Update On LDL-C Lowering During A Lifetime: How Low To Strive For With Intensive Drug Therapy: How Young To Start If High; How Old To Continue Statins: Why And How Often Should LDL-C Levels Be Measured

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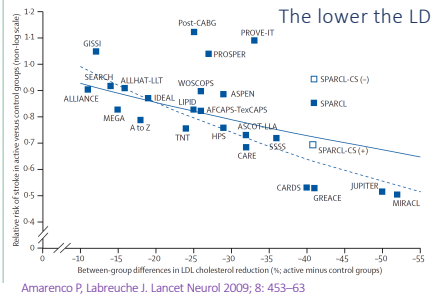
Lipid lowering and stroke risk

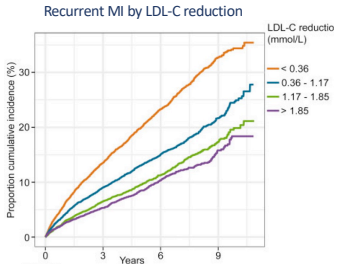
The lower the LDL-C, the better



Amarenco P, Labreuche J. Lancet Neurol 2009; 8: 453–63

The lower the LDL-C the better

A bit of statin is not the answer: Intensive statin therapy, plus ezetimibe, or ezetimibe + bempedoic acid or PCSK9-based Rx is much better

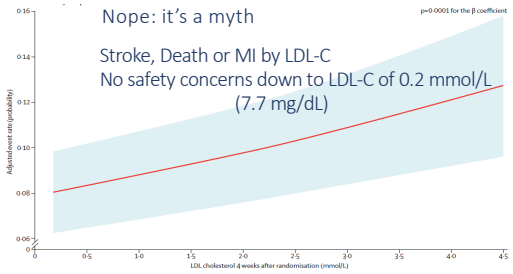


Schubert J et al. Eur Heart J 2020

Whoa! aren't you worried about very low LDL?

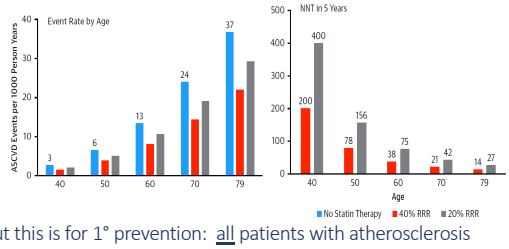
Nope: it's a myth

Stroke, Death or MI by LDL-C
No safety concerns down to LDL-C of 0.2 mmol/L (7.7 mg/dL)



Giugliano RP et al. Lancet. 2017;390:1962-1971.

Greater absolute risk reduction with statins with age

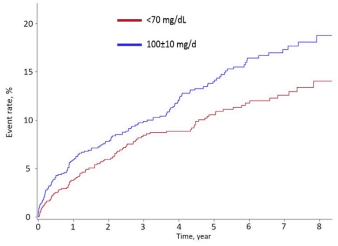


But this is for 1° prevention: all patients with atherosclerosis should be on intensive lipid lowering therapy

Mortensen BD, Falk E. JACC 2018; 71:85-94

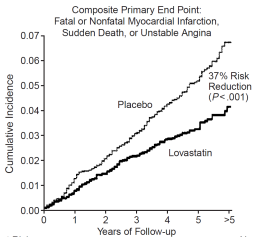
RCT of LDL-C <1.7 vs. 2.4 mmol/L post atherosclerotic stroke

French subgroup
Followed 5.3 years
n = 1073 Age 67 at baseline
1° outcome
stroke/MI/revasc/death
HR 0.74 [95% CI, 0.57–0.94]
P=0.019



Amarenco P et al. Stroke 2020 Online Feb 20

Cholesterol lowering

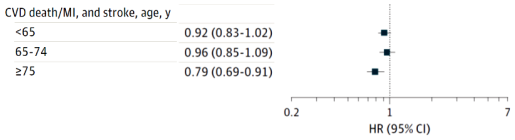


- Benefits of statins increase over time
- Estimates of benefit based on the short duration of studies underestimate lifetime benefit
- In AFCAPS/Texcaps[1], risk reduction was 37% over 5 years, but by year:[2]

Year	1	2	3	4
	12%	30%	41%	49%

1. Downs JL et al. JAMA. 1998;279:1615-162
2. Good CB et al. Ann Int Med 2019; 171: 72

Absolute risk reduction greater age ≥75 in Simvastatin/Ezetimibe RCT



Age Group	NNT for 1˚ endpoint
>75	11
<75	125

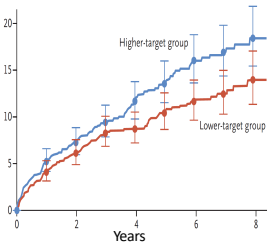
1˚ endpoint CVD death, MI, Stroke, hospitalized unstable angina, coronary revascularization; benefit was less for this endpoint so for stroke/MI/CVD death the NNT would have been even lower

Bach RG et al. JAMA Cardiol. 2019;4:846-854
Gotto A. JAMA Cardiol. 2019;4:855-856.

Treat to Target Trial

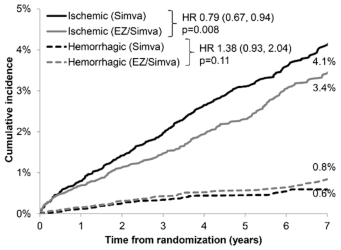
N = 2680 Ischemic stroke patients
Age 67 at baseline, followed 3.5 years
Target LDL-C <1.8 vs. 2.3-2.8 mmol/L

- Composite 1˚ outcome HR 0.78; 95% CI 0.61 to 0.98; P = 0.04)
- Greater benefit in patients with ischemic stroke (vs. TIA) at baseline: HR 0.67 (0.52–0.87)
- At sites with LDL in target >50% of the time HR 0.64 (0.48–0.85)



Amarenco P et al. N Engl J Med. 2020;382:9-19

Adding ezetimibe to statin reduces recurrent stroke; statins do not cause ICH

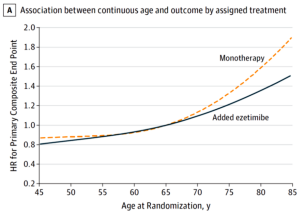


Bohula EA et al. Circulation. 2017;136:2440–2450.

Ezetimibe + simvastatin more beneficial in the elderly

Absolute risk reduction 8.7% above age 75, vs. 0.9% below age 65
NNT above age 75 was 11, vs. 125 below age 75
Greatest benefit in high-risk: HR 0.75 (0.63-0.89)

The older the patient, the greater the benefit of lowering LDL-C

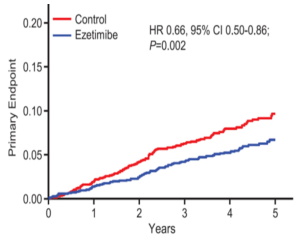


1. Gotto AM, Jr. Intensive lipid lowering in elderly. JAMA Cardiology, 2019 online July 17.
2. Bach RG, et al. Effect of simvastatin-ezetimibe compared with simvastatin monotherapy after acute coronary syndrome among patients 75 years or older: JAMA Cardiology, 2019 online July 17.

RCT of Diet + Ezetimibe in elderly Japanese

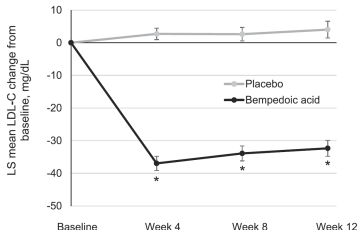
N = 3,796 with LDL-C ≥ 3.68 mmol/L,
No CAD, but risk factors present
Mean age at baseline 80.7 years;
followed 5 years

Primary outcome:
sudden cardiac death, MI, PCI or CABG, and/or stroke;
Reduced by 34%



Ouchi Y et al. Circulation 2019;140:992-1003.

Bempedoic acid added to ezetimibe



Ballantyne CM, et al. Atherosclerosis. 2018;277:195-203

Ezetimibe should routinely be added to statin or bempedoic acid

- It is synergistic with statin: more than doubles the effect
- Permits lower dose of statin in those with muscle problems
- Reduces the risk of stroke/MI/CVD death (including age ≥ 75)
- Is now recommended as Grade 1 in new European guideline [1]

1.Mach F, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias. European Heart Journal. ePub 2019 Aug 31 .

Conclusions

- LDL-C should be as low as possible; ezetimibe should be routinely added to statins or bempedoic acid
- Use PCSK9 agents for statin intolerant
- Age is not an issue; what matters is the presence of atherosclerosis
- LDL-C should be measured at baseline, and repeated occasionally to confirm adherence
- Better to measure plaque:
  - "Treating arteries instead of treating risk factors" [1,2]

1. Spence JD, Coates V, Li H, Tamayo A, Munoz C, Hackam DG, et al. Effects of intensive medical therapy on microemboli and cardiovascular risk in asymptomatic carotid stenosis. Arch Neurol. 2010;67(2):180-6.
2. Spence JD, Hackam DG. Treating arteries instead of risk factors: a paradigm change in management of atherosclerosis. Stroke. 2010;41(6):1193-9.

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