

Calcium Antagonists (“CCBs”) Clinical Pearls for the Washington Rx Therapeutic Interchange Program (TIP)

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Background

In 2003, the Washington State Pharmacy and Therapeutics Committee (P&T), the agency directors of the Department of Social and Health Services-Medical Assistance Administration (DSHS-MAA), Labor and Industries (L&I), and the Health Care Authority-Uniform Medical Plan (UMP) declared amlodipine, diltiazem, nifedipine and verapamil the “preferred” calcium antagonists for patients covered by their prescription insurance. Patients currently using “non-preferred” agents must be evaluated for conversion to preferred agents. Furthermore, patients presenting with prescriptions for non-preferred agents from endorsing practitioners (i.e., providers that have signed the TIP agreement) may be automatically converted to preferred agents by pharmacists.

Purpose

The purpose of this document is to inform pharmacists of the clinical, safety and cost rationale for these policy changes and to optimize their ability to assure safe and effective conversion of patients to the appropriate agent.

Calcium Antagonists available in US (oral formulations only)

Amlodipine* (Norvasc®)	Bepridil (Vascor)
Diltiazem* (generic) (immediate and ER)	Felodipine ER (Plendil)
Isradipine (DynaCirc) (immediate and ER)	Nifedipine* (generic) (immediate and ER)
Nicardipine (generic/immediate-release), (Cardene SR)	Nisoldipine ER (Sular)
	Verapamil* (generic) (immediate and SR)

* Washington State Evidence Based Preferred Drug List Agents

I. Overview of Calcium Antagonists or Calcium Channel Blockers (CCBs)

Calcium channel blocking agents are generally classified into three groups according to their chemical structure: benzothiazepines (diltiazem); phenylalkylamines (verapamil); and the dihydropyridines (amlodipine, bepridil, felodipine, isradipine, nicardipine, nifedipine, and nisoldipine). Dihydropyridines have greater selectivity for vascular smooth muscle than for myocardium and have little or no action at the SA or AV nodes; negative inotropic activity is rarely seen at therapeutic doses. Benzothiazepines and phenylalkylamines (“non-dihydropyridines”) 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 with Food and Drug Administration (FDA) indications for treating hypertension, angina, and supraventricular arrhythmias, depending on the specific drug.

A. Clinical Efficacy Comparison of CCBs

General Summary

There is scarce head-to-head data from well-designed clinical trials from which to directly compare the CCB agents. The results from 11 active-controlled trials suggest that the CCBs performed no better than ACE-inhibitors, diuretics, and/or beta-blockers for health outcomes. Based on this evidence identification of a superior CCB is not valid for several reasons: concern regarding sufficient power, varying use of additional anti-hypertensive medications, contrasting relative risks in the same trial, and limited or lack of any evidence for some CCBs. Some CCBs appeared to reduce risk for some health outcomes yet increase risk for other outcomes. One trial reported a low RR for MI (0.58) yet a high risk for stroke (2.3). The INSIGHT trial reported a high RR for CHF (2.17) yet a low RR for ESRD (0.62). In addition, it is not possible to separate the effects of supplemental antihypertensive medications from study medications; therefore, the type and prevalence of secondary medication use varied. All of these issues made it difficult to reach reliable conclusions concerning the comparative efficacy of the CCBs to improve CV health outcomes.

Efficacy in Heart Failure/Systolic Dysfunction

Perhaps one of the most controversial topics related to CCB safety concerns use of these agents in patients with heart failure or systolic dysfunction (EF < 45%). The role of ACE inhibitors, beta-blockers, diuretics and spironolactone are well established in treatment of systolic dysfunction. More recently angiotensin receptor antagonists have shown benefits

in this population. The role of CCBs in heart failure is that of adjunctive therapy, generally to treat hypertension. Common clinical opinion is that amlodipine is the most appropriate CCB in patients with systolic dysfunction (per the PRAISE trial) based on no worsening of CHF in treated patients.

The Prospective Randomized Amlodipine Survival Evaluation (PRAISE) study is the largest trial of a CCB for use in systolic dysfunction and included 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 non-ischemic cardiomyopathy (n = 421). There was a 9% difference in fatal and nonfatal events (95% CI -17.9,-0.1) and a 13% difference in all-cause mortality (95% CI - 21.8,- 4.8) in favor of amlodipine.

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.

Nine active or placebo-controlled studies of CCBs for the treatment of systolic dysfunction have been rated of good or fair quality: one each for nifedipine and nisoldipine, two for amlodipine and five with felodipine. 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. The question remains as to whether other CCBs would show a neutral, positive or negative impact on in this population of patients.

B. Safety and Adverse Effects with CCBs

The most common adverse effects related to CCBs are edema (peripheral and pedal), dizziness, headache, flushing, hypotension, and minor GI disturbances (nausea, constipation). The short-acting dihydropyridines agents are particularly associated with increased incidence of flushing and peripheral edema; however, these occurrences are notably less frequent with the more commonly prescribed extended-release preparations. Also, the immediate-release formulations of the short-acting dihydropyridines were implicated in cases of worsening angina and myocardial infarction in some patients with underlying ischemic disease. A National Heart, Lung, and Blood Institute panel recommends, "short-acting nifedipine preparations be used with great caution (if at all), especially at higher doses, in the treatment of high blood pressure, angina, and myocardial infarction.

Incidence of Common Adverse Effects Reported for CCB Agents (Facts & Comparisons)

ADR	Amlodipine	Bepridil	Diltiazem ¹	Felodipine	Isradipine ¹	Nicardipine	Nifedipine ¹	Nisoldipine	Verapamil ¹
Edema	1.8-14.6	<2	<6		3.5-35.9	0.6-1	10-30		1.7-3
Peripheral Edema			2-15	2-17.4		†	7-29	7-29	3.7
Dizziness	<3.4	11.6-27.3	<10	2.7-3.7	3.4-8	1.6-6.9	4-27	3-10	3.4-7
Headache	7.3	7-13.6	<12	10.6-14.7	10.3-22	6.2-8.2	10-23	22	2.2-12.1
Flushing	0.7-4.5		<3	3.9-6.9	1.2-5.1	5.6-9.7	<25		0.6-0.8

¹Data for oral formulations only and pooled from separate studies and are not necessarily comparable.

¹Includes data for SR/ER form.

† Occurs, no incidence reported.

Adverse Effects from Clinical Trials

It is important to note that in a large overview of clinical trials data for all approved indications, the quality of evidence for CCB-related adverse events is generally rated poor and at best fair. Trends were noted for less incidence of peripheral edema with the non-dihydropyridines, but this data was not seen as clinically significant.

Drug Interactions

CYP450:

CYP3A4 has a major role in the metabolism of all the calcium channel blockers. Inducers and inhibitors of CYP3A4 can affect the metabolism of the dihydropyridines as well as verapamil and diltiazem. In general, diltiazem and verapamil inhibit other CYP3A4 substrates (e.g., midazolam, carbamazepine), whereas the dihydropyridines do not.

C. Cost Comparisons of CCBs

Drug	Cost for Typical 30-day Supply [#]
Amlodipine*	\$58
Bepidil	\$58
Diltiazem ER*	\$30 - 40
Felodipine ER	\$31 - 56
Isradipine CR	\$70
Nicardipine ER	\$30
Nifedipine ER*	\$20 - 38
Nisoldipine	\$30
Verapamil SR*	\$21

* Washington State Evidence Based Preferred Drug List Agents

[#]Costs based on DSHS reimbursement formulas

V. Information on Converting Patients to Preferred Drug

Choosing a Preferred Agent

- Patients currently utilizing a non-dihydropyridine agent, verapamil or diltiazem, should not require conversion since both agents are preferred. It is not recommended to convert patients taking a non-preferred dihydropyridine (i.e., felodipine) to verapamil or diltiazem without consulting the prescriber as these agents have differing physiologic actions (i.e., AV nodal effects).
- Patients taking a non-preferred dihydropyridine CCB should be converted to a similar dosage of a preferred dihydropyridine CCB. The conversion guide below can help in selecting an agent and dose.

Conversion and Dosing Conversion Guide*[^]

Dihydropyridine CCB	Low	Med	High	Max Daily Dose
Amlodipine [#]	2.5mg	5mg	10mg	10mg
Felodipine ER	2.5mg	5mg	10mg	20mg
Isradipine CR	5mg	10mg	20mg	20mg
Nicardipine SR	30mg bid		60mg bid	120mg
Nifedipine ER [#]	30mg	60mg	90mg	120mg
Nisoldipine	20mg	30mg	40mg	60mg
Nondihydropyridine CCB	Low	Med	High	Max Daily Dose
Diltiazem ER [#]	180mg	240mg	360mg	540mg
Verapamil SR [#]	180mg	240mg	360mg	540mg

*This table does not represent exact or equivalent dosing conversions. It is based on FDA approved dosing ranges and comparative doses from clinical trials for treating hypertension. Practitioners should exercise common sense in the practical application of this guide, including consideration for the patient's history of response to specific agents and current clinical status.

[^]All doses are once daily unless stated otherwise.

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Considerations in Converting Patients

- Response to Therapy: The dihydropyridine CCBs are used to treat hypertension and angina, conditions whose control is dependent on appropriate drug-dose response. While most patients should be receiving CCBs as adjunctive therapy, assessment of patient response post-conversion is crucial to assure that clinical benefits are maintained. It is both a legal requirement and a clinical necessity that information regarding this conversion be related to the prescriber in a timely manner.

Patient Education and Counseling

- Patients should be counseled on appropriate use of their new agent and the rationale for conversion (i.e., equal effectiveness, increased cost-effectiveness).
- Patients should be instructed to follow the instructions for the new CCB and to not combine use with the old CCB agent. Instruct the patients that there is no advantage to combining two products and there is more likelihood of adverse effects.
- Patients should be advised to contact the prescriber if they experience therapeutic failure (i.e., increased frequency of anginal pain, loss of blood pressure control) to assure a complete review of the patient's condition and medication response.
- Patients should be counseled on the common side effects with CCB agents and to contact the pharmacy for any medication-related questions and/or the prescriber if any significant and persistent side effects are experienced.

VI. References and Resources

Oregon Health Policy and Research, Evidence-based Drug Reports (<http://www.ohpr.state.or.us/index.html>)

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