



Department of Vermont Health Access

Therapeutic Class Review Calcium-Channel Blocking Agents (Non-dihydropyridines)

Overview/Summary

Calcium-channel blocking agents have multiple roles in treating cardiovascular disease. 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.¹⁻² 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.^{3,4} In addition, calcium-channel blocking agents (also called calcium-channel blockers or CCBs) decrease peripheral vascular resistance by relaxing arteriolar smooth muscle.⁵ Both coronary and systemic vasodilation serve to reduce cardiac workload.⁶ There are two classes of CCBs dihydropyridines, which are similar in chemical structure, and non-dihydropyridines, which are a structurally miscellaneous group.

This review covers the non-dihydropyridine, or miscellaneous, CCBs. They have additional effects and thus a somewhat different therapeutic profile from the dihydropyridines.^{3,7} Generally, the miscellaneous agents produce less peripheral vasodilation than the dihydropyridines, with verapamil producing less than diltiazem. Additionally, diltiazem and verapamil slow conduction in the atrioventricular node, slowing the heart rate.^{1,8,9}

The primary effect of verapamil, a diphenylalkylamine CCB to slow conduction through the atrioventricular node. Verapamil has negative inotropic and chronotropic effects. Because of these properties, it reduces heart rate and systemic blood pressure.⁸ Verapamil is Food and Drug Administration (FDA) approved for the treatment of arrhythmias, chronic stable angina, hypertension, unstable and vasospastic angina.¹⁰⁻¹⁶

Diltiazem's effect on cardiac tissue is slightly different than that of verapamil. Diltiazem is a benzothiazepine and a potent vasodilator of coronary arteries. Although diltiazem does decrease atrioventricular node conduction, it does not have negative inotropic properties. Like verapamil, it reduces heart rate and systemic blood pressure.⁹ Diltiazem is FDA approved for the treatment of chronic stable and variant angina, arrhythmias, and hypertension.¹⁷⁻²⁹

Long-acting CCBs are recommended in patients with stable angina if β -adrenergic blocking agents (β -blockers) are contraindicated. Alternatively, they may be used with β -blockers if initial treatment was not successful.³⁰ Immediate-release and short-acting dihydropyridine CCBs can increase adverse cardiac events and should not be used. The European Society of Cardiology recommends the use of CCBs in patients with angina who can't tolerate β -blockers and who have had a myocardial infarction and who do not have heart failure.⁶ CCBs are recommended in patients with variant angina whose coronary angiogram shows no or non-obstructive coronary artery lesions.³¹

Rate limiting CCBs or β -blockers are recommended as initial monotherapy in patients with permanent atrial fibrillation requiring rate control. To control heart rate during both normal activities and during exercise, rate-limiting calcium antagonists should be given with digoxin. Where urgent rate control is indicated, intravenous treatment with β -blockers or rate-limiting calcium antagonists is recommended.³² Direct comparisons of verapamil and diltiazem have demonstrated similar effectiveness with preserved or improved exercise tolerance in most patients.³³

In general, hypertension guidelines recommend the use of CCBs in patients with certain compelling indications including high coronary disease risk and diabetes.^{34,35} Patients with hypertension and stable angina should be treated with a β -blocker or a long-acting CCB.³⁴

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Diltiazem (Cardizem [®] *, Cardizem CD [®] *, Cardizem LA [®] *, Cartia XT [®] *, Dilacor XR [®] *, Dilt-CD [®] *, Dilt-XR [®] *, Diltzac [®] *, Matzim LA [®] *, Tiazac [®] *, Taztia XT [®] *)	Calcium-channel blocking agent (non-dihydropyridine)	✓
Verapamil (Calan [®] *, Calan SR [®] *, Covera-HS [®] , Isoptin SR [®] *, Verelan [®] *, Verelan PM [®] *)	Calcium-channel blocking agent (non-dihydropyridine)	✓

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration (FDA) Approved Indications¹⁰⁻²⁹

Generic Name	Hypertension	Chronic Stable Angina	Unstable Angina	Vaso-spastic Angina (Prinzmetal's or Variant Angina)	Atrial Fibrillation/Atrial Flutter	Paroxysmal Supraventricular Tachycardia
Diltiazem IR tablets (Cardizem [®])		✓		✓*		
Diltiazem SR capsules, once-daily dosing (Dilacor XR [®] , Dilt-XR [®])	✓	✓				
Diltiazem SR capsules, twice-daily dosing	✓					
Diltiazem SR coated bead capsules (Cardizem CD [®] , Dilt-CD [®] , Cartia XT [®])	✓	✓		✓*		
Diltiazem SR coated beads tablets (Cardizem LA [®] , Matzim LA [®])	✓	✓				
Diltiazem ER capsules (Tiazac [®] , Diltzac [®] , Taztia XT [®])	✓	✓				
Diltiazem IV					✓†	✓‡
Verapamil IR tablets (Calan [®])	✓	✓	✓§	✓	✓	✓¶
Verapamil ER tablets (Calan	✓					

Generic Name	Hypertension	Chronic Stable Angina	Unstable Angina	Vaso-spastic Angina (Prinzmetal's or Variant Angina)	Atrial Fibrillation/Atrial Flutter	Paroxysmal Supraventricular Tachycardia
SR [®] , Ispodin SR [®])						
Verapamil osmotic-release ER tablets (Covera-HS [®])	✓	✓				
Verapamil ER capsules (Verelan [®] , Verelan PM [®])	✓					
Verapamil IV					✓ #	✓ **

ER=extended-release, IR=immediate-release, IV=intravenous, SR=sustained-release

*Angina due to coronary artery spasm.

† Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White syndrome or short PR syndrome.

‡ Rapid conversion of PSVT to sinus rhythm. This includes atrioventricular nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathway such as the Wolff-Parkinson-White syndrome or short PR syndrome.

§Crescendo, pre-infarction angina.

|| In association with digitalis for the control of ventricular rate at rest and during stress in patients with chronic atrial flutter and/or atrial fibrillation.

¶ Prophylaxis of repetitive paroxysmal supraventricular tachycardia.

Temporary control of rapid ventricular rate in atrial flutter or atrial fibrillation except when the atrial flutter and/or atrial fibrillation are associated with accessory bypass (Wolff-Parkinson-White and Lown-Ganong-Levine syndromes).

**Rapid conversion to sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory bypass tracts (Wolff-Parkinson-White and Lown-Ganong-Levine syndromes).

Pharmacokinetics

Table 3. Pharmacokinetics^{1,10-29}

Generic Name	Bio-availability (%)	Protein Binding (%)	Active Metabolites	Elimination (%)	Half-Life (hours)
Diltiazem IR tablets	40	70 to 80	Yes	Urine (2 to 4 unchanged)	3.0 to 4.5
Diltiazem SR capsules (once-daily dosing)	40 to 41	70 to 80	Yes	Urine (2 to 4 unchanged)	5 to 10
Diltiazem SR capsules (twice-daily dosing)	40	70 to 80	Yes	Urine (2 to 4 unchanged)	5 to 7
Diltiazem SR coated bead capsules	40	70 to 80	Yes	Urine (2 to 4 unchanged)	5 to 8
Diltiazem SR coated beads tablets	40	70 to 80	Yes	Urine (2 to 4 unchanged)	6 to 9
Diltiazem ER capsules	40	70 to 80	Yes	Urine (2 to 4 unchanged)	4.0 to 9.5
Diltiazem IV	100	70 to 80	Yes	Urine (2 to 4 unchanged)	3.4 to 4.9
Verapamil IR tablets	20 to 35	90	Yes	Feces (16 or greater); urine (70 as metabolites, 3 to 4 unchanged)	4.5 to 12.0
Verapamil ER tablets	20 to 35	90	Yes	Feces (16 or greater); urine (70 as metabolites, 3 to 4 unchanged)	4.5 to 12.0
Verapamil osmotic-release ER tablets	20 to 35	90	Yes	Feces (16 or greater); urine (70 as metabolites, 3 to 4 unchanged)	4.5 to 12.0

Generic Name	Bio-availability (%)	Protein Binding (%)	Active Metabolites	Elimination (%)	Half-Life (hours)
Verapamil ER capsules	20 to 35	90	Yes	Feces (16 or greater); urine (70 as metabolites, 3 to 4 unchanged)	4.5 to 12.0
Verapamil IV	100	90	Yes	Feces (16 or greater); urine (70 as metabolites, 3 to 4 unchanged)	2 to 5

ER=extended release, IR=immediate release, IV=intravenous, SR=sustained release

Clinical Trials

The non-dihydropyridine calcium channel blockers are indicated to treat hypertension and angina, in addition to slowing ventricular rate in patients with atrial fibrillation/atria 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.³⁶⁻³⁹ A direct comparison between diltiazem and verapamil found no significant differences between the agents in exercise tolerance, though resting heart rate, angina frequency and nitroglycerin use were all significantly lower in the diltiazem group.³⁶ Siu and colleagues compared the use of intravenous diltiazem with the use of intravenous digoxin or amiodarone in patients presenting to the emergency room with symptomatic acute atrial fibrillation. Significantly more patients in the diltiazem group achieved rate control compared to patients in the digoxin and amiodarone groups, in addition to a shorter average time to ventricular rate control and shorter hospital stay.⁴⁰ However, no significant difference was observed between groups in sinus rhythm conversion rate or time to sinus conversion.⁴⁰ Both diltiazem and verapamil have shown efficacy in the treatment of hypertension, though comparisons with other classes of medication have not consistently demonstrated “superiority” of either agent.^{41,42} 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 four hours after awakening in addition to greater reductions in heart rate; however mean 24-hour systolic blood pressure reductions were significantly greater with amlodipine.⁴¹ 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 β -blockers and diuretics.⁴³⁻⁴⁷

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Angina				
<p>De Rosa et al³⁶</p> <p>Diltiazem SR 300 mg Daily vs verapamil SR 240 mg Daily vs placebo</p>	<p>DB, XO</p> <p>Men and women 48 to 72 years of age, with stable exertional angina, a positive test for myocardial ischemia and documented coronary artery disease</p>	<p>N=20</p> <p>12 weeks</p>	<p>Primary: Exercise tolerance test: time to onset of angina, time to 1-mm ST-segment depression and total exercise duration</p> <p>Secondary: Heart rate, angina frequency, nitroglycerin use and adverse events</p>	<p>Primary: Time to onset of angina increased significantly in both groups compared to the placebo group (verapamil vs placebo; $P<0.05$ and diltiazem vs placebo; $P<0.005$).</p> <p>Time to 1-mm ST-segment depression increased significantly in both groups compared to the placebo group (verapamil vs placebo; $P<0.05$ and diltiazem vs placebo; $P<0.005$).</p> <p>Total exercise duration increased significantly in both groups compared to the placebo group (verapamil vs placebo; $P<0.05$ and diltiazem vs placebo; $P<0.005$).</p> <p>For each primary endpoint, there was no significant difference between the treatment groups.</p> <p>Secondary: Heart rates were similar between the treatment groups, except resting heart rate was significantly lower in the diltiazem group as compared to the verapamil group (68.5 vs 75.9; $P<0.05$).</p> <p>Angina frequency and nitroglycerin use decreased significantly in the diltiazem group compared to the placebo group ($P<0.05$) and to the verapamil group ($P<0.05$).</p> <p>Edema and flushing were most frequently reported. Similar rates of adverse events were reported for both treatments.</p>
<p>Chugh et al³⁷</p> <p>Diltiazem 240 mg Daily for 2 weeks then 360 mg Daily for 2 weeks vs</p>	<p>DB, DD, PG, RCT</p> <p>Patients with stable angina, BP in the range of 100/60 to 170/110 mm Hg and a positive ischemic</p>	<p>N=67</p> <p>4 weeks</p>	<p>Primary: Treadmill exercise test: time to onset of angina, time to 1-mm ST-segment depression</p> <p>Secondary:</p>	<p>Primary: Both treatment groups, and all doses, had significant increases in time to onset of angina from baseline ($P<0.001$ for all). There was no significant difference between the treatment groups ($P=0.838$) and between dose levels ($P=0.144$) in time to onset of angina.</p> <p>Both treatment groups, and all doses, had significant increases in time to 1-mm ST-segment depression from baseline, except the low-dose</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
amlodipine 5 mg Daily for 2 weeks then 10 mg Daily for 2 weeks	response on a treadmill test, history of angiography		Heart rate, BP, number of angina episodes and use of nitrates	<p>amlodipine group ($P < 0.004$, except $P = 0.063$). There was no significant difference between the treatment groups and between dose levels ($P = 0.114$) in time to 1-mm ST-segment depression ($P = 0.691$).</p> <p>Secondary: There was no significant difference between the groups in heart rate at rest or maximal exercise.</p> <p>There was no significant difference between the groups in BP at rest or maximal exercise, except SBP at rest was higher in the diltiazem group (137 to 143 vs 129 to 135 mm Hg; $P = 0.029$).</p> <p>Both treatments reduced the number of angina episodes and the use of nitrates, but these results were not statistically different between the groups (P value not reported).</p>
<p>van Kesteren et al³⁸</p> <p>Diltiazem CR 90 to 120 mg BID</p> <p>vs</p> <p>amlodipine 5 to 10 mg Daily</p>	<p>DB, MC</p> <p>Men and women 41 to 77 years of age with a history of stable angina pectoris, a positive exercise tolerance test, and positive thallium scan or positive coronary angiogram</p>	<p>N=132</p> <p>8 weeks</p>	<p>Primary: Exercise tolerance test: time to 1-mm ST-segment depression, time to onset of chest pain, time to end of exercise (exercise duration)</p> <p>Secondary: Safety</p>	<p>Primary: Diltiazem and amlodipine treatment resulted in significant increases in time to 1-mm ST-segment depression as compared to baseline ($P < 0.0001$). Treatments were not significantly different from each other ($P > 0.05$).</p> <p>Diltiazem and amlodipine treatment resulted in significant increases in time to onset of chest pain at four and eight weeks, (10 and 13% for amlodipine; $P < 0.0001$; 5 and 7% for diltiazem; $P = 0.009$). Treatments were not significantly different from each other ($P > 0.05$).</p> <p>Amlodipine treatment resulted in a significant increase in total exercise duration as compared to baseline ($P = 0.0002$), however the change from baseline for diltiazem was not significantly increased ($P = 0.43$). There was no significant difference between the treatment groups at endpoint.</p> <p>Secondary: Ten patients (15.2%) in the amlodipine group and 17 patients (25.8%) in the diltiazem group reported an adverse event; two patients from the amlodipine group and six patients from the diltiazem group</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				subsequently withdrew from the study.
<p>Frishman et al³⁹</p> <p>Verapamil 240 to 480 mg at bedtime</p> <p>vs</p> <p>amlodipine 5 to 10 mg Daily</p> <p>vs</p> <p>amlodipine 5 to 10 mg Daily plus atenolol 50 mg Daily</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 30 to 80 years of age with chronic stable angina pectoris, evidence of exercise-induced ST-segment depression ≥ 1 mm and other evidence of cardiac disease</p>	<p>N=551</p> <p>4 week</p>	<p>Primary: Exercise tolerance test (symptom-limited exercise duration, time ≥ 1-mm ST-segment depression and time to moderate angina)</p> <p>Secondary: 48-hour Holter-determined number of ischemic episodes, mean and total duration of ischemia, maximal depth of ST depression, heart rate at onset of ischemia</p>	<p>Primary: Treatment with verapamil, amlodipine, and amlodipine plus atenolol resulted in significantly better results than patients treated with placebo in: symptom-limited exercise duration, time ≥ 1-mm ST-segment depression and time to moderate angina ($P \leq 0.01$ for all vs placebo).</p> <p>Secondary: Treatment with verapamil, amlodipine, and amlodipine plus atenolol resulted in significantly fewer ischemic episodes in 48-hour Holter monitoring ($P = 0.003$ for verapamil vs placebo).</p> <p>Treatment with amlodipine monotherapy resulted in a significant increase in duration of ischemic episode ($P \leq 0.05$ vs verapamil vs amlodipine plus atenolol and vs placebo).</p> <p>Treatment with verapamil and amlodipine plus atenolol resulted in a decrease in duration of ischemic episodes as compared to treatment with amlodipine and placebo ($P \leq 0.05$ for each).</p> <p>Heart rate at the onset of ischemic episode was significantly lower in the verapamil group and in the amlodipine plus atenolol group ($P \leq 0.05$ vs amlodipine) and higher in the amlodipine group ($P \leq 0.05$ vs verapamil, vs amlodipine plus atenolol and vs placebo).</p>
Atrial Fibrillation				
<p>Siu et al⁴⁰</p> <p>Diltiazem 0.25 mg/kg bolus over 2 minutes followed by a second bolus of 0.35 mg/kg if ventricular rate remained >90 bpm after 15 minutes; maintenance infusion of 10 mg/hour for 24 hours</p>	<p>OL, RCT</p> <p>Patients presenting to the emergency room with symptomatic acute AF for <48 hours and a rapid ventricular rate >120 bpm</p>	<p>N=150</p> <p>24 hours</p>	<p>Primary: Ventricular rate control within the first 24 hours (sustained ventricular rate reduction <90 bpm for ≥ 4 hours)</p> <p>Secondary:</p>	<p>Primary: Ventricular rate control was achieved in 79% of patients.</p> <p>Significantly more patients in the diltiazem group achieved rate control compared to patients in the digoxin and amiodarone groups (90 compared to 74 and 74% respectively; $P = 0.047$).</p> <p>Patients in the diltiazem group had persistently lower ventricular rate after the first hour compared to the patients in the digoxin and amiodarone groups ($P < 0.05$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
<p>vs</p> <p>digoxin 0.5 mg bolus followed by 0.25 mg every 8 hours</p> <p>vs</p> <p>amiodarone 300 mg over the first hour followed by 10 mg/kg over 24 hours</p>	<p>necessitating hospitalization</p>		<p>Time to ventricular rate control, sinus rhythm conversion, symptom severity, hospital stay, adverse events</p>	<p>Secondary:</p> <p>The average time to ventricular rate control in the diltiazem group was three hours and was significantly shorter than the digoxin and amiodarone groups ($P<0.0001$).</p> <p>No significant differences were observed between groups in the sinus rhythm conversion rate within the first 24 hours or by discharge ($P>0.05$).</p> <p>No significant differences were observed between groups in the time to sinus conversion ($P>0.05$).</p> <p>Symptom severity and frequency scores were reduced in all treatment groups within 24 hours.</p> <p>Patients in the diltiazem group had significantly lower symptom severity scores at 24 hours compared to patients in the digoxin and amiodarone groups ($P=0.047$ and $P=0.01$ respectively).</p> <p>No significant difference was observed in symptom frequency scores at 24 hours.</p> <p>A significantly shorter hospital stay was observed in the diltiazem group compared to the digoxin and amiodarone groups ($P=0.023$).</p> <p>No bradycardia, hypotension, new onset congestive heart failure or myocardial infarction was observed in any of the patients.</p>
<p>Wyse et al⁴⁸</p> <p>Rhythm control therapy: amiodarone, disopyramide, flecainide, moricizine*, procainamide, propafenone, quinidine, sotalol, dofetilide and combinations of these drugs (doses not specified)</p>	<p>MC, RCT</p> <p>Patients ≥ 65 years of age who had AF that was likely recurrent, AF was likely to cause illness or death, long-term</p>	<p>N=4,060</p> <p>3.5 years</p>	<p>Primary:</p> <p>Overall mortality</p> <p>Secondary:</p> <p>Composite death, disabling stroke, disabling anoxic encephalopathy, major bleeding and</p>	<p>Primary:</p> <p>The difference in mortality between the two groups was not significant (HR, 1.15; 95% CI, 0.99 to 1.34; $P=0.08$).</p> <p>Secondary:</p> <p>The rates of the composite end point of death, disabling stroke, disabling anoxic encephalopathy, major bleeding or cardiac arrest were also similar in the two groups ($P=0.33$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
<p>and adjusted to maintain normal sinus rhythm)</p> <p>vs</p> <p>rate control therapy: β-blockers, calcium-channel blockers, digoxin and combinations of these drugs (doses not specified and adjusted to maintain normal sinus rhythm)</p>	<p>treatment for AF was warranted, no contraindication to anticoagulation therapy, eligible to undergo trials of ≥ 2 drugs in both treatment strategies and treatment with either strategy could be initiated immediately after randomization</p>		<p>cardiac arrest</p>	
<p>Van Gelder et al⁴⁹</p> <p>Rhythm control therapy: electrical cardioversion, then sotalol 160 to 320 mg (based on weight and renal function); if recurrence within 6 months, repeat electrical cardioversion, then flecainide 200 to 300 mg daily or propafenone 450 to 900 mg daily; if recurrence again, electrical cardioversion repeated along with amiodarone 600 mg daily for 4 weeks then 200 mg daily</p> <p>vs</p> <p>rate control therapy: digitalis, non-dihydropyridine calcium</p>	<p>MC, RCT</p> <p>Patients with recurrent persistent AF or AFL, who have undergone 1 electrical cardioversion during the previous 2 years, with a maximum of 2</p>	<p>N=522</p> <p>2 years</p>	<p>Primary: Composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, the need for implantation of a pacemaker or severe adverse effects of antiarrhythmic drugs</p> <p>Secondary: Not reported</p>	<p>Primary: The composite end point occurred in 44 (17.2%) patients receiving rate-control and in 60 (22.6%) patients receiving rhythm-control (absolute difference, -5.4; 90% CI, -11.0 to 0.4).</p> <p>Death from cardiovascular causes occurred in 18 (7.0%) patients receiving rate-control and in 18 (6.8%) patients receiving rhythm-control (absolute difference, 0.2; 90% CI, -3.4 to 3.9).</p> <p>Heart failure occurred in nine (3.5%) patients receiving rate-control and in 12 (4.5%) patients receiving rhythm-control (absolute difference, -1.0; 90% CI, -3.8 to 1.8).</p> <p>Thromboembolic complications occurred in 14 (5.5%) patients receiving rate-control and in 21 (7.9%) patients receiving rhythm-control (absolute difference, -2.4; 90% CI, -6.0 to 1.2).</p> <p>Bleeding occurred in 12 (4.7%) patients receiving rate-control and in nine (3.4%) patients receiving rhythm-control (absolute difference, 1.3; 90% CI, -1.5 to 4.1).</p> <p>Severe adverse effects of antiarrhythmic drugs occurred in two (0.8%)</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
channel blocker and β -blocker, alone or in combination				<p>patients receiving rate-control and in 12 (4.5%) patients receiving rhythm-control (absolute difference, -3.7; 90% CI, -6.0 to -1.4).</p> <p>A pacemaker was implanted in three (1.2%) patients receiving rate-control and in eight (3.0%) patients receiving rhythm-control (absolute difference, -1.8; 90% CI, -3.9 to 0.2).</p> <p>Secondary: Not reported</p>
<p>Opolski et al⁵⁰</p> <p>Rhythm control therapy: propafenone 450 to 600 mg/day, disopyramide 300 to 600 mg/day or sotalolol 160 to 320 mg/day</p> <p>vs</p> <p>rate control therapy: β-blockers, non-dihydropyridine calcium channel blockers, digoxin or a combination of these drugs</p> <p>All patients underwent electric cardioversion prior to the initiation of trial medication.</p> <p>Drug given to patient was determined by their arrhythmia etiology, concomitant heart diseases and age.</p> <p>If patient had recurrent AF,</p>	<p>MC, OL, RCT</p> <p>Patients 50 to 75 years of age with AF known to be present continuously for between 7 days and 2 years with acceptable etiology of the arrhythmia related to ischemic heart disease, arterial hypertension, hemo-dynamically insignificant valvular heart disease or lack of assessable etiology</p>	<p>N=205</p> <p>1 year</p>	<p>Primary: Composite of death from any cause (thromboembolic complications and intracranial or other major hemorrhage)</p> <p>Secondary: Rate control, sinus rhythm maintenance, discontinuation of therapy (proarrhythmic effects), hemorrhage, hospitalization, new or worsening CHF, changes in exercise tolerance</p>	<p>Primary: There was not a significant difference in composite of death from any cause between patients receiving rate control and patients receiving rhythm control (OR, 1.98; 95% CI, 0.28 to 22.3; $P>0.71$).</p> <p>Secondary: Patients receiving rhythm control had a significantly lower mean heart rate (79.1 ± 8.6 bpm) in 24 hour Holter monitoring compared to patients receiving rate control (85.8 ± 7.5 bpm; $P<0.003$).</p> <p>Four patients receiving rhythm control experienced proarrhythmic effects (P value not reported). Whether this lead to discontinuation of therapy was not mentioned.</p> <p>At the end of the trial, 66 patients (63.5%) receiving rhythm control were in sinus rhythm, with 27 of these patients successfully maintained with the first antiarrhythmic compound administered after the first cardioversion (P values not reported).</p> <p>There was not a significant difference seen in bleeding complications between the rhythm control group (eight patients) and rate control group (five patients; P value not reported).</p> <p>A significantly lower number of hospitalizations were seen with rate control compared to rhythm control (12 vs 74%, respectively; $P<0.001$).</p> <p>Both rhythm control and rate control had significant improvements in</p>

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cardioversion was repeated and an alternate antiarrhythmic agent was given in addition to amiodarone.				<p>CHF class at some point during follow up compared to baseline ($P<0.001$ and $P<0.05$, respectively). No difference in NYHA functional class between patients initially randomized to the two strategies was found at the end of the follow up period (P value not reported).</p> <p>At the end of the trial, both maximal workload and exercise duration were higher with rhythm control compared to rate control ($P<0.001$ and $P<0.001$, respectively).</p>
Hypertension				
<p>Wright et al⁴¹</p> <p>Diltiazem graded-release 360 to 540 mg Daily</p> <p>vs</p> <p>amlodipine 5 to 10 mg Daily</p>	<p>AC, DB, MC, PG, RCT</p> <p>Male and female African Americans patients 18 to 80 years of age with hypertension (DBP 85 to 109 mm Hg and SBP <180 mm Hg)</p>	<p>N=268</p> <p>12 weeks</p>	<p>Primary: Change from baseline in DBP during first four hours of awakening as recorded by ambulatory BP monitoring</p> <p>Secondary: Changes from baseline in BP, heart rate, rate-pressure product, safety</p>	<p>Primary: Reductions in DBP during the first four hours after awakening, and from 6AM to noon, were significantly greater in the diltiazem group than in the amlodipine group (-13.12 vs -9.65 mm Hg; $P=0.0049$ and -11.97 vs -8.75 mm Hg; $P=0.0019$).</p> <p>Secondary: Reductions in SBP during the first four hours after awakening and between 6AM and noon, were similar between the groups ($P<0.0768$ and $P<0.9470$).</p> <p>Mean 24-hour SBP reductions were significantly greater in the amlodipine group than in the diltiazem group (-14.08 vs -10.64; $P=0.0022$).</p> <p>Reductions in heart rate were significantly greater in the diltiazem group than in the amlodipine group (24 hour mean: -4.88 vs 1.77; $P<0.0001$).</p> <p>Reductions in rate-pressure product were significantly greater in the diltiazem group than in the amlodipine group (24 hour mean: -1,493 vs -881; $P<0.0008$).</p> <p>In the diltiazem and amlodipine groups respectively, 1.5 and 2.2% discontinued early due to adverse events.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
<p>Rosei et al⁴² VHAS</p> <p>Verapamil SR 240 mg Daily vs chlorthalidone 25 mg Daily</p>	<p>DB (1st 6 months), MC, PG, RCT</p> <p>Patients 40 to 65 years of age, with hypertension (SBP \geq160 mm Hg and DBP \geq95 mm Hg)</p>	<p>N=1,414</p> <p>2 years</p>	<p>Primary: BP</p> <p>Secondary: Cardiovascular events, adverse events</p>	<p>Primary: Both treatments significantly reduced SBP and DBP compared to baseline, however reductions did not significantly differ between treatments (verapamil reduction, 27.6/17.0 mm Hg vs chlorthalidone reduction, 28.6/16.6 mm Hg; $P < 0.01$ for each vs baseline).</p> <p>Goal DBP was achieved in 69.3% of patients receiving verapamil and 66.9% of patients receiving chlorthalidone (P value not reported).</p> <p>Secondary: Serum total cholesterol levels and heart rate decreased significantly in the verapamil group as compared to baseline and the chlorthalidone group (total cholesterol; $P < 0.01$ for both, heart rate; $P < 0.05$).</p> <p>The number of nonfatal cardiovascular events was similar between the groups, 37 in the verapamil group and 39 in the chlorthalidone group (P value not reported).</p> <p>The number of cardiovascular deaths was similar between the groups, five in the verapamil group and four in the chlorthalidone group (P value not reported).</p> <p>Hypokalemia and hyperuricemia occurred significantly more frequently in the chlorthalidone group than in the verapamil group ($P < 0.01$ for both).</p> <p>Two hundred and thirty six patients reported 403 adverse events in the chlorthalidone group and 230 patients reported 387 adverse events in the verapamil group. Asthenia was the most commonly reported adverse event in the chlorthalidone group and constipation was the most commonly reported adverse event in the verapamil group.</p>
<p>Van Bortel et al⁵¹</p> <p>Nebivolol vs</p>	<p>MA</p> <p>12 RCTs involving >25 patients with essential</p>	<p>N=2,653</p> <p>Duration varied</p>	<p>Primary: Antihypertensive effect and tolerability</p>	<p>Primary: Overall, higher response rates were observed with nebivolol than all other antihypertensive agents combined (OR, 1.41; 95% CI, 1.15 to 1.73; $P = 0.001$) and compared to the ACE inhibitors (OR, 1.92; 1.30 to 2.85; $P = 0.001$), but response rates to nebivolol were similar to β-</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
active comparator (ARB, β -blocker, calcium channel blocker or ACE inhibitor) or placebo	hypertension where nebivolol 5 mg Daily was compared to placebo or other active drugs for >1 month		Secondary: Not reported	<p>blockers (OR, 1.29; 95% CI, 0.81 to 2.04; $P=0.283$), calcium channel blockers (OR, 1.19; 95% CI, 0.83 to 1.70; $P=0.350$) and losartan (OR, 1.35; 95% CI, 0.84 to 2.15; $P=0.212$).</p> <p>Overall, a higher percentage of patients obtained normalized BP with nebivolol compared to the other antihypertensive agents combined (OR, 1.35; 95% CI, 1.07 to 1.72; $P=0.012$). A higher percentage of patients receiving nebivolol obtained normalized BP compared to patients receiving losartan (OR, 1.98; 95% CI, 1.24 to 3.15; $P=0.004$) and patients receiving calcium channel blockers (OR, 1.96; 95% CI, 1.05 to 1.96; $P=0.024$), but not when compared to patients receiving other β-blockers (OR, 1.29; 95% CI, 0.81 to 1.65; $P=0.473$).</p> <p>Overall, the percentage of adverse events was significantly lower with nebivolol compared to the other antihypertensive agents combined (OR, 0.59; 95% CI, 0.48 to 0.72; $P<0.001$) and similar to placebo (OR, 1.16; 95% CI, 0.76 to 1.67; $P=0.482$). In comparing nebivolol to the individual treatments, nebivolol had a lower percentage of adverse events compared to losartan (OR, 0.52; 95% CI, 0.30 to 0.89; $P=0.016$), the other β-blockers (OR, 0.56; 95% CI, 0.36 to 0.85; $P=0.007$) and calcium channel blockers (OR, 0.49; 95% CI 0.33 to 0.72; $P<0.001$), but was similar to ACE inhibitors (OR, 0.75; 95% CI 0.52 to 1.08).</p> <p>Secondary: Not reported</p>
Cardiovascular Outcomes				
Boden et al ⁵² INTERCEPT Diltiazem 300 mg Daily vs placebo Daily	DB, MC, PG, PRO, RCT Patients 75 years of age and younger, with acute MI, without CHF and who received a thrombolytic agent	N=874 Up to 6 months	Primary: Composite first-event rate of: cardiac death, nonfatal reinfarction or refractory ischemia Secondary: Composite of first	Primary: There was no significant difference between diltiazem treatment and placebo treatment in composite event rate (131 primary outcome events occurred in the placebo group and 97 occurred in the diltiazem group; $P=0.07$). Secondary: Rates of all composite nonfatal cardiac events (nonfatal reinfarction combined with refractory ischemia or all recurrent ischemia or need for revascularization) significantly favored the diltiazem group over the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			occurrence of cardiac death, nonfatal reinfarction, recurrent ischemia, composite of cardiac death, nonfatal reinfarction, need for myocardial revascularization, safety	<p>placebo group ($P=0.05$, $P=0.05$, $P=0.03$ respectively).</p> <p>Rates of cardiac death, nonfatal reinfarction, refractory ischemia and all recurrent ischemia were similar between the diltiazem group and the placebo group, however the need for revascularization favored the diltiazem group ($P=0.67$, $P=0.47$, $P=0.07$, $P=0.07$, $P=0.03$).</p> <p>There was no increase in rates of CHF, bleeding, cancer or cerebrovascular accidents in the diltiazem group.</p>
<p>Gibson et al⁵³</p> <p>Diltiazem 60 mg QID or verapamil 120 mg TID</p> <p>vs</p> <p>placebo</p>	<p>RETRO combined subgroup analysis of 2 RCT</p> <p>Patients suffering acute non-Q-wave MI</p>	<p>N=817</p> <p>12 to 18 months</p>	<p>Primary: All cause mortality</p> <p>Secondary: Combined cardiac events</p>	<p>Primary: Patients receiving treatment (either agent) had a 42% lower mortality rate than those receiving placebo ($P=0.010$).</p> <p>Secondary: Patients receiving treatment (either agent) had a 31% lower event rate (death or recurrent MI) than those receiving placebo ($P<0.006$).</p>
<p>Pepine et al⁴³</p> <p>INVEST</p> <p>Verapamil SR 120 to 480 mg Daily</p> <p>vs</p> <p>atenolol 25 to 200 mg Daily</p> <p>Trandolapril and/or HCTZ were added to control BP.</p>	<p>MC, open blinded endpoint, PRO, RCT</p> <p>Patients 50 years of age and older with hypertension requiring drug therapy (BP>140/90 or >130/80 mm Hg if diabetic or with renal impairment), and documented coronary artery disease</p>	<p>N=22,576</p> <p>24 months</p>	<p>Primary: First occurrence of combined death (all-cause), nonfatal MI, or nonfatal stroke</p> <p>Secondary: Occurrence of death (all-cause), nonfatal MI, nonfatal stroke; time to most serious event, cardiovascular death, angina, cardiovascular hospitalization, BP control, cancer, Alzheimer disease, Parkinson disease,</p>	<p>Primary: There was no significant difference between the verapamil group and the atenolol group in time to first occurrence of death, nonfatal MI and nonfatal stroke ($P=0.57$). One thousand one hundred and seventy one events were reported by 1,119 patients in the verapamil group and 1,209 events were reported by 1,150 patients in the atenolol group.</p> <p>Secondary: All cause death occurred in 873 patients in the verapamil group and 893 patients in the atenolol group ($P=0.72$). Equal number, 431 in each treatment group was classified as cardiovascular.</p> <p>Nonfatal MI were reported in 151 patients in the verapamil group and 153 patients in the atenolol group ($P=0.95$).</p> <p>Nonfatal strokes were reported in 131 patients in the verapamil group and 148 patients in the atenolol group ($P=0.33$).</p> <p>There was no significant difference between the verapamil group and</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			gastrointestinal tract bleeding, adverse events	<p>the atenolol group in cardiovascular related death or hospitalization ($P=0.94$, $P=0.59$).</p> <p>Reported angina decreased similarly in both groups ($P=0.18$), however the average frequency was lower in the verapamil group as compared to the atenolol group ($P=0.02$).</p> <p>There was no significant difference between the verapamil group and the atenolol group in reduction of SBP (verapamil, -18.7 vs -19.0 mm Hg; $P=0.41$) and DBP (verapamil, -10.0 vs -10.2 mm Hg; $P=0.26$).</p> <p>Overall, 71.7% of verapamil and 70.7% of atenolol treated patients achieved BP goal at 24 months ($P=0.18$).</p> <p>The average resting heart rate was lower in the atenolol group than the verapamil group (69.2 vs 72.8 bpm; $P<0.001$).</p> <p>Rates did not differ between the groups for rates of cancer, Alzheimer disease, Parkinson disease or gastrointestinal tract bleeding ($P>0.05$ for all).</p> <p>Constipation and cough were reported more frequently in the verapamil group and dyspnea, lightheadedness, symptomatic bradycardia and wheezing were more frequently reported in the atenolol group.</p>
<p>Bangalore et al⁴⁴ INVEST substudy</p> <p>Verapamil SR 120 to 480 mg Daily</p> <p>vs</p> <p>atenolol 25 to 200 mg Daily</p> <p>Trandolapril and/or HCTZ were added to control BP.</p>	<p>MC, open blinded endpoint, PRO, RCT</p> <p>Patients 50 years of age and older with hypertension requiring drug therapy (BP>140/90 or >130/80 mm Hg if diabetic or with</p>	<p>N=22,576</p> <p>24 months</p>	<p>Primary: First occurrence of death, nonfatal MI, nonfatal stroke</p> <p>Secondary: Death, total MI, total stroke</p>	<p>Primary: No significant difference was observed between groups in the primary endpoint ($P=0.30$).</p> <p>Among patients with the primary outcome, no significant difference was observed between groups in the risk of death ($P=0.94$).</p> <p>There was no significant difference between groups in the risk of nonfatal MI ($P=0.41$).</p> <p>There was a trend toward a 29% reduction in the risk of nonfatal stroke in the verapamil group compared to the atenolol group</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	renal impairment), and documented coronary artery disease			<p>($P=0.06$).</p> <p>Secondary: The risks of fatal and nonfatal MI were similar between groups.</p> <p>No significant differences were observed between groups in fatal and nonfatal stroke ($P=0.18$).</p>
<p>Mancia et al⁴⁵ INVEST</p> <p>Verapamil SR 120 to 480 mg Daily</p> <p>vs</p> <p>atenolol 25 to 200 mg Daily</p>	<p>MC, open blinded endpoint, PRO, RCT</p> <p>Patients with hypertension, requiring drug therapy (BP>140/90 or >130/80 mm Hg if diabetic or with renal impairment), and coronary artery disease</p>	<p>N=22,576</p> <p>24 months</p>	<p>Primary: Occurrence of death, nonfatal MI and nonfatal stroke</p> <p>Secondary: BP control rates</p>	<p>Primary: Rates (death, nonfatal MI and nonfatal stroke) were similar for both treatment groups (P value not reported).</p> <p>Secondary: Rates of death, MI and stroke declined as the number of office visits for which BP was controlled increased ($P<0.001$).</p>
<p>Hansson et al⁴⁶ NORDIL</p> <p>Diltiazem 180 to 360 mg Daily</p> <p>vs</p> <p>conventional (diuretic, β-blocker or both)</p>	<p>Blinded endpoint, MC, open, PRO, RCT</p> <p>Patients 50 to 74 years of age with DBP ≥ 100 mm Hg and previously untreated</p>	<p>N=10,881</p> <p>4.5 years</p>	<p>Primary: Combined fatal and nonfatal stroke, fatal and nonfatal MI, other cardiovascular death</p> <p>Secondary: Fatal plus nonfatal stroke and fatal plus nonfatal MI</p>	<p>Primary: The primary endpoint occurred in 403 of the diltiazem patients and 400 of the diuretic/β-blocker patients (RR, 1.00; 95% CI, 0.87 to 1.15; $P=0.97$).</p> <p>Secondary: Rates of secondary endpoints were similar between the groups. Fatal plus nonfatal stroke occurred in 159 of the diltiazem patients and 196 of the diuretic/β-blocker patients ($P=0.04$).</p> <p>Fatal plus nonfatal MI occurred in 183 of the diltiazem patients and 157 of the diuretic/β-blocker patients ($P=0.17$).</p> <p>Other endpoints were not statistically different between the groups including cardiovascular death ($P=0.41$), all cardiac events ($P=0.57$) and congestive heart failure ($P=0.42$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
<p>Black et al⁴⁷ CONVINCE</p> <p>Verapamil ER 180 mg Daily</p> <p>vs</p> <p>atenolol 50 mg Daily</p> <p>vs</p> <p>HCTZ 12.5 mg Daily</p>	<p>AC, DB, MC, RCT</p> <p>Patients 55 years of age and older with hypertension and at least one risk factor for cardiovascular disease</p>	<p>N=16,476</p> <p>3 years</p>	<p>Primary: Composite first occurrence of acute MI, stroke or cardiovascular disease-related death</p> <p>Secondary: Cardiovascular endpoints expanded, all-cause mortality, cancer, hospitalization for bleeding, incidence of primary endpoints between 6AM and noon, adverse events</p>	<p>Primary: There was no significant difference between the verapamil treatment group and the atenolol or HCTZ treatment groups in the composite primary endpoint (HR, 1.02; 95% CI, 0.88 to 1.18; <i>P</i>=0.77).</p> <p>Secondary: There was no significant difference between the verapamil treatment group and the atenolol or HCTZ treatment group in rates of cardiovascular-related hospitalization (<i>P</i>=0.31), death (all-cause mortality) (<i>P</i>=0.32) and cancer rates (<i>P</i>=0.46).</p> <p>Patients treated with verapamil experienced a significantly higher rate of death or bleeding unrelated to stroke (HR, 1.54; 95% CI, 1.15 to 2.04; <i>P</i>=0.003).</p> <p>Primary endpoints did not differ significantly based on time of day (<i>P</i>=0.43).</p> <p>Patients treated with verapamil were more likely to withdraw for adverse events or symptoms than those treated with atenolol or HCTZ (<i>P</i>=0.02).</p>
<p>Wiysonge et al⁵⁴</p> <p>β-blockers (atenolol, metoprolol, oxprenolol* or propranolol)</p> <p>vs</p> <p>other antihypertensive therapies (i.e., placebo, diuretics, calcium channel blockers or renin-angiotensin system inhibitors)</p>	<p>MA</p> <p>13 RCTs evaluating patients ≥18 years of age with hypertension</p>	<p>N=91,561</p> <p>Duration varied</p>	<p>Primary: All-cause mortality</p> <p>Secondary: Stroke, coronary heart disease, cardiovascular death, total cardiovascular disease, adverse reactions</p>	<p>Primary: There was not a significant difference observed in all-cause mortality between β-blockers and placebo (RR, 0.99; 95% CI, 0.88 to 1.11; <i>P</i> value not reported), diuretics (RR, 1.04; 95% CI, 0.91 to 1.19; <i>P</i> value not reported) or renin-angiotensin system inhibitors (RR, 1.10; 95% CI, 0.98 to 1.24; <i>P</i> value not reported). There was a significantly higher rate in all-cause mortality with β-blockers compared to calcium channel blockers (RR, 1.07; 95% CI, 1.00 to 1.14; <i>P</i>=0.04).</p> <p>Secondary: There was a significant decrease in stroke observed with β-blockers compared to placebo (RR, 0.80; 95% CI, 0.66 to 0.96). Also there was a significant increase in stroke with β-blockers compared to calcium channel blockers (RR, 1.24; 95% CI, 1.11 to 1.40) and renin-angiotensin system inhibitors (RR, 1.30; 95% CI, 1.11 to 1.53), but there was no difference observed compared to diuretics (RR, 1.17;</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				<p>95% CI, 0.65 to 2.09).</p> <p>Coronary heart disease risk was not significantly different between β-blockers and placebo (RR, 0.93; 95% CI, 0.81 to 1.07), diuretics (RR, 1.12; 95% CI, 0.82 to 1.54), calcium channel blockers (RR, 1.05; 95% CI, 0.96 to 1.15) or renin-angiotensin system inhibitors (RR, 0.90; 95% CI, 0.76 to 1.06).</p> <p>The risk of total cardiovascular disease was lower with β-blockers compared to placebo (RR, 0.88; 95% CI, 0.79 to 0.97). The effect of β-blockers on cardiovascular disease was significantly worse than that of calcium channel blockers (RR, 1.18; 95% CI, 1.08 to 1.29), but was not significantly different from that of diuretics (RR, 1.13; 95% CI, 0.99 to 1.28) or renin-angiotensin system inhibitors (RR, 1.00; 95% CI, 0.72 to 1.3).</p> <p>There was a significantly higher rate of discontinuation due to side effects with β-blockers compared to diuretics (RR, 1.86; 95% CI, 1.39 to 2.50) and renin-angiotensin system inhibitors (RR, 1.41; 95% CI, 1.29 to 1.54), but there was no significant difference compared to calcium channel blockers (RR, 1.20; 95% CI, 0.71 to 2.04). Actual side effects were not reported.</p>

*Agent not currently available in the United States.

Drug regimen abbreviations: BID=twice daily, CR=controlled release, ER=extended release, QID-four times daily, SR=sustained release, TID=three times a day

Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, MA=meta analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=risk ratio, XO=crossover

Miscellaneous abbreviations: ACE=angiotensin converting enzyme, AF=atrial fibrillation, AFL=atrial flutter, BP=blood pressure, ARB=angiotensin receptor blocker, bpm=beats per minute, CHD=coronary heart disease, CHF=congestive heart failure, DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, MI=myocardial infarction, NYHA=New York Heart Association, SBP=systolic blood pressure

Special Populations

Though different dosage forms exist for both diltiazem and verapamil, information regarding special populations is consistent for each medication.

Table 5. Special Populations⁸⁻²⁹

Generic Name	Population and Precaution				
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Diltiazem	Dose selection in elderly patients should be cautious. Safety and efficacy have not been established in pediatric patients.	No dosage adjustment required.	No dosage adjustment required; use with caution.	C	Yes
Verapamil	Dose selection in elderly patients should be cautious. Verelan PM [®] should be administered at 100 mg at bedtime in the elderly. Safety and efficacy have not been established in pediatric patients.	No dosage adjustment required; use with caution.	Use with caution. In patients with severe hepatic impairment, 30% of the normal dose should be administered. Verelan PM [®] should be administered at 100 mg at bedtime.	C	Yes

Adverse Drug Events**Table 6. Adverse Drug Events**¹⁰⁻²⁹

Adverse Event	Diltiazem	Verapamil
Cardiovascular		
Angina	<1	≤1
Arrhythmia	<1	-
Asystole	✓	-
Atrial fibrillation	1.4	✓
Atrioventricular block	<1.0 to 7.6	0.8 to 1.7
Atrioventricular dissociation	-	≤1
Bigeminal extrasystoles	<1	-
Bradycardia	<1 to 6	1.4
Bundle branch block	<1	-
Chest pain	<1	≤1
Claudication	-	≤1
Congestive heart failure	<1	≤1.9
Electrocardiogram abnormalities/changes	<1.0 to 4.1	-
Extrasystoles	<1 to 2	-
Hypertension	<1	-
Hypotension	<1	0.7 to 5.0
Myocardial infarction	<1	≤1
Myocardial ischemia	<1	-
Palpitations	<1 to 2	≤1

Therapeutic Class Review: calcium-channel blocking agents (non-dihydropyridines)

Adverse Event	Diltiazem	Verapamil
Postural hypotension	-	<1
ST elevation	<1	-
Tachycardia	<1	-
Vasculitis	✓	-
Ventricular extrasystoles	<1	-
Ventricular tachycardia	-	✓
Central Nervous System		
Abnormal dreams	≤1.4	-
Akathisia	✓	-
Amnesia	<1	-
Asthenia	1.2 to 5.0	≤2
Cerebrovascular accident	-	≤1
Confusion	-	≤1
Depression	<1	-
Dizziness	1.5 to 10.0	3.3 to 4.7
Equilibrium disorder	-	≤1
Fatigue	4.8	1.7 to 4.5
Hallucinations	<1	-
Headache	2.1 to 12.0	2.2 to 12.1
Insomnia	≤1	≤1
Lethargy	-	3.2
Hypertonia	<1	-
Nervousness	<1 to 3	-
Neuropathy	<1	-
Paresthesia	<1	1
Personality changes	<1	-
Psychotic symptoms	-	<1
Shakiness	-	≤1
Sleep disturbance	-	1.4
Somnolence	<1.0 to 1.3	≤1
Syncope	<1	≤1
Tremor	<1	<1
Vertigo	<1	<1
Dermatologic		
Alopecia	✓	≤1
Dermatitis	<1	-
Ecchymosis	<2	≤1
Erythema multiforme (including Stevens-Johnson syndrome)	✓	≤1
Exanthema	-	≤1
Exanthematous pustulosis	✓	-
Exfoliative dermatitis	✓	-
Generalized exanthematous pustulosis	✓	-
Flushing	<1 to 3	<1
Hair color change	-	✓
Hyperhidrosis	-	≤1
Hyperkeratosis	-	≤1
Petechiae	<1	-
Photosensitivity	<1	-
Pruritis	<1	-
Rash	1 to 2	≤1.4
Rash, maculopapular	-	≤1

Adverse Event	Diltiazem	Verapamil
Skin hypertrophy (nevus)	<1	-
Urticaria	<1	≤1
Endocrine and Metabolic		
Gout	<1 to 2	-
Gynecomastia	<2	≤1
Hyperglycemia	<1	-
Hyperprolactinemia/galactorrhea	-	≤1
Hyperuricemia	<1	-
Thirst	<1	-
Gastrointestinal		
Abdominal enlargement	2	-
Abdominal pain	1	-
Anorexia	<1	-
Constipation	<1.0 to 3.6	7.3 to 11.7
Diarrhea	<1 to 2	≤2.4
Dry mouth	<1	≤1
Dysgeusia	<1	-
Dyspepsia	<1 to 6	≤2.7
Eructation	<1	-
Gingival hyperplasia	✓	≤1
Hepatitis	✓	-
Nausea	1.3 to 2.2	1.7 to 2.7
Vomiting	<1 to 2	-
Genitourinary		
Acute renal failure	✓	✓
Albuminuria	<2	-
Crystalluria	<2	-
Cystitis	<1	-
Dysmenorrhea	<1	-
Impotence	<1 to 2	≤1
Kidney calculus	<1	-
Kidney failure	<1	-
Nocturia	<1	-
Polyuria	<1.0 to 1.3	≤1
Prostate disease	<1	-
Pyelonephritis	<1	-
Sexual dysfunction	<1	-
Spotty menstruation	-	≤1
Urinary tract infection	<1	-
Vaginitis	<1	-
Hematological		
Hemolytic anemia	✓	-
Increased bleeding time	✓	-
Leukopenia	✓	-
Photosensitivity	✓	-
Purpura	✓	≤1
Thrombocytopenia	✓	-
Laboratory Abnormalities		
Alkaline phosphatase increase	<1	-
Creatine phosphokinase elevation	<1	-
Hepatic enzyme elevations	<1	1.4
SGOT increased	<1	-

Adverse Event	Diltiazem	Verapamil
SGPT increased	<1	-
Musculoskeletal		
Arthralgia	1.4	≤1
Arthrosis	1	-
Bone pain	<1	-
Bursitis	<1	-
Extrapyramidal symptoms	✓	≤1
Gait abnormality	<1	-
Muscle cramps	<1	≤1
Myalgia	2.0 to 2.3	1.1
Myopathy	✓	-
Neck rigidity	<2	-
Osteoarthritis	<1	-
Respiratory		
Bronchitis	<1 to 4	-
Cough	2 to 3	✓
Dyspnea	1 to 6	1.4
Epistaxis	<1	-
Nasal congestion	<1 to 2	-
Pharyngitis	1.4 to 6.0	3
Respiratory disorder	<1	-
Respiratory distress	<1	-
Rhinitis	2.9 to 9.6	2.6
Sinusitis	1 to 2	3
Other		
Abnormal visual accommodation	<1	-
Accidental injury	1.3	1.5
Allergic reaction	✓	-
Allergy aggravated	-	≤2
Amblyopia	<1	-
Angioedema	✓	-
Blurred vision	-	≤1
Conjunctivitis	2	-
Ear pain	<1	-
Edema	2.4 to 15.0	1.7 to 3.7
Eye hemorrhage	<1	-
Eye pain	<1	-
Fever	<1	-
Flu syndrome	2.0 to 2.3	3.7
Hyperuricemia	<1	-
Infection	<1 to 6	12.1
Leukocytoclastic vasculitis	✓	-
Lymphadenopathy	<1	-
Malaise	<1	-
Ophthalmitis	<1	-
Otitis media	<1	-
Pain	1.7 to 6.0	2.4
Pallor	<1	-
Peripheral edema	✓	✓
Phlebitis	<1	-
Retinopathy	✓	-
Taste perversion	<1	-

Adverse Event	Diltiazem	Verapamil
Tinnitus	<1	<1
Vasodilatation	1.3 to 3.0	-
Weight gain	<1	-

- Event not reported.

✓ Percent not specified.

Contraindications/Precautions

Diltiazem¹⁷⁻²⁹

Diltiazem is contraindicated in patients with sick sinus syndrome or second- or third-degree heart block (except in the presence of a functioning ventricular pacemaker), patients with hypotension (<90 mm Hg systolic), patients who have demonstrated hypersensitivity to the drug and patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

Diltiazem prolongs atrioventricular node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This may rarely result in abnormally slow heart rates or second- or third-degree heart block. Concurrent use of diltiazem with β -blockers or digitalis may result in additive effects on cardiac conduction. Patients with Prinzmetal's angina developed periods of asystole (two to five seconds) after a single dose of diltiazem 60 mg.

Caution should be exercised when using diltiazem alone or in combination with β -blockers in patients with impaired ventricular function.

Diltiazem use may occasionally result in symptomatic hypotension.

Rare instances of significant elevations in alkaline phosphatase, lactate dehydrogenase, SGOT, SGPT and other phenomena consistent with acute hepatic injury have been observed with diltiazem use and are reversible upon discontinuation of the medication.

Diltiazem is extensively metabolized by the liver and excreted by the kidneys and in bile. Laboratory parameters of renal and hepatic function should be monitored regularly. Use diltiazem with caution in patients with renal or hepatic impairment.

Dermatological events associated with diltiazem may be transient and may disappear despite continued use of the medication. Skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatological reaction persist, the drug should be discontinued.

Verapamil¹⁰⁻¹⁶

Verapamil is contraindicated in patients with severe left ventricular dysfunction, hypotension (<90 mm Hg) or cardiogenic shock, sick sinus syndrome or second- or third-degree atrioventricular block (except in patients with a functioning artificial ventricular pacemaker), patients with atrial fibrillation or flutter and an accessory bypass tract (Wolff-Parkison-White, Lown-Ganong-Levine syndromes) and patients with a known hypersensitivity to verapamil.

Verapamil should be avoided in patients with severe left ventricular dysfunction (ejection fraction <30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are also receiving a β -blocker. It is recommended to stabilize patients with milder ventricular dysfunction with optimal doses of digitalis and/or diuretics prior to initiating verapamil treatment.

Verapamil use may occasionally result in symptomatic hypotension

Elevations in transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations have sometimes been transient and may disappear even with continued use of verapamil. Periodic monitoring of liver function is recommended.

Patients with paroxysmal and/or chronic atrial fibrillation or atrial flutter and a coexisting accessory atrioventricular pathway have developed increased antegrade conduction across the accessory pathway bypassing the atrioventricular node, producing a very rapid ventricular response or ventricular fibrillation after intravenous verapamil or digitalis. The risk of this occurring with oral verapamil has not been established, though patients receiving oral verapamil may still be at risk. Verapamil use in these patients is contraindicated.

The effect of verapamil on atrioventricular conduction and the sinoatrial node may cause asymptomatic first-degree atrioventricular block and transient bradycardia, sometimes accompanied by nodal escape rhythms. PR-interval prolongation is correlated with verapamil plasma concentrations especially during titration. Higher degrees of atrioventricular block were infrequent. Marked first-degree block or progression to second- or third-degree block requires a reduction in dose or discontinuation of verapamil and institution of appropriate therapy based on the clinical situation.

Patients with hypertrophic cardiomyopathy may experience serious adverse events with verapamil therapy, including pulmonary edema, severe hypotension, sinus bradycardia, second-degree atrioventricular block and sinus arrest. Most adverse events responded well to a dose reduction.

Use verapamil with caution in patients with hepatic impairment. Severe liver dysfunction prolongs the elimination half-life of verapamil to 14 to 16 hours and therefore 30% of the dose should be given to these patients. Careful monitoring of the PR interval and other signs of excessive pharmacological effects is recommended.

Verapamil decreases neuromuscular transmission in patients with Duchenne's muscular dystrophy, prolongs recovery from the neuromuscular blocker vecuronium and causes a worsening of myasthenia gravis. Dose reduction may be necessary in patients with attenuated neuromuscular transmission.

Use verapamil with caution in patients with renal impairment. Patients should be carefully monitored for PR interval prolongation and other signs of overdose.

Caution should be used when administering Covera-HS[®] to patients with preexisting severe gastrointestinal narrowing. Kinetic data are not available in patients with extremely short gastrointestinal transit time (<7 hours) and dose adjustment may be required.¹²

Drug Interactions

Table 7. Drug Interactions⁵⁵

Drug	Interaction	Mechanism
Non-dihydropyridines	β-Blockers (atenolol, metoprolol, pindolol, propranolol)	Increased serum levels of β-blockers may result if administered with non-dihydropyridines, increasing the risk of symptomatic bradycardia, due to decreased metabolism of β-blockers and additive pharmacologic effects. If bradycardia results, the consider using a lower dose of the β-blocker.
Non-dihydropyridines	Buspirone	Increased serum levels of buspirone may result if administered with non-dihydropyridines, due non-dihydropyridines inhibitory effect on CYP3A4. Close monitoring is recommended.
Non-dihydropyridines	Carbamazepine	Increased serum levels of carbamazepine may result if administered with non-dihydropyridines, increasing the risk of greater effect and toxicity, due to inhibition of carbamazepine metabolism by non-dihydropyridines. Close monitoring of carbamazepine levels is recommended and dose alterations may be required if diltiazem is discontinued.
Non-dihydropyridines	Cyclosporine	Increased serum levels of cyclosporine may result if administered with non-dihydropyridines, increasing the risk of nephrotoxicity, due to non-dihydropyridines inhibitory effect on cyclosporine

Drug	Interaction	Mechanism
		metabolism. Close monitoring is recommended and dose adjustments may be required.
Non-dihydropyridines	Digoxin	Increased serum levels of digoxin may result, increasing the risk of digoxin toxicity, if administered with non-dihydropyridines, due to decreased renal clearance of digoxin. Close monitoring of digoxin levels is recommended.
Non-dihydropyridines	HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	Increased serum levels of HMG-CoA reductase inhibitors may result, increasing the risk of toxicities, such as myositis and rhabdomyolysis, if coadministered with non-dihydropyridines, due to decreased metabolism of HMG-CoA reductase inhibitors. Close monitoring is recommended if co administered.
Non-dihydropyridines	Macrolide antibiotics	Increased serum levels of macrolide antibiotics may result if administered with non-dihydropyridines, due to non-dihydropyridines inhibitory effect on CYP3A4. Coadministration should be avoided.
Non-dihydropyridines	Quinidine	Increased effects of quinidine may occur if co administered with non-dihydropyridines, increasing the risk of bradycardia, hypotension and ventricular tachycardia, as well as atrioventricular block. Coadministration should be avoided.
Non-dihydropyridines	Ranolazine	Increased serum levels of ranolazine may result if administered with non-dihydropyridines, due to non-dihydropyridines inhibitory effect on CYP3A4. Coadministration should be avoided due to the increased risk of QTc prolongation, torsades-de-pointes arrhythmias and death.
Diltiazem	Benzodiazepines (diazepam, midazolam, triazolam)	Increased serum levels of benzodiazepines may result if administered with diltiazem, increasing the risk of central nervous system depression, due to decreased metabolism of benzodiazepines. If coadministered, the benzodiazepine dose should be decreased.
Diltiazem	Methylprednisolone	Increased effects of corticosteroids may be seen if administered with diltiazem, due to decreased metabolism of corticosteroids.
Diltiazem	Moricizine	Increase levels of moricizine may result, as diltiazem decreases the metabolism of moricizine. Additionally moricizine increases the metabolism of diltiazem, resulting in lower serum levels and effects of diltiazem. Close monitoring is recommended.
Diltiazem	Sirolimus	Increased serum levels of sirolimus may result if administered with diltiazem, due to inhibition of sirolimus metabolism by diltiazem due CYP3A4 inhibition. Close monitoring of sirolimus levels is recommended.
Diltiazem	Tacrolimus	Increased serum levels of tacrolimus may result if administered with diltiazem, due to inhibition of tacrolimus metabolism by diltiazem due CYP3A4 inhibition. Close monitoring of tacrolimus levels is recommended.
Diltiazem	Theophyllines (aminophylline, oxtriphylline, theophylline)	Increased effects of theophyllines may result if administered with diltiazem, due to inhibition of theophylline metabolism by diltiazem. Dose adjustments may be needed.
Verapamil	Calcium salts (acetate, carbonate, chloride, citrate, glubionate, gluceptate, gluconate,	Effects of verapamil may be decreased by calcium salts. Monitor closely if coadministered.

Drug	Interaction	Mechanism
	glycerophosphate, lactate, leulinate)	
Verapamil	Dofetilide	Increase serum levels and effects of dofetilide may occur if coadministered with verapamil, increasing the risk of arrhythmia. Coadministration is contraindicated.
Verapamil	Everolimus	Increased everolimus plasma concentrations may result. If coadministration can not be avoided, close monitoring for clinical response is recommended. Adjust the everolimus dose based on blood concentration monitoring and the verapamil dose based on blood pressure.
Verapamil	Grapefruit	Increased verapamil serum levels and effects may result if coadministered with grapefruit, due to grapefruit's inhibition of CYP3A4, reducing the metabolism of verapamil. Coadministration should be avoided.
Verapamil	Nondepolarizing muscle relaxants (atracurium, doxacurium, mivacurium, pancuronium, pipecuronium, tubocurarine)	Increased serum levels of nondepolarizing muscle relaxants may result, increasing the risk of respiratory depression, if coadministered with verapamil, due to calcium's role on muscle contraction. Coadministration should be avoided.
Verapamil	Prazosin	Prazosin serum concentrations and effects, decreases in blood pressure, may be increased if coadministered with verapamil. Patients should be monitored and warned about changes in blood pressure.
Verapamil	Rifampin	Decreased serum levels of verapamil may result if coadministered with rifampin, due to increased metabolism of verapamil. Dose adjustments or substitutions are recommended if coadministration is required.
Verapamil	St. John's Wort	Decreased serum levels of verapamil may result if coadministered with St. John's Wort, due to increased metabolism of verapamil by CYP3A4. Coadministration should be avoided.

Dosage and Administration

Table 8. Dosing and Administration¹⁰⁻²⁹

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Diltiazem IR tablets (Cardizem®)	<u>Chronic stable angina and angina due to coronary artery spasm:</u> Initial, 30 mg QID; maintenance, 180 to 360 mg daily	Safety and efficacy has not been established in pediatric patients.	Tablet: 30 mg 60 mg 90 mg 120 mg
Diltiazem SR capsules, once-daily dosing (Dilacor XR®, Dilt-XR®)	<u>Hypertension:</u> 180 to 240 mg Daily; maintenance, 180 to 480 mg Daily; maximum, 540 mg Daily <u>Chronic stable angina:</u> 120 mg Daily; maximum, 480 mg Daily	Safety and efficacy has not been established in pediatric patients.	Capsule: 120 mg 180 mg 240 mg
Diltiazem SR capsules, twice-daily dosing	<u>Hypertension:</u> 60 to 120 mg BID; total daily maintenance, 240 to 360 mg/day	Safety and efficacy has not been established in pediatric patients.	Capsule: 60 mg 90 mg 120 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Diltiazem SR coated bead capsules (Cardizem CD [®] , Dilt-CD [®] , Cartia XT [®])	<p><u>Hypertension:</u> 180 to 240 mg Daily; maintenance, 240 to 360 mg Daily; maximum, 480 mg Daily</p> <p><u>Chronic stable angina and angina due to coronary artery spasm:</u> 120 to 180 mg Daily; maximum, 480 mg Daily</p>	Safety and efficacy has not been established in pediatric patients.	Capsule: 120 mg 180 mg 240 mg 300 mg 360 mg
Diltiazem SR coated beads tablets (Cardizem LA [®] , Matzim LA [®])	<p><u>Hypertension:</u> 180 to 240 mg Daily; maximum, 540 mg Daily</p> <p><u>Chronic stable angina:</u> 180 mg Daily; maximum, 360 mg Daily</p>	Safety and efficacy has not been established in pediatric patients.	Tablet: 120 mg 180 mg 240 mg 300 mg 360 mg 420 mg
Diltiazem ER capsules (Tiazac [®] , Diltzac [®] , Taztia XT [®])	<p><u>Hypertension:</u> 120 to 240 mg Daily; maximum, 540 mg Daily</p> <p><u>Chronic stable angina:</u> 120 to 180 mg Daily; maximum, 540 mg Daily</p>	Safety and efficacy has not been established in pediatric patients.	Capsules: 120 mg 180 mg 240 mg 300 mg 360 mg 420 mg
Diltiazem IV	<p><u>Atrial fibrillation/atrial flutter and paroxysmal supraventricular tachycardia:</u> Direct IV bolus: 0.25 mg/kg actual body weight over two minutes; dose may be repeated after 15 minutes; if first dose was inadequate, the second dose should be 0.35 mg/kg</p> <p>Continuous IV infusion: 5 to 10 mg/hour; maximum, 15 mg/hour</p>	Safety and efficacy has not been established in pediatric patients.	Injection: 5 mg/mL 100 mg vial
Verapamil IR tablets (Calan [®])	<p><u>Hypertension:</u> 80 mg TID; maximum, 360 mg daily in divided doses</p> <p><u>Chronic stable angina, unstable angina and vasospastic angina (Prinzmetal's or variant angina):</u> 40 to 120 mg TID</p> <p><u>Digitalized patients with chronic atrial fibrillation:</u> 240 to 320 mg daily divided TID or QID</p> <p><u>Prophylaxis of paroxysmal supraventricular tachycardia:</u> 240 to 480 mg daily divided TID or QID</p>	Safety and efficacy has not been established in pediatric patients.	Tablets: 40 mg 80 mg 120 mg
Verapamil ER	<u>Hypertension:</u>	Safety and efficacy has	Tablets:

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
tablets (Calan SR [®] , Ispodin SR [®])	120 to 180 mg Daily; maximum, 240 mg BID	not been established in pediatric patients.	120 mg 180 mg 240 mg
Verapamil osmotic-release ER tablets (Covera-HS [®])	<u>Hypertension and chronic stable angina:</u> 180 mg at bedtime; maximum, 480 mg at bedtime	Safety and efficacy has not been established in pediatric patients.	Tablets: 180 mg 240 mg
Verapamil ER capsules (Verelan [®] , Verelan PM [®])	<u>Hypertension:</u> Verelan [®] : 120 to 240 mg Daily; maximum, 480 mg Daily Verelan PM [®] : 100 to 200 mg at bedtime; maximum, 400 mg at bedtime	Safety and efficacy has not been established in pediatric patients.	Capsules: Verelan [®] : 120 mg 180 mg 240 mg 360 mg Verelan PM [®] : 100 mg 200 mg 300 mg
Verapamil IV	<u>Atrial fibrillation and flutter and paroxysmal supraventricular tachycardia:</u> 5 to 10 mg as IV bolus over at least two minutes; if first dose is inadequate, a second 10 mg dose may be given after 30 minutes	Controlled trials have not been conducted in pediatric patients and caution should be used when administering verapamil IV to pediatric patients. <u>Atrial fibrillation and flutter and paroxysmal supraventricular tachycardia:</u> 0 to 1 year of age: 0.1 to 0.2 mg/kg over at least two minutes; if first dose is inadequate, a second dose may be given after 30 minutes; 1 to 15 years of age: 0.1 to 0.3 mg/kg over at least two minutes; the first dose should not exceed 5 mg; if first dose is inadequate, a second dose may be given after 30 minutes; the second dose should not exceed 10 mg	Injection: 2.5 mg/mL

BID=twice daily, ER=extended-release, IR=immediate-release, IV=intravenous, QID=four times daily, SR=sustained-release, TID=three times daily

Clinical Guidelines

Current guidelines are summarized in Table 9. Please note that guidelines addressing the treatment of hypertension and stable angina are presented globally, addressing the role of various medication classes in the treatment of the disease. Due to the complexity of treatment regimens for unstable angina and

atrial fibrillation, the associated guideline summaries focus on the role of the calcium channel blockers in disease management.

Table 9. Clinical Guidelines

Clinical Guideline	Recommendation
<p>American College of Cardiology/American Heart Association: 2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)³⁰</p>	<ul style="list-style-type: none"> • Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients, unless contraindicated. • Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. • Patients with hypertension and established coronary artery disease should be treated with blood pressure medication(s) as tolerated, including angiotensin converting enzyme (ACE) inhibitors and/or β-blockers with the addition of other medications as needed to achieve blood pressure goals of <140/90 or <130/80 mm Hg for patients with chronic kidney disease or diabetes. • Long-acting calcium-channel blocking agents or long-acting nitrates may be used if β-blockers are contraindicated. Immediate-release and short-acting dihydropyridine calcium channel blockers can increase adverse cardiac events and should not be used. • Long-acting calcium channel blockers or long-acting nitrates may be used with β-blockers if initial treatment is not successful. • ACE inhibitors should be used indefinitely in patients with a left ventricular ejection fraction (LVEF) \leq40% and in those with hypertension, diabetes or chronic kidney disease, unless contraindicated. • ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal LVEF in whom cardiovascular risk factors remain well controlled and revascularization has been performed), unless contraindicated. • Angiotensin receptor blockers (ARBs) are recommended in patients with hypertension, those who have an indication for an ACE inhibitor and are intolerant to them, who have heart failure, or who have had a myocardial infarction and have a LVEF \leq40%. • ARBs may be considered in combination with an ACE inhibitor for heart failure due to left ventricular systolic dysfunction. • Aldosterone blockade is recommended in patients post-myocardial infarction without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a LVEF \leq40% and have either diabetes or heart failure. • It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had a myocardial infarction, acute coronary syndrome or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. • Annual influenza vaccination is recommended in patients with cardiovascular disease.
<p>European Society of Cardiology: Management of Stable Angina Pectoris (2006)⁶</p>	<p><u>Therapy to improve prognosis</u></p> <ul style="list-style-type: none"> • Aspirin 75 mg once daily is recommended in all patients without contraindications. • Statin therapy is recommended for all patients with coronary disease. • ACE inhibitor therapy is recommended for patients with indications for ACE inhibition including hypertension, heart failure, left

Clinical Guideline	Recommendation
	<p>ventricular dysfunction and history of myocardial infarction with left ventricular dysfunction and diabetes.</p> <ul style="list-style-type: none"> • β-blocker therapy is recommended in patients with history of myocardial infarction or heart failure. • Class IIa evidence includes ACE inhibition in patients with angina and proven coronary disease, clopidogrel in patients with stable angina who are not candidates for aspirin and high dose statin therapy in high risk patients with proven coronary disease. • Class IIb evidence includes fibrates in patients with low high density lipoprotein cholesterol and high triglycerides who have diabetes or metabolic syndrome. • Calcium channel blockers may be recommended in patients with angina who cannot tolerate β-blockers and who have had a myocardial infarction and who do not have heart failure. <p><u>Therapy to improve symptoms and/or reduce ischemia</u></p> <ul style="list-style-type: none"> • Short-acting nitroglycerin therapy is recommended for acute symptom relief and situational prophylaxis. • Test the effects of a β1 blocker and titrate to full dose; consider the need for 24-hour protection against ischemia. • If β-blockers are not effective or not tolerated, attempt monotherapy with a calcium channel blocker, long-acting nitrate or nicorandil*. • If the effects of β-blocker therapy are insufficient, add a dihydropyridine calcium channel blocker. • Class IIa evidence includes a sinus node inhibitor in the case of β-blocker intolerance, or a long-acting nitrate or nicorandil* in place of a calcium channel blocker in the case of insufficient response to calcium channel blocker monotherapy or combination therapy with a calcium channel blocker and β-blocker. • Class IIb evidence includes the use of metabolic agents where available as add-on therapy or in place of conventional therapy when conventional therapy is not tolerated. <p><u>Treatment of syndrome X</u></p> <ul style="list-style-type: none"> • Therapy with nitrates, β-blockers and calcium channel blockers alone or in combination is recommended. • Statin therapy is recommended in patients with hyperlipidemia. • ACE inhibitors are recommended in patients with hypertension. • Class IIa evidence includes a trial of other anti-anginal agents such as nicorandil* and metabolic agents. <p><u>Treatment of vasospastic angina</u></p> <ul style="list-style-type: none"> • Treatment with calcium channel blockers is recommended in patients whose coronary arteriogram is normal or shows only non-obstructive lesions.
<p>American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Guideline Update for the Management of Patients With Unstable Angina and Non-ST-</p>	<ul style="list-style-type: none"> • Nitrates, morphine, β-blockers, calcium channel blockers, inhibitors of the renin-angiotensin-aldosterone system, antiplatelet agents, and GP IIb/IIIa receptor antagonists can be used in the acute setting during early hospitalization. • Calcium channel blockers are recommended for ischemic symptoms when β-blockers are not successful, contraindicated, or not tolerated. • Treatment with nitrates and calcium channel blockers is

Clinical Guideline	Recommendation
<p>segment Elevation Myocardial Infarction (2007)³¹</p>	<p>recommended in patients with variant angina whose coronary angiogram shows no or non-obstructive coronary artery lesions.</p> <ul style="list-style-type: none"> Nitrates, β-blockers, and calcium channel blockers (as monotherapy or combination therapy) are recommended in patients with cardiovascular syndrome X.
<p>European Society of Cardiology: Guidelines for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes (2007)⁵⁶</p>	<ul style="list-style-type: none"> Calcium channel blockers may provide additional symptomatic relief in patients already being treated with β-blockers and nitrates. They may also be used in patients who are intolerant to β-blockers and in patients with vasospastic/variant angina. Nondihydropyridine calcium channel blockers should not be used unless combined with β-blockers.
<p>National Institute for Health and Clinical Excellence: Atrial Fibrillation (2006)³²</p>	<ul style="list-style-type: none"> β-blockers or rate-limiting calcium antagonists should be the preferred initial monotherapy in adult patients with permanent atrial fibrillation who need rate control. Combination therapy of digoxin and either a β-blocker or a rate-limiting calcium antagonist should be considered if control is not achieved with monotherapy. If these two classes of drugs are ineffective or not tolerated, amiodarone or diltiazem/β-blocker combination are third line options. When used as monotherapy, β-blockers and calcium antagonists are more effective than digoxin in controlling heart rate at high levels of physical exertion but there was no difference during normal daily activities. To control heart rate during both normal activities and during exercise, rate-limiting calcium antagonists should be given with digoxin. Where urgent rate control is indicated, intravenous treatment with β-blockers or rate-limiting calcium antagonists are recommended. Amiodarone is indicated when β-blockers and calcium antagonists are not tolerated or ineffective. In patients undergoing cardiothoracic surgery, the risk of postoperative atrial fibrillation should be reduced by the administration of β-blockers, rate-limiting calcium antagonists, sotalol or amiodarone.
<p>American College of Cardiology Foundation/ American Heart Association/Heart Rhythm Society: Focused Update on the Management of Patients with Atrial Fibrillation (Updating the 2006 Guideline)³³ (2011)⁵⁷</p>	<ul style="list-style-type: none"> With regards to the use of calcium channel blockers, the full-text guideline (2006) remains current. Rate control using a β-blocker or a non-dihydropyridine calcium channel blocker is recommended as initial therapy in patients with persistent or permanent atrial fibrillation. In the acute setting, intravenous administration of β-blockers or non-dihydropyridine calcium channel blockers is recommended. The combination of digoxin and either a β-blocker or a non-dihydropyridine calcium channel blocker is recommended to control heart rate both at rest and during exercise. Intravenous administration of a non-dihydropyridine calcium channel blocker is not recommended in patients with decompensated heart failure and atrial fibrillation. Intravenous administration of a non-dihydropyridine calcium channel blocker is not recommended in patients with pre-excitation syndrome and atrial fibrillation. Non-dihydropyridine calcium channel blockers are the only agents which have shown an improvement in quality of life and exercise

Clinical Guideline	Recommendation
	<p>tolerance.</p> <ul style="list-style-type: none"> • Direct comparisons of verapamil and diltiazem have demonstrated similar effectiveness with preserved or improved exercise tolerance in most patients. These agents may be preferred for long-term use over β-blockers in patients with bronchospasm or chronic obstructive pulmonary disease. • In general, combination therapy with digoxin and β-blockers appears more effective than digoxin and calcium channel blockers. Intravenous β-blockers, digitalis, adenosine, lidocaine, and non-dihydropyridine calcium channel antagonists, all of which slow conduction across the atrioventricular node, are contraindicated in patients with the Wolff–Parkinson–White syndrome and tachycardia associated with ventricular pre-excitation. • There is no evidence to support the antiarrhythmic efficacy of calcium channel antagonist drugs in patients with paroxysmal atrial fibrillation, but they reduce heart rate during an attack such that symptoms may disappear despite recurrent atrial fibrillation. • Unless atrioventricular node conduction is impaired, a short-acting β-blocker or non-dihydropyridine calcium channel antagonist should be given at least 30 minutes before administration of a type IC antiarrhythmic agent to terminate an acute episode of atrial fibrillation. • Intravenous β-blockers or non-dihydropyridine calcium channel blockers are recommended to slow a rapid ventricular response to atrial fibrillation following an acute myocardial infarction in patients who do not have signs of left ventricular dysfunction, heart block or bronchospasm. • Non-dihydropyridine calcium channel blockers are recommended in patients with atrial fibrillation and thyrotoxicosis when β-blockers cannot be used. • Digoxin, β-blockers or non-dihydropyridine calcium channel blockers are recommended in pregnant patients with atrial fibrillation. • Non-dihydropyridine calcium channel blockers are recommended in patients with atrial fibrillation and obstructive pulmonary disease.
<p>National Heart, Lung, and Blood Institute: The Seventh Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (2004)³⁴</p>	<ul style="list-style-type: none"> • Thiazide-type diuretics should be used as initial therapy for most patients with hypertension, either alone or in combination with another class (ACE inhibitors, ARBs, β-blockers, calcium channel blockers) demonstrated to be beneficial in randomized controlled outcome trials. • Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs or calcium channel blockers. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from two drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with two

Clinical Guideline	Recommendation
	<p>antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic.</p> <ul style="list-style-type: none"> • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretics, ACE inhibitors, β-blockers, ARBs and aldosterone antagonists), post-myocardial infarction (β-blockers, ACE inhibitors and aldosterone antagonists), high coronary disease risk (diuretics, ACE inhibitors, β-blockers and calcium channel blockers), diabetes (diuretics, ACE inhibitors, ARBs, β-blockers and calcium channel blockers), chronic kidney disease (ACE inhibitors and ARBs) and recurrent stroke prevention (diuretics and ACE inhibitors). • The drug of choice in patients with hypertension and stable angina is a β-blocker. Long-acting calcium channel blockers may also be used. • For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers and aldosterone antagonists are recommended. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers and calcium channel blockers are beneficial in reducing cardiovascular disease and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to microalbuminuria. • Patients with chronic kidney disease often require treatment with three or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. ACE inhibitors and ARBs have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required, along with other medications. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs and β-blockers compared to calcium channel blockers and diuretics. The incidence of ACE-inhibitor-induced angioedema is two to four times higher in African Americans. • Calcium channel blockers may be useful in Raynaud's syndrome and certain arrhythmias. • ACE inhibitors and ARBs should not be given to women who are pregnant or may become pregnant.
<p>World Health Organization/ International Society of Hypertension: 2003 World Health Organization/ International Society of Hypertension Statement on Management of Hypertension (2003)⁵⁸</p>	<ul style="list-style-type: none"> • When used as monotherapy, a diuretic or a calcium channel blocker may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine calcium channel blockers), renal disease (ACE inhibitors and ARBs), post-myocardial infarction (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors and diuretics), left ventricular hypertrophy (ARBs) and cerebrovascular

Clinical Guideline	Recommendation
<p>European Society of Hypertension/European Society of Cardiology: 2007 Guidelines for the Management of Hypertension (2007)⁵⁹, Reappraisal of Guidelines on Hypertension Management (2009)³⁵</p>	<p>disease (diuretics and ACE inhibitors).</p> <ul style="list-style-type: none"> • In order to optimize treatment initiation, intensity and goals, it is important to assess total cardiovascular risk in patients with hypertension which must include a search for subclinical organ damage. • In general, early introduction of blood pressure lowering treatments, before organ damage develops or becomes irreversible or before cardiovascular events occur, is recommended. • There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs and calcium channel blockers), asymptomatic atherosclerosis (calcium channel blockers and ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous myocardial infarction (ACE inhibitors, β-blockers and ARBs), angina (calcium channel blockers and β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs and aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors and ARBs), permanent atrial fibrillation (β-blockers and nondihydropyridine calcium channel blockers), end stage renal disease/proteinuria (ACE inhibitors, ARBs and loop diuretics), metabolic syndrome (ACE inhibitors, ARBs and calcium channel blockers), diabetes (ACE inhibitors and ARBs), pregnancy (methyldopa, calcium channel blockers and β-blockers) and African American patients (calcium channel blockers and diuretics). • Available evidence justifies the use of aliskiren in hypertension, particularly in combination with other agents. • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, consider medications which have different and complementary mechanisms of action, and that there is evidence that the antihypertensive effect of the combination is greater than that of either combination component and the combination is likely to be well tolerated. <ul style="list-style-type: none"> • Combinations that can be recommended for priority use based on trial evidence of outcome reduction include a diuretic with an ACE inhibitor, ARB or calcium channel blocker and an ACE inhibitor with a calcium channel blocker. • Avoid β-blocker/diuretic combination unless required for other reasons. • If triple therapy is needed, the most rational combination is a blocker of the rennin-angiotensin system, a calcium channel blocker and a diuretic at effective doses. • A β- or α-blocker may be included in a triple therapy approach depending on clinical circumstances. • Antihypertensive treatment is highly beneficial in elderly patients and treatment may be initiated with a thiazide diuretic, ACE inhibitor,

Clinical Guideline	Recommendation
	<p>calcium channel blocker, ARB or β-blocker.</p> <ul style="list-style-type: none"> • Blood pressure lowering drugs should be continued or initiated in patients 80 years of age, starting with monotherapy and adding a second drug, if needed. The decision to treat should be made on an individual basis and patients should be carefully monitored. • Calcium channel blockers, ARBs and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension. • Antihypertensive treatment should always be initiated in diabetic patients when blood pressure is 140/90 mm Hg or higher; however, there is evidence in favor of initiating treatment with high normal blood pressure. • The blood pressure goal of <130/80 mm Hg is not supported by outcome evidence from trials and is difficult for the majority of patients to achieve; therefore, its realistic to recommend only to pursue a sizeable blood pressure reduction without indicating a goal that is unproven. • In hypertensive diabetic patients, tight blood glucose control (glycosylated hemoglobin to 6.5%) is beneficial, particularly in combination with effective blood pressure control, on improving microvascular complications. Tight glucose control should not be pursued abruptly and patients should be monitored closely due to the increased risk of severe hypoglycemic episodes.
<p>National Institute for Health and Clinical Excellence/ British Hypertension Society: Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)⁶⁰</p>	<ul style="list-style-type: none"> • Initial therapy in patients ≥ 55 years of age should be a calcium channel blocker or a thiazide diuretic. • Initial therapy in patients <55 years of age should be an ACE inhibitor or an ARB if the patient is intolerant to ACE inhibitors. • If a second medication is required and initial therapy was with a calcium channel blocker or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a calcium channel blocker or a diuretic should be added. • If three medications are required, a combination of calcium channel blocker, ACE inhibitor and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist.

*Agent not currently available in the United States.

Conclusions

The non-dihydropyridine calcium-channel blocking agents, diltiazem and verapamil, are Food and Drug Administration approved for the treatment of hypertension and some products have additional indications for the treatment of angina and arrhythmia. Evaluation of the available clinical trials comparing diltiazem and verapamil in the treatment of angina reveals that there is little or no difference in efficacy between the agents.³⁶ Clinical trials comparing diltiazem to agents in other classes showed that both treatments were effective at increasing exercise tolerance in patients with angina, with no significant differences reported.³⁷⁻³⁹

In the treatment of hypertension, clinical trials have compared diltiazem and verapamil to various comparator agents, including other calcium channel blockers such as amlodipine. The results of these trials show that both diltiazem and verapamil are effective at controlling both systolic and diastolic blood pressure.^{41,42} In one trial diltiazem was found to be more effective than amlodipine at controlling early morning diastolic blood pressure in African American patients; however in the same trial there was no difference found in effects on systolic blood pressure for early morning measurements, and averages of systolic blood pressures over 24-hours favored amlodipine.⁴¹ A comparison of verapamil to chlorthalidone revealed equally potent reductions in blood pressure.⁴²

Appendix I: Utilization Within This Drug Class for DVHA: January 1, 2011 to June 30, 2011

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Diltiazem ER	200	361	30.57%	\$23,394.23	\$64.80
Verapamil ER	158	298	25.23%	\$14,555.51	\$48.84
Diltiazem CD	76	129	10.92%	\$8,692.84	\$67.39
Diltiazem	78	126	10.67%	\$10,493.10	\$83.28
Cartia XT	59	99	8.38%	\$6,334.39	\$63.98
Verapamil	48	76	6.43%	\$1,107.26	\$14.57
Verapamil SR	35	57	4.83%	\$4,430.86	\$77.73
Taztia XT	18	25	2.12%	\$2,697.06	\$107.88
Dilt-XR	4	3	0.25%	\$236.14	\$78.71
Cardizem LA	1	2	0.17%	\$632.40	\$316.20
Covera-HS	1	2	0.17%	\$367.42	\$183.71
Cardizem CD	2	2	0.17%	\$1,176.94	\$588.47
Cardizem	1	1	0.08%	\$360.43	\$360.43
Class Total:	----	1,181	100%	\$74,478.58	\$63.06

Recommendations

No changes to the Department of Vermont Health Access (DVHA) approval criteria for non-dihydropyridine calcium channel blocking agents (see below) are proposed. All available generics, with the exception of diltiazem ER (compare to Cardizem LA[®]), are preferred agents.

Non-preferred drugs:

- The patient has had a documented side effect, allergy, or treatment failure to at least three preferred drugs. (If a medication has an AB rated generic, one trial must be the generic formulation.)

References

1. Micromedex[®] Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2011 [cited 2011 May 19]. Available from: <http://www.thomsonhc.com/>.
2. Kannam JP, Aroesty JM, Gersh BJ. Calcium channel blockers in the management of stable angina pectoris. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2011 [cited 2011 May 19]. Available from: <http://www.utdol.com/utd/index.do>.
3. Talbert RL. Ischemic heart disease. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: a pathophysiologic approach. 6th edition. New York (NY): McGraw-Hill; 2005. p. 273-90.
4. Michel T. Treatment of myocardial ischemia. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman and Gilman's The pharmacological basis of therapeutics [monograph on the Internet]. 11th ed. New York: McGraw-Hill; 2006 [cited 2008 Jun 5]. Available from: <http://online.statref.com/document.aspx?fxid=75&docid=305>.
5. Hoffmann BB. Therapy of hypertension. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman and Gilman's The pharmacological basis of therapeutics [monograph on the Internet]. 11th ed. New York: McGraw-Hill; 2006 [cited 2011 May 19]. Available from: <http://online.statref.com/document.aspx?fxid=75&docid=310>.
6. Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, et al. Guidelines on the management of stable angina pectoris: executive summary: the task force on the management of stable angina pectoris of the European Society of Cardiology. Eur Heart J. 2006 Jun;27(11):1341-81.
7. Saseen JJ, Carter BL. Hypertension. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: a pathophysiologic approach. 6th edition. New York (NY): McGraw-Hill; 2005. p. 185-217.
8. Verapamil: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2011 [cited 2011 May 19]. Available from: <http://www.utdol.com/utd/index.do>.
9. Diltiazem: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2011 [cited 2011 May 19]. Available from: <http://www.utdol.com/utd/index.do>.
10. Calan[®] [package insert]. New York (NY): Pfizer Inc.; 2010 Nov.
11. Calan SR[®] [package insert]. New York (NY): Pfizer Inc.; 2009 Oct.
12. Covera-HS[®] [package insert]. New York (NY): Pfizer Inc.; 2010 Feb.
13. Isoptin SR[®] [package insert]. North Chicago (IL): Abbott Laboratories; 2005 Jan.
14. Verapamil injection [package insert]. Shirley (NY): American Regent, Inc.; 2003 Jan.
15. Verelan[®] [package insert]. Smyrna (GA): Schwarz Pharma, LLC; 2010 Apr.
16. Verelan PM[®] [package insert]. Smyrna (GA): Schwarz Pharma, LLC; 2010 Apr.
17. Cardizem[®] [package insert]. Kansas City (MO): Sanofi-Aventis U.S. LLC; 2009 Nov.
18. Cardizem CD[®] [package insert]. Kansas City (MO): Sanofi-Aventis U.S. LLC; 2009 Nov.
19. Cardizem LA[®] [package insert]. North Chicago (IL): Abbott Laboratories; 2007 Sept.
20. Cartia XT[®] [package insert]. Corona (CA): Watson Laboratories, Inc.; 2006 Dec.
21. Dilacor XR[®] [package insert]. Corona (CA): Watson Laboratories, Inc.; 2010 Sept.
22. Dilt-XR[®] [package insert]. Weston (FL): Apotex Corp.; 2005 Sept.
23. Diltiazem injection [package insert]. Lake Forest (IL): Hospira, Inc.; 2006 Jun.
24. Diltiazem [package insert]. Morgantown (WV): Mylan Pharmaceuticals, Inc.; 2006 Jun.
25. Dilt CD[®] [package insert]. Weston (FL): Apotex Corp.; 2004 May.
26. Diltzac[®] [package insert]. Weston (FL): Apotex Corp.; 2008 Jul.
27. Matzim LA[®] [package insert]. Corona (CA): Watson Laboratories, Inc.; 2011 Feb.
28. Tiazac[®] [package insert]. St. Louis (MO): Forest Pharmaceuticals, Inc.; 2010 Mar.
29. Taztia XT[®] [package insert]. Corona (CA): Watson Laboratories, Inc.; 2006 Dec.
30. Fraker T, Fihn S, Gibbons RJ, Abrams J, Chatterjee K, Daley J et al. 2007 chronic angina focused update of the ACC/AHA 2002 guidelines for the management of chronic stable angina: a report of the American College of Cardiology/American Heart Association task force on practice guidelines writing group to develop the focused update of the 2002 guidelines for the management of patients with chronic stable angina. Circulation. 2007 Dec 4;116(23):2762-72.
31. Anderson J, Adams C, Antman E, Bridges CR, Califf RM, Casey DE Jr, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association task force on

- practice parameters (writing committee to revise the 2002 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. *J Am Coll Cardiol.* 2007 Aug 14;50(7):1-157.
32. National Institute for Health and Clinical Excellence (NICE). Atrial Fibrillation [guideline on the Internet]. London (UK): National Institute for Health and Clinical Excellence, 2006 Jun [cited 2011 May 19]. Available from: <http://www.nice.org.uk/nicemedia/pdf/cg036fullguideline.pdf>.
 33. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation.* 2006 Aug 15;114(7):e257-e354.
 34. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [Internet]. Bethesda (MD): Department of Health and Human Services (US), National Institutes of Health, National Heart, Lung and Blood Institute; 2004 Aug [cited 2011 May 19]. (NIH Publication No. 04-5230.) Available from: <http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf>.
 35. Mancia G, Laurent S, Agabiti-Rosei E, Ambosioni E, Burnier M, Caulfield M et al. Reappraisal of European guidelines on hypertension management: a European society of hypertension task force document. *Journal of Hypertension.* 2009;27(11):2121-58.
 36. De Rosa ML, Giordano A, Melfi M, Della Guardia D, Ciaburri F, Rengo F. Antianginal efficacy over 24 hours and exercise hemodynamic effects of once daily sustained-release 300 mg diltiazem and 240 mg verapamil in stable angina pectoris. *Int J Cardiol.* 1998;63(1):27-35.
 37. Chugh SK, Dignpal K, Hutchinson T, McDonald CJ, Miller AJ, Lahiri A. A randomized, double-blind comparison of the efficacy and tolerability of once-daily modified-release diltiazem capsules with once-daily amlodipine tablets in patients with stable angina. *J Cardiovasc Pharmacol.* 2001 38(3):356-64.
 38. van Kesteren HA, Withagen AJ. A comparative study of once-daily amlodipine versus twice-daily diltiazem controlled-release (CR) in the treatment of stable angina pectoris. *Amlodipine Study Group. Cardiovasc Drugs Ther.* 1998;12 Suppl 3:233-7.
 39. Frishman WH, Glasser S, Stone P, Deedwania PC, Johnson M, Fakouhi TD. Comparison of controlled-onset, extended-release verapamil with amlodipine and amlodipine plus atenolol on exercise performance and ambulatory ischemia in patients with chronic stable angina pectoris. *Am J Cardiol.* 1999 Feb 15;83(4):507-14.
 40. Siu C, Lau C, Lee W, Lam K, Tse H. Intravenous diltiazem is superior to intravenous amiodarone or digoxin for achieving ventricular rate control in patients with acute uncomplicated atrial fibrillation. *Crit Care Med.* 2009;37(7):2174-79.
 41. Wright JT Jr, Sica DA, Gana TJ, Bohannon K, Pascual LG, Albert KS. Antihypertensive efficacy of night-time graded-release diltiazem versus morning amlodipine in African Americans. *Am J Hypertens.* 2004;17(9):734-42.
 42. Rosei EA, Dal Palu C, Leonetti G, Magnani B, Pessina A, Zanchetti A. Clinical results of the Verapamil in Hypertension and Atherosclerosis Study. VHAS Investigators. *J Hypertens.* 1997;15(11):1337-44.
 43. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA.* 2003;290(21):2805-16.
 44. Bangalore S, Messerli F, Cohen J, Bacher P, Sleight P, Mancia G, et al. Verapamil-sustained release-based treatment strategy at reducing cardiovascular events in patients with prior myocardial infarction: an International Verapamil SR-Trandolapril (INVEST) substudy. *Am Heart J.* 2008;156:241-7.
 45. Mancia G, Messerli F, Bakris G, et al. Blood pressure control and improved cardiovascular outcomes in the international verapamil SR-trandolapril study. *Hypertension.* 2007;50:299-305.

46. Hansson L, Hedner T, Lund-Johansen P, et al. Randomized trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet*. 2000;356(9227):359-65.
47. Black HR, Elliott WJ, Grandits G, et al. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. *JAMA*. 2003;289(16):2073-82.
48. Wyse DG, Waldo AL, DiMarco JP, et al. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347(23):1825-33.
49. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347(23):1834-40.
50. Opolski G, Torbicki A, Kosior DA, et al. Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation: The results of the polish how to treat chronic atrial fibrillation (HOT CAFE) Study. *Chest*. 2004;126:476-86.
51. Van Bortel LM, Fici F, Mascagni F. Efficacy and tolerability of nebivolol compared with other antihypertensive drugs: a meta-analysis. *Am J Cardiovasc Drugs*. 2008;8(1):35-44.
52. Boden WE, van Gilst WH, Scheldewaert RG, et al. Diltiazem in acute myocardial infarction treated with thrombolytic agents: a randomized placebo-controlled trial. Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis post-Thrombolysis (INTERCEPT) *Lancet*. 2002;355(9217):1751-6.
53. Gibson RS, Hansen JF, Messerli F, Schechtman KB, Boden WE. Long-term effects of diltiazem and verapamil on mortality and cardiac events in non-Q-wave acute myocardial infarction without pulmonary congestion: post hoc subset analysis of the multicenter diltiazem post infarction trial and the second Danish verapamil infarction trial studies. *Am J Cardiol*. 2000;86(3):275-9.
54. Wiysonge CS, Bradley H, Mayosi BM, Maroney R, Mbewu A, Opie LH, et al. Beta-blockers for hypertension. *Cochrane Database Syst Rev*. 2007 Jan 24;(1):CD002003. doi: 10.1002/14651858.CD002003.pub2.
55. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2011 [cited 2011 May 19]. Available from: <http://online.factsandcomparisons.com>.
56. Bassand J, Hamm C, Ardissino D, Boersma E, Budaj A, Fernández-Avilés F, et al; Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of European Society of Cardiology. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J*. 2007 Jul;28(13):1598-660.
57. Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes NAM, et al. 2011 ACCF/AHA/HRS focused updated on the management of patients with atrial fibrillation (updating 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2011 Jan 11;57(2):223-42.
58. Whitworth JA; World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens*. 2003 Nov;21(11):1983-92.
59. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2007 Jun;25(6):1105-87.
60. National Institute for Health and Clinical Excellence, National Collaborating Centre for Chronic Conditions; British Hypertension Society. Hypertension: management of adults in primary care: pharmacological update [monograph on the Internet]. London (UK): Royal College of Physicians; 2006 Jun [cited 2011 May 19]. Available from: <http://www.nice.org.uk/guidance/index.jsp?action=download&o=30111>.