Calcium Channel Blockers

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Key Points and Practical Recommendations

- Calcium channel blockers, which dilate arteries by reducing calcium flux into cells, effectively lower blood pressure, especially in combination with other drugs, and some formulations of agents of this class are approved for treating angina or cardiac dysrhythmias.
- Calcium channel blockers reduce blood pressure across all patient groups, regardless of sex, race/ethnicity, age, and dietary sodium intake.
- Nondihydropyridine calcium channel blockers are more negatively chronotropic and inotropic than the dihydropyridine subclass, which is important for patients with cardiac dysrhythmias or who need β-blockers.
- Extensive experience in comparative randomized trials indicates that an initial calcium antagonist can prevent all major types of cardiovascular disease, except heart failure (for which a diuretic is superior). Initial dihydropyridine calcium channel blockers have not reduced the rate of progression of renal disease as well as inhibitors of the renin-angiotensin system, although members of the nondihydropyridine subclass can reduce albuminuria.
- High doses of dihydropyridine calcium channel blockers often cause edema, headache, flushing and tachycardia; high doses of verapamil can cause constipation. Diltiazem and verapamil have important drug interaction with digoxin and cyclosporine, among others. *J Clin Hypertens (Greenwich).* 2011;13:687–689. ©2011 Wiley Periodicals, Inc.

CELLULAR MECHANISM OF ACTION

Calcium channel blockers (CCBs) inhibit the flow of extracellular calcium through ion-specific channels that span the cell wall. Although several types of such channels have been identified, currently available CCBs inhibit the L-type channels in humans. When inward calcium flux is inhibited, vascular smooth muscle cells relax, resulting in vasodilation and a lowering of blood pressure (BP). In cardiac muscle, contractility is reduced and the sinus pacemaker and atrioventricular conduction velocities are slowed.[1]

SUBTYPES OF CCBS

Although many CCBs that share a dihydropyridine chemical structure and most pharmacologic effects have been developed as a group, they differ in important ways from the two ''nondihydropyridine'' compounds that are currently available (Table).[2] Drugs in these two subclasses bind to separate sites on the L-type calcium channel, so there is a pharmacologic rationale for their combination, especially for diltiazem and a dihydropyridine.

PHARMACOLOGIC PROFILES OF CCBS

All CCBs are peripheral arterial dilators. Dihydropyridines with short elimination half-lives typically cause reflex tachycardia (an adverse effect that has been largely mitigated by sustained-release preparations). Verapamil has more negative chronotropic effects than diltiazem, an effect that makes each useful for acute intravenous treatment and chronic prevention of atrial dysrhythmias. Both also are associated with negative inotropic effects, verapamil perhaps more than diltiazem. In the kidney, CCBs produce natriuresis by increasing renal blood flow, dilating afferent arterioles, and increasing glomerular filtration pressure. Nondihydropyridine CCBs reduce albuminuria by improving glomerular permselectivity and/or by lowering renal perfusion pressure.

FDA-APPROVED INDICATIONS FOR CCBS

With the exception of nimodipine (which was originally developed for treating hypertension, but is approved only for subarachnoid hemorrhage), all CCBs have been approved by the Food and Drug Administration (FDA) for lowering BP, alone or in combination with other antihypertensive drugs. All guideline committees consider CCBs a viable *option* for first-line treatment of hypertension.[3] In the United Kingdom, CCBs are recommended as initial therapy for black patients and those older than 55 years,[4] whereas in the United States and Canada, a diuretic is instead recommended for ''most'' patients.[3] Some CCBs have been approved for chronic stable angina and/or variant (Prinzmetal's) angina (Table). Some formulations of verapamil or diltiazem have been approved for treatment of atrial dysrhythmias.

CCBs are approved for marketing in the United States in combination with several other classes of drugs including: angiotensin-converting enzyme (ACE)

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TABLE. Calcium Channel Blockers

Name	Half-life, h	Dose, mg/times per day	Affect LV function	Market, %	Approved by FDA for	Major Outcome-Based Hypertension Trials
Verapamil	6–8	80–120/2	–	~8%	Hypertension, angina, atrial dysrhythmias	VHAS, CONVINCE,[10] INVEST[11]
(Calan, Isoptin)	12–24	80–480/1				
(Calan SR, Isoptin SR, Verelan)	24	180–300/1				
(Covera-HS, Verelan-PM)						
Diltiazem	6–8	30–90/3	–	~11%	Hypertension, angina, atrial dysrhythmias	NORDIL[12]
(Cardizem)	8–12	120–180/2				
(Cardizem SR, Tiazac, others)	18–24	120–480/1				
(Cardizem CD, Cartia XT, others)	24	120–540/1				
(Cardizem LA)						
Nifedipine	0.2–1	10–20/4–6	–	~5%	Hypertension, angina	INSIGHT,[13] STONE
(Procardia, Adalat)	24 (?)	30–120/1				
(Procardia XL, Adalat CC)						
Nicardipine	6–8	20–30/3	–	Small	Hypertension	NICS-EH
(Cardene)	8–12	30–60/2				
(Cardene SR)						
Isradipine	8–12	2.5–5/2	– or ±	Small	Hypertension	MIDAS
(DynaCirc)	12–18	5–10/1		Small		
(DynaCirc CR)						
Felodipine	11–16	2.5–10/1	± or 0	~3%	Hypertension	HOT,[14] FEVER[15] (second-line)
(Plendil)						
Amlodipine	44+	2.5–10/1	± or 0	~71%	Hypertension, angina	AASK,[8] IDNT,[9] ALLHAT,[5] VALUE, ASCOT,[16] CASE-J, ACCOMPLISH[17] (combination)
(Norvasc)						
Nisoldipine	7–12	10–40/1	– or ±	~2%	Hypertension	ABCD
(Sular)						
Clevidipine	0.25	1–2 mg/h, intravenously only	±	Tiny	Hypertensive emergencies	Reflex tachycardia, hypotension
(Cleviprex)						
Nimodipine	1–2	30/4–6	–	Tiny	Subarachnoid hemorrhage	Metabolized by CYP3A4; not approved for hypertension!
(generic only in United States after October 2009)						

Abbreviations: AASK, African American Study of Kidney Diseases and Hypertension; ABCD, Appropriate Blood Pressure Control in Diabetes; ACCOMPLISH, Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension; ALLHAT, Antihypertensive and Lipid Lowering to Prevent Heart Attack Trial; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; CASE-J, candesartan antihypertensive survival evaluation in Japan; CONVINCE, Controlled Onset Verapamil Investigation of Cardiovascular Endpoints; CYP3A4, 3A4 Isoform Of Hepatic Cytochrome P_{450} Enzyme System; FEVER, Felodipine Event Reduction; HOT, Hypertension Optimal Treatment Study; IDNT, Irbesartan Diabetic Nephropathy Trial; INSIGHT, International Nifedipine (Gastrointestinal Therapeutic System) Study: Intervention as a Goal in Hypertension Treatment; INVEST, International Verapamil-Sustained Release/Trandolapril Trial; MIDAS, Multicenter Isradipine Diuretic Atherosclerosis Study; NICS-EH, National Intervention Cooperative Study In Elderly Hypertensives; NORDIL, Nordic Diltiazem; STONE, Shanghai Trial of Nifedipine in the Elderly; VALUE, Valsartan Antihypertensive Long-Term Use Evaluation; VHAS, Verapamil Hypertension Atherosclerosis Study.

inhibitors, angiotensin receptor blockers, a renin inhibitor, and a statin.

OFF-LABEL USES FOR CCBS

CCBs have been studied in many other diseases. They may be beneficial in conditions involving peripheral vasospasm (Raynaud's phenomenon, migraine and cluster headaches, high-altitude pulmonary edema, and even premature labor). Hypertension associated with cyclosporine, nonsteroidal anti-inflammatory drugs, or widened pulse pressure is often improved by CCBs. Although a large clinical trials evidence base exists, no CCB is FDA-approved for prevention of cardiovascular or renal end points.

CONTRAINDICATIONS, ADVERSE EFFECTS, AND DRUG INTERACTIONS OF CCBS

All CCBs are contraindicated in patients who are allergic to any component of a given preparation. Verapamil and diltiazem are contraindicated in patients with hypotension, sick sinus syndrome (unless a permanent pacemaker is in place), second- or third-degree

atrioventricular block, and patients with atrial flutter or atrial fibrillation and an accessory bypass tract (eg, Wolff-Parkinson-White or Lown-Ganong-Levine syndromes). In addition, verapamil is contraindicated in patients with severe left ventricular dysfunction, whereas diltiazem is contraindicated in patients with acute myocardial infarction and pulmonary congestion on x-ray.

CCBs are generally not recommended for patients with, or at high risk for, heart failure due to reduced left ventricular function. When added to other therapies, long-acting dihydropyridine compounds did not significantly alter prognosis of patients with heart failure.[5] An initial diuretic was significantly more effective in preventing heart failure than any other drug class, including a CCB.[6,7] CCBs are generally not used alone in patients with renal disease. For example, amlodipine was inferior to an ACE inhibitor in preventing the decline in renal function in nondiabetic African Americans with hypertensive nephrosclerosis[8] and to an angiotensin receptor blocker in patients with hypertension and type 2 diabetic nephropathy.[9]

Common adverse effects of CCBs include edema, flushing, headache, dizziness, constipation (particularly with high-dose verapamil), nausea, rash, and drowsiness.

CCBs have many important drug interactions. Verapamil and diltiazem increase digoxin levels. Verapamil, diltiazem, and nicardipine increase plasma levels and decrease the dosing requirement for cyclosporine. Verapamil and diltiazem are metabolized by CYP3A4, therefore inducers (eg, rifampin) and inhibitors (eg, erythromycin, cimetidine) are likely to result in decreased and increased plasma levels of these two CCBs, respectively. Concomitantly administered grapefruit juice elevates the oral bioavailability of felodipine, nifedipine, nicardipine, nisoldipine, and verapamil. Because of their shared negative effects on heart rate and myocardial contractility, β-blockers and verapamil are not used simultaneously.

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