STATINS ADVERSE EFFECTS BEYOND MYOPATHY

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Proven Benefits of Statins :

Prospective meta-analysis: 90,056 participants in 14 randomized statin trials

For each 1 mmol/L LDL-C lowering

- 12% reduction in all-cause mortality (*P*<0.0001)
- 19% reduction in coronary mortality (*P*<0.0001)
- 23% reduction in MI and coronary death (*P*<0.0001)
- 24% reduction in revascularizations (*P*<0.0001)
- 17% reduction in fatal or non-fatal stroke (*P*<0.0001)
- 21% reduction in any major vascular event (*P*<0.0001)
- No increase in non-vascular mortality or cancers

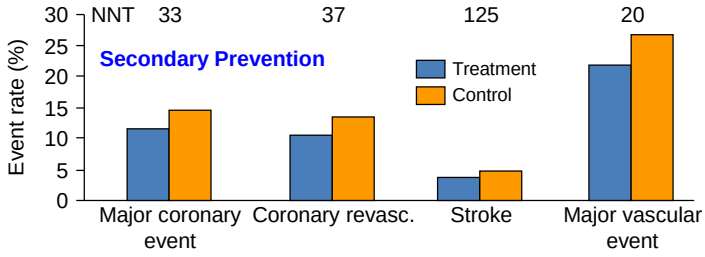
Adapted from Baigent C et al. Cholesterol Treatment Trialists' (CTT) Collaborators. *Lancet* 2005; 366:1267-78

Benefits of More vs Less Intensive Statin Therapy: (5 RCTs, N=39,612)

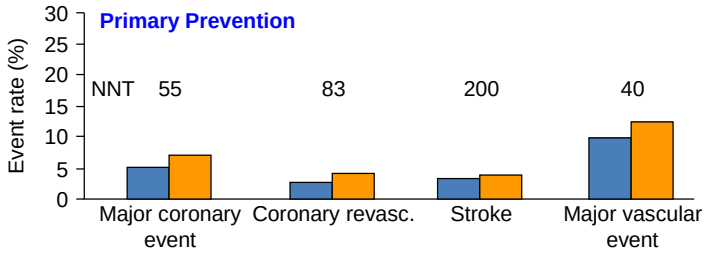
- Intensive therapy statin therapy resulted in a further reduction of LDL-C of 0.51mmol/L
- **After 1 year:**
  - 15% reduction in major vascular events
  - 13% reduction of coronary death or non-fatal MI
  - 16% reduction in ischaemic stroke

CTT *Lancet* 2010; 376: 1670-81

Absolute Benefit of Statins
Events Prevented by Reducing LDL 1 mmol for 5 yrs



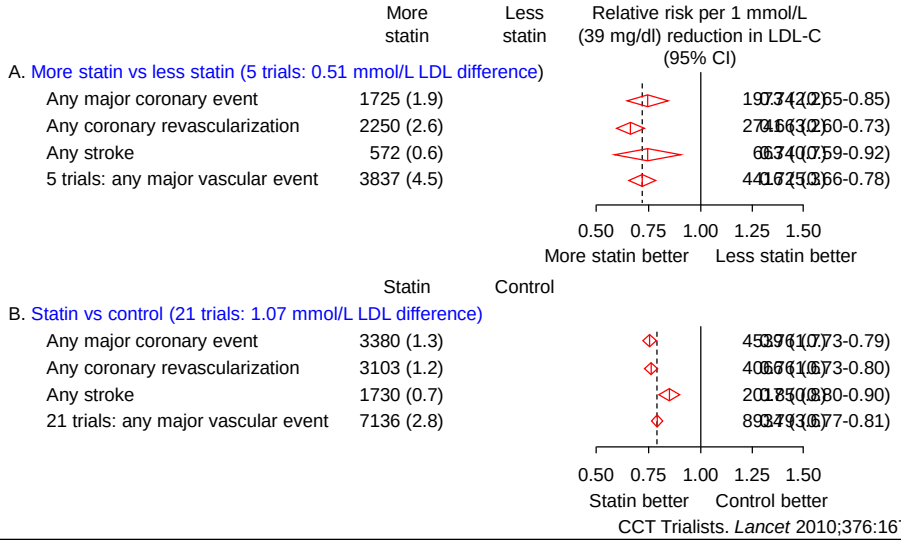
Outcomes avoided per 1000 (95% CI)	Major coronary event	Coronary revasc.	Stroke	Major vascular event
	30 (24-37)	27 (20-34)	8 (4-12)	48 (39-57)



Outcomes avoided per 1000 (95% CI)	Major coronary event	Coronary revasc.	Stroke	Major vascular event
	18 (14-23)	12 (9-16)	5 (1-8)	25 (19-31)

CTT *Lancet* 2005; 366:1267

Effect of Statins on CV Event Rates
Related to 1 mmol/l LDL Reduction



CCT Trialists. *Lancet* 2010;376:1670

Beyond Myopathy…
We should remember that

Muscle Disease Nomenclature

- Myalgia
  - Muscle aches or weakness in absence of CK rise
- Myositis
  - Elevated CK in presence of muscle symptoms
  - No absolute CK cut-off to define elevated
- Rhabdomyolysis
  - Pronounced CK elevation (> 10x ULN) with muscle symptoms
  - May be associated with urine myoglobin and renal dysfunction

Note CK elevation can be caused by multiple other causes

- Hypo or hyper thyroidism
- Renal dysfunction
- Artifactual elevation
- Physical exertion
- Seizures
- Trauma

Mancini GB et al. *CJC* 2011; 27:635-662

So ,,, What's statin adverse effects beyond myopathy?

Reported Adverse Effects of Statins

- Elevated hepato-cellular enzymes
- Cancer
- New diabetes
- Hemorrhagic stroke
- Fatigue
- Neuro-psychiatric effects and insomnia
- Proteinuria / hematuria
- Erectile dysfunction

Lack of Risk of Cancer with Statins

- Meta-analysis of 175,000 subjects in 27 trials

  5 years of statin therapy had no effect on the incidence of, or mortality from cancer

- Incidence of or mortality from cancer not related to
  - Age
  - Sex
  - Anatomical site of cancer
  - Type statin
  - Duration of treatment
  - Baseline LDL-C level
  - Risk of vascular event

CTT *Lancet* DOI:10.1016/S0140 -6736(12)60367-5

IJC
International Journal of Cancer

Effects of statins on cancer mortality and progression: A systematic review and meta-analysis of 95 cohorts including 1,111,407 individuals

Zubing Mei[1], Mining Liang[2,3], Lezhi Li[2,3,4], Yi Zhang[5], Qingming Wang[1] and Wei Yang[1]

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[5]Department of pharmacy, the First People's Hospital of Jiashan, Jiashan County, Jiaxing City, Zhejiang Province, China

A meta-analysis of 55 articles showed that statin use was significantly associated with decreased risk of all-cause mortality (HR 0.70, 95% CI 0.66 to 0.74) compared with nonusers
Subgroup analyses according to initiation of statins showed postdiagnosis statin users (HR 0.65, 95% CI 0.54 to 0.79) gained significantly more recurrence-free survival benefit than prediagnosis statin users (HR 0.86, 95% CI 0.77 to 0.96) (p for interaction 5 0.018).
Statin therapy has potential survival benefit for patients with malignancy.

Liver Injury Associated with Statin Use

Type of liver injury	Frequency	Comment
Asymptomatic elevations in aminotransferases	0.1%-3.0%	Dose-dependent; class effect; clinically not significant
Clinically significant acute liver injury	Very rare	May be seen in combination with other medications
Fulminant hepatic failure	Extremely rare (isolated case reports)	It was estimated that risk of fulminant liver failure is 2 per million
Autoimmune hepatitis	Case reports	Statins may induce AIH in genetically susceptible individuals

Bhardwaj SS et al. *Clin Liver Dis* 2007; 11:597-613

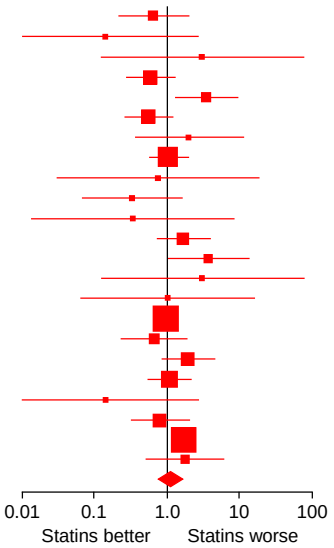
	Number of cases reported	Positive rechallenge	Fatal liver injury reported (yes/no)
Simvastatin	68	yes	yes
Atorvastatin	65	yes	yes
Fluvastatin	28	yes	no
Rosuvastatin	13	no	no
Lovastatin	12	no	no
Pravastatin	11	no	no

Number of case reports of DILI with different statins and whether cases of positive rechallenge and fatality from the liver injury has been reported
Björnsson ES[1,2].
Liver Int. 2017 Feb;37(2):173-178. doi: 10.1111/liv.13308. Epub 2016 Nov 27.

Statins and Intra-cerebral Hemorrhage
Meta-analysis of 23 RCTs shows no increased risk

Trial	RR (95% CI)	Weight
4D	0.64 (0.21-1.96)	3.9
ACAPS	0.14 (0.01-2.75)	0.7
AFCAPS	3.00 (0.12-3.62)	0.6
ALERT	0.59 (0.27-1.28)	6.5
ALLHAT	3.42 (1.26-9.27)	4.7
ASCOT	0.55 (0.26-1.14)	7.0
ASPEN	1.98 (0.36-10.9)	1.9
AURORA	1.04 (0.57-1.91)	8.8
Bone et al.	0.74 (0.03-18.3)	0.6
CARE	0.33 (0.07-1.65)	2.2
CLAPT	0.34 (0.01-8.34)	0.6
CORONA	1.66 (0.72-3.80)	6.1
GISSI-HF	3.69 (1.03-13.2)	3.2
GISSI-P	2.99 (0.12-73.6)	0.6
GREACE	1.00 (0.06-16.0)	0.8
HPS	0.96 (0.65-1.41)	12.5
JUPITER	0.67 (0.24-1.87)	4.4
LIPID	1.89 (0.84-4.24)	6.2
MEGA	1.09 (0.56-2.11)	7.9
MIRACL	0.14 (0.01-2.78)	0.7
PROSPER	0.81 (0.32-2.04)	5.2
SPARCL	1.68 (1.09-2.60)	11.6
SSSS	1.75 (0.51-6.00)	3.4
Overall	1.10 (0.86-1.42)	100

Median LDL-C reduction 1.03 mmol/L



Hackam DG et al. *Circulation* 2011; 124:2233-42

Statins and Neuropsychiatric Effects

- **Dementia**
  - Systematic review showed no increased risk of cognitive decline
    Law et al. *Am J Cardiol* 2006; 97:52C
- **Suicide / violent death**
  - Conflicting evidence on relationship between statin use mood states: depression, anxiety, fatigue, confusion and vigour
    While et al. *Eur J Cardiovasc Nurs* 2010
- **Insomnia**
  - Initial studies suggested insomnia with lovastatin compared with pravastatin
    Black et al. *JAMA* 1990; 264:1105
  - Study with objective measures of sleep showed no effect
    Ehrenberg et al. *Sleep* 1999; 22:117

Statins and Cognitive Impairment

FDA review of case reports, observational data and randomized clinical trials

FDA concluded:

- Some individuals over 50 years old suffer notable, but ill-defined memory loss / impairment
- Reversible on discontinuation of statin
- Variable time of onset (1 day to years)
- No fixed or progressive dementia
- Not related to specific statin

FDA Safety Communication http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm

Statins and Fatigue

- Randomised subset of a controlled trial (397 of 1016 subjects)
- Equal randomisation to simvastatin 20mg, pravastatin, or placebo
- 6 month follow-up

Table. Change in Energy and Exertional Fatigue Outcome (EnergyFatigueEx) for Placebo vs Statin Groups

	Placebo	Statin		Simvastatin		Pravastatin	
	Mean ± SD	Mean ± SD	*P* value	Mean ± SD	*P* value	Mean ± SD	*P* value
All	-0.06 ± 0.71	-0.21 ± 0.87	0.005	-0.25 ± 0.87	0.002	-0.17 ± 0.86	0.06
Women	-0.08 ± 0.72	-0.39 ± 1.14	0.01	-0.47 ± 1.20	0.004	-0.31 ± 0.72	0.07

- **Conclusions:**
  - Statins may worsen energy and or exertional fatigue
  - Women appear more affected than men
  - 40% women complain of worse or much worse fatigue

However this is a small study of randomized subset, with uncertain reproducibility or importance of metrics used

Golomb BA et al. *Arch Intern Med*. 2012; 172(15):1180-2. doi:10.1001/archinternmed.2012.2171

Dilemma of Statin use and New-onset DM

Statins and New-Onset Diabetes

Study	Proportion of patients with new-onset diabetes (%)		RR, statin vs placebo	95% CI
	Statins	Placebo		
WOSCOPS (N=5974)	1.9%	2.8%	0.69	0.49-0.96
HPS (N=14,543)	4.6%	4.0%	1.14	0.98-1.33
ASCOT (N=7773)	3.9%	3.5%	1.14	0.90-1.43
LIPID (N=7937)	4.3%	4.6%	0.95	0.77-1.16
CORONA (N=3534)	5.6%	5.0%	1.13	0.86-1.49
JUPITER (N=17,802)	3.0%	2.4%	1.25	1.05-1.49
Combined all above (N=57,593)	3.8%	3.5%	1.06	0.93-1.22 (*P*=0.38)
Combined all above except WOSCOPS (N=51,619)	4.0%	3.5%	1.13	1.03-1.23 (*P*=0.008)

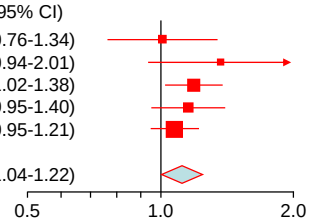
Absolute risk of developing DM 0.3-0.5%
Note
- Patient reported diabetes
- No formal testing for diabetes

Risk factors for Statin associated DM
- Obesity
- IFG
- Elevated TG / HDL

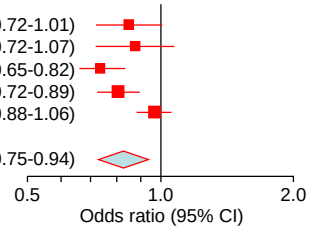
Sattar N et al. *Lancet* 2010; 375:735-42

Statins and New-Onset Diabetes In Context of Reduction of CV Events: 5 Trials Comparing Intensive- to Moderate-Dose Statin Therapy

Incident Diabetes	Cases/Total (%)		
	Intensive dose	Moderate dose	OR (95% CI)
PROVE-IT - TIMI 22, 2004	101/1707 (5.9)	99/1688 (5.9)	1.01 (0.76-1.34)
A to Z, 2004	65/1768 (3.7)	47/1736 (2.7)	1.37 (0.94-2.01)
TNT, 2005	418/3798 (11.0)	358/3797 (9.4)	1.19 (1.02-1.38)
IDEAL, 2005	240/3737 (6.4)	209/3724 (5.6)	1.15 (0.95-1.40)
SEARCH, 2010	625/5398 (11.6)	587/5399 (10.9)	1.07 (0.95-1.21)
Pooled odds ratio	1449/16,408 (8.8)	1300/16,344 (8.0)	1.12 (1.04-1.22)



Incident CVD			
PROVE-IT - TIMI 22, 2004	315/1707 (18.4)	355/1688 (21.0)	0.85 (0.72-1.01)
A to Z, 2004	212/1768 (12.0)	234/1736 (13.5)	0.87 (0.72-1.07)
TNT, 2005	647/3798 (17.0)	830/3797 (21.9)	0.73 (0.65-0.82)
IDEAL, 2005	776/3737 (20.8)	917/3724 (24.6)	0.80 (0.72-0.89)
SEARCH, 2010	1184/5398 (21.9)	1214/5399 (22.5)	0.97 (0.88-1.06)
Pooled odds ratio	3134/16,408 (19.1)	3550/16,344 (21.7)	0.84 (0.75-0.94)

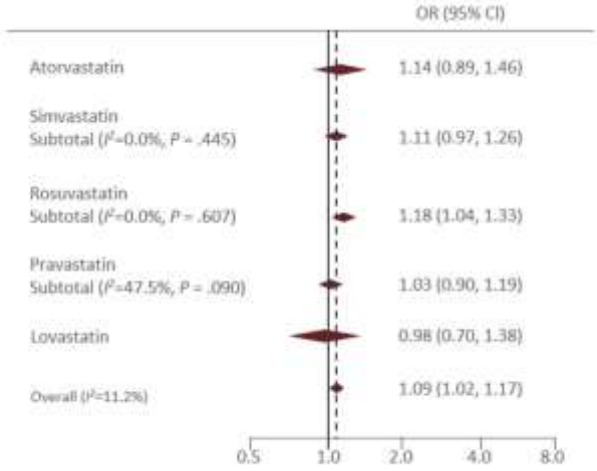


NTT/yr **155 for CV events**
NNH/yr **498 for new-onset diabetes**

Preiss D et al. *JAMA* 2011; 305:2556-64

T2D Risk: No Difference Between Statins

Meta-Analysis of 13 Clinical Trials



Sattar N, et al. *Lancet*. 2010;375:735-742.

Statins and New-Onset Diabetes

- Treatment of 255 patients with statins results in 1 additional case of diabetes over 4 years
- Statin treatment prevented of 5.4 vascular events in these 255 patients

Benefit of statin treatment exceeds risk
Monitor fasting glucose and A_1C

Statin-Associated T2D Implications for Clinical Care

- Do not discontinue statin
  - Exposes patients to CV risk
- Do not ignore elevated HbA_{1c}
  - Manage T2D according to treatment guidelines
- Monitor HbA_{1c}
- Counsel patients on lifestyle management
  - Diet, weight, exercise

The American Journal of Medicine
Available online 13 November 2017
In Press, Corrected Proof

Clinical Research Study

Statin Use in Men and New Onset of Erectile Dysfunction: A Systematic Review and Meta-Analysis

Akram Y. Elgendy MD, MRCP [a], Islam Y. Elgendy MD [a], Ahmed N. Mahmoud MD [a], Mohammad Al-Ani MD [a], Mohamed Moussa MD [b], Ahmad Mahmoud MD [c], Mohammad K. Mojadidi MD [a], R. David Anderson MD, FACC [a] ⁂, [d]

Three randomized trials and 3 observational studies were identified, with 69,448 men, of whom 24,661 were statin users. Statin use was not associated with an increased risk of new onset of erectile dysfunction by random effects model or fixed effect model (risk ratio 0.96; 95% confidence interval, 0.84-1.10; *P* = .58; and odds ratio 0.95; 95% confidence interval, 0.88-1.02; *P* = .20, respectively).

STATIN INTOLERANCE

Prevention of Statin Intolerance

- **Pre-treatment assessment**
  - Assess risk (e.g. elderly, prior muscle pains, FH of myopathy, renal disease, DM, hypothyroidism)
  - Consider exogenous factors (e.g. statin dose, alcohol use, drug-drug interactions, excessive grapefruit juice use)
  - Measure baseline CK, ALT, TSH, creatinine
- **Counseling**
  - Inform that statins are very well tolerated in most people
  - Inform about muscular symptoms and when to discontinue
- **Monitoring**
  - Check CK / ALT when monitoring lipid lowering efficacy
    - At 6-8 weeks after starting or with dose increase and then every 6-12 m
    - Avoid severe exercise for several days prior to testing

Therapeutic Options for Management of Statin "Intolerant" Patient

- Dietary and health behaviour measures
- Statin based strategies
  - Alternative statin
  - Alternative dosing
- Non-statin alternatives and adjuncts
  - Ezetimibe
  - Bile acid sequestrants
    - Fibrates
    - Niacin

Statin based Options for LDL-Cholesterol Lowering in Statin "Intolerant" Patient

- Lower statin dose
- Switch to alternative statin
- Altered dosing regimens
  - Rosuvastatin 2.5-10 mg 3 x weekly or alternate days
  - Rosuvastatin 5-20 mg once weekly
- Low dose / alternative statin /alternating day rosuvastatin

  +
  - Ezetimibe
  - Bile acid binding resin

Non-Statin Lipid Lowering Strategies

Ezetimibe
- Lowers LDL 15-20%
- Well tolerated
- May be added to low dose statin

Bile acid sequestrants
- Lowers LDL 15%
- May prevent diabetes
- Colesevalam better tolerated

Ezetimibe + Bile acid sequestrant
- 40-45% LDL reduction

Fibrates
- ↓ TG LDL little change
- ? Benefit when HDL low

Niacin
- Flushing/pruritus may limit tolerance
- Lowers LDL 20%
- TG ↓40%, HDL ↑30%

Future Non-Statin Strategies to Reduce LDL Cholesterol

- **CETP inhibitor**
  - Torcetrapib (increased mortality) and Dalcetrapib (no benefit)
  - Anacetrapib results awaited (↑ HDL 138%, ↓ LDL 40%)
  - Evacetrapib Phase 2 study presented 2010
- **Mipomersen**
  - Inhibits protein synthesis of apoB
  - Reduces LDL ~30%
  - Injected weekly
  - No outcomes trials
- **PCSK9 inhibitors**
  - Reduce LDL 50-60 %,
  - Injected q 2 weeks
  - No outcomes trials

To conclude :

Conclusions
Adverse Effects of Statin Treatment

- More common than clinical trials suggest
- Probably more frequent at higher doses
- Important cause of poor adherence to treatment
- Manage adverse events
  - Use alternative statin
  - Reduce frequency of statin
  - Use non-statin agents as monotherapy or together with reduced dose or frequency statin

Thanks for attention