Oregon Health Resources Commission

Calcium Channel Blocker

Subcommittee Report

Update #2, May 2005

This report is an update of the initial
CCB Subcommittee Report of October 2003.
All revisions are highlighted.

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Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-Managed Prescription Drug Plan (PMPDP). Statute specifically directs the Health Resources Commission (HRC) to advise the Department of Human Services on this Plan.

In the winter of 2003 the HRC appointed a subcommittee to perform an evidence-based review of calcium channel blockers. Members of the subcommittee consisted of physicians, a pharmacist and a family nurse practitioner. The subcommittee had four meetings from June 4, 2003 to September 17, 2003. All meetings were held in public with appropriate notice provided.

The subcommittee members initially worked with Oregon Health and Science University's Evidence-based Practice Center (OHSU-EPC) to formulate and finalize three key questions for drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity, age, demographics, other medications and co-morbidities.

Using standardized methods, the OHSU-EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The OHSU-EPC's draft report titled "Drug Class Review on Calcium Channel Blockers" was completed the week of May 5, 2003, circulated to subcommittee members for review and posted on the web. An Executive Summary on Calcium Channel Blockers was completed by Marian S. McDonagh, PharmD, OHSU-EPC, on the week of June 6, 2003. The OHSU-EPC's Addendum Evidence-based Report on Calcium Channel Blockers was completed the week of August 25, 2003. All available sources of information: the OHSU-EPC reports, documents and testimony presented by pharmaceutical companies were considered by the Calcium Channel Blocker (CCB) subcommittee in drawing the conclusions which comprise the body of this report. Time was allotted for public comment, questions and testimony at each meeting.

In April 2004 the HRC appointed a Standing Update Committee to perform an evidence-based review of the November 2003 *Calcium Channel Blocker Subcommittee Report* for new information or changes in FDA package inserts. Members of the Standing Update Committee consisted of one HRC member, one OSU pharmacist, one HRC Director, one EPC member, two previous MDs from subcommittees and one pharmacist from subcommittees. Kathy Crispell, MD, a Cardiologist, was also consulted.

This report does not recite or characterize all the evidence that was considered by the OHSU-EPC, the Standing Update Committee or the Health Resources Commission. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in

providing recommendations to the Department of Human Services. This report is the second update of the initial October 2003 Subcommittee Report. All revisions are highlighted.

At least once per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the Plan Drug List will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and FDA changes in indications and safety recommendations will be evaluated. The Calcium Channel Blocker report will be updated if indicated. Substantive changes will trigger the reconvening of the CCB Subcommittee Committee to revise the report that may effect the conclusions. The Standing Update Committee met twice on May 19, 2005 and June 7, 2005. The Second Update of the CCB report was accepted by the HRC on July 22. 2005.

The full OHSU-EPC report, *Drug Class Review on Calcium Channel Blockers Updated Final Report #2,* is available on the Office for Oregon Health Policy & Research (OHPR), Practitioner-Managed Prescription Drug Plan web site; www.oregonrx.org. Additional information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the OHPR website: www.ohpr.state.or.us/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml
You may also request copies of the report, and minutes or tapes of the subcommittee meetings from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from OHSU Center for Evidence-based Policy by contacting:

John Santa, MD
Assistant Director for Health Projects
OHSU-Center for Evidence-based Policy
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There will be a charge for copying and handling documents from OHPR and the Center.

Critical Policy:

- ***Senate Bill 819:***
  - "The Department of Human Services shall adopt a Practitioner-Managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price."
- ***Health Resources Commission:***

  "Clinical outcomes are the most important indicators of comparative effectiveness."
  - "If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed."

Definition of Calcium Channel Blockers

This review covers the eight calcium channel blockers used for cardiac conditions currently marketed in the United States:

Generic	Form	Brand
AMLODIPINE	TAB	NORVASC
BEPRIDIL*		*VASCOR*
DILTIAZEM	TAB	CARDIZEM
DILTIAZEM	12H SR CAP	CARDIZEM SR
DILTIAZEM	24H SR CAP	CARDIZEM CD, DILACOR XR, TIAZAC, OTHERS
DILTIAZEM	24H SR TAB	CARDIZEM LA
FELODIPINE	24H SR TAB	PLENDIL
ISRADIPINE	CAP	DYNACIRC
ISRADIPINE	24H GITS	DYNACIRC CR
NICARDIPINE	CAP	CARDENE
NICARDIPINE	12H SR CAP	CARDENE SR
NIFEDIPINE	CAP	PROCARDIA
NIFEDIPINE	24H GITS	PROCARDIA XL, AND OTHERS
NIFEDIPINE	24H SR TAB	ADALAT CC, AND OTHERS
NISOLDIPINE	24H SR TAB	SULAR
VERAPAMIL	TAB	CALAN, ISOPTIN
VERAPAMIL	24H SR CAP	VERELAN
VERAPAMIL	24H COER	COVERA-HS, VERELAN PM
VERAPAMIL	12H SR TAB	CALAN SR, ISOPTIN S.R.

SR = Slow Release
GITS = GastoIntestinal Therapeutic System
COER = Controlled-Onset, Extended-Release
*** = Voluntarily withdrawn from US market by manufacturer**

Calcium channel blocking agents (CCBs) inhibit the movement of calcium 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 primary actions of the CCBs include dilation of coronary and peripheral arterial vasculature, a negative inotropic action, reduction of heart rate, and slowing of AV conduction.

CCBs are classified into two major groups; the dihydropyridines and the non-dihydropyridines. The dihydropyridines (amlodipine, *bepridil**, felodipine, isradipine, nicardipine, nifedipine, and nisoldipine) have greater selectivity for the vascular smooth muscle than for myocardium and have little or no action at the SA and AV nodes. Negative inotropic activity rarely occurs with dihydropyridines at therapeutic doses in normal myocardium. Isradipine, nicardipine, nifedipine have both immediate and extended release formulations. Amlodipine and *bepridil** are a long acting drug (once daily) available as immediate release only.

Non-dihydropyridines (diltiazem, verapamil) have less selective vasodilator activity than dihydropyridines and have a direct effect on myocardium causing depression of SA and AV nodal conduction. Both diltiazem and verapamil have immediate and extended release formulations.

There are eight calcium channel blockers currently marketed in the United States having FDA indications for treating hypertension, angina, and supraventricular arrhythmias, depending on the specific drug. CCBs are accepted as first-line therapy alone or in combination with a thiazide diuretic for those with hypertension and at high risk of coronary artery disease and diabetes. [1] The use of CCBs in treating stable angina and the use of non-dihydropyridines in treating supraventricular arrhythmias are commonly accepted practices.

Congestive heart failure (CHF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricles to fill with or eject blood. The term systolic dysfunction refers to abnormal heart muscle contractility (decreased pumping function), and can lead to the syndrome of heart failure. Another form of heart muscle dysfunction with preserved contractility is called diastolic dysfunction; this can also lead to the syndrome of heart failure. Coronary artery disease is the underlying cause of CHF in approximately two thirds of patients with left ventricular systolic dysfunction. There are other potential identifiable causes (e.g. hypertension, valvular disease, myocardial toxins, myocarditis, or hereditary) or there may be no discernible cause (e.g. idiopathic dilated cardiomyopathy).

The use of CCBs in treating ventricular systolic dysfunction is an American College of Cardiology (ACC) and American Heart Association (AHA) Class III recommendation (there is evidence and/or general agreement that the treatment is not useful/effective and in some cases

* Voluntarily withdrawn from US market by manufacturer

[1] Chobanian AV, Bakris GI, Black HR, Cushman WC, Green LA, Izzo JLJ, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report [comment]. JAMA 2003;289(19):2560-72.

can be harmful).[2] Therefore, current practice guidelines do not support the use of CCBs as primary agents in the setting of ventricular systolic dysfunction. However, the use of CCBs may be necessary in persons with ventricular systolic dysfunction and co-morbid hypertension, angina, or supraventricular arrhythmias. Thus, it is for this reason that the subcommittee included a review of the evidence for CCB use in those with ventricular systolic dysfunction. The conclusions that are relevant to congestive heart failure (as defined by systolic dysfunction with left ventricular ejection fractions < 45%) are made within this background.

Because of differences in mechanism of action and side effects, **t**he subcommittee decided to examine the efficacy and safety between the two major groupings, dihydropyridines and non-dihydropyridines for hypertension and angina. A comparison for supraventricular arrhythmia was not made since only non-dihydropyridines have this indication.

Key Questions

1. For adult patients with hypertension (blood pressure ≥ 140/90 mm Hg), angina, supraventricular arrhythmias, or congestive heart failure (as defined by systolic dysfunction with left ventricular ejection fraction [LVEF <45%]) do calcium channel blockers differ in efficacy?

2. For adult patients with hypertension (blood pressure ≥ 140/90 mm Hg), angina, supraventricular arrhythmias or congestive heart failure (as defined by systolic dysfunction with LVEF <45%), do calcium channel blockers differ in safety or adverse effects?

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

Inclusion criteria

1. Populations

   Adult patients with hypertension (blood pressure ≥ 140/90 mm Hg), angina, supraventricular arrhythmias, or congestive heart failure (as defined by systolic dysfunction with LVEF <45%).

2. Interventions

   Interventions include a calcium channel blocker compared with another calcium channel blocker, another drug (such as beta blocker), or placebo. (Calcium channel blockers: amlodipine, *bepridil**, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, verapamil; extended release formulations to be considered separate to immediate release formulations).

* Voluntarily withdrawn from US market by manufacturer

[2] Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman, Francis GS, et al. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary A report of the American college of Cardiology/American Heart Association Task force on Practice Guidelines. Circulation 2001;104(24):2996-3007.

3. Efficacy Measures

Hypertension
All cause mortality
Cardiovascular (CV) disease mortality
CV events (stroke, MI< development of CHF)
Development of renal failure (end stage renal disease/dialysis/transplant, clinically significant permanent increase in serum creatinine or decrease in creatinine clearance)

Quality of life

Angina
All cause mortality
Cardiovascular
(CV) disease mortality
CV events (stroke, MI< development of CHF)
Symptoms
Quality of life

Supraventricular Arrhythmias
All cause mortality
Cardiovascular (CV) disease mortality
Stroke
Symptoms (rate or rhythm control)
Quality of life

Adverse Effects
Withdrawals
Withdrawals due to adverse effects
Specific adverse effects or withdrawals due to specific adverse events (for example, symptomatic hypotension).

4. Effectiveness

For effectiveness, study is a randomized controlled trial. Crossover trials will be included. Studies conducted entirely in the inpatient setting are excluded.

5. Adverse Effects

For adverse effects, study is a controlled clinical trial of a least 6 months duration. Drug-drug interaction studies of shorter duration will be included.

Exclusion criteria

1. No original data: Study does not contain original data (e.g., review, editorial, letter with no original data). Good quality systematic reviews will be used as appropriate to inform the current review.
2. Studies of combinations of interventions as initial therapy where the effect of the calcium channel blocker could not be delineated.

3. Angina with less than 2 months of follow-up.

Quality of the Evidence

The subcommittee utilized the EPCs ratings of good, fair or poor to weigh the body of evidence for each key question. They took into account the number of studies, the total number of patients in each study, the length of the study periods and the end-points of the studies. Statistical significance was an important consideration.

The subcommittee's task was to identify CCBs that would offer the greatest likelihood of success for the treatment of hypertension, angina and supraventricular arrhythmias. Additionally, it was our task to identify the safest CCBs for use in persons with ventricular systolic dysfunction with comorbid hypertension, angina and/or supraventricular arrhythmias.

Update #2 Findings

- Since October 2004 there have been no FDA changes.
- *Bepridil* (Vascor)* was voluntarily withdrawn from the market in 2004.
- The EPC invited Pharmaceutical manufacturers to submit dossiers, including citations, using a protocol issued by the Center for Evidence-based Policy. No new studies were identified through the dossier submission process.
- To evaluate adverse event rates, the EPC included observational studies as well as clinical trials.
- Using the same search strategy that was used in the original CCB report, the EPC found an additional 1,533 citations, but only 23 studies fully met inclusion criteria.
- Five active-control trials (in 7 publications) in patients with hypertension are included.
- One placebo-controlled trial in a patient with angina that reported long term health outcomes, cardiovascular events, and mortality is described.
- Five observational studies of other adverse events.

* Voluntarily withdrawn from US market by manufacturer

Amended Summary of Results

Key Question 1. For adult patients with hypertension (blood pressure ≥ 140/90 mm Hg), angina, supraventricular arrhythmias, or congestive heart failure (as defined by systolic dysfunction with LVEF <45%) do calcium channel blockers differ in efficacy?

1A. …with hypertension (blood pressure ≥ 140/90 mm Hg do calcium channel blockers differ in efficacy?

No head-to-head trials of patients with hypertension that reported health outcomes were found.

Sixteen active-controlled trials evaluated the efficacy of treating hypertensive patients with CCBs in order to reduce mortality, non-fatal cardiovascular (CV) events, and end stage renal disease (ESRD). These trials compared CCBs to angiotensin converting enzyme inhibitors (ACEI), diuretics, and beta-blockers. With the exception of the **ALLHAT**[3]**, FACET**[4]**,** and **VALUE**[5] trials, which were rated good quality, all other included trials were of fair quality. The trials differed greatly in the additional anti-hypertensive medications the patients could be given if the randomized study drug inadequately controlled blood pressure. Therefore, it was inappropriate to perform a meta-analysis as the effect of the study medication from the additional medications was impossible to quantify. No trials were found that compared the effect of *bepridil** or felodipine on health outcomes. A subgroup analysis of one trial focused on patients with both coronary artery disease and diabetes[6].

There were 14 active-controlled trials 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 no significant difference between the performance of the CCBs and their comparator drugs in reducing all cause mortality. There were 9 active-controlled studies of cardiovascular mortality; 11 active-controlled trials of myocardial infarction (MI); 11 active-controlled trials of stroke; 8 active-controlled trials of CHF, and 8 active-controlled trials of ESRD that failed to show significant difference between CCBs. The overall grade for the body of evidence is poor due to the heterogeneity of the studies.

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* Voluntarily withdrawn from US market by manufacturer

[3] Furberg CD, Wright Jr JT, Davis BR, et al. Major outcomes in high-risk hypertensive patients randomized to ACEI or CCB vs diuretic: The antihypertensive and lipid-lowering treatment to prevent hear attack trial (ALLHAT). *JAMA* 2002;288(23):2981-2997

[4] Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinorpil Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patientw with hypertension and NIDDM. *Diabetes Care.* 1998;21(4):597-603

[5] Kuwajima I, Kuramoto K. Ogihara T, et al. Tolerability and safety of a calcium channel blocker in comparison with a diuretic in the treatment of elderly patients with hypertension: secondary analysis of the NICS-EH. *Hypertension Research-Clinical & Experimental* 2001;24(5):474-480.

[6] Yui Y, Sumiyoshi T, Kodama K, et al. Nifedipine retard was as effective as angiotensin converting enzyme inhibitors in preventing cardiac events in high-risk hypertensive patients with diabetes and coronary artery disease: the Japan Multicenter Investigation for Cardiovascular Diseases-B (**JMIC-B**) subgroup analysis. *Hypertension Research Clinical & Experimental* 2004;27(7):449-456.

1B …with angina do calcium channel blockers differ in efficacy?

Eleven poor to fair quality head-to-head trials compared amlodipine, diltiazem, nisoldipine, nicardipine, and nifedipine to one another for the treatment of chronic stable angina. Only indirect evidence from active controlled trials could be found for *bepridil** and verapamil. No evidence was available for felodipine and isradipine. In summary head-to-head trials show no difference in efficacy in the comparisons made (amlodipine vs. diltiazem or diltiazem CR, amlodipine vs. nisoldipine, nisoldipine vs. diltiazem CR, and nicardipine vs. nifedipine.) Indirect comparisons between these 13 studies, as well as active and placebo-controlled studies, do not provide evidence of differences in clinical outcomes with amlodipine, *bepridil**, diltiazem, nicardipine, nifedipine, nisoldipine, or verapamil. One placebo-controlled trial of nifedipine GITS found no difference between groups on all-cause mortality, MI, refractory angina, or debilitating stroke. Overt heart failure was significantly reduced in the nifedipine group (HR 0.71)[7]. No evidence was found for the use of felodipine, diltiazem XR and TZ, verapamil HS and VR, and isradipine in angina.

1C …for patients with supraventricular arrhythmias do calcium channel blockers differ in efficacy?

Three fair quality head-to-head trials of diltiazem and verapamil for chronic atrial fibrillation gave consistent results, but no difference in efficacy. Twenty-two active and placebo controlled studies confirmed no difference in effectiveness 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. Evidence for other supraventricular arrhythmias was inadequate.

1D….for patients with CHF (LVEF < 45%) do calcium channel blockers differ in efficacy?

The overall grade of evidence was fair since there were no head-to-head trials to compare the various CCBs. There was consistent indirect evidence across six fair to good quality placebo-controlled trials that amlodipine, and felodipine showed that both CCBs had no significant effects (positive or negative) on all-cause mortality or combined cardiovascular events. Evidence for diltiazem, isradipine and nicardipine was poor. There was no evidence for *bepridil** or verapamil.

Evidence from 9 fair quality active or placebo-controlled trials could not demonstrate differences between amlodipine, felodipine, nifedipine, or nisoldipine in effects on cardiac symptoms or exercise tolerance.

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* Voluntarily withdrawn from US market by manufacturer

[7] Poole-Wilson PA, Lubsen J, Kirwan BA et al. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (**ACTION**) trial:randomized controlled trial. Lancet. 2004;364(9437):849-857.

Consensus

The Standing Update Committee agrees by consensus that:

1A. For Hypertension:

- *The evidence for amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nisoldipine and verapamil does not clearly differentiate one CCB from another for efficacy.*
- *No evidence was found for bepridil* or felodipine from studies that fulfilled our criteria.*

1B. For Chronic Stable Angina:

- *There is consistent evidence of equivalence for amlodipine, diltiazem, nicardipine, nisoldipine, and nifedipine to effectively treat chronic stable angina.*
- *There is only indirect evidence for bepridil* and verapamil.*
- *There is no evidence for felodipine and isradipine from studies that fulfilled criteria.*

1C. For Supraventricular Arrhythmias:

- *Only non-dihydropyridines were evaluated*
- *The evidence for the treatment of chronic atrial fibrillation shows no difference between diltiazem and verapamil.*
- *Evidence for other supraventricular arrhythmias was insufficient.*

1D. For Systolic Dysfunction in the clinical situation where hypertension, angina, or atrial fibrillation is co-morbid):

- *There is consistent indirect evidence for amlodipine and felodipine that showed both CCBs had neutral effects on all-cause mortality or combined fatal and nonfatal cardiovascular events.*
- *The evidence showed no difference among amlodipine, felodipine, nifedipine, or nisoldipine from effects on cardiac symptoms or exercise tolerance.*
- *The evidence for diltiazem, isradipine and nicardipine was poor.*
- *No evidence was found for bepridil* and verapamil.*

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Key Question 2. **For adult patients with hypertension (blood pressure ≥ 140/90 mm Hg), angina, or supraventricular arrhythmias, or congestive heart failure (as defined by systolic dysfunction with LVEF <45%) do calcium channel blockers differ in safety or adverse effects?**

2A … for hypertension do calcium channel blockers differ in safety or adverse effects?

The overall grade of evidence was poor due in part to the lack of head-to-head trials that reported clinical outcomes. There were 15 long-term active controlled trials that were insufficient to clearly differentiate one CCB from another for incidence or withdrawals due to adverse effects. No trials were found for *bepridil** or felodipine. Frequency of overall adverse events was reported in three trials**: INSIGHT**[8] 48.9% of patients taking verapamil had one or more adverse events compared to 41.9% of patients taking co-amilozide; **JMIC-B** trial where 9% of patients taking nifedipine retard had an adverse event, versus 15% of those taking an ACE inhibitor; and 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). In a trial measuring quality of life, there was a significantly higher rate of withdrawals due to adverse events in the nifedipine retard group compared with both cilazapril and atenolol.[9]

The trials that reported individual adverse event incidence were consistent in their findings that dizziness, edema, headache and flushing were most common.

Five trials reported the incidence of development of diabetes. When compared to a diuretic or beta blocker, patients taking amlodipine (**ALLHAT**), nifedipine GITS (**INSIGHT**), diltiazem (**NORDIL**), and amlodipine (**INVEST**) the incidence of new-onset diabetes was lower in the CCB groups, and similar across CCBs. In the **VALUE** trial, comparing an AIIRA 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).

2B …for angina do calcium channel blockers differ in safety or adverse effects?

Six short-term trials of amlodipine, diltiazem, nicardipine, nisoldipine, and nifedipine indicated no difference in adverse events or withdrawal rate overall. There was only indirect evidence for *bepridil** and verapamil.

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* Voluntarily withdrawn from US market by manufacturer

[8] Brown MJ, Palmer CR, Castaigne A., et al. Principle results from the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (**INSIGHT**). European Heart Journal Supplements. 2001;3(B):B-20-B26.

[9] Petersen LJ, Petersen JR, Talleruphuus U, et al. A randomized and double-blind comparison of isradipine and spirapril as monotherapy and in combination on the decline in renal function in patients with chronic renal failure and hypertension. *Clinical Nephrology* 2001;55(5):375-383.

2C …for supraventricular arrhythmias do calcium channel blockers differ in safety or adverse effects?

Three very short term (7-30 days) trials comparing verapamil and diltiazem showed no clear evidence in safety between these two drugs.

2D …for treatment of adult patients with systolic dysfunction (LVEF <45%)?

No head-to-head trials, and only two of three trials with active-controls reported adverse events. One compared felodipine to enalapril and the other compared nifedipine to isosorbide dinitrate. 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. Overall event rates were greater with nifedipine than with isosorbide dinitrate or the combination.

2E …for evidence on Long-Term Safety from Observational Studies

Seventeen observational studies of adverse effect from CCBs including: 9 studies of the risk of cancer, 3 studies of all-cause mortality, and 5 studies of various adverse effects are referenced.

Nine studies of total cancer incidence and cancer-related mortality do not provide convincing evidence of an increased risk of total cancer or cancer mortality. Two studies reported excess cancer risk with verapamil in older adults (≥ 71); however 3 other studies did not find a relationship. Excess risk with nifedipine was also found in the study of older persons, but not in 5 other studies. No increase risk was found with diltiazem in 6 studies. No increased risk of breast cancer occurred with nifedipine, diltiazem or verapamil in one study, or with CCBs as a group in 3 other studies.

Three studies among patients >65 years reported mortality rates, compared to no CCB use, BB use, and comparing rates amongst CCBs. Mortality was 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 dihyrdropyridines", or verapamil.[10] However, two small studies found opposing results.[11,12] Nifedipine was associated with a significantly higher risk of death relative to BB use in one study. When stratifying based on immediate release and extended release formulations, the increase in risk was associated only with the long-acting forms. This study found that the risk of mortality was higher with doses ≥ 40 mg/day, and with duration of use ≤ 6 months. In the other study, significantly *fewer* deaths and cardiac re-hospitalizations among patients who started a CCB post-MI were found with the extended release

[10] Jollis JG, Simpson Jr. RJ, Chowdhury MK, et al. Calcium channel blockers and mortality in elderly patients with myocardial infarction. Archives of Internal Medicine 1999;159(19):2341-2348.
[11] Maxwell CJ, Hogan DB, Campbell NRC, et al. Nifedipine and mortality risk in the elderly. Relevance of drug formulation, dose, and duration. Pharmacoepidemiology and Drug Safety. 2000;9(1):11-23.
[12] Gillman MW, Ross-Degnan D, McLaughlin TJ, et al. Effects of long-acting versus short-acting calcium channel blockers among older survivors of acute myocardial infarction. Journal of the American Geriatrics Society. 1999;47(5):512-517.

dihydropyridines than the short-acting formulations. This difference was not found with diltiazem and verapamil.

Related to risk of various adverse effects, two studies reported the 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 less severe or nuisance side effects such as flushing, headache and dizziness were higher with isradipine, compared to diltiazem, nicardipine, and amlodipine; while peripheral edema was higher with amlodipine compared to the others. 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.

Consensus

The Standing Update Committee agrees by consensus that:

2A For Hypertension:

- *The evidence is insufficient to clearly differentiate amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nisoldipine, and verapamil from one another for incidence of withdrawals due to adverse effects.*
- *No trials were found for bepridil* and felodipine.*

2B For Angina:

- *The evidence for amlodipine, diltiazem, nicardipine, nifedipine, and nisoldipine indicates no difference in adverse event or withdrawal rate overall.*
- *Only indirect evidence for bepridil* and verapamil exists.*
- *There is no evidence for felodipine and isradipine.*

2C For Supraventricular Arrhythmias:

- *There is insufficient evidence to differentiate between diltiazem and verapamil.*

2D For Systolic Dysfunction (in the clinical situation where hypertension, angina, or atrial fibrillation are co morbid):

- *Studies that met our criteria could not demonstrate clear differences in safety between felodipine and nifedipine in mild to moderate systolic dysfunction, or felodipine and amlodipine in severe systolic dysfunction.*
- *No evidence for other CCBs was found.*

2E For evidence of safety from long-term observational studies:

- *There is inconsistent evidence of any increased risk of cancer*
- *There is inconsistent evidence of any change in overall mortality with any CCB, whether long or short acting, or from non-dihyropyridine or dihydropyridine subgroups of CCBs; except limited evidence suggests a higher risk of mortality with bepridil* compared to no CCB.*

* Voluntarily withdrawn from US market by manufacturer

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one calcium channel blocker is more effective or associated with fewer adverse effects?

Consensus

The Standing Update Committee agrees by consensus that:

3A For Hypertension

- *The evidence for amlodipine, nicardipine, nifedipine, nisoldipine, and verapamil SR was insufficient to clearly differentiate one CCB from another for efficacy or adverse effects in subgroups of patients.*

3B For Angina:

- *There is no evidence for any of the included CCBs.*

3C For Supraventricular Arrhythmias

- *There is no evidence for any of the included CCBs.*

3D For Systolic Dysfunction (in the clinical situation where hypertension, angina, or atrial fibrillation are co morbid):

- *There is no evidence for any of the included CCBs.*

Conclusion

It is the decision of the Standing Update Committee that:

1. The current evidence does not allow for comparisons of CCBs for the treatment of hypertension and does not differentiate amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nisoldipine, or verapamil SR for efficacy, adverse effects and in subgroups for the treatment of hypertension. There is no evidence for *bepridil** and felodipine.

2. The current evidence does not differentiate amlodipine, diltiazem, nicardipine, nifedipine, and nisoldipine for efficacy in the treatment of chronic stable angina. There is no evidence for felodipine and isradipine. No difference in efficacy was found between dihydropyridines and non-dihydropyridines for the treatment of angina.

3. The current evidence does not differentiate between diltiazem or verapamil for efficacy and adverse effects in the treatment of supraventricular arrhythmias and there is no evidence in subgroups of patients.

4. In the setting of CHF (defined as systolic dysfunction with a LVEF of < 45%) there is evidence that amlodipine and felodipine do not decrease survival or cause harm in this patient population, but neither do they improve survival nor decrease nonfatal cardiovascular events. In patients with systolic dysfunction the evidence does not demonstrate differences between amlodipine, felodipine nifedipine and nisoldipine on symptoms and exercise tolerance.

* Voluntarily withdrawn from US market by manufacturer

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Health Resources Commission

The State of Oregon's Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.