Intensive Statin Therapy in Elderly Patients

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Outline

- Case / Clinical Scenario
- Role of Statin Therapy
  - Guidelines – General & in Patients with ACS
- Intensive Dose Statin Therapy
  - Efficacy
  - Safety
- Clinical Scenario – Wrap-Up
- Summary

Clinical Scenario

Case:

- Mr B, 79 y.o. male c/o chest pain x 8 hrs
- In ER, troponin elevated & ECG showed ST elevation in inferior leads: Dx ACS/STEMI
- STEMI order set initiated, TNK given
- Symptoms resolved & ECG normalized
- Transferred to CCU

- PMH:
  - Denied hx of CAD, HTN, chol, DM, FHx of CAD; ex-smoker (quit 20+yrs ago)
  - 5'11, 105kg; BMI 32.4 kg/m^2
  - Past GI bleed on high dose ASA (++ yrs ago)
- No home medications

- CCU Initial Management:
  - Antiplatelet combo: ECASA, clopidogrel & enoxaparin
  - Nitroglycerin drip
  - Metoprolol 12.5 mg bid
  - Perindopril 2 mg od
  - Atorvastatin 80 mg od
- Referred to NBHC for cardiac cath, angiography +/- PCI

Clinical Scenario (cont.)

- Should Mr.B have received intensive statin therapy post-MI?
- If so, what is the recommended duration of intensive statin therapy?

Clinical Question: In patients age 70 or more, what are the benefits and risks of intensive- versus lower-dose statin therapy?

Role of Statin Therapy

- HMG-CoA reductase inhibitors (a.k.a. statins) are among the most important medical therapies introduced into clinical practice in the past 2 decades
  - Widely viewed as very safe & effective
- Statins reduce morbidity & mortality related to atherosclerotic disease
  - Ability to alter lipid profiles (mainly LDL)
  - Less well understood anti-inflammatory properties
- Balance of benefit vs risk in the elderly
  - Is it less favorable compared to younger patients?

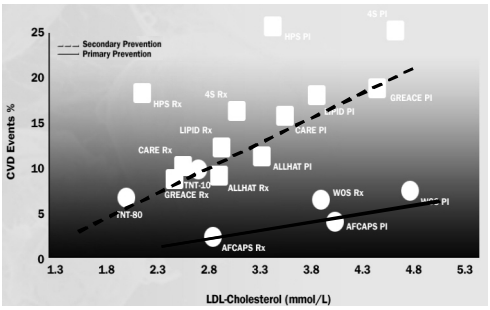
Lipid Management Pharmacotherapy

Therapy	TC	LDL	HDL	TG	Patient tolerability
Statins*	↓ 19-37%	↓ 25-50%	↑ 4-12%	↓ 14-29%	Good
Ezetimibe	↓ 13%	↓ 18%	↑ 1%	↓ 9%	Good
Bile acid sequestrants	↓ 7-10%	↓ 10-18%	↑ 3%	Neutral or ↑	Poor
Nicotinic acid	↓ 10-20%	↓ 10-20%	↑ 14-35%	↓ 30-70%	Reasonable to Poor
Fibrates	↓ 19%	↓ 4-21%	↑ 11-13%	↓ 30%	Good

HDL-C=High-density lipoprotein cholesterol, LDL-C=Low-density lipoprotein cholesterol, TC=Total cholesterol, TG=Triglycerides

*Daily dose of 40mg of each drug, excluding rosuvastatin.

LDL-C lowering and the associated reduction of CV outcomes



Fitchett DH, Leiter LA, et al. Can J Cardiol 2005;21:85-90

2006 Recommendations for the Diagnosis and Treatment of Dyslipidemia and Prevention of Cardiovascular Disease

Risk Categories and Treatment Recommendations

Risk level	10-year CAD risk	Recommendations	
High*	≥ 20%	Treatment targets†: Primary: LDL-C < 2.0 mmol/L Secondary: TC: HDL-C < 4.0	High risk patients should lower LDL-C by at least 50%
Moderate‡§	10%-19%	*Treat when:* LDL-C ≥ 3.5 mmol/L or TC:HDL-C ≥ 5.0	Low-Moderate risk, patients should lower LDL-C by at least 40%
Low‡§	<10%	*Treat when:* LDL-C ≥ 5.0 mmol/L or TC:HDL-C ≥ 6.0	

* High risk includes coronary artery disease (CAD), peripheral artery disease, cerebrovascular disease (CVD) and most patients with diabetes. Individuals younger than 40 years with recent-onset diabetes, a normal lipid profile and no require immediate lipid-lowering therapy. In patients with established atherosclerosis, treatment to lower low-density lipoprotein cholesterol (LDL-C) by at least 50% is generally appropriate.

† Apolipoprotein B may be used to determine CAD risk, especially in hypertriglyceridemic patients, and monitor adequacy of treatment. Optimal levels of apolipoprotein B are less than 0.65 g/L in high-risk patients; less than 1.05 g/L in intermediate-risk patients; and less than 1.2 g/L in low-risk patients.

‡ Treatment may be initiated at lower or higher levels if family history or other investigations indicate elevated or reduced risk. Patients with severe genetic lipoprotein disorders such as familial hypercholesterolemia or type 3 lipid patients should be treated because of their high risk of premature CAD.

§ Patients in low- or moderate-risk categories may be at high long-term cardiovascular risk. This group includes many patients with abdominal obesity (the metabolic syndrome). The reduction in CAD and stroke events, and overall cost-effectiveness of therapy is proportional to the decrease in LDL-C. Thus, for those low- or moderate-risk subjects who are candidates for statin therapy, treatment to lower LDL-C by at least 40% is generally appropriate.

HDL-C=High-density lipoprotein cholesterol; TC=Total cholesterol

McPherson R, Frohlich J, Fodor G, Genest J. Canadian Cardiovascular Society position statement – Recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. Can J Cardiol 2006;22(11):913-927.

Acute Coronary Care in the Elderly: Role of Statin Therapy

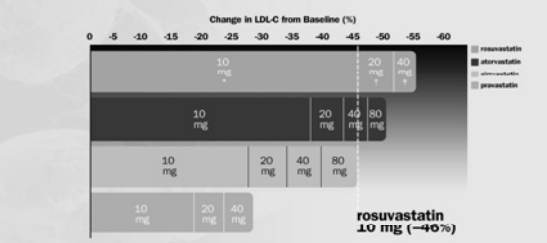
- Current American treatment guidelines & a recent AHA scientific statement recommend target LDL <100 mg/dL (2.6 mmol/L) in post-ACS patients <u>without regard to age</u>
  - Some secondary prevention trials excluded patients over 75 years but still demonstrated benefit of statins in younger elderly
- Summary: "Statins have greater benefit in the elderly for prevention of subsequent MI and death than in younger subgroups."

Alexander et al. Acute Coronary Care in the Elderly, Part II. Circulation 2007; 115: 2570-2589
DeBacker et al. NCEP ATPIII Guidelines. Circulation 2004; 110: 227-39

Intensive Dose Statin Therapy: Efficacy

- Definition of high or "intensive" dose statin therapy
- MIRACL trial (2001)
  - Atorva 80 mg vs placebo in patients with mean age 65 years
  - 16% decrease in combined endpoint (death, nonfatal MI, readmit for ischemia or resuscitated cardiac arrest) at 16 wks post-NSTEMI
- Clinical trials of intensive- vs standard-dose statins (2004-2007)
  - Significant results: PROVE IT-TIMI 22, TNT
  - Non-significant trends toward benefit: A-to-Z, IDEAL
  - Subgroup analyses provide some insight into potential benefits in elderly patients post-ACS or with chronic CAD (limited enrollment in many of these studies)

Statins & LDL-C Efficacy across Dose Range: What is "Intensive" Statin Therapy?



*p<0.002 vs atorvastatin 10 mg; simvastatin 10, 20, 40 mg; pravastatin 10, 20, 40 mg
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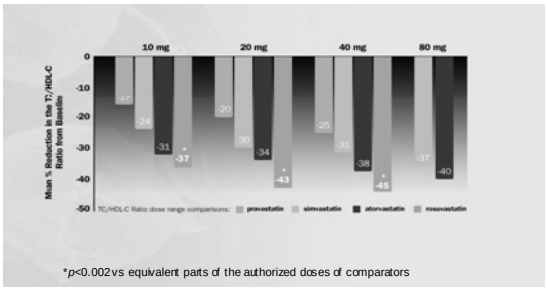
Adapted from Jones PH et al. STELLAR Study. Am J Cardiol 2003;92:152–160

Statins: TC/HDL-C Ratio Efficacy Across the Dose Range



*p<0.002 vs equivalent parts of the authorized doses of comparators

Jones PH, et al. for the Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) Study Group.Clinical Therapeutics 2004;26(9):1388-1399.

Proven Benefits of Statins in RCTs

- Prospective meta-analysis from 90,056 patients in 14 randomized trials of statins demonstrated:
  - Decreasing LDL-C with a statin by 1 mmol/L in patients with and without established cardiovascular disease, decreased the following:
    - All cause mortality – 12%
    - CHD – 19%
    - Major vascular event – 21%
    - Non-fatal MI – 26%
    - CHD death – 19%
    - Need for revascularization – 24%
    - Stroke – 17%

Cholesterol Treatment Trialist Collaboration: Lancet 2005;366:1267-78

Efficacy & Safety of Intensive Statin Therapy: A Meta-Analysis of RCTs

- Purpose: To compare more vs less intensive statin use in CAD reporting CV events or mortality
- Method: Searched electronic databases (Medline, Embase, Cochrane registry, Web of Science) for RCTs published up to July 19, 2007, for trials comparing statin regimens of different intensities in adults with CAD reporting CV events or mortality.

Josan et al. Can Med Assoc J 2008; 178: 576-584.

Efficacy & Safety of Intensive Statin Therapy: A Meta-Analysis of RCTs (cont…)

- Subjects:
  - 29,395 patients in 7 trials: 2 post-ACS, 5 chronic CAD
  - Mean age 56-62 yrs (mean 72 yrs, more females & diabetics in 1 small study)
  - Males predominant (75-80%) in most groups
  - Baseline mean LDL 2.74 to 3.9 mmol/L
  - Rx varied but atorva 80mg vs prava 40mg in several of these trials
  - Follow-up duration varied: 1 to 4.9 yrs

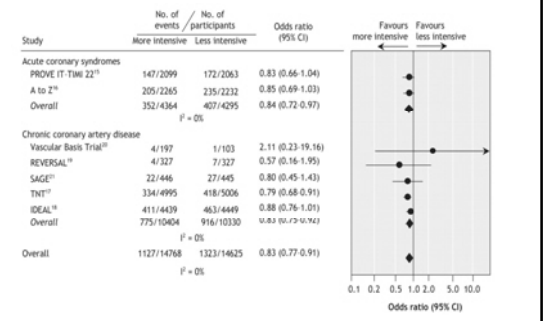
Efficacy & Safety of Intensive Statin Therapy: A Meta-Analysis of RCTs (cont…)

Results:

- Outcomes favoring more intensive statin therapy:
  - Lower LDL 0.39-1.0 mmol/L
    - Mean diff 0.72, 95% CI 0.60-0.84
  - MI or coronary death: OR 0.83, 95% CI 0.77-0.91 (NNT 70)
  - Stroke: OR 0.82, 95% CI 0.71-0.95 (NNT 250)
  - Major coronary events (MI/stroke/coronary death), OR 0.80, 95% CI 0.71-0.90 (NNT=33)
- No difference in all-cause mortality
  - OR 0.87, 95% CI 0.74-1.03

Josan et al. Can Med Assoc J 2008; 178: 576-584.

Risk of MI or coronary death among patients with ACS or chronic CAD in 7 studies of statin therapy intensity



Josan, K. et al. CMAJ 2008;178:576-584

CMAJ·JAMC

Efficacy & Safety of Intensive Statin Therapy: A Meta-Analysis of RCTs (cont…)

- Results (cont):
  - Safety aspects favored less intensive groups:
    - Discontinuation rate: 7.8 vs 5.3% NS
    - LFTs >3x ULN: 1.5 vs 0.4%, OR 4.14, 95%CI 2.30-7.44
  - Myopathic events: inconsistently reported
    - Not significantly more frequent in more intensive statin group

Clinical Implications

- Fixed doses used
  - Cannot use level of LDL lowering to define optimal target LDL
  - Less than 50% of all patients in intensive tx group achieved LDL <2.0 mmol/L
- Trials support intensive statin monotherapy
  - Combo tx targeting lower LDL needs further research
- Cost-effectiveness proven in ACS patients
  - But less certain in chronic CAD (sensitive to rx cost & long-term adherence).

Josan et al. CMAJ 2008; Chan et al. Circulation 2007

Clinical Implications (cont.)

- Age is a number
  - How to define "elderly" - chronological vs physiologic age
- What if your patient is other than a white male?
  - Most statin trials enrolled mainly white males (~75%)
  - Efficacy confirmed in women (similar to that found in men)
  - Patients from other races & those of advanced age remain underrepresented in trials
- Individual patient factors
  - Ability to pay/insurance, adherence, fear of side effects, etc.

Josan et al. CMAJ 2008; CTT Collaborators. Lancet 2005

Clinical Implications (cont.)

- Safety (cont.)
  - Well tolerated & relatively safe in clinical trials
  - Likely that adverse effects will be more common with intensive statin therapy in clinical practice
  - "Real world" patients may be at increased risk of adverse effects:
    - Advanced age, more co-morbidities (renal/liver dysfunction, alcohol abuse) or other medications (CYP450 inhibitors, other LLDs)

Intensive Dose Statin Therapy: Safety

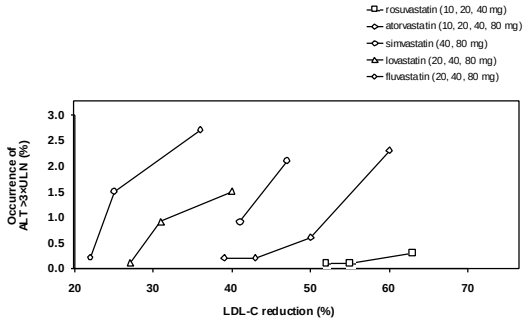
- What are common and/or major safety issues related to statin therapy in the elderly?
- Is there a relationship between dose and increasing incidence of statin adverse events (AEs)?

AEs Associated with Statin Therapy

- Serious AEs among statins are very low, <1%
  - Doug's "rule of 10" for statin safety/AEs
- Myalgia:
  - Patient-reported symptom in ~1 in 10 patients (~10%)
  - Most cases are not associated with CK rise
- Elevated ALT or AST >3x ULN
  - ~1 in 100 patients (avg 1%, range 0.2-2.3%)

Ballantyne et al. Arch Intern Med 2003; 163: 553-564

Benefit Versus Risk for Various Statins: LDL-C Reduction Versus Effect on ALT



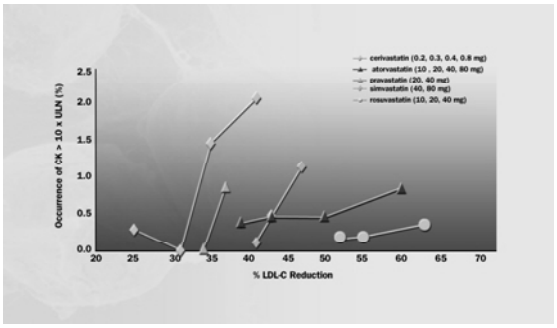
Brewer HB Jr. *Am J Cardiol* 2003;92(suppl):23K-29K

AEs Associated with Statin Therapy (cont)

- Myopathy:
  - Occurs in 1 in 1000 (0.1%) of all patients taking statins
  - "CK >10x ULN with symptoms of myalgia, fatigue or weakness"
  - CK 5-10x ULN require investigation
  - No symptoms & CK <5x ULN often considered benign

Ballantyne et al. Arch Intern Med 2003; 163: 553-564

Benefit Versus Risk for Various Statins: LDL-C Reduction Versus CK Elevation



Brewer HB Jr. *Am J Cardiol* 2003;92(suppl):23K-29K

AEs Associated with Statin Therapy (cont)

- Rhabdomyolysis:
  - Very rare: 1 in 10,000-1,000,000 patients receiving statins
    - Higher risk when combined with fibrates or niacin
    - Fatal cases are far fewer at 0.03 per 100,000 patient-years
  - "CK >10,000 U/L (100x ULN) with myoglobinuria, myoglobinemia and target-organ damage"
  - Progression from myopathy to rhabdo can almost always be reversed by early diagnosis & treatment
  - Incidence of myopathy & rhabdo difficult to determine due to variety of definitions used in studies & reports
    - But… remember cerivastatin (Baycol)?

Ballantyne et al. Arch Intern Med 2003; 163: 553-564

Factors that Increase the Risk of Statin-Induced Myopathy

Patient Characteristics	Statin Properties
Increasing age	High systemic exposure
Female sex	Lipophilicity
Renal insufficiency	High bioavailability
Hepatic dysfunction	Limited protein binding
Hypothyroidism	Potential for drug-drug interactions metabolized by CYP pathways (particularly CYP3A4)
Diet (grapefruit juice)	
Polypharmacy	

Rosenson RS, Current Overview of Statin-Induced Myopathy. *AM J Med*. 2004;116:408-416.

Statins and Drug/Food Interactions

- Caution when combining statins with:
  - Fibrates
  - Niacin (rare)
  - Verapamil, diltiazem
  - Amiodarone
  - Nefazodone, venlafaxine
  - Some SSRIs
  - Macrolide antibiotics
  - Azole antifungals
  - Cydosporine A
  - Protease inhibitors
  - Grapefruit juice (>1L/day)
- Most of these drugs are inhibitors of CYP3A4
- Atorva, simva & lova are 3A4 substrates
- Other CYP isoenzymes are likely less significant contributors to drug-drug interactions

Pasternak et al. JACC 2002; 40: 567-571

AEs Associated with Statin Therapy (cont)

- In the elderly, statins may cause adverse muscle effects presenting as shortness of breath (in setting of negative cardiopulmonary workup)
  - Have greater negative impact due to declined muscle strength & function -> affecting ADLs & independence
- Potential for deleterious effects on memory & cognition (in case reports/case series)
- Other: GI, psych, rash/skin & sleep problems

Golomb BA. Geriatric Times 2004

AEs Associated with Statin Therapy (cont)

Sober Second Thoughts!

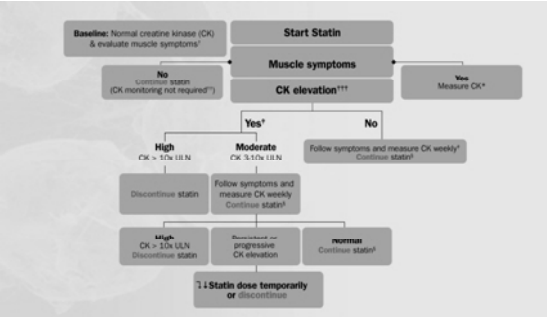
- In patients of all ages, the true incidence of statin AEs are confounded by study design, definitions, comorbidities, & interactions with drugs & food
- Most of these estimates are based on patients of all ages
  - Not exclusively studied in the elderly taking statins
  - Many patients with comorbidities, serious illness & interacting medications are excluded from statin RCTs

Prevention of Myopathies

- Coenzyme Q10
  - Recent review showed lack of proven benefit
  - Although safe for use, improvement in patients with muscle symptoms may be placebo effect
  - Suggest further studies needed to determine who may benefit & establish effective dosage

Marcoff & Thompson. JACC 2007; 49: 2231-2237

Statin Monitoring and Goals of Therapy



Statin Monitoring and Goals of Therapy. A Reference Guide. ACC Tool.

Clinical Scenario: Wrap-Up

- Should Mr.B have received intensive statin therapy post-MI?
  - On post-MI day#1, fasting lipid profile=LDL 2.37
  - TC 3.88 / HDL 0.77 (5.0); TG 1.64
- If so, what is the recommended duration of intensive statin therapy?
  - With ACS, at least 2 years
  - With chronic CAD, 1-5 years
  - Caveats: Patient tolerability & acceptability; greater cost-effectiveness with post-ACS patients

Summary

- Clinical trials demonstrate that, in patients of all ages, more intensive dose statin therapy is efficacious, safe & well tolerated in setting of post-ACS & chronic CAD
- Current practice in our CCU usually sees initiation of moderate to high dose statin in setting of ACS
  - Lower doses preferred in patients at risk of myopathies

Summary (cont.)

- In clinical practice, individual patient factors (tolerability, cost, etc.) may affect ability to continue at high doses for long periods or to achieve LDL or TC/HDL targets for high risk patients
- Very elderly patients may not derive the same balance of benefit vs risk compared to younger patients
- Need to recognize that some patients may be more susceptible to adverse effects of statins

Summary (cont.)

- When statin intolerances are identified, clinician can discuss options with patients including:
  - Use lowest effective dose to meet target(s)
  - Switch to a different statin
  - Alternative/off-label strategies (q2 day, 3x/wk)
- More evidence needed for:
  - Statin plus coenyzme Q10 or ezetimibe

Summary (cont.)

- Unanswered questions include:
  - Are results due to dose-intensity or are there differences between statins (molecules) used?
  - Are benefits due to LDL-lowering alone or pleotropic effects (anti-inflammatory, etc.) of statins?
  - Recognizing the challenge of achieving current targets (LDL, TC/HDL) in high risk patients with statin monotherapy, what is evidence for guiding therapy in those not meeting targets, with history of intolerance, or with mixed lipid disorders?

Questions?