

Consumer Reports BEST BUY DRUGS™

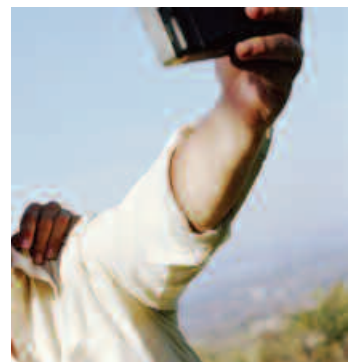


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Treating High Blood Pressure and Heart Disease: The Calcium Channel Blockers

Comparing Effectiveness, Safety, and Price



Our Recommendations

Calcium Channel Blockers (CCBs) are used by millions of Americans to treat high blood pressure, angina, and certain heart rhythm abnormalities.

The cost for CCBs varies from about \$22 to more than \$120 per month. This report presents information that will help you: (a) determine when you might need a CCB; (b) choose the right CCB and dose; and (c) save \$1,000 to \$1,700 a year if you have been prescribed an expensive brand-name CCB.

CCBs are effective medicines that lower blood pressure and help prevent and treat the symptoms of angina. Two CCBs are effective in controlling certain heart rhythm problems.

CCBs are typically *not* prescribed as initial or first-step treatment in people with high blood pressure who have no other form of heart disease. Instead, CCBs are often used as a second or third drug to help lower blood pressure when other medicines have failed to bring it down enough.

CCBs *should* be considered as initial medicine (usually in combination with other drugs) for people who have high blood pressure plus angina and/or a high risk of stroke. CCBs *should not* be taken by people with heart failure (often called congestive heart failure).

This report compares the effectiveness, safety, and cost of eight CCBs. We have chosen the following four as *Consumer Reports Best Buy Drugs* based on the weight of scientific evidence, dosing convenience, and cost in treating the following conditions:

- *For high blood pressure* – Diltiazem SR and Diltiazem CR, Felodipine SR, Nifedipine SR, Verapamil SR
- *For angina* – Nifedipine SR
- *For heart rhythm abnormalities* – Diltiazem SR and Diltiazem CR, Verapamil SR

All these medicines are available as low-cost or moderately priced generic drugs. All are as effective as other CCBs. (SR stands for “sustained release” and CR stands for “continuous release.”)

Welcome

This report on a class of drugs known as calcium channel blockers (CCBs) is part of a Consumers Union and *Consumer Reports* project to help you find safe, effective medicines that give you the most value for your health-care dollar. To learn more about the project and drugs we've evaluated, go to www.CRBestBuyDrugs.org.


CCBs are used by millions of people every day. They were the eighth most widely prescribed class of medicines in the United States in 2004, with almost 90 million prescriptions filled. CCBs are primarily used to treat people with high blood pressure, angina (the chest pain caused by reduced blood supply to the heart muscle), and certain heart rhythm abnormalities (especially those where the heart beats too fast). But doctors also prescribe CCBs to prevent migraines and treat inadequate blood flow to the hands and feet (called Raynaud's disease), as well as certain psychiatric disorders.

In this report, we focus on the use of CCBs to treat high blood pressure, angina, and abnormal heart rhythms.

Eight CCBs are available in the U.S. Five are available as lower-cost generic drugs in some dosage forms. And most are available as long-acting, sustained, or continuous release pills that need to be taken just once a day, instead of two to four times a day (which can be inconvenient and raise the risk of missed doses). The eight are:

Generic Name	Brand Name(s)	Available as a Prescription Generic Drug ¹
Amlodipine	Norvasc	No
Diltiazem	Cardizem, Cartia, Dilacor, Diltia, Taztia, Tiazac	Yes
Felodipine	Plendil	Yes
Isradipine	Dynacirc	No
Nicardipine	Cardene	Yes
Nifedipine	Adalat, Nifedical, Procardia	Yes
Nisoldipine	Sular	No
Verapamil	Calan, Covera-HS, Isoptin, Verelan	Yes

(1) Some dosage forms only



CCBs are just one class of prescription medicine used to treat heart problems. Five other classes are used to treat high blood pressure, for example. Those include diuretics, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), and alpha-blockers. Those five plus CCBs are often used in various combinations. Indeed, many people with high blood pressure will have to take two or more drugs to bring their blood pressure down to normal. Likewise, several other kinds of drugs are used to treat angina. The most commonly used are nitroglycerin and beta-blockers.

Talk with your doctor about the right mix of blood pressure and heart medicines for you, as well as lifestyle changes – such as a low saturated-fat diet, weight loss, getting more exercise, controlling alcohol use, and quitting smoking – *that could reduce your need for medicines and help enhance and preserve your health.*

You should know that high blood pressure in particular is one of the most significantly under-diagnosed and under-treated diseases in the U.S., in large part because it has no symptoms. High blood pressure is one of the most important risk factors for heart attack, heart failure, stroke, dementia, vision loss, and kidney failure. In most who have it, it is a lifelong chronic condition. Estimates vary, but at least 65 million Americans – including *one third* of adults aged 18 and over – have high blood pressure. Yet studies show that:

- 30% are *unaware* of their condition and not getting any treatment
- 15% are aware of their condition but not getting treatment or taking medicine
- 25% are getting treatment but their high blood pressure is *not* under control

That leaves only 30% of people with high blood pressure getting the medicines, care, and blood pressure control they need. Uncontrolled high blood pressure is a leading cause of death. In addition, high blood pressure's dangers are now believed to extend to an additional *45 to 60 million* Americans who have “prehypertension,” or borderline high blood pressure. (See Table 1 on page 6.)

The upshot: you should have your blood pressure checked often – at least once a year, more often if you are over age 50, and every time you visit a doctor no matter what your age is. Although high blood pressure can occur at any age, it is far more common in people 35 and over and among African-Americans.

To a lesser extent (mostly because they have symptoms), angina and heart rhythm abnormalities are also under-diagnosed and under-treated. If you experience occasional or frequent feelings of pressure in your chest, a sense of squeezing or actual pain (sometimes radiating to the jaw, shoulder, arms, or neck), you could have angina and should see a doctor as soon as possible. You may first notice such symptoms when exercising or physically active – such as walking up a flight of stairs. The symptoms usually ease when you are at rest, and can usually be managed with medicines.

But angina symptoms can also occur when you are doing nothing, and that is especially dangerous. In that case, *you should chew and swallow an aspirin tablet, and dial 911 for transportation to the nearest emergency room since you may be having a heart attack.*

Likewise, if you sense your heart is racing and/or you have heart palpitations (irregular beating of the heart), bouts of dizziness, shortness of breath, lightheadedness, or fainting, you may have what doctors call an arrhythmia (abnormal heart rhythm), of which there are several kinds. One common form is called atrial fibrillation; another is atrial flutter. All arrhythmias require *immediate* medical attention and can be treated successfully after identification of the particular kind.

This report is based on a comprehensive expert analysis of the medical evidence on CCBs. There's more information on page 20 and at www.CRBestBuyDrugs.org about how we conducted our evaluation.

This report was released and last updated in June 2005

Note to Readers: This is our third report on different classes of prescription medicines to treat high blood pressure and other heart conditions. A report on beta-blockers was released in March and one on the ACE inhibitor drugs in April. Both are available at www.CRBestBuyDrugs.org. In addition, we will soon post a report to help you make sense of all the classes of drugs used – often in combination – to treat high blood pressure. Sign up at www.CRBestBuyDrugs.org for an e-mail alert if you'd like us to tell you when that and other reports get posted on our Web site.



What Are Calcium Channel Blockers and Who Needs Them?

CCBs work by slowing the movement of calcium into the muscle cells of the heart and blood vessel walls. This relaxes blood vessels which makes it easier for the blood to flow. In turn, blood pressure declines. CCBs can directly affect the heart muscle as well. All affect the pumping action or contraction of the heart. And some CCBs reduce the heart rate by slowing the nerve impulse conduction that makes the heart contract.

Importantly, two CCBs (diltiazem and verapamil) have a stronger effect on the heart than on the blood vessels while the others listed in the Welcome section have a stronger effect on the blood vessels and less of an effect on the heart.

CCBs are not the best initial choice for many people with high blood pressure. A diuretic is the better (and least expensive) initial treatment, especially for people who have high blood pressure but no other

heart problems. CCBs are very often prescribed early, however, for people with high blood pressure who also have angina or are at high risk of stroke or coronary heart disease. In this case, CCBs are usually used along with other medicines such as diuretics or beta-blockers. Also, your doctor may recommend a CCB if you are already taking a diuretic and need a second drug to lower your blood pressure.

The box on page 7 and Table 1 on this page give you some basic information on high blood pressure and its treatment.

As with high blood pressure, CCBs are not usually recommended as the *initial* treatment of angina. Instead, your doctor may prescribe other medicines first, such as nitrates (nitroglycerin) or beta-blockers. But if you are taking one of those other medicines and you keep having angina symptoms, your doctor may prescribe a CCB, too.

Table 1. Blood Pressure Levels and Treatment Guidance

Blood Pressure Classification	Systolic Measure (mm Hg)	Diastolic Measure (mm Hg)	General Treatment Guidance
Normal	Below 120	Below 80	<ul style="list-style-type: none"> ■ No treatment needed ■ Healthy lifestyle encouraged to maintain normal blood pressure
Prehypertensive	120-139	80-89	<ul style="list-style-type: none"> ■ Lifestyle changes needed: weight loss, quitting smoking, low-salt and low-fat diet, curb excessive alcohol use, and increased exercise ■ Drug treatment not indicated except if you have diabetes, kidney or heart disease
Stage 1 High Blood Pressure	140-159	90-99	<ul style="list-style-type: none"> ■ Lifestyle changes urged, same as above ■ Drug treatment needed. Doctor may start with one medicine (usually a diuretic) to see if it does the job.
Stage 2 High Blood Pressure	160 or above	100 or above	<ul style="list-style-type: none"> ■ Lifestyle changes urged, same as above ■ Drug treatment needed. Two or more medicines usually required to bring blood pressure down.

Source: Chobanian AV, Bakris GL, Black HR, et al., "The seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure," *Journal of the American Medical Association*, 2003; 289(19):2560-2572

The Basics on High Blood Pressure

Americans' health could be markedly improved if they were more alert to the dangers and complications of high blood pressure and the need to have their blood pressure checked regularly.

Blood pressure is the force against the walls of your arteries when blood is pumped out of the heart. It's measured in millimeters of mercury (abbreviated as mm Hg) and the measurement consists of two numbers. One number, usually given first, is the pressure when the heart muscle contracts; that's called the systolic pressure. The second number is the pressure when the heart is at rest. That's called the diastolic pressure. Both matter. Your doctor may say or present them, for example, as "120 over 80" or 120/80 mm Hg.

High blood pressure – the causes of which are not well understood – is defined, for adults, as a systolic pressure of 140mm Hg or greater and/or a diastolic pressure of 90mm Hg or greater. Normal blood pressure is defined as a systolic reading of less than 120mm Hg and a diastolic reading of less than 80mm Hg.

That leaves a gap between "normal" and "high." That gap is now labeled "prehypertensive." Based on recent studies, if your blood pressure readings fall into that gap, you are at risk of developing high blood pressure and you already have some elevated risk of heart disease and stroke. You need to lower your blood pressure. Table 1 on page 6 presents these levels of blood pressure and general treatment guidance. If your blood pressure levels are prehypertensive and you have heart or kidney disease or diabetes, you may need drug treatment to lower your blood pressure.

Note: Both numbers – systolic and diastolic – don't have to be high at the same time, and often are not. Even if one is elevated, you are considered to have high blood pressure. Indeed, in people aged 50 and over, a high systolic reading appears to be much more strongly linked to a higher risk of heart disease and heart attack than a high diastolic blood pressure.

High blood pressure's relationship to stress, anxiety, nervousness, or feeling tense is often misunderstood. Feeling excited, anxious, or fearful can indeed raise blood pressure, but usually only temporarily – due to the surge of adrenaline that often accompanies those feelings. But they are *not* symptoms of high blood pressure. You can be a calm, relaxed person who never gets anxious or fearful and still have high blood pressure. And you may have absolutely no symptoms. The only way to detect your high blood pressure is to have it checked regularly using a blood pressure arm cuff.

Importantly, CCBs can help control or prevent the symptoms of angina, *but they do not stop it once it starts*. Your doctor will usually prescribe nitroglycerin for that.

If you have been diagnosed with a rapid heart arrhythmia – called a "supraventricular tachycardia" – your doctor may consider prescribing a CCB. Only two CCBs are indicated for this condition, however – diltiazem and verapamil. Both have been shown to effectively slow that particular abnormal heart rhythm.

Your doctor will also likely discuss with you alternative methods to change the heart rhythm back to normal. You should know that if you take a CCB for an abnormal heart rhythm, you should be monitored very closely by your physician. If you are also taking a beta-blocker (for any reason), discuss the choice of a CCB with your doctor: using these two types of medicines together can slow the heart rate excessively and lead to light-headedness and possible fainting spells.

Choosing a Calcium Channel Blocker – Our *Best Buy* Picks

The choice of a CCB depends on what you need it for. If you have two or more of the medical conditions for which CCBs are indicated – such as high blood pressure and angina or heart beat irregularities – your doctor will be making a judgment about which CCB and dose, and other medicines, are best for you.

The information in this report will help you discuss with your doctor which treatment is right for you,

and which may cost you the least amount of money out-of-pocket.

People respond to the various CCBs differently. So you may have to try more than one if your doctor judges that the one that was initially prescribed is not working. In addition, CCBs, while generally safe, can have side effects and you may respond to one CCB better than another. Side effects include

Table 2. Summary of Evidence on the CCBs

Generic Name (Daily Dose – Range)	Brand Name(s)	Proven to Lower Blood Pressure?	Proven to Reduce Angina?	Proven to Reduce Heart Rate?	Approved for Treatment of:
Amlodipine 5-10mg	Norvasc	Yes	Yes	No	<ul style="list-style-type: none"> ■ HBP¹ ■ Angina
Diltiazem 180-240mg	Cardizem, Cartia, Dilacor, Diltia, Taztia, Tiazac	Yes	Yes	Yes	<ul style="list-style-type: none"> ■ HBP ■ Angina ■ Fast irregular heart rhythms
Felodipine 5-10mg	Plendil	Yes	Likely ²	No	<ul style="list-style-type: none"> ■ HBP
Isradipine 5-10mg	Dynacirc	Yes	Likely	No	<ul style="list-style-type: none"> ■ HBP
Nicardipine 60-120mg	Cardene	Yes	Yes	No	<ul style="list-style-type: none"> ■ HBP ■ Angina
Nifedipine 30-60mg	Adalat, Nifedical, Procardia	Yes	Yes	No	<ul style="list-style-type: none"> ■ HBP ■ Angina
Nisoldipine 10-40mg	Sular	Yes	Likely	No	<ul style="list-style-type: none"> ■ HBP
Verapamil 120-240mg	Calan, Covera-HS, Isoptin, Verelan	Yes	Yes	Yes	<ul style="list-style-type: none"> ■ HBP ■ Angina ■ Fast irregular heart rhythms

(1) HBP stands for high blood pressure

(2) "Likely" means that studies have not yet proved effectiveness, but doctors may prescribe it for this condition.

dizziness, headache, constipation, flushing, and swollen ankles. Less frequently, they can cause diarrhea, drowsiness, fatigue and nausea. Also, some of the CCBs can cause dangerously slow heart rates.

Starting with as low a dose of a CCB as possible can reduce your risk of side effects. Indeed, doctors commonly start with a low dose of a CCB and then increase your dosage over time to get the best results without triggering side effects. It may take a couple of weeks before you start getting the full benefit of a CCB.

You and your doctor should be choosing a CCB based primarily on its potential benefits and risks to you (this must be individually determined), the strength of the evidence (it is both safe and works against a particular condition), and whether it is approved by the Food and Drug Administration (FDA) to treat that condition.

Where the evidence suggests equal effectiveness and safety, cost may be a deciding factor, especially if you have no drug coverage. The CCBs vary in cost from about \$22 to \$78 per month for most generics to over \$100 per month for many brand-name versions. Again, five of the CCBs are available as generics in most dose forms.

For many people, the convenience of once-a-day dosing of a CCB also may be important. Our *Best Buy* picks in this report give priority to once-a-day doses for two reasons: (a) people are more likely to comply with this dose regimen, and (b) evidence suggests that the once-a-day long-acting (or sustained release) formulations of CCBs may prove to have better results than short-acting formulations.

Table 2 and the discussion below summarize the strength of the evidence on CCBs and should help guide your choice. Note that the proof of effectiveness for some CCBs is confined to some dose strengths. That does not mean that lower or higher dose strengths aren't effective.

Taking effectiveness, safety, dosing convenience, and cost into account, we have selected the following CCBs as *Consumer Reports Best Buy Drugs* for these medical conditions:

- *For high blood pressure* – Diltiazem SR and Diltiazem CR, Felodipine SR, Nifedipine SR, Verapamil SR
- *For angina* – Nifedipine SR
- *For heart rhythm abnormalities* – Diltiazem SR and Diltiazem CR, Verapamil SR

Treating high blood pressure. As presented in Table 2, all the CCBs are approved for and have been shown to be effective in lowering blood pressure. However, no studies have directly compared the effectiveness and safety of one CCB with another as to how well they work or their track record in reducing the risk of heart attack or stroke in people with high blood pressure. Most of the evidence from studies suggests that, on average, people's response to the various CCBs (when they are taken to lower blood pressure) does not differ substantially.

Again, CCBs may not be optimal as a first line treatment if you have high blood pressure but no other form of heart disease. They are typically used as a second drug if you have especially high blood pressure or if your blood pressure has failed to be lowered by a single drug, such as a diuretic.

Our choice of four *Best Buy* CCBs for high blood pressure – Diltiazem SR and Diltiazem CR, Felodipine SR, Nifedipine SR, Verapamil SR – is based primarily on cost and dosing convenience. These four give you adequate choice if you need to try another CCB. All are available in relatively low-cost generic or “branded generic” formulations in one-a-day capsules or tablets. They range in cost from \$22 to \$76 a month, depending on dose. There is no reason to take the more expensive brand-name versions of any of these medicines. (Note: A branded generic is a generic copy of an original drug but one given a special name by its generic manufacturer. See Table 3.)

Treating angina. Five of the eight CCBs are FDA-approved for angina treatment. As with high blood pressure, CCBs are typically prescribed as a second- or third-tier treatment for angina, along with other drugs.

While no studies have shown any one CCB to be better than another in treating angina, less evidence exists for felodipine, isradipine, nisoldipine, and the

“sustained release” or “continuous release” formulations of diltiazem and verapamil. The effectiveness of these drugs is likely similar to other CCBs, but our analysis found the evidence lacking to date. So, you might want to talk to your doctor about alternatives if you are taking one of these medicines for angina. Also, if the only medicine you are currently taking for angina is a CCB, ask your doctor if a beta-blocker or a nitrate might be a more cost-effective alternative.

Our choice of one *Best Buy* CCB for treating angina – **Nifedipine SR** – is based on the strength of evidence, dosing convenience, and cost. This medicine is available in relatively low-cost generic or branded generic formulations that need to be taken just once a day. The various generic forms and doses range in cost from \$32 to \$77 a month.

Treating abnormal heart rhythms. Only two CCBs have been proven safe and effective for the treatment of rapid abnormal heart rate. These are diltiazem and verapamil. None of the other CCBs should be used for this purpose. Taken as a whole, studies do not indicate that one of these two drugs is better than another when used to treat rapid heart rate.

Our choice of three sustained release or continuous release versions of these two drugs as *Best Buys* – **Diltiazem SR, Diltiazem CR, and Verapamil SR** – is based on proof of effectiveness, dosing convenience, and cost. Cost-effective generic or branded generic formulations of all three are available that need to be taken just once a day. They range in cost from \$22 to \$66 a month.

Table 3 presents the average monthly costs for all the CCBs at a wide variety of doses, and their *Best Buy* indications.

Table 3. CCB Cost Comparison and Best Buy Indication

Generic Name and Dose	Brand Name(s) ¹	Drug a Generic (Yes) or Branded Generic (BG) ²	Frequency of Use (Per Day) ³	Average Monthly Cost ⁴	Best Buy Indication
Amlodipine 2.5mg tablet	Norvasc	No	One	\$56	
Amlodipine 5mg tablet	Norvasc	No	One	\$55	
Amlodipine 10mg tablet	Norvasc	No	One	\$73	
Diltiazem 30mg tablet	Cardizem	No	Four	\$81	
Diltiazem 30mg tablet	Generic	Yes	Four	\$34	
Diltiazem 60mg SR capsule ⁵	Cardizem SR	No	Two	\$68	
Diltiazem 60mg SR capsule	Generic	Yes	Two	\$44	
Diltiazem 60mg tablet	Cardizem	No	Four	\$124	
Diltiazem 60mg tablet	Generic	Yes	Four	\$40	
Diltiazem 90mg SR capsule	Cardizem SR	No	Two	\$78	
Diltiazem 90mg SR capsule	Generic	Yes	Two	\$49	
Diltiazem 90mg tablet	Cardizem	No	Four	\$193	

Table 3. CCB Cost Comparison and Best Buy Indication (continued)






Generic Name and Dose	Brand Name(s) ¹	Drug a Generic (Yes) or Branded Generic (BG) ²	Frequency of Use (Per Day) ³	Average Monthly Cost ⁴	Best Buy Indication
Diltiazem 90mg tablet	Generic	Yes	Four	\$61	
Diltiazem 120mg CR capsule ⁶	Cardizem CD	No	One	\$49	
 Diltiazem 120mg CR capsule	Cartia XT	BG	One	\$35	■ HBP ⁷ ■ HRAs ⁸
 Diltiazem 120mg CR capsule	Generic	Yes	One	\$32	■ HBP ■ HRAs
Diltiazem 120mg SR capsule	Cardizem SR	No	Two	\$78	
Diltiazem 120mg SR capsule	Dilacor XR	BG	One	\$58	
 Diltiazem 120mg SR capsule	Diltia XT	BG	One	\$25	■ HBP ■ HRAs
 Diltiazem 120mg SR capsule	Dilt-XR	BG	One	\$27	■ HBP ■ HRAs
 Diltiazem 120mg SR capsule	Generic	Yes	One	\$27	■ HBP ■ HRAs
 Diltiazem 120mg SR capsule	Taztia XT	BG	One	\$35	■ HBP ■ HRAs
Diltiazem 120mg SR capsule	Tiazac	BG	One	\$41	
Diltiazem 120mg SR tablet	Cardizem LA	No	One	\$50	
Diltiazem 120mg tablet	Cardizem	No	Four	\$208	
Diltiazem 120mg tablet	Generic	Yes	Four	\$78	
Diltiazem 180mg CR capsule	Cardizem CD	No	One	\$58	
Diltiazem 180mg CR capsule	Cartia XT	BG	One	\$40	
 Diltiazem 180mg CR capsule	Generic	Yes	One	\$37	■ HBP ■ HRAs
Diltiazem 180mg SR capsule	Dilacor XR	No	One	\$64	

Table 3. CCB Cost Comparison and Best Buy Indication (continued)








	Generic Name and Dose	Brand Name(s) ¹	Drug a Generic (Yes) or Branded Generic (BG) ²	Frequency of Use (Per Day) ³	Average Monthly Cost ⁴	Best Buy Indication
	Diltiazem 180mg SR capsule	Diltia XT	BG	One	\$27	■ HBP ■ HRAs
	Diltiazem 180mg SR capsule	Dilt-XR	BG	One	\$31	■ HBP ■ HRAs
	Diltiazem 180mg SR capsule	Generic	Yes	One	\$30	■ HBP ■ HRAs
	Diltiazem 180mg SR capsule	Taztia XT	BG	One	\$40	
	Diltiazem 180mg SR capsule	Tiazac	BG	One	\$48	
	Diltiazem 180mg SR tablet	Cardizem LA	No	One	\$52	
	Diltiazem 240mg CR capsule	Cardizem CD	No	One	\$79	
	Diltiazem 240mg CR capsule	Cartia XT	No	One	\$55	
	Diltiazem 240mg CR capsule	Generic	Yes	One	\$49	
	Diltiazem 240mg SR capsule	Dilacor XR	No	One	\$71	
	Diltiazem 240mg SR capsule	Diltia XT	BG	One	\$30	■ HBP ■ HRAs
	Diltiazem 240mg SR capsule	Dilt-XR	BG	One	\$31	■ HBP ■ HRAs
	Diltiazem 240mg SR capsule	Generic	Yes	One	\$35	■ HBP ■ HRAs
	Diltiazem 240mg SR capsule	Taztia XT	BG	One	\$55	
	Diltiazem 240mg SR capsule	Tiazac	BG	One	\$65	
	Diltiazem 240mg SR tablet	Cardizem LA	No	One	\$57	
	Diltiazem 300mg CR capsule	Cardizem CD	No	One	\$102	
	Diltiazem 300mg CR capsule	Cartia XT	BG	One	\$70	
	Diltiazem 300mg CR capsule	Generic	Yes	One	\$64	■ HBP ■ HRAs

Table 3. CCB Cost Comparison and Best Buy Indication (continued)






	Generic Name and Dose	Brand Name(s) ¹	Drug a Generic (Yes) or Branded Generic (BG) ²	Frequency of Use (Per Day) ³	Average Monthly Cost ⁴	Best Buy Indication
	Diltiazem 300mg SR capsule	Generic	Yes	One	\$66	■ HBP ■ HRAs
	Diltiazem 300mg SR capsule	Taztia XT	BG	One	\$71	
	Diltiazem 300mg SR capsule	Tiazac	BG	One	\$84	
	Diltiazem 300mg SR tablet	Cardizem LA	No	One	\$79	
	Diltiazem 360mg CR capsule	Cardizem CD	No	One	\$122	
	Diltiazem 360mg SR capsule	Generic	Yes	One	\$66	■ HBP ■ HRAs
	Diltiazem 360mg SR capsule	Taztia XT	BG	One	\$71	
	Diltiazem 360mg SR capsule	Tiazac	BG	One	\$85	
	Diltiazem 360mg SR tablet	Cardizem LA	No	One	\$79	
	Felodipine 2.5mg SR tablet	Generic	Yes	One	\$37	■ HBP
	Felodipine 2.5mg SR tablet	Plendil	No	One	\$47	
	Felodipine 5mg SR tablet	Generic	Yes	One	\$37	■ HBP
	Felodipine 5mg SR tablet	Plendil	No	One	\$46	
	Felodipine 10mg SR tablet	Generic	Yes	One	\$64	■ HBP
	Felodipine 10mg SR tablet	Plendil	No	One	\$80	
	Isradipine 2.5mg capsule	Dynacirc	No	Two	\$98	
	Isradipine 5mg capsule	Dynacirc	No	Two	\$145	
	Isradipine 5mg SR tablet	Dynacirc CR	No	One	\$66	
	Isradipine 10mg SR tablet	Dynacirc CR	No	One	\$102	
	Nicardipine 20mg capsule	Cardene	No	Three	\$70	
	Nicardipine 20mg capsule	Generic	Yes	Three	\$33	

Table 3. CCB Cost Comparison and Best Buy Indication (continued)






Generic Name and Dose	Brand Name(s) ¹	Drug a Generic (Yes) or Branded Generic (BG) ²	Frequency of Use (Per Day) ³	Average Monthly Cost ⁴	Best Buy Indication
Nicardipine 30mg capsule	Cardene	No	Three	\$99	
Nicardipine 30mg capsule	Generic	Yes	Three	\$51	
Nicardipine 30mg SR capsule	Cardene SR	No	Two	\$71	
Nicardipine 45mg SR capsule	Cardene SR	No	Two	\$108	
Nicardipine 60mg SR capsule	Cardene SR	No	Two	\$128	
Nifedipine 10mg capsule	Adalat	No	Three	\$57	
Nifedipine 10mg capsule	Generic	Yes	Three	\$38	
Nifedipine 10mg capsule	Procardia	No	Three	\$82	
Nifedipine 20mg capsule	Generic	Yes	Three	\$99	
Nifedipine 20mg capsule	Procardia	No	Three	\$175	
Nifedipine 30mg SR tablet	Adalat CC	No	One	\$50	
 Nifedipine 30mg SR tablet	Afeditab CR	BG	One	\$32	■ HBP ■ Angina
Nifedipine 30mg SR tablet	Generic	Yes	One	\$41	
 Nifedipine 30mg SR tablet	Nifediac CC	BG	One	\$35	■ HBP ■ Angina
Nifedipine 30mg SR tablet	Nifedical XL	BG	One	\$41	
Nifedipine 30mg SR tablet	Procardia XL	No	One	\$55	
Nifedipine 60mg SR tablet	Adalat CC	No	One	\$87	
 Nifedipine 60mg SR tablet	Afeditab CR	BG	One	\$56	■ HBP ■ Angina
 Nifedipine 60mg SR tablet	Generic	Yes	One	\$60	■ HBP ■ Angina
 Nifedipine 60mg SR tablet	Nifediac CC	BG	One	\$62	■ HBP ■ Angina
Nifedipine 60mg SR tablet	Nifedical XL	BG	One	\$69	

Table 3. CCB Cost Comparison and Best Buy Indication (continued)










Generic Name and Dose	Brand Name(s) ¹	Drug a Generic (Yes) or Branded Generic (BG) ²	Frequency of Use (Per Day) ³	Average Monthly Cost ⁴	Best Buy Indication
Nifedipine 60mg SR tablet	Procardia XL	No	One	\$94	
Nifedipine 90mg SR tablet	Adalat CC	No	One	\$101	
 Nifedipine 90mgSR tablet	Generic	Yes	One	\$77	■ HBP ■ Angina
 Nifedipine 90mg SR tablet	Nifediac CC	BG	One	\$76	■ HBP ■ Angina
Nifedipine 90mg SR tablet	Procardia XL	No	One	\$112	
Nisoldipine 10mg SR tablet	Sular	No	One	\$53	
Nisoldipine 20mg SR tablet	Sular	No	One	\$51	
Nisoldipine 30mg SR tablet	Sular	No	One	\$68	
Nisoldipine 40mg SR tablet	Sular	No	One	\$66	
Verapamil 40mg tablet	Calan	No	Three	\$59	
Verapamil 40mg tablet	Generic	Yes	Three	\$27	
Verapamil 80mg tablet	Calan	No	Three	\$82	
Verapamil 80mg tablet	Generic	Yes	Three	\$23	
Verapamil 100mg SR capsule	Verelan PM	No	One	\$53	
 Verapamil 120mg SR capsule	Generic	Yes	One	\$32	■ HBP ■ HRAs
Verapamil 120mg SR capsule	Verelan	No	One	\$71	
Verapamil 120mg SR tablet	Calan SR	No	One	\$53	
 Verapamil 120mg SR tablet	Generic	Yes	One	\$27	■ HBP ■ HRAs
Verapamil 120mg SR tablet	Isoptin SR	BG	One	\$50	
Verapamil 120mg tablet	Calan	No	Three	\$131	
 Verapamil 120mg tablet	Generic	Yes	Three	\$31	■ HBP ■ HRAs

Table 3. CCB Cost Comparison and Best Buy Indication (continued)

Generic Name and Dose	Brand Name(s) ¹	Drug a Generic (Yes) or Branded Generic (BG) ²	Frequency of Use (Per Day) ³	Average Monthly Cost ⁴	Best Buy Indication
Verapamil 180mg SR capsule	Generic	Yes	One	\$33	
Verapamil 180mg SR capsule	Verelan	BG	One	\$75	
Verapamil 180mg SR tablet	Calan SR	No	One	\$66	
Verapamil 180mg SR tablet	Covera HS	No	One	\$57	
 Verapamil 180mg SR tablet	Generic	Yes	One	\$22	■ HBP ■ HRAs
Verapamil 180mg SR tablet	Isoptin SR	BG	One	\$64	
Verapamil 200mg SR capsule	Verelan PM	BG	One	\$66	
 Verapamil 240mg SR capsule	Generic	Yes	One	\$36	■ HBP ■ HRAs
Verapamil 240mg SR capsule	Verelan	BG	One	\$84	
Verapamil 240mg SR tablet	Calan SR	No	One	\$74	
Verapamil 240mg SR tablet	Covera HS	No	One	\$92	
 Verapamil 240mg SR tablet	Generic	Yes	One	\$22	■ HBP ■ HRAs
Verapamil 240mg SR tablet	Isoptin SR	BG	One	\$69	
Verapamil 300mg SR capsule	Verelan PM	BG	One	\$96	
 Verapamil 360mg SR capsule	Generic	Yes	One	\$65	■ HBP ■ HRAs
Verapamil 360mg SR capsule	Verelan	BG	One	\$123	

(1) "Generic" indicates that this drug is sold as a generic under the generic or chemical name.

(2) "Yes" means it is a generic, sold under the chemical name. "BG" means it is a branded generic, which is a generic copy of an original drug but one given a special name by its generic manufacturer. "No" means it is a brand-name drug not yet available as a generic or a branded generic.

(3) Frequency of use reflects usual frequency; some medicines may be used more or less frequently.

(4) Prices reflect nationwide retail average for April 2005, rounded to the nearest dollar; data provided by NDCHealth, a healthcare information company.

(5) "SR" stands for sustained release

(6) "CR" stands for continuous delivery

(7) "HBP" stands for high blood pressure

(8) "HRAs" stands for heart rhythm or heart rate abnormalities

The Evidence

This section presents more information on the effectiveness and safety of calcium channel blockers.

This report is based on an analysis of the scientific evidence on calcium channel blockers. Almost 3,500 studies were identified that were published in peer-reviewed journals from 1970 to 2004, or submitted by pharmaceutical companies. An additional 1,533 studies were evaluated which contained references to calcium channel blockers. From both groups of studies, the analysis focused on the results of 188, most of which were medium- to large-scale controlled clinical trials or detailed “meta-analyses” of many clinical trials. A meta-analysis combines the results of previous individual studies and tries to draw conclusions based on all of them.

How Effective Are CCBs?

CCBs are widely accepted as effective medicines. They have been proven to lower blood pressure, help prevent and reduce angina pain, and slow the heart rate in people with certain heart rhythm abnormalities. Although none of the CCBs has been *proven to reduce deaths* from heart attack or stroke in people who have high blood pressure or angina, evidence points in that direction and such a benefit is assumed. Indeed, several important studies have shown CCBs to be superior at lowering the risk of strokes compared to other drugs to treat high blood pressure.

Even so, a vigorous debate continues about the relative merits of CCBs compared to other medicines, particularly in treating high blood pressure. That’s largely because a few studies indicate that CCBs (and particularly high doses taken over long periods) may be associated with a somewhat higher risk of heart attacks and heart failure compared to other medicines, such as diuretics, beta-blockers, and ACE inhibitors.

This does not mean that CCBs are *causing* heart attacks or heart failure (also called congestive heart failure, which occurs when the heart muscle weakens limiting the heart’s pumping ability). It means that

they may not be preventing as many deaths from these conditions as other medicines. It could also mean that some CCBs (diltiazem and verapamil, in particular, which slow heart rate) are given in some cases to the wrong patients, such as those with heart failure. Studies continue on this issue, and it’s generally agreed that more evidence is needed.

In the meantime, such concerns have led to more cautious use of CCBs, and are the reason many doctors avoid them as first line treatment. It is also why they are no longer advised for people with heart failure. ACE Inhibitors are the strongly preferred drug in such patients.

One problem in that regard is that heart failure often goes unrecognized, especially in its early stages. People commonly think its symptoms are a sign of normal aging, and nothing to worry about. In addition, doctors sometimes misdiagnose symptoms of heart failure, such as fatigue, weakness, shortness of breath, unexplained coughing or wheezing, and swelling of the legs.

If you have these symptoms, you should see a doctor as soon as possible.

Your doctor is likely to be aware of the debate over which drugs are best for high blood pressure, and he or she may well have an opinion about recent studies that have yielded conflicting results.

If you have significantly elevated blood pressure and one or more additional heart problems, this ongoing debate is of vital importance. *Taking the right medicines at the right doses can be literally a life-and-death issue.* Unfortunately, it is not possible yet to say with certainty what the best combination of heart drugs is for many people who have several heart ailments.

How Safe Are CCBs?

CCBs are generally safe medicines, with more than two decades of widespread use around the world. In general, other than those discussed above, no signif-

icant differences have been found among the CCBs in terms of their safety or the side effects they cause.

All the CCBs can cause side effects. Most are minor. The most common are: dizziness, headache, flushing, and mild ankle swelling. These side effects often go away as the body adjusts to the medicine but, if persistent, may require some adjustment in dose or even discontinuing the medicine. One side effect may be first noticed by your dentist. Enlargement of the gum tissue (called gingival hyperplasia) can lead to bleeding and further erosion of the gums. In such cases, you may have to stop taking your CCB.

More serious side effects can occur, however, especially if you have heart failure. If any of the following symptoms occur while taking a CCB, contact your doctor:

- Breathing problems
- Irregular, fast heart beat
- A slow heart beat (less than 50 beats per minute)

As mentioned above, people with heart failure should not be taking a CCB. And among the CCBs, diltiazem and verapamil are especially dangerous for those people because they are more likely to slow your heart rate.

In fact, if you are taking either of these two drugs, you should ask your doctor to instruct you on how to count your pulse rate and check it regularly. If it is much slower than usual, or less than 50 beats per minute, check with your doctor immediately. A pulse rate that is too slow can cause severe light-headedness and fainting.

Doctors and researchers have been looking closely at the relative merits of the shortacting versus the long-acting (extended, sustained or continuous release) versions of the CCB drugs. Most experts agree that the long-acting forms of CCBs are preferred in the treatment of chronic high blood pressure.

Since you will probably be taking a CCB along with other medicines, you should know that you are more likely to have side effects from taking any combination of drugs versus one drug alone. You may want to talk to your doctor about what side effects to watch for if a CCB is added to your prescription drug regimen. The chief reason to do this is to prevent you from discontinuing one or more of your medicines. *You should not stop taking your blood pressure medicines without consulting your doctor. This could lead to a fatal stroke or heart attack.*

In particular, diltiazem and verapamil can interact with beta-blockers to cause excessive slowing of the heart rate. CCBs also can have adverse interaction with the following medicines:

- Digitalis
- Drugs to correct irregular heartbeat, such as quinidine (Quinidex), disopyramide (Norpace), or procainamide (Procan, Pronestyl)
- Anti-seizure medications, such as carbamazepine (Tegretol)

Grapefruit and grapefruit juice can also increase the side effects of most CCBs.

Age, Race, and Gender Differences

Mounting evidence suggests that African-Americans with high blood pressure respond better to CCBs (usually combined with a diuretic) than they do to ACE inhibitors. This is emerging as conventional wisdom in clinical practice as well. Any African-American taking an ACE inhibitor who has struggled to control their blood pressure should discuss with their doctor switching to a CCB.

That said, people older than 65 and various ethnic groups have been under-represented in most studies of CCBs. Taken together, these studies could not detect if any one CCB is more or less effective in older patients or people of a particular race or gender.

Talking With Your Doctor

It's important for you to know that the information we present here is not meant to substitute for a doctor's judgment. But we hope it will help your doctor and you arrive at a decision about which CCB or dose is best for you, and which gives you the most value for your health-care dollar.

Bear in mind that many people are reluctant to discuss the cost of medicines with their doctors and that studies show doctors do not routinely take price into account when prescribing medicines. Unless you bring it up, your doctor may assume that cost is not a factor for you.

Many people (including physicians) also believe that newer drugs are always or almost always better. While that's a natural assumption to make, the fact is that it's not true. Studies consistently show that many older medicines are as good as, and in some cases better than, newer medicines. Think of them as "tried and true," particularly when it comes to their safety record. Newer drugs have not yet met the test of time, and unexpected problems can and do crop up once they hit the market.

Of course, some newer prescription drugs are indeed more effective and safer. Talk with your doctor about the pluses and minuses of newer versus older medicines, including generic drugs.

Prescription medicines go "generic" when a company's patents on a drug lapse, usually after about 12 to 15 years. At that point, other companies can make and sell the drug.

Generics are almost always much less expensive than newer brand name medicines, but they are not lesser quality drugs. Indeed, most generics remain useful medicines even many years after first being marketed. That is why today about 47% of all prescriptions in the U.S. are for generics.

Another important issue to talk with your doctor about is keeping a record of the drugs you are taking. There are several reasons for this:

- First, if you see several doctors, each may not be aware of medicines the others have prescribed.
- Second, since people differ in their response to medications, it is very common for doctors to prescribe several medicines before finding one that works well or best.
- Third, many people take several prescription medications, non-prescription drugs and dietary supplements at the same time. These can interact in ways that can either reduce the benefit you get from the drug, or be dangerous.
- And fourth, the names of prescription drugs — both generic and brand — are often hard to pronounce and remember.

For all these reasons, it's important to keep a written list of all the drugs and supplements you are taking, and to periodically review this list with your doctors.

Always be sure, too, that you understand the dose of the medicine being prescribed for you and how many pills you are expected to take each day. Your doctor should tell you this information. When you fill a prescription at the pharmacy, or if you get it by mail, you may want to check to see that the dose and the number of pills per day on the pill bottle match the amounts that your doctor told you.

How We Picked the *Best Buy* CCBs

Our evaluation is primarily based on an independent, scientific review of the evidence on the effectiveness, safety and adverse effects of the CCBs. A team of physicians and researchers at Oregon Health & Science University Evidence-based Practice Center conducted the analysis as part of the Drug Effectiveness Review Project, or DERP. DERP is a first-of-its-kind 12-state initiative to evaluate the comparative effectiveness and safety of hundreds of prescription drugs.

A synopsis of DERP's analysis of the CCBs forms the basis for this report. A consultant to *Consumer Reports Best Buy Drugs* is also a member of the Oregon-based research team, which has no financial interest in any pharmaceutical company or product.

The full DERP review of CCBs is available at <http://www.ohsu.edu/drugeffectiveness/reports/final.cfm>. (This is a long and technical document written for physicians.)

The drug costs we cite were obtained from a health-care information company which tracks the sales of

prescription drugs in the U.S. Prices for a drug can vary quite widely, even within a single city or town. All the prices in this report are national averages based on sales of prescription drugs in retail outlets. They reflect the cash price paid for a month's supply of each drug in April 2005.

Consumers Union and *Consumer Reports* selected the *Best Buy Drugs* using the following criteria. The drug (and dose) had to:

- Be approved by the FDA for treating the conditions addressed in this report
- Have a safety record equal to or better than other CCBs
- Have an average price for a 30-day supply that is substantially lower than the most costly CCB meeting the first two criteria

The *Consumers Reports Best Buy Drugs* methodology is described in more detail in the Methods section at www.CRBestBuyDrugs.org.

About Us

Consumers Union, publisher of *Consumer Reports* magazine, is an independent and nonprofit organization whose mission since 1936 has been to provide consumers with unbiased information on goods and services and to create a fair marketplace. It is solely responsible for the content of this report. Its main Web sites are www.consumersunion.org and www.consumerreports.org.

Consumer Reports Best Buy Drugs is a public education project administered by Consumers Union. Two outside sources of generous funding made the project possible. They are a major grant from the Engelberg Foundation, a private philanthropy, and a supporting grant from the National Library of Medicine, part of the National Institutes of Health. A more detailed explanation of the project is available at www.CRBestBuyDrugs.org.

We followed a rigorous editorial process to ensure that the information in this report and on the *Consumer Reports Best Buy Drugs* Web site is accurate and describes generally accepted clinical practices. If we find, or are alerted to, an error, we will correct this as quickly as possible. However, *Consumer Reports* and its authors, editors, publishers, licensors and any suppliers cannot be responsible for medical errors or omissions, or any consequences from the use of the information on this site. Please refer to our user agreement at www.CRBestBuyDrugs.org for further information.

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References

1. Agodoa LY, Appel L, Bakris GL, et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *JAMA*. 2001;285(21):2719-2728.
2. Armstrong C, Garnham J, Blackwood R. Comparison of the efficacy of nifedipine and nifedipine in patients with chronic stable angina. *British Journal of Clinical Pharmacology*. 1986;22(SUPPL. 3):325S-330S.
3. Armstrong C, Garnham J, Blackwood R. Comparison of the efficacy of nifedipine, a new calcium channel blocker, with nifedipine in the treatment of mild to moderate essential hypertension. *Postgraduate Medical Journal*. 1987;63(740):463-466.
4. Black HR, Elliott HL, Grandits G, et al. Principal results of the controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) Trial. *JAMA*. 2003;289(16):2073-2082.
5. Borhani NO, Mercuri M, Borhani PA, et al. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS). A randomized controlled trial. *JAMA*. 1996;276(19):785-791.
6. Botto GL, Bonini W, Broffoni T. Modulation of ventricular rate in permanent atrial fibrillation: randomized, crossover study of the effects of slow-release formulations of gallopamil, diltiazem, or verapamil. *Clinical Cardiology*. 1998;21(11):837-840.
7. Brown MJ, Palmer CR, Castaigne A, et al. Principal results from the International Nifedipine GITS Study: Invention as a Goal in Hypertension Treatment (INSIGHT). *European Heart Journal Supplements*. 2001;3(B):B20-B26.
8. Canale C, Terrachini C, Masperone MA, et al. Open comparative study to assess the efficacy and safety of two calcium antagonists: Amlodipine and diltiazem in the treatment of symptomatic myocardial ischemia. *Journal of Cardiovascular Pharmacology*. 1991;17(SUPPL.1):S57-S60.
9. Chan JC, Cockram CS, Nicholls MG, et al. Comparison of enalapril and nifedipine in treating non-insulin dependent diabetes associated with hypertension: one year analysis. *BMJ*. 1992;305(6860):981-985.
10. Dargie HJ, Ford I, Fox KM, et al. Total Ischaemic Burden European Trial (TIBET). Effects of ischaemia and treatment with atenolol, nifedipine SR and their combination on outcome in patients with chronic stable angina. *European Heart Journal*. 1996;17(1):104-112.
11. Devereux, R B, Dahlof, et al. Comparison of enalapril versus nifedipine to decrease left ventricular hypertrophy in systemic hypertension (the PRESERVE). *American Journal of Cardiology*. 1996;78(1):61-65.
12. Elkayam U, Armin J, Mehra A, et al. A prospective, randomized, double-blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with than of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. [see comments.]. *Circulation*. 1990;82(6):1954-1961.
13. Estacio RO, Jeffers BW, Hiatt WR, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. [see comments.]. *New England Journal of Medicine*. 1998;338(10):645-652.
14. Furberg CD, Wright Jr JT, Davis BR, et al. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The antihypertensive and lipid-lowering treatment to prevent heart attach trial (ALLHAT). *JAMA*. 2002;288(23):2981-2997.
15. Gillman MW, Ross-Degnan D, McLaughlin TJ, et al. Effects of long-acting versus short-acting calcium channel blockers among older survivors of acute myocardial infarction. *Journal of the American Geriatrics Society*. 1999;47(5):512-517.
16. Hall RJ. A multicenter study comparing the efficacy and tolerability of nisoldipine coat-core and amlodipine in patients with chronic stable angina. *Current Therapeutic Research, Clinical & Experimental*. 1998;59(7):483-497.
17. Hansson L, Hedner T, Lund-Johansen P, et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality of hypertension: the Nordic Diltiazem (NORDIL) study. [see comments.]. *Lancet*. 2000;356(9227):359-365.
18. Jonas M, Goldbourt U, Boyko V, et al. Nifedipine and cancer mortality: ten-year follow-up of 2607 patients after acute myocardial infarction. *Cardiovascular Drugs & Therapy*. 1998;12(2):177-181.
19. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomized trial. *Lancet*. 2004;363(9426):2022-2031.
20. Kanamasa K, Kimura A, Miyataka M, et al. Incidence of cancer in postmyocardial infarction patients treated with short-acting nifedipine and diltiazem. *Cancer*. 1999;85(6):1369-1374.
21. Kjeldsen SE, Hedner T, Syvertsen JO, et al. Influence of age, sex and blood pressure on the principal endpoints of the Nordic Diltiazem (NORDIL) study. *Journal of Hypertension*. 2002;20(6):1231-1237.
22. Knight CJ, Fox KM. Amlodipine versus diltiazem as additional antianginal treatment to atenolol. *American Journal of Cardiology*. 1998;81(2):133-136.
23. Kubota K, Pearce GL, Inman WH. Vasodilation-related adverse events in diltiazem and dihydropyridine calcium antagonists studied by prescription-event monitoring. *European Journal of Clinical Pharmacology*. 1995;48(1):1-7.
24. Littler WA, Sheridan DJ. Placebo controlled trial of felodipine in patients with mild to moderate heart failure. *British Heart Journal*. 1995;73(5):428-433.
25. Littler WA. Comparison of nisoldipine coat-core and diltiazem controlled-release tablets in the treatment of chronic stable angina in elderly patients: A multicenter study. *Current Therapeutic Research - Clinical and Experimental*. 1999;60(11):614-627.
26. Lundstrom T, Ryden L. Ventricular rate control and exercise performance in chronic atrial fibrillation: effects of diltiazem and verapamil. *Journal of the American College of Cardiology*. 1990;16(1):86-90.
27. Mancia G, Brown M, Castaigne A, et al. Outcomes with nifedipine GITS or Coamilofide in hypertensive diabetics and nondiabetics in Intervention as a Goal in Hypertension (INSIGHT). *Hypertension*. 2003;41(3):431-436.
28. O'Connor CM, Carson PE, Miller AB, et al. Effect of amlodipine on mode of death among patients with advanced heart failure in the PRAISE trial. *American Journal of Cardiology*. 1998;82(7):881-887.
29. Ogihara T, Kuramoto K. Effect of long-term treatment with antihypertensive drugs on quality of life of elderly patients with hypertension: a double-Blind comparative study between a calcium antagonist and a diuretic. NICS-EH Study Group. *Hypertension Research - Clinical & Experimental*. 2000;23(1):33-37.
30. Packer M, O'Connor CM, Ghali JK, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival

- Evaluation Study Group. *New England Journal of Medicine*. 1996;335(15):1107-1114.
31. Pahor M, Guralnik JM, Ferrucci L, et al. Calcium-channel blockade and incidence of cancer in aged populations. *Lancet*. 1996;348(9026):493-497.
 32. Pahor M, Manto A, Pedone C, et al. Age of severe adverse drug reactions caused by nifedipine and verapamil. *Journal of Clinical Epidemiology*. 1996;49(8):921-928.
 33. Palmer A, Fletcher A, Hamilton G, et al. A comparison of verapamil and nifedipine on quality of life. *British Journal of Clinical Pharmacology*. 1990;30(3): 365-370.
 34. Pepine CJ, Cooper-DeHoff RM, Weiss RJ, et al. Comparison of effects of nisoldipine-extended release and amlodipine in patients with systemic hypertension and chronic stable angina pectoris. *American Journal of Cardiology*. 2003;91(3):274-279.
 35. 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*.
 36. Pessina AC, Boari L, De Dominicis E, et al. Efficacy, tolerability and influence on quality of life of nifedipine GITS versus amlodipine in elderly patients with mild-moderate hypertension. *Blood Pressure*. 2001; 10 (3) : 176-183.
 37. Poole-Wilson PA, Lubsen J, Kirwan BA, et al. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet*. 2004;364(9437):849-857.
 38. Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA* 2003; 289:2534-44.
 39. Rehnqvist N, Hjelm Dahl P, Billing E, et al. Effects of metoprolol vs verapamil in patients with stable angina pectoris. The Angina Prognosis Study in Stockholm (APSIS). *European Heart Journal*. 1996;17(1):76-81.
 40. Rodriguez ML, Guillen F, Caballero JC, et al. A comparison of the efficacy, tolerability and effect on quality of life of nisoldipine CC and enalapril in elderly patients with mild-to-moderate hypertension. *Acta Therapeutica*. 1996;22(2-4):89-106.
 41. Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care*. 1998;21(4):597-603.
 42. Testa MA, Turner RR, Simonson DC, et al. Quality of life and calcium channel blockade with nifedipine GITS versus amlodipine in hypertensive patients in Spain. *Journal of Hypertension*. 1998; 16(12): 1839-1847
 43. Udelson JE, DeAbate CA, Berk M, et al. Effects of amlodipine on exercise tolerance, quality of life, and left ventricular function in patients with heart failure from left ventricular systolic dysfunction. *American Heart Journal*. 2000.;139(3):503-510.
 44. van Kesteren HA, Withagen AJ. Amlodipine versus diltiazem controlled release as monotherapy in patients with stable coronary artery disease. *Current Therapeutic Research, Clinical & Experimental*. 1998;59(3)139-148.
 45. Van Noord T, Van Gelder IC, Tieleman RG, et al. VERDICT: the Verapamil versus Digoxin Cardioversion Trial: A randomized study on the role of calcium lowering for maintenance of sinus rhythm after cardioversion of persistent atrial fibrillation. *Journal of Cardiovascular Electrophysiology*. 2001; 12(7):766-769.
 46. Verdecchia P, Schillaci G, Reboldi G, et al. Calcium antagonists and cardiovascular risk in patients with hypertension and Type 2 diabetes mellitus: Evidence from the PIUMA Study. *Diabetes, Nutrition and Metabolism - Clinical and Experimental*. 1999.12(4):292-299.
 47. Weir MR, Major outcomes in high risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or CCB vs diuretic: the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Current Hypertension Reports*. 2003;5(5):405-407.
 48. Yui Y, Sumiyoshi T, Kodama K, et al. Nifedipine retard was as effective as angiotensin converting enzyme inhibitors in preventing cardiac events in high-risk hypertensive patients with diabetes and coronary artery disease: The Japan Multicenter Investigation for Cardiovascular Diseases-B(JMIC-B) subgroup analysis. *Hypertension Research Clinical & Experimental*. 2004;27(7):449-456.