Therapeutic Class Overview
Calcium Channel Blocking Agents (Dihydropyridines)

INTRODUCTION

- Approximately 92.1 million American adults have at least 1 type of cardiovascular disease according to the American Heart Association Heart Disease and Stroke Statistics 2017 update (Benjamin et al, 2017). From 2004 to 2014, mortality associated with cardiovascular disease declined 25.3%.
- Calcium channel blockade has certain effects that are specific to cardiac function. Coronary vascular smooth muscle relaxes when calcium channels are blocked which increases the flow of oxygenated blood into the myocardium and lowers coronary vascular resistance. In addition, calcium channel blocking agents (also called calcium channel blockers) decrease peripheral vascular resistance by relaxing arteriolar smooth muscle. Both coronary and systemic vasodilation serve to reduce cardiac workload (Kannam et al, 2017; Dobesh PP, 2017; Michel T, 2011).
- The movement of calcium ions is essential for the function of all types of muscle, including cardiac muscle and vascular smooth muscle. For both cardiac and smooth muscle, the flow of calcium ions into the muscle cells through specific channels allows muscle contraction to occur. When this flow is reduced, the result is a weakening of muscle contraction and relaxation of muscle tissue (Micromedex® 2.0, 2017; Kannam et al, 2017).
- The calcium channel blocking agents include dihydropyridines, which are similar in chemical structure, and non-dihydropyridines, which are a structurally heterogeneous group. Although they have different binding sites on the L-type calcium channel, both block the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The non-dihydropyridines also block the T-type calcium channel in the atrioventricular node (Micromedex 2.0, 2017; Kannam et al, 2017; Dobesh PP, 2017; Michel T, 2011; Saseen, 2017).
- Dihydropyridines are more potent vasodilators than non-dihydropyridines due to greater selectivity for vascular smooth muscle. They have little effect on cardiac muscle contractility or conduction (Micromedex 2.0, 2017; Kannam et al, 2017).
- All available dihydropyridine calcium channel blocking agents can be used in the treatment of hypertension, with the exception of nimodipine. Although not a first-line treatment in all hypertensive patients, the dihydropyridines are generally effective but differ somewhat in other properties and effects. Guidelines do recommend thiazide-type diuretics or calcium channel blockers in Black hypertensive patients (James et al, 2014; Mancia et al, 2013; Weber et al, 2014). Blood pressure goals for older patients have been a point of debate. The recent SPRINT trial followed patients ≥ 50 years with high blood pressure and increased cardiovascular risks under intense-hypertensive treatment (with a goal of 120 mmHg) compared to standard hypertensive treatment (with a goal of 140 mmHg) over a period of 3.2 years. The trial did end early; however, results demonstrated a reduced primary composite of myocardial infarction (MI), acute coronary syndrome (ACS), stroke, heart failure (HF), or cardiovascular death driven mainly by reduced HF events and cardiovascular death with intense-treatment compared to standard treatment (goal 140 mmHg). SPRINT has pointed to potential clinical benefits associated with a more intensive treatment in certain patients (SPRINT Research Group, 2015).
- Amlodipine, oral nicardipine, and long-acting nifedipine are effective treatment options for chronic stable angina. Short-acting agents, such as short-acting nifedipine, should be avoided due to increased cardiovascular and mortality risks in some patients as well as significant adverse effects, such as reflex tachycardia. Amlodipine is also indicated to reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented coronary artery disease (CAD).
- The dihydropyridines are available in a variety of single entity formulations (Micromedex 2.0, 2017; Kannam et al, 2017). All of the single-entity dihydropyridine calcium channel blocking agents are available generically in at least 1 formulation (Drugs@FDA.com, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017).
- Amlodipine is also available in combination with benazepril, perindopril, olmesartan, valsartan, telmisartan, atorvastatin, valsartan/hydrochlorothiazide, or olmesartan/hydrochlorothiazide. However, these combination agents are not included in this review.
- This review will focus on the dihydropyridine calcium channel blocking agents which are Food and Drug Administration (FDA)-approved to treat hypertension and forms of angina, with the exception of nimodipine, which is only FDA-approved for the prophylaxis and treatment of ischemic defects due to vasospasm after a subarachnoid hemorrhage (SAH).

- Since there are several branded agents that contain the same generic component, the remaining tables in the review are organized by generic name. This review encompasses all dosage forms and strengths with the exception of injectable indications and formulations used primarily in an institutional setting.
- Medispan Therapeutic Class: Calcium Channel Blockers

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Adalat CC (nifedipine extended-release)	✔
Afeditab CR (nifedipine extended-release)*	✔
Amlodipine	✔
Felodipine extended-release	✔
Isradipine	✔
Nicardipine	✔
Nifedipine extended-release	✔
Nimodipine	✔
Nisoldipine extended-release	✔
Norvasc (amlodipine)	✔
Nymalize (nimodipine)	-
Procardia (nifedipine)	✔
Procardia XL (nifedipine extended-release)	✔
Sular (nisoldipine extended-release)	✔

(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Amlodipine	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Angina Pectoris							
Treatment of chronic stable angina	✔ *	-	-	✔ (IR)†	-	-	-
Treatment of chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents	-	-	-	-	✔ (capsule, ER tablet)	-	-
Treatment of vasospastic angina	✔ ‡	-	-	-	✔ (capsule, ER tablet)§	-	-
CAD							
Reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented CAD by angiography and without heart failure or an ejection fraction < 40%	✔	-	-	-	-	-	-
Hypertension							
Treatment of hypertension	✔ ‖	✔ ‖	✔ ¶	✔ ‖	✔ (ER tablet)‖	-	✔ ‖
Treatment of hypertension to lower blood pressure which reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions	✔ ‖	✔ ‖	-	-	✔ (ER tablet)‖	-	-
Miscellaneous							

Indication	Amlodipine	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in subarachnoid hemorrhage from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (ie, Hunt and Hess Grades I-V)	-	-	-	-	-	√	-

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

(Prescribing information: ADALAT CC, 2011; AFEDITAB CR, 2014; felodipine ER, 2014; isradipine, 2014; nicardipine capsule, 2016; nifedipine extended-release, 2016; nimodipine, 2012; nisoldipine extended-release tablet, 2010; NORVASC, 2017; NYMALIZE, 2013; PROCARDIA, 2016; PROCARDIA XL, 2016; SULAR, 2014)

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

CLINICAL EFFICACY SUMMARY

- Clinical trials have demonstrated the efficacy of these agents for their respective indications.
- In a crossover study for the treatment of angina, amlodipine and felodipine have been shown to be more effective than placebo, though no significant difference between the 2 active treatment groups was observed (Koenig, 1997).
- Numerous clinical trials have shown that the dihydropyridines can effectively lower systolic and diastolic blood pressure when administered alone or in combination with other agents. In trials comparing combination therapy to monotherapy, the more aggressive treatment regimens lowered blood pressure to a greater extent than the less intensive treatment regimens. Some comparative trials have demonstrated slight differences in blood pressure effects among the various dihydropyridines; however, the clinical significance of these differences remains to be established (Sheehy et al, 2000; Van der Krogt et al, 1996; Mounier-Vehier et al, 2002; Kes et al, 2003; Ryuzaki et al, 2007; Saito et al, 2007; Pepine et al, 2003; Whitcomb et al, 2000; White et al, 2003b; Lenz et al, 2001; Drummond et al, 2007; Benetos et al, 2000; Prisant et al, 1995; Mazza et al, 2002; Hollenberg et al, 2003; White et al, 2003a; Jordan et al, 2007; Messerli et al, 2002; Chrysant et al, 2012; Messerli et al, 2000; Jamerson et al, 2004; Neutel et al, 2005; Kuschnir et al, 1996; Chrysant et al, 2007; Chrysant et al, 2004; Fogari et al, 1997; Minami et al, 2007; Hilleman et al, 1999; Jamerson et al, 2007; Malacco et al, 2002; Kereiakes et al, 2007; Tatti et al, 1998; Miranda et al, 2008; Fogari et al, 2007; Ribeiro et al, 2007; Oparil et al, 1996; Chrysant et al, 2008; Chrysant et al, 2009; Oparil et al, 2009; Braun et al, 2009; Littlejohn et al, 2009a; Littlejohn et al, 2009b; Sharma et al, 2007; Neutel et al, 2012; Maciejewski et al, 2006; Ichihara et al, 2006; Karpov et al, 2012; Philipp et al, 2007; Philipp et al, 2011; Schunkert et al, 2009; Ke et al, 2010; Destro et al, 2008; Flack et al, 2009; Schrader et al, 2009; Sinkiewicz et al, 2009; Fogari et al, 2009; Poldermans et al, 2007; Calhoun et al, 2009a; Calhoun et al, 2009b; Crikelair et al, 2009; Pareek et al, 2010; Gustin et al, 1996; Karotsis et al, 2006; Manyemba et al, 1997; Lindholm et al, 2005; Van Bortel et al, 2008; Wiysonge et al, 2007; Baguet et al, 2007).
  - In-class comparisons for the treatment of hypertension have found better compliance and a higher response rate with amlodipine compared to felodipine, though van der Krogt and colleagues found similar decreases in overall systolic and diastolic blood pressures between groups (Sheehy et al, 2000; Van der Krogt et al, 1996).
  - The most clinical trial experience has been with amlodipine and nifedipine, which have been shown to have beneficial effects on cardiovascular and stroke outcomes in hypertension trials (Rahman et al, 2012; Black et al, 2008; ALLHAT, 2002; Julius et al, 2004; Zanchetti et al, 2006; Savanitto et al, 1996; Nissen et al, 2004; Ogihara et al, 2008; Jamerson et al, 2008; Weber et al, 2010; Weber et al, 2013; Brown et al, 2000).
- The dihydropyridines have been shown to have favorable effects on cardiovascular morbidity and mortality, and several studies have demonstrated comparable efficacy with beta blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) in select diseases (Pitt et al, 2000; Dahlöf et al, 2005; Chapman et

al, 2007; Nissen et al, 2004; ALLHAT, 2002; Black et al, 2008; Rahman et al, 2012; Ogihara et al, 2008; Julius et al, 2004; Zanchetti et al, 2006; Jamerson et al, 2008; Bakris et al, 2010; Weber et al, 2010; Weber et al, 2013; Hansson et al, 1999; Borhani et al, 1996; National Intervention Cooperative Study, 1999; Lichtlen et al, 1990; Brown et al, 2000; Estacio et al, 1998).
  - In the ALLHAT study, ACE inhibitors had a 51% higher rate (relative risk [RR], 1.51; 95% confidence interval [CI], 1.22 to 1.86) of stroke in patients of African or Caribbean descent (Black) when used as initial therapy compared to calcium channel blockers. ACE inhibitors were also less effective in reducing blood pressure in Black patients compared to a calcium channel blocker (Rahman et al, 2012; Black et al, 2008; ALLHAT, 2002).

CLINICAL GUIDELINES

- There are several national and international evidence-based antihypertensive guidelines that provide recommendations regarding the use of calcium channel blocking agents. Most recommend that the selection of an antihypertensive agent be based on compelling indications for use:
  - Most guidelines recommend a thiazide-type diuretic, an ACE inhibitor, an ARB, or a calcium channel blocker as first-line therapy (Go et al, 2014; James et al, 2014; Mancia et al, 2013; Weber et al, 2014). However, the 2013 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines also recommend beta blockers as a first-line therapy option (Mancia et al, 2013).
  - In Black hypertensive patients, thiazide-type diuretics or calcium channel blockers are recommended specifically as first-line therapy (James et al, 2014; Mancia et al, 2013; Weber et al, 2014).
  - In patients with chronic kidney disease, calcium channel blockers are generally recommended after ACE inhibitors or ARBs (KDIGO, 2012; Go et al, 2014; James et al, 2014; Mancia et al, 2013; Weber et al, 2014).
  - In patients with chronic aortic regurgitation (stages B and C), valvular disease, and hypertension, dihydropyridine calcium channel blockers, ACE inhibitors or ARBs are preferred treatment options (Nishimura et al, 2014).
  - Consensus guidelines recommend calcium channel blockers as an option in pregnant patients with severe hypertension to prevent stroke; nifedipine is one of the only dihydropyridines tested in these patients (Bushnell et al, 2014; Mancia et al, 2013).
  - There is no consensus on additional populations that calcium channel blockers should be prescribed in. However, other compelling indications that include calcium channel blockers as a first-line treatment option include elderly patients, diabetic patients, patients with asymptomatic organ damage and asymptomatic atherosclerosis, peripheral artery disease, and metabolic syndrome (Go et al, 2014; James et al, 2014; KDIGO, 2012; Mancia et al, 2013; Weber et al, 2014). A long-acting dihydropyridine calcium channel blocker may be added to a basic hypertensive regimen, particularly after a beta blocker and ACE inhibitor, in hypertensive patients with CAD and stable angina (Rosendorff et al, 2015).
  - The 2013 ESH/ESC guidelines do recommend calcium channel blockers in patients with asymptomatic organ damage and left ventricular (LV) hypertrophy (Mancia et al, 2013). However, in general, calcium channel blocking agents are not recommended for the routine treatment of heart failure (Ponikowski et al, 2016; Yancy et al, 2013; Yancy et al, 2016; Yancy et al, 2017), although, some guidelines agree that some dihydropyridine calcium channel blockers may be used in certain co-morbid conditions if the patient has preserved LV function (Ponikowski et al, 2016).
- For the treatment of chronic angina, beta blockers are recommended as initial therapy; however, long-acting calcium channel blocking agents may be used if beta blockers are contraindicated or if additional therapy is required (Fihn et al, 2012; Fihn et al, 2014; O'Gara et al, 2013; Montalescot et al, 2013). Beta blockers and calcium channel blockers have similar clinical outcomes, but beta blockers may have fewer adverse events in patients with stable angina. Long-acting calcium channel blockers may be used in combination with beta blockers when beta blocker monotherapy is unsuccessful (Montalescot et al, 2013; Amsterdam et al, 2014). Other guidelines recommend long-acting calcium channel blockers and nitrates as a treatment option for coronary artery spasm. For vasospastic (Prinzmetal) angina, guidelines recommend calcium channel blockers alone or in combination with nitrates (Amsterdam et al, 2014).
- For the treatment of aneurysmal SAH, oral nimodipine is recommended to reduce poor outcome related to SAH (Connolly et al, 2012; Diringer et al, 2011).

SAFETY SUMMARY

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

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

- Intravenous administration of the contents of nimodipine capsules has resulted in serious adverse consequences including death, cardiac arrest, cardiovascular collapse, hypotension and bradycardia. As such, nimodipine capsules have a boxed warning against the use of nimodipine capsules for intravenous administration.
- Hypotension may occur occasionally during the initial titration or with dosage increases, and hence, blood pressure should be monitored during initial administration and titration. Dihydropyridines, specifically felodipine and nisoldipine, should be used cautiously in patients with congestive heart failure.
- Dihydropyridine calcium channel blockers can produce negative inotropic effects and exacerbate heart failure and as a result, patients with heart failure should be monitored carefully.
- Caution should be exercised when using dihydropyridine calcium channel blockers in patients with impaired hepatic function or reduced hepatic blood flow as these agents are extensively metabolized by the liver.
- In general, patients should have their blood pressure (with initiation and titration), heart rate and anginal pain monitored. Patients should also be monitored for signs and symptoms of edema.
- (Facts and Comparisons®, 2017; Micromedex 2.0, 2017)

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Usual Recommended Frequency	Comments
Amlodipine	Tablet: 2.5 mg 5 mg 10 mg	Angina pectoris (chronic stable and vasospastic): Tablet: maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily CAD: Tablet: maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily Hypertension: Tablet: initial, 5 mg once daily; maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily Hypertension in children 6 to 17 years of age: Tablet: initial, 2.5 mg once daily; maintenance, 2.5 to 5 mg once daily; maximum, 5 mg once daily	Doses in excess of 5 mg daily have not been studied in pediatric patients. In general, wait 7 to 14 days between titration steps. Titrate more rapidly, however, if clinically warranted, provided the patient is assessed frequently.
Felodipine	Extended-release tablet: 2.5 mg 5 mg 10 mg	Hypertension: Extended-release tablet: initial, 5 mg once daily; maintenance, 2.5 to 10 mg once daily	Dose adjustments should occur generally at intervals of not less than 2 weeks. Should be swallowed whole and not crushed or chewed; take without food or with a light meal
Isradipine	Capsule: 2.5 mg 5 mg	Hypertension: Capsule: initial, 2.5 mg twice daily; maximum, 20 mg/day	Dose adjustments should occur in increments of 5 mg/day at 2 to 4 week intervals.
Nicardipine	Capsule:	Angina pectoris (chronic stable):	Allow at least 3 days before

Drug	Available Formulations	Usual Recommended Frequency	Comments
	20 mg 30 mg	Capsule: initial, 20 mg 3 times daily; maintenance, 20 to 40 mg 3 times daily Hypertension: Capsule: initial, 20 mg 3 times daily; maintenance, 20 to 40 mg 3 times daily	increasing the dose to ensure achievement of steady state plasma drug concentrations (capsule formulation).
Nifedipine	Immediate-release capsule: 10 mg 20 mg Extended-release tablet: 30 mg 60 mg 90 mg	Angina pectoris (chronic stable): Capsule: initial, 10 mg 3 times daily; maintenance, 10 to 20 mg 3 times daily; maximum, 180 mg/day Extended-release tablet: initial, 30 or 60 mg once daily; maintenance, 30 to 90 mg once daily; maximum, 120 mg/day Angina pectoris (vasospastic): Capsule: initial, 10 mg 3 times daily; maintenance, 20 to 30 mg 3 to 4 times daily; maximum, 180 mg/day Extended-release tablet: initial, 30 or 60 mg once daily; maintenance, 30 to 90 mg once daily; maximum, 120 mg/day Hypertension: Extended-release tablet: initial, 30 or 60 mg once daily; maintenance, 30 to 90 mg once daily; maximum, 120 mg/day	Titration should proceed over a 7- to 14-day period. Extended-release tablets should be swallowed whole, not bitten or divided and should be taken on an empty stomach; co-administration with grapefruit juice should be avoided.
Nimodipine	Capsule: 30 mg Oral solution: 60 mg/20 mL	Subarachnoid hemorrhage: Capsule: 60 mg every 4 hours for 21 consecutive days Oral solution: 20 mL (60 mg) every 4 hours for 21 consecutive days	Dosing should be started within 96 hours of subarachnoid hemorrhage. Capsules should be swallowed whole with a little liquid and oral solution should only be administered enterally, preferably not less than 1 hour before or 2 hours after meals; grapefruit juice should be avoided; capsules should not be administered intravenously or by other parenteral routes.
Nisoldipine	Extended-release tablet: 8.5 mg 17 mg 20 mg	Hypertension: Extended-release tablet: initial, 20 mg once daily; maintenance, 20 to 40 mg/day; maximum, 60 mg/day	Dose adjustments should occur at intervals of not less than 1 week.

Drug	Available Formulations	Usual Recommended Frequency	Comments
	25.5 mg 30 mg 34 mg 40 mg	Extended-release tablet (Sular and its generics): initial, 17 mg once daily; maintenance, 17 to 34 mg once daily; maximum, 34 mg once daily	Extended-release tablets should be swallowed whole, not bitten, divided or crushed; should be taken on an empty stomach (1 hour before or 2 hours after a meal); grapefruit products should be avoided; administration with a high fat meal can lead to excessive peak drug concentration and should be avoided.

See the current prescribing information for full details

CONCLUSION

- The majority of the single entity dihydropyridines are available in a generic formulation, although Nymalize oral solution is the only dihydropyridine formulation available as brand only.
- All of the dihydropyridines, with the exception of nimodipine, are approved for the treatment of hypertension. Amlodipine, nicardipine, and nifedipine are also indicated for the treatment of angina. Additionally, amlodipine reduces the risk of hospitalization due to angina and reduces the risk of coronary revascularization procedures in patients with recently documented coronary artery disease (CAD). Nimodipine improves the neurological outcome of patients with an SAH by reducing the incidence and severity of ischemic deficits in patients with ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (ie, Hunt and Hess Grades I-V).
- Numerous clinical trials have shown that the dihydropyridines can effectively lower systolic and diastolic blood pressure when administered alone or in combination with other agents. In trials comparing combination therapy to monotherapy, the more aggressive treatment regimens lowered blood pressure to a greater extent than the less intensive treatment regimens. Some comparative trials have demonstrated slight differences in blood pressure effects among the various dihydropyridines; however, the clinical significance of these differences remains to be established.
- The dihydropyridines have been shown to favorably affect cardiovascular morbidity and mortality, and several studies have demonstrated comparable efficacy with beta blockers, diuretics, ACE inhibitors, and ARBs in select diseases (Pitt et al, 2000; Dahlöf et al, 2005; Chapman et al, 2007; Nissen et al, 2004; ALLHAT, 2002; Black et al, 2008; Rahman et al, 2012; Ogihara et al, 2008; Julius et al, 2004; Zanchetti et al, 2006; Jaromerson et al, 2008; Bakris et al, 2010; Weber et al, 2010; Weber et al, 2013; Hansson et al, 1999; Borhani et al, 1996; National Intervention Cooperative Study, 1999; Lichtlen et al, 1990; Brown et al, 2000; Estacio et al, 1998). However, the ALLHAT study demonstrated that patients of African or Caribbean descent (Black) had a lower rate of stroke when therapy was initiated with a calcium channel blocker compared to an ACE inhibitor (Rahman et al, 2012; Black et al, 2008; ALLHAT, 2002).
- There is insufficient evidence to support that one dihydropyridine calcium channel blocker is safer or more efficacious than another, although most clinical trial experience has been with amlodipine and nifedipine (Rahman et al, 2012; Black et al, 2008; ALLHAT, 2002; Julius et al, 2004; Zanchetti et al, 2006; Savanitto et al, 1996; Nissen et al, 2004; Ogihara et al, 2008; Jamerson et al, 2008; Weber et al, 2010; Weber et al, 2013; Brown et al, 2000).

REFERENCES

- ADALAT CC prescribing information. Bayer HealthCare Pharmaceuticals Inc.; Wayne, NJ. April 2011.
- AFEDITAB CR prescribing information. Actavis Pharma, Inc. Parsippany, NJ. September 2014.
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. 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 Attack Trial (ALLHAT). JAMA. 2002 Dec 18;288(23):2981-97.
- Amsterdam E, Wenger N, Brindis R, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64(24):e139-228.
- Baguet JP, Legallicier B, Auquier P, et al. Updated meta-analytical approach to the efficacy of antihypertensive drugs in reducing blood pressure. Clin Drug Investig. 2007;27(11):735-53.

- Bakris GL, Sarafidis PA, Weir MR, et al. ACCOMPLISH Trial investigators. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomized controlled trial. Lancet. 2010 Apr 3;375(9721):1173-81.
- Benetos A, Consoli S, Safavian A, et al. Efficacy, safety, and effects on quality of life of bisoprolol/hydrochlorothiazide vs amlodipine in elderly patients with systolic hypertension. Am Heart J. 2000 Oct;140(4):E11.
- Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics – 2017 update: a report from the American Heart Association. Circulation. 2017;135(10):e146-e603.
- Black HR, Davis B, Barzilay J, et al. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Metabolic and clinical outcomes in nondiabetic individuals with the metabolic syndrome assigned to chlorthalidone, amlodipine, or lisinopril as initial treatment for hypertension: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Diabetes Care. 2008 Feb;31(2):353-60.
- 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;276:785-791.
- Braun N, Ulmer HJ, Handrock R, et al. Efficacy and safety of the single pill combination of amlodipine 10 mg plus valsartan 160 mg in hypertensive patients not controlled by amlodipine 10 mg plus olmesartan 20 mg in free combination (abstract). Curr Med Res Opin. 2009;25(2):421-30.
- Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomized to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the international nifedipine GTS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). Lancet. 2000; 356:366-72.
- Bushnell C, McCullough LD, Awad IA, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014 May;45(5):1545-88.
- Calhoun D, Crikelair N, Yen J, et al. Amlodipine/valsartan/hydrochlorothiazide triple combination therapy in moderate/severe hypertension: secondary analyses evaluating efficacy and safety. Adv Ther. 2009a;26(11):1012-23.
- Calhoun DA, Lacourciere Y, Chiang YT, et al. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide: a randomized controlled trial. Hypertension. 2009b;54:32-9.
- Chapman N, Dobson J, Wilson S, et al. Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Effect of spironolactone on blood pressure in subjects with resistant hypertension. Hypertension. 2007 Apr;49(4):839-45.
- Chrysant SG. Blood pressure effects of high-dose amlodipine-benazepril combination in black and white hypertensive patients not controlled on monotherapy. Drugs RD. 2012;12(2):57-64.
- Chrysant SG, Bakris GL. Amlodipine/benazepril combination therapy for hypertensive patients nonresponsive to benazepril monotherapy. Am J Hypertens. 2004 Jul;17(7):590-6.
- Chrysant SG, Melino M, Karki S, et al. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. Clin Ther. 2008 Apr;30(4):587-604.
- Chrysant SG, Oparil S, Melino M, et al. Efficacy and safety of long-term treatment with the combination of amlodipine besylate and olmesartan medoxomil in patients with hypertension. J Clin Hypertens (Greenwich). 2009;11:475-82.
- Chrysant SG, Sugimoto DH, Lefkowitz M, et al. The effects of high-dose amlodipine/benazepril combination therapies on blood pressure reduction in patients not adequately controlled with amlodipine monotherapy. Blood Press Suppl. 2007 Mar;1:10-7.
- Clinical Pharmacology online [database on the Internet]. Tampa, FL: Elsevier/Gold Standard; 2017. Available from: http://www.clinicalpharmacology-ip.com/default.aspx. Accessed June 5, 2017.
- Connolly ES, Rabinstein AA, Carhuapoma R, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage; a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012 Jun;43(6):1711-1737.
- Dahlöf B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required vs atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomized controlled trial. Lancet. 2005 Sep 10-16;366(9489):895-906.
- Destro M, Luckow A, Samson M, et al. Efficacy and safety of amlodipine/valsartan compared to amlodipine monotherapy in patients with stage 2 hypertension: a randomized, double-blind, multicenter study: the EX-EFFeCTS study. J Am Society Hypertension. 2008;2:294-302.
- Diringer MN, Bleck TP, Menon D, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care. 2011 Sep;15 (2):211-40.
- Dobesh PP. Stable ischemic heart disease. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: a pathophysiologic approach. 10th edition. New York (NY): McGraw-Hill; 2017.
- Drugs@FDA [database on the Internet]. Rockville, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed June 5, 2017.
- Drummond W, Munger M, Essop M, et al. Antihypertensive efficacy of the oral direct renin inhibitor aliskiren as add-on therapy in patients not responding to amlodipine monotherapy. J Clin Hypertens. 2007;9:742-50.
- Estacio RO, Schrier RW. Antihypertensive therapy in type 2 diabetes: implications of the appropriate blood pressure control in diabetes (ABCD) trial. Am J Cardiol. 1998;82(9B):9R-14R.
- Facts and Comparisons® eAnswers [database on the Internet]. St. Louis, MO: Wolters Kluwer Health, Inc.; 2017. Available from: http://online.factsandcomparisons.com. Accessed June 5, 2017.
- Felodipine ER prescribing information. Glenmark Generics Ltd. Mahwah, NJ. December 2014.
- Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice

Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2012;126:e354–e471.

- Fihn SD, Blankenship J, Alexander K, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2014 Nov 4;64(18):1929-49.
- Flack JM, Calhoun DA, Satlin L, et al. Efficacy and safety of initial combination therapy with amlodipine/valsartan compared to amlodipine monotherapy in black patients with stage 2 hypertension: the EX-STAND study. J Hum Hypertens. 2009;23:479-89.
- Fogari R, Corea L, Cardoni O, et al. Combined therapy with benazepril and amlodipine in the treatment of hypertension inadequately controlled by an ACE inhibitor alone. J Cardiovasc Pharmacol. 1997 Oct;30(4):497-503.
- Fogari R, Mugellini A, Derosa G; CANDIA (CANdesartan and DIuretic vs Amlodipine in hypertensive patients) Study Group. Efficacy and tolerability of candesartan cilexetil/hydrochlorothiazide and amlodipine in patients with poorly controlled mild-to-moderate essential hypertension. J Renin Angiotensin Aldosterone Syst. 2007 Sep;8(3):139-44.
- Fogari R, Zoppi A, Mugellini A, et al. Efficacy and safety of two treatment combinations of hypertension in very elderly patients. Archives of Gerontology and Geriatrics. 2009;48:401-5.
- Gustin G, White WB, Taylor S, et al. Clinical outcome of a mandatory formulary switch for dihydropyridine calcium-channel blocker therapy at a Veteran's Administration Medical Center. Am J Hypertens. 1996;9(4 Pt 1):312-6.
- Hansson L, Lindholm LH, Ekbom T, et al. Randomized trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet. 1999 Nov 20;354(9192):1751-6.
- Hilleman DE, Ryschon KL, Mohiuddin SM, et al. Fixed-dose combination vs monotherapy in hypertension: a meta-analysis evaluation. J Hum Hypertens. 1999;13:477-83.
- Hollenberg HK, Williams GH, Anderson R, et al. Symptoms and the distress they cause: comparison of an aldosterone antagonist and a calcium-channel blocking agent in patients with systolic hypertension. Arch Intern Med. 2003;163(13):1543-8.
- Ichihara A, Kaneshiro Y, Takemitsu T, et al. Effects of amlodipine and valsartan on vascular damage and ambulatory blood pressure in untreated hypertensive patients. J Hum Hypertens. 2006 Oct;20(10):787-94.
- Isradipine prescribing information. Actavis Pharma, Inc. Parsippany, NJ. June 2014.
- Jamerson K, Bakris GL, Dahlöf B, et al; for the ACCOMPLISH Investigators. Exceptional early blood pressure control rates: the ACCOMPLISH trial. Blood Press. 2007;16(2):80-6.
- Jamerson KA, Nwose O, Jean-Louis L, et al. Initial angiotensin-converting enzyme inhibitor/calcium-channel blocker combination therapy achieves superior blood pressure control compared to calcium-channel blocker monotherapy in patients with stage 2 hypertension. Am J Hypertens. 2004 Jun;17(6):495-501.
- Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high risk patients. N Engl J Med. 2008;359:2417-28.
- James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014 Feb 5;311(5):507-20.
- Jordan J, Engeli S, Boye SW, et al. Direct renin inhibition with aliskiren in obese patients with arterial hypertension. Hypertension. 2007 May;49:1047-55.
- Julius S, Kjeldsen SE, Weber M, et al; VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004 Jun 19;363(9426):2022-31.
- Kannam JP, Aroesty JM, Gersh BJ. Calcium-channel blockers in the management of stable angina pectoris. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2017. Available from: http://www.uptodate.com/contents/calcium-channel-blockers-in-the-management-of-stable-angina-pectoris?source=search_result&search=angina&selectedTitle=6~150. Accessed June 5, 2017.
- Karotsis AK, Symeonidis A, Mastorantonakis SE, et al. Additional antihypertensive effect of drugs in hypertensive subjects uncontrolled on diltiazem monotherapy: a randomized controlled trial using office and home blood pressure monitoring. Clin Exp Hypertens. 2006;28(7):655-62.
- Karpov Y, Dongre N, Vigdorchik A, et al. Amlodipine/valsartan single-pill combination: a prospective, observational evaluation of the real-life safety and effectiveness in the routine treatment of hypertension. Adv Ther. 2012;29(2):134-147.
- Ke Y, Zhu D, Hong H, et al. Efficacy and safety of a single-pill combination of amlodipine/valsartan in Asian hypertensive patients inadequately controlled with amlodipine monotherapy. Curr Med Res Opin. 2010;26:1705-13.
- Kereiakes DJ, Neutel JM, Punzi HA, et al. Efficacy and safety of olmesartan medoxomil and hydrochlorothiazide compared to benazepril and amlodipine besylate. Am J Cardiovasc Drugs. 2007;7(5):361-72.
- Kes S, Caglar N, Canberk A, et al. Treatment of mild-to-moderate hypertension with calcium-channel blockers: a multicentre comparison of once-daily nifedipine GITS with once-daily amlodipine. Curr Med Res Opin. 2003; 19(3):226-37.
- Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int Suppl. 2012 Dec;2(5):337-414.
- Koenig W, Hoher M. Felodipine and amlodipine in stable angina pectoris: results of a randomized double-blind crossover trial. J Cardiovasc Pharmacol. 1997;29(4):520-4.
- Kuschnir E, Acuña E, Sevilla D, et al. Treatment of patients with essential hypertension: amlodipine 5 mg/benazepril 20 mg compared to amlodipine 5 mg, benazepril 20 mg, and placebo. Clin Ther. 1996;18(6):1213-24.
- Lenz TL, Wurdeman RL, Hilleman DE. Comparison of 24-hour blood pressure profiles in patients with hypertension who were switched from amlodipine to nisoldipine. Pharmacotherapy. 2001;21(8):898-903.

- Lichtlen PR, Hugenholtz PG, Rafflenbeul W, et al. Retardation of coronary artery disease in humans by the calcium-channel blocker nifedipine: results of the INTACT study (International Nifedipine Trial on Antiatherosclerotic Therapy). Cardiovasc Drugs Ther. 1990 Aug;4 Suppl 5:1047-68.
- Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lancet. 2005 Oct 29-Nov 4;366(9496):1545-53.
- Littlejohn TW 3rd, Majul CR, Olvera R, et al. Telmisartan plus amlodipine in patients with moderate or severe hypertension: results from a subgroup analysis of a randomized, placebo-controlled, parallel-group, 4x4 factorial study. Postgrad Med. 2009a Mar;121(2):5-14.
- Littlejohn TW 3rd, Majul CR, Olvera R, et al. Results of treatment with telmisartan-amlodipine in hypertensive patients. J Clin Hypertens (Greenwich). 2009b Apr;11(4):207-13. .
- Maciejewski S, Mohiuddin SM, Packard KA, et al. Randomized, double-blind, crossover comparison of amlodipine and valsartan in African-Americans with hypertension using 24-hour ambulatory blood pressure monitoring. Pharmacotherapy. 2006 Jul;26(7):889-95.
- Malacco E, Piazza S, Carretta R, et al; Italian Blood Pressure Study Group. Comparison of benazepril-amlodipine and captopril-thiazide combinations in the management of mild-to-moderate hypertension. Int J Clin Pharmacol Ther. 2002 Jun;40(6):263-9.
- Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC 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). Eur Heart J. 2013;34(28):2159-219.
- Manyemba J. A randomized crossover comparison of reserpine and sustained-release nifedipine in hypertension. Cent Afr J Med. 1997 Dec;43(12):344-9.
- Mazza A, Gil-Extremera B, Maldonato A, et al. Nebivolol vs amlodipine as first-line treatment of essential arterial hypertension in the elderly. Blood Press. 2002;11(3):182-8.
- Medispan PriceRx [internet database]. Updated periodically. Available by subscription at: https://pricerx.medispan.com. Accessed June 5, 2017.
- Messerli FH, Oparil S, Feng Z. Comparison of efficacy and side effects of combination therapy of angiotensin-converting enzyme inhibitor (benazepril) with calcium antagonist (either nifedipine or amlodipine) vs high-dose calcium antagonist monotherapy for systemic hypertension. Am J Cardiol. 2000 Dec 1;86:1182-7.
- Messerli FH, Weir MR, Neutel JM. Combination therapy of amlodipine and benazepril vs monotherapy of amlodipine in a practice-based setting. Am J Hypertens. 2002 Jun;15(6):550-6.
- Michel T, Hoffmann BB. Treatment of myocardial ischemia and hypertension. In: Brunton LL, Chabner BA, Knollman BC, et al, editors. Goodman and Gilman's The pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill: 2011.
- Micromedex 2.0 [database on the Internet]. Greenwood Village, CO: Truven Health Analytics; Updated periodically. Available from: http://www.micromedexsolutions.com/home/dispatch. Accessed June 5, 2017.
- Minami J, Abe C, Akashiba A, et al. Long-term efficacy of combination therapy with losartan and low-dose hydrochlorothiazide in patients with uncontrolled hypertension. Int Heart J. 2007 Mar;48(2):177-86.
- Miranda RD, Mion D, Rocha JC, et al. An 18-week, prospective, randomized, double-blind, multicenter study of amlodipine/ramipril combination vs amlodipine monotherapy in the treatment of hypertension: the assessment of combination therapy of amlodipine/ramipril (ATAR) study. Clin Ther. 2008;30:1618-28.
- Montalescot G, Sechtem U, Achenback S, et al. 2013 ESC Guidelines on the management of stable coronary artery disease: The Task Force for the management of stable coronary artery disease of the European Society of Cardiology (ESC). Eur Heart J. 2013;34:2949-3003.
- Mounier-Vehier C, Jaboureck O, Emeriau JP, et al. Randomized, comparative, double-blind study of amlodipine vs nicardipine as a treatment of isolated systolic hypertension in the elderly. Fundam Clin Pharmacol. 2002;16(6):537-44.
- National Intervention Cooperative Study in Elderly Hypertensives Study Group. Randomized double-blind comparison of a calcium antagonist and a diuretic in elderly hypertensives. National Intervention Cooperative Study in Elderly Hypertensives Study Group. Hypertension. 1999 Nov;34(5):1129-33.
- Neutel JM, Mancia G, Black HR, et al. Single-pill combination of telmisartan/amlodipine in patients with severe hypertension: results from the TEAMSTA severe HTN study. J Clin Hypertens (Greenwich). 2012 Apr;14(4):206-215.
- Neutel JM, Smith DH, Weber MA, et al. Efficacy of combination therapy for systolic blood pressure in patients with severe systolic hypertension: the Systolic Evaluation of Lotrel Efficacy and Comparative Therapies (SELECT) study. J Clin Hypertens. 2005 Nov;7(11):641-6.
- Nicardipine capsule prescribing information. Mylan Pharmaceuticals, Inc. Morgantown, WV. September 2016.
- Nifedipine extended-release prescribing information. Oceanside Pharmaceuticals. Bridgewater, NJ. June 2016.
- Nimodipine prescribing information. Caraco Pharmaceutical Laboratories, Ltd.; Detroit, MI. January 2012.
- Nishimura R, Otto C, Bonow R, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jun 10;63(22):e57-185.
- Nisoldipine extended-release tablet prescribing information. Mylan Pharmaceuticals Inc.; Morgantown, WV. January 2010.
- Nissen SE, Tuzcu EM, Libby P, et al; CAMELOT Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA. 2004;292(18):2217-25.
- NORVASC prescribing information. Pfizer Inc.; New York, NY. March 2017.
- NYMALIZE prescribing information. Arbor Pharmaceuticals Inc.; Atlanta, GA. March 2017.
- O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. J Am Coll Cardiol. 2012. doi:10.1016/j.jacc.2012.11.019.

- Ogihara T, Nakao K, Fukui T, et al; Candesartan Antihypertensive Survival Evaluation in Japan Trial Group. Effects of candesartan compared to amlodipine in hypertensive patients with high cardiovascular risks: candesartan antihypertensive survival evaluation in Japan trial. Hypertension. 2008 Feb;51(2):393-8.
- Oparil S, Barr E, Elkins M, et al. Efficacy, tolerability, and effects on quality of life of losartan, alone or with hydrochlorothiazide, vs amlodipine, alone or with hydrochlorothiazide, in patients with essential hypertension. Clin Ther. 1996 Jul-Aug;18(4):608-25.
- Oparil S, Lee J, Karki S, et al. Subgroup analyses of an efficacy and safety study of concomitant administration of amlodipine besylate and olmesartan medoxomil: evaluation by baseline hypertension stage and prior antihypertensive medication use. J Cardiovasc Pharmacol. 2009;54(5):427-36.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring, MD : Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/. Accessed on June 5, 2017.
- Pareek A, Salkar H, Mulay P, et al. A randomized, comparative, multicenter, evaluation of atenolol/amlodipine combination with atenolol alone in essential hypertension patients. Am J Ther. 2010;17:46-52.
- Pepine CJ, Cooper-DeHoff RM, Weiss RJ, et al. Comparative Efficacy and Safety of Nisoldipine and Amlodipine (CESNA-II) Study Investigators. Comparison of effects of nisoldipine-extended-release and amlodipine in patients with systemic hypertension and chronic stable angina pectoris. Am J Cardiol. 2003; 91(3):274-9.
- Philipp T, Glazer RD, Wernsing M, et al. Initial combination therapy with amlodipine/valsartan compared to monotherapy in the treatment of hypertension (abstract). J Amer Soc Hypertens. 2011;5(5):417-424.
- Philipp T, Smith TR, Glazer R, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. Clin Ther. 2007 Apr;29(4):563-80.
- Pitt B, Byington RP, Furberg CD, et al. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. PREVENT Investigators. Circulation. 2000;102(13):1503-10.
- Poldermans D, Glazes R, Kargiannis S, et al. Tolerability and blood pressure-lowering efficacy of the combination of amlodipine plus valsartan compared to lisinopril plus hydrochlorothiazide in adult patients with stage 2 hypertension. Clin Ther. 2007 Feb;29(2):279-89.
- Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2016;37:2129-2200.
- Prisant LM, Weir MR, Papademetriou V, et al. Low-dose combination therapy: an alternative first-line approach to hypertension treatment. Am Heart J. 1995 Aug;130(2):359-66.
- PROCARDIA prescribing information. Pfizer Inc.; New York, NY. July 2016.
- PROCARDIA XL prescribing information. Pfizer Inc.; New York, NY. July 2016.
- Rahman M, Ford CE, Cutler JA, et al. Long-term renal and cardiovascular outcomes in antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) participants by baseline estimated GFR. Clin J Am Soc Nephrol. 2012;7:989-1002.
- Ribeiro AB, Mion D Jr, Marin MJ, et al; Latin American Hypertension Study (LAMHYST) Group. Antihypertensive efficacy of amlodipine and losartan after two 'missed' doses in patients with mild to moderate essential hypertension. J Int Med Res. 2007 Nov-Dec;35(6):762-72.
- Rosendorff C, Lackland DT, Allison M, et al. Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension (AHA/ACC/ASH). J Am Coll Cardiol. 2015;65(18):1998-2038. doi:10.1016/j.jacc.2015.02.038.
- Ryuzaki M, Nakamoto H, Nishida E, et al. Crossover study of amlodipine vs nifedipine CR with home blood pressure monitoring via cellular phone: internet-mediated open-label crossover trial of calcium-channel blockers for hypertension (I-TECHO trial). J Hypertens. 2007 Nov;25(11):2352-8.
- Saito I, Saruta T. Controlled release nifedipine and valsartan combination therapy in patients with essential hypertension: The Adalat CR and valsartan cost-effectiveness combination (ADVANCE-Combi) study. J Hypertens. 2007 Nov;25(11):2352-8.
- Saseen JJ, MacLaughlin EJ. Hypertension. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: a pathophysiologic approach. 10th edition. New York (NY): McGraw-Hill; 2017.
- Schrader J, Salvetti A, Calvo C, et al. The combination of amlodipine/valsartan 5/160 mg produces less peripheral oedema than amlodipine 10 mg in hypertensive patients not adequately controlled with amlodipine 5 mg. Int J Clin Pract. 2009;63:217-25.
- Schunkert H, Glazer RD, Wernsing M, et al. Efficacy and tolerability of amlodipine/valsartan combination therapy in hypertensive patients not adequately controlled on amlodipine monotherapy. Curr Med Res Opin. 2009;25:2655-62.
- Sharma A, Bagchi A, Kinagi SB, et al. Results of a comparative, phase III, 12-week, multicenter, prospective, randomized, double-blind assessment of the efficacy and tolerability of a fixed-dose combination of telmisartan and amlodipine vs amlodipine monotherapy in Indian adults with stage II hypertension. Clin Ther. 2007;29:2667-76.
- Sheehy O, LeLorier J. Patterns of amlodipine and felodipine use in an elderly Quebec population. Can J Cardiol. 2000;16(9):1109-17.
- Sinkiewicz W, Glazer RD, Kavoliuniene A, et al. Efficacy and tolerability of amlodipine/valsartan combination therapy in hypertensive patients not adequately controlled on valsartan monotherapy. Curr Med Res Opin. 2009;25:315-24.
- SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015 Nov 26; 373(22):2103-16.
- SULAR prescribing information. Shionogi Inc.; Florham Park, NJ. March 2014.
- Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinopril vs Amlodipine Cardiovascular Events Trial (FACET) in patients with hypertension and non-insulin dependent diabetes mellitus. Diabetes Care. 1998; 21:597-603.
- Van Bortel LM, Fici F, Mascagni F. Efficacy and tolerability of nebivolol compared to other antihypertensive drugs: a meta-analysis. Am J Cardiovasc Drugs. 2008;8(1):35-44.

- Van Der Krogt J, Brand R, Dawson E. Amlodipine vs extended-release felodipine in general practice: A randomized, parallel-group study in patients with mild-to-moderate hypertension. Curr Therap Res. 1996; 57 (3):145-58.
- Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension (ASH/ISH). J Hypertens. 2014 Jan;32(1):3-15.
- Weber MA, Bakris GL, Jamerson K, et al.; ACCOMPLISH Investigators. Cardiovascular events during differing hypertension therapies in patients with diabetes. J Am Coll Cardiol. 2010 Jun 29;56(1):77-85.
- Weber MA, Jamerson K, Bakris G, et al. Effects of body size and hypertension treatments on cardiovascular event rates: subanalysis of the ACCOMPLISH randomised controlled trial. Lancet. 2013;381:537-45.
- Whitcomb C, Enzmann G, Pershadsingh HA, et al. A comparison of nisoldipine ER and amlodipine for the treatment of mild to moderate hypertension. Int J Clin Pract. 2000;54(8):509-13.
- White WB, Duprez D, St Hillaire R, et al. Effects of the selective aldosterone blocker eplerenone vs the calcium antagonist amlodipine in systolic hypertension. Hypertension. 2003a;41(5):1021-6.
- White WB, Saunders E, Noveck RJ, et al. Comparative efficacy and safety of nisoldipine extended-release (ER) and amlodipine (CESNA-III study) in African American patients with hypertension. Am J Hypertens. 2003b;16(9 Pt 1):739-45.
- Wiysonge CS, Bradley H, Mayosi BM, et al. Beta-blockers for hypertension. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD002003. doi: 10.1002/14651858.CD002003.pub2.
- Yancy CW, Jessup M, Bozkurk B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16):e147-239.
- Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2016 Sep 27;68(13):1476-88.
- Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Failure Society of America. J Card Fail. 2017 Apr 25. doi: 10.1016/j.cardfail.2017.04.014.
- Zanchetti A, Julius S, Kjeldsen S, et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: An analysis of findings from the VALUE trial. J Hypertens. 2006 Nov;24(11):2163-8.

Publication Date: Month DD, YYYY