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, 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 subcommittee in drawing the conclusions which comprise the body of this report. Time was allotted for public comment, questions and testimony at each meeting.

This report does not recite or characterize all the evidence that was considered by the OHSU-EPC, the Calcium Channel Blocker Subcommittee 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, Oregon Medical Assistance Program.

The Calcium Channel Blocker Update Committee of the HRC, working together with the OHSU-EPC, OMAP, and the OSU College of Pharmacy will monitor medical evidence for new developments in this drug class. Approximately every six months 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 be brought to the attention of the HRC who may choose to approve the report, or reconvene a Calcium Channel Blocker Subcommittee.
The full OHSU-EPC report, *Drug Class Review on Calcium Channel Blockers*, is available on the Office for Oregon Health Policy & Research (OHPR), Practitioner-Managed Prescription Drug Plan web site: [http://www.oregonrx.org](http://www.oregonrx.org). Additional information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the OHPR website; [http://www.ohpr.state.or.us](http://www.ohpr.state.or.us). You may also request copies of the report, and minutes or tapes of the subcommittee meetings from:

Kathleen Weaver, MD, Director  
Health Resources Commission  
Office for Health Policy and Research  
255 Capitol St. NE, 5th Floor  
Salem, Oregon 97310  
503-378-2422 ext. 406  
Email: Kathy.Weaver@state.or.us

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

Jeani Crichlow  
Oregon Health & Science University  
Mailcode: BICC  
3181 SW Sam Jackson Park Road  
Portland, OR 97201-3098  
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There will be a charge for copying and handling in providing documents from Oregon Office for Oregon Health Policy & Research and from OHSU.

**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 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 nine calcium channel blockers currently marketed in the United States:

- Amlodipine: Norvasc
- Bepridil: Vascor
- Diltiazem: Cardizem, Diltia XT, Tiazac, Dilacor, Tiamate
- Felodipine: Plendil, Renedil
- Isradipine: DynaCirc, DynaCirc CR
- Nicardipine: Cardene
- Nifedipine: Procardia XL, Adalat CC
- Nisoldipine: Sular
- Verapamil: Isoptin, Calan, Covera-HS, Verelan PM, Chronovera

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 long acting drugs (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.

The nine calcium channel blockers currently marketed in the United States have 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. The use of CCBs in treating stable angina and the use of non-dihydropyridines in treating supraventricular arrhythmias are common accepted practices.

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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 can be harmful). 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, the 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.

**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 left ventricular ejection fraction [LVEF] <45%).

2. Interventions
   - Interventions include a calcium channel blocker compared with another 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).

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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 or observational study, of at 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.

**Weighing the Evidence**

The subcommittee 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.

**Key Questions**

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

2. For adult patients with hypertension (blood pressure $\geq 140/90$ 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?

**Summary of Results**

**Key Question 1.** For adults patients with hypertension (blood pressure $\geq 140/90$ 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 $\geq 140/90$ mm Hg do calcium channel blockers differ in efficacy?**

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

Eleven 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
These trials compared CCBs to angiotensin converting enzyme inhibitors (ACEI), diuretics, and beta-blockers. With the exception of the ALLHAT trial, which was 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.

There were 10 active-controlled trials of amlodipine, diltiazem, isradipine, nicardipine, nifedipine long-acting gastrointestinal transport-system (GITS), nisoldipine, and controlled-onset extended release (COER)-verapamil that reported no significant difference between the performance of the CCBs and their comparator drugs in reducing all cause mortality. There were eight active-controlled trials of myocardial infarction (MI); eight active-controlled trials of stroke; and six active-controlled trials of CHF or 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.

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

Thirteen good 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 or 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 studies, as well as active and placebo-controlled studies, do not provide evidence of differences in clinical outcomes with amlodipine, bepridil, diltiazem, nicardipine, nifedipine, nisoldipine, or verapamil. No evidence was found for the use of felodipine or isradipine in angina.

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. Active and placebo controlled studies confirmed this finding, allowing overall evidence to be considered fair to good. Evidence for other supraventricular arrhythmias was inadequate.

1D….for patients with CHF (left ventricular ejection fraction < 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.

Consensus

The Subcommittee 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 for diltiazem, isradipine and nicardipine was poor.
- No evidence was found for bepridil and verapamil.
- The evidence showed no difference among amlodipine, felodipine, nifedipine, or nisoldipine from effects on cardiac symptoms or exercise tolerance.

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. There were 12 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. The trials that reported individual adverse event incidence were consistent in their findings that dizziness, edema, headache and flushing were most common.

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.

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

Three very short term (7-21 days) trials comparing verapamil and diltiazem showed no clear evidence in safety between these two drugs.

Consensus
The subcommittee 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.

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 subcommittee agrees by consensus that:

3A For Hypertension

- The evidence for amlodipine, nicardipine, nifedipine, and nisoldipine 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 Calcium Channel Blocker Subcommittee 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, or nisoldipine, 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 left ventricular ejection fraction 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.
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.