



Senior Medicine Rotation: Evidence-Based Medicine Project

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Case SIGNOUT:

SB is a 71-year-old man with a history of nonischemic cardiomyopathy with an ejection fraction of 20% with an AICD placed in 2012 who presented to CUMC after an episode of substernal chest pain associated with shortness of breath following a physical altercation with his neighbors. His EKG was v-paced and three troponins were negative, thus ruling out acute coronary syndrome. A recent catheterization showed no angiographic evidence of coronary disease. The patient's symptoms were thought to be a result of increased myocardial demand in a high stress situation in the setting of chronic congestive heart failure. He was discharged on his home medication regimen of aspirin, losartan, and carvedilol (no spironolactone due to previous intolerance).

Clinical Question: Are statins beneficial in patients with nonischemic cardiomyopathy?

Background:

- Statins (HMG CoA reductase inhibitors) have been shown to reduce morbidity and mortality in patients with coronary artery disease
- Many statin trials in CAD patients have excluded those with known CHF → lack of safety and efficacy data on use with ischemic and nonischemic cardiomyopathy patients
- In addition to lowering serum cholesterol and LDL levels, statins have other beneficial effects including plaque stabilization
- Statins also improve endothelial function, facilitate NO synthesis (vasodilator), inhibit synthesis of inflammatory cytokines and chemokines, reverse myocardial remodeling
- Heart failure patients often have elevated levels of pro-inflammatory cytokines, which are involved in adverse LV remodeling and associated with increased morbidity and mortality
 - TNF alpha RII plays role in development of LV dysfunction, adverse remodeling, endothelial dysfunction, cardiac myocyte apoptosis, development of anorexia/cachexia
 - IL-6 involved in myocyte hypertrophy, myocardial dysfunction, muscle wasting
 - IL-6 and hsCRP associated with poorer prognosis on CHF patients
 - E-SOD (erythrocyte superoxide dismutase) catalyses reaction destruction of O₂ free radicals
- Hypothesis: statin therapy could potentially improve LV function and decrease inflammation (and potentially attenuate adverse LV remodeling) in patients with nonischemic cardiomyopathy
- Currently 20-30% of patients with nonischemic cardiomyopathy are on a statin compared with 50-55% with ischemic cardiomyopathy and 80-85% of patients with CAD

Search Strategy

Database: Pubmed. Search query: "nonischemic cardiomyopathy AND statins". 20 results.

Article chosen: Sola S, Mir M, Lerakis S, Tandon N, Khan B. Atorvastatin improves left ventricular systolic function and serum markers of inflammation in nonischemic heart failure. J Am Coll Cardiol 2006;47(2):332-7.



COLUMBIA UNIVERSITY MEDICAL CENTER
DIVISION OF GENERAL MEDICINE

Senior Medicine Rotation: Based Medicine Project (Cont)

Group	Criteria or definition	N
Population screened.	Men and women > age 18 with NYHA functional class II – IV heart failure due to a nonischemic etiology	?
Inclusion criteria	1) LVEF < 35% as documented by echo or ventriculography during 1 year prior to enrollment, 2) stable doses of heart failure medications for three months prior to enrollment, 3) nonischemic cardiomyopathy defined as no history of MI and no coronary artery stenoses > 50% on catheterization during 1 year prior to enrollment	108
Exclusion criteria	1) receiving statin during six months before enrollment, 2) prior adverse event related to statin use, 3) diabetes mellitus	?
Treatment group	Atorvastatin 20 mg/day for 12 months	54
No treatment group	Placebo	54

Primary endpoint: change in left ventricular ejection fraction

Secondary endpoint: change in markers of inflammation and oxidation (hsCRP, IL-6, TNF-alpha RII, E-SOD)

- Are the Results of the Trial Valid?
 - Randomized? Yes
 - All patients accounted for at end?
 - 89 patients (out of 108) completed the study; 19 dropped out (11 from placebo group, 8 from statin group) by their own choice or decision of their physician
 - Intention to treat? Yes
 - Blinding? Double-blinded
 - Groups similar at start of trial?
 - Yes, no significant difference between groups with regard to: age, gender, BMI, BP, NYHA functional class, LVEF, LDL, HDL, triglyceride levels, or baseline medication regimen
 - Equal treatment of groups?
 - Yes, patents had study visits at 0, 6, 12 months, TTE and lab work at each visit
 - Did randomization work? Yes
- Are the Results of the Trial important?
 - Number of subjects was small; study was not powered to evaluate effect of atorvastatin on clinical outcomes. However, this study is suggestive that use of a statin in this patient population might provide a benefit. A large-scale randomized trial is necessary to provide more robust evidence.

Endpoint	Result	Significance
LVEF	Increase in LVEF in treatment group from 0.33 +/- 0.05 to 0.37 +/- 0.05	p = 0.01
	Decrease in LVEF in placebo group from 0.33 +/- 0.04 to 0.31 +/- 0.03	p = 0.04
	At 12 months, treatment group had significantly higher LVEF (0.37 +/- 0.05) than placebo group (0.31 +/- 0.03)	ANOVA p = 0.004

Serum levels of inflammatory and anti-oxidation markers	At 12 months, treatment group had significantly lower serum levels of IL-6 than placebo group (13.3 +/- 0.8 ng/dl vs. 17.3 +/- 1.4 ng/dl)	p = 0.001
	At 12 months, treatment group had significantly lower serum levels of hsCRP than placebo group (1.7 +/- 0.2 mg/dl vs. 1.9 +/- 0.3 mg/dl)	p = 0.002
	At 12 months, treatment group had significantly lower serum levels of TNF-alpha RII than placebo group (24.3 +/- 2.3 ng/dl vs. 34.5 +/- 3.0 ng/dl)	p = 0.001
	At 12 months, treatment group had significantly increased serum levels of E-SOD than placebo group (649 +/- 43 U/g Hb vs. 577 +/- 38 U/g Hb), after starting out with significantly lower levels at baseline (550 +/- 58 U/g Hb vs. 580 +/- 60 U/g Hb)	p < 0.0001 p = 0.009
Morbidity	Result	Significance
NYHA functional class	At 12 months, mean NYHA functional class was less advanced in treatment group (2.2 +/- 0.3) compared to placebo group (2.9 +/- 0.3)	p = 0.001
Hospitalizations	At 12 months, no significant differences in number of hospitalizations between treatment group (n=8) and placebo group (n=13)	NS
Mortality	At 12 months, no difference in total mortality between treatment group (n=4) and placebo group (n=4)	NS

- Can I apply these results to my patient?
 - Comparison of my patient to trial patients.
 - My patient meets the definition of nonischemic cardiomyopathy (no history of clinical MI, cath with angiographically clean coronaries), had a documented EF of less than 35% and has been on a stable heart failure medication regimen. He has not been on a statin and thus has not had an adverse reaction to a statin. He is not a diabetic. He is similar to the patients in this trial.
 - All clinically important outcomes considered.
 - Left ventricular ejection fraction, changes in various inflammatory markers (possible mechanisms) and left ventricular remodeling were considered. However, the study was not powered to look at outcomes including mortality and clinical outcomes like hospitalizations and heart failure exacerbations. This suggests that statins would be beneficial in these patients; however a large-scale randomized trial is needed to further elucidate the extent of the benefit.
 - Likely benefits outweigh potential harms and cost?
 - Yes, the potential benefit of LVEF improvement and reduction in LV remodeling along with little potential harm (low financial cost, few adverse reactions to statins) suggests that this would be a low risk addition to my patient's medication regimen.

Other Trials

Node et al: RCT of 51 patients with NYHA class II or III NICM, randomized to simvastatin vs. placebo for 14 weeks → improvement in EF from 0.34 (+/- 0.03) to 0.41 (+/- 0.04) in treatment group, no change in placebo group. In treatment group, 39% experienced improvement in functional class, 4.3% experienced decline in functional class. In placebo group, 16% experienced improvement and 12% had decline in functional class. Also showed decrease in serum levels of IL-6, TNF-alpha, BNP in treatment group.

SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) sub-analysis: 2521 people (1211 with NICM) followed for 45.5 months. In this study, statin use decreased mortality by 33% (HR 0.67, 95% CI: 0.47-0.96, $p < 0.05$) in NICM patients— compared those taking statins to those not taking statins, after controlling for baseline differences (age, weight, race, EF, HR, Na, functional class, etc). Mortality benefit was NOT greater in patients with ischemic cardiomyopathy than NICM.

BEST (Beta blocker Evaluation of Survival) sub-analysis: 1024 people with NICM (NYHA class III/IV, EF < 35%), 74 received statin therapy and were followed for 2 years. Statin use was independently associated with significantly decreased all-cause mortality (HR 0.38; 95% CI, 0.18-0.82, $p = 0.0134$) and decreased cardiovascular death (HR 0.42, 95% CI 0.18-0.95, $p = 0.037$), after adjusting for age, gender, BP, cholesterol, medication regimen, etc.

DEFINITE (DEFibrillators in Non-Ischemic cardiomyopathy Treatment Evaluation) sub-analysis: 458 patients with NICM, EF < 35%, NSVT or 10 PVCs/hr on Holter. In this study, 78% reduction in mortality in patients on statin (HR 0.22, 95% CI: 0.09-0.55, $P=0.001$), larger than benefit attributed to ICD in this trial → in part due to reduction in arrhythmic sudden death as well as other mechanisms.

References

Dickinson MG, Ip JH, Olshansky B, et al. Statin use was associated with reduced mortality in both ischemic and nonischemic cardiomyopathy and in patients with implantable defibrillators: mortality data and mechanistic insights from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Am Heart J*. 2007 Apr;153(4):573-8.

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Frampton S. Statin use in nonischemic cardiomyopathy: review of the literature. *Prog Cardiovasc Nurs*. 2008 Spring;23(2):89-90.

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