Kjekshus J et al. Rosuvastatin in Older Patients with Systolic Heart Failure (CORONA). NEJM 2007;357:2248-61.

Clinical question posed by this trial: Is rosuvastatin safe and efficacious in patients with systolic heart failure of remote ischemic origin?

Context:

- Patients with heart failure (HF) have been systematically excluded from statin trials.
- Even in patients with HF due to ischemic heart disease, rates of myocardial infarction (MI) are low compared to other competing causes of death (e.g. pump failure or arrhythmic death)
- Statins also reduce synthesis of coenzyme Q10, which may lead to skeletal/cardiac myopathy → statins may be harmful in HF patients
- However, autopsy studies also suggest unrecognized ACS that leads to death are more common than originally thought – questioning if statins may play a role in HF

Methodology

Study design	RCT; follow-up 32.8months
Sequence generation	Randomization was based on optimal assignment procedure (minimization method) with a random element included. Optimally balanced allocation was achieved with score that included: • Age, ejection fraction, NYHA class, presence/absence of DM/MI/hypertension, use of beta-blockers, total cholesterol level
Allocation concealment	Adequate (Central randomization by phone)
Blinding	• All investigators blinded, except those on data and safety monitoring board • Matching placebo used
Loss to follow-up	Not reported
Population analyzed	Modified intention-to-treat (included all who received one bottle of study drug)
Intervention	• Rosuvastatin 10mg
Co-intervention	• 60 patients from rosuvastatin group and 120 patients in placebo group also received open-label statin
Outcomes	• All cause mortality • **Composite cardiovascular death, nonfatal MI, nonfatal stroke** (time to first event; primary outcome) • Nonfatal MI • Nonfatal stroke • Any coronary event • Hospitalization (all-cause, cardiovascular) • Adverse effects
Statistical power calculation	• N = 4950 to find 22% RRR assuming hazard rate of 10.4% in placebo group; alpha = 0.05, power = 90%
Funding	AstraZeneca

Participants

Setting	371 sites (Europe, Russia, South America)
Inclusion criteria	• >60 years old • NYHA II-IV from ischemic causes • EF ≤ 40% (≤ 35% if class II) • No other indication for cholesterol-lowering drug • Stable optimum treatment for at least 2 weeks prior to randomization
Relevant exclusion criteria	• **MI within past 6 months** • **Unstable angina or stroke within past 3 months** • **Percutaneous Coronary Intervention (PCI), Coronary-Artery Bypass Graft (CABG), or implantation of cardioverter-defibrillator or biventricular pacemaker within past 3 months, or planning of a device** • Decompensated HF • Previous statin-induced myopathy or hypersensitivity • Need for inotropic therapy • Previous/planned heart transplantation • Clinically significant, uncorrected primary valvular heart disease, or malfunctioning prosthetic valve • Hypertrophic cardiomyopathy • Acute endomyocarditis/myocarditis • Pericardial disease • Systemic disease • Acute/chronic liver disease • SCr >221umol/L • Chronic muscle disease or unexplained CK level more than 2.5x ULN • Previous tx with cyclosporine • Receipt of less than 80% of dispensed placebo tablets during run-in period
Study size	• 5459 assessed for eligibility & entered placebo period ○ 5011 eligible & randomized
"Average" patient	• Age 73 • Female: 24% • EF: 31% • NYHA class ○ II: 37%, III: 62%, IV: ~1.5% • Comorbidities ○ Smoker: 9% ○ MI: 60% ○ Angina pectoris: 72% ○ CABG/PCI: 26% ○ Hypertension: 63% ○ DM: 30% ○ Stroke: 13%
Medications Used	• ACEI/ARB: 92% • BB: 75% • Aldosterone antagonist: 39% • Loop diuretic/thiazide: 89% • Digitalis: ~33%

Results					
	Placebo	Rosuvastatin 10mg	RR	ARR	p-value
All cause mortality	12.2%	11.6	0.95 (0.86-1.05)	0.6%	NSS
Serious adverse events (% patients)	67.0%	64.7%	---	---	---
Primary outcome (first event of CV death, nonfatal MI, nonfatal stroke)	12.3%	11.4%	0.92 (0.83-1.02)	0.9%	NSS
Nonfatal MI	2.4%	1.9%	---	---	---
Nonfatal stroke	1.7%	1.5%	---	---	---
Any coronary event	10.0%	9.3%	0.92 (0.82-1.04)	0.7%	NSS
Any cause hospitalization	38.0%	35.6%	HR 0.94 (0.88-1.01)	2.4%	0.09
CV hospitalization	25.0%	22.9%	0.92 (0.85-0.99)	2.1%	0.04
• Adverse effects: More patients in placebo discontinued study drug, more due to 'adverse event'					
• Muscle pain: more incidence in rosuvastatin group					

Major Limitations:

Methods

- Although subjects were randomized to placebo or rosuvastatin, a portion of patients from each group (more in placebo group) received non-study statin therapy
  - This could bring the results closer to null
- Rosuvastatin dose could have been low to show effect
  - Equivalent to atorvastatin 20mg
  - Or possible that rosuvastatin doesn't share a beneficial class effect with other statins?

Results

- **"Negative" trial for major endpoints…but significantly different for hospitalizations**
  - Major endpoints were NSS, but there was a "trend" towards lower rates in rosuvastatin arm
    - (ie. Primary outcome NNT = 112)
    - Components of the primary endpoint: nonfatal MI less in rosuvastatin vs placebo (115 vs 141), nonfatal stroke less in rosuva vs placebo (89 vs 104)
  - SS differences in any cause hospitalization, cardiovascular causes, and worsening heart failure causes
    - But: how were the hospitalizations significantly different when there were no differences in nonfatal MI, any coronary event, and other endpoints?
    - Hospitalizations is not a 'hard outcome' – less objective
- **Placebo more adverse events than rosuvastatin?**
  - Nocebo effect? Or was it rosuvastatin 'protective' for some ADRs (ie. Cardiac)?

Generalizability

- Possibly able to be generalizable to our population in North America
- However, in North America, for patients who have previously had an MI (and thus caused HF due to ischemia), they likely would already be on a statin

Conclusions:

- Rosuvastatin 10mg does not seem to reduce cardiovascular death/nonfatal MI/nonfatal stroke in elderly patients with ischemic, systolic heart failure managed with other HF medications

Discussion: On another note, this may support not starting a statin in a simple HF patient if they presented to you without one to begin with. Food for thought!