Lipids: how low do you go

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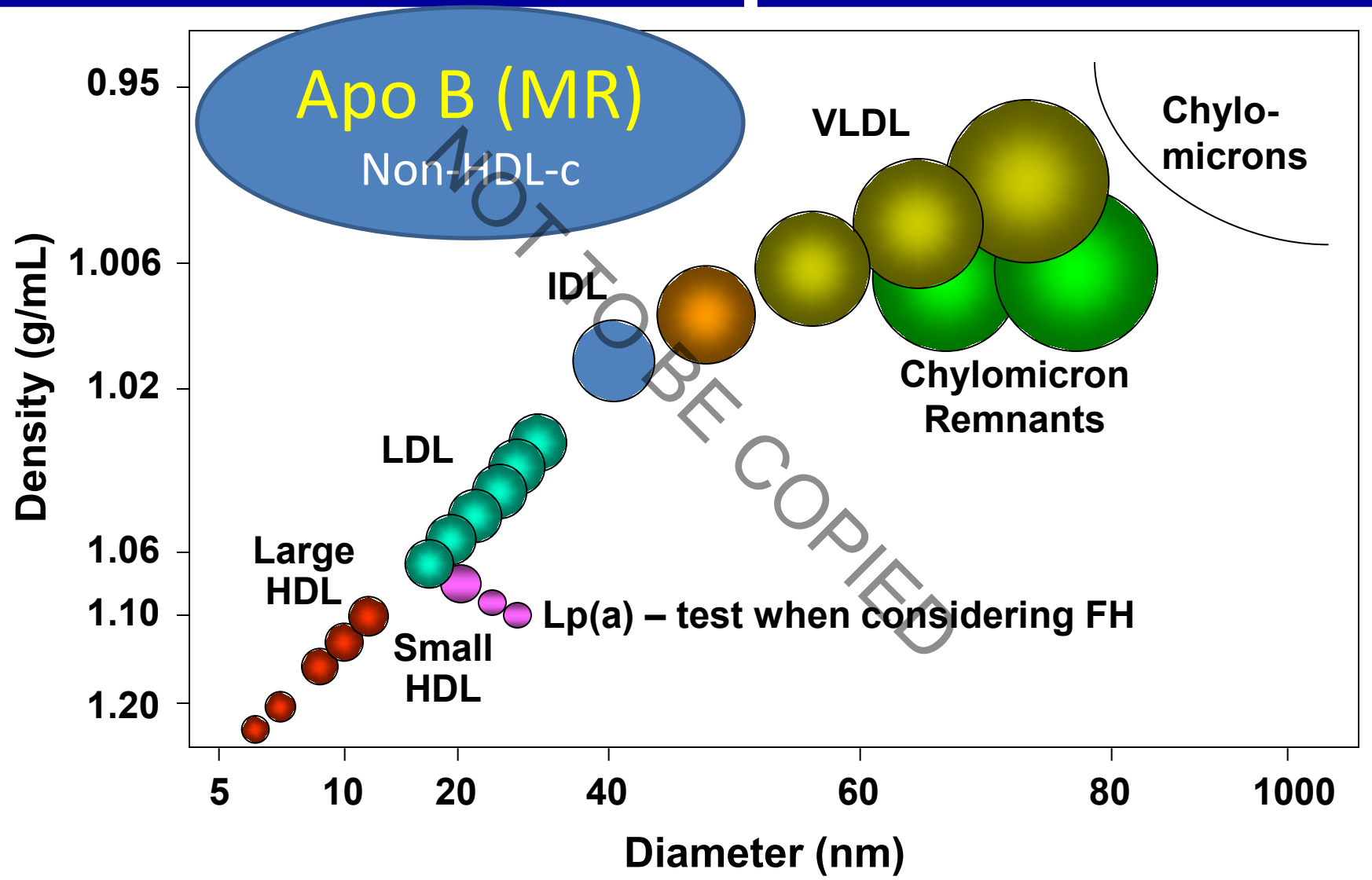
Cover

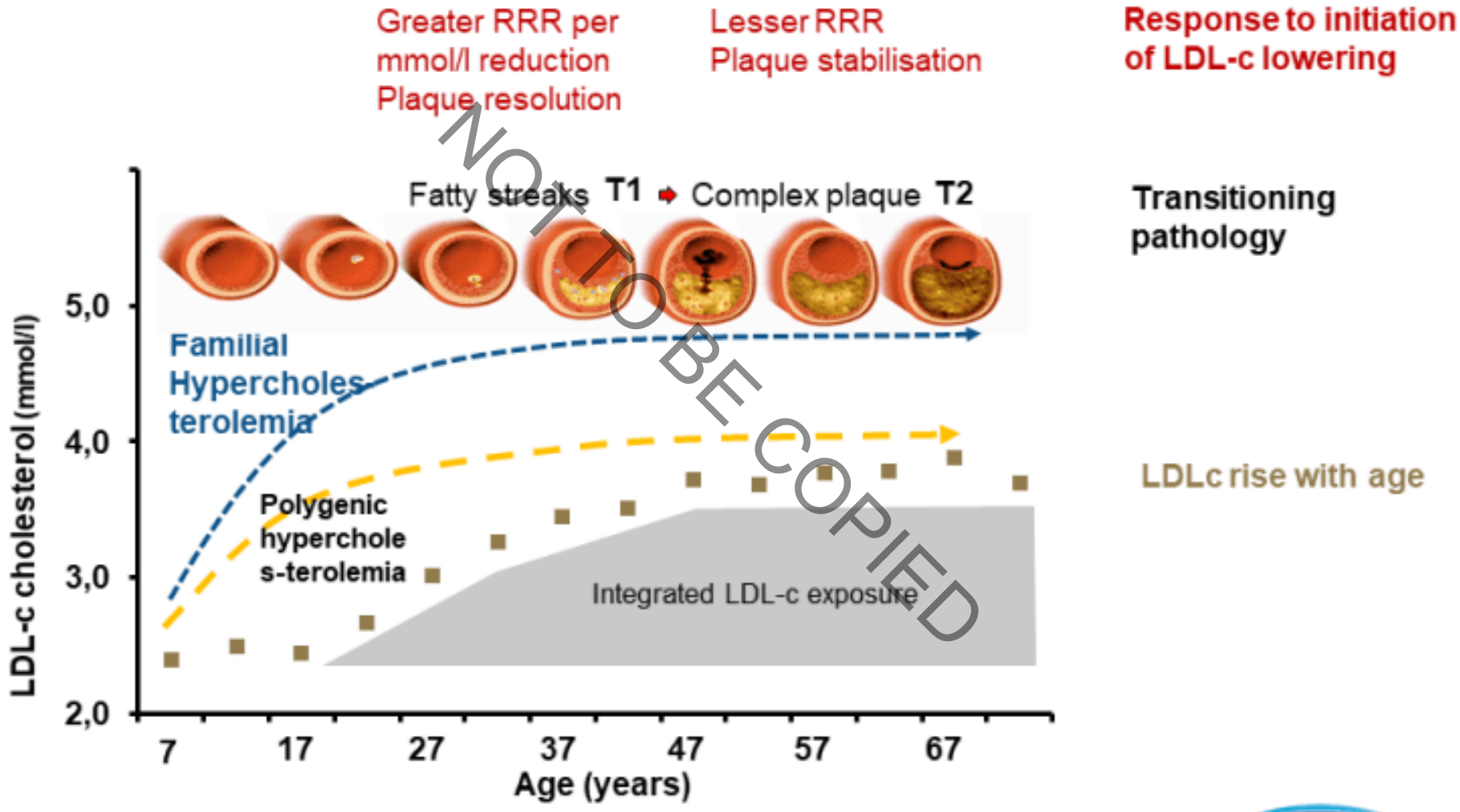
- When to give statin – single guideline preferable
- If in doubt on CV risk, consider statin
- Ezetimibe adds LDLc and outcomes benefit
- Muscle symptoms - >90% not statin-related
- Statins do increase HbA1c by 1-2 mmol/mol
- For high trigs – remember glucose control critical AND weight – plus some meds

Lipoproteins – increases in one but can be multiple



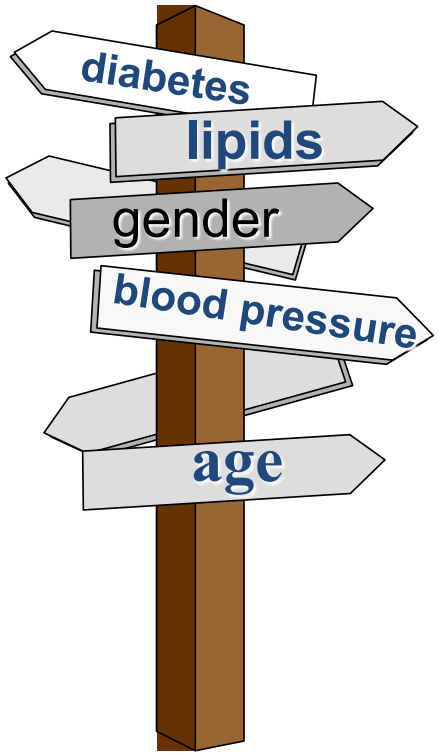
Adapted from Segrest JP. *Adv Protein Chem*. 1994;45:303-369.

The atherosclerosis disease process changes with time and LDL-c level, and treatment effect depends on the disease phase



Packard CJ. Trends Cardiovasc Med. 2018 Jul;28(5):348-354

Determining Heart disease risks



- Starting point - CHD event risk
  NOT simply cholesterol level
  - many factors combine to cause disease

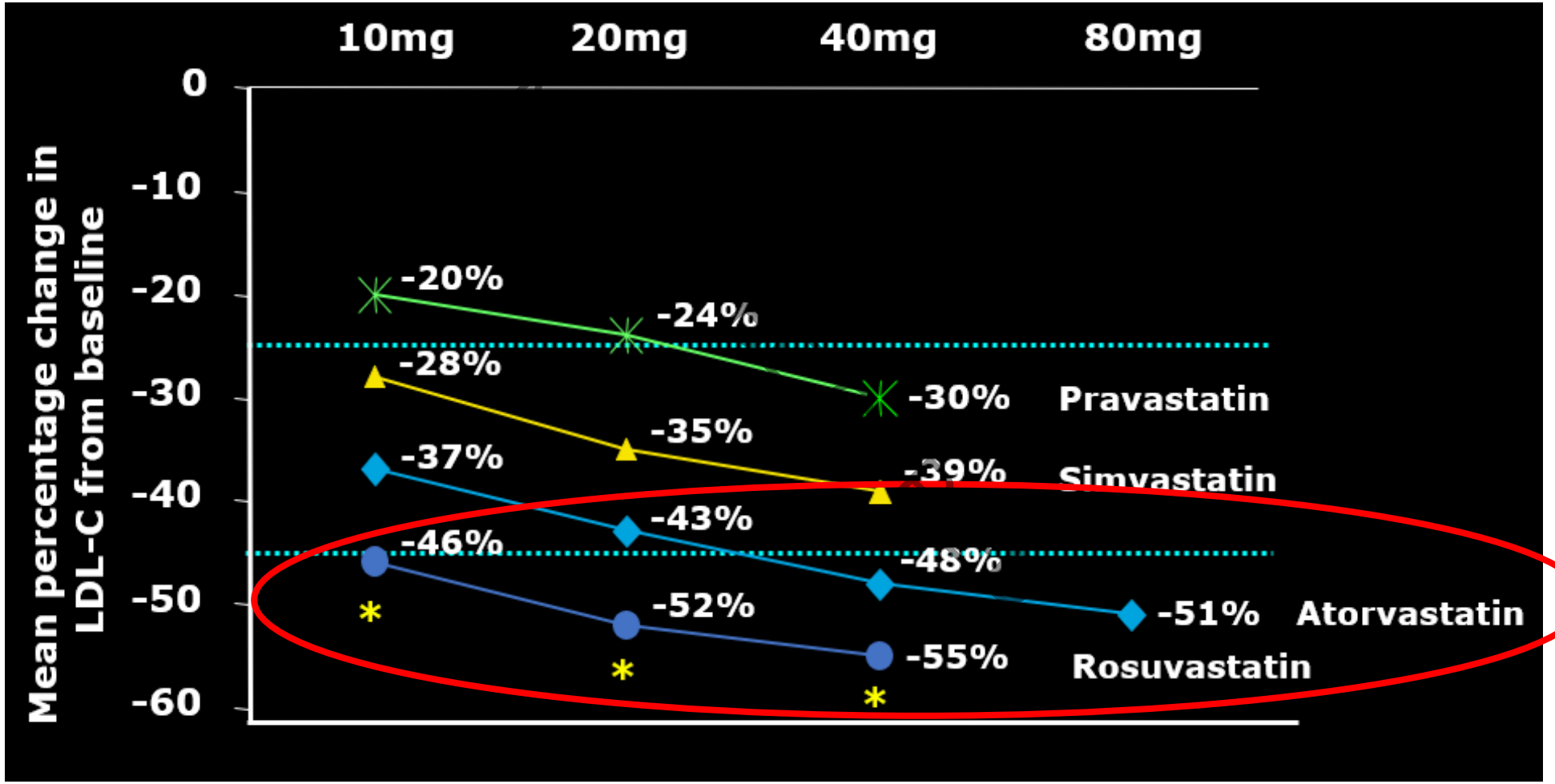
RISK CHARTS
OR CALCULATORS – GP SCREENS

<u>RISK OF CVD EVENTS NEXT 10 YEAR</u>

Treat >10% broadly QRISK2
ASSIGN2 will align

Effect of statins on LDL-C

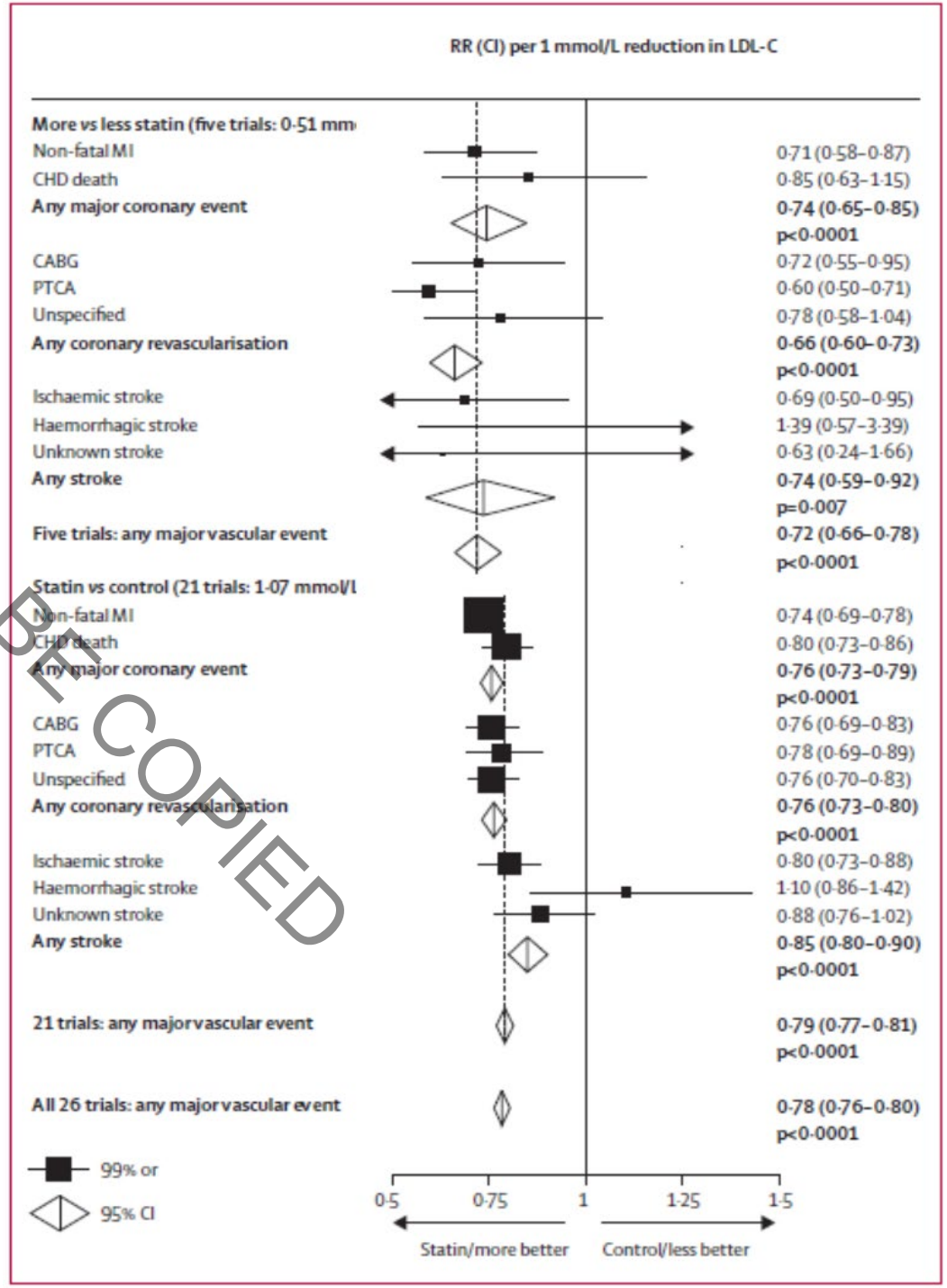
Dose response



Jones et al Am J Cardiol (2003) 92:152-160

Meta-Analysis of Statin Trials (N=170,000)

- 5 More vs. Less Statin Trials
  - Mean LDL-C reduction of ~1 to 2 mmol/l)
- 21 Statin vs. Placebo Trials
- 26 Total Trials
  - **22% CV risk reduction per 1 mmol reduction in LDL-C**
  - **Lifelong benefits greater so AUC**



CTT Collaboration. *Lancet*. 2010

NICE 2023 – T2 diabetes

- Use the QRISK3 tool for people with type 2 diabetes aged between 25 and 84
- Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a 10-year QRISK3 score of 10% or more

T1 DM

- Offer statin for primary prevention of CVD to adults with T1Ds who:
- are >40 years **or**
  - have had diabetes >10 years **or**
  - have established nephropathy **or**
  - have other CVD risk factors. **[May 2023]**
- Consider statin treatment for primary prevention for people 18 to 40 with T1D, including those who have had diabetes for 10 years or less. **[May 2023, amended December 2023]**
- When starting treatment with a statin for adults with type 1 diabetes, use atorvastatin 20 mg. **[May 2023]**
- https://diabepi.shinyapps.io/cvdrisk/ **app may help developed in Scotland**

Before starting statins perform baseline blood tests and clinical assessment. Include all of the following in the assessment:

- transaminase level (alanine aminotransferase or aspartate aminotransferase)
- thyroid-stimulating hormone level in people with symptoms of underactive or overactive thyroid. **[May 2023, amended December 2023]**

Primary prevention target

- **Primary prevention LDL-c target 2.5 mmol/l or 50% reduction from baseline**
- **Secondary prevention or severe Target Organ Damage**
  - **LDLc <1.8 or 1.4 mmol/l if very high risk (recurrent vascular or risk score high)**
- Severe TOD is defined as at least one of:
  - eGFR <45 mL/min/1.73 m^2
  - eGFR 46–59 mL/min/1.73 m2 + microalbuminuria (ACR 30–300 mg/g or 3–30 mg/mmol);
  - proteinuria (ACR >300 mg/g or >30 mg/mmol);
  - presence of microvascular disease in at least three different sites (e.g. microalbuminuria plus retinopathy plus neuropathy)

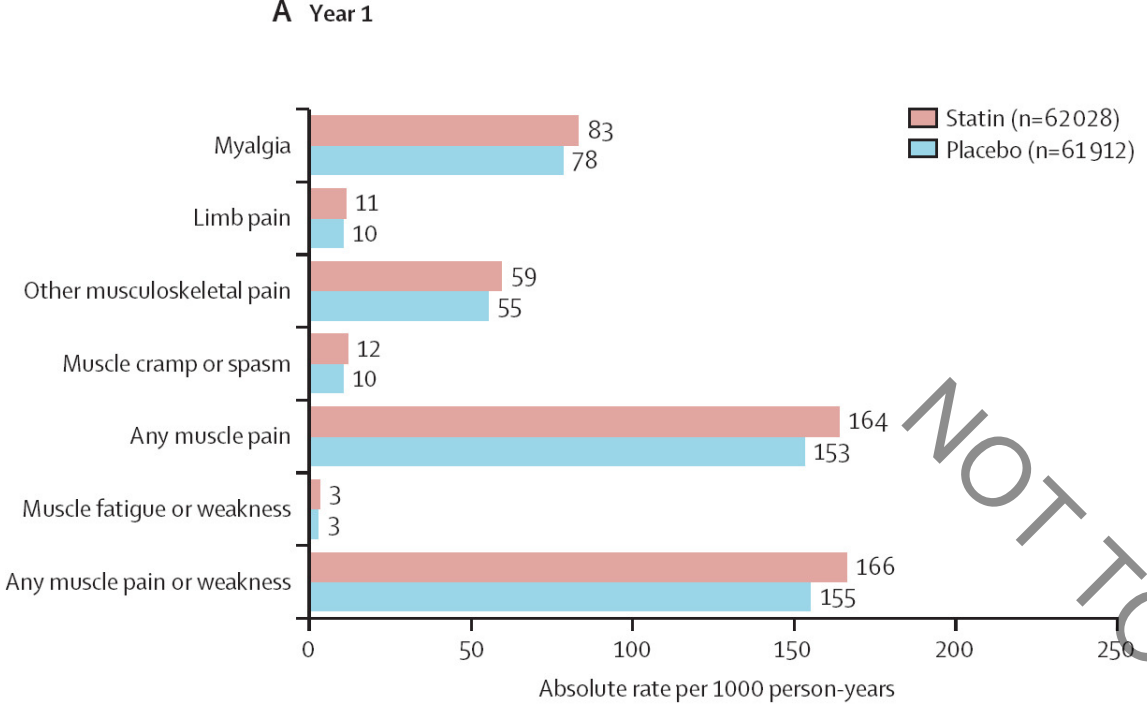
NNTs NNHs for statins

Table 11: Numbers needed to treat and harm for outcomes associated with five years of daily high-intensity statin therapy

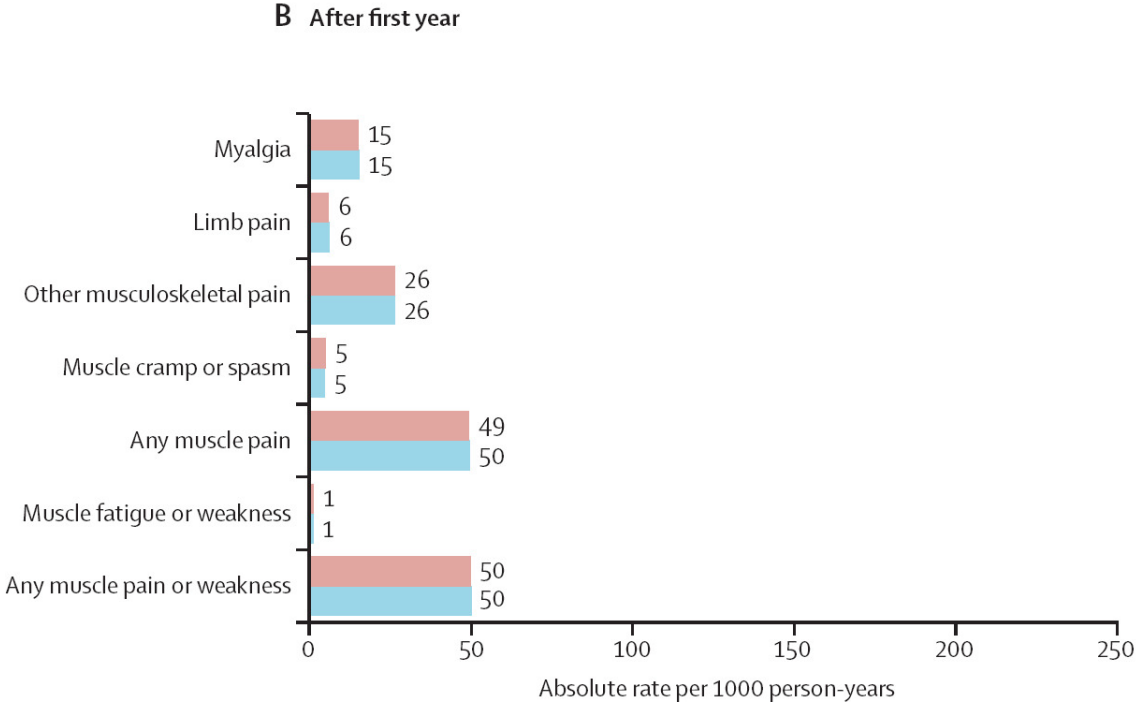
	Primary prevention		Secondary prevention	
	NNH	NNT	NNH	NNT
Major vascular events		20		10
New diabetes	100–200		100–200	
Haemorrhagic stroke	1,000–2,000		1,000–2,000	
Myopathy	2,000		2,000	

Based on data from Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016;388(10059):2532-61.

Check LFTs, and CK if muscle pain



Rate ratio (95% CI)	Absolute excess rate per 1000 person-years (95% CI)
1·06 (1·02 to 1·11)	5 (1 to 8)
1·08 (0·97 to 1·21)	1 (0 to 2)
1·08 (1·03 to 1·13)	4 (1 to 7)
1·14 (1·02 to 1·27)	1 (0 to 3)
1·07 (1·04 to 1·10)	11 (6 to 16)
1·14 (0·92 to 1·40)	0 (0 to 1)
1·07 (1·04 to 1·10)	11 (6 to 16)



Rate ratio (95% CI)	Absolute excess rate per 1000 person-years (95% CI)
0·99 (0·93 to 1·04)	0 (−1 to 1)
0·96 (0·89 to 1·04)	0 (−1 to 0)
1·00 (0·96 to 1·04)	0 (−1 to 1)
1·06 (0·97 to 1·16)	0 (0 to 1)
0·99 (0·96 to 1·03)	0 (−2 to 1)
1·07 (0·89 to 1·27)	0 (0 to 0)
0·99 (0·96 to 1·02)	0 (−2 to 1)

CTT (2022) Lancet

>90% of reports of muscle symptoms not due to the statin

Reassure patients

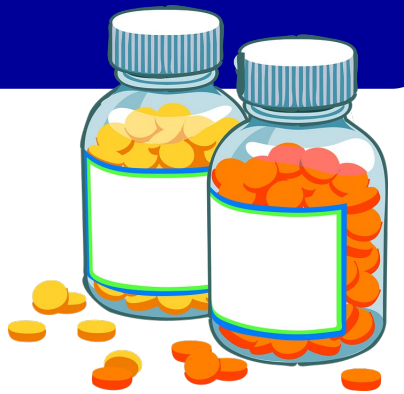
In 100 people
15 with statin
14 with placebo
muscle ache

So 1 extra per 100

Summary

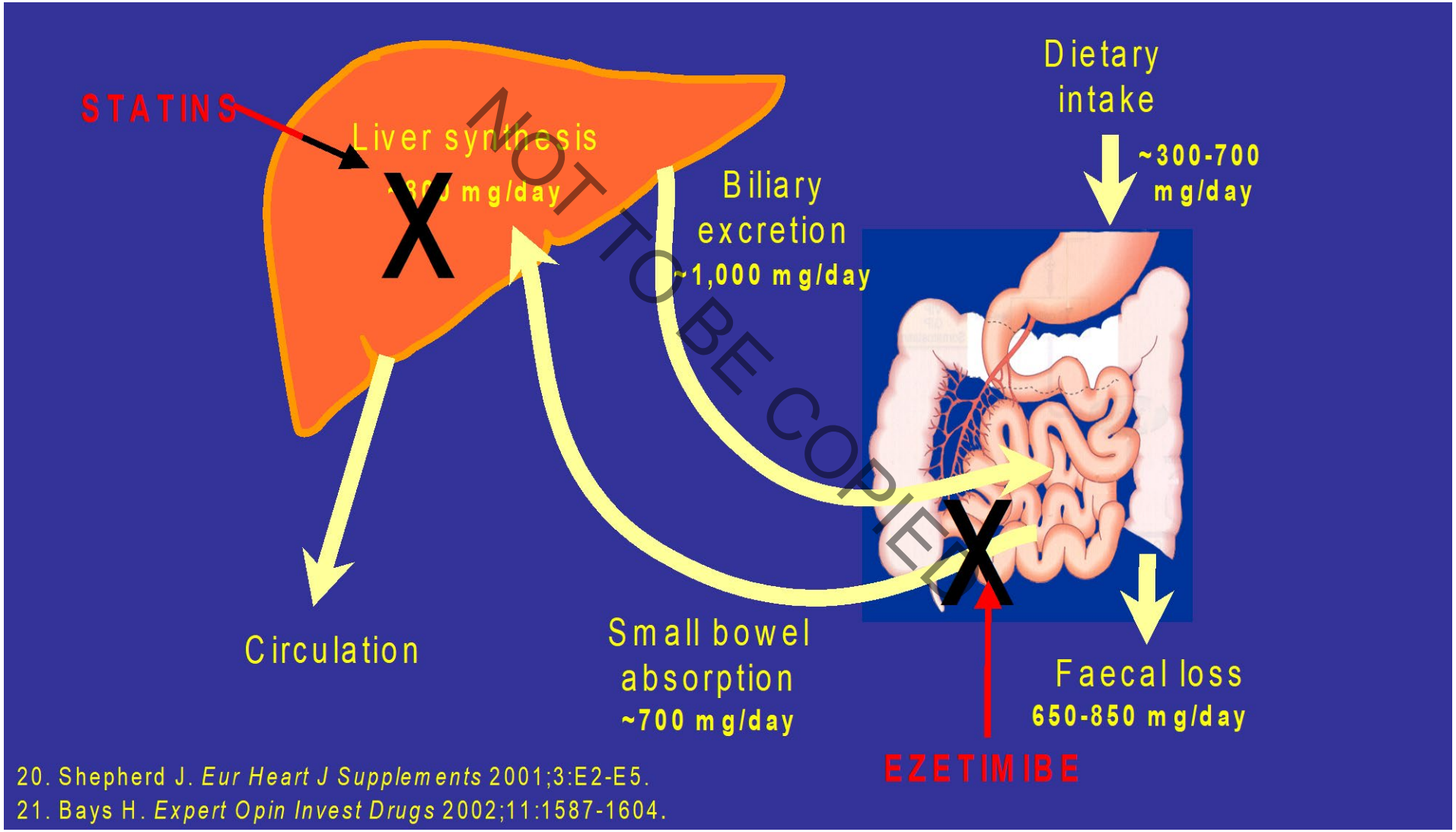
- Era of multiple LLT now in play
- Two somewhat distinct pathways –
  - LDLc or non-HDL-c – 4 drugs now
  - High Triglyceride (ectopic fat)
  - Lp(a) interest growing

Why do we need other LLT



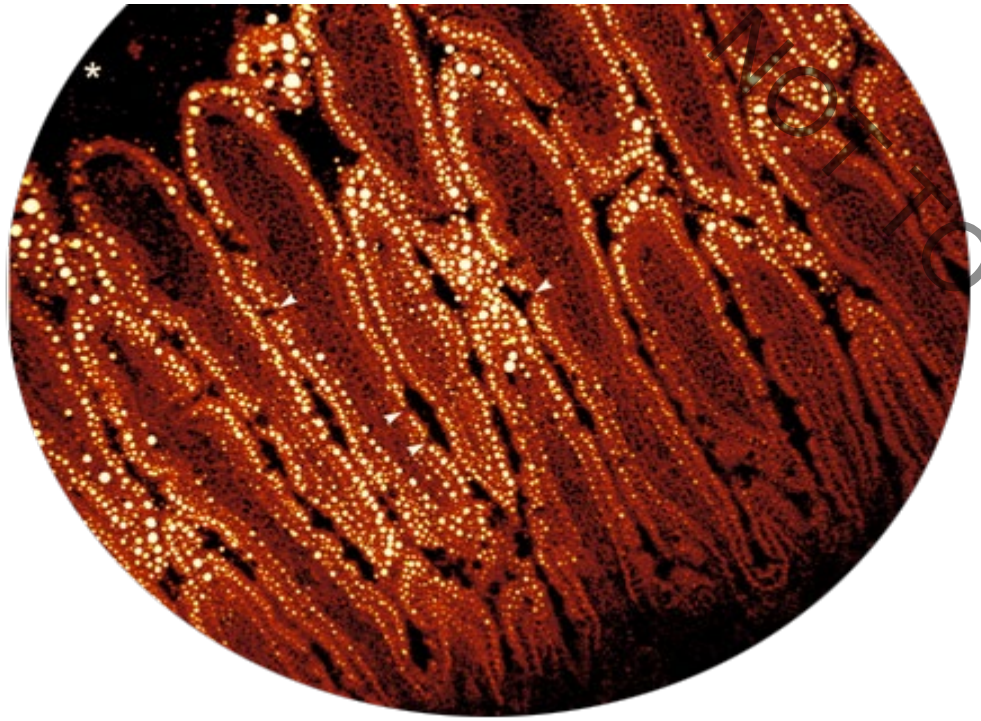
- Targets for LDL-c now much lower
- Primary prevention LDL-c target 2.5 mmol/l or 50% reduction from baseline
- If start LDL-c at >4mmol/l, hard to reach lower targets in many with just statins

Dual inhibition[20,21]

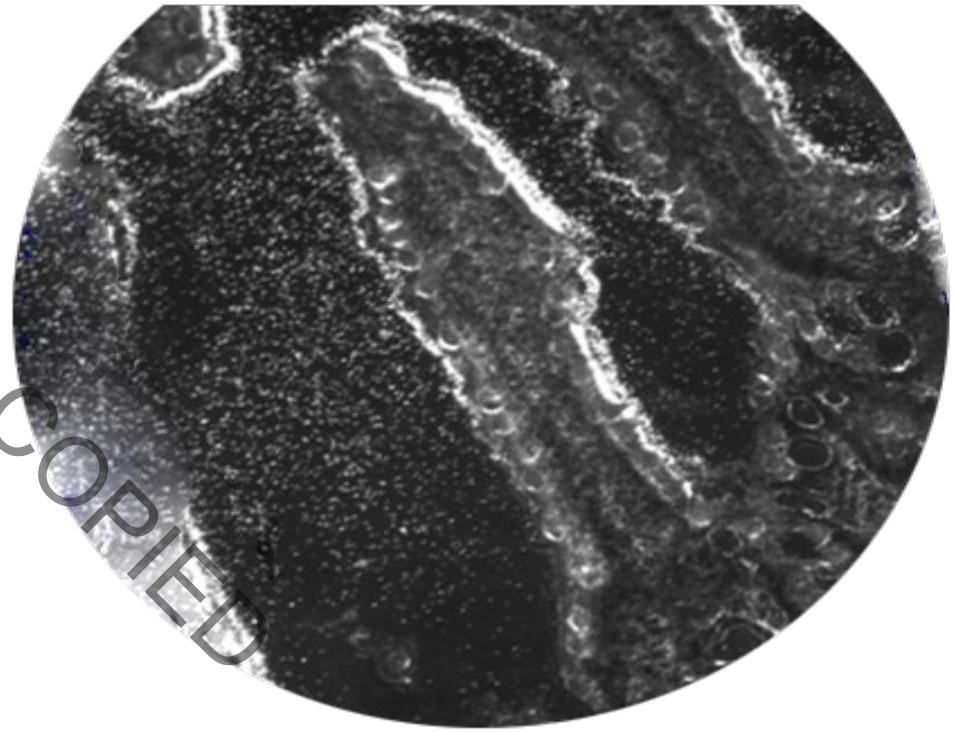


20. Shepherd J. *Eur Heart J Supplements* 2001;3:E2-E5.
21. Bays H. *Expert Opin Invest Drugs* 2002;11:1587-1604.

Localisation of ezetimibe at site of cholesterol absorption



Uptake of a fluorescent cholesterol analog in hamster small intestine



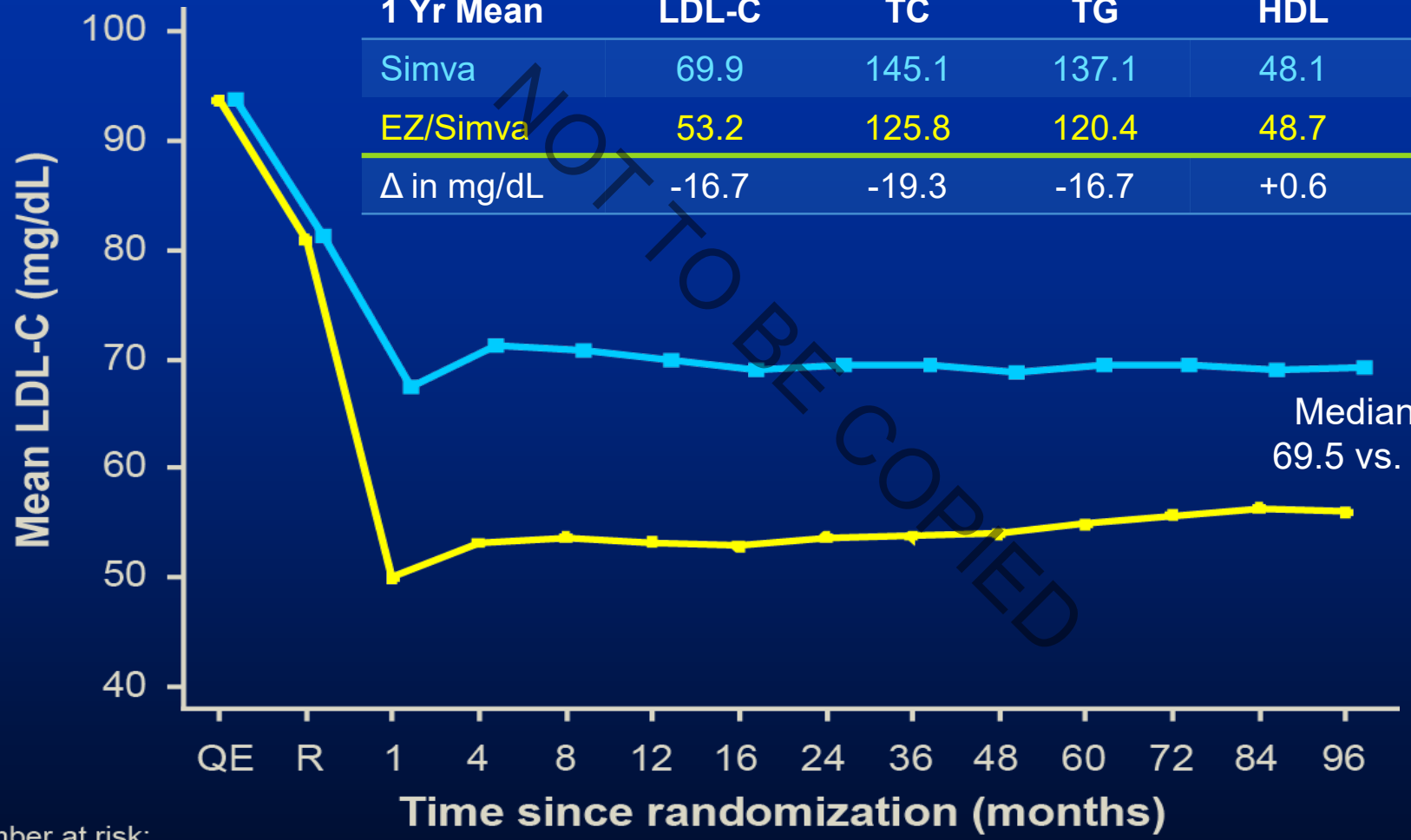
125 I-Gluc-Ezetimibe Delivered I.V. Localizes to the Intestinal Brush Border in Bile-Duct Cannulated Rats

Sparrow et al. *J Lipid Res.* 1999; 10:1747.

LDL-C and Lipid Changes

IMPROVE-IT

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5



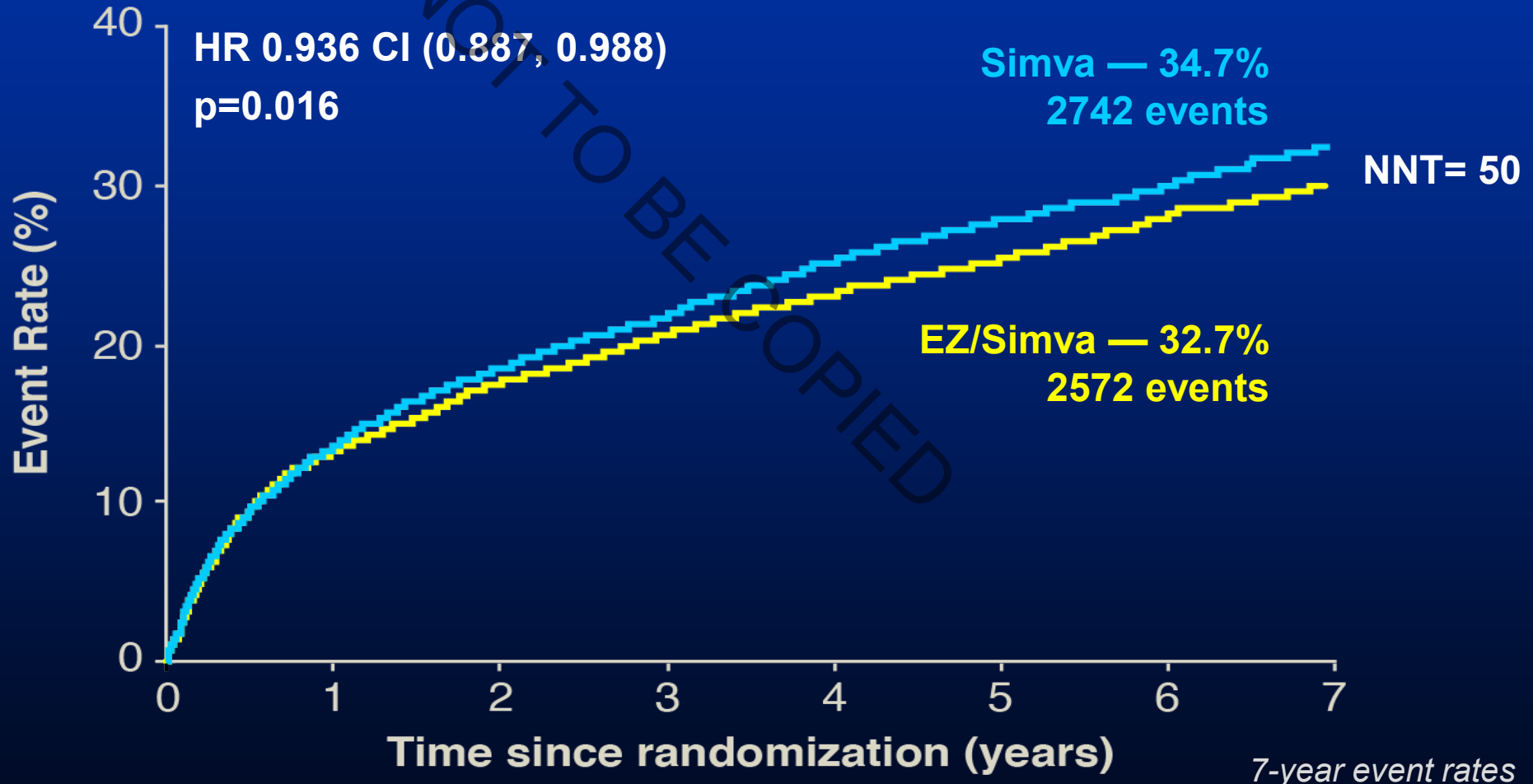
Median Time avg
69.5 vs. 53.7 mg/dL

Number at risk:

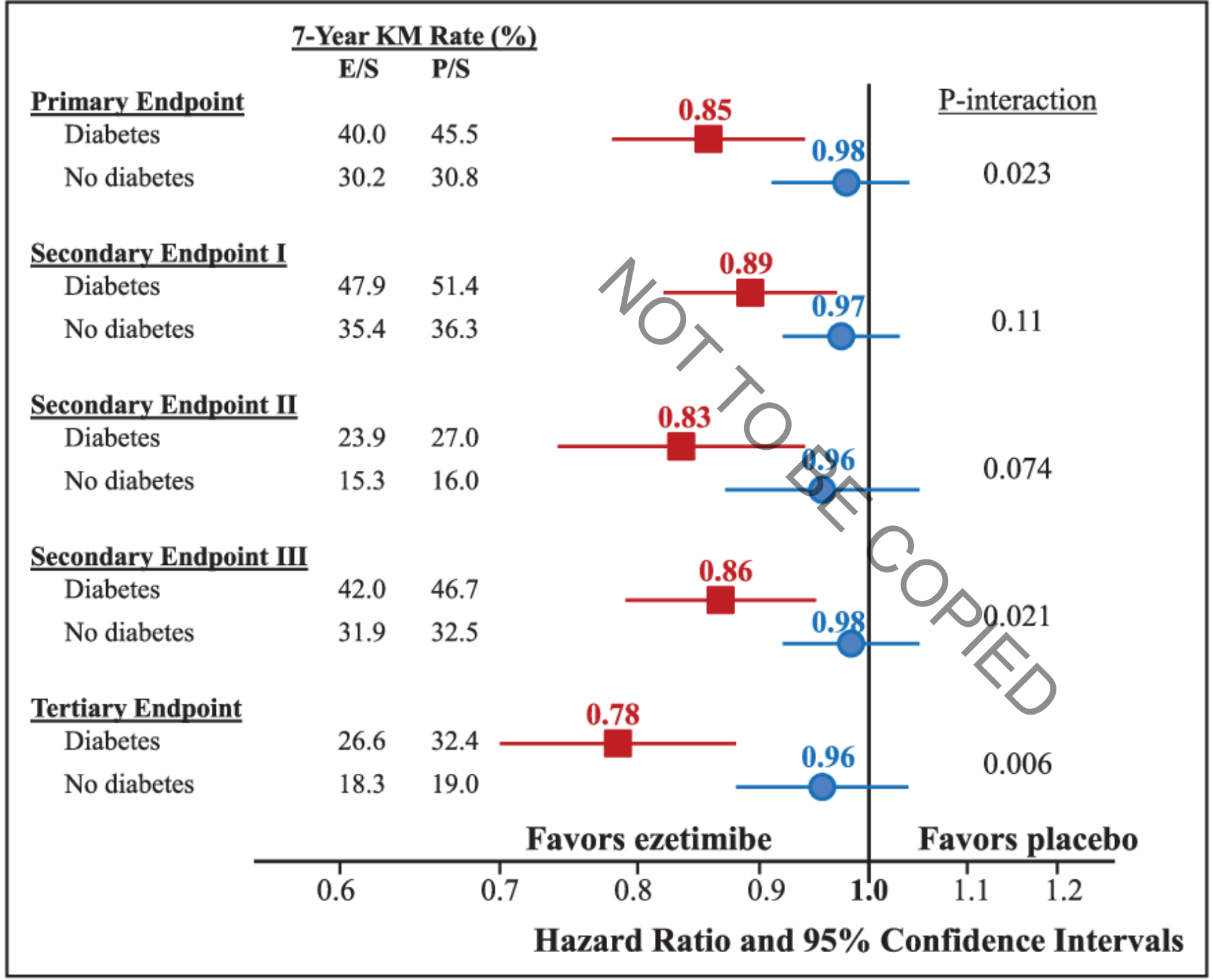
EZ/Simva	8990	8889	8230	7701	7264	6864	6583	6256	5734	5354	4508	3484	2608	1078
Simva	9009	8921	8306	7843	7289	6939	6607	6192	5684	5267	4395	3387	2569	1068

Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

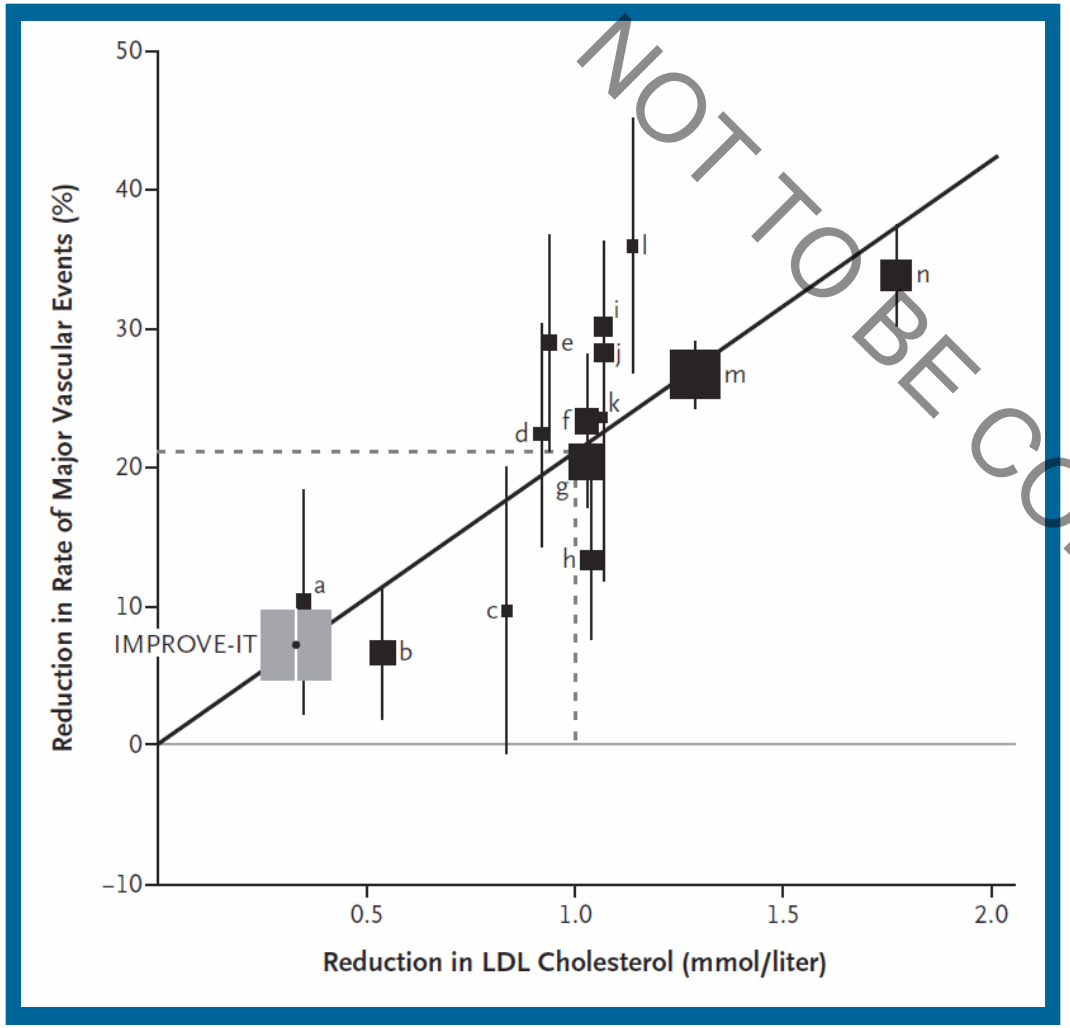


7-year event rates



Giuliano (2018) Circulation

Lessons from completed LDL lowering trials
Risk reduction is related to LDL decrease



Data from trials of:-

- Statin vs placebo
- More vs less intense statin therapy.
- Combination therapy with ezetimibe

Regression line reveals:-

1.0 mmol/l fall in LDLc translates into a 22% decrease in risk

CTTC Lancet (2005) 367;1267-78
Cannon et al NEJM (2015) 367; June

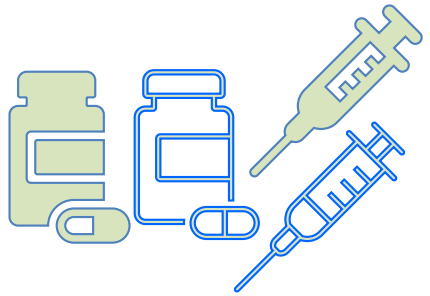
Other drugs to use

Drug	Mechanism of Action	Effect on LDL-c	Evidence for ↓ in MACE	Status in NHS
Ezetimibe	Oral Cholesterol Absorption Inhibitor	↓ LDL-c 15-20%	Yes (reduction in MI) One CVOT	NICE TA 2013 Generic
PCSK9 Inhibitors	Monoclonal AB that block PCSK9 in liver with resultant net upregulation LDL-R	↓ LDL-c ~50-60%	Yes (reduction in MI) 2 CVOTs	NICE TA 2016 LDL-c threshold 4 mmol/L or 3.5 if polyvascular or recurrent CVD
Bempedoic Acid	Inhibits ATP Citrate Lyase (2 steps before HMG Co A reductase in hepatic cholesterol production	↓ LDL-c ~ 15%	Not yet CVOT ongoing (CLEAR Outcomes)	NICE TA 2020 Not currently recommended (draft) SPC with ezetimibe
Incliseran	siRNA for PCSK9	↓ LDL-c 50%	Not yet Orion 4 Ongoing	EU License Dec 2020 *NHS plan to make inclisiran available through a population-level agreement with Novartis*

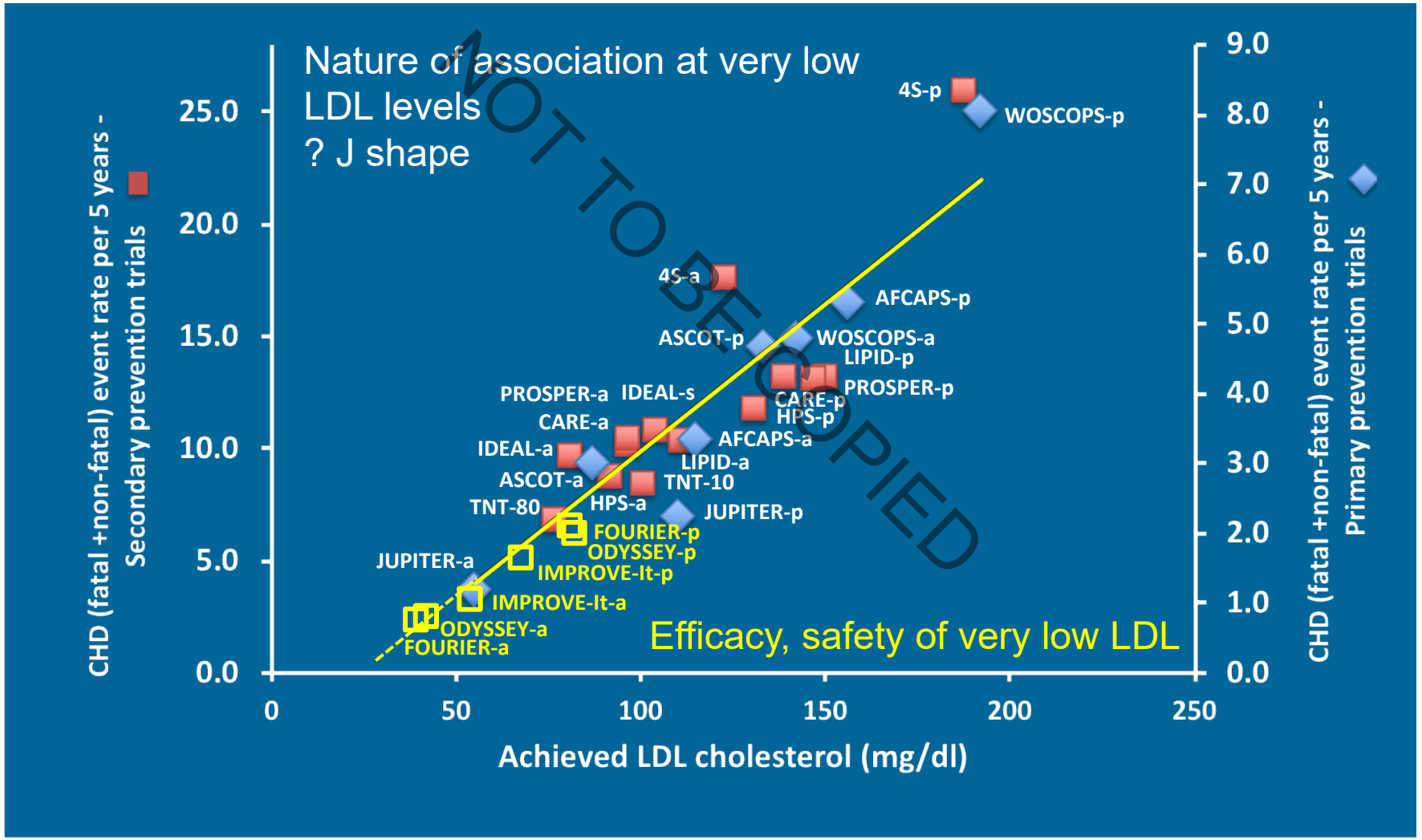
Improve It. NEJM 2015;372:2387-2397, Odyssey Outcomes N Engl J Med 2018; 379:2097-2107, Fourier N Engl J Med 2017;376:1713-22.
Clear Harmony N Engl J Med 2019; 380:1022-1032, Orion 9,10,11 N Engl J Med 2020; 382:1520-1530, N Engl J Med 2020; 382:1507-1519

New ways to lower lipids and lower targets in force now

- PCSK9 inhibitors –
- SC injection every 2 or 4 weeks
- Evolocumab or Alirocumab
  - >50% reduction on top statins
- Major trials FOURIER and ODYSSEY
- LDL-c as lower 0.2 mmol/L



Achieved LDL in primary and secondary prevention trials



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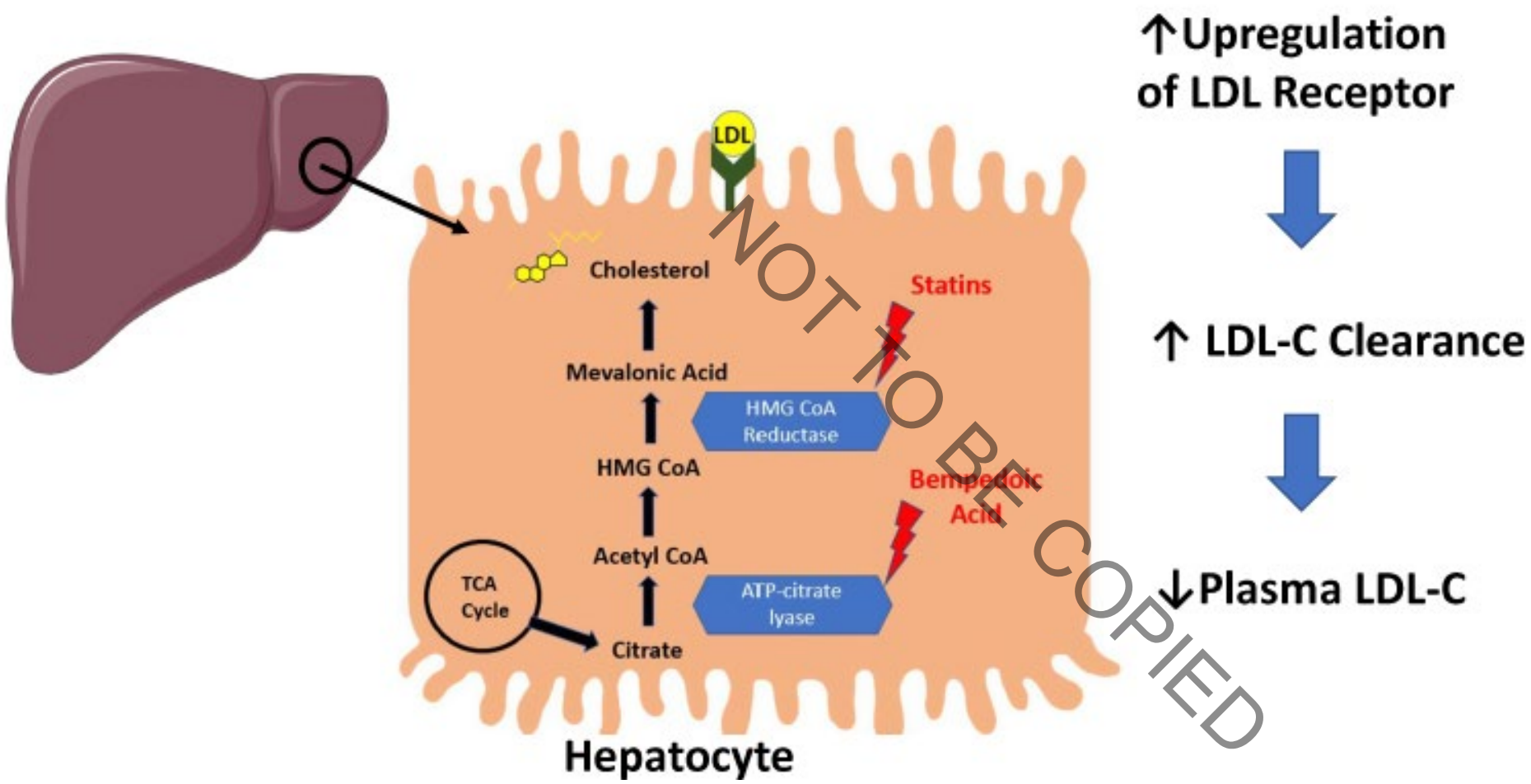
Bempedoic Acid: Mechanism of Action



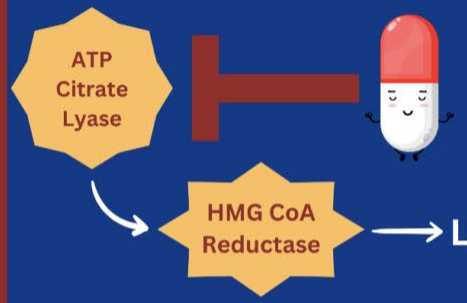
No muscle aches, but can increase uric acid –
CLEAR Outcomes trial 14K in statin intolerant patients –

CLEAR Outcomes Trial

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

Nissen et al. March 2023. NEJM.

BEMPEDOIC ACID



ATP Citrate Lyase inhibitor that targets cholesterol synthesis upstream of statins

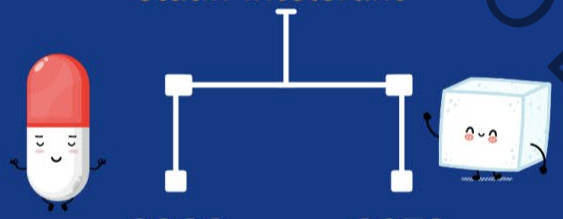
QUESTION

Does bempedoic acid decrease adverse CV events in patients who require 1* or 2* prevention of CV disease but are statin-intolerant?

METHODS

Randomized, double-blinded study

Patients were 18-85 years old, with or at high risk for CVD who were statin-intolerant*



6992 **6978**

1:1 ratio of bempedoic acid 180mg or placebo

Median follow-up for 40.6 months

(> 90% white in both arms)

*Statin intolerance defined as inability to tolerate ≥2 statins, one at a low dose

PRIMARY ENDPOINT

Composite MACE†

11.7% **13.3%**

HR 0.87, 95% CI 0.79-0.96 (p = 0.004)

†MACE: death from CV cause, nontal MI, nonfatal stroke, coronary revascularization

SECONDARY ENDPOINTS

Death from CV cause, nonfatal stroke, or nonfatal MI	**8.2%**	**9.5%**
Fatal or nonfatal MI	**3.7%**	**4.8%**
Coronary revascularization	**6.2%**	**7.6%**
	All significant	
Fatal or nonfatal stroke, death from CV cause, death from any cause	**Non-significant**	

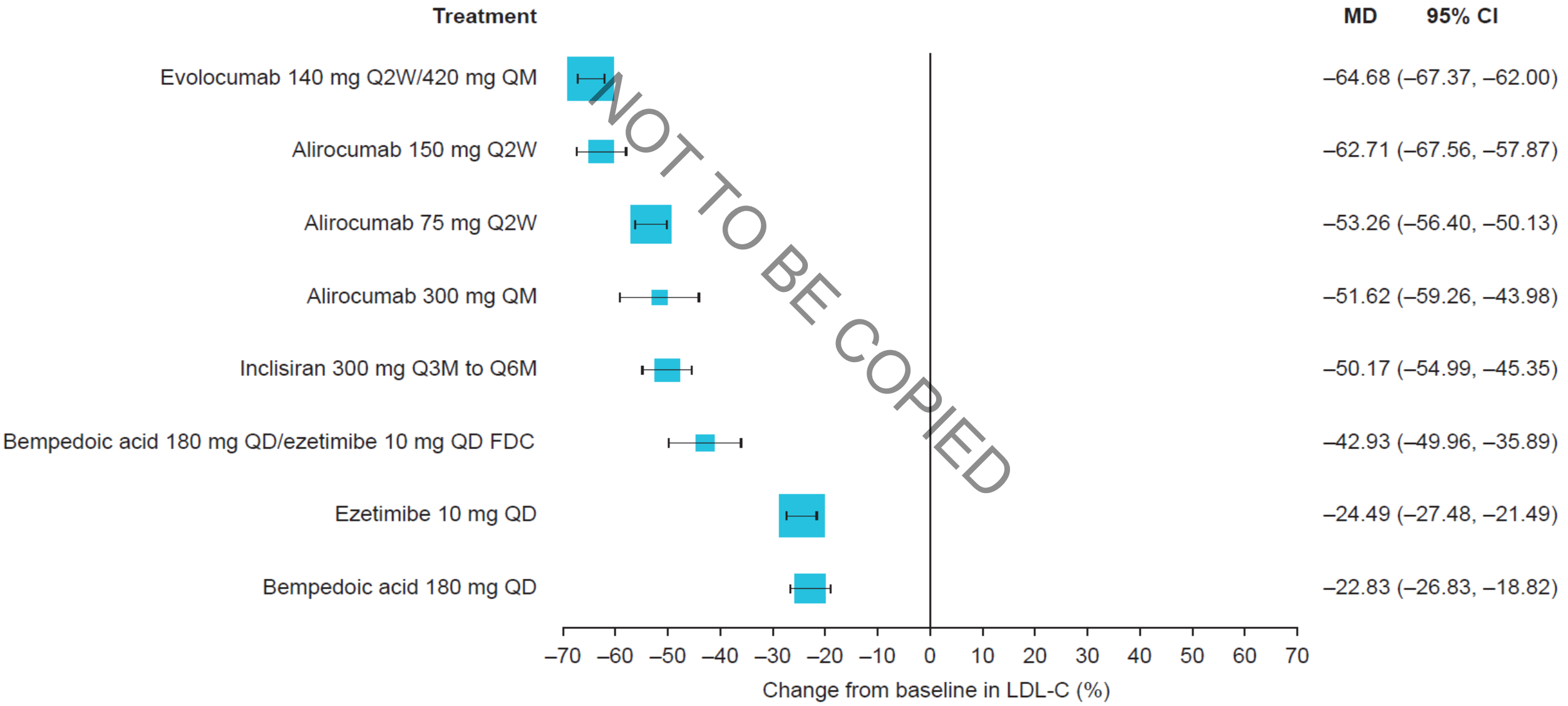
Adverse events: ↑ gout & cholelithiasis in bempedoic acid group

CONCLUSION

Use of bempedoic acid compared to placebo in patients with or at high risk for CVD resulted in a 13% relative risk reduction in composite MACE at 40 months.

Created by: @CaliRClark. Reviewed by @EuniceDuganMD, @DrAlaaDiab, @TySweeney6, @DeveshRaiMD

Network meta-analysis of LLT
Toth et al (2022) JAHA



Gain confidence in some with apparent intolerance

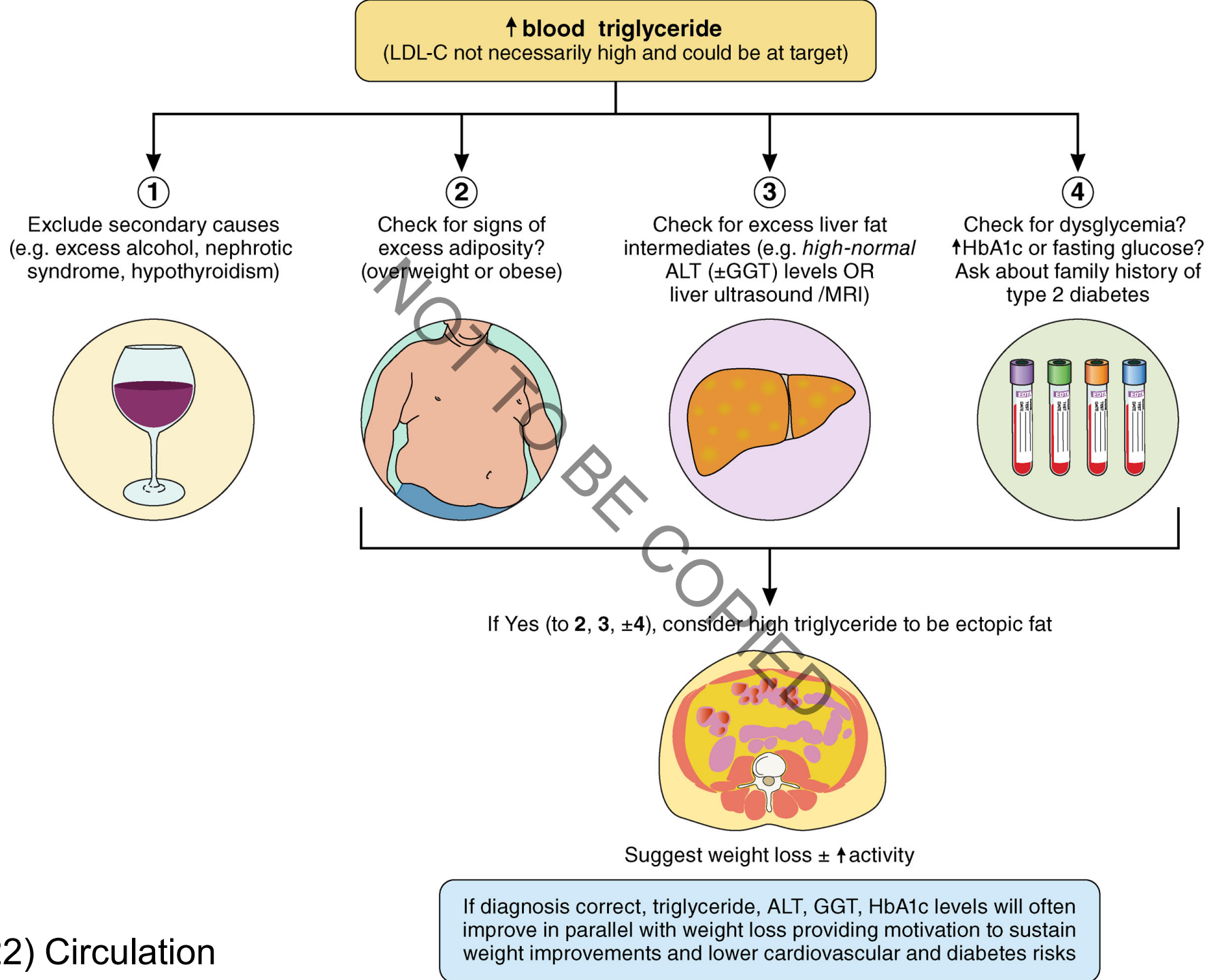
- If statin ‘intolerance’ – real or nocebo effect
  - Try low dose rosuvastatin (5mg twice per week) and build up and add ezetimibe
  - Or combo or ezetimibe and Bempedoic acid (~45% LDL-c reduction)

Summary LDL-c axis

- LDL-c causal for CVD (number of particles = apo B = nonHDL-c)
- Lower LDL-c lowers risk – absolute reduction best when LDL-c higher
- Statins, ezetimibe and PCSK9i licensed for lower LDL-c and mainstay treatment
- New kids on the block
  - Bempedoic acid: SMC approved - can↑ uric acid, myopathy risk, CK checks
  - Inclisiran – small iRNA – now also improved
- LLT in ASCVD / diabetes – like BP will be 2-3 drugs….
  - **MOSTLY STATIN +/- EZE**

Triglycerides (fat)

- **Higher with obesity, diabetes**
- **Correlate to lower HDL-cholesterol**
- **Drugs targeting TG lowering – fibrates – benefit for CVD risk reduction shaky**
- **When TG > 10 mmol/l**
  - Risk for pancreatitis
  - Think alcohol excess
  - **Poor diabetes control – excess sugar taken up liver to make fat**
  - Renal disease



Sattar et al (2022) Circulation

High triglyceride, when trigs >10-20mmol/l despite good HbA1c control, statin and other factors excluded

- **Fenofibrate if trigs >10 mmol/l despite statin; 200 mg per day or 160mg tablets Supralip version**
  - Renal impairment: Fenofibrate not to be used if eGFR <30
  - If eGFR 30 to 59, max dose 100mg standard or 67 mg micronized once daily

Summary

- T2D and T1D risks for CV higher
- Primary prevention guidance – distinct – risk score T2D from 25 years onwards; T1 diff approach, risk scores used less
- LDLc<2.5mmol/l – 2^0 prevention (or target organ damage – European guidelines) LDLc <1.8 and lower coming
- Statins mainstay / consider ezetimibe more often
- >90% intolerance is not genuine – explain and then retry – perhaps lower dose to gain confidence and then increase back
- Other drugs also available; PCSK9i, Bempedoic acid but expensive