Are you Following the Guidelines in Measuring and Managing Dyslipidemia?

A Focus on Secondary Prevention

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Presenter Disclosure

Dr. Shaun Goodman

Are you following the guidelines in measuring and managing dyslipidemia?

Relationships with financial sponsors:

- **Grants/Research Support:** Amgen, Anthos Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, CYTE Ltd., Daiichi-Sankyo/American Regent, Eli Lilly, Esperion, Ferring Pharmaceuticals, Idorsia, Merck, Novartis, Novo Nordisk A/C, Pendopharm/Pharmascience, Pfizer, Regeneron, Sanofi, Servier
- **Speakers Bureau/Honoraria:** Amgen, Canadian Heart Failure Society, Canadian Heart Research Centre and MD Primer, Canadian VIGOUR Centre, Cleveland Clinic Coordinating Centre for Clinical Research, Duke Clinical Research Institute, Jewish General Hospital\ CIUSSS Centre-Ouest-de-l'Ile-de-Montreal, New York University Clinical Coordinating Centre, PERFUSE Research Institute, Peter Munk Cardiac Centre Clinical Trials and Translation Unit, TIMI Study Group (Brigham Health), EOCI, LiV
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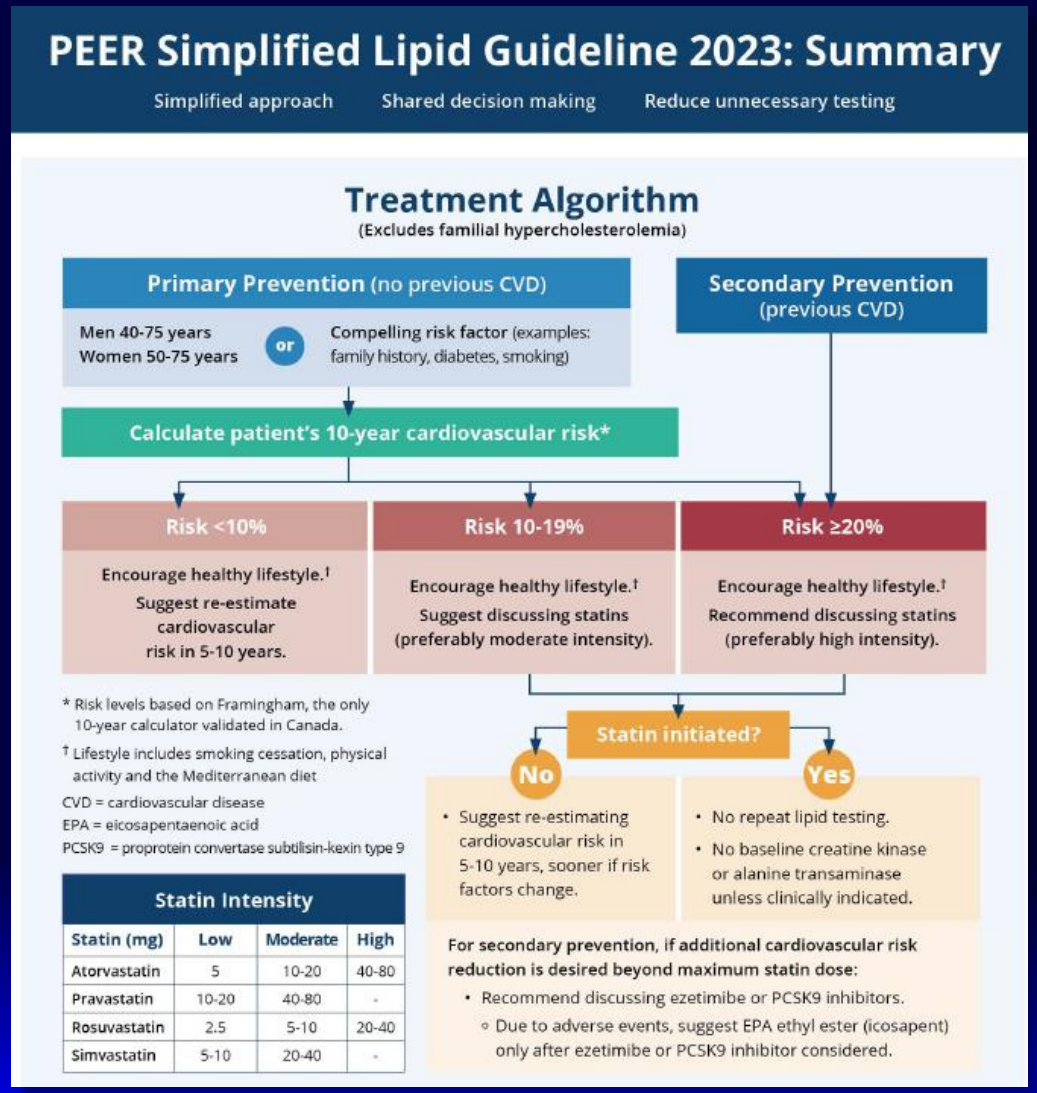
- **Patents:** N/A
- **Other:** N/A

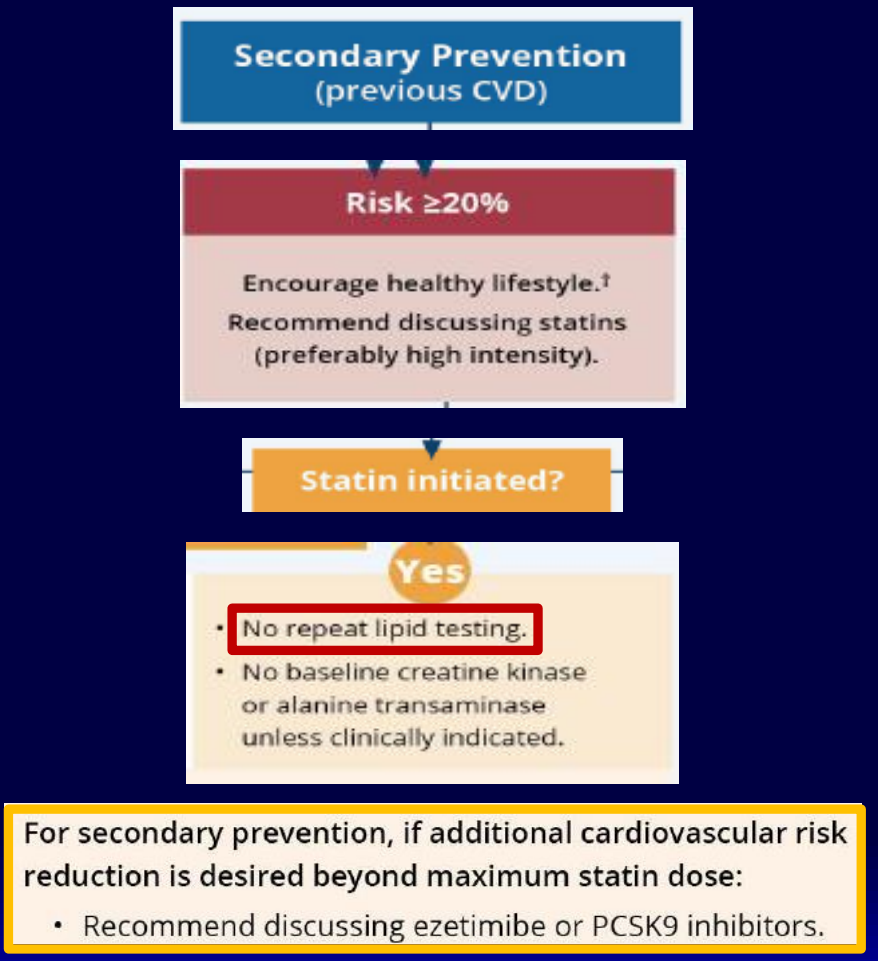
2023 PEER Simplified Lipid Guideline for the Prevention and Management of Cardiovascular Disease in Primary Care

- Family physicians deliver most health care services in Canada, including most primary prevention for CVD
  - intended audience = family physicians, primary care providers, and their teams
- Recommendations must be accessible, applicable, and feasible to implement in primary care settings
  - most primary care providers lack sufficient time to provide all the care required in their communities of practice, and most guidelines do not consider the time needed to implement recommendations for eligible patients
- "In our evidence-to-decision framework, based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, we considered the time needed for clinicians and patients to implement guideline recommendations in light of opportunity costs and competing demands."

Kolber et al *Can Fam Phys* 2023;69:675-86

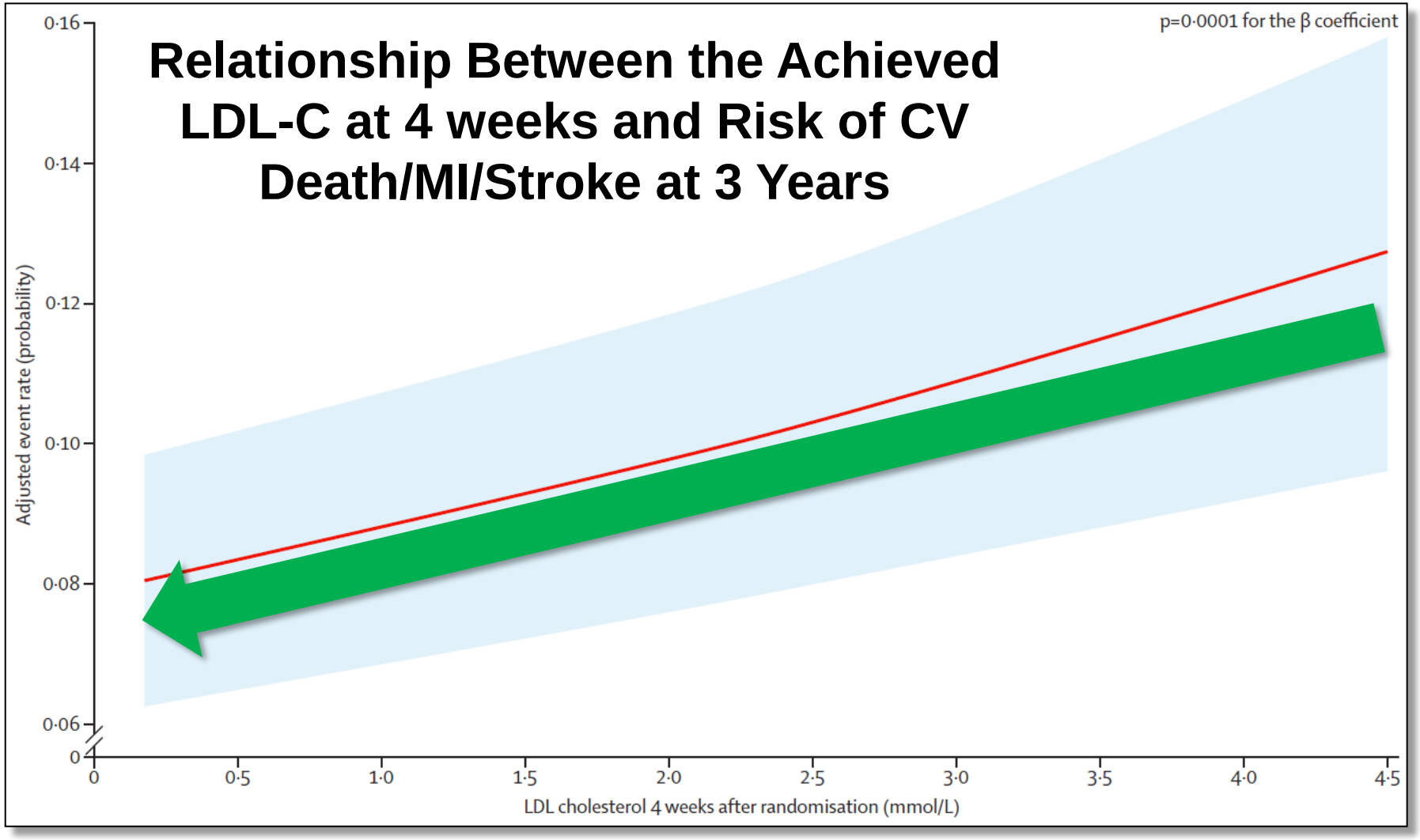
2023 PEER Simplified Lipid Guideline for the Prevention and Management of Cardiovascular Disease in Primary Care





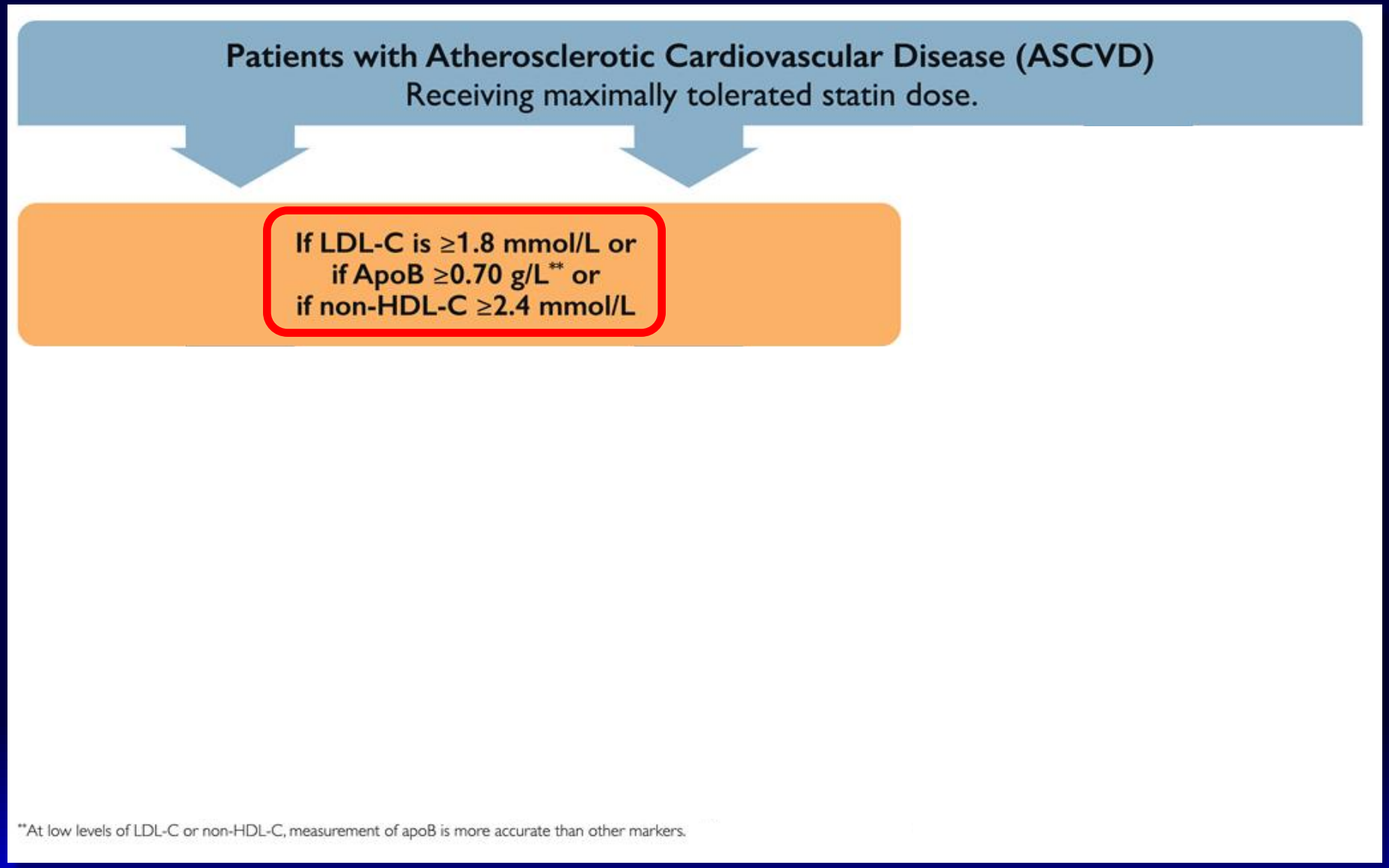
Kolber et al *Can Fam Phys* 2023;69:675-86

Lowest LDL-C Is Best



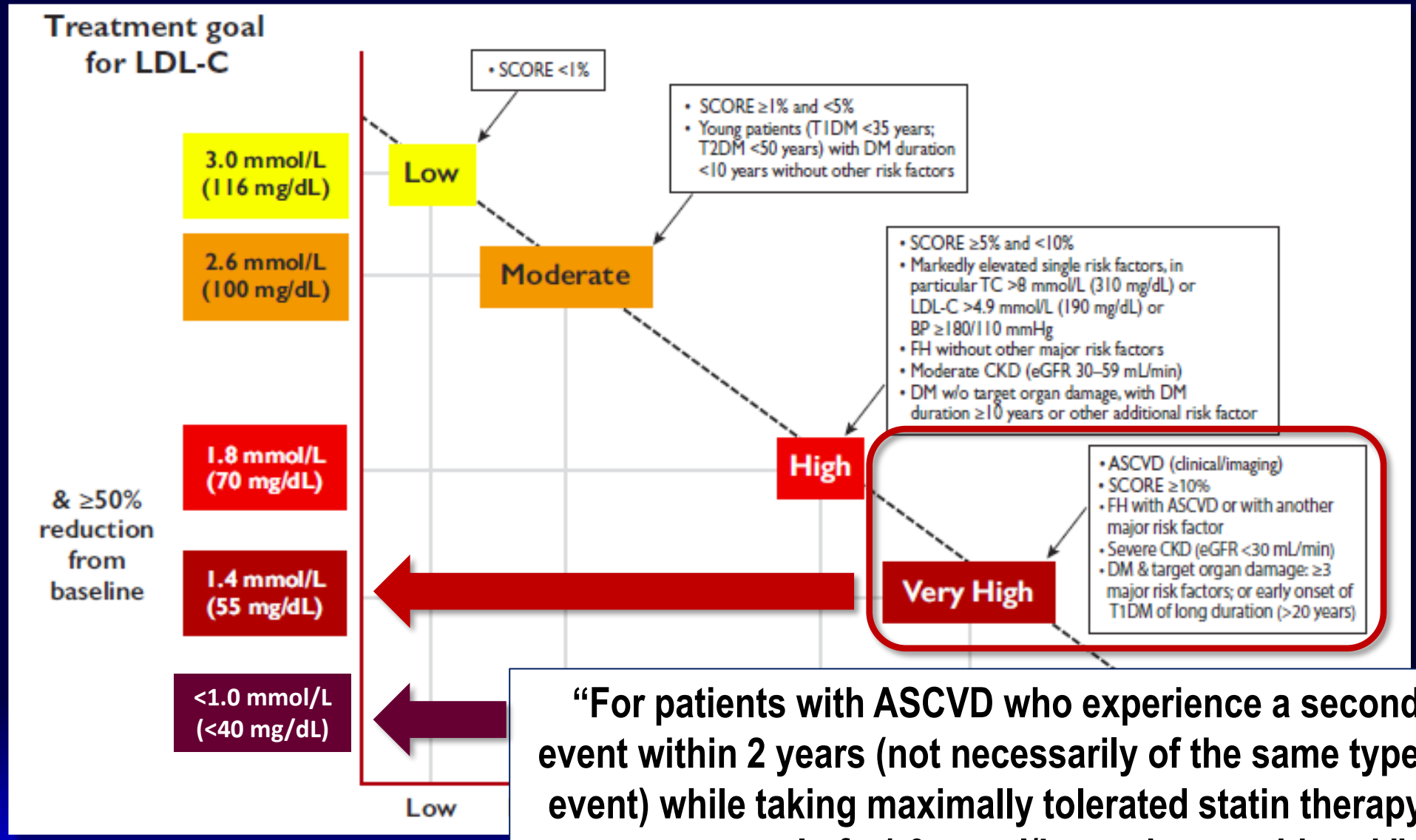
Giugliano et al *Lancet* 2017;390:1962-71

2021 CCS Guidelines for the Management of Dyslipidemia



Pearson et al *Can J Cardiol* 2021;37:1129-50

ESC/EAS Dyslipidemia Guidelines



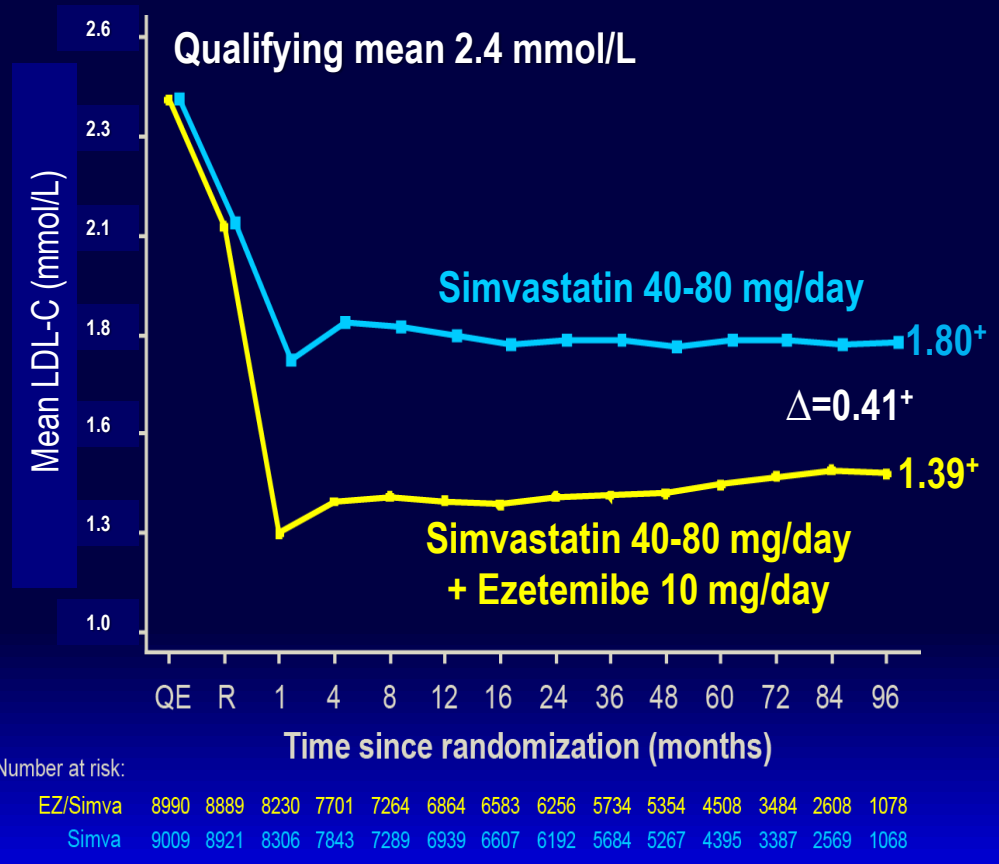
"For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin therapy, an LDL-C goal of <1.0 mmol/L may be considered."

Addition of Cholesterol Absorbtion Inhibition (Ezetimbe) to Moderate* Lipid Lowering Post-ACS

Pts ≥50 yrs hospitalized for ACS<10 days with ≥1 high risk feature and LDL-C >1.3 mmol/L

LDL-C Over Time

Median Time Average (mmol/L)+

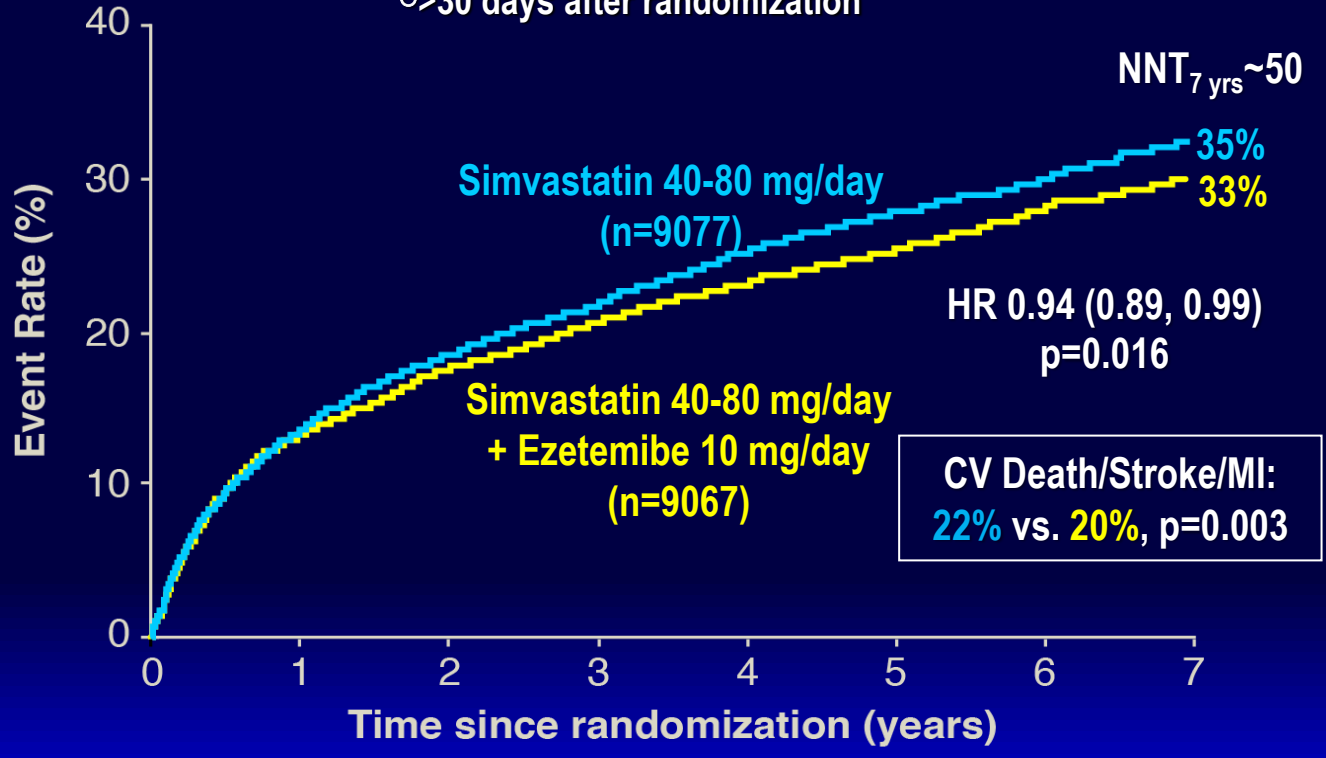


Number at risk:

EZ/Simva	8990	8889	8230	7701	7264	6864	6583	6256	5734	5354	4508	3484	2608	1078
Simva	9009	8921	8306	7843	7289	6939	6607	6192	5684	5267	4395	3387	2569	1068

CV Death, MI, UA Requiring Rehospitalization, ○Coronary Revascularization, or Stroke

○>30 days after randomization



Cannon et al *N Engl J Med* 2015;372:2387-97

Health professional risk communication

Health Canada Santé Canada

Ezetrol (ezetimibe) and the Risks of Drug-Induced Liver Injury and Severe Cutaneous Adverse Reactions

Last updated: 2024-03-27

Issue

Ezetrol (ezetimibe) may cause serious adverse reactions, including drug-induced liver injury (DILI) and severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilic and systemic symptoms (DRESS).

https://recalls-rappels.canada.ca/en/alert-recall/ezetrol-ezetimibe-and-risks-drug-induced-liver-injury-and-severe-cutaneous-adverse

Health professional risk communication

Health Canada Santé Canada

Ezetrol (ezetimibe) and the Risks of Drug-Induced Liver Injury and Severe Cutaneous Adverse Reactions

Last updated: 2024-03-27

The Market Authorization Holder conducted a review of international safety data and the scientific literature and identified 42 post-marketing cases of DILI in patients taking Ezetrol, including a Canadian case of liver injury associated with ezetimibe monotherapy. There was sufficient evidence to suggest a causal association between ezetimibe monotherapy and DILI.

The review also identified rare cases of SCARs in patients taking Ezetrol. There was sufficient evidence to suggest at least a reasonable possibility of a causal association with some cases of SJS, TEN, and DRESS.

https://recalls-rappels.canada.ca/en/alert-recall/ezetrol-ezetimibe-and-risks-drug-induced-liver-injury-and-severe-cutaneous-adverse

Addition of Cholesterol Absorbtion Inhibition (Ezetimbe) to Moderate* Lipid Lowering Post-ACS

Pts ≥50 yrs hospitalized for ACS<10 days with ≥1 high risk feature and LDL-C >1.3 mmol/L

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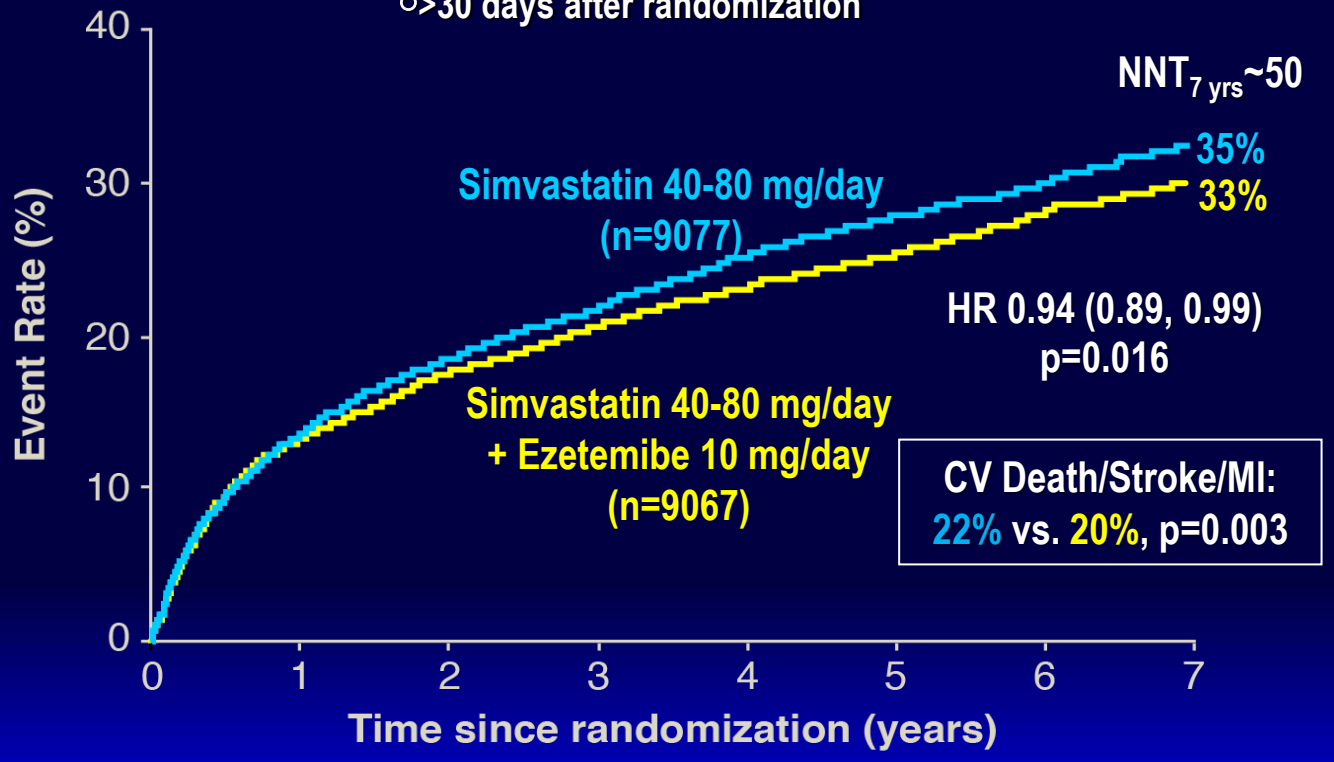

Well-tolerated and safe: no statistically significant differences in muscle-, liver- or gallbladder-related events, or cancer[1]

[1]Giugliano et al *JACC CardioOnc* 2020;2:385-96

Cannon et al *N Engl J Med* 2015;372:2387-97

Health professional risk communication

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Ezetrol (ezetimibe) and the Risks of Drug-Induced Liver Injury and Severe Cutaneous Adverse Reactions

Last updated: 2024-03-27

Healthcare professionals are advised to:

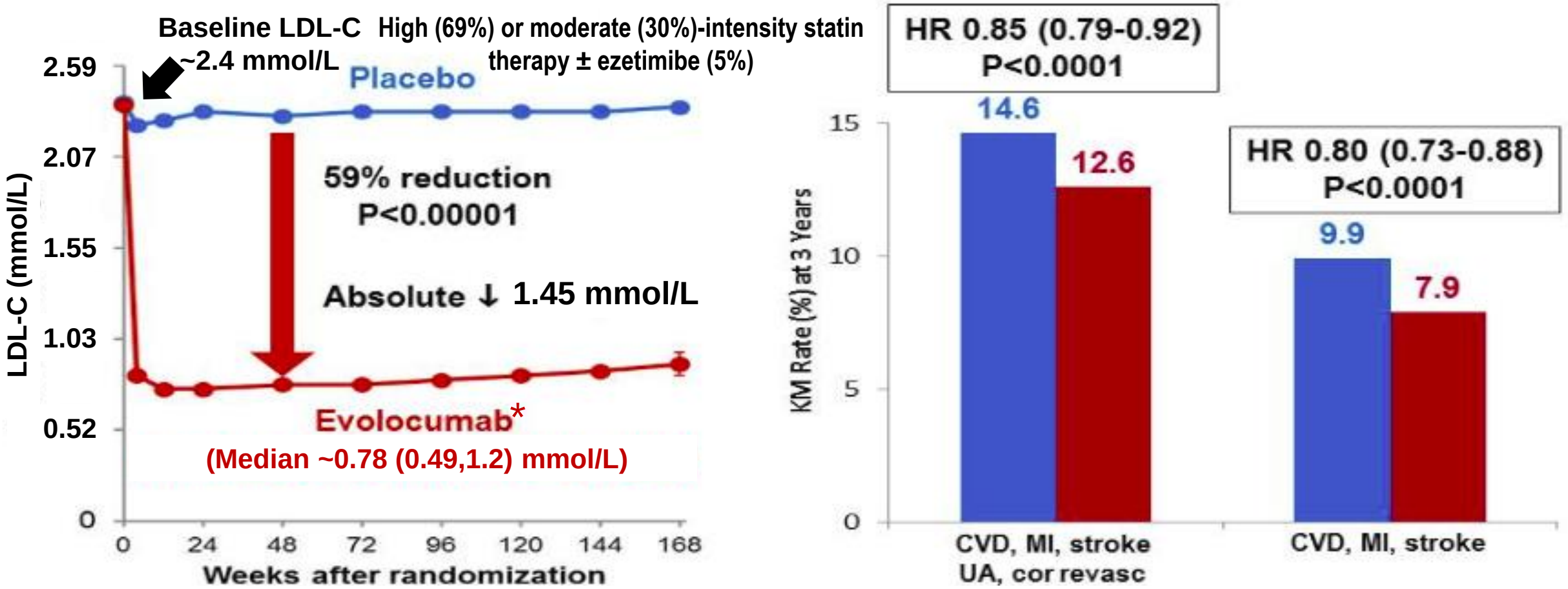
Consider performing liver function tests at the initiation of Ezetrol, whether administered as monotherapy or in combination with a statin or fenofibrate and subsequently as required.

https://recalls-rappels.canada.ca/en/alert-recall/ezetrol-ezetimibe-and-risks-drug-induced-liver-injury-and-severe-cutaneous-adverse

Summary of Effects of PCSK9i Evolocumab

fourier

27,564 high-risk, stable patients with established CVD: Prior MI (81%), prior non-hemorrhagic stroke (19%), or symptomatic PAD (13%) AND LDL-C ≥1.8 mmol/L or non-HDL-C ≥2.6 mmol/L



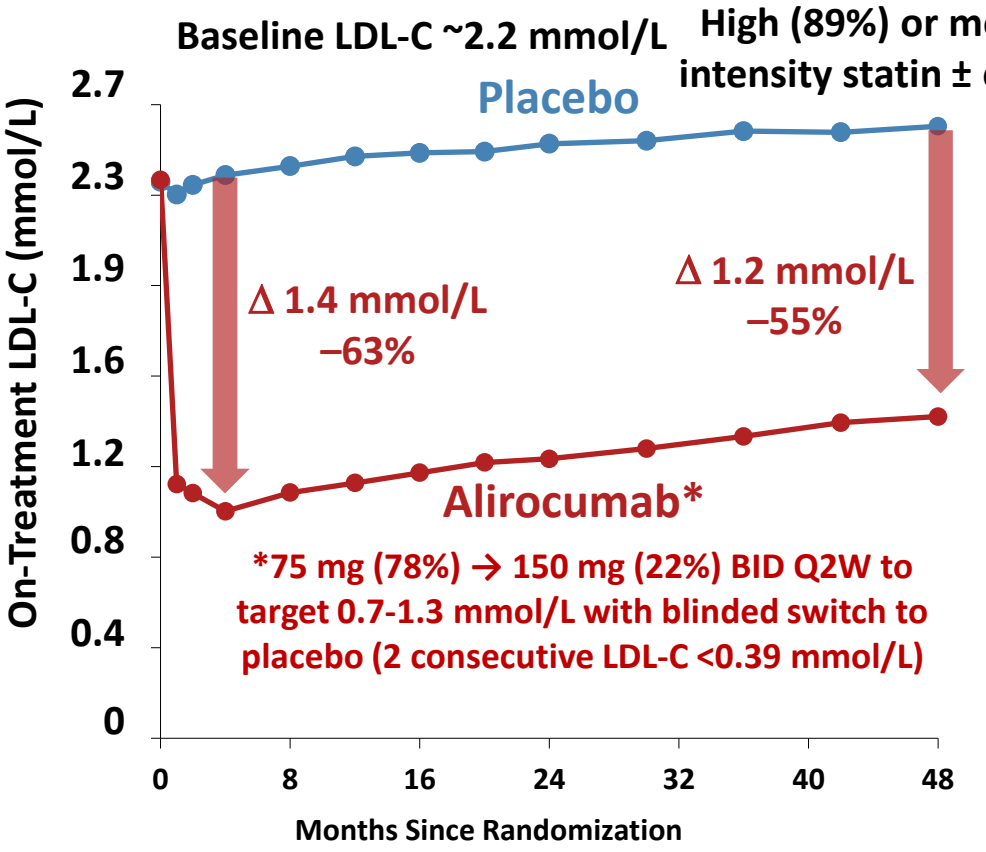
*140 mg Q2W or 420 mg SC Q4W

Sabatine et al *N Engl J Med* 2017;376:1713-22

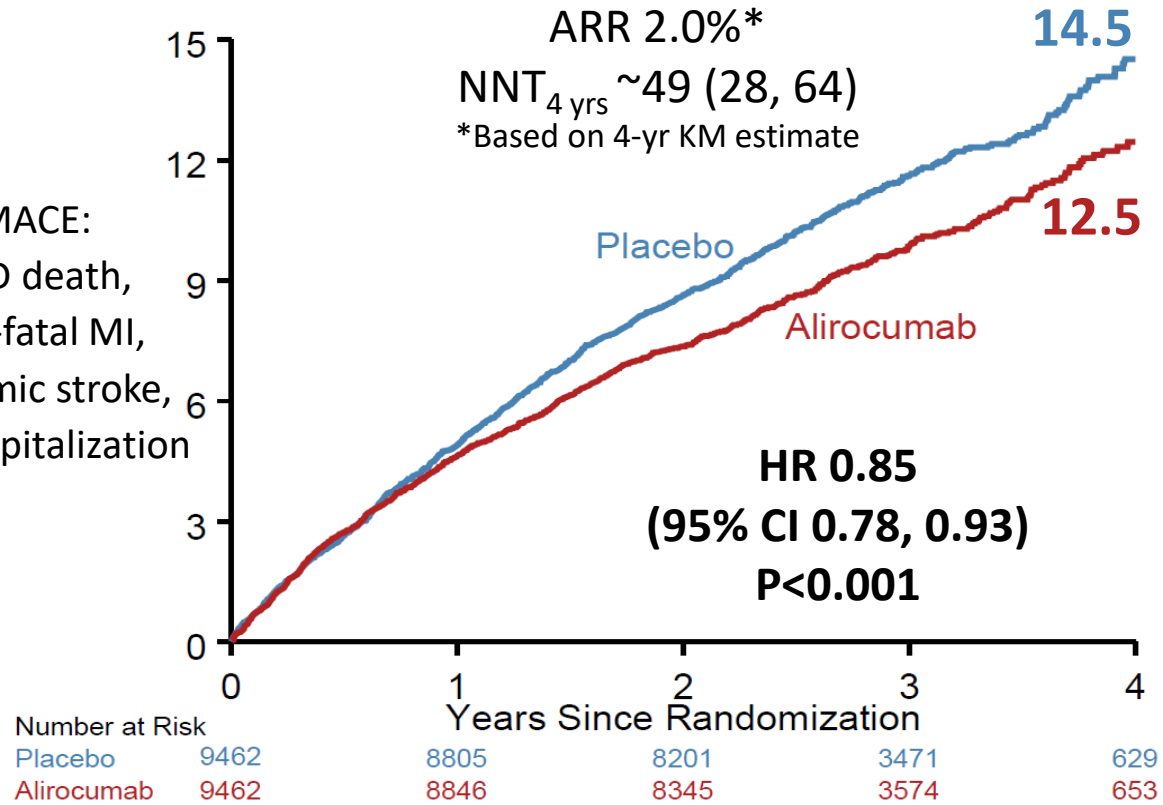
ODYSSEY OUTCOMES

PCSK9 Inhibition with Alirocumab

18,924 patients ≥40 years 1-12 (median 2.6) months post-ACS (34% STEMI, 48% NSTEMI, 17% UA) on maximally tolerated atorva/rosuvastatin AND LDL-C ≥1.8 mmol/L, non-HDL-C ≥2.6 mmol/L, or ApoB≥0.8 mg/dL



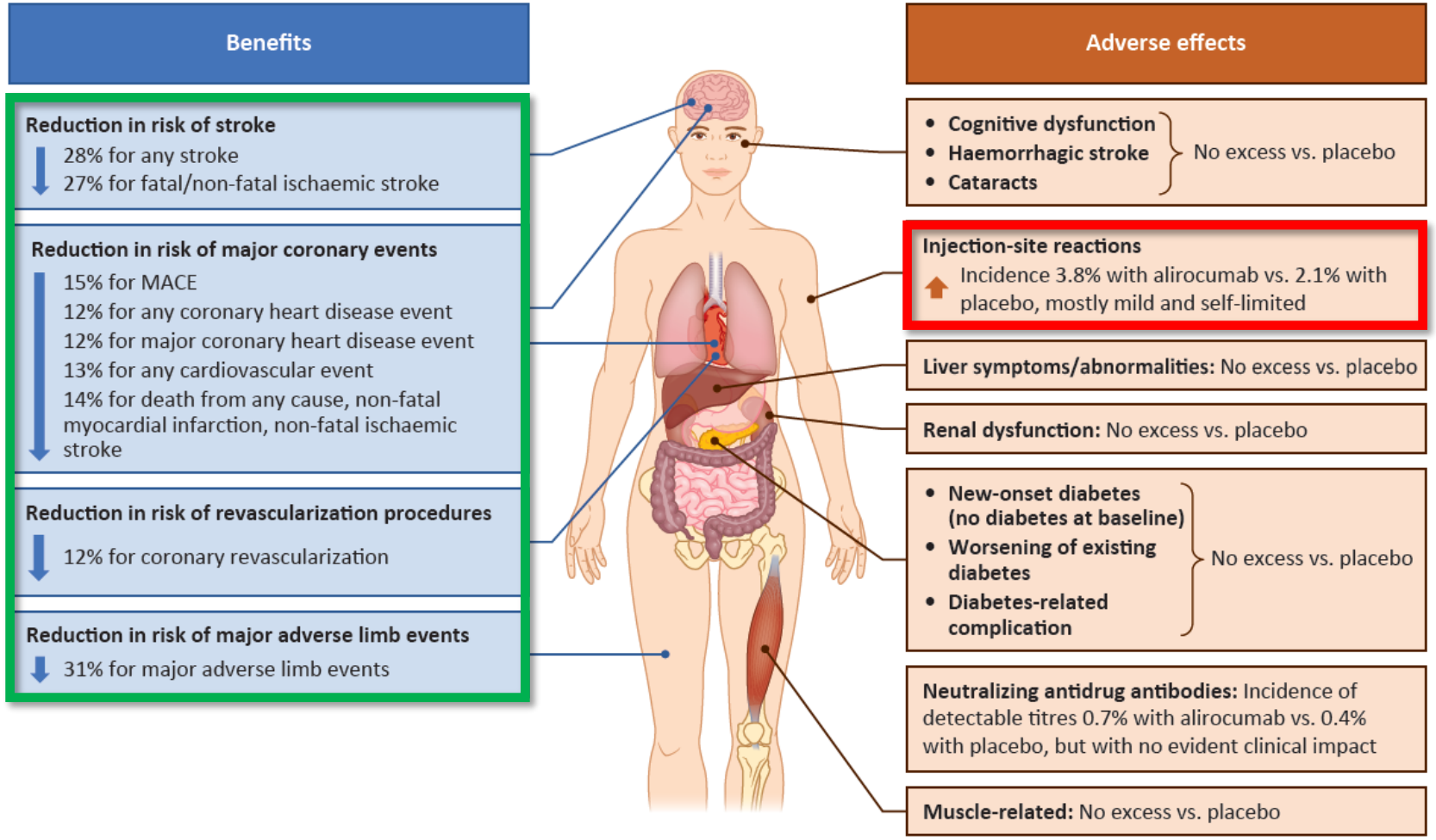
MACE:
CHD death,
non-fatal MI,
ischemic stroke,
UA hospitalization



Schwartz G et al *N Engl J Med* 2018;379:2097-107

ODYSSEY OUTCOMES

Efficacy, Safety, and Tolerability of Alirocumab

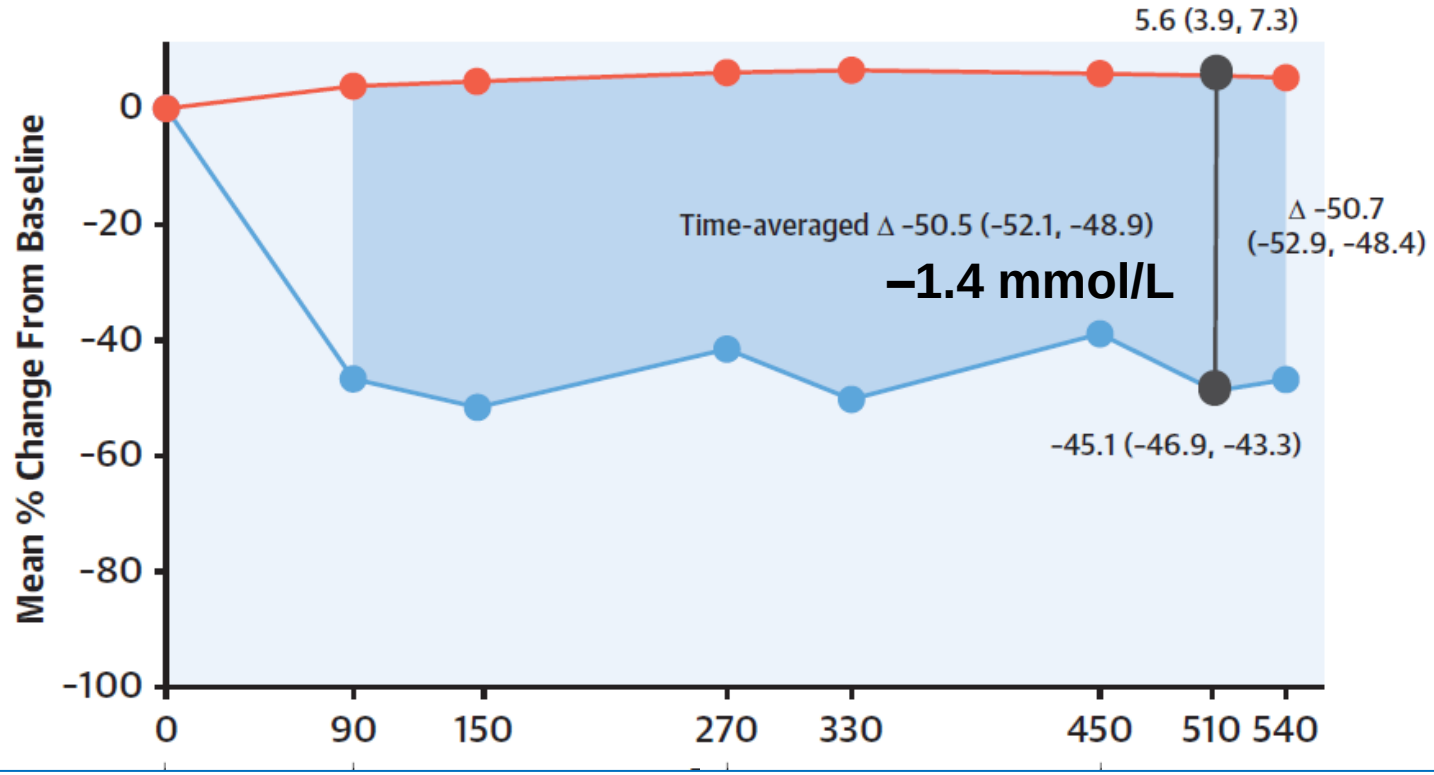


Goodman et al *Eur Heart J CV Pharmacother* 2024;doi.org/10.1093/ehjcvp/pvae025

Inclisiran: Durable and Potent with Consistent LDL-C Lowering Effect over 18 Months

n=3,660
mean age 64 yrs
33% women
85% ASCVD
20% HeFH
92% on statin (74% high-intensity)
14% ezetimibe
mean LDL-C 2.9 mmol/L

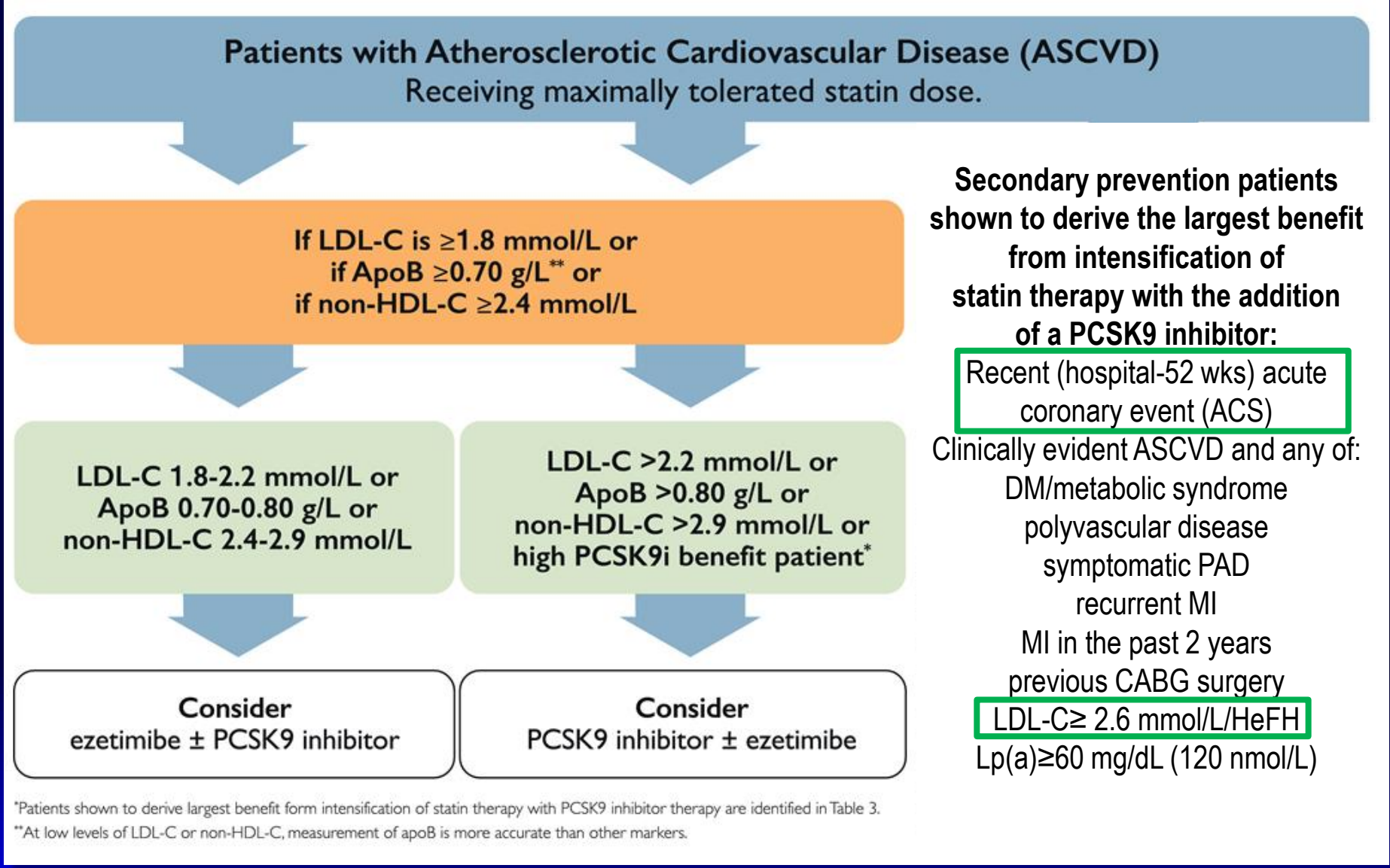
Pooled Data ORION-9, -10, -11



Pre-specified exploratory CV endpoint: 9.4% vs. 7.1%
Non-fatal MI: 7.8% vs. 5.2%

Wright et al *J Am Coll Cardiol* 2021;77:1182-93

2021 CCS Guidelines for the Management of Dyslipidemia



Secondary prevention patients shown to derive the largest benefit from intensification of statin therapy with the addition of a PCSK9 inhibitor:

Recent (hospital-52 wks) acute coronary event (ACS)

Clinically evident ASCVD and any of:

DM/metabolic syndrome

polyvascular disease

symptomatic PAD

recurrent MI

MI in the past 2 years

previous CABG surgery

LDL-C≥ 2.6 mmol/L/HeFH

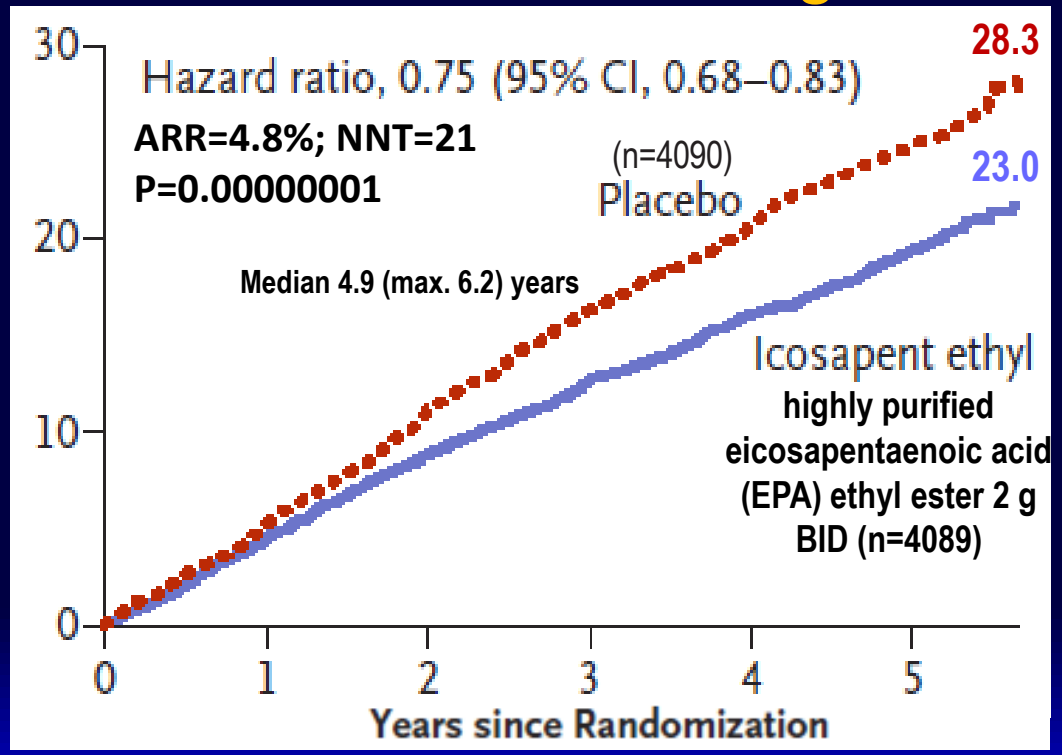
Lp(a)≥60 mg/dL (120 nmol/L)

Pearson et al *Can J Cardiol* 2021;37:1129-50

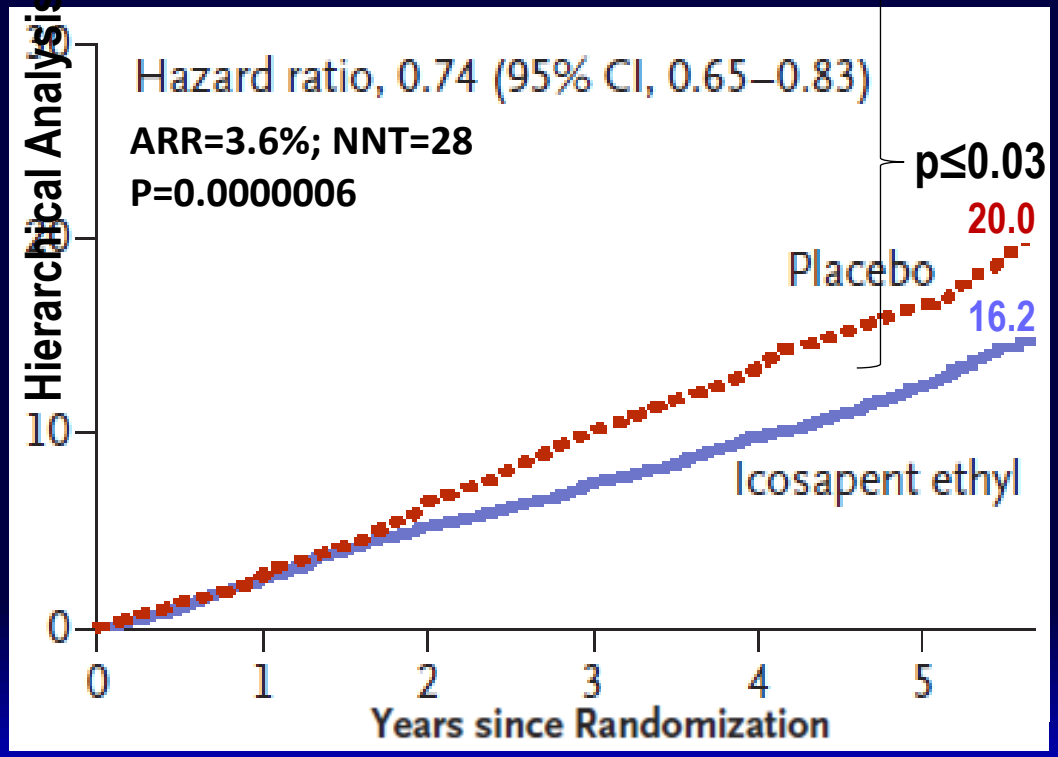
CV Risk Reduction with Icosapent Ethyl

8,179 pts with ASCVD (71%) or ≥50 yrs + DM + CVD risk factor,
fasting triglycerides 1.52-5.63 mmol/L and LDL-C 1.06-2.59 mmol/L on statin

CV Death/MI/Stroke/Coronary Revasc./Unstable Angina



CV Death/MI/Stroke



Bhatt et al *N Engl J Med* 2019;380:11-22

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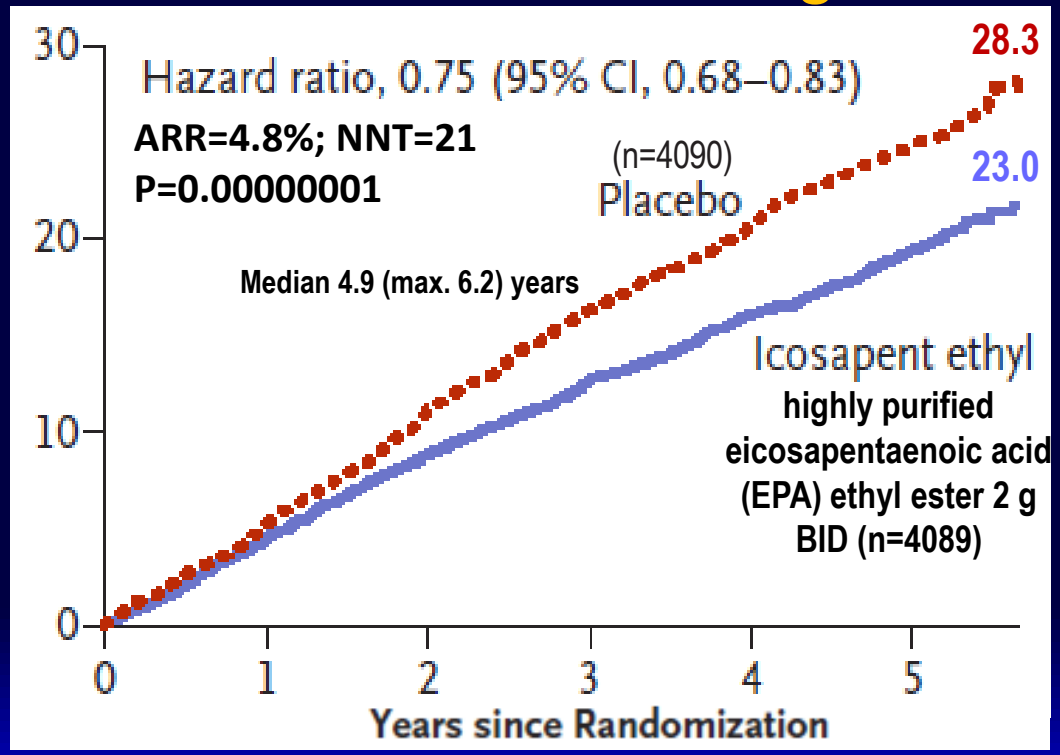


Hierarchical Analysis

- CV Death/MI -25%
- Fatal/Nonfatal MI -31%
- Urgent/Emergent Revasc -35%
- CV Death -20%
- Hosp. for UA -32%
- Fatal/Nonfatal Stroke -28%
- Death/MI/Stroke -23%
- Death -13% (p=0.09)

} p≤0.03

Bleeding 2.7% vs. 2.1%, p=0.06
Periph. Edema 6.5% vs. 5%, p=0.002
Constipation 5.4% vs. 3.6%, p<0.001
Atrial fibrillation 5.3% vs. 3.9%, p=0.003

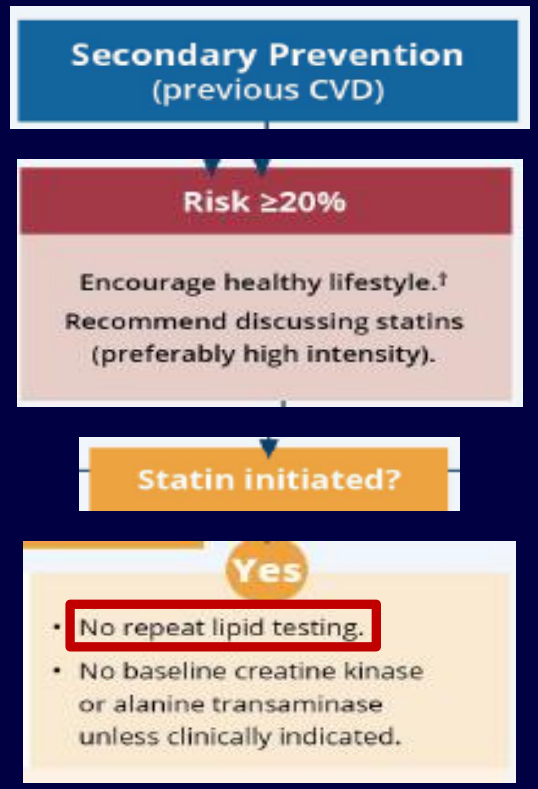
Bhatt et al *N Engl J Med* 2019;380:11-22

CV Risk Reduction with Icosapent Ethyl

- Benefit of icosapent ethyl (IPE)
  - consistent across subgroups, including sex, diabetes, renal function, prior revascularization, HF, smoking status → large absolute benefits in prior MI and recent ACS patients
  - not only for first CV events, but also recurrent and total ischemic events
  - regardless of baseline and achieved trigylceride (TG) levels
  - significant (~40% relative) reductions in hsCRP
  - significant (~360% relative) increase in EPA levels correlated strongly with CV events and all-cause mortality

Bhatt et al *N Engl J Med* 2019;380:11-22; *J Am Coll Cardiol* 2019;74:1159-61; *J Am Coll Cardiol* 2019;73:2791-802; Peterson et al *Circulation* 2021;143:33-44; Majithia et al *Circulation* 2021;144:1750-59; Verma et al *Circulation* 2021;144:1845-55; Peterson et al *JAHA* 2022;11:e022937; Boden et al *Eur Heart J* 2020; 41:2304-12; Gaba et al *J Am Coll Cardiol* 2022;79:1660-71; Selvaraj et al *JAHA* 2022;11:e024999; Miller et al *Eur Heart J CV Pharmacother* 2023;9:129-37; Sayah et al *Eur Heart J* 2024;45:1173-76

2023 PEER Simplified Lipid Guideline for the Prevention and Management of Cardiovascular Disease in Primary Care



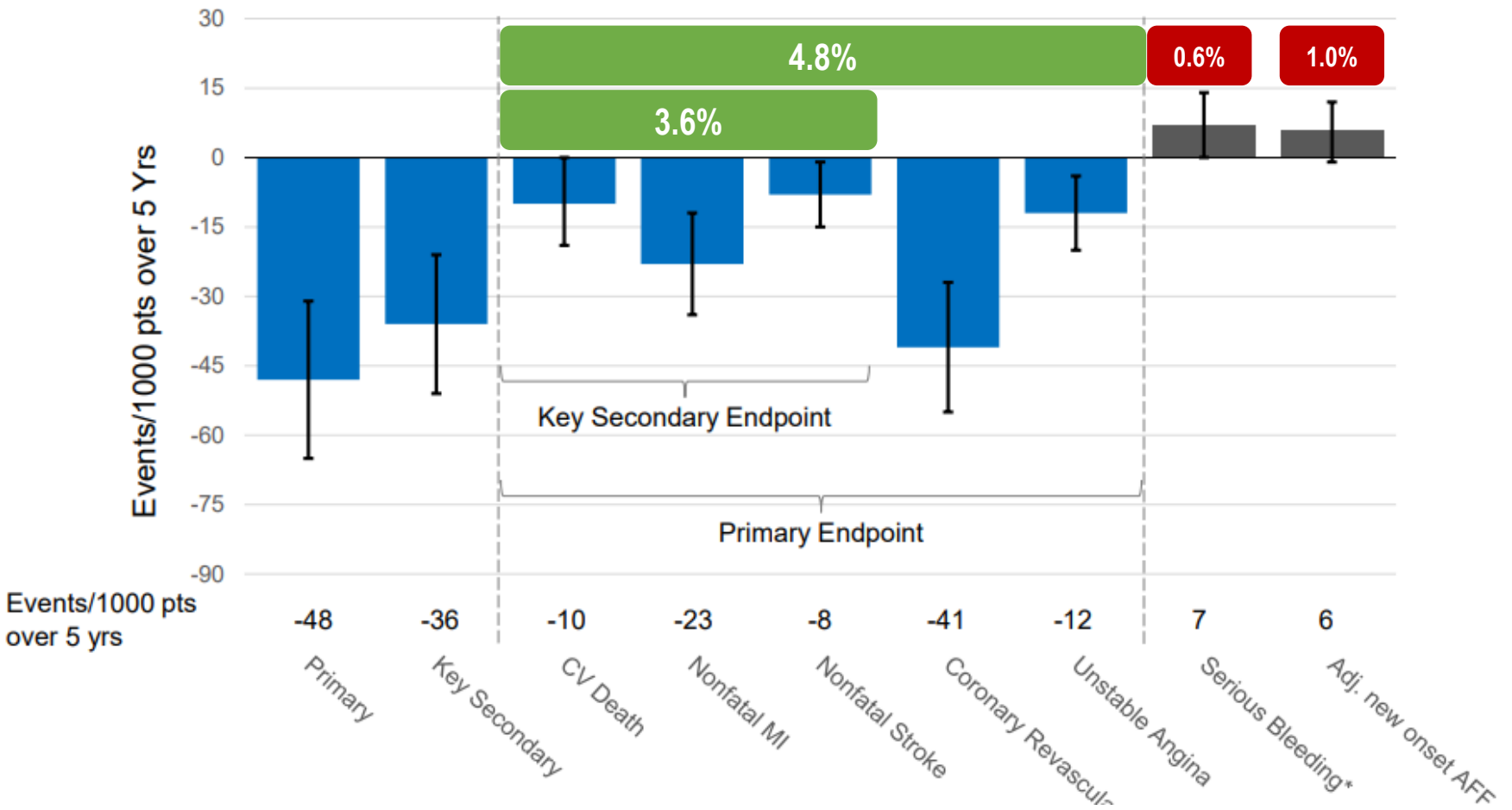
Given potential adverse effects (atrial fibrillation, bleeding), we **suggest** adding icosapent to statins only after considering ezetimibe or PCSK9 inhibitors

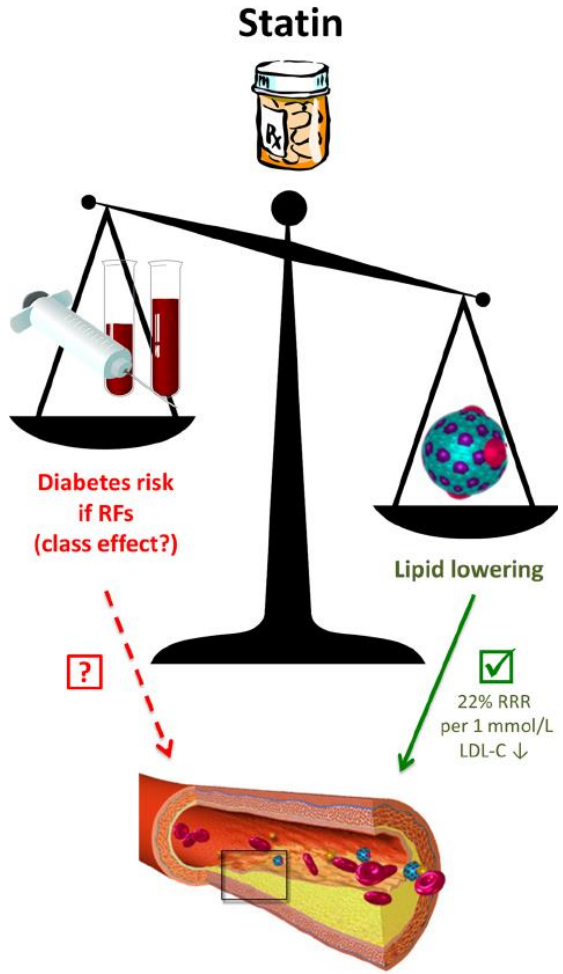
For secondary prevention, if additional cardiovascular risk reduction is desired beyond maximum statin dose:

- Recommend discussing ezetimibe or PCSK9 inhibitors.
  - Due to adverse events, suggest EPA ethyl ester (icosapent) only after ezetimibe or PCSK9 inhibitor considered.

Kolber et al *Can Fam Phys* 2023;69:675-86

Benefit / Risk Considerations
Full ITT Population





* Includes hemorrhagic stroke

Adapted from **FDA Advisory Committee (Nov. 19, 2019) and Bhatt et al *N Engl J Med* 2019;380:11-22**

2021 CCS Guidelines for the Management of Dyslipidemia

Patients with Atherosclerotic Cardiovascular Disease (ASCVD)
Receiving maximally tolerated statin dose.

RECOMMENDATION

We recommend the use of icosapent ethyl to lower the risk of CV events in patients with ASCVD, or with diabetes and ≥1 CVD risk factors, who have an elevated fasting triglyceride level of 1.5-5.6 mmol/L despite treatment with maximally tolerated statin therapy.
Strong Recommendation; High-Quality Evidence

Pearson, Thanassoulis, et al *Can J Cardiol* 2021;37:1129-50