What Is The Best Medical Treatment For Patients With Carotid Stenosis (Asymptomatic And Symptomatic): Can High Risk Plaques Be Made Low Risk And Smaller? All Stroke Patients Should Be On Statins Because They Decrease Recurrent Stroke And Mortality Rates Markedly

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Patients with carotid stenosis are at high risk

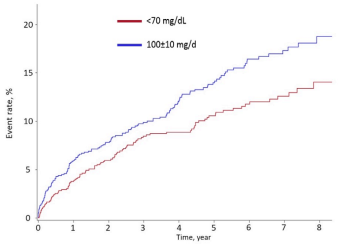
- Not just stroke
- They have a high risk of coronary disease
- They should all receive intensive medical therapy
- Age should not be an impediment to intensive medical Rx
- The best results are with "Treating Arteries" instead of merely treating risk factors
  - Target is plaque regression, not just lipid levels

Best medical therapy for carotid stenosis

- Smoking cessation
- Mediterranean diet
- Exercise
- Intensive lipid lowering therapy
- Antiplatelet agents
- Blood pressure control
  - Importance of measuring plasma renin and aldosterone
  - Individualized therapy for hypertension

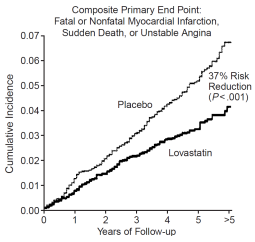
RCT of LDL-C <1.7 vs. 2.4 mmol/L post atherosclerotic stroke

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

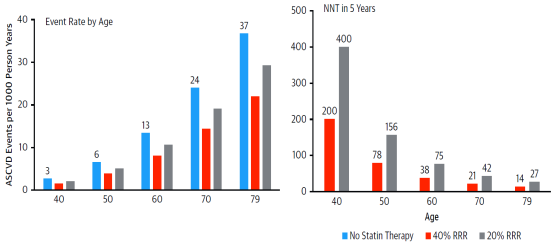


- Benefits of statins increase over time
- Estimates of benefit based on the short duration of studies underestimate lifetime benefit
- In AFCAPS/Texcaps[1], risk reduction was 37% over 5 years, but by year:[2]

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

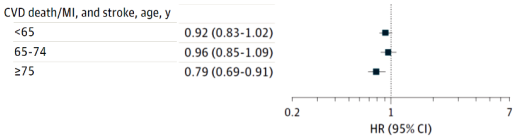
1. Downs JL et al. JAMA. 1998;279:1615-162
2. Good CB et al. Ann Int Med 2019; 171: 72

Greater absolute risk reduction with statins with age



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

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



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

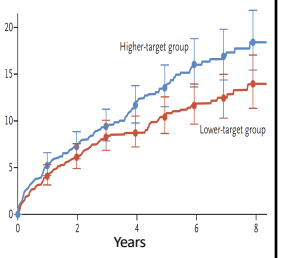
1˚ endpoint CVD death, MI, Stroke, hospitalized unstable angina, coronary revascularization; benefit was less for this endpoint so for stroke/MI/CVD death the NNT would have been even lower

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

Treat to Target Trial

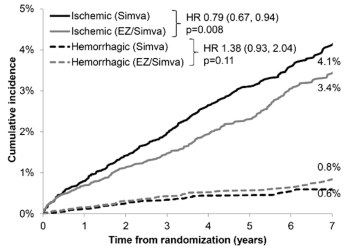
N = 2680 Ischemic stroke patients
Age 67 at baseline, followed 3.5 years
Target LDL-C <1.8 vs. 2.3-2.8 mmol/L

- 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

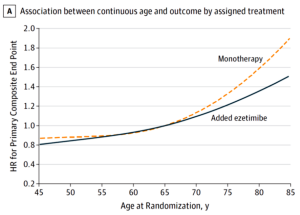


Bohula EA et al. Circulation. 2017;136:2440–2450.

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

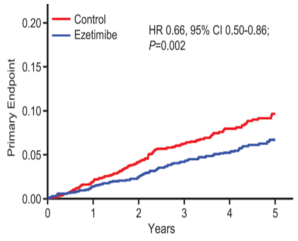


1. Gotto AM, Jr. Intensive lipid lowering in elderly. JAMA Cardiology, 2019 online July 17.
2. Bach RG, et al. Effect of simvastatin-ezetimibe compared with simvastatin monotherapy after acute coronary syndrome among patients 75 years or older: JAMA Cardiology, 2019 online July 17.

RCT of Diet ± Ezetimibe in elderly Japanese

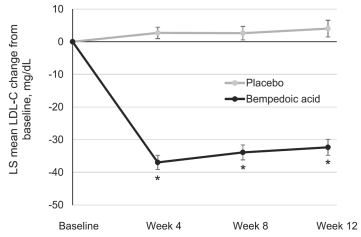
N = 3,796 with LDL-C ≥ 3.68 mmol/L, No CAD, but risk factors present
Mean age at baseline 80.7 years; followed 5 years

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



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

Bempedoic acid added to ezetimibe



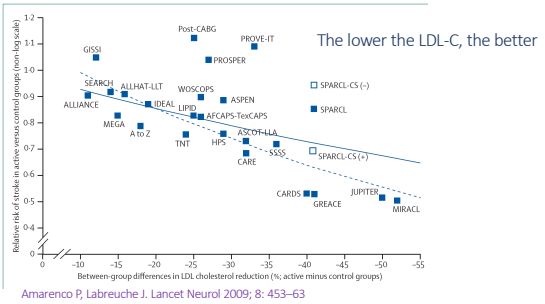
Ballantyne CM, et al. Atherosclerosis. 2018;277:195-203

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 .

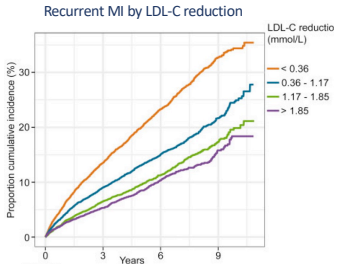
Lipid lowering and stroke risk



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, and maybe PCSK9-based Rx is much better

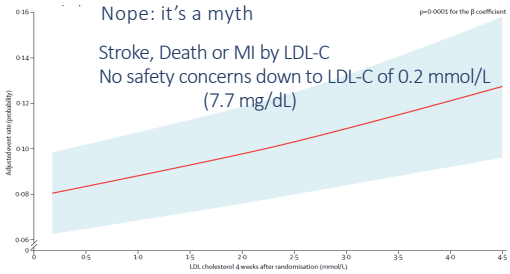


Schubert J et al. Eur Heart J 2020

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

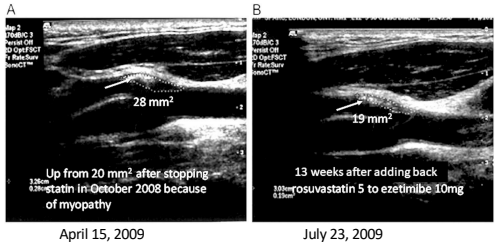
Nope: it's a myth

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.

Lipid lowering reduces plaque size and plaque risk within weeks



Spence JD. Atherosclerosis. 2019;287:179-80.

Effect of "Treating Arteries" in asymptomatic carotid stenosis

2-year risk	Before 2003 n = 199	After 2003 n = 269	p
Stroke	8.8%	1%	0.005
MI	7.6%	1%	0.005

Annual risk of stroke 0.5%

Spence JD et al. Arch Neurol. 2010;67:180-6

Best medical therapy for patients with carotid stenosis: Conclusions

- Mediterranean Diet, smoking cessation, exercise, antiplatelet agent
- Effective blood pressure control (with renin/aldosterone-based Rx)
- All patients with carotid stenosis should receive intensive lipid lowering Rx
- "Treating Arteries" instead of merely treating risk factors
- Ezetimibe should be routinely added to statin or bempedoic acid
- For statin-intolerant patients, use ezetimibe + bempedoic acid + PCSK9-based Rx
  - Such as evolocumab (Repatha)

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