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 atroventricular 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalat CC (nifedipine extended-release)</td>
<td>✓</td>
</tr>
<tr>
<td>Afeditab CR (nifedipine extended-release)</td>
<td>✓</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>✓</td>
</tr>
<tr>
<td>Felodipine extended-release</td>
<td>✓</td>
</tr>
<tr>
<td>Isradipine</td>
<td>✓</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>✓</td>
</tr>
<tr>
<td>Nifedipine extended-release</td>
<td>✓</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>✓</td>
</tr>
<tr>
<td>Nisoldipine extended-release</td>
<td>✓</td>
</tr>
<tr>
<td>Norvasc (amlodipine)</td>
<td>✓</td>
</tr>
<tr>
<td>Nymalize (nimodipine)</td>
<td>✓</td>
</tr>
<tr>
<td>Procardia (nifedipine)</td>
<td>✓</td>
</tr>
<tr>
<td>Procardia XL (nifedipine extended-release)</td>
<td>✓</td>
</tr>
<tr>
<td>Sular (nisoldipine extended-release)</td>
<td>✓</td>
</tr>
</tbody>
</table>

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

<table>
<thead>
<tr>
<th>Indication</th>
<th>Amlodipine</th>
<th>Felodipine</th>
<th>Isradipine</th>
<th>Nicardipine</th>
<th>Nifedipine</th>
<th>Nimodipine</th>
<th>Nisoldipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina Pectoris</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of chronic stable angina</td>
<td>✓</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Treatment of chronic stable angina</td>
<td></td>
<td>-</td>
<td>-</td>
<td></td>
<td>✓ (capsule, ER tablet)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of vasospastic angina</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of chronic stable angina</td>
<td></td>
<td>-</td>
<td>-</td>
<td></td>
<td>✓ (capsule, ER tablet)</td>
<td></td>
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<tr>
<td>Treatment of vasospastic angina</td>
<td>✓</td>
<td></td>
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<tr>
<td>CAD</td>
<td>✓</td>
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<tr>
<td>Reduce the risk of hospitalization due</td>
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<tr>
<td>to angina and to reduce the risk of</td>
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<tr>
<td>a coronary revascularization procedure</td>
<td></td>
<td>-</td>
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<tr>
<td>in patients with recently documented CAD by angiography and without heart failure or ejection fraction &lt; 40%</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>✓ (ER tablet)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Treatment of hypertension</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td>✓ (ER tablet)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Treatment of hypertension to lower</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td>✓ (ER tablet)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>blood pressure which reduces the risk</td>
<td></td>
<td></td>
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<tr>
<td>of fatal and nonfatal cardiovascular</td>
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<tr>
<td>events, primarily strokes and myocardial infarctions</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
<td></td>
<td></td>
<td>✓ (ER tablet)</td>
<td>-</td>
</tr>
</tbody>
</table>

Data as of June 5, 2017 SS-UICK-UJID
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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).
  - 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; Oghara 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
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 (Fiin 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).
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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Available Formulations</th>
<th>Usual Recommended Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>Tablet: 2.5 mg, 5 mg, 10 mg</td>
<td>Angina pectoris (chronic stable and vasospastic): Tablet: maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CAD: Tablet: maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypertension: Tablet: initial, 5 mg once daily; maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Felodipine</td>
<td>Extended-release tablet: 2.5 mg, 5 mg, 10 mg</td>
<td>Hypertension: Extended-release tablet: initial, 5 mg once daily; maintenance, 2.5 to 10 mg once daily</td>
<td>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</td>
</tr>
<tr>
<td>Isradipine</td>
<td>Capsule: 2.5 mg, 5 mg</td>
<td>Hypertension: Capsule: initial, 2.5 mg twice daily; maximum, 20 mg/day</td>
<td>Dose adjustments should occur in increments of 5 mg/day at 2 to 4 week intervals.</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Capsule:</td>
<td>Angina pectoris (chronic stable):</td>
<td>Allow at least 3 days before</td>
</tr>
<tr>
<td>Drug</td>
<td>Available Formulations</td>
<td>Usual Recommended Frequency</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Immediate-release capsule: 10 mg, 20 mg</td>
<td>Angina pectoris (chronic stable): Capsule: initial, 10 mg 3 times daily; maintenance, 20 to 30 mg 3 to 4 times daily; maximum, 180 mg/day</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Extended-release tablet: 30 mg, 60 mg, 90 mg</td>
<td>Extended-release tablet: initial, 30 or 60 mg once daily; maintenance, 30 to 90 mg once daily; maximum, 120 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypertension: Extended-release tablet: initial, 30 or 60 mg once daily; maintenance, 30 to 90 mg once daily; maximum, 120 mg/day</td>
<td></td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Capsule: 30 mg</td>
<td>Subarachnoid hemorrhage: Capsule: 60 mg every 4 hours for 21 consecutive days</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Oral solution: 60 mg/20 mL</td>
<td>Oral solution: 20 mL (60 mg) every 4 hours for 21 consecutive days</td>
<td></td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>Extended-release tablet: 8.5 mg, 17 mg, 20 mg</td>
<td>Hypertension: Extended-release tablet: initial, 20 mg once daily; maintenance, 20 to 40 mg/day; maximum, 60 mg/day</td>
<td>Dose adjustments should occur at intervals of not less than 1 week.</td>
</tr>
<tr>
<td>Drug</td>
<td>Available Formulations</td>
<td>Usual Recommended Frequency</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
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<tr>
<td></td>
<td>25.5 mg</td>
<td>Extended-release tablet (Sular and its generics): initial, 17 mg once daily; maintenance, 17 to 34 mg once daily; maximum, 34 mg once daily</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>30 mg</td>
<td></td>
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<tr>
<td></td>
<td>34 mg</td>
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<tr>
<td></td>
<td>40 mg</td>
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</tbody>
</table>

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).

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Messeter FH, Opalir S, Feng Z. Comparison of efficacy and side effects of combination therapy of angiotensin-converting enzyme inhibitor (benazepril) with calcium antagonist (either nifedipine or amlopidine) vs high-dose calcium antagonist monotherapy for systemic hypertension. Am J Cardiol. 2000 Dec 1;86:1182-7.


