

Criteria for Use of Long-Acting Dihydropyridine Calcium Antagonists in VA Patients

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of individual patient situations.

The role of the dihydropyridine (DHP) calcium antagonist class in the management of hypertension (HTN) and/or angina should be evaluated for each individual VA patient. The following recommendations are provided for clinicians considering the use of a long-acting DHP calcium antagonist for the treatment of HTN and/or angina.

I. Long-Acting DHP Calcium Antagonist Criteria for Use

A. Summary for the Treatment of Hypertension

- Diuretics and beta-blockers are the preferred agents for patients with uncomplicated HTN.
- Another class of agents may be considered in patients who have a contraindication to a diuretic and beta-blocker or who are inadequately controlled on these agents **OR** in patients who have an indication for an agent in another antihypertensive class. In addition, the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) suggests the combination of two agents at low doses may improve efficacy and minimize side effects.
- When a calcium antagonist is chosen, verapamil or diltiazem should be considered for patients with Stage I hypertension (unless contraindicated) due to the lower price of these agents compared with a long-acting DHP calcium antagonist. A long-acting DHP (VA National Formulary preferred agents are extended-release felodipine or long-acting nifedipine) may be considered in patients with Stage 2 or 3 HTN. Refer to the VHA/DoD Clinical Practice Guidelines for the Diagnosis and Management of Hypertension in the Primary Care Setting and PBM-MAP The Pharmacologic Management of Hypertension: Supplement to the VHA/DoD Clinical Practice Guidelines for the Diagnosis and Management of Hypertension in the Primary Care Setting at <http://www.vapbm.org> or <http://vaww.pbm.med.va.gov>.
- Short-acting nifedipine should **NOT** be used for the treatment of HTN.

B. Summary for the Treatment of Angina

- Patients with angina should be treated with a beta-blocker.
- A long-acting calcium antagonist or long-acting nitrate may be used if a beta-blocker is ineffective or contraindicated. A calcium antagonist may also be considered for additional blood pressure control, and in patients with variant angina. If a calcium antagonist is being considered for the treatment of angina, the nondihydropyridine calcium antagonists (diltiazem, verapamil) are preferred, unless the patient is already receiving therapy with a beta-blocker. Diltiazem and verapamil should be used with caution in patients already on a beta-blocker due to potential for additive negative effects on myocardial contractility, heart rate, and atrioventricular conduction.
- If a long-acting DHP calcium antagonist is considered appropriate, the preferred agents are extended-release felodipine or long-acting nifedipine.
- Amlodipine may be used when a long-acting DHP calcium antagonist is considered the most appropriate treatment for the patient based on the above recommendations for the treatment of angina **AND** the patient has a documented adverse reaction to extended-release felodipine **AND** long-acting nifedipine.

C. Summary for the Treatment of HTN and/or Angina in Patients with Chronic Heart Failure (HF)

- Felodipine may be considered for the treatment of HTN and/or angina in patients being treated with standard therapy for milder heart failure. Refer to PBM-MAP The Pharmacologic Management of Chronic Heart Failure at <http://www.vapbm.org> or <http://vaww.pbm.med.va.gov>.
- Amlodipine may be considered for the treatment of HTN and/or angina in patients with advanced HF who are already receiving appropriate therapy for chronic HF.

D. Precautions

1. Increased frequency, duration, and or severity of angina and/or acute myocardial infarction (MI) have rarely occurred when starting or increasing the dose of a calcium antagonist. Patients with angina being initiated on long-acting nifedipine should be warned that the drug may cause an increase in angina, especially if therapy with a beta-blocker is discontinued abruptly.
2. Due to safety concerns, most calcium antagonists should be avoided in patients with HF.¹ Long-term studies with felodipine and amlodipine have provided safety data in patients with chronic HF on optimal therapy [e.g., diuretics, angiotensin-converting enzyme inhibitor (ACEI), digoxin].²⁻⁴ Felodipine did not worsen HF or show a difference in mortality when compared to placebo in patients with primarily New York Heart Association (NYHA) class II HF. These endpoints were not primary objectives in the study which also was not powered to detect a difference in morbidity or mortality.² Amlodipine appears to be safe, showing no difference in mortality compared to placebo (a primary endpoint) in patients with advanced (NYHA class III-IV) HF.³ Peripheral^{2, 3} and pulmonary³ edema occurred significantly more frequently in patients on amlodipine or felodipine compared to placebo.
3. The potential for adverse cardiac outcomes in patients treated with a long-acting DHP calcium antagonist in patients with HTN and non-insulin dependent diabetes has yet to be resolved. Until additional information is available, ACEIs are preferred for the treatment of HTN in patients with diabetes with proteinuria. A low-dose diuretic or beta-blocker may also be appropriate for treating patients with HTN and non-insulin dependent diabetes mellitus.

II. Discussion

A. Hypertension

According to JNC VI,⁵ diuretics or beta-blockers are the preferred therapy for treating patients with uncomplicated HTN. These recommendations are based on the reduction in morbidity and mortality shown in randomized controlled trials where these agents were used to treat HTN.

Recent Outcome Studies in HTN: Since JNC VI, additional outcome studies have been published that evaluate initial therapy for HTN. The CAPPP⁶ trial evaluated the ACEI captopril vs. conventional therapy (diuretic or beta-blocker) in patients with HTN. The primary endpoint (composite fatal and non-fatal MI, stroke, and other cardiovascular deaths) did not differ significantly between treatment groups. Two trials compared treatment of HTN with a calcium antagonist (INSIGHT⁷ with extended-release nifedipine; NORDIL⁸ with long-acting diltiazem) to a diuretic (INSIGHT) or diuretic and beta-blocker (NORDIL). The primary outcomes were cardiovascular death, MI, HF, or stroke (INSIGHT) or fatal and non-fatal stroke, MI, and other cardiovascular death (NORDIL). These trials did not demonstrate a statistically significant difference in the primary outcomes compared to conventional therapy, although stroke rate was lower in the diltiazem group and HF was more common in the group treated with nifedipine. The difference in outcomes in these and other studies⁹⁻¹¹ indicate that the place of calcium antagonists in the treatment of HTN still remains to be defined.

In other outcome studies, an ACEI (ramipril) significantly decreased the primary endpoint of death rate, MI, and stroke in patients with evidence of vascular disease or diabetes and one other cardiovascular risk factor (HTN, among others) who did not have HF or a low ejection fraction in the HOPE¹² study. The HOT trial¹³ used a long-acting DHP calcium antagonist (felodipine) as initial treatment in determining the optimum target diastolic blood pressure (DBP). The lowest incidence of major cardiovascular events was at a mean DBP of 82.6 mm Hg; cardiovascular mortality was lowest at a DBP of 86.5 mm Hg.

Thus in the treatment of uncomplicated HTN, diuretics and beta-blockers are recommended as drugs of first choice. Other drug classes (e.g., ACEI, calcium antagonists) may be equally effective and we await the results of additional ongoing long-term outcome trials.

Calcium Antagonists in Older Patients with HTN: Other antihypertensive medications may be used for compelling reasons or to tailor therapy for selected patients. Thiazide diuretics are the preferred agents for the treatment of isolated systolic HTN although JNC VI recommends that a long-acting DHP calcium antagonist may

be considered in these patients.⁵ This recommendation is based on a 42% reduction in fatal and nonfatal stroke in patients with isolated systolic HTN found in the Syst-Eur study¹⁴ using nitrendipine (not available in the U. S.). This recommendation remains controversial therefore a long-acting DHP calcium antagonist should be considered in patients with isolated systolic HTN only when a thiazide diuretic is contraindicated. More recently, results from STOP-2¹⁵ showed that older patients with HTN treated with conventional therapy (diuretic and/or beta-blocker) compared with a long-acting DHP calcium antagonist (felodipine or isradipine) or an ACEI (enalapril or lisinopril) experienced a similar reduction in blood pressure and risk of major cardiovascular events. For the treatment of isolated systolic hypertension, diuretics are preferred therapy. Diuretics or beta-blockers are recommended as first-line for treating older persons with HTN, although other agents appear equally effective.

Calcium Antagonists in HTN and Diabetes: There has been discussion concerning whether DHP calcium antagonists may contribute to an increased risk of cardiovascular events in selected patient populations.¹⁶ Two studies with a long-acting DHP calcium antagonist in patients with HTN and non-insulin dependent diabetes showed an increased risk of major vascular events (FACET with amlodipine)¹⁷ and a higher incidence of fatal and nonfatal MI (ABCD with nisoldipine)¹⁸ compared to patients treated with an ACEI. In another trial (MIDAS)¹⁹ in patients with HTN, the primary endpoint of rate of progression of the mean maximum intimal-medial thickness in carotid arteries was not different in patients receiving isradipine compared to those on hydrochlorothiazide, however there was an increased incidence of vascular events in patients treated with isradipine compared to those receiving a thiazide diuretic. It should be noted that these outcome measures were secondary endpoints of these three trials. In a post hoc analysis of MIDAS,²⁰ it was found that patients with HTN and prediabetes treated with isradipine experienced more adverse cardiovascular events than patients treated with a thiazide diuretic. However, patients with diabetes receiving nitrendipine in the Syst-Eur study¹⁴ experienced a decrease in cardiovascular events and mortality. An improvement in cardiovascular outcomes was also seen in patients with diabetes treated with felodipine in the HOT trial.¹³ In the UK diabetes study,²¹ a comparison trial of an ACEI vs. a beta-blocker, outcomes were similar in patients with HTN and diabetes treated with these agents. At this time, ACEI are preferred therapy in patients with types 1 and 2 diabetes mellitus (DM) with proteinuria. Low dose thiazide diuretics may have a favorable effect in patients with DM.⁵ The potential benefit of beta-blockers is yet to be determined.²¹ The effect of a calcium antagonist compared to other antihypertensive therapy in patients with DM is yet to be determined.

B. Angina

According to a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, the ACC/AHA/ACP-ASIM Guidelines for the Management of Patients With Chronic Stable Angina²² states that the preferred treatment for patients with angina is a beta-blocker. A long-acting calcium antagonist or long-acting nitrate may be used if a beta-blocker is ineffective or contraindicated. It is unclear whether treatment with a long-acting calcium antagonist or long-acting nitrate leads to better outcomes, although a long-acting calcium antagonist may be preferable to a long-acting nitrate due to their duration of action. If a calcium antagonist is being considered for the treatment of angina, the nondihydropyridine calcium antagonists (diltiazem, verapamil) are preferred, unless the patient is already receiving therapy with a beta-blocker. The PBM-MAP recommends that the preferred long-acting DHP calcium antagonist is either extended-release felodipine²³⁻³⁶ or long-acting nifedipine.³⁶⁻⁴⁰

C. Treatment of Hypertension and/or Angina in Patients with Chronic Heart Failure

The Advisory Council to Improve Outcomes Nationwide in Heart Failure (ACTION-HF)¹ have indicated that two long-acting DHP calcium antagonists (felodipine and amlodipine) have been shown to be relatively safe in patients with chronic HF.²⁻⁴ Patients evaluated in V-HeFT III² on felodipine included approximately 79% patients in NYHA class II HF, 22% in class III, with a mean ejection fraction (EF) 29%. Patients enrolled in the PRAISE Study³ on amlodipine included approximately 81% patients in NYHA class III HF, 19% in class IV, with a mean EF 21%. PRAISE-2⁴ enrolled patients according to similar inclusion criteria as PRAISE, although only patients with chronic HF due to nonischemic dilated cardiomyopathy were included. The possibility that amlodipine decreases mortality in patients with nonischemic dilated cardiomyopathy³ was not demonstrated in the follow-up evaluation (PRAISE-2).⁴ Based on these data, felodipine or amlodipine may be considered for the treatment of HTN and/or angina only in patients who are receiving appropriate therapy for chronic HF (e.g., diuretics, ACEI,

digoxin, beta-blocker, spironolactone where indicated). However, evidence for their safety and efficacy in the treatment of HTN and/or angina in patients with HF is lacking.

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