Calcium Channel Blockers

December 1997[ii]

Calcium Channel Blockers (**CCBs**) are used in the treatment of many cardiovascular conditions. Although they have generally been effective and well tolerated, recent concerns about their safety await the results of well designed, long term clinical trials currently underway.

Comparative Pharmacology

The **Non-dihydropyridine CCBs** such as **verapamil** (Isoptin®) and **diltiazem** (Cardizem®) cause less vasodilation and more cardiac depression than dihydropyridine CCBs. They have negative effects at the SA and AV nodes, and cause reductions in heart rate and contractility. Verapamil has the most pronounced negative inotropic effect. Both are used in the treatment of hypertension (HTN), angina, and supraventricular tachycardias and non-obstructive cardiomyopathy.

The **Dihydropyridine CCBs, nifedipine** (Adalat®), **felodipine** (Renedil®/Plendil®), **amlodipine** (Norvasc®), and **nicardipine** (Cardene®) have more vascular selectivity and fewer cardiac effects. They are indicated in the treatment of HTN and angina. They do not suppress AV conduction or SA node automaticity. Dihydropyridines, especially short acting nifedipine, can cause a reflex tachycardia secondary to arterial vasodilation and stimulation of the sympathetic nervous system. They also activate the renin-angiotensin system.[1]

Newer agents such as amlodipine and felodipine have a more gradual onset and a longer duration of action resulting in less severe hypotension and less reflex tachycardia. Sustained release dosage forms of nifedipine, diltiazem, and verapamil have been developed to decrease adverse effects secondary to their rapid onset and short duration of action.

Two CCBs with specialized indications include nimodipine (Nimotop®) and flunarizine (Sibelium®). Nimodipine is unique in its ability to cross into the CNS and decrease cerebral vasospasm. Although data is limited, it is used for managing aneurysmal subarachnoid hemorrhage (SAH). Flunarizine, a highly selective cerebral vasodilator, is indicated for migraine prophylaxis.

Highlights

- CCBs are considered second line agents to thiazide diuretics and β-Blockers in patients with uncomplicated HTN, largely due to lack of morbidity & mortality data.
- CCBs are the **most expensive** class of antihypertensives.
- **Short acting CCBs** (e.g. regular nifedipine) are **no longer recommended** in the management of HTN
- Newer CCBs (felodipine, amlodipine, nicardipine) have increased vascular selectivity with less cardiac depressant effects. While not indicated in the treatment of CHF, they pose less risk than previous CCBs. Amlodipine may be beneficial in patients with CHF.
- **Cost** per 30 days of long-acting CCBs for hypertension:

felodipine ER 5-10mg/od	$ **31 - 43**
nifedipine XL 30-60mg/od	$ 41 - 60
amlodipine 5-10mg/od	$ 53 - 75

- Studies raising the possibility of a link between CCBs and an ↑ **risk of MI & cancer** have **many limitations**. While caution is warranted, CCBs are considered safe and effective when used as indicated in select patients.

Hypertension

CCBs are useful in the management of HTN and are usually considered *second line* agents.[2,3] Unlike CCBs, β-blockers and thiazide diuretics have the advantage of long term studies that demonstrate reductions in morbidity and mortality. The long term effects of CCBs on morbidity and mortality await the results of ongoing trials. CCBs are alternatives for patients who do not respond adequately or are intolerant to first line agents. CCBs may be preferred in patients with atrial fibrillation with a rapid ventricular rate, vasospastic angina, or other conditions in which CCBs are effective (Table 1). CCBs are generally neutral in their effect on lipid and glucose tolerance. All four major classes of antihypertensives

(diuretics, β-blockers, ACEI, & CCBs) have shown improvements in *quality of life* (QOL).[4,5] Attempts to show differences in the QOL between these classes have been inconsistent.[5,6,7,8] Although ACEIs and CCBs are often thought to be better tolerated, the recent TOMHS study found the diuretic chlorthalidone and β-blocker acebutolol appeared to improve QOL the most.[5]

Short acting CCBs such as nifedipine capsules are <u>not</u> indicated in either the acute reduction or long term management of hypertension.[3,9,10] They have been associated with serious adverse events such as MI, stroke and death. Alternative oral antihypertensives for hypertensive urgencies include captopril (6.25-25mg po), clonidine (0.1-0.2mg po), and labetalol (200-400mg po).[11,12,13] Long acting formulations of nifedipine such as Adalat XL® or newer CCBs such as felodipine ER offer a more gradual onset of effect and are preferred when CCBs are used for HTN.[14,15]

Although CCBs are effective and usually well tolerated, they should be used with caution. Given their uncertain long term efficacy, safety risks and higher cost (Table 2), other agents such as thiazides, β-blockers, and ACEIs may be preferred.

<u>Other Uses</u>

CCBs have been useful in the treatment of a variety of conditions.(Table 1) They are alternative agents in the treatment of **chronic stable angina** in patients without contraindications, who do not respond adequately to, or tolerate, nitrates and β-blockers. Dihydropyridine CCBs, especially nifedipine, may be given in combination with β-blockers to prevent reflex tachycardia. Angina secondary to **coronary artery spasm** may respond particularly well to verapamil, diltiazem, or nifedipine where these drugs are alternatives to nitrates. CCBs are <u>not</u> usually indicated in unstable angina, where ASA, nitrates, and β-blockers have definite therapeutic advantages.

CCBs are generally contraindicated after recent MI especially if accompanied by left ventricular failure and pulmonary edema. Post infarction studies have shown increased mortality with the use of nifedipine and other dihydropyridines; verapamil and diltiazem appear to have similar detrimental results in patients with left ventricular dysfunction and are of minimal benefit in patients without heart failure. CCBs are not routinely used in patients surviving MI since beta blockers, ASA, and ACE inhibitors have demonstrated greater clinical benefits.[16]

<u>Adverse Effects</u>

Although generally well tolerated, CCBs side effect profiles differ according to class and dosage form. Older dihydropyridines (nifedipine, nicardipine) cause significant headache, flushing, tachycardia and peripheral edema. Newer long acting dihydropyridines (nifedipine XL, felodipine, amlodipine) have a lower incidence of these side effects due in part to a more gradual onset of action.

Verapamil and diltiazem can cause bradycardia in patients with pre-existing heart block or those patients receiving β-blockers. They are usually contraindicated in patients with left ventricular dysfunction.

Some patients may experience **withdrawal reactions** such as angina, upon discontinuation of therapy. To minimize this risk, CCBs should be tapered gradually especially in high risk patients .[17]

Grapefruit juice may significantly affect the metabolism of CCBs possibly due to its inhibition of the isoenzyme CYP 3A4. The interaction is greatest with felodipine where bioavailability may be 2-3 times greater than when taken with water.[18] Several other CCBs show a similar interaction, but to a lesser extent: e.g. nifedipine (~33%), verapamil (~33%), amlodipine (~16%).[19] There is significant individual variation in the extent of the "grapefruit effect" and avoiding grapefruit juice is recommended for patients taking these agents. Orange juice is not associated with this interaction.

(Other contraindications, precautions and drug-interactions are listed in Tables 3 and 4.)

<u>Current Issues & Controversies</u>

Risk of MI: Concerns have arisen over CCB use in hypertension and a possible increase in the risk of MI.[20,21,22] Studies to date have had many limitations, been inconclusive, and await better designed clinical trials which are currently underway. Short acting CCBs (e.g. nifedipine caps) should be avoided in routine hypertensive management.

Cancer: One prospective cohort study in the elderly found a dose related increase in the risk of cancer in patients taking CCBs.[23] The controversy has grown with other investigators suggesting there is no increase in risk.[24]

Heart Failure (HF): CCBs are generally contraindicated in HF due to negative inotropic effects as well as undesirable stimulation of the sympathetic nervous system and renin-angiotensin system.[25] One study (PRAISE) found that amlodipine was safe in patients with severe HF, and of possible benefit in patients with <u>nonischemic dilated cardiomyopathy</u>.[26] Other studies are in progress to evaluate what, if any, role the newer CCBs have in HF.

Bleeding: Preliminary evidence indicates a possible association of bleeding with the CCBs.[27,28] At present

there is not enough information to fully evaluate this effect. Health Canada is currently collecting and evaluating data.

References available on request

The Rx Files: Calcium Channel Blockers
Supplementary Tables

Table 1

Other Potential Clinical Uses of CCBs[29]

- esophageal disorders {diltiazem may ↑ esophageal sphincter pressure (ESP) and is beneficial in conditions such as systemic scleroderma; in contrast, nifedipine ↓ ESP}[30]
- migraine prophylaxis
- panic attack prevention
- Raynaud's phenomenon
- perniosis (inflammatory cutaneous lesions secondary to cold environment)
- tardive dyskinesia
- thyrotoxicosis, symptomatic control
- Tourette's syndrome
- fetal tachycardia

Table 2

Comparative Cost For 30 Days Treatment With Commonly Used Antihypertensives

hydrochlorothiazide 12.5-25mg po daily	$8.00
atenolol 50mg po daily	$ 20.00
acebutolol 200mg po bid	$ 25.00
lisinopril 10mg po daily	$ 36.00
enalapril 10mg po daily	$ 42.00
enalapril 5mg po bid	$ 64.00
felodipine ER 10mg po daily	$ 43.00
diltiazem CD 180mg po daily	$ 50.00

Table 3

Contraindications and Precautions

Contraindications

- **Pregnancy** - FDA category C: animal studies show teratogenic and embryocidal effects
- **Severe hypotension** (SBP<90 mm)
- **Recent MI** with LVF or pulmonary edema
- **Sick sinus syndrome or 2nd/3rd degree AV block** - avoid use of CCBs with negative inotropic effects unless a ventricular pacemaker is in place

Precautions

- **Breastfeeding** - excreted in breast milk but no reported problems in humans
- **Pediatrics** - not officially approved in this age group
- **Geriatrics** - due to reduced drug elimination, initial doses should be low and titrated slowly to reduce side effects

Table 4

Drug Interactions[31]

Anticonvulsants

- enzyme inducers such as phenobarb, phenytoin, and carbamazepine may ↑ metabolism of CCBs resulting in ↓ CCB efficacy; this effect is highly variable but felodipine appears to be the most affected

⇒ adjust CCB dose as required

Beta-blockers

- verapamil and diltiazem add to beta blockers' effect on cardiac conduction while all CCBs enhance their hypotensive effects
- CCBs may also ↑conc. of β-blockers due to ↓ metabolism

⇒ monitor for enhanced effects such as severe hypotension, bradycardia, precipitation/exacerbation of angina, arrhythmia, or heart failure; reduce dose or discontinue as required

Cimetidine

- may ↑ CCB conc. due to ↓ metabolism and ↑ bioavailability secondary to ↑ gastric pH; ranitidine and famotidine have less effect on metabolism

⇒ monitor for enhanced CCB effects and reduce dose as required

Carbamazepine, Cyclosporine, Quinidine

- verapamil and diltiazem ↓ metabolism of these drugs resulting in ↑ conc. and potential toxicity

⇒ monitor levels and reduce dose as required

Digoxin

- verapamil, and to a lesser extent, diltiazem ↓ elimination of digoxin resulting in ↑ conc. and potential toxicity

⇒ monitor digoxin levels and reduce dose as required; consider alternate CCB

⇒ as both verapamil and diltiazem, and digoxin slow AV conduction, monitor for AV block and excessive bradycardia during first weeks of concurrent therapy

Disopyramide

- should not be administered 48 hrs before or 24 hrs after verapamil due to potentiated negative inotropic effect

Ethanol

- verapamil ↓ metabolism of ETOH resulting in increased and prolonged intoxication
- ETOH may ↑ felodipine levels requiring dose reduction

Grapefruit Juice

- decreases metabolism of most CCBs, especially felodipine.

⇒ grapefruit juice should be avoided in patients on dihydropyridine CCBs and verapamil.

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