Pharmacy Benefits Management and Medical Advisory Panel
Drug Class Review
Calcium Channel Blockers

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OBJECTIVES

1. To review the efficacy, safety, and administration of the currently available oral calcium channel blockers.

Generic Name	Brand Name (®)	Manufacturer
Amlodipine	Norvasc	Pfizer
Bepridil	Vascor	McNeil
Diltiazem	*various*	*various*
Felodipine	Plendil	Astra
Isradipine	DynaCirc	Sandoz
Nicardipine	Cardene	Syntex
Nifedipine	*various*	*various*
Nimodipine	Nimotop	Miles
Nisoldipine	Sular	Zeneca
Verapamil	*various*	*various*

2. To present criteria for determining the formulary status of calcium channel blockers for the Veterans Health Administration National Drug Formulary.

I. FDA INDICATIONS [1-20]

Indications		Hypertension	Angina Pectoris			Other
			Vasospastic	Stable	Unstable	
Amlodipine		x	x	x		
Bepridil				x		
Diltiazem	IR	x				
	SR	x				
	CD	x	x	x		
	XR	x		x		
	TZ	x		x		
Felodipine		x				
Isradipine	IR	x				
	SR	x				
Nicardipine	IR	x		x		
	SR	x				
Nifedipine	IR		x			
	XL	x	x			
	CC	x				
Nimodipine						Subarachnoid Hemorrhages
Nisoldipine		x				
Verapamil	HS	x		x		
	IR	x	x	x	x	Arrhythmias
	SR	x				
	VR	x				

CC = Adalat® CC nifedipine tablets, CD = Cardizem® CD diltiazem capsules, HS = Covera-HS® verapamil tablets, IR = immediate release formulation, SR = sustained release formulation, TZ = Tiazac® diltiazem capsules, VR = Verelan® verapamil capsules, XL = Procardia XL® nifedipine tablets, XR = Dilacor XR® diltiazem capsules; Verapamil SR = Calan® SR, Isoptin® SR, or various generic tablets

None of the calcium channel blockers are FDA-approved for use in congestive heart failure. Use for this indication is generally considered to be controversial, but not unusual. Calcium blocker use is commonly documented in CHF studies. A variety of unlabeled uses can be found in the literature. Some of the more encouraging calcium channel blocker, cardiovascular studies include: reinfarction reduction; arrhythmia suppression, both ventricular and supraventricular; congestive heart failure and cardiomyopathy management; and regression of coronary artery disease. Non-cardiovascular studies have investigated the agents' use in: retardation of diabetic proteinuria and renal failure, management of Raynaud's Phenomena, prevention of nocturnal leg cramps, and control of migraines and cluster headaches. Nonlabeled investigations have had varying degrees of success. [1-2, 23-32]

II. PHARMACOLOGY [1, 3-22]

A. Myocardial Effects

Calcium channel blockers competitively bind to the post-synaptic alpha$_1$-subunits of the L-type calcium channels called "slow current channels." This inhibits calcium's myocardial cellular influx during depolarization. The subunits are primarily located in the sinoatrial and atrioventricular nodes.

B. Vascular Effects

In the peripheral vasculature, calcium channel blockers competitively inhibit both post-synaptic alpha$_1$ and alpha$_2$ receptors to varying degrees. Dihydropyridines are considered to be more selective for the vascular smooth muscle than for cells in the myocardium; however, the degree of selectivity varies with the agent. The second generation dihydropyridines also appear to be more selective for vascular smooth muscle.

III. PHARMACOKINETICS [2-22, 24]

The calcium channel blockers undergo first pass metabolism that is extensive, but variable depending upon the agent. Bioavailability and therefore clinical response can be *significantly* altered in the elderly or in patients with hepatic dysfunction. Lower initial doses and extra care are recommended in these patients. Most metabolites are inactive and are eliminated in the urine or feces. However, diltiazem and verapamil produce active metabolites. Caution should be exercised when calcium channel blockers are given to patients with renal dysfunction, especially with agents having active metabolites.

Multiple, extended-release formulations are available for agents whose patents have expired. These include: Dilacor XR® (Rhone Poulenc Rorer) and Tiazac® (Forest) for diltiazem; Verelan® (Elan Pharmaceuticals) and Covera-HS® (Searle) for verapamil; and Adalat® CC (Bayer) and Procardia XL® (Pfizer) for nifedipine. The FDA considers these generics inequivalent to their original, immediate release counterparts and to each other (BC rated)[33], this does not discount therapeutic equivalence. In some cases, an agents' pharmacokinetics appear to change (see below), this is a result of the different formulations.

Measure	Verapamil/VR/HS	Diltiazem/XR/SR/CD/TZ	Bepridil	Nimodipine	Nisoldipine
Bioavailability [%]	20-35	40-67	59	13	5
Onset [min]	30/NA/delayed 4-5hrs	30-60	60	-	-
Peak [hrs]	1-2.2/7-9/11	2-4/4-6/6-11/10-14/6.8	2-3	1	6-12
Duration [hrs]	4/NA/24	6-8	-	-	-
Protein Binding [%]	83-92	70-80	> 99	> 95	> 99
Half-Life [hrs]	3-8/12/NA	3.5-6/5-10/5-7/5-8/4-9.5	24	1-2	7-12

VR = Verelan®, HS = Covera-HS®, XR = Dilacor XR®, SR = Cardizem® SR, CD = Cardizem® CD, TZ = Tiazac®
NA = information not available in manufacturer's package insert

Measure	Amlodipine	Felodipine	Isradipine/CR	Nicardipine‡	Nifedipine/XL/CC
Bioavailability [%]	64-90	20	15-24	35	45-70/86
Onset [min]	-	120-300	120-240	20	20
Peak [hrs]	6-12	2.5-5	1.5/8-10	0.5-2	0.5/6/2-5*
Duration [hrs]	> 24	22-24	12/24	6-8	4-8/-
Protein Binding(%)	> 93	> 99	95	> 95	92-98
Half-Life [hrs]	30-50	11-16	8	2-4	2-5/2-5/7

CR = DynaCirc® CR, XL = Procardia XL®, CC = Adalat® CC
* Adalat® CC has a second, smaller peak 6 to 12 hours after administration
‡ Pharmacokinetics are the same with immediate and sustained release formulation

IV. COMPARATIVE CLINICAL TRIALS

A. HYPERTENSION[34-42]

Design	Important Criteria	Drugs <n>	Outcome	Comments
random, double-blind, parallel[34]	age 21 to 65 yrs; SiDBP 95 to 115, British	Amlodipine 5 to 10 mg qd <53> Nifedipine ret 20 to 60 mg bid <58> (up titration after 2-wks if DBP > 90) 4-wk tx after titration	Sig BP decreases compared to placebo in both groups. No sig dif between agents (BP : 18/12--amlodipine; 17/12--nifedipine). No sig dif in HR between baseline and final measures or between the two groups. Max dose required in 45% of amlodipine; w/ nifedipine, 41% needed 40 mg bid, 2% needed 60 mg bid. No sig dif in ADRs.	All pts were caucasian. Excluded: CHF, angina, females of child bearing potential.
random, open-label, parallel[35]	age 21 to 65 yrs (ave 50); SiDBP 95 to 115 (some obesity, retinopathy, headache)	Felodipine 5 to 10 mg qd <126> Nifedipine GITS 30 to 90 mg qd <127> (up titration after 6-wks if DBP > 90 OR not decrease by 10 from baseline w/ a SiDBP <100) 6-wk tx after titration	Max dose required in: 63%-- felodipine (ave dose 8 mg); w/ nifedipine, 40% needed 60 mg, 14% needed 90 mg (ave 50 mg). No sig BP dif between groups at any time (SiBP: 14/12--felodipine; 16/13—nifedipine). Blacks &/or females tended to have greater response to active tx, but dif not statistically sig. # pts age >55 yrs attaining controlled SBP with nifedipine was sig greater than felodipine; both txs were sig better than placebo in all pts. No sig dif in ADRs.	Excluded: CHF; CVA; sick sinus syndrome or AV block > 1st degree w/o pacemaker; uncontrolled diabetes mellitus; alcohol or substance abuse; using > 10 cigarettes/day; women of child-bearing potential.
8-wk, random, double-blind, cross-over, fixed dose, stratified for race[36]	atenolol tx failures, age 25 to 75 yrs, SuSBP 170 & SuDBP 100, British	Nisoldipine 10 mg bid Nifedipine 20 mg bid <28>	Sig decreases in BP, compared to baseline, w/ both agents; no dif between the groups (SuBP : 37.2/22.5-nisol, 35.4/21-nifed). No sig dif in ADRs.	52 pts screened; 14 pts not analyzed-reasons & distribution not specified.
Random, double-blind[37]	age 22 to 78 yrs, DBP 95 to 115, Danish Responder if: decrease DBP 10 OR final DBP <90.	Amlodipine 5 to 10 mg qd <61> Felodipine ER 5 to 20 mg qd <57> (up titration if DBP >90 after: 4-wks -- felodipine, or 6 to 8-wks -- amlodipine) 4-wk tx after titration	Sig decreases in office measured BPs compared to baseline w/ both groups. No sig dif between groups (BP : 13.4/11.8--felodipine; 15.3/12.9--amlodipine). Ambulatory BP taken day 2, showed similar onsets; but SBP sig lower w/ amlodipine. Max dose required in 40% amlodipine (ave 7.4 mg); w/ felodipine, 57% needed 10 or 20 mg (ave 11.2 mg)—distribution not specified. Sig more felodipine pts got headache or flushing; no sig dif in other side effects.	Excluded: severe cardiac disease. Baseline, daytime SBP sig higher w/ amlodipine group (158.9) vs (154.3) felodipine.

A. HYPERTENSION (cont)[34-42]

Random, double-blind, parallel Also focused on ADRs associated w/ vasodilation (ankle edema, headache, flushing, dizziness, increased HR)[38]	age 18 to 65 yrs (ave 54), SuDBP 95 to 115, Australia	Isradipine 2.5 to 5 mg bid <72> Felodipine retard 2.5 to 5 mg bid <71> (up titration after 4-wks if SuDBP > 90; open-label enalapril 2.5 mg qd added if SuDBP > 90 at 8-wks) 4-wk tx after dosing adjustments.	Sig BP decrease, compared to baseline in both groups. Sig greater decrease in StDBP w/ isradipine compared to felodipine. No sig dif in SuBP at end (21/16—isradipine; 21/12--felodipine). Mean daily doses: isradipine 8.6 mg; felodipine 8.65. 35% isradipine and 24% felodipine needed max dose. Enalapril was added in 34% of isradipine and 13% of felodipine pts. Sig more felodipine pts developed ankle edema. Of those reporting ankle edema in both groups, 55% were women even though women were only 36% of the population. One felodipine pt died following a cerebral hemorrhage. No sig dif between groups for remaining targeted, vasodilation ADRs.	
6-wk, random, double-blind, parallel, fixed dose[39]	age ave 56.5 yrs, SiDBP 95 to 115, Belgium	Isradipine 5 mg qd <103> Amlodipine 5 mg qd <102>	No sig dif in BP decrease between groups (BP 19.9/10.4—isradipine, 18.4/10.1-amlodipine), both sig decreased compared to baseline. Sig more amlodipine pts reported ADRs considered to be associated with peripheral vasodilation (see above study).	Excluded: CHF NYHA Class III or IV; cardiac arrhythmia; history of alcohol or drug abuse, signs of mental dysfunction
Random, double-blind, cross-over, parallel, fixed dose[40]	age 30 to 68 yrs (ave 53); clinic pt 2 mos; using nifedipine 20 mg bid 2 to 4-wks	Nifedipine retard 20 mg bid; 4-wks Amlodipine 5 mg qd with pm placebo; 4-wks <13>	HR sig faster with amlodipine. No sig dif in SP between groups.	Excluded: S_{CR} > 150 mol/l, ischemic heart disease, diabetes mellitus, oral contraceptive
8-wk, random, double-blind, parallel[41]	age 18 to 75 yrs, SiDBP 95 to 114, Analgesic, antitussive, lipid lowering agent, any gastrointestinal medication types and distribution not specified	Nifedipine CC 30 to 60 mg qd <90> Amlodipine 5 to 10 mg qd <86> (up titration if Si DBP 90 after 4-wks) 4-wk tx after titration	65.6% nifedipine and 60.5% amlodipine patients remained on original doses. No sig dif in BP reduction (using office and 24-hr measurements) between the agents (BP 18.7/16.2-nifedipine, 18.9/15.4-amlodipine). No sig dif in HR between agents or compared to baseline. ADR withdrawals: 3 nifedipine (photosensitivity, ankle edema, hypertensive crisis-220/110 asymptomatic); 1 amlodipine (flushing). Trend toward more non-sig ADRs with amlodipine.	Excluded: CAD, CHF, hepatic or renal dysfunction, history of alcohol or drug abuse, tranquilizer or psychotropic drug, gastrointestinal disorder. Sig more females in amlodipine group (50%) than nifedipine (38%)
6-wk, random, double-blind, parallel, multicentre [42]	age 27 to 70 yrs, (mean 56), SiDBP 95-115, German Included pts w/ DM (13), angina (10), mild CHF (2), PVD (7)	Felodipine ER 5 to 10mg qd <59> Amlodipine 5 to 10mg qd <59> (up titration if SiDBP > 90 after 2-wks)	No sig dif in BP decrease between groups (BP 18/13 2-wks, 25/18 6-wks felodipine; 16/12 2-wks, 23/17 6-wks amlodipine), both sig decreased compared to baseline. Response rates (SiDBP $\leq$ 90) with 5mg at 2-wks 59% felodipine, 51% amlodipine; at 6-wks 76% felodipine, 75% amlodipine. ADRs reported by 8 felodipine, 11 amlodipine pts. HA, dizziness, flushing, palpitations most common.	Excluded: Secondary or malignant HTN, renal or hepatic dysfunction, severe CHF, MI past 3 months, valvular disease, CVA past 12 months, unstable angina, hypertrophic obstructive cardiomyopathy, hypersensitivity to either drug, pregnancy

B. ANGINA[43-51]

Design	Important Criteria	CCB <n>	Outcome	Comments
2-wk, random, double-blind, cross-over, parallel, fixed dose[43]	ave age 58.5 yrs, stable angina and CAD &/or (+) Bruce test for ischemia	Amlodipine 10 mg qd Diltiazem 120 mg tid <31>	No sig dif between groups in angina attacks, ischemic episodes, or BP. Diltiazem pts sig lower HR throughout study.	
random, double-blind, cross-over, parallel[44]	age 20 to 70 yrs, CHF NYHA II-III, >4 anginal attacks/wk despite β-blocker & nitrate therapy, Sweden Pts also on metoprolol or alprenolol	Felodipine 5 & 10 mg Nifedipine 10 & 20 mg Placebo Each dose given once in lab <24>	Sig increase in time on ergometer with felodipine and nifedipine compared to placebo; no sig dif between drugs or doses. Time to 1 mm ST depression sig longer with low doses of nifedipine vs felodipine; no dif between higher doses. SBP during exercise sig lower with active drugs compared to placebo; no sig difs between drugs or doses. No sig dif among groups in HR.	Excluded: women of child- bearing age 96% female; 88% w/hx of MI
6-wk random, double-blind, cross-over, parallel[45]	age 20 to 70 yrs (ave 56), 1 mm ST depression on bicycle ergometer lovastatin, sl ntg	Felodipine ER 10 mg qd; 2-wk Nifedipine retard 20 mg bid; 2-wk placebo bid; 2-wk <42>	Both sig increased exercise time, time to angina onset, and time to ST depression when compared to placebo. No sig dif between active agents in total exercise time, but time to angina onset and ST depression were sig longer w/ felodipine. Sig decrease in angina attacks and ntg intake w/ active meds compared to placebo; but, felodipine sig fewer than nifedipine. No sig dif in ADRs.	Excluded: women of child-bearing potential
2-wk, random, double-blind, parallel [46]	age range 30 to 88 yrs; 1 mm ST depression w/ treadmill test using modified Bruce Protocol sl ntg	Nisoldipine CC 20 mg qd <78> Nisoldipine CC 40 mg qd <75> Nisoldipine CC 60 mg qd <82> Placebo qd <77>	20 and 60 mg tx sig increased total exercise time compared to placebo; no sig dif between the two. Time to ST depression sig longer with 40 and 60 mg compared to placebo. No sig decrease in # anginal attacks or sl ntg use compared to baseline for any of the txs. 40 and 60 mg txs sig decreased BP compared to placebo. Sig increased HR w/ 40 and 60 mg compared to placebo. 10 pts left study due to potentially serious ADRs (2 placebo; 6, 40 mg; 2, 60 mg); including aMI and worsening angina.	Excluded: CHF, CVA

B. ANGINA (cont)[43-51]

Random, double-blind, cross-over, forced titration (every 2-wks)[47]	age 40 to 73 yrs (ave 57); 8 anginal attacks/wk; exercise-induced angina 3-mos and: previous aMI, >60% stenosis in at least one major coronary per angio, + exercise test, or thallium-201 scan; British. sl ntg	Isradipine 2.5 to 7.5 mg tid; 6-wks Nifedipine 10 to 30 mg tid; 6-wks <18>	Exercise duration increased 30% w/ isradipine and 34% w/ nifedipine. Time to angina onset increase 53% w/ isradipine and 62% w/ nifedipine. Sig decrease in angina frequency compared to baseline (11.4 attacks/wk baseline, 8.4--nifedipine, and 11-isradipine). SL ntg consumption decreased from 5.2 tablets/wk at baseline to 5.1--nifedipine and 6.4--isradipine. No sig dif in HR between groups. BP sig decreased in each group; no sig dif between agents (at exercise end point: isradipine 15/7 and nifedipine 10/8). Sig more ADRs w/ nifedipine. No sig dif in withdrawals due to ADRs. 34 pts originally, 16 withdrew (inc. 2, each w/ aMI; 2 isradipine and 1 nifedipine w/ increased unstable angina; 1 each dropped, at end of study, for non-specified protocol violations; & 2 isradipine and 1 nifedipine for non-specified miscellaneous reasons).	Excluded: women of child bearing potential, cardiac conduction defects, uncontrolled HTN, S_{CR} > 177 mol/l; users of digoxin or psychotropic medication.
3-day, random (to days order), double-blind (placebo given as single-blind), parallel, cross-over, fixed dose[48]	ave age 57.4 yrs; + exercise test; 70% w/ stenosis in at least one major coronary artery 8 bicycle ergometer tests during study anticoagulant	Day 1: placebo; placebo + ntg Day 2: ATE; ATE + ntg; ATE + NIC (or NIF) Day 3: ATE; ATE + ntg; ATE + NIC (or NIF) {NIC Nicardipine 40 mg; NIF Nifedipine 20 mg; ATE atenolol 100 mg; ntg as sl spray} <17>	All placebo tests ended in angina. ATE alone and w/ NIC did not sig affect ST depression compared to placebo at max exercise. Ischemia improvement w/ groups using ntg. ATE + ntg and ATE + NIC biked sig longer than ATE + NIF. At HR of 100 bpm, no sig dif in biking w/ any ATE group. Resting SBP was sig lower w/ ATE + NIF (113) and ATE + NIC (109) than ATE + ntg (126) or ATE alone (135). All sig lower than placebo (144). SBP at exercise end-point was sig higher w/ ATE + ntg (174) than ATE + NIC (162) or ATE + NIF (156). At rest, ATE groups had sig slower HR than placebo. No sig dif in HR w/ ATE + NIC or ATE + NIF groups.	Excluded: CHF, valvular disease, bundle branch block, AV block, renal or hepatic failure, peripheral vascular insufficiency All were in sinus rhythm and were male. None w/ history of coronary arterial bypass or transluminal coronary angioplasty.

B. ANGINA (cont)[43-51]

Random, double-blind, fixed dose[49]	age 46 to 66 yrs (ave 58), stable angina 3 mos sl ntg (angio proven coronary stenosis in 6 pts – distribution not specified)	Nisoldipine 5 mg Nisoldipine 10 mg Nifedipine 20 mg Placebo <10> {one time doses given in the lab}	At maximum exercise, time to ST depression and max exercise duration increased sig w/ all groups (including placebo). Both nisoldipine doses were sig better than placebo, but nifedipine was not. Rate/pressure products were sig higher with nifedipine and both nisoldipines when compared to placebo (at max exercise). The sum of ST depressions, at peak exercise when compared to baseline, was reduced w/ nifedipine and 20 mg nisoldipine. Compared to baseline, HR at rest, increased sig following 20 mg nisoldipine and nifedipine; also had sig decreases in SBP (11-nifedipine, 12-nisoldipine).	
Random, double-blind, crossover; w/ long-term follow-up (felodipine only).[50]	ave age 54 yrs, hospitalized w/ Prinzmetal's variant angina (+ ST elevation during attacks) sl ntg (25 w/smoking history, 16 w/ increased cholesterol, 3 w/diabetes mellitus, 5 w/ previous aMI	Nifedipine 20 mg qid; 6-days Felodipine 10 mg qd; 6-days Felodipine 20 mg qd; 6-days initially, then up to 6 mos <30>	Compared to baseline, all groups had equivalent reductions in: ST-depression during ergometer testing; ischemic episodes (symptomatic/ asymptomatic) per 24-hr holter monitor; angina attacks by pt report; and ntg consumption by pill count. Withdrawals: dizziness-one each, melena due to aspirin-one, non-Q-wave MI-one (nifedipine). 21 of 26 pts remained symptom free and without ST changes during 24-hr holter monitoring during long-term follow-up.	Excluded: CABG, angioplasty, CHF
Random, double-blind, crossover[51]	mean age 63 yrs, documented exercise-induced angina and myocardial ischemia during 24hr ECG monitoring sl ntg (14 w/smoking history, 6 w/PTCA, 1 w/ CABG, 9 w/ angio proven CAD, 10 w/previous MI, 4 w/minor stroke, 18 w/diabetes mellitus)	Placebo (9 days) and 2.5mg ntg tid (days 1 to 7) Felodipine or amlodipine 5mg qd; 7-days after placebo Felodipine or amlodipine 10mg qd; 21-days after 5mg qd <52>	Both amlodipine and felodipine showed similar reductions in mean number ischemic episodes/24 hr, total duration of ischemic episodes/24 hr, maximal ST-depression, number of anginal attacks, and nitrate consumption as compared to baseline ($p<0.001$ for all variables). Withdrawals: palpitations - two w/felodipine and one w/amlodipine, worsened angina - one (amlodipine), refused further treatment - one (amlodipine).	Excluded: antianginals other than ntg during run-in, unstable angina, MI, CABG, PTCA, or stroke w/in past 3 months, CHF, hypotension, LVH, BBB, severe liver disease, pregnancy, renal insufficiency

ATE = Atenolol, NIC = Nicardipine, NIF = Nifedipine

C. CONGESTIVE HEART FAILURE [52-64]

None of the calcium channel blockers are FDA-approved for the treatment of congestive heart failure. Use for this indication is generally considered to be controversial, but not unusual. Calcium blocker use is commonly documented in CHF studies involving other drugs. Typically, agents were added in an attempt to treat underlying coronary artery disease, not CHF. In theory, the pathophysiologic basis for use centers around the agents vasodilatory effects. It is thought that the resulting decrease in systemic vascular resistance (i.e., after load) would result in improved exercise tolerance, increase ejection fraction, and decreased mortality. Another unproven, but hoped for, benefit involves the prevention of calcium overload with a resulting decreased arrhythmia incidence. Early trials with the less vascular selective, first generation agents (verapamil, diltiazem, nifedipine) generally concluded negatively. This was frequently attributed to their more negative inotropic effects that were thought to increase with higher doses and more advanced disease. However, cardiac output or ejection fraction remained unchanged or improved with some first generation drugs in patients experiencing worsening heart failure. Another theory involved the activation of negative neurohormonal responses involving the renin-angiotensin aldosterone system and the sympathetic nervous system as a result of vasodilation. Several investigators have hypothesized that the hormonal effect could be neutralized through concomitant use of angiotensin converting enzyme inhibitors or beta-blockers. Additionally, the question of how CHF etiology predicts response was raised in a newer trial. Because many short-term studies show benefit that is ultimately lost in the long term, this review excludes them. Also excluded are most trials involving first generation agents, for reasons specified above. [52-64]

Design & Important Criteria	**Drugs <n>**	**Outcome**	**Comments**
4-month, randomized, double blind, age 55± 14 yrs, NYHA III (w/ LVEF 0.18±0.08)[57]	Nicardipine 60 mg qd Nicardipine 90 mg qd Placebo <20>	In pts w/ worsening of CHF (6 nicardipine and 2 placebo), renin levels increased from 4±4 to 21±15 ng/ml/hr (p=0.001). In those not worsening, no change in max treadmill time; ventriculography at rest or during exercise; 6-min walking test, or in norepinephrine, renin, or aldosterone levels.	[abstract] CHF causes not indicated
16-wk, randomized, double blind, Netherlands, age 18 to 75 (mean 65) yrs, NYHA II or III (w/ LVEF 0.25±0.10)[58]	Felodipine max 5 mg bid <22> Enalapril max 5 mg bid <24> (Titrated to max if SBP>95 mmHg & pt could tolerate)	Final doses: felodipine-13.3 ±5.5 mg & enalapril 15.4 ± 6.2 mg. No increase in resting HR or DBP w/ either group, but felodipine pt had sig reduced resting SBP (15 mmHg). Also no change in VO_2 max or exercise tolerance Six enalapril & 4 felodipine pts improved 1 NYHA Class. Enalapril sig decreased norepinephrine, renin, & aldosterone levels; no changes seen w/ felodipine. Withdrawals: for CHF felodipine 2 & enalapril 1 (pt died); Other- 1 felodipine for ankle edema & 1 enalapril for renal impairment	Excluded: MI w/in 3 mos; SBP < 100 mmHg; significant valvular disease. An additional enalapril pt w/ increased CHF did not withdraw CHF causes: CAD 17-enalapril, 18 felodipine; HTN 5-enalapril, 4-felodipine; cardiomyopathy 2-enalapril, 0-felodipine

C. CONGESTIVE HEART FAILURE (cont) [52-64]

randomized, (stratified by etiology), double blind, follow-up 6 to 33 mos (ave 13.8), age 64 to 68 yrs, NYHA IIIB or IV (LVEF <0.21±0.01)[59] PRAISE	Amlodipine max 10 mg qd <571> Placebo qd <582> [titrated to max dose if tolerated]	There were no sig dif between groups in *death from all causes* or incidence of *primary fatal or nonfatal events*. Sub Group Analysis (comparisons to placebo): 1) Etiology- amlodipine pts w/ CHF due to nonischemic dilated cardiomyopathy had a 46% decrease in risk of *death from all causes* (p<0.001) and a 31% decrease in risk of *primary & secondary events* (p= 0.04); no sig changes in pts w/ CHF due to ischemic heart disease. 2) Characteristic - slight reductions in hazard ratio [95%CI] were seen in women (r=0.62 [0.40-0.96]), pts w/ h/o angina (r=0.59 [0.44-0.81]), and those w/o h/o htn (r=0.75 [0.57-0.99]). Hazards ratios were not sig affected by age > vs. ≤ 65 yrs, male sex, LVEF > vs. ≤ 0.20, NYHA class, presence of angina, h/o HTN, or serum sodium concentration. Sig more pulmonary and peripheral edema, but less uncontrolled HTN and angina occurred in the amlodipine group. There was no sig dif in arrhythmia incidence or *all cause medication withdrawal* rate. Disorders involving the liver and gall bladder were sig less w/ amlodipine while those involving the kidneys were more.	Excluded:cardiac arrest; sustained VT or VF w/in 1 yr; unstable angina or MI w/in 1 mo; CVA or cardiac revascularization w/in 3-mos; severe lung, renal, hepatic dz; 85<SBP> 159 or DBP>89 (pulmonary edema, severe hypoperfusion, MI, sustained or hemodynamically destabilizing VT or VF).
randomized, cross-over, age 35 to 71 (mean 55±10) yrs, NYHA II or III (LVEF 0.08 to 0.35)[60]	<orig 28 pts> Nifedipine max 20 mg + placebo-ISDN qid <15> ISDN (max 40 mg) + placebo - nifedipine qid <19> Nifedipine + ISDN (both as above) <17> [Goal-all pts to get each tx for 8-wks ; doses titrated to max if tolerated.]	Baseline ETTs were 316 ±87 & 324±88 sec; after 8-wks tx, 2-hr & 4-hr-post dose ETTs were 398±118 & 413±121 sec w/ ISDN, 389±97 & 411±109 w/ nifedipine, and 372±92 & 384±100 w/ combination. Each 2 & 4-hr time was sig longer than placebo, but no sig dif among each other. No sig in VO2 Max occurred with any tx. DBP was sig reduced w/ nifedipine, but not ISDN. None of the txs affected SBP or HR. Hospitalizations for worsening CHF occurred in 5/21 nifedipine pts and 6/23 combination pts; both were significantly greater than w/ ISDN pts 0/20. There were no sig dif between groups needing additional diuretics for worsening of CHF.	Excluded: child bearing potential, MI w/in 1-mo of study, primary valvular disease, angina, cardiomyopathy (other than dilated); & sig pulmonary, hepatic, renal, or hematological disease. CHF Causes: CAD-9, cardiomyopathy-19.
randomized, double blind, cross-over, United Kingdom, age 50 to 69 (mean 61) years, NYHA III (LVEF 25±3%), CAD[61]	Felodipine max 10 mg qd Placebo qd <15> [pts got each tx for 3-wks; doses titrated to max where tolerated]	No sig dif between the groups in HR, but felodipine pts had sig higher systemic arterial pressures and sig greater cardiac outputs than did placebo pts. Ankle circumference and body weight sig increased w/ Felodipine tx. No sig dif between groups in ETT workload intensity or total. Pt QOL assessment shows worsening w/ felodipine tx, but dif not sig. No pts withdrew.	Excluded: not listed. CHF causes: not indicated
2-mo, randomized, double blind, NYHA II or III (LVEF 40%)[62]	Amlodipine 10 mg qd Placebo qd	Symptoms and exercise time sig increased after 8-wks of amlodipine tx, compared to placebo and baseline. Amlodipine pts taking an angiotensin converting enzyme inhibitor tended to have increased LVEF (dif not sig). Plasma norepinephrine levels were sig decreased w/ amlodipine and sig increased w/ placebo.	[Abstract] Excluded: not listed. CHF causes: not indicated

C. CONGESTIVE HEART FAILURE (cont) [52-64]

39-mo, randomized, double blind 24 VAMCs, Males, mean age 63.4 yrs, NYHA II or III (LVEF 18 to 42%), cardiothoracic ratio 0.55[63,64] V-HeFT III	Felodipine ER max 5 mg bid <224> Placebo <226> [doses titrated to max if tolerated]	There was no sig dif between txs in death from all causes, worsening CHF, or number of hospitalizations. Exercise tolerance increased w/ felodipine and decreased w/ placebo tx; dif was sig at 27 mos. Felodpine LVEF was sig better than placebo only at wk-12 (+2.1% ± 7%). There was no sig dif between groups in norepinephrine levels, but both were greater than baseline. ADRs: There were no sig difs between groups in incidence of PND, orthopnea, edema, or rales. Pt quality of life assessment was sig dif from placebo at 27 months.	Excluded:all women; severe COPD; hypertrophic cardiomyopathy; long acting nitrates or 4 < sl ntg/wk; MI, CABG, angioplasty w/in 3-mos; CVA w/in 6-mos; use of beta-blockers or vasodilators (except ACE inhibitors). CHF cause: CAD-55% . 45% non-ischemic.

Changes in blood pressure are expressed as (mean change in systolic)/(mean change in diastolic), BP = blood pressure, HR = heart rate, DBP = diastolic blood pressure, SBP = systolic blood pressure, SiDBP = sitting diastolic blood pressure, SuDBP = supine diastolic blood pressure, ADR = adverse drug reaction, ATE = atenolol, NIF = nifedipine, NIC = nicardipine, ETT = exercise treadmill test, SIG = significant, DIF = difference

V. ADVERSE EFFECTS[2-21]

Relatively Common Reactions *(listed as %)*

Effect	Verap	Dilti	Bepri	Nimo	Niso	Amlo	Felo	Nifed	Israd	Nicar
Peripheral Edema	2.1	2.4-9	2	0.4-1.2	22	1.8-14.6	2.0-17.4	10-30	7.2	7.1-8
Palpitations	<1	< 1	6.5	< 1	1	0.7-4.5	0.4-2.5	7	4	3.3-4.1
Congestive Heart Failure	1.8	< 1		< 1	1			2-6.7	1	
Angina		< 1			2		1.5	1	2.4	5.6
Flushing	< 1	1.7-3		1-2.1		0.7-4.5	3.9-6.9	< 3-25	2.6	5.6-9.7
Sexual Dysfunction	< 1	< 1	2		1	1-2	1.5	3	1	+
Dyspnea/Wheezing	1.4	< 1	8.7	1.2	1	1-2	0.5-3.9	8	1.8	0.6
Cough			2		1	0.1	0.8-1.7	6	1	
Myalgia/Cramping	< 1			0.2-1.4	1	1-2	1.9	8		
Headache	2.2	2.1-12	7-13.6	1.4-4.1	22	7.3	10.6-14.7	10-23	13.7	6.4-8.2
Dizziness	3.5	1.5-7	11.6-27	< 1	5	1.1-3.4	2.7-3.7	4.1-27	7.3	4-6.9
Nervousness		< 1	7.4-11.6		1	1	1.5	7	1	0.6
Asthenia/Jitteriness	>1-1.7	1.2-5	6.5-14		1	1-2	2.2-3.9	12	1.2	0.6-5.8
Nausea	2.7	1.6-1.9	7-26	0.6-1.4	2	2.9	1.0-1.7	3.3-11	1.8	1.9-2.2
Constipation	7.3	1.6	2.8			1	0.3-1.5	3.3	1	0.6

Verap = verapamil, Dilti = diltiazem, Bepri = bepridil, Nimo = nimodipine, Niso= nisoldipine, Amlo = amlodipine, Felo = felodipine, Nifed = nifedipine, Israd = isradipine, Nicar = nicardipine

Calcium channel blockers have been shown to be generally well tolerated in clinical trials (see above). Although a wide variety of adverse reactions frequently occur, they are usually mild enough to allow patients to continue therapy. Many reactions, particularly those relating to vasodilation, are dose related.

Bepridil's package insert has an FDA mandated boxed warning relating to its proarrhythmic effect. Because of class I anti-arrhythmic properties, use has resulted in prolonged QT intervals and torsades de pointe. The FDA recommends that bepridil only be given to patients with inadequate response to other anti-anginals. [4]

Nifedipine has been used, without ill effects in severe gestational hypertension. However, all calcium channel blockers are Pregnancy Category C: Animal studies have shown them to be teratogenic and embryotoxic. Most, but not all, studies were conducted at doses higher than would be used in humans. No well-controlled studies have been conducted in pregnant women; therefore the agents should only be used when the potential benefit to the mother exceeds the risk to the fetus. [3-20]

VI. CLINICALLY SIGNIFICANT DRUG INTERACTIONS[3-21, 65]

Calcium Channel Blocker	Interacting Drug	Result
Diltiazem, Felodipine, Nisoldipine, Verapamil, Bepridil	Digitalis	↑ digitalis levels 20% to 70 %; may result in toxicity, ↑ av block, bradycardia
Verapamil	Dantrolene	Hyperkalemia and myocardial depression
Verapamil, Nifedipine	Quinidine	Hypotension, bradycardia, ventricular tachycardia, AV block or pulmonary edema
Verapamil, Diltiazem	β-blockers	Myocardial depression and/or AV node block
Diltiazem, Felodipine, Verapamil	Carbamazepine	↑ carbamazepine levels may result in toxicity; felodipine bioavailability may be reduced
Diltiazem, Nicardipine, Verapamil	Cyclosporin	↑ cyclosporin levels may result in toxicity or be used for clinical benefit
Diltiazem	Imipramine	↑ imipramine levels
Diltiazem	Lovastatin	Potential for ↑ toxicity due to marked ↑ lovastatin concentration, verapamil likely to produce similar changes; simvastatin also likely to be affected
Verapamil	Rifampin	↓ verapamil levels
Verapamil, Diltiazem	Lithium	Neurotoxicity without attendant increase in serum level

In addition to the above clinically significant reactions, there is an increased risk of hypotension when calcium channel blockers are combined with other antihypertensives.

VII. DOSING AND AVAILABILITY[2-21]

Drug	Recommended Dose	Frequency	Availability	Comments
Amlodipine	htn 2.5-10	Qd	2.5, 5, 10 mg tablets	h, j
	angina 5-10	Qd	5, 10 mg tablets	h, j
Bepridil	200-400	Qd	200, 300, 400 mg tablets	s
Diltiazem	reg 30-120	Tid	reg 30, 60, 90, 120mg tablets	w
	SR 60-180	Bid	SR 60, 90, 120mg capsules	
	TZ 120-540	Qd	TZ 120,180, 240,300,360,420mg caps	
	CD htn 180-360	Qd	CD 180, 240, 300mg capsules	
	CD angina 120-480	Qd	CD 120, 180, 240, 300mg capsules	
	XR htn 180-360	Qd	XR 180, 240mg capsules	d, w
	XR angina 120-480	Qd	XR 120, 180, 240mg capsules	d, w
Felodipine	ER 2.5-10	Qd	2.5, 5, 10mg tablets	d, h, j
Isradipine	2.5-10	Bid	2.5, 5mg capsules	h, r
Isradipine	CR 5-10	Qd	CR 5, 10mg tablets	h, r
Nicardipine	reg 20-40	Tid	reg 20, 30mg capsules	h, j, r
	SR 30-60	Bid	SR 30, 45, 60mg capsules	h, j, r
Nifedipine	reg 10-60 (angina)	Tid	reg 10, 20mg capsules	j
	XL htn 30-120	Qd	XL 30, 60, 90mg tablets	d, j
	XL angina 30-90	Qd	XL 30, 60, 90mg tablets	d, j
	CC 30-90	Qd	CC 30, 60, 90mg tablets	d, j
Nimodipine	60	q4h (21 days)	30mg capsules	h
Nisoldipine	10-60	Qd	10, 20, 30, 40mg tablets	d, f, h, j
Verapamil	reg htn 80-120	Bid - Tid	reg htn 40, 80, 120mg tablets	h, r, s
	reg angina 80-120	Tid - Qid	angina 40, 80, 120mg tablets	h, r, s
	reg arrhythmia 80-120	Tid - Qid	arrhythmia 40, 80, 120mg tablets	h, r, s
	SR 180-480	Qd (Bid > 240mg)	SR 120, 180, 240mg capsules	e, h, r, s
	VR 120-480	Qd	VR 120, 180, 240, 360mg capsules	d, h, r, s
	HS 180-480	Qd	HS 180, 240mg tablet	d, h, r, s

d=do not crush, cut, or chew;**e**=take with food;**f=**avoid administration with high fat meals;**h**=small, frail, elderly, or hepatically impaired should be started at the lowest dose;**j**=grapefruit juice should be avoided before and after dosing;**r**=adjust dose in renal failure; **s**=scored; **w**=take on an empty stomach

IX. SUMMARY OF EFFICACY AND SAFETY [66-85]

The dihydropyridines have equivalent efficacy in the management of hypertension. At optimum doses, the agents showed equivalent and satisfactory antianginal effects; however, the higher doses tended to increase the incidence of vasodilatory associated adverse effects.

Calcium channel blockers have been the focus of controversial studies involving increased mortality and cancer risks. The immediate release formulations of nifedipine, verapamil and diltiazem were associated with an increased risk of first myocardial infarction in a retrospective, case-controlled study. Short acting nifedipine was also associated with increased mortality in a dose-response meta-analysis of 16 randomized prevention trials. Because of methodology, neither study established a cause-effect relationship; however, the FDA cautioned against using immediate release nifedipine for anything other than angina. Another prospective study with co-variate risk adjustments for high mortality diseases suggests that calcium antagonists have a protective effect. However the new study may be limited because it was conducted in a racially homogenous group. An *ad hoc* subcommittee, formed by the Liaison Committee of the World Health Organisation and the International Society of Hypertension, reviewed the available evidence regarding the risk of coronary heart disease, cancer and bleeding with the calcium antagonists. They concluded that the evidence reviewed did not confirm either a beneficial or harmful effect of the calcium antagonists on coronary heart disease risk, cancer or bleeding.[66-85]

Estimated Comparative Dihydropyridines Equivalents*

Dose (mg)	**Amlodipine**	**Felodipine**	**Isradipine CR**	**Nicardipine**		**Nifedipine (long acting)**	**Nisoldipine**
Low	2.5	2.5	5	20 tid	30 bid		
Medium	5	5	10	30 tid	45 bid	30, 60	10, 20
Moderate	5,10	10			60 bid	60	30, 40
High	10	10	20			90	

Estimated Comparative Benzothiazepines Equivalents*

Dose (mg)	**Diltiazem** Regular	**Diltiazem SR**	**Diltiazem XR**	**Diltiazem CD**	**Diltiazem TZ**
Very Low	30 qid	60 bid	120	120	120
Low	60 tid	90 bid	180	180	180
Medium	60 qid	120 bid	240	240	240
Moderate	90 qid	--	--	300	300
High	120 tid	--	--	--	360, 420

***** The equivalents are estimates based upon clinical trials and should only be used as a starting point for dosing conversions.

Even though similar blood pressure lowering would be expected with formulations containing the same active ingredients in equivalent amounts, the FDA does not consider any long acting formulations therapeutically equivalent to their immediate release counter-parts or to each other. Precautions are advisable when converting a patient from one agent to another. Therapeutic equivalence is accepted among the long acting and immediate release verapamil tablets, but not to the newer long acting capsules. However, a milligram to milligram potency should be expected.

X. CRITERIA FOR FORMULARY SELECTION

- Ability to significantly lower blood pressure and reduce angina is proven in randomized, double-blind, titratable dose, parallel trials which compare one agent to another. The study should include the pharmacologically active antihypertensives at their appropriate doses. The trial should be published in a peer reviewed journal (not supplement).

- Clinically acceptable safety profile, including drug and disease interactions.

- Convenience and compliance where preference will be given to agents that allow once daily dosing without food.

- Having indicated outcomes with sufficient literature support. Priority will be given to agents studied in the VA population.

- Clinical experience in the VA population, especially currently.

- Other considerations include special care groups such as patients with CHF, angina, and proteinuria. Inventory issues will also be considered.

XI. RECOMMENDATIONS

1. The formulary should exclude agents lacking sufficient efficacy data.

2. Verapamil is the only diphenylkylamine. It generally works well in mild to moderate hypertension and is much less expensive than other calcium channel blockers. Contraindications aside, the Pharmacy Benefits Management Group (PBM) and the Medical Advisory Panel (MAP) recommends that in patients needing calcium channel blocker therapy, it should be considered a first choice agent. One regular and one sustained release formulation should be established as formulary agents.

3. Diltiazem is the only benzothiazepine derivative. All the available products work well for both hypertension and angina, but are generally more expensive than verapamil. It should be considered an alternate choice unless the patient has an atrial arrhythmia, sinus tachycardia, and/or angina or asymptomatic ischemia. An immediate and a 24-hour sustained release formulation should be established as formulary agents.

4. Nimodipine is a dihydropyridine calcium channel blocker. It's only indication is in management of subarachnoid hemorrhages. Because of its uniqueness, this agent should be made available.

5. Bepridil has FDA approval for the management of chronic angina. Because of proarrhythmic effects, bepridil should only be used in patients failing therapy with safer methods. This agent is currently under FSS contract.

6. The dihydropyridines:

   - They have equivalent efficacy in the management of hypertension. Formulary selection should be defined by the above criteria for formulary selection and by cost.

   - At least one dihydropyridine should be selected for formulary inclusion. One alternate should be available for patients failing therapy (in terms of efficacy or intolerance) with the preferred agent(s). Presently none of the dihydropyridine derivatives have the FDA indication for the treatment of congestive heart failure. Both amlodipine and felodipine have data to substantiate their safe use in patients with underlying LV dysfunction, and for the treatment of concomitant diseases. Therefore, one of these agents should be established as a formulary agent.

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