

# **Drug Class Review on Calcium Channel Blockers**

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**A literature scan of this topic is done periodically**

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

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

## TABLE OF CONTENTS

<b>INTRODUCTION</b> .....	<b>4</b>
Scope and Key Questions.....	5
<b>METHODS</b> .....	<b>5</b>
Literature Search .....	5
Study Selection .....	5
Data Abstraction .....	6
Validity Assessment.....	7
Data Synthesis.....	7
<b>RESULTS</b> .....	<b>7</b>
<b>Overview</b> .....	<b>7</b>
<b>Key Question 1: Effectiveness</b> .....	<b>8</b>
Essential Hypertension.....	8
Angina.....	18
Supraventricular Arrhythmias.....	23
Systolic Dysfunction.....	25
<b>Key Question 2: Safety and Adverse Events</b> .....	<b>28</b>
Essential Hypertension.....	29
Angina.....	31
Supraventricular Arrhythmias.....	31
Systolic Dysfunction.....	32
Evidence from Observational Studies.....	34
<b>Key Question 3: Subgroups</b> .....	<b>39</b>
Essential Hypertension.....	39
Angina.....	41
Supraventricular Arrhythmias.....	41
Systolic Dysfunction.....	41
<b>SUMMARY</b> .....	<b>42</b>
<b>REFERENCES</b> .....	<b>44</b>

### IN-TEXT TABLES

Table 1. All-cause mortality in patients with hypertension .....	11
Table 2. Cardiovascular disease mortality in patients with hypertension .....	12
Table 3. Myocardial infarction in patients with hypertension .....	13
Table 4. Stroke in patients with hypertension .....	14
Table 5. Heart failure in patients with hypertension .....	15
Table 6. End stage renal disease in patients with hypertension .....	15
Table 7. Quality of life in patients with hypertension .....	16
Table 8. Active control trials of chronic stable angina .....	21
Table 9. Placebo-controlled trials of systolic dysfunction .....	28
Table 10. Observational studies of mortality .....	37
Table 11. Strength of the evidence by key question .....	42

### FIGURES

Figure 1. Results of literature search .....	56
Figure 2. All-cause mortality in hypertensives (CCB vs diuretic and/or beta-blocker).....	57
Figure 3. All-cause mortality in hypertensives (CCB vs ACE inhibitor) .....	58
Figure 4. Mean change in weekly angina attacks .....	59

Figure 5. Mean change in weekly nitroglycerin doses .....	60
Figure 6. Mean change in time to angina onset .....	61
Figure 7. Final ventricular rate plot .....	62
Figure 8. Flushing in hypertensives .....	63
Figure 9. Dizziness in hypertensives.....	64
Figure 10. Headache in hypertensives .....	65
Figure 11. Edema in hypertensives .....	66
Figure 12. Withdrawals due to adverse events in hypertension active-controlled trials of CCBs vs diuretics or beta-blockers.....	67
Figure 13. Withdrawals due to adverse events in hypertension active-controlled trials of CCBs vs ACE inhibitors.....	68
Figure 14. Overall AE incidence in head-to-head trials of patients with angina .....	69
Figure 15. Withdrawal due to AE in head-to-head trials of patients with angina.....	70
Figure 16. Edema incidence in head-to-head angina trials .....	71
Figure 17. Edema incidence in systolic dysfunction trials.....	72
Figure 18. Withdrawal rates in systolic dysfunction trials.....	73

## APPENDICES

Appendix A. Search strategy .....	74
Appendix B. Quality assessment methods for drug class reviews.....	77
Appendix C. Reports of trials excluded.....	81
Appendix D. Articles available as abstracts only.....	187
Appendix E. Studies of quality of life with duration less than 6 months.....	190
Appendix F. List of abbreviations.....	193

## EVIDENCE TABLES - Published in a separate document

Evidence Table 1. Quality assessment of randomized trials
Evidence Table 2. Hypertension active controlled trials
Evidence Table 3. Quality of life trials
Evidence Table 4. Angina head to head trials
Evidence Table 5. Angina active controlled trials
Evidence Table 6. Angina placebo controlled trials
Evidence Table 7. Supraventricular arrhythmia head to head trials
Evidence Table 8. Supraventricular arrhythmia active controlled trials
Evidence Table 9. Supraventricular arrhythmia placebo controlled trials
Evidence Table 10. Systolic dysfunction active controlled trials
Evidence Table 11. Systolic dysfunction placebo controlled trials
Evidence Table 12. Adverse events in hypertension active controlled trials
Evidence Table 13. Adverse events in angina head to head trials
Evidence Table 14. Adverse events in supraventricular arrhythmia trials
Evidence Table 15. Observational studies of cancer
Evidence Table 16. Observational studies of cardiovascular events
Evidence Table 17. Observational studies of other adverse events
Evidence Table 18. Quality assessment of observational studies

## 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 because they block smooth muscle calcium channels at concentrations below those required for significant cardiac effects; they have less negative inotropic activity than verapamil or diltiazem.<sup>1</sup> 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 and Canada: amlodipine, bepridil, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, and verapamil. Of these, diltiazem, isradipine, nicardipine, nifedipine, and verapamil have both immediate and extended release formulations available (ranging from one to four times daily), felodipine and nisoldipine have only extended release formulations (given once daily), and amlodipine and bepridil are long-acting drugs available as immediate release only (given once daily). These drugs have Food and Drug Administration (FDA) indications for treating hypertension, angina, and supraventricular arrhythmias, depending on the specific drug.

While the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure generally recommends a thiazide diuretic as first-line therapy for essential hypertension, CCBs are accepted as first-line therapy alone or in combination with a thiazide diuretic for those without compelling indications, and for patients with high coronary disease risk and diabetes.<sup>2</sup> The use of CCBs in treating stable angina and the use of non-dihydropyridines in treating supraventricular arrhythmias is common, accepted practice. While, the use of CCBs in treating systolic dysfunction is not recommended by the American College of Cardiologists and American Heart Association,<sup>3</sup> the question of the safety of their use in such cases still arises. This report assumes that the decision to use a CCB has been made; the remaining decision is to determine which CCB will be chosen.

### Dihydropyridines vs non-dihydropyridines

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

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

## Scope and Key Questions

1. Do CCBs differ in effectiveness in the treatment of adult patients with essential hypertension (blood pressure  $\geq$  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  $\geq$  140/90 mm Hg), angina, supraventricular arrhythmias, or systolic dysfunction (LVEF $<$ 45%)?
3. Based on demographics (age, racial groups, gender), other medications, or co-morbidities, are there subgroups of patients for which one CCB is more effective or is associated with fewer adverse effects?

## METHODS

### Literature Search

To identify articles relevant to each key question, we searched the Cochrane Central Register of Controlled Trials (4th Quarter 2003), MEDLINE (1996 to February Week 1 2004), EMBASE (1991 to 1st Quarter 2004), the International Pharmaceutical Abstracts (IPA) database (1970 to February 2003), reference lists of review articles, and the Cardiovascular Trials Review.<sup>4</sup> In electronic searches, we used broad searches, combining terms for drug names with terms for relevant research designs (see Appendix A for the complete search strategy). In addition, we searched the FDA website for any updates on the approved indications for each CCB. Pharmaceutical manufacturers were invited to submit dossiers, including citations, using a protocol issued by the Center for Evidence-based Policy (<http://www.ohsu.edu/drugeffectiveness/pharma/index.htm#2>). 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  $\geq$  140/90 mm Hg), angina, supraventricular arrhythmia or supraventricular tachycardia (SVT), and systolic dysfunction (LVEF  $<$ 45%). For studies of angina, we believed that longer-term studies were required to establish a difference in effectiveness: therefore, we only included studies with a duration of 2 months or longer as an arbitrary cutoff. *Interventions* included oral dosage forms of one of nine CCBs (amlodipine,

bepidil, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, and verapamil) compared with another CCB drug, another oral antihypertensive drug (i.e., ACE inhibitor, beta-blocker, diuretic), or a placebo. *Outcomes* for hypertension, angina, supraventricular arrhythmias and systolic dysfunction included all-cause mortality, cardiovascular (CV) disease mortality, CV events, and quality of life. Additional outcomes included the development of renal failure due to hypertension, symptoms of angina (e.g., episodes of chest pain, use of sublingual nitroglycerin), symptoms (rate or rhythm control) and incidence of stroke due to supraventricular arrhythmias, and symptoms (exercise tolerance, subjective assessments, and New York Heart Association [NYHA] classification) related to systolic dysfunction.

To evaluate effectiveness we included only controlled clinical trials. The validity of controlled trials depends on how they are designed. Randomized, properly blinded clinical trials are considered the highest level of evidence for assessing effectiveness.<sup>5,6</sup> 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 observational studies as well as clinical trials. 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. 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.

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

## Data Abstraction

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

## Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix B. These criteria are based on US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK) criteria.<sup>4,5</sup> We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more categories were rated “poor quality”; trials that met all criteria were rated “good quality”; the remainder were rated “fair quality.” As the fair quality category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A poor quality trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. External validity of trials was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the role of the funding source.

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

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

## Data Synthesis

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

# RESULTS

## Overview

Original searches identified 3,480 citations: 928 from the Cochrane Library, 1,764 from MEDLINE, 625 from EMBASE, 34 from IPA, 84 from reference lists, and 45 from two pharmaceutical company submissions (Figure 1).

Update searches, including a new search for observational studies of adverse events, identified an additional 1,533 citations. After a title and abstract review, we retrieved 165 full-text articles for detailed assessment, and included 23 new studies: five active-control trials (in 7 publications) in patients with hypertension (including one study of quality of life), one placebo-



controlled trial in patients with angina that reported long term health outcomes, nine observational studies of the risk of cancer, three observational studies of the risk of cardiovascular events and mortality, and five observational studies of other adverse events.

Excluded trials publications are listed in Appendix C, and results of trials published in abstract form are listed in Appendix D (individual trials may be represented by multiple publications, including abstracts).

Most of the randomized trials had fair internal validity, but their applicability to community practice was difficult to determine. The treatment and control groups generally received standard doses of CCB or comparator drug, with most studies of hypertension or angina allowing dose titration. Many studies did not state the funding source, but more than half were funded at least in part by the pharmaceutical industry, although a number of larger studies also reported other funding sources. Detailed quality assessments can be found in Evidence Table 1.

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

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

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

Head-to-head trials of the effects of CCBs on blood pressure control are numerous. It is our assumption that all of the approved CCBs lower blood pressure clinically significantly (as evidenced by FDA approval). However, these trials not often do not report health outcomes in addition to blood pressure lowering outcomes, and hence are not included in this review. We did not find any head-to-head trials that examined whether CCBs have different effects on all cause mortality, cardiovascular mortality, or cardiovascular events among patients with hypertension. The only health outcome reported in head-to-head trials was quality of life.

Quality of life (QOL) 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.<sup>7</sup> We found four head-to-head trials that examined quality of life in hypertensive patients.<sup>8-11</sup> We limited our analysis to only those 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. Only one trial met this criteria.<sup>8</sup> A bibliography of the other trials with durations less than 24 weeks can be found in Appendix E.

The one trial that met the follow-up duration criteria compared nifedipine GITS and amlodipine in 356 for 24 weeks.<sup>8</sup> It is unclear whether an intention-to-treat (ITT) analysis was used for the quality of life endpoints. The self-report quality of life questionnaire was comprised of items adapted from various scales. The scales 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 individual domains and a QOL summary score are reported.

A difference between groups was found 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 QOL 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. 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. Results from the Work Well-Being and Sexual Symptoms Distress domains were not reported.

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 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).

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

We identified 16 trials that evaluated the effectiveness of treating hypertensive patients with CCBs in order to reduce mortality, non-fatal CV events, and end stage renal disease (ESRD).<sup>12-30</sup> These trials compared CCBs to ACE inhibitors, angiotensin receptor antagonists, diuretics, and beta-blockers.<sup>12-23, 25, 29-34</sup> With the exception of the ALLHAT trial<sup>14</sup>, FACET trial<sup>15</sup> and the VALUE trial<sup>26</sup> which were 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.<sup>35</sup> We identified an additional three trials: ASCOT,<sup>36</sup> CASE-J,<sup>32</sup> and PRESERVE,<sup>37</sup> that have been launched but outcomes results have not yet been published.

The results of the 16 active-controlled trials are depicted in Tables 1-6 and Figures 2 and 3. Most trials recruited patients from the general population, although some trials focused on patients with renal decline,<sup>17, 29, 30, 38</sup> diabetes,<sup>15, 29, 30, 39</sup> or coronary artery disease.<sup>27, 33</sup> A subgroup analysis of one trial focused on patients with both coronary artery disease and diabetes.<sup>40</sup> 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.<sup>14</sup> All but two trials<sup>15, 16</sup> 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 14 active-controlled trials<sup>12, 14, 15, 17-22, 26, 27, 29, 30, 33, 41</sup> of amlodipine, diltiazem, isradipine, nicardipine, nifedipine long-acting gastrointestinal transport-system (GITS), nifedipine retard, nisoldipine, controlled-onset extended release (COER)-verapamil, and verapamil slow release (SR) that reported all-cause mortality. The study of nifedipine retard is

from Japan (JMIC-B) and it is not clear that the product used in this study is available in the US or Canada. We found nine active-controlled trials that reported CV disease mortality; 11 active-controlled trials of fatal and nonfatal MI; 11 active-controlled trials of fatal and nonfatal stroke; and eight active-controlled trials of fatal and nonfatal CHF or ESRD.<sup>12, 14-22, 25-30</sup>

Indirect comparisons across these trials are severely limited by heterogeneity and clinical differences. Data presented in tables and text below depict the range of outcomes found, but any indirect comparisons should be interpreted with caution.

### All-cause mortality

In the active-controlled trials there were no significant differences between the performance of the CCBs and their comparator drugs in reducing all-cause mortality (Table 1).<sup>12, 14-22, 26, 27, 29, 30, 33, 41</sup> The RR values and surrounding confidence intervals overlapped each other and all crossed 1.0 (see Figures 2 and 3).

When amlodipine, nifedipine GITS, nifedipine retard or nisoldipine were compared to ACE-inhibitors, the relative risks ranged from 0.76 to 1.73 (Table 1).<sup>15, 17, 21, 27, 42</sup> 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 (0.76) occurred in a 3-year, fair-quality study of Japanese patients with hypertension and coronary artery disease who took relatively low dosages of either nifedipine retard (10-20 mg) or an ACE inhibitor (enalapril 5-10 mg, imidapril 5-10 mg, or lisinopril 10-20 mg).<sup>27</sup> In contrast, 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.<sup>17</sup> This study was unique in that it recruited patients with a progressive decline in renal function.

Two trials compared amlodipine to angiotensin-II receptor antagonists (AIIRA).<sup>26, 29, 30</sup> These trials reported similar RR values despite heterogeneity in patient populations, AIIRA comparators, concomitant medication use, and duration of follow-up. The fair-quality, Irbesartan Diabetic Nephropathy Trial (IDNT) followed 1,715 patients taking amlodipine (2.5-10 mg), irbesartan (75 to 300 mg) or placebo for 2.5 years. In IDNT, significantly more patients taking amlodipine used concomitant potassium-sparing and combination diuretics than those taking irbesartan.<sup>29, 30</sup> The good-quality VALUE trial followed 15,000 high cardiovascular risk patients taking amlodipine 5 mg or valsartan 80 mg for 4 to 6 years.<sup>26</sup>

When patients taking amlodipine, diltiazem, isradipine, sustained release nicardipine, nifedipine GITS, COER-verapamil, or verapamil SR were compared with patients taking diuretics and/or beta-blockers, the relative risks ranged from 0.89 to 1.54. With one exception<sup>16</sup> 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.<sup>16</sup>

**Table 1. All-cause mortality in patients with hypertension**

CCB vs ACE Inhibitor or Angiotensin Receptor Antagonist				CCB vs Diuretic and/or Beta-blocker		
Drug	Studies	Comparison	RR (95% CI)	Studies	Comparison	RR (95% CI)
<b>Amlodipine</b>	AASK	Vs. Ramipril	1.45 (0.73-2.86)	ALLHAT	Vs. Chlorthalidone	0.96 (0.89-1.02)
	FACET	Vs. Fosinopril	1.24 (0.36-4.20)			
	VALUE	Vs. Valsartan	0.98 (0.89-1.07)			
	IDNT	Vs. Irbesartan	0.97 (0.74-1.28)			
<b>Diltiazem</b>				NORDIL	Vs. Combined diuretic and beta-blocker	1.00 (0.83-1.20)
<b>Isradipine</b>				MIDAS	Vs. HCTZ	0.89 (0.35-2.28)
<b>Nicardipine</b>				NICS-EH	Vs. Trichlormethiazide	1.54 (0.31-7.67)*
<b>Nifedipine GITS</b>	Marin	Vs. Fosinopril	1.73 (0.54-5.58)*	INSIGHT	Vs. Co-amiloride, HCTZ	1.01 (0.81-1.27)
	<b>Nifedipine retard</b>	JMIC-B	Vs. ACE inhibitor (enalapril, imidapril, or lisinopril)			
<b>Nisoldipine</b>	ABCD	Vs. Enalapril	1.30 (0.60-2.80)			
<b>COER-Verapamil</b>				CONVINCE	Vs. HCTZ or atenolol	1.08 (0.92-1.26)
<b>Verapamil SR</b>				INVEST	Vs. Atenolol	0.98 (0.90-1.07)

## Cardiovascular disease (mortality and events)

### Cardiovascular mortality

We found four trials that evaluated the effectiveness of CCBs in reducing CV mortality compared with ACE inhibitors<sup>17, 21, 27, 39</sup> or an angiotensin-II receptor antagonist<sup>26</sup> (Table 2). Two trials reported reduced effectiveness (relative risks of 2.00 and 2.30, respectively).<sup>17, 21, 39</sup> Each result should be considered with caution. One study had large withdrawal rates (55-60%) in the study medication rates,<sup>21, 39</sup> and the other was underpowered to detect CV outcomes.<sup>17</sup> This latter study contained only 241 patients.<sup>17</sup> Both of these studies included special populations: type 2 diabetes<sup>39</sup> and patients with progressive renal function decline<sup>17</sup>; this may make the results more difficult to compare with the studies of the general population. Two other trials found no difference in CV mortality in comparisons of amlodipine versus valsartan<sup>26</sup> and nifedipine retard versus either enalapril, imidapril, or lisinopril.<sup>27</sup>

**Table 2. Cardiovascular disease mortality in patients with hypertension**

\*Authors reported insufficient power

CCB vs ACE Inhibitor or Angiotensin Receptor Antagonist				CCB vs Diuretic and/or Beta-blocker		
Drug	Studies	Comparison	RR (95% CI)	Studies	Comparison	RR (95% CI)
<i>Amlodipine</i>	VALUE	Vs. Valsartan	1.01 (0.86-1.18)			
<i>Diltiazem</i>				NORDIL	Vs. Combined diuretic and beta-blocker	1.11 (0.87-1.43)
<i>Nicardipine</i>				NICS-EH	Vs. Trichlormethiazide	1.54 (0.31-7.67)*
<i>Nifedipine GITS</i>	Marin	Vs. Fosinopril	2.30 (0.65-8.26)*	INSIGHT	Vs. Co-amiloride, HCTZ	1.18 (0.78-1.78)
<i>Nifedipine retard</i>	JMIC-B	Vs. ACE inhibitor (enalapril, imidapril, or lisinopril)	0.96 (0.31-3.04) (sudden death/ cardiac death)			
<i>Nisoldipine</i>	ABCD	Vs. Enalapril	2.00 (0.70-6.10)			
<i>COER-Verapamil</i>				CONVINCE	Vs. HCTZ or atenolol	1.09 (0.87-1.37)
<i>Verapamil SR</i>				INVEST	Vs. Atenolol	1.00 (0.88-1.14)

The relative risks for CV mortality comparing CCBs to diuretics and/or beta-blockers again center around 1.0,<sup>18, 20, 33, 41, 43</sup> with the exception of one underpowered trial.<sup>16</sup>

#### Myocardial Infarction (fatal and nonfatal)

The relative risks for myocardial infarction for CCBs compared with ACE inhibitors are mixed and were tested only in special populations (Table 3). Both trials that compared a CCB with fosinopril reported lowered risk with the CCB (nifedipine GITS vs. fosinopril, 0.58; amlodipine vs. fosinopril, 0.77)<sup>15, 17</sup> although these differences were not statistically significant. In one study the patients had diabetes<sup>15</sup> and in the other, the patients had chronic renal failure.<sup>17</sup> In contrast, when nisoldipine was compared with enalapril in another diabetic population, the RR increased (2.25)<sup>39</sup> 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.<sup>21, 39</sup>

Amlodipine reduced the risk of MI when compared to AIIRAs in two studies in special populations (hypertensive comorbid with either CAD or diabetic nephropathy).<sup>26, 29, 30</sup> It is unclear as to whether the MI rates reported in the IDNT included both nonfatal and fatal types.<sup>29, 30</sup>

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.<sup>18</sup> 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.”<sup>18</sup>.

**Table 3. Myocardial infarctions (fatal and nonfatal) in patients with hypertension**

CCB vs ACE Inhibitor or Angiotensin Receptor Antagonist				CCB vs Diuretic and/or Beta-blocker		
Drug	Studies	Comparison	RR (95% CI)	Studies	Comparison	RR (95% CI)
<b>Amlodipine</b>	FACET	Vs. Fosinopril	0.77 (0.34-1.75)			
	VALUE	Vs. Valsartan	0.85 (0.74-0.99)			
	IDNT	Vs. Irbesartan	0.62 (0.39 to 0.99)			
<b>Diltiazem</b>				NORDIL	Vs. Combined diuretic and beta-blocker	1.16 (0.94-1.44)
<b>Nicardipine</b>				NICS-EH	Vs. Trichlormethiazide	1.03 (0.18-5.79)*
<b>Isradipine</b>				MIDAS	Vs. HCTZ	1.20 (0.37-3.89)
<b>Nifedipine GITS</b>	Marin	Vs. Fosinopril	0.58 (0.08-4.34)*	INSIGHT	Vs. Co-amiloride, HCTZ	1.27 (0.91-1.76)
	<b>Nifedipine retard</b>	JMIC-B	Vs. ACE inhibitor (enalapril, imidapril, or lisinopril)			
<b>Nisoldipine</b>	ABCD	Vs. Enalapril	2.25 (0.75-8.82)			
<b>Verapamil</b>				CONVINCE	Vs. HCTZ or atenolol	0.82 (0.65-1.03)
<b>Verapamil SR</b>				INVEST	Vs. Atenolol	1.03 (0.90-1.17)

\*Authors reported insufficient power

### Stroke (fatal and nonfatal)

The relative risks in seven of 12 trials center around 1.0 (0.88 to 1.15), regardless of comparison drugs (Table 4).<sup>14, 18, 26, 27, 29, 30, 33, 39, 41, 43</sup> The results of two trials (FACET, MIDAS) suggest that, again, dosage influenced the result.<sup>15, 19</sup> The lowest RR (0.39) of stroke occurred when patients taking a high dose (10 mg) of amlodipine were compared with patients taking a relatively low dose (20 mg) of fosinopril, as evidenced by the significantly greater reduction in blood pressure from baseline with amlodipine vs fosinopril (p,0.05).<sup>15</sup> The trial (again thought to be underpowered) with the highest risk of stroke (3.09) had the lowest risk of CHF (0.15).<sup>16</sup>

**Table 4. Stroke (fatal and nonfatal) in patients with hypertension**

CCB vs ACE Inhibitor or Angiotensin Receptor Antagonist				CCB vs Diuretic and/or Beta-blocker		
Drug	Studies	Comparison	RR (95% CI)	Studies	Comparison	RR (95% CI)
<b>Amlodipine</b>	FACET	Vs. Fosinopril	0.39 (0.12-1.23)	ALLHAT	Vs. Chlorthalidone	0.93 (0.82-1.06)
	VALUE	Vs. Valsartan	0.88 (0.75-1.03)			
	IDNT	Vs. Irbesartan	0.54 (0.30-1.0)			
<b>Nicardipine</b>				NICS-EH	Vs. Trichlormethiazide	3.09 (0.13- 75.36)*
<b>Isradipine</b>				MIDAS	Vs. HCTZ	2.00 (0.50-7.93)
<b>Nifedipine GITS</b>	Marin	Vs. Fosinopril	2.30 (0.30-17.45)*	INSIGHT	Vs. Co-amiloride HCTZ	0.91 (0.66-1.26)
<b>Nifedipine retard</b>	JMIC-B	Vs. ACE inhibitor (enalapril, imidapril, or lisinopril)	1.00 (0.50-2.02)			
<b>Nisoldipine</b>	ABCD	Vs. Enalapril	1.00 (0.18-5.63)			
<b>COER-Verapamil</b>				CONVINCE	Vs. HCTZ or atenolol	1.15 (0.90-1.48)
<b>Verapamil SR</b>				INVEST	Vs. Atenolol	0.88 (0.72-1.07)

\*Authors reported insufficient power

#### Congestive heart failure (fatal and nonfatal)

The RR for CHF ranged from 0.15 in an underpowered trial of sustained release nicardipine to 2.17 in a trial of nifedipine GITS (INSIGHT), compared with co-amiloride in an older population (76% of patients over 60 years) (Table 5).<sup>16, 43</sup> With the exception of the one underpowered study, seven studies found point estimates indicating an increased risk of CHF with the CCB than with the comparator (AIIRA, ACE-Inhibitor, diuretic and/or beta blocker); with 3 of these being statistically significant. Three studies finding a significant increase in risk studied dihydropyridines (2 of amlodipine, 1 of nifedipine GITS). Two studies that either required or allowed a beta-blocker in the diuretic arm, compared to a non-dihydropyridine CCB found non-significant increases in risk. Two large trials of a CCB versus a diuretic found the risk of heart failure significantly greater with the CCB, one of amlodipine in a general population (ALLHAT) and the other of nifedipine GITS in older patients (INSIGHT). Amlodipine was also associated with a significantly greater risk of heart failure than irbesartan in patients with hypertension and diabetic nephropathy in the IDNT.<sup>29, 30</sup> One very large AIIRA study and one ACE-Inhibitor study of dihydropyridines found non-significant increases in risk.

**Table 5. Heart failure (fatal and nonfatal) in patients with hypertension**

CCB vs ACE Inhibitor or Angiotensin Receptor Antagonist				CCB vs Diuretic and/or Beta-blocker		
Drug	Studies	Comparison	RR (95% CI)	Studies	Comparison	RR (95% CI)
<b>Amlodipine</b>	VALUE	Vs. Valsartan	1.14 (0.99-1.31)	ALLHAT	Vs. Chlorthalidone	<b>1.38</b> <b>(1.25-1.52)</b>
	IDNT	Vs. Irbesartan	<b>1.6 (1.17-2.14)</b>			
<b>Nicardipine</b>				NICS-EH	Vs. Trichlormethiazide	0.15 (0.01-2.83)*
<b>Nifedipine GITS</b>				INSIGHT	Vs. Co-amiloride, HCTZ	<b>2.17</b> <b>(1.11-4.24)</b>
<b>Nisoldipine</b>	ABCD	Vs. Enalapril	1.14 (0.44-2.99)			
<b>Diltiazem</b>				NORDIL	Vs. Combined diuretic and beta-blocker	1.16 (0.81-1.67)
<b>COER-Verapamil</b>				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)<sup>43</sup> 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.<sup>42</sup> The trial (INSIGHT) that had the highest RR for CHF (2.17) also had the lowest RR for ESRD (0.62).<sup>43</sup>

**Table 6. End stage renal disease in patients with hypertension**

CCB vs ACE Inhibitor or Angiotensin Receptor Antagonist				CCB vs Diuretic &/or Beta-blocker		
Drug	Studies	Comparison	RR (95% CI)	Studies	Comparison	RR (95% CI)
<b>Amlodipine</b>	AASK	Vs. Ramipril	1.37 (0.90-2.07)	ALLHAT	Vs. Chlorthalidone	1.12 (0.89-1.40)
	IDNT	Vs. Irbesartan	1.29 (0.99-1.69)			
<b>Isradipine</b>	Petersen	Vs. Spirapril	1.00 (0.31-3.25)			
<b>Nifedipine SR</b>	Chan	Vs. Enalapril	0.80 (0.27-2.33)			
<b>Nifedipine GITS</b>				INSIGHT	Vs. Co-amiloride, HCTZ	0.62 (0.26-1.44)
<b>COER-Verapamil</b>				CONVINCE	Vs. HCTZ or atenolol	0.81 (0.49-1.35)



## Quality of life

Three studies discussed above (TOMHS, AASK, NICS-ES), as well as seven other long-term, active-controlled trials reported quality of life outcomes.<sup>7, 44-49</sup>

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<sup>49</sup> reported declines in mean scores from the total psychological, somatic and cognitive subscale baselines, as did patients in one amlodipine treatment group<sup>44</sup> 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.

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.

**Table 7. Effects of CCBs on the quality of life in patients with hypertension**

Trial	Intervention	Sample Size	QOL Outcome Summary
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
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
Fletcher, 1992	Nifedipine retard	n=179	↑ on 1/12 subscales ↓ on 1/12 subscales no change on 10 subscales (compared with cilazapril or atenolol)
Metelitsa	Nifedipine	n=89	↑ on 4/8 main GWBQ scales
Fletcher, 1992	Nifedipine	n=130	↑ on 5/8 subscales; ↓ on 3/8
Boissel	Verapamil	n=163	No significant differences for 16/16 QOL items

## Summary

Overall, the results from active-controlled trials suggest that the CCBs performed no better than diuretics and/or beta-blockers for health outcomes. In indirect comparison of studies of CCBs compared to ACE-inhibitors, no differences among the CCBs were discernable but in general the CCBs resulted in higher risk for health outcomes than ACE-inhibitors (although not statistically significant). The reasons for these differences in individual studies is not clear. Results were mixed across two trials that compared amlodipine to AIIRAs in different

hypertensive subgroups.<sup>26, 29, 30</sup> The INDT of hypertensives with diabetic nephropathy reported that amlodipine was associated with a significantly lower risk of myocardial infarction and a significantly higher risk of heart failure than irbesartan.<sup>29, 30</sup> The other trial found no difference between treatments in patients with coronary artery disease.<sup>26</sup> Based on this evidence it is not possible to identify a superior CCB 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.<sup>16, 17</sup> 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.<sup>17, 43</sup> One trial reported a low RR for MI (0.58) yet a high risk for stroke (2.3).<sup>17</sup> The INSIGHT trial reported a high RR for CHF (2.17) yet a low RR for ESRD (0.62), although none of these differences were statistically significant.<sup>43</sup> In addition, it is not possible to separate the effects of supplemental antihypertensive medications from study medications; therefore, the type and prevalence of secondary medication use varied. All of these issues made it difficult to reach reliable conclusions concerning the comparative effectiveness of the CCBs to improve CV health outcomes.

### **Dihydropyridines vs non-dihydropyridines**

One trial using diltiazem<sup>20</sup> and two trials using verapamil<sup>18, 33, 41</sup> were found. All three studies compared a non-dihydropyridine to a diuretic and/or beta-blocker; no significant difference was documented. On the outcome measure of heart failure, two trials of non-dihydropyridine CCBs showed no significant increase in risk, while 3 trials of dihydropyridine CCBs did report an increase in risk. Due to important differences in patient populations, co-interventions, and comparator drugs, it is not possible to make indirect comparisons across this study set, and no further assessment of differences between dihydropyridines and non-dihydropyridines can be made.

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

Placebo-controlled trials did not examine mortality and cardiovascular morbidity outcomes, but one trial of felodipine vs placebo assessed quality of life over 52 weeks of follow-up.<sup>50</sup> 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%).

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

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

We found 11 trials comparing one CCB to another for the treatment of chronic stable angina (see Evidence Table 4); however five of these were rated poor quality and are not discussed here (see study quality assessments, Evidence Table 1). The poor quality studies suffered from lack of details on randomization, allocation concealment and baseline characteristics, lack of an intention to treat analysis, and/or differences in potentially important baseline characteristics. The remaining six trials studied amlodipine (four trials), diltiazem immediate release (three trials), diltiazem controlled release (CR) (one trial), nisoldipine core coat (CC) (two trials), and nicardipine and nifedipine (one trial each). All were of fair quality.<sup>51-56</sup> It is not clear whether the diltiazem CR formulation used in one study conducted in the UK is available in the US.<sup>55</sup> These studies ranged in duration from 2-3 months. These studies were not long enough to report health outcomes of mortality and CV events, rather they report symptom related outcomes and those are reported here. There were no head-to-head studies of bepridil, felodipine, isradipine, or verapamil.

These studies enrolled patients with chronic stable angina, although one study<sup>52</sup> also enrolled patients with coronary artery narrowing (based on angiography) or a non-Q wave MI. Two studies required the concomitant use of a beta-blocker (atenolol)<sup>53, 55</sup> and a third allowed continued use of beta-blockers or long-acting nitrates if the dose was stable.<sup>51</sup> 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<sup>51, 57</sup> 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<sup>51, 52</sup> 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.<sup>56</sup>

Based on treadmill exercise testing, the mean change in time to the onset of angina was available from three studies (Figure 6).<sup>52, 53, 55</sup> These studies compared amlodipine to diltiazem, amlodipine to nisoldipine, and nisoldipine to diltiazem CR. The range of improvement in time to onset of angina was 16 to 85 seconds. Again, no significant difference was found between drugs in these studies, although amlodipine and nisoldipine tended to be superior to diltiazem.

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

We found 15 trials of a CCB vs an active control from another drug class for the treatment of angina. Two of these were poor quality (see Evidence Table 1).<sup>58, 59</sup> These studies had significant problems; they did not report methods of randomization and allocation concealment, and had potentially important differences at baseline in CV characteristics, lack of blinding of patients, and/or lack of description of withdrawals. The remaining studies were all fair quality, and assessed amlodipine (four studies), bepridil (one study), diltiazem (two studies), diltiazem CR (one study), nifedipine (two studies), nifedipine SR (one study) and verapamil (two studies) in patients with chronic stable angina (see Evidence Table 5 and Table 8 below). The patient populations enrolled were typical of chronic stable angina, with a mean age of approximately 60 years, more males than females, and a significant proportion of positive histories for evidence of coronary artery disease. The comparator drugs were primarily beta-blockers. The studies ranged from 8 weeks to 75 months, and daily doses of CCBs were amlodipine 5-10mg, bepridil 100-400mg, diltiazem 180-360mg, diltiazem CR 240mg, nifedipine 40mg, nifedipine SR 40mg, and verapamil 360 to 480mg. Two of the 13 studies were conducted in the US, with others largely conducted in European countries. There were no studies of felodipine, isradipine, nicardipine, or nisoldipine.

In the group of CCBs studied in active-controlled trials, only bepridil and verapamil are not also represented in the head-to-head comparisons. The study of bepridil<sup>60</sup> 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<sup>61-63</sup> reported very different outcome measures. One followed patients for 6-75 months and reported fatal and non-fatal events.<sup>61, 62</sup> 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<sup>63</sup> 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<sup>64, 65</sup> 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).<sup>61, 62</sup> Again, however, the verapamil study followed patients for up to 75 months. It is not clear that the formulation of nifedipine SR used in this study is one that is available in the US.

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

**Table 8. Active-controlled trials of chronic stable angina**

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

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

We found four fair quality studies of a CCB compared to placebo (Evidence Tables 1 and 6). One of these trials reported long-term health outcomes.<sup>66</sup>

### **Health Outcomes**

A placebo-controlled trial of nifedipine GITS (30-60 mg) in 7,665 patients with stable angina pectoris<sup>66</sup> found no difference between groups in all-cause mortality (Hazard Ratio {HR} 1.07; 95% CI 0.91-1.25; p=0.41), myocardial infarction (HR 1.04; 95% CI 0.88-1.24; p=0.62), refractory angina (HR 0.86 95% CI 0.69-1.07; p=0.18), or debilitating stroke (HR 0.78; 95% CI 0.58-1.05; p=0.10) after an average followup period of 4.9 years. The only health outcome that was significantly reduced in the nifedipine group was overt heart failure (HR 0.71; 95% CI 0.54-0.94; p=0.015). Hazard ratios for undergoing the procedures coronary angiography (0.82; 95% CI 0.75-0.90), and coronary bypass surgery (0.79; 95% CI 0.68-0.92) were significantly reduced, but not percutaneous coronary intervention (0.92; 0.80-1.06) or peripheral revascularization (1.25; 95% CI 0.98-1.59),.

### **Symptoms**

Two studies are reports written by the same investigator using verapamil vs placebo for treating Prinzmetal's variant angina pectoris.<sup>67, 68</sup> 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.

Another trial 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 do not show difference in efficacy in the comparisons made (amlodipine vs diltiazem or diltiazem CR, amlodipine vs nisoldipine, nisoldipine vs diltiazem CR, and nifedipine 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, 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<sup>51, 52, 56</sup>, nisoldipine in 1<sup>55</sup>) to a non-dihydropyridine (diltiazem). No differences

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

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

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

We found three head-to-head studies comparing one CCB to another for the treatment of a supraventricular arrhythmia (see Evidence Table 7). Two studies compared immediate release formulations of diltiazem and verapamil<sup>69, 70</sup>, while one compared the SR formulations of these drugs.<sup>71</sup> All three studies were fair quality (see Evidence Table 1), and none were conducted in the US. The studies ranged from 1<sup>70, 71</sup> to 3 weeks.<sup>69</sup> 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<sup>70, 71</sup> and 1 month.<sup>69</sup> 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,<sup>71</sup> 11% had corrected or uncorrected mitral valve disease<sup>69</sup> and 47% had mitral valve disease.<sup>70</sup> The proportion of patients with lone AF was similar in the two studies reporting these data (56 and 61%).<sup>69, 71</sup> The primary outcome measure was mean ventricular rate at rest, although two studies also reported these data during exercise<sup>69, 71</sup>. However, different methods of exercise testing were used (walking test and ergonometric bicycle), and one study<sup>70</sup> also reported the rate of conversion to normal sinus rhythm.

One of these studies only reported the ventricular rate at final testing<sup>71</sup> 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.<sup>69, 71</sup> 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.<sup>69</sup>



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

We found 16 studies comparing a CCB to a drug from another class, six studies of diltiazem and 10 of verapamil (see Evidence Table 8). These studies compared the CCB to a beta-blocker, digoxin, or an antiarrhythmic drug (quinidine, flecainide, amiodarone). All but one study was fair quality (see Evidence Table 1). The one poor quality trial<sup>72</sup> 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<sup>73</sup> (Cardizem CD) used the immediate release formulation, with doses ranging from 180 to 360mg daily. Of the verapamil studies, one used verapamil SR,<sup>74</sup> 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.<sup>73-85</sup> 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),<sup>86</sup> patients with new-onset rapid AF ( $\leq 24$  hours duration, verapamil vs clonidine or digoxin),<sup>87</sup> and patients with paroxysmal SVT (verapamil vs flecainide).<sup>88</sup> No comparative analysis can be made of the effectiveness of CCBs in these three groups of patients, except to report that no studies of diltiazem were found.

For the studies of chronic AF, the mean age across studies ranged from 50 to 67 years, and more men than women were enrolled in 9 of 13 studies. The proportions of patients with valvular disease ranged from 11 to 75%, and those with lone AF ranged from 8 to 33%. These studies enrolled 12 to 97 patients. The study ranged from 2 weeks to 12 months, and one study<sup>78</sup> 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).<sup>80, 81, 85</sup>

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,<sup>78, 84</sup> one using diltiazem 270 to 350mg and the other using verapamil 120 to 360mg daily. These studies had similar inclusion/exclusion criteria and reported similar outcomes. The mean resting ventricular rate with diltiazem was 91, and 102 with verapamil (although rate varied depending on dose); the post-exercise rate was 140 with diltiazem and 127 to 149 with verapamil. Visual analog scale assessments of overall well-being were 23 with diltiazem, and ranged from 13 to 18 with verapamil. The baseline scores were not presented. Using the Borg scale (6 – 20 points), patient perception of exertion with exercise was assessed, with scores of 3.7 for diltiazem, and 3.7 to 4.5 for verapamil.

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

We found seven placebo-controlled studies of a CCB to treat a supraventricular arrhythmia (see Evidence Table 9). Three of these studies<sup>89-91</sup> 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<sup>92,93</sup> 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<sup>94</sup> used verapamil 360 mg daily, and the seventh study was in patients with paroxysmal SVT,<sup>95</sup> using diltiazem in doses of 240-360mg daily. Because there are only single studies of post-MI prophylaxis and paroxysmal SVT, no comparison can be made between the CCBs.

In the three chronic AF studies, the duration of treatment using verapamil or placebo was 2-12 weeks. At the end of active treatment, the mean ventricular rate at rest ranged from 66 to 87 bpm with verapamil, compared to 87 to 125 bpm with placebo, in the two trials reporting these data, with higher rates for patients with resting rates > 100 bpm at baseline.<sup>90,91</sup> These rates are similar to the rates seen in head-to-head and active-controlled trials. Ventricular rate during exercise ranged from 101 to 126 bpm, and was somewhat lower than the rates seen in the verapamil arms of the head-to-head and active-control trials, which were 137 to 158 and 127 to 149 bpm, respectively.

## Summary

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

## Dihydropyridines vs non-dihydropyridines

No trials using a dihydropyridine were found.

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

Fourteen studies of a CCB for the treatment of systolic dysfunction (LVEF <45%) were found.<sup>96-111</sup> 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<sup>103, 104, 110-112</sup>. 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.<sup>96, 97, 113, 114</sup> 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,<sup>98, 108</sup> and one to isosorbide dinitrate.<sup>101</sup>

### 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.<sup>108</sup> 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.<sup>98</sup> The third study<sup>101</sup> 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.<sup>107</sup> 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.<sup>97, 109, 115</sup>

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<sup>109</sup> 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.<sup>100, 102, 105, 106</sup>

The Prospective Randomized Amlodipine Survival Evaluation (PRAISE) study<sup>105, 106</sup> is the largest trial of a CCB for systolic dysfunction included, with 1153 patients randomized to amlodipine or placebo and followed up for a mean of 13.8 months. In this study, the results for the overall group did not show any difference in fatal or nonfatal events (nonfatal events: pulmonary edema, severe hypoperfusion, MI, sustained ventricular tachycardia/fibrillation) or all-cause mortality (secondary outcome). In a subgroup analysis, there was also no difference among those patients with ischemic disease (n = 732); however there were significant differences in the group with nonischemic cardiomyopathy (n = 421). There was a 9% reduction in fatal and nonfatal events (95% CI -17.9,-0.1) and a 13% reduction in all-cause mortality (95% CI -21.8,-4.8) in the amlodipine group. While randomization was stratified by etiology, the results pertain to a subgroup. This study was followed up by a second PRAISE study, which included only patients with nonischemic cardiomyopathy. This study has not been published in its entirety, but reports from cardiology conferences in 2000 indicated that 1652 patients were randomized, using a protocol similar to the original study. In this larger study no significant difference was found in all-cause mortality, with a 2% difference between amlodipine and placebo being reported.

Two small studies using felodipine vs placebo enrolled patients with LV dysfunction due to ischemic etiology. One study followed patients for two months (n = 23)<sup>99</sup> and the other for six months (n = 20).<sup>102</sup> The 6-month study<sup>102</sup> found no difference in mortality or subjective assessment after six months. The 2-month study<sup>99</sup> found patients to have a significantly increased exercise duration in the felodipine group (mean difference of change = 125 seconds, p<0.05) but worse subjective assessments of improvement compared to placebo. The scale used to assess subjective improvement was 1=markedly worse, 7=markedly improved; at 8 weeks the mean score in the felodipine group was 2.9 and 4.4 in the placebo group (p<0.01). Dyspnea was measured on a 3-point scale: 0=no dyspnea, 3=marked dyspnea. At 2 months, it was reported that 91% of patients on felodipine had diminished dyspnea while only 41% in the placebo group noted any improvement, but the scores are not reported.

### Summary

Nine active or placebo-controlled studies of CCBs for the treatment of systolic dysfunction were rated good or fair quality: one each of nifedipine and nisoldipine, two of amlodipine and five of felodipine. In active-controlled trials of felodipine, nifedipine, and

nisoldipine no differences in the effect on symptoms or exercise tolerance were found, however the trials results are limited by small sample sizes and short follow-up periods.

Data regarding mortality and/or CV events are available for amlodipine and felodipine from placebo-controlled trials. Overall, the evidence suggests that neither of these CCBs have an important impact (positive or negative) on all-cause mortality or combined fatal and nonfatal CV events. While amlodipine was shown to reduce combined events and all-cause mortality in idiopathic systolic dysfunction, the evidence is weakened by the fact that these findings were in a subgroup, with the reports from a larger follow-up trial showing no effect. Minor improvements in various symptom-based measures seen with amlodipine and felodipine in placebo-controlled trials are limited by small sample sizes and short follow-up periods. In general, no evidence of a difference in response could be found between amlodipine and felodipine. No other dihydropyridine CCB was studied in a fair- or good-quality study. No fair or good-quality study of a non-dihydropyridine CCB was found.

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

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

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

### Evidence from clinical trials

We included evidence from controlled clinical trials that reported data on adverse events of CCBs when used to treat hypertension, angina, or supraventricular arrhythmias. This evidence pertains to the populations specifically selected for these trials, and often excludes patients at higher risk for developing serious adverse events. These data provide a comparison of adverse

event and safety data for CCBs in shorter duration studies using somewhat healthier populations. However, the active-controlled hypertension studies provide data for longer time periods (2-6 years). Because the indication for using CCBs may have an effect on the adverse events experienced therefore leading to withdrawals, we initially present adverse event data by disease. Data regarding withdrawals due to adverse events are given greater weight because they capture the magnitude of effect and relate to reductions in effectiveness.

Evidence about adverse events from observational studies is presented in section 2E, below.

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

We found no head-to-head studies designed to assess the adverse events of CCBs. Adverse event evaluations reported in 15 active-controlled trials are summarized in Evidence Table 12.<sup>12, 14-17, 19-22, 25-30, 33, 39, 41-43, 116-140</sup> These evaluations included data for amlodipine, diltiazem, isradipine, 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 reported in three trials. In the INSIGHT trial, 48.9% of patients taking verapamil had one or more adverse events, compared to 41.9% of patients taking co-amiloride. In the JMIC-B trial,<sup>27</sup> 9% of patients taking nifedipine retard had an adverse event, versus 15% of those taking an ACE inhibitor. In a trial of nifedipine retard versus a beta blocker or an ACE inhibitor, designed to measure quality of life, overall adverse event rates were high in all three groups (64% nifedipine, 62% atenolol, and 52% cilazapril). Both of these studies were conducted in countries outside North America, and it is not clear that the formulation of nifedipine is available in the US or Canada.

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. The figures also include rates of adverse events from one trial designed to measure quality of life.<sup>48</sup> Data from the INSIGHT, MIDAS, NORDIL, and TOMHS trials suggest similarity between amlodipine, diltiazem, isradipine and nifedipine for risk of headache, and between amlodipine and nifedipine for risk of flushing when compared to a diuretic. Risk of dizziness compared to a diuretic is similar for amlodipine and nifedipine and similar for diltiazem and verapamil when compared to a beta blocker.

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

Withdrawals due to adverse events were reported by five active-controlled trials in which a CCB was compared to an ACE-inhibitor (ALLHAT, Chan, ABCD, JMIC-B, Fletcher), and

seven trials in which a CCB was compared to a diuretic/beta-blocker (ALLHAT, NICS-EH, INSIGHT, MIDAS, CONVINCENCE, INVEST, Fletcher). 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<sup>25, 40</sup> and nisoldipine (ABCD) or amlodipine (ALLHAT).

When comparing nisoldipine to enalapril, the risk difference in the ABCD study was not significant (risk difference= +5.5, 95% CI -1.7% to +12.8%), while in the ALLHAT study there was a significant difference between amlodipine and lisinopril (risk difference= -9.2, 95% CI -10.5 to -7.8).

Comparison of CCBs with diuretic comparators suggests similarity in adverse event withdrawal rates for amlodipine vs chlorthalidone (ALLHAT), nicardipine vs trichlormethiazide (NICS-EH), isradipine vs HCTZ (MIDAS), COER verapamil vs HCTZ or atenolol (CONVINCE), and verapamil SR vs atenolol (INVEST). Patients in the nifedipine GITS group in the INSIGHT trial showed a significantly higher adverse event withdrawal risk difference (+6.5%) than seen in the other trials: nicardipine in NICS-EH (-1.4%) and COER verapamil in CONVINCENCE (+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.

In a trial measuring quality of life,<sup>48</sup> there was a significantly higher rate of withdrawals due to adverse events in the nifedipine retard group compared with both cilazapril (risk difference +1.2%) and atenolol (risk difference +9.1%).

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

Five trials (ALLHAT, INSIGHT, NORDIL, INVEST, VALUE) reported the incidence of development of diabetes. When compared to a diuretic or beta blocker, patients taking amlodipine in the ALLHAT study (risk difference -1.8; 95% CI -2.6 to -1.0), nifedipine GITS in the INSIGHT study (risk difference -1.3; 95% CI -2.2 to -0.4), diltiazem in the NORDIL study (risk difference -0.7; 95% CI -1.5 to 0.05) and amlodipine in the INVEST study (risk difference -1.2; 95% CI -1.9 to -0.5) the incidence of new-onset diabetes was lower in the CCB groups, and similar across CCBs. In the VALUE trial, comparing an angiotensin-II receptor antagonist with amlodipine in patients at high cardiovascular risk, the risk of new onset diabetes was lower in the valsartan group than the amlodipine group (Hazard Ratio 0.77; 95% CI 0.69-0.86).

In summary, indirect analysis of data for amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nisoldipine, and verapamil from 15 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) and formulations of drugs 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<sup>51-56</sup> no significant difference in overall adverse event rates or withdrawals due to adverse events was found between amlodipine, diltiazem, 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.<sup>61, 62</sup> 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.<sup>60, 63</sup>

## **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).<sup>69-71</sup> These were very short duration trials, two only lasting 7 days<sup>70, 71</sup> and the third lasting 3 weeks.<sup>69</sup> 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).<sup>69</sup> 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).<sup>70</sup> 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.<sup>71</sup>

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, 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,<sup>141</sup> and the other comparing nifedipine to isosorbide dinitrate.<sup>101</sup> Felodipine was similar to enalapril in overall adverse event rates, but more patients experienced peripheral edema with felodipine, while more had cough and dizziness with enalapril. No withdrawals were reported in this crossover trial. Reports of overall adverse events were greater with nifedipine than with isosorbide dinitrate or the combination (68% vs 35% vs 48%, respectively). Withdrawals due to adverse events were also higher in the nifedipine alone group (29% vs 19% vs 5%); however, these numbers include withdrawals due to worsening heart failure (failure of effectiveness).

### Placebo-controlled trials

One study of mild systolic dysfunction reported that 17% of patients experienced dizziness due to hypotension and ankle edema with felodipine, vs none with placebo.<sup>107</sup> 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 ( $p = 0.02$ ).<sup>97</sup> 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<sup>109</sup> 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.<sup>99, 106</sup> 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.<sup>99</sup> 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.<sup>106</sup> 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.<sup>102</sup>

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%).

## **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.

## 2E. Evidence on Long-Term Safety from Observational Studies

Seventeen observational studies of adverse effects from CCBs met the criteria for this review. These included 9 studies of the risk of cancer,<sup>142-150</sup> and 3 studies of all-cause mortality.<sup>151-153</sup> The remaining five studies examined various adverse effects, including depression,<sup>154</sup> congenital abnormalities,<sup>155</sup> and vasodilation-related events,<sup>156</sup> among others.<sup>157, 158</sup> Further details about the methods and results of these studies are found in Evidence Table 17.

There were additionally 2 studies of cancer risk<sup>159, 160</sup> and 3 studies of cardiovascular events<sup>161-163</sup> that were not included in this review, because the reports did not separate outcomes by drug.

### Studies of cancer incidence and cancer-related mortality

Six cohort studies<sup>144-148, 150</sup> and one case-control study<sup>149</sup> evaluated the association between CCB use and total cancer incidence or cancer-related mortality. Breast cancer risk was evaluated in two case-control studies,<sup>142, 143</sup> and three of the studies on total cancer reported results for breast cancer, among other sites.<sup>146, 148, 149</sup>

Eight of the 9 cancer studies were rated fair-quality because the methods did not fully characterize exposure or the effects of confounding factors.<sup>142, 144-150</sup> One case-control study that characterized CCB exposure and the effects of confounders in depth was rated good-quality.<sup>143</sup> However, the cohort design is preferred to the case-control study design for most outcomes, except for rarely occurring events.

Six fair-quality cohort studies of the association between CCB use and the total incidence of cancer or cancer-related mortality reported mixed results. In a cohort of 5052 persons in the U.S. *aged 71 or older*, the hazard ratio for cancer incidence was significantly increased for verapamil (HR 2.49, 95% CI 1.54-4.01) and nifedipine (HR 1.74, 95% CI 1.05-2.88), and non-significantly increased for diltiazem use (HR 1.22, 95% CI 0.70-2.12) compared with patients not taking CCBs, and a significant ( $p=0.0094$ ) dose-response gradient emerged for CCBs as a group.<sup>146</sup> A population-based cohort (N=3204) in the Netherlands found an increased risk of total cancer with verapamil but not with nifedipine, diltiazem, or amlodipine, compared with no CCB use.<sup>145</sup> The risk for verapamil in this study was statistically significant only with use greater than 2 years (RR 2.4, 95% CI 1.2-4.9), and was not significantly increased with use of 2 years or less (RR 1.4, 95% CI 0.8-2.5). A population-based cohort (N=17911) in Denmark found no increases in the age- and sex-standardized incidence of total cancer for verapamil (SIR 1.09, 95% CI 0.92-1.27), diltiazem (SIR 1.04, 95% CI 0.85-1.25), or dihydropyridines as a group (SIR 0.87, 95% CI 0.72-1.05).<sup>148</sup> A cohort study of 1054 post-MI patients in Japan found no excess risk of total cancer with either nifedipine (RR 1.34, 0.63-2.85) or diltiazem (RR 0.89, 95% CI 0.27-2.93), compared with patients who received no CCBs.<sup>150</sup> A 3-year cohort study in Israel (N=5543) found no excess risk for cancer-related mortality with nifedipine (RR 1.34, 95% CI 0.90-1.98), diltiazem (RR 0.78, 95% CI 0.52-1.17), or verapamil (RR 1.22, 95% CI 0.53-2.81), compared with no CCB use at baseline.<sup>144</sup> Another cohort study from Israel assessed cancer mortality after 10 years among 2607 hospital survivors of acute MI, and found no excess risk with nifedipine use at the time of discharge (RR 1.05, 95% CI 0.52-2.18).<sup>147</sup>

A case-control study in the U.S (cases n=9513, controls n=6492) reported no increased risks for total cancer with diltiazem, nifedipine, or verapamil.<sup>149</sup> Further analysis in this study found increased risks for cancers of the colon (OR 1.7, 95% CI 1.0-2.8) and kidney (OR 1.9,

95% CI 0.9-3.9) with 5 or more years of CCB use, but these results were not reported by drug. Further details about the methods and results of these studies are provided in Evidence Table 15.

### Breast Cancer

A good-quality case-control study of breast cancer among women aged 65-79 in the U.S. compared the use of CCBs among 975 cases and 1007 population-based controls.<sup>143</sup> In-person interviewers collected information about the dose, duration, and timing of exposure, and the following potential confounders: race, income, marital status, education, age at menarche, parity, age at first birth, type of menopause, age at menopause, duration of oral contraceptive use, ever use of hormone replacement therapy, first-degree family history of breast carcinoma, smoking status, average daily alcohol intake, and body mass index. The study found that users of the immediate-release non-dihydropyridines had an increased risk of breast cancer (OR 1.6, 95% CI 1.1-2.5) compared with never use of antihypertensive medications. A trend of increased risk with increased duration of use, however, did not emerge. No excess risk was found for immediate-release dihydropyridines, or the sustained-release forms of dihydropyridines and nondihydropyridines. Results by individual CCB drug were not reported.

A fair-quality case-control study of breast cancer in the UK compared 3706 cases of breast cancer with 14,155 controls.<sup>142</sup> All subjects were derived from a database of medical information submitted by general practitioners (GPRD), and controls were matched with cases based on age, physician practice, calendar date, and number of years of medical history in the GPRD. Smoking status, body mass index, history of alcohol abuse, previous hysterectomy, and history of benign breast disease, and estrogen replacement therapy were evaluated as potential confounders. The study found that the use of nifedipine, diltiazem, or verapamil did not significantly differ between cases of breast cancer and controls, and that increasing duration of use did not affect risk. Further analysis of nifedipine found no differences in risk among users of short-acting (OR 1.0, 95% CI 0.7-1.4) and long-acting formulations (OR 1.0, 95% CI 0.8-1.3). Three other studies found no increased risk between breast cancer and CCB use, but did not differentiate the results by drug.<sup>146, 148, 149</sup>

### Observational studies of all-cause mortality

A good-quality, population-based, retrospective cohort study in the U.S. examined mortality among elderly patients (mean age 76.1) who received CCBs after hospitalization due to acute MI.<sup>153</sup> Patients who were prescribed diltiazem (N=21175), nifedipine (N=12670), amlodipine (N=11683), verapamil (3639), or bepridil (N=116) at discharge were compared with 89,120 patients who were not prescribed CCBs at discharge. The study included all Medicare patients in 46 states, diagnosed with acute myocardial infarction (MI) and consecutively discharged during an 8-month period. Mortality was analyzed at 30 days and at 1 year after discharge, and adjusted for age, sex, race, descriptors of MI and coronary disease severity, comorbid illnesses, mobility at discharge, discharge destination, and propensity for CCB treatment. The study found no statistically significant differences in mortality among patients who received diltiazem (30-day 3.8%/1-year 18.3%), nifedipine (3.8%/18.3%), amlodipine (5.1%/22.0%), verapamil (4.3%/19.2%), or no CCB treatment at discharge (5.7%/21.5%). Patients who received bepridil, however, had significantly higher mortality compared with

controls matched for age and illness severity (30-day 13.8% vs 4.3%,  $p < 0.01$ ; 1-year 52.6% vs 27.6%,  $p < 0.001$ ).

Another good-quality, population-based, retrospective cohort study in the U.S. followed survivors of acute MI for two years to assess mortality and cardiac rehospitalization.<sup>152</sup> Patients who were prescribed long-acting CCBs within 90 days of discharge were compared with those who were prescribed short-acting CCBs. The study included Medicare recipients aged 65 or older who were consecutively discharged with a principal diagnosis of acute MI during a 1-year period, and who were also enrolled in Medicaid or the Program of Pharmaceutical Assistance for the Aged and Disabled. The analysis adjusted for demographics, severity, and comorbidity, and grouped together the dihydropyridines (nifedipine, nicardipine) and non-dihydropyridines (diltiazem, verapamil), rather than reporting results for each drug. Compared with their short-acting counterparts, the long-acting forms of the dihydropyridines were associated with significantly lower risks of death (RR 0.42, 95% CI 0.21-0.86) and cardiac rehospitalization (RR 0.57, 95% CI 0.34-0.94). For the non-dihydropyridines, the long-acting forms had a non-significantly higher risk of death (RR 0.65, 95% CI 0.40-1.05), and a non-significantly lower risk of cardiac rehospitalization (1.43, 95% CI 0.88-2.32), compared with short-acting forms.

A good-quality prospective cohort study of mortality in Canada compared beta-blockers with diltiazem, verapamil, and nifedipine.<sup>151</sup> Subjects were elderly patients (mean age 80.4) without dementia, who reported use of one or more antihypertensive medications or diuretics at screening. Vital status, and date and cause of death were assessed 5 years later. The study grouped diltiazem and verapamil users together, but further analyzed nifedipine users by formulation (short- vs. long-acting), dose, and duration of use, and compared with beta-blocker users. The results were adjusted for digoxin and nitrate use, age, sex, history of stroke, diabetes, arterial hypertension, intermittent claudication, cardiac symptoms, Modified Mini-Mental State Examination score, and diastolic blood pressure. The adjusted mortality among diltiazem and verapamil users was similar to that of beta-blocker users (HR 0.96, 95% CI 0.58-1.60), but significantly increased among nifedipine users (HR 1.82, 95% CI 1.09-3.04). Mortality was significantly high among users of the long-acting form of nifedipine (RR 2.07, 95% CI 1.11-3.85) but not the short-acting form (RR 1.64, 95% CI 0.88-3.03). Most short-acting users reported a dose of 30 mg/day or less, whereas most long-acting reported a dose of 40 mg/day or greater. An analysis by formulation-dose category revealed a two-fold increased risk of mortality for users of both short- and long-acting nifedipine at doses  $\geq 40$ mg/day, but this finding was statistically significant among long-acting nifedipine users only. No clear trend emerged with duration of nifedipine use.

**Table 10. Summary of results from observational studies of mortality and CCB use**

Author, year	CCB	Comparator	Adjusted comparison (95% CI or p-value)
Results for nifedipine			
Jollis, 1999	Nifedipine	No CCB use	0.98 (0.93-1.05)
Gillman, 1999	Long-acting dihydropyridines (nifedipine, nicardipine)	Short-acting dihydropyridines (nifedipine, nicardipine)	<b>0.42 (0.21-0.86)</b>
Maxwell, 2000	Long-acting nifedipine	Beta-blockers	<b>2.07 (1.11-3.85)</b>
	Short-acting nifedipine	Beta-blockers	1.64 (0.88-3.03)
Results for diltiazem and verapamil			
Jollis, 1999	Diltiazem	No CCB use	1.02 (0.97-1.07)
	Verapamil	No CCB use	0.93 (0.83-1.02)
Gillman, 1999	Long-acting non-dihydropyridines (diltiazem, verapamil)	Short-acting non-dihydropyridines (diltiazem, verapamil)	1.43 (0.88-2.32)
Maxwell, 2000	Diltiazem or verapamil	Beta-blockers	0.96 (0.58-1.60)
Results for other CCBs			
Jollis, 1999	Amlodipine	No CCB use	1.04 (0.98-1.10)
	Bepidril	No CCB use	52.6% v. 27.6% at 1 year ( <b>p&lt;0.001</b> )

### Observational studies of other adverse effects

A fair-quality case-control study in Hungary investigated the association between congenital limb deficiencies and the use of verapamil, nifedipine, and felodipine during pregnancy.<sup>155</sup> Twenty-two thousand eight hundred sixty-five cases were identified from a population-based registry of congenital abnormalities, and 38,151 matching controls were selected from the national birth registry based on gender, week of birth, and district of parents' residence. Mailed questionnaires collected information about maternal health and prenatal drug use, but did not assess smoking and alcohol consumption. Among cases, 2.6% of mothers received CCBs during pregnancy, compared with 2.4% of controls. The unadjusted odds for congenital limb deficiencies were similar between cases and controls with respect to prenatal use of verapamil, nifedipine, and felodipine. Calcium channel blockers as a group, however, were associated with significantly increased odds of undescended testis (OR 1.5, 95% CI 1.1-1.9), cardiovascular- (OR 1.4, 95% CI 1.2-1.7), and multiple congenital abnormalities (OR 1.4, 95% CI 1.0-1.9) between the fourth and ninth months of gestation. The latter results were not reported separately by CCB drug.

A fair-quality, post-marketing surveillance study of lisinopril in the UK reported adverse events with nifedipine (N=1759) as a comparator drug.<sup>157</sup> The study included patients with hypertension and/or ischemic heart disease who were prescribed medication for the first time and followed for 1 year. The following adverse events led to withdrawals in the nifedipine group: hypotension (0.23%), dyspepsia or other digestive symptoms (0.38%), genitourinary conditions (0.23%), joint effusions and other limb symptoms (1.08%), malaise and fatigue (0.62%), headaches (4.85%), edema (1.77%), pallor and flushings (3.16%), and palpitations (0.85%).

A fair-quality study in the UK compared CCBs with ACE-Inhibitors on event rates of depression (e.g. neurotic depression, manic depression, postnatal depression, depressed mood, suicide, and suicide attempts), as recorded by general practitioners during patients' first 6 months of treatment.<sup>154</sup> Prescription-event monitoring on the first 10,000 patients receiving newly marketed drugs allowed for the calculation of crude event rates for depression per 1000 patient-

months of treatment. Rate ratios adjusted for age, gender, season, and indication (4 categories: ischemic heart disease, hypertension, cardiac failure, and others) revealed no significant differences between diltiazem, nifedipine, and ACE-Inhibitors.

Another fair-quality, prescription-event monitoring study in the UK determined the incidence of flushing, headache, dizziness, and edema among patients treated with diltiazem (N=10112), nifedipine (N=10910), isradipine (N=3679), or amlodipine (N=12969).<sup>156</sup> The study found significant variation between drugs in the rates of the selected vasodilation-related events. The highest rates (per 100 patients per 6 months) occurred with isradipine: flushing 6.5, headache 7.5, dizziness 4.2, edema 4.7. The lowest rates occurred with diltiazem: 0.4, 1.5, 1.6, and 1.1 respectively. The rates for these events with amlodipine varied from 1.4 (flushing) to 6.3 (edema), while with nifedipine the rates for each event were similar in range (2.6 to 3.0). Statistical analyses of these data were not conducted.

A fair-quality study among hospitalized patients in Italy examined severe adverse events (SADRs) associated with nifedipine (N=2381), verapamil (n=862), diltiazem (n=455), nifedipine (n=374), and amlodipine (N=327).<sup>158</sup> The total rate of severe adverse drug reactions was highest with diltiazem (19.8 per 1000), followed by verapamil (16.2), amlodipine (15.2), nifedipine (11.0), and nifedipine (10.7). Severe hypotension occurred most frequently with amlodipine (15.2 per 1000) followed by nifedipine (9.3). Rates of bradycardia were highest with diltiazem (11.0), followed by verapamil (10.4). No statistical analyses of these rates were conducted. The rate of acute renal failure was 0.4 with nifedipine, and not reported for other drugs. Further analysis by age found that SADRs increased with age among nifedipine users. This relationship was not seen with verapamil use; however, the risk for adverse events was lower among users of extended release verapamil compared to immediate release.

## Summary of Observational Studies

Three studies among patients > 65 years reported mortality rates, comparing to no CCB use, beta-blocker use, and comparing rates among CCBs. Mortality was found to be nearly twice as high with bepidril relative to no CCB use in a very large study of post-MI patients, while this study found no increase in risk with amlodipine, diltiazem, “other dihydropyridines”, or verapamil.<sup>153</sup> Two small studies found opposing results.<sup>151, 151, 152</sup> Nifedipine was associated with a significantly higher risk of death, relative to beta-blocker use in one study.<sup>151</sup> When stratifying based on immediate release and extended release formulations, the increase in risk was associated only with the long-acting forms. This study also found that the risk of mortality was higher with doses  $\geq 40$  mg/day, and with duration of use  $\leq 6$  months. In the other study, significantly *fewer* deaths and cardiac rehospitalizations among patients who started a CCB post-MI were found with the extended release “dihydropyridines” than the short-acting formulations.<sup>151, 152</sup> This difference was not found with the non-dihydropyridine drugs studied.

Studies of total cancer incidence and cancer-related mortality varied in their findings. Two studies reported excess cancer risk with verapamil, one in older adults ( $\geq 71$  years) that also found a dose-response relationship, and in the other the increase in risk occurred after 2 years of use.<sup>145, 146</sup> However, 3 other studies, including one very large study, did not find a relationship.<sup>144, 148, 149</sup> Excess risk with nifedipine was also found in the study of older persons,<sup>146</sup> but not in 5 other studies.<sup>144, 145, 147, 149, 150</sup> No increase in risk was found with diltiazem in 6 studies. It is assumed that the drugs used during these studies were primarily

immediate release formulations, although the study dates did overlap the date of introduction of extended release products in some cases.

No increased risk of breast cancer occurred with nifedipine, diltiazem, or verapamil in one study,<sup>142</sup> or with CCBs as a group, in three other studies.<sup>146, 148, 149</sup> One study of breast cancer incidence reported increased risk with use of immediate-release non-dihydropyridines versus no antihypertensive medication use, while noting the absence of a trend of increasing risk with duration of use.<sup>143</sup> Both of these studies reported no increased risk with extended release formulations of dihydropyridines or non-dihydropyridines studied.

Five other studies assessed various adverse effects.<sup>154-158</sup> Two studies reported the rates of adverse events with various CCBs.<sup>156,158</sup> Rates of severe adverse events were highest with diltiazem, followed in order by verapamil, amlodipine, nifedipine and nicardipine. Severe hypotension was reported most often with amlodipine, and bradycardia with verapamil. Rates of flushing, headache and dizziness were higher with isradipine, compared to diltiazem, nicardipine and amlodipine, while peripheral edema was higher with amlodipine compared with diltiazem, isradipine, and nicardipine. Due to important differences in study design, populations, and reporting, no indirect comparisons of the risks with different CCBs can be made across these studies.

**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

Eleven 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), three enrolled patients with renal insufficiency (Marin, AASK, Petersen), one enrolled patients with type II diabetes and proteinuria (IDNT), two enrolled patients with CAD (INVEST, JMIC-B), one enrolled patients with various cardiovascular disease risk factors (VALUE), 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 trials of CCB vs ACE inhibitor or AIIIRA comparisons among diabetic, renal insufficiency, and African American subgroups. All-cause mortality RR's for the trial comparing nicardipine to a trichlormethiazide in elderly Japanese patients and the trial comparing verapamil SR to atenolol in patients with CAD showed no differences in rates from the other five CCB vs diuretic and/or beta-blocker trials.<sup>33</sup>

A subanalysis of patients with diabetes in the JMIC-B trial found no difference in total mortality in patients taking nifedipine retard or an ACE inhibitor (enalapril, imidapril, or lisinopril) for 3 years (RR 0.76; 95% CI: 0.35-1.63; p=0.48).<sup>40</sup>



## Cardiovascular mortality

Evidence of CV mortality rates for CCB vs ACE inhibitor comparisons was found only in the renal insufficiency (Marin), diabetic (ABCD and JMIC-B), and CAD subpopulations (see section 1A under Key Question 1 for detailed results). Trials of target population groups are not available; no meaningful indirect comparison to differentiate one CCB from another can be made. Cardiovascular mortality RR's for the trial comparing nifedipine to a trichlormethiazide (RR 1.54; 95% CI, 0.31-7.67) in elderly Japanese patients<sup>16</sup> and the trial comparing verapamil SR to atenolol (RR 1.00; 95% CI, 0.88-1.14)<sup>33</sup> showed no difference from rates of the other three CCB vs diuretic and/or beta-blocker comparisons. In the subanalysis of patients with diabetes in the JMIC-B trial, cardiac/sudden death rates were similar in patients taking nifedipine retard or an ACE inhibitor (RR 0.31; 95% CI 0.03-3.37; p=0.7332).<sup>40</sup>

## Myocardial infarction

The only studies of CCBs vs ACE-Inhibitor reporting rates of MI were in special populations, three in persons with diabetes and one in patients without diabetes, but with renal insufficiency, and the relative risks for MI were mixed. Both trials that compared a CCB with fosinopril reported lowered risk (nifedipine GITS vs. fosinopril, 0.58; and amlodipine vs. fosinopril, 0.77).<sup>15, 164</sup> In one study the patients were diabetic<sup>15</sup> and in the other, the patients had chronic renal failure.<sup>164</sup> By contrast, when nisoldipine was compared with enalapril in another population with diabetes, the RR for MI was increased (2.25).<sup>39</sup> In the JMIC-B trial, comparing nifedipine with ACE inhibitors, there was no difference in MI rates in the overall population with CAD,<sup>27</sup> or in the subgroup with both CAD and diabetes.<sup>40</sup> Differences in study design and conduct made a simple comparison impossible. Without the opportunity to compare these results to patients without diabetes or renal-failure, very little can be concluded from these studies regarding the relative effectiveness of CCBs in these subgroups. Cardiovascular mortality RR's for the trial comparing nifedipine to a trichlormethiazide (RR 1.03; 95% CI, 0.18-5.79) in elderly Japanese patients<sup>16</sup> and the trial comparing verapamil SR to atenolol (RR 0.99; 95% CI, 0.79-1.24) showed no difference from rates of the other four CCB vs diuretic and/or beta-blocker comparisons.<sup>33</sup>

Amlodipine was associated with a lower risk of MI than AIIRAs in two trials of hypertensive subgroups.<sup>29, 30</sup> In the VALUE trial<sup>26</sup> (patients at high cardiovascular risk), patients taking valsartan had a higher risk of MI compared with those taking amlodipine (Hazard Ratio 1.19; 95% CI 1.02-1.38; p=0.02); most other health outcomes were not significantly different between the groups, however (see Key Question 1). In the IDNT of patients with type II diabetes and overt nephropathy, patients taking amlodipine also had a reduced risk of MI compared with those taking irbesartan (Hazard Ratio 0.65, 95% CI 0.48 to 0.87, p=0.004)

## Stroke

The evidence of stroke rates in active-controlled trials is insufficient to differentiate between CCBs in any subgroup. Stroke rates (fatal and nonfatal) for CCB vs ACE inhibitor comparisons were only found in renal insufficiency,<sup>17, 164</sup> diabetic,<sup>21, 39, 40, 133, 134</sup> and CAD<sup>26</sup> subpopulations (see section 1A under Key Question 1 for detailed results). Stroke rates for amlodipine vs AIIRA comparisons were found in subpopulations of hypertensives with high

cardiovascular risk<sup>26</sup> and in those with type II diabetes and overt nephropathy.<sup>29, 30</sup> 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**

Evidence of ESRD rates in active-controlled trials is insufficient to differentiate between CCBs in any subgroups. ESRD rates were found in trials of CCB vs ACE-Inhibitor comparisons in groups of African Americans with renal insufficiency<sup>12, 28, 42, 116, 165</sup> and patients with diabetes<sup>25, 126</sup> and in a trial of amlodipine vs irbesartan in patients with Type II Diabetes and over nephropathy.<sup>29, 30</sup> Detailed results of these can be found in section 1A under Key Question 1.

### **Quality of life**

We found two randomized active-controlled trials that evaluated the benefit of CCBs in improving quality of life in racial subgroups.<sup>165, 166</sup> The AASK pilot trial<sup>165</sup> 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).<sup>167</sup> 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<sup>165, 166</sup> was designed to measure the effects of nicardipine and trichlormethiazide on quality of life in elderly Japanese patients with hypertension using an unspecified scale comprised of 28 items. In summary, a comparison between pretreatment and posttreatment quality of life scores within the nicardipine group showed significant deterioration in the cognitive function category and no change in the other eight categories. No other trial that used this same quality of life measure was found to be available for comparison. As a result, evidence from both the AASK and NICS-EH is insufficient to address whether CCBs differ in their affect on quality of life in African American or elderly Japanese patients with hypertension.

### **3B. Angina**

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

### **3C. Supraventricular arrhythmias**

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

### 3D. Systolic dysfunction

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

## SUMMARY

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

**Table 11. Summary of the comparative evidence on CCBs and the overall strength of the evidence by key question**

Key Question 1: Comparative Effectiveness	Grade of Evidence**	Conclusion
a. Hypertension	Overall grade: Poor	No head-to-head trials. Evidence for amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nisoldipine, and verapamil from 16 long-term, active-controlled trials was insufficient to clearly differentiate one CCB from another for effectiveness. No evidence was found for bepridil or felodipine.
b. Angina	Overall grade: Good for chronic stable angina  Poor for Prinzmetal's variant angina	Chronic stable angina: One placebo-controlled trial of nifedipine GITS found no difference between groups on all-cause mortality, myocardial infarction, refractory angina, or debilitating stroke. Overt heart failure was significantly reduced in the nifedipine group.  For symptoms, consistent evidence from 13 head-to-head trials of amlodipine, diltiazem, nisoldipine, nicardipine, and nifedipine does not show a difference between these drugs. Only indirect evidence for bepridil and verapamil. No evidence for felodipine and isradipine. Prinzmetal's variant angina: 2 placebo-controlled trials of verapamil only – no comparative evidence.
c. Supraventricular arrhythmias	Overall grade: Fair to good for AF	3 fair quality head-to-head trials of diltiazem and verapamil for chronic AF, found no difference in rate control. Active- and placebo-controlled studies confirm this finding. Evidence for other supraventricular arrhythmias was inadequate.
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 CCBs 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 15 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 CCBs was found.
e. Evidence from observational studies	Fair	9 studies do not provide convincing evidence of an increased risk of total cancer, cancer mortality or breast cancer with individual CCBs, although 2 found an increase in risk for any cancer, 1 found an increase in risk of kidney cancer, and 1 found an increase in risk of breast cancer (immediate release non-dihydropyridines only). Observational studies of all cause mortality provide a mixed picture, with some evidence that long-acting formulations of nifedipine result in lower risk when compared directly, but when compared to beta blockers the risk is higher with the long-acting form. Limited evidence suggests a higher risk of mortality with bepridil compared to no CCB, while no increased risk with amlodipine.
<b>Key Question 3: Subgroups</b>	<b>Quality of Evidence</b>	<b>Conclusion</b>
a. Hypertension	Overall grade: Poor	Evidence for amlodipine, nicardipine, nifedipine, and nisoldipine and verapamil SR from long-term, active-controlled trials was insufficient to clearly differentiate one CCB from another for effectiveness or adverse effects in subgroups of diabetics; patients with renal insufficiency; patients with CAD; and older Japanese patients.
b. Angina	Overall grade: Poor	We found no evidence regarding the effectiveness or safety of any of the included CCBs for treatment of angina in subgroups.
c. Supraventricular arrhythmias	Overall grade: Poor	We found no evidence regarding the effectiveness or safety of any of the included CCBs for treatment of supraventricular arrhythmia in subgroups.
d. Systolic dysfunction	Overall grade: Poor	We found no evidence about effectiveness or safety of any of the CCBs for treatment of systolic dysfunction in subgroups.
		No evidence for diltiazem XL or TZ, felodipine, or verapamil HS or VR was found for any question

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

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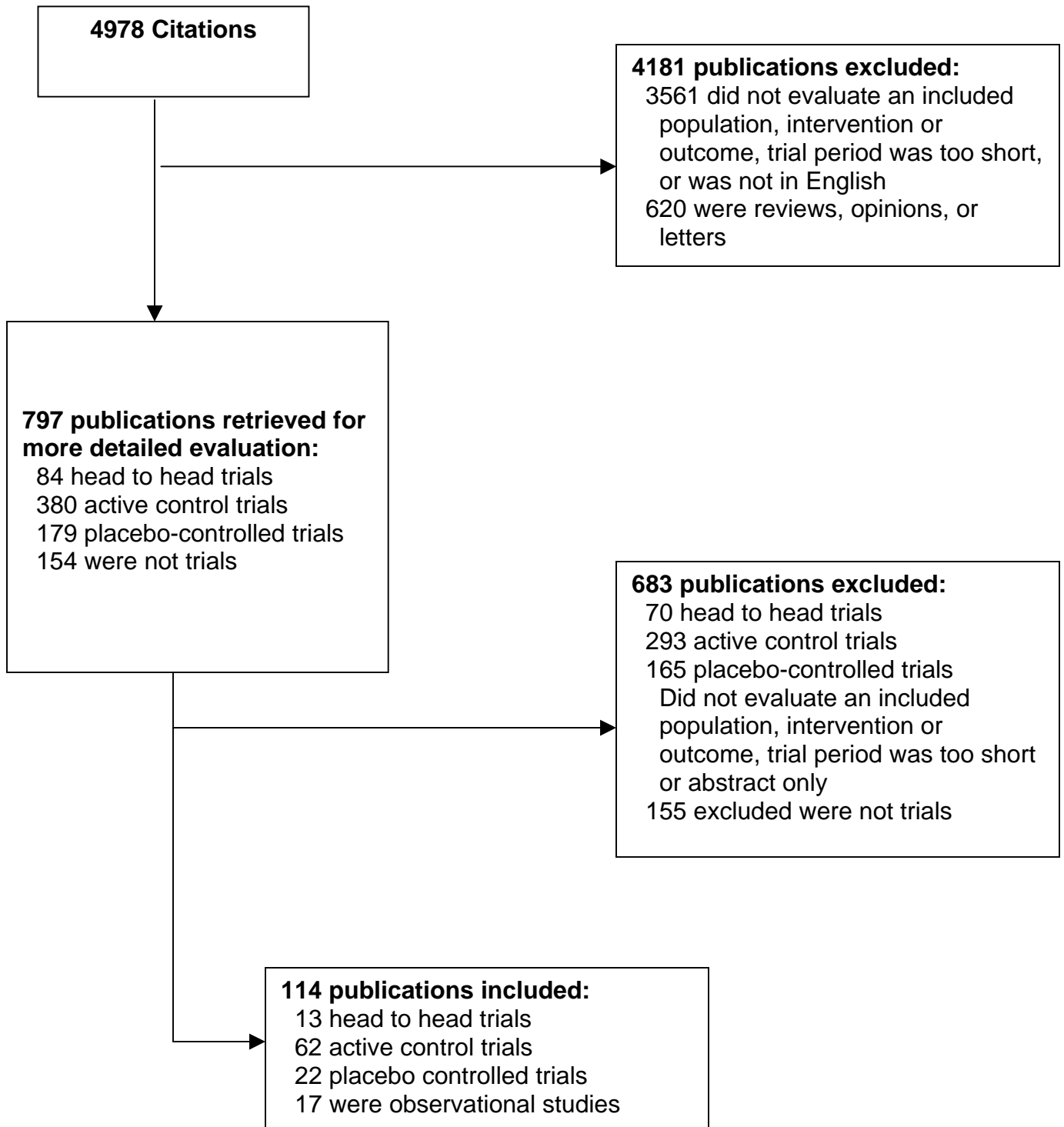
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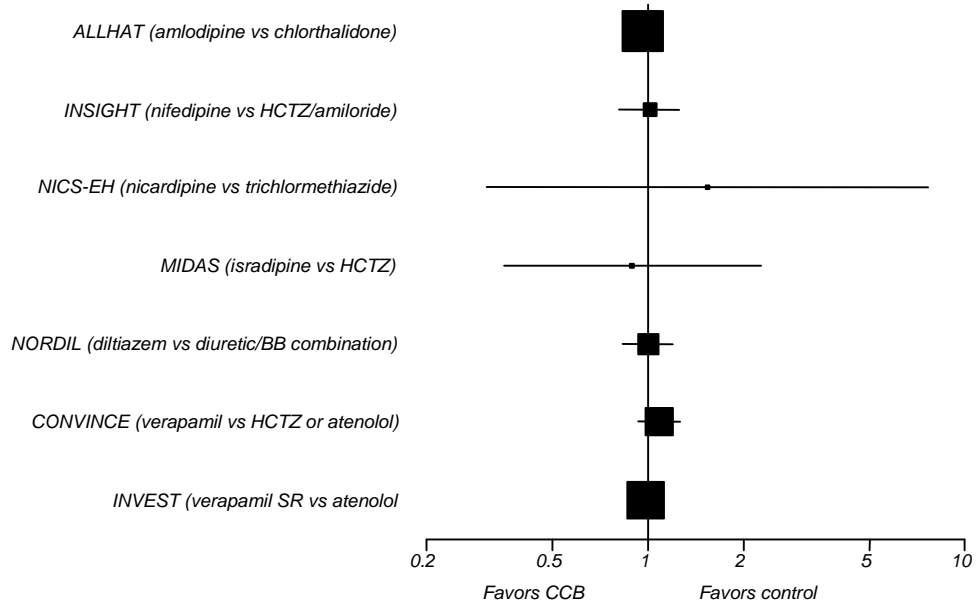
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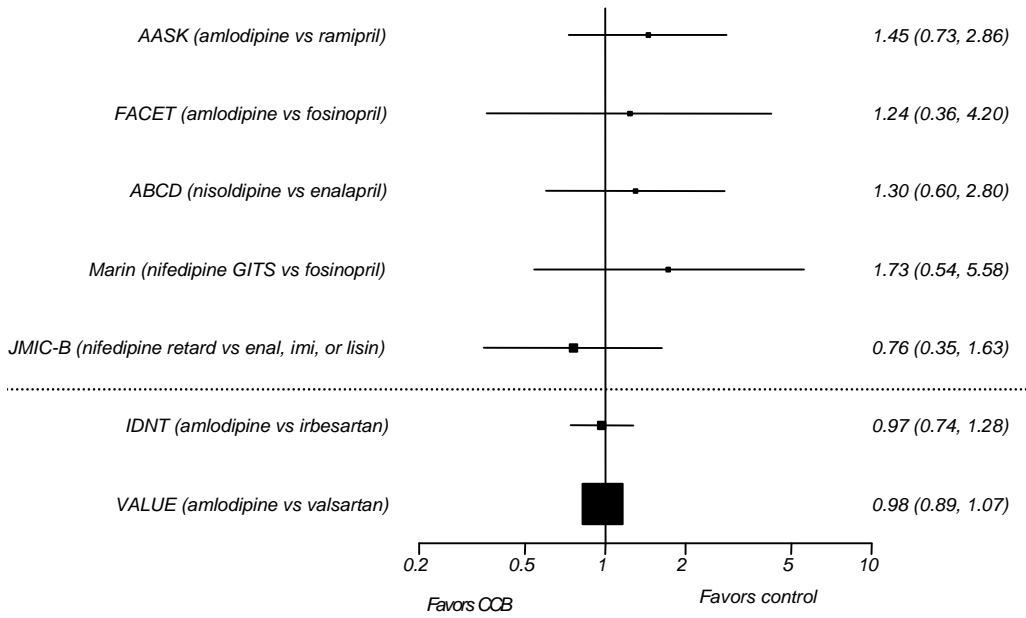
**Figure 1. Calcium Channel Blocker Literature Search Results**



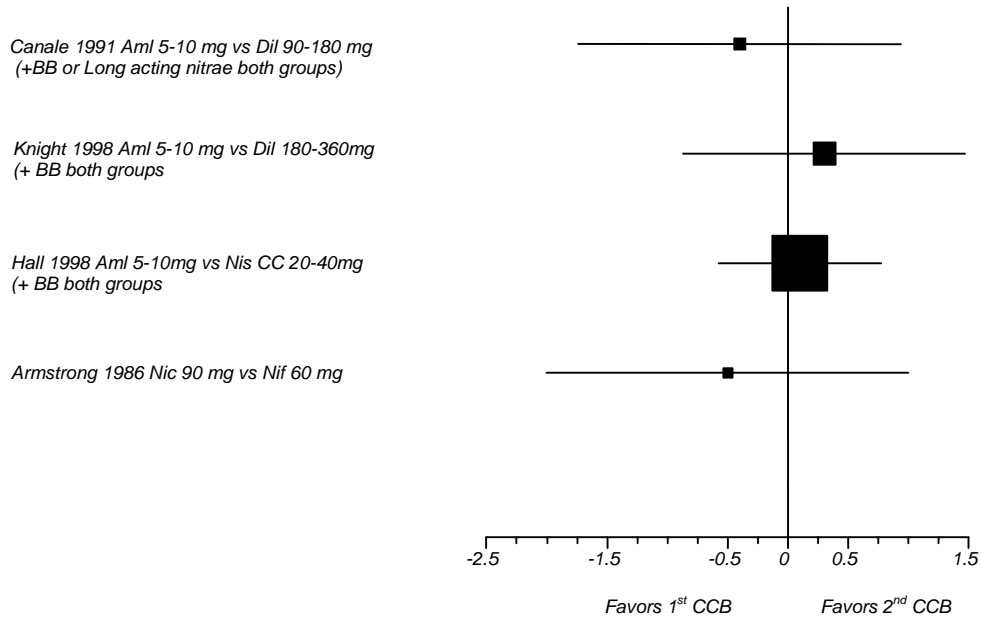
**Figure 2. All-cause Mortality in Hypertensives in Active Treatment Controlled Trials of CCB's vs Diuretic and/or Beta Blocker (95% CI)**



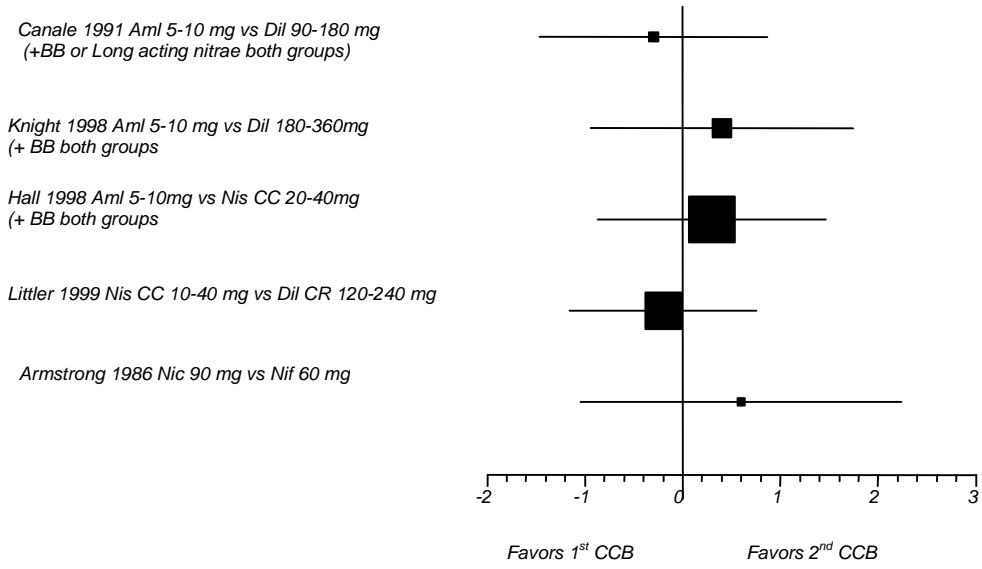
**Figure 3. All-cause Mortality in Hypertensives in Active Treatment Controlled Trials of CCB's vs. ACE Inhibitors**



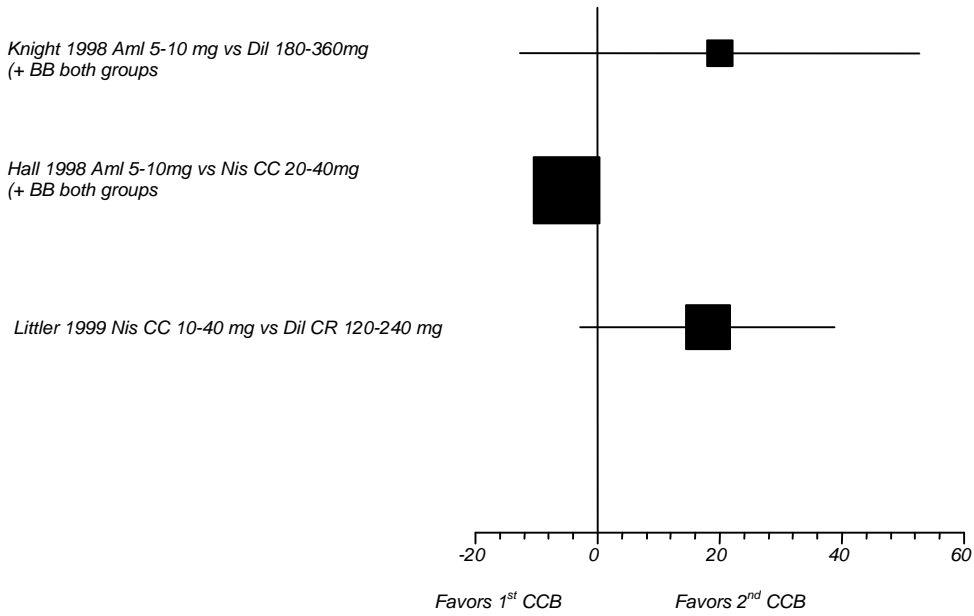
**Figure 4. Mean Change in Number of Angina Attacks Per Week in Head to Head Trials (weighted mean difference, 95% CI)**



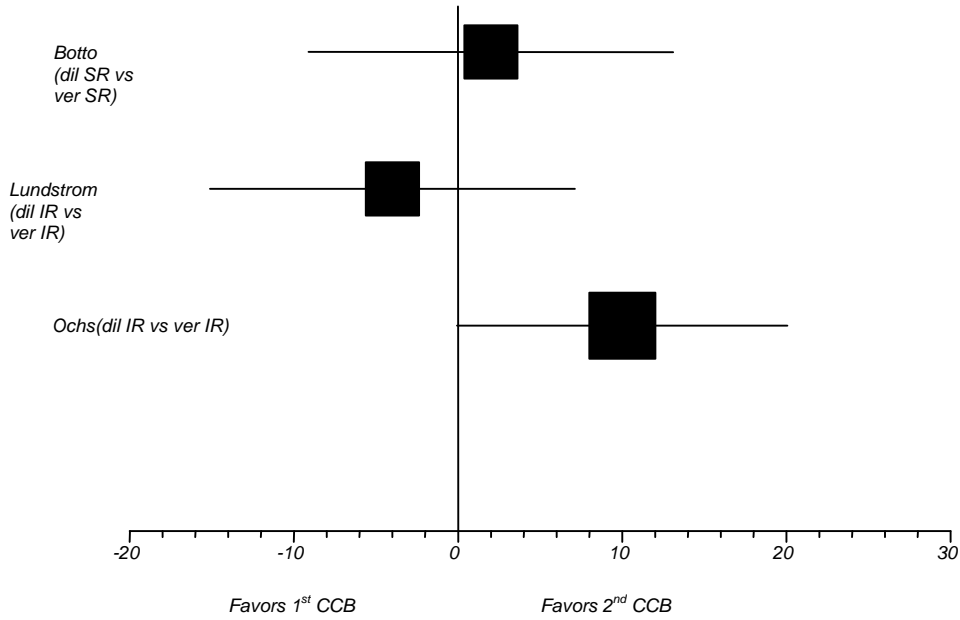
**Figure 5. Mean Change in Number of Nitroglycerin Doses Per Week in Head to Head Trials (weighted mean difference, 95% CI)**



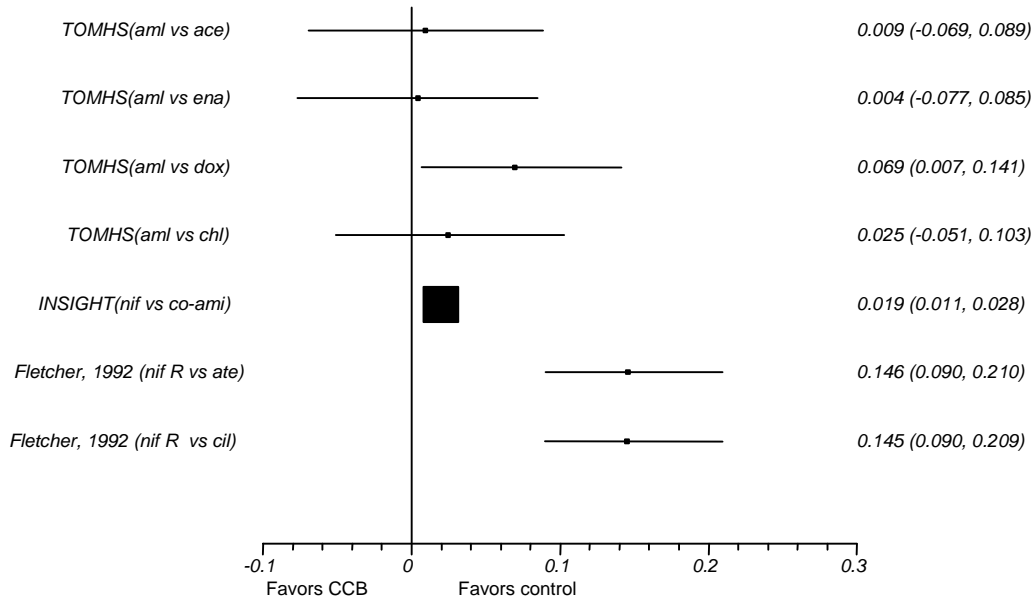
**Figure 6. Mean Change in Time to Onset of Angina with Exercise (sec) in Head to Head Trials (weighted mean difference, 95% CI)**



**Figure 7. Final Ventricular Rates in Supraventricular Arrhythmia Head to Head Trials (weighted mean difference, 95% CI)**

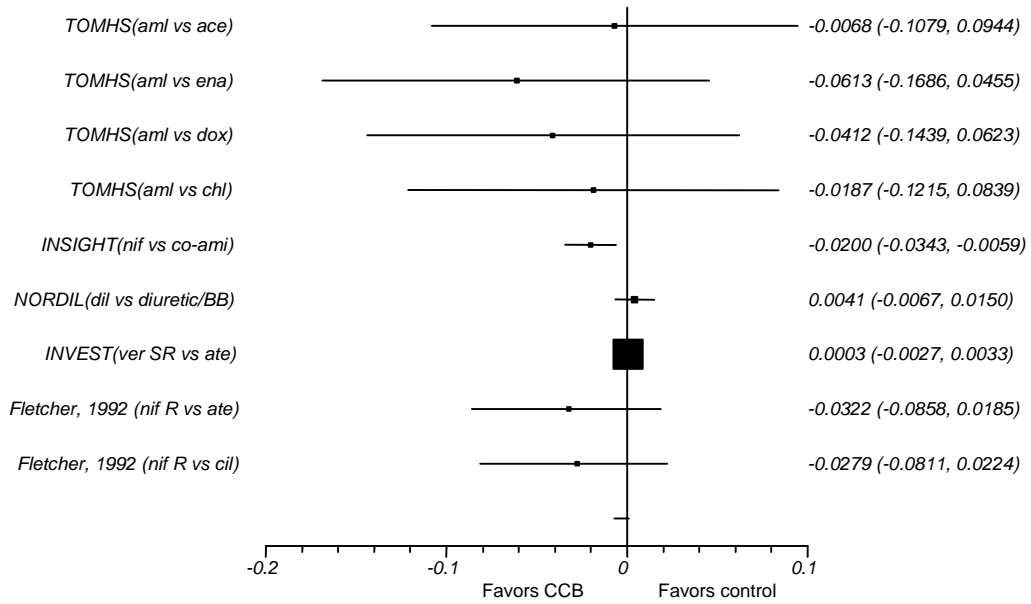


**Figure 8. Risk of Flushing in Active Controlled Trials of Hypertensives (risk difference, 95% CI)**

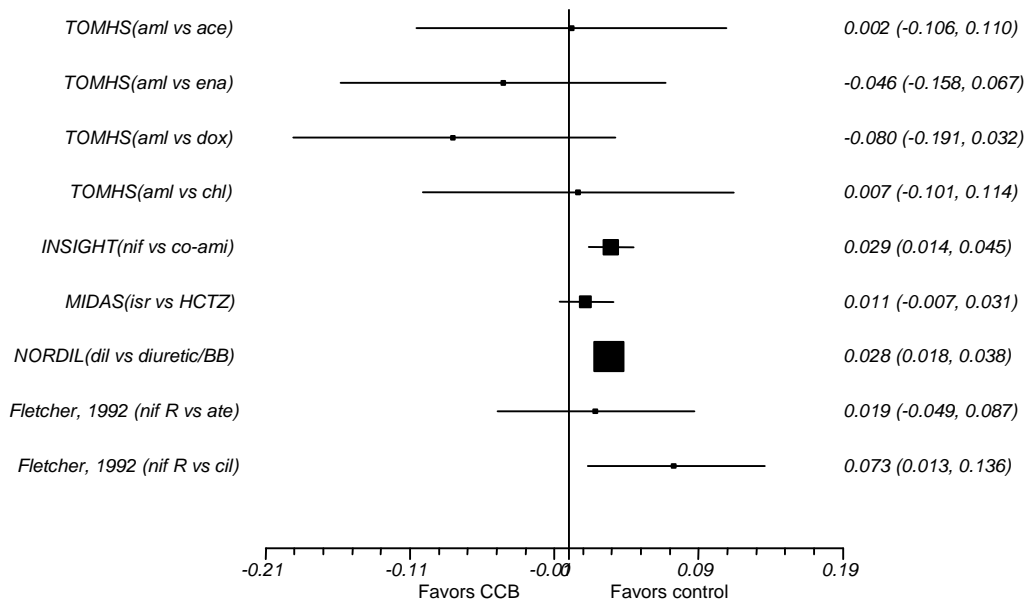




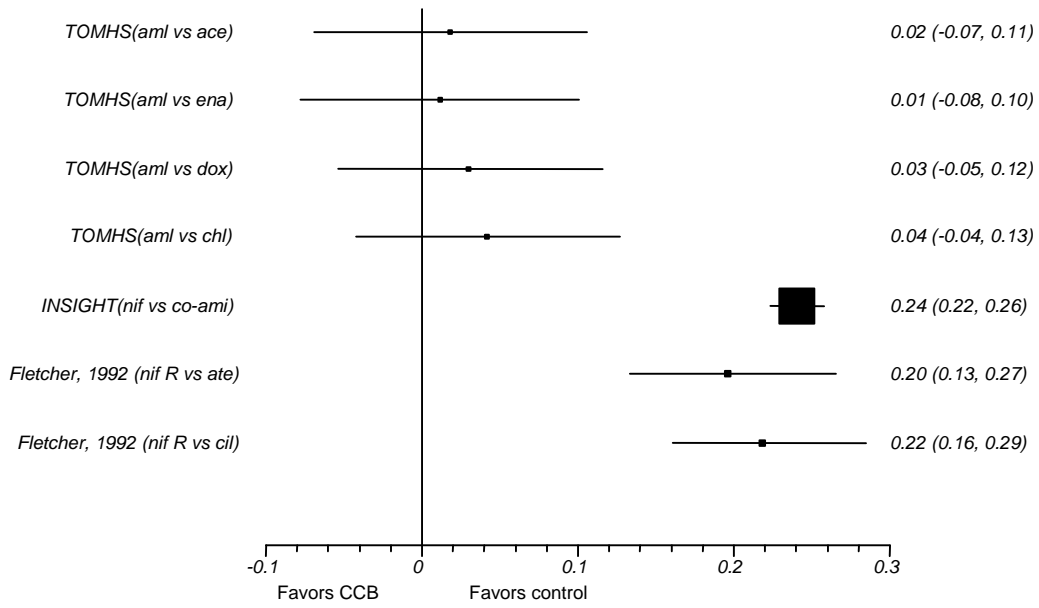
**Figure 9. Risk of Dizziness in Active Controlled Trials of Hypertensives (risk difference, 95% CI)**



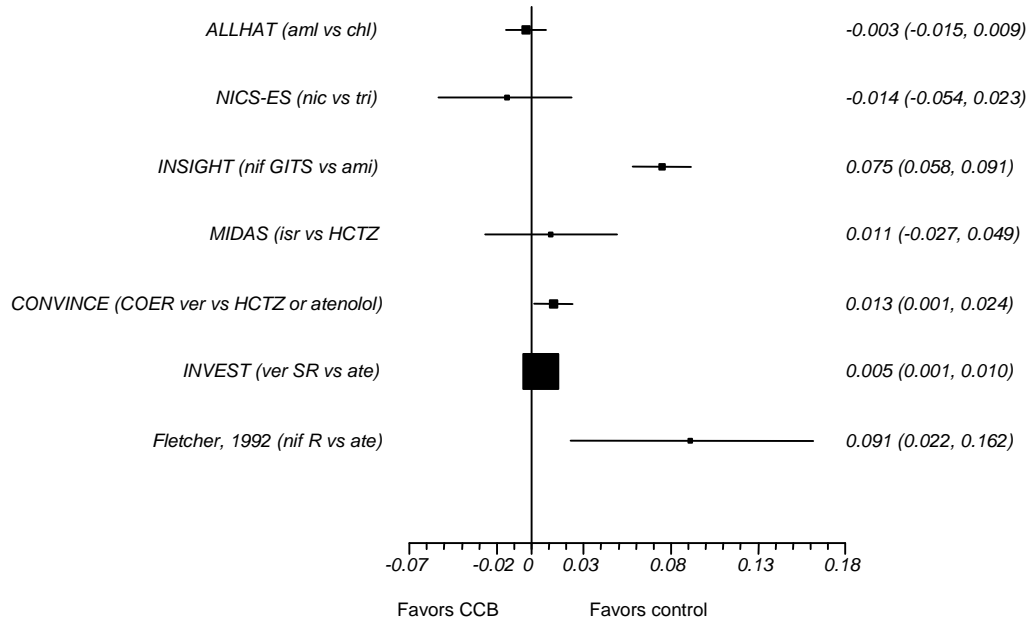
**Figure 10. Risk of Headache in Active Controlled Trials of Hypertensives (risk difference, 95% CI)**



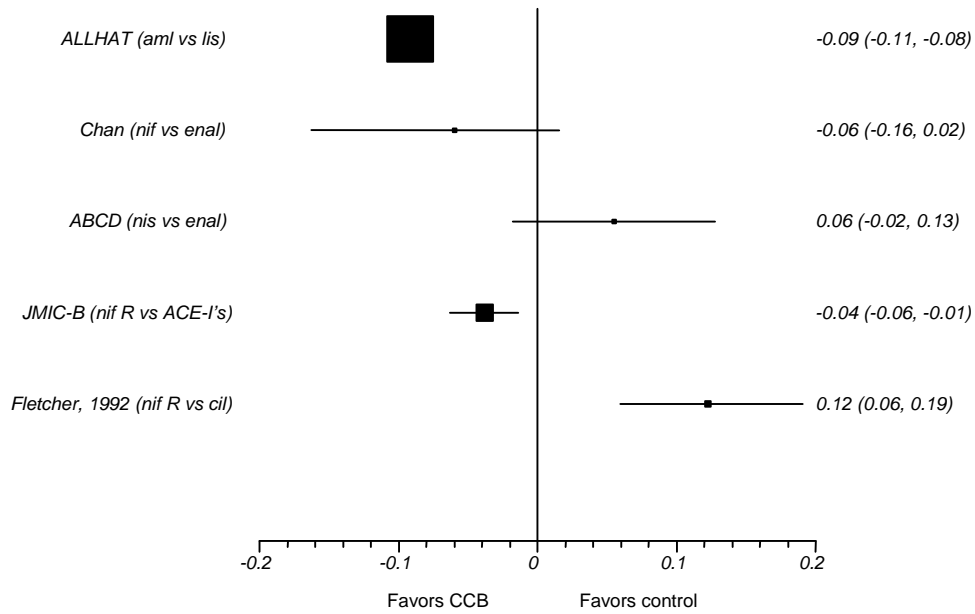
**Figure 11. Risk of Edema in Active Controlled Trials of Hypertensives (risk difference, 95% CI)**



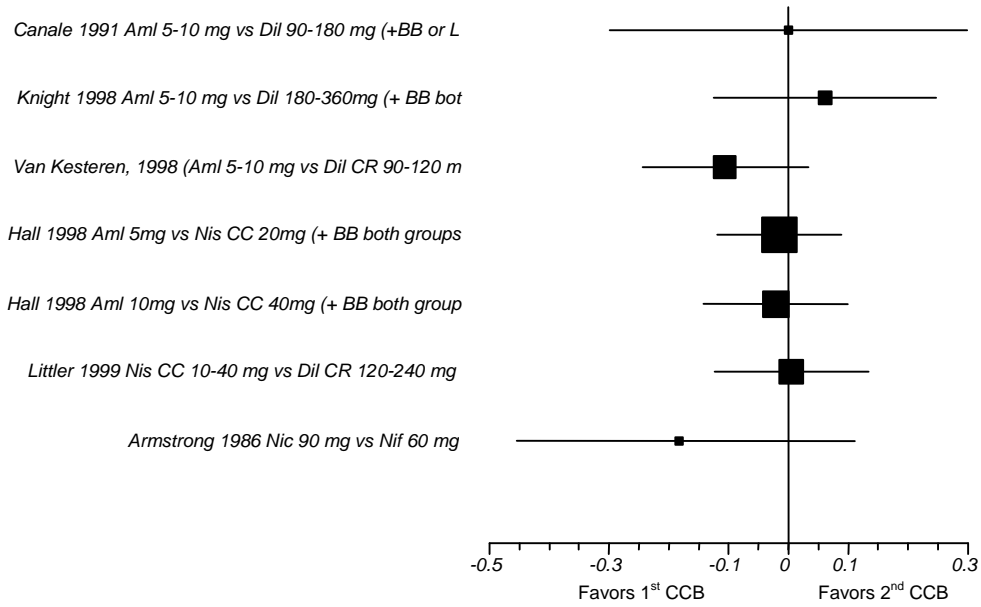
**Figure 12. Withdrawals Due to AEs for Hypertension Active Controlled Trials of CCBs vs Diuretics or Beta Blockers (risk difference, 95% CI)**



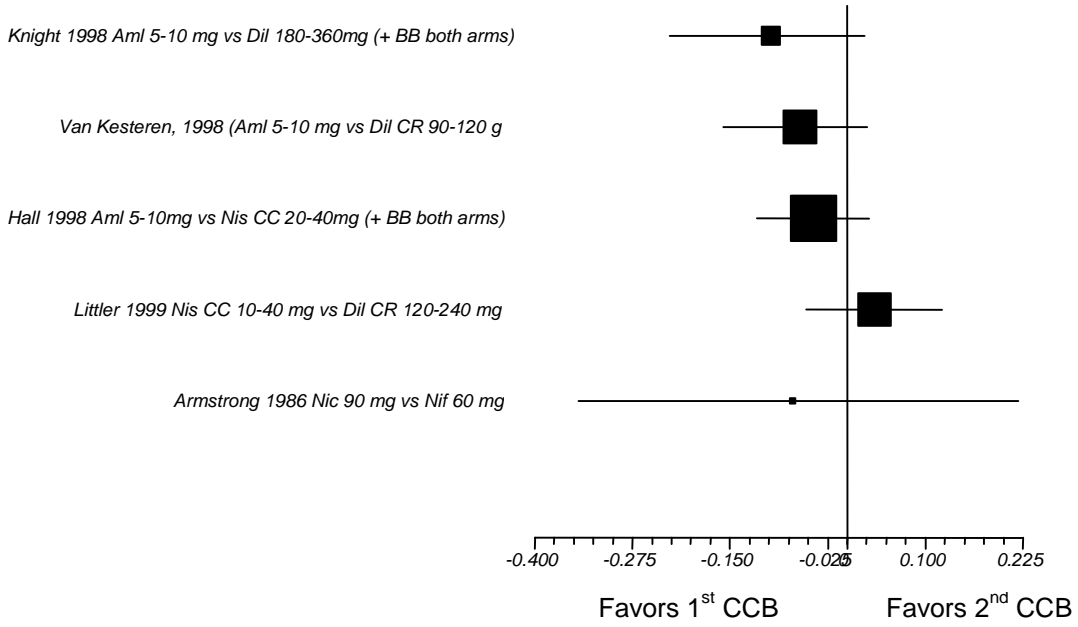
**Figure 13. Withdrawals Due to Adverse Events in Active Controlled Trials of Hypertensives Comparing CCBs to ACE Inhibitors (risk difference, 95% CI)**



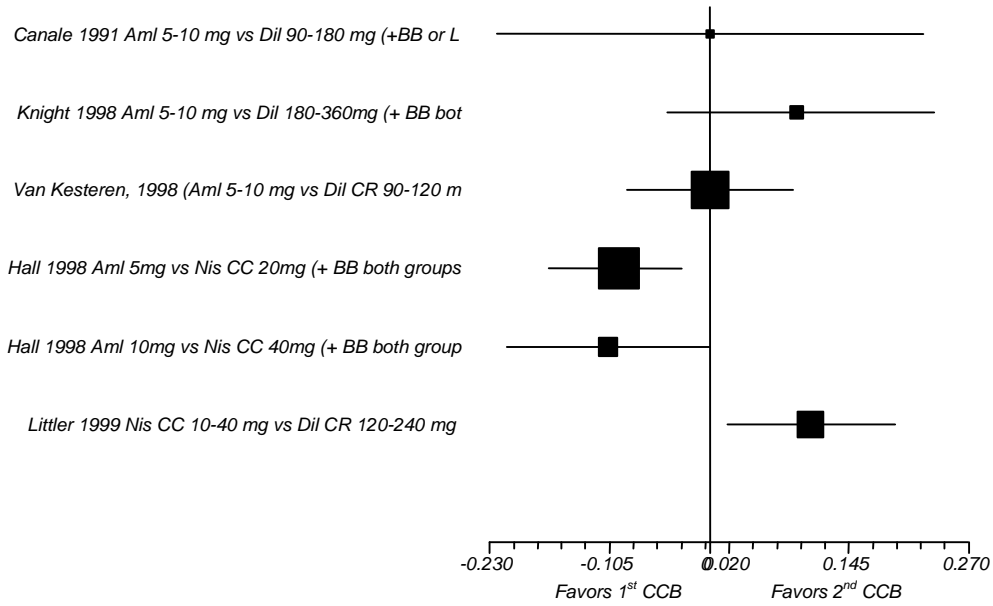
**Figure 14. Any Adverse Event in Head to Head Trials of Patients with Angina (risk difference, 95% CI)**



**Figure 15. Withdrawals Due to Adverse Events in Head to Head Trials of Patients with Angina (risk difference, 95% CI)**

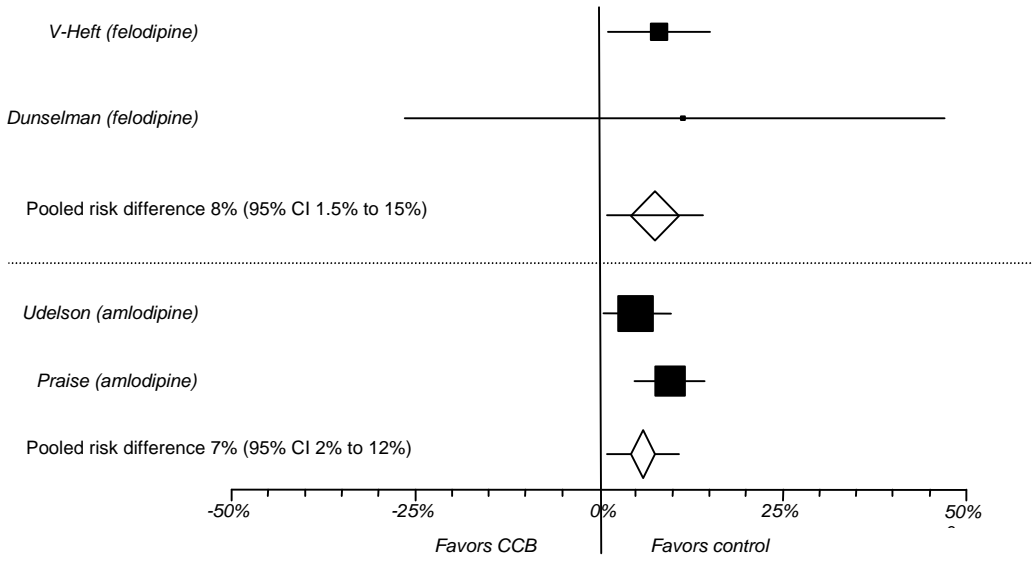


**Figure 16. Peripheral Edema in Angina Head to Head Trials (risk difference, 95% CI)**

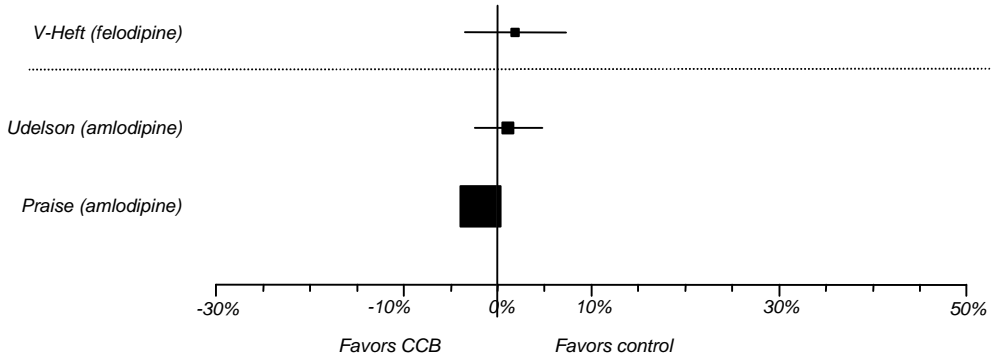




**Figure 17. Risk of Peripheral Edema (risk difference, 95% CI)**



**Figure 18. Risk of Withdrawal from Study (risk difference, 95% CI)**



## Appendix A. Calcium Channel Blockers Search Strategies Update #2

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2003>

Search Strategy:

- 1 (amlodipine or bepridil or diltiazem or felodipine or isradipine or nicardipine).ti.
- 2 (nifedipine or nisoldipine or verapamil).ti.
- 3 1 or 2
- 4 (angina\$ or supraventricular tachycardia\$ or supraventricular arrhythmia\$ or hypertensi\$ or high blood pressure or heart failure\$.ti.
- 5 3 and 4

Database: Ovid MEDLINE(R) <1996 to February Week 1 2004>

Search Strategy:

- 1 exp \*AMLODIPINE/
- 2 exp \*BEPRIDIL/
- 3 exp \*DILTIAZEM/
- 4 exp \*FELODIPINE/
- 5 exp \*ISRADIPINE/
- 6 exp \*NICARDIPINE/
- 7 exp \*NIFEDIPINE/
- 8 exp \*NISOLDIPINE/
- 9 exp \*VERAPAMIL/
- 10 exp AMLODIPINE/
- 11 exp BEPRIDIL/
- 12 exp DILTIAZEM/
- 13 exp FELODIPINE/
- 14 exp ISRADIPINE/
- 15 exp NICARDIPINE/
- 16 exp NIFEDIPINE/
- 17 exp NISOLDIPINE/
- 18 exp VERAPAMIL/
- 19 exp \*HYPERTENSION/
- 20 exp \*ANGINA PECTORIS/
- 21 exp \*Tachycardia, Supraventricular/
- 22 exp \*exp heart failure, congestive/ or exp cardiac output, low/
- 23 exp HYPERTENSION/
- 24 exp ANGINA PECTORIS/
- 25 exp Tachycardia, Supraventricular/ or supraventricular arrhythmia\$.mp.
- 26 exp heart failure, congestive/ or exp cardiac output, low/
- 27 amlodipine.mp. or exp AMLODIPINE/
- 28 bepridil.mp. or exp BEPRIDIL/

- 29 diltiazem.mp. or exp DILTIAZEM/
- 30 felodipine.mp. or exp FELODIPINE/
- 31 isradipine.mp. or exp ISRADIPINE/
- 32 nicardipine.mp. or exp NICARDIPINE/
- 33 nifedipine.mp. or exp NIFEDIPINE/
- 34 nisoldipine.mp. or exp NISOLDIPINE/
- 35 verapamil.mp. or exp VERAPAMIL/
- 36 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
- 37 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
- 38 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
- 39 19 or 20 or 21 or 22
- 40 23 or 24 or 25 or 26
- 41 38 and 40
- 42 limit 41 to (human and yr=2002-2004 and (clinical trial or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial))
- 43 limit 42 to english language
- 44 limit 42 to abstracts
- 45 43 or 44
- 46 from 45 keep 1-167

Database: EMBASE Drugs & Pharmacology <1991 to 1st Quarter 2004>  
 Search Strategy:

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- 1 exp \*AMLODIPINE/
  - 2 exp \*BEPRIDIL/
  - 3 exp \*DILTIAZEM/
  - 4 exp \*FELODIPINE/
  - 5 exp \*ISRADIPINE/
  - 6 exp \*NICARDIPINE/
  - 7 exp \*NIFEDIPINE/
  - 8 exp \*NISOLDIPINE/
  - 9 exp \*VERAPAMIL/
  - 10 exp AMLODIPINE/
  - 11 exp BEPRIDIL/
  - 12 exp DILTIAZEM/
  - 13 exp FELODIPINE/
  - 14 exp ISRADIPINE/
  - 15 exp NICARDIPINE/
  - 16 exp NIFEDIPINE/
  - 17 exp NISOLDIPINE/
  - 18 exp VERAPAMIL/
  - 19 exp \*HYPERTENSION/
  - 20 exp \*ANGINA PECTORIS/
  - 21 exp \*Tachycardia, Supraventricular/
  - 22 exp \*heart failure/

- 23 exp HYPERTENSION/
- 24 exp ANGINA PECTORIS/
- 25 exp Tachycardia, Supraventricular/ or supraventricular arrhythmia\$.mp.
- 26 exp heart failure/
- 27 amlodipine.mp. or exp AMLODIPINE/
- 28 bepridil.mp. or exp BEPRIDIL/
- 29 diltiazem.mp. or exp DILTIAZEM/
- 30 felodipine.mp. or exp FELODIPINE/
- 31 isradipine.mp. or exp ISRADIPINE/
- 32 nicardipine.mp. or exp NICARDIPINE/
- 33 nifedipine.mp. or exp NIFEDIPINE/
- 34 nisoldipine.mp. or exp NISOLDIPINE/
- 35 verapamil.mp. or exp VERAPAMIL/
- 36 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
- 37 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
- 38 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
- 39 19 or 20 or 21 or 22
- 40 23 or 24 or 25 or 26
- 41 38 and 40
- 42 exp controlled study/
- 43 41 and 42
- 44 limit 43 to (human and yr=2002-2004)
- 45 limit 44 to english language
- 46 limit 44 to abstracts
- 47 45 or 46
- 48 from 47 keep 1-343

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## Appendix B. Quality Assessment Methods for Drug Class Reviews for the Drug Effectiveness Review Project

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

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

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

### For Controlled Trials

#### Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?

Adequate approaches to sequence generation:

Computer-generated random numbers

Random numbers tables

Inferior approaches to sequence generation:

Use of alternation, case record numbers, birth dates or week days

Not reported

2. Was the treatment allocation concealed?

Adequate approaches to concealment of randomization:

Centralized or pharmacy-controlled randomization

Serially-numbered identical containers

On-site computer based system with a randomization sequence that is not readable until allocation

Other approaches sequence to clinicians and patients

Inferior approaches to concealment of randomization:

Use of alternation, case record numbers, birth dates or week days  
Open random numbers lists  
Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient kept unaware of the treatment received?
8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?
9. Did the study maintain comparable groups?
10. Did the article report attrition, crossovers, adherence, and contamination?
11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

#### Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?
2. How many patients were recruited?
3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)
4. What was the funding source and role of funder in the study?
5. Did the control group receive the standard of care?
6. What was the length of followup? (Give numbers at each stage of attrition.)

## **For Studies Reporting Complications/Adverse Effects**

### Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?
2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)
3. Were the events investigated specified and defined?
4. Was there a clear description of the techniques used to identify the events?
5. Was there non-biased and accurate ascertainment of events (independent ascertainment; validation of ascertainment technique)?
6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?
7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

### Assessment of External Validity

1. Was the description of the population adequate?
2. How similar is the population to the population to whom the intervention would be applied?
3. How many patients were recruited?
4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)
5. What was the funding source and role of funder in the study?

## **Systematic Reviews**

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

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



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

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

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

3. Is the validity of included studies adequately assessed?

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

4. Is sufficient detail of the individual studies presented?

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

5. Are the primary studies summarized appropriately?

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

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

## Appendix C. Reports of Trials Excluded

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[In Process Citation]. Ter Arkh  
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## Appendix D. Articles Available as Abstracts Only

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## Appendix E. Quality of Life Studies Under Six Months Duration

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

### Head to Head

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

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### **Active Control**

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**Appendix F. List of Abbreviations for Tables**

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

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