Lipid Management in Diabetes
Focus on Recent Advances

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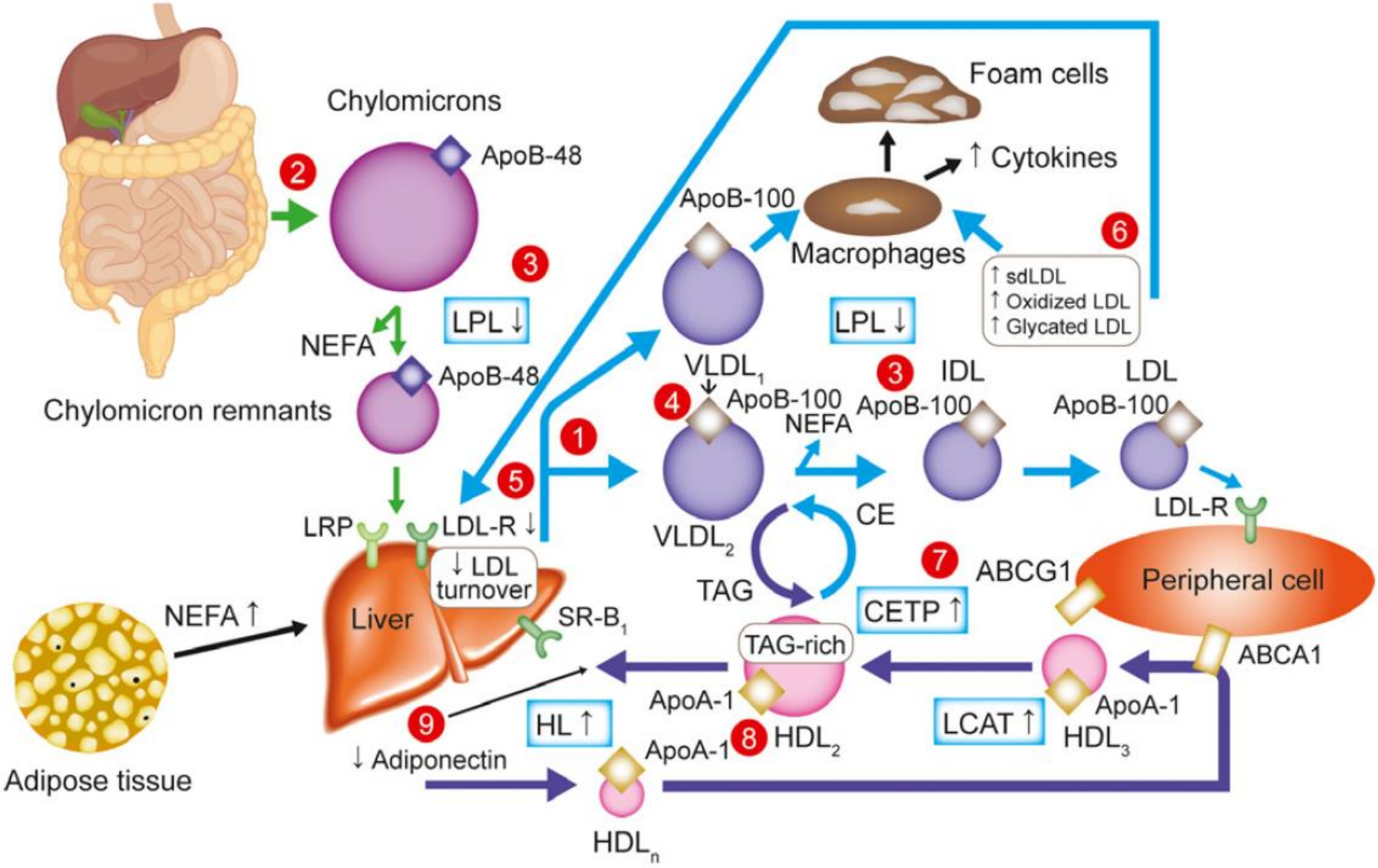
Agenda

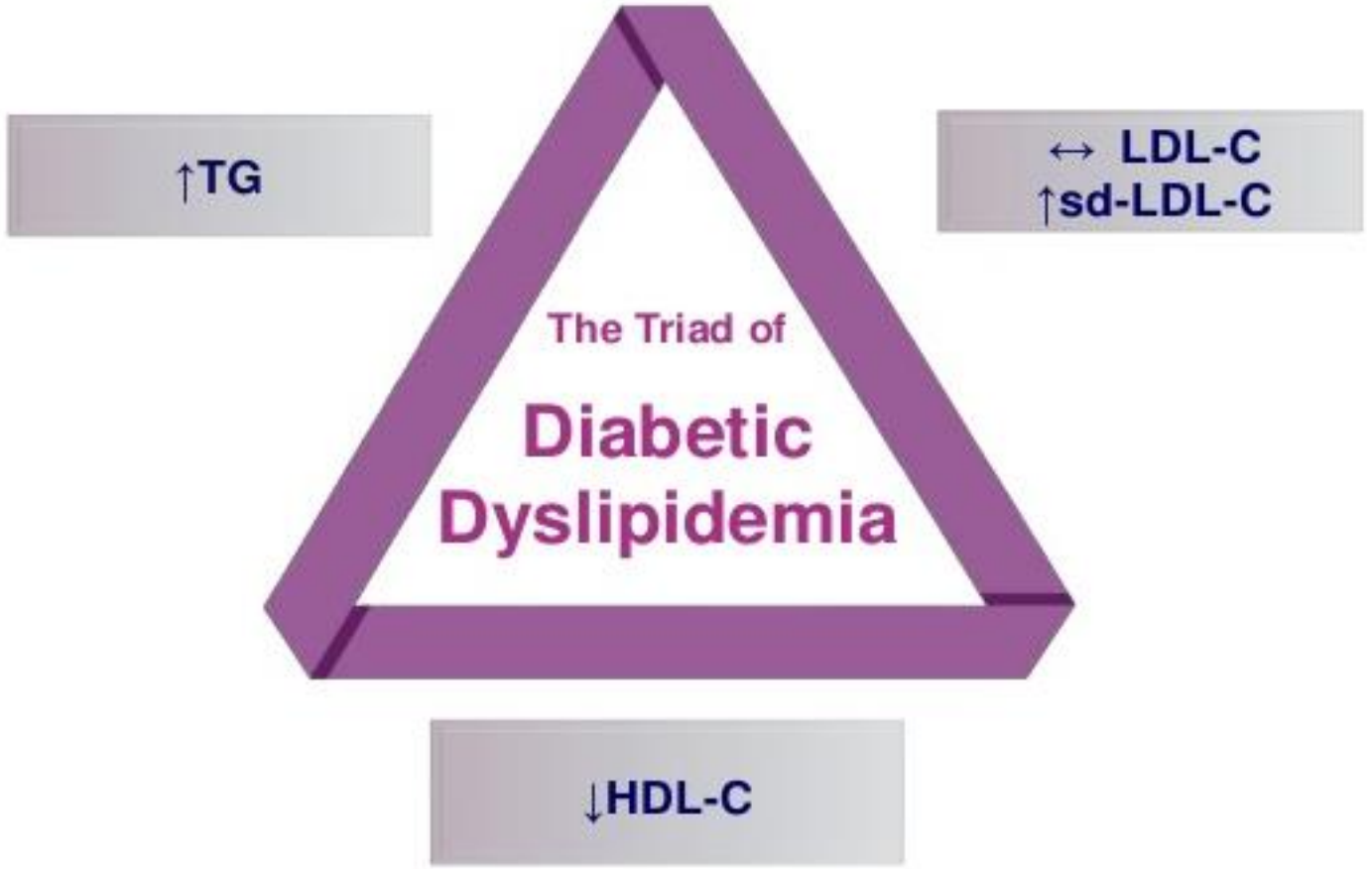
- Introduction
- Statin treatment in diabetes
- Combination therapy for LDL-C lowering in diabetes
  - Ezetimibe
  - PCSK9 inhibitors
- Hypertriglyceridemia in diabetes
- Conclusions

Lipid abnormalities in diabetes



Handelsman Y, et al. J Am Heart Assoc 2018;7:e008953.

Diabetic Dyslipidemia



sd-LDL-C: small dense LDL-C

AMERICAN COLLEGE of CARDIOLOGY

ASCVD Risk Estimator Plus

Estimate Risk | Therapy Impact | Advice

Current Age *

Age must be between 20-79

Sex *

Male | Female

Race *

White | African American | Other

Systolic Blood Pressure (mm Hg) *

Value must be between 90-200

Diastolic Blood Pressure (mm Hg)

Value must be between 60-130

Total Cholesterol (mg/dL) *

Value must be between 130 - 320

HDL Cholesterol (mg/dL) *

Value must be between 20 - 100

LDL Cholesterol (mg/dL)

Value must be between 30-300

History of Diabetes? *

Yes | No

Smoker? *

Current | Former | Never

On Hypertension Treatment? *

Yes | No

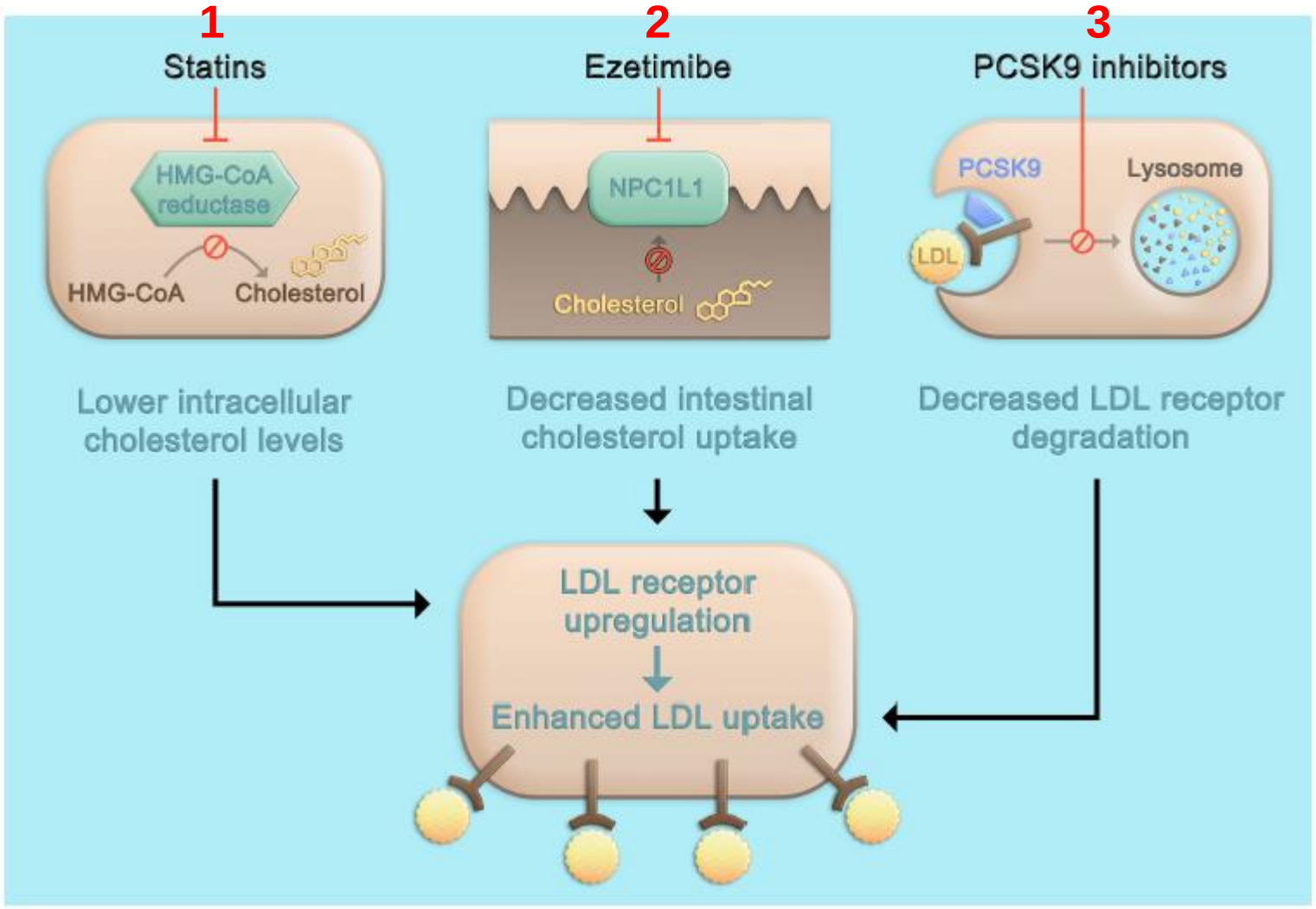
On a Statin?

Yes | No

On Aspirin Therapy?

Yes | No

Pharmacologic approaches to lower LDL-C



Katzmann JL, et al. Front. Physiol 2020;11:595819.

Intensity of lipid lowering treatment

Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30–49%)
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 1–4 mg

*Once-daily dosing. XL, extended release.

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Statin treatment in diabetes

- Patients with ASCVD or LDL-C ≥190 mg/dL:
  - High-intensity statin (A)

- Patients aged 20-39 years:
  - It may be reasonable to initiate statin (C) if any of the following risk factors is present:
    - long duration (≥10 years of type 2 DM, ≥ 20 years of type 1 DM), albuminuria (≥30 mg/g), estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m², retinopathy, neuropathy, ankle-brachial index (ABI) <0.9

ADA-2021 endorsed by ACC.

Statin treatment in diabetes

- Patients aged >75 years:
  - Already on statin therapy:
    - It is reasonable to continue statin treatment. (B)
  - Not on statin therapy:
    - It may be reasonable to initiate statin therapy after discussion of potential benefits and risks. (C)

Statin treatment in diabetes

- Patients aged 40-75 years:
  - Moderate-intensity statin (A)
  - ASCVD risk ≥20% or multiple ASCVD risk factors:
    - High-intensity statin (B)

ADA-2021 endorsed by ACC.

Combination therapy for LDL-C lowering

- Patients with diabetes and very high risk* ASCVD:
  - If LDL-C is ≥70 mg/dL on maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor). (A)
  - Ezetimibe may be preferred due to lower cost.

*Very high-risk of future ASCVD events:

- History of multiple major ASCVD events
- One major ASCVD event and multiple high-risk conditions

ADA-2021 endorsed by ACC.

- **Major ASCVD events:**
  - Recent ACS (within the past 12 months)
  - History of MI (other than recent ACS event listed above)
  - History of ischemic stroke
  - Symptomatic PAD (history of claudication with ankle-brachial index (ABI) < 0.85, or previous revascularization or amputation)
- **High-risk conditions:**
  - Age ≥ 65 y
  - Heterozygous familial hypercholesterolemia
  - History of prior CABG or PCI outside of the major ASCVD event(s)
  - Diabetes mellitus
  - Hypertension
  - Chronic kidney disease (eGFR 15-59 mL/min/1.73 m^2)
  - Current smoking
  - Persistently elevated LDL-C (LDL-C ≥ 100 mg/dL) despite maximally tolerated statin therapy and ezetimibe
  - History of congestive heart failure

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Combination therapy for LDL-C lowering

- Patients with diabetes and 10-year ASCVD risk of ≥20%:
  - It may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL-C levels by ≥50%. (C)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 18, 2015 VOL. 372 NO. 25

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S., Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D., Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D., Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., Paul De Lucca, Ph.D., KyungAh Im, Ph.D., Erin A. Bohula, M.D., D.Phil., Craig Reist, Ph.D., Stephen D. Wiviott, M.D., Andrew M. Tershakovec, M.D., M.P.H., Thomas A. Musliner, M.D., Eugene Braunwald, M.D., and Robert M. Califf, M.D., for the IMPROVE-IT Investigators*

Circulation

ORIGINAL RESEARCH ARTICLE

Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With Versus Without Diabetes Mellitus

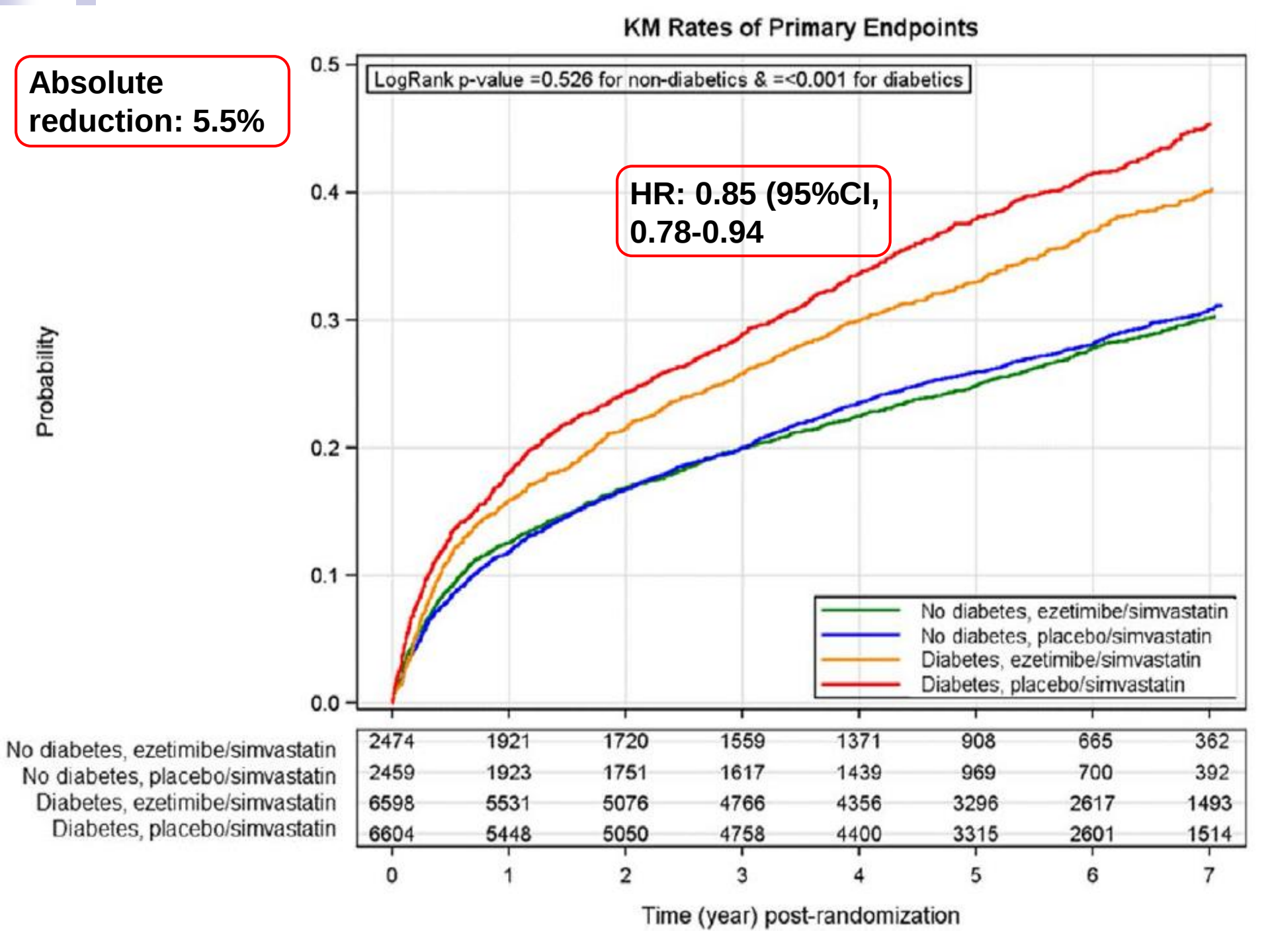
Results From IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)

Prespecified analysis of the IMPROVE-IT

- **Study population:** 18,144 patients after acute coronary syndrome with LDL-C 50 to 125 mg/dL including 4933 (27%) patients with diabetes (mean age: 65 y)
- **Intervention:** 40 mg ezetimibe/simvastatin versus 40 mg placebo/simvastatin
- **Primary end point:** a composite of CV death, major coronary event or stroke
  - Major coronary events: MI, unstable angina requiring hospital admission, coronary revascularization occurring ≥30 days after randomization

Giugliano RP, et al. Circulation 2018;137:1571-1582.

Absolute reduction: 5.5%



Prespecified analysis of the IMPROVE-IT

- **Conclusion**
  - In the IMPROVE-IT, the benefit of adding ezetimibe to statin appeared to be enhanced among patients with diabetes, with no adverse effect in safety.
  - A number needed to treat of 18 to prevent one CVD event over seven years.

Giugliano RP, et al. Circulation 2018;137:1571-1582.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 4, 2017 VOL. 376 NO. 18

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

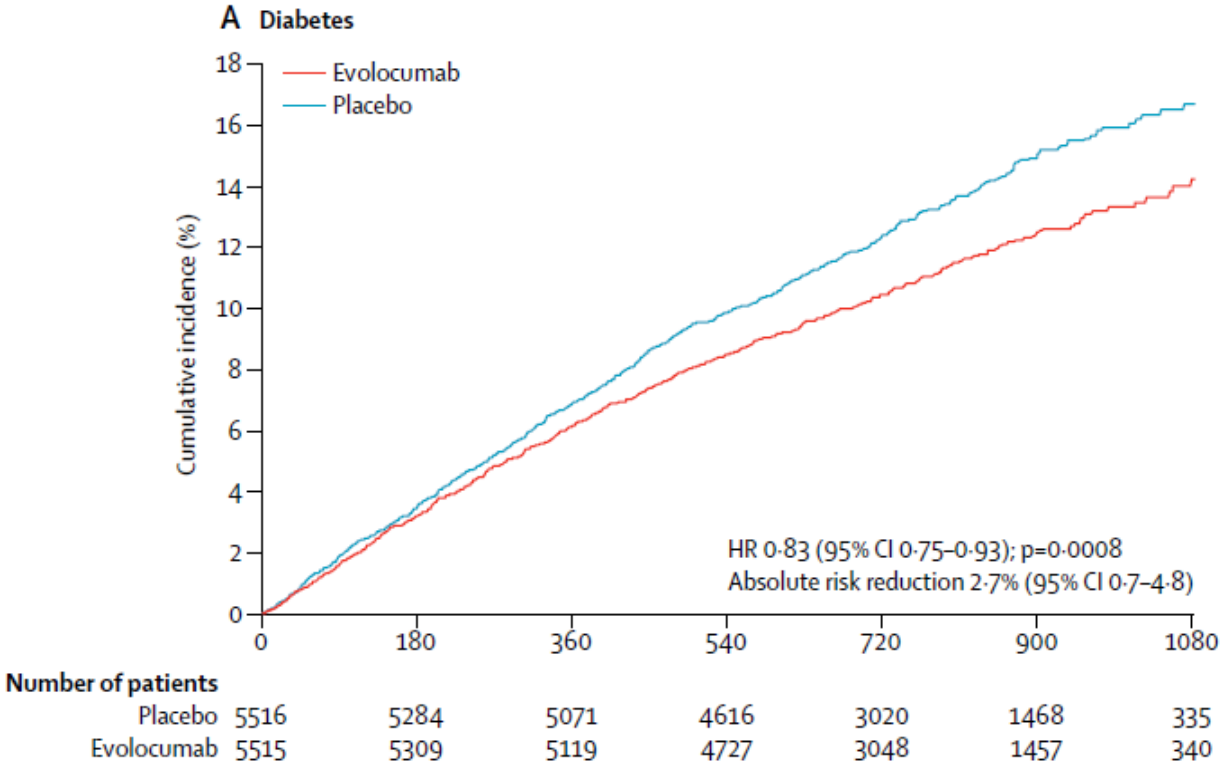
Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial

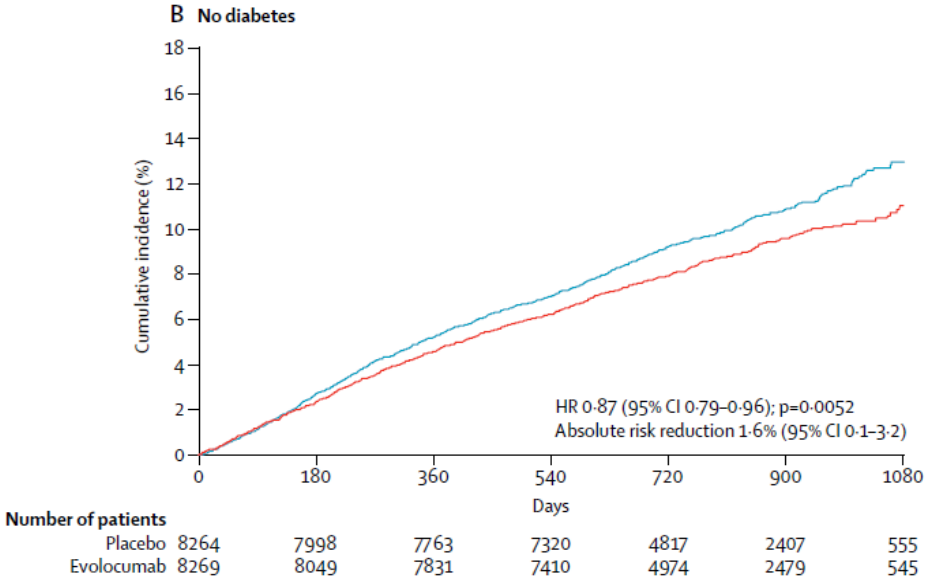
Marc S Sabatine, Lawrence A Leiter, Stephen D Wiviott, Robert P Giugliano, Prakash Deedwania, Gaetano M De Ferrari, Sabina A Murphy, Julia F Kuder, Ioanna Gouni-Berthold, Basil S Lewis, Yehuda Handelsman, Armando Lira Pineda, Narimon Honarpour, Anthony C Keech, Peter S Sever, Terje R Pedersen

Prespecified analysis of the FOURIER

- **Study population:** 27,564 patients with clinically evident ASCVD and additional risk factors with LDL-C ≥70 mg/dL while taking an optimised lipid-lowering regimen including 11,031 (40%) patients with diabetes (mean age: 62 y)
- **Intervention:** evolocumab (140 mg sc q 2 weeks or 420 mg monthly) versus placebo
- **Primary end point:** a composite of CV death, MI, stroke, hospital admission for unstable angina, or coronary revascularisation



Absolute risk reduction: 2.7%



Prespecified analysis of the FOURIER

- **Conclusion**
  - In the FOURIER, evolocumab lowered LDL-C and significantly reduced CV risk with similar relative efficacy in patients with and without diabetes.
  - Due to their heightened baseline risk of CV events, patients with diabetes tended to have a greater absolute risk reduction.
  - A number needed to treat of 37 over three years.
  - Evolocumab did not increase the risk of new-onset diabetes, nor did it worsen glycaemia.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 29, 2018 VOL. 379 NO. 22

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

G.G. Schwartz, P.G. Steg, M. Szarek, D.L. Bhatt, V.A. Bittner, R. Diaz, J.M. Edelberg, S.G. Goodman, C. Hanotin, R.A. Harrington, J.W. Jukema, G. Lecorps, K.W. Mahaffey, A. Moryusef, R. Pordy, K. Quintero, M.T. Roe, W.J. Sasiela, J.-F. Tamby, P. Tricoci, H.D. White, and A.M. Zeiher, for the ODYSSEY OUTCOMES Committees and Investigators*

Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial

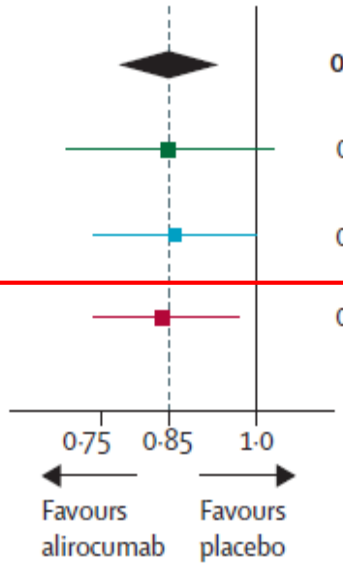
Kausik K Ray, Helen M Colhoun*, Michael Szarek*, Marie Baccara-Dinet, Deepak L Bhatt, Vera A Bittner, Andrzej J Budaj, Rafael Diaz, Shaun G Goodman, Corinne Hanotin, Robert A Harrington, J Wouter Jukema, Virginie Loizeau, Renato D Lopes, Angèle Moryusef, Jan Murin, Robert Pordy, Arsen D Ristic, Matthew T Roe, José Tuñón, Harvey D White, Andreas M Zeiher, Gregory G Schwartz*, Philippe Gabriel Steg*, for the ODYSSEY OUTCOMES Committees and Investigators†*

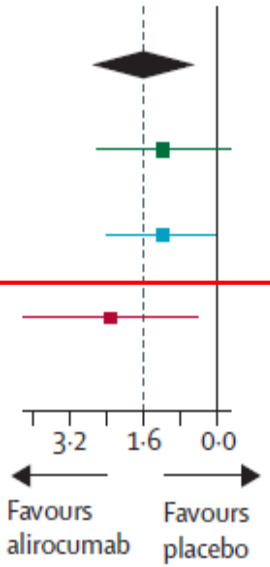
Prespecified analysis of the ODYSSEY OUTCOMES

- **Study population:** 18,924 patients with an acute coronary syndrome 1 to 12 months earlier, and a LDL-C of at least 70 mg/dL while taking an optimised lipid-lowering regimen including 5444 (29%) patients with diabetes (mean age: 59 y)
- **Intervention:** alirocumab (75 mg sc q 2 weeks) versus placebo
- **Primary end point:** composite of death from CHD, non-fatal MI, fatal or non-fatal ischemic stroke, or unstable angina requiring hospital admission

Ray KK, et al. Lancet Diabetes Endocrinol 2019;7:618-28.

	MACE incidence		Relative risk reduction $p_{interaction}$=0·98	Hazard ratio (95% CI)	Absolute risk reduction $p_{interaction}$=0·0019	Absolute risk reduction (95% CI)
	Alirocumab n/N (%)	Placebo n/N (%)				
Overall	**903/9462 (9·5%)**	**1052/9462 (11·1%)**		**0·85 (0·78–0·93)**		**1·6% (0·7 to 2·4)**
Normoglycaemia	192/2639 (7·3%)	220/2595 (8·5%)		0·85 (0·70–1·03)		1·2% (–0·3 to 2·7)
Prediabetes	331/4130 (8·0%)	380/4116 (9·2%)		0·86 (0·74–1·00)		1·2% (0·0 to 2·4)
Diabetes	380/2693 (14·1%)	452/2751 (16·4%)		0·84 (0·74–0·97)		2·3% (0·4 to 4·2)





Prespecified analysis of the ODYSSEY OUTCOMES

- **Conclusion**
  - The patients with diabetes derived twice as much benefit when alirocumab was used to target an LDL-C between 25 and 50 mg/dL with a median follow-up of 2.8 years.
  - A number needed to treat of 43 over three years.

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Hypertriglyceridemia

- Moderate hypertriglyceridemia:
  fasting or nonfasting triglycerides 175-499 mg/dL

- Severe hypertriglyceridemia:
  fasting triglycerides ≥ 500 mg/dL

Hypertriglyceridemia

- Address and treat:
  - Lifestyle factors:
    - obesity
    - metabolic syndrome
  - Secondary factors:
    - diabetes mellitus
    - chronic liver or kidney disease
    - nephrotic syndrome
    - hypothyroidism
  - Medications that increase triglycerides

Hypertriglyceridemia

- Adults aged 40-75 years:
  - ASCVD risk ≥7.5%:
    - Initiate moderate-intensity statin therapy

- Serum TG ≥500 mg/dL, especially ≥1000 mg/dL:
  - Very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate (preferably fenofibrate) therapy.

Hypertriglyceridemia

- In patients with ASCVD or other cardiovascular risk factors on a statin with controlled LDL cholesterol but elevated triglycerides (135-499 mg/dL), the addition of icosapent ethyl can be considered to reduce cardiovascular risk. (A)

The NEW ENGLAND JOURNAL of MEDICINE

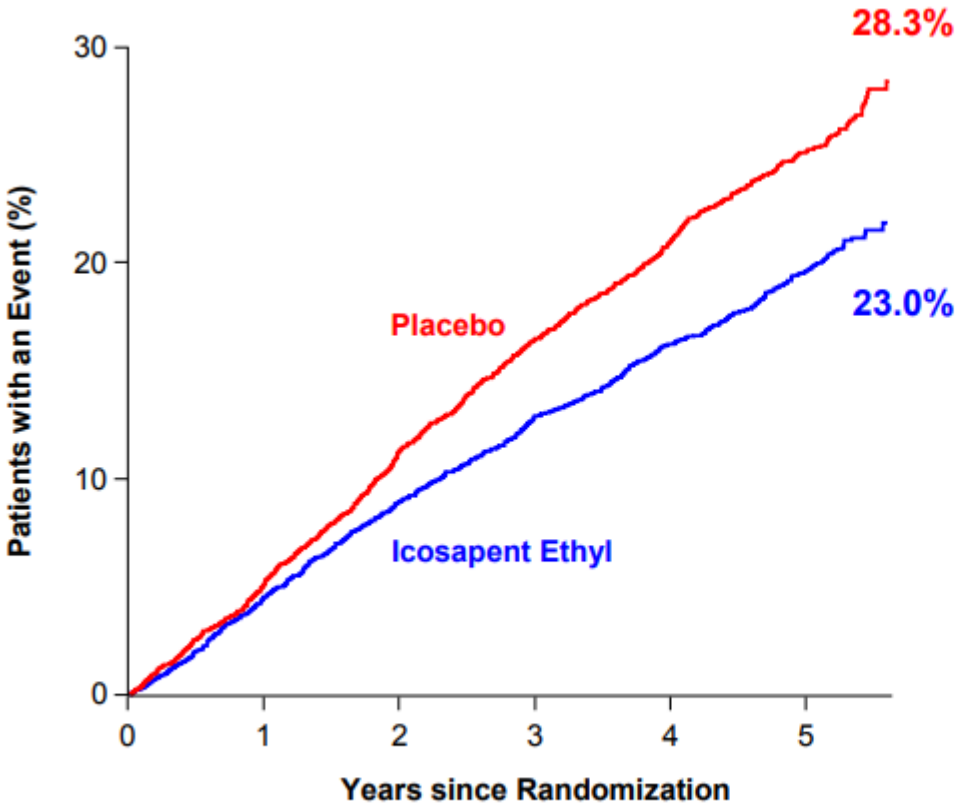
ESTABLISHED IN 1812 JANUARY 3, 2019 VOL. 380 NO. 1

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

- **Study population:**
  - 8179 patients on stabilized statin therapy for ≥4 weeks with 40< LDL-C ≤100 mg/dL and 135≤ TG <500 mg/dL including 4787 (58%) patients with diabetes
  - CV risk cohort 1: Age ≥45 y and established CVD (~71%)
  - CV risk cohort 2: Age ≥50 y and diabetes and ≥1 additional CVD risk factor
  - Median follow-up: 4.9 years

Among patients with elevated TG levels despite statin therapy, the risk of primary endpoint events was significantly lower with 2 g of icosapent ethyl twice daily than with placebo.



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)
RRR = 24.8%
ARR = 4.8%
NNT = 21 (95% CI, 15–33)
P=0.00000001

Primary endpoint: a composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina

Estimated Kaplan-Meier event rate at approximately 5.7 years

ESC European Society of Cardiology
European Heart Journal (2020) **41**, 3925–3932
doi:10.1093/eurheartj/ehaa652

Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial

Matthew J. Budoff [1]*, Deepak L. Bhatt [2], April Kinninger [1], Suvasini Lakshmanan[1], Joseph B. Muhlestein[3], Viet T. Le [3,4], Heidi T. May [3], Kashif Shaikh[1], Chandana Shekar[1], Sion K. Roy[1], John Tayek[1], and John R. Nelson[5]

[1]Department of Medicine, Lundquist Institute at Harbor-UCLA Medical Center, 1124 W Carson Street, Torrance, CA 90502, USA; [2]Department of Medicine, Brigham and Women's Hospital Heart & Vascular Center and Harvard Medical School, Boston, MA, USA; [3]Intermountain Heart Institute, Intermountain Medical Center, Salt Lake City, UT, USA; [4]Department of Medicine, Rocky Mountain University of Health Profession, Provo, UT, USA; and [5]California Cardiovascular Institute, Fresno, CA, USA

- Icosapent ethyl demonstrated significant regression of low-attenuation plaque volume on multidetector CT compared with placebo over 18 months.
- EVAPORATE provides important mechanistic data on plaque characteristics that may have relevance to the REDUCE-IT results and clinical use of IPE.

Hypertriglyceridemia

- Statin plus fibrate combination therapy has not been shown to improve ASCVD outcomes and is generally not recommended. (A)
- Statin plus niacin combination therapy has not been shown to provide additional CV benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. (A)

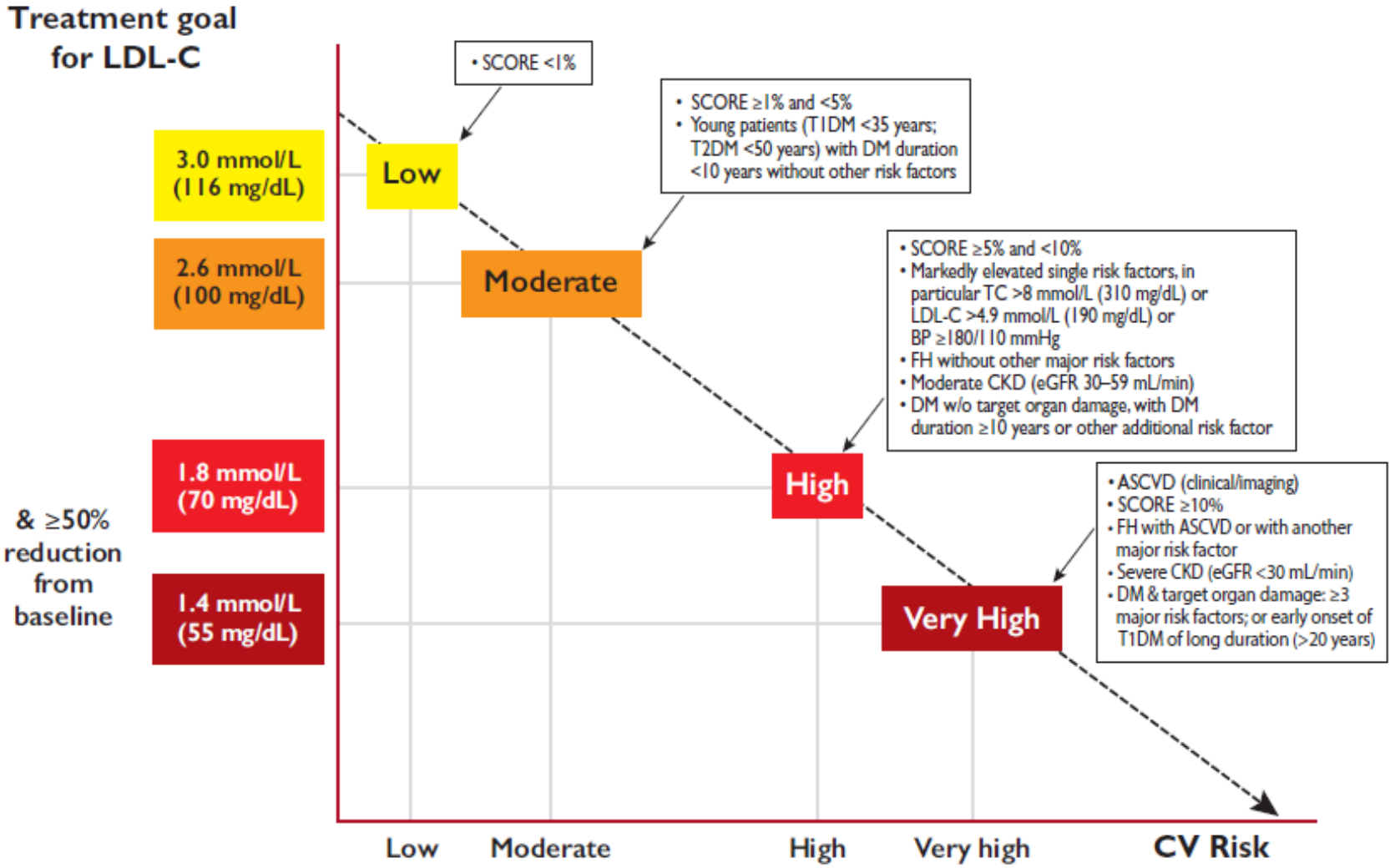
We don’t forget other guidelines!

Cardiovascular risk categories in patients with diabetes

Category	Criteria
Very high risk	- Established CVD or - other target organ damage or - ≥3 major risk factors 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

- Target organ damage: Proteinuria, renal impairment (eGFR <30 mL/min/1.73 m²), left ventricular hypertrophy, or retinopathy.
- Major risk factors: Age, hypertension, dyslipidemia, smoking, obesity.

Cosentino F, et al. Eur Heart J 2020;41:255-323.



Cosentino F, et al. Eur Heart J 2020;41:255-323.

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Take-home message

- Statin therapy is the first-line lipid-lowering drug therapy for the management of dyslipidemia in individuals with diabetes mellitus.

- Other lipid lowering agents can (should) be used to achieve adequate LDL-C reductions and additional cardiovascular risk reduction in specific clinical settings especially in those with higher cardiovascular risk.

Thanks for your patience.

Photo by Majid Valizadeh, MD