The interplay of dysglycemia and dyslipidemia: Managing cardiovascular burden in individuals with high CV risk

Wednesday, September 18, 2019

18:45–20:15

Hortega Hall

This Evening Symposium is organized and sponsored by
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SAGLB.PRL.19.08.1167
August 2019

Disclosures

Professor Luis Masana

Professor Luis Masana has received fees for lectures or advisory work from: Amgen, Sanofi-Regeneron, Merck & Co., Mylan and Daichii/Sankyo

Professor Helen Colhoun

Professor Helen Colhoun has received research support, honorarium, and is also a member of the advisory panels or speaker's bureaus for Sanofi Aventis, Regeneron, Novartis Pharmaceuticals, Novo-Nordisk and Eli Lilly. Professor Colhoun also receives or has recently received a non-binding research support from Pfizer Inc., and AstraZeneca LP and Novo-Nordisk. Professor Colhoun is a shareholder of Roche Pharmaceuticals and Bayer

Assistant Professor Ann Marie Navar

Professor Ann Marie Navar has consulted and recieved research support from: Amarin, Amgen, Sanofi, Regeneron and Janssen. Consulting from NovoNordisk and AstraZeneca

Housekeeping

Agenda

Time	Item	Presenter
18:45–18:50	Welcome and introductions	**Professor Luis Masana** (Chair, Spain)
18:50–19:10	Urgency in treating dyslipidemia in individuals with diabetes and high CV risk	**Professor Helen Colhoun** (UK)
19:10–19:30	Individuals with diabetes and high CV risk who may benefit the most from PCSK9 inhibition in your clinical practice	**Professor Luis Masana** (Spain)
19:30–19:50	Evaluating the benefit/risk and safety profile of PCSK9 inhibitors: implications in clinical practice	**Asst. Professor Ann Marie Navar** (USA)
19:50–20:10	Question and answer/panel discussion	**All panellists**
20:10–20:15	Conclusion and key take-away messages	**Professor Luis Masana** (Spain)

Faculty

Name	Affiliation	Country
Professor Luis Masana, MD, PhD	University Rovira i Virgili, CIBERDEM	Spain
Professor Helen Colhoun, MD, PhD	University of Edinburgh	UK
Assistant Professor Ann Marie Navar, MD, PhD	Duke University School of Medicine	USA

Questions to faculty

There are 3 ways to interact with the faculty:

- Questions via keypads provided
  - Post your questions to faculty throughout the Symposium, for consideration during the question and answer/panel discussion
- Questions via question cards
  - Complete and hand in to a hostess at any time during the Symposium
- Questions via microphone
  - Faculty will invite questions during the question and answer/panel discussion

Polling

Use the keypads to answer polling questions

- The presenter will alert you to the polling question
- The question will appear on the keypad screen
- Use the roller ball to select the answer you think is most appropriate
  - To change your mind, press the red triangle to clear then input your new choice
  - Press the green square to submit your answer

Press ‘send’ when finished

Welcome and introductions

Professor Luis Masana (Chair)
University of Rovira i Virgili, CIBERDEM
Spain

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Symposium objectives

- Understand the CV risk profile and need for prompt lipid-lowering therapy in individuals with diabetes and dyslipidemia at high CV risk
- Identify the most appropriate individuals with diabetes and high CV risk who may benefit the most from PCSK9 inhibition and how clinical trial evidence directs best clinical practice use of alirocumab in this population
- Review the clinical implications of PCSK9i use based on its benefit/risk and safety profile, and overall value

CV, cardiovascular; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibition

Interactivity polling test

What region are you from?

A. Europe
B. North America
C. South America
D. Australia/New Zealand
E. Middle East
F. Asia
G. Africa

VOTE
Choose the best option

Interactivity polling test

What is your primary speciality?

A. Endocrinologist/Diabetologist
B. Lipidologist
C. Cardiologist
D. Internist
E. General practitioner
F. Other

VOTE
Choose the best option

Interactivity polling test

In what year was the construction of the Montjuïc Communications Tower completed?

A. 1989

B. 1990

C. 1991

D. 1992

E. 1993

F. 1994

VOTE

Choose the best option

Interactivity polling test

In what year was the construction of the Montjuïc Communications Tower completed?

A. 1989
B. 1990
C. 1991
D. 1992
E. 1993
F. 1994

The tower was built for the 1992 Summer Olympic Games in Barcelona

- The structure is **136m tall** and is located in the Olympic park
- It represents an athlete holding the **Olympic flame**
- Because of the tower's orientation, it also works as a giant sundial!

Diabetes increases CVD risk about 2-fold on average

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Mach F, *et al. European Heart Journal*. 2019;00:1–78.

Urgency in treating dyslipidemia in individuals with diabetes and high CV risk

Professor Helen Colhoun
University of Edinburgh
UK

Disclosures

Professor Colhoun receives research support and honorarium and is a member of the advisory panels or speaker's bureaus for Sanofi Aventis, Regeneron, Novartis Pharmaceuticals, Novo-Nordisk and Eli Lilly. Professor Colhoun also receives, or has recently received, a non-binding research support from Pfizer Inc., AstraZeneca LP and Novo-Nordisk. Professor Colhoun is a shareholder of Roche Pharmaceuticals and Bayer.

According to the 2019 ESC/EASD guidelines, for individuals with diabetes, with persistent high LDL-C despite treatment with a maximum tolerated statin dose, in combination with ezetimibe, or in patients with statin intolerance, treatment with PCSK9 inhibitor is recommended. What class and level of evidence is this recommendation?

1. Class Ia
2. Class Ib
3. Class IIa
4. Class IIb
5. None of the above

VOTE

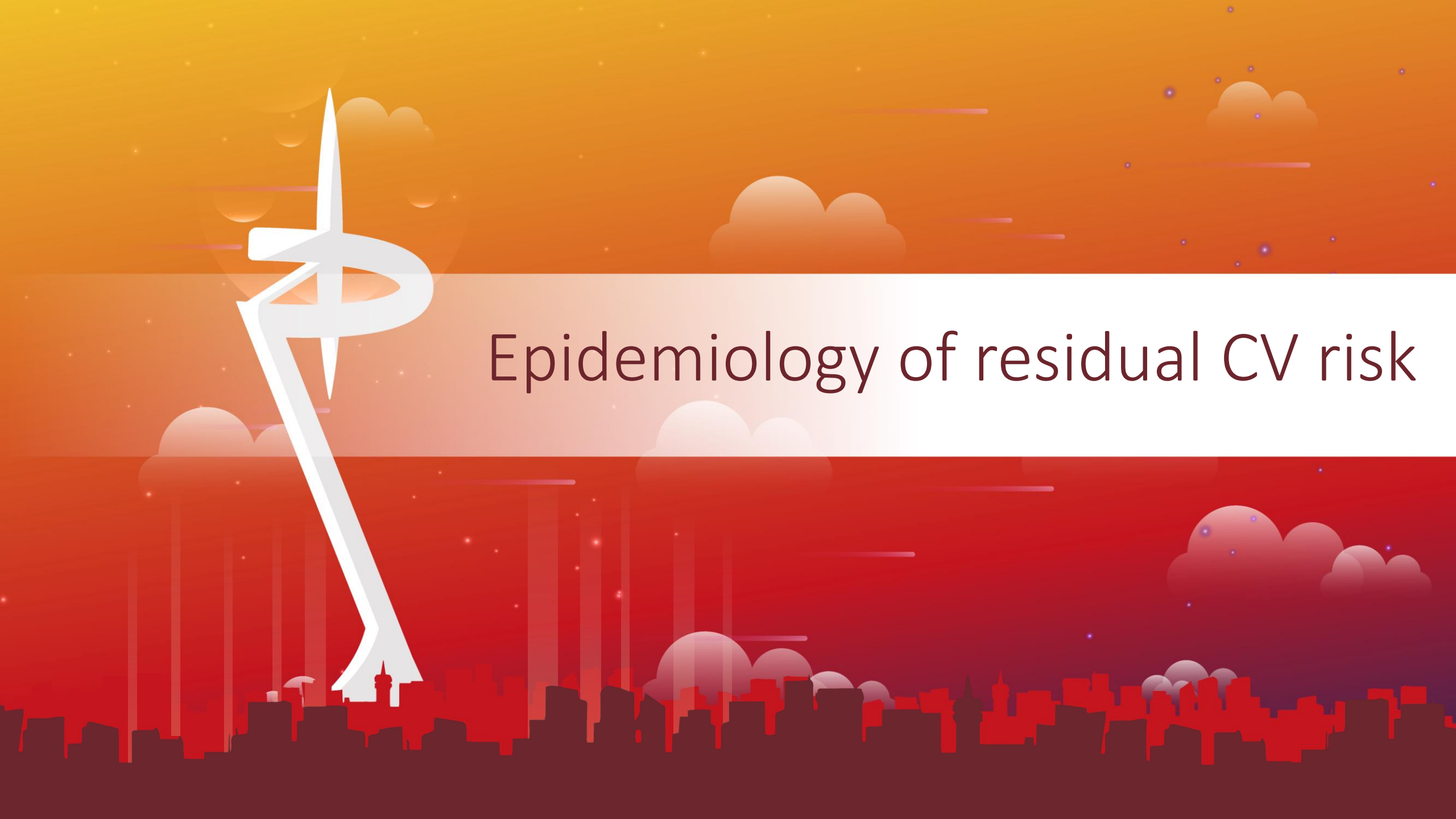
Choose the best option

Introduction

- Total mortality rates are 40% higher in men and 50% higher in women with type 2 diabetes mellitus compared with people without diabetes[1]
- CVD remains the leading cause of loss of life expectancy in type 2 diabetes and rates remain elevated compared to those without diabetes[2]
- Ongoing elevations in CV risk have been reported in recent data from Scotland, Sweden and the USA[3,4,5]

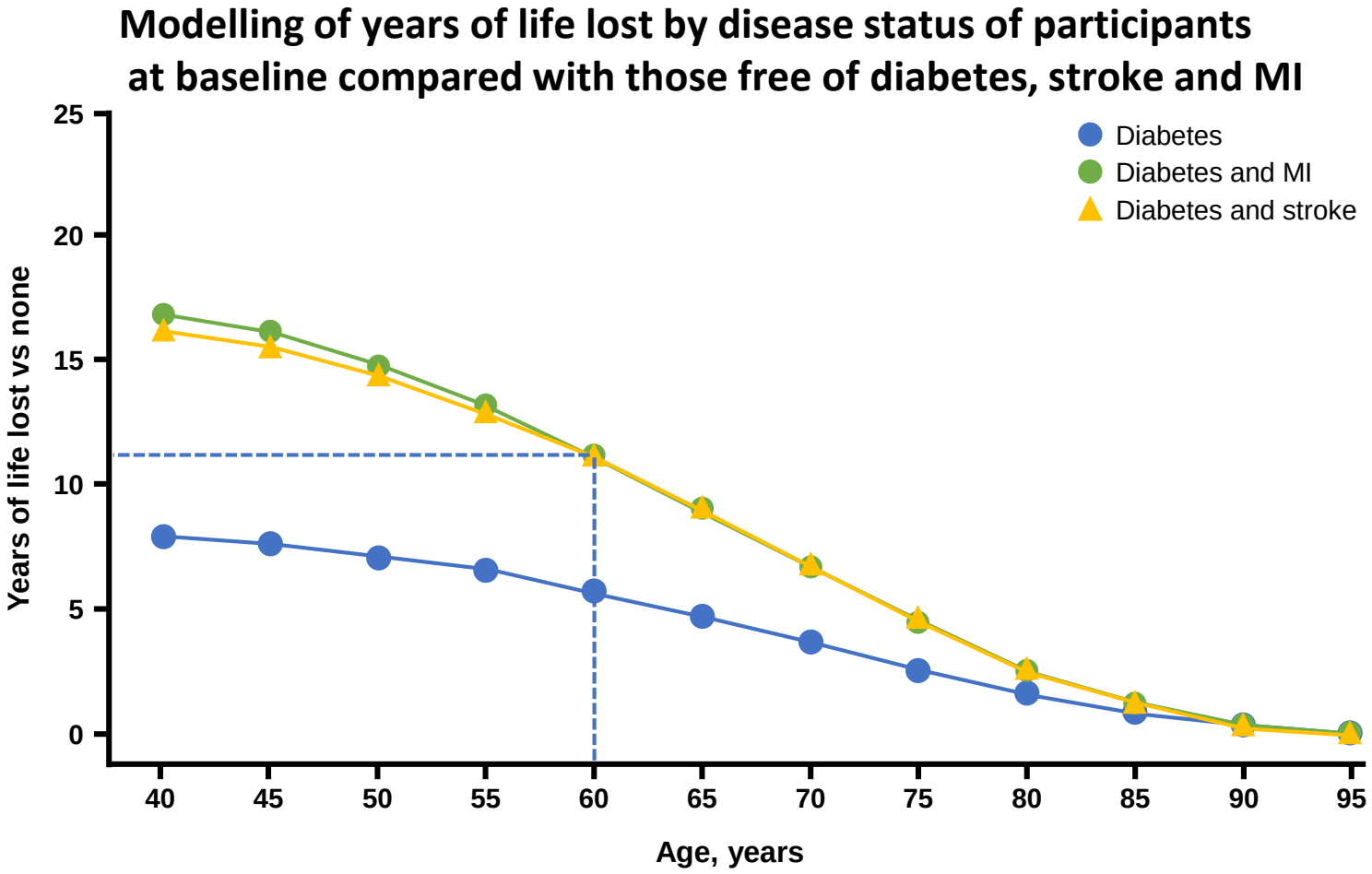
CVD, cardiovascular disease

1. Read SH, *et al. Diabetologia.* 2016;59:2106–13; 2.McGurnaghan S, *et al. Diabet Med*. 2019;36:718–25; 3.Read SH, *et al. Diabet Med.* 2018;35:99–106; 4. Rawshani A et al N Engl J Med 2017; 377: 300–301; 5. Burrows NR, *et al. Diabetes Care.* 2018; 41:293–302.



Epidemiology of residual CV risk

Life expectancy is reduced by ~12 years in people with diabetes with previous CVD[a]

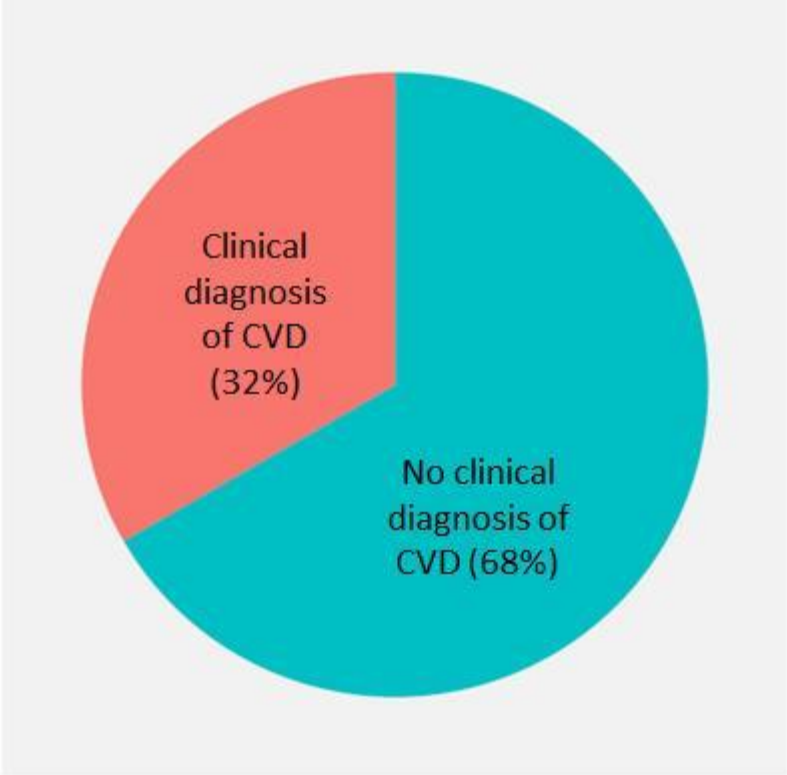


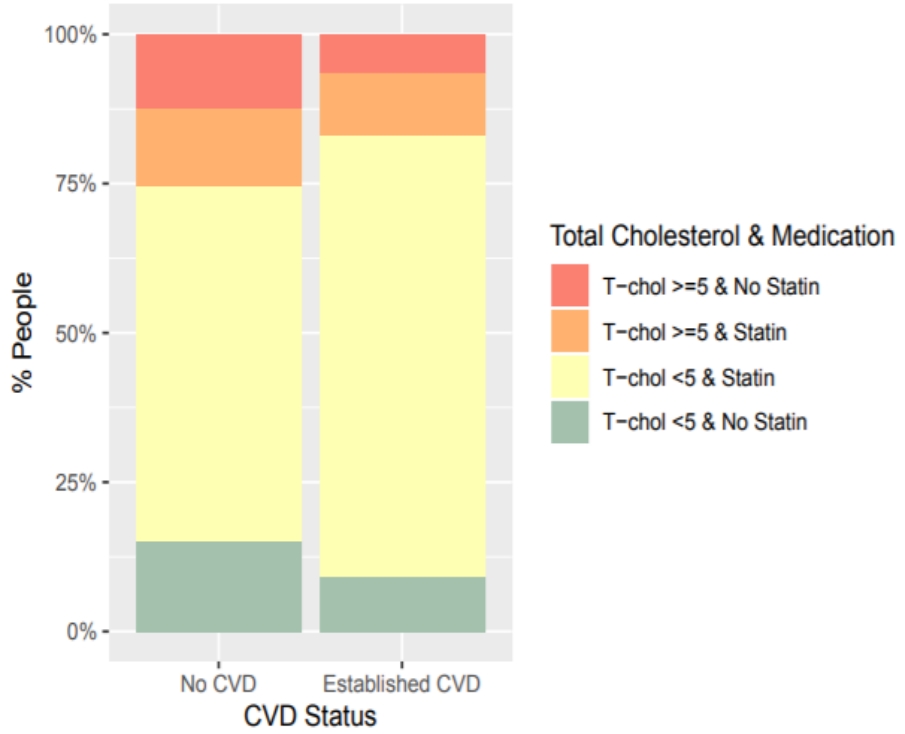
Emerging Risk Factors Collaboration: 689,300 participants; 91 cohorts; years of baseline surveys: 1960–2007; latest mortality follow-up: April 2013; 128,843 deaths.

[a]Male, 60 years of age with history of MI or stroke.
MI, myocardial infarction

Adapted from The Emerging Risk Factors Collaboration. *JAMA* 2015;314:52–60.

Current CVD prevalence and statin use: example of Scottish population data

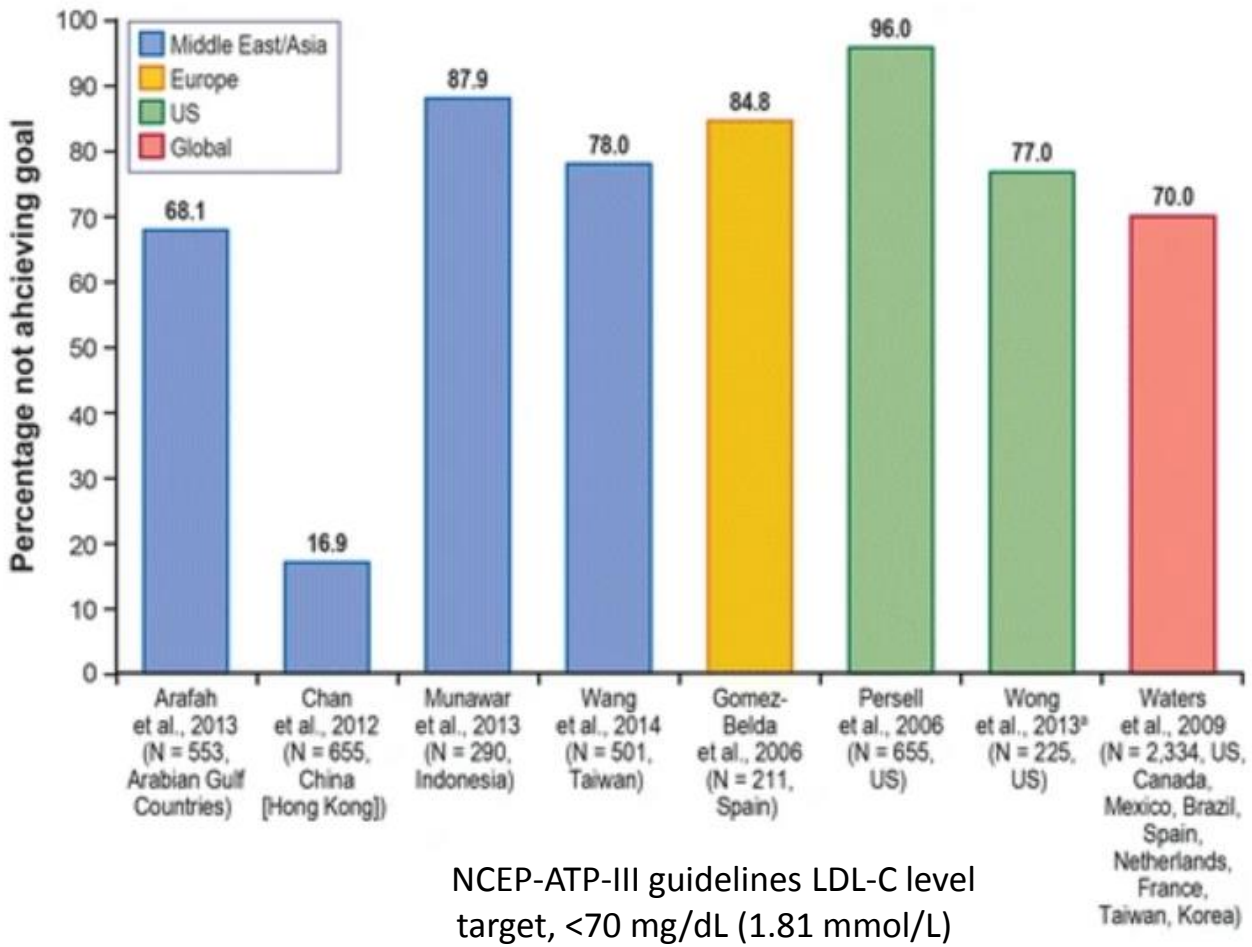




- Among 248,400 people with type 2 diabetes, 32% had prior clinical diagnosis of CVD
- Despite 75% currently being on a statin, a quarter (23%) had total cholesterol of 5 mmol/L (193 mg/dL) or more

McGurnaghan S, *et al. Diabet Med.* 2019;36:718–25.

Majority (68–96%) of very high-risk CVD patients do not attain LDL-C goals



NCEP-ATP-III guidelines LDL-C level target, <70 mg/dL (1.81 mmol/L)

LDL-C, low-density lipoprotein cholesterol;
NCEP-ATP-III, National Cholesterol Education Program–Adult Treatment Panel III

Mitchell S, *et al. BMC Cardiovascular Disorders.* 2016;16:74.

Statin intolerance

Statins are recommended as first-line lipid-lowering therapy in patients with ASCVD[1]

Recent guidelines and/or consensus statements recommend the use of ezetimibe or PCSK9is in certain patients who are unable to achieve therapeutic goals with statins alone or who are statin intolerant[1]

Although no definitive rate of statin intolerance has been established, 6–8 observational studies suggest that up to 25% of patients initiating statins experience some degree of statin intolerance, which contributes to non-adherence, increased incidence of ASCVD events and higher healthcare costs[1]

In the overall population, 20–30% of subjects are suspected to be statin intolerant[2]

A study of 32,000 patients reported that 5.8% and 6.7% of individuals with and without diabetes, respectively, had statin-related myalgia[3]

ASCVD, atherosclerotic cardiovascular disease;
PCSK9, proprotein convertase subtilisin/kexin type 9

1. Cannon CP, *et al. Am J Cardiol.* 2019;123:1202–7; 2. Mancini GB, *et al. Can J Cardiol.* 2016;32(Suppl. 7):S35–65; 3. Nichols GA, Koro CE. *Clin Ther*. 2007;29(8):1761–70.

Residual risk

Patients adherent to lifestyle modifications and statins retain significant residual risk. Despite being on statin therapy, 1 in 7 people with diabetes experience a major CV event within 5 years[1]

Patients with T2DM remain at increased risk for CVD, despite the rise in LDL-C–lowering therapies and impressive reductions in LDL-C[2]

Therapeutic strategies targeted towards multiple CVD risk factors will help minimise residual risk[2]

PCSK9 inhibition achieved through alirocumab or evolocumab can play an important role in reducing residual risk in selected, high-risk individuals with diabetes[1]

Whilst additional PCSK9 inhibition can alleviate/further reduce residual risk, it does not reduce it to zero

T2DM, type 2 diabetes mellitus

1. Warraich HJ, *et al*. *Curr Cardiol Rep*. 2018;20(12):125; 2. Dash S, *et al. Diabetes Obes Metab*. 2019;21(Suppl. 10):28–38.

ESC/EAS 2019 dyslipidemia and ESC/ EASD DM, pre-DM and CVD guidelines

DM, diabetes mellitus; EAS, European Atherosclerosis Society; EASD, European Association for the Study of Diabetes; ESC, European Society of Cardiology

ESC/EASD 2019 DM, pre-DM and CVD guidelines: CV risk categories in patients with diabetes

Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

[b]Proteinuria, renal impairment defined as eGFR ≥30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy.
[c]Age, hypertension, dyslipidemia, smoking, obesity.
T1DM, type 1 diabetes mellitus

Cosentino F, *et al. European Heart Journal*. 2019;00:1–69.

Recommended treatment goals for LDL-C–lowering therapy in 2019 ESC/EAS and ESC/EASD guidelines

ESC/EAS 2019 dyslipidemia guidelines[1]

Risk category	LDL goals (starting with untreated LDL-C)	
	2016	2019
Very-high-risk	<1.8 mmol/L (70 mg/dL) or >50% ↓ if LDL-C 1.8-3.5 (70 - 135 mg/dL)	<1.4 mmol/L (55 mg/dL) and >50% ↓
High-risk	<2.6 mmol/L (100mg/dL) or >50% ↓ if LDL-C 2.6-5.2 (100 - 200 mg/dL)	<1.8 mmol/L (70 mg/dL) and >50% ↓
Moderate-risk	<3.0 mmol/L (115 mg/dL)	< 2.6 mmol/L (100 mg/dL)
Low-risk	<3.0 mmol/L (115 mg/dL)	<3.0 mmol/L (115 mg/dL)

ESC/EASD 2019 DM, pre-DM and CVD guidelines[2]

Recommendations	Class[a]	Level[b]
Targets		
In patients with T2DM at moderate CV risk,[c] an LDL-C target of <2.6 mmol/L (<100 mg/dL) is recommended.	I	A
In patients with T2DM at high CV risk,[c] an LDL-C target of <1.8 mmol/L (<70 mg/dL) and LDL-C reduction of at least 50% is recommended.[d]	I	A
In patients with T2DM at very high CV risk,[c] an LDL-C target of <1.4 mmol/L (<55 mg/dL) and LDL-C reduction of at least 50% is recommended.[d]	I	B
In patients with T2DM, a secondary goal of a non-HDL-C target of <2.2 mmol/L (<85 mg/dL) in very high CV-risk patients, and <2.6 mmol/L (<100 mg/dL) in high CV-risk patients, is recommended.[d,]	I	B

[a]Class of recommendation; [b]Level of evidence
HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein

1. Mach F, *et al*. *European Heart Journal*. 2019;00:1–78; 2. Cosentino F, *et al. European Heart Journal*. 2019;00:1–69.

2019 ESC/EASD DM, pre-DM and CVD guidelines: recommendations for the management of dyslipidemia with lipid-lowering drugs

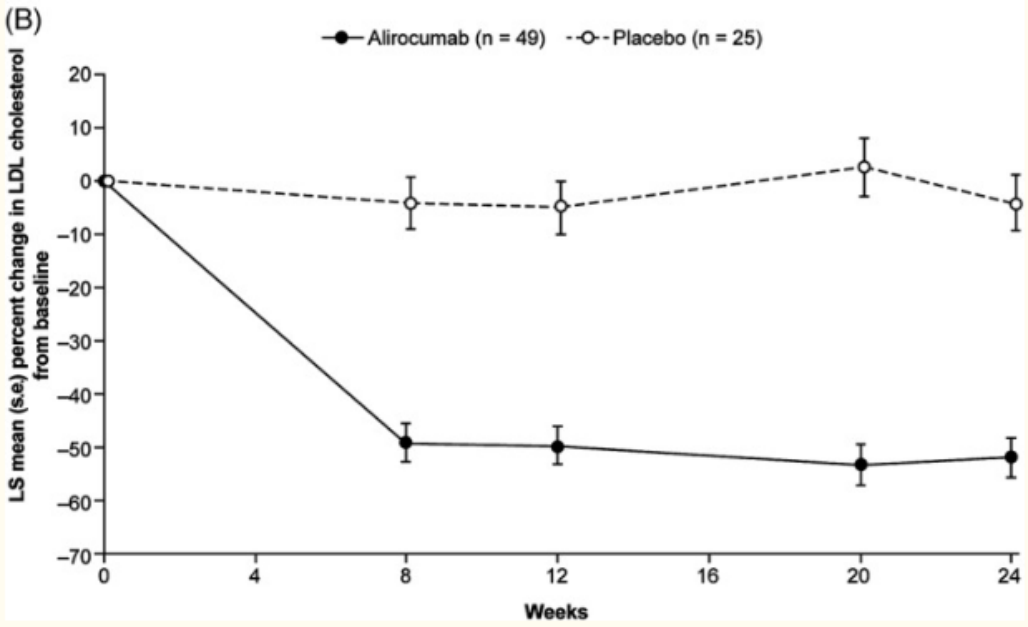
Treatment		
Statins are recommended as the first-choice lipid-lowering treatment in patients with DM and high LDL-C levels: administration of statins is defined based on the CV risk profile of the patient[c] and the recommended LDL-C (or non-HDL-C) target levels.	I	A
If the target LDL-C is not reached, combination therapy with ezetimibe is recommended.	I	B
In patients at very high CV risk, with persistent high LDL-C despite treatment with a maximum tolerated statin dose, in combination with ezetimibe, or in patients with statin intolerance, a PCSK9 inhibitor is recommended.	I	A
Lifestyle intervention (with a focus on weight reduction, and decreased consumption of fast-absorbed carbohydrates and alcohol) and fibrates should be considered in patients with low HDL-C and high triglyceride levels.	IIa	B
Intensification of statin therapy should be considered before the introduction of combination therapy.	IIa	C
Statins should be considered in patients with T1DM at high CV risk,[c] irrespective of the baseline LDL-C level.	IIa	A
Statins may be considered in asymptomatic patients with T1DM beyond the age of 30 years.	IIb	C
Statins are not recommended in women of childbearing potential.	III	A

Cosentino F, *et al. European Heart Journal*. 2019;00:1–69.

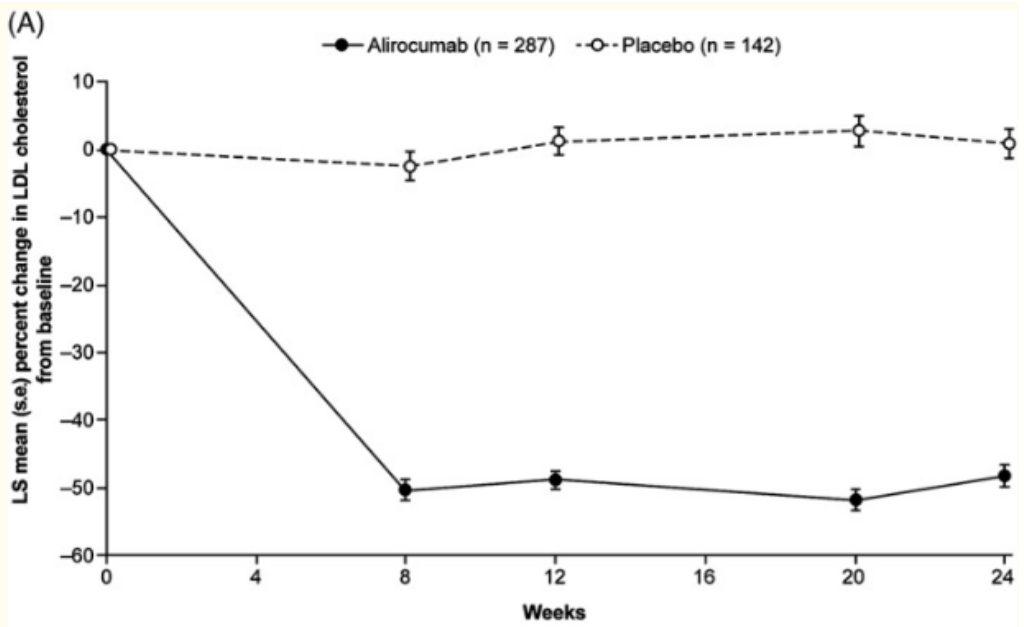
Evidence-based use of PCSK9i in 2019 ESC/EASD DM, pre-DM and CVD guidelines[1]

ODYSSEY DM-INSULIN trial: Phase IIIb, randomised, double-blind, placebo-controlled, multicentre trial. Primary endpoints were percentage change in calculated LDL-C levels from baseline to Week 24[2]

ODYSSEY DM-INSULIN trial: in insulin-treated individuals with T1DM or T2DM and high CV risk, alirocumab vs placebo reduced LDL-C by 50% after 24 weeks[1]



T1DM



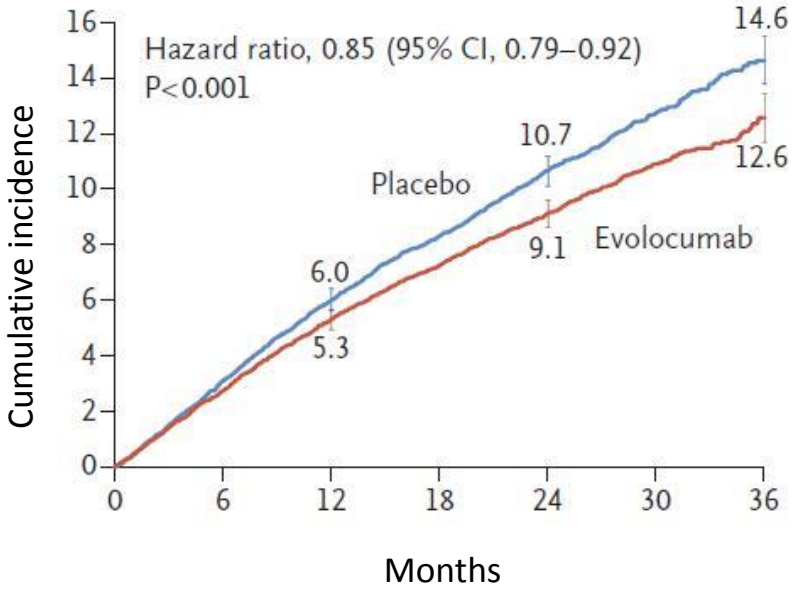
T2DM

1. Cosentino F, *et al. European Heart Journal*. 2019;00:1–69; 2. Leiter LA, *et al. Diabetes Obes Metab*. 2017;19(12):1781–92.

Evidence-based use of PCSK9i in 2019 ESC/EASD DM, pre-DM and CVD guidelines[1]

FOURIER trial: randomised, double-blind, placebo-controlled trial of evolocumab involving 27,564 patients with ASCVD and LDL-C levels of ≥70 mg/dL (1.8 mmol/L) who were receiving statin therapy[2]

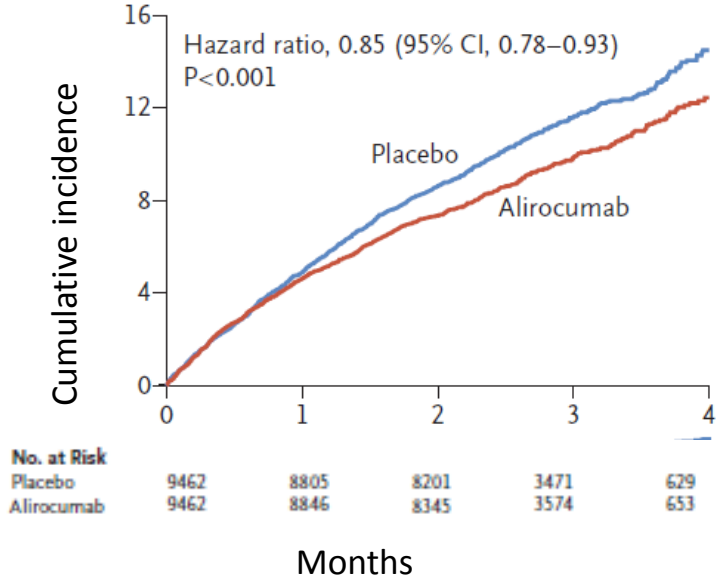
FOURIER trial: results demonstrated that primary endpoint (CV death, MI, stroke, hospital admission for UA or coronary revascularisation) significantly reduced with evolocumab vs placebo[2]



In both studies, similar safety vs placebo except for injection-site reactions[2,3]

ODYSSEY OUTCOMES: multicentre, **treat-to-target***, randomised, double-blind, placebo-controlled trial involving 18,924 patients who had an ACS 1–12 months earlier, LDL-C levels of ≥70 mg/dL (1.8 mmol/L), and were receiving maximum-tolerated statin[3]

ODYSSEY OUTCOMES trial: alirocumab significantly reduced risk of primary endpoint (CV death, MI, stroke, or hospital admission for UA) vs placebo[3]



***treat-to-target approach (LDL-C 25-50 mg/dL)**

CI, confidence interval;
UA, unstable angina

1. Cosentino F, *et al. European Heart Journal*. 2019;00:1–69; 2. Sabatine MS, et al. *NEJM.* 2017;376:1933-42; 3. Schwartz GG, *et al. NEJM*. 2018;379(22):2097–107.

ODYSSEY OUTCOMES study: diabetes subgroup

Background to the ODYSSEY OUTCOMES diabetes sub-analysis

- A majority of patients with ACS have a glucometabolic abnormality (prediabetes or diabetes)
- ACS patients with diabetes are at higher risk for recurrent ischemic CV events than ACS patients without diabetes, and derive greater absolute benefit from high-intensity statin therapy or ezetimibe + statin
- Pre-specified sub-analyses to investigate the effect of alirocumab on:
  - CV events by glycaemic status at baseline (diabetes, prediabetes or normoglycaemia)
  - The risk of new-onset diabetes among those without diabetes at baseline

ACS, acute coronary syndrome

Ray KK, *et al*. *Lancet Diabetes Endocrinol.* 2019;7(8):618–28.

Incidence of CV events in *placebo group* was greater in people with vs without diabetes at baseline

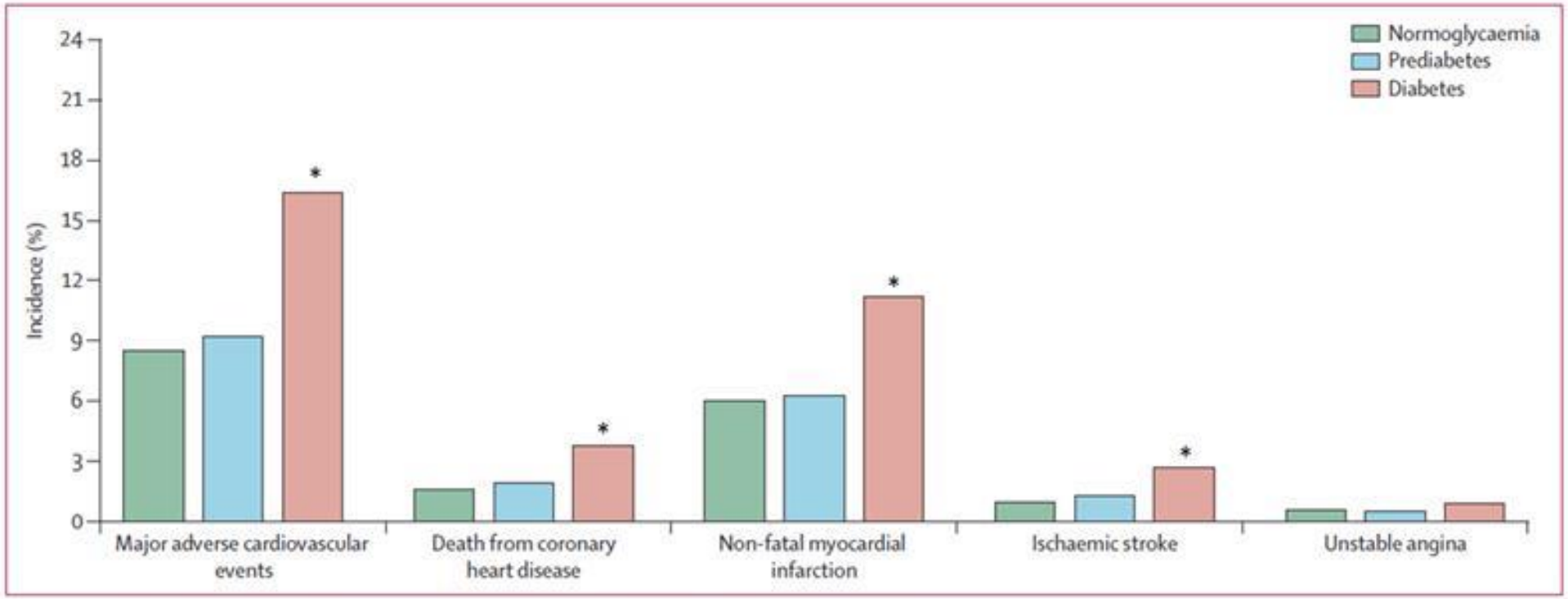


***Figure 1*: Incidence of cardiovascular events in the placebo group, by baseline glycaemic status**
Median follow-up was 2·8 years (IQR 2·3–3·4). There were no significant differences between participants with normoglycaemia and those with prediabetes for any of the outcomes (data not shown).

Pre-specified analysis: normoglycaemia (28%, n=5,234); pre-diabetes (43%, n=8,246); diabetes (29%, n=5,444).
***p<0.0001** comparing diabetes vs normoglycaemia or prediabetes.
IQR, interquartile range

Adapted from Ray KK, *et al*. *Lancet Diabetes Endocrinol.* 2019;7(8):618–28.

No significant difference across glycaemic categories in lipid concentrations at 4 months

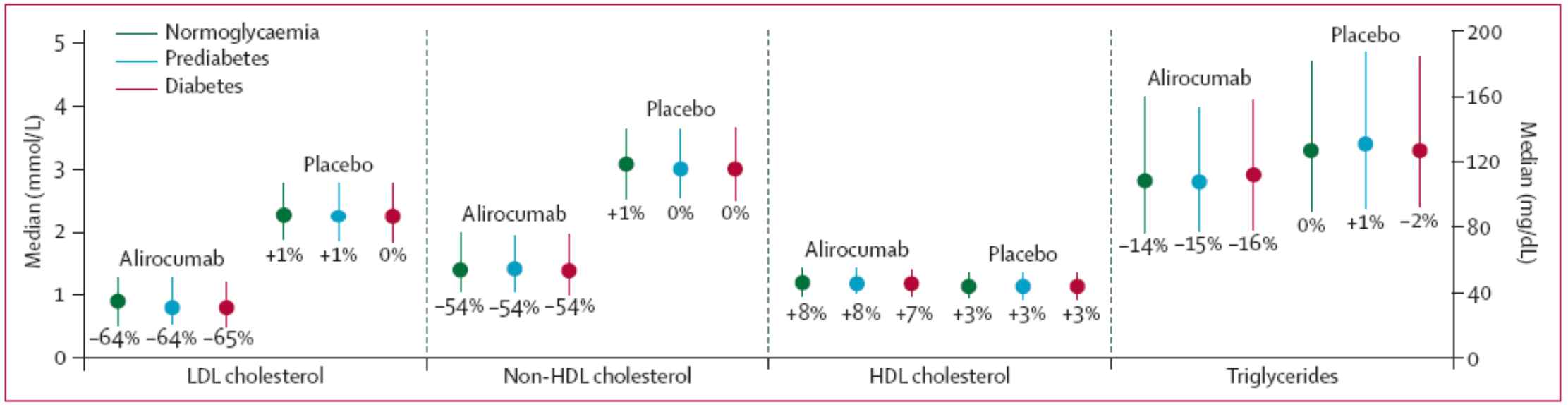


Figure 2: **Lipid concentrations at 4 months after randomisation, by baseline glycaemic status (intention-to-treat analysis)**
Error bars are IQRs. Median within-patient percentage changes from baseline are shown below each data point.

HDL, high-density lipoprotein

Ray KK, *et al. Lancet Diabetes Endocrinol.* 2019;7(8):618–28.

Relative and absolute risk reduction with alirocumab on primary MACE by glucometabolic status

A pre-specified analysis of the ODYSSEY OUTCOMES

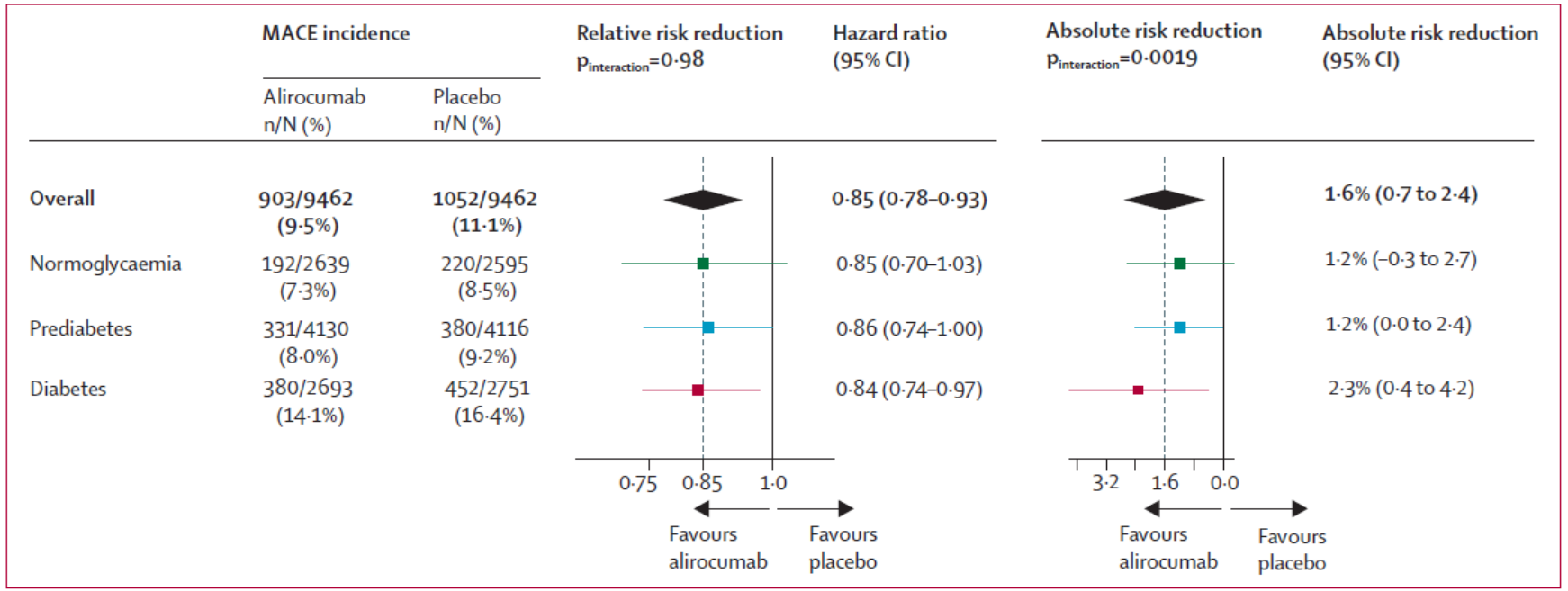


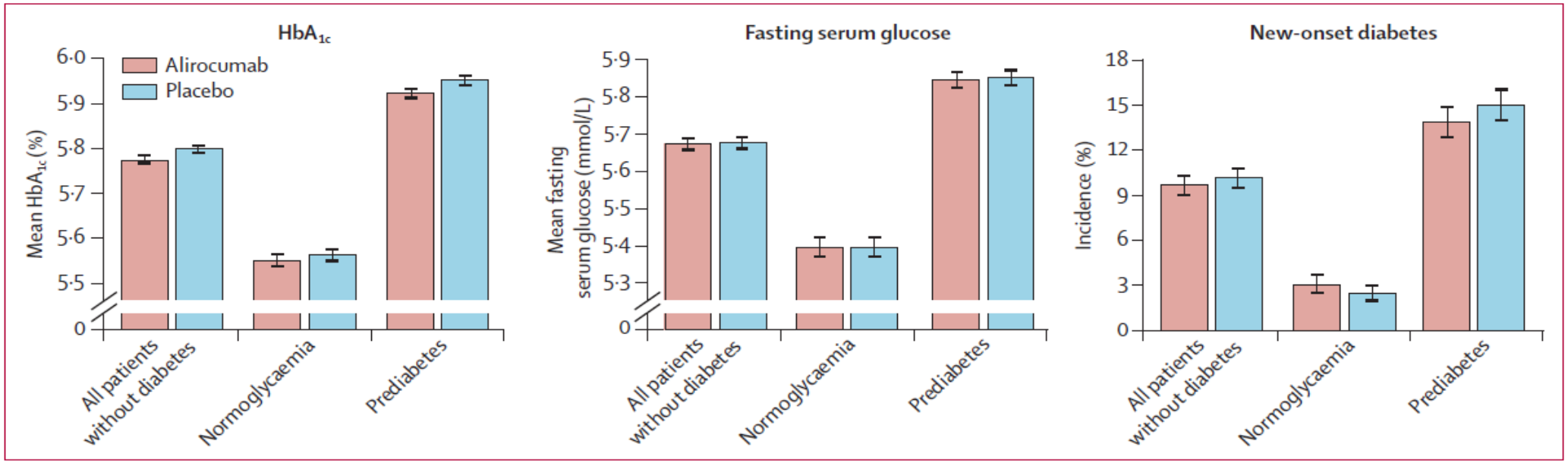
Figure 4: **Relative and absolute risk reduction with alirocumab, by baseline glycaemic status**
Median follow-up was 2·8 years (IQR 2·3–3·4). MACE=major adverse cardiovascular events.

Subgroup analysis of ODYSSEY OUTCOMES trial, patients with DM: **x2** absolute risk reduction (2.3%) vs pre-DM, non-DM subjects (1.2%)[2]

Median (Q1, Q3) follow-up: 2.8 (2.3, 3.4) years.
MACE, major adverse cardiovascular events

1. Ray KK, *et al. Lancet Diabetes Endocrinol*. 2019;7(8):618–28; 2. Cosentino F, *et al. European Heart Journal*. 2019;00:1–69.

Post-randomisation HbA_{1c}, fasting glucose and new-onset diabetes by baseline glucometabolic status



Post-randomisation HbA_{1c}, fasting serum glucose and NOD, by baseline glycaemic status

Error bars: 95% CI. Only post-randomisation values before DM medication started and included in the analysis.

New-onset diabetes mellitus:

- **All patients without DM*:** alirocumab 9.6% (95% CI 8.9–10.3) vs placebo 10.1% (9.4–10.8; p=0.98)
- **Pre-DM subgroup:** alirocumab 13.8% (12.8–14.9) vs placebo 15.3% (13.9–16.1; p=0.60)
- **Normoglycaemia subgroup:** alirocumab 3.0% (2.4–3.7) vs placebo 2.4% (1.9–3.0; p=0.15)

Analysis method for A1c and fasting glucose: repeated-measures mixed-effects model; random effects = slope, intercept; fixed effects = treatment, baseline value and time.*Without diabetes = prediabetes or normoglycaemia.

HbA_{1c}, haemoglobin A_{1c}; NODM, new-onset diabetes mellitus

Ray KK, *et al. Lancet Diabetes Endocrinol.* 2019;7(8):618–28.

Conclusions

Conclusions (1)

There have been substantial advances in the management and prevention of CVD in patients with diabetes

However, there continues to be a high prevalence (32%) of CVD among people with type 2 diabetes and a high level of unmet need for CV risk factor control[1]

There is substantial scope for reducing the excess risk of CVD in diabetes, through improved management of known risk factors

In secondary prevention for patients at very high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) is recommended[2]

The new guidelines state prevention strategies should not be glucose centric, but a multifactorial approach with combined reduction in HbA_{1c}, SBP and lipids[3]

SBP, systolic blood pressure

1. McGurnaghan S, *et al. Diabet Med.* 2019;36:718–25; 2. Mach F, *et al*. *European Heart Journal*. 2019;00:1–78; 3. Cosentino F, *et al. European Heart Journal*. 2019;00:1–69.

Conclusions (2)

In ODYSSEY OUTCOMES, treatment with alirocumab to target LDL-C levels of 25–50 mg/dL (0.65–1.30 mmol/L) produced:

- the same relative risk reduction
- and twice the absolute risk reduction

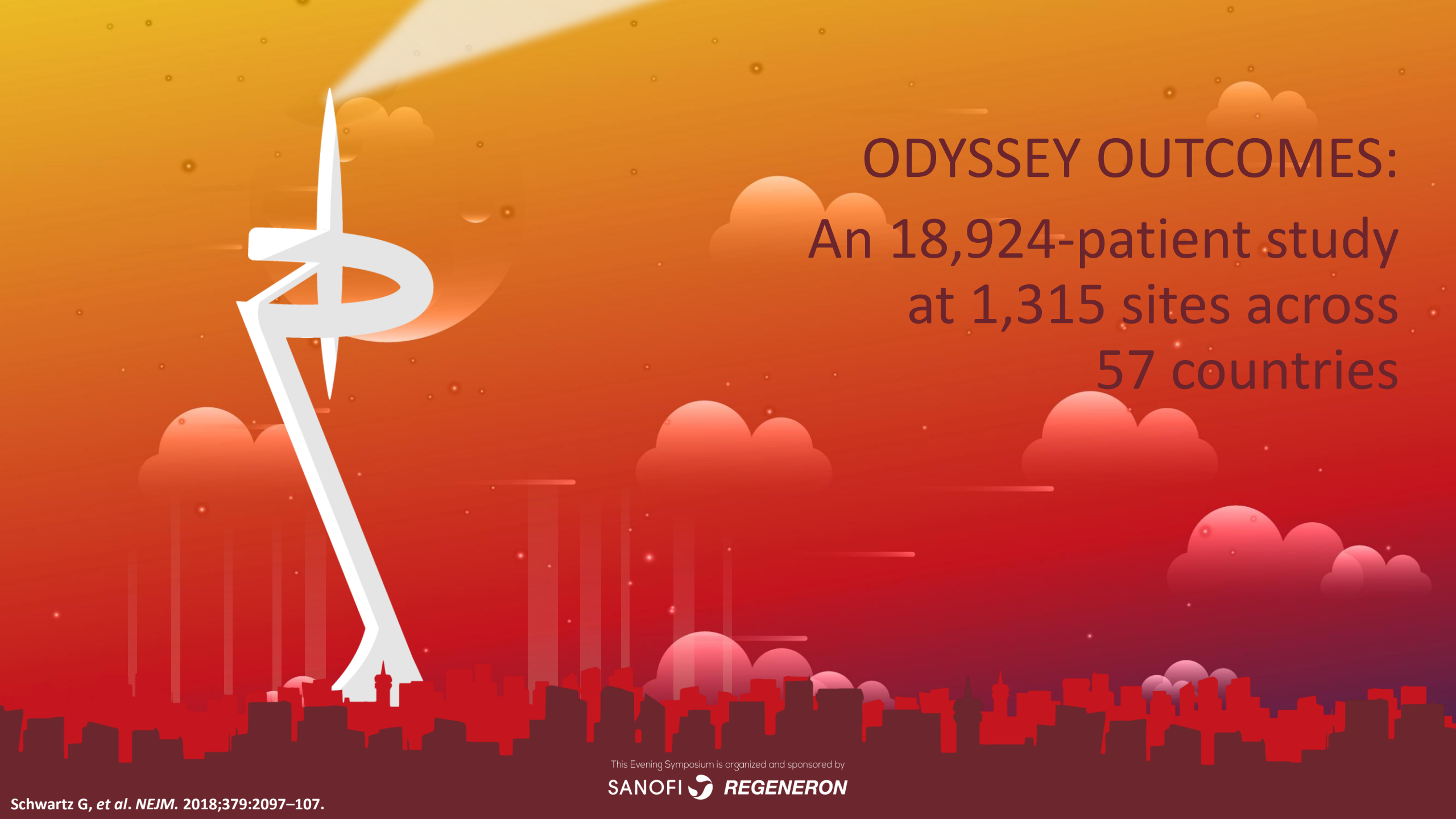
in CV events among people with diabetes as in those without

Clearly, there is a need to easily identify very high-risk groups who derive greater absolute benefits from more intensive therapies

Ray KK, *et al*. *Lancet Diabetes Endocrinol.* 2019;7(8):618–28.

ODYSSEY OUTCOMES:

An 18,924-patient study at 1,315 sites across 57 countries



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Schwartz G, *et al*. *NEJM.* 2018;379:2097–107.

Individuals with diabetes and high CV risk who may benefit the most from PCSK9 inhibition in your clinical practice

Professor Luis Masana (Chair)
University of Rovira i Virgili, CIBERDEM
Spain

Disclosures

Fees for lectures or advisory work from:

Amgen; Sanofi-Regeneron; MSD; Mylan; Daichii/Sankyo

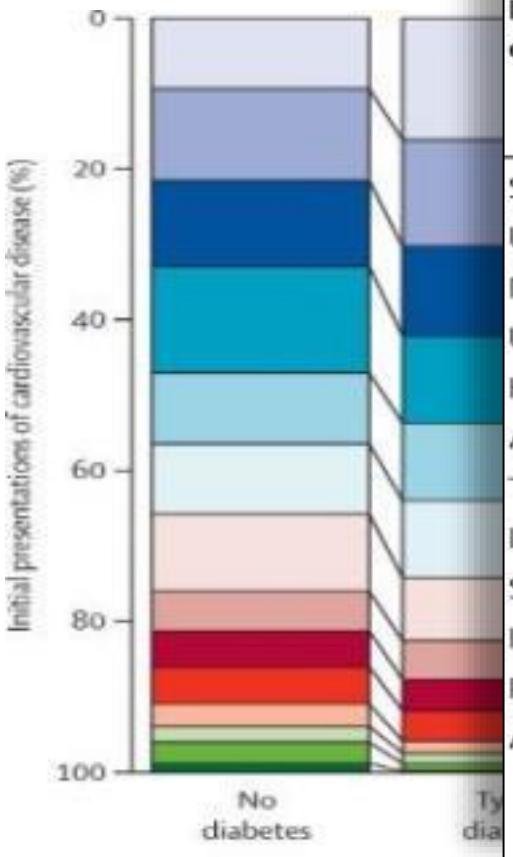
Alongside people with diabetes, which other patient populations have shown benefit from treatment with PCSK9i?

1. Polyvascular disease (PVD)
2. Peripheral artery disease (PAD)
3. Prior CABG
4. PAD and PVD
5. All of the above

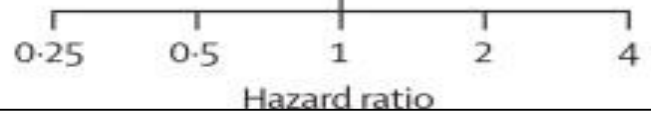
VOTE

Choose the best option

Type 2 diabetes increases the risk of CV diseases: a cohort study in 1.9 million people



Initial presentation of cardiovascular disease	Number of events: No diabetes	Number of events: Type 2 diabetes	Hazard ratio (95% CI)	p value
Stable angina	12 232	728	1·62 (1·49–1·77)	<0·0001
Unstable angina	5286	245	1·53 (1·32–1·76)	<0·0001
Non-fatal myocardial infarction	15 191	706	1·54 (1·42–1·67)	<0·0001
Unheralded coronary death	5101	255	1·43 (1·23–1·65)	<0·0001
Heart failure	13 072	866	1·56 (1·45–1·69)	<0·0001
Arrhythmia or sudden cardiac death	3218	100	0·95 (0·76–1·19)	0·65
Transient ischaemic attack	10 990	513	1·45 (1·31–1·60)	<0·0001
Ischaemic stroke	5643	316	1·72 (1·52–1·95)	<0·0001
Subarachnoid haemorrhage	1260	11	0·48 (0·26–0·89)	0·020
Intracerebral haemorrhage	2265	84	1·28 (1·02–1·62)	0·035
Peripheral arterial disease	10 074	992	2·98 (2·76–3·22)	<0·0001
Abdominal aortic aneurysm	3051	62	0·46 (0·35–0·59)	<0·0001

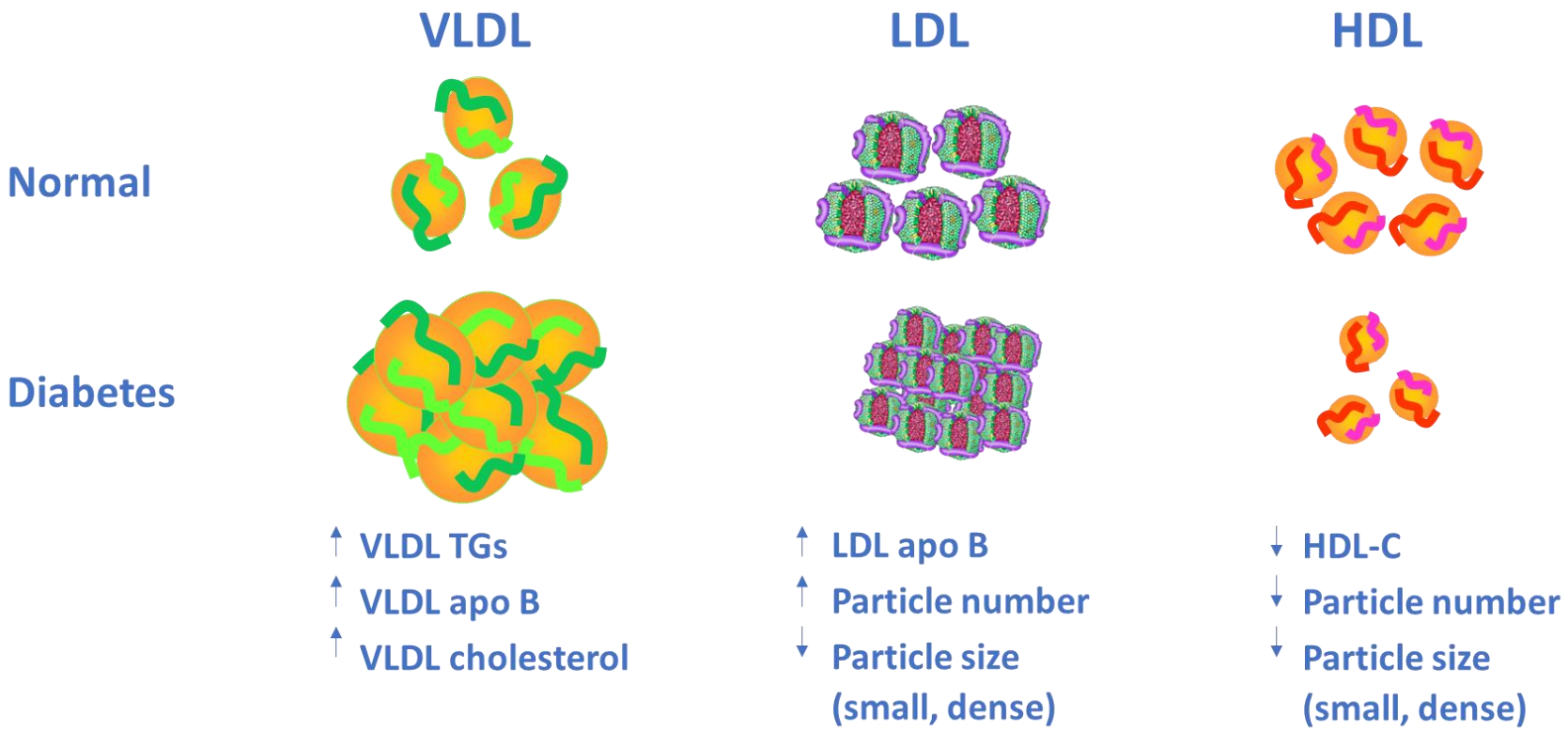


Cohort study: to assess associations between T2DM and initial manifestations of CVD in the UK (from 4 electronic health data sources) in people free from baseline CVD. Primary endpoint: first record of 1 of 12 CV presentations in any of the data sources. N=1,921,260 individuals, of whom 1,887,062 (98.2%) without DM and 34,198 (1.8%) with DM. Follow-up 5.5 years.

Anoop Dinesh Shah, *et al*. *The Lancet Diabetes & Endocrinology*. 2015;3:105–13.

Type 2 diabetes is often associated with a mixed dyslipidemia profile

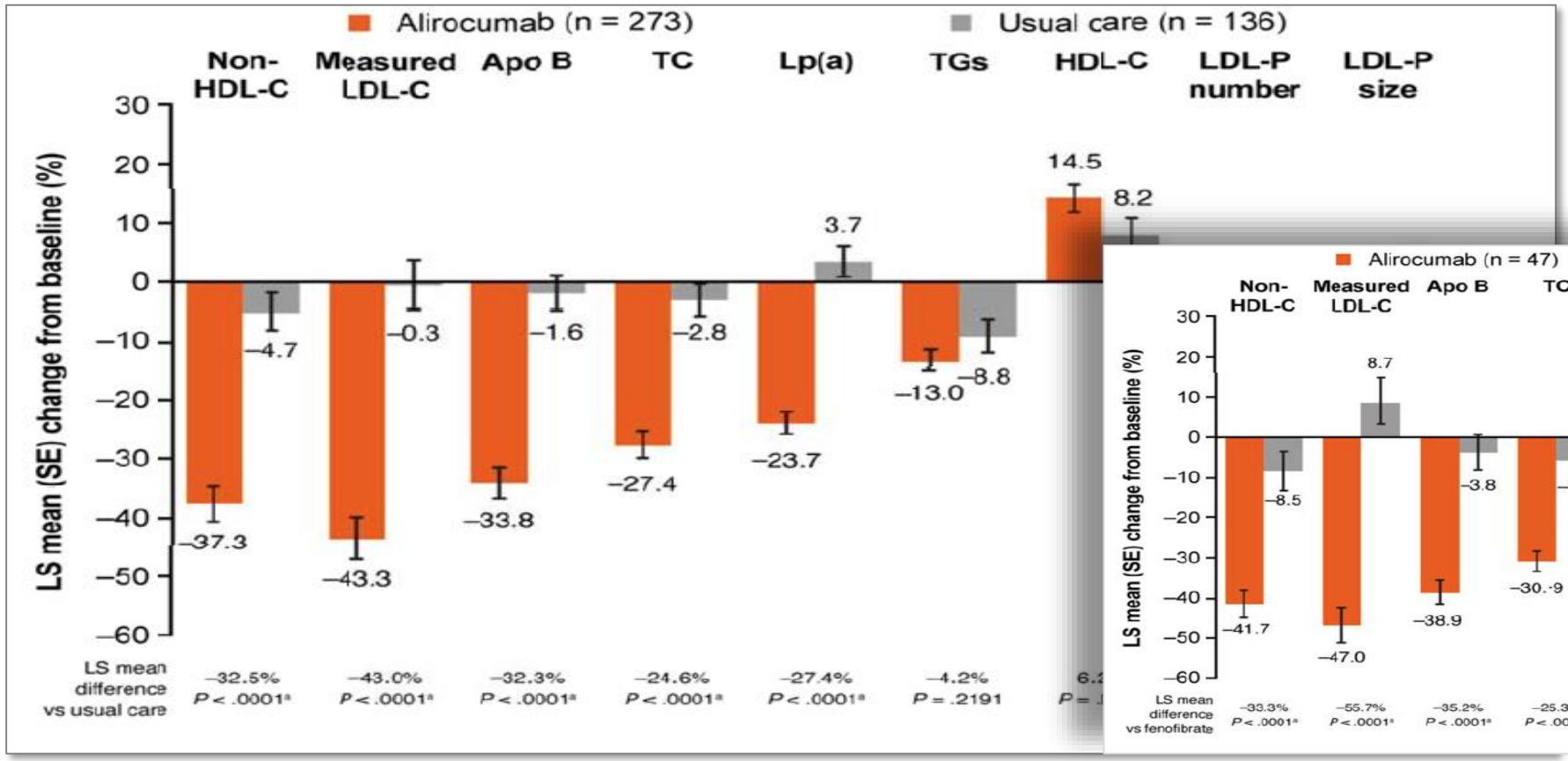
Diabetic dyslipidemia: not only quantitative lipoprotein abnormalities, but also qualitative and kinetic abnormalities, resulting in a shift towards a more atherogenic lipid profile[1]

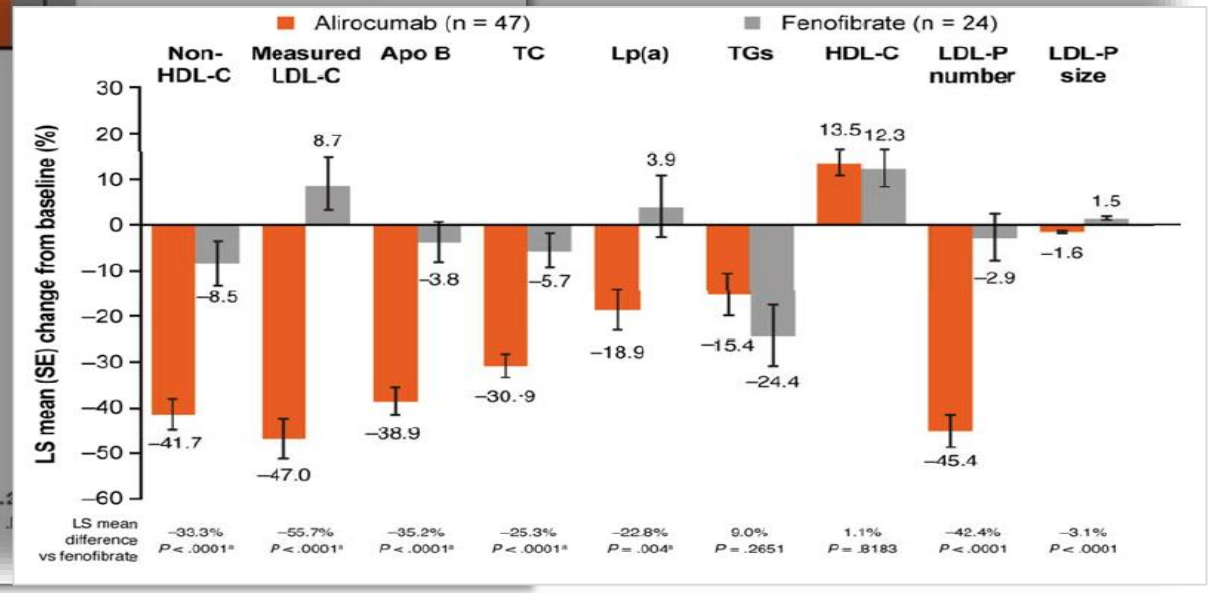


Apo, apolipoprotein; HDL, high-density lipoprotein; HDL-C, HDL cholesterol; LDL, low-density lipoprotein; T2DM, type 2 diabetes mellitus; TG, triglyceride; VLDL, very-low density lipoprotein

1. Verges B. *Diabetologia.* 2015;58:886–99; Figure adapted from: Diapedia. Treatment of Diabetic Dyslipidaemia. 2014. Available online: https://www.diapedia.org/associated disorders/61040851150/diabetic-dyslipidaemia-origins-and-treatment [Last accessed September 2019].

Alirocumab add-on statin therapy improves the overall lipoprotein profile in patients with T2DM





Safety: incidence of treatment-emergent adverse events similar in both groups. No clinically meaningful effect on glycaemic parameters or change in number of glucose-lowering agents.

ODYSSEY DM-DYSLIPIDEMIA study: open-label randomised study to compare alirocumab 75 mg Q2W/150 mg Q2W, with usual care (UC: no additional lipid-lowering therapy; fenofibrate; ezetimibe; omega-3 fatty acid; nicotinic acid) in individuals with T2DM, and mixed dyslipidemia not optimally managed by maximally tolerated statins. Primary efficacy endpoint: % change in non-HDL-C from baseline to Week 24. N=413.
LDL-P, low-density lipoprotein particle; Lp(a), lipoprotein(a); LS, least square; SE, standard error; TC, total cholesterol

Ray K, *et al*. *Diabetes Obes Metab*. 2018;20(6):1479–89.

Diabetes sub-analyses from most recent PCSK9i CVOT studies

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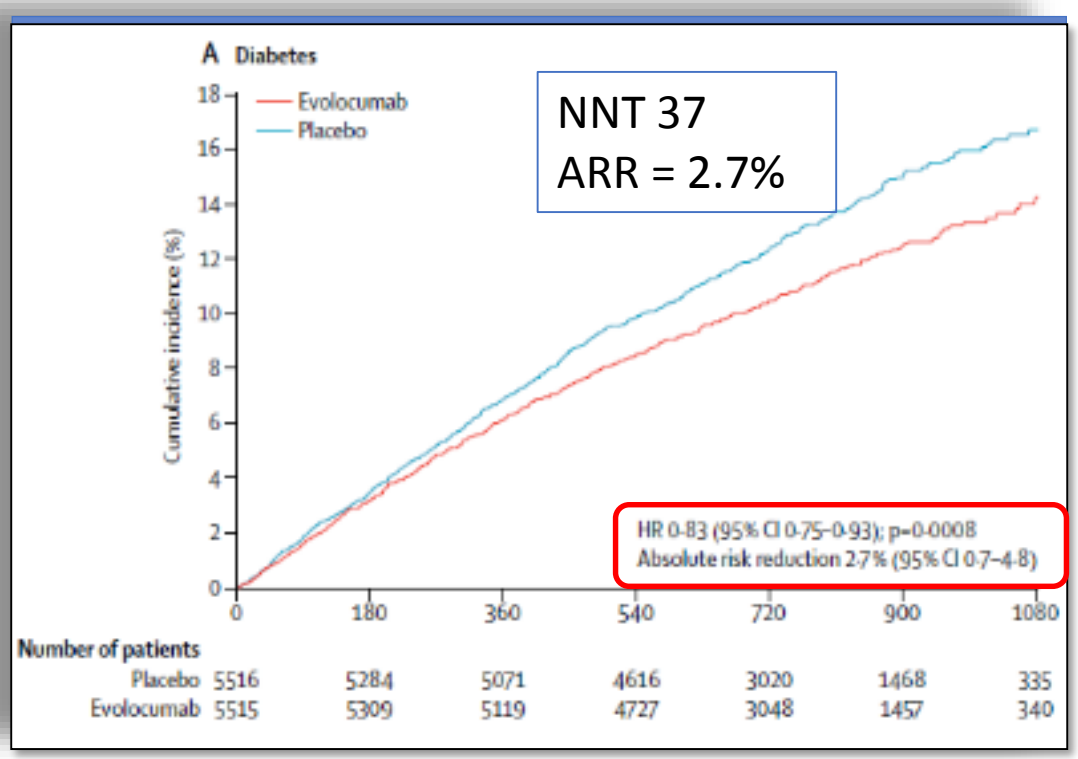
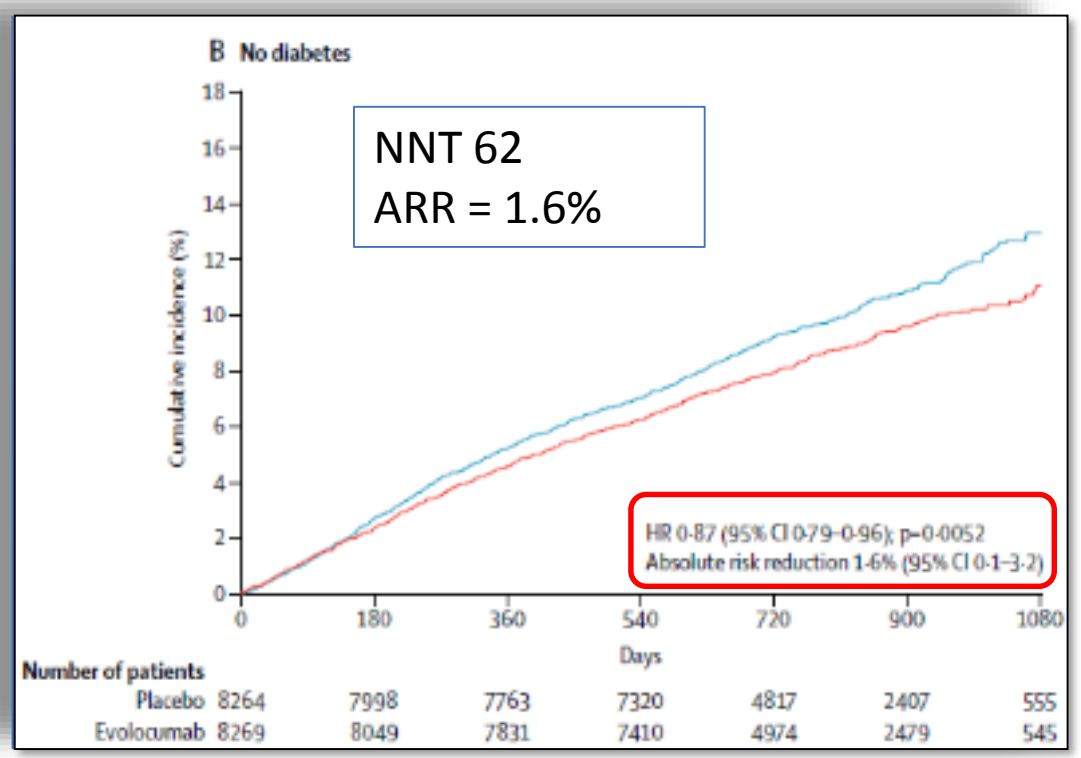
CVOT, cardiovascular outcomes trial

FOURIER: evolocumab significantly reduced primary MACE in people with and without diabetes



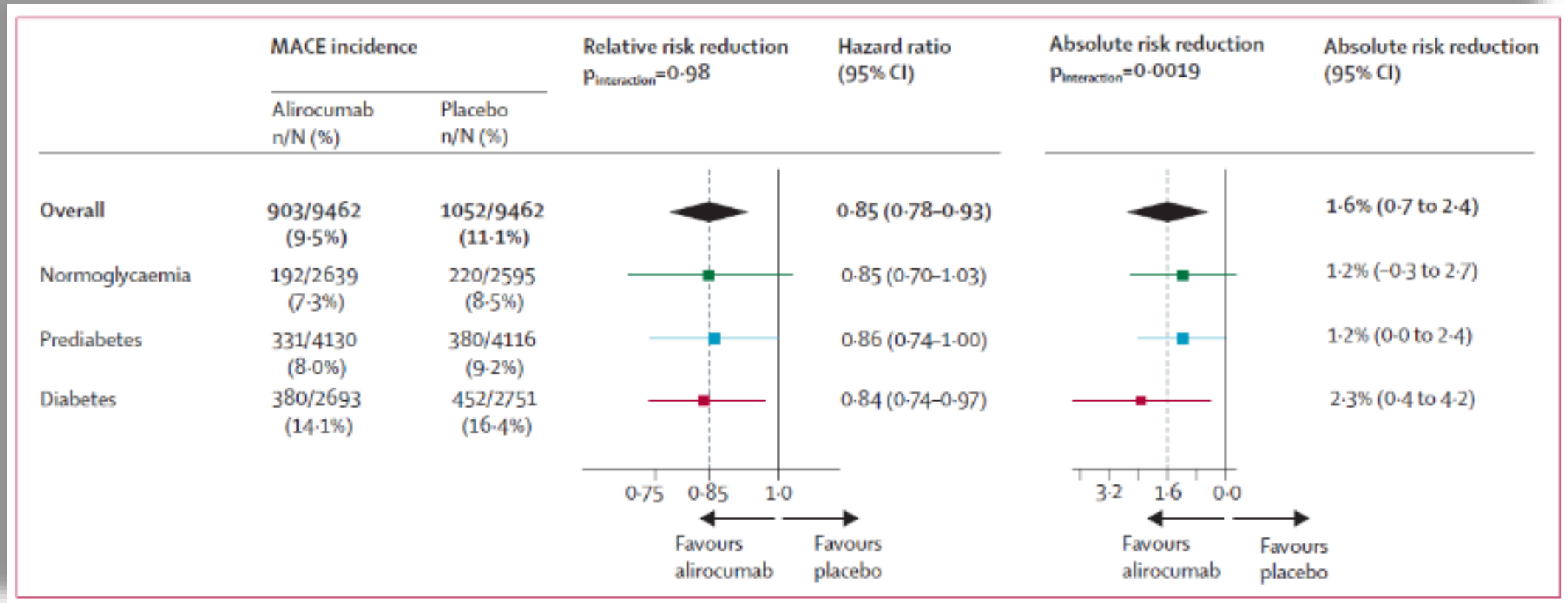


Primary efficacy endpoint (CV death, MI, stroke, hospital admission for UA or coronary revascularisation)
The p-interaction value between baseline diabetes status and efficacy of evolocumab was 0.60

FOURIER study design and primary endpoint (overall) provided in Pr. Colhoun's presentation.
Overall safety, and safety in people with and without diabetes, will be shown in Pr. Navar's presentation.
ARR, absolute risk reduction; HR, hazard ratio; NNT, number needed to treat

Sabatine MS, *et al. Lancet Diabetes Endocrinol.* 2017;5:941–50.

ODYSSEY OUTCOMES DM study: greater CV risk and ARR with alirocumab in DM vs non-DM



Pre-specified analysis.
Median (Q1, Q3) follow-up: 2.8 (2.3, 3.4) years.

ODYSSEY OUTCOMES study design and primary endpoints provided in Pr. Colhoun's presentation.
Overall safety, and safety in people with and without diabetes, will be shown in Pr. Navar's presentation.

Ray KK, *et al. Lancet Diabetes Endocrinol.* 2019;7(8):618–28.

The higher the baseline CV risk, the greater the potential absolute risk reduction

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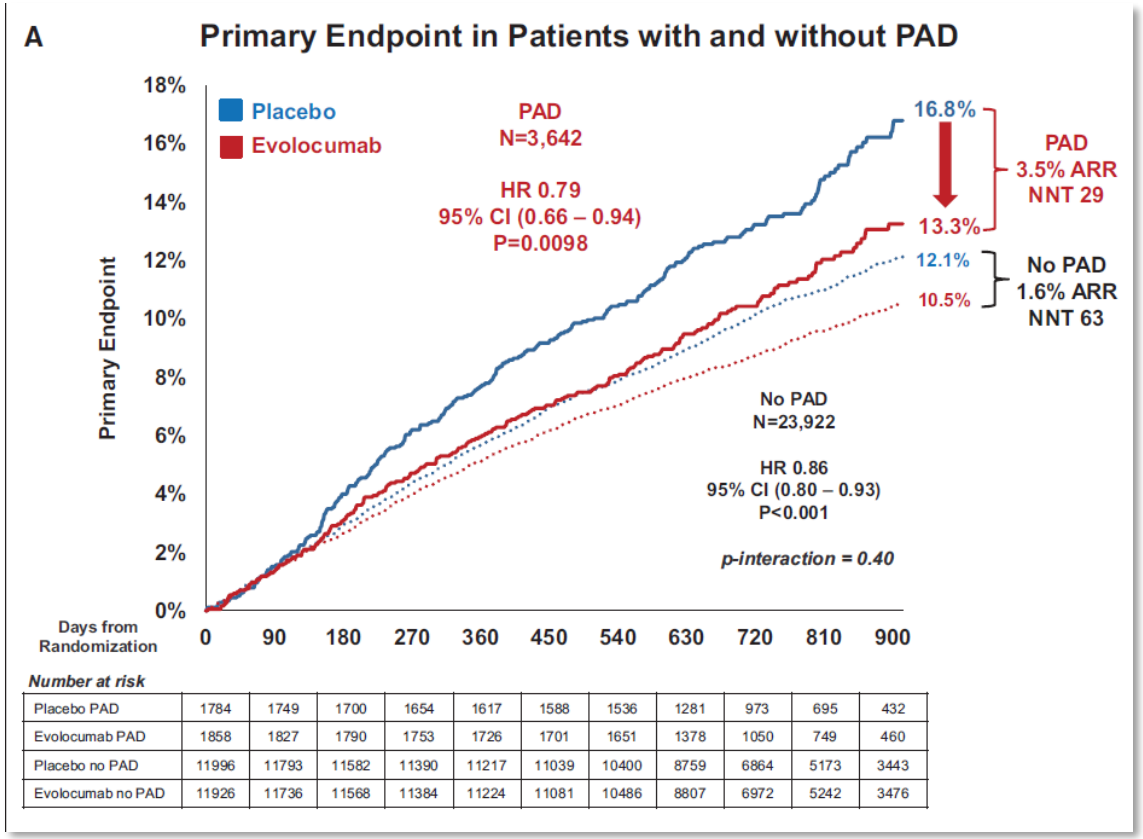
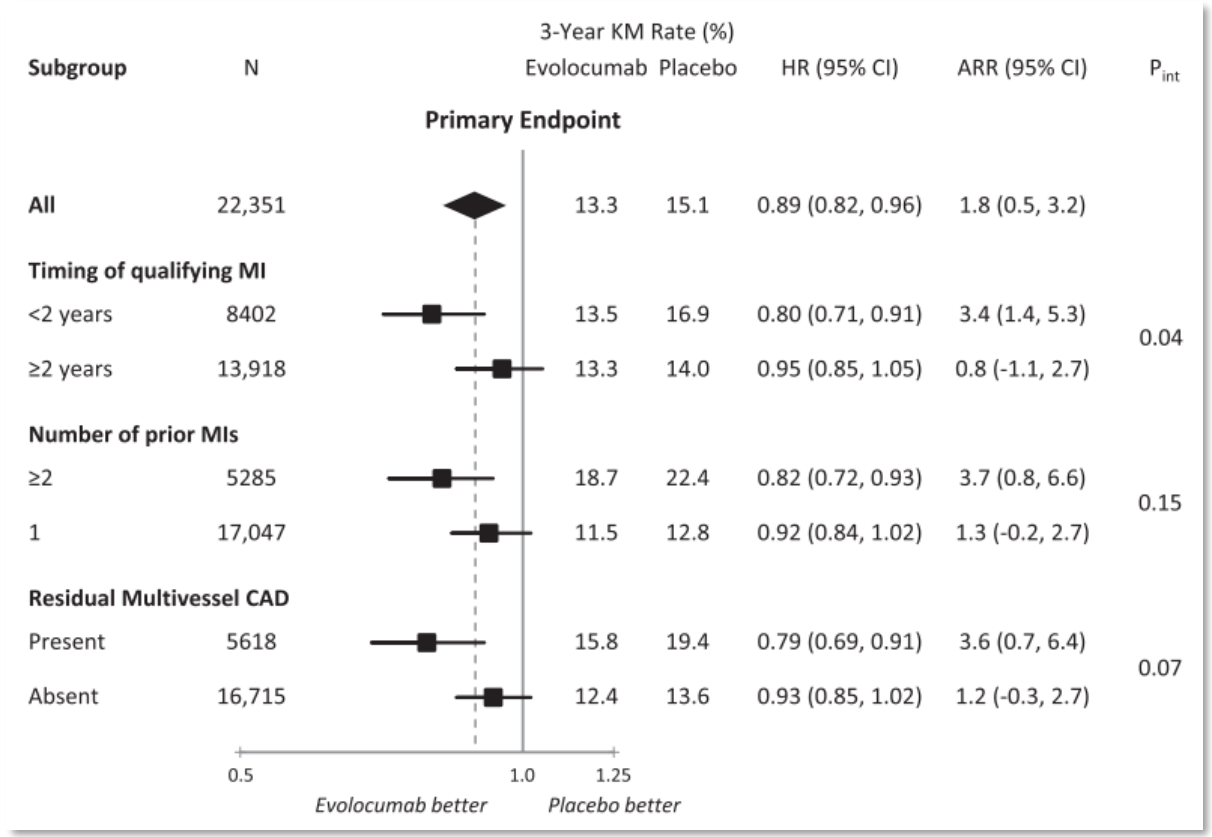
Greater absolute benefit* on primary MACE† observed in other sub-groups: additional analysis from FOURIER





- With PAD, 13% of overall population, of whom **43% had DM[1]**

- With recent MI <2 years, 38% of overall population, of whom **31% had DM[2]**
- With >2 prior MI, 24% of overall population, of whom **36% had DM[2]**
- With multivessel CAD, 25% of overall population, of whom **35% had DM[2]**

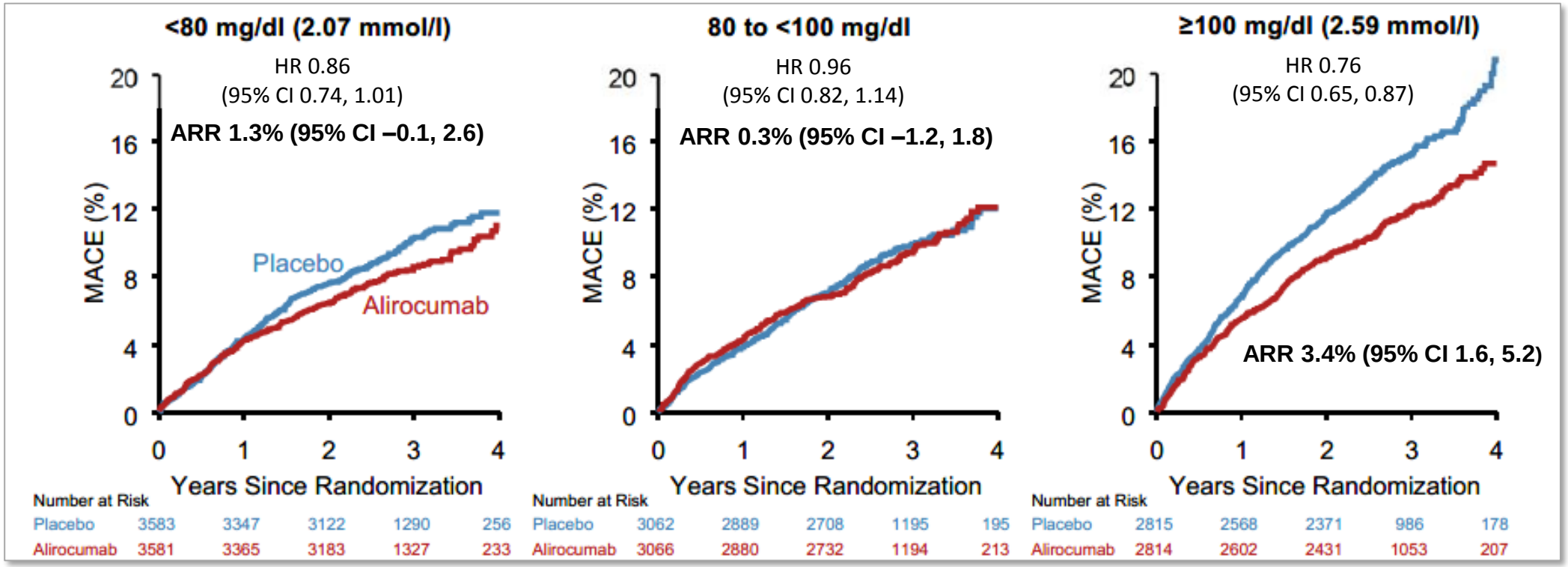
*Versus other subgroups; †Composite of CV death, MI, stroke, hospitalisation for UA or coronary revascularisation.
CAD, coronary artery disease; KM, Kaplan–Meier; PAD, peripheral arterial disease

1. Bonaca MP, *et al. Circulation.* 2018;137:338–50; 2. Sabatine MS, *et al. Circulation.* 2018;138(8):756–66.

ODYSSEY OUTCOMES: Patients with a baseline LDL-C level of ≥100 mg/dL derived a greater absolute benefit on primary MACE with alirocumab vs those with lower baseline LDL-C

Primary endpoint by LDL-C at baseline

(RRR interaction p-value = 0.09 [pre-specified]*; ARR interaction p-value <0.001 [post-hoc analysis]†)



<u>NNT</u> (to prevent one primary MACE) in patients with baseline LDL-C ≥100 mg/dL: 16 (95% CI 11–34) patients for 4 years

*Based on median follow-up for 2.8 years; †Based on median follow-up for 2.8 years.
RRR, relative risk reduction

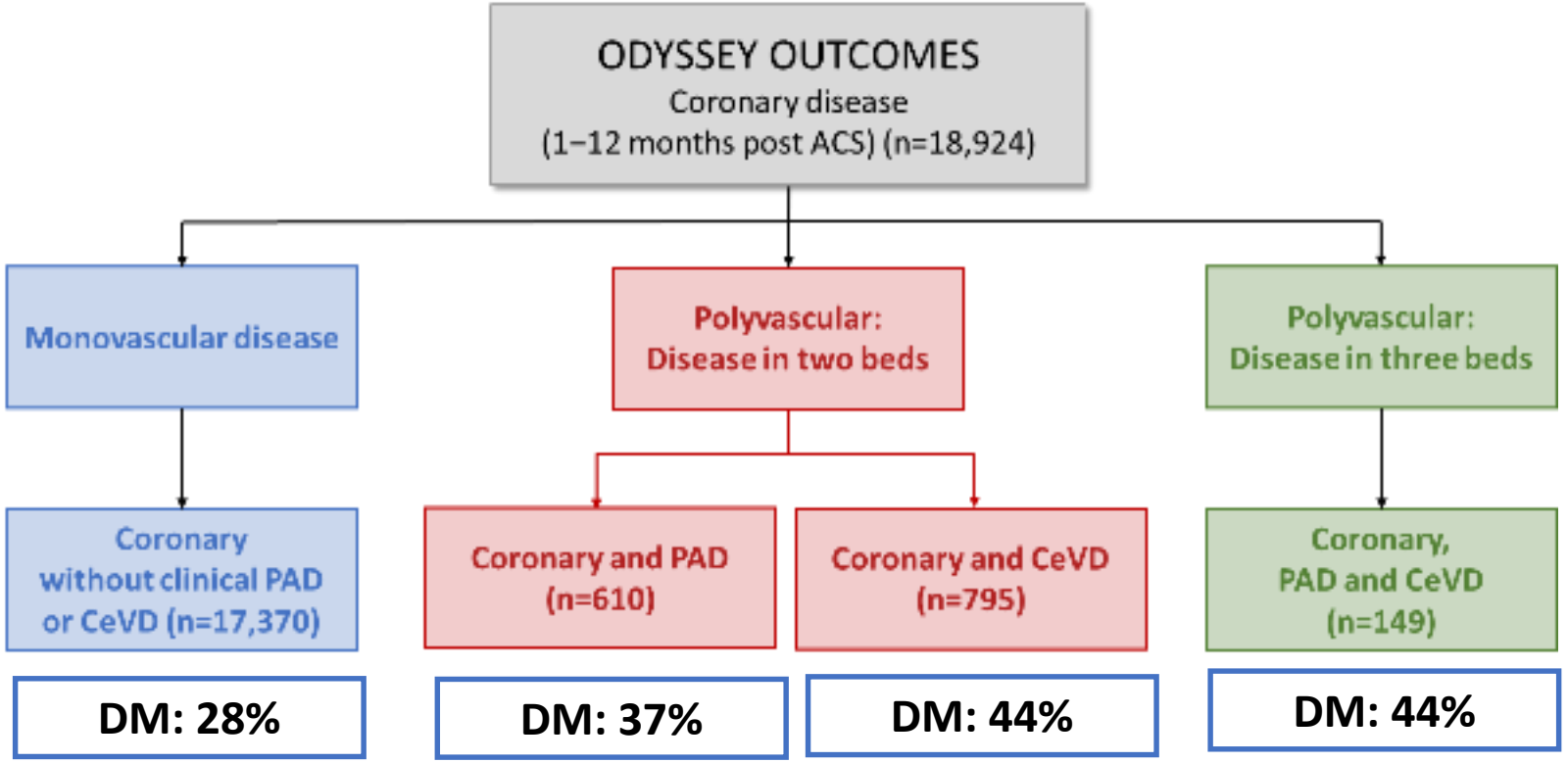
Schwartz GG, *et al. NEJM.* 2018;279:2097–107.

Alirocumab in patients with polyvascular disease and recent ACS

ODYSSEY OUTCOMES prespecified analysis of influence of polyvascular disease on primary MACE and death

p<0.0001

Categories of polyvascular disease

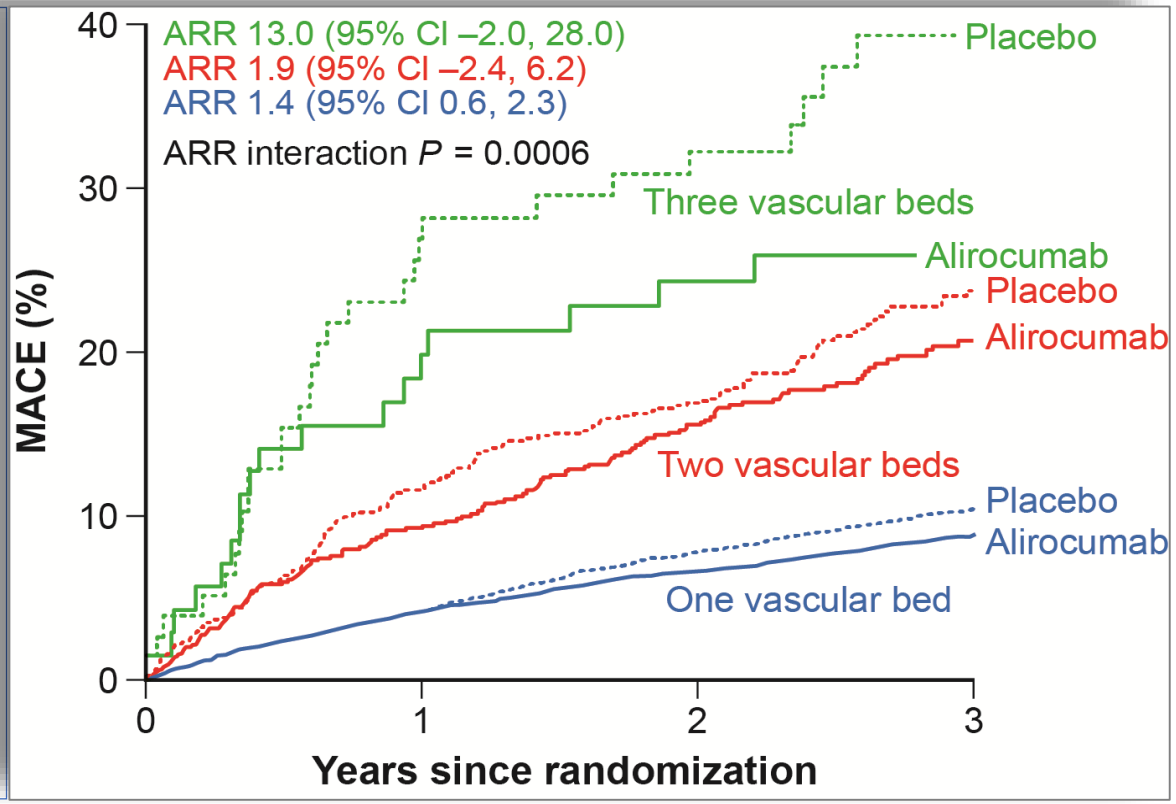


CeVD, cerebrovascular disease

Jukema JW, *et al. JACC.* 2019;74(9):1167–76.

Primary MACE: one, two or three vascular beds, greater ARR in polyvascular disease

Primary composite	HR (95% CI)	HR interaction p-value
Monovascular disease	0.85 (0.77, 0.93)	0.40
Disease in 2 vascular beds		
Coronary and PAD	0.93 (0.67, 1.30)	
Coronary and CeVD	0.87 (0.63, 1.19)	
Disease in 3 vascular beds	0.64 (0.35, 1.12)	
All patients	0.85 (0.78, 0.93)	



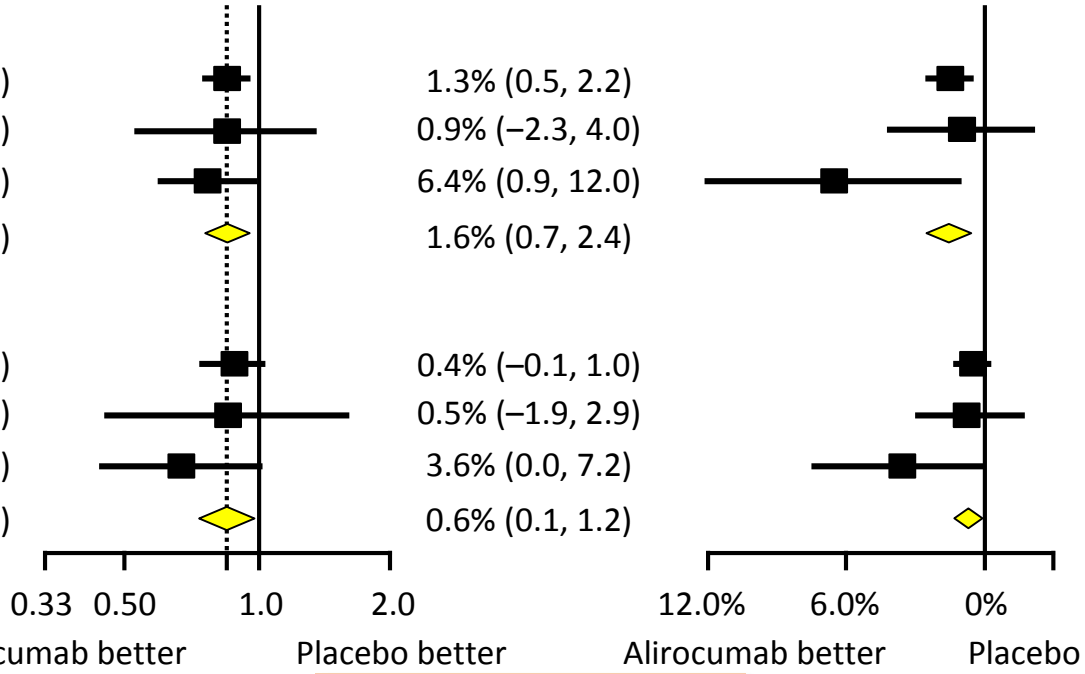
Safety: No major differences in safety outcomes among the three subgroups

Overall safety from ODYSSEY OUTCOMES will be reported in Dr. Navar's presentation.
ODYSSEY OUTCOMES prespecified analysis of the influence of polyvascular disease on MACE and death.

Jukema JW, *et al. JACC.* 2019;74(9):1167–76.

Patients with ACS and prior CABG derived greater absolute benefit from alirocumab vs other subgroups

	Alirocumab % (n)	Placebo % (n)	HR (95% CI)	ARR (95% CI)
Primary endpoint				
No CABG	8.8 (747)	10.2 (857)	0.86 (0.78, 0.95)	1.3% (0.5, 2.2)
Index CABG[a]	6.7 (33)	7.5 (40)	0.85 (0.54, 1.35)	0.9% (–2.3, 4.0)
Prior CABG[b]	24.5 (123)	30.9 (155)	0.77 (0.61, 0.98)	6.4% (0.9, 12.0)
All patients	9.5 (903)	11.1 (1,052)	0.85 (0.78, 0.93)	1.6% (0.7, 2.4)
All-cause death				
No CABG	3.3 (278)	3.7 (314)	0.88 (0.75, 1.03)	0.4% (–0.1, 1.0)
Index CABG[a]	3.6 (18)	4.1 (22)	0.85 (0.46, 1.59)	0.5% (–1.9, 2.9)
Prior CABG[b]	7.6 (38)	11.2 (56)	0.67 (0.44, 1.01)	3.6% (0.0, 7.2)
All patients	3.5 (334)	4.1 (392)	0.85 (0.73, 0.98)	0.6% (0.1, 1.2)



Pre-planned ODYSSEY OUTCOMES sub-analysis to determine clinical benefit of adding alirocumab to statin therapy in patients with recent ACS and prior CABG.

No CABG (n=16,896), index CABG (n=1,025), prior CABG (n=1,003)*

HR interaction p-values
- Primary endpoint: p=0.71
- All-cause death: p=0.48

ARR interaction p-values
- Primary endpoint: p=0.0007
- All-cause death: p=0.03

*No CABG: 27.8% DM; index CABG: 33.8% DM,; prior CABG: 40.6% DM, 38.1% prediabetes, 21.3% normoglycemia.
[a]Index CABG is CABG between the index ACS event and randomization (including 44 patients with prior CABG); [b]Prior CABG is CABG prior to the index ACS event. CABG, coronary artery bypass graft

Goodman SG, *et al.* Poster presentation at the American College of Cardiology, March 16–18, 2019. Poster number: 1045-07.

Additional analyses from ODYSSEY OUTCOMES

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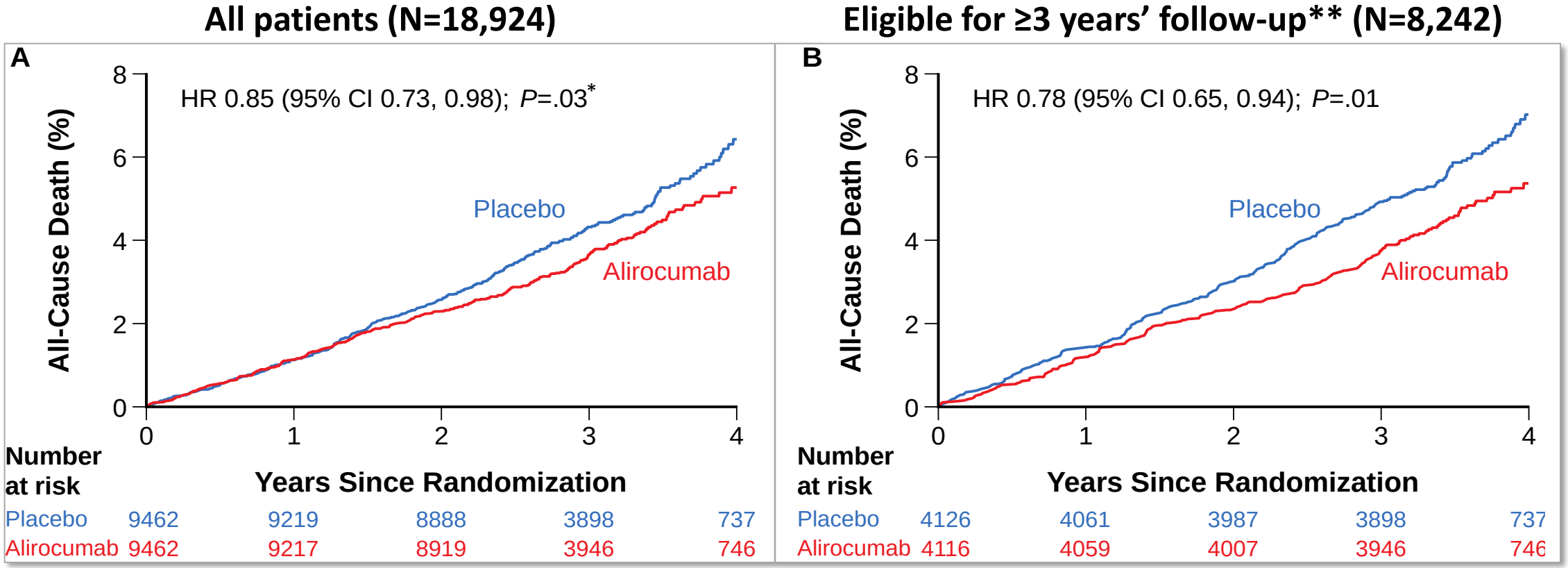
All-cause death in ODYSSEY OUTCOMES: all patients vs patients eligible for ≥3 years of follow-up



In overall population, 28% had DM at baseline; in population eligible for >3 years' follow-up, 30% had DM at baseline

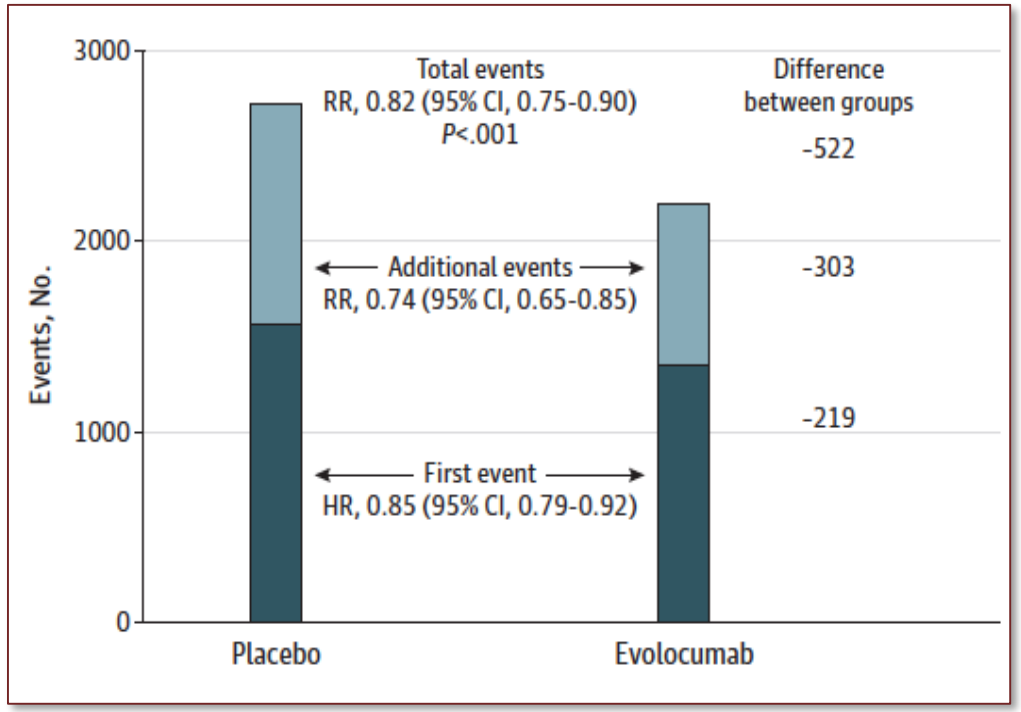
*Because all-cause death followed CHD death and CV death in the prespecified hierarchy of main secondary endpoints, the p-value for all-cause death was considered nominal. Alirocumab is associated with lower all-cause death as compared to placebo. Patients were eligible for ≥3 years' follow-up if randomised ≥3 years before the common study end date. CHD, coronary heart disease

** Patients were eligible for ≥3 years' follow-up if randomised ≥3 years before the common study end date

Steg PG, *et al. Circulation.* 2019;140(2):103–12.

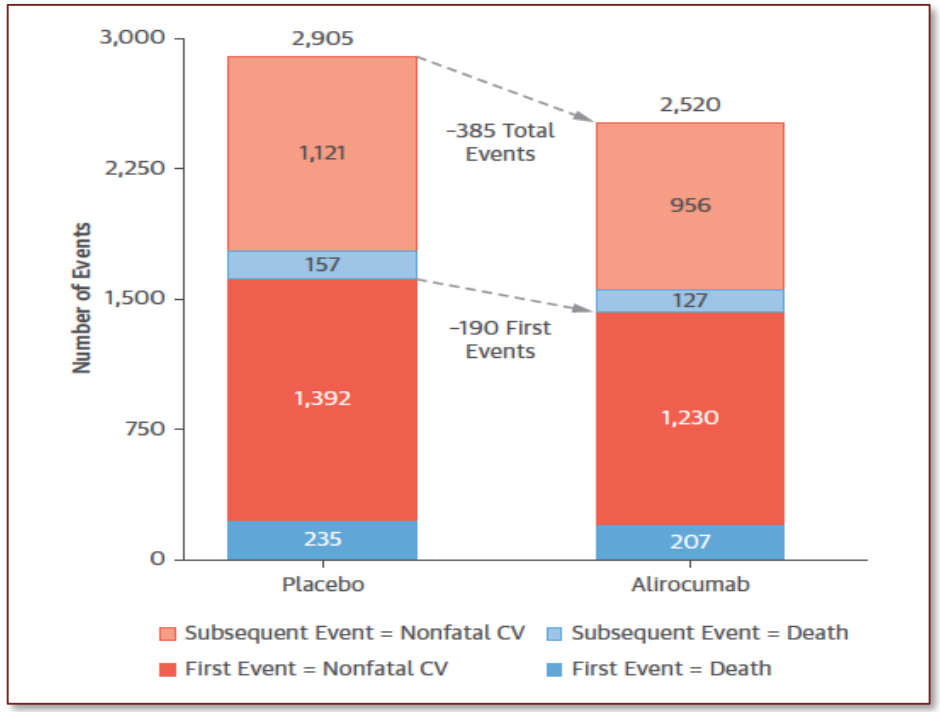
Pre-specified analysis on total CV events in FOURIER and ODYSSEY OUTCOMES

FOURIER (stable ASCVD)[1a]



Evolocumab improved clinical outcomes with significant reductions in total primary endpoint events, driven by decreases in MI, stroke, and coronary revascularisation, which revealed more than double the number of events prevented compared with an analysis of only first events

ODYSSEY OUTCOMES (ACS)[2b]



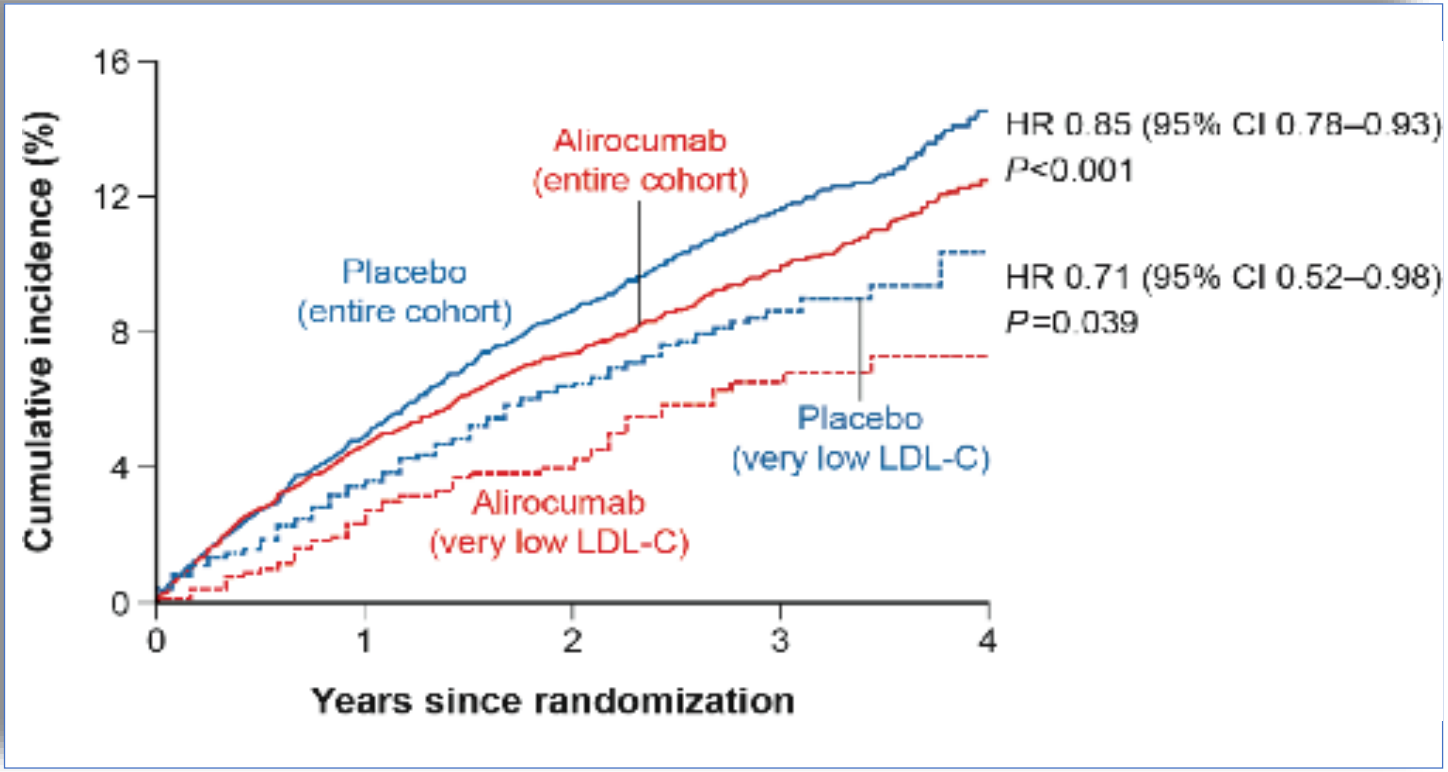
Alirocumab was associated with twice the reduction in total number of events (nonfatal CV events and death) than the reduction in first events. Alirocumab reduced total non-fatal CV events (HR: 0.87; 95% CI: 0.82 to 0.93) and death (HR: 0.83; 95% CI 0.71 to 0.97)

[a] Analysis using the Wei et al method, total events : all CV events

[b] **Non-fatal CV event:** non-fatal primary endpoints, haemorrhagic stroke, heart failure requiring hospitalisation, and ischaemia-driven coronary revascularisation. Hazard functions for total nonfatal CV events and death were jointly estimated, linked by a shared frailty accounting for patient risk heterogeneity and correlated within-patient nonfatal events. An association parameter also quantified the strength of the linkage between risk of nonfatal events and death. The model provides accurate relative estimates of nonfatal event risk if nonfatal events are associated with increased risk for death.

1. Murphy S, et al. JAMA Cardiol. 2019; 4(7): 613-619; 2. Szarek, et al. JACC. 2019; 73: 387-396.

ODYSSEY OUTCOMES: MACE in patients with very low LDL-C on alirocumab compared with PSM patients from placebo group



Post-randomisation LDL-C is confounded by differences in baseline characteristics. Propensity score matching (PSM) reduces this confounding

Analysis evaluated efficacy and safety* of very low achieved LDL-C (<15 mg/dL, median 9 mg/dL) with alirocumab (ALI, n=730, blinded substitution of placebo (PBO) at median of 8.3 months from randomisation using PSM to similar patients treated with PBO (n=2,152)

DM at baseline: 35% in ALI very low LDL-C and 34% in PBO PSM

Despite blinded substitution of placebo for alirocumab, patients with very low achieved LDL-C on alirocumab had reduced MACE compared with PSM patients from the placebo group. These patients did not diminish overall efficacy of alirocumab in ODYSSEY OUTCOMES

*Predefined safety: neurocognitive events; haemorrhagic stroke; new-onset diabetes in patients without diabetes at baseline (blindly adjudicated).
PSM, propensity score matching

Schwartz G, *et al*. Oral presentation at the European Society of Cardiology, September 1, 2019. Poster number: P1226.

ODYSSEY OUTCOMES: adverse events with very low LDL-C on alirocumab compared with PSM patients from placebo group

Adverse events in patients with very low LDL-C on alirocumab compared with placebo group before and after PSM

Table 2. Adverse events in patients with very low LDL-C on alirocumab compared with the placebo group before and after PSM								
	ALI with very low LDL-C		PBO (all)	HR (95% CI)	P-value	PBO PSM	HR (95% CI)	P-value
N	730		9443			2152		
Neurocognitive events, n (%)	10 (1.4)		167 (1.8)	0.71 (0.38, 1.35)	0.30	31 (1.4)	0.84 (0.41, 1.72)	0.88
Hemorrhagic stroke, n (%)	0 (0.0)		16 (0.2)	0.00	0.99	6 (0.3)	0.00	0.99
N	525		6696			1575		
New-onset diabetes, n (%)	79 (15.1)		676 (10.1)	1.46 (1.16, 1.85)	0.001	204 (13.0)	1.10 (0.85, 1.43)	0.46

In PSM comparisons, there was no evidence of association between very low LDL-C levels and increased risk of neurocognitive events, haemorrhagic stroke or new-onset diabetes with very low achieved LDL-C on alirocumab

Schwartz G, *et al*. Oral presentation at the European Society of Cardiology, September 1, 2019. Poster number: P1226.

2019 dyslipidaemia guidelines: (ESC/EAS, SEA)

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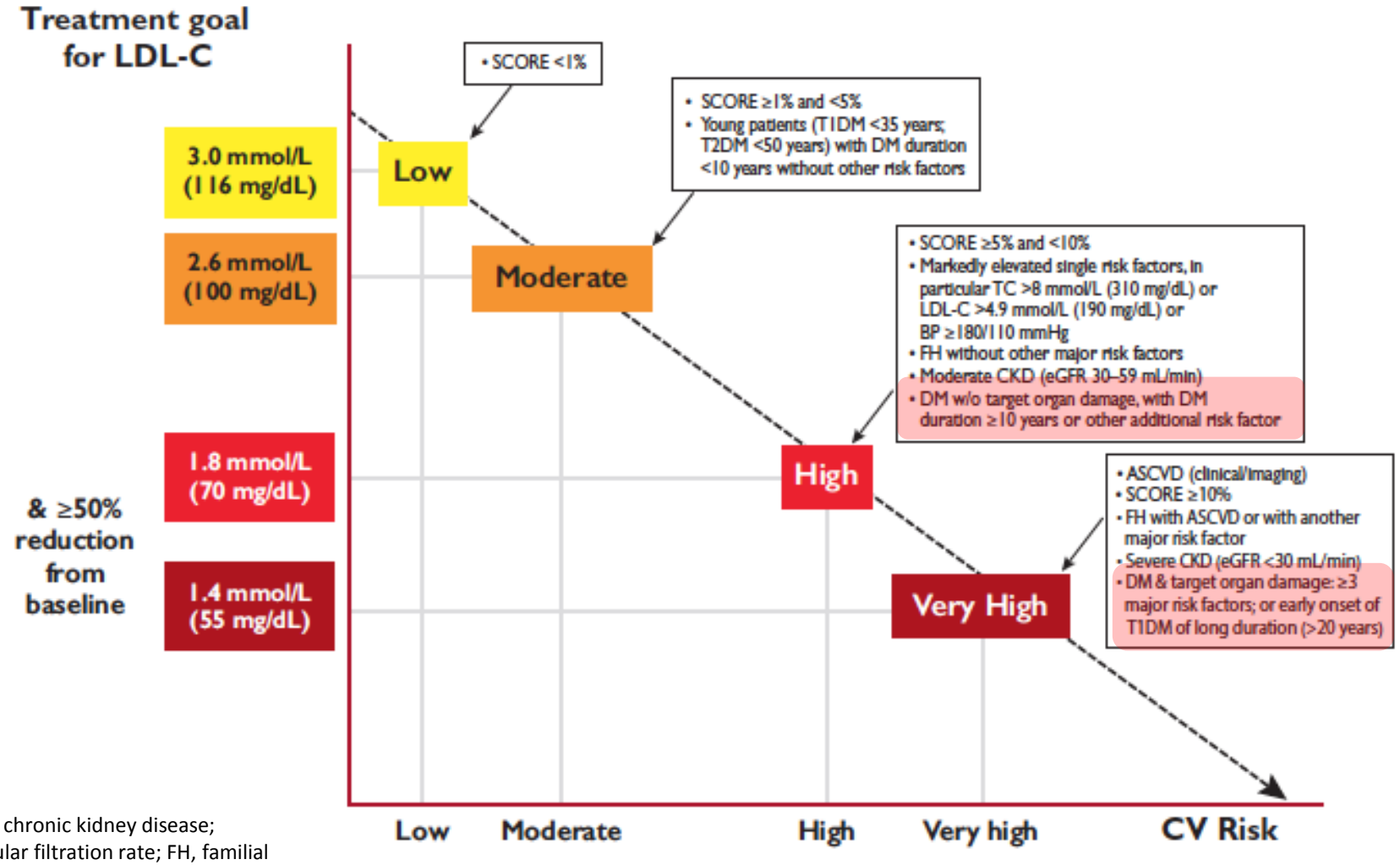
SEA, Spanish Society of Arteriosclerosis

2019 ESC/EAS dyslipidemia guidelines: treatment goal for LDL-C across CV risk categories



BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolaemia

Mach F, *et al*. *European Heart Journal*. 2019;00:1–78.

2019 ESC/EAS dyslipidemia guidelines: recommendations for the management of dyslipidaemia with lipid-lowering drugs

Recommendations	Class[a]	Level[b]
It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk.	I	A
If the goals[c] are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.	I	B
For primary prevention patients at very-high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered.	IIb	C
For secondary prevention, patients at very-high risk not achieving their goal[c] on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	A
For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal[c] on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered.	IIa	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may also be considered.	IIb	C
If the goal[c] is not achieved, statin combination with a bile acid sequestrant may be considered.	IIb	C

[a]Class of recommendation; [b]Level of evidence; [c]For definitions, see Table 7.

Mach F, *et al*. *European Heart Journal*. 2019;00:1–78.

2019 ESC/EAS dyslipidemia guidelines: recommendations for lipid-lowering therapy in very high-risk patients **with ACS**

Recommendations	Class	Level
In all ACS patients without any contra-indication or definite history of intolerance, it is recommended to initiate or continue high dose statin as early as possible, regardless of initial LDL-C values.	I	A
Lipid levels should be re-evaluated 4–6 weeks after ACS to determine whether a reduction of at least 50% from baseline and goal levels of LDL-C <1.4 mmol/L (<55 mg/dL) have been achieved. Safety issues need to be assessed at this time and statin treatment doses adapted accordingly.	IIa	C
If the LDL-C goal is not achieved after 4–6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended.	I	B

Recommendations	Class	Level
If the LDL-C goal is not achieved after 4–6 weeks despite maximal tolerated statin therapy and ezetimibe, adding a PCSK9 inhibitor is recommended.	I	B
In patients with confirmed statin intolerance or in patients in whom a statin is contra-indicated, ezetimibe should be considered.	IIa	C
For patients who present with an ACS and whose LDL-C levels are not at goal despite already taking a maximally tolerated statin dose and ezetimibe, adding a PCSK9 inhibitor early after the event (if possible, during hospitalization for the ACS event) should be considered.	IIa	C

Mach F, *et al*. *European Heart Journal*. 2019;00:1–78.

Recommendations of the 2019 SEA for the clinical use of PCSK9i

Clinical situation	Conditions	LDL	Recommendation	Evidence level
Familial hypercholesterolaemia				
	Homozygous		Strong	Low
	<4 risk factors (males <30 y/o, females <45 y/o)	**>160**	Strong	Low
	≥4 risk factors	**>130**	Strong	Moderate
	Diabetes	**>100**	Strong	Moderate
	ASCVD	**>70**	Strong	Moderate

Ascaso J, *et al. Clin Invest Arteriosclerosis*. 2019;31(3):128–39.

Recommendations of the 2019 SEA for the clinical use of PCSK9i

Clinical situation	Condition	LDL	Recommendation	Evidence level
Atherosclerotic cardiovascular disease	Stable	>130	Strong	Strong
	Diabetes + 1 risk factor	>100	Strong	Moderate
	ACS (<1 year)	>100	Strong	Moderate
	Lp(a) >50 mg/dL	>100	Strong	Moderate
	More than 2 risk factors	>100	Weak	Low
	Multivessel coronary heart disease	>70	Strong	Moderate
	Peripheral artery disease	>70	Strong	Moderate
	Polyvascular disease (more than one territory)	>70	Strong	Moderate
	Recurrent CHD	>70	Strong	Low
	CKD ≥3 + 1 risk factor	>70	Weak	Low
Primary prevention	Diabetes + CKD >3b	>130	Weak	Low

Ascaso J, *et al. Clin Invest Arteriosclerosis*. 2019;31(3):128–39.

PCSK9 inhibitor use in the real world

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PCSK9i use in Catalonia (Official Register 2016–2019)

Condition	Total (%)
Patients (% women)	983 (41%)
Age (median IQR)	59 (52–66)
Hypertension	501 (51%)
Diabetes	**198 (20.1%)**
Obesity	247 (25.1%)
Smoking	140 (14.2)
ASCVD family history	433 (44%)
CHD	589 60%)
Ischemic stroke	97 (9.9%)
PAD	156 (15.9%)

Condition	Total (%)
LDL-C <100 mg/dL 100–129 130–159 160–190 >190	 66 (6.7%) 252 (25.6%) 295 (30.0%) 167 (17.0%) 203 (20.7%)
FH	493 (49.3%)
Statin Intolerance	445 (45%)
Statin/high-intensity statin (%)	701(71%)/(81%)
+ ezetimibe	677 (92%)
Alirocumab/evolocumab	529 (53.8%)/ 454 (46.2%)

CatSalut. Servei Català de la Salut. Inici. http://catsalut.gencat.cat/ca/inici/.

Conclusions

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Conclusions

There is a need to clearly identify populations with the highest CV risk that may benefit the most from PCSK9 inhibition

The ODYSSEY OUTCOMES and FOURIER sub-analyses in people with diabetes with higher baseline risk have shown similar relative CV risk reduction and greater ARR on primary MACE versus in those without diabetes

- Additional secondary prevention patient populations with high baseline CV risk who benefited from greater ARR in primary MACE with PCSK9 inhibition were: recurrent CVD, recent MI, recurrent MI and PAD for FOURIER and LDL-C>=100 mg/dl, PVD and previous CABG for ODYSSEY OUTCOMES

The 2019 guidelines (ESC/EAS, ESC/EASD) now recommend for very high-risk populations:

- a new LDL-C target of <55 mg/dL
- PCSK9i if target is not achieved on MTD statin and ezetimibe

In real-life clinical practice, the use of PCSK9is remains clearly far from optimal

Recent CVOTs have highlighted efficacy and safety of PCSK9 inhibitors for high CV risk patients

Schwartz G, *et al*. *NEJM.* 2018;379:2097–107;
Sabatine MS, *et al*. *NEJM.* 2017;376(18):1713–23.

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Evaluating the benefit/risk and safety profile of PCSK9 inhibitors: implications in clinical practice

Assistant Professor Ann Marie Navar
Duke University School of Medicine
USA

Disclosures

Professor Ann Marie Navar has consulted and recieved research support from: Amarin, Amgen, Sanofi, Regeneron and Janssen. Consulting from NovoNordisk and AstraZeneca

PCSK9 inhibitors have a similar safety profile compared to placebo except for which of the following:

1. New-onset diabetes
2. HbA1c
3. Local injection-site reactions
4. New-onset diabetes and HbA1c
5. None of the above

VOTE

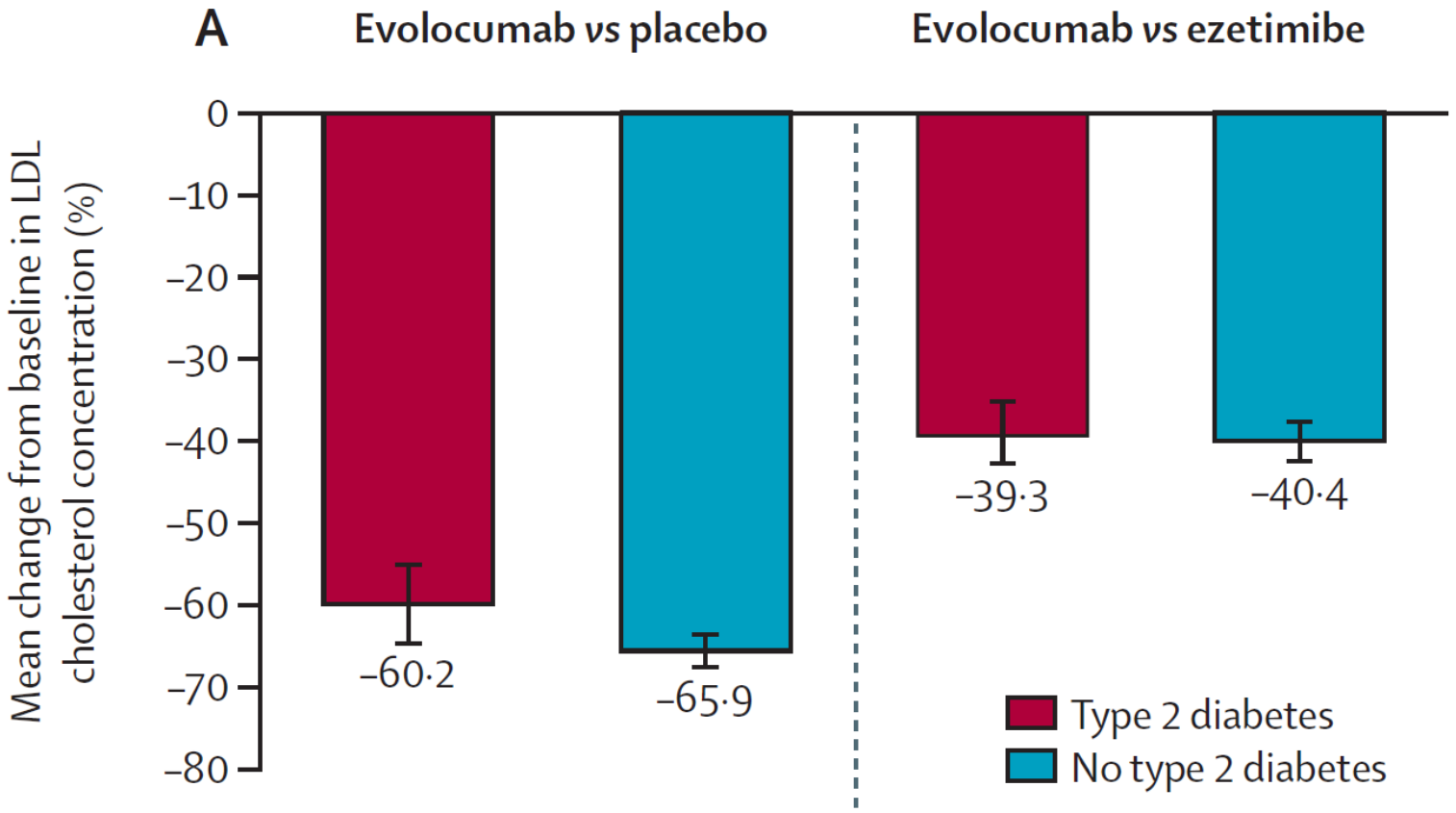
Choose the best option

Evolocumab in individuals with type 2 diabetes

Post-hoc meta-analysis of Phase III trials (12 weeks' duration) comparing the efficacy of evolocumab, placebo and ezetimibe to improve lipid parameters in adult patients with or without type 2 diabetes

Safety: similar frequency of adverse events, in evolocumab vs placebo or ezetimibe in both subpopulations

Changes in lipid concentrations from baseline to 12 weeks with evolocumab relative to placebo or ezetimibe in patients with or without type 2 diabetes*



*N=413 patients with type 2 diabetes and 2,119 patients without type 2 diabetes

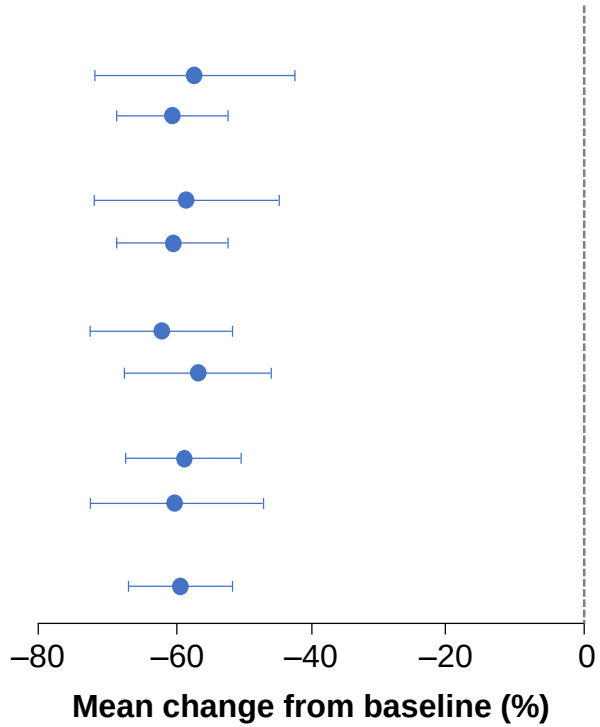
Sattar N, *et al*. *Lancet Diabetes Endocrinol*. 2016;4:403–10.

Evolocumab vs placebo: subgroup analysis in people with T2DM

LDL-C reductions in patients taking evolocumab were comparable at about 50–60% across all diabetes subgroups

Reductions in LDL-C in subgroups of patients with T2DM

	Number of patients		Mean percentage change from baseline (95% CI)
	Evolocumab	Placebo	
Baseline insulin use			
Yes	23	16	–57.4% (–72.0 to –42.8)
No	174	73	–60.5% (–68.8 to –52.2)
History of CVD			
Yes	88	36	–58.6% (–72.2 to –45.0)
No	109	53	–60.5% (–68.4 to –52.5)
Baseline HbA_{1c}			
< median	94	44	–62.1% (–72.4 to –51.7)
≥ median	102	45	–56.8% (–67.4 to –46.1)
Baseline eGFR			
≥ 60 mL/min/1.73 m^2	160	77	–58.9% (–67.3 to –50.4)
< 60 mL/min/1.73 m^2	37	12	–60.1% (–72.9 to –47.3)
Overall	**197**	**89**	**–59.4% (–66.7 to –52.0)**

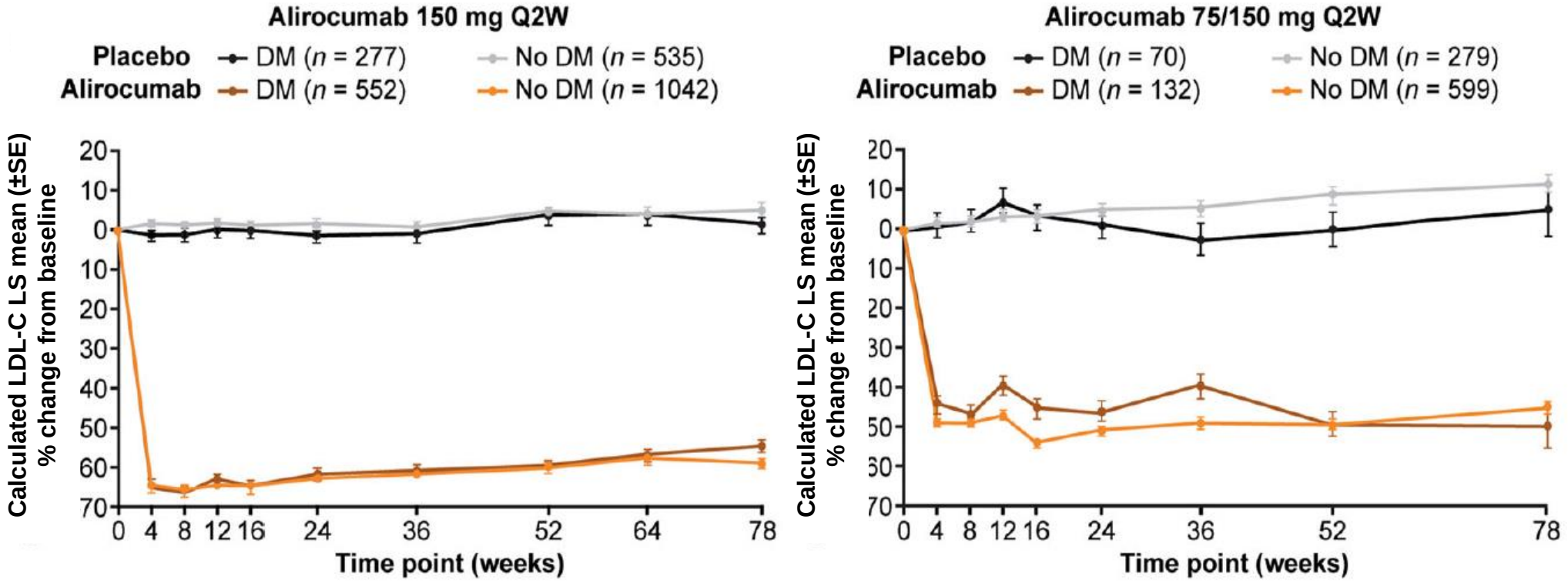


Meta-analysis of Phase III trials (12 weeks' duration) comparing the efficacy of evolocumab, placebo and ezetimibe to improve lipid parameters in adult patients with or without T2DM. N=413 patients with T2DM and 2,119 patients without T2DM. Error bars show 95% CIs.

Sattar N, *et al*. *Lancet Diabetes Endocrinol*. 2016;4:403–10.

Similar reduction of LDL-C with alirocumab in DM vs non-DM

Pooled analysis of five Phase III trials in ODYSSEY programme

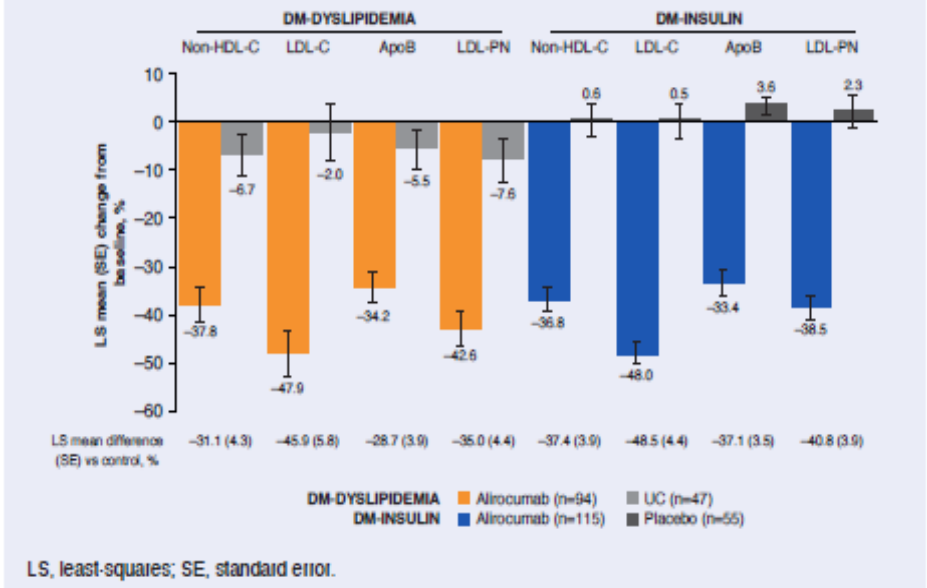


Assessment of alirocumab efficacy and safety in people with/without DM from five placebo-controlled ODYSSEY Phase III studies (data from up to 78 weeks analysed in individuals on maximally tolerated background statin, three studies with alirocumab 75/150 mg Q2W, two studies with alirocumab 150 mg Q2W. **Primary endpoint**: percentage change in LDL-C from baseline to Week 24.
Adverse event groups were generally comparable in all groups (79.8–82.0%).
Q2W, every 2 weeks

Ginsberg HN, *et al*. *Diabetes Ther*. 2018;9:1317–34.

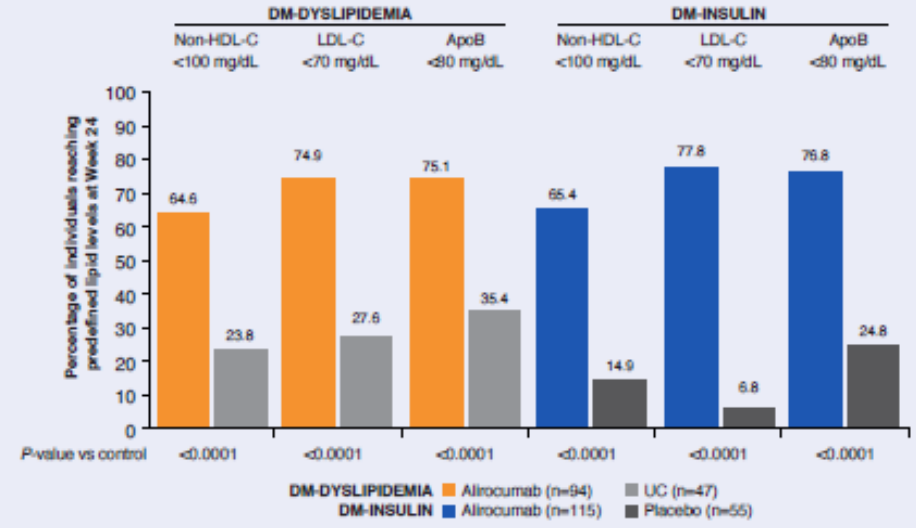
Alirocumab in T2DM and ASCVD: ODYSSEY DM-DYSLIPIDEMIA and DM-INSULIN[1–3]

Figure 1. Percentage change from baseline to Week 24 in non-HDL-C, LDL-C, ApoB, and LDL-PN (ITT analysis)



LS, least-squares; SE, standard error.

Figure 2. Percentage of individuals achieving non-HDL-C <100 mg/dL, LDL-C <70 mg/dL and ApoB <80 mg/dL at Week 24 (ITT analysis)



Non-HDL-C: 100 mg/dL = 2.59 mmol/L; LDL-C: 70 mg/dL = 1.81 mmol/L.

Assessment of efficacy and safety of alirocumab in individuals with T2DM, high LDL-C, or non–HDL-C, and established ASCVD receiving MTD.

Safety: 66.7% (alirocumab) and 67.3% (control) of individuals reported adverse events, similar adverse event pattern in both groups.

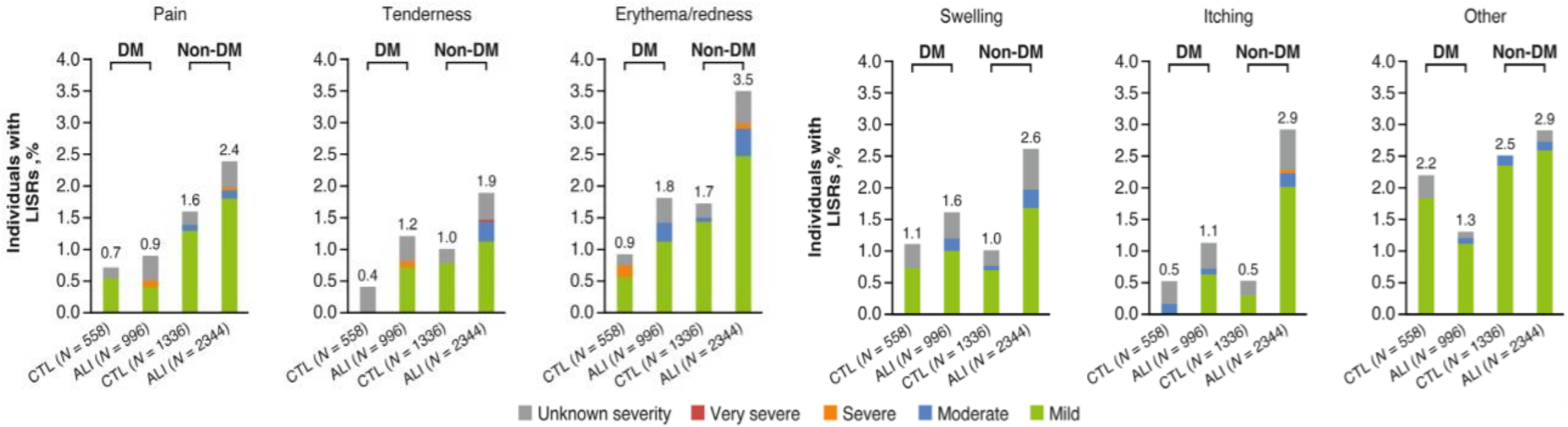
Individuals with ASCVD and T1DM enrolled in ODYSSEY DM-INSULIN not included in analysis due low number of individuals in this group (alirocumab: n=11; placebo: n=5)

In ODYSSEY DM-DYSLIPIDEMIA, alirocumab significantly reduced non–HDL-C (primary endpoint) and LDL-C vs UC in individuals with T2DM and mixed dyslipidemia on maximally tolerated statin (p<0.0001)[2]. In ODYSSEY DM-INSULIN, alirocumab treatment resulted in insignificant LDL-C reductions in insulin-treated individuals with T2DM and T1DM (p<0.0001)[3]. ITT, intention-to-treat

1. Ray KK, *et al*. Presented at the XVIII[th] International Symposium on Atherosclerosis, June 9–12, 2018, Toronto, Ontario, Canada;
2. Ray KK, *et al*. *Diabetes Obes Metab.* 2018;20(6):1479–89;
3. Leiter LA, *et al*. *Diabetes Obes Metab.* 2017;19(12):1781–92.

Alirocumab safety in diabetes

Comparison of LISRs according to diabetes status



- Pooled data from 14 ODYSSEY trials, N=5234 trial participants, 29.7% (N=1554) with DM
- Overall, treatment-emergent adverse events similar in alirocumab vs control groups, except for more frequent local injection-site reactions with alirocumab
- **Less LISRs in DM [HR 1.24 (95% CI 0.68–2.25)] vs non-DM [HR 1.51 (95% CI 1.13–2.01)]**

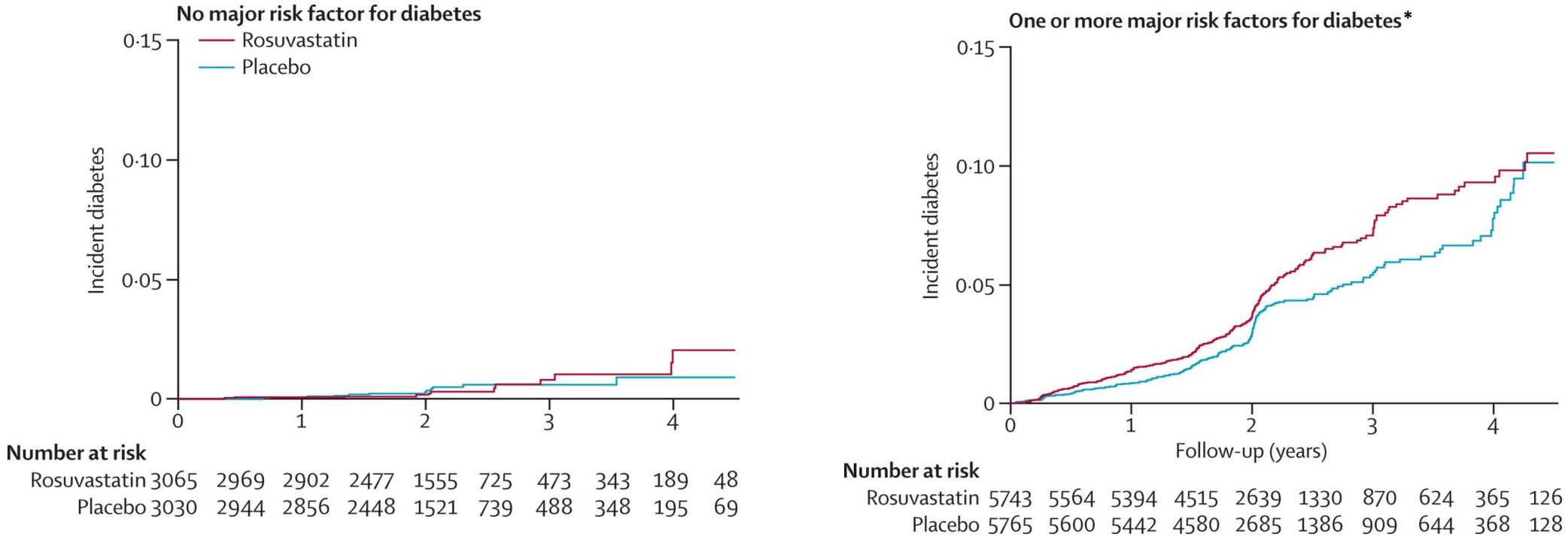
In DM, greater number of serious adverse events ([ALI, 19.4%; CTL, 19.7%] vs non-DM [ALI, 14.5%; CTL, 13.5%]).
No increase in HbA_{1c} or fasting plasma glucose vs control treatment groups observed, regardless of diabetes status.
CTL, control; LISR, local injection-site reaction

Leiter LA, *et al. Diabet Med.* 2018;35:1742–51.

Statin–diabetes link well documented

Statins increase risk of T2DM: JUPITER trial

Cumulative incidence of diabetes among those with and without major risk factors for diabetes.



JUPITER trial: 17,603 individuals without prior CVD or DM randomly allocated to rosuvastatin 20 mg or placebo and followed for up to 5 years for the trial primary endpoint (MI, stroke, hospitalisation for UA, arterial revascularisation or CV death). *metabolic syndrome, impaired fasting glucose, body mass index >30 kg/m2, or HbA1c > 6 percent.
CVD, cardiovascular disease; CV, cardiovascular; MI, myocardial infarction; T2DM, type 2 DM; UA, unstable angina

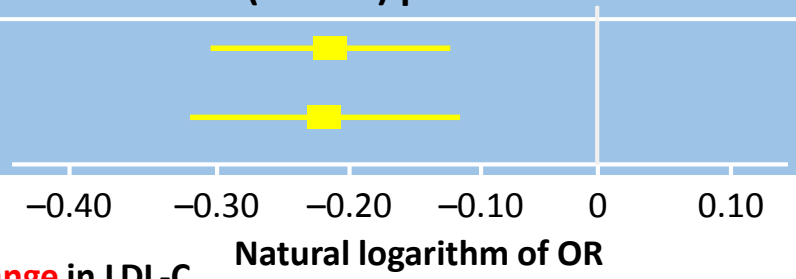
Ridker PM, *et al. Lancet.* 2012;380(9841):566–71.

Recent Mendelian randomisation studies suggest a potential link between genetic PCSK9 deficiency and the risk of diabetes

112,772 participants (14 trials); 14,120 CV events, 10,635 cases of DM

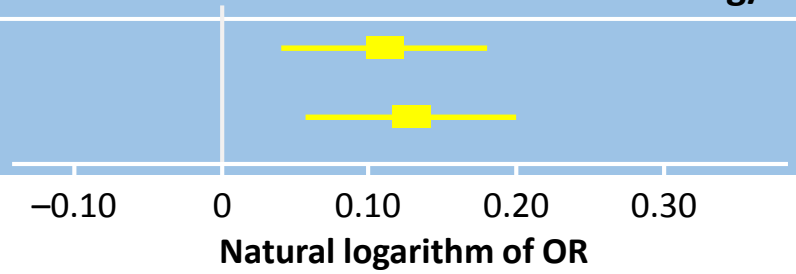
Effect of *PCSK9* and *HMGCR* scores on risk of MI or death from CHD per unit change in LDL-C

	Standardised difference in LDL-C (mg/dL)	OR for myocardial infarction or death from CHD (95% CI) per decrease in LDL-C of 10 mg/dL
PCSK9 genetic score	–10.0	0.81 (0.74–0.89)
HMGCR genetic score	–10.0	0.81 (0.72–0.90)



Effect of *PCSK9* and *HMGCR* scores on risk of diabetes per unit change in LDL-C

	Standardised difference in LDL-C (mg/dL)	OR for diabetes (95% CI) per decrease in LDL-C of 10 mg/dL
PCSK9 genetic score	–10.0	1.11 (1.04–1.19)
HMGCR genetic score	–10.0	1.13 (1.06–1.20)



Variants in *PCSK9* and *HMGCR* associated with protective effects on CV risk and potential risk of diabetes. Authors highlighted that monoclonal PCSK9 antibodies bind to extra-cellular PCSK9 => therefore may not have same biological effect as *PCSK9* genetic variants that lower LDL-C

OR, odds ratio

Ference BA, *et al*. *NEJM*. 2016;375:2144–53.

Analysis of transition to NODM in Phase III PCSK9i trials in patients without DM at baseline

In a pooled analysis of 10 Phase III ODYSSEY trials:

- No evidence was found that alirocumab affects incidence of NODM (n=3,448; follow-up 6–18 months)[1]

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo (n=818)	Alirocumab (n=1620)	Ezetimibe (n=428)	Alirocumab (n=582)
Transition from baseline pre-diabetes to new-onset diabetes†				
% (n)	10.4 (47)	9.3 (84)	5.5 (14)	7.2 (26)
HR versus control (95% CI)	0.90 (0.63–1.29)		1.10 (0.57–2.12)	
Transition from baseline normoglycemic to pre-diabetes				
% (n)	31.5 (115)	36.4 (261)	24.1 (42)	26.5 (59)
HR versus control (95% CI)	1.20 (0.96–1.49)		0.88 (0.59–1.32)	

In CVOT trials with PCSK9i:

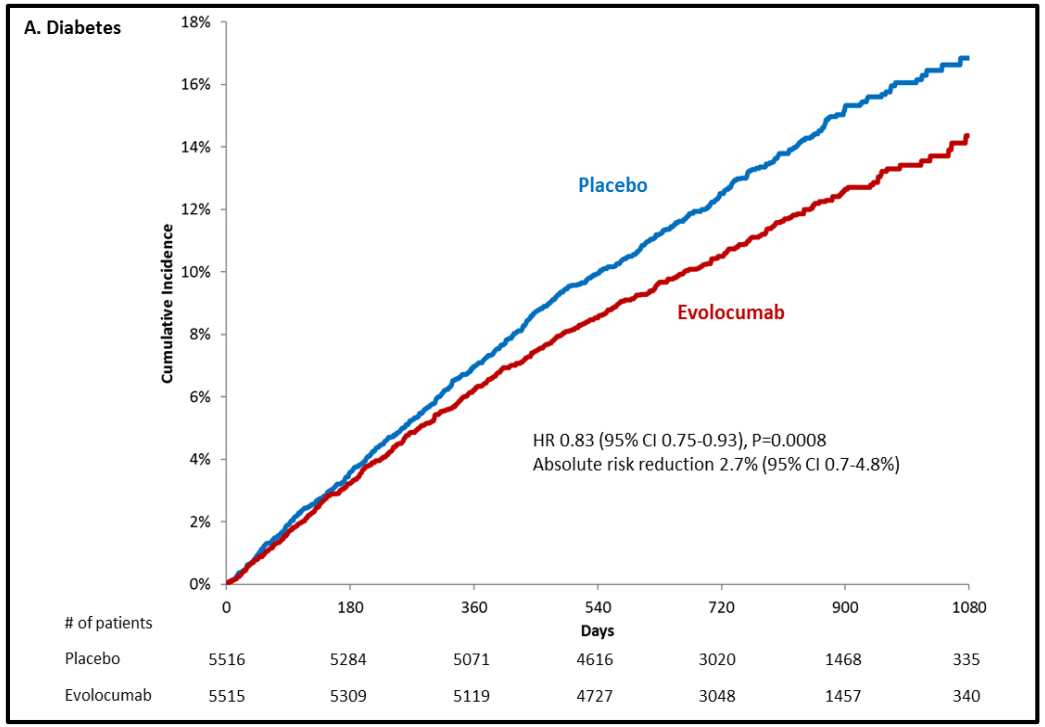
- Overall incidence of NODM did not differ between placebo and evolocumab in FOURIER trial (median follow-up 2.2 years); HR 1.05 (95% CI, 0.94–1.17)[2]
- No impact of alirocumab on NODM in 13,480 patients without DM in ODYSSEY OUTCOMES study (median follow-up 2.8 years); HR 1.00 (95% CI 0.89–1.11)[3]

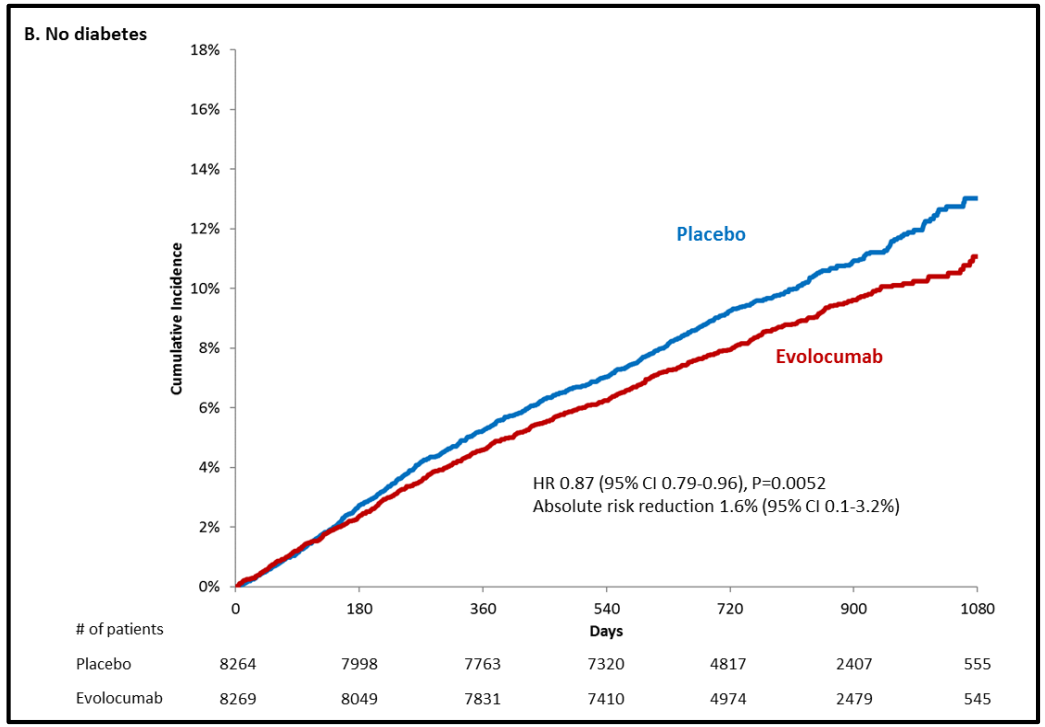
*NODM assessed by adverse event or laboratory parameters.

1. Colhoun HM, *et al*. *Eur Heart J*. 2016;37:2981–89; 2. Sabatine MS, *et al*. *Lancet Diabetes Endocrinol*. 2017;5:9141–50; 3. Schwartz GG, *et al*. *N Engl J Med.* 2018;279:2097–107.

FOURIER: evolocumab efficacy in DM

Primary MACE





- 40% (n=11,031) with diabetes at baseline
  - HR 0.83 with diabetes; HR 0.87 without diabetes (p-interaction DM vs non-DM = 0.60)

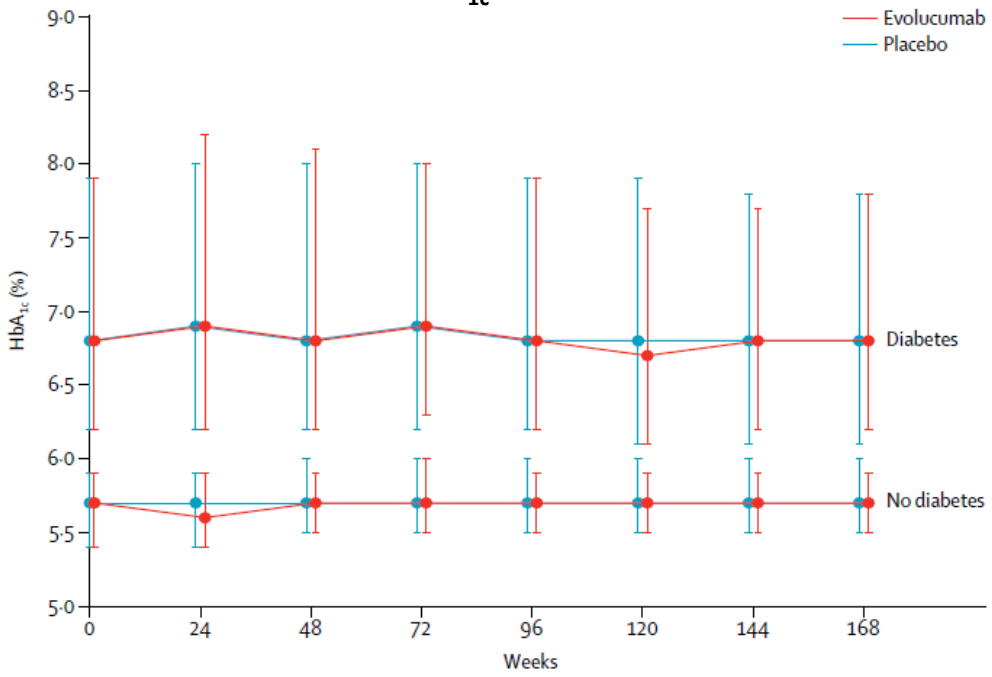
Study design of FOURIER shown in Professor Colhoun's presentation.

Sabatine MS, *et al*. *Lancet Diabetes Endocrinol.* 2017;5:941–51.

FOURIER: glycaemic parameters and NOD

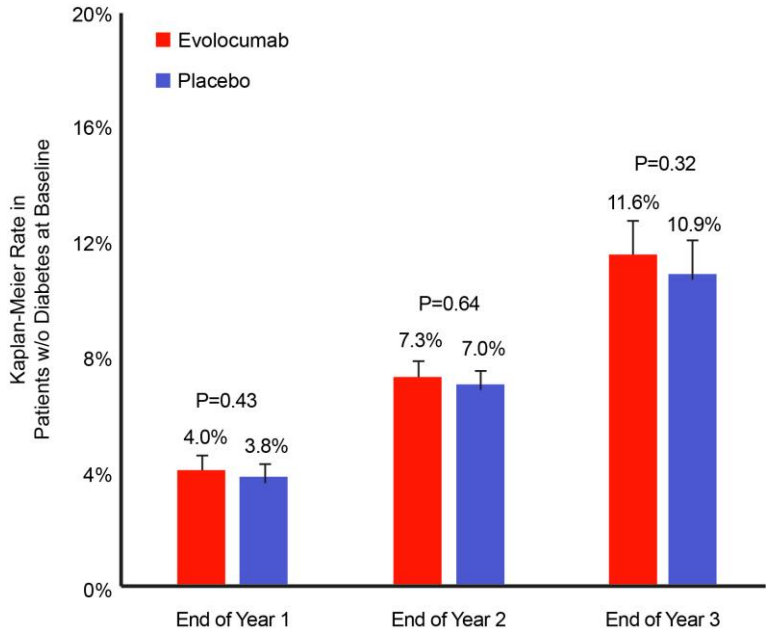
No impact on glycaemic parameters in individuals with DM and pre-DM

HbA_{1c} over time



Overall, evolocumab did not increase risk of NODM in participants without DM at baseline: HR 1.05 (95% CI 0.94–1.17)

Cumulative incidence of NODM at end of 1, 2 and 3 years of follow-up (in evolocumab and placebo) among patients without DM at baseline



Conversion to diabetes on other subgroups: post-hoc analyses:

- Pre-DM: in evolocumab vs placebo group, HR 95% CI 1.00 (0.89–1.13)
- Normoglycaemia: in evolocumab vs placebo, HR 95% CI 1.60 (1.13–2.28)

Sabatine MS, *et al*. *Lancet Diabetes Endocrinol.* 2017;5:941–51.

Evolocumab safety in FOURIER

AE and laboratory	Evolocumab N=13,769	Placebo N=13,756
Adverse events %		
Any	77.4	77.4
Serious	24.8	24.7
AE related or leading to discontinuation	1.6	1.5
Injection-site reaction*	2.1	1.6
Allergic reaction	3.1	2.9
Muscle-related events	5.0	4.8
Rhabdomyolysis	0.1	0.1
Cataract	1.7	1.8
Adjudicated NODM**	8.1	7.7
Neurocognitive event	1.6	1.5
Laboratory results %		
Aminotransferase >3 ULN	1.8	1.8
CK >5 ULN	0.7	0.7
Antidrug antibodies	0.3	0
Neutralising antibodies	0	0

- Similar safety profile **except injection-site reactions** which were more frequent with evolocumab (2.1% vs 1.6%) p<0.001

**Between-group difference nominally significant p<0.001.*
***Total N=8,337 in evolocumab and 8,339 in placebo.*
AE, adverse event; CK, creatine kinase; ULN, upper limits of normal

Sabatine MS, *et al. NEJM*. 2017;376:1933–42.

ODYSSEY OUTCOMES DM study: similar RRR and greater ARR with alirocumab in the DM population versus placebo

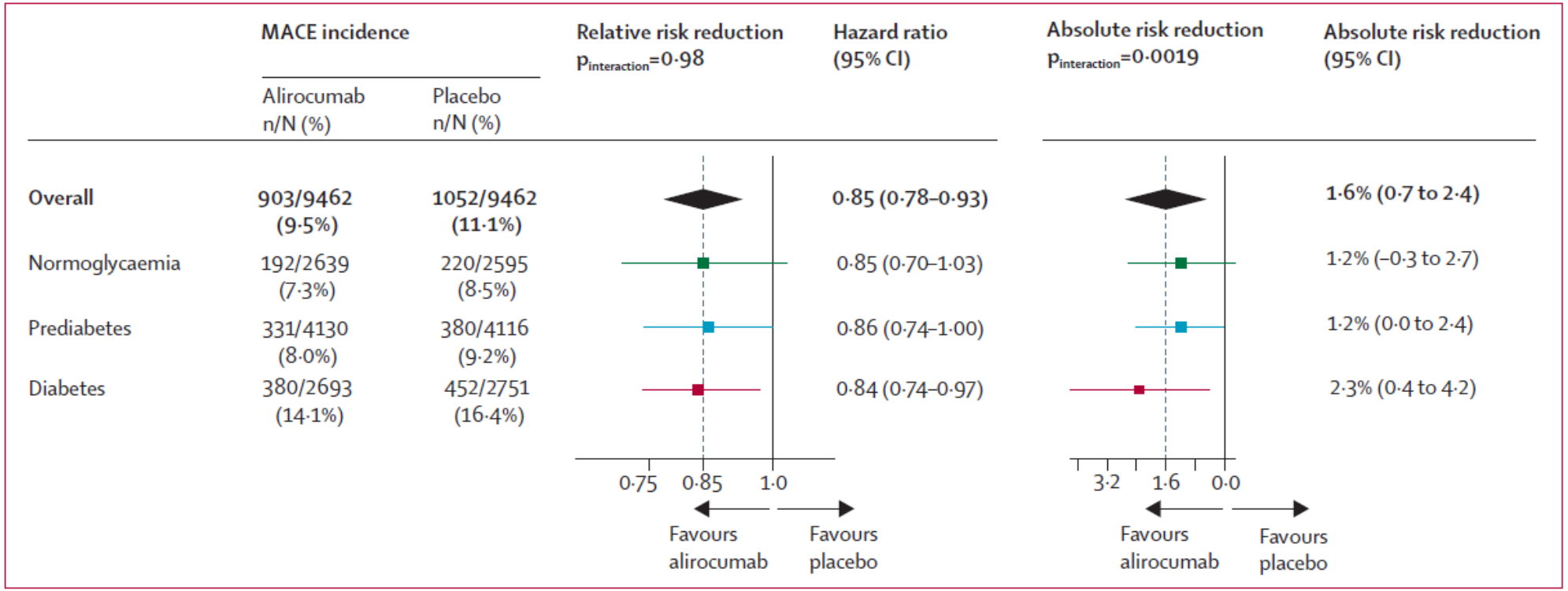
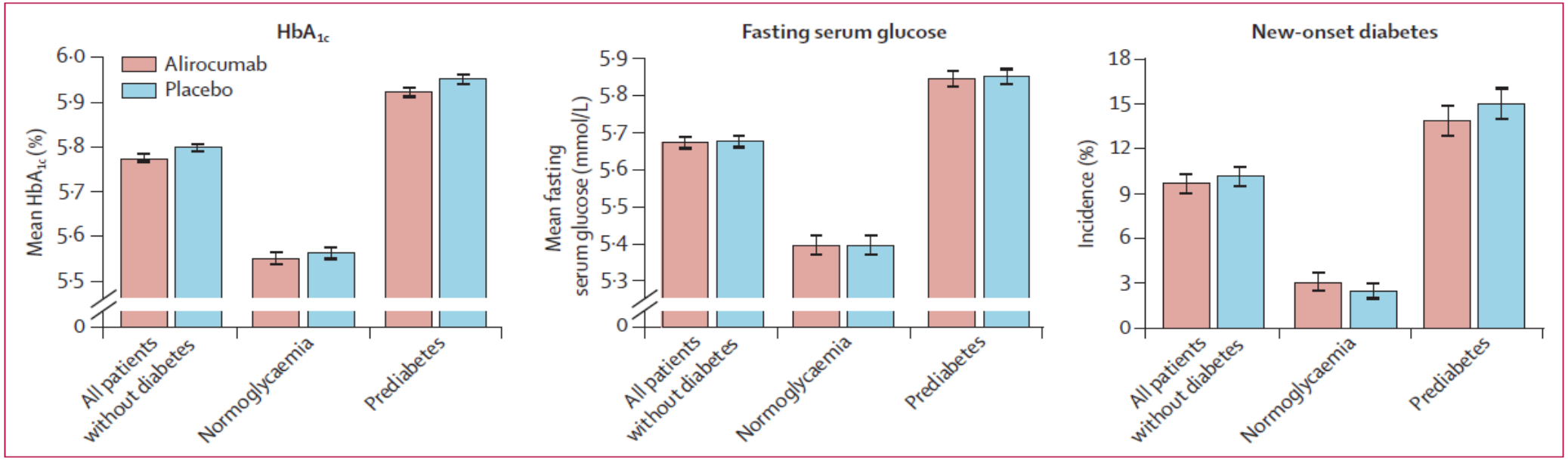


Figure 4: Relative and absolute risk reduction with alirocumab, by baseline glycaemic status

Pre-specified analysis. Study design provided in Professor Colhoun's presentation.
Median (Q1, Q3) follow-up: 2.8 (2.3, 3.4) years.

Ray KK, *et al. Lancet Diabetes Endocrinol.* 2019;7(8):618–28.

ODYSSEY OUTCOMES: no increased risk of DM, change in A_{1c}, glucose



Post-randomisation HbA_{1c}, fasting serum glucose and NOD, by baseline glycaemic status
Error bars: 95% CIs. Only post-randomisation values before DM medication started and included in the analysis

Alirocumab did not adversely affect measures of glycaemia or increase the risk of NOD

Analysis method for A_{1c} and fasting glucose: repeated-measures mixed-effects model; random effects = slope, intercept; fixed effects = treatment, baseline value and time

Ray KK, *et al*. *Lancet Diabetes Endocrinol.* 2019;7(8):618–28.

Alirocumab safety in ODYSSEY OUTCOMES[1]

AE and laboratory	Alirocumab (N=9,451)	Placebo (N=9,443)
Adverse events %		
Any	75.8	77.1
Serious	23.3	24.9
AE leading to death	1.9	2.4
AE leading to discontinuation	3.6	3.4
Injection-site reaction	3.8	2.1
General allergic reaction	7.9	7.8
DM worsening or DM complications*	18.8	21.2
NOD in patients without baseline DM**	9.6	10.1
Neurocognitive event	1.5	1.8
Hepatic disorder	5.3	5.7
Cataract	1.3	1.4
Haemorrhagic stroke (adjudicated)	<0.1	0.2
Laboratory results %		
ALAT >3 ULN	2.3	2.4
ASAT >3 ULN	1.7	1.8
Bilirubin >2 ULN	0.7	0.8
CK >10 ULN	0.5	0.5
Antidrug antibodies	0.7	0.4
Neutralising antibodies	0.5	<0.1

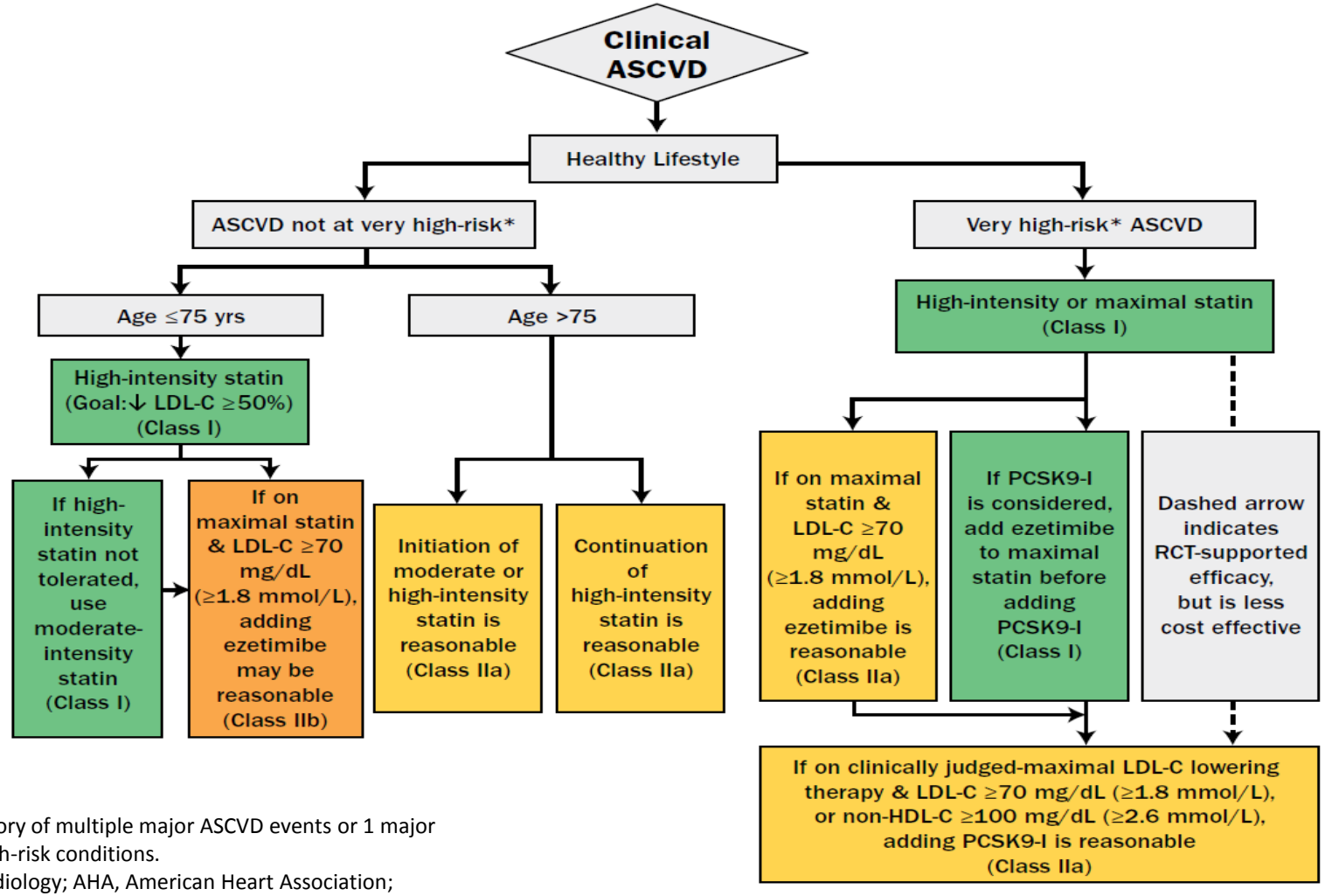
- Similar safety profile **except injection-site reactions** which were more frequent with alirocumab (3.8% vs 2.1%) p<0.001

*In patients with baseline DM; N=2,688 (alirocumab), N=2,747 (placebo)
**N=6,763 (alirocumab), N=6,696 (placebo)

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase

1. Schwartz G, *et al*. *New Eng J Med.* 2018;379:2097–107.

2018 ACC/AHA guidelines: secondary prevention in patients with clinical ASCVD



*Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.
ACC, American College of Cardiology; AHA, American Heart Association; RCT, randomised controlled trial

Grundy SM, *et al*. *J Am Coll Cardiol.* 2019;73(24):e285–e350.

2018 ACC/AHA guidelines: focus on new 'very high-risk' group in secondary prevention

Clinical ASCVD

Healthy lifestyle

Very high-risk ASCVD
Includes history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions

- **High-intensity statin therapy** is indicated for clinical ASCVD
- **Patients at very high risk** of future ASCVD events **have multiple high-risk clinical factors**
- **If very high risk and LDL-C ≥70 mg/dL** on maximally tolerated statin, **non-statin therapy** should be considered

Major ASCVD events

- Recent ACS (within past 12 months)
- History of MI (other than recent ACS event listed above)
- History of ischemic stroke
- Symptomatic PAD (history of claudication with ABI <0.85, or previous revascularisation or amputation)

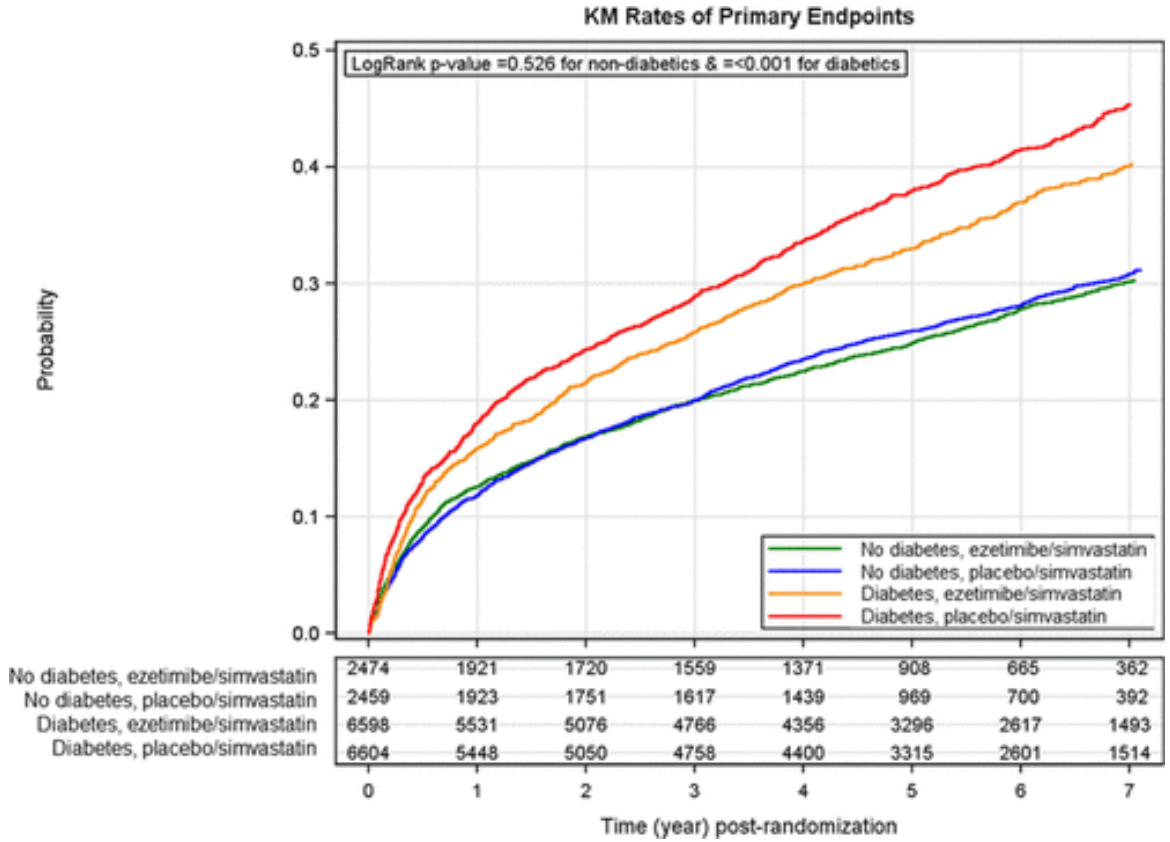
High-risk conditions

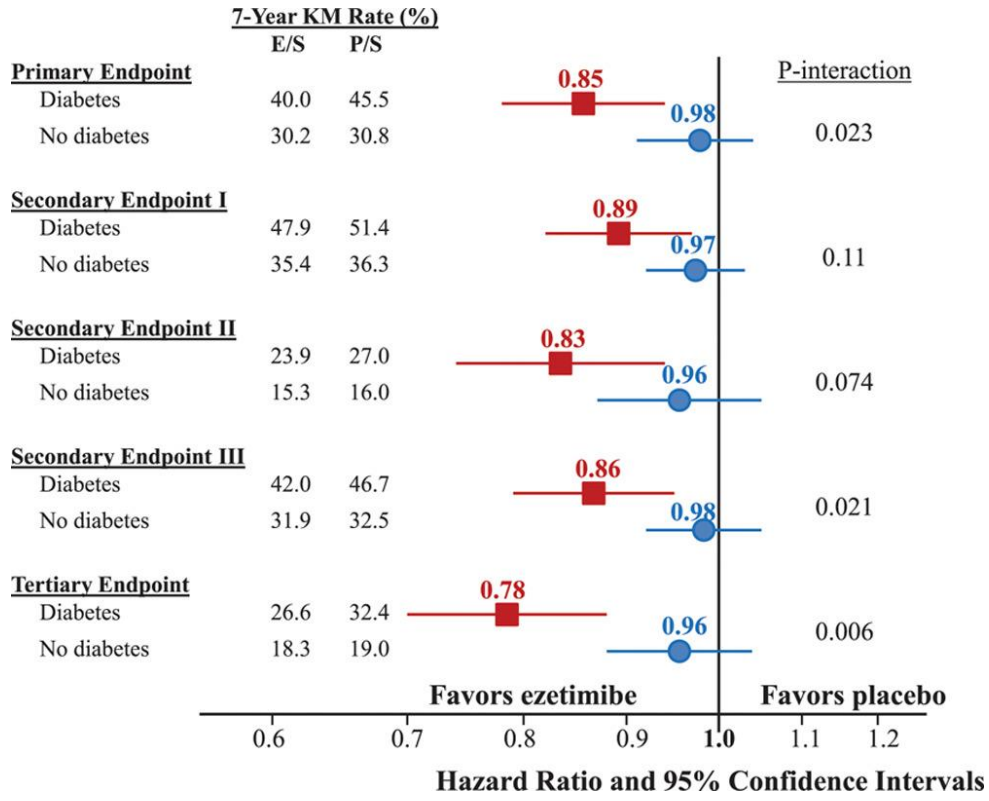
- Age ≥65 years
- HeFH
- Prior CABG or PCI outside of the major ASCVD event(s)
- DM
- Hypertension
- CKD (eGFR 15–59 mL/min/1.73 m^2)
- Currently smoking
- Persistent LDL-C ≥100 mg/dL (≥ 2.6 mmol/L) despite maximally tolerated statin therapy and ezetimibe
- History of congestive HF

*Symptomatic PAD indicates history of claudication with ABI <0.85, or previous revascularisation or amputation.
ABI, ankle–brachial index; HeFH, heterozygous familial hypercholesterolaemia; HF, heart failure; PCI, percutaneous coronary intervention

Grundy SM, *et al*. *J Am Coll Cardiol.* 2019;73(24):e285–e350.

Ezetimibe in diabetes: IMPROVE-IT





IMPROVE-IT: 18,144 patients after ACS with LDL-C, 50–125 mg/dL randomised to 40 mg ezetimibe/simvastatin (E/S) or 40 mg placebo/simvastatin (P/S). **Primary endpoint:** CV death, major coronary events and stroke (DM prespecified subgroup). Rates of prespecified safety events of special interest similar between E/S and P/S, irrespective of DM status, with possible exception of haemorrhagic stroke (DM: 0.9% with E/S versus 0.4% with P/S (p=0.023); however, p-interaction not statistically significant (p=0.092).

Guigliano RP, *et al. Circulation*. 2018;137(15):1571–82.

2019 ESC/EAS dyslipidemia guidelines

Recommendations for pharmacological LDL-C lowering

Recommendations	Class[a]	Level[b]
It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk.	I	A
If the goals[c] are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.	I	B
For primary prevention patients at very-high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered.	IIb	C
For secondary prevention, patients at very-high risk not achieving their goal[c] on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	A
For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal[c] on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered.	IIa	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may also be considered.	IIb	C
If the goal[c] is not achieved, statin combination with a bile acid sequestrant may be considered.	IIb	C

Recommendations for lipid-lowering therapy in very high-risk patients with ACS

Recommendations	Class	Level
If the LDL-C goal is not achieved after 4–6 weeks despite maximal tolerated statin therapy and ezetimibe, adding a PCSK9 inhibitor is recommended.	I	B
In patients with confirmed statin intolerance or in patients in whom a statin is contra-indicated, ezetimibe should be considered.	IIa	C
For patients who present with an ACS and whose LDL-C levels are not at goal despite already taking a maximally tolerated statin dose and ezetimibe, adding a PCSK9 inhibitor early after the event (if possible, during hospitalization for the ACS event) should be considered.	IIa	C

Mach F, *et al*. *Eur Heart J*. 2019;00:1–78.

How can we use PCSK9 inhibition most effectively in patients with established ASCVD, recent ACS?

- **Clinical studies demonstrated that PCSK9 inhibitors (evolocumab in stable ASCVD and alirocumab in recent ACS) significantly reduced CV risk in people with, and without, diabetes:[1,2]**
  - Without adversely affecting measures of glycaemic parameters
  - Without increasing the risk of new-onset DM in patients with no diabetes at baseline
- **Higher absolute CV risk associated with higher* absolute CV benefit on primary MACE in the following subpopulations:**

FOURIER[1]	ODYSSEY OUTCOMES[6]
DM[2,3]	
PAD[4]	LDL-C >100 mg/dL[6]
Recent MI[5]	PVD[7]
Multivessel CAD[5]	CABG[8]

*Higher absolute risk in comparison to other subgroups. **PAD, recent MI, >2 prior MI and multivessel CAD presented in Professor Masana's presentation.**
PVD, peripheral vascular disease

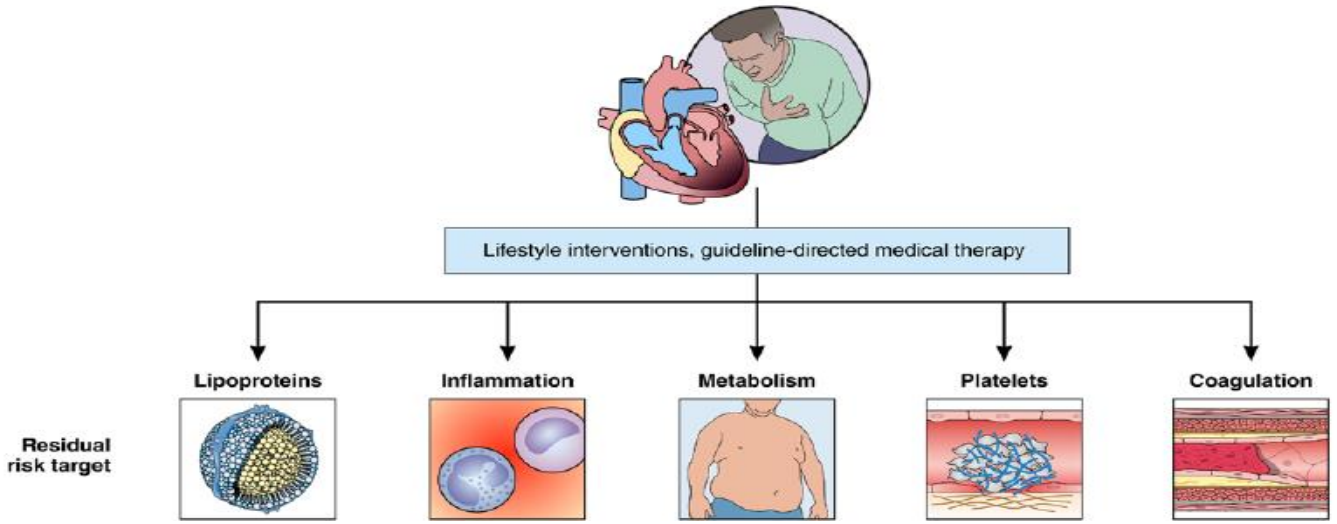
1. Sabatine MS, et al. NEJM. 2017;376:1933–42; 2. Sabatine MS, *et al. Lancet Diabetes Endocrinol.* 2017;5:9141–50; 3. Ray KK, *et al. Lancet Diabetes Endocrinol.* 2019;7(8):618–28; 4. Bonaca MP, *et al. Circulation.* 2018;137:338–50; 5. Sabatine MS, *et al. Circulation.* 2018;138(8):756–66; 6. Schwartz GG, *et al. NEJM.* 2018;279:2097–107; 7. Jukema JW,*et al. JACC.* 2019 [Epub ahead of print]; 8. Goodman SG, *et al.* Poster presentation at the American College of Cardiology, March 16–18, 2019. Poster number: 1045-07.

My approach to lipids in DM + CVD

- **<u>Start with a high-intensity statin</u>**
  - Consider immediate initiation of statin + ezetimibe if LDL↑↑↑ to shorten time to goal
- If LDL-C is above goal, add ezetimibe, then add PCSK9i
  - If LDL-C <30 mg/dL, may stop ezetimibe to prevent polypharmacy
- If LDL-C >100 mg/dL, unlikely to reach target on ezetimibe alone
  - Consider PCSK9i before ezetimibe
- If TGs ≥135 mg/dL after treatment of secondary causes,* add icosapent ethyl

*Secondary causes could include excessive alcohol intake, untreated diabetes, endocrine conditions, renal or liver disease, pregnancy, autoimmune disorders and use of certain medications.

Multiple therapeutic targets for residual risk in T2DM and CVD: patient-centred decision-making



Adapted from: Patel KV, *et al*. *Circulation.* 2018;137:2551–53.

Multiple options for CV risk reduction beyond 'the basics'

- Aspirin, statin, beta blocker, ACE inhibitor, P2Y12 inhibitor
- PCSK9i, ezetimibe, rivaroxaban, icosapent ethyl, SGLT2i, GLP1-RA

Factors to consider

- A_{1c} control → SGLT2i, GLP1-RA lower A_{1c} in addition to CV risk reduction
- Preferred administration route → SC vs PO choice
- Price → out-of-pocket costs impact adherence/ persistence
- Preferences → risks of therapies (bleeding, atrial fibrillation, infections)
- Comorbidities → heart failure, diabetic kidney disease

ACE, angiotensin-converting enzyme; GLP1-RA, glucagon-like peptide 1 receptor agonist; PO, oral; SC, subcutaneous; SGLT2i, sodium-glucose co-transporter 2 inhibitor

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Cosentino F, *et al*. *Eur Heart J.* 2019;00:1–69.

Question and answer/panel discussion

All panellists

Alirocumab new EU indication: approved to reduce CV risk in adult patients with established ASCVD*

***Indicated in adults with established ASCVD to reduce CV risk by lowering LDL-C levels, as an adjunct to correction of other risk factors, and in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidemia, as an adjunct to diet: in combination with the maximum-tolerated dose of a statin with or without other lipid-lowering therapies, or alone, or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.**

Primary hypercholesterolaemia and mixed dyslipidemia (previous lipid indication): in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidemia, as an adjunct to diet: in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum-tolerated dose of a statin, or alone, or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom a statin is contra-indicated.

Sanofi and Regeneron. Alirocumab EU Summary of Product Characteristics, March 2019.

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Conclusion and key take-away messages

Professor Luis Masana (Chair)
University of Rovira i Virgili, CIBERDEM
Spain

Conclusions and key take-away messages

There is a need to clearly identify populations with the highest CV risk that may benefit the most from PCSK9 inhibition

There continues to be a high prevalence (32%) of CVD among people with type 2 diabetes and a high level of unmet need for CV risk factor control, and through improved management of known risk factors, there is substantial scope for reducing the excess risk of CVD in diabetes

Clinical studies demonstrated that PCSK9 inhibitors significantly reduced CV risk in people with, and without, diabetes:

- Without adversely affecting measures of glycaemic parameters
- Without increasing the risk of NOD in patients with no diabetes at baseline

The 2019 guidelines (ESC/EAS, ESC/EASD) now recommend in very high risk populations:

- a new LDL-C target of <55 mg/dL
- PCSK9 inhibitor if target is not achieved on MTD statin and ezetimibe

Evaluation form

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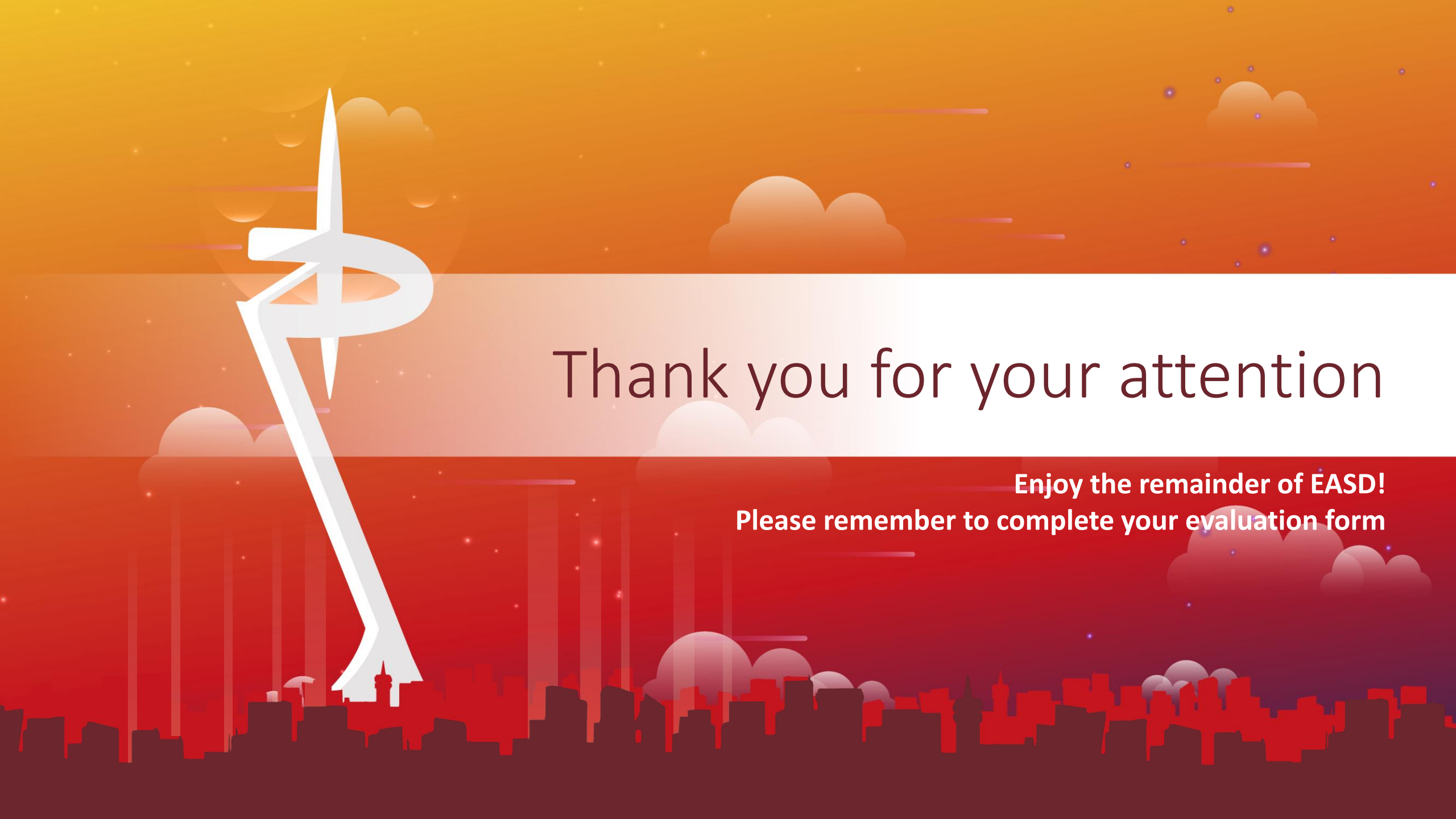
Thank you for your attention
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