Congresso della Diabetologia Toscana

Nodi ed intrecci di una rete:
evidenze scientifiche ed esperienze a confronto
Grosseto, 30 novembre/1 dicembre 2018

Terapia ipolipemizzante nel paziente diabetico: nuovi farmaci, appropriatezza prescrittiva ed aderenza

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dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

Background

• I pazienti con diabete tipo 2 presentano un rischio di morte e di eventi cardiovascolari 2-4 volte più alto di quello della popolazione generale. *(Rawshani A. N Engl J Med 2017; 376: 1407-18).*

• Una significativa riduzione della spettanza di vita si osserva anche nel diabete tipo 1 *(Livingstone SJ. JAMA 2015; 313: 37–44).* In tali pazienti la malattia cardiovascolare è il maggiore determinante della mortalità e della morbilità. *(Rawshani A. Circulation 2017; 135: 1522–31).*

• I risultati dei trial randomizzati dimostrano l'utilità di implementare una serie di interventi mirati al controllo dei fattori di rischio cardiovascolari, quali HbA1c, pressione arteriosa, colesterolo, per prevenire o ritardare le complicanze sia nel diabete tipo 1 sia nel diabete tipo 2.

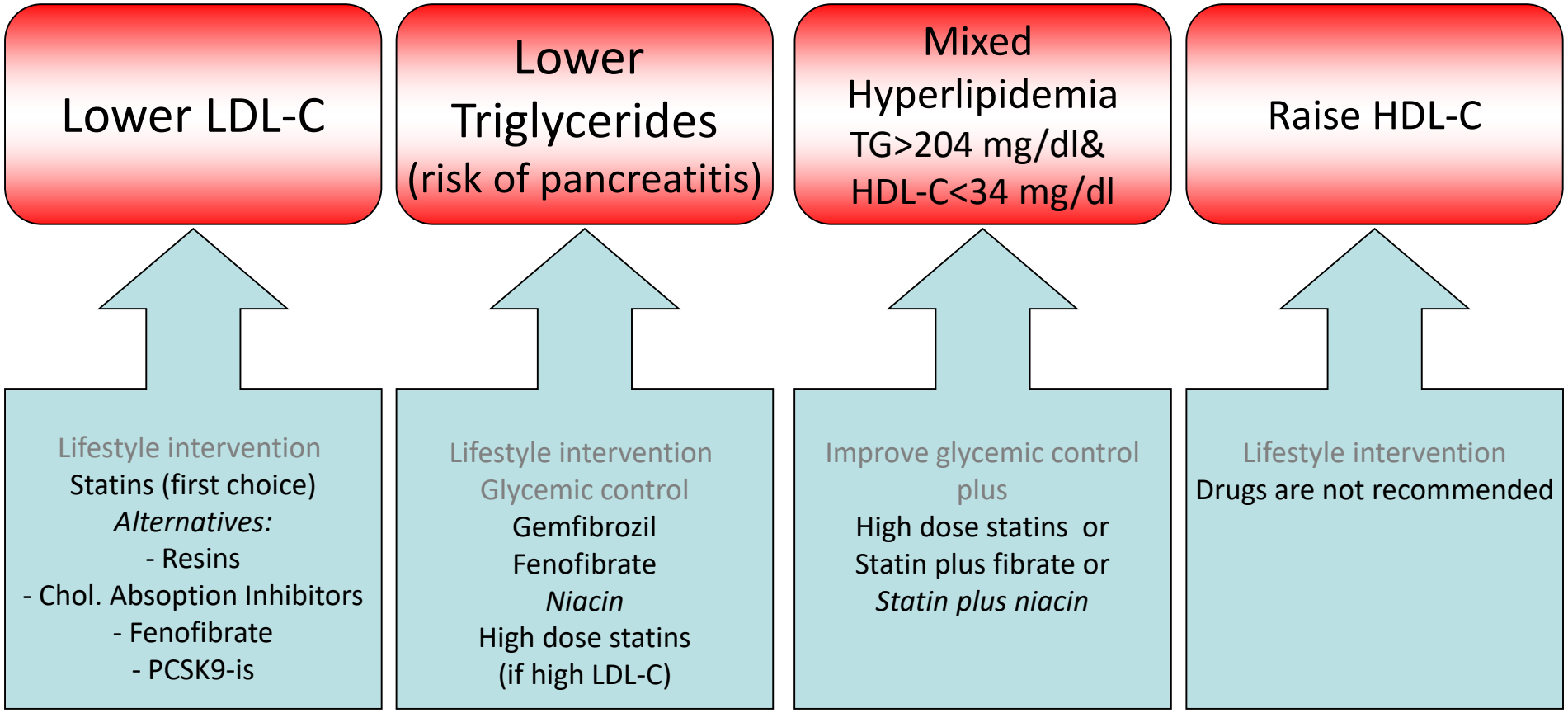
Characteristics of dyslipidaemia in type 2 diabetes mellitus

- Dyslipidemia is a major risk factor for CVD
- Dyslipidemia represents a cluster of lipid and liporotein abnormalities including elevation of both fasting and post-prandial TG, Apo B, small dense LDL particles, low HDL-C and Apo A

ESC-EASD Task Force. European Heart Journal (2013) 34, 3035–3087

The management of lipid levels in patients with diabetes

First priority



Adapted from ADA Recommendations 2016 - ESC Guidelines 2016

www.thelancet.com Vol 371 January 12, 2008

Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis

*Cholesterol Treatment Trialists' (CTT) Collaborators**

RISULTATI Durante un follow-up medio di 4,3 anni, si sono verificati 3247 eventi vascolari maggiori nelle persone con diabete.

• Riduzione proporzionale del 9% nella mortalità per tutte le cause per ogni mmol/L (38 mg/dl) di riduzione del colesterolo LDL nei soggetti diabetici (vs 13% di riduzione in quelli senza diabete). Questo risultato rifletteva una diminuzione significativa nella mortalità vascolare e *nessun effetto sulla mortalità non vascolare* (RR 0,97; 0,82-1,16; p=0,7) nei diabetici.

• Riduzione proporzionale significativa del 21% negli eventi vascolari maggiori per mmol/L di diminuzione del colesterolo LDL nei partecipanti con diabete, che era simile all'effetto osservato in quelli senza diabete.

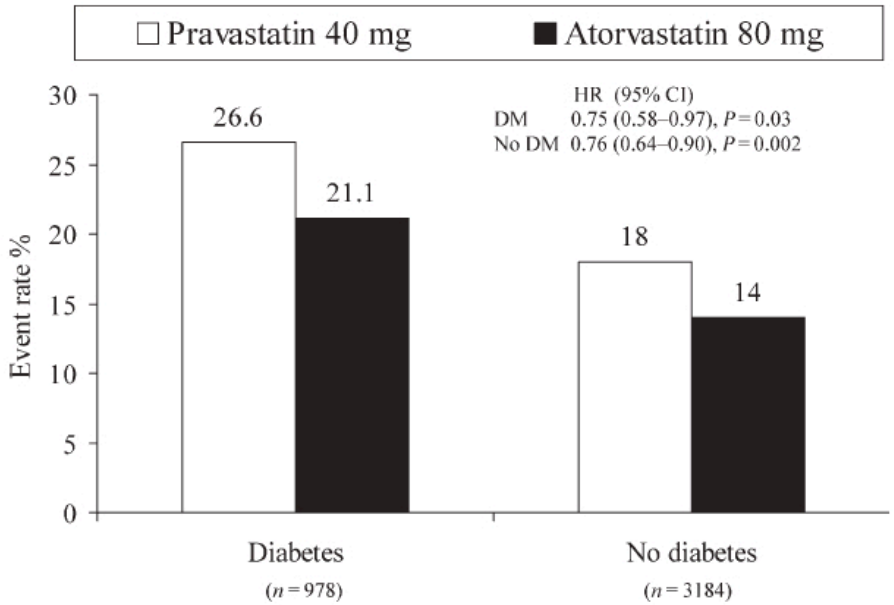
• Riduzione di: infarto miocardico, morte coronarica (-22%), rivascolarizzazione coronarica (-25%) e ictus (-21%).

• Gli effetti del trattamento con statine sono presenti a prescindere dalla presenza di una storia precedente di malattie vascolari e di altre caratteristiche basali.

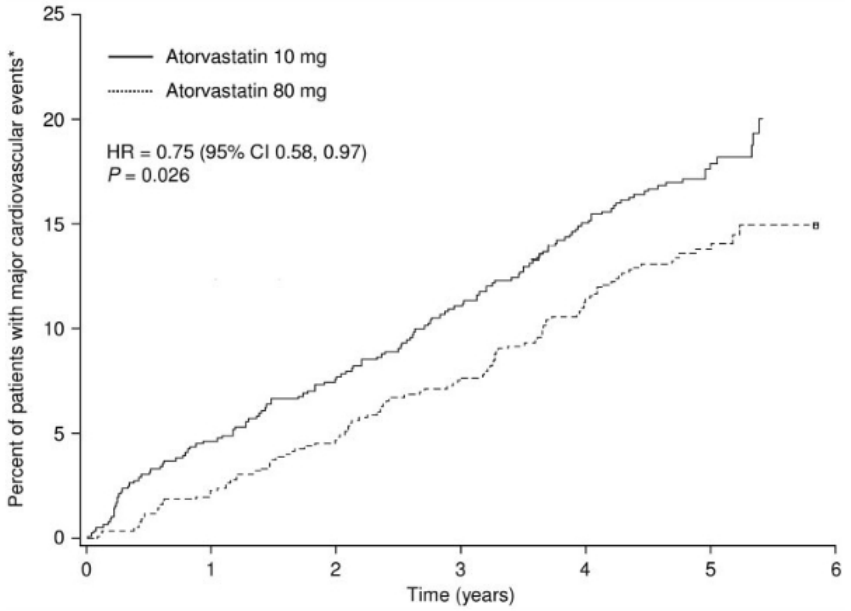
CONCLUSIONE La terapia con statine dovrebbe essere presa in considerazione per tutti i diabetici che presentano un rischio sufficientemente elevato di eventi vascolari.

LDL-C less than 100 mg/dl is beneficial in patients with diabetes and coronary heart disease

PROVE-IT study



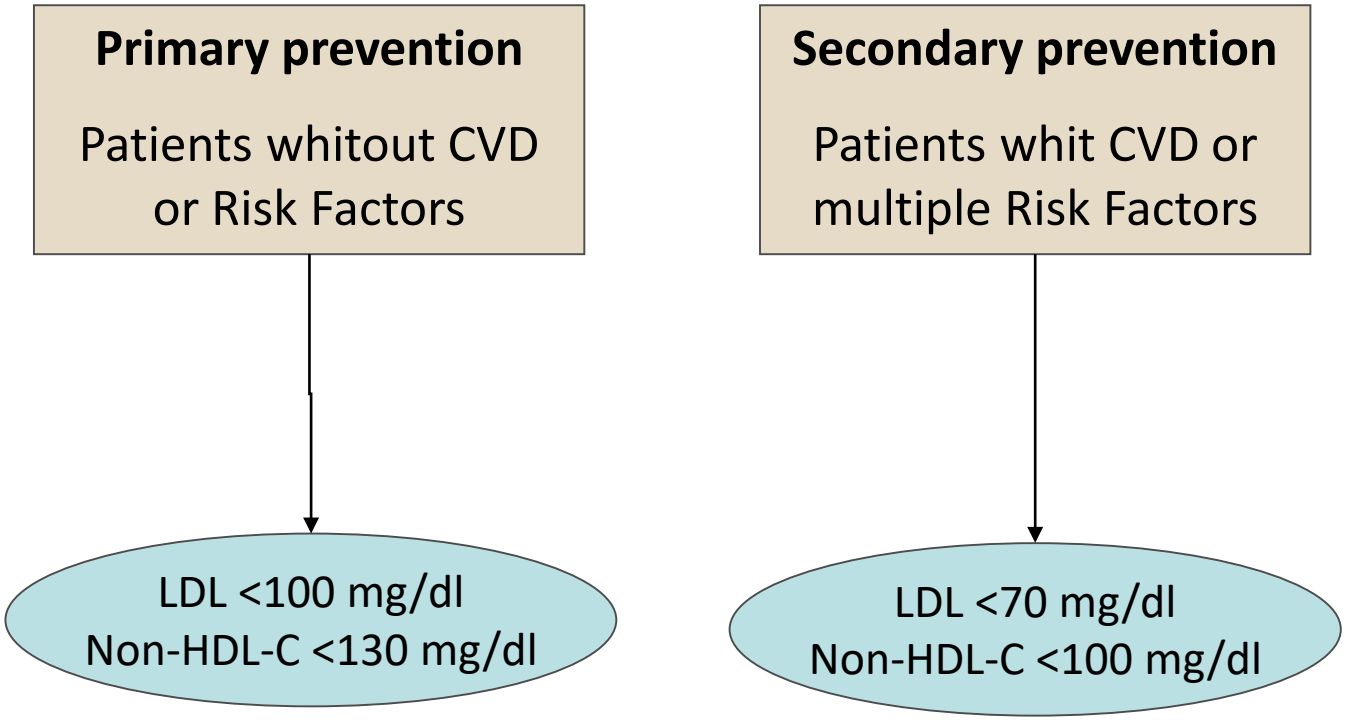
TNT study



These data suggest that patients with DM (with previous CHD) benefit from an LDL-C that is considerably less than 100 mg/dL, and in the post-ACS setting, the achieved level should be 70 mg/dL

Shepherd J. Diabetes Care 2006; 29:1220 –1226 - Ahmed S. Eur Heart Journal 2006; 27, 2323–2329

LDL-cholesterol targets in patients with diabetes



Standard italiani per la cura del Diabete Mellito AMD-SID 2018

Recommendations for statin and combination treatment in adults with diabetes

Age	ASCVD	Recommended statin intensity^ and combination treatment*
<40 years	No	None†
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#
≥40 years	No	Moderate‡
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30% to 50%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 2–4 mg

*Once-daily dosing. XL, extended release.

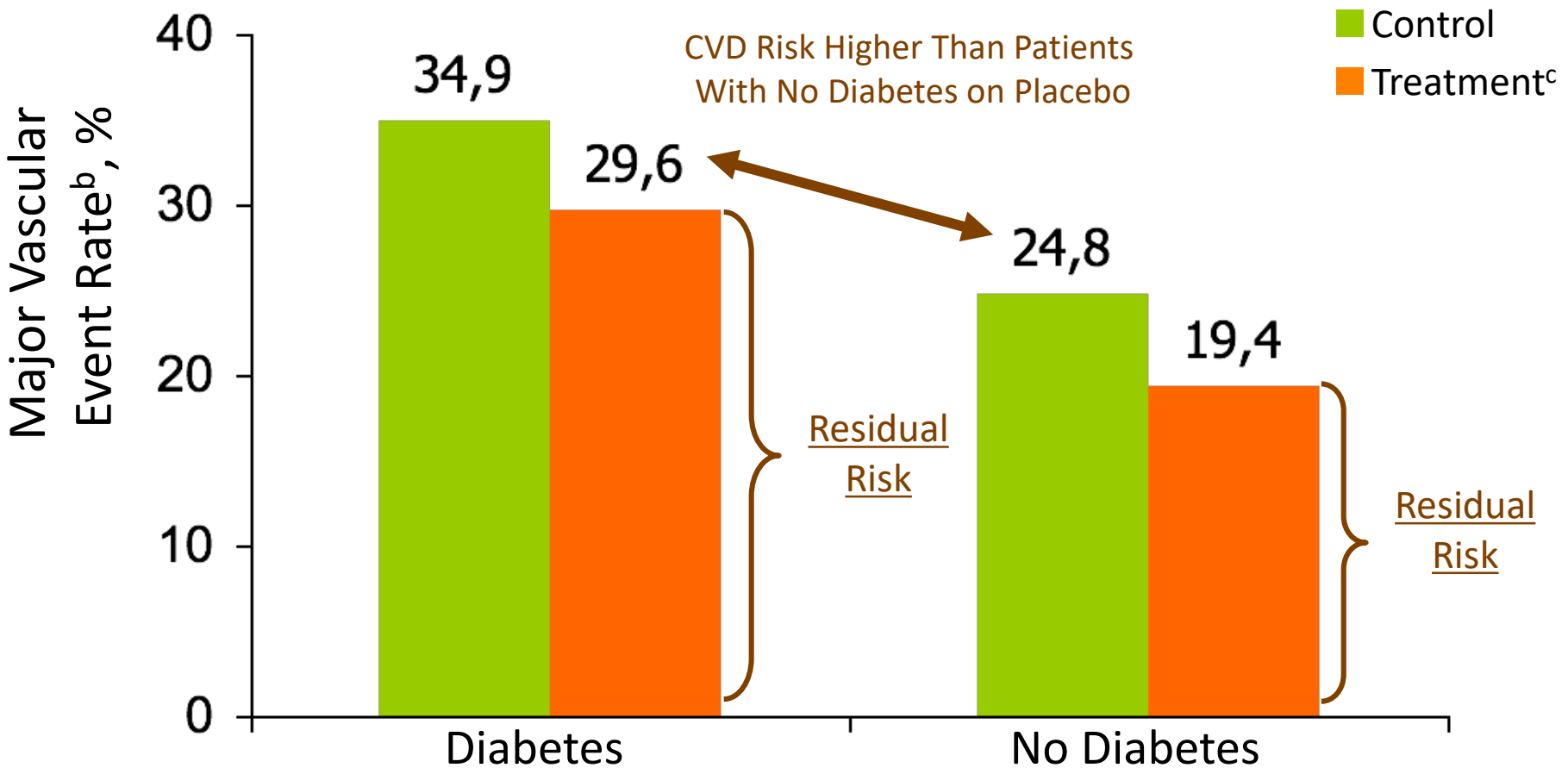
†Moderate-intensity statin may be considered based onrisk-benefit profile andpresence of ASCVD risk factors. ASCVD risk factors include LDLcholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD.

‡High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors.

Adapted from ADA Standard of Medical Care in Diabetes 2018 - Diabetes Care: 41, Suppl. 1

Statin Therapy Reduces CVD Events in DM Approximately to Un-Rx'd Risk in Non-Diabetics

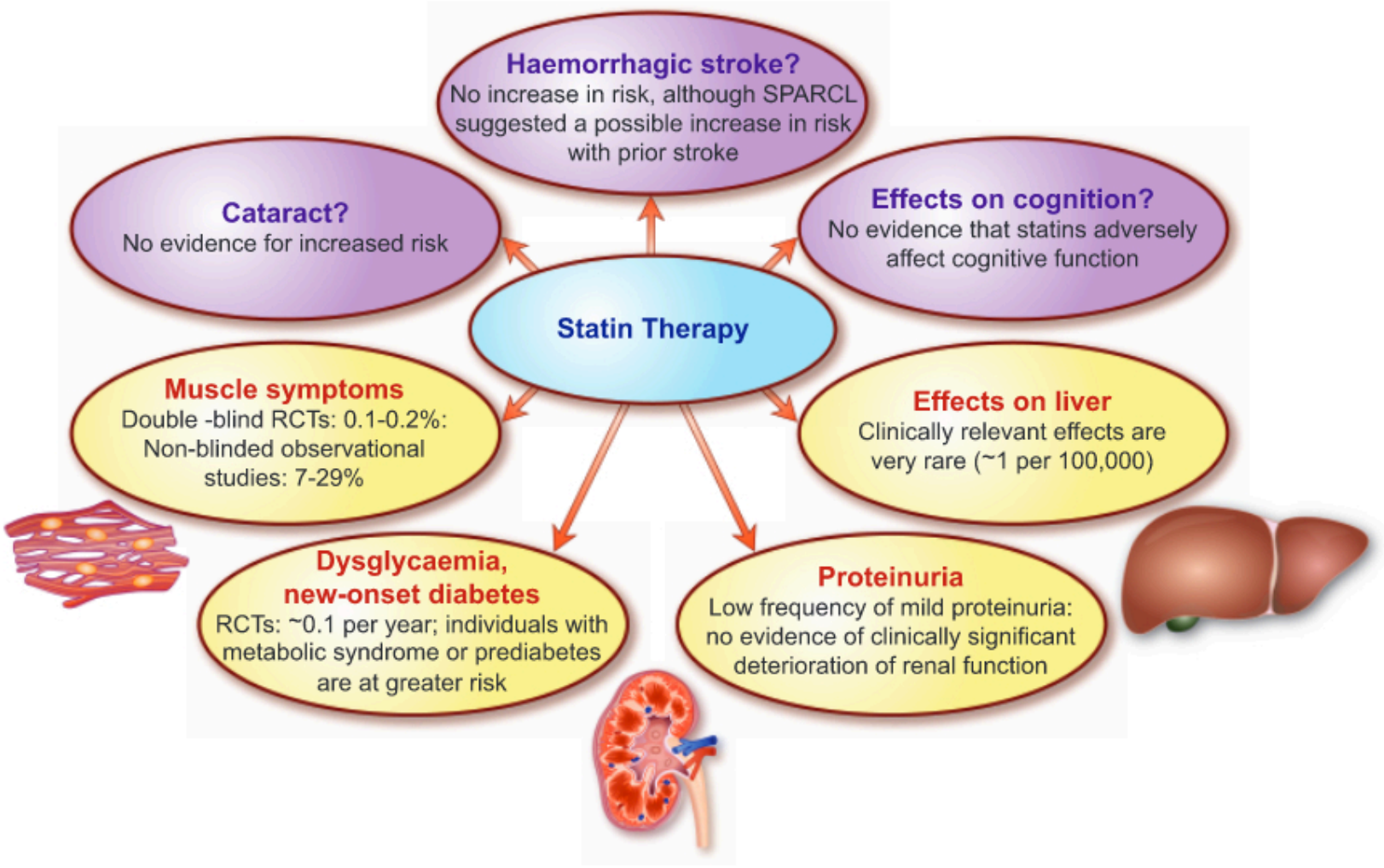
CTT Meta-Analysis of 14 Statin Trials[a]



[a]4.3-year mean follow-up of 18 686 patients with diabetes; n = 71 370 patients with no diabetes
[b]Nonfatal MI, CHD death, stroke, or coronary revascularization
[c]Event rate per 1 mmol/L (39 mg/dL) reduction in LDL-C

CTT Collaborators. Lancet. 2008;371:117-125.

Overview of the relative prevalence of the main types of adverse effects reported with statin therapy



European Atherosclerosis Society Consensus Panel. European Heart Journal (2018) 39, 2526–2539

Take home messages

Rischio di diabete

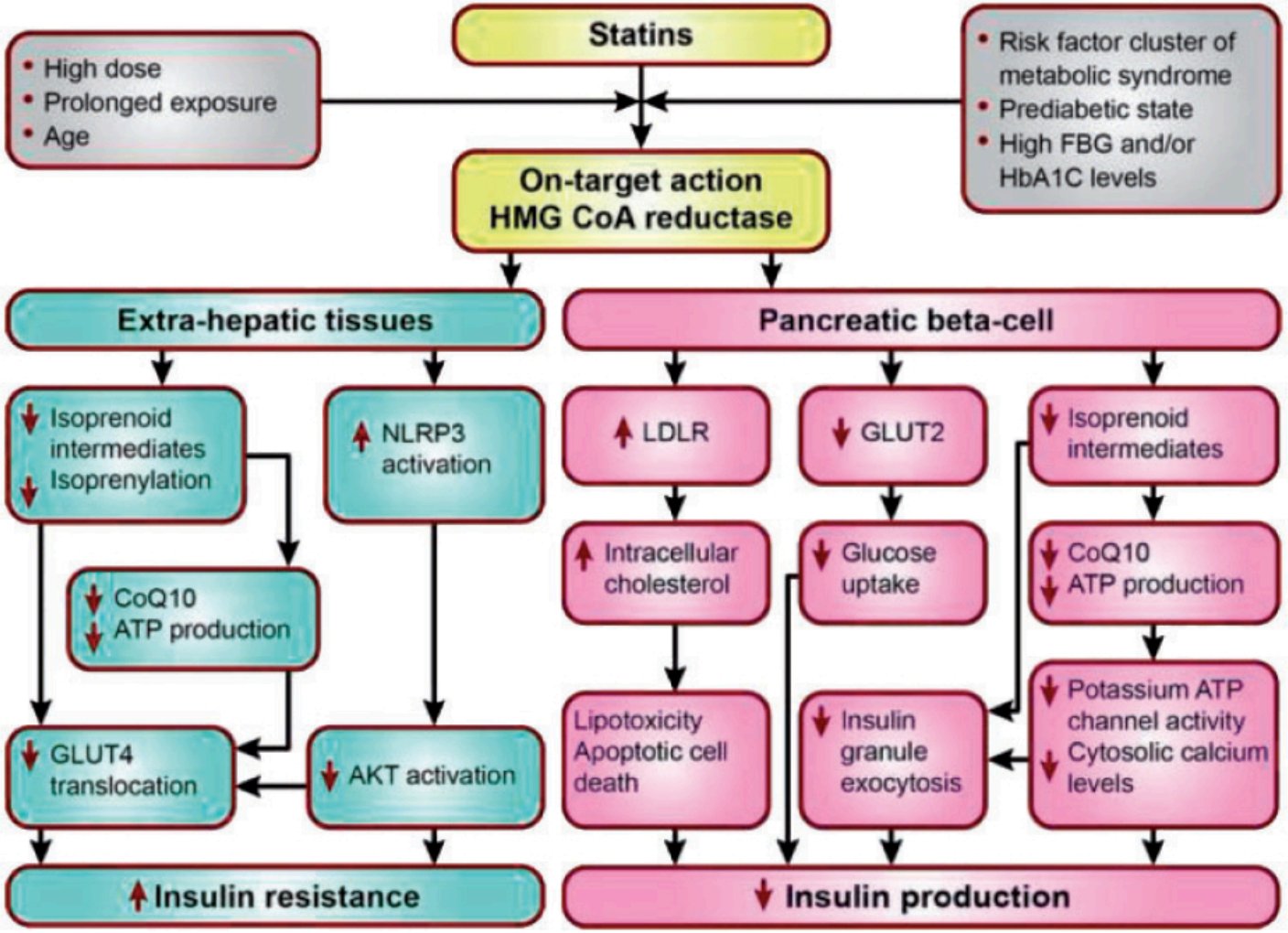
• Evidenze concordanti derivanti dai trial randomizzati e dagli studi genetici indicano che la terapia con statine si associa con un modesto aumento del rischio di nuovi casi di diabete pari a circa *1 caso ogni 1000 pazienti/anno*, ma che è in grado di prevenire 5 nuovi eventi CV.

• Gli individui con sindrome metabolica o prediabete sono a rischio più elevato, sebbene il loro tasso di progressione a diabete sia alto anche in assenza di statine.

• I pazienti dovrebbero essere riassicurati sul fatto che i benefici delle statine nella prevenzione CV superano il rischio potenziale di peggioramento della regolazione glicemica o di progressione a diabete.

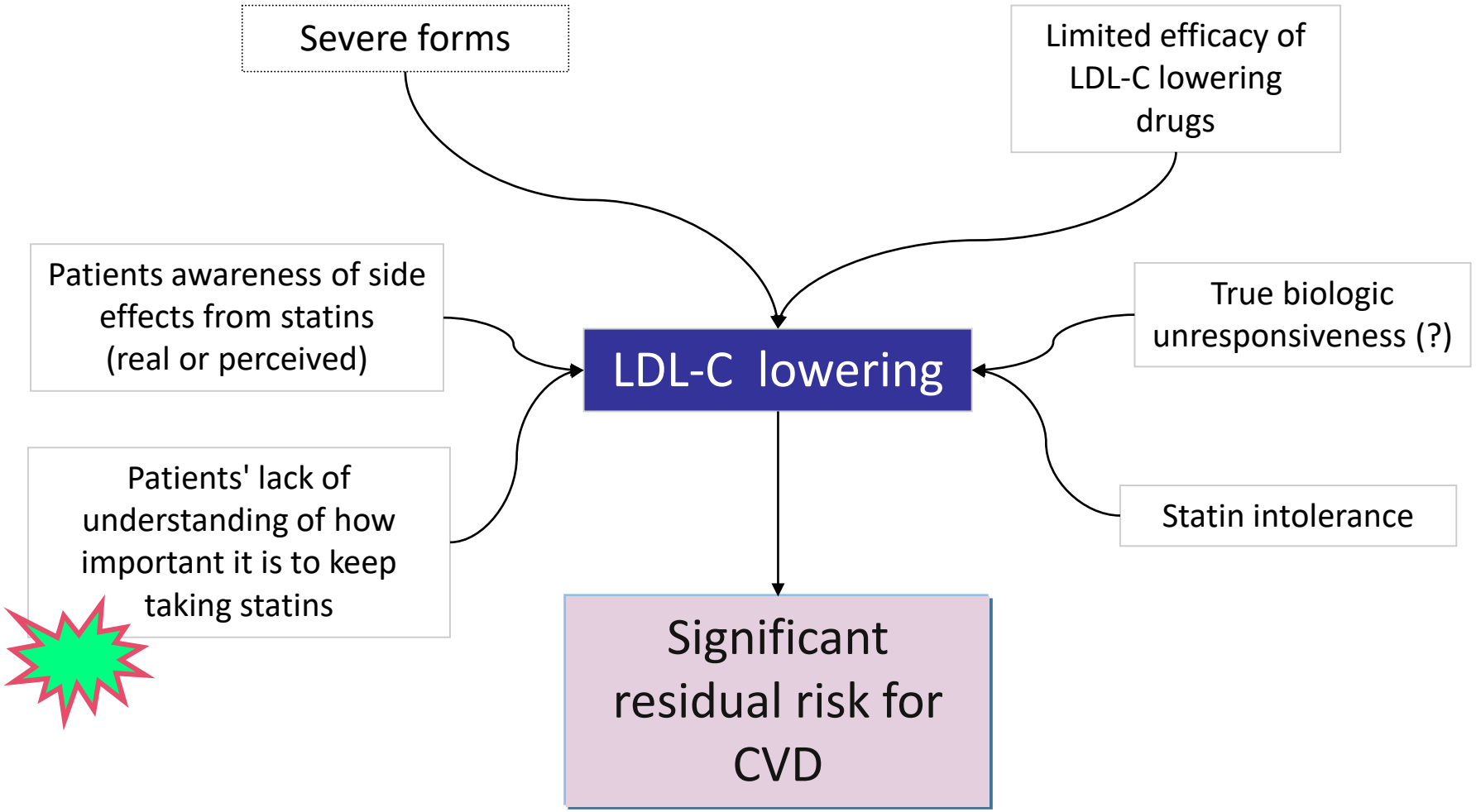
European Atherosclerosis Society Consensus Panel. European Heart Journal (2018) 39, 2526–2539

Factors favouring diabetogenic effects of statins and candidate mechanisms in extrahepatic tissues and pancreatic β-cells



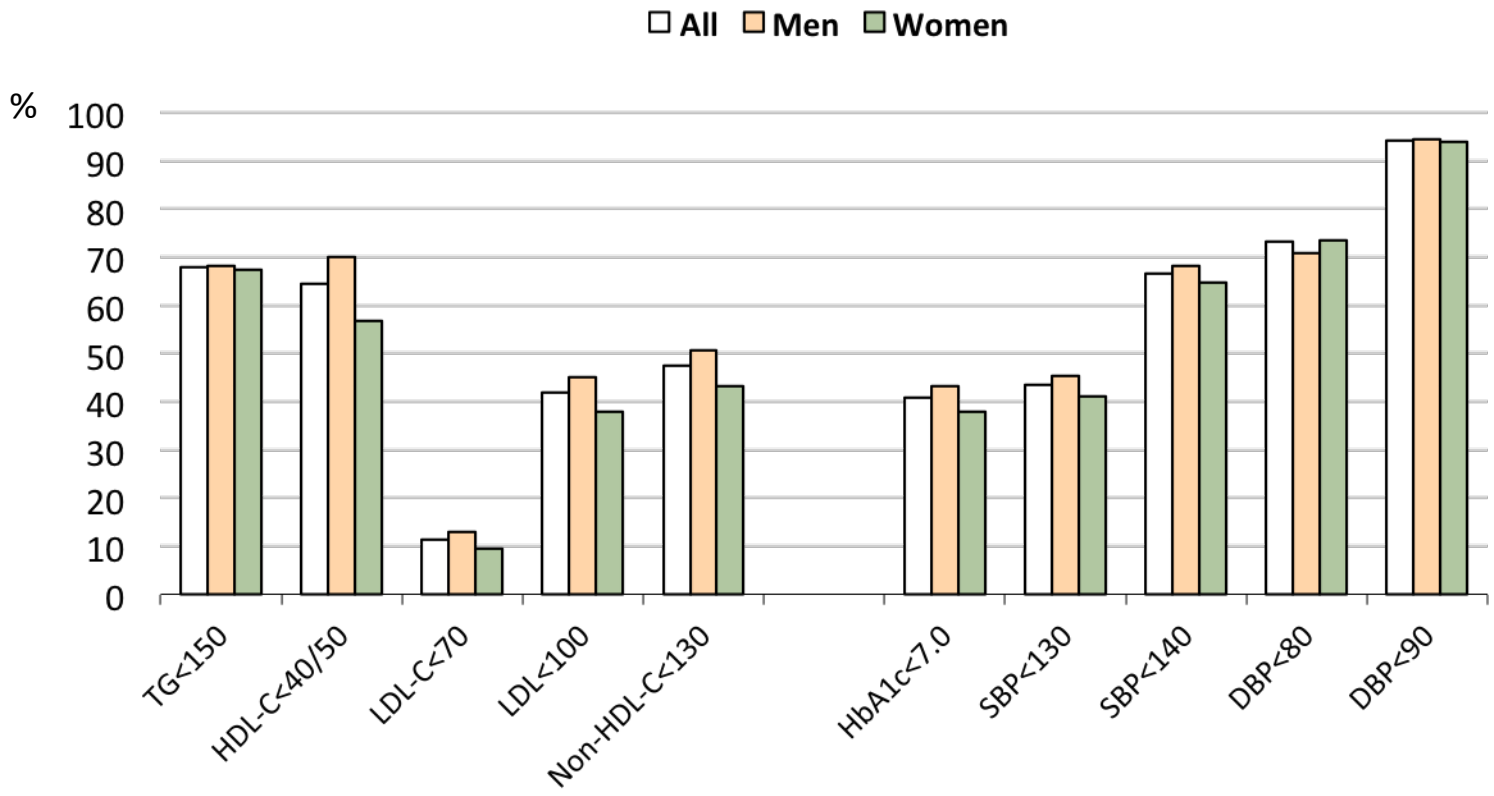
Adapted from Betteridge DJ. Nat Rev Endocrinol 2016;12:90–110

Unmet need in cholesterol lowering therapy



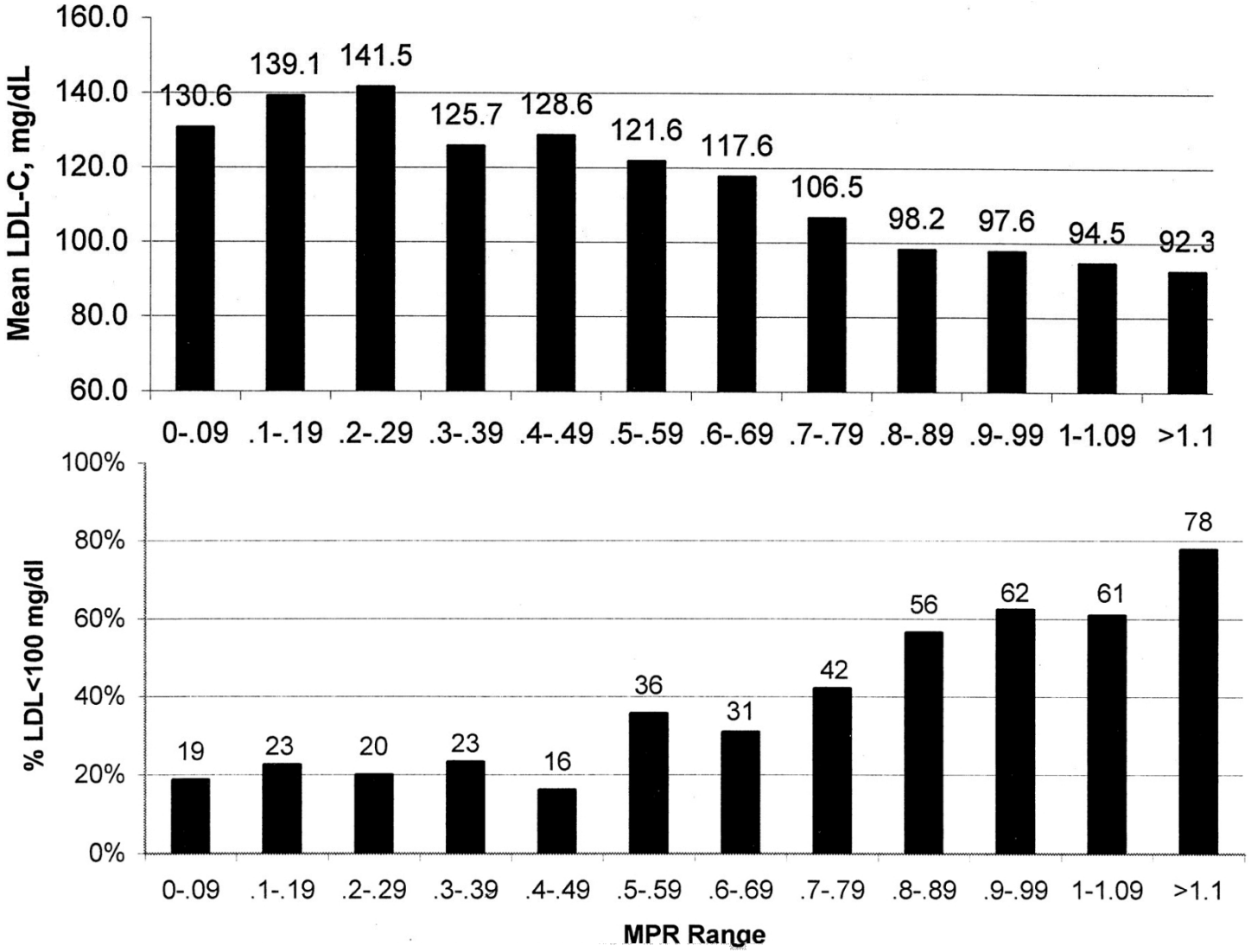
The achievement of guideline derived targets in patients wth type diabetes 2

The RIACE Study; n. 15.773



Penno G, J Intern Med 2013; 274: 176-191

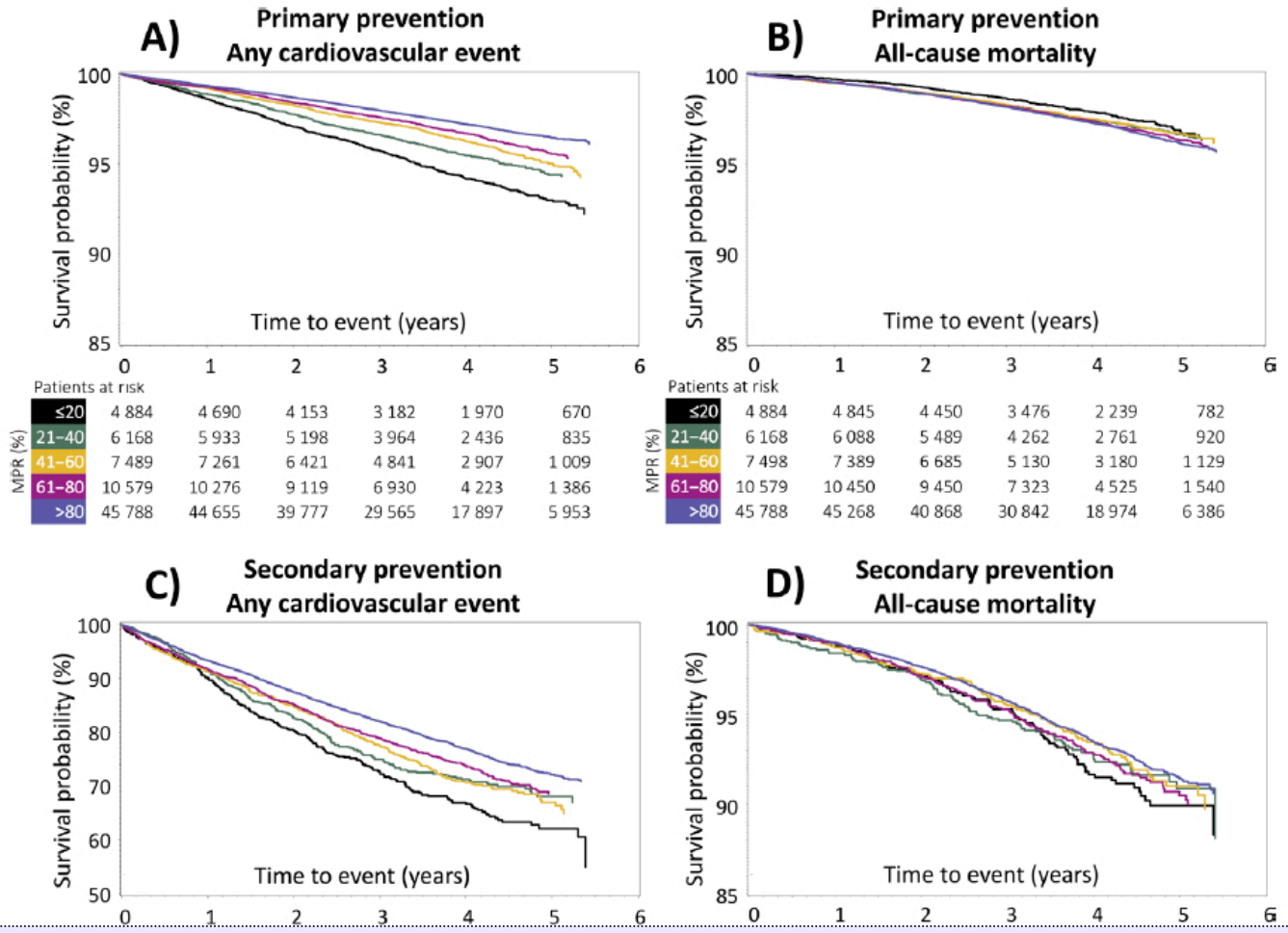
Adherence to Statin Therapy and LDL Cholesterol Goal Attainment by Patients With Diabetes



Parris ES, Diabetes Care 2005 Mar; 28(3): 595-599

Higher levels of refill adherence are associated with lower risk of CVD in patients with type 2 diabetes mellitus

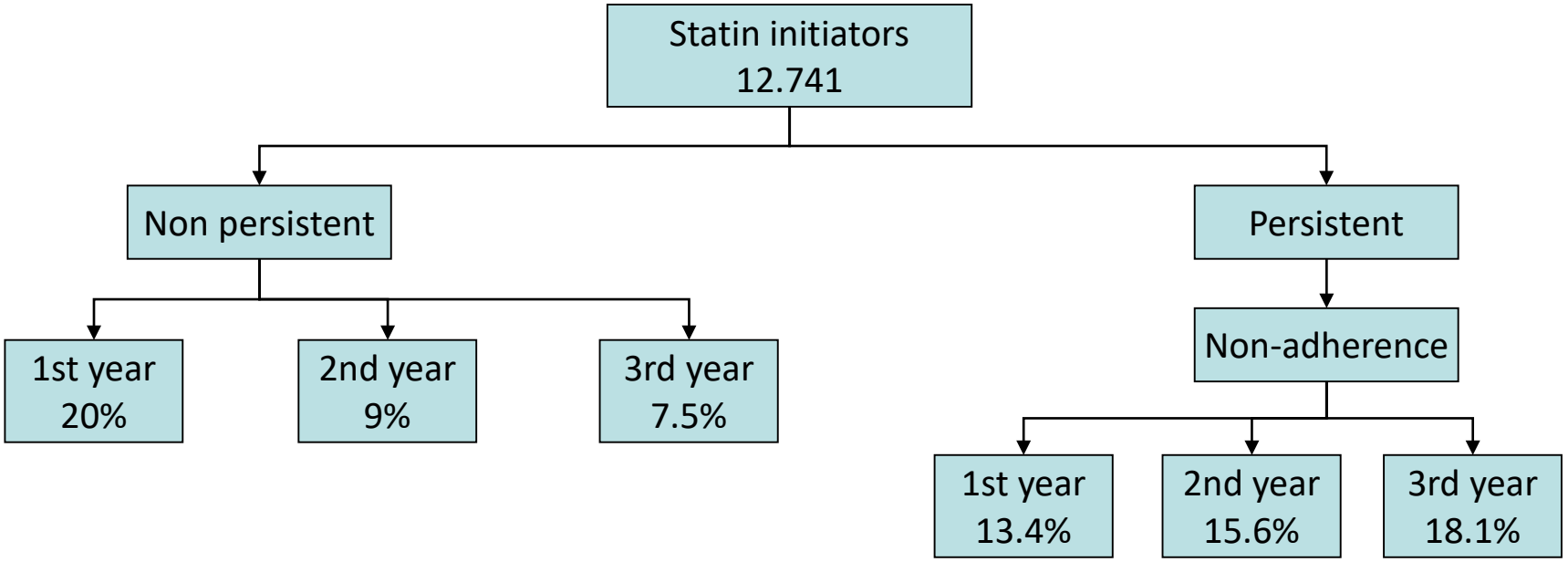
86.568 patients aged ≥18 years, registered with type 2 diabetes mellitus in the Swedish National Diabetes Register



- Higher levels of refill *adherence* are associated with lower risk of CVD in patients with type 2 diabetes mellitus, who commence lipid-lowering medications for primary or secondary prevention.
- *Non-persistence* to treatment was associated with a higher risk of CVD and mortality as well.

lsson SA. BMJ Open 2018;8:e020309. i:10.1136/bmjopen-2017-020309

Pharmacy-based predictors of non-persistence and non-adherence to statin treatment among patients on oral diabetes medication



Predictors of non-Persistence

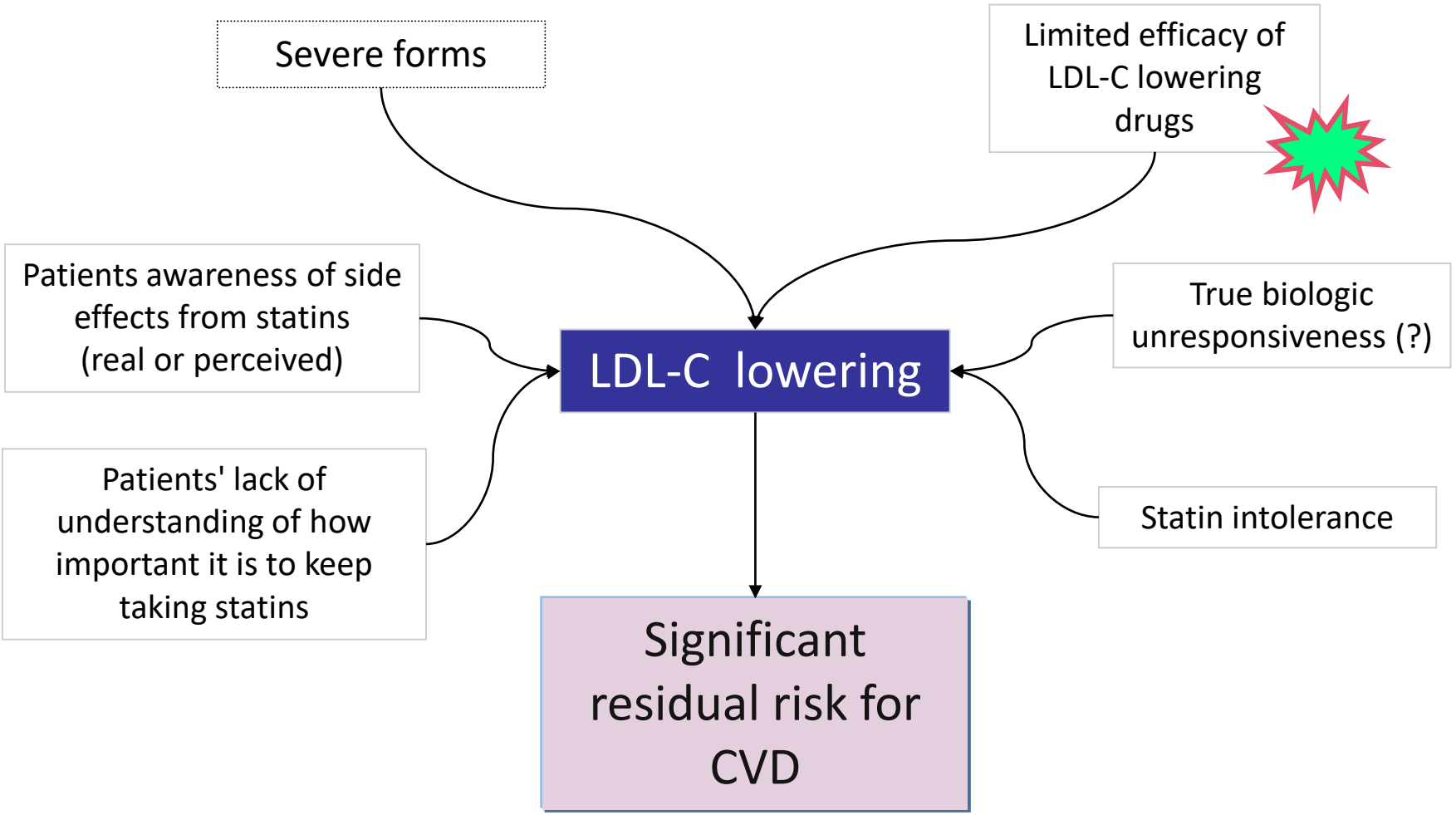
- female gender (HR:1.10; 95%CI:1.01-1.19)
- older age (HR:1.52; 95%CI:1.31-1.75)
- primary prevention (HR:1.10; 95%CI:1.00-1.20)
- initiating on low-dose (HR:1.44; 95%CI:1.07-1.94) or standard-dose (HR:1.56; 95%CI:1.16-2.10)
- no cardiovascular co-medication (HR:1.19; 95%CI:1.07-1.33), patients with 4 or more other medications were more likely to be persistent.

Predictors of non-Aderence

- age <50 years (OR:1.47; 95%CI:1.22-1.77)
- low socioeconomic status (OR:1.27; 95%CI:1.12-1.45)
- primary prevention (OR:1.21; 95%CI:1.07-1.38)
- females were more likely to be adherent (OR:0.87; 95%CI: 0.77-0.98

Curr Med Res Opin. 2018; 34: 1013-1019

Unmet need in cholesterol lowering therapy

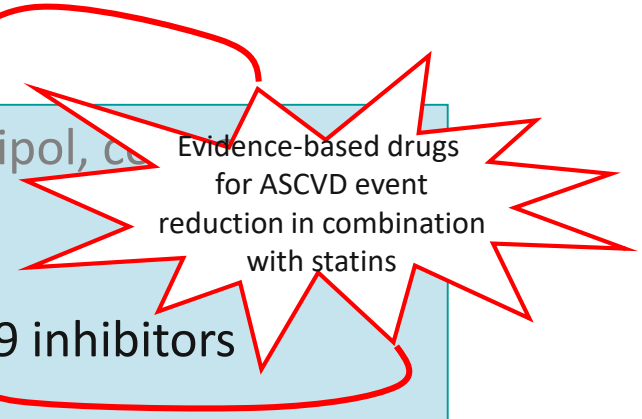


Therapeutic agents to lower LDL-C beyond statins

- Bile acid sequestrants (cholestyramine, colestipol, c
- Cholesterol absorption inhibitor, ezetimibe
- Nicotinic acid (niacin)
- Proprotein convertase subtilisin/kexin 9 PCSK-9 inhibitors (evolocumab, alirocumab)
- Microsomal transfer protein (MTP) inhibitor (lomitapide)
- Apolipoprotein B synthesis inhibitor (mipomersen)
- Red yeast rice

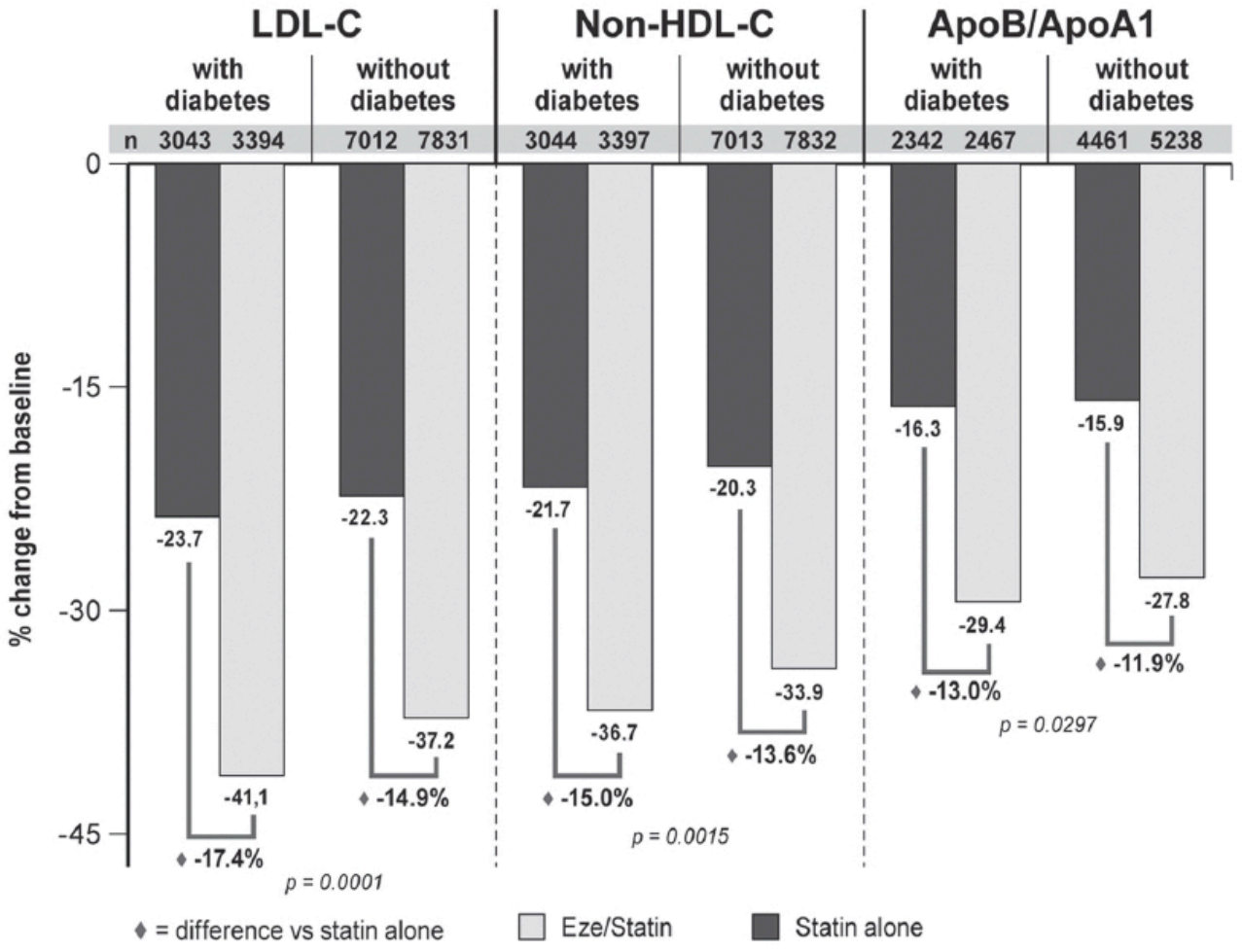
New agents in development:

- ATP citrate lyase inhibitor (ETC 1002)
- Dialkyl ether dicarboxylic acid (gemcabene)
- Angiopoietin-like protein3 (ANGPLP3) inhibitors
- THR-β agonist (MGL-3196)



Adapted from Ganda O. Current Diabetes Reports (2018) 18:126

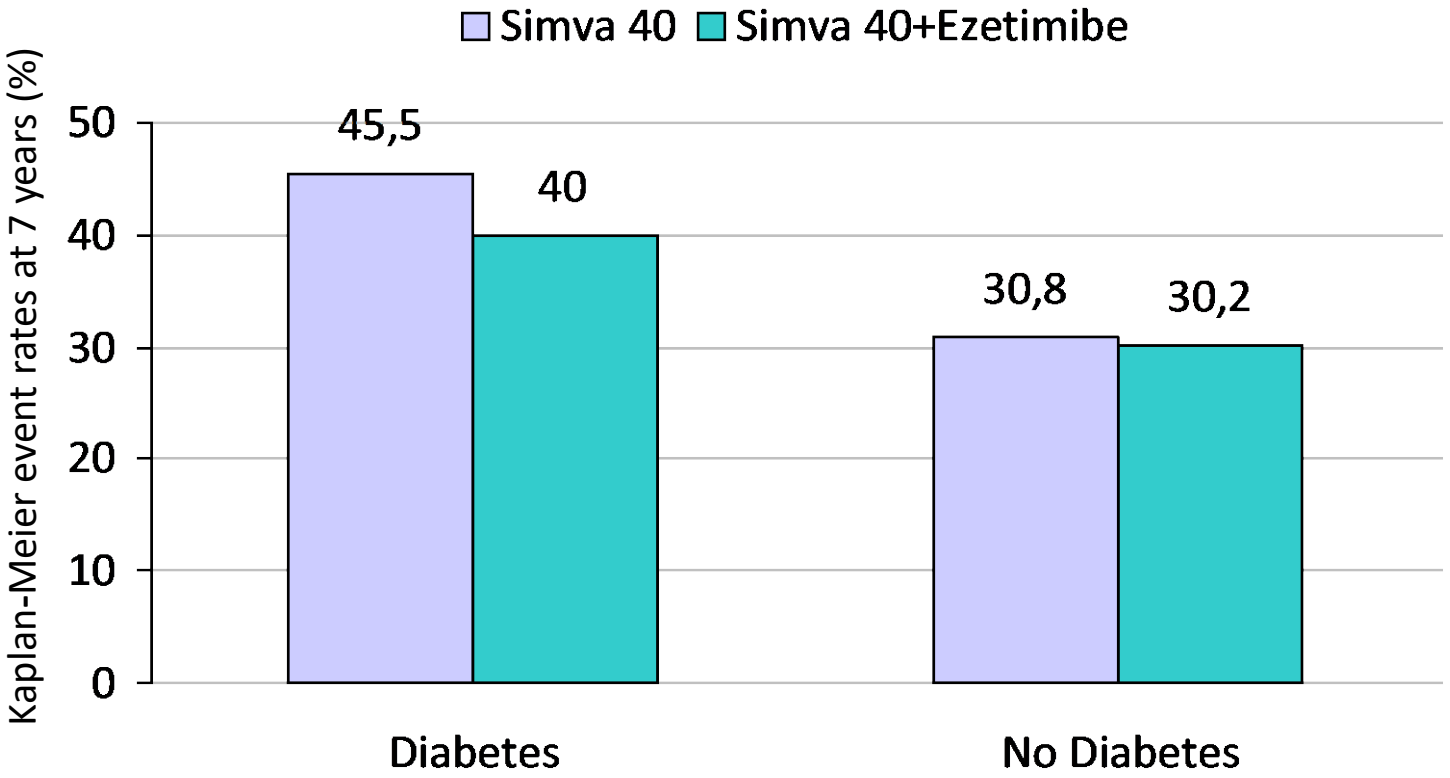
Pooled-analysis of 27 clinical trials comparing the efficacy of ezetimibe/statin vs statin therapies in patients with and without diabetes



Leiter et al. Diabetes Obes Metab 2011; 13: 615–28

IMPROVE-IT Substudy: greater CV event reduction with combo EZE+SIMVA in diabetic patients

18.144 patients (4.933 with T2D) after ACS with LDL-C 50-125 mg/dl

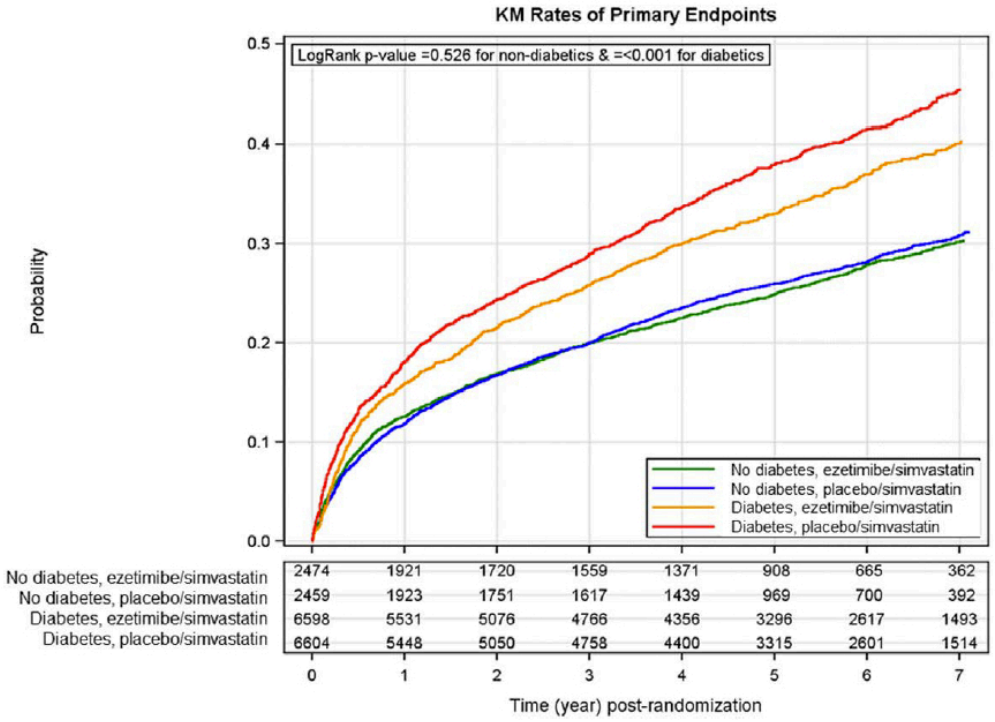


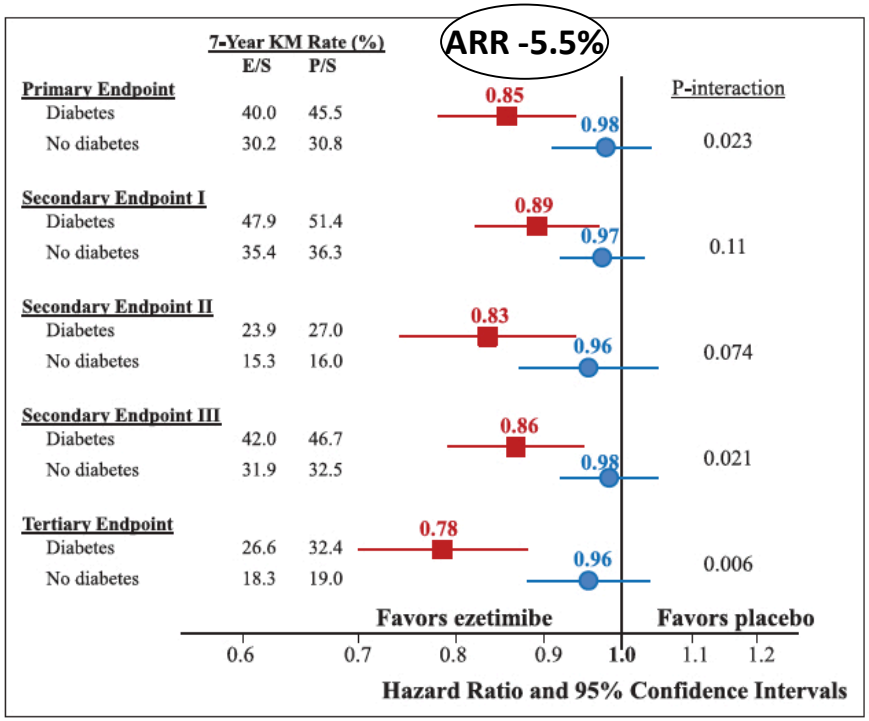
Primary endpoint (cardiovascular death, myocardial infarction, documented unstable angina requiring hospitalization, coronary revascularization after 1 month of treatment, or stroke):
↓14% among diabetic subjects (HR 0.86, p<0.023)

Giugliano RP. Circulation. 2018; 137:1571-1582

Benefit of adding ezetimibe to statin therapy oncardiovascular outcomes and safety in patients with versus without diabetes mellitus results from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)

Pre-specified subgroup with DM (n = 4933)





- The *largest relative reductions* in patients with DM were in myocardial infarction (24%) and ischemic stroke (39%).
- *Mortality end points* and hospitalization for unstable angina were not reduced with E/S versus P/S in patients with or without DM

Giugliano RP. Circulation. 2018;137:1571–1582

Statin and Fibrate

Recommendations

Combination therapy (statin/fibrate) has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended.

A

…

In the ACCORD study, the combination of fenofibrate and simvastatin in prespecified subgroup analyses, suggested heterogeneity in treatment effects with possible benefit for men with both a triglyceride level ≥204 mg/dL and an HDL cholesterol level ≤34 mg/dL.

…

Severe hypertriglyceridemia (>1.000 mg/dL) may warrant pharmacologic therapy (fibric acid derivatives and/or fish oil) to reduce the risk of acute pancreatitis.

Therapeutic agents to lower LDL-C beyond statins

- Bile acid sequestrants (cholestyramine, colestipol, c
- Cholesterol absorption inhibitor, ezetimibe
- Nicotinic acid (niacin)
- Proprotein convertase subtilisin/kexin 9 PCSK-9 inhibitors (evolocumab, alirocumab)
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New agents in development:

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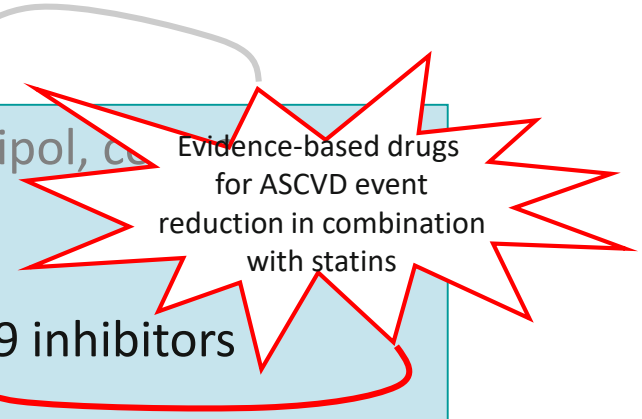
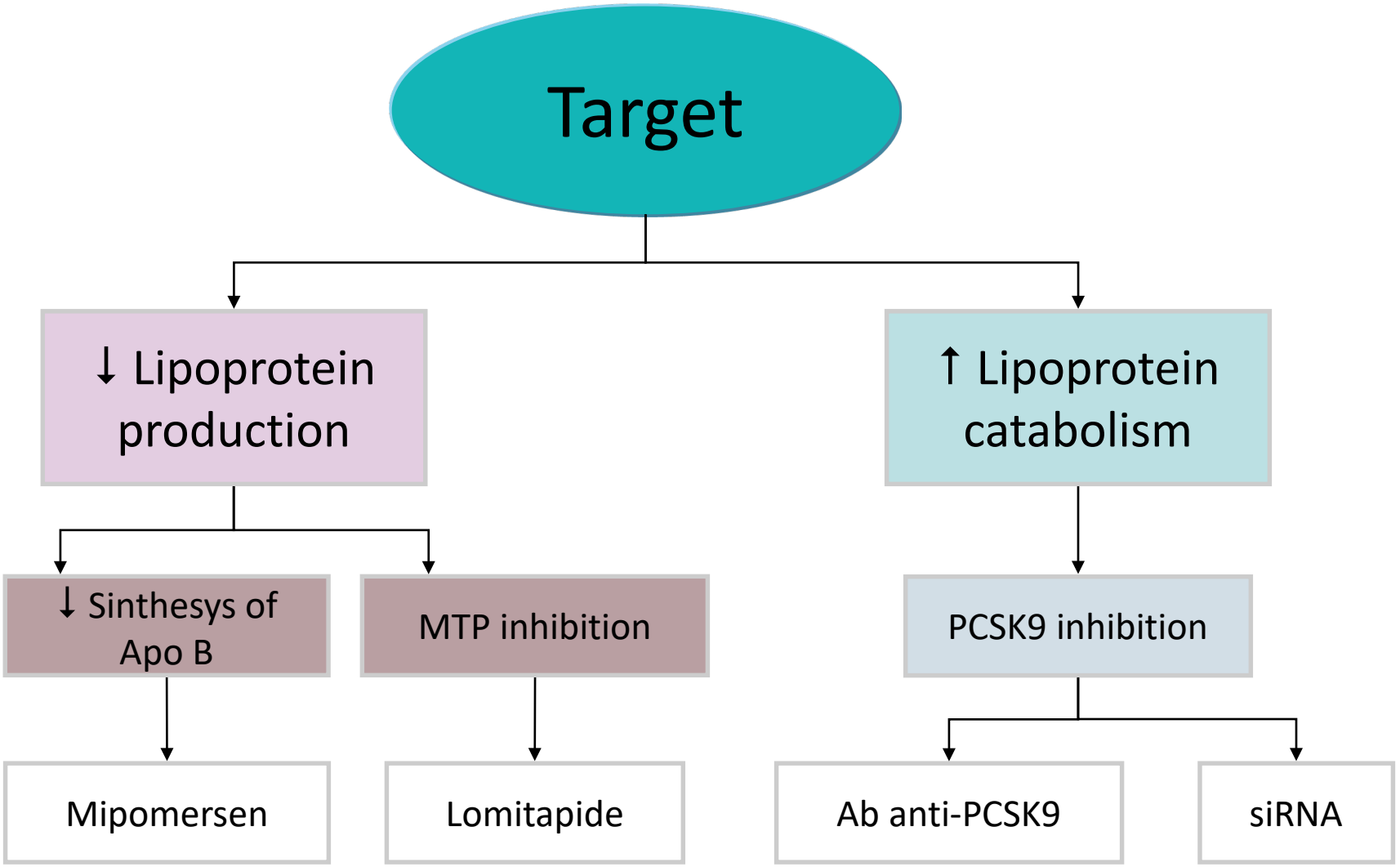


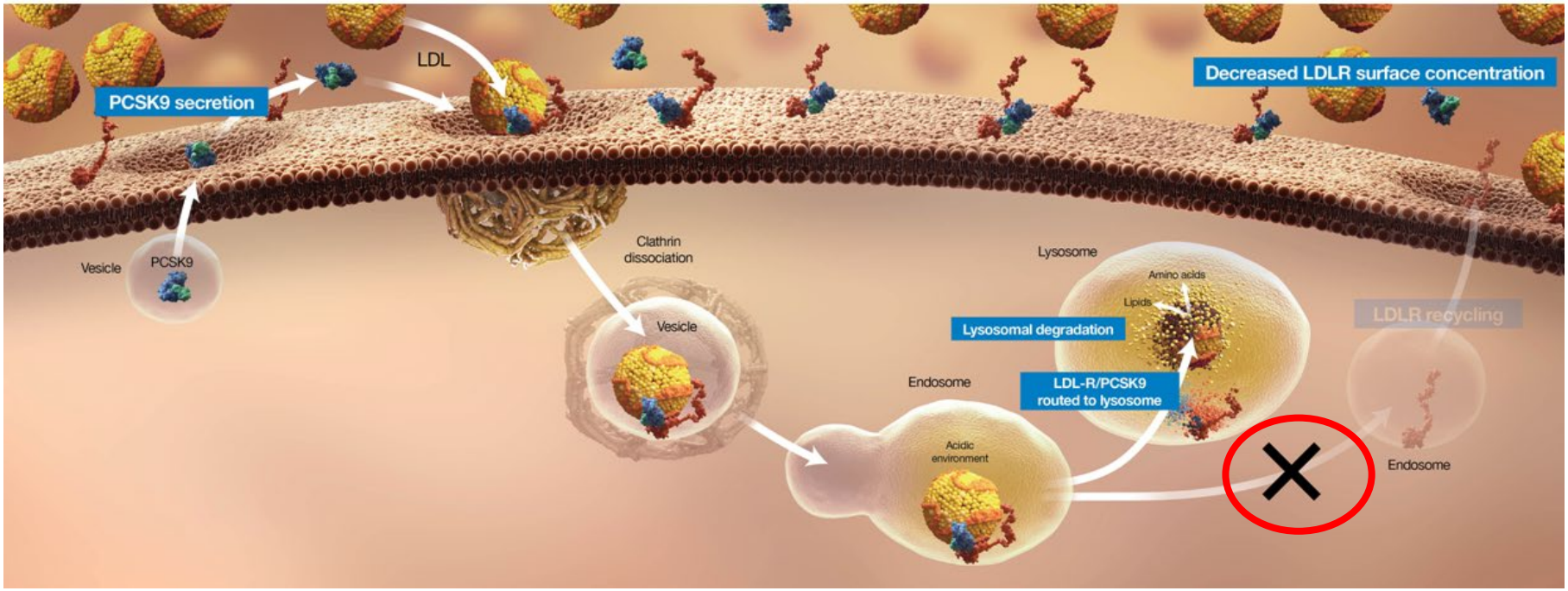
Adapted from Ganda O. Current Diabetes Reports (2018) 18:126

New cholesterol lowering drugs: mechanism of action



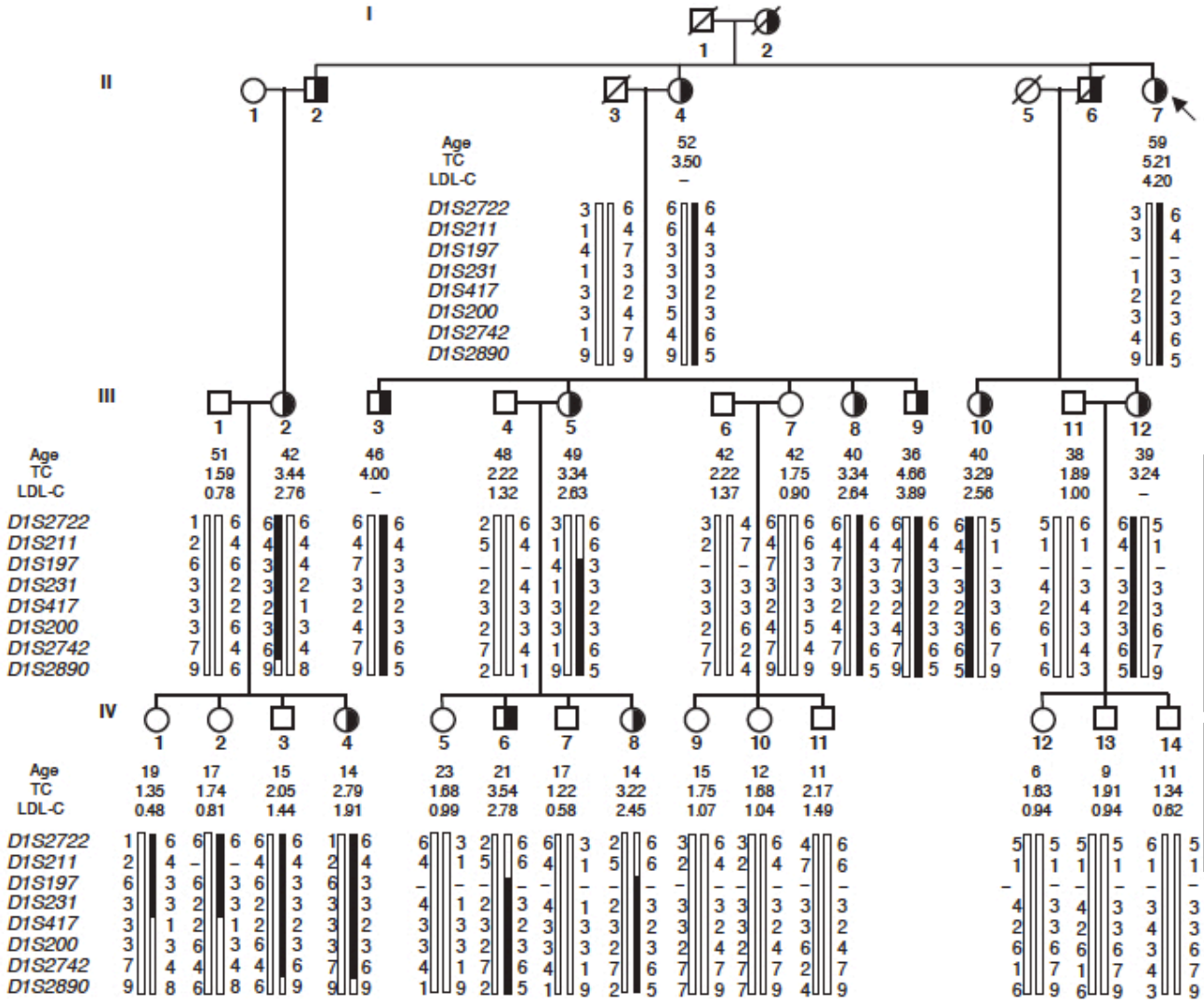
PCSK9 is a Key Regulator of LDL-R recycling

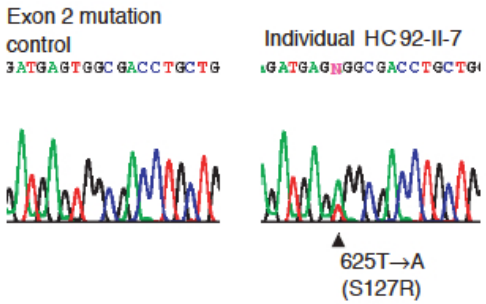
PCSK9 mediates degradation of the LDL-R by interacting with the extracellular domain and targeting the receptor for degradation[1]



1. Horton JD, et al. *J Lipid Res*. 2009;50:S172-S177. **2.** Qian YW, et al. *J Lipid Res.* 2007;48:1488-1498. **3.** Zhang DW, et al. *J Biol Chem.* 2007;282:18602-18612.

Discovery of PCSK9 as a Regulator of Cholesterol Homeostasis





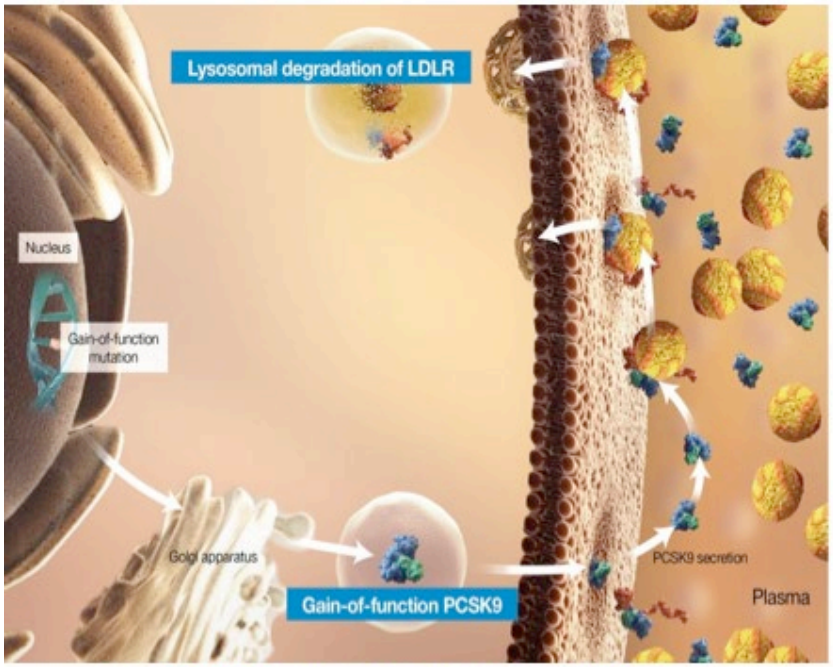
Affected family members with:

- Total cholesterol in 90th percentile
- Tendon xanthomas
- CHD, Early MI
- Stroke

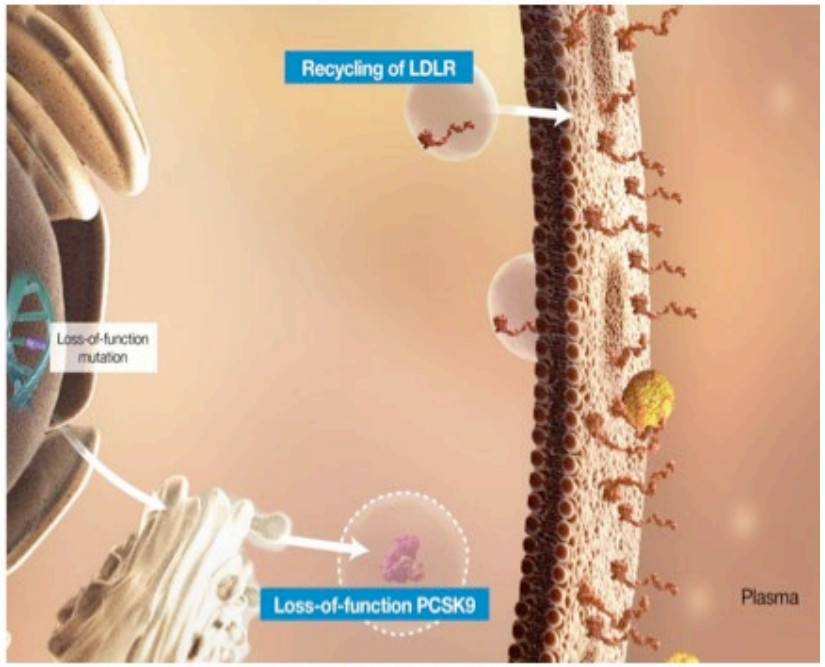
Gain-of-function mutations in PCSK9 cause autosomal dominant hypercholesterolemia

Abifadel M, et al. Nature Genet. 34: 154-156, 2003

Genetic Variants of PCSK9 Demonstrate Its Importance in Regulating LDL Levels



PCSK9 Gain of Function (GOF) = Less LDL-Rs[1,3,5]

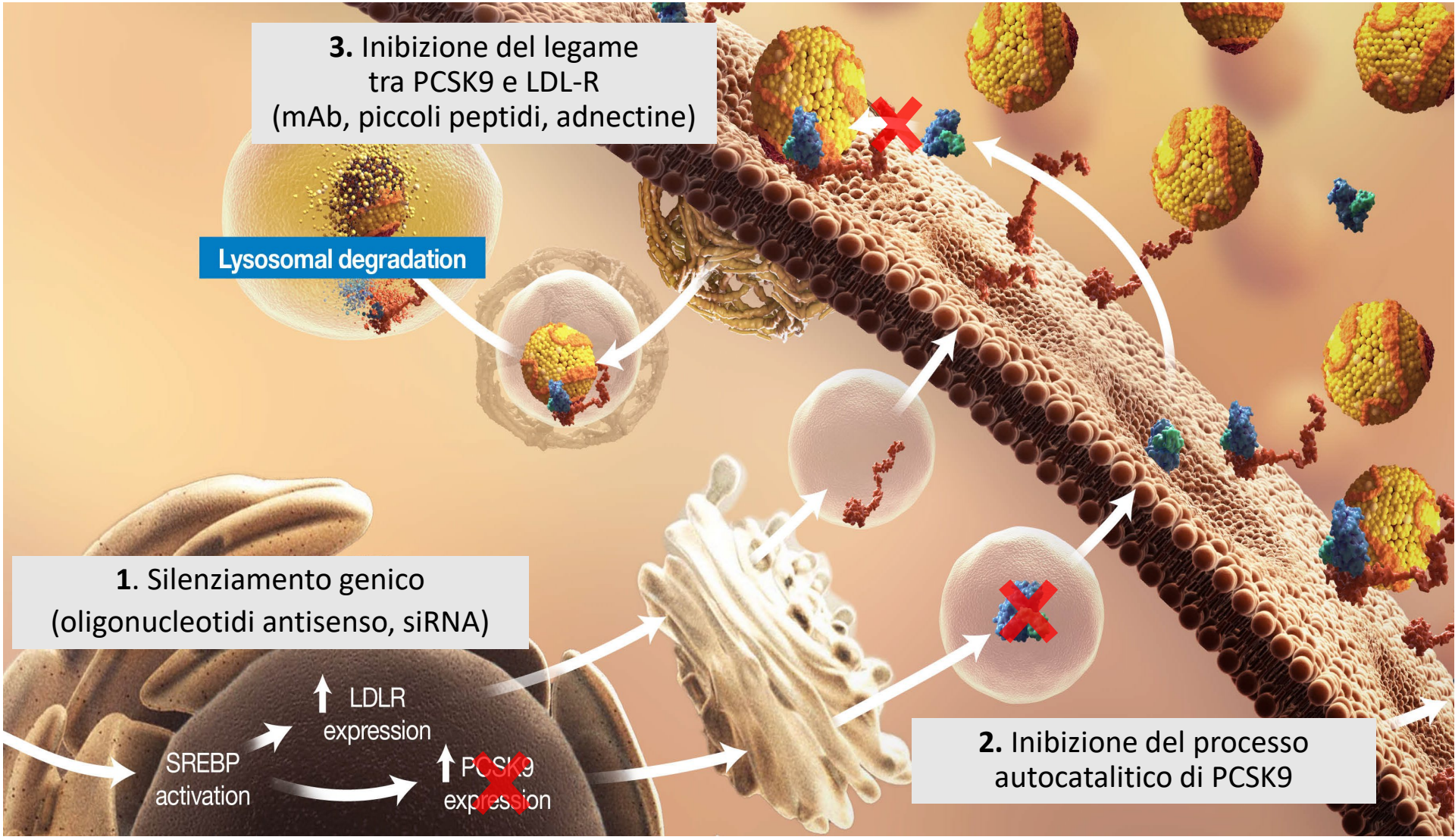


PCSK9 Loss of Function (LOF) = More LDL-Rs[2,4,5]

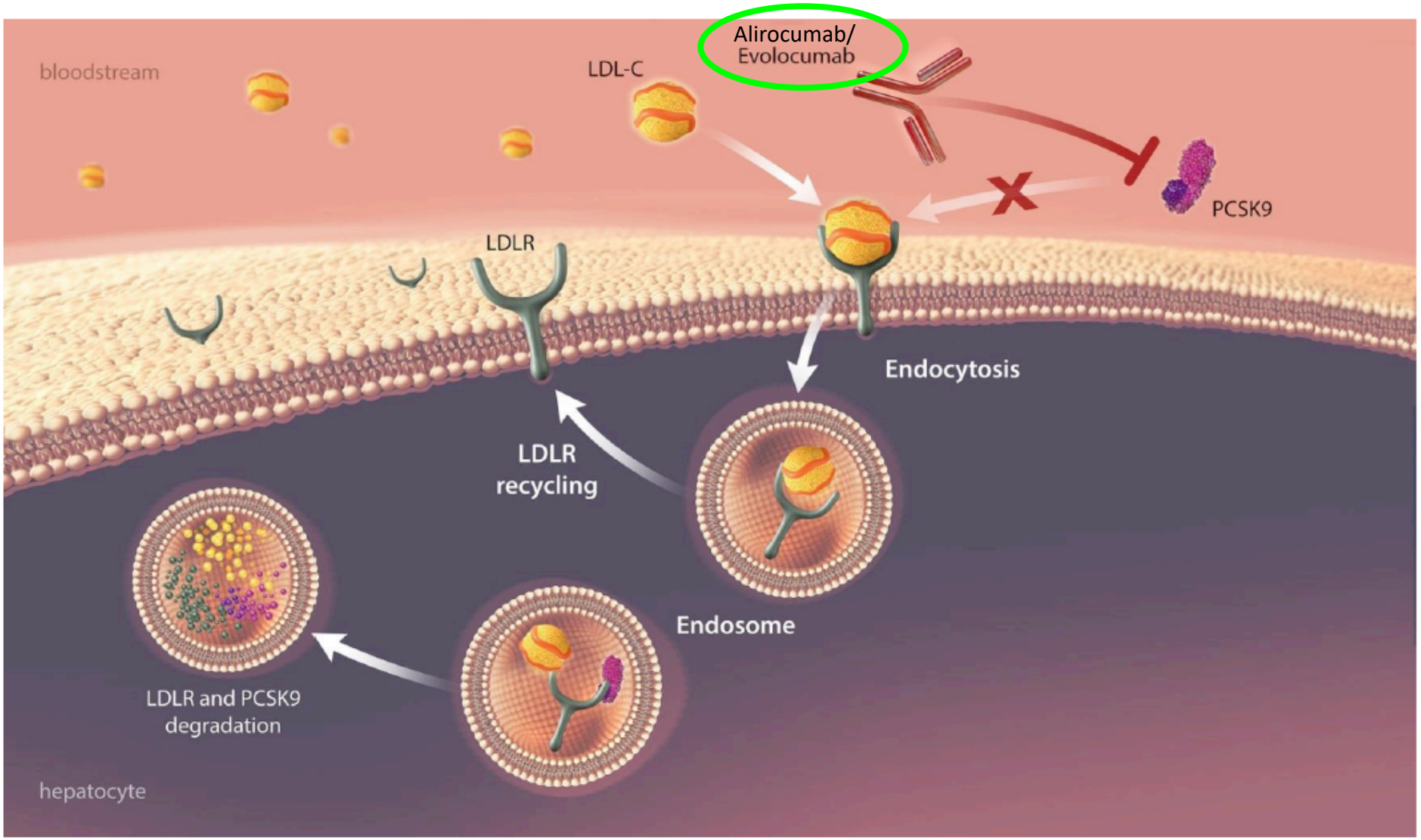
Mutations in the human PCSK9 gene that lead to a loss of PCSK9 function are found in 1% to 3% of the population[6,7]

Elaborated from **: 1.** Horton JD, et al. *J Lipid Res*. 2009;50:S172-S177. **2.** Lakoski SG, et al. *J Clin Endocrinol Metab.* 2009;94:2537-2543. **3.** Abifadel M, et al. *Hum Mutat.* 2009;30:520-529. **4.** Cohen J, et al. *Nat Genet.* 2005;37:161-165. **5.** Steinberg D, et al. *PNAS.* 2009;106:9546-9547. **6.** Cohen JC, et al. *N Engl J Med*. 2006;354:1264-1272. **7.** Benn M, et al. *J Am Coll Cardiol*. 2010;55:2833-2842.

Strategies for PCSK9 inhibition



Fully Human Monoclonal Antibody Against PCSK9 and Inhibits PCSK9/LDL-R Interaction



Chan JC, Piper DE, Cao Q, et al. Proc Natl Acad Sci U S A. 2009;106:9820-9825

Pharmacokinetic properties of PCSK9 inhibitors

Agent	Bioavailability	Distribution	Time to Peak	Elimination Half-life	Metabolism	Excretion
Alirocumab	85%	0.04-0.05 L/kg	Peak effect on PCSK9 suppression • 4 – 8 hours Cmax (SQ): • 3 – 7 days	17-20 days 12 days when combined with a statin	Proteolysis and degradation to small peptides and amino acids	Feces: 41.5% as unchanged drug, 7% as hydroxylated metabolite, 3.2% as *O*-glucuronide metabolite Urine: ~33%; 30.5% as *O*-glucuronide metabolites, <1% as unchanged drug
Evolocumab	72%	3.3 L	Peak effect on PCSK9 suppression • 4 hours Cmax (SQ): • 3-4 days	11-17 days	Non-saturable proteolysis	Feces: 21% ~15% as parent drug Urine: 75% < 2% as parent drug

Lexi-Drugs. Wolters Kluwer; 2015. http://online.lexi.com/lco/action/index/dataset/patch_f -AHFS-DI. Hudson, OH: Wolters Kluwer; 2015: http://online.lexi.com/lco/action/index/dataset/complete_ashp- Gilman Ga. The Pharmacologic Basis of Therapeutics. In: Laurence L. Brunton BAC, Björn C. Knollmann ed. China2011.

Populations studied with PCSK9 inhibitors

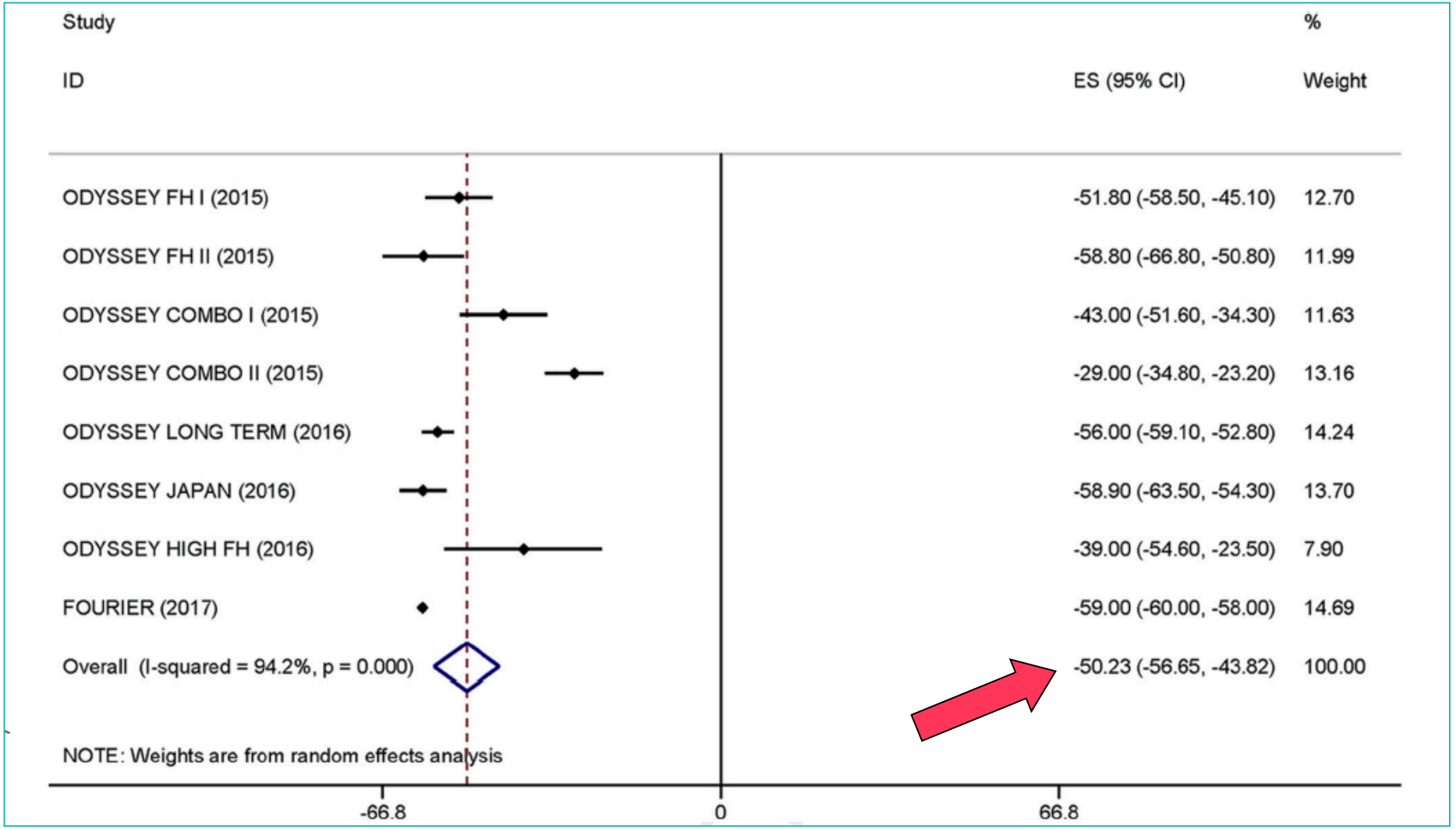
Familial Hypercholesterolaemia

CVD and high LDL-C

Statin intolerance

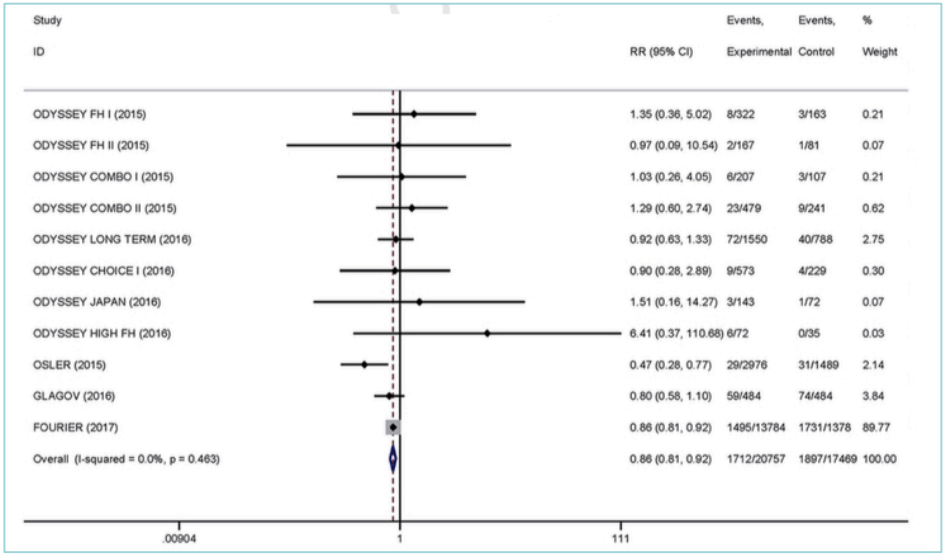
Long-term efficacy and safety of PCSK9is A meta-analysis of 11 randomized controlled trials

Effect on LDL-C



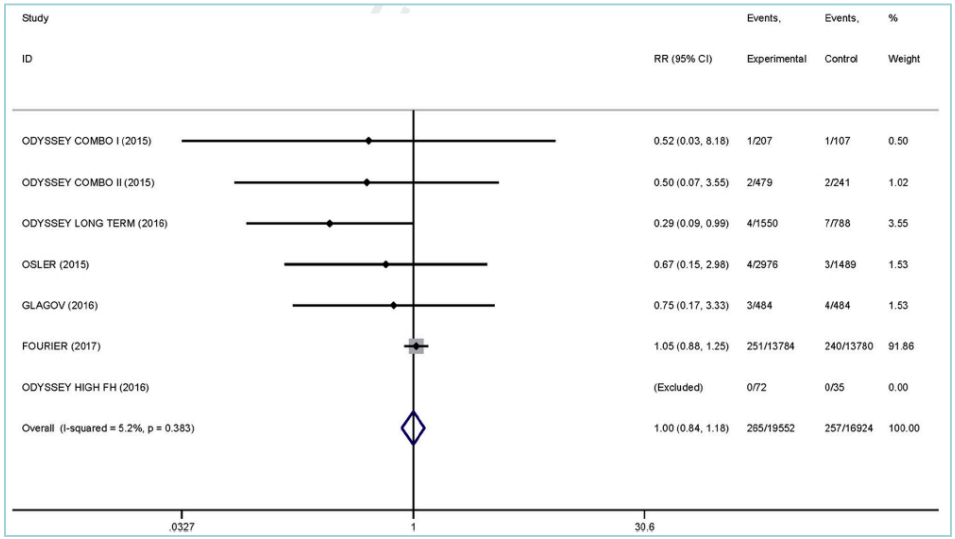
Bai J. Journal of Clinical Lipidology 2018; 12: 277-291

Long-term efficacy and safety of PCSK9is
A meta-analysis of 11 randomized controlled trials
Effect on cardiovascular outcomes



Cardiovascular events

RR, 0.86 (95% CI, 0.81–0.92)

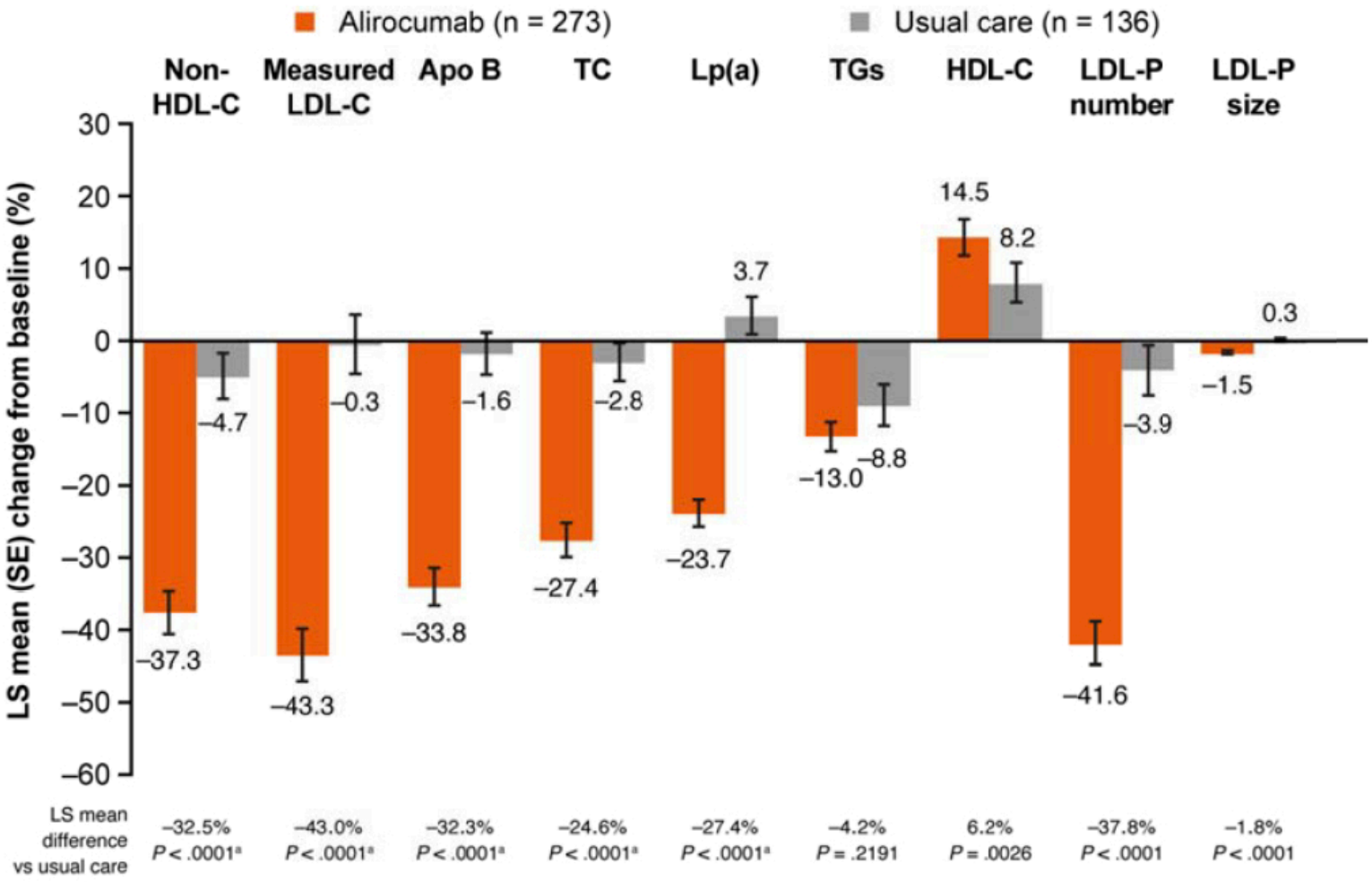


Cardiovascular mortality

RR, 1.00 (95% CI, 0.84–1.18)

Bai J. Journal of Clinical Lipidology 2018; 12: 277-291

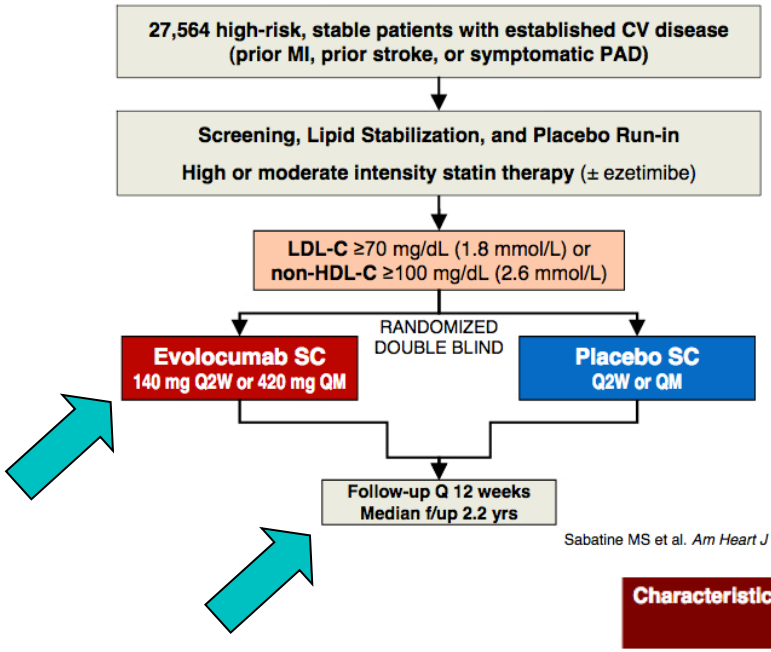
Alirocumab versus usual lipid-lowering care as add-on to statin therapy in individuals with type 2 diabetes and mixed dyslipidaemia
The ODYSSEY DM-DYSLIPIDEMIA randomized trial
*N. 413 - Alirocumab 75-150 mg - 24 weeks**



*ITT analysis

Ray KK, Del Prato S. et al. Diabetes Obes Metab. 2018; 20: 1479-1489

Trial Design



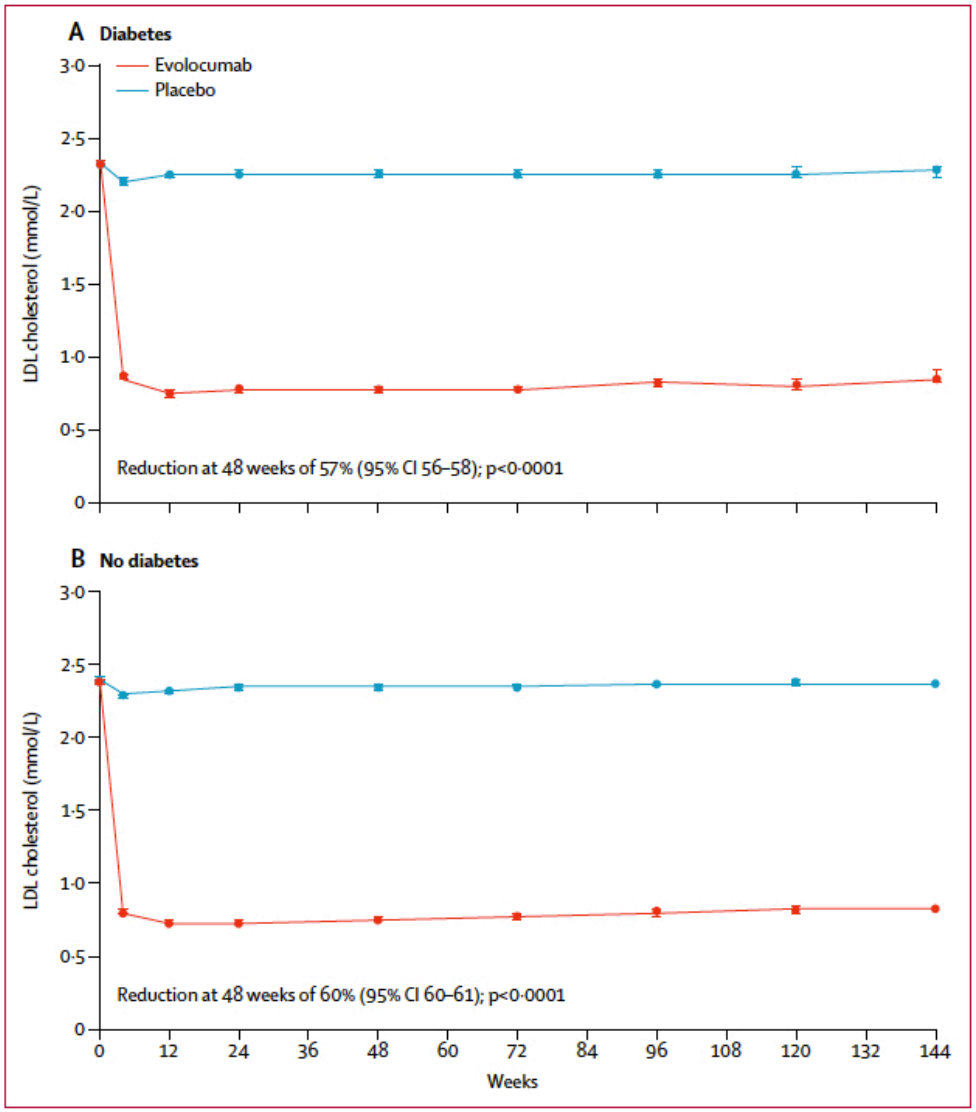
Sabatine MS et al. *Am Heart J* 2016;173:94-101

Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk

Characteristic	Diabetes (N=11,031)	No Diabetes (N=16,533)
Age, years, mean (SD)	63 (9)	62 (9)
Female sex (%)	27	23
White race (%)	80	88
Weight, kg, mean (SD)	88 (19)	83 (16)
Type of cardiovascular disease (%)		
Myocardial infarction	79	83
Stroke (non-hemorrhagic)	22	18
Symptomatic PAD	15	12
Cardiovascular risk factor (%)		
Hypertension	87	75
Current cigarette use	22	32
eGFR, mL/min per 1.73 m^2 (SD)	75 (21)	76 (17)

Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes

The FOURIER randomised controlled trial

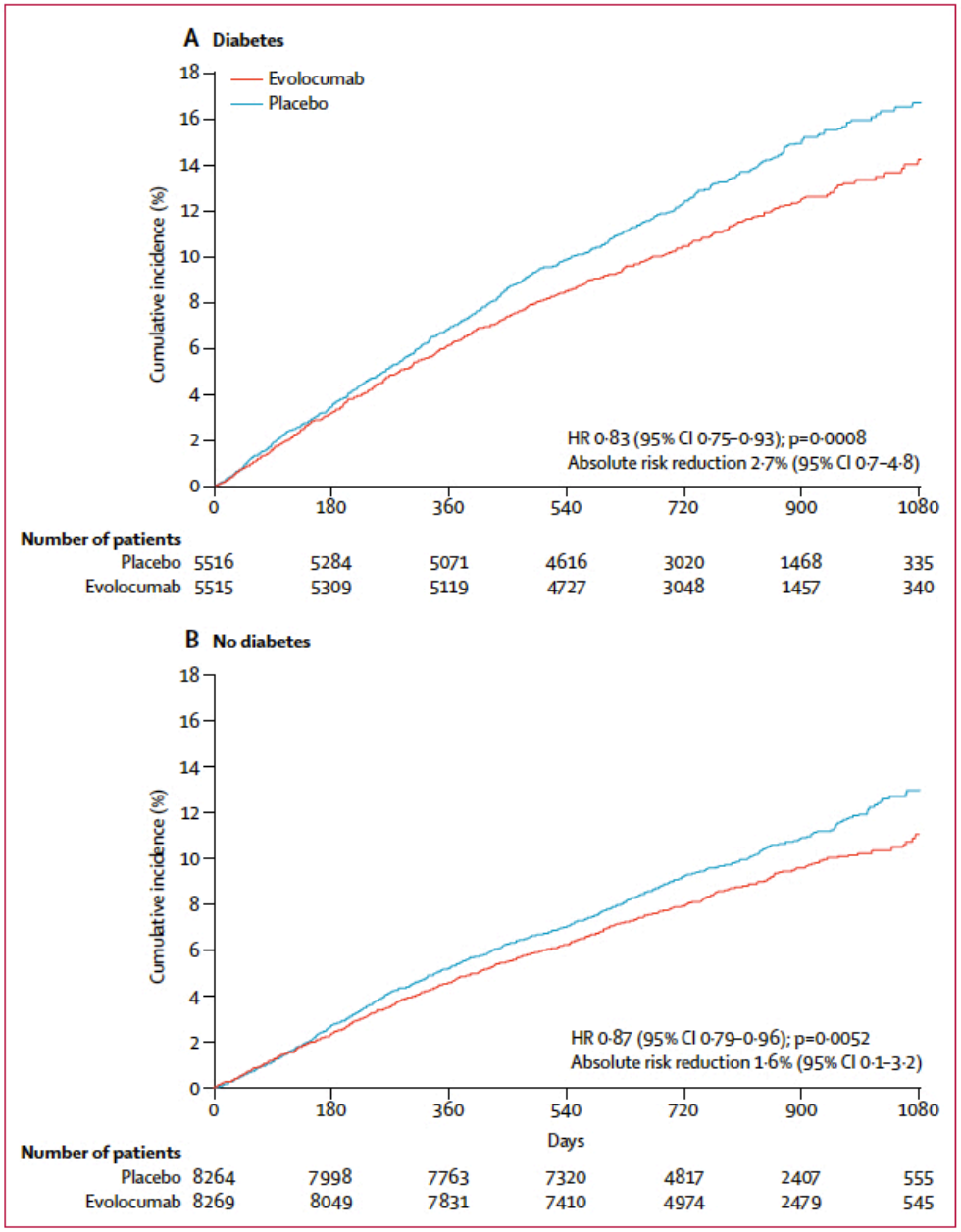


- **27.564 patients with atherosclerotic disease** (*40% with diabetes, n. 11.031*) on statin therapy,
- **Follow-up median 2·2 years**
- Primary endpoint (composite): cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina, or coronary revascularisation.
- Secondary endpoint: composite of cardiovascular death, myocardial infarction, or stroke.

- Compared with placebo, **evolocumab lowered LDL cholesterol** by 57% (95% CI 56–58; p<0.0001) in the diabetes subgroup and 60% (60–61; p<0.0001) in the non-diabetes subgroup at 48 weeks.
- non-HDL-C: -50% vs -53%
- apo B - 48% vs -50%
- TG: -16% vs -17%

(p<0.0001 vs placebo)

Sabatine MS. Lancet Diabetes Endocrinol. 2017;5:941–950.



Evolocumab significantly reduces cardiovascular risk in patients with diabetes

The FOURIER randomised controlled trial

Primary Composite Endpoint (HR)
0·83 (95% CI 0·75–0·93; p=0·0008) vs
0·87 (0·79–0·96; p=0·0052) (p interaction=0·60)

Secondary Endpoint (HR)
HRs **0·82** (0·72–0·93; p=0·0021) vs **0·78** (0·69–0·89; p=0·0002) (p interaction=0·65)

- **Absolute Risk Reduction 2.7% vs 1.6%**
- **NNT (3 years) 37 vs 62**

Sabatine MS. Lancet Diabetes Endocrinol. 2017;5:941–950

Alirocumab and Cardiovascular Outcomes in Patients with Acute Coronary Syndrome (ACS) and Diabetes—Prespecified Analyses of ODYSSEY OUTCOMES

18.924 patients (diabetes 28%) with recent ACS and LDL-C≥70mg/dL on a maximum-tolerated dose of atorvastatin or rosuvastatin

End Point	Alirocumab (N=9462)	Placebo (N=9462)	Hazard Ratio (95% CI)	P Value
	number of patients (percent)			
Primary end point: composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization	903 (9.5)	1052 (11.1)	0.85 (0.78–0.93)	<0.001
Major secondary end points, in order of hierarchical testing				
Any coronary heart disease event*	1199 (12.7)	1349 (14.3)	0.88 (0.81–0.95)	0.001
Major coronary heart disease event†	793 (8.4)	899 (9.5)	0.88 (0.80–0.96)	0.006
Any cardiovascular event‡	1301 (13.7)	1474 (15.6)	0.87 (0.81–0.94)	<0.001
Composite of death from any cause, nonfatal myocardial infarction, or nonfatal ischemic stroke§	973 (10.3)	1126 (11.9)	0.86 (0.79–0.93)	<0.001
Death from coronary heart disease	205 (2.2)	222 (2.3)	0.92 (0.76–1.11)	0.38¶
Death from cardiovascular causes	240 (2.5)	271 (2.9)	0.88 (0.74–1.05)	
Death from any cause	334 (3.5)	392 (4.1)	0.85 (0.73–0.98)	
Other end points‖				
Nonfatal myocardial infarction	626 (6.6)	722 (7.6)	0.86 (0.77–0.96)	
Fatal or nonfatal ischemic stroke	111 (1.2)	152 (1.6)	0.73 (0.57–0.93)	
Unstable angina requiring hospitalization	37 (0.4)	60 (0.6)	0.61 (0.41–0.92)	
Ischemia-driven coronary revascularization procedure	731 (7.7)	828 (8.8)	0.88 (0.79–0.97)	
Hospitalization for congestive heart failure	176 (1.9)	179 (1.9)	0.98 (0.79–1.20)	

Schwartz G.G N Engl J Med 2018 Nov 7 [Epub ahead of print]

Incidence of MACE with Alirocumab added to maximum-tolerated statin in Patients with Acute Coronary Syndrome (ACS) and Diabetes Prespecified Analyses of ODYSSEY OUTCOMES

Category	N. (% of cohort)	MACE cumulative incidence		ARR	Hazard ratio (% 95% CI)	P interaction
		Alirocumab n/N (%)	Placebo n/N (%)			
All subjects	18.924 (100)	903/9462 (9.5)	1052/9462 (11.1)	1.6	0.85 (0.78-0.93)	NA
Normoglycemia	5234 (27.7)	192/2639 (7.3)	220/2595 (8.5)	1.2	0.85 (0.70-1.03)	

THM 1 - Patients with recent ACS and diabetes derived greater absolute benefit from ALI added to maximum-tolerated statin.

THM2 - All-cause mortality was reduced (HR 0.85; 95% CI, 0.73–0.98; nominal p = 0.026) and confined to those with LDL-C ≥ 100 mg/dl at baseline.

Median follow-up: 34 months. ARR, absolute risk reduction; NA, not applicable.

Ray KK. Diabetes 2018 Jul; 67(Supplement 1):

Alirocumab and Cardiovascular Outcomes in Patients with Acute Coronary Syndrome (ACS) and Diabetes—Prespecified Analyses of ODYSSEY OUTCOMES

Safety

	Alirocumab (N = 9451)	Placebo (N = 9443)
Diabetes worsening or diabetic complications pts w/DM at baseline, n/N (%)	506/26.88 (18.8)	583/2747 (21.2)
New onset diabetes pts w/o DM at baseline, n/N (%)	648/6763 (9.6)	676 /6696 (10.1)
General allergic reaction, n (%)	748 (7.9)	736 (7.8)
Hepatic disorder, n (%)	500 (5.3)	534 (5.7)
Local injection site reaction, n (%)	360 (3.8)	203 (2.1)
Neurocognitive disorder, n (%)	143 (1.5)	167 (1.8)
Cataracts, n (%)	120 (1.3)	134 (1.4)
Hemorragic stroke, n (%)	9 (<0.1)	16 (0.2)

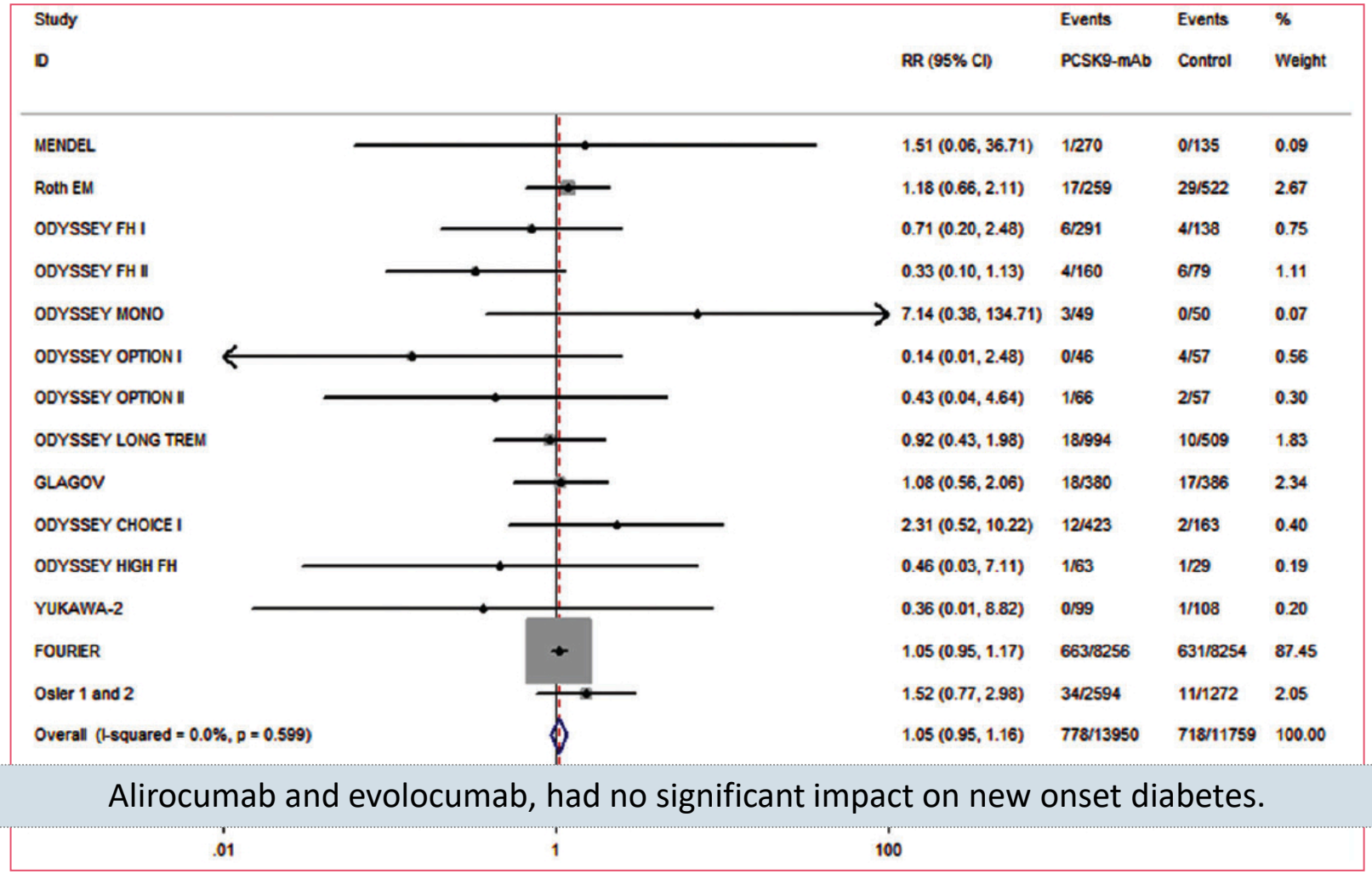
https://seekingalpha.com/article/4155622-sanofi-sny-updates-results-odyssey-outcomes-trial - Accessed 5 November 2018

Effect of PCSK9is on new-onset diabetes

A

systematic review and meta-analysis

18 studies including 26 123 participants without diabetes



Alirocumab and evolocumab, had no significant impact on new onset diabetes.

Cao YX. Diabetes Obes Metab. 2018;20:1391–1398

PCSK9 inhibitors in lipid management of patients with diabetes mellitus and high cardiovascular risk: a review

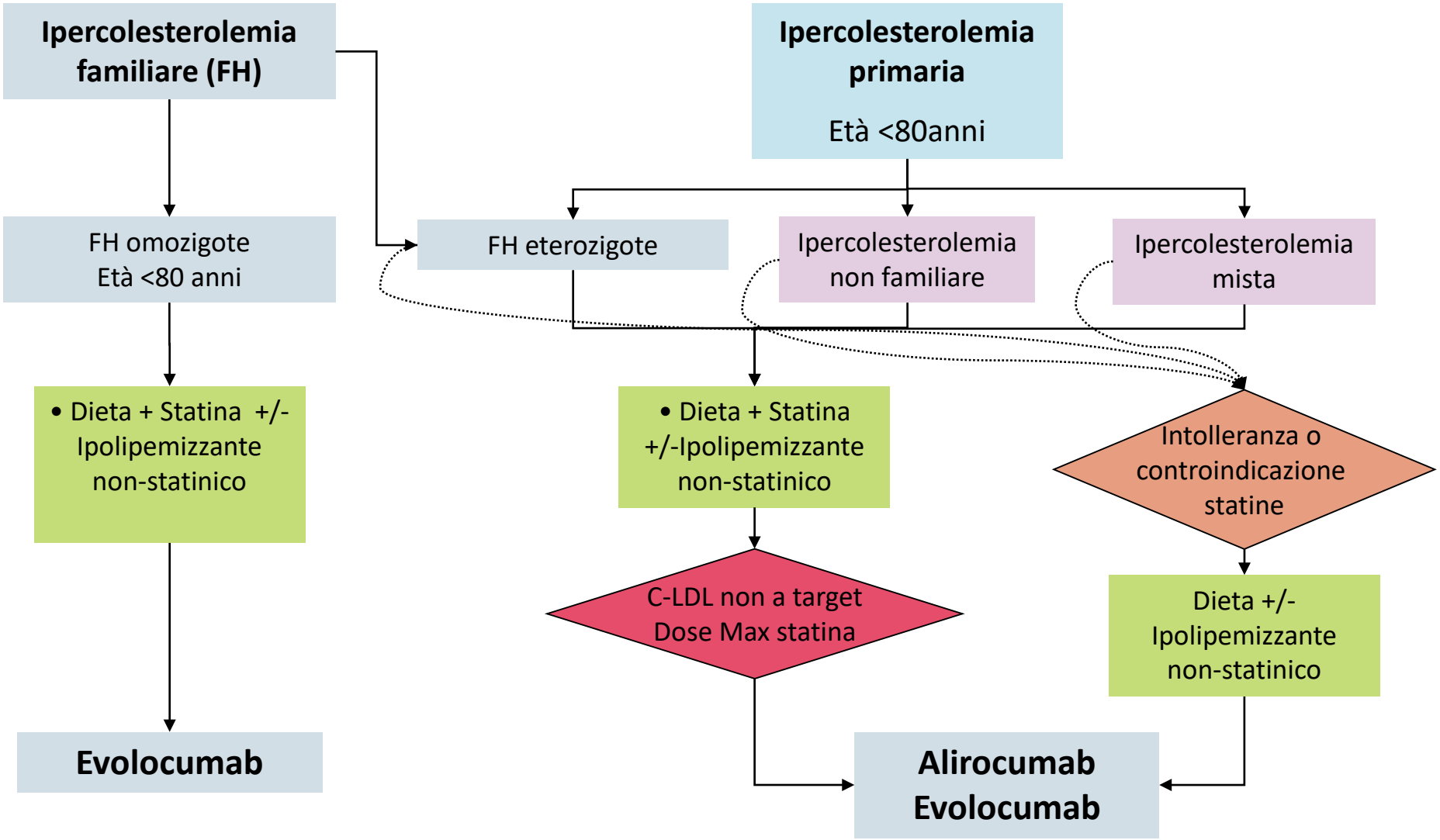
Conclusions

In individuals with hyperlipidemia and diabetes mellitus on top of maximally tolerated statin therapy PCSK9 inhibitors

- are well tolerated
- provide significant LDL-C lowering in without loss of glycemic control or increased risk of developing diabetes mellitus in those without pre-existing diabetes mellitus
- can prevent or reduce further cardiovascular events

Handelman Y. J Am Heart Assoc. 2018;7:e008953. DOI: 10.1161/JAHA.118.008953.

Indicazioni autorizzate e rimborsate dal Sistema Sanitario Nazionale per i farmaci inibitori di PCSK-9



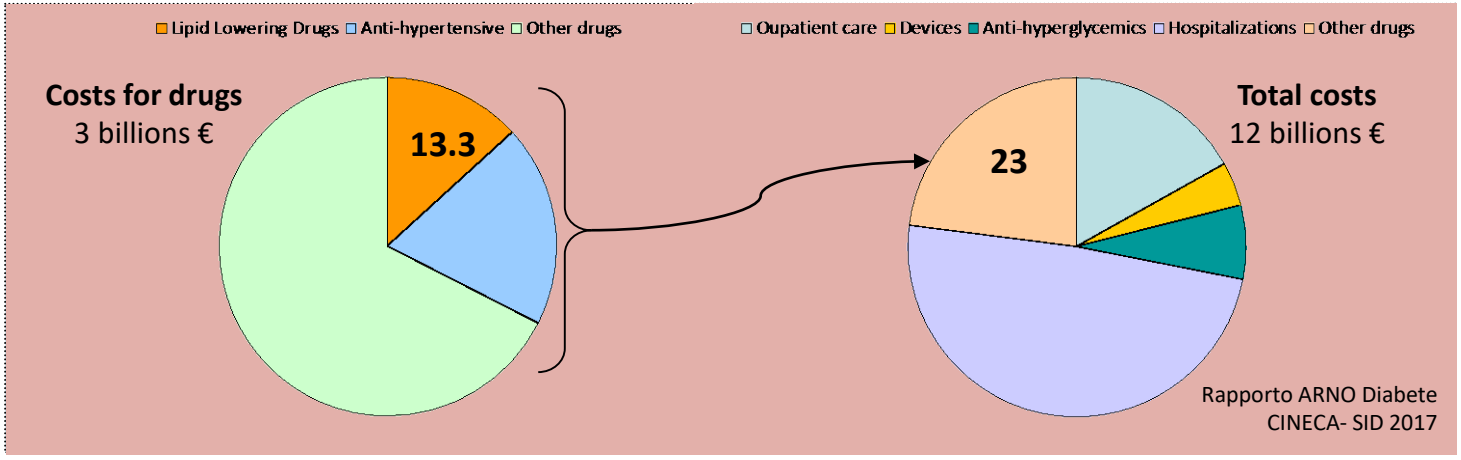
Adattata da RCP: https://ec.europa.eu/health/documents/community-register/2015

Unit cost and daily cost of lipid lowering drugs

Drug	Pack	Unit cost*	Cost per day
Atorvastatin 40 mg	30 tablets	11.95	0.39
Rosuvastatin 40 mg	28 tablets	12.23	0.43
Ezetmibe 10 mg	30 tablets	24.5	0.81
Alirocumab 150 mg	2 prefilled pen	716.26	24
Evolocumab 140 mg	2 prefilled pen	717.40	24

4700€/ year

*Reference price from List of class A drugs by AIFA



Are PCSK9 Inhibitors Cost Effective?

At present, PCSK9 inhibitors are expensive and are utilized modestly. Patients with the highest risk of CVD are likely those who will get the drugs first, particularly patients who cannot achieve acceptable LDL-C levels with other drugs and have FH, established CVD, or both.

Korman J. PharmacoEconomics 2018 https://doi.org/10.1007/s40273-018-0671-0

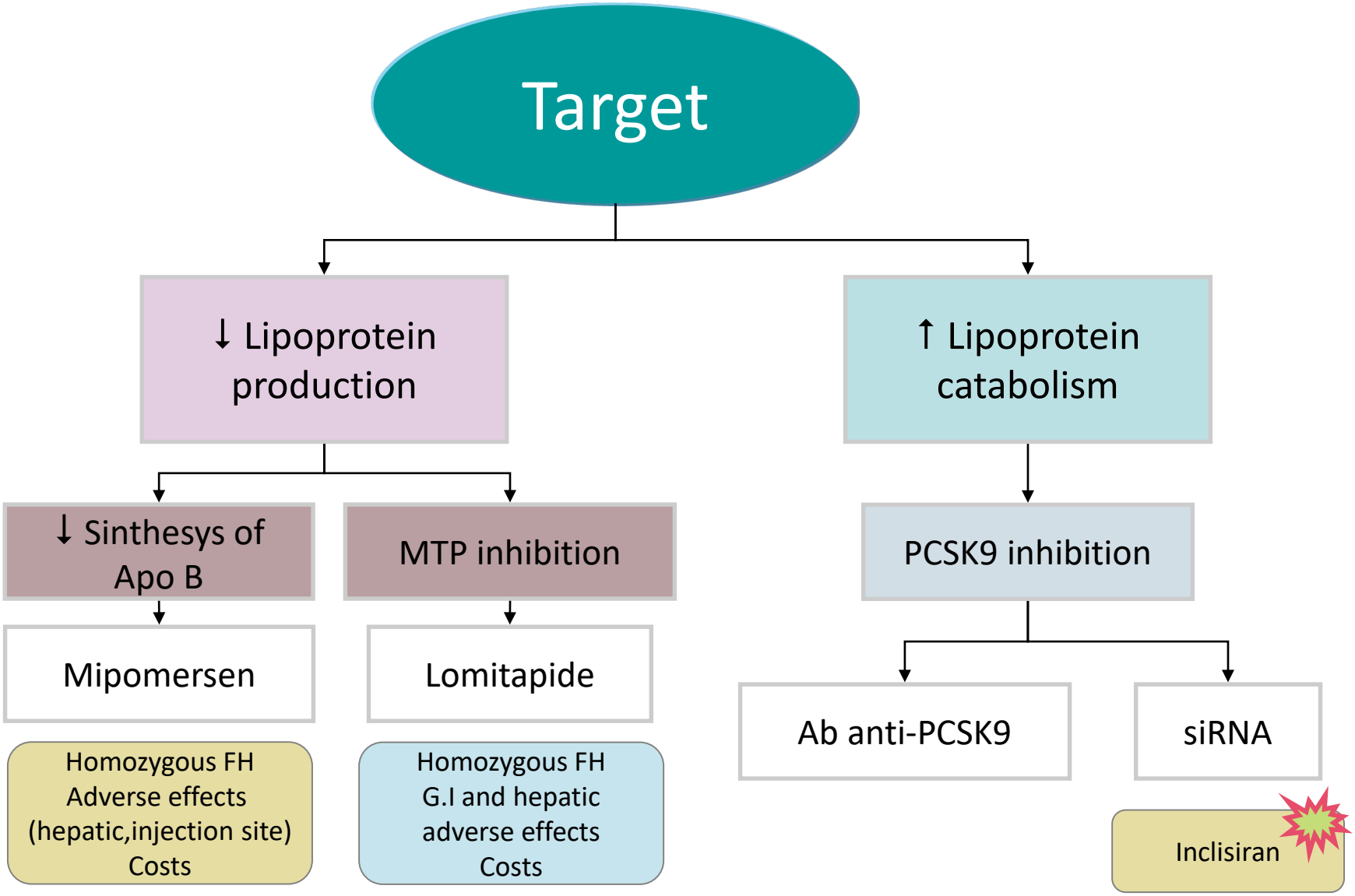
…

At current acquisition prices (AU$8174 per person per year), the incremental cost effectiveness ratio (ICER)was AU$308,558 per quality-adjusted life year (QALY) saved. Acquisition priceswould need to be reduced to approximately AU$1500 per person per annum for PCSK9i to reach the arbitrary cost-effectiveness threshold of AU$50,000 per QALY saved.

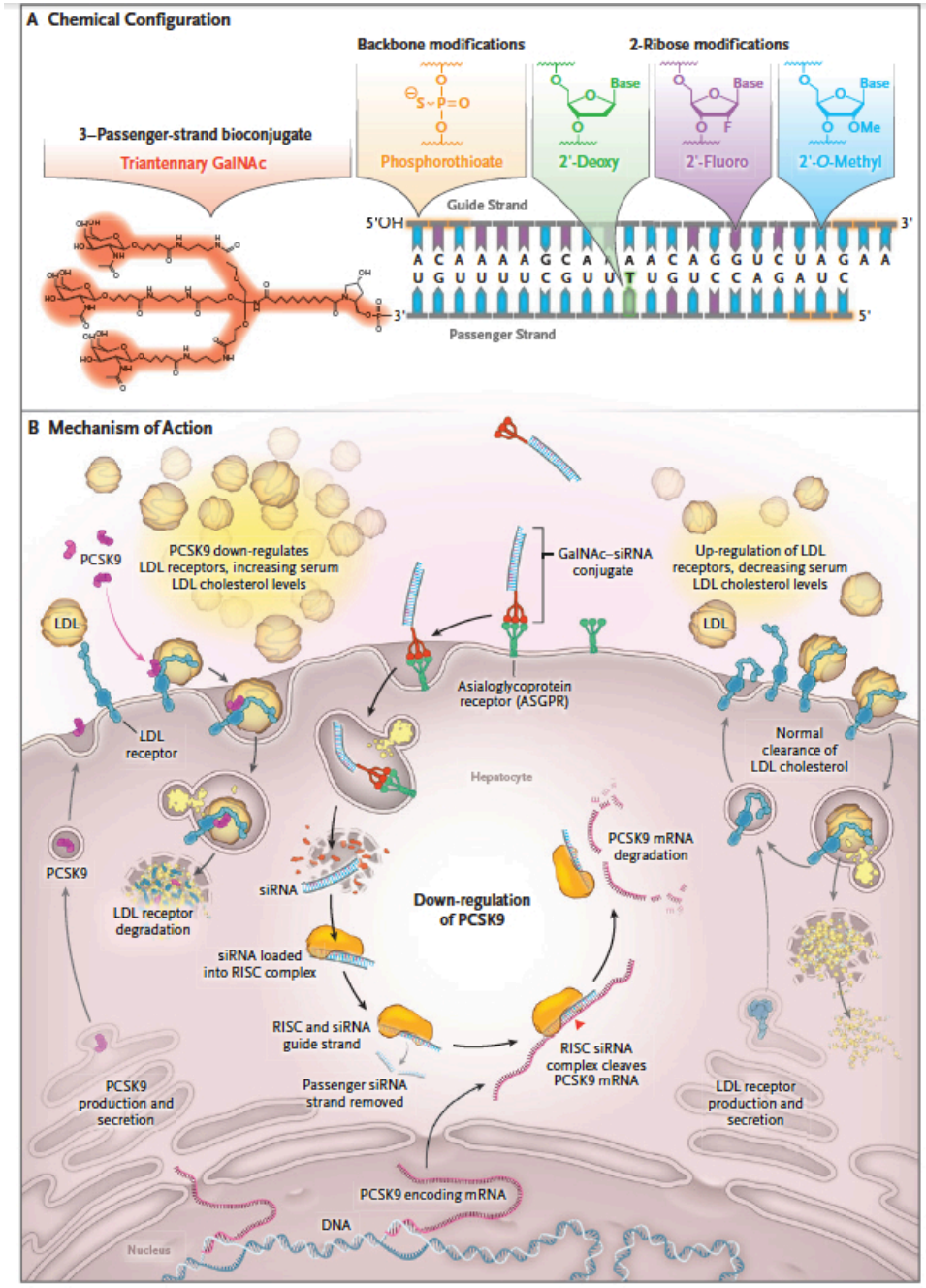
Conclusion(s): **PCSK9i are an effective alternative** for those with existing CVD or at high risk of CVD in whom statin therapy alone is ineffective, **but are not cost-effective** to the Australian healthcare system based on current prices.

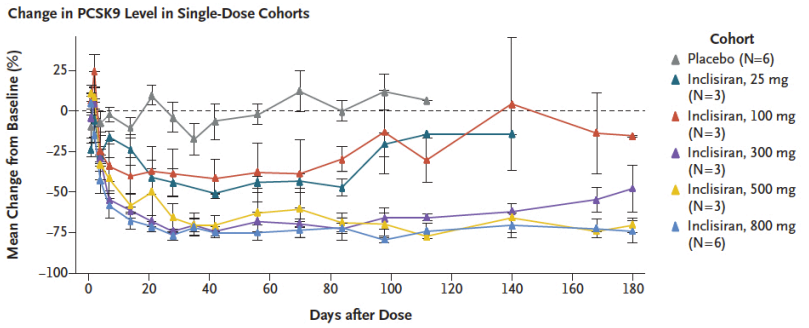
Kumar R. I. .J.Cardiol 2018 https://doi.org/10.1016/j.ijcard.2018.04.122

New cholesterol lowering drugs: mechanism of action



Inclisiran (ALN-PCSsc): a long-acting RNA interference (RNAi) therapeutic agent that inhibits the synthesis of PCSK9





In this phase 1 trial, no serious adverse events were observed with inclisiran.

- Doses of 300 mg or more (in single or multiple doses) significantly reduced levels of PCSK9 and LDL cholesterol for at least 6 months.

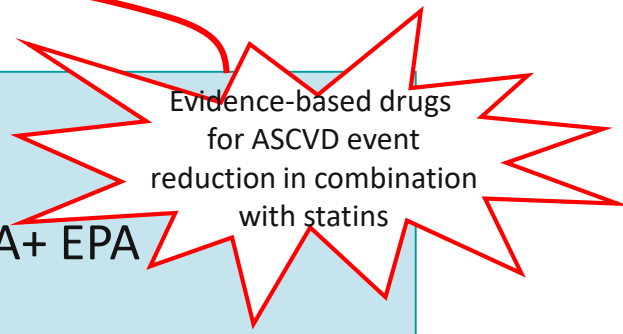
Fitzgerald K. N Engl J Med 2017;376:41-5

Therapeutic agents targeting triglyceride-rich lipoproteins and HDL-C

- Fibrates
- Nicotinic acid (niacin)
- Omega-3 fatty acids (DHA, *EPA, DHA+ EPA, DHA+ EPA carboxylic acids)
- Microsomal transfer protein (MTP) inhibitors (lomitapide)

Newer agents in development:

- Pemafibrate (a novel selective PPARα modulator
- Apolipoprotein C-3 antagonists (volanesorsen, ISIS 304801)
- Angiopoietin like protein 3 (ANGPLP3) inhibitors
- Angiopoietin like protein 4 (ANGPLP4) inhibitors
- Lipoprotein lipase (LPL) gene therapy



Adapted from Ganda O. Current Diabetes Reports (2018) 18:126

REDUCE-IT

Trial Design

Eligibility	• LDL-C 41-100 mg/dl (median baseline 75 mg/dl controlled with statin
	• CV risk factors : persistent elevated triglycerides (TGs) between 150-499 mg/dL (median baseline 216 mg/dL) AND either established CVD (secondary prevention cohort) OR diabetes and at least one CV RF (primary prevention cohort)
Participants	• 8.179 statin treated patients
Randomization	• 4.0 gm EPA, compared to placebo
Follow-up	• 4.9 years

https://investor.amarincorp.com/- Accessed 06 November 2018

REDUCE-IT: main results

Efficacy: Approximately **25% relative risk reduction** ($p<0.001$), in the **primary endpoint composite** of the first occurrence of MACE (cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization).

Safety: 4 gm EPA have been well tolerated with a safety profile consistent with clinical experience associated with omega-3 fatty acids and current FDA-approved labeling. The proportions of patients experiencing adverse events and serious adverse events in REDUCE-IT were similar between the active and placebo treatment groups.

https://investor.amarincorp.com/- Accessed 06 November 2018

A reduction in coronary heart disease with CETP inhibition is revealed

Trial	Patients	Lipoprotein changes	Duration	Outcome	Comments
Illuminate (Torcetrapib) 2011	15.067 High CV Risk	HDL-C↑72% LDL-C↓*	1-2 years	CV events Death SBP (5 mmHg)	Electrolyte disturbances, hyeraldosteronism identified as off-target effects *LDL measured indirectly
Dal-Outcomes (Dalcetrapib) 2012	15.871 post ACS	HDL-C ~↑30% LDL-C ↔	31 months	CV events ↔ ↑SBP (0.6 mmHg)	Trial stopped early for futility. Possible benefit in a genetic subgroup
Accelerate (Evacetrapib) 2017	12.092 High CV risk	HDL-↑133% LDL-C ↓*	26 months	↔CV events ↑SBP (1.2 mmHg)	Trial stopped early for futility ↓ Deaths (not pre-specified) *LDL measured indirectly
Reveal (Anacetrapib) 2017	30.449 High CV Risk	HDL-C↑ 104% LDL-C↓ 17%	4.1 years	↓Coronary events (9%) ↑SBP (0.7 mmHg)	Trial went to planned completion New onset diabetes

Finally, the REVEAL trial has shown that the CETP inhibitor anacetrapib decreased coronary heart disease when added to statin therapy.

Conclusioni

• Forti evidenze sostengono il ruolo delle statine nel ridurre in maniera efficace e sicura i livelli di C-LDL e gli eventi cardiovascolari nei pazienti con diabete. L'associazione con ezetimibe si dimostra più efficace nei pazienti con diabete vs quelli senza.
Il trattamento del rischio residuo post-statine potrebbe risentire favorevolmente dell'associazione con EPA.
• I rischi associati alla terapia con statine sono superati dai numerosi effetti cardiovascolari protettivi.

• Sebbene restino controversi i goal di C-LDL, circa il 50% dei soggetti non riescono ad abbassare adeguatamente il C-LDL, probabilmente a causa della mancanza di aderenza o intolleranza al trattamento con statine.

• I farmaci inibitori di PCSK9 si sono dimostrati efficaci nel ridurre gli eventi cardiovascolari nei pazienti con diabete ed altre co-morbidità. Ulteriori studi di outcome sono necessari per avere conferma della validità di tale approccio.
• La sicurezza di tali farmaci necessita ulteriori conferme a lungo termine (>3 anni) ed il loro rapporto costo/efficacia, attualmente, non risulta favorevole.