Hyperlipidemia and Stroke

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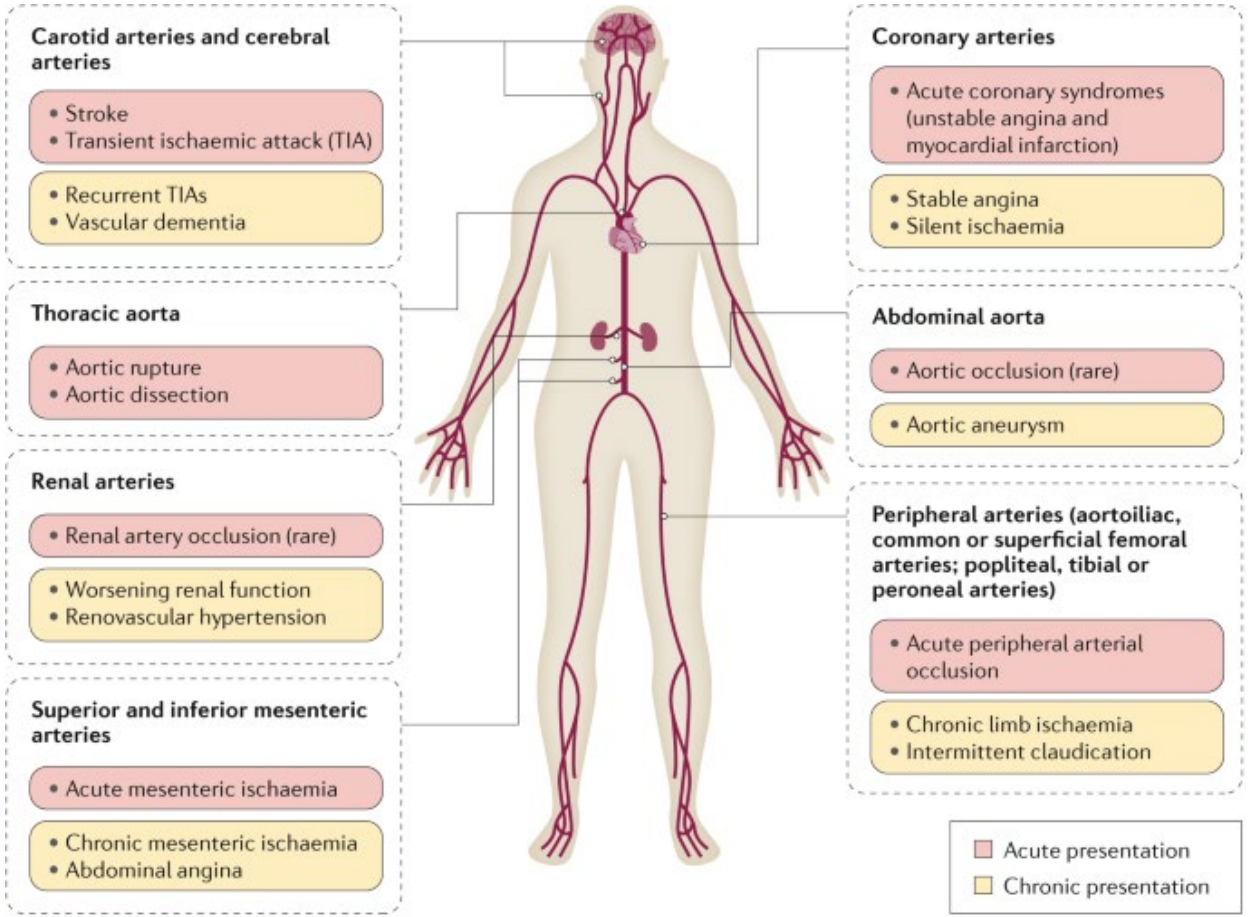
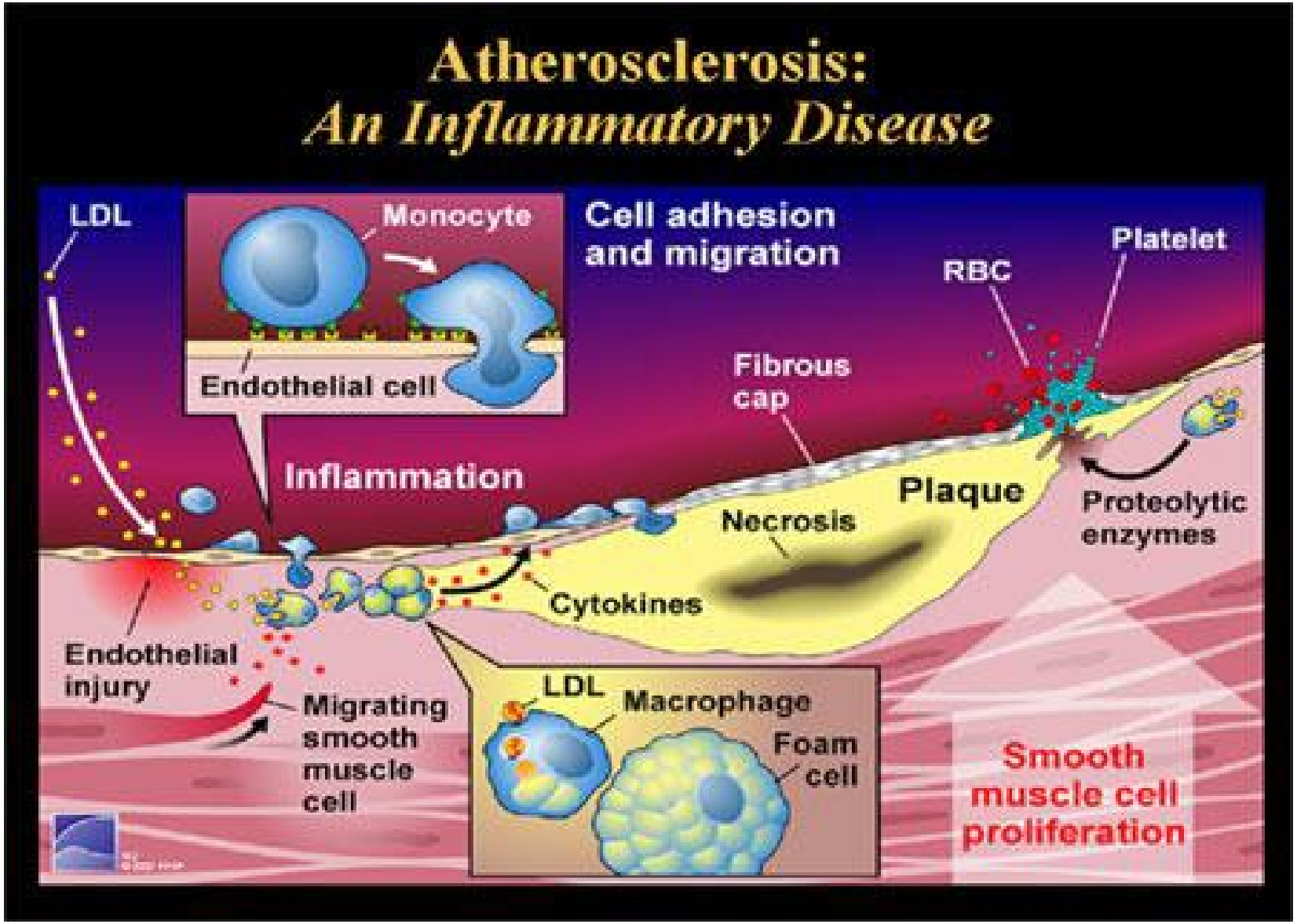
Agenda

- Discuss the pathophysiology of atherosclerosis
- Review the data for lipid lowering therapies in stroke patients
- Briefly summarize the Stroke AHA Guidelines
- Appreciate the recent published data from 2022
- Discuss systems of care issues to address guidelines

Atherosclerosis is a Systemic Disease

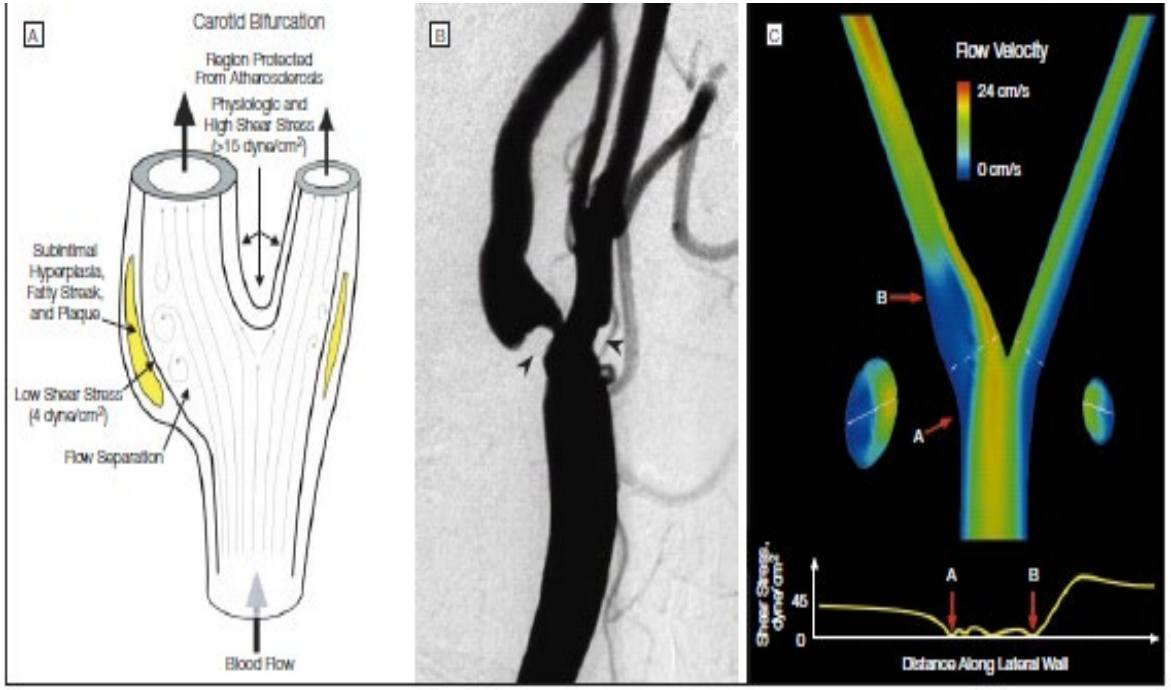


Libby, P., Buring, J.E., Badimon, L. *et al.* Atherosclerosis. *Nat Rev Dis Primers* **5**, 56 (2019)

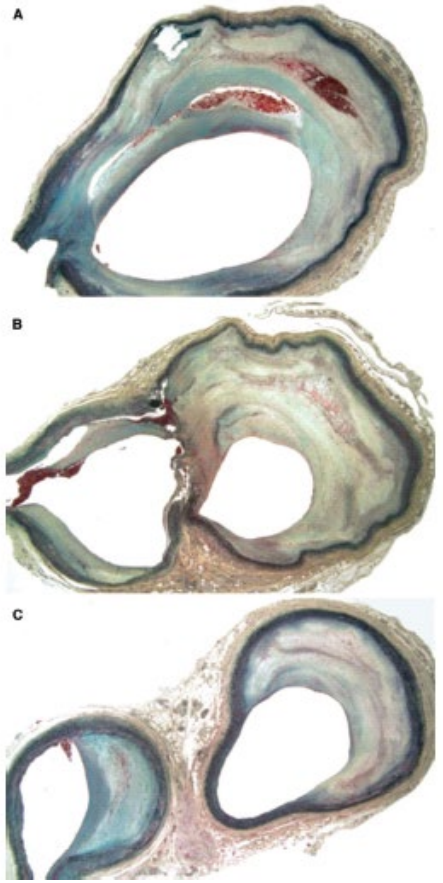


Ross, R. N Eng J Med 1999;340:115-126.

Localization of Atherosclerosis

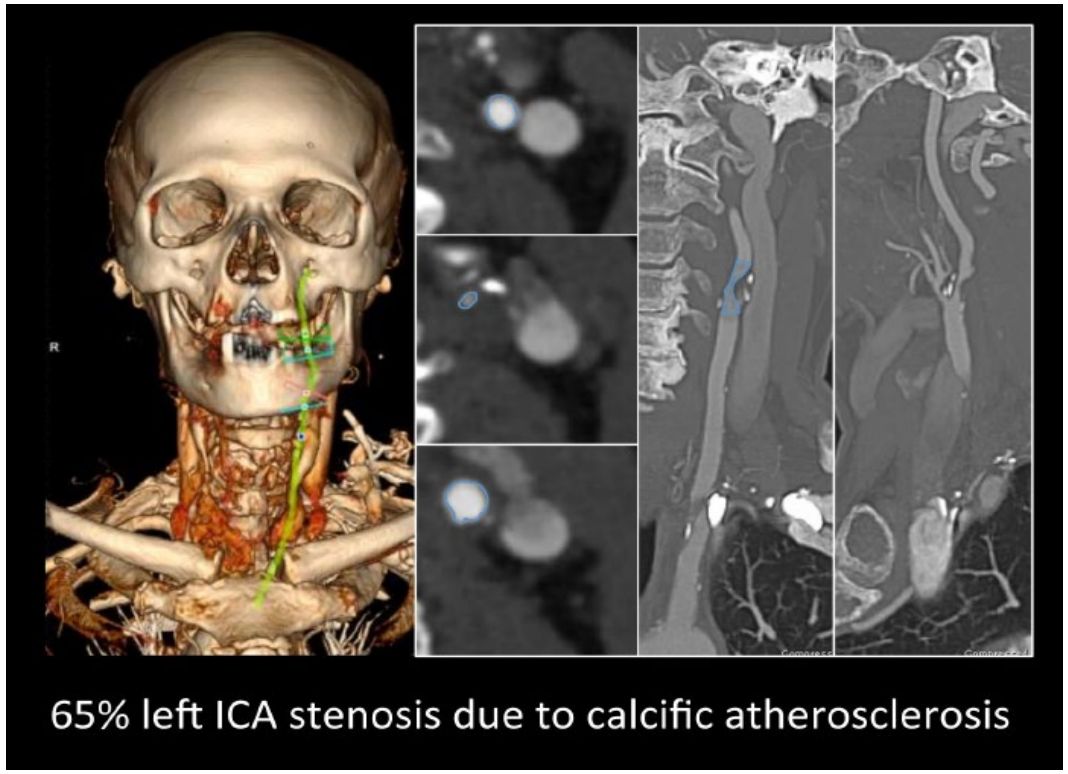


JAMA 1999;282:2035-2042

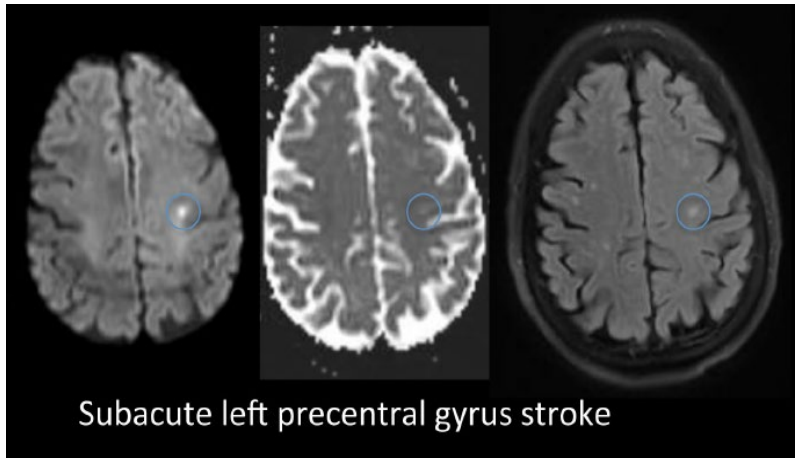


Neurosurgery 59:53-219-53-227,2006

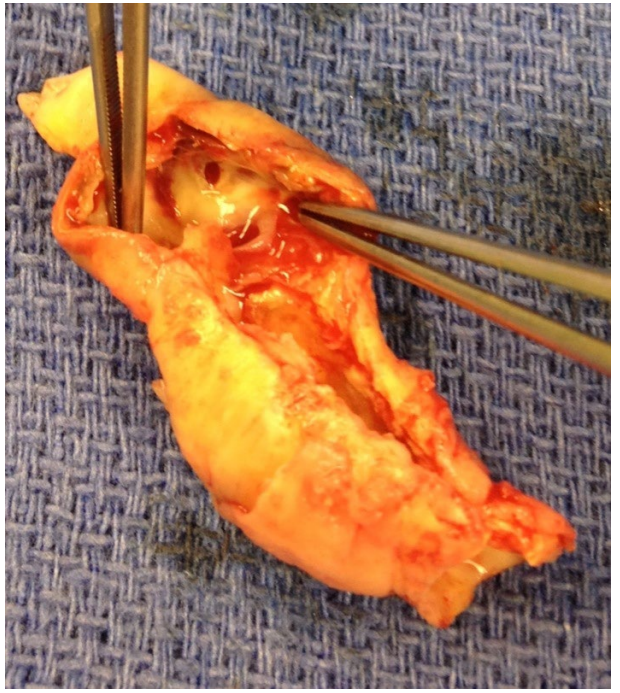
Carotid Disease



65% left ICA stenosis due to calcific atherosclerosis

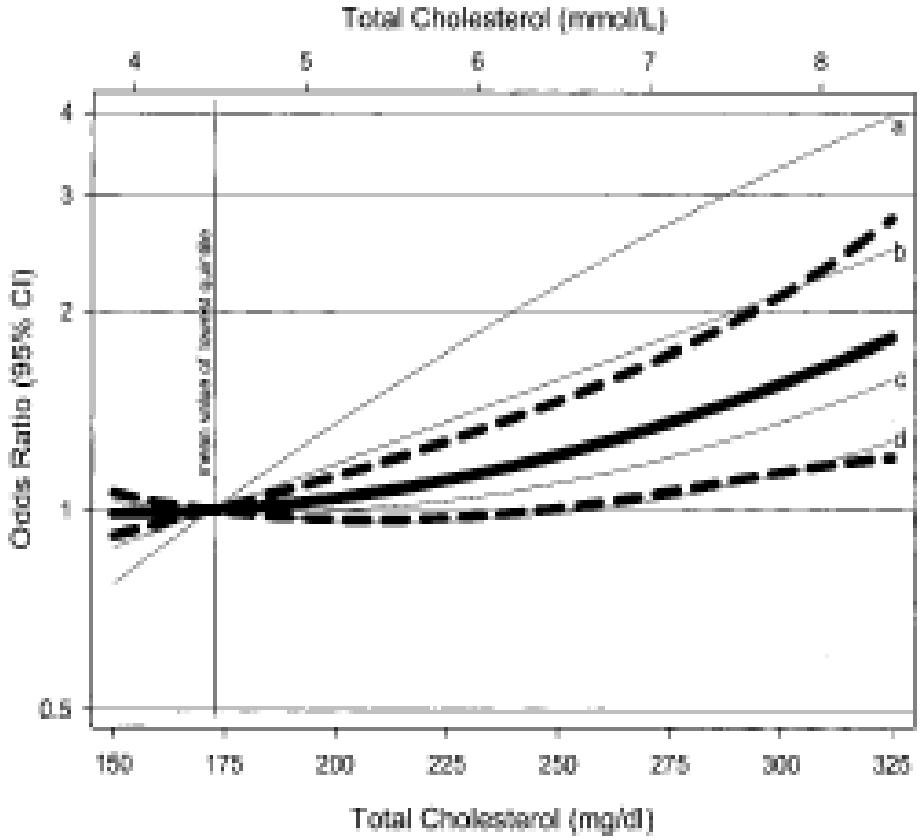


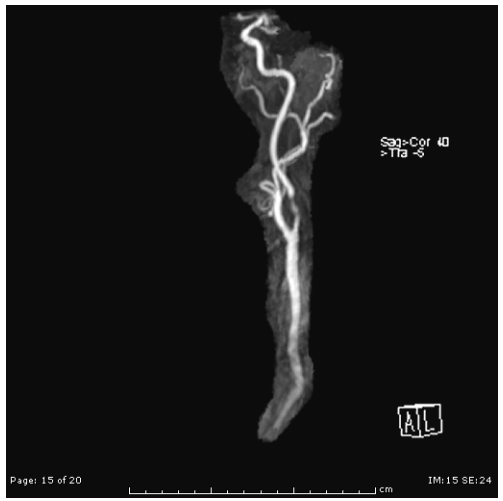
Subacute left precentral gyrus stroke



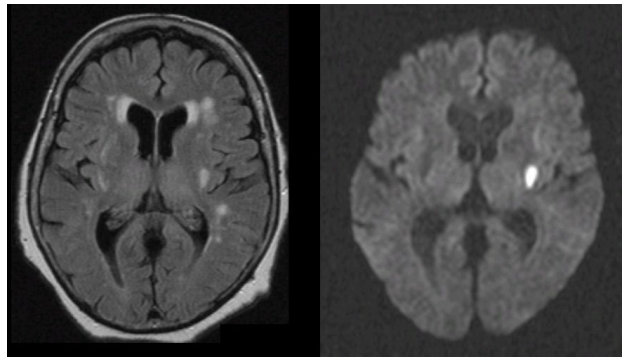
Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups

D.L. Tirschwell, MD, MSc; N.L. Smith, PhD; S.R. Heckbert, MD, PhD; R.N. Lemaitre, PhD, MPH; W.T. Longstreth, Jr., MD, MPH; and B.M. Psaty, MD, PhD





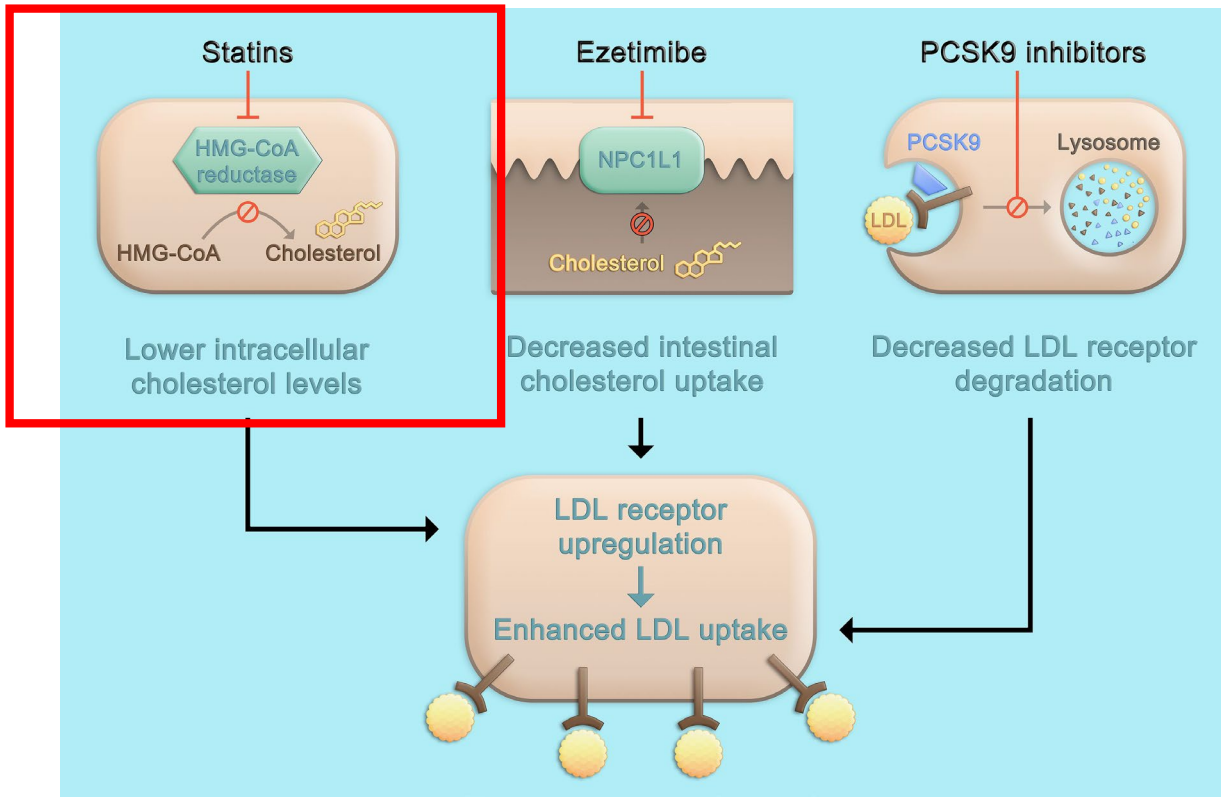
(a)



(b)

Tirschwell, D. L., et al. "Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups." *Neurology* 63.10 (2004): 1868-1875.

Statin Pharmacology



Katzmann, Julius L., Ioanna Gouni-Berthold, and Ulrich Laufs. "PCSK9 inhibition: insights from clinical trials and future prospects." *Frontiers in Physiology* 11 (2020): 595819.

Statins

Cholesterol Treatment Trialist Collaboration	Effect on Ischemic Stroke	Effect on Hemorrhagic Stroke
Statin vs Control (21 trials)	RR 0.8 per 1 –mmol/L reduction in LDL-C	RR 1.10 per 1-mmol/L reduction in LDL-C
More vs Less (5 trials)	RR 0.69 per 1-mmol/L reduction in LDL-C	RR 1.39 per 1-mmol/L reduction in LDL-C
All Trials (26 Trials)	RR 0.79 per 1-mmol/L reduction in LDL-C	RR 1.12 per 1-mmol/L reduction in LDL-C

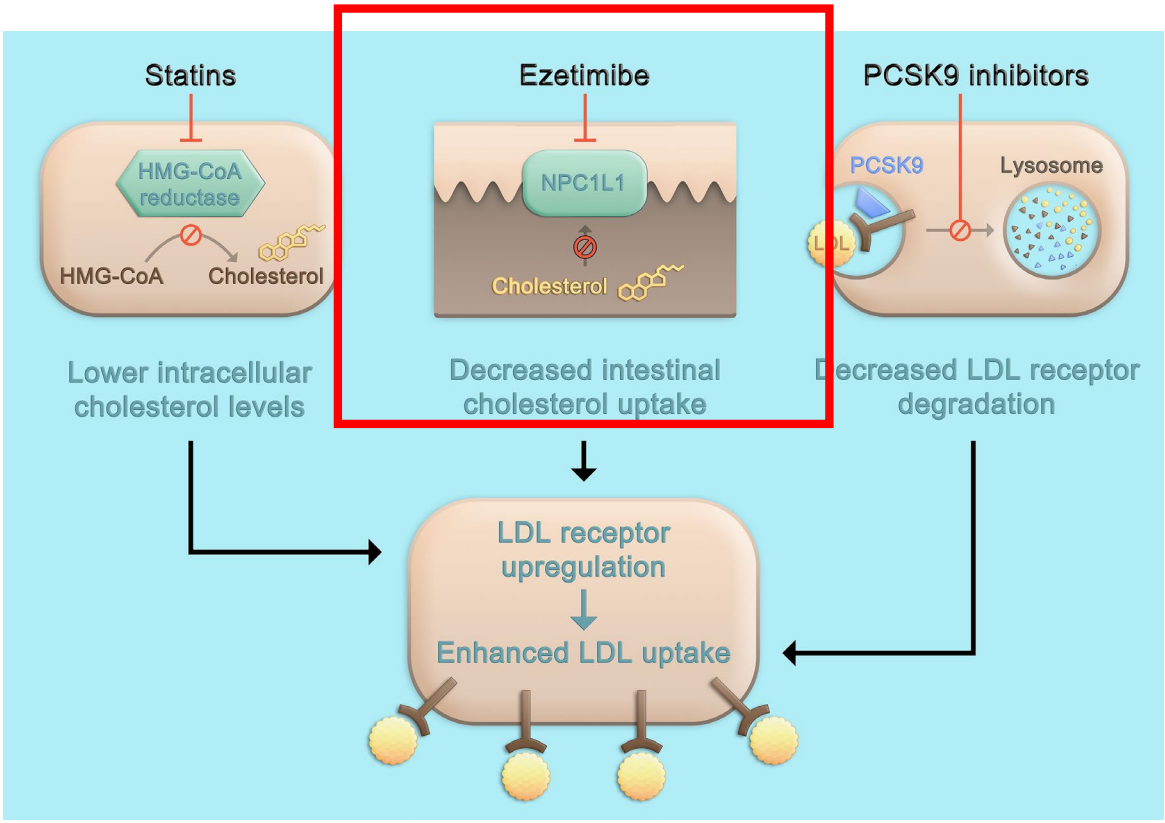
Baigent, C., et al. "Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials." *Lancet (London, England)* 376.9753 (2010): 1670-1681.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

- Recent stroke or TIA but no coronary disease randomized to 80mg/d Atorvastatin or placebo
- Followed for median 4.9 years
- 16 % RRR in statin group for first fatal stroke or nonfatal stroke
- 22% RRR ischemic stroke
- 66% increase in hemorrhagic stroke
- Hemorrhagic stroke more common in men, advanced age, previous hemorrhage, stage 2 hypertension
- Difference in absolute risk for hemorrhagic stroke was small (0.9% - 2.3% statin v 1.4% placebo)

Stroke 38.12 (2007): 3198-3204.

Ezetimibe Pharmacology



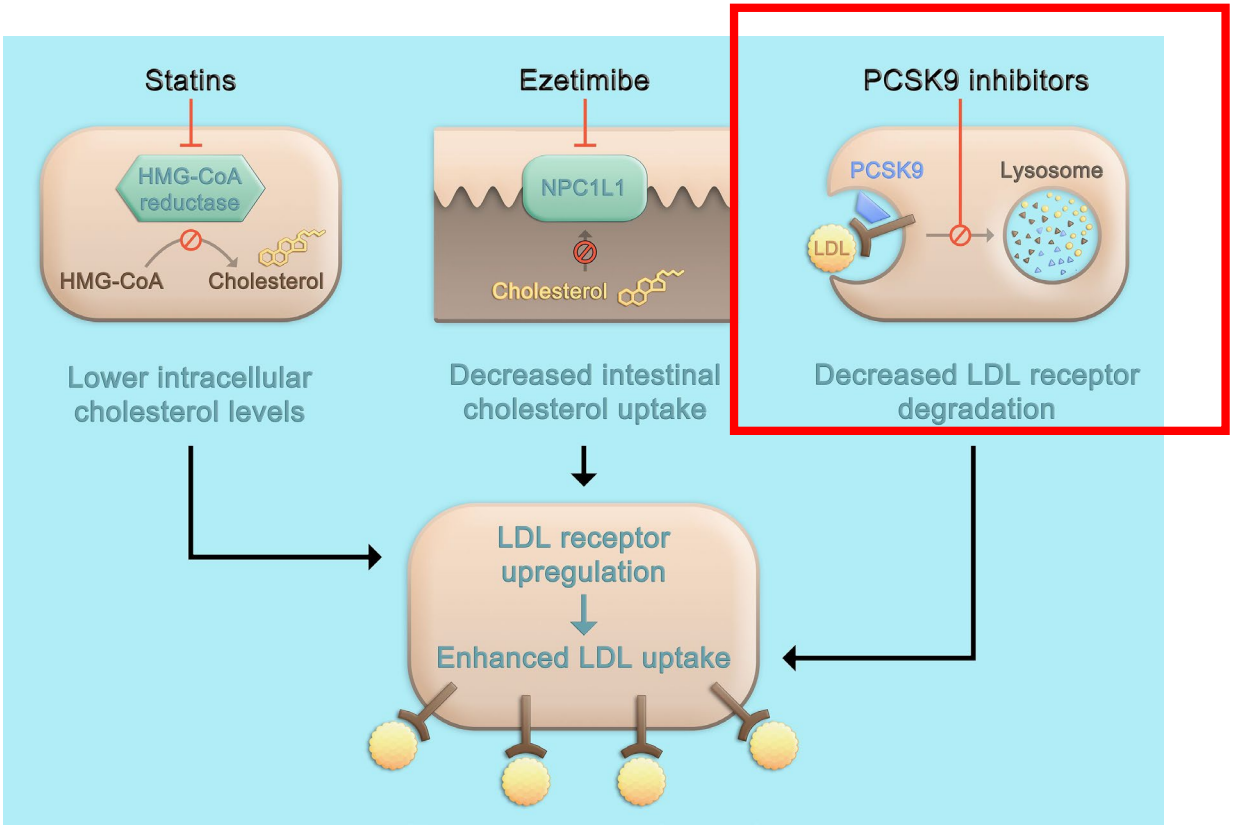
Katzmann, Julius L., Ioanna Gouni-Berthold, and Ulrich Laufs. "PCSK9 inhibition: insights from clinical trials and future prospects." *Frontiers in Physiology* 11 (2020): 595819.

Improved Reduction of Outcomes: Vytorin Efficacy International Trial (Improve-IT)

- 18,144 patients stabilized after acute coronary syndrome randomized to either ezetimibe + statin or statin alone
- Primary endpoint was a composite of cardiovascular outcomes including nonfatal stroke
- Composite endpoint reduced 6% in ezetimibe arm
- During the trial, a total of 641 patients experienced 1 stroke during median f/u of 6 years
- Treatment with ezetimibe was protective (HR, 0.79)
- Patients with previous stroke were especially likely to benefit, with a 40% reduction in stroke, NNT 12 to prevent any stroke
- Greatest benefit in 6 months after index acute coronary syndrome
- Nonsignificant increase in hemorrhagic stroke

Circulation 130.23 (2014): 2109.

PCSK9 Inhibitor Pharmacology



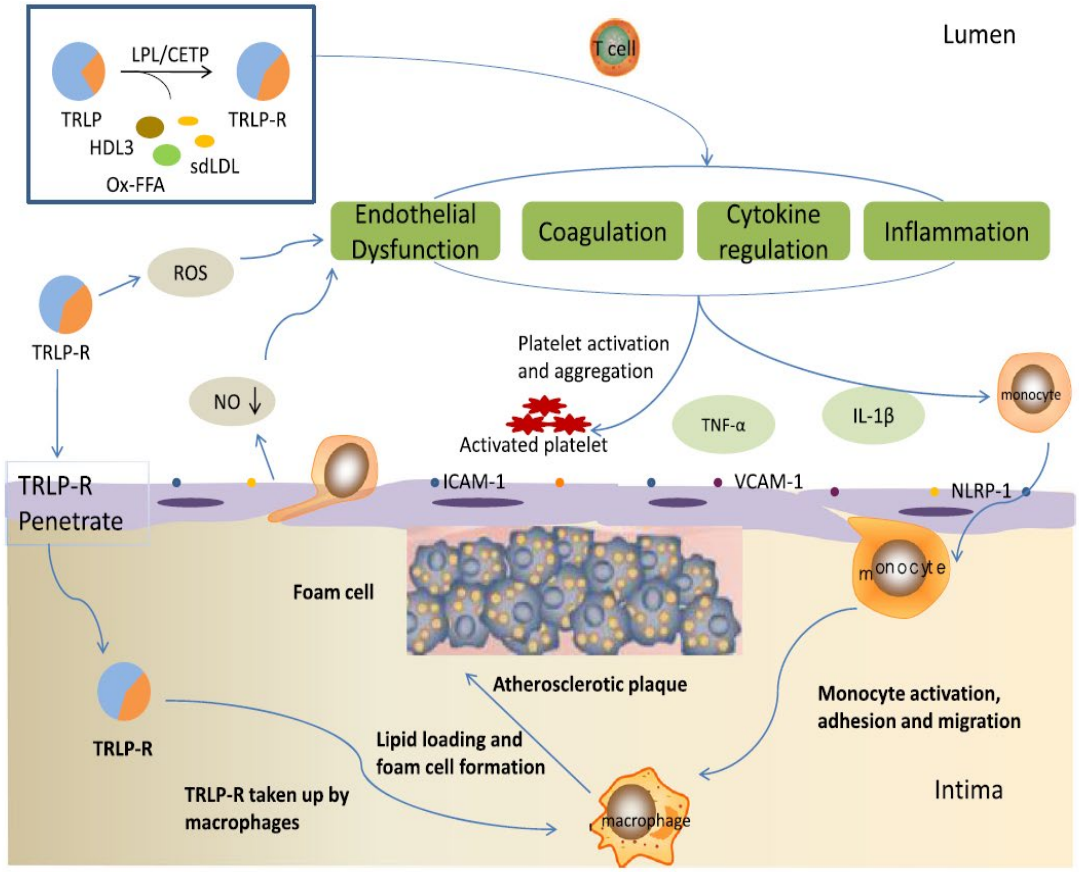
Katzmann, Julius L., Ioanna Gouni-Berthold, and Ulrich Laufs. "PCSK9 inhibition: insights from clinical trials and future prospects." *Frontiers in Physiology* 11 (2020): 595819.

Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects with Elevated Risk (Fourier trial)

- 27,564 patients with atherosclerotic disease and LDL-C >70 on statin therapy were randomized to evolocumab or placebo as SC injections
- Primary endpoint was a composite of cardiovascular death, MI, stroke, coronary revascularization
- Composite endpoint was reduced (HR, 0.85) in PCSK9 arm
- Total stroke (HR, 0.79) and Ischemic Stroke (HR, 0.75) were also reduced in PCSK 9 arm
- Patients (n=3366) who qualified for trial based on IS alone saw a significant benefit in primary endpoint (6% PCSK9 arm vs 8.5% placebo)

Circulation. 2018;138(8):756-766.

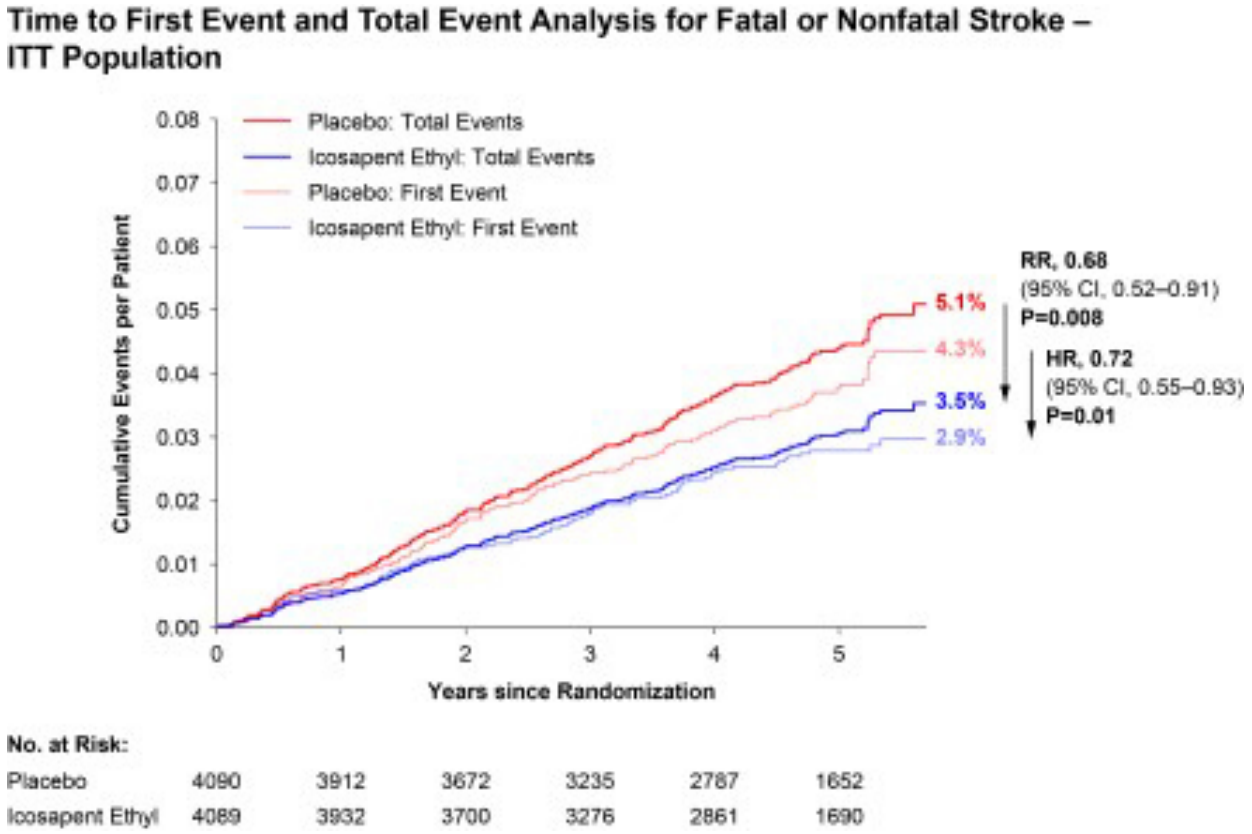
Triglyceridemia and Atherosclerosis



Eicosapentaeonoic Acid Ethyl Ester

- Highly purified form of omega-3 fatty acid eicosapentaenoic acid ester
- Appears to reduce the production of triglycerides in the liver and to enhance the clearance of triglycerides from circulating very low-density lipoprotein
- REDUCE-IT Trial, 8,000 multinational study showed that icosapent ethyl could benefit people with heart disease, diabetes or TG levels >150 whose LDL was already under control with a statin. Cardiovascular events were reduced by 25%.
- Dec 2019 FDA approved icosapent ethyl as a secondary treatment to reduce cardiovascular events
- Re-analysis done in 2021

Reduction in Ischemic Stroke with Icosapent Ethyl



- Compared with placebo, IPE 4 grams/day significant reduced first and total strokes by 28% and 32 % respectively
- NNT 114
- For every 1,000 patients treated for 5 years with IPE, about 14 strokes were averted
- Hemorrhagic stroke occurred at low rates IPE vs placebo (0.3% vs 0.2%)

Bhatt, Deepak L., et al. "Reduction in Ischemic Stroke With Icosapent Ethyl-Insights From REDUCE-IT." *Stroke* 52.Suppl_1 (2021): A57-A57.

AHA Stroke Guidelines

Very High Risk for Atherosclerotic Cardiovascular Disease(ASCVD) Events

Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions:
Major ASCVD events
History of ischemic stroke
Recent acute coronary syndrome (within the past 12 mo)
History of MI (other than recent ACS event listed above)
Symptomatic peripheral arterial disease (history of claudication with ankle-brachial index <0.85 or previous revascularization or amputation
High-risk conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD events
Diabetes
Hypertension
Chronic kidney disease (estimated glomerular filtration rate, 15–59 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$)
Current smoking

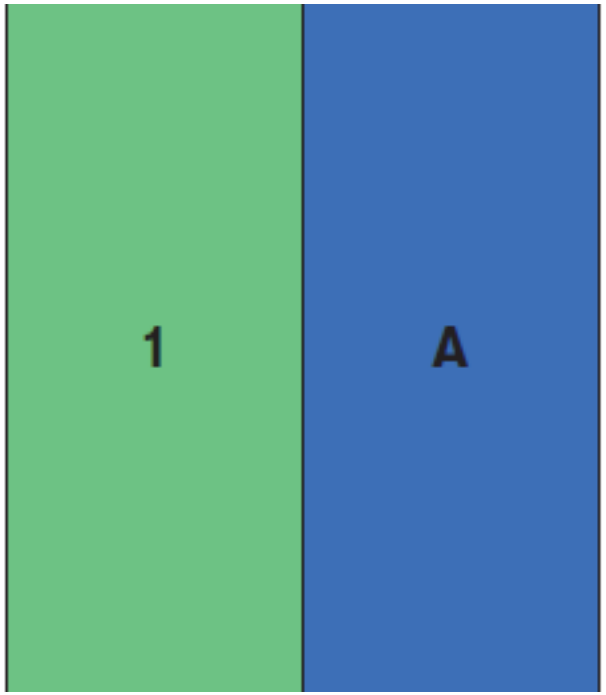
Stroke 52.7 (2021): e364-e467.

Recommendations for Treating Hyperlipidemia

COR	LOE	Recommendations
		Treatment
1	A	1. In patients with ischemic stroke with no known coronary heart disease, no major cardiac sources of embolism, and LDL cholesterol (LDL-C) >100 mg/dL, atorvastatin 80 mg daily is indicated to reduce risk of stroke recurrence.[208,209]
1	A	2. In patients with ischemic stroke or TIA and atherosclerotic disease (intracranial, carotid, aortic, or coronary), lipid-lowering therapy with a statin and also ezetimibe, if needed, to a goal LDL-C of <70 mg/dL is recommended to reduce the risk of major cardiovascular events.[210]
2a	B-NR	3. In patients with ischemic stroke who are very high risk (defined as stroke plus another major ASCVD or stroke plus multiple high-risk conditions), are taking maximally tolerated statin and ezetimibe therapy and still have an LDL-C >70 mg/dL, it is reasonable to treat with PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor therapy to prevent ASCVD events.[211–213]

Stroke 52.7 (2021): e364-e467.

Monitoring



4. In patients with stroke or TIA and hyperlipidemia, patients' adherence to changes in lifestyle and the effects of LDL-C–lowering medication should be assessed by measurement of fasting lipids and appropriate safety indicators 4 to 12 weeks after statin initiation or dose adjustment and every 3 to 12 months thereafter, based on need to assess adherence or safety.[214,215]

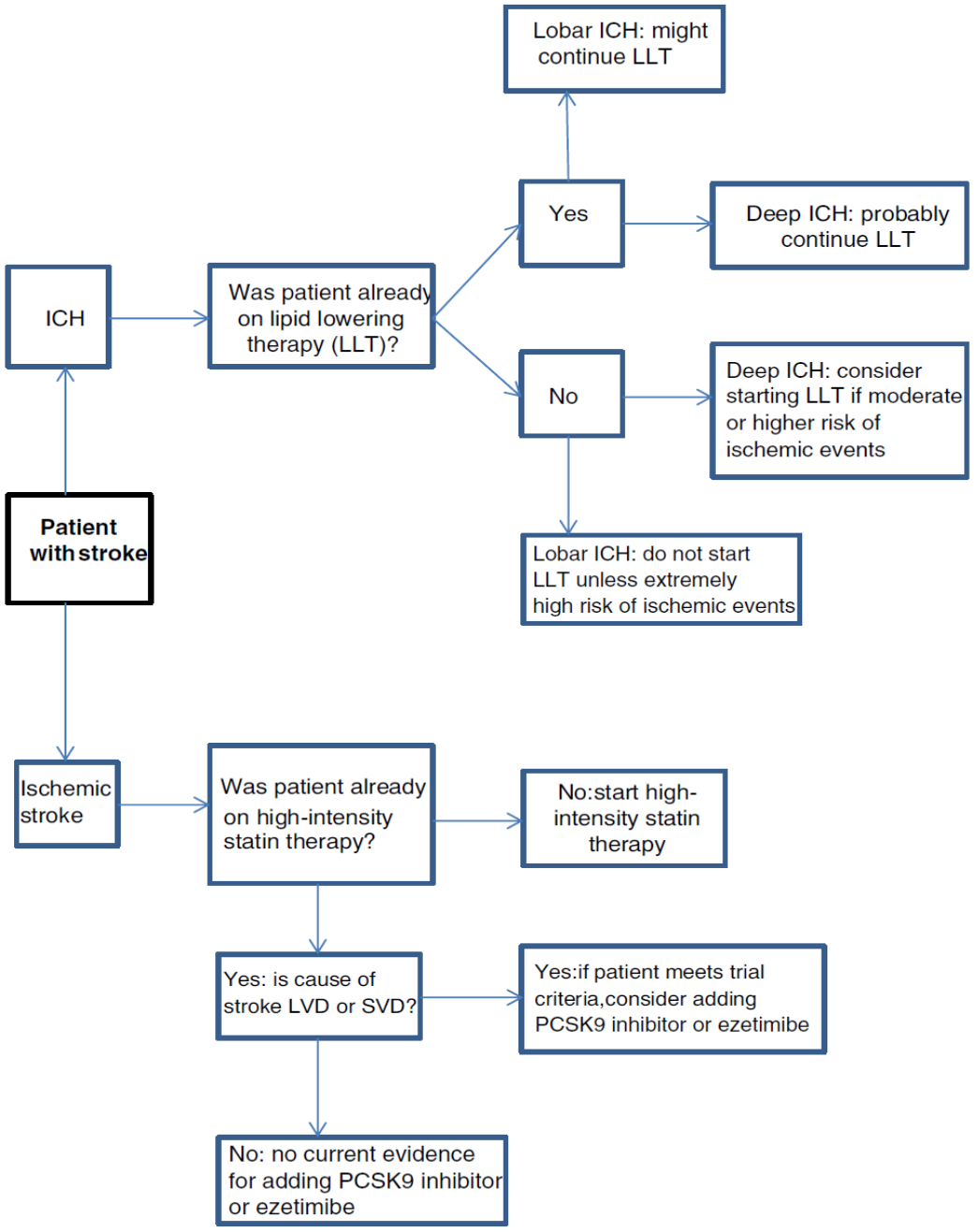
Stroke 52.7 (2021): e364-e467.

Hypertriglyceridemia

COR	LOE	Recommendations
2a	B-R	1. In patients with ischemic stroke or TIA, with fasting triglycerides 135 to 499 mg/dL and LDL-C of 41 to 100 mg/dL, on moderate- or high-intensity statin therapy, with HbA1c <10%, and with no history of pancreatitis, AF, or severe heart failure, treatment with icosapent ethyl (IPE) 2 g twice a day is reasonable to reduce risk of recurrent stroke.[219,220]
2a	B-NR	2. In patients with severe hypertriglyceridemia (ie, fasting triglycerides ≥500 mg/dL [≥5.7 mmol/L]), it is reasonable to identify and address causes of hypertriglyceridemia and, if triglycerides are persistently elevated or increasing, to further reduce triglycerides in order to lower the risk of ASCVD events by implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate therapy.[221–223]

Stroke 52.7 (2021): e364-e467.

Flowchart for Dyslipidemia Management after TIA or Stroke



Current treatment options in cardiovascular medicine 21.12 (2019): 1-15.

Beyond the Guidelines (publications in 2022)

- Cholesterol Trial Treatment Collaboration evaluated effect on statin therapy on muscle symptoms
- 19 double blinded trials of statin therapy were reviewed (n=123,940)
- Meta-analysis on pre-specified muscle outcomes
- Participants on statin therapies had 7% relative increase in muscle complaints by year 1
- Only 1/15 participant complaints were related to the statin
- Concluding that statin therapy caused a small excess of mild muscle pain
- Greater than 90% of complaints were not due to the statin

The Lancet 400.10355 (2022): 832-845.

Beyond the Guidelines (2022)

- Recent meta-analysis evaluate continued intensification of statin dosing vs less intensive dosing
- 11 trials evaluated over 4 years (n=20,163)
- More intensive statin treatment showed greater reduction in absolute risk (absolute risk, 8.1% vs 9.3%). NNT=90
- Also, reduced risk of Major Adverse Cardiac Events(MACE) (absolute risk 13.9% vs 16.7%)
- Pooled analysis from two trials showed no difference in cognitive adverse effects

JAMA Neurol. 2022;79(4):349-358

Deintensification or No Statin Treatment Is Associated With Higher Mortality in Patients With Ischemic Stroke or Transient Ischemic Attack

Jennifer L. Dearborn-Tomazos, MD; Xin Hu, MSPH; Dawn M. Bravata, MD; Manali A. Phadke, MS; Fitsum M. Baye, MS; Laura J. Myers, PhD; John Concato, MD; Alan J. Zillich, PharmD; Mathew J. Reeves, BVSc, PhD; Jason J. Sico, MD

RESULTS: The population included 9380 predominately White (71.1%) men (96.3%) who were hospitalized for stroke or TIA. In this sample, 34.1% of patients (n=3194) were discharged off a statin medication. Deintensification occurred in 14.0% of patients (n=1312) and none to none in 20.5% (n=1924). Deintensification and none to none were associated with a higher odds of mortality as compared with goal to goal (adjusted odds ratio 1-year mortality: deintensification versus goal to goal, 1.26 [95% CI, 1.02–1.57]; none to none versus goal to goal, 1.59 [95% CI, 1.30–1.93]). Adjustments for differences in baseline characteristics using propensity weighted scores demonstrated similar results.

CONCLUSIONS: Underutilization of statins, including no treatment or underdosing after stroke (deintensification), was observed in approximately one-third of veterans with ischemic stroke or TIA and was associated with higher mortality when compared with patients who were at goal for statin prescription dosing.

Crossing the Chasm in Lipid Management

- Increase grassroots education of guidelines
- Developing consensus of quality measures on lipid parameters (intensity, frequency of testing)
- Health systems need to gather stakeholders to develop implementation strategies
- Electronic Health Records need to make clinical workflow efficient
- Focus on education around the use of the term statin intolerance for patients and providers