Drug Class Review
on Calcium Channel Blockers

FINAL REPORT

September 2003

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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 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 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 efficacy 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.

Key Questions and Scope of Paper

1. Do CCBs differ in efficacy 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 Library (2002, Issue 4), MEDLINE (1966-February 2003), EMBASE (1980-1st Quarter 2003), 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, only combining terms for drug names with terms for relevant research designs (see Appendix A for the complete search strategy). Subcommittee members were invited to provide additional citations. Pharmaceutical manufacturers were invited to submit dossiers, including citations, using a protocol issued by the State of Oregon (http://www.ohppr.state.or.us /index.htm). 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 efficacy: 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 efficacy 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 efficacy.[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 time constraints.

Trials that evaluated one CCB against another provided direct evidence of comparative efficacy 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 efficacy. 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 is used to support direct comparisons, where they exist, and is also used as the primary comparison where no direct comparisons exist. Such indirect comparisons should be interpreted with caution.

Data Abstraction

The following data was 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 if available and if the trial did not report high overall loss to follow-up.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix B, which were submitted to the Health Resources Commission in December, 2001 and updated in February, 2003. 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 efficacy 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 2,988 citations: 914 from the Cochrane Library, 1,536 from MEDLINE, 376 from EMBASE, 34 from IPA, 83 from reference lists, and 45 from two pharmaceutical company submissions. We included 88 randomized controlled trials (in 120 publications), and one systematic review. We excluded 2,876 studies for the reasons detailed in Figure 1. Excluded trials publications are listed in Appendix E, and results of trials published in abstract form are listed in Appendix F (individual trials may be represented by multiple publications, including abstracts). An additional 59 citations provided background information, including 18 meta-analyses. We excluded 26 reports that were published in abstract form only. Figure 1 summarizes the flow of study inclusions.

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 efficacy 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 efficacy in the treatment of patients with essential hypertension?

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

We identified 11 trials that evaluated the efficacy of treating hypertensive patients with CCBs in order to reduce mortality, non-fatal CV events, and end stage renal disease (ESRD).[7-18] These trials compared CCBs to ACE inhibitors, diuretics, and beta-blockers.[7-16, 18] With the exception of the ALLHAT trial,[8] 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.[19] We identified an additional four trials: ASCOT,[20] INVEST,[21] PRESERVE,[22] and VALUE[23] that have been launched but outcomes results have not yet been published.

The results of the 11 active–controlled trials are depicted in Tables 1-6 and Figures 2 and 3. Most trials recruited patients from the general population, although two trials focused on patients with renal decline[11, 24] or diabetes.[9, 25] 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.[8] All but two trials[9, 10] 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 10 active-controlled trials[7-9, 11-16] of amlodipine, diltiazem, isradipine, nicardipine, nifedipine long-acting gastrointestinal transport-system (GITS), nisoldipine, and controlled-onset extended release (COER)-verapamil that reported all-cause mortality. We found 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.[7-16, 18]

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).[7-16] The RR values and surrounding confidence intervals overlapped each other and crossed at 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).[9, 11, 15, 26] 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.[9] 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.[11] 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

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)

When patients taking amlodipine, diltiazem, isradipine, sustained release nicardipine, nifedipine GITS, or COER-verapamil were compared with patients taking diuretics and/or beta-blockers, the relative risks ranged from 0.89 to 1.54. With one exception[10] 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.[10]

Cardiovascular Disease (Mortality and Events)

Cardiovascular Mortality

We found only two trials that evaluated the efficacy of CCBs in reducing CV mortality compared with ACE inhibitors (Table 2).[11, 15, 25] Both trials reported reduced efficacy (relative

risks of 2.00 and 2.30, respectively).[11, 15, 25] Each result should be considered with caution. One study had large withdrawal rates (55-60%) in the study medication rates,[15, 25] and the other was underpowered to detect CV outcomes.[11] This latter study contained only 241 patients.[11] Both of these studies included special populations: type 2 diabetes[25] and patients with progressive renal function decline[11]; this may make the results more difficult to compare with the studies of the general population.

Table 2. Cardiovascular Disease Mortality

*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)

The relative risks for CV mortality comparing CCBs to diuretics and/or beta-blockers again center around 1.0,[12, 14, 27], with the exception of one underpowered trial.[10]

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 (nifedipine GITS vs. fosinopril, 0.58; amlodipine vs. fosinopril, 0.77)[9, 11]. In one study the patients were diabetic[9] and in the other, the patients had chronic renal failure.[11] By contrast, when nisoldipine was compared with enalapril in another diabetic population, the RR increased (2.25)[25] 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.[15, 25]

Table 3. Myocardial Infarctions (fatal and nonfatal)

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)

*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.[12] 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."[12].

Stroke (fatal and nonfatal)

The relative risks in four of eight trials center around 1.0 (0.91-1.15), regardless of comparison drugs (Table 4).[8, 12, 25, 27] The results of two trials (FACET, MIDAS) suggest that, again, dosage influenced the result.[9, 13] 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.[9] The trial (again thought to be underpowered) with the highest risk of stroke (3.09) had the lowest risk of CHF (0.15).[10]

Table 4. Stroke (Fatal and nonfatal)

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)

*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).[10, 27]

Table 5. Congestive Heart Failure (fatal and nonfatal)

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)[27] 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.[26] The trial (INSIGHT) that had the highest RR for CHF (2.17) also had the lowest RR for ESRD (0.62).[27]

Table 6. End Stage Renal Disease

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 11 active-controlled trials suggest that the CCBs performed no better than ACE-inhibitors, diuretics, and/or beta-blockers for health outcomes. 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.[10, 11] 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.[11, 27] One trial reported a low RR for MI (0.58) yet a high risk for stroke (2.3).[11] The INSIGHT trial reported a high RR for CHF (2.17) yet a low RR for ESRD (0.62).[27] 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 efficacy of the CCBs to improve CV health outcomes.

Dihydropyridines vs non-dihydropyridines

One trial using diltiazem[14] and one trial using verapamil[12] were found. Both 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 efficacy of CCBs in the treatment of essential hypertension?

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

What is the comparative efficacy 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.[28] 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.[28-38] 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 C.

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.[29]

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 the scales when compared to those in the medium and high subgroups. However, there was one

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

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[33] reported declines in mean scores from the total psychological, somatic and cognitive subscale baselines, as did patients in one amlodipine treatment group[32] 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. Results of Quality of Life Assessments in Active Controlled HTN Studies

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 efficacy 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 efficacy in the treatment of adult patients with angina?

In head-to-head trials what is the comparative efficacy 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.[39-44] It is not clear whether the diltiazem CR formulation used in one study conducted in the UK is available in the US.[43] 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[40]also enrolled patients with coronary artery narrowing or a non-Q wave MI. Two studies required the concomitant use of a beta-blocker (atenolol)[41, 43] and a third allowed continued use of beta-blockers or long-acting nitrates if the dose was stable.[39] 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[39, 45] 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[39, 40] 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.[44]

Based on treadmill exercise testing, the mean change in time to the onset of angina was available from three studies (Figure 6).[40, 41, 43] 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 efficacy 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).[46, 47] 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). 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[48] 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[49-51] reported very different outcome measures. One followed patients for 6-75 months and reported fatal and non-fatal events.[49, 50] 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[51] 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[52, 53]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).[49, 50] 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.

In placebo-controlled trials what is the comparative efficacy 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 .[54, 55] 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 efficacy 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[39, 40, 44], nisoldipine in 1[43]) 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 efficacy 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 efficacy for the treatment of angina can be seen between dihydropyridines and non-dihydropyridines.

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

In head-to-head trials what is the comparative efficacy 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[56, 57], while one compared the SR formulations of these drugs.[58] All three studies were fair quality (see Evidence Table 1), and none were conducted in the US. The studies ranged from 1[57, 58] to 3 weeks.[56] 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[57, 58] and 1 month.[56] 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,[58], 11% had corrected or uncorrected mitral valve disease[56] and 47% had mitral valve disease.[57] The proportion of patients with lone AF was similar in the two studies reporting these data (56 and 61%).[56, 58] The primary outcome measure was mean ventricular rate at rest, although two studies also reported these data during exercise[56, 58]. However, different methods of exercise testing were used (walking test and ergonometric bicycle), and one study[57] also reported the rate of conversion to normal sinus rhythm.

One of these studies only reported the ventricular rate at final testing[58] 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.[56, 58] 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.[56]

In active-controlled trials what is the comparative efficacy 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[59] 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[60] (Cardizem CD) used the immediate release formulation, with doses ranging from 180 to 360mg daily. Of the verapamil studies, one used verapamil SR,[61] 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.[60-72] 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),[73] patients with new-onset rapid AF (≤ 24 hours duration, verapamil vs clonidine or digoxin),[74] and patients with paroxysmal SVT (verapamil vs flecainide).[75] 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 and lone AF ranged from 11 to 75%, and 8 to 33%, respectively. These studies enrolled 12 to 97 patients. The study ranged from 2 weeks to 12 months, and one study[65] 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).[67, 68, 72]

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,[65, 71] 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 ranged from 96 to 102 with verapamil (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 efficacy 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[76-78] 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[79, 80] 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[81] used verapamil 360 mg daily, and the seventh study was in patients with paroxysmal SVT,[82] 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 in the two trials reporting these data, with higher rates for patients with resting rates > 100 bpm at baseline.[77, 78] 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 efficacy 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 efficacy 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.[83-98] 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[90, 91, 97-99]. 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.[83, 84, 100, 101] 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,[85, 95] and one to isosorbide dinitrate.[88]

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.[95] 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.[85]The third study[88] 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.[94] 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.[84, 96, 102]

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[96]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.[87, 89, 92, 93]

The Prospective Randomized Amlodipine Survival Evaluation (PRAISE) study[92, 93]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% difference in fatal and nonfatal events (95% CI -17.9,-0.1) and a 13% difference in all-cause mortality (95% CI -21.8,-4.8). 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)[86] and the other for six months (n = 20).[89] The 6-month study[89] found no difference in mortality or subjective assessment after six months. The 2-month study[86] 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 8. 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 mortaltiy 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 efficacy.

A. 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 12 active-controlled trials are summarized in Evidence Table 12.[7-11, 13-16, 18, 25-27, 37, 103-126] 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 and dizziness when compared to a diuretic.

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 five trials in which a CCB was compared to a diuretic/beta-blocker (ALLHAT, NICS-EH, INSIGHT, MIDAS, CONVINCE). 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[18] 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 isradipine vs HCTZ (MIDAS), nicardipine vs trichlormethiazide (NICS-EH), and COER verapamil vs HCTZ or atenolol (CONVINCE). 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.

Three trials (Marin, MIDAS, ALLHAT) 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. Differences in study duration, case identification, and reporting make comparisons across these three studies ambiguous.

In summary, indirect analysis of data for amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nisoldipine, and verapamil from 12 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[39-44] 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.[49, 50] 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.[48, 51]

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).[56-58] These were very short duration trials, two only lasting 7 days [57, 58]and the third lasting 3 weeks.[56] 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) .[56] 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).[57] 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.[58]

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[127], and the other comparing nifedipine to isosorbide dinitrate.[88] 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 efficacy).

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.[94] 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 ($p = 0.02$).[84] 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[96] 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.[86, 93] 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.[86] 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.[93] 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.[89]

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

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 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 for the single trial comparing nicardipine to a trichlormethiazide in elderly Japanese patients showed no difference in rates from the other five CCB vs diuretic and/or beta-blocker trials.

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 for the single trial comparing nicardipine to a trichlormethiazide (RR 1.54; 95% CI, 0.31-7.67) in elderly Japanese patients 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 diabetics and one in non-diabetic patients 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).[9, 128] In one study the patients were diabetic[9]and in the other, the patients had chronic renal failure.[128] By contrast, when nisoldipine was compared with enalapril in another diabetic population, the RR for MI was increased (2.25).[25] Differences in study design and conduct made a simple comparison impossible. Without the opportunity to compare these results to non-diabetic, non-renal failure patients, very little can be concluded from these studies regarding the relative efficacy of CCBs in these subgroups.

Stroke

Stroke rates (fatal and nonfatal) for CCB vs ACE inhibitor comparisons were only found in renal insufficiency[11, 128] and diabetic[15, 25, 119, 120] 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, 26, 34, 103] and patients with diabetes[18, 112] 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.[34, 38] The AASK pilot trial[34] 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).[129] 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[34, 38] 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 efficacy 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 efficacy 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 9. Strength of the evidence

Key Question 1: Comparative Efficacy	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 11 long-term, active-controlled trials was insufficient to clearly differentiate one CCB from another for efficacy. 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 Efficacy	**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 11 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 from 5 long-term, active-controlled trials was insufficient to clearly differentiate one CCB from another for efficacy or adverse effects in subgroups of diabetics, patients with renal insufficiency, and older Japanese patients.
b. Angina	Overall grade: Poor	We found no evidence regarding the efficacy 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 efficacy 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 efficacy 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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