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DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

3 – Calcium channel blockers

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> *"Calcium antagonists have assumed a major role in the treatment of patients with hypertension or coronary heart disease."*
>
> *Abernethy and Schwartz, 1999[1]*
>
> *"There are none of the widely trumpeted dangers from dihydropyridine calcium channel blockers."*
>
> *Kaplan, 2003, commenting on the results of ALLHAT[2]*

Calcium channel blockers (CCBs; calcium antagonists) act chiefly by vasodilation and reduction of the peripheral vascular resistance. They remain among the most commonly used agents for hypertension and angina. Their major role in these conditions is now well understood, based on the results of a series of large trials. CCBs are a heterogeneous group of drugs that can chemically be classified into the dihydropyridines (DHPs) and the non-DHPs (Table 3-1), their common pharmacologic property being selective inhibition of L-type channel opening in vascular smooth muscle and in the myocardium (Fig. 3-1). Distinctions between the DHPs and non-DHPs are reflected in different binding sites on the calcium channel pores, and in the greater vascular selectivity of the DHP agents.[3] In addition, the non-DHPs, by virtue of nodal inhibition, reduce the heart rate (heart rate–lowering [HRL] agents). Thus verapamil and diltiazem more closely resemble the β-blockers in their therapeutic spectrum with, however, one major difference: CCBs are contraindicated in heart failure.

Table 3-1 -- Binding Sites for CCBs, Tissue Specificity, Clinical Uses, and Safety Concerns

Site	Tissue Specificity	Clinical Uses	Contraindications	Safety Concerns
DHP Binding				
Prototype: nifedipine Site 1	Vessels > myocardium > nodes Vascular selectivity 10× N, A 100× Nic, I, F 1000× Nis	Effort angina (N, A) Hypertension (N,* A, Nic, I, F, Nis) Vasospastic angina (N, A) Raynaud phenomenon	Unstable angina, early phase AMI, systolic heart failure (possible exception: amlodipine)	Nifedipine capsules: excess BP fall especially in older adults; adrenergic activation in ACS Longer acting forms: safe in hypertension, no studies on ACS
Non-DHP Binding				
"Heart rate lowering" Site 1B, D Site 1C, V	SA and AV nodes > myocardium = vessels	Angina: effort (V, D), unstable (V), vasospastic (V, D) Hypertension (D,*V) Arrhythmias, supraventricular (D,[†] V) Verapamil: postinfarct patients (no US license)	Systolic heart failure; sinus bradycardia or SSS; AV nodal block; WPW syndrome; acute myocardial infarction (early phase)	Systolic heart failure, especially diltiazem. Safety record of verapamil may equal that of β-blockade in older adult patients with hypertension

FDA-approved drugs for listed indications in parentheses.

A, Amlodipine; *ACS,* acute coronary syndrome; *AMI,* acute myocardial infarction; *AV,* atrioventricular; *BP,* blood pressure; *CCB,* calcium channel blocker; *D,* diltiazem; *DHP,* dihydropyridine; *F,* felodipine; *FDA,* Food and Drug Administration; *I,* isradipine; *N,* nifedipine; *Nic,* nicardipine; *Nis,* nisoldipine; *SA,* sinoatrial; *SSS,* sick sinus syndrome; *V,* verapamil; *WPW,* Wolff-Parkinson-White syndrome.

* Long-acting forms only.

† Intravenous forms only.

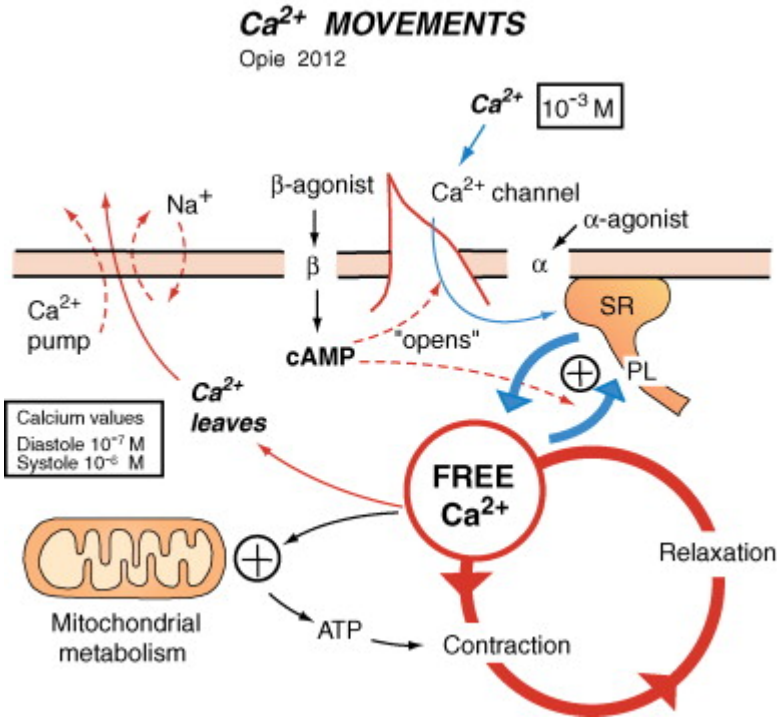

Figure 3-1 Role of calcium channel in regulating myocardial cytosolic calcium ion movements. *α,* alpha-adrenergic receptor; *β,* beta-adrenergic receptor; *cAMP,* cyclic adenosine monophosphate; *P,* phospholamban; *SR,* sarcoplasmic reticulum.
(Figure © L.H. Opie, 2012.)

Pharmacologic properties

Calcium channels: L and T types

The most important property of all CCBs is selectively to inhibit the inward flow of charge-bearing calcium ions when the calcium channel becomes permeable or is "open." Previously, the term *slow channel* was used, but now it is realized that the calcium current travels much faster than previously believed, and that there are at least two types of calcium channels, the L and T. The conventional long-lasting opening calcium channel is termed the *L-type channel,* which is blocked by CCBs and increased in activity by catecholamines. The function of the L-type is to admit the substantial amount of calcium ions required for initiation of contraction via calcium-induced calcium release from the sarcoplasmic reticulum (see Fig. 3-1). The T-type (*T* for transient) channel opens at more negative potentials than the L-type. It plays an important role in the initial depolarization of sinus and atrioventricular (AV) nodal tissue and is relatively upregulated in the failing myocardium. Currently there are no specific T-type blockers clinically available.

Cellular mechanisms: β-blockade versus CCBS

Both these categories of agents are used for angina and hypertension, yet there are important differences in their subcellular mode of action. Both have a negative inotropic effect, whereas only CCBs relax vascular and (to a much lesser extent) other smooth muscle (Fig. 3-2). CCBs "block" the entry of calcium through the calcium channel in both smooth muscle and myocardium, so that less calcium is available to the contractile apparatus. The result is vasodilation and a negative inotropic effect, which in the case of the DHPs is usually modest because of the unloading effect of peripheral vasodilation.

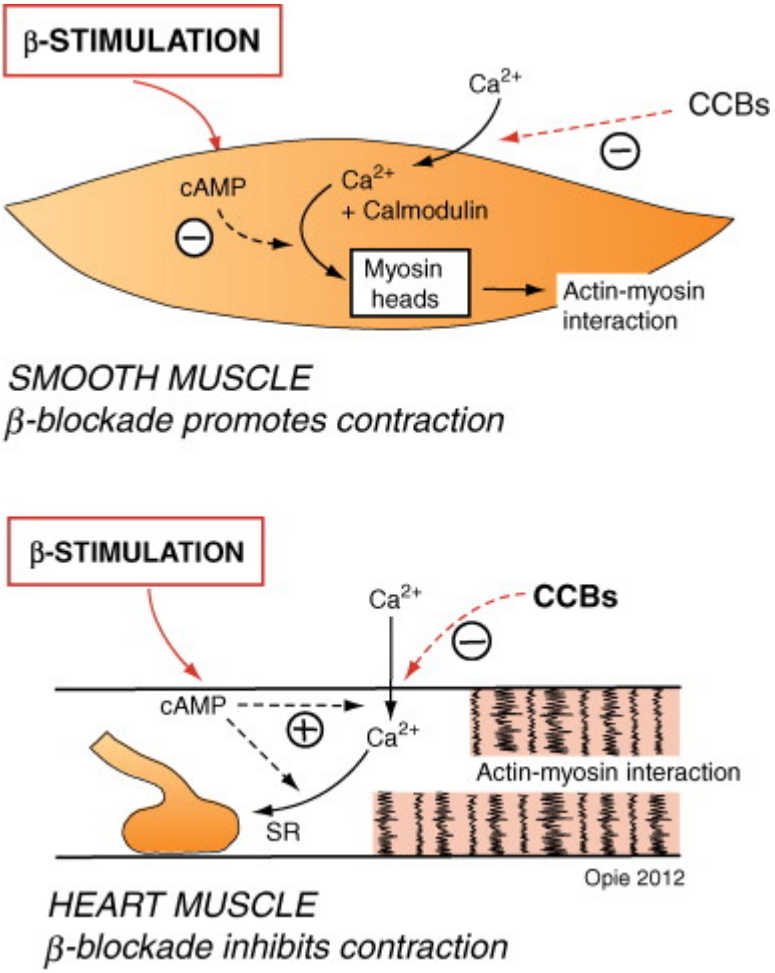

Figure 3-2 Proposed comparative effects of β-blockade and calcium channel blockers (CCBs) on smooth muscle and myocardium. The opposing effects on vascular smooth muscle are of critical therapeutic importance. *cAMP,* Cyclic adenosine monophosphate; *SR,* sarcoplasmic reticulum.
(Figure © L.H. Opie, 2012.)

CCBs inhibit vascular contraction.

In smooth muscle (see Fig. 3-2), calcium ions regulate the contractile mechanism independently of troponin C. Interaction of calcium with calmodulin forms calcium-calmodulin, which then stimulates myosin light chain kinase (MLCK) to phosphorylate the myosin light chains to allow actin-myosin interaction and, hence, contraction. Cyclic adenosine monophosphate (AMP) inhibits the MLCK. In contrast, β-blockade, by lessening the formation of cyclic AMP, removes the inhibition on MLCK activity and therefore promotes contraction in smooth muscle, which explains why asthma may be precipitated, and why the peripheral vascular resistance often rises at the start of β-blocker therapy (Fig. 3-3).

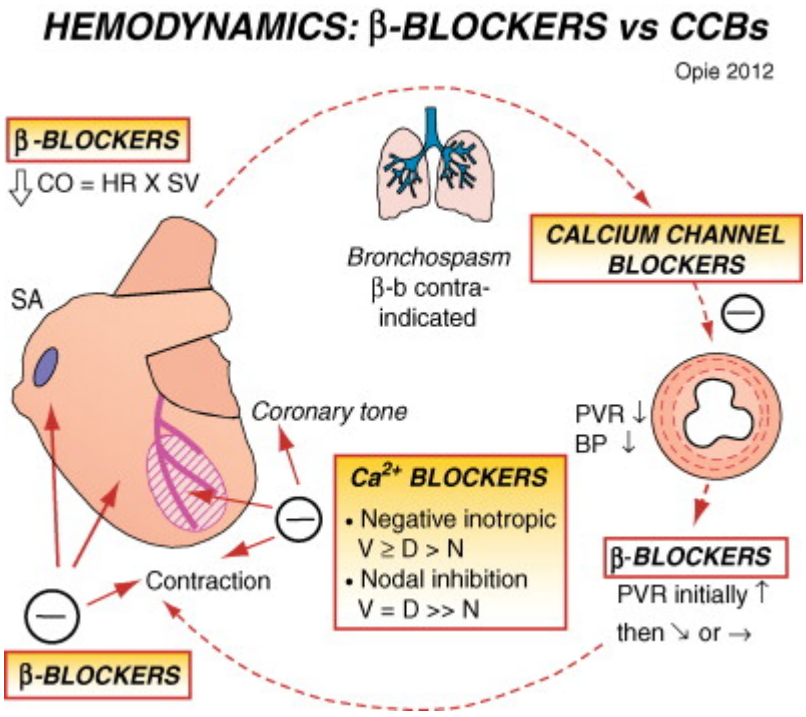

Figure 3-3 Comparison of hemodynamic effects of β-blockers and of CCBs, showing possibilities for combination therapy. *BP,* blood pressure; *CO,* cardiac output; *D,* diltiazem; *HR,* heart rate; *N,* nifedipine as an example of dihydropyridines; *PVR,* peripheral vascular resistance; *SA,* sinoatrial node; *SV,* stroke volume; *V,* verapamil.
(Figure © L.H. Opie, 2012.)

CCBs versus β-blockers.

CCBs and β-blockers have hemodynamic and neurohumoral differences. Hemodynamic differences are well defined (see Fig. 3-3). Whereas β-blockers inhibit the renin-angiotensin system by decreasing renin release and oppose the hyperadrenergic state in heart failure, CCBs as a group have no such inhibitory effects.[4] This difference could explain why β-blockers but not CCBs are an important component of the therapy of heart failure.

CCBs and carotid vascular protection.

Experimentally, both nifedipine and amlodipine give endothelial protection and promote formation of nitric oxide. Furthermore, several CCBs including amlodipine, nifedipine, and lacidipine have inhibitory effects on carotid atheromatous disease.[5],[6] Similar protective effects have not consistently been found with β-blockers. There is increasing evidence that such vascular protection may be associated with improved clinical outcomes.

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Classification of calcium channel blockers

Dihydropyridines

The DHPs all bind to the same sites on the α_1-subunit (the N sites), thereby establishing their common property of calcium channel antagonism (Fig. 3-4). To a different degree, they exert a greater inhibitory effect on vascular smooth muscle than on the myocardium, conferring the property of vascular selectivity (see Table 3-1, Fig. 3-5). There is nonetheless still the potential for myocardial depression, particularly in the case of agents with less selectivity and in the presence of prior myocardial disease or β-blockade. For practical purposes, effects of DHPs on the sinoatrial (SA) and AV nodes can be ignored.

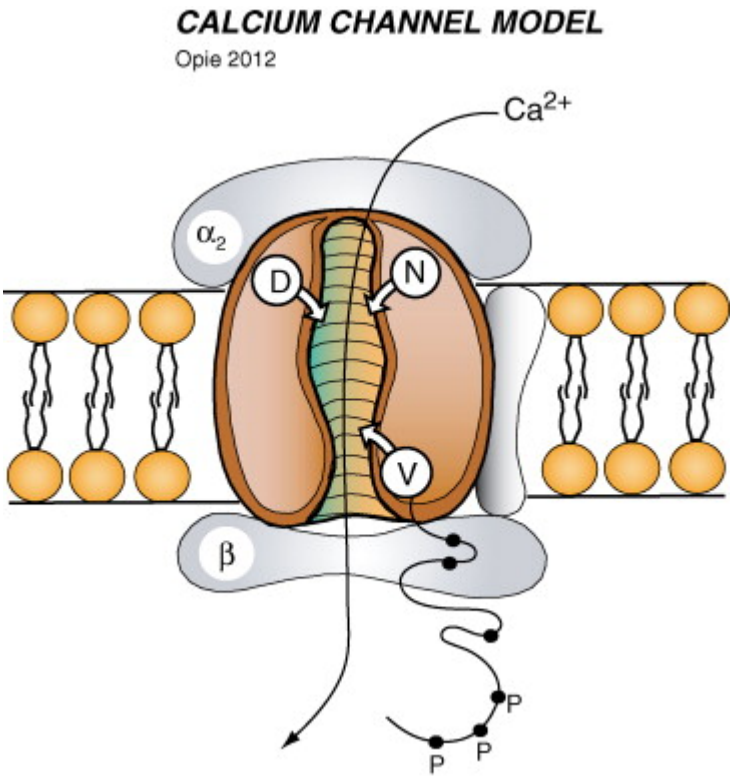

Figure 3-4 Proposed molecular model of calcium channel α1-subunit with binding sites for nifedipine (N), diltiazem (D), and verapamil (V). It is thought that all dihydropyridines bind to the same site as nifedipine. Amlodipine has additional subsidiary binding to the V and D sites. *P* indicates sites of phosphorylation in response to cyclic adenosine monophosphate (see Fig. 3-1), which acts to increase the opening probability of the calcium channel.
(Figure © L.H. Opie, 2012.)

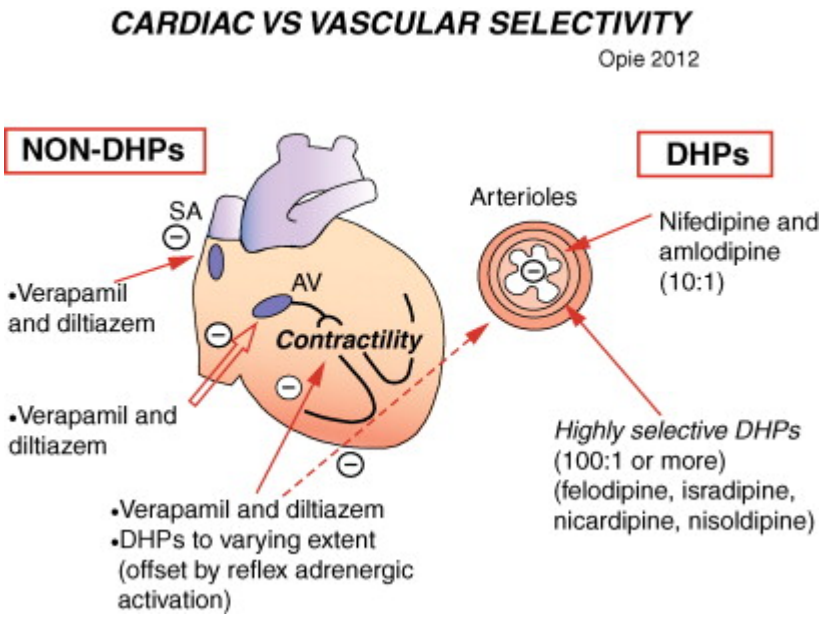

Figure 3-5 As a group, the dihydropyridines (DHPs) are more vascular selective, whereas the non-DHPs verapamil and diltiazem act equally on the heart and on the arterioles. *AV,* Atrioventricular; *SA,* sinoatrial.
(Figure © L.H. Opie, 2012.)

Nifedipine was the first of the DHPs. In the short-acting capsule form, originally available, it rapidly vasodilates to relieve severe hypertension and to terminate attacks of coronary spasm. The peripheral vasodilation and a rapid drop in blood pressure (BP) led to rapid reflex adrenergic activation with tachycardia (Fig. 3-6). Such proischemic effects probably explain why the short-acting DHPs in high doses have precipitated serious adverse events in unstable angina. The inappropriate use of short-acting nifedipine can explain much of the adverse publicity that once surrounded the CCBs as a group,[7] so that the focus has now changed to the long-acting DHPs, which are free of such dangers.[2]

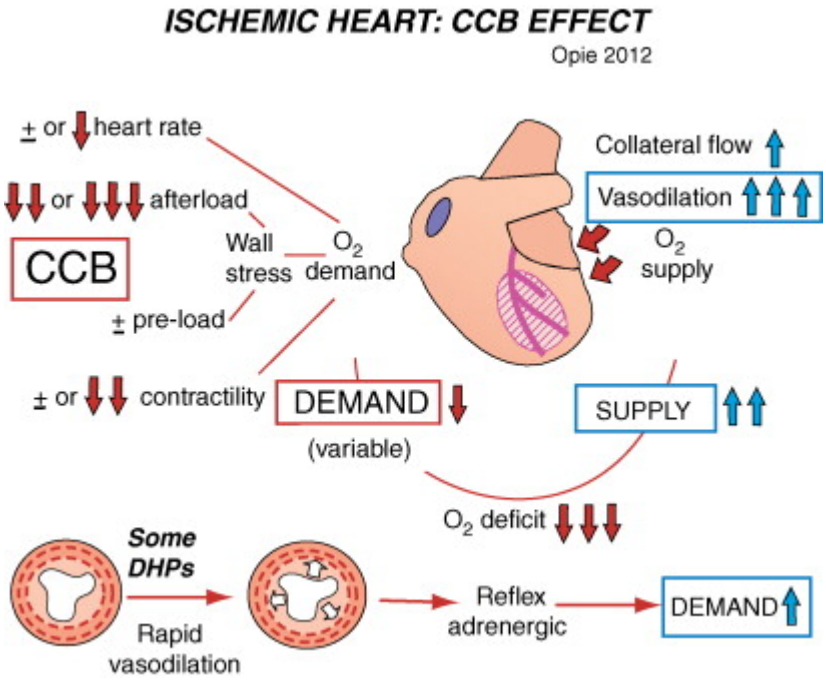

Figure 3-6 Mechanisms of antiischemic effects of calcium channel blockers. Note that the rapid arteriolar vasodilation resulting from the action of some short-acting dihydropyridines (DHPs) may increase myocardial oxygen demand by reflex adrenergic stimulation. *CCB,* Calcium channel blocker.

(Figure © L.H. Opie, 2012.)

Hence, the introduction of truly long-acting compounds, such as amlodipine or the extended-release formulations of nifedipine (GITS, XL, CC) and of others such as felodipine and isradipine, has led to substantially fewer symptomatic side effects. Two residual side effects of note are headache, as for all arteriolar dilators, and ankle edema, caused by precapillary dilation. There is now much greater attention to the appropriate use of the DHPs, with established safety and new trials in hypertension such as ACCOMPLISH suggesting a preeminent place for initial dual therapy by DHP and CCBs with an angiotensin-converting enzyme (ACE) inhibitor.[8],[9]

Nondihydropyridines: Heart rate–lowering agents

Verapamil and diltiazem bind to two different sites on the α_1-subunit of the calcium channel (see Fig. 3-4), yet have many properties in common with each other. The first and most obvious distinction from the DHPs is that verapamil and diltiazem both act on nodal tissue, being therapeutically effective in supraventricular tachycardias. Both tend to decrease the sinus rate. Both inhibit myocardial contraction more than the DHPs or, put differently, are less vascular selective (see Fig. 3-5). These properties, added to peripheral vasodilation, lead to substantial reduction in the myocardial oxygen demand. Such “oxygen conservation” makes the HRL agents much closer than the DHPs to the β-blockers, with which they share some similarities of therapeutic activity. Two important exceptions are (1) the almost total lack of effect of verapamil and diltiazem on standard types of ventricular tachycardia, which rather is a contraindication to their use; and (2) the benefits of β-blockade in heart failure, against which the HRL agents are also clearly contraindicated. The salient features for the clinical use of these agents is shown in Table 3-2.

Table 3-2 -- Oral Heart Rate–Lowering CCBs: Salient Features for Cardiovascular Use

Agent	Dose	Pharmacokinetics and Metabolism	Side Effects and Contraindications	Kinetic and Dynamic Interactions
Verapamil				
Tablets (for IV use, see p. 78)	180-480 mg daily in two or three doses (titrated)	Peak plasma levels with 1-2 h. Low bioavailability (10%-20%), high first-pass metabolism to long-acting norverapamil Excretion: 75% renal; 25% GI; t½ 3-7 h	Constipation; depression of SA, AV nodes, and LV; CI sick sinus syndrome, digoxin toxicity, excess β-blockade, LV failure; obstructive cardiomyopathy	Levels ↑ in liver or renal disease. Hepatic interactions; inhibits CYP3A4, thus decreases breakdown of atorvastatin, simvastatin, lovastatin/St. John’s wort reduces plasma verapamil. Digoxin levels increased.
Slow release (SR) Verelan (Ver) Covera-HS (timed)	As above, two doses (SR) Single dose (Ver) Single bedtime dose	Peak effects: SR 1-2h, Ver 7-9h, t½ 5-12 h Co-delayed 4- to 6-h release	As above	As above
Diltiazem				
Tablets (for IV use see p. 79)	120-360 mg daily in three or four doses	Onset: 15-30 min. Peak: 1-2 h; t½ 5 h. Bioavailable 45% (hepatic). Active metabolites. 65% GI loss.	As for verapamil, but no constipation	As for verapamil, except little or no effect on digoxin levels, liver interactions less prominent. Cimetidine and liver disease increase blood levels. Propranolol

Agent	Dose	Pharmacokinetics and Metabolism	Side Effects and Contraindications	Kinetic and Dynamic Interactions
				levels increased.
Prolonged SR, CD, XR Tiazac	As above, 1 (XR, CD, Tiazac) or 2 doses	Slower onset, longer t½, otherwise similar	As above	As above

AV, Atrioventricular; *CCB,* calcium channel blocker; *CI,* confidence intervals; *GI,* gastrointestinal; *IV,* intravenous; *LV,* left ventricular; *SA,* sinoatrial; *SR,* slow release; *t½,* plasma elimination half-life; *Ver,* Verelan.

For supraventricular tachycardias, a frequency-dependent effect is important, so that there is better access to the binding sites of the AV node when the calcium channel pore is “open.” During nodal reentry tachycardia, the channel of the AV node opens more frequently and the drug binds better, and hence specifically inhibits the AV node to stop the reentry path.

Regarding side effects, the non-DHPs, being less active on vascular smooth muscle, also have less vasodilatory side effects than the DHPs, with less flushing or headaches or pedal edema (see later, Table 3-4). Reflex tachycardia is uncommon because of the inhibitory effects on the SA node. Left ventricular (LV) depression remains the major potential side effect, especially in patients with preexisting congestive heart failure (CHF). Why constipation occurs only with verapamil of all the CCBs is not known.

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Major indications for CCBs

Stable effort angina.

Common to the effects of all types of CCBs is the inhibition of the L-calcium current in arterial smooth muscle, occurring at relatively low concentrations (see Table 3-2). Hence coronary vasodilation is a major common property (see Fig. 3-3). Although the antianginal mechanisms are many and varied, the shared effects are (1) coronary vasodilation and relief of exercise-induced vasoconstriction, and (2) afterload reduction resulting from BP reduction (see Fig. 3-6). In addition, in the case of verapamil and diltiazem, slowing of the sinus node with a decrease in exercise heart rate and a negative inotropic effect probably contribute (Fig. 3-7).

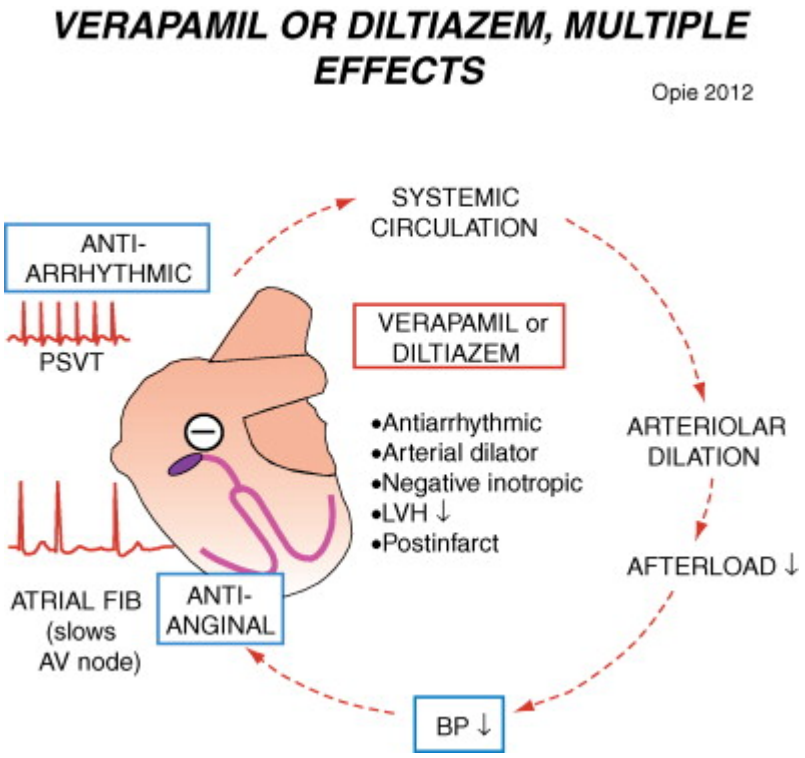

Figure 3-7 Verapamil and diltiazem have a broad spectrum of therapeutic effects. *Atrial fib,* Atrial fibrillation; *AV,* atrioventricular; *BP,* blood pressure; *LVH,* left ventricular hypertrophy; PSVT, paroxysmal supraventricular tachycardia.
(Figure © L.H. Opie, 2012.)

Unstable angina at rest.

Of the major CCBs, *only verapamil* has a license for unstable angina, although intravenous diltiazem has one good supporting study.[10] Importantly the DHPs should not be used without concurrent β-blockade (risk of reflex adrenergic activation, see Fig. 3-6).

Coronary spasm.

The role of spasm as a major cause of the anginal syndromes has undergone revision. Once seen as a major contributor to transient ischemic pain at rest, coronary spasm is now relatively discounted because

β-blockade was more effective than nifedipine in several studies.[11] The role of coronary spasm in unstable angina has also been downplayed because nifedipine, in the absence of concurrent β-blockade, appeared to be harmful.[12] Coronary spasm remains important as a cause of angina precipitated by cold or hyperventilation, and in Prinzmetal's variant angina. All CCBs should be effective. Among those specifically licensed are verapamil and amlodipine.

Hypertension.

CCBs are excellent antihypertensive agents, among the best for older adult and black patients (see Chapter 7). Overall, they are at least as effective as other antihypertensive classes in treating CHD and more effective than others in preventing stroke.[13] Furthermore, they are almost as good as other classes in preventing heart failure. Their effect is largely independent both of sodium intake, possibly because of their mild diuretic effect, and of the concurrent use of antiinflammatory agents such as nonsteroidal antiinflammatory drugs. In hypertension with nephropathy, both DHPs and non-DHPs reduce the BP, which is the primary aim, but non-DHPs reduce proteinuria better.[14]

Supraventricular tachycardia.

Verapamil and diltiazem inhibit the AV node, which explains their effect in supraventricular tachycardias. Nifedipine and other DHPs are clinically ineffective.

Postinfarct protection.

Although β-blockers are drugs of choice, both verapamil and diltiazem give some protection in the absence of prior LV failure. Verapamil is better documented.[15],[16]

Vascular protection.

Increased nitric oxide formation in cultured endothelial cells[17] and improved endothelial function in patients[18] may explain why CCBs slow down carotid atherosclerosis,[6] which in turn may be explain decreased stroke.[19] In CAMELOT, amlodipine slowed coronary atheroma and reduced cardiovascular events more than enalapril.[20]

Safety and efficacy

The ideal cardiovascular drug is both efficacious in reducing hard end points, such as mortality, stroke, and myocardial infarction (MI), and safe. Safety, which is not generally well defined, may be regarded as the absence of significant adverse effects when the drug is used with due regard for its known contraindications. In the case of CCBs, previous controversy regarding both efficacy and safety has been laid to rest by new studies that strongly and beyond doubt support the safety of long-acting CCBs.[21-25]

Safety and efficacy in ischemic heart disease.

In stable effort angina, imperfect evidence based on randomized controlled trials and a metaanalysis suggests equivalent safety and efficacy of CCBs (other than short-acting nifedipine) to β-blockers. Nonetheless, CCBs remain underused in stable effort angina, especially in the United States.[26] The largest angina trial, ACTION, found that adding long-acting nifedipine to existing β-blocker therapy in effort angina decreased new heart failure and the need for coronary angiography.[27] In unstable angina, a small trial supports the use of diltiazem.[10] There are no data to back the use of DHPs in unstable angina.[12] In postinfarct follow-up, β-blockers remain the agents of choice, with the non-DHP HRL agents (especially verapamil) the second choice if β-blockers are contraindicated or not tolerated. DHPs lack good evidence for safety and efficacy in post-MI patients.

In hypertension, seven large outcome trials in which more than 50,000 patients received long-acting DHPs, often amlodipine, provide overwhelming proof of the safety and efficacy of these CCBs. Verapamil-based therapy had similar effects on coronary disease with hypertension to therapy based on atenolol in the INVEST trial, the primary end-points being all-cause deaths, nonfatal MI, or nonfatal stroke.[25] In diabetic hypertensives long-acting DHPs are also able to improve outcome.[28],[29] In ALLHAT, amlodipine gave similar results in the diabetic and nondiabetic subgroups.[30] These findings make it difficult to agree with the view that CCBs have adverse effects in diabetics, in whom the major issue is adequate BP reduction. In fact, diabetes may rather be a positive indication for preferential use of a CCB.[31] Cancer, bleeding, and increased all-cause mortality, once incorrectly proposed as serious and unexpected side effects of the CCBs, are now all discounted.[2],[30]

Verapamil

Verapamil (Isoptin, Calan, Verelan), the prototype non-DHP agent, remains the CCB with the most licensed indications. Both verapamil and diltiazem have multiple cardiovascular effects (see Fig. 3-7).

Electrophysiology.

Verapamil inhibits the action potential of the upper and middle regions of the AV node where depolarization is calcium mediated. Verapamil thus inhibits one limb of the reentry circuit, believed to underlie most paroxysmal supraventricular tachycardias (see Fig. 8-4). Increased AV block and the increase in effective refractory period of the AV node explain the reduction of the ventricular rate in atrial flutter and fibrillation. Verapamil is ineffective and harmful in the treatment of ventricular tachycardias except in certain uncommon forms. Hemodynamically, verapamil combines arteriolar dilation with a direct negative inotropic effect (see Table 3-2). The cardiac output and LV ejection fraction do not increase as expected following peripheral vasodilation, which may be an expression of the negative inotropic effect. At rest, the heart only drops modestly with a greater inhibition of exercise-induced tachycardia.

Pharmacokinetics and interactions.

Oral verapamil takes 2 hours to act and peaks at 3 hours. Therapeutic blood levels (80 to 400 ng/mL) are seldom measured. The elimination half-life is usually 3 to 7 hours, but increases significantly during chronic administration and in patients with liver or advanced renal insufficiency. Despite nearly complete absorption of oral doses, bioavailability is only 10% to 20%. There is a high first-pass liver metabolism by multiple components of the P-450 system, including CYP 3A4, the latter explaining why verapamil increases blood levels of several statins such as atorvastatin, simvastatin, and lovastatin, as well as ketoconazole. Because of the hepatic CYP3A4 interaction, the Food and Drug Administration (FDA) warns that the10-mg dose of simvastatin should not be exceeded in patients taking verapamil. Ultimate excretion of the parent compound, as well as the active hepatic metabolite norverapamil, is 75% by the kidneys and 25% by the gastrointestinal (GI) tract. Verapamil is 87% to 93% protein bound, but no interaction with warfarin has been reported. When both verapamil and digoxin are given together, their interaction causes digoxin levels to rise, probably as a result of a reduction in the renal clearance of digoxin. Norverapamil is the long-acting hepatic metabolite of verapamil, which appears rapidly in the plasma after oral administration of verapamil and in concentrations similar to those of the parent compound; like verapamil, norverapamil undergoes delayed clearance during chronic dosing.

Verapamil doses.

The usual total oral daily dose is 180-360 mg daily, no more than 480 mg given once or twice daily (long-acting formulations) or three times daily for standard short-acting preparations (see Table 3-2). Large differences of pharmacokinetics among individuals mean that dose titration is required, so that 120 mg daily may be adequate for those with hepatic impairment or for older adults. During chronic oral dosing, the formation of norverapamil metabolites and altered rates of hepatic metabolism suggest that less frequent or smaller daily doses of short-acting verapamil may be used.[32] For example, if verapamil has been given at a dose of 80 mg three times daily, then 120 mg twice daily should be as good. Lower doses are required in older adult patients or those with advanced renal or hepatic disease or when there is concurrent β-blockade. Intravenous verapamil is much less used for supraventricular arrhythmias since the advent of adenosine and the ultra–short acting β-blocker, esmolol.

Slow-release preparations.

Calan SR or Isoptin SR releases the drug from a matrix at a rate that responds to food, whereas Verelan releases the drug from a rate-controlling polymer at a rate not sensitive to food intake. The usual doses are 240 to 480 mg daily. The SR preparations are given once or twice daily and Verelan once daily. A

controlled-onset, extended-release tablet (Covera-HS; COER-24; 180 or 240 mg tablets) is taken once daily at bed time, with the (unproven) aim of lessening adverse cardiovascular events early next morning.

Outcome studies.

Verapamil was the antihypertensive equivalent of atenolol in hypertension, with coronary artery disease (CAD) regarding major outcomes with three extra benefits: less new diabetes, less angina, and less psychological depression.[25]

Side effects.

Class side effects are those of vasodilation causing headaches, facial flushing, and dizziness. These may be lessened by the long-acting preparations, so that in practice they are often not troublesome. Tachycardia is not a side effect. Constipation is specific and causes most trouble, especially in older adult patients. Rare side effects may include pain in the gums, facial pain, epigastric pain, hepatotoxicity, and transient mental confusion. In older adults, verapamil may predispose to GI bleeding.[21]

Contraindications to verapamil

(Fig. 3-8, Table 3-3). Contraindications, especially in the intravenous therapy of supraventricular tachycardias are sick sinus syndrome; preexisting AV nodal disease; excess therapy with β-blockade, digitalis, quinidine, or disopyramide; or myocardial depression. In the Wolff-Parkinson-White (WPW) syndrome complicated by atrial fibrillation, intravenous verapamil is contraindicated because of the risk of anterograde conduction through the bypass tract (see Fig. 8-14). Verapamil is also contraindicated in ventricular tachycardia (wide QRS-complex) because of excess myocardial depression, which may be lethal. An exception to this rule is exercise-induced ventricular tachycardia. Myocardial depression, if secondary to the supraventricular tachycardia, is not a contraindication, whereas preexisting LV systolic failure is. Dose reduction may be required in hepatic or renal disease (see “Pharmacokinetics and Interactions” earlier in this chapter).

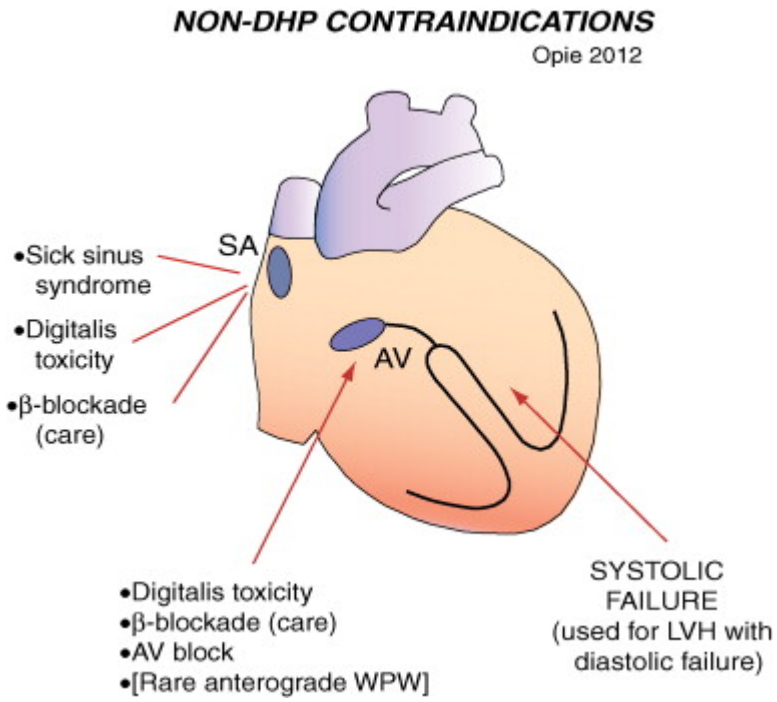

Figure 3-8 Contraindications to verapamil or diltiazem. For use of verapamil and diltiazem in patients already receiving β-blockers, see text. *AV,* Atrioventricular; *LVH,* left ventricular hypertrophy; *SA,* sinoatrial; *WPW,* Wolff-Parkinson-White preexcitation syndrome.
(Figure © L.H. Opie, 2012.)

Table 3-3 -- Comparative Contraindications of Verapamil, Diltiazem, Dihydropyridines, and β-Adrenergic Blocking Agents

Contraindications	Verapamil	Diltiazem	DHPs	β-Blockade
Absolute				
Severe sinus bradycardia	0/+	0/+	0	++
Sick sinus syndrome	++	++	0	++
AV conduction defects	++	++	0	++
WPW syndrome	++	++	0	++
Digoxin toxicity, AV block*	++	++	0	++
Asthma	0	0	0	+++
Bronchospasm	0	0	0	0/++
Heart failure	+++	+++	++	Indicated
Hypotension	+	+	++	+
Coronary artery spasm	0	0	0	+
Raynaud and active peripheral vascular disease	0	0	0	+
Severe mental depression	0	0	0	+
Severe aortic stenosis	+	+	++	+
Obstructive cardiomyopathy	0/+	0/+	++	Indicated
Relative				
Insulin resistance	0	0	0	Care
Adverse blood lipid profile	0	0	0	Care
Digoxin nodal effects	Care	Care	0	Care
β-blockade	Care	Care	BP↓	—
Disopyramide therapy	Care	Care	0	Care
Unstable angina	Care	Care	++	0
Postinfarct protection	May protect	0 (+ if no LVF)	++	Indicated

AV, Atrioventricular; *DHP,* dihydropyridine; *FDA,* Food and Drug Administration; *LVF,* left ventricular failure; *WPW,* Wolff-Parkinson-White syndrome.

+++ = Absolutely contraindicated; ++ = strongly contraindicated; + = relative contraindication; 0 = not contraindicated.

“Indicated” means judged suitable for use by author (L.H. Opie), not necessarily FDA approved.

* Contraindication to rapid intravenous administration

Drug interactions with verapamil

β-blockers.

Verapamil by intravenous injection is now seldom given, so that the potentially serious interaction with preexisting β-adrenergic blockade is largely a matter of history. Depending on the dose and the state of the sinus node and the myocardium, the combination of oral verapamil with a β-blocker may be well tolerated or not. In practice, clinicians can often safely combine verapamil with β-blockade in the therapy of angina pectoris or hypertension, provided that due care is taken (monitoring for heart rate and heart block). In older adults, prior nodal disease must be excluded. For hypertension, β-blocker plus verapamil works well, although heart rate, AV conduction, and LV function may sometimes be adversely affected. To avoid any hepatic pharmacokinetic interactions, verapamil is best combined with a hydrophilic β-blocker such as atenolol or nadolol, rather than one that is metabolized in the liver, such as metoprolol, propranolol, or carvedilol.

Digoxin.

Verapamil inhibits the digoxin transporter, P-glycoprotein, to increase blood digoxin levels, which is of special relevance when both are used chronically to inhibit AV nodal conduction. In digitalis toxicity, rapid intravenous verapamil is absolutely contraindicated because it can lethally exaggerate AV block. There is no reason why, in the absence of digitalis toxicity or AV block, oral verapamil and digoxin should not be combined (checking the digoxin level). Whereas digoxin can be used for heart failure with atrial fibrillation, verapamil is negatively inotropic and should not be used.

Antiarrhythmics.

The combined negative inotropic potential of verapamil and disopyramide is considerable. Co-therapy with flecainide may also give added negative inotropic and dromotropic effects.

Statins.

Verapamil inhibits the hepatic CYP3A isoenzyme, and therefore potentially increases the blood levels of atorvastatin, simvastatin, and lovastatin, which are all metabolized by this isoenzyme.[21]

Other agents.

Phenobarbital, phenytoin, and rifampin induce the cytochrome systems metabolizing verapamil so that its blood levels fall. Conversely, verapamil inhibits hepatic CYP3A to increase blood levels of cyclosporin, carbamazepine (Tegretol) and theophylline, as mentioned in the package insert. This inhibition is also expected to increase blood levels of ketoconazole and sildenafil. Cimetidine has variable effects. Alcohol levels increase. Verapamil may sensitize to neuromuscular blocking agents, and to the effects of lithium (neurotoxicity).

Therapy of verapamil toxicity.

There are few clinical reports on management of verapamil toxicity. Intravenous calcium gluconate (1 to 2 g) or half that dose of calcium chloride, given over 5 minutes, helps when heart failure or excess hypotension is present. If there is an inadequate response, positive inotropic or vasoconstrictory catecholamines (see Chapter 5, p. 180) are given, or else glucagon. An alternative is hyperinsulinemic-euglycemic therapy.[33] Intravenous atropine (1 mg) or isoproterenol is used to shorten AV conduction. A pacemaker may be needed.

Clinical indications for verapamil

Angina.

In chronic stable effort angina, verapamil acts by a combination of afterload reduction and a mild negative inotropic effect, plus reduction of exercise-induced tachycardia and coronary vasoconstriction. The heart rate usually stays the same or falls modestly. In a major outcome study in patients with CAD with hypertension, INVEST, verapamil-based therapy was compared with atenolol-based therapy, the former supplemented by the ACE inhibitor trandolapril, and the latter by a thiazide if required to reach the BP goal.[25] Major outcomes were very similar but verapamil-based therapy gave less angina and new diabetes. Verapamil doses of 240 to 360 mg daily were the approximate equivalent of atenolol 50-100 mg daily. In unstable angina at rest with threat of infarction, verapamil has not been tested against placebo, although licensed for this purpose in the United States. In Prinzmetal's variant angina therapy is based on CCBs, including verapamil, and high does may be needed.[34] Abrupt withdrawal of verapamil may precipitate rebound angina.

Hypertension.

Verapamil is approved for mild to moderate hypertension in the United States. Besides the outcome study in CAD with hypertension (preceding section), in a long-term, double-blind comparative trial, mild to moderate hypertension was adequately controlled in 45% of patients given verapamil 240 mg daily,[35] versus 25% for hydrochlorothiazide 25 mg daily, versus 60% for the combination. Higher doses of verapamil might have done even better. Combinations can be with diuretics, β-blockers, ACE inhibitors, angiotensin receptor blockers (ARBs), or centrally acting agents. During combination with α-blockers, a hepatic interaction may

lead to excess hypotension.

Verapamil for supraventricular arrhythmias.

Verapamil is licensed for the prophylaxis of repetitive supraventricular tachycardias, and for rate control in chronic atrial fibrillation when given with digoxin (note interaction). For acute attacks of supraventricular tachycardias, when there is no myocardial depression, a bolus dose of 5 to 10 mg (0.1 to 0.15 mg/kg) given over 2 minutes restores sinus rhythm within 10 minutes in 60% of cases (package insert). However, this use is now largely supplanted by intravenous adenosine (see Fig. 8-7). When used for uncontrolled atrial fibrillation but with caution if there is a compromised LV failure, verapamil may safely be given (0.005 mg/kg/min, increasing) or as an intravenous bolus of 5 mg (0.075 mg/kg) followed by double the dose if needed. In atrial flutter, AV block is increased. In all supraventricular tachycardias, including atrial flutter and fibrillation, the presence of a bypass tract (WPW syndrome) contraindicates verapamil.

Other uses for verapamil.

In hypertrophic cardiomyopathy, verapamil has been the CCB best evaluated. It is licensed for this purpose in Canada. When given acutely, it lessens symptoms, reduces the outflow tract gradient, improves diastolic function, and enhances exercise performance by 20% to 25%. Verapamil should not be given to patients with resting outflow tract obstruction. No long-term, placebo-controlled studies with verapamil are available. In retrospective comparisons with propranolol, verapamil appeared to decrease sudden death and gave better 10-year survival.[36] The best results were obtained by a combination of septal myectomy and verapamil. A significant number of patients on long-term verapamil develop severe side effects, including SA and AV nodal dysfunction, and occasionally overt heart failure.

Atypical ventricular tachycardia.

Some patients with exercise-induced ventricular tachycardia caused by triggered automaticity may respond well to verapamil, as may young patients with idiopathic right ventricular outflow tract ventricular tachycardia (right bundle branch block and left axis deviation). However, verapamil can be lethal for standard wide complex ventricular tachycardia, especially when given intravenously. Therefore, unless the diagnosis is sure, verapamil must be avoided in ventricular tachycardia.

For postinfarct protection, verapamil is approved in the United Kingdom and in Scandinavian countries when β-blockade is contraindicated. Verapamil 120 mg three times daily, started 7 to 15 days after the acute phase in patients without a history of heart failure and no signs of CHF (but with digoxin and diuretic therapy allowed) was protective and decreased reinfarction and mortality by approximately 25% over 18 months.[15]

In intermittent claudication, carefully titrated verapamil increased maximum walking ability.[37]

Summary.

Among CCBs, verapamil has the widest range of approved indications, including all varieties of angina (effort, vasospastic, unstable), supraventricular tachycardias, and hypertension. Indirect evidence suggests good safety, but nonetheless with risks of heart block and heart failure. Compared with atenolol in hypertension with CAD, there was less new diabetes, fewer anginas, and less psychological depression. Verapamil combined with β-blockade runs the risk of heart block; thus a DHP with β-blockade is much better.

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Diltiazem

Although molecular studies show different channel binding sites for diltiazem and verapamil (see Fig. 3-4), in clinical practice they have somewhat similar therapeutic spectra and contraindications, so that they are often classified as the non-DHPs or HRL agents (see Fig. 3-5). Clinically, diltiazem is used for the same spectrum of disease as is verapamil: angina pectoris, hypertension, supraventricular arrhythmias, and rate control in atrial fibrillation or flutter (see Fig. 3-7). Of these, diltiazem is approved in the United States to treat angina (effort and vasospastic) and hypertension, with only the intravenous form approved for supraventricular tachycardias and for acute rate control. Diltiazem has a low side-effect profile, similar to or possibly better than that of verapamil; specifically the incidence of constipation is much lower (Table 3-4). On the other hand, verapamil is registered for more indications. Is diltiazem less a cardiodepressant than verapamil? There are no strictly comparable clinical studies to support this clinical impression.

Table 3-4 -- Reported Side Effects of the Three Prototypical CCBs and Long-Acting Dihydropyridines

	Verapamil Covera-HS (%)	Diltiazem Short-Acting (%)	Diltiazem XR or CD (%)	Nifedipine Capsules* (%)	Nifedipine XL, CC, GITS (%)	Amlodipine 10 mg (%)	Felodipine ER 10 mg (%)
Facial flushing	<1	0-3	0-1	6-25	0-4	3	5
Headaches	< placebo	4-9	< placebo	3-34	6	< placebo	4
Palpitation	0	0	0	Low-25	0	4	1
Lightheadedness, dizziness	5	6-7	0	12	2-4	2	4
Constipation	12	4	1-2	0	1	0	0
Ankle edema, swelling	0	6-10	2-3	6	10-30	10	14
Provocation of angina	0	0	0	Low-14	0	0	0

Data from Opie LH. Clinical use of calcium antagonist drugs. Boston: Kluwer; 1990, p. 197, and from package inserts.

CCB, Calcium channel blocker.

Side effects are dose related; no strict direct comparisons between the CCBs. Percentages are placebo-corrected.

* No longer used in the United States.

Pharmacokinetics.

Following oral administration of diltiazem, more than 90% is absorbed, but bioavailability is approximately 45% (first-pass hepatic metabolism). The onset of action of short-acting diltiazem is within 15 to 30 minutes (oral), with a peak at 1 to 2 hours. The elimination half-life is 4 to 7 hours; hence, dosage every 6 to 8 hours of the short-acting preparation is required for sustained therapeutic effect. The therapeutic plasma concentration range is 50 to 300 ng/mL. Protein binding is 80% to 86%. Diltiazem is acetylated in the liver to deacyldiltiazem (40% of the activity of the parent compound), which accumulates with chronic therapy. Unlike verapamil and nifedipine, only 35% of diltiazem is excreted by the kidneys (65% by the GI tract). Because of the hepatic CYP3A4 interaction, the FDA warns that the10-mg dose of simvastatin should not

be exceeded in patients taking diltiazem.

Diltiazem doses.

The dose of diltiazem is 120 to 360 mg, given in four daily doses of the short-acting formulation or once or twice a day with slow-release preparations. Cardizem SR permits twice-daily doses. For once-daily use, Dilacor XR is licensed in the United States for hypertension and Cardizem CD and Tiazac for hypertension and angina. Intravenous diltiazem (Cardizem injectable) is approved for arrhythmias but not for acute hypertension. For acute conversion of paroxysmal supraventricular tachycardia, after exclusion of WPW syndrome (see Fig. 8-14) or for slowing the ventricular response rate in atrial fibrillation or flutter, it is given as 0.25 mg/kg over 2 minutes with electrocardiogram and BP monitoring. If the response is inadequate, the dose is repeated as 0.35 mg/kg over 2 minutes. Acute therapy is usually followed by an infusion of 5 to 15 mg/hr for up to 24 hrs. Diltiazem overdose is treated as for verapamil (see p. 77).

Side effects.

Normally side effects of the standard preparation are few and limited to headaches, dizziness, and ankle edema in approximately 6% to 10% of patients (see Table 3-4). With high-dose diltiazem (360 mg daily), constipation may also occur. When the extended-release preparation is used for hypertension, the side-effect profile resembles placebo. Nonetheless, bradycardia and first-degree AV block may occur with all diltiazem preparations. In the case of intravenous diltiazem, side effects resemble those of intravenous verapamil, including hypotension and the possible risk of asystole and high-degree AV block when there is preexisting nodal disease. In postinfarct patients with preexisting poor LV function, mortality is increased by diltiazem, not decreased. Occasionally, severe skin rashes such as exfoliative dermatitis are found.

Contraindications.

Contraindications resemble those of verapamil (see Fig. 3-8, Table 3-3): preexisting marked depression of the sinus or AV node, hypotension, myocardial failure, and WPW syndrome. Postinfarct LV failure with an ejection fraction of less than 40% is a clear contraindication.[38]

Drug interactions and combinations.

Unlike verapamil, the effect of diltiazem on the blood digoxin level is often slight or negligible. As in the case of verapamil, there are the expected hemodynamic interactions with β-blockers. Nonetheless, diltiazem plus β-blocker may be used with care for angina watching for excess bradycardia or AV block or hypotension. Diltiazem may increase the bioavailability of oral propranolol perhaps by displacing it from its binding sites (package insert). Occasionally diltiazem plus a DHP is used for refractory coronary artery spasm, the rationale being that two different binding sites on the calcium channel are involved (see Fig. 3-4). Diltiazem plus long-acting nitrates may lead to excess hypotension. As in the case of verapamil, but probably less so, diltiazem may inhibit CYP3A cytochrome, which is expected to increase blood levels of cyclosporin, ketoconazole, carbamazepine (Tegretol), and sildenafil.[21] Conversely, cimetidine inhibits the hepatic cytochrome system breaking down diltiazem to increase circulating levels.

Clinical uses of diltiazem

Ischemic syndromes.

The efficacy of diltiazem in chronic stable angina is at least as good as propranolol, and the dose is titrated from 120 to 360 mg daily (see Table 3-2). In unstable angina at rest, there is one good albeit small study showing that intravenous diltiazem (not licensed for this purpose in the United States) gives better pain relief than does intravenous nitrate, with improved 1-year follow up.[10] In Prinzmetal's variant angina, diltiazem 240 to 360 mg/day reduces the number of episodes of pain.

Diltiazem for hypertension.

In the major long-term outcome study on more than 10,000 patients, the Nordic Diltiazem (NORDIL) trial, diltiazem followed by an ACE inhibitor if needed to reach BP goals was as effective in preventing the primary combined cardiovascular endpoint as treatment based on a diuretic, a β-blocker, or both.[39] In the smaller multicenter VA study, diltiazem was the best among five agents (atenolol, thiazide, doxazosin, and

captopril) in reducing BP, and was especially effective in older adult white patients and in black patients.[40] Nonetheless, reduction of LV hypertrophy was poor at 1 year of follow-up, possibly because a short-acting diltiazem formulation was used.[41]

Antiarrhythmic properties of diltiazem.

The main electrophysiologic effect is a depressant one on the AV node; the functional and effective refractory periods are prolonged by diltiazem, so that diltiazem is licensed for termination of an attack of supraventricular tachyarrhythmia and for rapid decrease of the ventricular response rate in atrial flutter or fibrillation. Only intravenous diltiazem is approved for this purpose in the United States (see “Diltiazem Doses” earlier in this chapter). Oral diltiazem can be used for the elective as well as prophylactic control (90 mg three times daily) of most supraventricular tachyarrhythmias (oral diltiazem is not approved for this use in the United States or United Kingdom). WPW syndrome is a contraindication to diltiazem.

Cardiac transplantation.

Diltiazem acts prophylactically to limit the development of posttransplant coronary atheroma, independently of any BP reduction.[42]

Summary.

Diltiazem, with its low side-effect profile, has advantages in the therapy of angina pectoris, acting by peripheral vasodilation, relief of exercise-induced coronary constriction, a modest negative inotropic effect, and sinus node inhibition. There are no outcome studies comparing diltiazem and verapamil. As in the case of verapamil, combination with β-blockade is generally not advised.

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Nifedipine, the first DHP

The major actions of the DHPs can be simplified to one: arteriolar dilation (see Fig. 3-5). The direct negative inotropic effect is usually outweighed by arteriolar unloading effects and by reflex adrenergic stimulation (see Fig. 3-6), except in patients with heart failure.

Short-acting capsular nifedipine was first introduced in Europe and Japan as Adalat, and then became the best-selling Procardia in the United States. In angina, it was especially used for coronary spasm, which at that time was thought to be the basis of unstable angina. Unfortunately not enough attention was paid to three important negative studies,[12],[43],[44] which led to warnings against use in unstable angina in previous editions of this book. Capsular nifedipine is now only the treatment of choice when taken intermittently for conditions such as attacks of vasospastic angina or Raynaud phenomenon.

Long-acting nifedipine formulations

The rest of this section largely focuses on long-acting nifedipine formulations (Procardia XL in the United States, Adalat LA elsewhere; Adalat CC) that are now widely used in the treatment of hypertension, in effort angina, and in vasospastic angina.

Pharmacokinetics.

Almost all circulating nifedipine is broken down by hepatic metabolism by the cytochrome P-450 system to inactive metabolites (high first-pass metabolism) that are largely excreted in the urine. The long-acting, osmotically sensitive tablet (nifedipine GITS, marketed as Procardia XL or Adalat LA) releases nifedipine from the inner core as water enters the tablet from the GI tract (see Table 3-2). This process results in stable blood therapeutic levels of approximately 20 to 30 ng/mL over 24 hours. With a core-coat system (Adalat CC), the blood levels over 24 hours are more variable, with the trough-peak ratios of 41% to 91%.

Doses of nifedipine.

In effort angina, the usual daily dose 30 to 90 mg of Procardia XL or Adalat LA (Adalat CC is not licensed in the United States for angina). Dose titration is important to avoid precipitation of ischemic pain in some patients. In cold-induced angina or in coronary spasm, the doses are similar and capsules (in similar total daily doses) allow the most rapid onset of action. In hypertension, standard doses are 30 to 90 mg once daily of Procardia XL or Adalat CC. In older adults or in patients with severe liver disease, doses should be reduced.

Contraindications and cautions

(Fig. 3-9, Table 3-5). These are tight aortic stenosis or obstructive hypertrophic cardiomyopathy (danger of exaggerated pressure gradient), clinically evident heart failure or LV dysfunction (added negative inotropic effect), unstable angina with threat of infarction (in the absence of concurrent β-blockade), and preexisting hypotension. Relative contraindications are subjective intolerance to nifedipine and previous adverse reactions. In pregnancy, nifedipine should only be used if the benefits are thought to outweigh the risk of embryopathy (experimental; pregnancy category C, see Table 12-10).

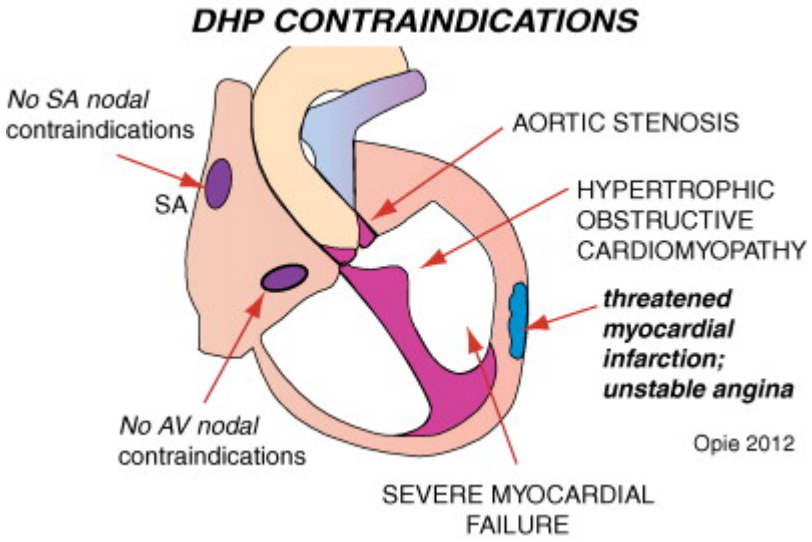

Figure 3-9 Contraindications to dihydropyridines (DHPs) are chiefly obstructive lesions such as aortic stenosis or hypertrophic obstructive cardiomyopathy, and heart failure. Unstable angina (threatened infarction) is a contraindication unless combined nifedipine plus β-blockade therapy is used or unless (rarely) coronary spasm is suspected. *AV,* Atrioventricular; *SA,* sinoatrial. *(Figure © L.H. Opie, 2012.)*

Table 3-5 -- Long-Acting Dihydropyridines for Oral Use

Agent	Dose and Major Trials	Pharmacokinetics and Metabolism	Side Effects and Contraindications	Interactions and Precautions
Amlodipine (Norvasc, Istin)	5-10 mg once daily (ALLHAT, VALUE, ASCOT)	t_{max} 6-12 h. Extensive but slow hepatic metabolism, 90% inactive metabolites; 60% renal; t½ 35-50 h. Steady state in 7-8 days	Edema, dizziness, flushing, palpitation. CI: severe aortic stenosis, obstructive cardiomyopathy, LVF, unstable angina AMI. May use amlodipine in CHF class 2 or 3, but best avoided.	Prolonged t½ up to 56 h in liver failure. Reduce dose, also in older adults and in patients with heart failure. Hepatic metabolism via CYP3A4, interaction with simvastatin (do not exceed 20 mg simvastatin, FDA recommendation), atorvastatin and lovastatin. Grapefruit juice: caution, interaction not established.
Nifedipine prolonged release XL, LA, GITS, Adalat CC; Procardia XL	30-90 mg once daily (INSIGHT, ACTION)	Stable 24-h blood levels. Slow onset, approximately 6 h.	S/E: headache, ankle edema. CI: severe aortic stenosis, obstructive cardiomyopathy, LVF. Unstable angina if no β-blockade	Added LV depression with β-blockade. Avoid in unstable angina without β-blockade. Nifedipine via CYP 3A4 interacts with simvastatin (limit simvastatin to 20 mg) and probably atorvastatin, lovastatin. Cimetidine and liver disease increase blood levels.
Felodipine ER (Plendil)	5-10 mg once daily (HOT)	t_{max}, 3-5 h. Complete hepatic metabolism (P-450) to inactive metabolites 75% renal loss, t½ 22-27 h	Edema, headache, flushing. CI as above except for CHF class 2 and 3 (mortality neutral).	Reduce dose with cimetidine, age, liver disease. Anticonvulsants enhance hepatic metabolism; grapefruit juice decreases CYP3A4 and markedly increases blood felodipine.

AMI, Acute myocardial infarction; *CHF,* congestive heart failure; *CI*, confidence intervals; *FDA,* Food and

Drug Administration; *LV,* left ventricular; *LVF,* left ventricular failure; *S/E,* side effect; *t1/2,* plasma elimination half-life; t_{max}, time to peak blood level.

Minor side effects.

The bilateral ankle edema caused by nifedipine is distressing to patients but is not due to cardiac failure; if required, it can be treated by dose reduction, by conventional diuretics, or by an ACE inhibitor. Nifedipine itself has a mild diuretic effect. With extended-release nifedipine preparations (Procardia XL), the manufacturers claim that side effects are restricted to headache (nearly double that found in controls) and ankle edema (dose-dependent, 10% with 30 mg daily, 30% with 180 mg daily). The low incidence of acute vasodilatory side effects, such as flushing and tachycardia, is because of the slow rate of rise of blood DHP levels.

Severe or rare side effects.

In patients with LV dysfunction, the direct negative inotropic effect can be a serious problem. Rarely, side effects are compatible with the effects of excess hypotension and organ underperfusion, namely myocardial ischemia or even infarction, retinal and cerebral ischemia, and renal failure. Other unusual side effects include muscle cramps, myalgia, hypokalemia (via diuretic effect), and gingival swelling.

Drug interactions.

Cimetidine and grape fruit juice (large amounts) inhibit the hepatic CYP3A4 P-450 enzyme system breaking down nifedipine, thereby substantially increasing its blood levels. Phenobarbital, phenytoin, and rifampin induce this system metabolizing so that nifedipine blood levels should fall (not mentioned in package insert). In some reports, blood digoxin levels rise. Volatile anesthetics interfere with the myocardial calcium regulation and have inhibitory effects additional to those of nifedipine.

Rebound after cessation of nifedipine therapy.

In patients with vasospastic angina, the manufacturers recommend that the dose be tailed off.

Nifedipine poisoning.

In one case there was hypotension, SA and AV nodal block, and hyperglycemia. Treatment was by infusions of calcium and dopamine (see also “Amlodipine: The First of the Second-Generation DHPs” later in this chapter).

Combination with β-blockers and other drugs.

In patients with reasonable LV function, nifedipine may be freely combined with β-blockade (Fig. 3-10), provided that excess hypotension is guarded against. In LV dysfunction, the added negative inotropic effects may precipitate overt heart failure. In the therapy of effort or vasospastic angina, nifedipine is often combined with nitrates. In the therapy of hypertension, nifedipine may be combined with diuretics, β-blockers, methyldopa, ACE inhibitors, or ARBs. Combination with prazosin or (by extrapolation) other α-blockers may lead to adverse hypotensive interactions.

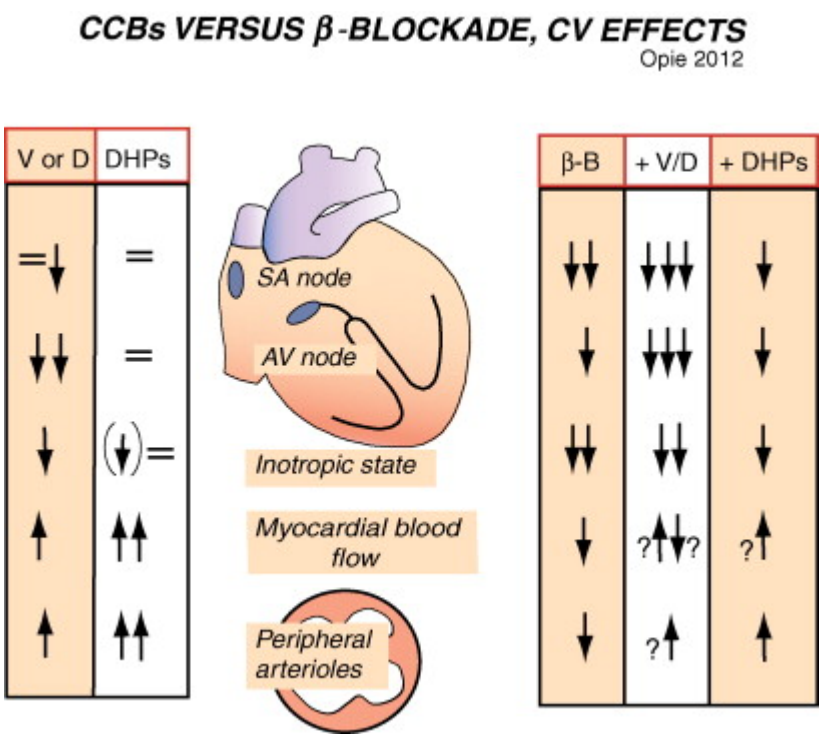

Figure 3-10 Proposed hemodynamic effects of calcium channel blockers (CCB), singly or in combination with β-blockade (β2B). Note that some of these effects are based on animal data and extrapolation to humans needs to be made with caution. *AV,* Atrioventricular; *D,* diltiazem; *DHP,* dihydropyridines; *SA,* sinoatrial; *V,* verapamil.
(Figure © L.H. Opie, 2012.)

Clinical uses of long-acting nifedipine

Effort angina.

In the United States only Procardia XL and not Adalat CC is licensed for effort angina, when β-blockade and nitrates are ineffective or not tolerated. Whereas capsular nifedipine modestly increases the heart rate (that may aggravate angina), the extended-release preparations leave the heart rate unchanged.[45] Their antianginal activity and safety approximates that of the β-blockers, albeit the cost of more subjective symptoms.[46] In the ACTION study on patients with stable coronary disease, one of the largest studies on effort angina (N ≈7,800), 80% already receiving β-blockade, the major benefits of added long-acting nifedipine were less new heart failure, less coronary angiography and less bypass surgery.[27] In the retrospective substudy on hypertensives (mean initial 151/85 mm Hg falling to 136/78 mm Hg) new heart failure decreased by 38% and major stroke by 32%, without altering cardiovascular death.[24]

Acute coronary syndromes.

In Prinzmetal's vasospastic angina, nifedipine gives consistent relief. In other acute coronary syndromes, nifedipine should not be used.

Systemic hypertension.

Long-acting nifedipine and other DHPs are increasingly used. The major outcome study with nifedipine GITS, the INSIGHT study, showed equivalence in mortality and other major outcomes to the diuretic, with less new diabetes or gout or peripheral vascular disease and more heart failure.[5] Capsular forms are not licensed for hypertension in the United States because of intermittent vasodilation and reflex adrenergic discharge, as well as the short duration of action. Procardia XL and Adalat CC are, however, approved and the dose is initially 30 mg once daily up to 90 mg daily.

Vascular protection.

Intriguing basic and clinical work suggests that nifedipine and other CCBs have vascular protective qualities, especially in the carotid vessels.[47]

Summary.

Long-acting nifedipine is widely used as a powerful arterial vasodilator with few serious side effects and is now part of the accepted therapy of hypertension and of effort or Prinzmetal's vasospastic angina. In hypertension, it gives equivalent outcomes to a diuretic. Long-acting nifedipine is especially well-tested in hypertensive anginal patients when added to β-blockade, as in the ACTION study. However, in unstable angina at rest, nifedipine in any formulation should not be used as monotherapy, unless vasospastic angina is the working diagnosis. Contraindications to nifedipine are few (apart from severe aortic stenosis, obstructive cardiomyopathy, or LV failure), and careful combination with β-blockade is usually feasible. Vasodilatory side effects include headache and ankle edema.

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Amlodipine: The first of the second-generation DHPS

The major specific advantages of amlodipine (Norvasc; Istin in the United Kingdom) are (1) the slow onset of action and the long duration of activity (see Table 3-5) and (2) the vast experience with this drug in hypertension. It was the first of the longer-acting "second-generation" CCBs. It binds to the same site as other DHPs (labeled *N* in Fig. 3-4). The charged nature of the molecule means that its binding is not entirely typical, with very slow association and dissociation, so that the channel block is slow in onset and offset. Additionally, it also binds to the same sites as verapamil and diltiazem, albeit to a lesser degree, so that with justification its binding properties are regarded as unique.[48]

Pharmacokinetics.

Peak blood levels are reached after 6 to 12 hours, followed by extensive hepatic metabolism to inactive metabolites. The plasma levels increase during chronic dosage probably because of the very long half-life. The elimination half-life is 35 to 48 hours, increasing slightly with chronic dosage. In older adults, the clearance is reduced and the dose may need reduction. Regarding drug interactions, no effect on digoxin levels has been found, nor is there any interaction with cimetidine (in contrast to verapamil and nifedipine). Because of the hepatic CYP3A4 interaction, the FDA warns that the 20-mg dose of simvastatin should not be exceeded in patients taking amlodipine. There is no known effect of grapefruit juice.

Hypertension.

Amlodipine has an outstanding record in major BP trials (Table 3-6).[49] As initial monotherapy, a common starting dose is 5 mg daily going up to 10 mg. In a large trial on mild hypertension in a middle-aged group over 4 years, amlodipine 5 mg daily was the best tolerated of the agents compared with an α-blocker, a β-blocker, a diuretic, and an ACE inhibitor.[50] In the largest outcome study, ALLHAT, amlodipine had the same primary outcome (fatal and nonfatal coronary heart disease) as the diuretic and ACE-inhibitor groups, but with modestly increased heart failure while decreasing new diabetes.[30] In another mega-trial, ASCOT-BP Lowering Arm, amlodipine usually in combination with the ACE inhibitor perindopril gave much better outcomes than a β-blocker usually combined with a diuretic.[23] Specifically, all cardiovascular events were decreased including heart failure, new diabetes was less, and decreased mortality led to premature termination of the trial.

Table 3-6 -- Amlodipine: Major Outcome Trials in Hypertension

Acronym	Numbers and Duration	Comparison	End Points
ALLHAT[30]	9048 in amlodipine arm	Amlodipine vs others (diuretic, ACE inhibitor, α-blocker)	Equal CHD, stroke, all-cause mortality, at same BP target; more HF, less new diabetes
ASCOT[23]	18,000 patients, 5 years, BP > 160/100 or 140/90 on drug; age 40-80; 3+ risk factors for CHD	Amlodipine vs atenolol 2nd: A + perindopril vs atenolol + thiazide	Mortality reduced, major fall in all CV events
VALUE, Amlodipine[49]	15,245 patients, age 50+, initial BP 155/87 mm Hg	Amlodipine vs valsartan ± thiazide	Equal cardiac and mortality outcomes
ACCOMPLISH[8],[9]	11,506 patients, at high risk for events	Benazepril + amlodipine vs benazepril + hydrochlorothiazide	Hazard ratio 0.79 for CV death, nonfatal MI, and nonfatal stroke (CI, 0.67-0.92; P=0.002)

ACCOMPLISH, Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension; *ACE,* angiotensin-converting enzyme; *ALLHAT,* Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial; *ASCOT,* Anglo Scandinavian Cardiac Outcomes Trial; *BP,* blood pressure; *CHD,* coronary heart disease; *CI,* confidence intervals; *CV,* cardiovascular; *HF,* heart failure; *MI,* myocardial infarction; *VALUE,* Valsartan Antihypertensive Long-term Use Evaluation Trial.

The decisive ACCOMPLISH study, comparing initial antihypertensive treatment with benazepril plus amlodipine versus benazepril plus hydrochlorothiazide, was terminated early as the CCB–ACE inhibitor combination was clearly superior to the ACE inhibitor-diuretic.[8] Both primary and secondary end-points were reduced by approximately 20%. For cardiovascular deaths, nonfatal MI, and nonfatal stroke, heart rate was 0.79 (95% cardiac index, 0.67-0.92; P = 0.002).[8] When matching the BP reductions exactly, the benefits were the same.[9] The progression of nephropathy was slowed to a greater extent with this combination.[51]

In diabetic type 2 hypertensives, ALLHAT showed that amlodipine was as effective as the diuretic in the relative risk of cardiovascular disease.[52] In advanced diabetic nephropathy, amlodipine compared with irbesartan protected from MI, whereas irbesartan decreased the heart failure and the progression of nephropathy.[53]

Effort angina and coronary artery disease.

Amlodipine is well tested in effort angina, with an antianginal effect for 24 hours, and often better tolerated than β-blockers. In CAMELOT amlodipine was given for 2 years to 663 patients with angiographic CAD; amlodipine decreased cardiovascular events by 31% versus enalapril despite similar BP reduction.[20],[54] Although atheroma volume fell in this trial, arterial lumen dimensions were unchanged. In PREVENT, amlodipine given to patients with coronary angiographic disease had reduced outcome measures after 3 years.[55] Exercise-induced ischemia was more effectively reduced by amlodipine than by the β-blocker atenolol, whereas ambulatory ischemia was better reduced by atenolol, and for both settings the combination was the best.[56] However, the CCB–β-blocker combination is often underused, even in “optimally treated” stable effort angina, as incorrectly claimed in COURAGE.[26] Exercise-induced ischemia is at the basis of effort angina. After the anginal pain is relieved by nitrates, the ejection fraction takes approximately 30 min to recover, a manifestation of postischemic stunning. Amlodipine markedly attenuates such stunning,[57] hypothetically because cellular calcium overload underlies stunning. In Prinzmetal’s vasospastic angina, another licensed indication, amlodipine 5 mg daily lessens symptoms and ST changes. For cardiovascular protection in hypertension, amlodipine was the major drug in the notable ASCOT study reducing strokes, total major events, and mortality.[23]

Contraindications, cautions, and side effects.

Amlodipine has the same contraindications as other DHPs (see Fig. 3-9). It is untested in unstable angina, acute myocardial infarction and follow-up. First principles strongly suggest that it should not be used in the absence of concurrent β-blockade. In heart failure CCBs as a group are best avoided but amlodipine may be added, for example, for better control of angina. In liver disease the dose should be reduced. Of the side effects, peripheral edema is most troublesome, occurring in approximately 10% of patients at 10 mg daily (see Table 3-4). In women there is more edema (15%) than in men (6%). Next in significance are dizziness (3% to 4%) and flushing (2% to 3%). Compared with verapamil, edema is more common but headache and constipation are less common. Compared with placebo, headache is not increased (package insert). Amlodipine gave an excellent quality of life compared with other agents in the TOMH study.[50]

Summary.

The very long half-life of amlodipine, good tolerability, and virtual absence of drug interactions (exception: high-dose simvastatin) makes it an effective once-a-day antianginal and antihypertensive agent, setting it apart from agents that are either twice or thrice daily. Side effects are few; ankle edema is the chief side effect. Exercise-induced ischemia is more effectively reduced by amlodipine than by the β-blocker atenolol, and the combination is even better. However, the CCB–β-blocker combination is often underused, even in

some studies reporting “optimally treated” stable effort angina. Amlodipine-based therapy in the notable ASCOT study in hypertension gave widespread cardiovascular protection, thereby dispelling the once-held belief that CCBs had some adverse outcome effects.

Felodipine

Felodipine (Plendil ER) shares the standard properties of other long-acting DHPs. In the United States, it is only licensed for hypertension in a starting dose of 5 mg once daily, then increasing to 10 mg or decreasing to 2.5 mg as needed. As monotherapy, it is approximately as effective as nifedipine. Initial felodipine monotherapy was the basis of a very large outcome study (Height of Hypertension [HOT]) in Scandinavia in which the aim was to compare BP reduction to different diastolic levels, 90, 85, or 80 mm Hg.[28] Combination with other agents such as ACE inhibitors and β-blockers was often required to attain the goals. Best results were found with the lowest BP group in diabetics, in whom hard end points such as cardiovascular mortality were reduced. Felodipine, like other DHPs, combines well with β-blockers.[58] There are two drug interactions of note: cimetidine, which increases blood felodipine levels, and anticonvulsants, which markedly decrease levels, both probably acting at the level of the hepatic enzymes. Grapefruit juice markedly inhibits the metabolism. The high vascular selectivity of felodipine led to extensive testing in heart failure, yet achieving no sustained benefit in the large Ve-HeFT-III trial in which it was added to conventional therapy.[59]

Other second-generation dihydropyridines

Other second-generation DHPs include, in alphabetical order, benidipine, cilnidipine, isradipine, lacidipine, lercanidipine, nicardipine, and nisoldipine. There appears to be no particular reason for choosing any of these instead of the much better studied agents with outcome results such as amlodipine, nifedipine, and felodipine except that (1) cilnidipine was more renoprotective than amlodipine in a small study that should be extended[60] and (2) use of lacidipine is strengthened by a large scale study with long-term follow up. *Lacidipine* (2-6mg daily, only in Europe and the United Kingdom) is highly lipophilic and may therefore exert vascular protection. In the ELSA trial the progression of carotid atherosclerosis was slowed when compared with atenolol, even though the ambulatory BP reduction of –7/–5 mm Hg was less than with the β-blocker (–10/–9 mm Hg).[6] Lacidipine also limited the development of new metabolic syndrome and new diabetes.[61] Lacidipine caused less ankle edema in a small direct comparison with amlodipine. *Benidipine,* well-studied in Japan, counters cardiac remodeling partially through nitric oxide,[62] and in hypertension (dose 4 mg/day) when combined with an ARB, β-blocker, or thiazide diuretic was similarly effective for the prevention of the major cardiovascular events and the achievement of target BP.[63] In a small post-MI trial, benidipine was as effective as β-blockade in reducing cardiovascular events.[64]

Third-generation dihydropyridines

Third-generation DHP CCBs inhibit T-type calcium channels on vascular muscular cells such as those localized on postglomerular arterioles. Sadly, they had a somewhat rocky start when the prototype agent, mibefradil, had to be withdrawn after a series of successful studies because of hepatic side effects. Now there is interest in a newer agent, *manidipine*.[65] In the DEMAND study on 380 subjects for a mean of 3.8 years, combined manidipine and ACE-inhibitor therapy reduced both macrovascular events and albuminuria in hypertensive patients with type 2 diabetes mellitus, whereas the ACE inhibitor did not. The proposed mechanism was reduced postglomerular resistance and decreased intraglomerular pressure. Cardioprotective effects extended beyond improved BP and metabolic control. Worsening of insulin resistance was almost fully prevented in those on combination therapy, which suggested additional effects possibly manidipine-mediated activation of adipocyte peroxisome proliferator-activated receptor-γ. The authors estimated that approximately 16 subjects had to be treated with the combined therapy to prevent one major cardiovascular event. Much larger trials are required to place the third-generation CCBs firmly on the therapeutic map.

Summary

1. ***Spectrum of use.*** CCBs (calcium antagonists) are widely used in the therapy of hypertension and underused in effort angina. The major mechanism of action is by calcium channel blockade in the arterioles, with peripheral or coronary vasodilation thereby explaining the major effects in hypertension and in effort angina. The HRL CCBs have a prominent negative inotropic effect, and inhibit the sinus and the AV nodes. These inhibitory cardiac effects are absent or muted in the DHPs, of which nifedipine is the prototype, now joined by amlodipine, felodipine, and others. Of these, amlodipine is very widely used in hypertension with proven outcome benefit. As a group, the DHPs are more vascular selective and more often used in hypertension than the HRL agents, also called the non-DHPs. Only the non-DHPs, verapamil and diltiazem, have antiarrhythmic properties by inhibiting the AV node. Both DHPs and non-DHPs are used against effort angina, albeit acting through different mechanisms and often underused especially in the United States.
2. ***Safety and efficacy.*** Previous serious concerns about the long-term safety of the CCBs as a group have been annulled by seven large outcome studies in hypertension, with one in angina pectoris. Nonetheless, as with all drugs, cautions and contraindications need to be honored.
3. ***Ischemic heart disease.*** All the CCBs work against effort angina, with efficacy and safety rather similar to β-blockers. The largest angina outcome study, ACTION, showed the benefits of adding a long acting DHP to prior β-blockade. In unstable angina the DHPs are specifically contraindicated in the absence of β-blockade because of their tendency to vasodilation-induced reflex adrenergic activation. Although the use of the HRL non-DHPs in unstable angina is relatively well supported by data, they have in practice been supplanted by β-blockers. In postinfarct patients, verapamil may be used if β-blockade is not tolerated or contraindicated, provided that there is no heart failure, although it is not licensed for this purpose in the United States. DHPs do not have good postinfarct data.
4. ***Hypertension.*** Strong overall evidence from a series of large outcome studies favors the safety and efficacy on hard end points, including coronary heart disease, of longer-acting DHPs. One large outcome study on coronary heart disease shows that the non-DHP verapamil gives results overall as good as atenolol with less new diabetes.
5. ***Diabetic hypertension.*** ALLHAT showed that amlodipine was as effective as the diuretic or the ACE inhibitor in the relative risk of cardiovascular disease. Other data suggest that initial antihypertensive therapy in diabetics should be based on an ACE inhibitor or ARB, especially in those with nephropathy. To achieve current BP goals in diabetics, it is almost always necessary to use combination therapy, which would usually include an ACE inhibitor or ARB, and a CCB besides a diuretic or β-blocker.
6. ***Heart failure.*** Heart failure remains a class contraindication to the use of all CCBs, with two exceptions: diastolic dysfunction based on LV hypertrophy, and otherwise well-treated systolic heart failure when amlodipine may be cautiously added if essential, for example, for control of angina

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