Drug Class Review
on
Calcium Channel Blockers

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Introduction

Calcium channel blocking agents (CCBs) inhibit the movement of calcium ions across the cell membrane by blocking the L-type (slow) calcium ion channel. This blockade reduces contraction of both smooth and cardiac muscle, and cells within the sinoatrial (SA) and atrioventricular (AV) nodes. The main actions of the CCBs include dilatation of coronary and peripheral arterial vasculature, a negative inotropic action, reduction of heart rate, and slowing of AV conduction. However, the effects of individual drugs vary by their degrees of selectivity at different tissue sites and by baroreceptor responses to vasodilation caused by the CCB. Calcium channel blocking agents are generally classified into three groups according to their chemical structure: benzothiazepines (diltiazem); phenylalkylamines (verapamil); and the dihydropyridines (amlodipine, bepridil, felodipine, isradipine, nicardipine, nifedipine, and nisoldipine). Dihydropyridines have greater selectivity for vascular smooth muscle than for myocardium and have little or no action at the SA or AV nodes; negative inotropic activity is rarely seen at therapeutic doses. Benzothiazepines and phenylalkylamines have less selective vasodilator activity than dihydropyridines and have a direct effect on myocardium causing depression of SA and AV nodal conduction.

There are nine CCBs currently marketed in the US: amlodipine, bepridil, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, and verapamil. Of these, diltiazem, isradipine, nicardipine, nifedipine, and verapamil have both immediate and extended release formulations available (ranging from one to four times daily), felodipine and nisoldipine have only extended release formulations (given once daily), and amlodipine and bepridil are long-acting drugs available as immediate release only (given once daily). These drugs have Food and Drug Administration (FDA) indications for treating hypertension, angina, and supraventricular arrhythmias, depending on the specific drug.

While the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure generally recommends a thiazide diuretic as first-line therapy for essential hypertension, CCBs are accepted as first-line therapy alone or in combination with a thiazide diuretic for those without compelling indications, and for patients with high coronary disease risk and diabetes.[1] The use of CCBs in treating stable angina and the use of non-dihydropyridines in treating supraventricular arrhythmias is common, accepted practice. However, the use of CCBs in treating systolic dysfunction is not currently recommended by the American College of Cardiologists and American Heart Association,[2] although the question of the safety of their use in such cases still arises. This report assumes that the decision to use a CCB has been made; the remaining decision is to determine which CCB will be chosen.

Dihydropyridines vs non-dihydropyridines

Dihydropyridines include amlodipine, bepridil, felodipine, isradipine, nicardipine, nifedipine, and nisoldipine. Non-dihydropyridines include benzothiazepines (diltiazem) and phenylalkylamines (verapamil). Because these groups are included in the same drug class but have some differences in both mechanisms of action and side effects, there is concern that the effectiveness and safety may vary by dihydropyridine and non-dihydropyridine groupings. Therefore, a discussion of the data based on this viewpoint is presented. Supraventricular

arrhythmia is not discussed, as only non-dihydropyridines (verapamil and diltiazem) are used for this indication.

Scope and key questions

1. Do CCBs differ in effectiveness in the treatment of adult patients with essential hypertension (blood pressure ≥ 140/90 mm Hg), angina, supraventricular arrhythmias, or systolic dysfunction (left ventricular ejection fraction [LVEF] <45%)?

2. Do CCBs differ in their safety or adverse effects in the treatment of adult patients with essential hypertension (blood pressure ≥ 140/90 mm Hg), angina, supraventricular arrhythmias, or systolic dysfunction (LVEF<45%)?

3. Based on demographics (age, racial groups, gender), other medications, or co-morbidities, are there subgroups of patients for which one CCB is more effective or is associated with fewer adverse effects?

Methods

Literature search

To identify articles relevant to each key question, we searched the Cochrane Central Register of Controlled Trials (4th Quarter 2003), MEDLINE (1996 to February Week 1 2004), EMBASE (1991 to 1st Quarter 2004), the International Pharmaceutical Abstracts (IPA) database (1970 to February 2003), reference lists of review articles, and the Cardiovascular Trials Review.[3] In electronic searches, we used broad searches, combining terms for drug names with terms for relevant research designs (see Appendix A for the complete search strategy). Pharmaceutical manufacturers were invited to submit dossiers, including citations, using a protocol issued by the Center for Evidence-based Policy (http://www.ohsu.edu/drugeffectiveness/pharma/Final_Submission_Protocol_Ver1_1.pdf). All citations were imported into an electronic database (EndNote 6.0).

Study selection

Two reviewers independently assessed for inclusion a sample equaling 10% of the citations, establishing an acceptable level of agreement (90%) by resolving disagreements through consensus. The remaining citations were divided between two reviewers and assessed for inclusion. One reviewer then assessed for inclusion full articles, with consultation from a second reviewer where necessary. We included English-language reports of controlled clinical trials in adults with hypertension (blood pressure ≥ 140/90 mm Hg), angina, supraventricular arrhythmia or supraventricular tachycardia (SVT), and systolic dysfunction (LVEF <45%). For studies of angina, we believed that longer-term studies were required to establish a difference in effectiveness: therefore, we only included studies with a duration of 2 months or longer as an arbitrary cutoff. *Interventions* included oral dosage forms of one of nine CCBs (amlodipine, bepridil, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, and verapamil) compared with another CCB drug, another oral antihypertensive drug (i.e., ACE inhibitor, beta-

blocker, diuretic), or a placebo. *Outcomes* for hypertension, angina, supraventricular arrhythmias and systolic dysfunction included all-cause mortality, cardiovascular (CV) disease mortality, CV events, and quality of life. Additional outcomes included the development of renal failure due to hypertension, symptoms of angina (e.g., episodes of chest pain, use of sublingual nitroglycerin), symptoms (rate or rhythm control) and incidence of stroke due to supraventricular arrhythmias, and symptoms (exercise tolerance, subjective assessments, and New York Heart Association [NYHA] classification) related to systolic dysfunction.

To evaluate effectiveness we included only controlled clinical trials. The validity of controlled trials depends on how they are designed. Randomized, properly blinded clinical trials are considered the highest level of evidence for assessing effectiveness.[4, 5] Clinical trials that are not randomized or blinded, and those that have other methodological flaws, are less reliable, but are also discussed in our report.

To evaluate adverse event rates, we included clinical trials. Clinical trials are often not designed to assess adverse events and may select low-risk patients (in order to minimize dropout rates) or utilize inadequately rigorous methodology for assessing adverse events. Observational studies designed to assess adverse event rates are preferred for this assessment because they typically include broader populations, carry out observations over a longer time period, utilize higher quality methodological techniques for assessing adverse events, or examine larger sample sizes. However, these have not been included in this review due to budget and time constraints.

Trials that evaluated one CCB against another provided direct evidence of comparative effectiveness and adverse event rates. Where possible, these data are the primary focus. In theory, trials that compare these drugs to other drugs used to treat hypertension, angina or supraventricular arrhythmias, or placebos can also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily issues of heterogeneity between trial populations, interventions, and assessment of outcomes. Indirect data are used to support direct comparisons, where they exist, and are also used as the primary comparison where no direct comparisons exist. Such indirect comparisons should be interpreted with caution.

Data abstraction

The following data were abstracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. We recorded intention-to-treat results when reported. If true intention-to-treat results were not reported, but loss to follow-up was very small, we considered these results to be intention-to-treat results. In cases where only per-protocol results are reported, we calculated intention-to-treat results if the data for these calculations were available.

Validity assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix B. These criteria are based on US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK) criteria.[4, 6] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and

blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more categories were rated "poor quality"; trials that met all criteria were rated "good quality"; the remainder were rated "fair quality." As the fair quality category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A poor quality trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. External validity of trials was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the role of the funding source.

Appendix B also shows the criteria we used to rate observational studies of adverse events. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met six or more of the seven predefined criteria, fair quality if they met three to five criteria, and poor quality if they met two or fewer criteria.

Overall quality ratings for the individual study were based on internal and external validity ratings for that trial. A particular randomized trial might receive two different ratings: one for effectiveness and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Data synthesis

In addition to the overall discussion of the study findings, meta-analyses were attempted, where possible. Forest plots of the relative risk (RR), and percent risk difference or standardized effect size are presented, where possible, to display data comparatively. Forest plots were created using StatsDirect (CamCode, UK) software.

Results

Overview

Searches identified 3,480 2,988 citations: 928 914 from the Cochrane Library, 1,764 1,536 from MEDLINE, 625 376 from EMBASE, 34 from IPA, 84 83 from reference lists, and 45 from two pharmaceutical company submissions. We included 91 88 randomized controlled trials (in 127 120 publications), and one systematic review. The flow of study inclusion or exclusion is detailed in Figure 1. Excluded trials publications are listed in Appendix C, and results of trials published in abstract form are listed in Appendix D (individual trials may be represented by multiple publications, including abstracts). An additional 59 citations provided background information, including 18 meta-analyses.

Most of the randomized trials had fair internal validity, but their applicability to community practice was difficult to determine. The treatment and control groups generally received standard doses of CCB or comparator drug, with most studies of hypertension or angina allowing dose titration. Many studies did not state the funding source, but more than half were

funded at least in part by the pharmaceutical industry, although a number of larger studies also reported other funding sources. Detailed quality assessments can be found in Evidence Table 1.

Key Question 1: Do CCBs differ in effectiveness in the treatment of adult patients with essential hypertension (blood pressure ≥ 140/90 mm Hg), angina, supraventricular arrhythmias, or systolic dysfunction (LVEF <45%)?

1A. Do CCBs differ in effectiveness in the treatment of patients with essential hypertension?

In head-to-head trials what is the comparative effectiveness of CCBs in the treatment of essential hypertension?

No head-to-head trials of patients with hypertension were found.

In active-controlled trials what is the comparative effectiveness of CCBs in the treatment of essential hypertension?

We identified 12 11 trials that evaluated the effectiveness of treating hypertensive patients with CCBs in order to reduce mortality, non-fatal CV events, and end stage renal disease (ESRD).[7-20] These trials compared CCBs to ACE inhibitors, diuretics, and beta-blockers.[7-18, 20-24] With the exception of the ALLHAT trial,[9] which was rated good quality, all other included trials were of fair quality. We found one abstract of an active-controlled trial with CV events but it lacked sufficient detail for inclusion.[25] We identified an additional four trials: ASCOT,[26] CASE-J,[22] PRESERVE,[27] and VALUE[28] that have been launched but outcomes results have not yet been published.

The results of the 12 active–controlled trials are depicted in Tables 1-6 and Figures 2 and 3. Most trials recruited patients from the general population, although three trials focused on patients with renal decline,[12, 29] diabetes,[10, 30] or coronary artery disease.[23] The results for all trials have been grouped by outcomes: all-cause mortality, CV mortality, myocardial infarction (MI), stroke, congestive heart failure (CHF), and ESRD. The trials differed greatly in the additional anti-hypertensive medications the patients could be given if the randomized study drug inadequately controlled blood pressure (Evidence Table 2). One trial allowed patients assigned to amlodipine to switch to a different CCB but still be included in the analysis.[9] All but two trials[10, 11] allowed the administration of additional medications but none of these trials presented the outcomes results according to study medication adherence. Therefore, it was impossible to quantitatively separate the effect of the study medication from the additional medications. Many of the CCBs were evaluated in only one trial. For these reasons, meta-analysis was inappropriate. Given this limitation, the outcomes results are presented in a descriptive fashion.

We found no trials that reported the effect of bepridil or felodipine on health outcomes. We found 11 10 active-controlled trials[7, 9, 10, 12-17, 23, 31] of amlodipine, diltiazem, isradipine, nicardipine, nifedipine long-acting gastrointestinal transport-system (GITS), nisoldipine, controlled-onset extended release (COER)-verapamil, and verapamil slow release (SR) that reported all-cause mortality. We found seven six active-controlled trials that reported CV disease mortality; eight active-controlled trials of fatal and nonfatal MI; eight active-controlled

trials of fatal and nonfatal stroke; and six active-controlled trials of fatal and nonfatal CHF or ESRD.[7, 9-17, 20]

All-cause mortality

In all of the active-controlled trials their was no significant difference between the performance of the CCBs and their comparator drugs in reducing all-cause mortality (Table 1).[7, 9-17, 23, 31] The RR values and surrounding confidence intervals overlapped each other and all crossed 1.0 (see Figures 2 and 3). When amlodipine, nifedipine GITS or nisoldipine were compared to ACE-inhibitors, the relative risks ranged from 1.24 to 1.73 (Table 1).[10, 12, 16, 32] When CCBs were compared to ACE inhibitors the large range in relative risks may have been related to the dosage levels, differences in population, and/or size of the study. The lowest RR (1.24) occurred when patients taking a high dose (10 mg) of amlodipine were compared with patients taking a relatively low dose (20 mg) of fosinopril.[10] The highest RR (1.73) for all-cause mortality occurred when patients took either 20-60 mg of nifedipine GITS daily or 10-30 mg of fosinopril daily – both are considered to be medium doses.[12] This study was unique in that it recruited patients with a progressive decline in renal function. The authors of this study stated that it was underpowered to assess CV outcomes.

Table 1. All-cause mortality in hypertensives

CCB vs ACE Inhibitor				CCB vs Diuretic and/or Beta-blocker		
Drug	**Studies**	**Comparison**	**RR (95% CI)**	**Studies**	**Comparison**	**RR (95% CI)**
Amlodipine	AASK FACET	Vs. Ramipril Vs. Fosinopril	1.45 (0.73-2.86) 1.24 (0.36-4.20)	ALLHAT	Vs. Chlorthalidone	0.96 (0.89-1.02)
Diltiazem				NORDIL	Vs. Combined diuretic and beta-blocker	1.00 (0.83-1.20)
Isradipine				MIDAS	Vs. HCTZ	0.89 (0.35-2.28)
Nicardipine				NICS-EH	Vs. Trichlormethiazide	1.54 (0.31-7.67)*
Nifedipine GITS	Marin	Vs. Fosinopril	1.73 (0.54-5.58)*	INSIGHT	Vs. Co-amiloride, HCTZ	1.01 (0.81-1.27)
Nisoldipine	ABCD	Vs. Enalapril	1.30 (0.60-2.80)			
COER-Verapamil				CONVINCE	Vs. HCTZ or atenolol	1.08 (0.92-1.26)
Verapamil SR				INVEST	Vs. Atenolol	0.98 (0.90-1.07)

When patients taking amlodipine, diltiazem, isradipine, sustained release nicardipine, nifedipine GITS, COER-verapamil, or verapamil SR were compared with patients taking diuretics and/or beta-blockers, the relative risks ranged from 0.89 to 1.54. With one exception[11] the RR centered around 1.0. In this study, which compared a sustained release nicardipine with trichlormethiazide, the RR was 1.54 (95% confidence interval [CI], 0.31-7.67). Unlike the other five trials that compared CCBs with diuretics, no other anti-hypertensive medications were

allowed. The authors of this trial reported that it was underpowered to detect individual outcomes.[11]

Cardiovascular disease (mortality and events)

Cardiovascular mortality

We found only two trials that evaluated the effectiveness of CCBs in reducing CV mortality compared with ACE inhibitors (Table 2).[12, 16, 30] Both trials reported reduced effectiveness (relative risks of 2.00 and 2.30, respectively).[12, 16, 30] Each result should be considered with caution. One study had large withdrawal rates (55-60%) in the study medication rates,[16, 30] and the other was underpowered to detect CV outcomes.[12] This latter study contained only 241 patients.[12] Both of these studies included special populations: type 2 diabetes[30] and patients with progressive renal function decline[12]; this may make the results more difficult to compare with the studies of the general population.

Table 2. Cardiovascular disease mortality in hypertensives

*Authors reported insufficient power

CCB vs ACE Inhibitor				CCB vs Diuretic and/or Beta-blocker		
Drug	**Studies**	**Comparison**	**RR (95% CI)**	**Studies**	**Comparison**	**RR (95% CI)**
Diltiazem				NORDIL	Vs. Combined diuretic and beta-blocker	1.11 (0.87-1.43)
Nicardipine				NICS-EH	Vs. Trichlormethiazide	1.54 (0.31-7.67)*
Nifedipine GITS	Marin	Vs. Fosinopril	2.30 (0.65-8.26)*	INSIGHT	Vs. Co-amiloride, HCTZ	1.18 (0.78-1.78)
Nisoldipine	ABCD	Vs. Enalapril	2.00 (0.70-6.10)			
COER-Verapamil				CONVINCE	Vs. HCTZ or atenolol	1.09 (0.87-1.37)
Verapamil SR				INVEST	Vs. Atenolol	1.00 (0.88-1.14)

The relative risks for CV mortality comparing CCBs to diuretics and/or beta-blockers again center around 1.0,[13, 15, 23, 31, 33], with the exception of one underpowered trial.[11]

Myocardial Infarction (fatal and nonfatal)

The relative risks for myocardial infarction for CCBs compared with ACE inhibitors are mixed and were tested only in special populations (Table 3). Both trials that compared a CCB with fosinopril reported lowered risk with the CCB (nifedipine GITS vs. fosinopril, 0.58; amlodipine vs. fosinopril, 0.77)[10, 12] although these differences were not statistically significant. In one study the patients had diabetes[10] and in the other, the patients had chronic renal failure.[12] By contrast, when nisoldipine was compared with enalapril in another diabetic population, the RR increased (2.25)[30] The design of the study limited the authors' ability to determine whether enalapril was protective and/or nisoldipine increased risk, or a combination of both.[16, 30]

Table 3. Myocardial infarctions (fatal and nonfatal) in hypertensives

CCB vs ACE Inhibitor				CCB vs Diuretic and/or Beta-blocker		
Drug	**Studies**	**Comparison**	**RR (95% CI)**	**Studies**	**Comparison**	**RR (95% CI)**
Amlodipine	FACET	Vs. Fosinopril	0.77 (0.34-1.75)			
Diltiazem				NORDIL	Vs. Combined diuretic and beta-blocker	1.16 (0.94-1.44)
Nicardipine				NICS-EH	Vs. Trichlormethiazide	1.03 (0.18-5.79)*
Isradipine				MIDAS	Vs. HCTZ	1.20 (0.37-3.89)
Nifedipine GITS	Marin	Vs. Fosinopril	0.58 (0.08-4.34)*	INSIGHT	Vs. Co-amiloride, HCTZ	1.27 (0.91-1.76)
Nisoldipine	ABCD	Vs. Enalapril	2.25 (0.75-8.82)			
Verapamil				CONVINCE	Vs. HCTZ or atenolol	0.82 (0.65-1.03)
Verapamil SR				INVEST	Vs. Atenolol	1.03 (0.90-1.17)

*Authors reported insufficient power

The RR of a patient experiencing an MI while on CCBs compared with diuretics and/or beta-blockers centered around 1.0 (range of 0.82-1.20). The lowest relative risk was found in the CONVINCE trial and should be considered with caution, since it may have been underpowered to show a difference in CV events.[13] The objective of this very large study (n=16,602) was to determine if COER-verapamil was equivalent to either atenolol or hydrochlorothiazide (the choice of which was selected by the investigator prior to randomization). The study was powered to obtain 2,024 CV events (MI, stroke, or CV related death) over 5 years. The sponsor stopped the trial 2 years early "for commercial reasons."[13].

Stroke (fatal and nonfatal)

The relative risks in five four of nine eight trials center around 1.0 (0.72 0.91-1.15), regardless of comparison drugs (Table 4).[9, 13, 23, 30, 31, 33] The results of two trials (FACET, MIDAS) suggest that, again, dosage influenced the result.[10, 14] The lowest RR (0.39) of stroke occurred when patients taking a high dose (10 mg) of amlodipine were compared with patients taking a relatively low dose (20 mg) of fosinopril, as evidenced by the significantly greater reduction in blood pressure from baseline with amlodipine vs fosinopril (p,0.05).[10] The trial (again thought to be underpowered) with the highest risk of stroke (3.09) had the lowest risk of CHF (0.15).[11]

Table 4. Stroke (fatal and nonfatal) in hypertensives

CCB vs ACE Inhibitor				CCB vs Diuretic and/or Beta-blocker		
Drug	**Studies**	**Comparison**	**RR (95% CI)**	**Studies**	**Comparison**	**RR (95% CI)**
Amlodipine	FACET	Vs. Fosinopril	0.39 (0.12-1.23)	ALLHAT	Vs. Chlorthalidone	0.93 (0.82-1.06)
Nicardipine				NICS-EH	Vs. Trichlormethiazide	3.09 (0.13- 75.36)*
Isradipine				MIDAS	Vs. HCTZ	2.00 (0.50-7.93)
Nifedipine GITS	Marin	Vs. Fosinopril	2.30 (0.30-1.75)*	INSIGHT	Vs. Co-amiloride HCTZ	0.91 (0.66-1.26)
Nisoldipine	ABCD	Vs. Enalapril	1.00 (0.18-5.63)			
COER-Verapamil				CONVINCE	Vs. HCTZ or atenolol	1.15 (0.90-1.48)
Verapamil SR				INVEST	Vs. Atenolol	0.88 (0.72-1.07)

*Authors reported insufficient power

Congestive heart failure (fatal and nonfatal)

The RR for CHF ranged from 0.15 in an underpowered trial of sustained release nicardipine to 2.17 in a trial (INSIGHT) of nifedipine GITS, compared with co-amiloride in an older population (76% of patients over 60 years) (Table 5).[11, 33]

Table 5. Congestive heart failure (fatal and nonfatal) in hypertensives

CCB vs ACE Inhibitor				CCB vs Diuretic and/or Beta-blocker		
Drug	**Studies**	**Comparison**	**RR (95% CI)**	**Studies**	**Comparison**	**RR (95% CI)**
Amlodipine				ALLHAT	Vs. Chlorthalidone	1.38 (1.25-1.52)
Diltiazem				NORDIL	Vs. Combined diuretic and beta-blocker	1.16 (0.81-1.67)
Nicardipine				NICS-EH	Vs. Trichlormethiazide	0.15 (0.01-2.83)*
Nifedipine GITS				INSIGHT	Vs. Co-amiloride, HCTZ	2.17 (1.11-4.24)
Nisoldipine	ABCD	Vs. Enalapril	1.14 (0.44-2.99)			
COER-Verapamil				CONVINCE	Vs. HCTZ or atenolol	1.30 (1.00-1.69)

*Authors reported insufficient power

End stage renal disease

The relative risks for ESRD ranged from 0.62 in a trial (INSIGHT)[33] comparing nifedipine GITS to co-amiloride in older adults, to 1.37 in a trial (AASK) comparing amlodipine to ramipril in an African American patient population in renal decline.[32] The trial (INSIGHT) that had the highest RR for CHF (2.17) also had the lowest RR for ESRD (0.62).[33]

Table 6. End stage renal disease in hypertensives

CCB vs ACE Inhibitor				CCB vs Diuretic &/or Beta-blocker		
Drug	**Studies**	**Comparison**	**RR (95% CI)**	**Studies**	**Comparison**	**RR (95% CI)**
Amlodipine	AASK	Vs. Ramipril	1.37 (0.90-2.07)	ALLHAT	Vs. Chlorthalidone	1.12 (0.89-1.40)
Nifedipine SR	Chan	Vs. Enalapril	0.80 (0.27-2.33)			
Nifedipine GITS				INSIGHT	Vs. Co-amiloride, HCTZ	0.62 (0.26-1.44)
COER-Verapamil				CONVINCE	Vs. HCTZ or atenolol	0.81 (0.49-1.35)

Summary

Overall, the results from 12 active-controlled trials suggest that the CCBs performed no better than diuretics, and/or beta-blockers for health outcomes. In studies of CCBs compared to ACE-inhibitors, no differences among the CCBs were discernable but in general the CCBs resulted in higher risk for health outcomes than ACE-inhibitors (although not statistically significant). Based on this evidence identification of a superior CCB is not valid for several reasons: concern regarding sufficient power, varying use of additional anti-hypertensive medications, contrasting relative risks in the same trial, and limited or lack of any evidence for some CCBs. The outcomes results from two trials are included even though the authors indicated that the outcomes are underpowered.[11, 12] Although only two trials stated this concern, most of the trials included in this review were powered for combined CV events and contained patient samples of similarly small sizes. Since the event combinations all varied, we broke out the analysis by individual CV events. This approach likely included additional trials that were underpowered suggesting caution in placing importance on any single relative risk.

Some CCBs appeared to reduce risk for some health outcomes yet increase risk for other outcomes.[12, 33] One trial reported a low RR for MI (0.58) yet a high risk for stroke (2.3).[12] The INSIGHT trial reported a high RR for CHF (2.17) yet a low RR for ESRD (0.62), although none of these differences were statistically significant.[33] In addition, it is not possible to separate the effects of supplemental antihypertensive medications from study medications; therefore, the type and prevalence of secondary medication use varied. All of these issues made it difficult to reach reliable conclusions concerning the comparative effectiveness of the CCBs to improve CV health outcomes.

Dihydropyridines vs non-dihydropyridines

One trial using diltiazem[15] and two one trials using verapamil[13, 23, 31] were found. All three studies compared a non-dihydropyridine to a diuretic and/or beta-blocker; no significant difference was documented. These results do not differ from results found with the dihydropyridines, and the comparison suffers from the same heterogeneity thereby making indirect comparisons impractical. Due to important differences in patient populations, co-interventions, and comparator drugs, it is not possible to make indirect comparisons across this study set, and no further assessment of differences between dihydropyridines and non-dihydropyridines can be made.

In placebo-controlled trials what is the comparative effectiveness of CCBs in the treatment of essential hypertension?

No placebo-controlled trials in patients with hypertension were found.

What is the comparative effectiveness of CCBs for quality of life measures in hypertensive patients?

Quality of life in hypertensive patients has been shown to be significantly lower than those of normotensive patients in areas including mood, physical health, and sexual, cognitive and work functioning.[34] We found 39 trials that assessed quality of life in patients who were assigned to take a CCB for essential hypertension. We analyzed trials with follow-up periods of at least 24 weeks based on the hypothesis that longer-term assessments are superior in capturing the stabilized effects of treatment on quality of life. Eleven trials met this criteria.[34-44] These trials included assessing the quality of life of patients receiving amlodipine, felodipine, isradipine, three formulations of nifedipine (immediate release, GITS and retard*), and verapamil .(see Evidence Table 3). No long-term trials of bepridil, diltiazem, nicardipine, or nisoldipine for hypertensive patients were found. A bibliography of the 28 trials with durations less than 24 weeks can be found in Appendix E.

Head-to-head trials

We found six head-to-head trials that examined quality of life in hypertensive patients. The trial durations ranged from 10-24 weeks, with only one trial meeting the criteria of at least 24 weeks duration.[35]

This trial compared nifedipine GITS and amlodipine in 178 patients per treatment group for a duration of 24 weeks. This trial was assessed as fair quality. It is unclear whether an intention-to-treat (ITT) analysis was used for the quality of life endpoints. The self-reporting quality of life questionnaire was specifically developed for this trial and was comprised of items adapted from various scales based on previous studies. The scales were standardized to a 100-600 range and were designed to measure five domains (e.g., General Perceived Health, Psychological Well-Being, Psychological Distress, Work Well-Being, and Sexual Symptom Distress). Absolute mean change scores for the first three domains and a summary composite were presented for analysis.

An important difference between groups was noted in the General Perceived Health scale results. Patients in the nifedipine GITS group showed a positive change (+6.5) from baseline to endpoint on this scale, while those taking amlodipine showed a decline (-6.6). A similar, but smaller, difference in effect was seen in the Quality of Life Summary scale results. Nifedipine GITS patients showed a positive mean change of +5.65, while those taking amlodipine declined from baseline by a mean of -0.22. Finally, positive mean changes were seen for patients in both groups on both the Psychological Well-Being (+5.14; +5.13) and Psychological Distress (+9.8; +6.5) scales.

When considering the baseline quality of life ranking (low, medium, or high), patients in both treatment groups presenting with low baseline scores experienced the largest increases on

* This is a formulation of nifedipine in the United Kingdom.

the scales when compared to those in the medium and high subgroups. However, there was one exception; the amlodipine patients with a low General Perceived Health baseline score experienced a negative mean decline at the endpoint on this scale (-11.5). The treatment groups were found to be equivalent (p 0.76) with regard to the number of patients withdrawn due to adverse events (nifedipine GITS 26; amlodipine 24).

Active-controlled trials

We found eight long-term trials that compared the effects of a CCB to another active antihypertensive drug regimen using the quality of life as an outcome measure.

We found a great deal of heterogeneity in the scales that were used to measure quality of life and this eliminated the opportunity for comparing effects across trials. Only one trial (TOMHS) evaluated quality of life using the SF-36 Health Survey. The quality of life domains studied in most of the trials include psychological and general health, well-being, and sexual, cognitive, social and work functioning.

The results of the change in mean quality of life subscale scores were slightly mixed for hypertensive patients across the four CCB groups as reflected in Table 7. In summary, patients in one nifedipine treatment group[39] reported declines in mean scores from the total psychological, somatic and cognitive subscale baselines, as did patients in one amlodipine treatment group[38] using sexual functioning and health outlook subscales. Improvements in all remaining mean quality of life subscale scores from baseline to endpoint were seen for patients in all four CCBs treatment groups.

Table 7. Effects of CCBs on the quality of life in hypertensives

Trial	Intervention	Sample Size	QOL Outcome Summary
Testa, 1998	Amlodipine	aml=178	↑ on 2/4 scales ↓ on 2/4 scales
TOMHS	Amlodipine	n=131	↑ on 7/7 subscales
Omvik	Amlodipine	n=208	PGWB: ↑ on 6/6 indices GHRI: ↑ on 4/6 indices; ↓ on 2/6
AASK	Amlodipine	n=27	↑ on 8/8 scales
Black, 2001	Felodipine ER	n=851	↑ on 7/7 subscales
LOMIR-MCT-IL	Isradipine	n=124	↑ on subjective QOL and semantic memory measures; no change in other 6 variables
NICS-EH	Nicardipine HCL	n=176	↑ on 1/9 QOL categories; no change on the other 8
Bulpitt	Nifedipine retard	n=379	↑ on 13/13 subscales
Testa, 1998	Nifedipine GITS	nif GITS=178	↑ on 4/4 scales
Metelitsa	Nifedipine	n=89	↑ on 4/8 main GWBQ scales
Fletcher	Nifedipine	n=130	↑ on 5/8 subscales; ↓ on 3/8
Boissel	Verapamil	n=163	No significant differences for 16/16 QOL items

The most meaningful result for making indirect comparisons across these trials would be the mean change within groups using the same quality of life measurement tool. This comparison is not possible with these studies due to reporting differences in the few studies that use the same measure. Also, it is not always clear if changes reported are statistically or clinically significant. Conclusions regarding the magnitude of effect from these data cannot be made; even the direction of effect should be interpreted with caution.

Placebo-controlled trials

Quality of life of felodipine vs placebo was assessed in one randomized trial with 52 weeks of follow-up. This trial used the Psychological General Well-Being (PGWB) questionnaire to assess quality of life in 171 patients with isolated systolic hypertension (sitting systolic blood pressure [SBP] between 140 and 159 mmHg and sitting diastolic blood pressure [DBP] <90 mmHg). The PGWB is a measure comprised of six subscales (Anxiety, Depression, Positive Well-being, Self-control, Health and Total Vitality) and an overall composite score (Total PGWB Index). It appears that this trial did not attempt to assess changes in all patients who withdrew from the trial. After 52 weeks, felodipine patients had significantly greater positive mean changes than those taking placebo on three of seven quality of life subscales. No between-group differences in adverse event discontinuation rates were found. After 52 weeks, patients taking felodipine reported significantly greater positive mean changes than those taking placebo on the Anxiety (+1.7 vs +0.3; $p \leq 0.01$) and Depression (+1.7 vs –0.4; $p \leq 0.05$) subscales and the Total PGWB Index (+3.0 vs –0.8; $p \leq 0.01$). Felodipine ER patients demonstrated positive mean improvement scores on the remaining four subscales; however, these did not differ from the mean change scores of the patients taking placebo. The effects of treatment on the Anxiety, Depression and Total PGWB mean change scores did not appear to be impacted by adverse events as the adverse event discontinuation rates were not significantly different ($p=0.25$) between felodipine ER (2%) and placebo (6%).

In summary, the only evidence of direct comparative quality of life effectiveness was provided by one fair quality, head-to-head trial comparing nifedipine GITS and amlodipine. A difference favoring nifedipine GITS on one of five quality of life subscales was found. Meaningful indirect comparisons of the CCB cohorts (amlodipine, isradipine, three formulations of nifedipine, verapamil) studied in the long-term active-controlled trials is impossible due to heterogeneity among the quality of life measurement instruments used, the reporting methods, and the included patient populations. Results of one placebo controlled trial favored felodipine on three quality of life subscales.

1B. Do CCBs differ in effectiveness in the treatment of adult patients with angina?

In head-to-head trials what is the comparative effectiveness of CCBs in the treatment of angina?

We found 11 trials comparing one CCB to another for the treatment of chronic stable angina (see Evidence Table 4); however five of these were rated poor quality and are not discussed here (see study quality assessments, Evidence Table 1). The poor quality studies suffered from lack of details on randomization, allocation concealment and baseline characteristics, lack of an intention to treat analysis, and/or differences in potentially important baseline characteristics. The remaining six trials studied amlodipine (four trials), diltiazem immediate release (three trials), diltiazem controlled release (CR) (one trial), nisoldipine core coat (CC) (two trials), and nicardipine and nifedipine (one trial each). All were of fair quality.[45-50] It is not clear whether the diltiazem CR formulation used in one study conducted in the UK is available in the US.[49] These studies ranged in duration from 2-3 months. These studies were not

long enough to report outcomes of mortality and CV events. There were no head-to-head studies of bepridil, felodipine, isradipine, or verapamil.

These studies enrolled patients with chronic stable angina, although one study[46] also enrolled patients with coronary artery narrowing (based on angiography) or a non-Q wave MI. Two studies required the concomitant use of a beta-blocker (atenolol)[47, 49] and a third allowed continued use of beta-blockers or long-acting nitrates if the dose was stable.[45] The studies reflect the underlying population with chronic stable angina, with mean ages of approximately 60 years and more men than women. None of the studies were conducted in the US: three were done in the UK, and one each in Italy and the Netherlands. Doses of included CCBs started in the medium dose range, and were generally increased according to tolerance and response to a higher dose. Amlodipine was dosed at 5-10mg, diltiazem at 90 to 360mg, nisoldipine at 10 to 40mg, nifedipine 60mg, and nicardipine at 90mg, total daily dose.

Based on patient diary information in five of the six studies, the mean change in number of weekly angina attacks and number of nitroglycerin doses used for symptoms were reduced in both CCB groups, with no statistically significant differences between groups (see Figures 4 and 5). The range in mean reduction was 1 to 3.4 attacks per week, while the mean reduction in number of nitroglycerin doses was 0.3 to 2.5 per week. Two studies[45, 51] reported higher responses in both drug groups (amlodipine vs diltiazem and nicardipine vs nifedipine) than were reported in the other studies. However, the reason for this was not clear, based on the eligibility and exclusion criteria, or baseline characteristics presented. No differences were apparent between drugs in these studies.

Two studies[45, 46] compared amlodipine to diltiazem (immediate release). The studies used the same doses of amlodipine, but different doses of diltiazem (the Canale study used 90 to 180mg diltiazem daily, which is not considered equivalent to amlodipine 5 to 10mg daily). Neither study found a significant difference between the drugs, but in the study that used lower doses of diltiazem, amlodipine reduced the number of angina attacks and use of sublingual nitroglycerin tablets more than diltiazem did. The sixth study did not report baseline data, but reported no difference in angina attacks or nitroglycerin use between amlodipine and diltiazem CR at 8 weeks.[50]

Based on treadmill exercise testing, the mean change in time to the onset of angina was available from three studies (Figure 6).[46, 47, 49] These studies compared amlodipine to diltiazem, amlodipine to nisoldipine, and nisoldipine to diltiazem CR. The range of improvement in time to onset of angina was 16 to 85 seconds. Again, no significant difference was found between drugs in these studies, although amlodipine and nisoldipine tended to be superior to diltiazem.

In active-controlled trials what is the comparative effectiveness of CCBs in the treatment of angina?

We found 15 trials of a CCB vs an active control from another drug class for the treatment of angina. Two of these were poor quality (see Evidence Table 1).[52, 53] These studies had significant problems; they did not report methods of randomization and allocation concealment, and had potentially important differences at baseline in CV characteristics, lack of blinding of patients, and/or lack of description of withdrawals. The remaining studies were all fair quality, and assessed amlodipine (four studies), bepridil (one study), diltiazem (two studies), diltiazem CR (one study), nifedipine (two studies), nifedipine SR (one study) and verapamil (two studies) in patients with chronic stable angina (see Evidence Table 5 and Table 8 below). The

patient populations enrolled were typical of chronic stable angina, with a mean age of approximately 60 years, more males than females, and a significant proportion of positive histories for evidence of coronary artery disease. The comparator drugs were primarily beta-blockers. The studies ranged from 8 weeks to 75 months, and daily doses of CCBs were amlodipine 5-10mg, bepridil 100-400mg, diltiazem 180-360mg, diltiazem CR 240mg, nifedipine 40mg, nifedipine SR 40mg, and verapamil 360 to 480mg. Two of the 13 studies were conducted in the US, with others largely conducted in European countries. There were no studies of felodipine, isradipine, nicardipine, or nisoldipine.

In the group of CCBs studied in active-controlled trials, only bepridil and verapamil are not also represented in the head-to-head comparisons. The study of bepridil[54] compared it to propranolol, and followed patients for a total of 24 weeks. Based on patient diaries, the mean reduction in angina attacks per week from baseline was 69% for bepridil (63% propranolol, 77% placebo) and mean reduction in number of nitroglycerin tablets used per week of 71% (74% propranolol, 79% placebo). Only the relative change from baseline was reported, so comparison to the results in the head-to-head trials was not possible. During the course of the study, there was one death in the bepridil (1.2%), two in propranolol, and none in placebo groups. Eight percent of the bepridil group experienced a non-fatal CV event (including worsening angina), compared to 10% with propranolol and 6% with placebo. The two studies of verapamil[55-57] reported very different outcome measures. One followed patients for 6-75 months and reported fatal and non-fatal events.[55, 56] This study found a rate of death from all causes of 6.2% in the verapamil group and 5.4% in the metoprolol group, CV deaths of 4.7% in each group, and non-fatal CV events of 24.3 and 26.1%, respectively. These numbers are higher than those seen in the bepridil trial (above) but the follow-up time differed greatly (24 weeks vs up to 75 months). The other verapamil study[57] followed patients for 12 weeks and reported the change in angina attacks and nitroglycerin use (verapamil –3.2/2 weeks for both). These numbers are not different to those seen in the head-to-head trials. The change in time to onset of anginal attacks was +41 seconds for verapamil, which is also within the range reported in the head-to-head trials.

The study of nifedipine SR[58, 59] followed patients for at least 1 year and reported rates of cardiac death of 2.6% (1.3% atenolol) and non-fatal MI of 6.5% (6.2% atenolol). These rates are higher than those reported in the (above) verapamil trial for the same outcomes (4.1%, 4.2%, respectively).[55, 56] Again, however, the verapamil study followed patients for up to 75 months. It is not clear that the formulation of nifedipine SR used in this study is one that is available in the US.

Results of studies using amlodipine, diltiazem immediate and sustained release, and nifedipine immediate release were not meaningfully different to those seen in the head-to-head trials. This is based on similar outcome measures for the number of angina attacks, number of nitroglycerin tablets per week, and onset of exercise-induced angina (see Table 8).

Table 8. Active-controlled trials of chronic stable angina

Study	Intervention, n	Outcomes
AMSA 2000	Amlodipine vs metoprolol 8 weeks N = 127	Mean change in time to onset of angina during exercise amlodipine 60.2 sec metoprolol 59 sec
APSIS 1996	Metoprolol vs Verapamil 6-75 months N = 809	Overall mortality (%): Metoprolol 5.4; Verapamil 6.2 AMI: Metoprolol 2.9; Verapamil 2.7 Non-fatal cardiovascular events (%): Metoprolol 26.1; Verapamil 24.3
Destors 1989	Bepridil vs propranolol 32 weeks N = 191	Mean change in number of attacks/week: bepridil-69%, propranolol -71%, Change in nitroglycerin consumption/week: bepridil -71%, propranolol - 74% All cause mortality: bepridil 1, propranolol 2 CV events (including angina deterioration): bepridil 8%, propranolol 10%
Hall 2001	Amlodipine vs Isosorbide mononitrate 28 weeks N = 196	Median number angina attacks: Amlodipine 0; Iso 0
Hauf-Zachariou 1997	Carvedilol Verapamil 12 weeks N = 313	Total exercise time(s): Carvedilol 436; Verapamil 438 Change in time to angina(s): Carvedilol +58; Verapamil +41 Mean change in number of angina attacks/week: Carvedilol -0.1; Verapamil -3.2 Mean # nitroglycerin doses: Carvedilol -1.1; Verapamil -3.2
Kawanishi 1992	Nifedipine vs Propranolol 6 months N = 74	Angina episodes/week: Nifedipine 2.7; Propranolol 2 Nitroglycerin use(tablets/week): Nifedipine 0.7; Propranolol 0.7 Change in time to onset of angina(seconds): Nifedipine +105, Propranolol +91
Lee 2002	Mibefradil vs diltiazem 8 weeks N = 234	Episodes of angina: stated that both groups had fewer weekly episodes Weekly nitroglycerin consumption: reported no significant difference
Meyer 1991	Bopindolol vs Diltiazem 8 weeks N = 31	Decrease in number of pain episodes/month: diltiazem 1.65; bopindolol 2.2 Number of pain episodes x duration (min): diltiazem 129.3; bopindolol 256.5 Change in anginal index: diltiazem 11.1; bopindolol 7.6 Average time free of pain(min): diltiazem 0.75; bopindolol 2.2
Pehrsson 2000	Amlodipine vs atenolol 10 weeks N = 351	Change in time to onset of angina (min): amlodipine 0.8; atenolol 1.0 Average anginal attacks/week: amlodipine 3.4; atenolol 3.7 Average nitroglycerin/week: amlodipine 2.2; atenolol 2.2
Singh 1993	Amlodipine vs nadolol 24 weeks N = 80	Mean change in time to angina onset: amlodipine +72 sec, nadolol +31 Median change in angina attacks/week: amlodipine -3.7, nadolol -2.7 Median change in nitroglycerin tabs used/week: amlodipine -1.7, nadolol -1.5
TIBET Dargie, 1996	nifedipine SR vs atenolol 100 vs 1 year + N = 682	Cardiac death (%): atenolol 1.3; nifedipine SR 2.6 Non-fatal MI (%): atenolol 6.2; nifedipine SR 6.5 Unstable angina (%): atenolol 5.3; nifedipine SR 1.7 CABG(%): atenolol 3.1; nifedipine SR 2.6
Ulvenstam 1992	Nicorandil vs Nifedipine 8 weeks N = 58	*Mean change in angina episodes/week: Nicorandil –2.2, Nifedipine –0.2 *Change in time to onset of angina (min) Nicorandil 2.8; Nifedipine 1.5 *(Significant differences existed at baseline)
Vliegen 1991	Diltiazem CR vs Metoprolol 32 weeks N = 56	Mean frequency of anginal attacks/week: NR Mean change in time to angina (min): Diltiazem CR 1.1; Metoprolol 1.4

In placebo-controlled trials what is the comparative effectiveness of CCBs in the treatment of angina?

We found three fair quality studies of a CCB compared to placebo (see Evidence Tables 1 and 6). Two are reports written by the same investigator using verapamil vs placebo for treating Prinzmetal's variant angina pectoris .[60, 61] Both trials used 240-480 mg daily for 2 months, had similar exclusion criteria, and enrolled similar patient populations (more than 50% males, with a mean age of 52 years). The findings were similar between these two studies; with the mean change in number of angina episodes per week of 11 and 14 for verapamil. The mean change in number of nitroglycerin doses per week was 12 and 15. These point estimates are higher than those seen in the head-to-head and active-controlled trials, but involve a different patient population.

The third study compared amlodipine to placebo over an 8-week time period in patients with chronic stable angina pectoris. The mean age of patients was 59, with a mean duration of angina for 4.5 years; the patients had at least three angina attacks per week at baseline. Patients continued using other anti-anginal drugs. Compared to placebo, a significant difference in number of attacks and number of nitroglycerin doses per week was seen.

In summary, head-to-head trials show no difference in effectiveness in the comparisons made (amlodipine vs diltiazem or diltiazem CR, amlodipine vs nisoldipine, nisoldipine vs diltiazem CR, and nicardipine vs nifedipine). Indirect comparisons between these studies, as well as active and placebo-controlled studies, do not provide evidence of differences in clinical outcomes with amlodipine, bepridil, diltiazem, nicardipine, nifedipine, nisoldipine, or verapamil. No evidence was found for the use of felodipine or isradipine in angina. Likewise, no evidence was found for using the following extended release formulations: diltiazem XR or TZ and verapamil HS and VR. It is unclear if the extended release formulation of nifedipine used was the XL or CC product or a product not marketed in the US.

Dihydropyridines vs non-dihydropyridines

Among the six head-to-head angina trials, four studies compared a dihydropyridine (amlodipine in 3[45, 46, 50], nisoldipine in 1[49]) to a non-dihydropyridine (diltiazem). No differences were found in the mean change in number of angina attacks, use of nitroglycerin, or time to onset of chest pain with exercise. Comparing the risk differences found in these studies to the dihydropyridine vs dihydropyridine studies, no difference in effectiveness is apparent (see Figures 4, 5, and 6). The ability to conduct an indirect comparison across active- and placebo-controlled trials is not possible due to the significant heterogeneity in patient populations. No difference in effectiveness for the treatment of angina can be seen between dihydropyridines and non-dihydropyridines.

1C. Do CCBS differ in effectiveness in the treatment of adult patients with supraventricular arrhythmias?

In head-to-head trials what is the comparative effectiveness of CCBs in the treatment of supraventricular arrhythmias?

We found three head-to-head studies comparing one CCB to another for the treatment of a supraventricular arrhythmia (see Evidence Table 7). Two studies compared immediate release formulations of diltiazem and verapamil[62, 63], while one compared the SR formulations of these drugs.[64] All three studies were fair quality (see Evidence Table 1), and none were conducted in the US. The studies ranged from 1[63, 64] to 3 weeks.[62] Daily doses ranged from 180 to 360mg of diltiazem, and 240 to 480mg of verapamil, and all of the patients also received digoxin throughout the studies. Enrolled patients had documented histories of stable chronic atrial fibrillation (AF), defined as present for greater than 6 months[63, 64] and 1 month.[62] The patient populations were somewhat dissimilar among the studies, with mean age ranging from 51 to 66 years and the proportion of male patients ranging from 40 to 83%. The proportion of patients with mitral valve disease also varied; 28% had mitral regurgitation,[64], 11% had corrected or uncorrected mitral valve disease[62] and 47% had mitral valve disease.[63] The proportion of patients with lone AF was similar in the two studies reporting these data (56 and 61%).[62, 64] The primary outcome measure was mean ventricular rate at rest, although two studies also reported these data during exercise[62, 64]. However, different methods of exercise testing were used (walking test and ergonometric bicycle), and one study[63] also reported the rate of conversion to normal sinus rhythm.

One of these studies only reported the ventricular rate at final testing[64] with no baseline data; final ventricular rates are compared in Figure 7. Resting ventricular rates at 7 days or 3 weeks ranged from 73 to 82 beats per minute (bpm) for diltiazem, and 63 to 80 bpm for verapamil. Using this information, verapamil appears to be slightly superior, but did not reach statistical significance. The two studies that reported changes from baseline also reported no statistically significant differences between the drugs, although verapamil again appeared to be somewhat superior. There was not a statistically significant difference in peak ventricular rate during exercise , using either the 6-minute walking test or ergonometric bicycle, with rates ranging from 142 to 159 for diltiazem and 137 to 158 for verapamil.[62, 64] Based on conversion to normal sinus rhythm, no differences were seen between diltiazem and verapamil alone, although the addition of quinidine appeared to improve the effectiveness of verapamil to some extent. Patient perception of exertion after exercise was not different between the two drugs.[62]

In active-controlled trials what is the comparative effectiveness of CCBs in the treatment of supraventricular arrhythmias?

We found 16 studies comparing a CCB to a drug from another class, six studies of diltiazem and 10 of verapamil (see Evidence Table 8). These studies compared the CCB to a beta-blocker, digoxin, or an antiarrhythmic drug (quinidine, flecainide, amiodarone). All but one study was fair quality (see Evidence Table 1). The one poor quality trial[65] lacked details for randomization and allocation concealment; it was not blinded and an intention to treat analysis

was not conducted. Of the diltiazem trials, all but one[66] (Cardizem CD) used the immediate release formulation, with doses ranging from 180 to 360mg daily. Of the verapamil studies, one used verapamil SR,[67] and the others used immediate release formulations. The doses ranged from 120 to 480mg daily. Thirteen studies enrolled patients with pre-existing AF ranging from 7 days to 1 year.[66-78] A single study was found for each of the following indications: patients with post-coronary artery bypass graft AF that was restored to normal sinus rhythm prior to randomization (verapamil vs quinidine or amiodarone),[79] patients with new-onset rapid AF (≤ 24 hours duration, verapamil vs clonidine or digoxin),[80] and patients with paroxysmal SVT (verapamil vs flecainide).[81] No comparative analysis can be made of the effectiveness of CCBs in these three groups of patients, except to report that no studies of diltiazem were found.

For the studies of chronic AF, the mean age across studies ranged from 50 to 67 years, and more men than women were enrolled in 9 of 13 studies. The proportions of patients with valvular disease ranged from 11 to 75%, and those with lone AF ranged from 8 to 33%. These studies enrolled 12 to 97 patients. The study ranged from 2 weeks to 12 months, and one study[71] compared a CCB to digoxin, while the others allowed or required digoxin use in all patients at some point during the study (e.g., crossover design with CCB vs digoxin vs CCB plus digoxin). Three studies included planned electrical cardioversion during the course of the study in those who had not spontaneously converted (on drug therapy).[73, 74, 78]

Most studies reported outcomes related to ventricular rate or success of conversion to a sustained normal sinus rhythm; however, variations in how these data were reported and the lack of baseline data in some instances make comparisons difficult. The two drugs appear to be successful in reducing mean, mean maximum, and mean minimum ventricular rate at rest and during exercise. Two studies were conducted by the same investigator,[71, 77] one using diltiazem 270 to 350mg and the other using verapamil 120 to 360mg daily. These studies had similar inclusion/exclusion criteria and reported similar outcomes. The mean resting ventricular rate with diltiazem was 91, and 102 with verapamil (although rate varied depending on dose); the post-exercise rate was 140 with diltiazem and 127 to 149 with verapamil. Visual analog scale assessments of overall well-being were 23 with diltiazem, and ranged from 13 to 18 with verapamil. The baseline scores were not presented. Using the Borg scale (6 – 20 points), patient perception of exertion with exercise was assessed, with scores of 3.7 for diltiazem, and 3.7 to 4.5 for verapamil.

In placebo-controlled trials what is the comparative effectiveness of CCBs in the treatment of supraventricular arrhythmias?

We found seven placebo-controlled studies of a CCB to treat a supraventricular arrhythmia (see Evidence Table 9). Three of these studies[82-84] used verapamil 240-480 mg daily to treat patients with persistent AF (ranging from > 72 hours to > 6 months duration) . Two studies by one author[85, 86] enrolled patients who had undergone pacemaker implantation for recurrent AF, one using diltiazem 240mg daily and one using verapamil 230mg daily. A trial of prophylaxis of AF in patients recently experiencing an MI[87] used verapamil 360 mg daily, and the seventh study was in patients with paroxysmal SVT,[88] using diltiazem in doses of 240-360mg daily. Because there are only single studies of post-MI prophylaxis and paroxysmal SVT, no comparison can be made between the CCBs.

In the three chronic AF studies, the duration of treatment using verapamil or placebo was 2-12 weeks. At the end of active treatment, the mean ventricular rate at rest ranged from 66 to

87 bpm with verapamil, compared to 87 to 125 bpm with placebo, in the two trials reporting these data, with higher rates for patients with resting rates > 100 bpm at baseline.[83, 84] These rates are similar to the rates seen in head-to-head and active-controlled trials. Ventricular rate during exercise ranged from 101 to 126 bpm, and was somewhat lower than the rates seen in the verapamil arms of the head-to-head and active-control trials, which were 137 to 158 and 127 to 149 bpm, respectively.

Summary

Based on direct evidence from three head-to-head trials, and indirect evidence from 22 active- or placebo-controlled trials, no difference in effectiveness can be demonstrated between diltiazem immediate release, SR or CD and verapamil immediate release or SR formulations. No evidence was found for the following extended release formulations: diltiazem XL or TZ and verapamil HS or VR.

Dihydropyridines vs non-dihydropyridines

No trials using a dihydropyridine were found.

1D. Do CCBs differ in effectiveness and safety (for major events) in the treatment of adult patients with systolic dysfunction (LVEF <45%)?

Fourteen studies of a CCB for the treatment of systolic dysfunction (LVEF <45%) were found.[89-104] Ten of these compared the addition of a CCB to existing therapy currently using a placebo control. An additional four compared adding a CCB to adding an ACE-inhibitor, beta-blocker or nitrate to existing therapy (see Evidence Tables 1, 10 and 11). These studies included patients with a range of severity of symptoms, based on the New York Heart Association (NYHA) Classification. Co-interventions were used in all studies, with ACE-inhibitors being used in five of ten placebo-controlled studies. Two studies reported mortality as a primary outcome measure, while the others reported outcomes related to symptom assessment (e.g., change in NYHA classification or exercise tolerance). Five studies were poor quality[96, 97, 103-105]. They lacked sufficient details regarding randomization and concealment of allocation, combined with either lack of an intention to treat analysis clinical differences between groups at baseline, and/or high attrition rates. Because of these serious flaws, the results of these studies are not discussed. One study (VHeFT III) was good quality.[89, 90, 106, 107] The remaining studies were fair quality.

Head-to-head trials

No head-to-head trials comparing one CCB to another for systolic dysfunction were found.

Active-controlled trials

Three fair-quality trials comparing a CCB to a drug from another class were included; two compared a CCB to an ACE-inhibitor,[91, 101] and one to isosorbide dinitrate.[94]

Mild - NYHA Class II-III

Two trials compared a CCB to an ACE-Inhibitor. One randomized 24 subjects to nisoldipine or captopril and found no differences in response at three months based on changes in the NYHA classification.[101] The other randomized 46 patients to felodipine or enalapril and also found no difference at three months based on treadmill duration and quality of life scores.[91]The third study[94] reported no difference between isosorbide dinitrate, nifedipine or the combination in improvement in exercise tolerance.

Placebo-controlled trials

Six fair quality trials comparing a CCB to either a placebo or the current standard of care for systolic dysfunction were included (Table 8 and Evidence Tables 1 and 11). In all of these trials the CCB was added to existing therapy compared to placebo. The drugs studied included amlodipine, felodipine, isradipine, and nicardipine.

Mild – NYHA classes I-II

One study of patients with mild heart failure based on the NYHA classification was included.[100] This was a small study (n=23), lasting 12 months, that randomized patients to felodipine or placebo, in addition to standard therapy including enalapril. The addition of felodipine improved the NYHA classification, but the study size limits the reliability of these data. Twenty five percent of patients in the felodipine group moved from NYHA class II to class I, while 0% changed in the placebo group.

Moderate – NYHA classes II-III

Two studies included patients with moderate heart failure symptoms (NYHA classes II-III) and mixed etiology.[90, 102, 108]

One good-quality study, VHeFT III, randomized 450 patients to felodipine or placebo with up to 42 months of follow-up (mean 18 months) and reported no significant difference in the mortality rate. This study found significant differences in exercise duration and quality of life measures at the 27-month follow-up. The number of hospitalizations due to worsening heart failure was also significant, but the small number of subjects available for these comparisons reduces the reliability of these findings. The other study[102]was actually two studies that randomized a total of 437 patients to amlodipine or placebo for three months. One protocol started with 5mg amlodipine and increased to 10mg as tolerated, while the other started at 10mg; otherwise the protocols were similar with patients using digoxin, diuretics, and ACE-Inhibitor at baseline. Both protocols reported symptom-related outcomes (exercise duration, NYHA class,

symptom score and QOL) and found no differences. Results are presented for each protocol both separately and combined.

Severe – NYHA Class III-IV

Three studies enrolled patients with severe heart failure symptoms; two included patients with any etiology.[93, 95, 98, 99]

The Prospective Randomized Amlodipine Survival Evaluation (PRAISE) study[98, 99] is the largest trial of a CCB for systolic dysfunction included, with 1153 patients randomized to amlodipine or placebo and followed up for a mean of 13.8 months. In this study, the results for the overall group did not show any difference in fatal or nonfatal events (nonfatal events: pulmonary edema, severe hypoperfusion, MI, sustained ventricular tachycardia/fibrillation) or all-cause mortality (secondary outcome). In a subgroup analysis, there was also no difference among those patients with ischemic disease (n = 732); however there were significant differences in the group with nonischemic cardiomyopathy (n = 421). There was a 9% reduction in fatal and nonfatal events (95% CI -17.9,-0.1) and a 13% reduction in all-cause mortality (95% CI -21.8,-4.8) in the amlodipine group. While randomization was stratified by etiology, the results pertain to a subgroup. This study was followed up by a second PRAISE study, which included only patients with nonischemic cardiomyopathy. This study has not been published in its entirety, but reports from cardiology conferences in 2000 indicated that 1652 patients were randomized, using a protocol similar to the original study. In this larger study no significant difference was found in all-cause mortality, with a 2% difference between amlodipine and placebo being reported.

Two small studies using felodipine vs placebo enrolled patients with LV dysfunction due to ischemic etiology. One study followed patients for two months (n = 23)[92] and the other for six months (n = 20).[95] The 6-month study[95] found no difference in mortality or subjective assessment after six months. The 2-month study[92] found patients to have a significantly increased exercise duration in the felodipine group (mean difference of change = 125 seconds, $p<0.05$) but worse subjective assessments of improvement compared to placebo. The scale used to assess subjective improvement was 1=markedly worse, 7=markedly improved; at 8 weeks the mean score in the felodipine group was 2.9 and 4.4 in the placebo group ($p<0.01$). Dyspnea was measured on a 3-point scale: 0=no dyspnea, 3=marked dyspnea. At 2 months, it was reported that 91% of patients on felodipine had diminished dyspnea while only 41% in the placebo group noted any improvement, but the scores are not reported.

Summary

Nine active or placebo-controlled studies of CCBs for the treatment of systolic dysfunction were rated good or fair quality: one each of nifedipine and nisoldipine, two of amlodipine and five of felodipine. In active-controlled trials of felodipine, nifedipine, and nisoldipine no differences in the effect on symptoms or exercise tolerance were found, however the trials results are limited by small sample sizes and short follow-up periods.

Data regarding mortality and/or CV events are available for amlodipine and felodipine from placebo-controlled trials. Overall, the evidence suggests that neither of these CCBs have an important impact (positive or negative) on all-cause mortality or combined fatal and nonfatal CV events. While amlodipine was shown to reduce combined events and all-cause mortality in

idiopathic systolic dysfunction, the evidence is weakened by the fact that these findings were in a subgroup, with the reports from a larger follow-up trial showing no effect. Minor improvements in various symptom-based measures seen with amlodipine and felodipine in placebo-controlled trials are limited by small sample sizes and short follow-up periods. In general, no evidence of a difference in response could be found between amlodipine and felodipine. No other dihydropyridine CCB was studied in a fair- or good-quality study. No fair or good-quality study of a non-dihydropyridine CCB was found.

Table 9. Summary of placebo-controlled trials of CCBs for systolic dysfunction

Study	LVEF	NYHA Classes	Drug	Months Follow-Up	Number enrolled	Outcomes measured	Main findings
Russo 1998	mean 30%	I-II	Felodipine	12	23	NYHA Classification	**Improved NYHA**
Udelson 2000	<35%	II-III	Amlodipine	3	437	Symptoms	NS
V-Heft 1996, 1997	< 45%	II-III	Felodipine	18	450	**Mortality**, exercise duration, QOL, NYHA	NS mortality small differences in exercise duration, QOL and hospitalizations (seen after 15 months)
Praise Packer 1996	<30%	III-IV	Amlodipine	13.8	1153	**Mortality,** combined events	Overall NS NS in ischemic subgroup **SS in non-ischemic subgroup**
Kassis 1990	mean 26%	III-IV	Felodipine	6		**Mortality** and symptoms	NS
Dunselman 1989, 1990	mean 26%	III-IV	Felodipine	2	23	Exercise duration and subjective assessment of symptoms	**Increased exercise time (SS)** **Worse on subjective assessment of improvement**

Key Question 2: Do CCBs differ in safety or adverse effects in the treatment of adult patients with essential hypertension (blood pressure ≥140/90 mm Hg), angina, supraventricular arrhythmias, or systolic dysfunction (LVEF <45%)?

We included evidence from controlled clinical trials that reported data on adverse events of CCBs when used to treat hypertension, angina, or supraventricular arrhythmias. We did not include observational studies of populations using CCBs in a natural setting. Hence, the evidence included pertains to the populations specifically selected for these trials, and often excludes patients at higher risk for developing serious adverse events. These data provide a comparison of adverse event and safety data for CCBs in shorter duration studies using somewhat healthier populations. However, the active-controlled hypertension studies provide data for longer time periods (2-6 years). Because the indication for using CCBs may have an effect on the adverse events experienced therefore leading to withdrawals, we initially present adverse event data by disease. Data regarding withdrawals due to adverse events are given greater weight because they capture the magnitude of effect and relate to reductions in effectiveness.

2A. Do CCBs differ in safety or adverse effects in the treatment of patients with essential hypertension?

We found no head-to-head studies designed to assess the adverse events of CCBs. Adverse event evaluations reported in 13 12 active-controlled trials are summarized in Evidence Table 12.[7, 9-12, 14-17, 20, 23, 30-33, 43, 109-132] These evaluations included data for amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nisoldipine, and verapamil. Data were not available for either bepridil or felodipine. All trials were long-term with durations ranging from 2-6 years. Frequency of overall adverse events was only reported by the INSIGHT trial in which 48.9% of patients taking verapamil had one or more adverse events, compared to 41.9% of patients taking co-amilozide.

The most common adverse events in all trials were dizziness, peripheral edema, headache, and flushing. Comparisons of the rates of these adverse events are presented in Figures 8-11. Data from the INSIGHT, MIDAS, NORDIL, and TOMHS trials suggest equivalency between amlodipine, diltiazem, isradipine and nifedipine for risk of headache, and between amlodipine and nifedipine for risk of flushing when compared to a diuretic. Risk of dizziness compared to a diuretic is similar for amlodipine and nifedipine and similar for diltiazem and verapamil when compared to a beta blocker.

Upon comparing the rates of edema for CCBs between the INSIGHT and TOMHS trials, the difference in risk of developing edema was higher for the comparison of nifedipine GITS to HCTZ/amiloride (risk difference= +24%) than for the comparison of amlodipine to chlorthalidone (risk difference= +4.1%). The discrepancy in the risk of developing edema between the two CCBs vs diuretic groups should be interpreted with caution in light of the important between-group differences in patient characteristics. Patients in the INSIGHT group (nifedipine GITS) were older (75.9% were between 60 and 80 years old vs a mean age of 58.8), were comprised of a lower percentage of males (46.1% vs 58.8%), had a higher mean BP (173/99 vs 138.1/90.9), and had a greater proportion of CV risk factors than patients in the TOMHS trial (amlodipine). These differences may account for the higher proportion of patients experiencing edema with nifedipine GITS in the INSIGHT study.

Withdrawals due to adverse events were reported by three active-controlled trials in which a CCB was compared to an ACE-inhibitor (ALLHAT, Chan, ABCD), and six five trials in which a CCB was compared to a diuretic/beta-blocker (ALLHAT, NICS-EH, INSIGHT, MIDAS, CONVINCE, INVEST). Comparison of these rates can be found in Figures 12 and 13. Indirect comparison of the adverse event withdrawal rates for the CCBs with ACE inhibitor comparators show no difference between slow release nifedipine[20] and nisoldipine (ABCD) or amlodipine (ALLHAT). When compared to an ACE inhibitor, nisoldipine patients in the ABCD study had a higher risk difference for adverse event withdrawals than enalapril (risk difference= +5.5, 95% CI –1.7% to +12.8%), while in the ALLHAT study there was no significant difference between amlodipine and lisinopril (risk difference= -9.2, 95% CI –10.5 to –7.8). It is important to note that the withdrawal rate reported in the ABCD study combines withdrawals due to intercurrent diseases in addition to withdrawals due to adverse events. The effects of this variation in reporting and the difference in the prevalence of diabetes among the ABCD patients (100%) compared to the ALLHAT patients (36.7%) on the higher rate of withdrawals cannot be ruled out.

Comparison of CCBs with diuretic comparators suggests equivalency in adverse event withdrawal rates for amlodipine vs chlorthalidone (ALLHAT), nicardipine vs trichlormethiazide (NICS-EH), isradipine vs HCTZ (MIDAS), COER verapamil vs HCTZ or atenolol (CONVINCE), and verapamil SR vs atenolol (INVEST). Patients in the nifedipine GITS group in the INSIGHT trial showed a significantly higher adverse event withdrawal risk difference (+6.5%) than seen in the other trials: nicardipine in NICS-EH (-1.4%) and COER verapamil in CONVINCE (+1.1%) and are equivalent (the overlap of the 95% CIs) to isradipine in MIDAS (+1.1). The effect of the inclusion of patients with high CV risk factors in the INSIGHT trial (nifedipine GITS) on the rate of adverse event withdrawals cannot be ruled out.

Four Three trials (Marin, MIDAS, ALLHAT, INVEST) reported the incidence of cancer in patients receiving a CCB for treating hypertension. Over a 6-year period in the ALLHAT study, 10 patients per 100 were reported in the amlodipine group (compared to 9.7 with diuretic and 9.9 with ACE inhibitor). In MIDAS, 13 of 442 patients taking isradipine (compared to 20 of 441 taking diuretic) developed cancer (fatal and non-fatal combined). These numbers translate to 2.9 per 100, and 4.5 per 100 over three years. The third study (Marin) reported the number of withdrawals due to cancer as 1 of 112 taking nifedipine (compared to 1 of 129 taking ACE inhibitor) over 3 years. In INVEST, cancer was reported in 192 of 11,267 (1.70%) patients taking verapamil SR compared with 186 of 11309 (1.64%) patients in the atenolol group. Differences in study duration, case identification, and reporting make comparisons across these three studies ambiguous.

Four trials (ALLHAT, INSIGHT, NORDIL, INVEST) reported the incidence of development of diabetes. When compared to a diuretic or beta blocker, patients taking amlodipine in the ALLHAT study (risk difference –1.8; 95% CI –2.6 to –1.0), nifedipine GITS in the INSIGHT study (risk difference –1.3; 95% CI –2.2 to –0.4), diltiazem in the NORDIL study (risk difference –0.7; 95% CI –1.5 to 0.05) and amlodipine in the INVEST study (risk difference –1.2; 95% CI –1.9 to –0.5) the incidence of new-onset diabetes was lower in the CCB groups, and similar across CCBs.

In summary, indirect analysis of data for amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nisoldipine, and verapamil from 13 active-controlled trials was made. Evidence was insufficient to clearly differentiate one CCB from another for overall adverse event incidence. The trials that reported individual adverse event incidence were consistent in their findings that dizziness, edema, headache, and flushing were most common. Important differences in CCB treatment group characteristics (e.g., comorbidities) make it impossible to interpret the differences seen in risk of edema and adverse event withdrawals as being caused by the CCB.

2B. Do CCBs differ in safety or adverse effects in the treatment of adult patients with angina?

In six head-to-head trials[45-50] no significant difference in overall adverse event rates or withdrawals due to adverse events was found between amlodipine, diltiazem, nicardipine, nifedipine, or nisoldipine (see Evidence Table 13 and Figures 14 and 15). The difference in risk of withdrawal due to an adverse event appeared slightly lower for amlodipine compared to diltiazem or nisoldipine, and nisoldipine slightly lower than diltiazem. However, the differences were not statistically significant, with the difference in risk of withdrawal less than 10% in all studies. Incidence of peripheral edema was the same for amlodipine and diltiazem, but lower for amlodipine compared to nisoldipine (see Figure 16). Similarly, edema incidence was lower for

diltiazem, compared to nisoldipine. However, an effect of these differences was not apparent in the withdrawal rates (Figure 15).

Although comparison across studies is difficult, active- and placebo-controlled trials do not provide clear evidence of a difference between the CCBs studied (amlodipine, bepridil, diltiazem, diltiazem CR, nifedipine, nifedipine SR and verapamil). Two of these, bepridil and verapamil, were not studied in head-to-head trials. One of these trials covered a much longer time period (up to 75 months) so adverse event and withdrawal rates were higher.[55, 56] This study reported a 15% withdrawal rate and a malignancy rate of 1.5% for verapamil (rates for metoprolol were 11% and 0.7%, respectively). The other two studies reported withdrawal rates similar to each other (approximately 2%) and within the range of rates seen in head-to-head trials.[54, 57]

2C. Do CCBs differ in safety or adverse effects in the treatment of adult patients with supraventricular arrhythmias?

Adverse events were reported in three head-to-head trials of diltiazem and verapamil (immediate release or extended release) for AF (see Evidence Table 14).[62-64] These were very short duration trials, two only lasting 7 days [63, 64]and the third lasting 3 weeks.[62] The longer study reported similar total numbers of adverse events (36 with diltiazem vs 41 with verapamil in 18 patients each) and withdrawal rates (one patient with edema on diltiazem and none on verapamil) .[62] One 7-day study found higher overall adverse event and withdrawal rates for verapamil compared to diltiazem (90 vs 27% and 27 vs 7%, respectively).[63] This study used 180-360 mg of diltiazem and 240-480 mg of verapamil daily. It is unclear if adverse events and withdrawals were higher in the verapamil group due to intolerance of aggressive dosing in a short time-frame. In the other short-term study only adverse events recorded by ECG were reported, with rates of bradycardia and RR cycles greater than 2 seconds similar between the two drugs.[64]

Of 23 active- and placebo-controlled studies, nine did not report either specific adverse event data or withdrawals due to adverse events. Reported adverse event and withdrawal rates varied somewhat with duration, but are similar across studies for the diltiazem and verapamil arms. While edema was more commonly reported in diltiazem trials and constipation more common in verapamil trials, it is not clear if this is the result of guided questioning or spontaneous reporting.

In summary, no clear evidence of a difference in safety between the CCBs (amlodipine, bepridil, diltiazem, nicardipine, nifedipine, nisoldipine and verapamil) used to treat patients with hypertension, angina or supraventricular arrhythmias was found. No studies of felodipine, diltiazem XR or TZ and verapamil HS and VR meeting inclusion criteria were found, so no conclusion about their relative safety can be made.

2D. Do CCBs differ in safety or adverse effects in the treatment of adult patients with systolic dysfunction (LVEF <45%)?

Head-to-head trials

No head-to-head trials using a CCB to treat systolic dysfunction were found.

Active-controlled trials

Two of three trials with active-controls reported adverse events, one comparing felodipine to enalapril,[133] and the other comparing nifedipine to isosorbide dinitrate.[94] Felodipine was similar to enalapril in overall adverse event rates, but more patients experienced peripheral edema with felodipine, while more had cough and dizziness with enalapril. No withdrawals were reported in this crossover trial. Reports of overall adverse events were greater with nifedipine than with isosorbide dinitrate or the combination (68% vs 35% vs 48%, respectively). Withdrawals due to adverse events were also higher in the nifedipine alone group (29% vs 19% vs 5%); however, these numbers include withdrawals due to worsening heart failure (failure of effectiveness).

Placebo-controlled trials

One study of mild systolic dysfunction reported that 17% of patients experienced dizziness due to hypotension and ankle edema with felodipine, vs none with placebo.[100] A significant difference in the reports of peripheral edema was found in a good quality study, with 21% among those on felodipine and 13% among those on placebo ($p = 0.02$).[90] This study also found an increased incidence of fatigue and a decreased incidence of chest pain with felodipine compared to placebo. The withdrawal rate was 10% in the felodipine group over a mean of 18 months; however, there was no difference in withdrawal rates between felodipine and placebo. A three-month study of amlodipine[102] found an increased incidence of overall adverse events (13% vs 8%); and specifically edema (8% vs 3%) with amlodipine, as compared to placebo. The only withdrawals reported were those related to worsening heart failure, with 3.3% in the amlodipine groups and 2.2% in the placebo groups.

Two trials of patients with severe systolic dysfunction reported adverse events.[92, 99] A two-month study compared felodipine to placebo in 23 patients with ischemic systolic dysfunction; more reports of peripheral edema, flushing, tachycardia, palpitations, dizziness, and blurred vision were found with felodipine, while more reports of muscle weakness, fatigue, insomnia, pruritus, nausea, conjunctivitis, and sweating were found with placebo.[92] Peripheral edema occurred in 36% of patients taking felodipine 10-20mg daily, and in 17% of patients taking placebo. Flushing occurred in 27% taking felodipine and 0% on placebo. Dose reduction due to severe adverse events occurred in 27% taking felodipine and 8% on placebo, but withdrawals were not reported. The longer trial compared amlodipine to placebo in 1153 patients with mixed etiology of systolic dysfunction, with a mean of 13.8 months of follow-up.[99] The total number of adverse events reported was 2576 with amlodipine (mean 4.5 per patient randomized), and 1599 with placebo (mean 2.7 per patient randomized). Peripheral (27% vs 18%) and pulmonary (15% vs 10%) edemas were reported significantly more often in the amlodipine group, while uncontrolled hypertension and liver or biliary disorders were reported

significantly more often with placebo. Withdrawals due to adverse events, however, were reported more often in the placebo group (2.7% vs 0.9%, p=0.02). One trial of felodipine in class III-IV heart failure did not report adverse event data.[95]

The comparison of CCBs based on adverse events reported is hampered by the lack of description of the methods for collecting and the inconsistent reporting of these data. Amlodipine and felodipine were reported to cause peripheral edema significantly more often than placebo (Figure 17), with a pooled risk difference of 8% (95% CI 1.5 to 15%) for felodipine, and 7% (95% CI 2% to 12%) for amlodipine. The remaining studies did not report adverse events or were poor quality, so a comparison of the rate of peripheral edema cannot be made. Figure 18 displays the risk difference for withdrawal due to adverse events in those studies reporting these data. The risk of withdrawal with felodipine compared to placebo in a good quality study was 1.8% (95% CI –3.5 to 7.3%), while the pooled risk difference for amlodipine was –0.7% (95% CI –3.6% to .1%).

Summary

From the limited study data available, no important difference can be demonstrated between felodipine and amlodipine in the overall rates of adverse events, specific adverse events, or withdrawals due to adverse events among patients with systolic dysfunction. The data do indicate that amlodipine and felodipine have higher rates of peripheral edema than placebo.

Dihydropyridines vs non-dihydropyridines

Based on head-to-head trials in patients with angina, diltiazem appears to cause a lower rate of peripheral edema than the dihydropyridines amlodipine and nisoldipine, but the difference was not significant in the amlodipine trials (see Figure 16). Peripheral edema was not reported with non-dihydropyridines in the hypertension or heart failure studies. Other adverse events peculiar to either dihydropyridines and non-dihydropyridines were not reported with enough frequency or in a way that could be compared. While the dihydropyridines and non-dihydropyridines have differing side effect profiles, no difference in overall adverse event rates or withdrawal rates due to side effects can be seen between the two groups in head-to-head studies of patients with angina (see Figures 14 and 15). The hypertension studies did not provide adequate information to compare overall adverse event and withdrawal rates between dihydropyridines and non-dihydropyridines. Studies of supraventricular arrhythmias or systolic dysfunction did not compare these two groups.

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

3A. Hypertension

Seven Six of the included active-controlled trials using CCBs for treating hypertensive patients enrolled patients from subgroups with specific comorbidities, or from specific racial/ethnic categories. While these studies were designed to compare a CCB to another drug class in specific subgroups, they were not designed to compare across the CCBs. Three studies

only enrolled patients with diabetes (ABCD; FACET; Chan), two enrolled patients with renal insufficiency (Marin, AASK), one enrolled patients with CAD (INVEST), one enrolled only African Americans (AASK), and one was conducted using older Japanese patients (NICS-EH). Evidence for other racial subgroups, gender or age was not found for any of the included CCBs.

All-cause mortality

Analysis of all-cause mortality rates showed no significant differences in RR across all four trials of CCB vs ACE inhibitor comparisons among diabetic, renal insufficiency, and African American subgroups. All-cause mortality RR's for the trial comparing nicardipine to a trichlormethiazide in elderly Japanese patients and the trial comparing verapamil SR to atenolol in patients with CAD showed no differences in rates from the other five CCB vs diuretic and/or beta-blocker trials.[23]

Cardiovascular mortality

Evidence of CV mortality rates for CCB vs ACE inhibitor comparisons were only found in the renal insufficiency (Marin) and diabetic (ABCD) subpopulations (see section 1A under Key Question 1 for detailed results). Trials of target population groups are not available; no meaningful indirect comparison to differentiate one CCB from another can be made. Cardiovascular mortality RR's for the trial comparing nicardipine to a trichlormethiazide (RR 1.54; 95% CI, 0.31-7.67) in elderly Japanese patients[11] and the trial comparing verapamil SR to atenolol (RR 1.00; 95% CI, 0.88-1.14)[23] showed no difference from rates of the other three CCB vs diuretic and/or beta-blocker comparisons.

Myocardial infarction

The only studies of CCBs vs ACE-Inhibitor reporting rates of MI were in special populations, two in persons with diabetes and one in patients without diabetes, but with renal insufficiency, and the relative risks for MI were mixed. Both trials that compared a CCB with fosinopril reported lowered risk (nifedipine GITS vs. fosinopril, 0.58; and amlodipine vs. fosinopril, 0.77).[10, 134] In one study the patients were diabetic[10]and in the other, the patients had chronic renal failure.[134] By contrast, when nisoldipine was compared with enalapril in another population with diabetes, the RR for MI was increased (2.25).[30] Differences in study design and conduct made a simple comparison impossible. Without the opportunity to compare these results to patients without diabetes or renal-failure, very little can be concluded from these studies regarding the relative effectiveness of CCBs in these subgroups. Cardiovascular mortality RR's for the trial comparing nicardipine to a trichlormethiazide (RR 1.03; 95% CI, 0.18-5.79) in elderly Japanese patients[11] and the trial comparing verapamil SR to atenolol (RR 0.99; 95% CI, 0.79-1.24) showed no difference from rates of the other four CCB vs diuretic and/or beta-blocker comparisons.[23]

Stroke

Stroke rates (fatal and nonfatal) for CCB vs ACE inhibitor comparisons were only found in renal insufficiency[12, 134] and diabetic[16, 30, 125, 126] subpopulations (see section 1A under Key

Question 1 for detailed results). The evidence is insufficient to differentiate between CCBs for either subgroup. Relative risks of fatal/nonfatal stroke were also available for the nicardipine vs trichlormethiazide comparison in elderly Japanese patients (RR 1.03; 95% CI, 0.18-5.97). The risk for the elderly Japanese patients in the nicardipine group of fatal/nonfatal stroke was not different to that of the other three CCB vs diuretic and/or beta-blocker comparisons in target populations.

End stage renal failure

ESRD rates for CCB vs ACE-Inhibitor comparisons were only found in groups of African Americans with renal insufficiency[7, 32, 40, 109] and patients with diabetes[20, 118] Detailed results of these can be found in section 1A under Key Question 1. This evidence is insufficient to differentiate between CCBs for either subgroup. Relative risk of ESRD was not found in any of the six active-controlled trials of subpopulations.

Quality of life

We found two randomized active-controlled trials that evaluated the benefit of CCBs in improving quality of life in racial subgroups.[40, 44] The AASK pilot trial[40] was designed to compare the effects of amlodipine, ramipril, and metoprolol on quality of life in African Americans with hypertension as measured by the SF-36. The SF-36 was also used in a study of amlodipine in a predominantly Caucasian sample (TOMHS).[135] However, because the TOMHS trial used and reported effects on only selected indices from the larger SF-36 scales that were not reported for AASK, a comparison was not possible.

The NICS-EH trial[40, 44] was designed to measure the effects of nicardipine and trichlormethiazide on quality of life in elderly Japanese hypertensives using an unspecified scale comprised of 28 items. In summary, a comparison between pretreatment and posttreatment quality of life scores within the nicardipine group showed significant deterioration in the cognitive function category and no change in the other eight categories. No other trial that used this same quality of life measure was found to be available for comparison. As a result, evidence from both the AASK and NICS-EH is insufficient to address whether CCBs differ in their affect on quality of life in African American or elderly Japanese patients with hypertension.

3B. Angina

We found no evidence concerning the effectiveness or safety of any of the included CCBs in subgroups. Although the studies were conducted in a variety of countries, data on subgroups were either not reported or not analyzed separately.

3C. Supraventricular arrhythmias

We found no evidence concerning the effectiveness or safety of any of the included CCBs in subgroups. Although the studies were conducted in a variety of countries, data on subgroups were either not reported or not analyzed separately.

3D. Systolic dysfunction

Data regarding subpopulations were not sufficiently reported in any study to assess differences by CCB selection. Enrolled patients were generally older males, but results were not stratified by age or gender in any study. Ethnicity was not reported in any study. Differential effects based on type and severity of systolic dysfunction is discussed above, with no apparent differences.

Summary

The table below summarizes the overall strength of evidence for each question, by indication. Publication bias is a concern for angina and supraventricular arrhythmia, because trials not fully published (e.g., conducted for FDA approval) or those that are currently available only as abstracts cannot be fully assessed for inclusion.

Table 10. Strength of the evidence

Key Question 1: Comparative Effectiveness	Grade of Evidence**	Conclusion
a. Hypertension	Overall grade: Poor	No head-to-head trials. Evidence for amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nisoldipine, and verapamil from 12 long-term, active-controlled trials was insufficient to clearly differentiate one CCB from another for effectiveness. No evidence was found for bepridil or felodipine.
b. Angina	Overall grade: Good for chronic stable angina Poor for Prinzmetal's variant angina	Chronic stable angina: Consistent evidence of equivalence from 13 head-to-head trials of amlodipine, diltiazem, nisoldipine, nicardipine, and nifedipine. Only indirect evidence for bepridil and verapamil. No evidence for felodipine and isradipine. Prinzmetal's variant angina: 2 placebo-controlled trials of verapamil
c. Supraventricular arrhythmias	Overall grade: Fair to good for AF	Consistent results in 3 fair quality head-to-head trials of diltiazem and verapamil for chronic AF, with no difference found. Active- and placebo-controlled studies confirm this finding. Evidence for other supraventricular arrhythmias was inadequate.
Key Question 1: Comparative Effectiveness	**Grade of Evidence****	**Conclusion**
d. Systolic dysfunction	Overall grade: Fair	No head to head trials. Consistent indirect evidence across six fair-good quality placebo-controlled trials of amlodipine (2 trials) and felodipine (4 trials) showed that both CCB's had no significant effects (positive or negative) on all-cause mortality or combined fatal and nonfatal cardiovascular events. Evidence from nine fair quality active or placebo-controlled trials indicates no difference among amlodipine, felodipine, nifedipine or nisoldipine in effects on symptoms or exercise tolerance. Evidence for diltiazem, isradipine and nicardipine was poor. No evidence was found for bepridil, nifedipine, nisoldipine or verapamil.

Key Question 2: Adverse Effects	**Quality of Evidence**	**Conclusion**
a. Hypertension	Overall grade: Poor	No head-to-head trials. Indirect analysis of data for amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nisoldipine,and verapamil from 13 long-term, active-controlled trials was insufficient to clearly differentiate one CCB from another for incidence or withdrawals due to adverse effects. No trials were found for either bepridil or felodipine.
b. Angina	Overall grade: Fair	13 short-term head-to-head trials of amlodipine, diltiazem, nisoldipine, nicardipine, and nifedipine indicate no difference in adverse event or withdrawal rate overall. Only indirect evidence for bepridil and verapamil. No evidence for felodipine and isradipine
c. Supraventricular arrhythmias	Overall grade: Poor	No long-term studies included. Evidence from three head-to-head trials of diltiazem and verapamil is mixed.
d. Systolic dysfunction	Overall grade: Poor	No head to head trials. Data from five active and placebo-controlled trials of mixed durations did not clearly differentiate the safety of felodipine and nifedipine in mild-moderate systolic dysfunction or felodipine and amlodipine in severe systolic dysfunction. No evidence for other CCB's was found.
Key Question 3: Subgroups	**Quality of Evidence**	**Conclusion**
a. Hypertension	Overall grade: Poor	Evidence for amlodipine, nicardipine, nifedipine, and nisoldipine and verapamil SR from 6 long-term, active-controlled trials was insufficient to clearly differentiate one CCB from another for effectiveness or adverse effects in subgroups of diabetics; patients with renal insufficiency; patients with CAD; and older Japanese patients.
b. Angina	Overall grade: Poor	We found no evidence regarding the effectiveness or safety of any of the included CCBs for treatment of angina in subgroups.
c. Supraventricular arrhythmias	Overall grade: Poor	We found no evidence regarding the effectiveness or safety of any of the included CCBs for treatment of supraventricular arrhythmia in subgroups.
d. Systolic dysfunction	Overall grade: Poor	We found no evidence about effectiveness or safety of any of the CCBs for treatment of systolic dysfunction in subgroups.
		No evidence for diltiazem XL or TZ, felodipine, or verapamil HS or VR was found for any question

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

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Figure 1: Calcium channel blocker drug class review flow diagram

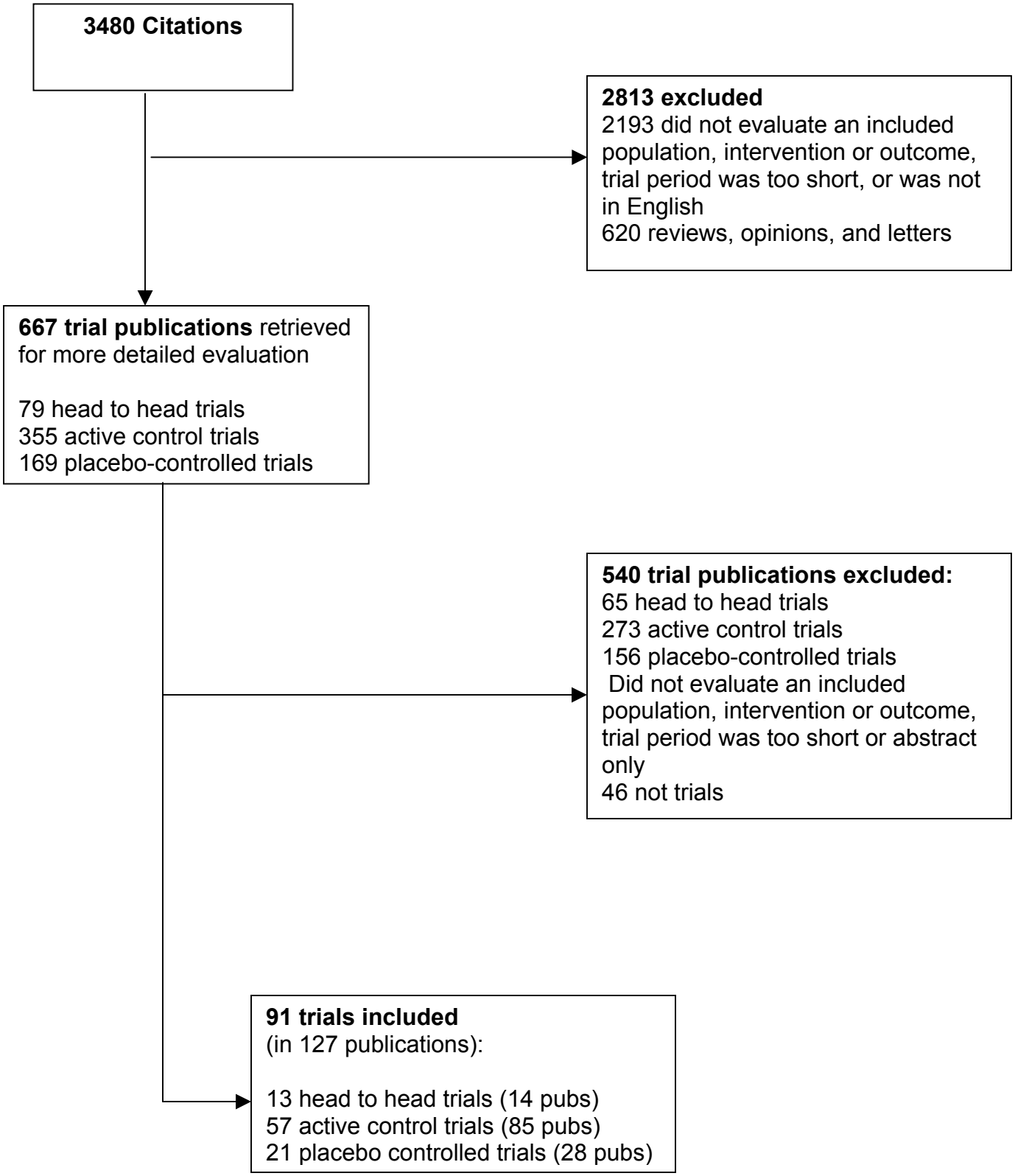


Figure 2.

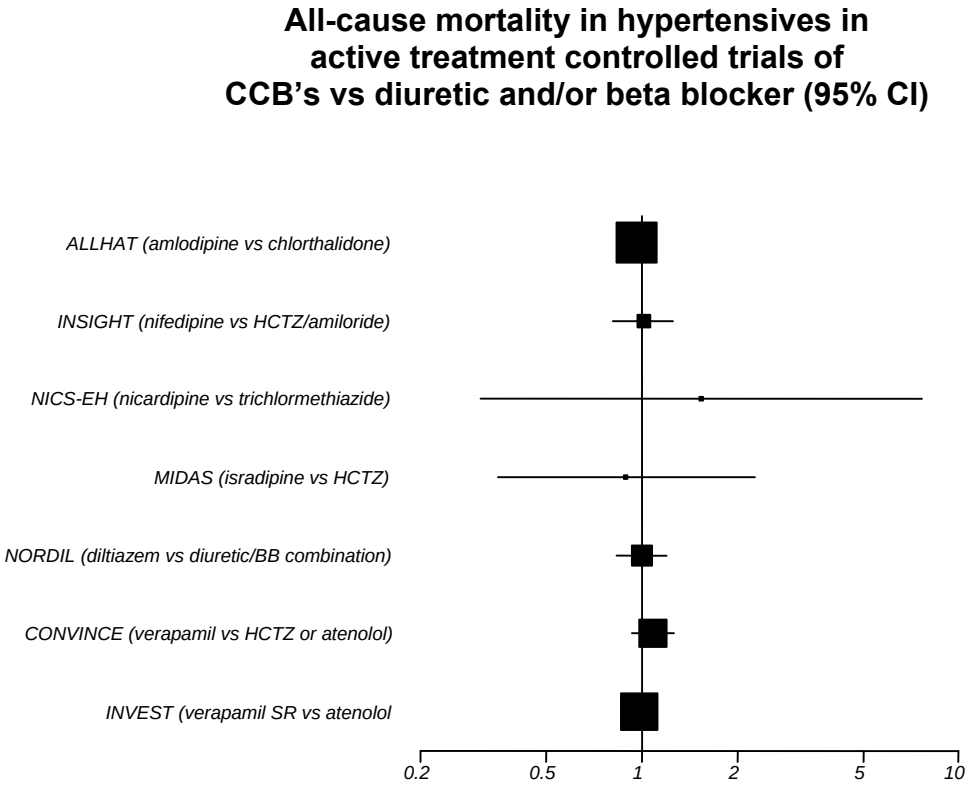

All-cause mortality in hypertensives in active treatment controlled trials of CCB's vs diuretic and/or beta blocker (95% CI)
ALLHAT (amlodipine vs chlorthalidone)
INSIGHT (nifedipine vs HCTZ/amiloride)
NICS-EH (nicardipine vs trichlormethiazide)
MIDAS (isradipine vs HCTZ)
NORDIL (diltiazem vs diuretic/BB combination)
CONVINCE (verapamil vs HCTZ or atenolol)
INVEST (verapamil SR vs atenolol
0.2
0.5
1
2
5
10

Figure 3.

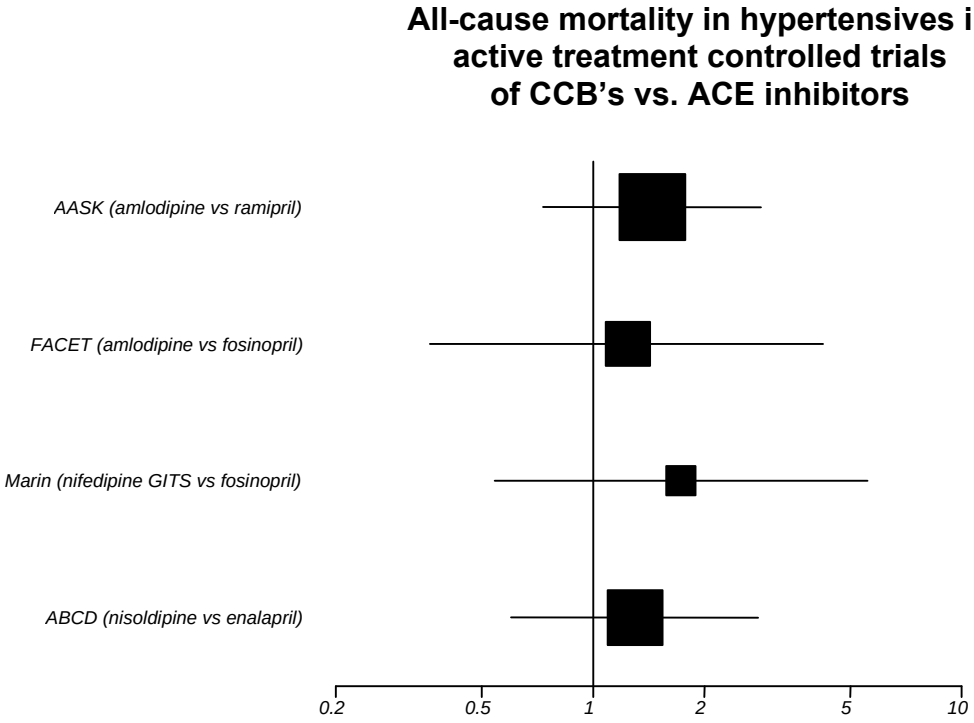

All-cause mortality in hypertensives in active treatment controlled trials of CCB's vs. ACE inhibitors
AASK (amlodipine vs ramipril)
FACET (amlodipine vs fosinopril)
Marin (nifedipine GITS vs fosinopril)
ABCD (nisoldipine vs enalapril)
0.2
0.5
1
2
5
10

Figure 4.

Mean change in number of angina attacks per week in head to head trials (weighted mean difference, 95% CI)

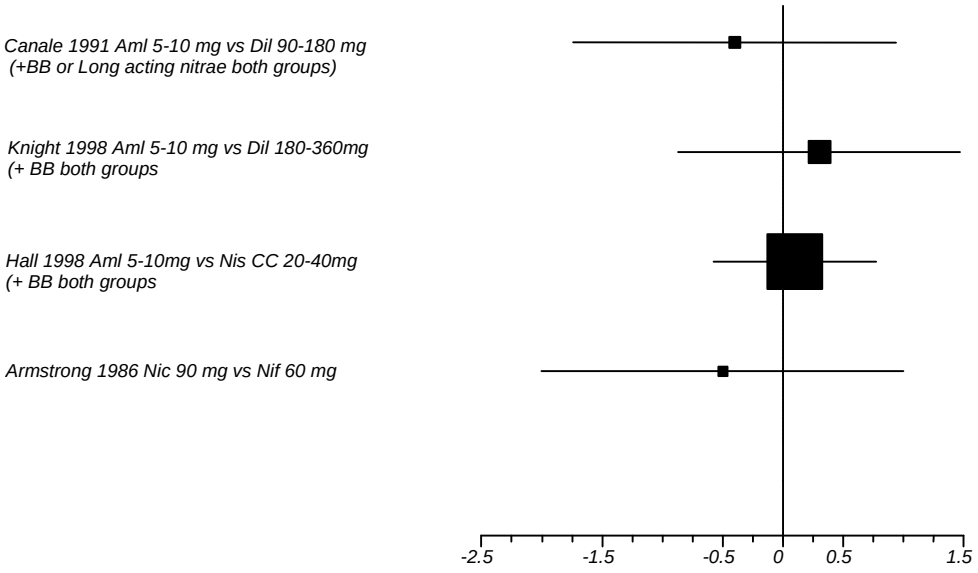


Figure 5.

Mean change in number of nitroglycerin doses per week in head to head trials (weighted mean difference, 95% CI)

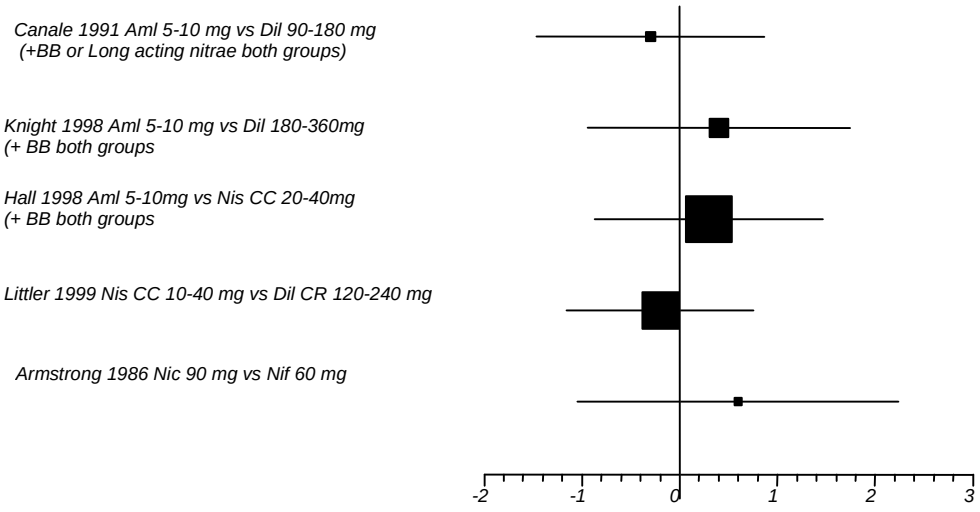


Figure 6.

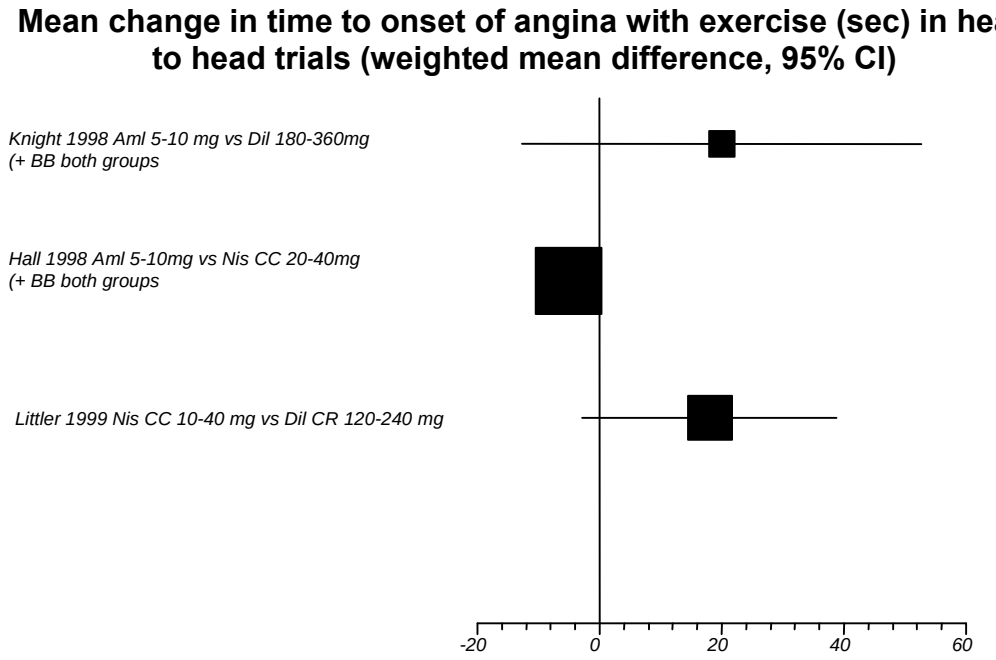

Mean change in time to onset of angina with exercise (sec) in head to head trials (weighted mean difference, 95% CI)
Knight 1998 Aml 5-10 mg vs Dil 180-360mg (+ BB both groups
Hall 1998 Aml 5-10mg vs Nis CC 20-40mg (+ BB both groups
Littler 1999 Nis CC 10-40 mg vs Dil CR 120-240 mg
-20
0
20
40
60

Figure 7.

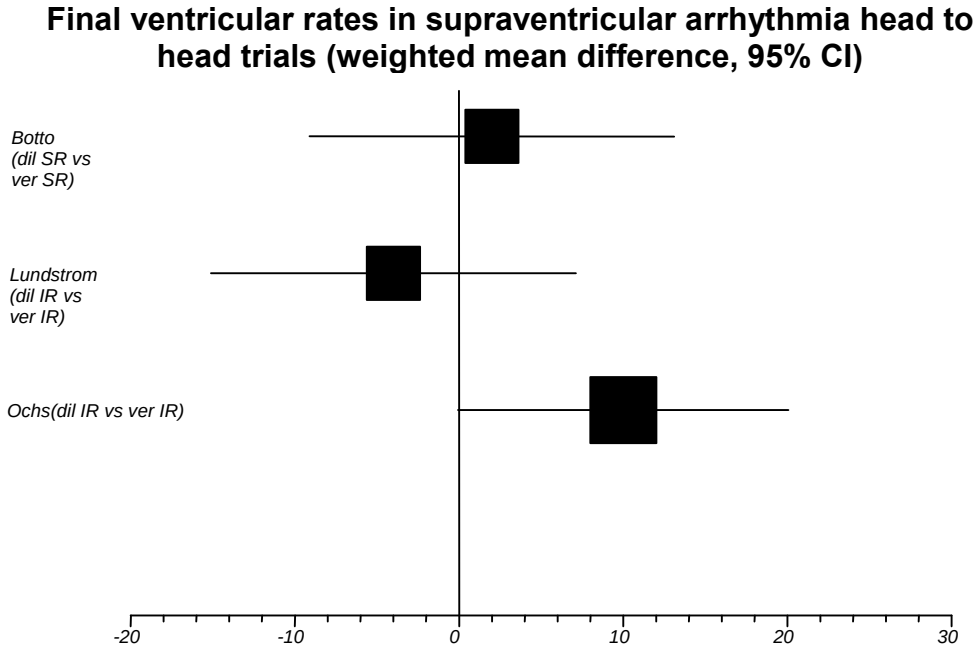

Final ventricular rates in supraventricular arrhythmia head to head trials (weighted mean difference, 95% CI)
Botto (dil SR vs ver SR)
Lundstrom (dil IR vs ver IR)
Ochs(dil IR vs ver IR)
-20
-10
0
10
20
30

Figure 8.

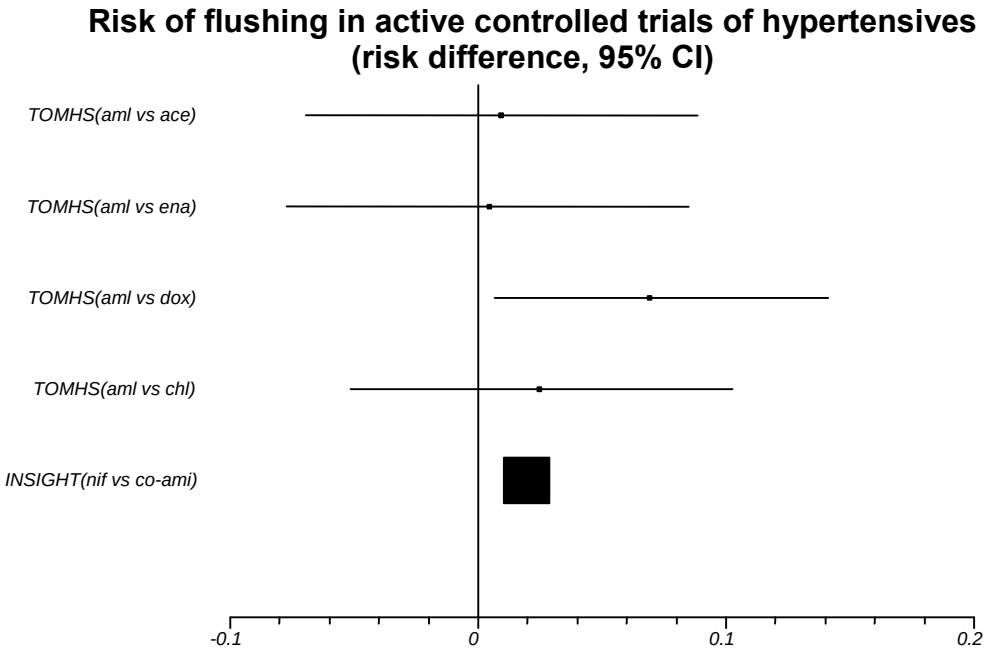

Risk of flushing in active controlled trials of hypertensives
(risk difference, 95% CI)
TOMHS(aml vs ace)
TOMHS(aml vs ena)
TOMHS(aml vs dox)
TOMHS(aml vs chl)
INSIGHT(nif vs co-ami)
-0.1
0
0.1
0.2

Figure 9.

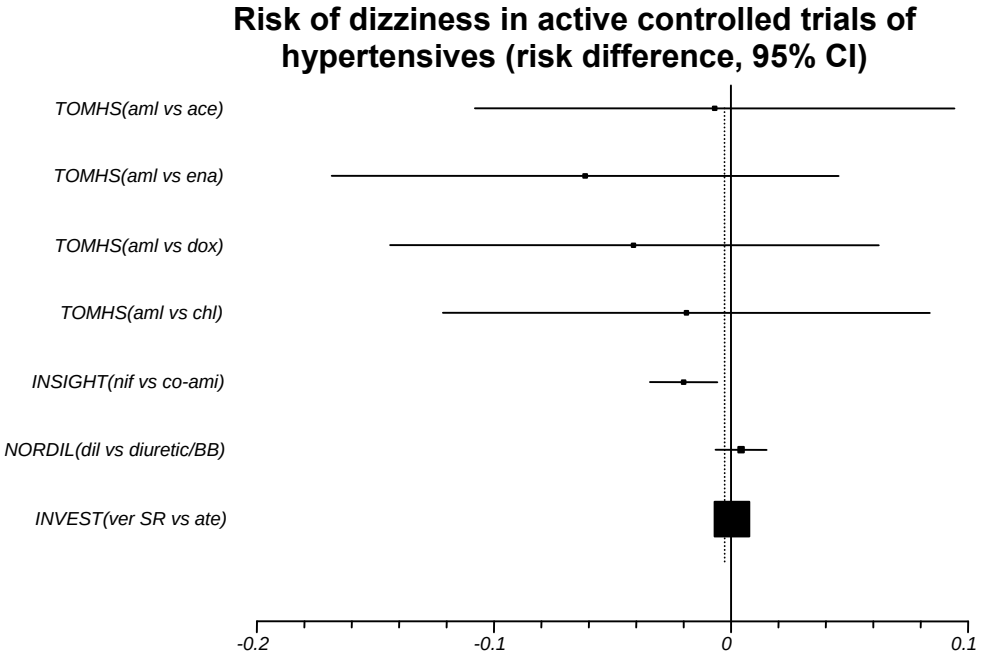

Risk of dizziness in active controlled trials of hypertensives (risk difference, 95% CI)
TOMHS(aml vs ace)
TOMHS(aml vs ena)
TOMHS(aml vs dox)
TOMHS(aml vs chl)
INSIGHT(nif vs co-ami)
NORDIL(dil vs diuretic/BB)
INVEST(ver SR vs ate)
-0.2
-0.1
0
0.1

Figure 10.

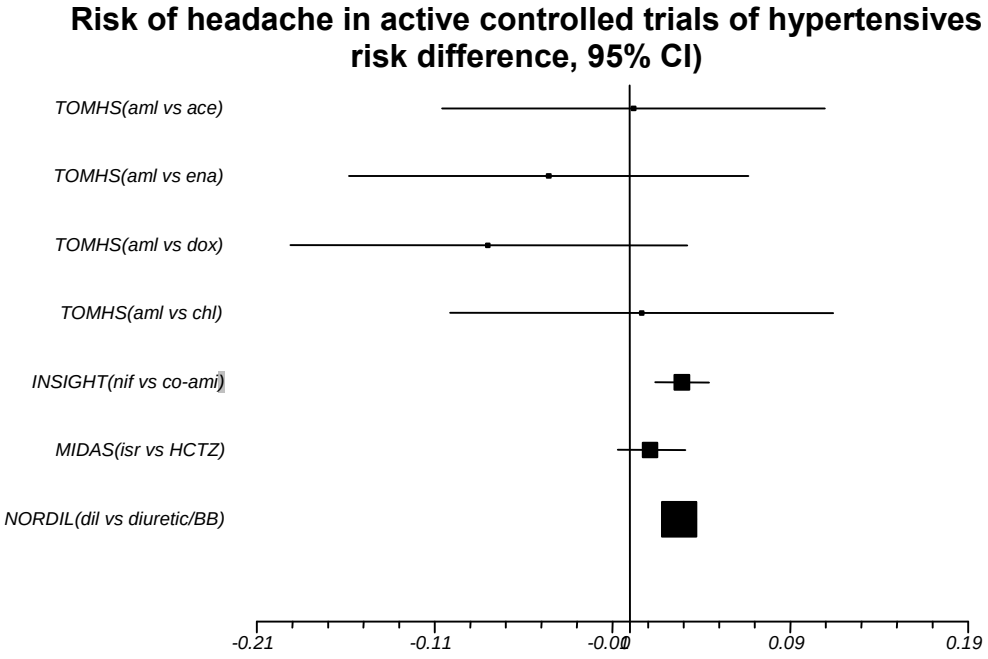

Risk of headache in active controlled trials of hypertensives
risk difference, 95% CI)
TOMHS(aml vs ace)
TOMHS(aml vs ena)
TOMHS(aml vs dox)
TOMHS(aml vs chl)
INSIGHT(nif vs co-ami)
MIDAS(isr vs HCTZ)
NORDIL(dil vs diuretic/BB)
-0.21
-0.11
-0.00
0.09
0.19

Figure 11.

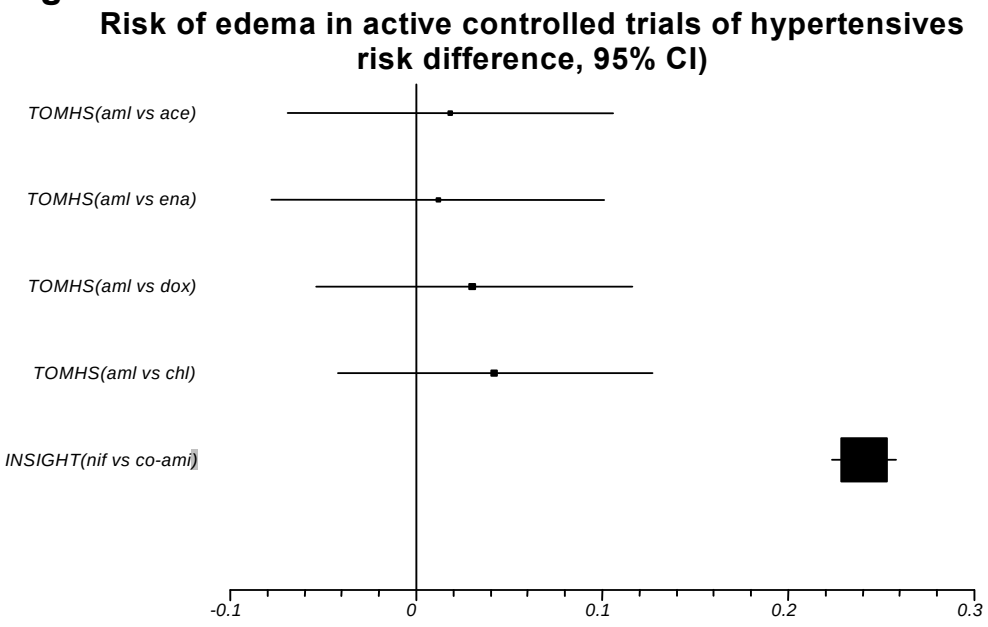

Risk of edema in active controlled trials of hypertensives
risk difference, 95% CI)
TOMHS(aml vs ace)
TOMHS(aml vs ena)
TOMHS(aml vs dox)
TOMHS(aml vs chl)
INSIGHT(nif vs co-ami)
-0.1
0
0.1
0.2
0.3

Figure 12.

Withdrawals due to AEs for hypertension active controlled trials of CCBs vs diuretics or beta blockers (risk difference, 95% CI)

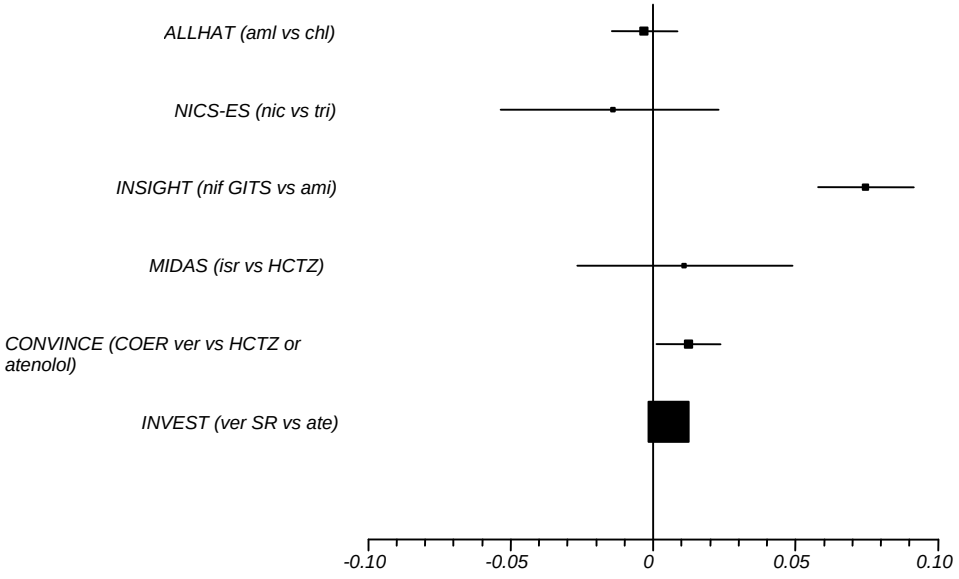


Figure 13.

Withdrawals due to adverse events in active controlled trials of hypertensives comparing CCBs to ACE inhibitors (risk difference, 95% CI)

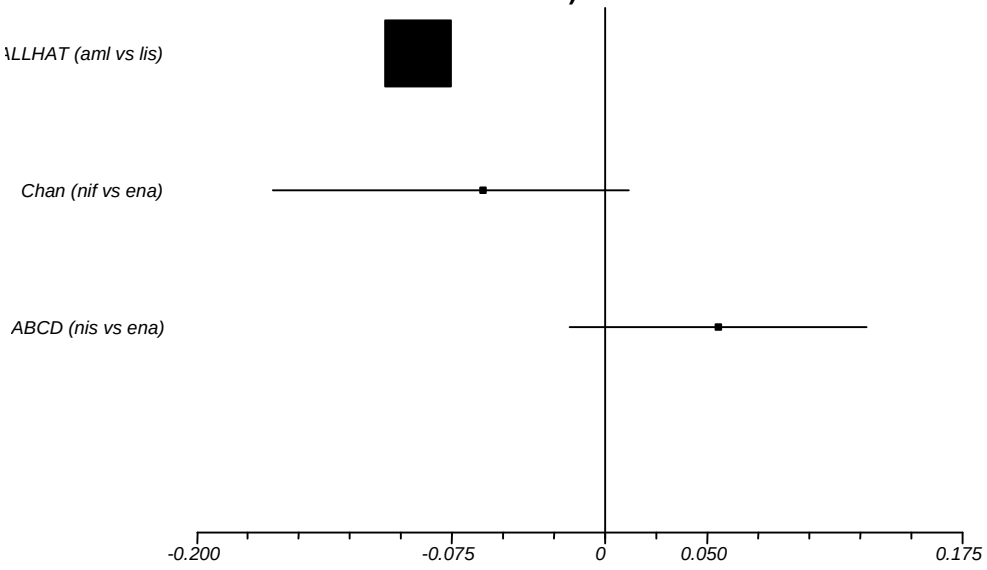


Figure 14.

Any adverse event in head to head trials of patients with angina (risk difference, 95% CI)

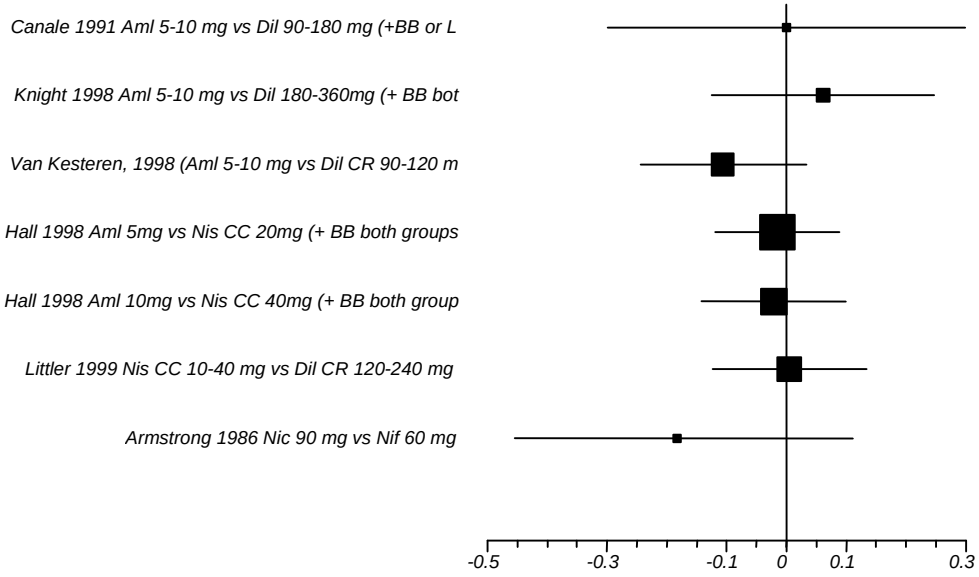


Figure 15.

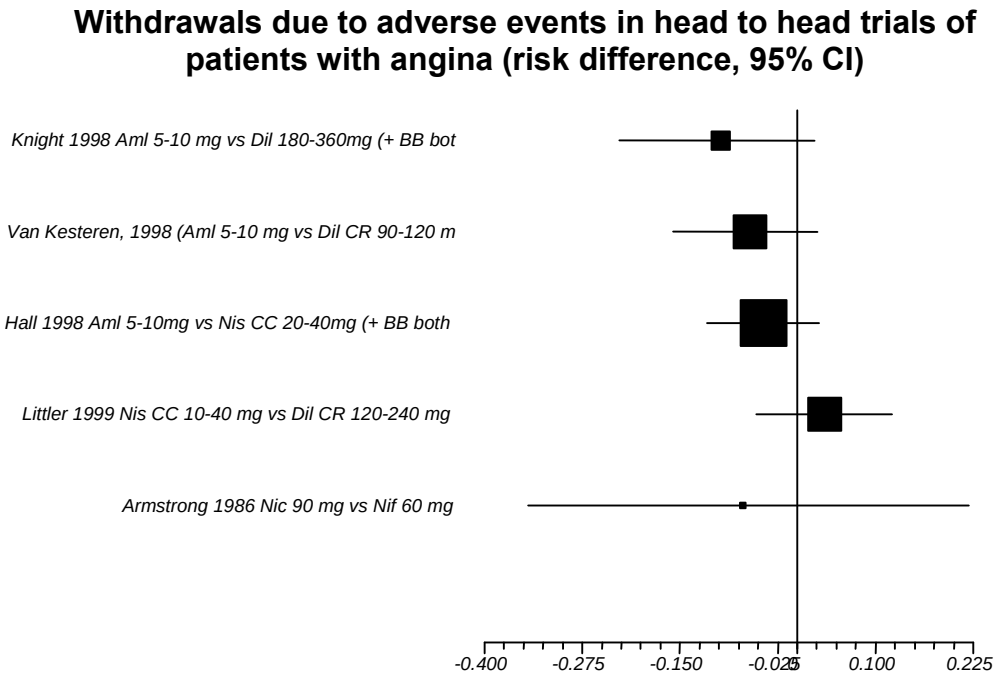

Withdrawals due to adverse events in head to head trials of patients with angina (risk difference, 95% CI)
Knight 1998 Aml 5-10 mg vs Dil 180-360mg (+ BB bot
Van Kesteren, 1998 (Aml 5-10 mg vs Dil CR 90-120 m
Hall 1998 Aml 5-10mg vs Nis CC 20-40mg (+ BB both
Littler 1999 Nis CC 10-40 mg vs Dil CR 120-240 mg
Armstrong 1986 Nic 90 mg vs Nif 60 mg
-0.400
-0.275
-0.150
-0.025
0.100
0.225

Figure 16.

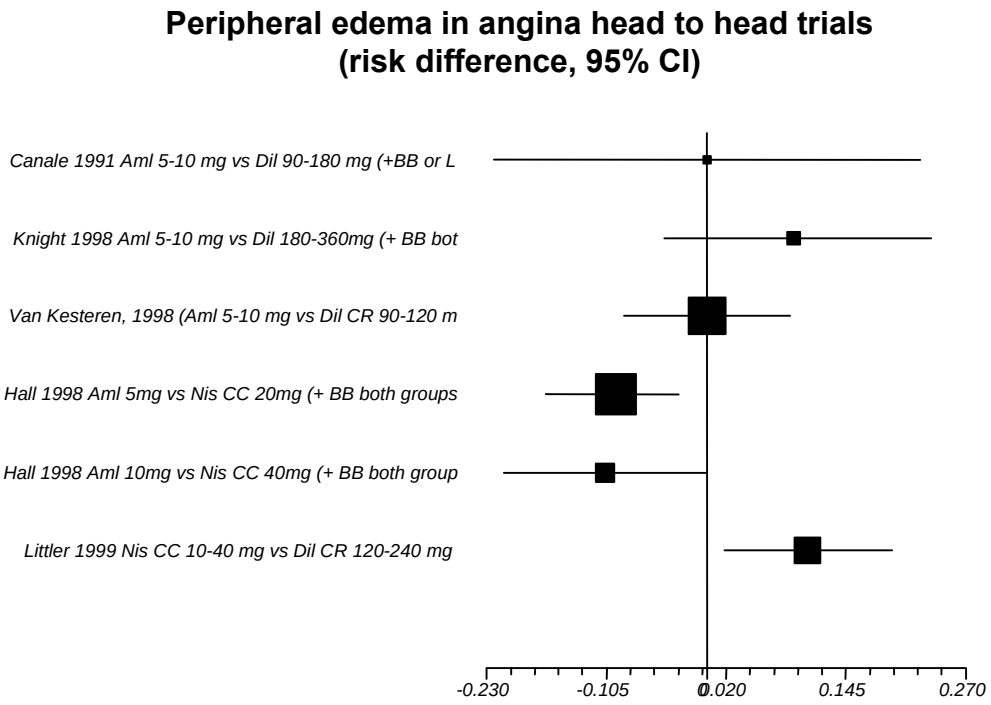

Peripheral edema in angina head to head trials
(risk difference, 95% CI)
Canale 1991 Aml 5-10 mg vs Dil 90-180 mg (+BB or L
Knight 1998 Aml 5-10 mg vs Dil 180-360mg (+ BB bot
Van Kesteren, 1998 (Aml 5-10 mg vs Dil CR 90-120 m
Hall 1998 Aml 5mg vs Nis CC 20mg (+ BB both groups
Hall 1998 Aml 10mg vs Nis CC 40mg (+ BB both group
Littler 1999 Nis CC 10-40 mg vs Dil CR 120-240 mg
-0.230
-0.105
0
0.020
0.145
0.270

Figure 17.

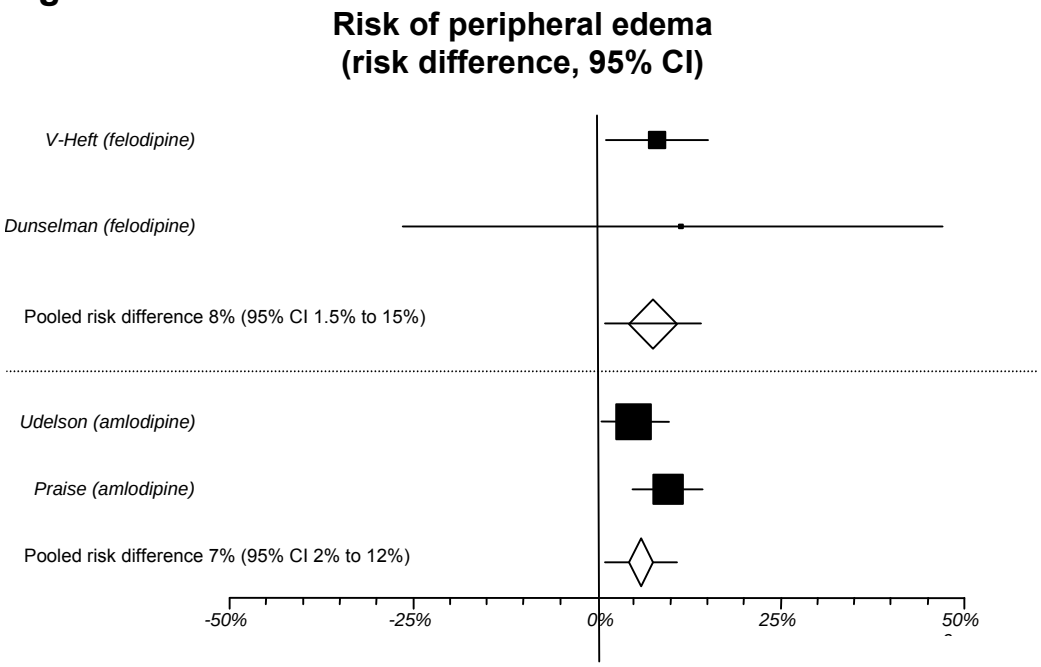
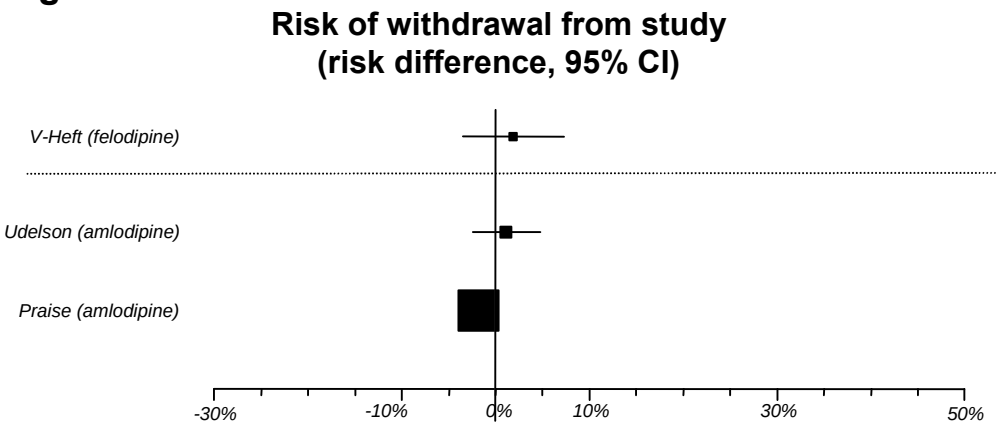

Risk of peripheral edema
(risk difference, 95% CI)
V-Heft (felodipine)
Dunselman (felodipine)
Pooled risk difference 8% (95% CI 1.5% to 15%)
Udelson (amlodipine)
Praise (amlodipine)
Pooled risk difference 7% (95% CI 2% to 12%)
-50%
-25%
0%
25%
50%

Figure 18.


Risk of withdrawal from study
(risk difference, 95% CI)
V-Heft (felodipine)
Udelson (amlodipine)
Praise (amlodipine)
-30%
-10%
0%
10%
30%
50%

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
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
Omvik, 1993 Norway	NR	NR	Yes	Yes	Yes	Yes
Nifedipine comparisons						
Metelitsa, 1996	NR	NR	Absolute data NR, but described homogeneity between groups	Yes	Yes	Yes
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

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
Amlodipine comparisons						
TOMHS (Treatment of Mild Hypertension Study) Mascioli, 1990 Treatment of Mild Hypertension Research Group, 1991 Neaton, 1993 Grimm, 1997 United States	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	Unclear	Attrition, adherence, contamination clearly reported in Neaton, 1993	No	Fair	Good Average age: 55 years Gender: 62% male Race: 54.6% white
Omvik, 1993 Norway	No	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
Nifedipine comparisons						
Metelitsa, 1996	No	Unclear	Attrition reported clearly Others NR	No	Fair-Poor	Not clear Absolute data NR
Bulpitt, 2000 Austria, Italy, Germany, Netherlands, Poland, Spain, Switzerland, and the UK	No	Unclear	Attrition clearly reported Others NR	No	Fair	Good for elderly population Mean age: bis=67.9; nif r=68.5

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	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	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	Yes	At least 4 years	National Heart, Lung and Blood Institute, Merck, Harp and Dohme Research Laboratories and Pfizer, Inc.
Omvik, 1993 Norway	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	Yes	50 weeks	NR
Nifedipine comparisons					
Metelitsa, 1996	345 enrolled	NR	Yes	8 months	Bristol-Meyers
Bulpitt, 2000 Austria, Italy, Germany, Netherlands, Poland, Spain, Switzerland, and the UK	771 enrolled 747 randomized	NR	Yes	6 months	Merck

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
Fletcher, 1992 Europe	NR	NR	Yes	Yes	Yes	Yes
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
Isradipine comparisons						
LOMIR-MCT-IL trial Amir, 1994 Bar-On, 1993 Yodfat, 1996 Israel	NR	NR	Yes	Yes	Yes	Yes

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
Fletcher, 1992 Europe	No	Unclear	Attrition clearly reported Others NR	No	Fair	Good Average age: pin=55.9; nif=56.4 Gender(%male): pin=54; nif=48
Verapamil comparisons						
Boissel, 1995	No	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
Isradipine comparisons						
LOMIR-MCT-IL trial Amir, 1994 Bar-On, 1993 Yodfat, 1996 Israel	Unclear; suspected that patients who were lost to follow-up and who refused to continue were not included in analysis	Unclear	Attrition clearly reported; others NR	No	Fair	100% male

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Fletcher, 1992 Europe	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	Yes	6 months	Leo Pharmaceutical Products
Verapamil comparisons					
Boissel, 1995	722 enrolled	NR	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	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	Yes	1 year	Sandoz Pharma

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
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
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
Destors 1989 4 European countries	Inadequate (sealed envelope)	NR	Small difference in duration of angina (months): bep 52, pro 67	Yes	Yes	Yes

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
AMSA (Amlodipine vs slow release Metoprolol in the treatment of Atable exertional Angina) Midtbo 2000 Norway	No	Not clear	Yes	No	Fair-Poor	Good
APSIS (The Angina Prognosis Study in Stockholm) Sweden Rehnqvist, 1994 Rehnqvist, 1996	Yes for fatal and non-fatal CV events No for psychological variables	Not clear	Withdrawals due to AEs and other administrative reasons clearly reported. Others not reported.	No	Fair-Poor	Good; older population, greater proportion male
Destors 1989 4 European countries	Yes	Not clear	Unclear	Overall 20% bep 19%, pro 22%, pla 17%	Fair-Good	Good

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
AMSA (Amlodipine vs slow release Metoprolol in the treatment of Atable exertional Angina) Midtbo 2000 Norway	NR/31 randomized	Unstable angina within preveious 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 dergree AV-block; electrocardiograph pattersn 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	Yes	2 months	Pfizer
APSIS (The Angina Prognosis Study in Stockholm) Sweden Rehnqvist, 1994 Rehnqvist, 1996	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		Median 3.4 years	Swedish Heart Lung Foundation; Swedish Research Medical Council; Knoll AG
Destors 1989 4 European countries	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	Yes	6 months	possibly Organon

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
Hall, 2001 UK	NR	NR	Yes	Yes	Yes	Yes
Hauf-Zachariou, 1997 Great Britain	NR	NR	Yes	Yes	Yes	Yes

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
Hall, 2001 UK	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)	Not clear	Attrition reported. Others NR	No	Fair	Good; older population, greater proportion male
Hauf-Zachariou, 1997 Great Britain	Reported ITT as including all patients randomized (248); however, outcome results provided for *per protocol* population (212) only	Not clear	Attrition reported Others NR	No	Fair	Good; older population, greater proportion male

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Hall, 2001 UK	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	Yes	28 weeks	NR
Hauf-Zachariou, 1997 Great Britain	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	Yes	12 weeks	Boehringer Mannheim GmbH

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
Kawanishi, 1992 United States	NR	NR	Yes	Yes	Yes	Yes
Lee, 2002 Canada	adequate (block randomization)	NR	Yes	Yes	Yes	Yes
Meyer, 1991 Israel	NR	NR	No; differences in 1) angina duration and 2) frequency of previous MI's	Yes	Yes	Yes

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
Kawanishi, 1992 United States	Not clear	Not clear	None reported	NR	Fair	Yes
Lee, 2002 Canada	Not clear	Not clear	Withdrawals due to AEs and compliance clearly reported. Others NR	Not clear	Fair	
Meyer, 1991 Israel	No; analysis did not include 3 patients who withdrew due to lack of efficacy	Not clear	Withdrawals due to lack of efficacy clearly reported. Others NR	No	Poor	Good; Average age >50; higher proportion male

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Kawanishi, 1992 United States	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	Yes	3 months	Pfizer
Lee, 2002 Canada		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	Yes		
Meyer, 1991 Israel	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	Yes	8 weeks	NR

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
Myers 1988 Canada	NR	NR	No, number on nitrate therapy = nif 17%, pro 36%	Yes	Yes	no
Pandhi, 1991 India	NR	NR	Yes	Yes	Yes	Yes
Pehrsson, 2000 Sweden	NR	NR	Yes	Yes	Yes	Yes

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
Myers 1988 Canada	primary outcomes and adverse events yes, secondary outcomes no.	Not clear	Attrition reported Others NR	loss = 0, withdrawals nif 17%, pro 29%	Poor	Fair, more women than men
Pandhi, 1991 India	No; analysis did not include patients who became lost-to-followup or withdrew due to worsening of angina	Not clear	Attrition reported Others NR	No	Fair	Good; older population, greater proportion male
Pehrsson, 2000 Sweden	Not clear	Not clear	Attrition clearly reported. Others NR	No	Fair	Good; Average age >50; higher proportion male

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Myers 1988 Canada	NR/27 randomized	Evidence of aortic valve disease; cardiovasclar 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	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	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	Yes	8 weeks	NR
Pehrsson, 2000 Sweden	442 screened/351 randomized	Significant hepatic, renal, cardiac, brochospastic disease; major concurrent disease; women of childbearing potential	Yes	10 weeks	NR

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
Singh 1993 USA	NR	NR	yes, but very few measured presented	Yes	NR	Yes

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
Singh 1993 USA	Not clear	Not clear	Attrition clearly reported. Others NR	Overall 24%; aml 20%, nad 28%	Fair-Poor	Fair

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Singh 1993 USA	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	Yes	24 weeks	NR

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
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
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

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
SWAN study group 1999 Switzerland, Austria	no, stated to be but 3 patients not accounted for	Not clear	Not clearly reported	No	Poor	Good
TIBET (Total Ischaemic Burden European Trial) 9 European countries Dargie, 1996 The TIBET Study Group, 1992	Yes	Not clear	Overall attrition clearly reported. Others NR	No	Fair-Good	Good; Average age >50; higher proportion male

Evidence Table 1. Quality assessment

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

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
Ulvenstam; 1992 Europe (Norway, Sweden, Iceland)	NR	NR	No; differences in history of MI and weekly anginal attack rate	Yes	Yes	Yes
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
Armstrong, 1986 UK	NR	NR	Yes	Yes	Yes	Yes

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
Ulvenstam; 1992 Europe (Norway, Sweden, Iceland)	Yes for safety(n=58); no for efficacy(n=55); reason for 3-patient discrepancy NR	Not clear	only withdrawals due to AEs reported	No	Fair-Poor	Good; older population, greater proportion male
Vliegen, 1991 The Netherlands	No	Not clear	Attrition clearly reported; others NR	No	Fair-Poor	Good; older population, greater proportion male
Armstrong, 1986 UK	No; analysis did not include 12 patients that withdrew "early on" due to adverse events	Not clear	Attrition reported Others NR	No	Fair	Good; older population, greater proportion male

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Ulvenstam; 1992 Europe (Norway, Sweden, Iceland)	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	Yes	8 weeks	NR
Vliegen, 1991 The Netherlands	NR/56 ernolled	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	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	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.	Yes	8 weeks	NR

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
Bernink, 1991 The Netherlands	NR	NR	Some differences; % male higher and angina attack severity lower in Aml group	Yes	Yes	Yes
Canale, 1991 Italy	NR	NR	Yes	Yes	Yes	Yes

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
Bernink, 1991 The Netherlands	No	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
Canale, 1991 Italy	Yes	Yes	Reported that adverse events did not require discontinuation. Others NR	No	Fair	Good; older population, greater proportion male

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Bernink, 1991 The Netherlands	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; cardoivascular 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	Yes	8 weeks	NR
Canale, 1991 Italy	40	NR	Yes	10 weeks	NR

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
Hall, 1998 UK	NR	NR	Yes	Yes	Yes	Yes
Knight, 1998 UK	NR	NR	Yes	Yes	Yes	Yes

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
Hall, 1998 UK	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	Not clear	Attrition reported Others NR	No	Fair	Good; older population, greater proportion male
Knight, 1998 UK	Yes	Yes	Not clear	No	Fair	Good; older population, greater proportion male

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Hall, 1998 UK	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.	Yes	8 weeks	Bayer AG
Knight, 1998 UK	109	NR	Yes	8 weeks	Pfizer

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
Littler, 1999 UK	NR	NR	Yes	Yes	Yes	Yes
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

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
Littler, 1999 UK	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	Not clear	Attrition reported Others NR	No	Fair	Good; older population, greater proportion male
Pehrsson 1996 Sweden	Unclear	NR	Yes	16% overall, and per group	Poor	Good

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Littler, 1999 UK	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.	Yes	12 weeks	Bayer
Pehrsson 1996 Sweden	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.	Yes	8 weeks	Pfizer

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
Radice 1991 Italy	NR (met and nif randomized, dil added later)	NR	no, but very little data presented	Yes	No	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
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
Van Kesteren	NR	NR	Yes	Yes	Yes	Yes

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
Radice 1991 Italy	NR	NR	NR	NR	Poor	Unclear
Reicher-Reiss 1992 Israel	Unclear	NR	Yes	no, only 1 drop out in nis group	Poor	Unclear
Singh 1991 USA	No	NR	Yes	Overall 16% loss, bep 20%, dil 12%	Poor	Good
Van Kesteren	Stated ITT, but not clear	Not clear	Attrition reported Others NR	No	Fair	Good; older population, greater proportion male

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Radice 1991 Italy	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.	Yes	3 months	NR
Reicher-Reiss 1992 Israel	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.	Yes	8 weeks	Bayer
Singh 1991 USA	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 tranquelizers, nonnarcotic analgesic and diuretic drugs, other calcium antagonists, antiarrhythmic drugs, cardiac glycosides, tricyclic antidepressants, and neuroleptics.	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	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	Yes	8 weeks	Pfizer

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
Johnson, 1981 United States	NR	NR	Crossover	Yes	Yes	NR
Johnson, 1981 United States	NR	NR	N/A	Yes	NR	NR
AASK Agodoa, 2001 Wright, 2002 US	NR	double-masked	Yes	Yes	Yes, double-masked	Yes to study drugs
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
FACET Tatti, 1998 Pahor, 1998 Italy	Computer-generated random number sequence	Yes	Yes	Yes	Yes	N, open-label
NICS-EH NICS-EH Study Group, 1999;	Controller in central office	NR	Yes	NR	Yes, steering committee	double-dummy

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
Johnson, 1981 United States	No	Crossover	Yes	No	Fair	Yes
Johnson, 1981 United States	Yes	Crossover	No	No	Fair	Yes
AASK Agodoa, 2001 Wright, 2002 US	Yes	Yes	Yes	No Total 8.1%	Fair	Yes
ALLHAT Furberg, 2002; Grimm, 2001; Vidt, 2000; HALLHAT Officers, 2002; US	Yes	Yes	Yes	No Aml 2.8% Chl 2.7% Lis 3.0%	Good	Yes
FACET Tatti, 1998 Pahor, 1998 Italy	Yes	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
NICS-EH NICS-EH Study Group, 1999;	Yes, 'Per protocol"	Yes	Yes	No	Fair	Yes

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Johnson, 1981 United States	19	Yes	Yes	9 months	NIH Ischemic Heart Disease Specialized Center of Research grant
Johnson, 1981 United States	10		Yes	8 months	NIH; Knoll Pharmaceutical Company; Pfizer Phamaceutical Company supplied tablets
AASK Agodoa, 2001 Wright, 2002 US	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	Yes	2-5 years	NIH, National Institute of Diabtes and Digestive and Kidney Diseases, Pfizer, Astra-Zeneca King Pharmaceuticals
ALLHAT Furberg, 2002; Grimm, 2001; Vidt, 2000; HALLHAT Officers, 2002; US	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.	Yes	6 years	National Heart, Lung and Blood Institute, AstraZeneca, Bristol-Myers Squibb and Pfizer, Inc.
FACET Tatti, 1998 Pahor, 1998 Italy	380	Stated	Yes	3 years	Bristol-Myers Squibb, Pfizer
NICS-EH NICS-EH Study Group, 1999;	414/429	NR	Yes		NR

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
Marin, 2001 Spain	NR	NR	Yes	Yes	No, open trial	No, open trial
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
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

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
Marin, 2001 Spain	Stated ITT, unclear	Yes	Attrition reported Others NR	No	Fair	Good Mean age: Fos=53; Nif GITS=56 Gender(%male): Fos=60.5; Nif GITS: 57.1
Chan, 1992 Chan, 2000 Hong Kong	Yes	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
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	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	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

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Marin, 2001 Spain	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	Yes	A minimum of 3 years	NR
Chan, 1992 Chan, 2000 Hong Kong	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	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	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	Yes	48 months	Bayer AG

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
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
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
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

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
NORDIL (Nordic Diltiazem Study) The NORDIL Group, 1993 Hedner, 1999 Hansson, 2000 Kjeldsen, 2002 Norway/Sweden	Data from 35 patients from one center were not included in analysis because of uncertainty about data quality	Unclear	Attrition, crossovers, contramination 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
ABCD (Appropriate Blood Pressure Control in Diabetes) Savage, 1993 Schrier, 1996 Estacio, 1998a Estacio, 1998b United States	Yes	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
MIDAS (Multicenter Isradipine Diuretic Atherosclerosis Study) The MIDAS Research Group, 1989 Borhani, 1990 Borhani, 1991 Borhani, 1992 Furberg, 1993 Borhani, 1996 United States	Yes	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

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	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	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 cerebrovacular disease or MI within the previous 6 months; present congestive heart failure	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	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	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	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	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

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
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
Testa, 1998 Spain	NR	NR	No; mean age higher in nif group(p=0.023)	Yes	Yes	Yes
Black, 2001	NR	NR	Yes	Yes	Yes	Yes

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
CONVINCE Black, 1998, 2001, US	Y, although 62 (ver) and 64 (HCTZ and ate) patients excluded due to data integrity concerns at 2 sites.	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
Testa, 1998 Spain	Unclear Randomized: nif=178; aml=178 ITT: nif=172; aml=175 Table 4 results: nig=161; aml=174	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
Black, 2001	Yes for safety; no for QOL	Unclear	Attrition clearly reported; others NR	No	Fair	Good; nearly half age>65 years, which the paper reported as being typical of this population

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
CONVINCE Black, 1998, 2001, US	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.	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	430 screened 356 randomized	NR	Yes	24 weeks	Quimica Farmaceutics Bayer
Black, 2001	250 screened 171 enrolled	NR	Yes	52 weeks	AstraZeneca, LP

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
Yilmaz	NR	NR	Yes	Yes	NR	NR
Botto, 1998 Italy	NR	NR	N/A - crossover study	Yes	Yes	no
Lundstrom, 1990 Sweden	NR	nr	na - crossover study	yes, but extermely vague	Yes	Yes
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%)			

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
Yilmaz	NR	NR	NR	NR	Fair	Fair
Botto, 1998 Italy	Yes	Yes	Yes	None	Fair	Good
Lundstrom, 1990 Sweden	No	Yes	Yes	Yes, 1 lost during dil, none in ver or placebo. But overall rate is low.	Fair	Fair
Ochs 1985 Germany						

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Yilmaz	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	Yes	Extremely short	NR
Botto, 1998 Italy	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.	Yes	Extremely short	NR
Lundstrom, 1990 Sweden	NR	NR	Yes	Extremely short	Swedish Heart and Lung Foundation, and Ferrosan (Swedish medical device and nutritional supplement co.)
Ochs 1985 Germany					

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
Dahlstrom 1992 Sweden	NR	NR	N/A - crossover study	Yes	NR	NR
Farshi, 1999 US	NR	NR	N/A - crossover study	Yes	No	No
Koh, 1995 Korea	NR	NR	Yes	Yes	No	No
Koh, 1995 Korea	NR	NR	Yes	Yes	No	No

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
Dahlstrom 1992 Sweden	No	NA	Yes	Overall withdrawal rate 23% dil 0% pro 8% dil + pro 15%	Fair	Unclear
Farshi, 1999 US	No	NA	No	None	Fair	Fair
Koh, 1995 Korea	No	NR	Yes	NR	Fair	Fair
Koh, 1995 Korea	No	NR	Yes	NR	Fair	Fair

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Dahlstrom 1992 Sweden	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, inlcudings calcium entry blockers, c) beta blockers, d) tricyclic antidepressants, pehnothiazines, and diazepam and MI within preceding 6 months.	Yes	Extremely short	KABI-Pharmacia, Swedish Heart Lung Foundation and the Gothenburg Medical Faculty
Farshi, 1999 US	NR	LVEF <35% by Echo, HR < 55 bpm, Wolff-Parkinson-White syndrome, clinically signifcant renal thryoud or heparic dyusfunction, uncontrolled hypertension, sick sinus syndrome, implanted pacemaker, unstable angina or acute MI or persistent suystolic blood pressure <95 mmHg, taking theophylline, clonidine,or inhaled beta-agonists, or with previous exposure to amiodarone.	Yes	Extremely short	Friends of Research
Koh, 1995 Korea	NR	HR at rest < 60 bpm, ejection fraction <30%, diabetes mellitus, bronchial asthma, crhonic obstructive lung disease, untreated thyrotoxicosis < 2 months after myocardial infarction, and SBP < 90 mmHg	Yes	Moderate	NR
Koh, 1995 Korea	NR	HR at rest <60 bpm, ejection fraction <30%, diabetes mellitus, bronchial asthma, crhonic obstructive lung disease, untreated thyrotoxicosis <2 months after MI, and SBP <90 mmHg	Yes	Moderate	Inha University grants

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
Hohnloser 2000 Germany	NR	NR	some differences: dil group longer duration AF, more recurrent AF at baseline, higher proportion with hypertension.	Yes	No	No
Lewis 1988 Scotland	NR	NR	N/A - crossover study	Yes, but extremely vague	NR	Yes
Ahuja 1989 India	NR	NR	N/A - crossover study	Yes, but extremely vague	No	No
Channer 1987 UK	NR	NR	N/A - crossover study	Yes, but extremely vague	Yes	No
Dorian, 1996 multiple countries	NR	NR	Yes	yes	no	No
James, 1989 UK	NR	NR	N/A - crossover study	Yes, but extremely vague	Yes	No
Lewis 1987 Scotland	adequate (random numbers)	NR	N/A - crossover study	Yes, but extremely vague	Yes	No

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
Hohnloser 2000 Germany	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)	NR	Yes	Yes - high loss to follow up in ami group	Fair	Good
Lewis 1988 Scotland	No	NA	Yes	3 withdrew during treatment with dil	Fair	Unclear
Ahuja 1989 India	No	NA	Yes	None	Poor	Fair
Channer 1987 UK	No	NA	Yes	None	Fair	Poor, very high proportion of women, high proportion of valve disease
Dorian, 1996 multiple countries	Yes	NR	Yes	NR	Fair	NR
James, 1989 UK	No	NR	Yes	NR	Fair	Fair
Lewis 1987 Scotland	No	NR	Yes	NR	Fair	Good

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Hohnloser 2000 Germany	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 intrcardiac 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.	Yes	Good	Sanofil Synthelabo Research, and Parke Davis Research
Lewis 1988 Scotland	NR	NR	Yes	Extremely short	NR
Ahuja 1989 India	NR	NR	Yes	Extremely short	NR
Channer 1987 UK	NR	NR	Yes	Extremely short	NR
Dorian, 1996 multiple countries	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 thrid degree AV block, or a PR interval >0.28 seconds or QRS interval >0.15 seconds during sinus rhythm	Yes	Good	3M Pharmaceuticals
James, 1989 UK	NR	NR	Yes	Extremely short	Wellcome Trust
Lewis 1987 Scotland	NR	NR	Yes	Extremely short	NR

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
Lewis, 1989 Scotland	NR	NR	N/A - crossover study	Yes	Yes	No
Lundstrom, 1992 Sweden	NR	NR	N/A - crossover study	Yes, but extremely vague	Yes	No
Rasmussen	NR	NR	NR	Yes, but extremely vague	NR	No
Van Nord	NR	NR	Yes	Yes, but extremely vague	NR	No
Clair, 1992	NR	NR	NR	Yes	Yes	Yes

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
Lewis, 1989 Scotland	No	NR	Yes	None	Fair	Good
Lundstrom, 1992 Sweden	No	NR	Yes	None	Fair	Good
Rasmussen	No	NR	Yes	None	Fair	Fair
Van Nord	Yes	Yes	Yes	None	Fair	Good
Clair, 1992	Unclear	Unclear	Attrition and compliance clearly reported. Others NR	No	Fair	NR

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
Lewis, 1989 Scotland	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	Yes	Extremely short	Tablets provided by ICI plc
Lundstrom, 1992 Sweden	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	Yes	Extremely short	Swedish Heart and Lung Foundation, Clinical Research Unit, ICI Pharma
Rasmussen	NR	NR	Yes	Good	NR
Van Nord	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; contraindictions for oral anticoagulant agents; age <18 or >85 years	Yes	Extremely short	The Netherlands Heart Foundation Grant 98.105
Clair, 1992	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	Yes	4 months	NR

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
DAVIT II (Part of the Danish Verapamil Infarction Trial II) Jespersen 1992 Denmark	NR	NR	Yes	Yes	Yes	Yes
Bertaglia 2001	NR	NR	Yes	NR	Yes	Yes
Stern, 1982 United States	NR	NR	N/A-crossover; charateristics reported for group overall	Yes	Yes	Yes
Tse, 2001 China	NR	NR	N/A-crossover; charateristics reported for group overall	Yes	Yes	Yes
Suwa 1996	Inferior: according to month of birth	NR	Yes	Minimal	NR	Yes
Schofer 1990	NR	NR	NR	Yes	Yes	Yes

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
DAVIT II (Part of the Danish Verapamil Infarction Trial II) Jespersen 1992 Denmark	Unclear	Unclear	None reported	Unclear	Fair	Good Mean age: plac=60; ver=59 Gender(%male): plac=76; ver=75
Bertaglia 2001	Stated ITT, but excluded 13 patients having spontaneous conversion to sinus rhytym and 6 patients that refused internal electrical cardioversion following unsuccessful external cardioversion	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
Stern, 1982 United States	Efficacy analysis did not include 1 patient for unspecified reason	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
Tse, 2001 China	Unclear	N/A-crossover trial	None reported	Not suspected	Fair	Good Mean age: 60 Gender(%male): 81.8%
Suwa 1996	No	NR	Withdrawals=5/18 (27.8%); others NR	No	Poor	Mean age 53.5 68.2% male
Schofer 1990	Yes	NR	NR	NR	Fair	Mean age=55.4 75% male

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
DAVIT II (Part of the Danish Verapamil Infarction Trial II) Jespersen 1992 Denmark	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	Yes	1 month	NR
Bertaglia 2001	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%	Yes	8 weeks	NR
Stern, 1982 United States	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	Yes	7-8 months	NR
Tse, 2001 China	11 enrolled	NR	Yes	3 months	NR
Suwa 1996	18	NR	Yes	10.5 months; crossover duration unclear	NR
Schofer 1990	24	Significant hematopoietic, liver and renal dysfunction (serum creatinine >2 mg%.	Yes	3 months	NR

Evidence Table 1. Quality assessment

Author, Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Outcome assessors blinded	Patient unaware of treatment
de Vries 1995	NR	NR	Yes	Yes	Yes	Yes
Agostoni 1986	NR	NR	Yes, crossover	Yes	NR	Yes
Elkayam 1990 USA	Adequate - Latin square design, computer-generated code	NR	NR	Yes	NR - says double blind, No details	Yes
INVEST Pepine, 2003 Pepine, 1998 International	Adequate	Adequate	Yes	Yes	Yes	N-open

Evidence Table 1. Quality assessment

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score	Similarity to target population
de Vries 1995	Yes	NR	NR	NR	Fair	Mean age=65 84.5% male
Agostoni 1986	No	NR	Attrition Yes others NR	high overall loss (31%), group assignment NR	Fair to poor	Selected for dilated cardiomyopathy
Elkayam 1990 USA	No	NR	attrition, NR on crossover details or contamination	No 5/28 (18%) overall	Fair	Unclear
INVEST Pepine, 2003 Pepine, 1998 International	Yes	Unclear	Y Y N Y	No	Fair	Yes

Evidence Table 1. Quality assessment

Author, Year Country	Number recruited	Exclusion criteria for recruitment	Control group standard of care	Length of follow-up	Funding
de Vries 1995	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.	Yes	16 weeks	ASTRA
Agostoni 1986	n = 26	Supine systolic BP <100 mm Hg; angina pectoris; history or ECG signs of MI; hepatic or renal impairment.	Yes, crossover	8 wks (x2)	NR
Elkayam 1990 USA	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.	Yes	24 weeks	NR
INVEST Pepine, 2003 Pepine, 1998 International	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	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	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 Agodoa, 2001 Wright, 2002 Douglas, 2003 US	Addition of in order furosemide, doxazosin mesylate, clonidine hydrochloride, hydralazine hydrochloride, minoxidil to maximum tolerated dose before adding next agent	During study Mean no. of drug classes: 2.65 (1.24) Level 1 (aml): 83.4% Level 2 (fur): 70.8% Level 3 (dox): 46.3% Level 4 (clo): 44.4% Level 5 (min): 24.1% Crossover: 6.4%	NR	During study Mean no. of drug classes: 2.66 (se 1.23) Level 1 (met): 83.6% Level 2 (fur): 74.0% Level 3 (dox): 42.0% Level 4 (clo): 34.4% Level 5 (min): 27.5% Crossover: 7.6%	During study Mean no. of drug classes: 2.66 (se 1.23) Level 1 (ram):76.8% Level 2 (fur): 74.0% Level 3 (dox):42.0% Level 4 (clo):34.4% Level 5 (min):27.5% 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	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, analyzed	Number withdrawn/ lost to fu/ analyzed	CCB Outcomes	Diuretic Outcomes	Beta Blocker Outcomes
Amlodipine					
AASK Agodoa, 2001 Wright, 2002 Douglas, 2003 US	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	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

Evidence Table 2. Hypertension active controlled trials

Study, Author, Year Country	Ace Inhibitor Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Amlodipine					
AASK Agodoa, 2001 Wright, 2002 Douglas, 2003 US	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	NR	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	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	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	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, analyzed	Number withdrawn/ lost to fu/ analyzed	CCB Outcomes	Diuretic Outcomes	Beta Blocker Outcomes
ALLHAT, Furberg, 2002 Grimm, 2001 Vidt, 2000 Vidt, 2003 US	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)	NR

Evidence Table 2. Hypertension active controlled trials

Study, Author, Year Country	Ace Inhibitor Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
ALLHAT, Furberg, 2002 Grimm, 2001 Vidt, 2000 Vidt, 2003 US	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%	Searches of Medicare and Medicaid and VA databases for angioedema and hospitalization for gastrointestinal bleeding.	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	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.
Nicardipine *NICS-EH* NICS-EH Study Group 1999 Kuwajima 2001 Kuramoto 1994 Ogihara 2000, Tokyo	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**
FACET Tatti, 1998 Pahor, 1998 Italy	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
Nicardipine					
NICS-EH NICS-EH Study Group 1999 Kuwajima 2001 Kuramoto 1994 Ogihara 2000, Tokyo	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)
FACET Tatti, 1998 Pahor, 1998 Italy	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)
Nicardipine *NICS-EH* NICS-EH Study Group 1999 Kuwajima 2001 Kuramoto 1994 Ogihara 2000, Tokyo		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, analyzed	Number withdrawn/ lost to fu/ analyzed	CCB Outcomes	Diuretic Outcomes	Beta Blocker Outcomes
FACET Tatti, 1998 Pahor, 1998 Italy	1172 380 376	4 4 276	Any major CV event Over 3 years followup Note: not intent to treat Aml 27/141 (19.2%) Aml + Fos 4/108 (3.7%) 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)	N/A	N/A
Nicardipine *NICS-EH* NICS-EH Study Group 1999 Kuwajima 2001 Kuramoto 1994 Ogihara 2000, Tokyo	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	N/A

Evidence Table 2. Hypertension active controlled trials

Study, Author, Year Country	Ace Inhibitor Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
FACET Tatti, 1998 Pahor, 1998 Italy	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)	NR	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.
Nicardipine					
NICS-EH NICS-EH Study Group 1999 Kuwajima 2001 Kuramoto 1994 Ogihara 2000, Tokyo	N/A	Judged by attending physician	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	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
Chan, 1992 Chan, 2000 Hong Kong	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
Nifedipine					
Marin, 2001 Spain	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		
Chan, 1992 Chan, 2000 Hong Kong	*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*				

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		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
Chan, 1992 Chan, 2000 Hong Kong	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, analyzed	Number withdrawn/ lost to fu/ analyzed	CCB Outcomes	Diuretic Outcomes	Beta Blocker Outcomes
Nifedipine					
Marin, 2001 Spain	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)		
Chan, 1992 Chan, 2000 Hong Kong	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%)		

Evidence Table 2. Hypertension active controlled trials

Study, Author, Year Country	Ace Inhibitor Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Nifedipine					
Marin, 2001 Spain	*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%)	NR	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 (n=50)* *At 5 years:* Renal events: 6(12%)			*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	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	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				

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	% 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, analyzed	Number withdrawn/ lost to fu/ analyzed	CCB Outcomes	Diuretic Outcomes	Beta Blocker 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	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	N/A

Evidence Table 2. Hypertension active controlled trials

Study, Author, Year Country	Ace Inhibitor Outcomes	Method of adverse effects assessment?	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	N/A	NR	*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 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	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	*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	*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, analyzed	Number withdrawn/ lost to fu/ analyzed	CCB Outcomes	Diuretic Outcomes	Beta Blocker Outcomes
Diltiazem					
NORDIL (Nordic Diltiazem Study) The NORDIL Group, 1993 Hedner, 1999 Hansson, 2000 Kjeldsen, 2002 Norway/Sweden	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	*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	Ace Inhibitor Outcomes	Method of adverse effects assessment?	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	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	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	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	*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				

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	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, analyzed	Number withdrawn/ lost to fu/ analyzed	CCB Outcomes	Diuretic Outcomes	Beta Blocker Outcomes
Nisoldipine					
ABCD (Appropriate Blood Pressure Control in Diabetes) Savage, 1993 Schrier, 1996 Estacio, 1998a Estacio, 1998b United States	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	N/A

Evidence Table 2. Hypertension active controlled trials

Study, Author, Year Country	Ace Inhibitor Outcomes	Method of adverse effects assessment?	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	*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	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)*	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)*	*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)*	*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, analyzed	Number withdrawn/ lost to fu/ analyzed	CCB Outcomes	Diuretic Outcomes	Beta Blocker 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)*	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 procedures* Fatal: 0.2 Nonfatal: 19.5	N/A

Evidence Table 2. Hypertension active controlled trials

Study, Author, Year Country	Ace Inhibitor Outcomes	Method of adverse effects assessment?	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)*	N/A	NR	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)
Verapamil					
CONVINCE Black, 1998, US	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, US	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, US	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, analyzed	Number withdrawn/ lost to fu/ analyzed	CCB Outcomes	Diuretic Outcomes	Beta Blocker Outcomes
Verapamil					
CONVINCE Black, 1998, US	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%)	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	Ace Inhibitor Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Verapamil					
CONVINCE Black, 1998, US	n/a	nr	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	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	*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	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, analyzed	Number withdrawn/ lost to fu/ analyzed	CCB Outcomes	Diuretic Outcomes	Beta Blocker Outcomes
INVEST	nr	2662(11.8%) withdrawn	*Number(%)*	n/a	*Number(%)*
	23,482	568(2.5%) lost to fu	*24-month outcomes*		*24-month outcomes*
Pepine, 2003	22,576	22576 analyzed			
Pepine, 1998			Primary outcome=data nr		Primary outcome=data nr
International			First event=1119(9.93%)		First event=1150(10.17%)
			Death=873(7.75%)		Death=893(7.90%)
			Nonfatal MI=151(1.34%)		Nonfatal MI=153(1.35%)
			Nonfatal stroke=131(1.16%)		Nonfatal stroke=148(1.31%)
			CV-related death=431(3.83%)		CV-related death=431(3.81%)
			CV-related hospitalization=726(6.44%)		CV-related hospitalization=709(6.27%)

Evidence Table 2. Hypertension active controlled trials

Study, Author, Year Country	Ace Inhibitor Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
INVEST Pepine, 2003 Pepine, 1998 International	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	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

Hypertension

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
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	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	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

Evidence Table 3. Quality of life trial summary

Hypertension

Author, Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
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	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	*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)

Evidence Table 3. Quality of life trial summary

Hypertension

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
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	11,914 screened/eligible NR/902 randomized	53(6%) withdrawn prior to 12-month visit/lost NR/	*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

Evidence Table 3. Quality of life trial summary

Hypertension

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

Hypertension

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Omvik 1993 Norway	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	*HCTZ 25-50 mg daily added at 12 weeks for nonresponders (DBP >/= 95 mmHg)* HCTZ addition: aml=11%; ena=20% (p<0.01)
Nifedipine comparisons					
Metelitsa 1996	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)*	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%)

Evidence Table 3. Quality of life trial summary

Hypertension

Author, Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Omvik 1993 Norway	*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	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
Nifedipine comp.			
Metelitsa 1996	General Well-Being Questionnaire (GWBQ) at month 8	Absolute data NR; data presented in graphical format; stated no differences in age	Absolute data NR Data presented in graphical format Stated no differences in height, body weight and HTN duration

Evidence Table 3. Quality of life trial summary

Hypertension

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Omvik 1993 Norway	NR/NR/461	Withdrawn: aml=3; ena=7/Lost NR/Analyzed: aml=228; ena=223	*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*
Nifedipine comparisons			
Metelitsa 1996	Screened NR/Eligible NR/345 enrolled	49 withdrawn Lost NR	Absolute data NR

Evidence Table 3. Quality of life trial summary

Hypertension

Author, Year Country	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Omvik 1993 Norway	Recorded by type, onset, degree of severity and relationship to treatment	*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)	
Nifedipine comparisons				
Metelitsa 1996	NR	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

Hypertension

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Bulpitt 2000 Austria, Italy, Germany, Netherlands, Poland, Spain, Switzerland, and the UK	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	HCTZ 25 mg daily added after 4 weeks for nonresponders (> 90 mmHg)

Evidence Table 3. Quality of life trial summary

Hypertension

Author, Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Bulpitt 2000 Austria, Italy, Germany, Netherlands, Poland, Spain, Switzerland, and the UK	*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	Mean age: bis=67.9; nif r=68.5 Gender NR Race NR NR

Evidence Table 3. Quality of life trial summary

Hypertension

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Bulpitt 2000 Austria, Italy, Germany, Netherlands, Poland, Spain, Switzerland, and the UK	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	*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

Evidence Table 3. Quality of life trial summary

Hypertension

Author, Year Country	Method of adverse effects assessment?	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	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)	*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

Hypertension

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Fletcher 1992 Europe	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*	Bendrofluazide 5 mg daily or equivalent doses of another thiazide diuretic

Evidence Table 3. Quality of life trial summary

Hypertension

Author, Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Fletcher 1992 Europe	*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	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%

Evidence Table 3. Quality of life trial summary

Hypertension

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Fletcher 1992 Europe	281 screened/eligible NR/257 randomized	Overall withdrawals: pin=23; nif=18	*Mean changes from 0-6 months* Complaint rate: pin=(-2.01); nif=(-3.14) Health index: pin=1.07; nif=2.62 *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) *% 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)

Evidence Table 3. Quality of life trial summary

Hypertension

Author, Year Country	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Fletcher 1992 Europe	Information collected via spontaneous patient report to physician	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

Hypertension

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Verapamil comparisons					
Boissel 1995	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	NR

Evidence Table 3. Quality of life trial summary

Hypertension

Author, Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Verapamil comparisons			
Boissel 1995	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	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)

Evidence Table 3. Quality of life trial summary

Hypertension

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Verapamil comparisons			
Boissel 1995	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)	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

Evidence Table 3. Quality of life trial summary

Hypertension

Author, Year Country	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Verapamil comparisons				
Boissel 1995	Evaluated using the ABOF questionnaire and spontaneous patient report	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

Hypertension

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Isradipine comparisons					
LOMIR-MCT-IL trial Bar-On, 1993 Amir, 1994 Yodfat, 1996 Israel	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)	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)

Evidence Table 3. Quality of life trial summary

Hypertension

Author, Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Isradipine comparisons			
LOMIR-MCT-IL trial Bar-On, 1993 Amir, 1994 Yodfat, 1996 Israel	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	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

Evidence Table 3. Quality of life trial summary

Hypertension

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Isradipine comparisons			
LOMIR-MCT-IL trial Bar-On, 1993 Amir, 1994 Yodfat, 1996 Israel	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	Data 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

Hypertension

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

Evidence Table 3. Quality of life trial summary

Supraventricular arrhythmia

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
PIAF (Pharmacological Intervention in Atrial Fibrillation Trial) Hohnloser 2000 Germany	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	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

Evidence Table 3. Quality of life trial summary

Supraventricular arrhythmia

Author, Year Country	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
PIAF (Pharmacological Intervention in Atrial Fibrillation Trial) Hohnloser 2000 Germany	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	% *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

Evidence Table 3. Quality of life trial summary

Supraventricular arrhythmia

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
PIAF (Pharmacological Intervention in Atrial Fibrillation Trial) Hohnloser 2000 Germany	NR/NR/252	Overall withdrawals NR/Lost NR/Analyzed not clear, but states ITT(252)	*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

Evidence Table 3. Quality of life trial summary

Supraventricular arrhythmia

Author, Year Country	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
PIAF (Pharmacological Intervention in Atrial Fibrillation Trial) Hohnloser 2000 Germany	NR	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	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	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	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 (continued)

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	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	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	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 (continued)

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	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	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	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 Gastrointenstinal: aml 0; dil 10 Other: aml 6.4; dil 16	aml 4.3% dil 14.0%	

Evidence Table 4. Angina head to head trials (continued)

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Pehrsson 1996 Sweden	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	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 (continued)

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	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	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 (continued)

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	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	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 (continued)

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Nisoldipine vs amlodipine			
Hall 1998 UK	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	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 (continued)

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	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	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 (continued)

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	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	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 (continued)

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Littler 1999 UK	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-an
Radice 1991 Italy	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 (continued)

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	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	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 (continued)

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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	NR/NR/31
Myers 1988 Canada	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	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	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	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	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
Singh 1993 USA	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

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	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)
Singh 1993 USA	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

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	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%	
Singh 1993 USA	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%)	

Evidence Table 5. Angina active controlled trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
SWAN study group 1999 Switzerland, Austria	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
TIBET (Total Ischaemic Burden European Trial) 9 European countries Dargie, 1996 The TIBET Study Group, 1992	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 and resting ST-T wave abnormalities on the electrocardiogram, predominant cardiac rhythm other than sinus rhythm, concurrent treatment with digoxin

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
SWAN study group 1999 Switzerland, Austria Poor quality	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
TIBET (Total Ischaemic Burden European Trial) 9 European countries Dargie, 1996 The TIBET Study Group, 1992	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

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
SWAN study group 1999 Switzerland, Austria Poor quality	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%	
TIBET (Total Ischaemic Burden European Trial) 9 European countries Dargie, 1996 The TIBET Study Group, 1992	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

Evidence Table 5. Angina active controlled trials

Author, Year Country	Study Design	Eligibility criteria	Exclusion criteria
Ulvenstam 1992 3 European countries	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
Vliegen 1991 The Netherlands	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
Ulvenstam 1992 3 European countries	*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
Vliegen 1991 The Netherlands	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
Ulvenstam 1992 3 European countries	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%	
Vliegen 1991 The Netherlands	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	Interventions (drug, regimen, duration)
Variant angina pectoris				
Johnson 1981 United States		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	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
Johnson 1981 United States	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	Ver 240-480 mg daily Placebo x 8 months (consisting of four 2-month periods; double crossover)

Evidence Table 6. Angina 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
Variant angina pectoris						
Johnson 1981 United States	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%	NR/NR/19	Withdrawn 2/ Lost 0/ Analyzed 16
Johnson 1981 United States	Oral isosorbide dinitrate	Daily patient diary Ambulatory electrocardiographic monitoring(calibrated two channel) for 24 hours during each week	Average age 52 60% male Race NR	NR	NR/NR/10	NR/NR/analyzed 10

Evidence Table 6. Angina placebo controlled trials

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

Evidence Table 7. Supraventricular arrhythmia head to head 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 Verapamil					
Botto, 1998 Italy	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	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	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	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

Amlodipine = aml, Bepridil = bep, Diltiazem = dil, Felodipine = fel, Isradipine = isa, Nicardipine = nic, Nifedipine = nif, Nisoldipine = nis, Verapamil = ver

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
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

Amlodipine = aml, Bepridil = bep, Diltiazem = dil, Felodipine = fel, Isradipine = isa, Nicardipine = nic, Nifedipine = nif, Nisoldipine = nis, Verapamil = ver

Evidence Table 7. Supraventricular arrhythmia head to head trials

Author, Year Country	Outcomes	Method of adverse effects assessment?	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Ochs 1985 Germany	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)	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

Amlodipine = aml, Bepridil = bep, Diltiazem = dil, Felodipine = fel, Isradipine = isa, Nicardipine = nic, Nifedipine = nif, Nisoldipine = nis, Verapamil = 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, decompesnsated 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

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

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	

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
Verapamil vs Other Medications					
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
Verapamil vs Other Medications					
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
Verapamil vs Other Medications					
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

Amlodipine = aml, Bepridil = bep, Diltiazem = dil, Felodipine = fel, Isradipine = isa, Nicardipine = nic, Nifedipine = nif, Nisoldipine = nis, Verapamil = ver

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

Amlodipine = aml, Bepridil = bep, Diltiazem = dil, Felodipine = fel, Isradipine = isa, Nicardipine = nic, Nifedipine = nif, Nisoldipine = nis, Verapamil = ver

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)	

Amlodipine = aml, Bepridil = bep, Diltiazem = dil, Felodipine = fel, Isradipine = isa, Nicardipine = nic, Nifedipine = nif, Nisoldipine = nis, Verapamil = ver

Evidence Table 9. Supraventricular arrhythmia placebo controlled trials

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Clair 1992	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	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	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	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	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	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	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	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	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	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	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	*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	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	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	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	RCT Crossover	Patients treated with an Implantable Atrial Defibrillator (IAD) for symptomatic, recurrent AF	NR
Tse 2001 China	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

Amlodipine = aml, Bepridil = bep, Diltiazem = dil, Felodipine = fel, Isradipine = isa, nicardipine = nic, Nifedipine = nif, Nisoldipine = nis, Verapamil = ver

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	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	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

Amlodipine = aml, Bepridil = bep, Diltiazem = dil, Felodipine = fel, Isradipine = isa, nicardipine = nic, Nifedipine = nif, Nisoldipine = nis, Verapamil = ver

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	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	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	

Amlodipine = aml, Bepridil = bep, Diltiazem = dil, Felodipine = fel, Isradipine = isa, nicardipine = nic, Nifedipine = nif, Nisoldipine = nis, Verapamil = ver

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 $\leq$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
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

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)
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
Schofer 1990 Fair	NR	Standard exercise test 1, 4, 8 and 12 weeks	Mean age=55.4 75% male Race nr	NR
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

Evidence Table 10. Systolic dysfunction active controlled trials

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment	Adverse Effects Reported	Withdrawals due to adverse events
Suwa 1996 Poor	NR/NR/ Enrolled=18	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	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
de Vries 1995 Fair	NR/52 eligible/46 randomized	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

Evidence Table 10. Systolic dysfunction active controlled trials

Author, Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Agostoni 1986 Italy	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)
Agostoni 1986 Italy	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

Evidence Table 10. Systolic dysfunction active controlled trials

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment	Adverse Effects Reported	Withdrawals due to adverse events
Agostoni 1986 Italy	nr/26/26	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 hypotention; 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)
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 stablization 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%)

Evidence Table 10. Systolic dysfunction active controlled trials

Author, Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment	Adverse Effects Reported	Withdrawals due to adverse events
Elkayam 1990 USA *Fair*	initial screening nr 51 began stabilization period to confirm eligibility 28 began randomized trial	Stabilization period withdrawn total = 23/51 (45%) -noncompliance = 8 -ineligible = 6 -worsening heart failure = 4 -chronic obstructive pulmonary disease = 2 -angina limiting ETT = 2 -inablity 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 hypotanesion (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; velvular 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	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

Fair

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*	Mortality 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 Exercise duration: 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. QOL: 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*	Protocol 174 Digoxin Diuretics ACE inhibitors (only if tolerated) Protocol 175 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-Inhibitorty; 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;aml 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
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 ischemis attack, stoke within 3 months prior to the study; atrial-ventricular block greater than first degree or high ventricular ectopy; left ventricular aneurysm; aniarrhythmis agents (other than Class I agents); diabetes, significant renal, hepatic, or hematoligical disorders; primary pulmonary hypertension.	Nicardipine (Nic) 60 - 90mg/d titration not described Placebo three times daily x 4 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
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

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) <u>Ischemic heart disease strata:</u> 45% in both groups (NS) <u>Nonischemic Cardiomyopathy strata:</u> 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) <u>Ischemic heart disease strata:</u> 40% in both groups (NS) <u>Nonischemic Cardiomyopathy strata</u>: 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
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

Evidence Table 11. Systolic dysfunction placebo controlled trials

Author, Year Country	Heart Failure Severity	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
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
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
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	
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)
Kassis 1990 Denmark *Fair*	Death (# pts; %) fel=5/10(50%) pla=3/10(30%) (NS) Subjective improvement 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
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)
Nicardipine				
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%)
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

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)
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)
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* Diltiazem group Step 2: Dil dose increment Step 3: Other antihypertensive drug add-on (preferably ACE inhibitors) Step 4: Diuretics Conventional treatment group: 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

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)
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%
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 Gastrointenstinal: 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%)
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%

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
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%)
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
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

Amlodipine = aml, Bepridil = bep, Diltiazem = dil, Felodipine = fel, Isradipine = isa, Nicardipine = nic, Nifedipine = nif, Nisoldipine = nis, Verapamil = ver

Appendix A. Calcium channel blockers search strategies:

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2003>
Search Strategy:
---
1 (amlodipine or bepridil or diltiazem or felodipine or isradipine or nicardipine).ti. (2462)
2 (nifedipine or nisoldipine or verapamil).ti. (2979)
3 1 or 2 (5103)
4 (angina or supraventricular arrhythmia$ or hypertension or high blood pressure or heart failure$).ti. (12653)
5 3 and 4 (1936)
6 from 5 keep 1-1936 (1936)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2003>
Search Strategy:
---
1 (amlodipine or bepridil or diltiazem or felodipine or isradipine or nicardipine).ti. (2462)
2 (nifedipine or nisoldipine or verapamil).ti. (2979)
3 1 or 2 (5103)
4 (angina or supraventricular arrhythmia$ or hypertension or high blood pressure or heart failure$).ti. (12653)
5 3 and 4 (1936)
6 (angina$ or supraventricular tachycardia$ or supraventricular arrhythmia$ or hypertensi$ or high blood pressure or heart failure$).ti. (15411)
7 3 and 6 (2402)
8 limit 7 to yr=1994-2003 (815)
9 from 8 keep 1-815 (815)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2003>
Search Strategy:
---
1 (amlodipine or bepridil or diltiazem or felodipine or isradipine or nicardipine).ti. (2462)
2 (nifedipine or nisoldipine or verapamil).ti. (2979)
3 1 or 2 (5103)
4 (angina or supraventricular arrhythmia$ or hypertension or high blood pressure or heart failure$).ti. (12653)

5 3 and 4 (1936)
6 (angina$ or supraventricular tachycardia$ or supraventricular arrhythmia$ or hypertensi$ or high blood pressure or heart failure$).ti. (15411)
7 3 and 6 (2402)
8 limit 7 to yr=2002-2004 (31)
9 from 8 keep 1-31 (31)

Database: Ovid MEDLINE(R) <1996 to February Week 1 2004>
Search Strategy:
---
1 exp *AMLODIPINE/ (585)
2 exp *BEPRIDIL/ (120)
3 exp *DILTIAZEM/ (707)
4 exp *FELODIPINE/ (195)
5 exp *ISRADIPINE/ (143)
6 exp *NICARDIPINE/ (227)
7 exp *NIFEDIPINE/ (1151)
8 exp *NISOLDIPINE/ (105)
9 exp *VERAPAMIL/ (1089)
10 exp AMLODIPINE/ (841)
11 exp BEPRIDIL/ (234)
12 exp DILTIAZEM/ (1252)
13 exp FELODIPINE/ (288)
14 exp ISRADIPINE/ (303)
15 exp NICARDIPINE/ (528)
16 exp NIFEDIPINE/ (2932)
17 exp NISOLDIPINE/ (171)
18 exp VERAPAMIL/ (2882)
19 exp *HYPERTENSION/ (30609)
20 exp *ANGINA PECTORIS/ (4915)
21 exp *Tachycardia, Supraventricular/ (1661)
22 exp *exp heart failure, congestive/ or exp cardiac output, low/ (1646)
23 exp HYPERTENSION/ (42479)
24 exp ANGINA PECTORIS/ (7312)
25 exp Tachycardia, Supraventricular/ or supraventricular arrhythmia$.mp. (2348)
26 exp heart failure, congestive/ or exp cardiac output, low/ (19064)
27 amlodipine.mp. or exp AMLODIPINE/ (1118)
28 bepridil.mp. or exp BEPRIDIL/ (270)
29 diltiazem.mp. or exp DILTIAZEM/ (1919)
30 felodipine.mp. or exp FELODIPINE/ (398)
31 isradipine.mp. or exp ISRADIPINE/ (389)
32 nicardipine.mp. or exp NICARDIPINE/ (887)
33 nifedipine.mp. or exp NIFEDIPINE/ (4861)
34 nisoldipine.mp. or exp NISOLDIPINE/ (257)

35 verapamil.mp. or exp VERAPAMIL/ (4774)
36 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (4044)
37 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (8404)
38 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 (12529)
39 19 or 20 or 21 or 22 (38695)
40 23 or 24 or 25 or 26 (69387)
41 38 and 40 (2308)
42 limit 41 to (human and yr=2002-2004 and (clinical trial or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial)) (168)
43 limit 42 to english language (154)
44 limit 42 to abstracts (162)
45 43 or 44 (167)
46 from 45 keep 1-167 (167)

Database: EMBASE Drugs & Pharmacology <1991 to 1st Quarter 2004>
Search Strategy:
---
1 exp *AMLODIPINE/ (1320)
2 exp *BEPRIDIL/ (148)
3 exp *DILTIAZEM/ (2848)
4 exp *FELODIPINE/ (730)
5 exp *ISRADIPINE/ (842)
6 exp *NICARDIPINE/ (1162)
7 exp *NIFEDIPINE/ (5095)
8 exp *NISOLDIPINE/ (482)
9 exp *VERAPAMIL/ (4987)
10 exp AMLODIPINE/ (3804)
11 exp BEPRIDIL/ (579)
12 exp DILTIAZEM/ (9257)
13 exp FELODIPINE/ (2181)
14 exp ISRADIPINE/ (2044)
15 exp NICARDIPINE/ (3434)
16 exp NIFEDIPINE/ (15897)
17 exp NISOLDIPINE/ (1282)
18 exp VERAPAMIL/ (15491)
19 exp *HYPERTENSION/ (36871)
20 exp *ANGINA PECTORIS/ (5722)
21 exp *Tachycardia, Supraventricular/ (896)
22 exp *heart failure/ (20920)
23 exp HYPERTENSION/ (64099)
24 exp ANGINA PECTORIS/ (11544)
25 exp Tachycardia, Supraventricular/ or supraventricular arrhythmia$.mp. (1810)
26 exp heart failure/ (38424)
27 amlodipine.mp. or exp AMLODIPINE/ (3905)

28 bepridil.mp. or exp BEPRIDIL/ (591)
29 diltiazem.mp. or exp DILTIAZEM/ (9441)
30 felodipine.mp. or exp FELODIPINE/ (2213)
31 isradipine.mp. or exp ISRADIPINE/ (2070)
32 nicardipine.mp. or exp NICARDIPINE/ (3536)
33 nifedipine.mp. or exp NIFEDIPINE/ (16541)
34 nisoldipine.mp. or exp NISOLDIPINE/ (1314)
35 verapamil.mp. or exp VERAPAMIL/ (16138)
36 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (14728)
37 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (37615)
38 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 (38951)
39 19 or 20 or 21 or 22 (62679)
40 23 or 24 or 25 or 26 (107320)
41 38 and 40 (12974)
42 exp controlled study/ (935719)
43 41 and 42 (4021)
44 limit 43 to (human and yr=2002-2004) (352)
45 limit 44 to english language (322)
46 limit 44 to abstracts (301)
47 45 or 46 (343)
48 from 47 keep 1-343 (343)

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

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

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

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

For Controlled Trials:

Assessment of Internal Validity

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

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

Use of alternation, case record numbers, birth dates or week days
Open random numbers lists
Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
Not reported

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

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

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

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

9. Did the study maintain comparable groups?

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

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

Assessment of External Validity (Generalizability)

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

2. How many patients were recruited?

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

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

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

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

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

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

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

3. Were the events investigated specified and defined?

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

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

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

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

Assessment of External Validity

1. Was the description of the population adequate?

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

3. How many patients were recruited?

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

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

Systematic Reviews:

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

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

study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

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

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

3. Is the validity of included studies adequately assessed?

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

4. Is sufficient detail of the individual studies presented?

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

5. Are the primary studies summarized appropriately?

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

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

Appendix C. Reports of trials excluded

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Appendix D. Articles available as abstracts only

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Appendix E. Quality of life studies under six months duration

Citation	Duration
Head to Head	
(Palmer, Fletcher et al. 1990)	4 months
(Pessina, Boari et al. 2001)	16 weeks
(Rodriguez, Guillen et al. 1996)	14 weeks
Active Control	
(Applegate, Phillips et al. 1991)	16 weeks
(Benetos, Consoli et al. 2000)	12 weeks
(Benetos, Adamopoulos et al. 2002)	12 weeks
(Croog, Elias et al. 1994)	22 weeks
(Croog, Kong et al. 1990)	8 weeks
(de Hoon, Vanmolkot et al. 1997)	8 weeks
(Fletcher, Chester et al. 1989)	4 months
(Jern, Hansson et al. 1991)	8 weeks
(Os, Bratland et al. 1991)	10 weeks
(Pirrelli and Nazzaro 1989)	12 weeks
(Prisant, Weir et al. 1995)	12 weeks
(Scuteri, Cacciafesta et al. 1992)	4 weeks
(Sundar, Rajan et al. 1991)	4 weeks
(Skinner, Futterman et al. 1992)	10 weeks
(Testa, Hollenberg et al. 1991)	20 weeks
(Van de Ven 1997)	8 weeks
(Weir, Josselson et al. 1991)	12 weeks
(Weir, Prisant et al. 1996)	12 weeks
(Zanchetti, Omboni et al. 2001)	12 weeks
Placebo	
(Dimenas, Wallander et al. 1991)	4 weeks
(van Ree and van der Pol 1996)	6 weeks

Head to Head

Palmer, A., A. Fletcher, et al. (1990). "A comparison of verapamil and nifedipine on quality of life." British Journal of Clinical Pharmacology **30**(3): 365-70.

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Placebo

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Appendix F. List of abbreviations for tables

Abbreviation	Definition
AE	Adverse Events
AMI	Acute Myocardial Infarction
AF or AFI	Atrial Fibrillation
AV	Atrial Ventricular
BMI	Body Max Index
BP	Blood Pressure
CHF	Congestive Heart Failure
CABG	Coronary Artery Bypass Graft
CHD	Chronic Heart Disease
CV	Cardiovascular
CVD	Cardiovascular Disease
DPB	Diastolic Blood Pressure
ECG	Electrocardiogram
ETT	Ergonometic Treadmill Test
FU	Followup
GTN	Glyceryl trinitrate
HDL	High Density Lipoprotein
HTN	Hypertension
HR	Heart Rate
Hosp	Hospital
IAD	Implant able Atrial Defibrillation
IDDM	Insulin Dependent Diabetes Mellitus
ITT	Intention to Treat
JNC V	Joint National Committee V
LDL	Low Density Lipoprotein
LV	Left Ventricular
LVH	Left Ventricular Hypertrophy
LVEF	Left Ventricular Ejection Fraction
Meds	Medication
MI	Myocardial Infarction
Min	Minutes
Mod	Moderate
N	Number of patients
NA	Not Applicable
NR	Not Reported
NSAIDS	Nonsteriodial Anti-inflammatory Drugs
NIDDM	Non-Insulin Dependent Diabetes
NTG	Nitroglycerin
NS	Not significant
NSR	Normal Sinus Rhythm
Plac	Placebo
Pts	Patients

QOL	Quality of Life
RCT	Random Controlled Trial
RR	Relative Risk
SBP	Systolic Blood Pressure
Sl	Sublingual
SVT	Supraventricular Tachycardia
TIA	Transient Ischaemic Attack
VPB	Ventricular Premature Beats
VAS	Visual Analog Scale
VR	Ventricular Rate
Wks	Weeks