head Trials

Author, Year Country	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Diltiazem vs Verapamil				
Botto, 1998 Italy	Active questioning	Adverse events (n/30) RR cycles > 2 seconds: dil SR 240mg: 254 ver SR 240mg: 203 gal SR 200mg: 125 dig 0.25mg: 137 Bradycardia episodes (bpm < 50) dil SR 240mg: 261 ver SR 240mg: 262 gal SR 200mg: 168 dig 0.25mg: 170 NS for all comparisons None others reported	None	Although stated that adverse events were monitored by active questioning, only those seen on ECG are reported.
Lundstrom, 1990 Sweden	Direct questioning	Number of adverse events reported by 18 patients: dil 36 most common: ankle edema, fatigue, dizziness ver 41 most common: ankle edema, fatigue, constipation pla 25 most common: ankle edema, fatigue, dizziness	1/19 (5%) dil group due to ankle edema	short time frame

Evidence Table 7. Supraventricular Arrhythmia Head to Head Trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Ochs 1985 Germany	RCT	Atrial fibrillation of more than 6 months duration, atrial size no larger than 45mm by echo, receiving digitalis, NYHA Class I or II heart failure, no evidence of pulmonary congestion and had cardiothoracic ratio within normal limits by chest x-ray	Serious concomitant diseases, hyperthyroidism	dil 180mg daily ver 240mg daily If not in NSR after 6 days increase doses to: dil 360mg daily ver 480mg daily if not in NSR at 6 days decreases doses to: dil 180mg daily ver 240mg daily quinidine 750mg daily	digoxin

Evidence Table 7. Supraventricular Arrhythmia Head to Head Trials

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	Outcomes
Ochs 1985 Germany	conversion to NSR by day 6	51.6 dil, 50.6 ver 40% male NR	Duration of AF: 4.6 yr dil, 2.4 yr ver mitral valve disease: 47%	NR/NR/30	5/0/30	Conversion to NSR by day 6 dil 180mg 6.7% (1/15), ver 240mg 6.7% (1/15) dil 360mg 0/13, ver 480mg 10% (1/10) dil 180mg + qui 0/13 ver 240mg + qui 33% (3/9) Mean VR : dil 360mg 73 (mean change from baseline 12) ver 480mg 63 (mean change from baseline 24)

Evidence Table 7. Supraventricular Arrhythmia Head to Head Trials

Author, Year Country	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Ochs 1985 Germany	NR	Number of patients reporting 1 or > adverse event: dil acute pancreatitis 1/15 (7%) bradycardia/fatigue 3/15 (20%) dil + qui diarrhea 2/13 (15%) ver dyspnea/nausea 1/15 (7%) pulmonary congestion/skin reaction 1/15 (7%) hepatomegaly/increase SGT, SGPT, GGT 1/15 (7%) acute cholecystitis 1/15 (7%) bradycardia 3/10 (30%) bigeminal rhythm 1/10 (10%) pulmonary congestion 1/10 (10%)	dil 7%, 1/15 ver 27% 4/15	The higher dose of both drugs was not well tolerated and resulted in a shortened course in 1/13 dil, 5/10 ver

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Diltiazem vs Other Medications					
Dahlstrom 1992 Sweden	RCT, crossover	Chronic AF > 6 mos duration, digoxin therapy, males aged 30 - 70 and postmenopausal females	angina pectoris, decompensated heart disease NYHA classes III-IV, severe ventricular arrhythmias, untreated thyureotoxicosis, marked anemia, glaucoma, advanced pulmonary disease, systolic blood pressure <95 or >160/95 mmHg (before or during the prestudy period), diabetes mellitus, severe hepatic or renal disease, inability to withdraw a) other antiarrhythmic drugs, other than digoxin; b) vasodilators, including calcium entry blockers, c) beta blockers, d) tricyclic antidepressants, phenothiazines, and diazepam and myocardial infarction within the preceding 6 months.	dil 180mg daily pro 60mg daily dil 180mg + pro 60mg daily x 4 weeks each All patients taking digoxin	NR

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

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
Diltiazem vs Other Medications					
Dahlstrom 1992 Sweden	Holter monitor and exercise test at end of week 4 Patient diary scored for sensation of arrhythmia, fatigue, breathlessness, dizziness (graded as not at all, sometimes, often, all the time), and general health (better, usual, worse) at week 4 of each 4 week period.	mean age 61 (range 35 to 74) 69% male NR	NR	NR/28/13 main reason for not enrolling was low blood pressure or heart rate during 2-day test of dil + pro	1/3/13

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Diltiazem vs Other Medications					
Dahlstrom 1992 Sweden	Mean HR at rest dil 84 (change from baseline = 11) pro 86 (change from baseline = 9) dil + pro 69 (change from baseline = 26) Max HR during exercise: dil 164 (change from baseline = 15) pro 163 (change from baseline = 14) dil + pro 135 (change from baseline = 44) Patient Diary: Sensation of tachyarrhythmia significantly more frequent during dil than other therapies (data not reported) No statistically significant differences in other parameters.	spontaneously reported or on direct questioning	Adverse events dil 20 events pro 24 events dil + pro 13 events Events for dil include: edema (20% of events) fatigue (20% of events) Paraesthesia (20% of events) Flushing, constipation, palpitations (10% of events each) Headache, dyspnea (5% of events each)	3/13 (23% withdrew due to AE dil : 0 pro: 1 dil + pro: 2	Unclear how many patients could be analyzed for each drug group, due to drop-outs and loss to follow-up.

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Farshi 1999 US	RCT, crossover	Documented chronic AF, resistant to attempted cardioversion, of at least one year duration.	LVEF <35% by Echo, HR < 55 bpm, Wolff-Parkinson-White syndrome, clinically significant renal thyroid or hepatic dysfunction, uncontrolled hypertension, sick sinus syndrome, implanted pacemaker, unstable angina or acute myocardial infarction or persistent systolic blood pressure < 95 mmHg, taking theophylline, clonidine, or inhaled beta-agonists, or with previous exposure to amiodarone.	dil ER 240mg daily dig 0.25mg daily ate 50mg daily dig + dil dig + ate x 2 weeks each	NR
Koh, 1995 Korea	RCT	AF > 1month duration	HR at rest < 60 bpm, ejection fraction <30%, diabetes mellitus, bronchial asthma, chronic obstructive lung disease, untreated thyrotoxicosis < 2 months after myocardial infarction, and SBP < 90 mmHg	no treatment dig 0.125 to 0.5 mg daily dig + dil 180mg daily x 4 weeks	none

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

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
Farshi 1999 US	24 hour Holter monitor at end of 2 week period, treadmill test (Naughton protocol),	mean age 69 (range 57 to 87) 92% male NR	58% lone AF Underlying cardiac disorders: 42% (5/12) HTN 8% (1/12) mitral stenosis 17% (2/12) ischemic heart disease	NR/NR/12	NR/NR/NR 3 (25%) did not receive ate due to chronic obstructive pulmonary disease
Koh, 1995 Korea	HR at rest Exercise treadmill test (Bruce protocol)	mean age 59 (range 29 to 82) 49% male NR	Mean Ejection fraction = 63% 64% valvular heart disease 13% hypertension 9% lone AF	NR/45/45	3/NR/42

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Farshi 1999 US	*Mean VR (bpm)/24 hr:* dil 80 dig 78.9 ate 75.9 dig + dil 67.3 dig + ate 65 *Daytime mean VR:* dil 83.8 dig 84.7 ate 77 dig + dil 71/8 dig + ate 64.7 *Nighttime VR:* dil 76.3 dig 72.8ate 74.8 dig + dil 62.9 dig + ate 65.4 *Mean peak VR (in those exercising for >/= 5 min):* dil 151 dig 175 ate 130 dig + dil 146 dig + ate 126	NR	NR	NR	
Koh, 1995 Korea	*HR at rest after 4 weeks (change from baseline):* no meds 105 (-3) dig 84 (-19) dig + dil 75 (-32) *HR at max exercise after 4 weeks (change from baseline):* no meds 196 (+4) dig 163 (-7) dig + dil 172 (-9)	questionnaire	NR		

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Koh, 1995 Korea	RCT, crossover	AF > 1month duration	HR at rest < 60 bpm, ejection fraction <30%, diabetes mellitus, bronchial asthma, chronic obstructive lung disease, untreated thyrotoxicosis < 2 months after myocardial infarction, and SBP < 90 mmHg	dig 0.125 to 0.5 mg + dil 180mg daily dig 0.125 to 0.5 mg + bet 20mg daily x 4 weeks each	NR
Hohnloser, 2000 Germany	RCT	Age 18 to 75, symptomatic persistent AF of between 7 days and 360 days duration.	NYHA class IV heart failure, unstable angina, acute MI within 30 days, AF with an average of fewer than 50 BPM, known sick-sinus syndrome, AF in setting of Wolff-Parkinson-White syndrome, CABG or valve replacement within past 3 months, echo documentation of intracardiac thrombus formation, central or peripheral embolization within the past 3 months, hypertrophic cardiomyopathy, amiodarone therapy within the last 6 months, acute thyroid dysfunction, pacemaker therapy, contraindications for systemic anticoagulation therapy.	dil 180 - 270mg daily ami 200mg daily (after NSR achieved with ami 600mg daily +/- electrical cardioversion) e. X 12 months	dil group: If rate not controlled adequately, other drugs added per treating physician choice. Ami group: recurrent AF treated per treating physician choice Digoxin allowed

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

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
Koh, 1995 Korea	HR at rest Exercise treadmill test (Bruce protocol)	mean age 52 (range 24 top 81) 60% male NR	Lone AF 14% valvular heart disease 51% mean ejection fraction 58%	NR/37/37	2/0/35
Hohnloser, 2000 Germany	AF-related symptoms (palpitations, dyspnea, dizziness) 6 minute walking test 24 hour Holter monitor Number of hospital admissions Assessments at 3 wks, 3, 6 and 12 months	mean age 60 1 (dil), 60 (ami) 74% (dil) and 72% (ami) male NR	Lone AF 17% (dil), 14% (ami) Valve disease 15% (dil), 17% (ami) Hypertension 54% (dil), 46% (ami) % taking dig:dil 70%, ami 72% Duration of AF(days): 118 (dil)103 (ami)	NR/NR/252 dil 125 ami 127	50/6/242 dil 122 ami 120 4 crossed over from dil to ami 6 crossed over from ami to dil

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Koh, 1995 Korea	*HR at rest after 4 weeks (change from baseline):* dig + dil 80 (-31) dig + bet 67 (-44) *HR at max exercise after 4 weeks (change from baseline):* dig + dil 154 (-37) dig + bet 135 (-56)	questionnaire	dig + dil 9 dig + bet 15 dil: dizziness, gastric pain, headache, fatigue, nausea, edema	2 due to cerebral infarction (group assigned not reported)	
Hohnloser, 2000 Germany	Drugs added: ACE-Inhibitors: dil 46%, ami 44% Beta blockers: 9%, 10% Class I or II antiarrhythmics: 0%, 0% *Proportion reporting improvement in symptoms (3wk, 3, 6, 12mths):* dil: 55%, 58%, 58%, 61% ami: 57%, 63%, 60%, 55% *Mean HR (BPM):* dil: 88 at baseline, 81 at 12 months ami: 86 at baseline, 78 at 3 weeks, afterwards "majority in sinus rhythm" *Maintenance of sinus rhythm:* dil: 10% at 12 months ami: 56% at 12 months *Change from baseline in 6 min walking test: (meters)* dil: 5 ami: 50 *Hospitalizations:* dil: 25% (68% due to adverse drug events) ami 69% (67% for cardioversion, 27% for adverse drug events)	NR	Proportion with at least one adverse event: dil 47% ami 64% Most common event: dil: edema, 17/125 (14%) ami: corneal deposits 10/127 (8%)	dil 14%, 17/125 ver 25%, 31/127	

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Lewis, 1988 Scotland	RCT, crossover	AF >= 1 year duration	NR	dil 270mg daily x 2 wks, then 360mg daily dig dosed to 1.3 - 2.6 nmol-1 (dose determined during run-in phase) dig (same dose)+ dil 270mg daily x 4 weeks total each then crossover	none
Verapamil vs Other Medications					

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

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
Lewis, 1988 Scotland	At 2 wks and 4 wks: Resting HR Symptoms assessed by VAS Exercise tolerance by 6-min walking test + ECG at end Patient evaluation of exertion on exercise test (Borg scale 6-20 points) At 4 wks: VR by 24-hour Holter monitor	mean age 62 (range 52 to 69) 71% male NR	14% (2) long AF ischemic heart disease 57% (8) mitral valve disease 29% (4) All NYHA Functional Class I 93% taking digoxin at baseline	NR/NR/14	4/0/10
Verapamil vs Other Medications					

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Lewis, 1988 Scotland	Mean resting HR: dil 91 dig 100 dig + dil 83 Mean post-exercise HR: dil 140 dig 152 dig + dil 141 Mean 24-hour HR: dil 90 dig 87 dig + dil 70 Mean walking distance (m): dil 554 dig 545 dig + dil 550 Patients perception of exertion (after walk test): dil 3.65 dig 3.5 dig + dil 3.4 VAS scores: Dyspnea dil 33, dig 26, both 24 tiredness dil 29, dig 24, both 31 well being dil 23, dig 17, both 25	Degree of constipation assessed by VAS	Assessment of Constipation by VAS dil 11 dig 10 dig + dil 14	3 withdrew during dil treatment: 1 ankle edema 1 breathlessness 1 severe chest pain (thought to be unrelated to study drug) 1 withdrew during dig run-in - converted to NSR	
Verapamil vs Other Medications					

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Ahuja 1989 India	RCT, crossover	isolated rheumatic mitral stenosis	NR	ver 120mg daily dig 0.25 mg daily met 100 daily x 2 wks each then ver 240mg daily dig 0.5mg daily met 200mg daily x 2 wks, decrease dose if symptoms	NR

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

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
Ahuja 1989 India	Subjective improvement using VAS Treadmill at 2 wks	mean age 27 60% male NR	10 NSR/10 AF Mean duration of illness 3.5 yr History of right heart failure 55% All treated with diuretics 70% NYHA Class II, 30% Class III	NR/24/24	4/0/20

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Ahuja 1989 India	Patients in AF: >= 50% subjective improvement: ver 80% dig 40% met 30% *Mean HR at rest:* ver 65 (change from baseline 51) dig 80 (change from baseline 36) met 72 (change from baseline 44) Mean HR during exercise ver 138 (change from baseline 52) dig 182 (change from baseline 8) met 149 (change from baseline 41) Patients in NSR: >= 50% subjective improvement: ver 40% dig 0 met 90% Mean HR at rest: ver 75 (change from baseline 13) dig 84 (change from baseline 4) met 65 (change from baseline 23) Mean HR during exercise ver 148 (change from baseline 6) dig 142 (change from baseline 12) met 127 (change from baseline 27)	NR	35% fatigue on met	NR	

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Channer 1987 UK	RCT, crossover	chronic AF (not defined)	NR	dig + ver 120mg daily dig maintenance dose (defined during run-in phase) dig double maintenance dose (max 0.5mg daily) x 1 month each, then crossover	NR
Dorian, 1996 multiple countries	RCT Open	Recurring paroxysmal SVT, requiring therapy, deigned as a regular tachycardia (adjacent RR intervals varying by </= 0.02 sec) at a rate of at least 120 beats/min, with normal QRS morphology or with functional bundle branch block, and without evidence of AV dissociation during tachycardia	Patients with coexisting paroxysmal atrial fibrillation or flutter, prior history of MI or unstable angina, a history of sustained ventricular tachycardia, NYHA class III or IV CHF, second or third degree AV block, or a PR interval > 0.28 seconds or QRS interval > 0.15 seconds during sinus rhythm	Flecainide (Fle) 100-300 mg daily Verapamil (Ver) 240-480 mg daily x up to 1 years	

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

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
Channer 1987 UK	At end of each treatment period palpitation and dyspnea assessed by VAS 6 minute walking test x 2 (separate days) 24-hour ambulatory ECG	mean age 60 (range 52 to 74) 21% male NR	All patients taking digoxin at baseline 57% taking diuretic mitral valve disease 65% aortic valve disease 14% Lone AF 21%	NR/NR/14	0/0/12 2 patients maintenance dose of dig was 0.5mg daily, so only dig + ver phase completed for these patients
Dorian, 1996 multiple countries	Patient diary ECG	Mean age: Fle=52; Ver=49 Gender (%male): Fle=25; Ver=33 Race NR	HTN(%): Fle=21; Ver=24 Cardiomegaly(%): Fle=8; Ver=7 Proportion with > 30 PVCs/hr(%): Fle=6; Ver=9	NR/NR/121	Overall withdrawals (before end of 1 year): Fle=29(46%); Ver=29(50%) Lost NR Analyzed: Unclear

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Channer 1987 UK	Mean max HR area under the curve: ver + dig: 2124 dig maint: 2451 Double dig: 2103 VAS of palpitations, breathlessness: ver + dig: 6.5, 22 dig maint: 24.5, 34 double dig: 15.5, 26 Walking test (m): dig + ver: 454 dig maint: 461 double dig: 463	NR	NR	NR	
Dorian, 1996 multiple countries	% patients showing 0-1 attacks/month: Fle=86%; Ver=73%	NR	Constipation: Ver=21%; Fle=3% Chest pain: Ver=7%; Fle=19% Headache: Ver=33%; Fle=23% Tachycardia: Ver=10%; Fle=0% Dizziness: Ver=9%; Fle=21%	Fle=12(19%) Ver=14(24%)	

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
James, 1989 UK	RCT Crossover	Chronic atrial fibrillation and were symptomatic with palpitation and/or breathlessness	NR	Pindolol (Pin) 10-30 mg daily Verapamil (Ver) 120 mg daily	NR

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

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
James, 1989 UK	VAS 24-h ambulatory ECG	33.3% male Mean age: 58.4 Race NR	All patients taking digoxin 58.3% taking diuretic *Etiology(%)* Mitral valve disease: 75 Ischaemic heart disease: 8.3 Thyroid disease: 8.3 Lone AF: 8.3	NR/NR/12	1 withdrawn/lost NR/10 analyzed

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
James, 1989 UK	*Mean max, min HR (AUC):* Dig alone=2570, 1798 Dig+Ver=2431, 1685 Dig+Pin=2340, 1817 *Mean daytime, nighttime pauses:* Dig alone=1.85, 2.25 Dig+Ver=1.92, 2.05 Dig+Pin=1.69, 1.78 *VAS palpitation, breathlessness* Dig alone=35.2, 39.1 Dig+Ver=20.7, 34.7 Dig+Pin=21.4, 40.1	NR	Pin: wakefulness(1), headaches/sweatiness(1), feeling 'on-edge'(1) Ver: NR	Pin=1(due to bout of nausea, vomiting and abdominal pain) Ver=0	

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Lewis 1989 Scotland	RCT Crossover	Chronic atrial fibrillation of at least 1 year's duration	History of uncontrolled cardiac failure, "sick-sinus syndrome", obstructive airways disease, insulin-dependent diabetes mellitus, or angina pectoris of a severity sufficient to limit exercise tolerance	Ate 100 mg daily Ver 160 mg daily Xam 400 mg daily Pla x 4 weeks, then crossover	Digoxin

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

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
Lewis 1989 Scotland	Treadmill (modified Bruce protocol) Continuous ECG	60% male Mean age: 61 Race NR	*Etiology* Rheumatic heart disease: 60% Atrial fibrillation: 33.3% Thyrotoxicosis: 6.7% NYHA class I: 93.3% All patients taking digoxin Diuretic use: 53.3% Warfarin: 33.3%	NR/NR/15	Withdrawn 5/15(33.3%); 0 lost/10 analyzed

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Lewis 1989 Scotland	*Resting HR(bpm)* Pla=90 Ate=68 Ver=68 Xam=83 *Postexercise HR(bpm)* Pla=164 Ate=120 Ver=131 Xam=130 *Mean hourly rate* Pla=86 Ate=67 Ver=77 Xam=80 *Mean min/max rate* Pla=49/172 Ate=44/140 Ver=49/148 Xam=58/136 *Max treadmill walking distance(m)* Pla=421 Ate=356 Ver=439 Xam=402	NR	No other patients reported any side effects	1 patient on Ate (dizziness/lightheadedness)	

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Lundstrom, 1992 Sweden	RCT Crossover	Chronic atrial fibrillation	Complete AV block, severe ventricular arrhythmias, bronchopulmonary disease, thyrotoxicosis, myocardial infarction that occurred less than 2 months before entry into the study, hepatic or renal disease or any other disease that would be likely to interfere with the evaluation of the drug effects	Xam 200 mg daily Ver slow-release 240 mg daily Plac x 2 weeks, then crossover	Digoxin

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

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
Lundstrom, 1992 Sweden	Bicycle ergometer 24-hour ECG Evaluation of subjective well being (VAS)	Mean age 67 66.7% male Race NR	Mean duration of AF(yrs): 5.5 Mitral valve disease: 28.6% Aortic valve disease: 4.8% Tricuspid insufficiency: 28.6% Hypertension: 28.6% Previous MI: 9.5% Cardiomyopathy: 9.5% CHF: 19.0% Idiopathic: 33.3% NYHA Class I, II, III: 28.6%, 38.1%; 33.3% Concomitant digoxin treatment: 80.9%	NR/NR/21	3 withdrawn/0 lost/18 analyzed

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Lundstrom, 1992 Sweden	*Workload(W)* Pla=122 Xam 100/200 mg=121/119 Ver=119 *Ventricular rate(beats/min)* Pla=171 Xam 100/200 mg=146/138 Ver=137 *Borg scale* Pla=18.5 Xam 100/200 mg=18.2/18.6 Ver=18.4 *Oxygen uptake (ml/min/kg)* Pla=20.2 Xam 100/200 mg=20.6/19.8 Ver=20.3 *Ventilation(L/min)* Pla=62.5 Xam 100/200 mg=62.1/59.9 Ver=60.3	NR	*Fatigue(%)* Pla=80 Xam 100/200 mg=57.1/66.7 Ver=70 *Dizziness(%)* Pla=20 Xam 100/200 mg=14.3/0 Ver=40 *Headache(%)* Pla=20 Xam 100/200 mg=28.6/33.3 Ver=30 *Nausea(%)* Pla=20 Xam 100/200 mg=14.3/16.7 Ver=20 *Edema(%)* Pla=20 Xam 100/200 mg=28.6/16.7 Ver=20 *Constipation(%)* Pla=20 Xam 100/200 mg=14.3/16.7 Ver=20	Xam=1(pneumonia) Ver=2(signs of liver toxicity)	

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Rasmussen 1981	RCT Crossover	Chronic stable atrial fibrillation with a documented duration of more than ten days in which a conversion trial was found to be indicated	NR	Qui 800 mg daily Ver 240 mg daily Cardioversion after at least 2 days of drug therapy. Then followed at 1 month, and then 3 month intervals	Dig stopped before cardioversion
Van Noord 2001	RCT Open	Persistent AF with a ventricular rate > 90 beats/min documented on resting ECG and planned ECV within 1 month	History of 2nd or 3rd degree AV conduction block; known sick sinus syndrome; heart failure according to NYHA functional class III or IV; unstable angina pectoris; current treatment with CCBs, digoxin, Class I or III antiarrhythmic drugs (amiodarone within last 3 months); untreated hyperthyroidism or hypothyroidism; serious pulmonary, hepatic, hematologic, metabolic, renal, gastrointestinal, central nervous system, or psychiatric disease; pacemaker treatment; contraindications for oral anticoagulant agents; age <18 or >85 years	ver 120-360 mg daily dig 0.125-0.25 mg x 1 month prior to electrical cardioversion (ECV) and 1 month after ECV	Acenocoumarol or Fenprocoumon initiated at least 4 wks before ECV and continued for at least 1 month after restoration of sinus rhythm

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

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
Rasmussen 1981	Occurrence of atrial fibrillation assessed by ECG	Age NR Gender NR Race NR	*AF duration* <1 mo: 8(15.1%) 1-6 mo.:10(18.9%) 6-12 mo.: 8(15.1%) 1-2 yr: 5(9.4%) >2 yrs.: 7(13.2%) Unknown: 15(28.3%) *Diagnosis* CHF: 16(30.2%) HTN: 12(22.6%) Valvular heart disease: 6(11.3%) Congenital heart disease: 1(1.9%) Constrictive pericarditis: 1(1.9%) Lone: 16(30.2%)	NR/NR/53	Withdrawn during first intervention (prior to crossover): Qui=11/25; Ver=0 Lost: 0 Analyzed: 50 at first drug/DC conversions
Van Noord 2001	24-hour Holter monitor	Mean age: Ver=66; Dig=66 Gender(%male): Ver=56%; Dig=75.5% Race NR	Coronary artery disease(%): Ver=25; Dig=16 Valvular disease(%): Ver=19; Dig=6 Mitral regurgitation(%): Ver=8; Dig=0 Systematic HTN(%): Ver=40; Dig=47 Chronic Obstructive Pulmonary Disease(%): Ver=19; Dig=22 Other(%): Ver=10; Dig=8 Lone AF(%): Ver=19; Dig=22 Duration of AF(days): Ver=18; Dig=21 NYHA HF class I/II(%): Ver=72.9/27.1; Dig=81.6/18.4 BB therapy(%): Ver=8; Dig=12 Left atrial long axis(mm): Ver=46; Dig=45	NR/NR/97	54(55.7%) withdrawn/0 lost/97 analyzed per ITT; 43 analyzed per protocol

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Rasmussen 1981	*Sinus rhythm during first intervention period* Drug conversion: Qui=8/26(31%); Ver=2/25(8%) Electrical conversion: Qui=16/17(94.1%); Ver=22/23(95.6%) Follow-up 6-33 mo.: Qui=2/24(8.3%); Ver=2/24(8.3%)	NR	NR	*During first intervention period* Withdrawal due to AE: Qui=5; Ver=0 Death: Qui=2; Ver=0	
Van Noord 2001	*Results per ITT* Spontaneous conversion: Ver=29%; Dig=27% Successful ECV: Ver=74%; Dig=84% Joules (mean): Ver=664; Dig=526 Relapse <1 month: Ver=40%; Dig=50% Days to relapse (median): Ver=6; Dig=11	NR	NR	Ver=4 (constipation in 2; heart failure in 2) Dig=1 (paroxysmal atrial tachycardia due to digoxin intoxication)	

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Yilmaz 1996	RCT	Patients with atrial fibrillation that occurred immediately after coronary artery bypass surgery and was returned to normal sinus rhythm by electrical or pharmacological agents	*Preoperative* Rhythm/conduction disturbances; BB agents; hyperthyroidism; GI diseases causing absorption dysfunction; LV aneurysm; severe LV dysfunction *Operative* Surgical interventions added to coronary artery surgery (e.g., aneurysmectomy, valve procedures) *Postoperative* MI; renal insufficiency; low cardiac output; severe respiratory complications; ventricular arrhythmias; symptomatic sinus bradycardia	No treatment *(n=30)* Quinidine 500 mg daily *(n=30)* *v* er 250 mg daily *(n=30)* Amiodarone 200 mg daily *(n=30) x 90 days*	Unspecified antianginal therapy and diuretics

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

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
Yilmaz 1996	24-hour Holter monitor x weekly for 1 month; monthly thereafter for a total of 90 days fu	Mean age: None=55; Qui=57; Ver=54; Ami=59 Gender(%male): None=86.7; Qui=93.3; Ver=90; Ami=86.7 Race NR	Hyperlipidemia(%): None=43; Qui=33.3; Ver=40; Ami=33.3 Smoking(%): None=66.7; Qui=60; Ver=63.3; Ami=56.7 Preoperative MI: None=30; Qui=26.7; Ver=30; Ami=36.7 Preoperative angina(Class III-IV): None=6.7; Qui=3.3; Ver=3.3; Ami=3.3 Preoperative normal ventricle: None=80; Qui=83.3; Ver=80; Ami=80 Three vessel disease: None=76.7; Qui=80; Ver=73.3; Ami=83.3 Number of distal anastomoses: None=2.5; Qui=2.6; Ver=2.4; Ami=2.7 Perfusion period (min): None=86; Qui=89; Ver=81; Ami=93	NR/124 eligible/120 enrolled	Withdrawn NR/Lost NR/Analyzed NR

Evidence Table 8. Supraventricular Arrhythmia Active Controlled Trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Yilmaz 1996	*Post discharge period* AF incidence: None=1; Qui=2; Ver=2; Ami=2 Time of first occurrence of AF(days): None=9; Qui=5.1; Ver=14.56; Qmi=7.13 Ventricular rate (beats/min): None=120; Qui=135; Ver=85; Ami=79 Number of relapses: None=0; Qui=0; Ver=0; Ami=0	NR	NR	Qui=5(16.6%)(vomiting, nausea, diarrhea, skin rash, and QT interval prolongation)	

Evidence Table 9. Supraventricular Arrhythmia Placebo Controlled Trials

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Clair 1992 Fair	RCT Crossover	History of at least three symptomatic attacks of paroxysmal supraventricular tachycardia within the previous 6 months; one of these attacks was required to have been documented by ECG; the ECG criteria for paroxysmal supraventricular tachycardia were as follows: (1) ventricular rate greater than 120/min, (2) QRS morphology that was normal or functional bundle branch block, (3) less than 0.02 second variation in successive RR intervals, (4) no evidence of atrioventricular dissociation, and (5) episodic occurrence	Left ventricular failure of NYHA functional class III or IV; medically required beta-blockers, digitalis glycosides, or other antiarrhythmic agents; required treatment with other investigational drugs; unstable angina; Wolff-Parkinson-White syndrome with antidromic reciprocating tachycardia; myocardial infarction within the 3 months before enrollment in the study; terminal illness; or women capable of bearing children
DAVIT II (Part of the Danish Verapamil Infarction Trial II) Jespersen 1992 Denmark Fair	RCT	Patients below 76 years of age with the diagnosis of AMI	Heart failure requiring more than 160 mg furosemide daily; systolic blood pressure <90 mmHg; second or third degree atrioventricular block; sinoatrial block; heart rate below 45 b.min-1; treatment with beta blockers or calcium antagonists; treatment with digoxin or anti-arrhythmics and patients with atrial flutter or fibrillation or an electrocardiogram with ventricular hypertrophy, strain or intraventricular block

Evidence Table 9. Supraventricular Arrhythmia Placebo Controlled Trials

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
Clair 1992 Fair	Open diltiazem (dil) 240-360mg daily x 3 months Double-blind dil at same maximum dose taken in open phase or placebo until first recurrence of tachycardia or up to 2 months, then crossover	NR	Time interval to first recurrence of tachycardia	NR	NR	NR/NR/17
DAVIT II (Part of the Danish Verapamil Infarction Trial II) Jespersen 1992 Denmark Fair	Verapamil (ver) 360 mg daily Placebo (plac) x 1 month	NR	Holter monitoring Exercise testing	Mean age: plac=60; ver=59 Gender(%male): plac=76; ver=75 Race NR	*Prior MI(%)* Anterior Q-wave: plac=36; ver=31 Inferoposterior Q-wave: plac=30; ver=37 Non Q-wave: plac=34; ver=32 *Other* Heart failure(%): plac=24; ver=23 Exercise, daily number (CL-95%): plac=10; ver=10 ST segment depression: plac=29; ver=26 Holter, day number(CL-95%): plac=7; ver=7 SVT(%): plac=13; ver=16	NR/NR/157

Evidence Table 9. Supraventricular Arrhythmia Placebo Controlled Trials

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)	Comments
Clair 1992 Fair	1 withdrawn/0 lost/16 analyzed	Time to tachycardia: dil vs plac hazard ratio=2.7(p=0.11)	NR	Overall AE incidence: dil=2/16(12.5%); plac=0 Type of AEs: Headache: dil=1/16(6.3%) Localize rash: dil=1/16(6.3%)	dil=0 plac=0	Relatively low dose
DAVIT II (Part of the Danish Verapamil Infarction Trial II) Jespersen 1992 Denmark Fair	NR	Change in SVT prevalence from baseline to one-month after discharge: ver=16%(n=10) vs 14%(n=9); plac=14%(n=9) vs 31%(n=19) Patients *with* SVT at 2nd monitoring who had been without at 1st monitoring: ver=5 of 53; plac=13 of 53(p<0.04) Patients *without* SVT at 2nd monitoring who had been with at 1st monitoring: ver=6 of 10; plac=3 of 9	NR	NR	NR	

Evidence Table 9. Supraventricular Arrhythmia Placebo Controlled Trials

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Bertaglia 2001 Fair	RCT	Persistent AF (>72 hours)	Treatment with intracellular calcium lowering drugs; mean ventricular rate < 60 beats/min; previous side effects of verapamil; left ventricular ejection fraction < 40%

Evidence Table 9. Supraventricular Arrhythmia Placebo Controlled Trials

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
Bertaglia 2001 Fair	Verapamil (ver) 240 mg daily+amiodarone (ami) 200 mg daily Amiodarone (ami) 200 mg daily x 4 wks before and 4 wks after electrical cardioversion	NR	ECG x 6 hours, 7 days and 30 days after electrical cardioversion	ver+ami *n* =39; ami *n* =42 Mean age: ver+ami=65.9; ami=65.3 Gender(%male): ver+ami=64; ami=64 Race NR	Coronary heart disease%: ver+ami=18; ami=12 Systemic HTN%: ver+ami=33; ami=23 Dilated cardiomyopathy%: ver+ami=8; ami=7 Valvar heart disease%: ver+ami=10; ami=17 Cor pulmonale%: ver+ami=0; ami=5 Lone atrial fibrillation%: ver+ami=31; ami=36 Atrial fibrillation relapses(n): ver+ami=1.5; ami=3.4 Previous electrical cardioversion(n): ver+ami=1.5; ami=1.5 Previous unsuccessful electrical cardioversion(n): ver+ami=0.5; ami=0.4 Atrial fibrillation episode duration(days): ver+ami=276; ami=228 Digoxin%: ver+ami=41; ami=55 Mean ventricular rate(bpm): ver+ami=78.5; ami=82.4 Left atrial size(mm): ver+ami=48.2; ami=47.7 Left ventricular end diastolic diameter(mm): ver+ami=54.9; ami=52.6 Left ventricular ejection fraction%: ver+ami=55.6; ami=56.5 Internal electrical cardioversion%: ver+ami=21; ami=26	189 patients referred/133 eligible/100 randomized

Evidence Table 9. Supraventricular Arrhythmia Placebo Controlled Trials

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)	Comments
Bertaglia 2001 Fair	Overall withdrawals(%): ver+ami=22; ami=16/0 lost/81 analyzed	*AF relapse* Within 6 hrs%: ver+ami=23; ami=12 Within 7 days%: ver+ami=46; ami=31 Within 30 days%: ver+ami=54; ami=43	NR	NR	ver+ami=1 ami=0	

Evidence Table 9. Supraventricular Arrhythmia Placebo Controlled Trials

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Panidis 1983 Fair	RCT	Patients with a history of stable, nonhemodynamically important chronic AF of AFI; documented by 24-hour ambulatory electrocardiographic (Holter) monitoring recorded within 4 weeks before the beginning of the study; maximal ventricular rate >100 beats/min between the second and third minute of a standarized exercise test	Clinically overt congestive heart failure; unstable angina; uncontrolled severe hypertension; Wolff-Parkinson-White Syndrome; renal or hepatic failure; insulin-dependent diabetes mellitus; sick sinus syndrome without a functioning implanted pacemaker; use of beta-blocking drugs and antiarrhythmic medications within 5 half-lives before entering study
Stern 1982 United States Fair	RCT Crossover	*Chronic atrial fibrillation* (n=9) Patients with atrial fibrillation of at least six months' duration and who were receiving digoxin Group 1: Patients with chronic atrial fibrillation and resting heart rates > 100/min Group 2: Patients with chronic atrial fibrillation and resting heart rates </= 100/min, but heart rates > 100/min during modest exercise *Paroxysmal atrial fibrillation* (n=4) Group 3: Patients with rapid paroxysmal atrial fibrillation	*Chronic atrial fibrillation groups (1 and 2):* significant congestive heart failure (any combination of cardiomegaly, hepatomegaly, rales, S3 gallop, venous hypertension); hypotension (SBP < 90 mmHg); severe hypertension (DBP > 115 mmHg); severe bradycardia at rest (HR < 50/min) *Paroxysmal atrial fibrillation group:* NR

Evidence Table 9. Supraventricular Arrhythmia Placebo Controlled Trials

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
Panidis 1983 Fair	*Open phase:* verapamil dose-titration phase (240-480 mg daily) *Double-blind phase:* verapamil at optimal dose as determined in open phase or placebo x 15 days, then crossover	NR	ECG at rest 24-hour Holter recording	Mean age: 57 Gender: 80% male Race NR	Mean AF duration(years): 6.4 NYHA class I or II(%): 96.7% Previous digitalis therapy: 100% Serum digoxin level >1 ng/ml: 90%	NR/NR/30 enrolled
Stern 1982 United States Fair	Verapamil 240-480 mg daily (lowest dose which reduced ventricular response during peak exercise by 15% as determined in open-label titration) Placebo x 14 days, then crossover	Digoxin	Exercise with continuous ECG monitoring on either treadmill or upright bicycle	Mean age: Group 1=53.5; Group 2=49.2; Group 3=54.5 Gender(%male): Group 1=75; Group 2=60; Group 3=50 Race NR	NYHA functional class Group 1: 100% class 2 Group 2: 60% class 2; 40% class 1 Group 3: 100% class 2	NR/NR/13

Evidence Table 9. Supraventricular Arrhythmia Placebo Controlled Trials

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)	Comments
Panidis 1983 Fair	3 withdrawn/0 lost/27 analyzed for efficacy	Mean heart rate at rest(beats/min): ver=69; plac=87(p<0.01) Mean maximal heart rate attained(beats/min): ver=104; plac=136(p<0.01) Change from baseline to maximal heart rate: ver=35; plac=49(p<0.01) >/= 15% reduction in exercise-induced heart rate: ver=96.3%; plac=29.6%	NR	*Open ver titration phase* AE incidence: ver=12/30(40%) Facial flushing: 13.3% Peripheral edema: 10% Headaches: 10% Constipation: 10% *Double-blind phase* AE incidence: ver= 3/27(11.1%); plac=3/27(11.1%)	*Open ver titration phase:* Withdrawal: 1 patient due to edema/general bruising *Double-blind phase* Withdrawals NR	
Stern 1982 United States Fair	Withdrawn: Group 1=0; Group 2=1; Group 3=0/0 lost/analyzed=12 overall	Groups 1 and 2 *Resting HR* Group 1: plac=125; ver=87 Group 2: plac=90; ver=66 Groups 1+2: plac=108; ver=76 *Peak exercise HR* Group 1: plac=162; ver=126 Group 2: plac=126; ver=101 Groups 1+2: plac=144; ver=113 *Group 3* Attacks per month: plac=5.3; ver=4 Heart rate: plac=160; ver=72	NR	AEs(all during ver therapy): Symptomatic bradycardia: 1 patient Right upper quadrant pain/mild hepatomegaly: 1 patient Impotence/decreased libido: 2 patients	2/13(15.4%)	

Evidence Table 9. Supraventricular Arrhythmia Placebo Controlled Trials

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Tse 2001 China Fair	RCT Crossover	Patients treated with an Implantable Atrial Defibrillator (IAD) for symptomatic, recurrent AF	NR
Tse 2001 China Fair	Crossover trial, dil vs no drug therapy	Successful AV junction ablatin and pacemaker implantation (due to drug resistant paroxysmal AF with uncontrolled ver=ventricular rate)	Amiodarone within previous 3 months

Evidence Table 9. Supraventricular Arrhythmia Placebo Controlled Trials

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
Tse 2001 China Fair	Verapamil 240 mg daily Placebo x 8 weeks, then crossover	Antiarrhythmic agents (amiodarone=5; sotalol=2) IV midazolam for sedation during shock therapy as needed	IAD	Mean age: 60 Gender(%male): 81.8% Race NR	Mean AF duration(years): 32 years Cardiovascular disease: 54.5% HTN: 54.5% Mean left ventricular ejection fraction: 0.54 Mean left atrial diameter by ECG: 4.5	NR/NR/11 enrolled
Tse 2001 China Fair	dil 240mg daily no drug therapy x 3 months, then crossover	none	Mode switch event counter	mean age 71 40% male NR	Mean duration of paroxysmal AF: 60 months 35% with cardiovascular disease 35% essential HTN mean LVEF 0.58	NR/NR/20

Evidence Table 9. Supraventricular Arrhythmia Placebo Controlled Trials

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)	Comments
Tse 2001 China Fair	Withdrawn NR/Lost NR/Analyzed NR	Efficacy of cardioversion: ver=86%; plac=100% Mean number of atrial defibrillation shocks: ver=1.7; plac=1.8 Mean number of AF episodes: ver=8; plac=9.1 Mean duration of AF episodes(hours): ver=44; plac=45 Total duration of AF(hours): ver=418; plac=586 Median AF-free interval for first episode(hours): ver=262, plac=114 and second episode: ver=130; plac=104	NR	NR	NR	
Tse 2001 China Fair	0/0/16 or 19 depending on outcome	Number with persistent AF: dil 5%, no treatment 16% Of those with persistent AF: Mean number of mode switch episodes: dil 109, no treatment 97 % with > 254 mode switch episodes/3 months (exceeds pacemaker capacity to record): dil 25%, no treatment 69%	NR	NR	NR	

Evidence Table 10. Systolic Dysfunction Active Controlled Trials

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Suwa 1996 Poor	RCT Crossover (only under lack of efficacy conditions)	14-68 years; congestive heart failure; diagnosed nonischemic dilated cardiomyopathy after thorough evaluation including ECG, chest roentgenography, echocardiography, cardiac catheterization, endomyocardial biopsy.	NR	Diltiazem (dil) 5-120 mg daily Bisoprolol (bis) 0.5-5 mg daily *Inpatient* 6-week titration 4-week observed maintenance *Outpatient* x 9 months; non-responsive patients crossed over after 2-month washout
Schofer 1990 Fair	RCT	Symptoms of heart failure (NYHA class II or III) as the main reason for exercise limitation; global ejection fraction ≤40%; digitalis and diuretics for at least 3 months.	Significant hematopoietic, liver and renal dysfunction (serum creatinine >2 mg%.	Nisoldipine (nis) 20 mg daily Captopril (cap) 75 mg daily x 3 months

Evidence Table 10. Systolic Dysfunction Active Controlled Trials

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
Suwa 1996 Poor	NR	*"Response":* 1) improvement by more than one NYHA functional class; 2) LVFS increased to above 20% with a reduction in left ventricular dimension	Mean age: dil=54; bis=53 Gender(% male): dil=75%; bis=61.5% Race nr	*NYHA functional class(# pts/%)* III: dil=4/8(50%); bis=7/13(53.8%) IV: dil=4/8(50%); bis=6/13(46.1%) *LVEDD(mm):* dil=65; bis=69 *LVFS(%):* dil=13; bis=11	NR/NR/ Enrolled=18
Schofer 1990 Fair	NR	Standard exercise test 1, 4, 8 and 12 weeks	Mean age=55.4 75% male Race nr	NR	NR/NR/24

Evidence Table 10. Systolic Dysfunction Active Controlled Trials

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment	Adverse Effects Reported	Withdrawals due to adverse events
Suwa 1996 Poor	Withdrawn=5/18(27.8%)/ Lost to fu NR/Analyzed: dil=8; bis=10	"Response"(# pts; %): Overall group: dil=3/8(37.5%); bis=9/13(69%)(NS) Class III patients: dil=2/4(50%); bis=7/7(100%)(p<0.05) Class IV patients: dil=1/4(25%); bis=2/6(33%)(NS)	NR	NR	NR
Schofer 1990 Fair	nr/nr/24	Improvement of one NYHA functional class (# pts; %): nis=7/12(58.3%); cap=5/12(41.7%) NYHA functional class unchanged (# pts; %): nis=5/12(41.7%); cap=6/12(50%) Decline in NYHA functional class(# pts; %): nis=0; cap=1/12(8.3%)	NR	NR	NR

Evidence Table 10. Systolic Dysfunction Active Controlled Trials

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
de Vries 1995 Fair	RCT	Clinically stable chronic CHF (NYHA functional class II or III) while taking fixed oral medication for >4 weeks (except digoxin for >12 weeks); LVEF by radionuclide ventriculography <0.40 within previous 3 months; age 18-75; valid cardiopulmonary exercise test, limited by dyspnea or fatigue with peak oxygen consumption >10 and <20 $ml \cdot kg^{1} \cdot min^{-1}$; sinus rhythm.	Active myocarditis; obstructive cardiomyopathy, hemodynamically significant valvular disease; hypotension (systolic BP <100 mm Hg), MI; coronary angioplasty or cardiac surgery <3 months; severe obstructive pulmonary disease; known intolerance to study drugs; treatment with ACEIs or dihydropyridines within previous 6 months.	Felodipine (fel) 5-10 mg daily Enalapril (ena) 5-10 mg daily with goal of SBP </= 95 mm Hg
Agostoni 1986 Italy Fair to Poor	RCT Crossover	Chronic CHF caused by unknown dilated cardiomyopathy of unknown cause; capable of exercising for at least 3 and no more than 12 minutes on a treadmill.	Supine systolic BP <100 mm Hg; angina pectoris; history or ECG signs of MI; hepatic or renal impairment.	nifedipine (nif) 60mg daily captopril (cap) 150mg daily 2 months

Evidence Table 10. Systolic Dysfunction Active Controlled Trials

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
de Vries 1995 Fair	NR	Treadmill (modified Naughton) Ambulatory ECG Severe heart failure questionnaire Sleep dysfunction scale Psychological general well-being index x 2, 4, 8, and 12 weeks after randomization Questionnaire responses rated using 6-point scale (0=no; 5=very much)	Mean age: ena=65; fel=65 % male: ena=83; fel=86 Race nr	*Etiology of heart failure(%)* Coronary artery disease: ena=71; fel=82 Systemic hypertension: ena=5; fel=4 Idiopathic cardiomyopathy: ena=8; fel=0 *Duration of heart failure (mean yrs):* ena=2.5; fel=2.7 *NYHA Class(%)* II: ena=83; fel=73 III: ena=17; fel=27 *History of MI(%):* ena=71; fel=82 *Smoking history(%):* ena=67; fel=73 *History of diabetes mellitus(%):* ena=8; fel=9	NR/52 eligible/46 randomized
Agostoni 1986 Italy Fair to Poor	Vasodilators (nitrates) stopped. Digitalis and diuretics regimen kept constant through trial.	Exercise test (not described) at start of first period, then weekly	Mean age: 52.6 years % Male: 83% Race: NR	Cardiac symptoms for >2 years = 61% Dyspnoea for at least 10 months = 39% NYHA class IV = 61% NYHA class III = 39% baseline mean = NYHA Class 3.6	nr/26/26

Evidence Table 10. Systolic Dysfunction Active Controlled Trials

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment	Adverse Effects Reported	Withdrawals due to adverse events
de Vries 1995 Fair	NR/NR/46 analyzed	Exercise tolerance(s): fel=(+61); ena=(+64) *Quality of life (mean change in units)* *(estimates from graphic display of results)* Severe heart failure questionnaire: ena=(+0.2); fel=(+0.3) General well-being questionnaire: ena=(-0.1); fel=0 Sleep dysfunction: ena=0; fel=(+0.7)	NR	Overall incidence (# pts; %): fel=16/22(72.7%); ena=18/24(75%) Incidence of most common adverse events (%) Peripheral edema: ena=0; fel=23% Dizziness/vertigo: ena=14%; fel=9% Coughing: ena=11%; fel=9% Atrial fibrillation: ena=7%; fel=5%	NR
Agostoni 1986 Italy Fair to Poor	Withdrawn = 5 (19%) Lost = 3 (12%) Analyzed = 18/26 (69%)	Mean NYHA Class: nif = 3.6 cap = 3.1 (p<0.01) Mean change in exercise time nif = approx 10 sec cap = approx 270 sec (numbers taken from graph) 1 death occurred during nif treatment Subjective clinical assessment in diary - results nr	Clinical for hypotension; and patient report	Hypotension: nif = 3/26 (12%) cap = 2/26 (8%) Headache:nif = 5/18 (28%); cap 0 Palpitation: nif = 11/18 (61%); cap 0 Taste alteration: nif 0; cap 2/18 (11%) edema: nif 11/18 (61%), cap 0 increase in weight: nif 12/18 (67%), cap 0 Death: nif = 1/26 (4%)	Hypotension = 4/26 (15%) Death = 1/26 (4%)

Evidence Table 10. Systolic Dysfunction Active Controlled Trials

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Elkayam 1990 USA Fair	NYHA II-III	18-75 years; well-documented history of CHF at least 1 month in duration, symptoms being NYHA class II or III and LVEF <40%; capable of performing treadmill exercise testing and remaining clinically stable on constant maintenance dose of digitalis and diuretics during ≤2 week stabilization period.	Pregnancy; childbearing potential; currently nursing; history of acute MI within first month before study entry; primary valvular disease as a reason of symptoms; angina pectoris; cardiomyopathy other than dilated congestive cardiomyopathy; significant primary pulmonary, hepatic, renal or hematological disease; inability to give informed consent.	Nifedipine (nif)(n=15 completed) 80 mg ISDN (n=19 completed) 160 mg nif/ISDN (n=17 completed) nif 80 mg + ISDN 160mg 8 wks each x 3 crossover periods (n=28)

Evidence Table 10. Systolic Dysfunction Active Controlled Trials

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
Elkayam 1990 USA Fair	Digoxin and diuretics allowed initial diuretic dose held constant - CHF worsening treated with hydrochlorothiazide (50 mg per day) or metolazone (5 mg per day) x 3 days all other vasodilators discontinued during 2-wk stabilization period	Exercise treadmill test (ETT) to exhaustion at end of first week of stabilization period on placebo, and end of second week, at 2 and 4 hours after dose administration; repeated end of each 8-wk period.	Mean age: 55 89% Male Race: NR	CHF cause: coronary artery disease = 9/28 (32%) congestive cardiomyopathy = 19/28 (68%) NYHA class: II = 8/28 (29%) III = 20/28 (71%)	initial screening nr 51 began stabilization period to confirm eligibility 28 began randomized trial

Evidence Table 10. Systolic Dysfunction Active Controlled Trials

Author, Year Country	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment	Adverse Effects Reported	Withdrawals due to adverse events
Elkayam 1990 USA Fair	Stabilization period withdrawn total = 23/51 (45%) -noncompliance = 8 -ineligible = 6 -worsening heart failure = 4 -chronic obstructive pulmonary disease = 2 -angina limiting ETT = 2 -inability to walk on ETT = 1 Randomized phase withdrawn total = 5 - noncompliance = 2 - psychiatric disorder = 1 - lost to followup = 2 23 patients analyzed for adverse events; 3 withdrawn (for adverse events) before ETT and other tests at end of first 8-wk period	ETT in seconds: ISDN = 316 -> 398 nif = 316 -> 389 nif/ISDN = 316 -> 372 (within groups p<0.05, between groups NS)	NR	Hospitalized, worsening CHF: nif = 5/21 (24%) nif/ISDN = 6/23 (26%) ISDN = 0/20 Add diuretic, worsening CHF: nif = 3/21 (14%) nif/ISDN = 2/23 (9%) ISDN = 3/20 (15%) Total heart-failure worsening episodes: nif = 9, nif/ISDN = 21, ISDN = 3 Other adverse signs or symptoms: nif = 68% - esp. weakness (4), noncardiac leg edema (2), nausea (2), dizziness (2) nif/ISDN = 48% - esp. noncardiac leg edema (2), dizziness (2) ISDN=35%- esp. headache (4)	Did not complete first 8-wk test period: Total = 3/23 (13%) = worsening heart failure (2), death (1) Premature discontinuation of drug: nif = 29% = severe fatigue or worsening CHF (3), symptomatic orthostatic hypotension (1), severe leg edema and dizziness (1), sudden death (1) nif/ISDN = 19% (?- 3/23 is 13%) = symptomatic hypotension (1), sudden death (1), severe worsening of CHF and cardiopulmonary arrest (1) ISDN = 5% = symptomatic orthostatic hypotension (1)

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

Author, Year Country	Heart Failure Severity	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
New York Heart Association class I-II				
Russo 1998 Italy *Fair*	NYHA Class I or II	Ischemic, dilated cardiomyopathy; chronic, stable, mild CHF.	Acute MI within previous 12 months; unstable angina; arterial hypertension; atrial fibrillation or severe ventricular arrythmias; renal failure; recent acute cardiac decompensation; valvular disease or significant mitral regurgitation; cardiac anatomy not allowing satisfactory and reproducible ECG recordings; any other major disease.	Felodipine (fel) 5mg daily Placebo (pla) x 12 months

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

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
New York Heart Association class I-II						
Russo 1998 Italy *Fair*	Enalapril x 6 mos minimum ASA, antiarrhythmics allowed	NYHA Classification	*Felodipine:* Mean age: 56.4 *67% Male* *Race: NR* *Placebo:* Mean age: 57.4 73% Male Race: NR	74% NYHA Class II (Fel 67%, Pla 82%) Mean LVEF: 30%	NR/NR/23	0/0/23

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
New York Heart Association class I-II				
Russo 1998 Italy *Fair*	NYHA Class II: Fel 42% (mean change 25%) Pla 82% (mean change 0%)	NR	Dizziness due to hypotension and premalleolar edema Fel: 2/12 (17%) Pla 0	0

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

Author, Year Country	Heart Failure Severity	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
New York Heart Association class II-III				
V-HeFT III Boden, 1996 Cohn, 1997 Wong 2000 Smith 2000 USA *Good*	Moderate - NYHA II or III	Males >18 years; history and physical findings of heart failure, including limited exercise tolerance caused by dyspnea or fatigue plus documentation of ventricular enlargement or dysfunction if they exhibited reduction in peak exercise performance (<14 minutes on a treadmill, modified Naughton protocol) and had a radiographic cardiothoracic ratio of >0.55, echocardiographic LV internal dimension at end diastole >2.7 cm.m3, or resting LVEF of <0.45 by radionuclide scan or contrast ventriculogram.	clinically important renal, hepatic or hematologic disorders; sever obstructive bronchopulmonary disease; inability to perform exercise test due to causes other than heart failure; symptomatic hypotension; aortic or mitral stenosis; hypertrophic cardiomyopathy; sever aortic or mitral regurgitation; severe hypertension; hemodynamically significant pericardial disease; sever angina pectoris; acute MI, CABG or angioplasty within 3 months of screening; cerebrovascular accident within 6 months of screening; symptomatic or life-threatening arrythmias not controlled medically or by a defibrillator; allergy or intolerance to calcium antagonists; use of beta blockers, long acting nitrates or other vasodilators (except ACEIs); treatment with an investigational drug within 4 weeks of screening; other significant comorbidity that made survival or compliance with the protocol unlikely.	Felodipine ER (fel) 5mg daily x 2 wks, then 10mg daily if tolerated Placebo (pla) x 3 months minimum, up to 42 months Mean 18 months

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

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
New York Heart Association class II-III						
V-HeFT III Boden, 1996 Cohn, 1997 Wong 2000 Smith 2000 USA *Good*	Enalapril, digoxin and loop diuretic. First 144 enrolled also randomized to digoxin or placebo but later switched to all taking digoxin	Mortality Treadmill test (Naughton protocol) Quality of life (Minnesota Living with Heath Failure questionnaire) NYHA Functional class	*Felodipine:* Mean age: 63 Gender: NR Race: 74% White *Placebo:* Mean age: 64 Gender: NR Race: 72% White	NYHA Class: II 79% III: 21% CAD: 55% Tobacco use: fel 70%, pla 75% Diabetes: fel 26%, pla 34% LV ejection fraction: 0.30 Other meds: digoxin 76%, diuretics 89%, ACE inhibitors 97%	5890 screened 1127 eligible 450 enrolled	39 withdrawn (8.7%) overall fel 10%, pla 7.8% 0 lost to f/u 450 analyzed

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
New York Heart Association class II-III				
V-HeFT III Boden, 1996 Cohn, 1997 Wong 2000 Smith 2000 USA *Good*	<u>Mortality</u> fel 31/224 (13.8%), pla 29/226 (12.8%) RR 1.08 (95% CI 0.65, 1.79) CHF due to CAD: fel 15/128 (12%), pla 17/120 (14%) NS CHF due to non-CAD: fel 16/96 (17%), pla 12/106 (11%) NS Mortality also NS by NYHA class <u>Exercise duration:</u> Small increase (approx. 20 secs) in both groups in first 3 mos. No difference between groups until 15 months, then trend toward decreased exercise time in pla group (Difference approx. 75 secs, p = 0.01 at 27 months) but only 44 (fel) and 42 (pla) patients evaluable at 27 months. <u>QOL:</u> Both groups show decline in QOL over time. No difference at baseline or until 9 months, then a trend towards lower scores in pla group (Difference of 6 points on MLWHF scale, p = 0.038 at 27 months) but only 52 (fel) and 50 (pla) patients evaluable at 27 months NHYA: reported as no significant difference in change between groups, data not presented. Hospitalization: NYHA Class III: fel 19/48 (40%), pla 26/45 (58%) p = 0.038, Not ITT	NR	Edema fel 21%, pla 13% (p = 0.02) nausea fel 6%, pla 7% fatigue fel 12%, pla 7% chest pain fel 9%, pla 12% hypotension fel 6.3%, pla 5.3% dizziness fel 16.1%, pla 14.6%	Overall withdrawal fel 10%, pla 7.8% - reasons not reported

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

Author, Year Country	Heart Failure Severity	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Udelson 2000 USA *Fair*	NYHA Class II-IV	≥18 years; clinical diagnosis of stable chronic heart failure for 3+ months; NYHA class II, III or IV; receiving treatment with digoxin, diuretics or ACEIs at stable doses for at least 2 months; LVEF of ≤35%.	Heart failure of predominant diastolic cause; unstable angina; inability to exercise; systolic BP <85 mm Hg or >160 mm Hg; history of resuscitation from sudden death or sustained ventricular tachycardia; serum creatinine level >3.0 mg/dL; severe primary lung disease that would limit exercise tolerance; need for treatment with vasodilators, other calcium channel blockers or beta blockers; antiarrhythmic therapy.	Protocol 174 amlodipine 5-10 mg daily (titrated) placebo Protocol 175 amlodipine 10 mg daily (not titrated) placebo 12 weeks

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

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
Udelson 2000 USA *Fair*	<u>Protocol 174</u> Digoxin Diuretics ACE inhibitors (only if tolerated) <u>Protocol 175</u> Digoxin Diuretics ACE inhibitors (required)	*Exercise* : Treadmill (Naughton protocol) and 6-minute walk test *NYHA classification* *Quality of life* : Living with Heart Failure questionnaire; Health Perception Scale; Alertness Behavior Scale; # of bed days	Protocol 174/Protocol 175/Pooled Amlodipine: Mean age: aml=63/63/63 % male: aml=78/78/78 Placebo: Mean age: pla=66/64/65 % male: pla=72/78/75	Values are expressed as Protocol 174/Protocol 175/Pooled CHF etiology(%) CAD: aml=60/51/55; pla=58/47/51 DCM: aml=35/40/38; pla=39/48/44 Other: aml=5/9/7; pla=3/5/5 History of MI(%) aml=43/50/47; pla=56/44/49 Background therapy(%) ACEI: aml=82/100/92; pla=84/100/93 Digitalis: aml=90/100/96; pla=87/100/94 Diuretic: aml=87/100/94; pla=87/100/95 Triple therapy: aml=66/100/85; pla=66/100/86	nr/784 eligible/437 randomized	nr/nr/437 analyzed

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Udelson 2000 USA *Fair*	Values are expressed as Protocol 174/Protocol 175/Pooled Exercise time(s): aml=(+63)/(+44)/(+53); pla=(+61)/(+69)/(+66)(NS) 6-minute walk distance(yards): aml=(+7)/(+7)/(+7); pla=(+17)/(+10)/(+13)(NS) Pooled only (aml n=208; pla n=216) (per protocol analysis) NYHA class change % improved at least 1 class: aml=16; pla=15 % worsening by at least 1 class: aml=8; pla=9 no change: aml=24.5; pla=76.4 Symptom score: data nr; aml=pla Living with Heart Failure questionnaire: data nr; aml=pla Health Perception Scale: data nr; aml=pla Alertness Behavior: data nr; aml=pla Bed days: data nr; aml=pla	NR	Pooled analysis: aml n=214; pla n=223 Overall adverse event incidence: aml=28(13%); pla=17(8%) Edema incidence: aml=17(7.9%); pla=7(3.1%) Change in body weight: data nr; aml=pla Worsening CHF(# pts; % in protocol 174/protocol 175/pooled): aml=10(10.6)/11(9.2%)/21(9.8%); pla=3(3.1%)/11(8.8%)/14(6.3%) Mortality(# pts; % in protocol 174/protocol 175/pooled): aml=1(1.1%)/2(1.7%)/3(1.4%); pla=1(1.0%)/0/1(0.4%)	Discontinued study due to worsening CHF(# pts; % in protocol 174/protocol 175/pooled): aml=4(4.2%)/3(2.5%)/7(3.3%); pla=2(2.0%)/3(2.4%)/5(2.2%)

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

Author, Year Country	Heart Failure Severity	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Littler 1995 UK *Poor*	NYHA Class(%) II-IV	18-75 years; LVEF ≤40%; heart failure stable during preceding 2 months caused by ischemic heart disease, hypertensive heart disease or dilated cardiomyopathy with or without secondary mitral insufficiency; subjective and objective evidence of reduced effort tolerance despite treatment for at least 2 months with an ACE-Inhibitors, diuretic or digoxin or any combination of these.	Exercise limited by claudication; unstable angina pectoris; MI; coronary bypass surgery or angioplasty within previous 3 months; significant obstructive pulmonary disease limiting exercise capACE-Inhibitory; uncontrolled atrial or ventricular arrhythmic within previous 4 weeks; systolic BP <100 mm Hg; diastolic BP > 114 mm Hg; medication with vasodilators which could not be withdrawn two weeks before entry; severe concomitant disease interfering with assessment; primary liver or renal disorder; abnormal laboratory findings suggesting unstable disease; known intolerance to dihydropyridines; child bearing potential; conditions associated with poor compliance.	Felodipine ER (fel-ER) 5 mg daily Placebo (pla) Single blind run-in x 2 weeks; then 12-weeks active treatment
van den Toren 1996 The Netherlands *Poor*	NYHA Class II-III	Mild to moderate CHF, NYHA class II-III due to documented coronary artery disease; MI >3 months previous; LVEF ≤0.40; sinus rhythm; peak VO2 <20mlO2/kg/min.	Clinically significant obstructive valvular disease; obstructive or restrictive heart disease; recent (<3 months) MI or CABG; significant renal, hepatic, pulmonary, psychiatric or other illness.	Isradipine (isr) 7.5-15 mg daily Placebo (pla) x 12 weeks First dose iv to study hemodynamic effects; then oral

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

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
Littler 1995 UK *Poor*	Any combination of angiotensin converting enzyme (ACE) inhibitor, diuretic or digoxin ACEI treatment(%): fel-ER=61; pla=61	Treadmill (Naughton protocol)	*Felodipine:* Mean age: 62 80% Male Race: NR *Placebo:* Mean age: 62.2 87% Male Race: NR	Etiology(%) Ischemic heart disease: fel-ER=77; pla=75 Dilated cardiomyopathy: fel-ER=20.3; pla=20.7 Mean duration of diagnosis(months): fel-ER=29.1; pla=42.4 Mean LVEF: fel-ER=25.6; pla=27.6	nr/322 eligible/252 randomized	Withdrawn: 56/252(22.2%)/0 lost to fu/Analyzed(Efficacy/Safety): fel-ER=113/132; pla=111/120
van den Toren 1996 The Netherlands *Poor*	Digoxin Diuretics Sodium restricted to 3 grams daily	Treadmill (modified Naughton protocol) to dyspnea or fatigue Follow-up visits every 2 weeks	Mean age 56 84% male Race nr	Mean LVEF=0.18	nr/nr/19 enrolled	Withdrawn=2(10.5%)/0 lost to fu/17 analyzed

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Littler 1995 UK *Poor*	Improvement in exercise time(s): fel-ER=(+107); pla=(+128)	Adverse event defined as any unfavourable, unintended event temporally associated with the administration of the study drug irrespective of whether or not it was considered to be drug related	Overall incidence(# pts; %): fel-ER=101/132(76.5%); pla=84/120(70%) Incidence of most common AE's (# pts; %) *fel-ER n=132; pla n=120* Death: fel-ER=3(2.3); pla=2(1.7) Edema: fel-ER=31(23); pla=6(5) Dyspnea: fel-ER=19(14); pla=13(11) Dizziness/vertigo: fel-ER=10(8); pla=13(11) Angina(new or aggravated): fel-ER=13(10); pla=8(7)	Fel-ER: 29/132(21.9%) Pla=17/120(14.2%)
van den Toren 1996 The Netherlands *Poor*	Data nr From narrative: Body weight: isr=pla Diuretic use: isr=pla Functional class: isr=pla	NR	Data nr From narrative: Adverse event incidence: isr=pla	nr

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

Author, Year Country	Heart Failure Severity	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Kukin 1999 USA *Poor*	NYHA II-IV	>18 years; symptomatic heart failure (NYHA class II-IV) despite diuretics, digoxin and ACE-Inhibitor therapy; nuclear LVEF <30%, left ventricular filling pressure of ≥14mm Hg	MI within 6 weeks; active angina requiring therapy; obstructive valvular disease; systolic BP <85 mm Hg; serum creatinine >3.5 mg/dL; asthma; known allergies to study medications; taking calcium channel blockers or long-acting nitrates.	Metoprolol (met)(n=14) Day 1 = 6.25 mg metoprolol+amlodipine (m/aml)(n=15) = met 6.25 mg + 10 mg aml Day 2 = met 6.25 mg twice daily both groups. Followup visits over 4 weeks = reduced, maintained or increased met to 12.5 mg, 25 mg and 50 mg x twice daily as tolerated; mL remains 10 mg x 3 months

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

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
Kukin 1999 USA *Poor*	Prior heart medications and diuretics	NYHA classifications and 6-minute walking test - baseline to 3-month outcome	Metoprolol plus amlodipine: Mean age: 50.9 93% Male Race: NR Metoprolol alone: Mean age: 48.8 78% Male Race: NR	CAUSE OF HEART FAILURE ischemic met = 3/14 (21%) m/aml = 6/15 (40%) idiopathic met = 11/14 (79%) m/aml 8/15 (53%) valvular met = 0 m/aml = 1/15 (7%) NYHA Class - II: met = 2/14 (14%) m/aml = 1/15 (7%) III: met = 9/14 (64%) m/aml = 14/15 (93%) IV: met = 3/14 (21%) m/aml = 0 met group had worse overall hemodynamic profile at baseline	nr/nr/29	overall 8/29 (28%) withdrawn met = 3/14 (21%) m/aml = 5/15 (33%) 8 lost 21 analyzed

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Kukin 1999 USA *Poor*	NYHA Class(I/II/III/IV) improved both groups: met = (0/2/7/2) -> (3/6/2/0) m/aml = (0/1/9/0) -> (3/6/1/0) Significant exercise improvement within groups (NS between groups) - 6-min walking test: met = 1194 ft baseline + 191 ft m/aml = 1137 ft baseline + 165 ft	NR	met = 1 death 1 persistent heart failure symptoms w/ transplant 1 reactive airway disease m/aml = 2 deaths (1 hospitalized for worsening CHF during uptitration) 3 increased symptoms of fatigue or intolerance of meds (1 hospitalized for worsening CHF during uptitration)	met = 3/14 (21%) m/aml = 5/15 (33%) overall 8/29 (28%)

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

Author, Year Country	Heart Failure Severity	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
New York Heart Association class III-IV				
PRAISE Packer, 1996 O'Connor, 1998 USA *Fair*	NYHA IIIb or IV	Dyspnea or fatigue at rest or on minimal exertion (NYHA class IIIB or IV); LVEF of <30% despite digoxin, diuretics and an ACE-Inhibitor; no intravenous diuretics or vasodilators within 24 hours before enrollment or intravenous positive inotropic agents within 72 hours.	Uncorrected primary valvular disease; active myocarditis; constrictive pericarditis; history of cardiac arrest or had sustained ventricular tachycardia or fibrillation within previous year; unstable angina or an acute MI within previous month; cardiac revascularization procedure or stroke within previous 3 months; severe pulmonary, renal or hepatic disease; systolic BP <85mm Hg or >159 mm Hg; diastolic BP >89 mm Hg; serum creatinine concentration >3.0 mg per deciliter; potassium concentration <3.5 or >5.5 mmol per liter; treatment with beta blockers, calcium channel blockers or class IC antiarrhythmic agents.	Amlodipine (aml) 5mg daily x 2 wks, then 10mg daily placebo daily (pla) x 6 to 33 months

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

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
New York Heart Association class III-IV						
PRAISE Packer, 1996 O'Connor, 1998 USA *Fair*	Digoxin, diuretic, ACE inhibitors,	Primary outcome: Combined all cause mortality and cardiovascular morbidity (hospitalization for at least 24 hrs for: acute pulmonary edema, severe hypoperfusion, acute MI, sustained or hemodynamically destabilizing ventricular tachycardia or fibrillation) Secondary outcomes: All cause mortality	*Amlodipine:* Mean age: 64.7 74% Male Race: NR *Placebo:* Mean age: 64.7 78% Male Race: NR	NYHA Class: III 81% IV: 19% LV ejection fraction: 0.21 Other meds: digoxin 99%, diuretics 100%, ACE inhibitors 99% randomization stratified by ischemic heart disease and non-ischemic dilated cardiomyopathy	NR/NR/1153	176/0/1153

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
New York Heart Association class III-IV				
PRAISE Packer, 1996 O'Connor, 1998 USA *Fair*	**Fatal or non-fatal event:** aml: 222/571 (39%) pla: 246/582 (42%) Risk difference -3% (95% CI -9, 2.2) Ischemic heart disease strata: 45% in both groups (NS) Nonischemic Cardiomyopathy strata: aml 58/209 (27.8%) pla 78/212 (36.8%) Risk difference: -9% (95% CI -17.9,-0.1) **All cause mortality:** aml: 190/571 (33%) pla: 223/582 (38%) Risk difference -5% (95% CI -10.5, 0.5) Ischemic heart disease strata: 40% in both groups (NS) Nonischemic Cardiomyopathy strata: aml 45/209 (21.5%) pla 74/212 (34.9%) Risk difference: -13.4% (95% CI -21.8,-4.8) Subgroup analyses underpowered.	NR	Total reported events: aml 2576 pla 1599 Cardiovascular disorders most commonly reported in both groups (includes markers of progression of CHF) Peripheral edema: aml 156 (27%), pla 103 (18%)p< 0.05 Pulmonary edema aml 85 (15%), pla 58 (10%) p< 0.05	Withdrawals due to adverse events: aml 5 (0.88%), pla 16 (2.7%) p=0.02

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

Author, Year Country	Heart Failure Severity	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Benatar 1998 USA *Poor*	NYHA Class III and IV	History of CHF in the preceding 6 months; age 21-79; NYHA class III or IV; third heart sound; physical findings consistent with CHF; cardiomegaly on chest x-ray; EF ≤35%; stabilized on digoxin, furosemide, and captopril.	Congenital, valvular, hypertropic heart disease; Hypotension (BP <90 mmHg); pregnancy or lactation; unstable angina, acute myocardial infarction, transient ischemic attack, stoke within 3 months prior to the study; atrial-ventricular block greater than first degree or high ventricular ectopy; left ventricular aneurysm; antiarrhythmic agents (other than Class I agents); diabetes, significant renal, hepatic, or hematological disorders; primary pulmonary hypertension.	Nicardipine (Nic) 60 - 90mg/d titration not described Placebo three times daily x 4 months
Kassis 1990 Denmark *Fair*	NYHA Class III	41-68 years; severe CHF (NYHA class III) despite treatment with digoxin and diuretics; past history of MI; ECG evidence of myocardial dyssynergy.	MI within 3 months; systolic BP <100 mm Hg; angiographic ejection fraction of >30%.	Felodipine (fel) 10-20 mg daily Placebo (pla) with goal of SBP </= 90 mm Hg x 6 months

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

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
Benatar 1998 USA *Poor*	Captopril, digoxin, and furosemide required	Exercise tolerance: Treadmill test (Naughton protocol) and 6-minute walk test CHF deterioration recorded based on symptoms, physical exam, and increasing dose of diuretic and/or hospitalization	Mean age: 55 ± 13 years % Male: 95 Race: NR	Ischemic cause of CHF: 30% idiopathic cause of CHF: 55% Hypertension cause of CHF: 15% Ventricular ejection fraction: Nic 17%, pla 20	NR/NR/20	Withdrawn: 40% (nic 40%, pla 40%) lost to f/u : 1 (pla) Analyzed: differs by outcome: CHF worsening n = 20, Treadmill n = 5, walk test n = 8
Kassis 1990 Denmark *Fair*	Digoxin Diuretics	Primary endpoint: self-assessment: better. no change. worse Secondary endpoint: death	*Felodipine:* Mean age: 54.6 Gender: NR Race: NR *Placebo:* Mean age: 52.5 Gender: NR Race: NR	Symptom duration(months): fel=16.7; pla=15.5 Previous MI(no.): fel=1.7; pla=1.6 LVEF(%): fel=25; pla=26	nr/nr/20 enrolled	

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Benatar 1998 USA *Poor*	Mean change in Treadmill exercise time: Nic 34 sec, Pla -23 sec (mean diff = 57 sec) Mean change in 6-minute walk test: Nic +189 feet, Pla +277 feet (mean diff = 88 ft) Proportion with worsening CHF: Nic 6/10 (60%), Pla 2/10 (20%) p = 0.06	NR	NR	NR
Kassis 1990 Denmark *Fair*	<u>Death (# pts; %)</u> fel=5/10(50%) pla=3/10(30%) (NS) <u>Subjective improvement</u> Felt better: fel=5/5(100%); pla=2/7(28.6%) No change: fel=0; pla=2/7(28.6%) Felt worse: fel=0; pla=3/7(42.8%)	NR	NR	nr

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

Author, Year Country	Heart Failure Severity	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Dunselman 1989, 1990 The Netherlands *Fair*	NYHA class III	CHF caused by coronary artery disease documented by MI <3 months previous; NYHA class III; sinus rhythm; regimen of digitalis & diuretics for 2+ months	NR	Felodipine (fel) 1 mg iv as inpatient x 3 days; 10-20 mg daily orally as outpatient x 8 weeks Placebo (pla) SBP goal </= 90 mm Hg

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

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
Dunselman 1989, 1990 The Netherlands *Fair*	NR	Treadmill Patient assessment of improvement: scale 1-7 (1 = markedly worse, 7 = markedly improved)	Felodipine: Mean age: 62 82% Male Race: NR Placebo: Mean age: 59 50% Male Race: NR	LVEF(%): fel=27; pla=26 Exercise duration(s): fel=587; pla=525	nr/nr/23 enrolled	0 withdrawn/0 lost to fu/23 analyzed

Evidence Table 11. Systolic Dysfunction Placebo Controlled Trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Dunselman 1989, 1990 The Netherlands *Fair*	Increase in exercise duration(s): pla=(+30); fel=(+155)(p<0.05) Subjective improvement(7-grade scale) at 2 weeks: fel=2.7; pla=4.1(p<0.05) at 4 weeks: fel=2.7; pla=4.4(p<0.05) at 6 weeks: fel=2.6; pla=4.3(p<0.01) at 8 weeks: fel=2.9; pla=4.4(p<0.01)	NR	Dose reduction due to severe AE's(%): fel=27.3; pla=8.3 Most common AE's(mild+severe)(# pts; %) Peripheral edema: fel=4/36.4; pla=3/16.7 Flushing: fel=3/27.3; pla=0 Tachycardia: fel=2/18.2; pla=0 Palpitations: fel=1/9.1; pla=0 Dizziness: fel=1/9.1; pla=0 Blurred vision: fel=1/9.1; pla=0 Muscle weakness: fel=1/9.1; pla=2/16.7 Fatigue: fel=0; pla=1/8.3 Insomnia: fel=0; pla=3/25 Pruritus: fel=0; pla=2/16.7 Nausea: fel=0; pla=2/16.7 Conjunctivitis: fel=0; pla=1/8.3 Sweating: fel=0; pla=1/8.3	nr

Evidence Table 12. Adverse Events in Active Controlled Trials of Essential Hypertension

Study, Author, Year Country	Interventions (drug, regimen, duration, n)	Allowed other medications/ interventions	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Amlodipine				
AASK Agodoa, 2001 Wright, 2002 US	aml 5 to 10 mg daily, n=194 ram 2.5 to 10 mg daily, n=400 met 50 to 200 mg daily, n=411	Addition of in order furosemide, doxazosin mesylate, clonidine hydrochloride, hydralazine hydrochloride, minoxidil to maximum tolerated dose before adding next agent	NR	NR
ALLHAT, Furberg, 2002 Grimm, 2001 Vidt, 2000 US	Amlodipine (aml) 2.5 to 10 mg daily, n=15,255 Lisinopril (lis) 10 to 40 mg daily, n=9048 Chlorthalidone (chl) 12.5 to 25 mg daily, n=9054 Doxazosin (dox) 2 to 8 mg daily, n=8619 No other antihypertensive initially after randomization	Addition of Step 2: ate 25-100 mg/d, Step 2: clo 0.2 to 0.6 mg daily Step 2: res 0.05 to 0.2 mg daily Step 3: hyd 50 to 200 mg daily Other drugs at physician's discretion	6 year rate per 100 patients(se) aml cancer 10.0 (0.4) gastrointestinal bleeds 8.0 (0.4) chl cancer 9.7 (0.3) gastrointestinal bleeds 8.8 (0.3) lis cancer 9.9 (0.4) gastrointestinal bleeds 9.6 (0.4)	aml (27%,2409/9048) chl (27%,4108/15255) lis (36%,3241/9054)
FACET Tatti, 1998 Pahor, 1998 Italy	aml 10 mg daily, n=191 fos 20 mg daily, n=189 If BP not at goal, other study drug at full dose also given.	None	NR	Withdrawals reasons not stated aml 52/191 fos 36/189

Evidence Table 12. Adverse Events in Active Controlled Trials of Essential Hypertension

Study, Author, Year Country	Interventions (drug, regimen, duration, n)	Allowed other medications/ interventions	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
VALUE Julius 2004 Multinational (US and Europe)	isradipine 5 mg or spirapril 6 mg daily, or spirapril 3 mg plus isradipine 2.5 mg	None	Valsartan vs amlodipine Prespecified Adverse Events: Peripheral edema: 14.9% vs 32.9% (p<0.0001) Dizziness: 16.5% vs 14.3% (p<0.0001) Headache: 14.7% vs 12.5% (p<0.0001) Fatigue: 9.7% vs 8.9% (p<0.0001) Additional Common Adverse Events: Diarrhea: 8.8% vs 6.8% (p<0.0001) Angina: 9.3% vs 6.4% (p<0.0001) Serious angina: 4.4% vs 3.1% (p<0.0001) Edema other: 3.2% vs 6.1% (p<0.0001) Hypokalemia: 3.5% vs 6.2% (p<0.0001) Atrial fibrillation: 2.4% vs 2.0% (p=0.1197) Syncope: 1.7% vs 1.0% (p<0.0001)	11.9% valsartan, 12.9% amlodipine
Lewis 2001 Berl 2003 International Irbesartan Diabetic Nephropathy Trial (IDNT)	Amlodipine (aml) 2.5 to 10 mg daily, n=567 Irbesartan (irb) 75 to 300 mg daily, n=579 Placebo (pla), n=569 Mean duration=932 days	Antihypertensive agents other than ACE-Is, ARBS, and CCBs were used as needed in each group	NR	Overall withdrawals due to adverse events: NR Withdrawal due to hyperkalemia: aml=3 (0.5%) vs irb=11 (1.9%) (p=0.01 for both comparisons) vs pla=2 (0.4%)
Nicardipine				

Evidence Table 12. Adverse Events in Active Controlled Trials of Essential Hypertension

Study, Author, Year Country	Interventions (drug, regimen, duration, n)	Allowed other medications/ interventions	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
NICS-EH NICS-EH Study Group 1999 Kuwajima 2001 Kuramoto 1994 Ogihara 2000, Tokyo	nic 40 mg sustained release daily, n=215 tri 2 mg daily, n=214 Doubling of study medication as needed	None	Nic 6/215 (2.8%) Tri 9/214 (4.2%)	5 year followup Nic headache1/204 (0.5%) fatigue 0/204 (0,0%) rash 1/204 (0.5%) joint pain 1/204 (0.5%) gastrointestinal complaint 1/204 (0.5%) Tri headache1/210 (0.5%) fatigue 2/210 (1.0%) rash 2/210 (1.0%) joint pain 0/204 (0.0%) gastrointestinal complaint 1/204 (0.5%)

Evidence Table 12. Adverse Events in Active Controlled Trials of Essential Hypertension

Study, Author, Year Country	Interventions (drug, regimen, duration, n)	Allowed other medications/ interventions	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Nifedipine				
Marin, 2001 Spain	Fos 10-30 mg daily *(n=129)* Nif GITS 30-60 mg daily *(n=112)* *+lifestyle modifications:* moderate sodium restriction (4-8 g/day of salt) protein intake around 0.8-1 g/kg per day	BP goal: <140/90 mmHg Step 2: Furosemide up to 100 mg daily Step 3: Atenolol up to 100 mg daily Step 4: Doxazosin up to 12 mg daily	Most common AEs and overall incidence NR	Cancer: Fos=1; Nif GITS=1 Edema(%): Fos=0.8; Ni GITS=8.9 Hyperkalemia: Fos=4.6; Nif GITS=0 Impaired renal function: Fos=3.1; Nif GITS=0.9 Cough: Fos=2.3; Nif GITS=0
Chan, 1992 Chan, 2000 Hong Kong	ena 10-40 mg daily, n=41 Modified Release Nifedipine (Nif) 40-80 mg daily x one year, n=49	*Target supine SBP:* < 140 mmHg Step 2: Indapamide 2.5 mg daily Step 3: Frusemide up to 120 mg daily *replacing* Indapamide *Additional, unspecified antihypertensive drugs were used as well, with the exception of ACEI in the Nif group*		*Ena* Overall withdrawals due to AEs: 3/50(6%), all due to cough *Nif* Overall withdrawals due to AEs: 0

Evidence Table 12. Adverse Events in Active Controlled Trials of Essential Hypertension

Study, Author, Year Country	Interventions (drug, regimen, duration, n)	Allowed other medications/ interventions	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
INSIGHT (International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment) Brown, 1996 Brown, 1997 Mancia, 1998 Brown, 2000 Brown, 2001 Brown, 2001 UK, France, Israel, Netherlands, Spain, Italy, Sweden, Denmark, Norway	Nifedipine GITS (Nif GITS) 30-60 mg daily, n=3157 Amiloride/HCTZ 2.5/25 (Co-ami - 5/50 mg daily, n=3164 3-year treatment period	Step 2: atenolol 25-50 mg or enalapril 5-10 mg (if beta-blockers are contraindicated) Step 3: unspecified additional antihypertensive drug (chosen by investigator); with the exclusion of diuretics in the Nif GITS group and calcium antagonists in the Ami/HCTZ group	*Serious AEs(%):* Nif GITS=25; Co-ami=28 *Most commonly reported AEs(%)* Edema: Nif GITS=28; Co-ami=4.3 Syncope: Nif GITS=1.5; Co-ami=2.8 Headache: Nif GITS=12; Co-ami=9.2 Palpitation: Nif GITS=2.5; Co-ami=2.7 Peripheral vascular disorder: Nif GITS=3.0; Co-ami=5.3 Impotence: Nif GITS=1.6; Co-ami=1.9 Flushing: Nif GITS=4.3; Co-ami=2.3 Diabetes: Nif GITS=3.0; Co-ami=4.3 Dizziness: Nif GITS=8.0; Co-ami=10.0 Gout: Nif GITS=1.3; Co-ami=2.1 Accidental injury: Nif GITS=1.2; Co-ami=2.2 Depression: Nif GITS=3.9; Co-ami=5.7 Hypokalemia: Nif GITS=1.9; Co-ami=6.2 Hyponatremia: Nif GITS=0.2; Co-ami=1.9 Hyperlipidemia: Nif GITS=4; Co-ami=6.3 Hyperglycemia: Nif GITS=5.6; Co-ami=7.7 Hyperuricemia: Nif GITS=1.3; Co-ami=6.4 Impaired renal function: Nif GITS=1.8; Co-ami=4.6	Per-protocol analysis: Any AE(%): Nif GITS=539/3157(17.1%); Co-ami=304/3164(9.6%) Serious AE(%): Nif GITS=6.3; Co-ami=7.7 Peripheral edema(%): Nif GITS=8.4; Co-ami=0.4 Headache(%): Nif GITS=1.9; Co-ami=1.0 Flushing(%): Nif GITS=1.3; Co-ami=0.6 Dizziness(%): Nif GITS=0.7; Co-ami=0.5

Evidence Table 12. Adverse Events in Active Controlled Trials of Essential Hypertension

Study, Author, Year Country	Interventions (drug, regimen, duration, n)	Allowed other medications/ interventions	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
JMIC-B Yui, 2004a Japan	nifedipine retard 10mg-20 mg or an ACE inhibitor (enalapril 5-10 mg, imidapril 5-10 mg, or lisinopril 10-20 mg) for 3 years.	If BP reduction was unsatisfactory, an alpha blocker (doxazosin, bunazosin, or prazosin) was administered concomitantly. If the antianginal effect of the treatment was inadequate, long-acting or short-acting nitrates and/or beta blockers were used concomitantly.	76 nifedipine, 121 ACE inhibitors. Major adverse events occurring in the nifedipine group were those related to vasodilatory effect, including hypotension, facial erythema, and hot flushes. Dry cough accounted for most of the adverse events occurring in the ACE inhibitor group.	nifedipine (n=828) vs amlodipine (n=822), n (%) withdrawn due to AEs: Hypotension: 8 (1.0%) vs 2 (0.2%) (p<0.01) Palpitations, tachycardia: 7 (0.8%) vs 0 (p<0.01) Edema: 7 (0.8%) vs 0 (p<0.01) Facial erythema, hot flushes: 6 (0.7%) vs 0 (p<0.05) Dry cough: 0 vs 60 (7.3%) (p<0.01) Headache, dull headache: 3 (0.4%) vs 3 (0.4%) Gingival hypertrophy: 3 (0.4%) vs 1 (0.1%) Digestive, intestinal disorder: 2 (0.2%) vs 3 (0.4%) Malaise, fatigue: 3 (0.4%) vs 0 Others: 2 (0.2%) vs 3 (0.4%) Total: 41 (5.0%) vs 72 (8.8%) (p<0.01)

Evidence Table 12. Adverse Events in Active Controlled Trials of Essential Hypertension

Study, Author, Year Country	Interventions (drug, regimen, duration, n)	Allowed other medications/ interventions	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Diltiazem				
NORDIL (Nordic Diltiazem Study) The NORDIL Group, 1993 Hedner, 1999 Hansson, 2000 Kjeldsen, 2002 Norway/ Sweden	Diltiazem (Dil) 180-360 mg daily; short-acting formulation used initially; replace by a longer-acting formulation in 1997, n=5410 Non-calcium antagonist group: Beta-blockers or diuretics used as first-line therapy (Conventional treatment=Con), n=5471	*Goal DBP: </= 90 mmHg* <u>Diltiazem group</u> Step 2: Dil dose increment Step 3: Other antihypertensive drug add-on (preferably ACE inhibitors) Step 4: Diuretics <u>Conventional treatment group</u>: Step 2: Combined thiazide diuretic/beta-blocker Step 3: Other antihypertensive drug add-on (preferably beta-blocker and diuretic) Step 4: Other drugs added, with exception of calcium antagonists	Most frequently reported AEs(%) Dizziness: Dil=9.3; Con=8.9 Arthralgia: Dil=7.7; Con=7.1 Headaches: Dil=8.5; Con=5.7 Chest discomfort: Dil=5.7; Con=5.9 Coughing: Dil=5.6; Con=5.4 Fatigue: Dil=4.4; Con=6.5 Back pain: Dil=4.7; Con=5.4 Depression: Dil=3.7; Con=3.4 Abdominal pain: Dil=3.5; Con=3.4 Dyspnea: Dil=2.9; Con=3.9 Myalgia: Dil=3.2; Con=3.4 Impotence: Dil=2.3; Con=3.7 Diabetes mellitus: Dil=3.9; Con=4.6	NR
Nisoldipine				
ABCD (Appropriate Blood Pressure Control in Diabetes) Savage, 1993 Schrier, 1996 Estacio, 1998a Estacio, 1998b United States	Nis 10-60 mg daily, n=235 Ena 5-40 mg daily, n=235	*Intensive goal:* DBP=75.0 mmHg *Moderate goal:* DBP=89.0 mmHg *Open-blind medications in stepwise order:* Metoprolol 100-200 mg daily HCTZ 12.5-25 mg daily Clonidine 0.2-0.6 mg daily Doxazosin 1-16 mg daily Minoxidil 5-40 mg daily Additional antihypertensive medications were added at the discretion of the medical director, but these did not include a calcium-channel blocker or ACE inhibitor	Incidence NR	Total withdrawals due to AEs: Nis=54(22.9%); Ena=41(17.4%) Edema withdrawals: Nis=20(8.5%); Ena=11(4.7%) Headache withdrawals: Nis=10(4.2%); Ena=1(0.4%)

Evidence Table 12. Adverse Events in Active Controlled Trials of Essential Hypertension

Study, Author, Year Country	Interventions (drug, regimen, duration, n)	Allowed other medications/ interventions	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Isradipine				
The MIDAS Research Group, 1989 Borhani, 1990 Borhani, 1991 Borhani, 1992 Furberg, 1993 Borhani, 1996 United States *Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS)*	Isr 5-10 mg daily, n=442 HCTZ 25-50 mg dailyn=441	*Goal DBP:* For patients with DBP </= 105 at baseline=a reduction of at least 10 mmHg and DBP<90 mmHg; For patients with DBP between 105 and 115 mmHg at baseline=a reduction of at least 10 mmHg and DBP<95 mmHg Open-label Enalapril 5-20 mg daily	Severe adverse event incidence: Isr=183(41.1%); HCTZ=172(39.0%) Chest pain: Isr=0.7%; HCTZ=0.8% Other cardiovascular-related adverse reactions: Isr=3.0%; HCTZ=0.9% Central nervous system adverse reactions: Isr=6.2%; HCTZ=4.4% (primarily due to more reports of headaches in the Isr groupx Kidney stones: Isr=0.4%; HCTZ=0.0% Headache: Isr=2.2%; HCTZ=1.1% Faintness: Isr=0.0%; HCTZ=0.4%	*3-year cumulative incidence* Isr=9.3% HCTZ=8.2%
Petersen, 2001 Denmark	isradipine 5 mg or spirapril 6 mg daily, or spirapril 3 mg plus isradipine 2.5 mg	14 patients were on a protein-controlled diet because their serum creatinine level increased to more than 500 mol/l; 5 patients received erythropoietin treatment because the hemoglobin level decreased to less than 6 mmol/l. Patients with secondary hyperparathyroidism were treated with -calcidol, and patients with edema were treated with loop diuretics. Loop diuretics and labetolol were the only drugs accepted as additional antihypertensive treatment when the study medication was insufficient in controlling blood pressure.	NR	NR

Evidence Table 12. Adverse Events in Active Controlled Trials of Essential Hypertension

Study, Author, Year Country	Interventions (drug, regimen, duration, n)	Allowed other medications/ interventions	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Verapamil				
CONVINCE Black, 1998, US	COER verapamil daily, n=8241 HCTZ or atenolol, n=8361 Before randomization, investigator assigned each patient to be HCTZ or ate based on suitability. If the patient was selected as control, he/she began the assigned control drug.	Step 1: If study medication is not tolerated or BP not controlled (<140/90), study medication doubled. Step 2: Added up to 25 mg HCTZ daily to Verapimil or Atenolol groups (blinded) Added 50 mg of atenolol to HCTZ group (blinded Step 3: Any other antihypertensive (other than CCB, diuretic or beta blocker) (unblinded)	Death or hospitalization due to adverse effect 1381/8179 (ver) 1363/8297 (HCTZ or ate)	16.5%, 1353/8179 (ver) 15.3%, 1278/8361 (HCTZ or ate)

Evidence Table 12. Adverse Events in Active Controlled Trials of Essential Hypertension

Study, Author, Year Country	Interventions (drug, regimen, duration, n)	Allowed other medications/ interventions	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
INVEST Pepine, 2003 Pepine, 1998 International	*Step 1* Verapamil SR 240-360 mg, n=11,267 Atenolol 50-100 mg, n=11,309 2-3 years	*Target: SBP<140 mm Hg and DBP<90 mm Hg or SBP<130 mm Hg and DBP<85 mm Hg when diabetes or renal impairment is present* *Step 2 Add drug* Verapamil SR 240 mg/trandolapril 2 mg combination product (Tarka) Atenolol 50 mg + HCTZ 25 mg *Step 3 Increase dose* Verapamil SR 180 mg/trandolapril 2 mg combination product (Tarka) twice daily Atenolol 100 mg + HCTZ 50 mg *Step 4 Add drug* Verapamil SR 180 mg/trandolapril 2 mg combination product (Tarka) twice daily + HCTZ 25 mg Atenolol 100 mg + HCTZ 50 mg + trandolapril 2 mg *Step 5* Add nonstudy antihypertensive medication	Development of diabetes Verapamil SR=569/8098(7.03%) Atenolol=665/8078(8.23%) (RR=0.85; 95% CI 0.77-0.95) Cancer Verapamil SR=192(1.70%) Atenolol=186(1.64%);NS Constipation Verapamil SR=195(1.73%) Atenolol=15(0.13%) Dizziness Verapamil SR=154(1.37%) Atenolol=151(1.34%) Dyspnea Verapamil SR=82(0.73%) Atenolol=114(1.01%) Lightheadedness Verapamil SR=48(0.43%) Atenolol=70(0.63%) Symptomatic bradycardia Verapamil SR=74(0.66%) Atenolol=143(1.26%) Wheezing Verapamil SR=17(0.15%) Atenolol=4(0.39%) Other Verapamil SR=1158(10.28%) Atenolol=1180(10.43%)	Verapamil SR=327(2.9%) Atenolol=267(2.4%)

Evidence Table 13. Adverse Events in Angina Head to Head Trials

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications	Adverse Effects Reported	Withdrawals due to adverse events
Amlodipine vs Diltiazem				
Bernink 1991	aml 2.5-10 mg daily *n=39* dil 180-360 mg daily *n=41* x 8 weeks	sl ntg	Overall incidence: aml 41.0%; dil 41.5%	dil 4.9% aml 0%
Canale 1991	aml 5-10 mg daily *n=20* dil 90-180 mg daily *n=20* x 10 weeks	sl ntg	Overall: aml 55%; dil 55% Headache: aml 40%; dil 25% Flushing: aml 20%; dil 0% Edema: aml 10%; dil 10% Gastric pyrosis: aml 0%; dil 15%	Total: 0
Knight 1998	aml 5-10 mg daily *n=47* dil 180-360 mg daily *n=50* x 4-8 weeks	Atenolol 50 mg daily sl GTN	% Total cardiovascular: aml 19.1; dil 20 Syncope: aml 0; dil 2 Atrial fibrillation: aml 0; dil 2 Bradycardia: aml 0; dil 4 Palpitations: aml 0; dil 2 Hypotension: aml 2.1; dil 2 Edema: aml 17.0; dil 8 Nervous system: aml 10.6; dil 14 Gastrointestinal: aml 0; dil 10 Other: aml 6.4; dil 16	aml 4.3% dil 14.0%
Pehrsson 1996	aml 5mg daily x 2 wks, then aml 10mg daily x 2 wks (*n=61)* dil 180mg daily x 2 wks then 360mg daily x 2 wks *(n=58)* dose reduced if higher dose not tolerated after 2 wks Final dose x 8 weeks	NR	Adverse events reported by 36/61 (59%) aml, 29/58 (50%) dil (NS) Reported that total number of events was significantly higher in aml group (p 0.017), data not reported. Most commonly reported events: aml: swollen legs 26/61 (43%) dil dizziness 13/58 (22%)	Overall 7 (6%) aml 4/61 (7%) dil 3/58 (5%)

Evidence Table 13. Adverse Events in Angina Head to Head Trials

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications	Adverse Effects Reported	Withdrawals due to adverse events
Van Kesteren 1998	aml 5-10 mg daily *(n=66)* dil CR 90-120 mg daily (n=66) x 8 weeks	sl ntg	Overall: aml 15%; dil CR 26% Headache aml 4.5%; dil CR 6.1% Edema: aml 4.5%; dil CR 4.5% GI complaints: aml 0; dil CR 4.5% Dizziness: aml 0; dil CR 3% Flushes: aml 1.5%; dil CR 1.5% Rash: aml 0; dil CR 1.5%	Withdrawals: aml 3%; dil CR 9%
Nisoldipine vs amlodipine				
Hall 1998	Nis CC 20-40 mg (n=140) Aml 5-10 mg daily *(n=148) x* 4 weeks Atenolol (25, 50 or 100 mg daily) taken concomitantly at an unaltered dose throughout the duration of the study	GTN	First 4-wk dose phase data(%)/Second 4-wk dose phase data(%) Asthenia: NisCC 2.1/5.6; aml 1.4/2.2 Dizziness: NisCC 2.1/4.8; aml 2.7/3.0 Dyspnea: NisCC 1.4/1.6; aml 2.7/3.0 Peripheral edema: NisCC 14.3/30.6; aml 4.7/20.0 Headache: NisCC 6.4/3.2; aml 4.1/5.9 Pain: NisCC 0.0/0.8; aml 2.7/4.4 Somnolence: NisCC 0.7/0.8; aml 2.7/2.2 Vasodilation: NisCC 0.7/1.6; aml 1.4/3.0 Any event: NisCC 28.6/44.4; aml 27.0/42.2	N 288(NisCC 140; aml 148) NisCC 12.8% aml 7.4%
Other CCBs vs diltiazem				
Singh 1991	bep 200-400 mg daily *(n=46)* dil 360mg daily *(n=40)*	Long acting nitrates, beta blockers at previously established doses, SL NTG for symptoms	Patients reporting at least one adverse event: bep 75%, dil 86% Most common: bep nausea, asthenia, dizziness, headache, diarrhea dil : asthenia, nausea, headache, edema, constipation and dizziness	bep: 4 (9%) dil: 1 (3%)

Evidence Table 13. Adverse Events in Angina Head to Head Trials

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications	Adverse Effects Reported	Withdrawals due to adverse events
Littler 1999	Nis CC 10-40 mg daily *(n=118)* dil CR 120-240 mg daily *(n=109)* x 12 weeks All patients were required to take concomitant beta blocker therapy at a constant dosage throughout the study.	sl ntg	Any adverse event incidence: Nis CC 49.2%; dil CR 48.6% Asthenia: Nis CC 5.9%; dil CR 0.9% Dizziness: Nis CC 3.4%; dil CR 5.5% Headache: Nis CC 5.9%; dil CR 4.6% Infection: Nis CC 7.6%; dil CR 0.9% Peripheral edema: Nis CC 17.8%; dil CR 7.3%	(n 227) Nis CC 10.2% dil CR 10.1%
Radice 1991	nif 40 to 200mg daily *(n=19)* dil 180 to 360mg daily *(n=12)* met 100 to 200mg daily *(n=19)* dose increased weekly to max tolerated. X 3 months	nr	nr	nr
Armstrong 1986	Nic 90 mg daily *(n=19)* Nif 60 mg daily *(n=21)* x 8 weeks	sl GTN	Overall: NCI 58%; Nif 76% Specific adverse event incidence NR	NCI 26.3% Nif 33.3%
Reicher-Reiss 1992	nis 10mg daily *(n=15)* nif 30mg daily *(n=15)* x 8 weeks	sl NTG	Adverse events reported by 2/15 (13%) nis, 2/15 nif (13%) sinus tachycardia and increased chest pain, headache, mild leg edema, nausea and palpitations	1/15 (7%) nis, 0 nif

Evidence Table 14. Adverse Events in Supraventricular Arrhythmia Head to Head Trials

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Diltiazem vs Verapamil					
Botto 1998 Italy	dil ER 240mg daily ver ER 240 mg daily gal ER 200 mg daily x 7 days each then crossed over *(n=18)*	dig to achieve serum concentration 0.8 - 1.4 mcg/ml (mean dose 0.25mg daily)	Active questioning	*Adverse events (n/30):* RR cycles > 2 seconds: dil SR 240mg: 254 ver SR 240mg: 203 gal SR 200mg: 125 dig 0.25mg: 137 *Bradycardia episodes (bpm < 50):* dil SR 240mg: 261 ver SR 240mg: 262 gal SR 200mg: 168 dig 0.25mg: 170 NS for all comparisons None others reported	None
Lundstrom 1990 Sweden	dil 270mg daily ver 240mg daily placebo x 3 weeks each then crossover *(n=19)*	digoxin all antiarrhythmic drugs discontinued prior to study	Direct questioning	*Number of adverse events reported by 18 patients:* dil 36 most common: ankle edema, fatigue, dizziness ver 41 most common: ankle edema, fatigue, constipation pla 25 most common: ankle edema, fatigue, dizziness	1/19 (5%) dil group due to ankle edema

Evidence Table 14. Adverse Events in Supraventricular Arrhythmia Head to Head Trials

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Ochs 1985 Germany	dil 180-360 mg daily *(n=15)* ver 240-480 mg daily *(n=15)*	digoxin	NR	*Number of patients reporting 1 or > adverse event:* dil acute pancreatitis 1/15 (7%) bradycardia/fatigue 3/15 (20%) dil + qui diarrhea 2/13 (15%) ver dyspnea/nausea 1/15 (7%) pulmonary congestion/skin reaction 1/15 (7%) hepatomegaly/increase SGT, SGPT, GGT 1/15 (7%) acute cholecystitis 1/15 (7%) bradycardia 3/10 (30%) bigeminal rhythm 1/10 (10%) pulmonary congestion 1/10 (10%)	dil 7%, 1/15 ver 27% 4/15

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Study design, setting	Number of subjects	Description of subjects	Exposure Duration, P
Beiderbeck-Noll, 2002 Netherlands (Fair)	Prospective population-based cohort study	3204	Eligible subjects were all inhabitants of Ommoord aged 71 and older. Excluded patients with a history of cancer before 1992, or who had filled a cytostatic agent before 1992.	Exposure to CCBs was assessed interview in 1991; all prescription the 2 weeks before the interview assessed. Dose and cumulative during the study period was asse pharmacy records since 1991. CCB users at baseline, n=262

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Dose	Confounding factors assessed	Method
Beiderbeck-Noll, 2002 Netherlands (Fair)		Separate analyses adjusted for baseline age, gender, heart failure, current smoking status, prior number of hospital admissions, and alcohol intake in Model 1; Model 2 adjusted for age, gender, ischaemic heart disease, total cholesterol, and diabetes mellitus; Model 3 adjusted for age, gender, ischaemic heart disease, total cholesterol, diabetes mellitus, diuretics, beta-blocking agents, and ACE-inhibitors. Other factors assessed at baseline: hypertension, ischemic heart disease, coronary bypass, PTCA, history of stroke, angina pectoris, peripheral artery disease, medication use (during 2 weeks prior to baseline interview), age at menopause, health complaints, socioeconomic status, body mass index, alcohol, food questionnaire.	In-person home interviews. Outcomes of interest: a registration of malignant cancer, death, transfer to another area, or end of the stu period. Data sources: all patients obtain their prescribed medicines through 7 networked area pharmacies; national hospitalization data Study period was 1991-1999.

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Results

Beiderbeck-Noll, 2002
Netherlands
(Fair)

	N	Model 1 RR (95% CI)	Model 2 RR (95% CI)
Non-users	273	--- Reference	--- Reference
CCB users	29	1.4 (0.9-2.0)	1.2 (0.8-1.8)
Verapamil	9	2.1 (1.1-4.0)	2.0 (1.01-3.9)
Diltiazem	10	1.5 (0.8-2.9)	1.3 (0.7-2.4)
Nifedipine	9	0.9 (0.5-1.8)	0.8 (0.4-1.6)

Cumulative time of exposure	Model 3 Reference group: non-use of CCBs
All CCBs	
<=2 years	1.0 (0.7-1.5)
>2 years	1.3 (0.8-2.0)
Verapamil	
<=2 years	1.4 (0.8-2.5)
>2 years	2.4 (1.2-4.9)
Diltiazem	
<=2 years	1.0 (0.6-1.7)
>2 years	0.7 (0.2-1.8)
Nifedipine	
<=2 years	0.8 (0.4-1.5)
>2 years	1.3 (0.7-2.5)
Amlodipine	
<=2 years	0.4 (0.1-1.6)
>2 years	0.7 (0.1-5.3)

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Study design, setting	Number of subjects	Description of subjects	Exposure Duration, P
Braun, 1998 Israel (Fair)	Retrospective cohort study	11575	Patients aged 45-74, mean age 60, with chronic CHD screened for but not included in the Bezafibrate Infarction Prevention study, approximately half of whom were treated at the time of screening with CCBs. Excluded those with an acute coronary event or intervention within 6 months before screening, severe congestive heart failure, cancer, or chronic liver or renal disease. Concurrent use of beta blockers by 29%, ACE inhibitors by 39%, diuretic drugs by 16%.	Mean follow-up for incidence 2.8 Mean follow-up for mortality 5.2 y Sept 1996.
Jonas, 1998 Israel (Fair)	Retrospective cohort study	2670	Hospitalized survivors of acute MI who were screened but not included in the Secondary Prevention Reinfarction Israeli Nifedipine Trial. Patients older than age 74 were excluded.	Nifedipine, n=526 Nifedipine plus verapamil, n=7 No nifedipine, n=2081 Verapamil without nifedipine, n=3 Cumulative dose and duration of not quantified.

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Dose	Confounding factors assessed	Method
Braun, 1998 Israel (Fair)	Not quantified	Age, gender, smoking current and past, past MI, hypertension, NYHA functional class, peripheral vascular disease, COPD, diabetes mellitus, diuretic drugs, beta-blockers, ACE inhibitors	Patients who were screened but not included in BIP study were link to the National Cancer Registry and National Death Registry. Cox proportional hazards model used for risk of cancer, total mortality, a cancer-related mortality. Screening included a complete medical e recording of medication use; CHD diagnosis determined by documented MI or angina within 2 years before screening, positive exercise test, positive radionuclear study or at least 60% stenosis c one major coronary artery.
Jonas, 1998 Israel (Fair)	Not quantified	Demographic, historical, and medical variables	Demographic, historical, medical variables, and use of nifedipine w collected during hospitalization. Vital status after 10 years of follow was obtained via the Israeli Population Registry.

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality) | **Results**

Braun, 1998
Israel
(Fair)

RR for cancer (excludes patients with cancer at screening)		
CCB status (total N)	N cancers	RR (95% CI)
CCB nonusers (5543)	117	1.00 Reference
All CCB users (5611)	129	1.07 (0.83-1.37)
Nifedipine (1913)	47	1.12 (0.80-1.57)
Diltiazem (3193)	69	1.04 (0.77-1.40)
Verapamil (336)	8	1.16 (0.56-2.38)
Combination (169)	5	1.36 (0.56-3.27)
RR for cancer-related mortality (excludes cancers at screening)		
CCB status (total N)	N cancer deaths	RR (95% CI)
CCB nonusers (5543)	75	1.00 Reference
All CCB users (5611)	83	1.03 (0.75-1.41)
Nifedipine (1913)	38	1.34 (0.90-1.98)
Diltiazem (3193)	35	0.78 (0.52-1.17)
Verapamil (336)	6	1.22 (0.53-2.81)
Combination (169)	4	1.72 (0.63-4.70)
RR for total mortality (excludes cancers at screening)		
CCB status (total N)	N total deaths	RR (95% CI)
CCB nonusers (5732)	730	1.00 Reference
All CCB users (5843)	840	0.94 (0.85-1.04)
Nifedipine (1999)	303	0.97 (0.84-1.12)
Diltiazem (3320)	444	0.89 (0.79-1.01)
Verapamil (350)	54	1.04 (0.79-1.39)
Combination (174)	39	1.28 (0.91-1.80)

Jonas, 1998
Israel
(Fair)

% of patients who died due to cancer during the 10-year follow-up, nifedipine vs non-nifedipine groups:
4.2% vs 5.5% (p=0.23)
Two of 30 (6.7%) patients on verapamil without nifedipine died of cancer.

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Study design, setting	Number of subjects	Description of subjects	Exposure Duration, P
Kanamasa, 1999 Japan (Fair)	Case-control	566 cases 488 controls	Patients being treated for myocardial infarction. 838 males, 216 females, age 60.1 ± 11.5 years. Post-MI patients were divided randomly to treatment with CCBs, or controls (no CCBs). Excluded patients who died within 7 days of onset of acute-MI. Prior use of CCBs is not reported. Duration of study (mean 26.3 months) may limit the ability to detect potential increased risk of cancer.	Mean observation period 26.3 m Nifedipine n=425, diltiazem n=14

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Dose	Confounding factors assessed	Method
Kanamasa, 1999 Japan (Fair)	nifedipine 30 mg/day (10 mg tid) diltiazem 90 mg/day (30 mg tid)	Univariate analyses only: gender, age, blood pressure, heart rate, atrial fibrillation, coronary thrombolysis, Forrester class, Killip class, Wall motion index by echo, ECG QRS score, angina after infarction, variant angina, hyperlipidemia, hypertension, smoking, diabetes mellitus, obesity, gout, positive exercise ECG test, combined medications (antiplatelets, cholesterol lowering drugs, beta-blockers, warfarin, ACE inhibitors, nitrates, antiarrhythmic drugs).	Patients enrolled January 1986 through June 1994. Each patient assigned 8-digit ID number and study drug assigned according to 5 digit. Selection of nifedipine or diltiazem was left to the doctor. Outpatient visits scheduled monthly. Data shown as mean $\pm$ standard deviation. Differences in patient characteristics between any two groups were tested by two-tailed c square tests, and a probability value of P<0.5 was considered significant. ORs and 95% CIs were also calculated for all patient ris

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Results
Kanamasa, 1999 Japan (Fair)	Of patients not treated with a calcium antagonist, 26 (5.3%) experienced cardiac events. 24 (5.6%) nifedipine patients (OR 1.07; 95% CI 0.6 to 1.89) and 6 (4.3%) diltiazem patients (OR 0.79; 95% CI, 0.32 to 1.96) experienced cardiac events. During follow-up, 31 (2.9%) patients were found to have newly developed cancers; 13 (2.7%) controls, 15 (3.5%) nifedipine patients (OR 1.34; 95% CI, 0.63 to 2.85), and 3 (2.1%) diltiazem patients (OR 0.89; 95% CI, 0.27 to 2.93). No significant difference in the site specific incidence of cancer among the 3 groups. Incidence of cancer was slightly higher in nifedipine patients compared with those not treated, but difference was not statistically significant. Diltiazem had no effect on risk of cancer.

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Study design, setting	Number of subjects	Description of subjects	Exposure Duration, P
Li, 2003 USA (Good)	Population-based case-control study	1982	Women in western Washington State, aged 65-79. 975 were cases of invasive breast carcinoma diagnosed during 1997-1999; 1007 controls were identified from a list of Social Security recipients provided by Medicare and Medicaid Services (cases also had to occur on this list). Users of antihypertensive medications for less than 6 months were excluded from analysis.	Dose, duration, and timing of exp relation to reference date were a

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Dose	Confounding factors assessed	Method
Li, 2003 USA (Good)	CCBs were divided into 4 groups: Immediate release = IR Sustained release = SR 1) IR nondihydropyridines (diltiazem and verapamil) 2) IR dihydropyridines (isradipine, nifedipine, and nisoldipine) 3) SR nondihydropyridines (diltiazem SR and verapamil SR) 4) SR dihydropyridines (amlodipine, felodipine, and nicardipine)	Analyzed as potential confounders: race, income, marital status, education, age at menarche, parity, age at first birth, type of menopause, age at menopause, duration of oral contraceptive use, ever use of hormone replacement therapy, first-degree family history of breast carcinoma, smoking status, average daily alcohol intake, and body mass index. None of these factors changed the OR estimates by more than 10% when included in the model. Analyses were adjusted only for age, because controls were matched to cases on age.	In-person interviews. Logistic regression using never-users as refe category, comparing all breast cancer cases with controls. Users = women who had used HTN medication for 6 months or lon Former users = ever-users who had stopped taking the medication more than 6 months prior to reference date Current users: ever-users who had used the medication within 6 months of reference date.

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Results		
Li, 2003 USA (Good)		Among ever and never users of anti-hypertensives (cases n=975, controls n=1007)	Among ever users of anti-hypertensives (cases n=512, controls n=489)
	Regimen	OR (95% CI)	OR (95% CI)
	Never used antihypertensives	1.0 Reference	---
	Never used CCBs	---	1.0 Reference
	Ever used CCBs	1.2 (0.9-1.5)	1.0 (0.8-1.3)
	6 mos to 5 yrs	1.2 (0.8-1.7)	1.0 (0.7-1.5)
	5-15 years	1.2 (0.8-1.8)	5+yr: 0.9 (0.6-1.3)
	15+ years	0.6 (0.3-1.3)	---
	Ever used IR CCBs	1.4 (1.0-2.1)*	1.3 (0.9-1.8)
	6 mos to 5 yrs	2.1 (1.2-3.8)*	1.9 (1.6-3.4)
	5+ years	1.1 (0.7-1.8)	1.0 (0.1-1.6)
	Ever used SR CCBs	1.0 (0.7-1.4)	0.9 (0.6-1.3)
	6 mos to 5 yrs	1.0 (0.7-1.5)	0.9 (0.6-1.3)
	5+ years	1.0 (0.6-1.6)	0.9 (0.5-1.4)
	Ever used IR nondihydropyridines	1.6 (1.1-2.5)*	1.4 (0.9-2.2)
	6 mos to 5 yrs	2.6 (1.4-5.1)*	2.4 (1.2-4.6)
	5+ years	1.1 (0.6-1.9)	1.0 (0.6-1.7)
	Ever used SR nondihydropyridines	1.1 (0.7-1.6)	0.9 (0.6-1.4)
	6 mos to 5 yrs	1.1 (0.6-1.9)	1.0 (0.5-1.7)
	5+ years	1.0 (0.5-1.8)	0.8 (0.4-1.5)
	Ever used IR dihydropyridines	1.1 (0.6-2.1)	1.0 (0.5-1.8)
	6 mos to 5 yrs	1.3 (0.5-3.5)	1.1 (0.4-3.1)
	5+ years	1.2 (0.5-2.8)	1.0 (0.5-2.4)
	Ever used SR dihydropyridines	1.1 (0.7-1.7)	0.9 (0.6-1.5)
	6 mos to 5 yrs	1.1 (0.6-1.9)	0.9 (0.5-1.6)
	5+ years	1.0 (0.5-2.0)	0.8 (0.4-1.7)
	Ever use of IR CCBs associated with a 1.4-fold increased risk of breast cancer, but there was no clear pattern of increasing risk with increasing duration of use. Former use of IR CCBs was associated with a heightened risk of breast cancer (n=134, OR 2.0, 95% CI 1.0-3.8) although few women were ever users of IR dihydropyridines (n=40, OR 1.1, 95% CU 0.6-2.1). Women who took SR CCBs, whether SR dihydropyridines or non-dihydropyridines, had a breast cancer risk that was similar to women who never used antihypertensives		

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Study design, setting	Number of subjects	Description of subjects	Exposure Duration, P
Meier, 2000 UK (Fair)	Case-control	3706 cases 14155 controls	Women in UK ≥50 years old at date of first-time breast cancer diagnosis (index date), and who had a drug prescription history in the General Practice Research Database (GPRD) of 3 years or more. 32% were 50-59 years old at index date, 26% were between 60 and 69 and 42% were ≥70.	Exposure assessed from comput Subjects classified as users of A only, users of CCBs only, users only, mixed users if they used m nonusers if they had no exposure antihypertensive drugs of interes date. Users were further stratified by d treatment and recency of use. Us classified according to number o exposed: 2 or less, 3 to 4, 5 or m unknown duration. Users were classified as current a prescription for a study drug wi prior to the index date and as pa last prescription preceded the inc more than 1 year.

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Dose	Confounding factors assessed	Method
Meier, 2000 UK (Fair)	NR	Independent effect of a number of covariates on the risk of developing breast cancer was evaluated for the following potential confounders: smoking status, BMI, history of alcohol abuse, previous hysterectomy, and a history of benign breast disease.	Patient records of potential cases were reviewed. Based on availat information from the computer records of patient profiles, potential cases were categorized into 1 of 3 groups: 1) uncertain - subjects whose index date was unclear (prevalent or incident cancer?) or fo whom there was weak evidence for diagnosis (no confirmation recorded and no action taken) or diagnosis was a chance finding a autopsy; 2) probable - subjects who were hospitalized at first-time diagnosis and for whom some treatment information was recorded patient record lacked further evidence of final confirmation; and 3) definite - subjects who underwent mastectomy, radiotherapy, and/c chemotherapy or whose details were noted with regard to staging, localization, or histological analysis of the cancer after diagnosis. Definite cases were included without further validation. 30 probable cases were confirmed by copies of hospital discharge letters, and uncertain cases were eliminated from further analysis. Conditional logistic regression models were used to analyze risk of developing breast cancer in relation to previous use of antihyperter drugs of various duration and to adjust for potential confounders.

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Results
Meier, 2000 UK (Fair)	Compared with nonusers, RR estimates for having ever used ACE inhibitors, CCBs, β-blockers, or a combination of the above were 1.0 (95% CI, 0.9 to 1.2), 1.0 (95% CI, 0.8 to 1.1), 1.0 (95% CI, 0.9 to 1.1), and 0.9 (95% CI, 0.8 to 1.0), respectively, adjusted for smoking status and BMI. Approximately 80% of users across all drug groups were current users at index date; risk of developing breast cancer did not differ between current and past users. Compared with non users, adjusted RR estimates for users of ACE inhibitors, CCBs, or β-blockers of <2 years, 3 to 4 years, or ≥5 years were all equal or close to 1. Direct comparison of longer-term users did not yield a decreased risk for users of ACE inhibitors (adjusted OR, 1.0; 95% CI, 0.6 to 1.6) or an increased risk for users of CCBs (adjusted OR 0.9; 95% CI, 0.6 to 1.3). Compared with nonusers, adjusted ORs for longer-term users (≥5 years) of nifedipine, diltiazem, or verapamil were 1.0 (95% CI, 0.7 to 1.4), 0.8 (95% CI, 0.2 to 3.6), and 1.0 (95% CI, 0.4 to 2.4), respectively.

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Study design, setting	Number of subjects	Description of subjects	Exposure Duration, P
Olsen, 1997 Denmark (Fair)	Population-based	17911	Subjects recruited from population-based Pharmaco-Epidemiological Prescription Database of the County of Nort Jutland, Denmark from 1/1/91 up to 12/31/93. 49% men, 51% women, age range NR	Prescription data shows: verapamil n=4879 (27%) dihydropyridines only n=7370 (41 amlodipine - 31%, felodipine - 26 22%, nitrendipine - 11%, isradipi nicardipine - 4%) diltiazem only n=4247 (24%) mixed use n=1415 (8%) 32,540 person-years follow-up a 1.8 years; range, >0 to 3 years)

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Dose	Confounding factors assessed	Method
Olsen, 1997 Denmark (Fair)	NR	Demographics (age, sex), prevalent vs. new patients	Information transferred to prescription database from pharmacy accounting system includes PIN (including DOB), type of drug prescribed according to anatomical therapeutical chemical (ATC) classification system, and date of prescription. The Central Populat Register (CPR) was used to determine vital status and migration. Cohort was then linked to files of the Danish Cancer Registry (DCF Number of cancer cases observed was compared with number of c expected on basis of rates from DCR. Standardized incidence ratio (SIR) was calculated as ratio of observed to expected number of ca Statistical methods used assume that observed number of cancer cases in any specific category followed a Poisson distribution. Test significance and CI for the SIR were calculated from an accurate asymptotic approximation.

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Results
Olsen, 1997 Denmark (Fair)	About 80% of patients included during the first study year remained on treatment until death or end of study period. 412 cancers were diagnosed vs. 413.9 expected (SIR 1.00; 95% CI, 0.90 to 1.10). SIR was 1.02 (95% CI, 0.89 to 1.16) for men and 0.97 (95% CI, 0.83 to 1.12) for women. Only statistically significant association was seen for tumors of the urinary bladder with 47 cases observed vs. 30.5 expected. Elevated risk was confined to men who received diltiazem exclusively (SIR = 2.1; 95% CI, 1.2 to 3.4) or multiple CA2+ channel blockers (SIR = 2.6; 95% CI, 1.1 to 5.0). No evidence of an excess cancer risk was found in more than 5500 prevalent users with longer periods of exposure.

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Study design, setting	Number of subjects	Description of subjects	Exposure Duration, P
Pahor, 1996 USA (Fair)	Prospective cohort study	5052	EPESE study. People aged 71 or older who lived in three regions of Massachusetts, Iowa, and Connecticut.	Mean followup (observation time Cumulative dose and duration of not quantified.

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Dose	Confounding factors assessed	Method
Pahor, 1996 USA (Fair)	Daily dose was calculated; Median dose by drug: verapamil 240 mg/day nifedipine 30 mg/day diltiazem 180 mg/day Dose groups ranked by low (below median), median, and high (above median)	Confounders were assessed at baseline interview: demographics (age, sex, ethnicity), coronary heart disease, heart failure, hypertension, stroke, diabetes, use of beta-blockers, ACE inhibitors, diuretics, digoxin, nitrates, NSAIDS, aspirin, corticosteroids, estrogens, coumarin; smoking status; alcohol intake; physical disability; blood pressure, BMI; also the number of hospital admissions before the qualifying event or before end of followup.	Based on EPESE study of persons aged 65 or older: in-person interviews 1982-1983, followed by telephone followup interviews. Health outcome data obtained through Medicare MEDPAR files, ca registries. Vital status assessed in 1992. The use and dosages of medications taken over the past 2 weeks was assessed at baseline classification of CCB use versus non-use was based on this baseli assessment.

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality) | **Results**

Pahor, 1996
USA
(Fair)

	Adjusted HR (95% CI)	P-value
All CCBs:		
Non-users (n=4601)	1.00 (reference)	---
Users (n=451)	1.72 (1.27-2.34)	0.0005
Individual CCBs:		
Verapamil (n=118)	2.49 (1.54-4.01)	0.0002
Nifedipine (n=146)	1.74 (1.05-2.88)	0.031
Diltiazem (n=184)	1.22 (0.70-2.12)	ns
CCB use vs. non-use, by type of cancer:		
Stomach	3.64 (0.96-13.76)	
Colon	1.98 (0.90-4.38)	
Rectum	1.32 (0.31-5.74)	
Liver, gallbaldder, pancreas	1.15 (0.26-4.96)	
Lung	0.21 (0.03-1.52)	
Skin	1.11 (0.14-8.62)	
Breast	1.65 (0.49-5.55)	
Uterus, adnexa	3.69 (1.22-11.14)	
Prostate	1.99 (0.93-4.27)	
Bladder, ureter, kidney	1.57 (0.55-4.47)	
Lymphatic, haemopoietic	2.57 (1.13-5.83)	
CCB use vs. non-use, by dose stratum; test for trend, p=0.0094		
Non-use	1.0 (reference)	
Low dose	1.2 (0.6-2.5)	
Median dose	1.7 (0.8-3.0)	
High dose	2.1 (1.1-4.0)	

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Study design, setting	Number of subjects	Description of subjects	Exposure Duration, P
Rosenberg, 1998 USA (Fair)	Case-control	9513 cases 6492 controls	People <70 years old admitted for first occurrences of cancer (cases) or for any of a variety of nonmalignant conditions (controls). Interviews took place in New York, NY, Philadelphia, PA, and Baltimore, MD. *Cases* : Age range 40-69 (mean = 56). 41% male; 84% White; 29% current smokers; 27% had BMI ≥28. *Controls* : Age range 40-69 (mean = 52). 42% male; 68% White; 32% current smokers; 35% had BMI >28.	Use of CCBs and β-blockers and were assessed separately. Only preceded onset of cancer is etiol relevant, therefore, focus was on begun at least a year before adm diltiazem any use: cases n=142, controls (RR 1.0; 95% CI, 0.8 to 1.4) ≥5 year duration: cases n=44, c (RR1.0; 95% CI, 0.6 to 1.6) nifedipine any use: cases n=163, controls r (RR 1.0; 95% CI, 0.8 to 1.3) >5 year duration: cases n=53, c (RR 1.5; 95% CI, 0.9 to 2.3) verapamil any use: cases n=172, controls r (RR 1.2; 95% CI, 0.9 to 1.5) >5 year duration: cases n=51, c (RR 1.1; 95% CI, 0.7 to 1.8)

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Dose	Confounding factors assessed	Method
Rosenberg, 1998 USA (Fair)	NR	Confounders were assessed at baseline interview: demographic data, reproductive and medical history, cigarette smoking, alcohol use, family history of cancer, lifetime history of medication use before admission to hospital (includes fluid retention, high blood pressure, heart conditions, and angina pectoris).	Patients interviewed by nurses between 1983 and 1996 with standa questionnaire. Patients <40 years old excluded due to uncommon use. Unconditional multiple logistic regression analysis used to estimate RRs for categories of drug use controlling for multiple factors. Indic terms were included for correlates of antihypertensive drug use and risk factors for the cancers. Use of CCBs was greater in men and increased with age, interview year, BMI, and annual visits to a physician 2 years before admission. Terms for these factors and fo race and years of education were included in the regressions. Age controlled in 5-year categories. Additional terms were included in th logistic regressions: regressions for all cancers combined, lung car nonlung respiratory cancers, urinary bladder cancer, esophogeal cancer (including pack-years of cigarette smoking), breast cancer (including breast cancer in mother or sister, benign breast disease at menarche, age at first birth, parity, age at menopause, alcohol consumption, duration of oral contraceptive use and parity, and dur prostate cancer (including prostate cancer in father or brother), ova cancer (including duration of oral contraceptive use and duration of estrogen supplement use).

Evidence Table 15. Observational Studies of Cancer

Author, year, location (Quality)	Results
Rosenberg, 1998 USA (Fair)	Use of CCBs compared with use of β-blockers. For CCB use that began at least a year before admission, RR estimate for cancer overall was 0.9 (95% CI, 0.8 to 1.1). Of those who had used 1 drug class exclusively: CCB use (126 cases, 113 controls) relative to no CCB use, RR estimate for cancer overall was 0.9 (95% CI, 0.6 to 1.1) RR estimates based on 5 or more cases (CCB users): Kidney cancer: 1.8 (95% CI 1.1 to 2.7. 22 other sties NS. Data on ≥5 years use of CCBs Colon Caner 1.7 (95% CI 1.0, 2.8); all others NS

Evidence Table 16. Observational Studies of Cardiovascular Events

Author, year, location	Study design, setting	Number of subjects	Description of subjects	Study period, d followu
Gillman, 1999 US Good	Retrospective database review, New Jersey Medicare population	833	Medicare patients from one state enrolled in either Medicaid or the Program of Pharmaceutical Assistance for the Aged and Disabled. Included were subjects aged 65 years or older who were discharged with a principal diagnosis of acute MI (ICD-9 codes 410.0-410.9) between January 1, 1999 and December 31, 1990, and who had filled a prescription for a calcium channel blocker within 90 days after discharge.	Study period Januar December 31, 1990, followup.

Evidence Table 16. Observational Studies of Cardiovascular Events

Author, year, location	Dose	Comparator	Results
Gillman, 1999 US Good	Not reported	Compared short-acting vs long-acting CCBs, and dihydropyridines and non-dihydropyridines.	Occurrence of death over 2 years of followup: Long-acting dihydropyridines: 11/81 (13.6%) Short-acting dihydropyridines: 49/172 (28.5%) Long acting non-dihydropyridines: 21/79 (26.6%) Short-acting non-dihydropyridines: 140/501 (27.9%) Occurrence of cardiac rehospitalization over 2 years of followup: Long-acting dihydropyridines: 25/76 (32.9%) Short-acting dihydropyridines: 73/165 (44.2%) Long acting non-dihydropyridines: 20/73 (27.4%) Short-acting non-dihydropyridines: 182/470 (38.7%) **Relative risk** (95% CI) of death for long-acting compared with short-acting CCBs (adjustec for demographics, severity, comorbidity) Dihydropyridines (nifedipine, nicardipine): 0.42 (0.21, 0.86) Non-dihydropyridines (diltiazem, verapamil): 1.43 (0.88, 2.32) **Relative risk** (95% CI) of cardiac rehospitalization for long-acting compared with short-acting CCBs (adjusted for demographics, severity, comorbidity) Dihydropyridines (nifedipine, nicardipine): 0.57 (0.34, 0.94) Non-dihydropyridines (diltiazem, verapamil): 0.65 (0.40, 1.05)

Evidence Table 16. Observational Studies of Cardiovascular Events

Author, year, location	Study design, setting	Number of subjects	Description of subjects	Study period, d followu
Jollis, 1999 US Good	Retrospective database review; medicare patients in 46 states	141,041 (51,921 prescribed calcium channel blockers at discharge: 21,175 diltiazem, 12,670 nifedipine, 11,683 amlodipine, 3,639 verapamil)	Medicare patients with a principal diagnosis of acute MI (ICD-9 codes 410.x0 and 410.x1) consecutively discharged from the hospital alive during 8-month periods between 1994 and 1995 in 46 states,	8-month periods bet\ and 1995, 1-year foll

Evidence Table 16. Observational Studies of Cardiovascular Events

Author, year, location	Dose	Comparator	Results
Jollis, 1999 US Good	Not reported	Patients not prescribed calcium channel blockers at hospital discharge.	Crude 30-day; 1-year mortality rate: Any calcium channel blocker: 4.3%; 19.6% No calcium channel blocker: 5.7%; 21.5% nifedipine: 3.8%; 18.3% amlodipine: 5.1%; 22.0% other dihydropteridines: 5.1%; 21.9% diltiazem: 3.8%; 18.3% verapamil: 4.3%; 19.2% bepridil: 13.8%; 52.6% (p-value for comparisons not reported) Adjusting for illness severity, medications used, and treatment propensity, no statistically significant differences in mortality at 30 days and 1 year for patients prescribed calcium channel blockers vs those not. However, trends for mortality for amlodipine-treated patient were somewhat higher at 30 days and, for verapamil-treated patients, were somewhat lowe at 1 year. Bepridil (n=116) was the exception: 30-day mortality: 13.8% vs 4.2%; p<0.01 1-year mortality: 52.6% vs 27.6%; p<0.001

Evidence Table 16. Observational Studies of Cardiovascular Events

Author, year, location	Study design, setting	Number of subjects	Description of subjects	Study period, d followu
Maxwell, 2000 Canada Good	Population-based, prospective cohort study.	837	Subjects taken from a representative sample of Canadians aged 65 and older (N=10,263), identified at baseline as not having dementia and reporting use of one or more antihypertensive medications.	Subjects enrolled in followup in 1996; 5-y

Evidence Table 16. Observational Studies of Cardiovascular Events

Author, year, location	Dose	Comparator	Results
Maxwell, 2000 Canada Good	Mean dose not reported, but sub-analysis by dose and duration of use reported for nifedipine.	Nifedipine, non-dihydropyridine CCBs, ACE inhibitors, loop diuretics, and other diuretics or anthypertensives compared with beta blockers.	<u>Hazard ratio (95% CI) for mortality</u> (adjusted for digoxin, nitrate, age, sex, history of stroke, history of diabetes, intermittent claudication, cardiac symptoms, 2MS score, diastolic BP, history of arterial hypertension): Beta blocker (reference group): 1.00 ACE inhibitor: 0.98 (0.54,1.78) Other diuretic/antihypertensive: 1.10 (0.70,1.72) Loop diuretic: 1.84 (1.21, 2.82) Nifedipine: 1.82 (1.09, 3.04) Diltiazem/verapamil: 0.96 (0.58,1.60) <u>Hazard ratio (95% CI) for mortality by dose and duration of use of nifedipine</u> (adjusted for digoxin and nitrate use, age, sex, history of stroke, diabetes, and arterial hyperetension, intermittent claudication, cardiac symptoms, MMMS score, and diastolic BP): (Reference group beta blocker users) Nifedipine formulation short-acting (n=41): 1.64 (0.88, 3.03) long-acting (n=35): 2.07 (1.11, 3.85) <u>Nifedipine dose</u> < 30 mg/day (n=33): 1.50 (0.74, 3.02) > 40 mg/day (n=35): 2.19 (1.19, 4.03) <u>Nifedipine duration of use</u> < 6 months (n=11): 3.75 (1.54, 9.13) 7-12 months (n=11): 0.82 (0.25, 2.74) >12 months (n=43): 1.70 (0.92, 3.12)

Evidence Table 17. Observational Studies of Other Adverse Events

Author, year, location	Study design, setting	Outcome	Number of subjects	Description of subjects
Dunn, 1999 UK	Retrospective database	Depression	81,677 (16,582 diltiazem, 19,144 nicardipine, 25,221 enalapril, 20,730 lisinopril)	Patients prescribed nicardipine, diltiazem, lisinopril, or enalapril.
Fallowfield, 1993 UK	Retrospective database	Deaths, serious adverse events, withdrawals, any adverse events	6,435 (1,759 nifedipine, 4,676 lisinopril)	Patients with hypertension and/or ischemic heart disease prescribed lisinopril or nifedipine for the first time. Indications: nifedipine: 77.4% hypertension only, 8% hypertension with ischemic heart disease, 11.7% ischemic heart disease without hypertension lisinopril: 97.8% hypertension only

Evidence Table 17. Observational Studies of Other Adverse Events

Author, year, location	Study period, duration of followup	Dose	Comparator
Dunn, 1999 UK	September 1984-March 1989; followup was 6 months.	Not reported.	ACE Inhibitors enalapril and lisinopril
Fallowfield, 1993 UK	Recruitment September 19, 1988 to October 23, 1990. Followup was 12 months.	At registration most patients received lowest doses (nifedipine 10 mg twice daily, lisinopril 2.5 mg once daily, nifedipine retard 20 mg twice daily) and were titrated upwards Median dose at end of followup: Nifedipine 10 mg 4 times daily; lisinopriil 10 mg once daily; nifedipine retard dose remained unchanged, at 20 mg twice daily.	Lisinopril (study was designed to examine the tolerability of lisinopril, nifedipine was the comparator)

Evidence Table 17. Observational Studies of Other Adverse Events

Author, year, location	Results
Dunn, 1999 UK	Crude rate of depression per 1000 patient months of treatment: ACE inhibitors 1.89 diltiazem: 1.92 nicardipine: 1.62 Crude rate ratio of depression (relative to ACE inhibitors): diltiazem: 1.00 nicardipine: 0.84 Rate ratio (relative to ACE inhibitors) of depression (95% CI), adjusted for age, sex, season, and indication (ischemic heart disease, hypertension, cardiac failure, and others): diltiazem: 1.07 (0.82-1.40) nicardipine: 0.86 (0.69-1.08)
Fallowfield, 1993 UK	Patients with hypertension: Deaths: 1.8% nifedipine, 1.5% lisinopril Serious adverse events: 0.5% nifedipine, 0.8% lisinopril Withdrawals due to adverse events: 19.7% nifedipine, 15.1% lisinopril Withdrawals due to specific adverse events: angina: 0 nifedipine, 0.18% lisinopril hypotension: 0.23% nifedipine, 0.25% lisinporil digestive system (mainly dyspepsia): 0.38% nifedipine, 0.44% lisinopril genitourinary system: 0.23% nifedipine, 0.25% lisinopril musculoskeletal system: 1.08% nifedipine, 0.16% lisinopril symptoms and ill-defined conditions: 16.08% nifedipine, 12.5% lisinopril

Evidence Table 17. Observational Studies of Other Adverse Events

Author, year, location	Study design, setting	Outcome	Number of subjects	Description of subjects
Kubota, 1995 UK	Retrospective database	Vasodilation-related events: flushing, headache, dizziness, and edema	3,670 (10,112 diltiazem, 10,910 nicardipine, 3,679 isradipine, 12,969 amlodipine)	Patients receiving a first-time prescription for diltiazem, nicardipine, isradipine, or amlodipine. Indications: hypertension: 1.4% diltiazem, 48.8% nicardipine, 82% isradipine, 70.8% amlodipine ischemic heart disease: 53.3% diltiazem, 35.4% nicardipine, 2.8% isradipine, 14.9% amlodipine chest pain: 2.7% diltiazem, 1.3% nicardipine, 0.1% isradipine, 0.6% amlodipine cardiac failure: 0.3% diltiazem, 0.6% nicardipine, 0.1% isradipine, 0.3% amlodipine Raynaud's phenomenon: 0 diltiazem, 0.4% nicardipine, 0.1% isradipine, 0.1% amlodipine Other: 2.4% diltiazem, 1.3% nicardipine, 0.3% isradipine, 0.5% amlodipine Unknown: 39.8% diltiazem, 12.3% nicardipine, 14.6% isradipine, 12.9% amlodipine

Evidence Table 17. Observational Studies of Other Adverse Events

Author, year, location	Study period, duration of followup	Dose	Comparator
Kubota, 1995 UK	diltiazem: September 1984-October 1986 nicardipine: November 1986-May 1988 Isradipine: March 1989-February 1991 amlodipine: March 1990-March 1991 Questionnaires sent to physicians 6 to 12 months after prescription issued	Daily dose based on random sample of 1,000 patients. diltiazem: 60 mg-480 mg nicardipine: 20 mg-180 mg isradipine: 1.25 mg-15 mg amlodipine: 2.5 mg-15 mg	Compared to 28 pooled non-cardiovascular drugs

Evidence Table 17. Observational Studies of Other Adverse Events

Author, year, location	Results
Kubota, 1995 UK	Flushing: 0.4% diltiazem, 3% nicardipine, 6.5% isradipine, 1.4% amlodipine Headache: 1.5% diltiazem, 3.7% nicardipine, 7.5% isradipine, 2.8% amlodipine Dizziness: 1.6% diltiazem, 2.4% nicardipine, 4.2% isradipine, 1.6% amlodipine Edema: 1.1% diltiazem, 2.6% nicardipine, 4.7% isradipine, 6.3% amlodipine All p<0.01 compared to 28 pooled non-cardiovascular drugs.

Evidence Table 17. Observational Studies of Other Adverse Events

Author, year, location	Study design, setting	Outcome	Number of subjects	Description of subjects
Pahor, 1996 Italy	prospective cohort	In-hospital adverse events	5,088 (2,371 nifedipine, 862 verapamil, 699 nimodipine, 455 diltiazem, 374 nicardipoine, 327 amlodipine)	Patients admitted to hospital wards during specified time periods at 79 clinical centers throughout Italy. New intake was considered present when the drug was prescribed in a patient who did not take that drug for at least 2 weeks prior to admission. Remaining patients who used the drugs prior to and during hospital stays were defined as continued users.

Evidence Table 17. Observational Studies of Other Adverse Events

Author, year, location	Study period, duration of followup	Dose	Comparator
Pahor, 1996 Italy	Time periods for enrollment: May 1- June 30, 1988 November 1-December 31, 1988 May 15-June 14, 1991 May 1- June 30, 1993 September 1-October 31, 1993 Patients followed until discharge from hospital.	Mean daily dose by age group (estimated from Figure 2): < 50: 33 mg nifedipine, 250 mg verapamil 50-59: 38 mg nifedipine, 210 mg verapamil 60-69: 36 mg nifedipine, 205 mg verapamil 70-79: 35 mg nifedipine, 200 mg verapamil >79: 34 mg nifedipine, 190 mg verapamil Slow-release preparatins taken more frequently in verapamil than nifedipine group (31.7% vs 7.3%) 63.3% nifedipine, 60% verapamil considered new intake.	Uncontrolled

Evidence Table 17. Observational Studies of Other Adverse Events

Author, year, location	Results

Pahor, 1996
Italy

	Nifedipine (n=2371)	Verapamil (n=862)	Diltiazem (n=455)	Nicardipine (n=374)	Amlodipine (n=327)
Severe AEs	N (rate/1000)	N (rate/1000)	N (rate/1000)	N (rate/1000)	N (rate/1000)
Hypotension	22 (9.3)	3 (3.4)	1 (2.2)	2 (5.3)	5 (15.2)
Tachycardia	3 (1.3)			2 (5.3)	
Acute renal failure	1 (0.4)		5 (11.0)		
Bradycardia		9 (10.4)			
Atrioventricular blocks		2 (2.3)	3 (6.6)		
Other AEs	49 (20.6)	6 (7.0)	5 (11.0)	5 (13.4)	5 (15.3)

Evidence Table 17. Observational Studies of Other Adverse Events

Author, year, location	Study design, setting	Outcome	Number of subjects	Description of subjects
Sorenson, 2001 Hungary	Population=based case-control study	Congenital abnormalities	22,865 cases, 31,151 controls	Cases were newborns with isolated and multiple congenital abnormalities. Excluded congenital dislocation of the hip based on the Ortolani click, congenital inguinal hernia and hemangiomas. Syndromes of known origin also excluded (e.g., Down Syndrome or rubella). Data entered in a population-based registry. Sources were obstetricians, pediatricians working in neonatal units of obstetric inpatient clinics and various inpatient and outpatients obstetric clinics, and consultants at six prenatal diagnostic centers where severe fetal defects are diagnosed and pregnancies subsequently terminated.

Evidence Table 17. Observational Studies of Other Adverse Events

Author, year, location	Study period, duration of followup	Dose	Comparator
Sorenson, 2001 Hungary	Study period 1980-1996. Intake data on 3 gestational time intervals: 1) first month after the last menstrual period, 2) second and third gestational months, and 3) fourth to ninth gestational months. Exposure measured through mailed, self-administered questionnaire to women and/or reported by the perinatal care physician in the personal prenatal care logbook.	Not reported.	Controls selected from the National Birth Registry.Two newborn infants without congenital abnormalities matched to every case according to sex, date of birth (week), and district of the parents' residence.

Evidence Table 17. Observational Studies of Other Adverse Events

Author, year, location	Results
Sorenson, 2001 Hungary	Among cases, 586 mothers (2.6%) had been exposed to calcium channel blockers compared to 907 controls (2.4%). Crude Odds Ratio (95% CI) for congenital abnormalities (CAs): verapamil: 0.6 (0.2-1.9) nifedipine 2.1 (0.7-6.1) felodipine 0.3 (0.0-8.2) Odds Ratios (95% CI) with significant increase (adjusted for maternal age, maternal disease, birth order, and intake of other drugs): Undescended testis, use in 4th-9th month of gestation: 1.5 (1.1-1.9) Cardiovascular CAs, use in 4th-9th month of gestation: 1.4 (1.2-1.7) Multiple CAs, use in 4th-9th month of gestation: 1.4 (1.0-1.9) Matched pairs analysis Odds Ratios (95% CI) with significant increase (adjusted for maternal age, maternal disease, birth order, and intake of other drugs): Club foot, use over whole pregnancy: 1.8 (1.1-2.7) Cardiovascular CAs, use over whole pregnancy: 1.3 (1.0-1.7) Multiple CAs, use over whole pregnancy: 1.5 (1.0-2.4)

Evidence Table 18. Quality Assessment of Observational Studies of Other Adverse Events

Author, year	Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall adverse event assessment quality
Dunn, 1999	Yes	Yes	Yes	Yes	No	Yes (some)	Yes	Fair
Fallowfield, 1993	Yes	Yes	No	Yes	No	No	Yes	Fair
Gillman, 1999	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Jollis, 1999	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Kubota, 1995	Yes	Yes	Yes	Yes	No	No	Yes	Fair
Maxwell, 2000	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Pahor, 1996	Yes	Yes	Yes	Yes	No	No	No (only followed through hospital discharge)	Fair
Sorenson, 2001	Yes	Yes	Yes	Yes	No (collection of data on drug use based partially on recall after outcome had occurred)	Some	Yes	Fair

Evidence Table 18. Quality Assessment of Observational Studies of Other Adverse Events

Author, year	Notes	Funding source
Dunn, 1999		Drug Safety Research Unit (UK)
Fallowfield, 1993		Zeneca Pharmaceuticals
Gillman, 1999		AHRQ
Jollis, 1999		HCFA
Kubota, 1995		Drug Safety Research Unit (UK)
Maxwell, 2000		NHRDP of Health Canada, Pfizer and Bayer
Pahor, 1996		Consiglio Nathonale delle Ricershe
Sorenson, 2001		EU BIOMED Program

Evidence Table 18. Quality Assessment of Observational Studies of Other Adverse Events

Author, year	Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall adverse event assessment quality
Beiderbeck-Noll, 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Braun, 1998	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Jonas, 1998	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Kanamasa, 1999	Yes	Yes	Yes	Yes	Yes	Partial (univariate analyses only)	Yes	Fair
Li, 2003	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Meier, 2000	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair

Evidence Table 18. Quality Assessment of Observational Studies of Other Adverse Events

Author, year	Notes	Funding source
Beiderbeck-Noll, 2002	Partial exposure assessment.	NR
Braun, 1998	Partial exposure assessment.	Boehringer-Mannheim
Jonas, 1998	Cumulative dose and duration of exposure were not quantified. Effect of nifedipine not clearly differentiated from verapamil (the only two CCBs in Israel at the time of study, and	NR
Kanamasa, 1999	Partial exposure assessment. Use of CCBs prior to randomization is not reported. Duration of followup (mean 26.3 months) may limit the ability to detect potential	NR
Li, 2003	Detailed exposure asses:	NCI
Meier, 2000	Partial exposure assessment: duration of use	NR

Evidence Table 18. Quality Assessment of Observational Studies of Other Adverse Events

Author, year	Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall adverse event assessment quality
Olsen, 1997	Yes	Yes	Yes	Yes	Yes	Partial (age and sex-standardized incidence ratios)	Unclear; end date of range for exposure same as end of followup (simultaneous)	Fair
Pahor, 1996	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Rosenberg, 1998	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair

Evidence Table 18. Quality Assessment of Observational Studies of Other Adverse Events

Author, year	Notes	Funding source
Olsen, 1997	Partial exposure assessment: ever use of CCBs between 1991-1993.	NR
Pahor, 1996	Cumulative dose and duration of exposure were not quantified. CCB use or non-use were determined at baseline.	National Institute on Aging
Rosenberg, 1998	Partial exposure assessment: duration of use	NCI