Month/Year of Review: January 2012
PDL Class: Calcium Channel Blockers (CCB)

Date of Last Review: 2005
Source Document: DERP Report

Current Preferred Agents:
Dihydropyridines:
amlodipine
nicardipine
nifedipine ER 24
nifedipine ER SA

Non-dihydropyridines:
diltiazem SR 24 HR
diltiazem ER
diltiazem HCL
verapamil HCL
verapamil HCL 24H

Current Non-Preferred Agents:
feldipine
isradapine
nisoldipine
Nimotop (nimodipine)

Previous Recommendations:

1. The current evidence does not allow for comparisons of CCBs for the treatment of hypertension and does not differentiate amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nisoldipine, or verapamil SR for efficacy, adverse effects and in subgroups for the treatment of hypertension. There is no evidence for bepridil and felodipine.

2. The current evidence does not differentiate amlodipine, diltiazem, nicardipine, nifedipine, and nisoldipine for efficacy in the treatment of chronic stable angina. There is no evidence for felodipine and isradipine. No difference in efficacy was found between dihydropyridines and non-dihydropyridines for the treatment of angina.

3. The current evidence does not differentiate between diltiazem or verapamil for efficacy and adverse effects in the treatment of supraventricular arrhythmias and there is no evidence in subgroups of patients.

4. In the setting of CHF (defined as systolic dysfunction with a LVEF of < 45%) there is evidence that amlodipine and felodipine do not decrease survival or cause harm in this patient population, but neither do they improve survival nor decrease nonfatal cardiovascular events. In patients with systolic dysfunction the evidence does not demonstrate differences between amlodipine, felodipine nifedipine and nisoldipine on symptoms and exercise tolerance.
**PA Criteria/QL:** Patient must have a covered ICD9 diagnosis.

**Background:**

Since the DERP report and OHP review of the CCB medications in 2005 there have been 3 DERP CCB class scans conducted in 2006, 2007, and 2009. Based on a defined search criteria a total of 40 potentially relevant trials were identified in those 3 scans (Appendix B - D). The majority of these were identified in the first year following the DERP report. New drugs, indications, and safety alerts found in these scans (2006-2009) since the 2005 report are summarized as follows:

**New drugs:**

**2006 scan**  
Bepridil discontinued due to ventricular arrhythmias

**2009 scan**  
FDA approved a change in the formulation of extended-release nisoldipine to lower the strengths and replace all current tablets with new lower, bioequivalent strengths.

**New FDA Indications:**

**2006 scan**  
Amlodipine indicated for use in patients with angiographically documented coronary artery disease–expanded population

**New FDA safety alerts:**

**2007 scan**  
New information was added to the Precautions section for 4 CCBs:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardizem LA (diltiazem hydrochloride) Extended Release Tablets</td>
<td>Bispirone, Quinidine, Buspirone</td>
</tr>
<tr>
<td>Tiazac (diltiazem hcl) ER</td>
<td>Bispirone, Quinidine Buspirone: Drug Interactions :</td>
</tr>
<tr>
<td>Verelan PM (verapamil hydrochloride) Extended-Release Capsules Controlled Onset</td>
<td>Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent telithromycin, an antibiotic in the ketolide class of antibiotics</td>
</tr>
</tbody>
</table>
Methods:

Search Strategy
A search was conducted to identify newly published high quality systematic reviews, new randomized controlled trials, new FDA approved drugs, indications, and safety alerts since the last DERP update scan (2009) was conducted. A MEDLINE OVID search was conducted using the following search terms: Amlodipine, diltiazem, felodipine, nicardipine, nisoldipine, verapamil, bepridil, isradipine, nifedipine, angina pectoris, supraventricular tachycardia, hypertension, heart failure.

The following limitations were used for the search:
All controlled clinical trials or randomized controlled trials
English language
Humans
2010-present

Results:

The MEDLINE search retrieved 217 full citations. These were reviewed for inclusion by evaluating citations and abstracts for head to head trials of CCB’s evaluating outcomes of interest. 6 new studies were included and are listed in Appendix A. This includes only 1 head to head trial that compared two CCB’s, Nifedipine CR and Diltiazem R in vasopastic angina.

The search of the Cochrane, AHRQ, DERP, and VA/DoD websites did not identify any relevant new systematic reviews.

The FDA website was reviewed for new FDA approved drugs, indications, and safety alerts.

New FDA-approved drugs:
Procardia XL (nifedipine gastrointestinal therapeutic system (GITS)) – once-a-day controlled-release tablet

New FDA Indications:
None identified.

New FDA safety alerts:
None identified.

New Systematic Reviews:
None identified.
Appendix A: New literature from current scan


Objectives: Evaluate efficacy of antihypertensive agents on central blood pressure in African Americans.
Design: 8-week double-blind, randomized study of African American patients with stage 2 hypertension that compared brachial and central BP responses to combination aliskiren/HCTZ and amlodipine monotherapy.
Results: Mean seated systolic BP reductions from baseline was similar with both treatments (-28.6 mm Hg with aliskiren/HCTZ vs -28.2 mm Hg with amlodipine). In the substudy, significantly greater reductions in central systolic BP was observed with aliskiren/HCTZ vs amlodipine (-30.1 mm Hg vs -21.2; P=.031), although 24-hour mean ambulatory BP reductions between the two groups were similar.
Conclusions: Central pressure is considered an important risk factor in African Americans, and these findings may suggest a new treatment option for these patients.


Objectives: Examine the effects of candesartan and amlodipine on cardiovascular events in hypertensive patients with chronic kidney disease (CKD) using the data from the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial.
Design: CKD was defined as proteinuria and/or decreased GFR (<60 ml per min per 1.73 m(2)) at enrollment. Among 2720 subjects with CKD, there were 1376 and 1344 patients in the candesartan and the amlodipine group, respectively.
Results: During a 3.2-year follow-up, cardiovascular event rate did not differ in the two groups (7.2% for candesartan and 7.6% for amlodipine). In the subgroup analysis based on the CKD stage, there were no significant differences in the incidence rates of cardiovascular events between the two groups in stages 1+2 and 3 CKD. In stage 4 CKD, however, candesartan reduced the incidence of cardiovascular events (55% risk reduction), particularly of renal events (81% risk reduction), compared with amlodipine. Furthermore, composite cardiovascular events were increased as the CKD stage progressed, and this effect was exaggerated in the presence of proteinuria. Finally, the new onset of diabetes was less in the candesartan-based regimen in stage 3 CKD.
Conclusions: candesartan protected hypertensive patients with CKD more potently against renal events, particularly in moderately-to-severely impaired CKD. Furthermore, candesartan prevented a new onset of diabetes in CKD, which would be favorable for the long-term management of CKD


Objectives: Compare the efficacy of once-daily administration of nifedipine CR 40 mg (N) with that of twice-daily diltiazem R 100mg (D) in patients with vasospastic angina (VSA) registered in 8 cardiovascular institutes in Aomori Prefecture.
Design: VSA was diagnosed by the ischemic ST segment changes during chest pain attacks at rest and/or acetylcholine induction test done during coronary angiography. Thirty-seven patients were randomly allocated to either the N (n=20) or D group (n=17). The number of symptomatic attacks and amount of short-acting nitrate use were examined based on data in diaries written by the patients.

Results: There were no significant differences in the baseline characteristics between the two groups. The mean number (median number) of attacks per week was significantly decreased in the N group from 2.56 (2.0) at baseline to 0.41 (0.0) after 4 weeks of treatment, to 0.24 (0.0) after 8 weeks, and to 0.36 (0.0) after 12 weeks (all p<0.05 vs. baseline). It was also decreased in D group from 2.71 (2.0) at baseline to 0.55 (0.0) after 4 weeks, to 0.32 (0.0) after 8 weeks, and to 0.27 (0.0) after 12 weeks (all p<0.05 vs. baseline). The numbers of attacks before and after treatment were comparable between N and D groups. In one patient in each of the N and D groups, the allocated drug was crossed over to the other due to recurrence of the attacks. One patient in each group experienced adverse effects and the drug was changed to the other.

Conclusions: Once-daily administration of nifedipine CR was as effective as twice-daily diltiazem R in the prevention of VSA attacks.


Objectives: Hypertension is particularly prevalent in patients aged ≥65 years, those with a body mass index ≥30 kg m(-2), Blacks and those with type II diabetes. Here we report a prespecified secondary analysis of the efficacy of amlodipine (10 mg day(-1)), olmesartan medoxomil (40 mg day(-1)), a combination of the two and placebo in these subgroups.

Design: Patients were randomized to treatment for 8 weeks. The primary efficacy endpoint was the change from baseline in mean seated diastolic blood pressure (DBP). Secondary efficacy endpoints included the change from baseline in mean seated systolic BP (SBP), proportions of patients achieving BP goal (<140/90 mm Hg or <130/80 mm Hg in patients with diabetes), and the number and percentage of patients achieving a range of BP targets. Safety and tolerability of amlodipine 5 and 10 mg, olmesartan medoxomil 10, 20 and 40 mg, and all possible combinations of the two were also assessed.

Results: For each prespecified subgroup, all active treatments resulted in significant BP reductions from baseline (P<0.05). The antihypertensive effect of the combination of amlodipine+olmesartan medoxomil was generally greater than the constituent amlodipine or olmesartan medoxomil monotherapies, regardless of subgroup. In general, more patients receiving combination therapy achieved BP goal than those treated with monotherapies. The safety and tolerability of combinations were similar to monotherapies across the subgroups.

Conclusions: These results suggest that the combination of amlodipine+olmesartan medoxomil provides a safe and effective option for the treatment of hypertension in challenging patient populations.


Objectives: Retrospective analyses of specific subgroups of patients from the database of the ACTION study have evaluated the effectiveness of a nifedipine gastrointestinal therapeutic system (GITS) on clinical outcomes. These subgroups included those patients receiving: 1) full "optimal" therapy at baseline; 2) full "optimal" therapy at baseline but excluding renin angiotensin system (RAS)-blocking drugs; 3) treatment with nifedipine GITS who were not treated with RAS blockers versus those treated with RAS blockers but not nifedipine GITS.
**Design:** Analyses were performed on an intention-to-treat basis. Treatment groups were compared by log-rank test without adjustment for covariates. Hazard ratios with 95% confidence intervals were obtained using Cox proportional hazards models with treatment allocation as the only covariate.

**Results:** 2461 patients randomized in ACTION were receiving optimal therapy (beta blockers, nitrates, aspirin, statins) excluding RAS blockers at baseline. There were reductions associated with nifedipine GITS compared with placebo in all prespecified endpoints but statistical significance was only achieved for debilitating stroke (48%; P<0.02) and coronary angiography (14%; P<0.05). These benefits were paralleled by a -4.1 and -2.8 mmHg difference between the groups for systolic and diastolic blood pressure, respectively. Patients randomized to nifedipine GITS but no RAS blockers (n=2966) when compared to those receiving RAS blockers but no nifedipine GITS (n=880) had highly statistically significant reductions in cardiovascular events (22%), new-onset heart failure (53%), and debilitating stroke (45%). However, the groups differed in their baseline characteristics.

**Conclusions:** Addition of nifedipine GITS to the treatment regimen of selected patient groups with symptomatic coronary artery disease results in a significant reduction of cardiovascular morbidity. While the interpretation of these subgroup analyses must obviously be cautious, there is a clear message relating to "best practice" treatment of angina, which suggests that "reliance" on RAS blockade may be misplaced and greater attention should be directed towards control of blood pressure.


**Objectives:** Test whether a combination of aliskiren and amlodipine is superior to each monotherapy in early control of blood pressure without excess of adverse events, and if initial control by monotherapy impairs subsequent control by combination therapy.

**Design:** Double-blind, randomized, parallel-group, superiority trial at 146 care sites in ten countries, with enrolment from Nov 28, 2008, to July 15, 2009. Patients eligible for enrolment had essential hypertension, were aged 18 years or older, and had systolic blood pressure between 150 and 180 mm Hg. Patients were randomly assigned (1:1:2) to treatment with 150 mg aliskiren plus placebo, 5 mg amlodipine plus placebo, or 150 mg aliskiren plus 5 mg amlodipine. Random assignment was through a central interactive voice response system and treatment allocation was masked from the patients. From 16-32 weeks, all patients received combination therapy with 300 mg aliskiren plus 10 mg amlodipine. Our primary endpoints, assessed on an intention-to-treat basis (ie, in patients who received the allocated treatment), were the adjusted mean reduction in systolic blood pressure from baseline over 8 to 24 weeks, and then the final reduction at 24 weeks.

**Results:** 318 patients were randomly assigned to aliskiren, 316 to amlodipine, and 620 to aliskiren plus amlodipine. 315 patients initially allocated to aliskiren, 315 allocated to amlodipine, and 617 allocated to aliskiren plus amlodipine were available for analysis. Patients given initial combination therapy had a 6·5 mm Hg (95% CI 5.3 to 7.7) greater reduction in mean systolic blood pressure than the monotherapy groups (p<0.0001). At 24 weeks, when all patients were on combination treatment, the difference was 1·4 mm Hg (95% CI -0.05 to 2·9; p=0·059). Adverse events caused withdrawal of 85 patients (14%) from the initial aliskiren plus amlodipine group, 45 (14%) from the aliskiren group, and 58 (18%) from the amlodipine group. Adverse events were peripheral oedema, hypotension, or orthostatic hypotension.

**Conclusions:** Routine initial reduction in blood pressure with a combination such as aliskiren plus amlodipine can be recommended.
Appendix B: New literature from scan #3 (13)


Appendix C: New literature from scan #2 (3)


Appendix D: New literature from scan #1 (24)


