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Month/Year of Review: January 2012 **Date of Last Review:** 2005
PDL Class: Calcium Channel Blockers (CCB) **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:
felodipine
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:

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

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, supreventricular 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

1. Ferdinand KC, Pool J, et al. Peripheral and central blood pressure responses of combination aliskiren/hydrochlorothiazide and amlodipine monotherapy in African American patients with stage 2 hypertension: the ATLAAST trial. J Clin Hypertens 2011 May;13(5):366-75

Objectives: Evaluate efficacy of antihypertneisve 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.

2. Saruta, T., K. Hayashi, et al. (2009). "Effects of candesartan and amlodipine on cardiovascular events in hypertensive patients with chronic kidney disease: subanalysis of the CASE-J Study." Hypertension Research - Clinical & Experimental **32**(6): 505-12.

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

3. Higuma, T., Oikawa, K., Kato, T., Mori, Y., Kudo, T., Yamamoto T., et al. (2010). Comparison of the effects of long-acting nifedipine CR and diltiazem R in patients with vasospastic angina: Aomori coronary spastic angina study. *Journal of Cardiology, 56*(3), 354-60.

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

4. Chrysant, S.G., Lee, J., Melino, M., Karki, S., & Heyrman, R. (2010). Efficacy and tolerability of amlodipine plus olmesartan medoxomil in patients with difficult-to-treat hypertension. *Journal of Human Hypertension, 24*(11), 730-8.

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.

5. Meredith, P.A., & Elliott, H.L. (2010). Benefits of nifedipine GITS in stable coronary artery disease: Further analysis of the "ACTION" database. *Advances in Therapy, 27*(5), 297-306.

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

6. Brown MJ. McInnes GT. Papst CC. Zhang J. MacDonald TM. Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial. Lancet. 377(9762):312-20, 2011 Jan 22

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)

1. Jamerson, K., M. A. Weber, et al. (2008). "Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients.[see comment]." New England Journal of Medicine **359**(23): 2417-28.

2. Nakamura, T., T. Inoue, et al. (2008). "Comparison of renal and vascular protective effects between telmisartan and amlodipine in hypertensive patients with chronic kidney disease with mild renal insufficiency." Hypertension Research - Clinical & Experimental **31**(5): 841-50.

3. Nakayama, K., Y. Kuwabara, et al. (2008). "Valsartan Amlodipine Randomized Trial (VART): design, methods, and preliminary results." Hypertension Research - Clinical & Experimental **31**(1): 21-8.

4. Tepel, M., W. Hopfenmueller, et al. (2008). "Effect of amlodipine on cardiovascular events in hypertensive haemodialysis patients." Nephrology Dialysis Transplantation **23**(11): 3605-12.

5. Ogihara, T., A. Fujimoto, et al. (2008). "ARB candesartan and CCB amlodipine in hypertensive patients: the CASE-J trial." Expert Review of Cardiovascular Therapy **6**(9): 1195-201.

6. Ogihara, T., K. Nakao, et al. (2008). "Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks: candesartan antihypertensive survival evaluation in Japan trial." Hypertension **51**(2): 393-8.

7. Ostergren, J., N. R. Poulter, et al. (2008). "The Anglo-Scandinavian Cardiac Outcomes Trial: blood pressure-lowering limb: effects in patients with type II diabetes." Journal of Hypertension **26**(11): 2103-11.

8. Bangalore, S., F. H. Messerli, et al. (2008). "Verapamil-sustained release-based treatment strategy is equivalent to atenolol-based treatment strategy at reducing cardiovascular events in patients with prior myocardial infarction: an INternational VErapamil SR-Trandolapril (INVEST) substudy." American Heart Journal **156**(2): 241-7.

9. Black, H. R., B. Davis, et al. (2008). "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 **31**(2): 353-60.

10. Davis, B. R., J. B. Kostis, et al. (2008). "Heart failure with preserved and reduced left ventricular ejection fraction in the antihypertensive and lipid-lowering treatment to prevent heart attack trial.[see comment]." Circulation **118**(22): 2259-67.

11. Schmieder, R. E., S. E. Kjeldsen, et al. (2008). "Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial." Journal of Hypertension **26**(3): 403-1

12. Wright, J. T., Jr., S. Harris-Haywood, et al. (2008). "Clinical outcomes by race in hypertensive patients with and without the metabolic syndrome: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[see comment]." Archives of Internal Medicine **168**(2): 207-17.

13. Yui, Y., E. Shinoda, et al. (2007). "Nifedipine retard prevents hospitalization for angina pectoris better than angiotensin-converting enzyme inhibitors in hypertensive Japanese patients with previous myocardial infarction (JMIC-B substudy)." Journal of Hypertension **25**(10): 2019-26.

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

1. Cooper-DeHoff, R. M., Q. Zhou, et al. (2007). "Influence of Hispanic ethnicity on blood pressure control and cardiovascular outcomes in women with CAD and hypertension: findings from **INVEST**." Journal of Women's Health **16**(5): 632-40.

2. Ruilope, L. M., B.-A. Kirwan, et al. (2007). "Uric acid and other renal function parameters in patients with stable angina pectoris participating in the **ACTION** trial: impact of nifedipine GITS (gastro-intestinal therapeutic system) and relation to outcome." Journal of Hypertension **25**(8): 1711-8.

3. Ruzyllo, W., M. Tendera, et al. (2007). "Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: a 3-month randomised, double-blind, multicentre, noninferiority trial." Drugs **67**(3): 393-405.

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

1. Black HR, Elliott WJ, Grandits G, et al. Results of the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) trial by geographical region. *Journal of Hypertension.* May 2005;23(5):1099-1106.

2. Cooper-Dehoff R, Cohen JD, Bakris GL, et al. Predictors of development of diabetes mellitus in patients with coronary artery disease taking antihypertensive medications (findings from the INternational VErapamil SR-Trandolapril STudy [INVEST]). *American Journal of Cardiology*. Oct 1 2006;98(7):890-894.

3. de Leeuw PW, Ruilope LM, Palmer CR, et al. Clinical significance of renal function in hypertensive patients at high risk: results from the INSIGHT trial.[see comment]. *Archives of Internal Medicine.* Dec 13-27 2004;164(22):2459-2464.

4. Derosa G, Cicero AFG, Bertone G, et al. Comparison of the effects of telmisartan and nifedipine gastrointestinal therapeutic system on blood pressure control, glucose metabolism, and the lipid profile in patients with type 2 diabetes mellitus and mild hypertension: a 12-month, randomized, double-blind study. *Clinical Therapeutics.* Aug 2004;26(8):1228-1236.

5. Frishman WH, Hainer JW, Sugg J, Group MFS. A factorial study of combination hypertension treatment with metoprolol succinate extended release and felodipine extended release results of the Metoprolol Succinate-Felodipine Antihypertension Combination Trial (M-FACT). *American Journal of Hypertension.* Apr 2006;19(4):388-395.

6. Hemels MEW, Van Noord T, Crijns HJGM, et al. Verapamil versus digoxin and acute versus routine serial cardioversion for the improvement of rhythm control for persistent atrial fibrillation. *Journal of the American College of Cardiology.* Sep 5 2006;48(5):1001-1009.

7. Inoue S, Tomino Y. Effects of calcium antagonists in hypertensive patients with renal dysfunction: a prospective, randomized, parallel trial comparing benidipine and nifedipine. *Nephrology.* Oct 2004;9(5):265-271.

8. Investigators JE, Investigators JE. Effect of Losartan and Amlodipine on Left Ventricular Diastolic Function in Patients With Mild-to-Moderate Hypertension (J-ELAN): rationale and design. *Circulation Journal.* Jan 2006;70(1):124-128.

9. Jerums G, Allen TJ, Campbell DJ, et al. Long-term renoprotection by perindopril or nifedipine in non-hypertensive patients with Type 2 diabetes and microalbuminuria. *Diabetic Medicine.* Nov 2004;21(11):1192-1199.

10. Koylan N, Bilge AK, Adalet K, Mercanoglu F, Buyukozturk K, Group TTS. Comparison of the effects of trimetazidine and diltiazem on exercise performance in patients with coronary heart disease. The Turkish trimetazidine study (TTS). *Acta Cardiologica.* Dec 2004;59(6):644-650.

11. Leenen FHH, Nwachuku CE, Black HR, et al. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the antihypertensive and lipid-lowering treatment to prevent heart attack trial.[see comment]. *Hypertension.* Sep 2006;48(3):374-384.

12. Mancia G, Ruilope L, Palmer C, et al. Effects of nifedipine GITS and diuretics in isolated systolic hypertension--a subanalysis of the INSIGHT study. *Blood Pressure.* 2004;13(5):310-315.

13. Messerli FH, Mancia G, Conti CR, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Annals of Internal Medicine.* Jun 20 2006;144(12):884-893.

14. Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial.[see comment]. *JAMA.* Nov 10 2004;292(18):2217-2225.

15. Ried LD, Tueth MJ, Taylor MD, Sauer BC, Lopez LM, Pepine CJ. Depressive symptoms in coronary artery disease patients after hypertension treatment. *Annals of Pharmacotherapy.* Apr 2006;40(4):597-604.

16. Ruggenenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes.[see comment]. *New England Journal of Medicine.* Nov 4 2004;351(19):1941-1951.

17. Vranic II, Matic M, Perunicic J, Simic T, Soskic L, Milic N. Adenosine cardioprotection study in clinical setting of paroxysmal supraventricular tachycardia. *Prostaglandins Leukotrienes & Essential Fatty Acids.* Jun 2006;74(6):365-371

18. Whelton PK, Barzilay J, Cushman WC, et al. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Archives of Internal Medicine.* Jun 27 2005;165(12):1401-1409.

19. Kojima S, Shida M, Yokoyama H. Comparison between cilnidipine and amlodipine besilate with respect to proteinuria in hypertensive patients with renal diseases. *Hypertension Research - Clinical & Experimental.* Jun 2004;27(6):379-385.

20. Vora A, Karnad D, Goyal V, et al. Control of rate versus rhythm in rheumatic atrial fibrillation: a randomized study.[see comment]. *Indian Heart Journal.* Mar-Apr 2004;56(2):110-116.

21. Hjemdahl P, Eriksson SV, Held C, Forslund L, Nasman P, Rehnqvist N. Favourable long term prognosis in stable angina pectoris: an extended follow up of the angina prognosis study in Stockholm (APSIS). *Heart.* Feb 2006;92(2):177-182.

22. Liu L, Zhang Y, Liu G, et al. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients.[see comment]. *Journal of Hypertension.* Dec 2005;23(12):2157-2172.

23. Lubsen J, Wagener G, Kirwan B-A, de Brouwer S, Poole-Wilson PA, investigators A. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with symptomatic stable angina and hypertension: the ACTION trial.[see comment]. *Journal of Hypertension.* Mar 2005;23(3):641-648.