COLUMBIA UNIVERSITY MEDICAL CENTER

DIVISION OF GENERAL MEDICINE

Senior Medicine Rotation: Evidence-Based Medicine Project

Student Name: Rachel Weiss **Block: August 2011** **Date: August 30, 2011**

Case SIGNOUT:

Patient is a 66 year old woman with past medical history significant for CAD s/p 3v CABG in 2002 and BMS x2 in 2007, CHF with LVEF 35% (2007) by TTE and 51% by MUGA (2008), DM type 2 (HgbA1C 6.6 in 8/2011), severe PAD s/p L femoral bypass and right AKA in 2006, presenting with neuropathic leg pain not relieved with her home dose of Gabapentin. On arrival to the ED, her BP was 193/88 with HR 101, which subsequently improved over the course of the hospitalization. Her outpatient cardiac medication regimen is as follows: Metoprolol Tartrate 100mg BID, Lisinopril 40mg daily, previously HCTZ 25mg daily (recently discontinued), and Amlodipine 5mg daily.

Clinical Question: It has been shown that beta-blockers and ACE Inhibitors reduce mortality in patients with CHF, while diuretics reduce morbidity and overall number of hospitalizations. Many patients with CHF remain hypertensive despite being on appropriate CHF regimens. In the past, evidence has shown that CCBs can lead to worsening HF, and have been associated with increased risk of cardiovascular events. Newer CCBs are vasoselective and do not negatively impact cardiac contractility, unlike earlier CCBs. Does amlodipine, a long-acting dihydropyridine CCB, reduce morbidity or mortality in patients with CHF?

Search Strategy

Database: PubMed
Search terms: "amlodipine morbidity and mortality heart failure" → 8 results
Limits: Clinical Trial or Meta-Analysis, English Language

Chosen Article:

Effect of **amlodipine** on **morbidity and mortality** in severe chronic **heart failure**. Prospective Randomized **Amlodipine** Survival Evaluation Study Group.
Packer M, O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, Miller AB, Neuberg GW, Frid D, Wertheimer JH, Cropp AB, DeMets DL.
N Engl J Med. 1996 Oct 10;335(15):1107-14.

Senior Medicine Rotation: Based Medicine Project (Cont)

Group	Criteria or definition	n
Population screened.	Patients with severe chronic heart failure and EF <30%, from 105 participating institutions	?
Inclusion criteria	New York Heart Association class IIIB or IV (dyspnea at rest or on minimal exertion) AND LVEF <30% despite treatment with digoxin, diuretics and an angiotensin-converting-enzyme inhibitor.	1153
Exclusion criteria	Treatment with nitrites was allowed, but *other vasodilator drugs were not permitted*; uncorrected primary valvular disease, active myocarditis, or constrictive pericarditis; history of cardiac arrest or had had sustained Vtach or fibrillation within the previous year, unstable angina or an acute myocardial infarction within the previous month, or a cardiac revascularization procedure or stroke within the previous three months; severe pulmonary, renal, or hepatic disease; *systolic BP <85mmHg or >159mmHg; diastolic BP >89mmHg*; a serum Cr >3.0mg/dL or a K <3.5 or >5.5mmol/L; *treatment with beta-blockers*, CCBs, or class 1C antiarrhythmic agents; IV diuretics or vasodilators within 24 hours before enrollment or IV positive inotropic agents within 72 hours.	?
Treatment group	5mg Amlodipine PO daily for 2 weeks, up-titrated as tolerated to 10mg PO for the remainder of the study.	571
No treatment group	Placebo 5mg PO daily for 2 weeks, "up-titrated" as tolerated to 10mg PO for the remainder of the study.	582

**If side-effects occurred, the dose of the medication could be reduced or discontinued, but investigators were encouraged to reinstitute treatment at a later time.
**If the patient's condition changed, the physician could use *any clinically indicated interventions*, including adjustments of concomitant treatment with other drugs (*digoxin, diuretics, ACE-Is*; NO vasodilator medications that were not nitrites). Patients could NOT receive open-label amlodipine.
**Trial was continued until 190 events occurred in the placebo group, with subsequent follow-up for 6 months.

Primary endpoint:
Combined all-cause mortality and cardiovascular morbidity - defined as hospitalization for at least 24 hrs with acute pulmonary edema, severe hypoperfusion, acute myocardial infarction, or sustained or hemodynamically destabilizing ventricular tachycardia or fibrillation.

Secondary endpoint:
Mortality from all causes.

- Prospective sub-group analyses, effect of amlodipine on survival:
  - sex, ejection fraction, NYHA class, serum Na concentration, presence/absence of history of angina or a history of hypertension.
  -

Patients were also stratified according to the etiology of their heart failure, ischemic vs. non-ischemic, but this paper will not focus on that arm of the study, given the subsequent results of the PRAISE II trial, which contradict its significant findings.

- **Are the Results of the Trial Valid?** Yes.
    - **Randomized?** Yes.
    - **All patients accounted for at end?** Duration of follow-up ranged from 6 to 33 months, with no patients lost to follow-up. 94 patients from the control arm and 82 patients from the study arm discontinued the medications.
    - **Intention to treat?** Yes.
    - **Blinding?** Yes, double blinded.
    - **Groups similar at start of trial?** Yes. Patients were equivalent with respect to age, heart failure class, average blood pressure, heart rate, cardiothoracic ratio, LVEF (avg 21%), number of patients on digitalis, diuretics and ACE Inhibitors, and doses of those medications.
    - **Equal treatment of groups?** Maybe. One month after randomization, patients were receiving an average daily dose of 8.8 +/- 0.6 mg of amlodipine or 8.9 +/- 0.6 mg of placebo. Compliance, assessed by pill counts at visits, averaged over 90%. However, whether or not patients had the same degree of follow-up between the two groups, or what that follow-up was, is not addressed in the study. Also, "cointerventions" allowed by study clinicians were not standardized, with exception of their inability to use open-label amlodipine; given that there are multiple proven effective medications for the treatment of heart failure and of hypertension, discrepant use of these medications between the two groups could have led to biased results. This was not addressed in the study.
    - **Did randomization work?** Yes. There was no significant difference between group characteristics at the start of the trial.
- **Are the Results of the Trial important?** Yes. The authors set out with the hypothesis that amlodipine would reduce the occurrence of both mortality and morbidity in patients with severe heart failure (HF), and although the risk reduction for all-cause mortality and morbidity was 9% in the amlodipine group, and for all-cause mortality was 16% in the amlodipine group, their results were not significant. However, they were able to demonstrate 1) that using amlodipine to treat patients with HF is safe, contradicting the results of many earlier trials, and 2) that worsening angina and hypertension were reported less frequently in patients with HF taking amlodipine as compared to placebo. This suggests a role for amlodipine in the treatment of patients with concomitant HF and hypertension or HF and angina.
    - Size of treatment effect? There was not a significant difference in morbidity or mortality in patients with HF treated with amlodipine vs. placebo, although there was significant data reported from sub-group analyses.
    - Precision of the estimate of the effect? Large trial size, but with CI for primary and secondary endpoints crossing zero.

Endpoint	**Result**	**Significance**	**ARR**	**NNT**
Primary fatal or nonfatal event (death or CV morbidity)	222/571 (39%) Amlodipine 246/582 (42%) Placebo	RR = 0.09 P = 0.31 95% CI: (-0.10-0.24)	3%	33
Death from all causes	190/571 (33%) Amlodipine 223/582 (38%) Placebo	RR = 0.16 P = 0.07 95% CI: (-0.02-0.31)	5%	20
Morbidity	**Result**	**Significance**	**ARI**	**NNH**
Peripheral Edema	Placebo 103/582 (18%) Amlodipine 155/571 (27%)	P < 0.001		
Pulmonary Edema	Placebo 58/582 (10%) Amlodipine 85/571 (15%)	P = 0.01		
Frequency of MI	No significant difference observed (P and A: 3%)			
Frequency of worsening HF	No significant difference observed (P 41%, A 42%)			
Hypotension	No significant difference observed (P 10%, A 12%)			

Uncontrolled HTN	Placebo 9/582 (2%) Amlodipine 2/571 (<1%)	P = 0.03		
Reduction in Systolic and Diastolic BP	Amlodipine > Placebo by 2mmHg	P < 0.01		
Symptomatic cardiac ischemia (angina and chest pain)	Placebo 148/582 (25%) Amlodipine 127/571 (22%)			
Subgroup: patients with ischemic HD - Risk of angina or chest pain	Placebo 31% Amlodipine 25%	P = 0.07		
Liver and Biliary Disorders	Placebo 27/582 (5%) Amlodipine 11/571 (2%)	P = 0.01		
Worsening Renal Function	Placebo 3.6% Amlodipine 7.7%	P = 0.002		

- **Can I apply these results to my patient?**
  - Comparison of my patient to trial patients.
    - Based on the inclusion and exclusion criteria detailed for the study, my patient, a 66 year old woman with ischemic heart disease and CHF with *most recent LVEF estimated at 51%, taking a beta-blocker* and with SBP averaging 146 over the course of the admission, would not be a candidate for this study. There are several other medication options, besides amlodipine, available for patients with HTN and anginal symptoms in the setting of heart failure, including hydralazine, potassium-sparing diuretics, and long-acting nitrates, which would all be alternative options in this patient. Amlodipine might still be a good choice, however, as long as the patient is not already affected by symptoms of pulmonary or pedal edema.
  - All clinically important outcomes considered. Yes, apparently.
    - The authors' primary outcome examined the impact of amlodipine on common, devastating and potentially avoidable complications in patients with heart failure: cardiovascular mortality and morbidity. Their secondary endpoint broadened this to death from all-causes, which is important in a medication that has the potential to affect many organ systems. The authors also looked comprehensively at a broad range of relevant adverse reactions across cardiovascular and non-cardiovascular systems.
    - It is strange that while amlodipine did not significantly affect the occurrence of "worsening heart failure" in this study, it did lead to significantly more pulmonary and pedal edema, which are clinical indicators of heart failure. In addition, the study shows only an average 2mmHg reduction in systolic and diastolic BP, but a significant reduction in the occurrence of uncontrolled hypertension. This can be attributed, perhaps, to the study clinicians' ability to use other BP reducing agents, potentially obscuring the BP effect that was due to amlodipine.
    - It would have been interesting if the authors had stratified patients based on the type of their underlying cardiac dysfunction, primarily systolic or diastolic heart failure, and had then examined if there was a different effect of amlodipine vs. placebo in these populations.
  - Likely benefits outweigh potential harms and cost? Yes. Amlodipine did reduce both combined all-cause mortality and cardiovascular morbidity, as well as all-cause mortality alone in patients with severe heart failure, although the observed trend was not significant. In addition, Amlodipine was not associated with the poor cardiovascular outcomes that had been attributed to CCBs in the past: worsening symptoms of HF, increased frequency of MI and hypotension. As a relatively inexpensive drug (the brand name, Norvasc, is around $40-60 for 30 10mg tabs, with less expensive generics available) that has proven efficacy in managing hypertension, the long-term potential benefits of amlodipine in reducing the incidence of uncontrolled hypertension and symptomatic cardiac ischemia may in fact outweigh the risks/morbidity of peripheral and

pulmonary edema in patients with ischemic heart failure. Amlodipine should be considered as an alternative to hydralazine and long-acting nitrates in patients with heart failure.

- **Weaknesses and limitations**:
  - The study did not address or standardize follow-up received by patients in the trial.
  - There was limited restriction of the alternative agents study physicians were able to use concomitant with amlodipine. The agents used were not documented or compared between the two arms, with exception of ensuring adequate randomization at the beginning.
  - While finding patients with LVEF <30% and BPs within the indicated range for the study would not be difficult in modern patient populations, finding a patient with diagnosed CHF and documented LVEF low enough for participation in this study and who is not on a beta-blocker would be very hard, as beta-blockade is considered a standard of care in CHF patients and has been proven to reduce mortality in those populations.
  - The study was supported by a grant from Pfizer Central Research, the company that produces the brand name amlodipine, Norvasc, leading to potential conflict of interest.

References:

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