OPTUMRx

Therapeutic Class Overview
Calcium Channel Blockers

INTRODUCTION

- Approximately 121.5 million American adults are living with some form of cardiovascular disease (consisting of coronary heart disease, heart failure, stroke, and hypertension) according to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2020 update. The age-adjusted prevalence of all types of heart disease was 10.6% in 2017. Deaths related to cardiovascular disease were most often caused by coronary heart disease (42.6%), followed by stroke (17.0%), high blood pressure (10.5%), heart failure (9.4%) and other causes (17.6%) *(Virani et al 2020)*.
- Calcium channel blockade has certain effects that are specific to cardiac function. Coronary vascular smooth muscle relaxes when calcium channels are blocked, which increases the flow of oxygenated blood into the myocardium and lowers coronary vascular resistance. In addition, calcium channel blocking agents (also called calcium channel blockers) decrease peripheral vascular resistance by relaxing arteriolar smooth muscle. Both coronary and systemic vasodilation serve to reduce cardiac workload (*Kannam et al 2019, Dobesh PP 2017, Michel T 2011*).
- The movement of calcium ions is essential for the function of all types of muscle, including cardiac muscle and vascular smooth muscle. For both cardiac and smooth muscle, the flow of calcium ions into the muscle cells through specific channels allows muscle contraction to occur. When this flow is reduced, the result is a weakening of muscle contraction and relaxation of muscle tissue (*Micromedex 2.0 2020, Kannam et al 2019*).
- The calcium channel blocking agents include dihydropyridines, which are similar in chemical structure, and non-dihydropyridines, which are a structurally heterogeneous group. Although they have different binding sites on the L-type calcium channel, both block the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The non-dihydropyridines also block the T-type calcium channel in the atrioventricular (AV) node (*Micromedex 2.0 2020, Kannam et al 2019, Dobesh PP 2017, Michel T 2011, Saseen 2017*).
- Dihydropyridines are more potent vasodilators than non-dihydropyridines due to greater selectivity for vascular smooth muscle. They have little effect on cardiac muscle contractility or conduction (*Micromedex 2.0 2020, Kannam et al 2019*).
  - All available dihydropyridine calcium channel blocking agents can be used in the treatment of hypertension, with the exception of nimodipine and immediate release nifedipine capsules. Although not a first-line treatment in all hypertensive patients, the dihydropyridines are generally effective but differ somewhat in other properties and effects.
  - Amlodipine, oral nicardipine, and long-acting nifedipine are effective treatment options for chronic stable angina. Short-acting agents, such as short-acting nifedipine, should be avoided due to increased cardiovascular and mortality risks in some patients as well as significant adverse effects, such as reflex tachycardia. Amlodipine is also indicated to reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented coronary artery disease (CAD).
  - Amlodipine is the only calcium channel blocker that is Food and Drug Administration (FDA)-approved in combination with a nonsteroidal anti-inflammatory drug (NSAID). Consensi (amlodipine/celecoxib) was FDA-approved on May 31, 2018 for the treatment of hypertension and osteoarthritis.
- The non-dihydropyridine calcium channel blocking agents include diltiazem and verapamil and both agents are available in a variety of modified-release delivery systems that alter their pharmacokinetic properties, including onset and duration of action (*Micromedex 2.0 2020*). Non-dihydropyridines dilate the arteries somewhat less than dihydropyridines, but they also reduce heart rate and contractility (*Micromedex 2.0 2020, Kannam et al 2019, Weber et al 2014*).
  - The non-dihydropyridine calcium channel blocking agents are indicated for use in the treatment of angina, arrhythmias, and hypertension. Diltiazem is a potent coronary vasodilator but is only a mild arterial vasodilator. Although it decreases AV node conduction, diltiazem does not have negative inotropic properties. Verapamil dilates coronary and peripheral arteries. It also slows conduction through the AV node and has negative inotropic and chronotropic effects (*Micromedex 2.0 2020*).
  - Guidelines stipulate that a non-dihydropyridine calcium channel blocker may be prescribed in certain patients, often with co-morbid indications. Non-dihydropyridine calcium-channel blocking agents are not recommended for the routine treatment of heart failure because of their negative inotropic action and risk of worsening heart failure *(Yancy et al 2013, Yancy et al 2016, Yancy et al 2017)*. Caution is also advised in elderly patients. Guidelines generally

reserve non-dihydropyridine calcium channel blockers for patients with high-risk cardiovascular diseases and arrhythmias; therefore, they are usually reserved for progressive cardiovascular and heart disease (*Al-Khatib et al 2017, American Geriatrics Society 2015, Amsterdam et al 2014, Fihn et al 2014, Go et al 2014, January et al 2019, KDIGO 2012, Williams et al 2018, Montalescot et al 2013, Page et al 2016, Rosendorff et al 2015, Weber et al 2014*).

- Calcium channel blockers are also included in various combination products (eg, amlodipine-benazepril); however, these combination agents are not included in this review.
- Since there are several branded agents that contain the same generic component, the remaining tables in the review are organized by generic name. This review encompasses all dosage forms and strengths with the exception of injectable indications and formulations used primarily in an institutional setting.
- Medispan Therapeutic Class: Calcium Channel Blockers

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Dihydropyridines	
Adalat CC (nifedipine extended-release)	✔
Consensi (amlodipine/celecoxib)	-
Conjupri (levamlodipine)	-
Felodipine extended-release	✔
Isradipine	✔
Katerzia (amlodipine suspension)	-
Nicardipine	✔
Nimodipine	✔
Nisoldipine extended-release	✔
Norvasc (amlodipine)	✔
Nymalize (nimodipine)	-
Procardia (nifedipine)	✔
Procardia XL (nifedipine extended-release)	✔
Sular (nisoldipine extended-release)	✔
Non- dihydropyridines	
Calan (verapamil) tablet	✔
Calan SR (verapamil extended-release) tablet	✔
Cardizem (diltiazem) tablet	✔
Cardizem CD* (diltiazem extended-release) capsule	✔
Cardizem LA† (diltiazem extended-release) tablet	✔
Dilacor XR‡ (diltiazem extended-release) capsule	✔
Tiazac§ (diltiazem extended-release) capsule	✔
Verelan (verapamil sustained-release) capsule	✔
Verelan PM (verapamil extended-release) capsule	✔

*Cartia XT is a branded generic of Cardizem CD.
†Matzim LA is the branded generic of Cardizem LA.
‡Dilacor XR is no longer manufactured, but included in this review because its branded generic, DILT-XR, is still on the market.
§Taztia XT and Diltzac are branded generics of Tiazac.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. FDA-Approved Indications – Dihydropyridines

Indication	Amlodipine	Consensi (amlodipine/ Celecoxib)	Felodipine	Isradipine	Levamlodipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
	Angina Pectoris								
Treatment of chronic stable angina	✔ *					✔ †			
Treatment of chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents							✔ (capsule, ER tablet [Procardia XL])		
Treatment of vasospastic angina	✔ ‡						✔ (capsule, ER tablet [Procardia XL])§		
	CAD								
Reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented CAD by angiography and without heart failure or an ejection fraction < 40%	✔								
	Hypertension								
Treatment of hypertension	✔ ‖	✔	✔ ‖	✔ ¶	✔ ‖	✔ ‖	✔ (ER tablet)‖		✔ ‖
Treatment of hypertension to lower blood pressure which reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions	✔ ‖		✔ ‖				✔ (ER tablet [Procardia XL])‖		
	Miscellaneous								
Improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in subarachnoid hemorrhage from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (ie, Hunt and Hess Grades I-V)								✔	
Management of the signs and symptoms of osteoarthritis		✔							

*Alone or in combination with other antianginal agents.
†Alone or in combination with beta blockers.
‡Confirmed or suspected vasospastic angina. May be used alone or in combination with other antianginal agents.
§Vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm.
‖Alone or in combination with other antihypertensive agents.
¶Alone or in combination with thiazide-type diuretics.

(Prescribing information: Adalat CC 2016, Conjupri 2019, Consensi 2020, felodipine ER 2018, isradipine 2017, Katerzia 2019, nicardipine capsule 2017, nimodipine 2017, nisoldipine extended-release tablet 2017, Norvasc 2019, Nymalize 2020, Procardia 2016, Procardia XL 2016, Sular 2017)

Table 3. Food and Drug Administration Approved Indications – Non-Dihydropyridines

Indication	Diltiazem	Verapamil
Angina Pectoris		
Angina due to coronary artery spasm or vasospastic angina	✔ (tablet [Cardizem], extended-release capsule [Cardizem CD])	✔ (Calan)
Chronic stable angina	✔	✔ (Calan)
Unstable angina		✔ (Calan)
Arrhythmias		
Control of ventricular rate at rest and during stress in patients with chronic atrial flutter and/or atrial fibrillation in association with digitalis		✔ (Calan)
Prophylaxis of repetitive paroxysmal supraventricular tachycardia		✔ (Calan)
Hypertension		
Hypertension	✔ *(with the exception of Cardizem)	
Hypertension to lower blood pressure which reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.	✔ *(Cardizem LA)	✔

*May be used alone or in combination with other antihypertensive agents.

(Prescribing Information: Calan 2017, Calan SR 2019, Cardizem 2016, Cardizem CD 2020, Cardizem LA 2019, DILT-XR 2012, Tiazac 2016, Verelan 2019, Verelan PM 2019)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Dihydropyridines

- Clinical trials have demonstrated the efficacy of these agents for their respective indications.
- Amlodipine oral suspension has a pharmacokinetic profile comparable to the tablet formulations, and received FDA approval based on these pharmacokinetic parameters and the efficacy of amlodipine tablet (*Katerzia prescribing information 2019)*.
- In a crossover study for the treatment of angina, amlodipine and felodipine have been shown to be more effective than placebo, though no significant difference between the 2 active treatment groups was observed (*Koenig 1997*).
- Numerous clinical trials have shown that the dihydropyridines can effectively lower systolic and diastolic blood pressure when administered alone or in combination with other agents. In trials comparing combination therapy to monotherapy, the more aggressive treatment regimens lowered blood pressure to a greater extent than the less intensive treatment regimens. Some comparative trials have demonstrated slight differences in blood pressure effects among the various dihydropyridines; however, the clinical significance of these differences remains to be established (*Sheehy et al 2000, Mounier-Vehier et al 2002, Kes et al 2003, Ryuzaki et al 2007, Saito et al 2007, Pepine et al 2003, Whitcomb et al 2000, White et al 2003b, Lenz et al 2001, Drummond et al 2007, Mazza et al 2002, Hollenberg et al 2003, White et al 2003a, Jordan et al 2007, Messerli et al 2002, Chrysant et al 2012, Messerli et al 2000, Jamerson et al 2004, Neutel et al 2005, Chrysant et al 2007, Chrysant et al 2004, Minami et al 2007, Jamerson et al 2007, Malacco et al 2002, Kereiakes et al 2007, Tatti et al 1998, Miranda et al 2008, Fogari et al 2007, Ribeiro et al 2007, Chrysant et al 2008, Chrysant et al 2009, Oparil et al 2009, Braun et al 2009, Littlejohn et al 2009a, Littlejohn et al 2009b, Sharma et al 2007, Neutel et al 2012, Maciejewski et al 2006, Ichihara et al 2006, Karpov et al 2012, Philipp et al 2007, Philipp et al 2011, Schunkert et al 2009, Ke et al 2010, Destro et al 2008, Flack et al 2009, Schrader et al 2009, Sinkiewicz et al 2009, Fogari et al 2009, Poldermans et al 2007, Calhoun et al 2009a, Calhoun et al 2009b, Crikelair et al 2009, Pareek et al 2010, Gustin et al 1996, Karotsis et al 2006, Lindholm et al 2005, Van Bortel et al 2008, Wiysonge et al 2007, Baguet et al 2007*).
  - In-class comparisons for the treatment of hypertension have found better compliance and a higher response rate with amlodipine compared to felodipine, though van der Krogt and colleagues found similar decreases in overall systolic and diastolic blood pressures between groups (*Sheehy et al 2000, Van der Krogt et al 1996*).

- The most clinical trial experience has been with amlodipine and nifedipine, which have been shown to have beneficial effects on cardiovascular and stroke outcomes in hypertension trials (*Rahman et al 2012, Black et al 2008, ALLHAT 2002, Julius et al 2004, Zanchetti et al 2006, Nissen et al 2004, Ogihara et al 2008, Jamerson et al 2008, Weber et al 2010, Weber et al 2013, Brown et al 2000*).

- The dihydropyridines have been shown to have favorable effects on cardiovascular morbidity and mortality, and several studies have demonstrated comparable efficacy with beta blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) in select diseases (*Pitt et al 2000, Dahlöf et al 2005, Chapman et al 2007, Nissen et al 2004, ALLHAT 2002, Black et al 2008, Rahman et al 2012, Ogihara et al 2008, Julius et al 2004, Zanchetti et al 2006, Jamerson et al 2008, Bakris et al 2010, Weber et al 2010, Weber et al 2013, Hansson et al 1999, National Intervention Cooperative Study 1999, Brown et al 2000, Estacio et al 1998*).
  - In the ALLHAT study, ACE inhibitors had a 51% higher rate (relative risk [RR], 1.51; 95% confidence interval [CI], 1.22 to 1.86) of stroke in patients of African or Caribbean descent (Black) when used as initial therapy compared to calcium channel blockers. ACE inhibitors were also less effective in reducing blood pressure in Black patients compared to a calcium channel blocker (*Rahman et al 2012, Black et al 2008, ALLHAT 2002*).
- An unpublished phase III randomized controlled trial compared amlodipine/celecoxib (Consensi) with its individual components and matching placebo in 152 patients with hypertension *(Smith et al, 2018)*. After 2 weeks of treatment, the primary endpoint of change in mean daytime ambulatory systolic blood pressure was noninferior with amlodipine/celecoxib vs amlodipine (-10.6 vs -8.8 mmHg; $p < 0.001$), and the secondary endpoint of mean 24-hour diastolic blood pressure was superior with amlodipine/celecoxib vs amlodipine (-7.1 vs -4.8 mmHg; $p = 0.38$).
- A Cochrane review determined that calcium channel blockers do not have a role in the management of patients with acute ischemic stroke (*Zhang et al 2019*).
- Levamlodipine, the pharmacologically active isomer of amlodipine, was recently approved for the treatment of hypertension (*Conjupri prescribing information 2019*). Approval of this agent is based on historical clinical trials demonstrating the efficacy and safety of amlodipine in adult and pediatric patients.

Non-dihydropyridines

- The non-dihydropyridine calcium channel blockers are indicated to treat hypertension and angina, in addition to slowing ventricular rate in patients with atrial fibrillation/atrial flutter. Clinical trials demonstrate the efficacy of these agents for their respective indications.
- For the treatment of angina, diltiazem and verapamil have been shown to be effective in improving exercise tolerance and reducing heart rate, angina frequency and nitroglycerin use *(De Rosa et al 1998, Chugh et al 2001, van Kesteren et al 1998, Frishman et al 1999).*
  - A direct comparison between diltiazem and verapamil found no significant differences between the agents in exercise tolerance; however, resting heart rate, angina frequency and nitroglycerin use were all significantly lower in the diltiazem group *(De Rosa et al 1998).*
- Both diltiazem and verapamil have shown efficacy in the treatment of hypertension, but comparisons with other classes of medications have not consistently demonstrated “superiority” of either agent (*Wright et al 2004, Rosei et al 1997*).
  - Wright and colleagues compared diltiazem and amlodipine in African American patients with hypertension and demonstrated significantly greater reductions in diastolic blood pressure during the first 4 hours after awakening in addition to greater reductions in heart rate with diltiazem; however, mean 24-hour systolic blood pressure reductions were significantly greater with amlodipine *(Wright et al 2004).*
- Studies evaluating the efficacy of the non-dihydropyridine calcium channel blockers for various cardiovascular outcomes generally demonstrated no significant difference between verapamil or diltiazem compared to other agents including beta blockers and diuretics *(Hansson et al 2000, Pepine et al 2003, Mancia et al 2007, Bangalore et al 2008, Black et al 2003).*

CLINICAL GUIDELINES

- There are several national and international evidence-based antihypertensive guidelines that provide recommendations regarding the use of calcium channel blocking agents. Most recommend that the selection of an antihypertensive agent be based on compelling indications for use:
  - Most guidelines recommend a thiazide-type diuretic, an ACE inhibitor, an ARB, or a calcium channel blocker as first-line therapy (*Go et al 2014, James et al 2014, Williams et al 2018, Weber et al 2014, Carey et al 2018*). The 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guideline generally recommends that

combination therapy include an ACE inhibitor or ARB with a calcium channel blocker and/or a thiazide-type diuretic *(Williams et al 2018)*.
  - In Black hypertensive patients, thiazide-type diuretics or calcium channel blockers are recommended specifically as first-line therapy *(James et al 2014, Williams et al 2018, Weber et al 2014*).
  - In patients with chronic kidney disease, calcium channel blockers are generally recommended after ACE inhibitors or ARBs (*KDIGO 2012, Go et al 2014, Williams et al 2018, Weber et al 2014*).
  - Consensus guidelines recommend calcium channel blockers as an option in pregnant patients with severe hypertension to prevent stroke; nifedipine is one of the only dihydropyridines tested in these patients *(Bushnell et al 2014, Williams et al 2018).*
  - A long-acting dihydropyridine calcium channel blocker may be added to a basic hypertensive regimen, particularly after a beta blocker and ACE inhibitor, in hypertensive patients with CAD and stable angina *(Rosendorff et al 2015).*
  - A non-dihydropyridine calcium channel blocker may be prescribed for hypertensive patients with CAD who have an intolerance or contraindication to a beta blocker; however, a combination of a beta blocker and a non-dihydropyridine calcium channel blocker may increase the risk of bradyarrhythmias and heart failure *(Rosendorff et al 2015)*.
  - Non-dihydropyridine calcium-channel blocking agents are not recommended for the routine treatment of heart failure because of their negative inotropic action and risk of worsening heart failure *(Yancy et al 2016, Yancy et al 2017).*
  - The 2018 ESC/ESH guidelines recommend calcium channel blockers, ACE inhibitors, and ARBs over beta-blockers or diuretics in patients with left ventricular (LV) hypertrophy *(Williams et al 2018)*. However, in general, calcium channel blocking agents are not recommended for the routine treatment of heart failure *(Ponikowski et al 2016, Yancy et al 2013, Yancy et al 2016, Yancy et al 2017)*, although, some guidelines agree that some dihydropyridine calcium channel blockers may be used in certain co-morbid conditions if the patient has preserved LV function *(Ponikowski et al 2016).*
  - In November 2017, the American College of Cardiology (ACC)/AHA released the 2017 Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults. For initial first-line therapy for stage 1 hypertension, they list thiazide diuretics, calcium channel blockers, and ACE inhibitors or ARBs. In African American adults with hypertension but without heart failure or CKD, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or calcium channel blocker. Two or more antihypertensive medications are recommended to achieve a BP target of < 130/80 mm Hg in most adults, especially in African American adults, with hypertension *(Whelton et al 2017)*.
  - In August 2017, the American Academy of Pediatrics (AAP) published practice guidelines for screening and management of high blood pressure in children and adolescents. In hypertensive children and adolescents who have failed lifestyle modifications (particularly those who have LV hypertrophy on echocardiography, symptomatic hypertension, or stage 2 hypertension without a clearly modifiable factor [eg, obesity]), the guidelines recommend initiating pharmacologic treatment with an ACE inhibitor, ARB, long-acting calcium channel blocker, or thiazide diuretic *(Flynn et al 2017).*
- For the treatment of chronic angina, beta blockers are recommended as initial therapy; however, long-acting calcium channel blocking agents may be used if beta blockers are contraindicated or if additional therapy is required *(Fihn et al 2012, Fihn et al 2014, Knuuti et al 2019, O'Gara et al 2013, Montalescot et al 2013).* Beta blockers and calcium channel blockers have similar clinical outcomes, but beta blockers may have fewer adverse events in patients with stable angina. Long-acting calcium channel blockers may be used in combination with beta blockers when beta blocker monotherapy is unsuccessful *(Montalescot et al 2013, Amsterdam et al 2014)*. Other guidelines recommend long-acting calcium channel blockers and nitrates as a treatment option for coronary artery spasm. For vasospastic (Prinzmetal) angina, guidelines recommend calcium channel blockers alone or in combination with nitrates *(Amsterdam et al 2014).*
- For the treatment of aneurysmal SAH, oral nimodipine is recommended to reduce poor outcome related to SAH *(Connolly et al 2012, Diringer et al 2011).*
- For patients with ventricular tachycardias, non-dihydropyridine calcium channel blockers have a limited role and administration of these agents can lead to further cardiovascular decompensation (*Al-Khatib et al 2017)*. Verapamil is effective in treating idiopathic interfascicular reentrant left ventricular tachycardia.

SAFETY SUMMARY

Dihydropyridine

- All of the dihydropyridine calcium channel blocking agents are contraindicated in patients with hypersensitivity to any component of the medication. Nicardipine is contraindicated in patients with advanced aortic stenosis. The Adalat CC

formulation of nifedipine is contraindicated in patients with cardiogenic shock and in patients who are concomitantly using strong CYP450 inducers such as rifampin. Nimodipine capsule is contraindicated for concomitant administration with strong CYP3A4 inhibitors such as some macrolide antibiotics, some anti-HIV protease inhibitors, some azole antimycotics and some antidepressants because of risk of significant hypotension.

- Intravenous administration of the contents of nimodipine capsules has resulted in serious adverse consequences including death, cardiac arrest, cardiovascular collapse, hypotension and bradycardia. As such, nimodipine capsules have a boxed warning against the use of nimodipine capsules for intravenous administration.
- Hypotension may occur occasionally during the initial titration or with dosage increases, and hence, blood pressure should be monitored during initial administration and titration. Dihydropyridines, specifically felodipine and nisoldipine, should be used cautiously in patients with congestive heart failure.
- Dihydropyridine calcium channel blockers can produce negative inotropic effects and exacerbate heart failure and as a result, patients with heart failure should be monitored carefully.
- Caution should be exercised when using dihydropyridine calcium channel blockers in patients with impaired hepatic function or reduced hepatic blood flow because these agents are extensively metabolized by the liver.
- In general, monitoring should be performed for blood pressure (with initiation and titration), heart rate and anginal pain. Patients should also be monitored for signs and symptoms of edema.
- Consensi (amlodipine/celecoxib) carries a boxed warning for the risk of serious cardiovascular and gastrointestinal (GI) events. Consensi is contraindicated in the setting of coronary artery bypass surgery. The celecoxib component is associated with serious GI adverse events, such as bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal.

Non-dihydropyridine

- Diltiazem is contraindicated in patients with i) acute myocardial infarction and pulmonary congestion documented by X-ray on admission, ii) hypersensitivity to the drug, iii) hypotension (< 90 mm Hg systolic), iv) second or third degree AV block except in the presence of a functioning ventricular pacemaker, and v) sick sinus syndrome except in the presence of a functioning ventricular pacemaker. Verapamil is contraindicated in patients with i) atrial fibrillation or flutter and an accessory bypass tract (Wolff-Parkinson-White, Lown-Ganong-Levine syndromes), ii) hypersensitivity to the drug, iii) hypotension (< 90 mm Hg systolic), iv) second or third degree AV block except in the presence of a functioning ventricular pacemaker, v) severe left ventricular dysfunction, and vi) sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
- The precautions for diltiazem include the following: may have an additive effect on heart rate with concomitant use of beta blockers or digitalis; dermatologic reactions leading to erythema multiforme and/or exfoliative dermatitis have been reported; increased risk of toxicity with hepatic and/or renal impairment; hypotension; impaired ventricular function and worsening congestive heart failure have also been reported. The precautions for verapamil include the following: concomitant use of a beta blocker in patients with any degree of ventricular dysfunction and concomitant use of quinidine in patients with hypotrophic cardiomyopathy should be avoided; congestive heart failure may occur; elevated liver enzymes, particularly serum transaminase levels, have been reported; first-degree AV block, marked, or progression to second- or third-degree block may occur; hepatic function impairment may occur; sinus bradycardia, pulmonary edema, severe hypotension, second-degree AV block, sinus arrest, and death have been reported in patients with hypertrophic cardiomyopathy; hypotension and/or dizziness may occur; pulmonary edema may occur.
- In general, patients taking non-dihydropyridine calcium channel blocking agents should have their blood pressure monitored weekly during the initial period of titration. Heart rate and anginal pain should also be monitored. Patients should have their liver function monitored periodically. Electrocardiogram (ECG) should be monitored for PR interval prolongation in patients with impaired renal or hepatic function using verapamil. If the medication is being used for arrhythmia, then ECG and reduction in signs and symptoms should be monitored.
- The common adverse effects of diltiazem include bradyarrhythmia, cough, dizziness, fatigue, headache and peripheral edema. The common adverse effects of verapamil include constipation, dizziness, edema, headache, hypotension, influenza-like symptoms, pharyngitis, and sinusitis.

(Facts and Comparisons 2020, Micromedex 2.0 2020)

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration - Dihydropyridine

Drug	Available Formulations	Usual Recommended Frequency	Comments
Amlodipine	Oral tablets Oral suspension	Angina pectoris (chronic stable and vasospastic): Tablet, suspension: maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily CAD: Tablet, suspension: maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily Hypertension: Tablet, suspension: initial, 5 mg once daily; maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily Hypertension in children 6 to 17 years of age: Tablet, suspension: initial, 2.5 mg once daily; maintenance, 2.5 to 5 mg once daily; maximum, 5 mg once daily	Doses in excess of 5 mg daily have not been studied in pediatric patients. In general, wait 7 to 14 days between titration steps. Titrate more rapidly, however, if clinically warranted, provided the patient is assessed frequently.
Consensi (amlodipine/celecoxib)	Oral tablets	Hypertension and osteoarthritis: Initial, 5 mg/200 mg once daily (or 2.5 mg/200 mg in small, elderly, or frail patients or those with hepatic impairment); titrate to 5 mg/200 mg or 10 mg/200 mg once daily as needed.	The lowest effective dose of celecoxib for the shortest duration should be used. Consensi may be substituted for its individual components.
Felodipine	Oral extended-release tablets	Hypertension: Extended-release tablet: initial, 5 mg once daily; maintenance, 2.5 to 10 mg once daily	Dose adjustments should occur generally at intervals of not less than 2 weeks. Should be swallowed whole and not crushed or chewed; take without food or with a light meal.
Isradipine	Oral capsules	Hypertension: Capsule: initial, 2.5 mg twice daily; maximum, 20 mg/day	Dose adjustments should occur in increments of 5 mg/day at 2 to 4 week intervals.
Levamlodipine	Oral tablets	Hypertension: Tablets: initial, 2.5 mg once daily; maximum, 5 mg once daily	Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 1.25 mg once daily.

Drug	Available Formulations	Usual Recommended Frequency	Comments
			Pediatric starting dose is 1.25 mg to 2.5 mg once daily; doses above 2.5 mg daily have not been studied in pediatric patients.
Nicardipine	Oral capsules	Angina pectoris (chronic stable): Capsule: initial, 20 mg 3 times daily; maintenance, 20 to 40 mg 3 times daily Hypertension: Capsule: initial, 20 mg 3 times daily; maintenance, 20 to 40 mg 3 times daily	Allow at least 3 days before increasing the dose to ensure achievement of steady state plasma drug concentrations (capsule formulation).
Nifedipine	Immediate-release capsules Extended-release tablets	Angina pectoris (chronic stable): Capsule: initial, 10 mg 3 times daily; maintenance, 10 to 20 mg 3 times daily; maximum, 180 mg/day Extended-release tablet: initial, 30 or 60 mg once daily; maximum, 90 mg/day Angina pectoris (vasospastic): Capsule: initial, 10 mg 3 times daily; maintenance, 20 to 30 mg 3 to 4 times daily; maximum, 180 mg/day Extended-release tablet: initial, 30 or 60 mg once daily; maximum, 90 mg/day Hypertension: Extended-release tablet: initial, 30 or 60 mg once daily; maintenance, 30 to 90 mg once daily; maximum, 120 mg/day	Titration should proceed over a 7- to 14-day period. Extended-release tablets should be swallowed whole, not bitten or divided and should be taken on an empty stomach; co-administration with grapefruit juice should be avoided.
Nimodipine	Oral capsules Oral solution	Subarachnoid hemorrhage: Capsule: 60 mg every 4 hours for 21 consecutive days Oral solution: 20 mL (60 mg) every 4 hours for 21 consecutive days	Dosing should be started within 96 hours of subarachnoid hemorrhage. Capsules should be swallowed whole with a little liquid and oral solution should only be administered enterally, preferably not less than 1 hour before or 2 hours after meals; grapefruit juice should be avoided; capsules should not be

Drug	Available Formulations	Usual Recommended Frequency	Comments
			administered intravenously or by other parenteral routes.
Nisoldipine	Extended-release tablets	Hypertension: Extended-release tablet: initial, 20 mg once daily; maintenance, 20 to 40 mg/day; maximum, 60 mg/day Extended-release tablet (Sular and its generics): initial, 17 mg once daily; maintenance, 17 to 34 mg once daily; maximum, 34 mg once daily	Dose adjustments should occur at intervals of not less than 1 week. Extended-release tablets should be swallowed whole, not bitten, divided or crushed; should be taken on an empty stomach (1 hour before or 2 hours after a meal); grapefruit products should be avoided; administration with a high fat meal can lead to excessive peak drug concentration and should be avoided.

See the current prescribing information for full details

Table 5. Dosing and Administration – Non-dihydropyridine

Drug	Available Formulations	Usual Recommended Frequency	Comments
Diltiazem	Extended-release capsules Extended-release tablets Tablets	Angina pectoris (chronic stable): Extended-release capsule: initial, 120 or 180 mg once daily; maintenance, 180 to 540 mg once daily; maximum, 540 mg once daily Extended-release tablet: initial, 180 mg once daily; maximum, 360 mg once daily Tablet: initial, 30 mg 4 times daily; maintenance, 180 to 360 mg/day (divided in 3 to 4 doses) Angina pectoris (due to coronary artery spasm): Extended-release capsule (Cardizem CD): initial, 120 or 180 mg once daily; maintenance, adjust dosage to each patient's needs up to 480 mg once daily Tablet: initial, 30 mg 4 times daily; maintenance, 180 to 360 mg/day (divided in 3 to 4 doses) Hypertension:	Tablet formulation should be taken before meals and at bedtime. Tiazac (extended-release) capsule formulation may also be administered by opening the capsule and sprinkling the capsule contents on a spoonful of applesauce; the applesauce should be swallowed immediately without chewing and followed with a glass of cool water to ensure complete swallowing of the capsule contents. Cardizem LA (extended-release) tablets should be swallowed whole and not chewed or crushed.

Drug	Available Formulations	Usual Recommended Frequency	Comments
		Extended-release capsule: initial, 120 to 240 mg once daily; maintenance, 120 to 540 mg once daily; maximum, 540 mg once daily Extended-release tablet: initial, 180 to 240 mg once daily, although some patients may respond to lower doses; maximum, 540 mg once daily	
Verapamil	Extended-release capsules Extended-release tablets Sustained-release capsules Tablets	Angina pectoris (chronic stable, unstable, and vasospastic): Tablet: maintenance, 80 to 120 mg 3 times daily Arrhythmias: Tablet: maintenance, 240 to 320 mg/day, divided in 3 to 4 doses; maximum, 480 mg/day Hypertension: Sustained-release capsule: initial, 120 to 240 mg once daily; maintenance, 180 mg to 480 mg/day; maximum, 480 mg/day Extended-release capsule: initial, 100 mg to 200 mg once daily at bedtime; maintenance, 200 mg to 400 mg once daily; maximum, 400 mg/day Extended-release tablet: initial, 120 to 180 mg in the morning; maintenance, 180 to 480 mg/day in 1 to 2 divided doses, maximum, 480 mg/day Tablet: initial, 80 mg 3 times daily; maintenance, 360 to 480 mg/day divided (3 to 4 times daily); maximum, 480 mg/day	Calan 80 mg tablets are scored and can be divided into halves to provide a 40 mg dose. Calan SR should be administered with food and if needed the caplets can be divided in half without compromising the sustained-release properties of the drug. Verelan and Verelan PM capsules should not be crushed or chewed and they may be administered by opening the capsule and sprinkling the capsule contents on a spoonful of applesauce; the applesauce should be swallowed immediately without chewing and followed with a glass of cool water to ensure complete swallowing of the capsule contents.

See the current prescribing information for full details

CONCLUSION

- All of the dihydropyridines, with the exception of nimodipine, are approved for the treatment of hypertension. Amlodipine, nicardipine, and nifedipine are also indicated for the treatment of angina. Additionally, amlodipine reduces the risk of hospitalization due to angina and reduces the risk of coronary revascularization procedures in patients with recently documented CAD. Consensi, a combination of amlodipine and celecoxib, was recently FDA-approved for the treatment of patients with hypertension and osteoarthritis. Nimodipine improves the neurological outcome of patients with an SAH by reducing the incidence and severity of ischemic deficits in patients with ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (ie, Hunt and Hess Grades I-V).

- Numerous clinical trials have shown that the dihydropyridines can effectively lower systolic and diastolic blood pressure when administered alone or in combination with other agents. In trials comparing combination therapy to monotherapy, the more aggressive treatment regimens lowered blood pressure to a greater extent than the less intensive treatment regimens. Some comparative trials have demonstrated slight differences in blood pressure effects among the various dihydropyridines; however, the clinical significance of these differences remains to be established.
- The dihydropyridines have been shown to favorably affect cardiovascular morbidity and mortality, and several studies have demonstrated comparable efficacy with beta blockers, diuretics, ACE inhibitors, and ARBs in select diseases. However, the ALLHAT study demonstrated that patients of African or Caribbean descent (Black) had a lower rate of stroke when therapy was initiated with a calcium channel blocker compared to an ACE inhibitor.
- There is insufficient evidence to support that one dihydropyridine calcium channel blocker is safer or more efficacious than another, although most clinical trial experience has been with amlodipine and nifedipine.
- The non-dihydropyridine calcium channel blocking agents are approved for the treatment of angina, arrhythmias, and hypertension. Diltiazem and verapamil are available in a variety of modified-release delivery systems that alter their pharmacokinetic properties, including onset and duration of action.
- Clinical trials demonstrate that diltiazem and verapamil can effectively treat angina and improve blood pressure. Both agents have been shown to reduce mortality and cardiovascular event rates compared to placebo. Evidence suggests that there is no overall difference between diltiazem and verapamil compared to other antihypertensive agents (beta blockers, diuretics) in reducing cardiovascular events and mortality in patients with hypertension. There is insufficient evidence to support that one non-dihydropyridine calcium channel blocking agent is safer or more efficacious than another.
- For the treatment of chronic angina, beta blockers are recommended as initial therapy; however, long-acting calcium-channel blocking agents may be used if beta blockers are contraindicated or if additional therapy is required. Beta blockers and calcium channel blockers have similar clinical outcomes, but beta blockers may have fewer adverse events in patients with stable angina. Long-acting calcium channel blockers may be used in combination with beta blockers when beta blocker monotherapy is unsuccessful. Long-acting calcium-channel blocking agents are also recommended in patients with variant angina and for patients with coronary artery spasm(s), known as vasospastic angina, with or without nitrates.
- Treatment options for atrial fibrillation include ventricular rate control or drug therapy to maintain sinus rhythm. The AFFIRM, RACE and HOT CAFE trials demonstrated similar outcomes with rate control compared to rhythm control strategies. Beta blockers or non-dihydropyridine calcium channel blockers are recommended for patients with persistent, paroxysmal, or permanent atrial fibrillation; however, in patients with decompensated heart failure or pre-excitation and atrial fibrillation, non-dihydropyridine calcium channel blockers should not be administered. Propafenone or flecainide (“pill-in-the-pocket”) in combination with a beta blocker or non-dihydropyridine calcium channel blocker are options to terminate atrial fibrillation outside of a hospital for select patients. Non-dihydropyridine calcium channel blockers may also be prescribed as monotherapy or in combination with other treatment in patients with atrial fibrillation and co-morbid hypertrophic cardiomyopathy, certain acute coronary syndrome patients, or chronic obstructive pulmonary disease. In cases of ventricular and supraventricular arrhythmias, intravenous non-dihydropyridine calcium channel blockers are recommended. Oral non-dihydropyridine calcium channel blockers may be used for the chronic management of patients with symptomatic supraventricular tachycardia without ventricular excitation.
- Caution is advised with use in elderly patients with systolic heart failure; non-dihydropyridine calcium channel blockers have the potential to promote fluid retention and/or exacerbate heart failure.

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