Lipid management – Case Studies: Primary & Secondary Prevention

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Objectives

- Brief review of primary prevention of CVD (no case study)
  - New ASSIGN 2.0 tool (primary prevention)
  - Statins (including intolerance)
- Discuss the evidence and decision making for secondary prevention of CVD, through a few case studies
  - Ezetimibe
  - Bempedoic Acid
  - PSCK9is
  - Inclisiran
  - Icosapent ethyl
- Q&A

Primary Prevention, including new ASSIGN 2.0 tool

ASSIGN- Background to the Update (1)

- ASSIGN 1.0 was launched in February 2007 with SIGN Guideline 97
  - https://www.sign.ac.uk/our-guidelines/sign-97-risk-estimation-and-the-prevention-of-cardiovascular-disease/
- This was reaffirmed in SIGN 149 'Risk estimation and the prevention of cardiovascular disease'
  - https://www.sign.ac.uk/assets/qrg149.pdf

R Asymptomatic individuals should be considered at high risk if they are assessed as having a ≥20% risk of a first cardiovascular event within ten years.

R Adults who are assessed as being at high cardiovascular risk, but with no established CVD, should be offered treatment with atorvastatin 20 mg/day following an informed discussion of risks and benefits between the individual and their responsible clinician. In those already taking an alternative regimen due to reported intolerance with atorvastatin, there is no need to change their current regimen.

ASSIGN- Background to the Update (2)

- In recent years, MHRA judged that ASSIGN was a Medical Device (as it directly influenced patient treatment) and therefore needed regular recalibration

- 'The ASSIGN tool was recalibrated in 2024 to acknowledge changing trends in population cardiovascular event rates and risk and the **threshold defining high-risk is now 10%,** consistent with the 10% risk threshold applied to the QRISK cardiovascular disease risk score by NICE. In the short term, this will mean inconsistency with SIGN 149: risk estimation and the prevention of cardiovascular disease, which recommends a 20% threshold for the original ASSIGN calculator'
    - https://www.sign.ac.uk/our-guidelines/risk-estimation-and-the-prevention-of-cardiovascular-disease/

ASSIGN- Background to the Update (3)

Updating the Scottish national cardiovascular risk score: ASSIGN version 2.0

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ABSTRACT

Background The Assessing cardiovascular risk using Scottish Intercollegiate Guidelines Network (ASSIGN) risk score, developed in 2006, is used in Scotland for estimating the 10-year risk of first atherosclerotic cardiovascular disease (ASCVD). Rates of ASCVD are decreasing, and an update is required. This study aimed to recalibrate ASSIGN (V.2.0) using contemporary data and to compare recalibration with other potential approaches for updating the risk score.

Methods Data from Scotland-resident participants from UK Biobank (2006–2010) and the Generation Scotland Scottish Family Health Study (2006–2010), aged 40–69 and without previous ASCVD, were used for the derivation of scores. External evaluation was conducted on UK Biobank participants who were not residents of Scotland. The original ASSIGN predictor variables and weights formed the basis of the new sex-specific risk equation to predict the 10-year risk of ASCVD. Different approaches for updating ASSIGN (recalibration, rederivation and regression adjustment) were tested in the evaluation cohort.

Results The original ASSIGN score overestimated ASCVD risk in the evaluation cohort, with median predicted 10-year risks of 10.6% for females and 15.1% for males, compared with observed risks of 6% and 11.4%, respectively. The derivation cohort included 44 947 (57% females and a mean age of 55) participants. The recalibrated score, ASSIGN V.2.0, improved model fit in the evaluation cohort, predicting median 10-year risk of 4% for females and 8.9% for males. Similar improvements were achieved using the regression-adjusted model. Rederivation of ASSIGN using new beta coefficients offered only modest improvements in calibration and discrimination beyond simple recalibration. At the current risk threshold of 20% 10-year risk, the original ASSIGN equation yielded a positive predictive value (PPV) of 16.3% and a negative predictive value (NPV) of 94.4%. Recalibrated ASSIGN V.2.0 showed similar performance at a 10% threshold, with a PPV of 16.8% and an NPV of 94.6%.

Conclusions The recalibrated ASSIGN V.2.0 will give a more accurate estimation of contemporary ASCVD risk in Scotland.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The Assessing cardiovascular risk using Scottish Intercollegiate Guidelines Network (ASSIGN) risk score is a tool for atherosclerotic cardiovascular disease (ASCVD) risk estimation in Scotland developed in 2006. However, declines in ASCVD rates have rendered the original score prone to overestimation of risk, necessitating an update.

WHAT THIS STUDY ADDS

⇒ ASSIGN version 2.0 derived using contemporary data provides recalibrated risk estimates that align with current ASCVD incidence rates. This version offers improved calibration and comparable discrimination without altering the established predictor variables, ensuring a smoother transition to clinical practice.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ By improving accuracy in ASCVD risk prediction, ASSIGN version 2.0 optimises ASCVD risk estimation in Scotland.

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of morbidity and mortality worldwide, including in the UK,[1] necessitating effective risk estimation systems to guide primary preventive interventions.[2 3] In Scotland, the Assessing cardiovascular risk using Scottish Intercollegiate Guidelines Network (SIGN (ASSIGN) guidelines to assign preventive treatment score has been a cornerstone in primary care for estimating the 10-year risk of a primary ASCVD event, thus guiding clinical decisions on preventive treatments, including lifestyle interventions and pharmacotherapy.[3] The original ASSIGN score, developed in 2006,[4] was pioneering in incorporating socioeconomic deprivation, family history of ASCVD and detailed smoking history into cardiovascular risk assessment, distinguishing it from earlier clinically applied risk scores.[5] The ASSIGN score was derived using the nationally representative Scottish Heart Health Extended Cohort recruited between 1984 and 1995.

Since the development of the ASSIGN score, there have been significant changes in the landscape of cardiovascular disease and its associated risk factors. Notably, there has been a decline in ASCVD event rates in Scotland, with the incidence of coronary heart disease (CHD) falling by around 17% in the last decade alone,[1 6] attributed to improvements in early intervention strategies, enhanced

Welsh P, Kimenai DM, Woodward M. Updating the Scottish national cardiovascular risk score: ASSIGN version 2.0. *Heart*. 2025 May 23;111(12):557-564. doi: 10.1136/heartjnl-2024-324852.

New ASSIGN 2.0

- ASSIGN 2.0 now launched and hosted on the ‘Right Decision’ platform
  - https://rightdecisions.scot.nhs.uk/assign-v20/

ASSIGN: Cardiovascular risk score calculator

ASSIGN (v2.0)

The ASSIGN cardiovascular risk score estimates the 10 year percentage risk of developing cardiovascular disease (diseases of the heart and blood vessels including coronary heart disease, stroke, and transient ischaemic attack) for individuals in Scotland, who do not currently have a diagnosis of CVD. **It is not appropriate to use it in those with known CVD.**

The score is a number between 0 and 100. Those with a score of >= 10 are considered high risk and should be offered targeted risk reduction advice and treatments in line with current guidelines. Those with a score less than ten are not necessarily risk-free and should be offered general advice on risk reduction. The tool has been developed using Scottish data and therefore should be used with caution in populations outside Scotland.

This ASSIGN calculator has been produced for use by qualified healthcare professionals and is not a substitute for seeking medical advice.

This calculator is CA marked as a class 1 device. See below for regulatory information.

Current age

Age at last birthday.

▶ Notes

60

Sex

Select a sex.

(•) Male ( ) Female

Please select one of the following

Select 'Scottish postcode' to insert a postcode and generate an SIMD score. If SIMD is already known, this can be entered directly by selecting SIMD.

(•) Scottish postcode ( ) Or SIMD

Enter a valid Scottish postcode.

▶ Notes

G21 3UZ

Family history

Has the person had a parent or sibling with a diagnosis of coronary heart disease or stroke?

▶ Notes

(•) Yes ( ) No

Does the person have a clinical diagnosis of diabetes?

▶ Notes

( ) Yes (•) No

Is the person a smoker?

( ) Yes (•) No

Systolic blood pressure

Enter systolic blood pressure in millimetres of mercury (mmHg).

▶ Notes

50 mmHg

Total cholesterol

Enter total cholesterol in millimoles per litre (mmol/l).

▶ Notes

6.5 mmol/l

HDL cholesterol

Enter High density lipoprotein (HDL) cholesterol in millimoles per litre (mmol/l).

▶ Notes

2.3 mmol/l

ASSIGN Score: 13

ASSIGN score of 10 or above is currently considered to be high risk. Offer targeted lifestyle information and medical treatment to reduce risk. No need to repeat the scoring on another occasion.

NB- Dummy case, using post-code of Stobhill Hospital where I work

Statins in Primary Prevention

For patients with a 10-year cardiovascular event risk ≥ 10%, first line treatment is to offer atorvastatin 20mg daily as primary prevention

See BNF for cautions, contraindications, and clinically important drug interactions

- **All patients should be advised of the benefits of lifestyle modification including smoking cessation, diet, weight loss, increased activity, and reduced alcohol consumption and manage other modifiable cardiovascular risk factors.**
- **Recheck lipids and LFTs within 3 months then annually as best practice to optimise compliance. Check CK if patient reports myalgia.**
- **Best practice suggests aim for 40% or greater reduction in LDL cholesterol for primary prevention. Statin therapy can be intensified to achieve this.**

NHS GGC Guidelines, 2025

Lipid target for people taking statins

1.6.1 For primary prevention of CVD aim for a greater than 40% reduction in non-HDL cholesterol. **[May 2023]**

https://www.nice.org.uk/guidance/ng238

Expected Lipid Lowering with Statins

EXTENT OF LIPID LOWERING WITH AVAILABLE THERAPIES

	Approximate reduction in LDL-C				
Statin dose mg/day	5	10	20	**40**	**80**
Fluvastatin			21%	27%	3%
Pravastatin		20%	24%	29%	
Simvastatin		27%	32%	37%	
Atorvastatin		37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	
Atorvastatin + Ezetimibe 10mg		52%	54%	57%	61%

Low intensity statins will produce an LDL-C reduction of 20-30%

Medium intensity statins will produce an LDL-C reduction of 31-40%

High intensity statins will produce an LDL-C reduction above 40%

Simvastatin 80mg is not recommended due to risk of muscle toxicity

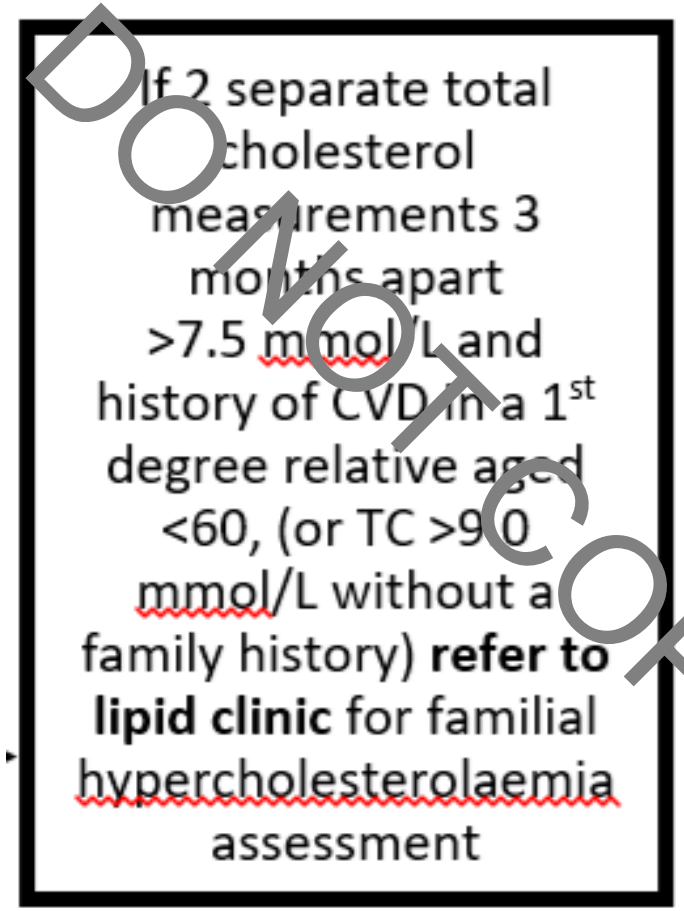
- **Rosuvastatin** may be used as an alternative to atorvastatin if compatible with other drug therapy. Some people may need a lower starting dose (see BNF).
- Low/medium intensity statins should only be used if intolerance or drug interactions.
- **Ezetimibe** when combined with any statin is likely to give greater reduction in non-HDL-C or LDL-C than doubling the dose of the statin.

https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/04/lipid-management-pathway-v7.pdf

PRIMARY PREVENTION

- Is the patient adherent with statins?
  - They should achieve the recommended 40% LDL-c reduction !
- If adherent and 40% LDL-c reduction is not met then intensifying statin therapy in primary prevention should be effective (e.g. increasing Atorvastatin to 40mg or 80mg)

Consider FH and Lipid Clinic Referral if TC >7.5mmol/l



NHS GGC Guidelines, 2025

Statin Intolerance (1)

9. STATIN INTOLERANCE

The majority of side-effects attributed to statins are due to "nocebo" effect (i.e. an expectation of adverse side-effects purely related to the act of taking a tablet, rather than an adverse effect of the active ingredient *per se*). The following paper provides a useful reference for discussions with patients:

"Statin therapy caused a small excess of mostly mild muscle pain. Most (>90%) of all reports of muscle symptoms by participants allocated statin therapy were not due to the statin. The small risks of muscle symptoms are much lower than the known cardiovascular benefits."
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01545-8/fulltext

NB The evidence base for improved cardiovascular outcomes with the use of statins is much more robust than for other agents for both primary and secondary prevention of cardiovascular disease. It is important to emphasise this to patients, and to ensure that there is genuine intolerance before considering an alternative.

Note rosuvastatin has a maximum licensed dose of 20mg daily in patients of Asian origin.

Statin Intolerance (2)

Primary prevention

Ensure patients are genuinely intolerant of statin before making any changes. If necessary patients should be encouraged to try different statin preparations and/or lower than usual doses - for example:- if intolerant of Atorvastatin (20, 40 or 80mg dose), stop statin therapy for 2-3 weeks and then recommence Atorvastatin 10mg. If intolerant, stop for 2-3 weeks then trial rosuvastatin at 2.5mg daily (half a 5mg tablet) for 4 weeks and titrate up to 5mg and then 10mg at 4 weekly intervals until a maximally tolerated dose is determined. If a higher dose is not tolerated, stop for 2-3 weeks and recommence at the last tolerated dose and recheck lipid profile.

If familial hypercholesterolaemia is suspected, the patient should be referred to a lipid clinic for specialist advice.

Secondary prevention

Ensure patients are genuinely intolerant of statin before making any changes. Patients should be encouraged to retry same statin after period of abstinence first and if side effects remerge then try different statin preparations and/or lower than usual doses - for example:- if intolerant of Atorvastatin (20, 40 or 80mg dose), stop statin therapy for 2-3 weeks and then recommence Atorvastatin 10mg. If intolerant, stop for 2-3 weeks then trial rosuvastatin at 2.5mg daily (half a 5mg tablet) for 4 weeks and titrate up to 5mg and then 10mg at 4 weekly intervals until a maximally tolerated dose is determined. If a higher dose in not tolerated, stop for 2-3 weeks and recommence at the last tolerated dose and recheck lipid profile. If necessary combine a lower dose of statin with ezetimibe.

Special Populations / Realistic Medicine

- **Young**

It should be noted that both these models may underestimate lifetime risk in younger patients. These tools should inform discussions with younger patients who may be approaching risk thresholds and who may wish to consider statin therapy if lifestyle measures do not sufficiently improve their lipid profile.

- **Frail**

Treatment of frail or very elderly people with statins should be guided by individual circumstances and co-morbidities and need not follow guideline recommendations. Review statin if limited life expectancy or if falling due to weakness. Additional considerations in severe frailty: Review statin/do not initiate if limited life expectancy or if the priority is symptomatic relief.

- **Women**

Statins in Pregnancy and Lactation

Statins should be stopped 3 months before attempting to conceive and not be restarted until breastfeeding is finished. Stop statins if pregnancy is a possibility.

https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/04/lipid-management-pathway-v7.pdf

Case Study 1 & 2:

What's the Target in Secondary Prevention and What to Do Next?

Statins in Secondary Prevention

For patients with atherosclerotic disease offer atorvastatin 80mg daily as secondary prevention

See BNF for cautions, contra-indications, and clinically important drug interactions

- **All patients should be advised of the key benefits of lifestyle modification including smoking cessation, diet, weight loss, increased activity and reduced alcohol consumption, as appropriate.**
- **Ensure optimal management of other modifiable cardiovascular risk factors including left ventricular systolic dysfunction, blood pressure and glycaemic control if appropriate.**
- **For patients with coronary artery calcification, give 40mg or 80mg atorvastatin depending on patient characteristics (Refer to Appendix 3).**
- **Recheck lipids and LFTS within 3 months then annually as best practice to optimise compliance. Check CK if patient complains of myalgia.**

NHS GGC Guidelines, 2025

Secondary Prevention

Treatment targets are LDL-C goal of <2 mmol/L (non-HDL <2.6 mmol/L)

Failure to reduce cholesterol concentrations significantly may be a marker of poor concordance.

If cholesterol targets are not met offer ezetimibe 10mg daily in addition to the maximal tolerated dose of high-intensity statin.

NHS GGC Guidelines, 2025

Lipid target for people taking lipid-lowering treatments

1.7.1 For secondary prevention of CVD, aim for LDL cholesterol levels of 2.0 mmol per litre or less, or non-HDL cholesterol levels of 2.6 mmol per litre or less. **[December 2023]**

https://www.nice.org.uk/guidance/ng238

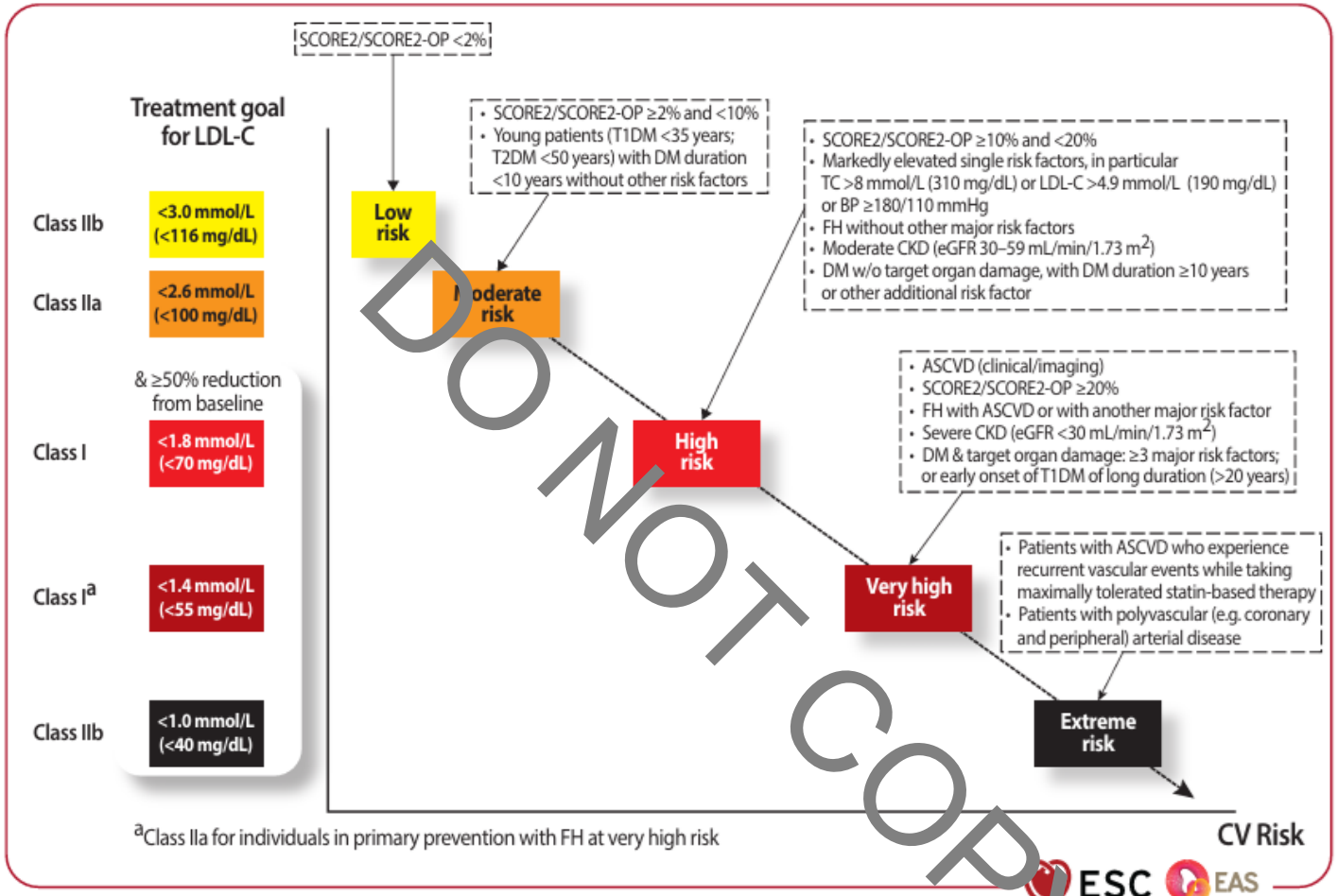


Figure 1 Treatment goals for low-density lipoprotein cholesterol across categories of total cardiovascular risk. ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; SCORE2, Systematic Coronary Risk Evaluation 2; SCORE2-OP, Systematic Coronary Risk Evaluation 2-Older Persons; T1DM, type 1 DM; T2DM, type 2 DM; TC, total cholesterol.

Mach F, et al; ESC/EAS Scientific Document Group. 2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias. Atherosclerosis. 2025 Oct;409:120479. doi: 10.1016/j.atherosclerosis.2025.120479. Epub 2025 Aug 29. PMID: 40885687.

Case Study 1: Secondary Prevention

- LAD proximal
Severity of Stenosis: Plaque Disease.

- Mid Circumflex
Severity of Stenosis: Plaque Disease.

- RCA mid
Severity of Stenosis: Occluded.

Intervention

Devices:	☑ Thrombus removal	Export Aspiration Catheter		
	☑ Balloon catheter	Emerge	2.5/15	
	☑ Coronary DE Stent	Xience Pro	[size not listed]	3.5 x 48 mm
	☑ Balloon catheter	NC Trek	4.0/20	16 atms

Outcome: Complete success:- stenosis from Occluded to 0%

Inf STE with Q waves already

RRA 6F

LMS: Ok

LAD: Prox plaque

Cx: Plaque

Test	Result	Ref. Range (Units)
Cholesterol	4.5	(mmol/L)
Triglycerides	2.3	0.2 - 2.3 mmol/L (mmol/L)
HDL Cholesterol	1.5	(mmol/L)
LDL-Cholest (calc'd)	1.9	(mmol/L)
VLDL-Chol (calc'd)	1.1	(mmol/L)
Chol/HDL ratio	3.0	

- 83yr old male
- Inferior STEMI
- Mild LVSD EF 48%

- PMHx- Ex-Smoker, Oesteo-arthritis, Frailty, Depression, Cognitive Impairment (mild)

- Aspirin 75mg daily
- Clopidogrel 75mg daily (6 months)
- Atorvastatin 80mg daily
- Ramipril 2.5mg twice daily
- Bisoprolol 2.5mg daily
- Co-codamol 30/500mg PRN
- Sertraline 50mg daily

Case Study 2: Secondary Prevention

- LAD proximal
Severity of Stenosis: Occluded.
Thrombus Present, Vessel Occlusion < 3 months, Length Of Lesion > 20mm, Lesion Calcification Moderate, Lesion Angulation 45-90°.

Intervention

Devices:	☑ Balloon catheter	NC Trek	3.0/15	16
	☑ IVUS	IVUS Catheter		
	☑ Coronary DE Stent	Promus Premier	3.0/28	14
	☑ Balloon catheter	NC Trek	3.5/15	20
	☑ Balloon catheter	Emerge NC	4.0/12	20

Outcome: Complete success:- stenosis from Occluded to 0%

- Left Main
Severity of Stenosis: 50-74%.
Thrombus Present, Length Of Lesion 10-20mm, Lesion Calcification Moderate.

Intervention

Devices:	☑ Balloon catheter	NC Trek	3.0/15	16
	☑ Coronary DE Stent	Promus Premier	4.0/24	14
	☑ Balloon catheter	Emerge NC	4.0/12	20 - 12 FKB
	☑ Balloon catheter	Emerge NC	5.0/08	16

Outcome: Complete success:- stenosis from 50-74% to 0%

- Proximal Circumflex
Severity of Stenosis: 75-94%.
Length Of Lesion 10-20mm, Lesion Calcification Moderate.

Intervention

Devices:	☑ Balloon catheter	NC Trek	3.0/15	14
	☑ Coronary DE Stent	Promus Premier	4.0/12	14
	☑ Balloon catheter	Emerge NC	4.0/12	20 - 12 FKB

Outcome: Complete success:- stenosis from 75-94% to 0%

- Obtuse Marginal 1
Severity of Stenosis: 50-74%.

- LAD mid
Severity of Stenosis: 50-74%.

- RCA mid
Severity of Stenosis: 25-49%.

- 43yr old male
- South Asian
- BMI 23 and cycles 5 miles a day to work
- PMHx- Three first degree relatives with CVD in 50s, high cholesterol (untreated)

Test	Result	Ref. Range (Units)
Cholesterol	4.5	(mmol/L)
Triglycerides	2	0.2 - 2.3 mmol/L (mmol/L)
HDL Cholesterol	1.5	(mmol/L)
LDL-Cholest (calc'd)	1.9	(mmol/L)
VLDL-Chol (calc'd)	1.1	(mmol/L)
Chol/HDL ratio	3.0	

Ezetimibe – Evidence Secondary Prevention (Post-ACS)

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., Brian 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*

ABSTRACT

BACKGROUND

Statin therapy reduces low-density lipoprotein (LDL) cholesterol levels and the risk of cardiovascular events, but whether the addition of ezetimibe, a nonstatin drug that reduces intestinal cholesterol absorption, can reduce the rate of cardiovascular events further is not known.

METHODS

We conducted a double-blind, randomized trial involving 18,144 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and had LDL cholesterol levels of 50 to 100 mg per deciliter (1.3 to 2.6 mmol per liter) if they were receiving lipid-lowering therapy or 50 to 125 mg per deciliter (1.3 to 3.2 mmol per liter) if they were not receiving lipid-lowering therapy. The combination of simvastatin (40 mg) and ezetimibe (10 mg) (simvastatin–ezetimibe) was compared with simvastatin (40 mg) and placebo (simvastatin monotherapy). The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization (≥30 days after randomization), or nonfatal stroke. The median follow-up was 6 years.

RESULTS

The median time-weighted average LDL cholesterol level during the study was 53.7 mg per deciliter (1.4 mmol per liter) in the simvastatin–ezetimibe group, as compared with 69.5 mg per deciliter (1.8 mmol per liter) in the simvastatin-monotherapy group (P<0.001). The Kaplan–Meier event rate for the primary end point at 7 years was 32.7% in the simvastatin–ezetimibe group, as compared with 34.7% in the simvastatin-monotherapy group (absolute risk difference, 2.0 percentage points; hazard ratio, 0.936; 95% confidence interval, 0.89 to 0.99; P=0.016). Rates of prespecified muscle, gallbladder, and hepatic adverse effects and cancer were similar in the two groups.

CONCLUSIONS

When added to statin therapy, ezetimibe resulted in incremental lowering of LDL cholesterol levels and improved cardiovascular outcomes. Moreover, lowering LDL cholesterol to levels below previous targets provided additional benefit. (Funded by Merck; IMPROVE-IT ClinicalTrials.gov number, NCT00202878.)

From the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Brigham and Women's Hospital, and Harvard Medical School, Boston (C.P.C., C.P.G., A.M., K.M., E.A.B., S.D.W., E.B.); Duke Clinical Research Institute (DCRI), Durham, NC (M.A.B., J.A.W., C.R., R.M.C.); Montreal Heart Institute, Montreal (P.T.); Vivantes Neukolln Medical Center, Berlin (H.D.); Lady Davis Carmel Medical Center, Haifa, Israel (B.S.L.); Canisius-Wilhelmina Ziekenhuis, Nijmegen (T.O.O.), and the Netherlands Leiden University Medical Center, Leiden (J.W.J.) — both in the Netherlands; Fondazione IRCCS Policlinico San Matteo and University of Pavia, Pavia, Italy (G.M.D.F.); National Institute of Cardiology, Warsaw, Poland (W.R.); and Merck, Kenilworth, NJ (P.D.L., A.M.T., T.A.M.). Address reprint requests to Dr. Cannon at the Cardiovascular Division, Brigham and Women's Hospital, 350 Longwood Ave., 1st Fl., Boston, MA 02115, or at cpcannon@partners.org.

*A complete list of investigators in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on June 3, 2015, at NEJM.org.

N Engl J Med 2015;372:2387-97.
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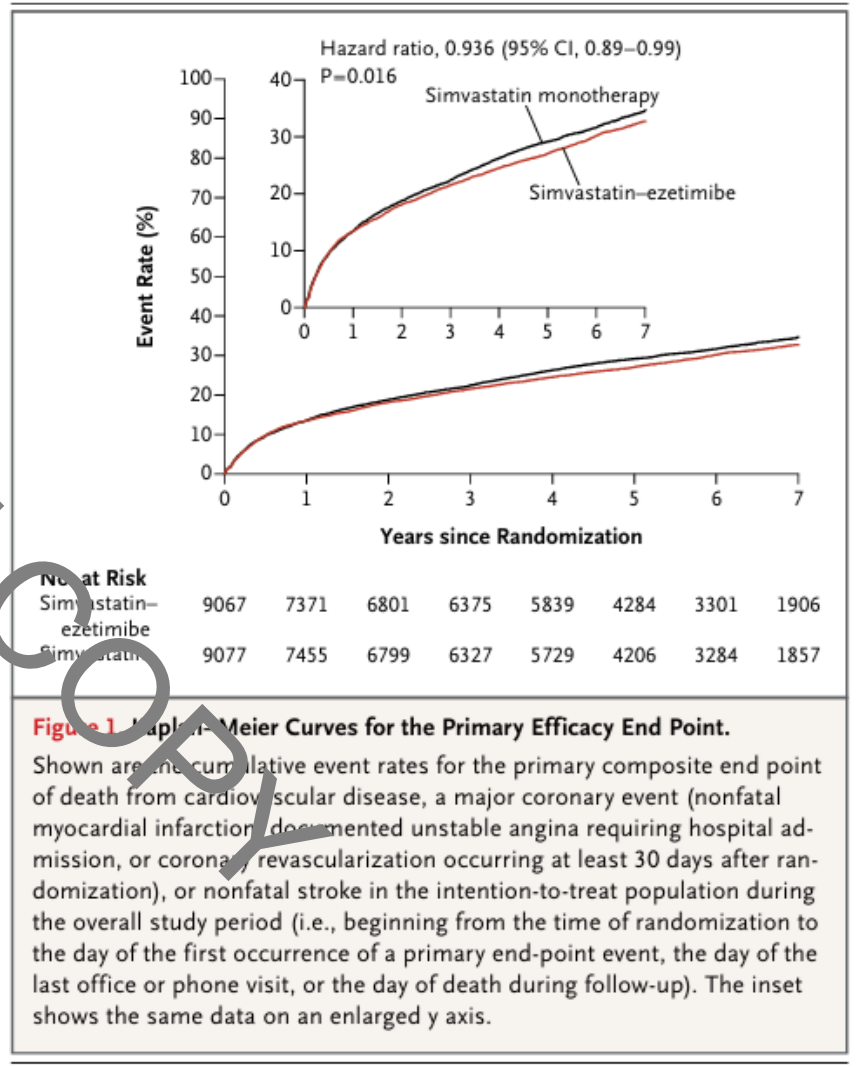

Figure 1. Kaplan–Meier Curves for the Primary Efficacy End Point.

Shown are the cumulative event rates for the primary composite end point of death from cardiovascular disease, a major coronary event (nonfatal myocardial infarction, documented unstable angina requiring hospital admission, or coronary revascularization occurring at least 30 days after randomization), or nonfatal stroke in the intention-to-treat population during the overall study period (i.e., beginning from the time of randomization to the day of the first occurrence of a primary end-point event, the day of the last office or phone visit, or the day of death during follow-up). The inset shows the same data on an enlarged y axis.

Cannon CP, et al ; IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015 Jun 18;372(25):2387-97. doi: 10.1056/NEJMoa1410489. Epub 2015 Jun 3. PMID: 26039521.

Ezetimibe – Evidence Secondary Prevention (Post-ACS)

Table 2. Primary, Secondary, and Individual End Points.*

Outcome	Simvastatin Monotherapy (N=9077)	Simvastatin–Ezetimibe (N=9067)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Primary end point: death from cardiovascular causes, major coronary event, or nonfatal stroke	2742 (34.7)	2572 (32.7)	0.936 (0.89–0.99)	0.016
Secondary end points				
Death from any cause, major coronary event, or nonfatal stroke	3246 (40.3)	3089 (38.7)	0.95 (0.90–1.0)	0.03
Death from coronary heart disease, nonfatal MI, urgent coronary revascularization ≥30 days	1448 (18.9)	1322 (17.5)	0.91 (0.85–0.98)	0.02
Death from cardiovascular causes, nonfatal MI, hospitalization for unstable angina, all revascularization ≥30 days, nonfatal stroke	2869 (36.2)	2716 (34.5)	0.95 (0.90–1.0)	0.04
Tertiary end points†				
Death from any cause	1231 (15.3)	1215 (15.4)	0.99 (0.91–1.07)	0.78
Death from cardiovascular causes	538 (6.8)	537 (6.9)	1.00 (0.89–1.13)	1.00
Death from coronary heart disease	461 (5.8)	440 (5.7)	0.96 (0.84–1.09)	0.50
Any MI	1118 (14.8)	977 (13.1)	0.87 (0.80–0.95)	0.002
Nonfatal MI	1083 (14.4)	945 (12.8)	0.87 (0.80–0.95)	0.002
Fatal MI	49 (0.7)	41 (0.5)	0.84 (0.55–1.27)	0.41
Any stroke	345 (4.8)	296 (4.2)	0.86 (0.73–1.00)	0.05
Ischemic stroke	297 (4.1)	236 (3.4)	0.79 (0.67–0.94)	0.008

Table 3. Prespecified Safety End Points.*

End Point	Simvastatin Monotherapy (N=9077)	Simvastatin–Ezetimibe (N=9067)	P Value
	no. of patients (%)		
ALT, AST, or both ≥3×ULN	208 (2.3)	224 (2.5)	0.43
Cholecystectomy	134 (1.5)	133 (1.5)	0.96
Gallbladder-related adverse events	321 (3.5)	281 (3.1)	0.10
Rhabdomyolysis	18 (0.2)	13 (0.1)	0.37
Myopathy	10 (0.1)	15 (0.2)	0.32
Rhabdomyolysis or myopathy	28 (0.3)	27 (0.3)	0.90
Rhabdomyolysis, myopathy, myalgia with creatine kinase elevation ≥5×ULN	58 (0.6)	53 (0.6)	0.64
Cancer†	732 (10.2)	748 (10.2)	0.57
Death from cancer†	272 (3.6)	280 (3.8)	0.71

* Adverse events were assessed in the intention-to-treat population. The database for the analysis presented here was locked on October 21, 20[illegible]. Skeletal muscle and cancer events were adjudicated by a clinical events committee, whose members were unaware of the study-group assignments. Detailed definitions of the adverse events are provided in the Supplementary Appendix. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.

† Percentages for cancer are 7-year Kaplan–Meier estimates. Cancer includes any new, relapsing, or progressing cancer, excluding nonmelanoma skin cancer. Death from cancer includes death from nonmelanoma skin cancer.

Cannon CP, et al ; IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015 Jun 18;372(25):2387-97. doi: 10.1056/NEJMoa1410489. Epub 2015 Jun 3. PMID: 26039521.

Case Study 3: Secondary Prevention

Secondary Prevention

Patients who are intolerant of atorvastatin should be trialled on rosuvastatin (Refer to Appendix 9).

Refer to lipid clinic if LDL remains >3.5mmol/l despite optimised lipid lowering therapy for consideration of PCSK9-inhibitor or other drug therapy.

Note that coronary calcification or atherosclerosis reported on CT alone is insufficient indication for consideration of PCSK9 inhibitor therapy.

NHS GGC Guidelines, 2025

- **MIND THE GAP !!!! (i.e. LDL-c ≥2 mmol/l, but <3.5mmol/l)**

Case Study 3: Secondary Prevention

- 64yr old
- Male
- STEMI
- PPCI mRCA DES x 1 and dRCA DES x 1
- Staged PCI pLAD / D1 - V stenting
- Moderate LVSD

- PMHx- NSTEMI 2019 (PCI dRCA DES x1), hypertension, hyperlipidaemia, T2DM, Obesity

Test	Result	Ref. Range (Units)	Abnormality
Cholesterol	6.2	(mmol/L)	
Triglycerides	* 3.5	0.2 - 2.3 mmol/L (mmol/L)	**Abnormal - high**
HDL Cholesterol	1.0	(mmol/L)	
LDL-Cholest (calc'd)	3.6	(mmol/L)	
VLDL-Chol (calc'd)	1.6	(mmol/L)	
Chol/HDL ratio	6.2		

- Losartan 100mg daily
- Bisoprolol 2.5mg daily
- Amlodipine 5mg daily
- Prasugrel 10mg daily
- Aspirin 75mg daily
- Ezetimibe 10mg daily
- Bendroflumethiazide 2.5mg daily
- Sitagliptin 100mg daily
- Empagliflozin 25mg daily
- Metformin MR 1g twice daily
- Omeprazole 20mg
- **<u>STATIN INTOLERANCE x 3</u>**

Newer Therapies

PCSK9i (1)

Table 1. Characteristics of the Patients at Baseline.*

Characteristics	Evolocumab (N=13,784)	Placebo (N=13,780)
Age — yr	62.5±9.1	[illegible]±8.9
Male sex — no. (%)	10,397 (75.4)	[illegible],398 ([illegible].5)
White race — no. (%)†	11,748 (85.2)	11,710 ([illegible].0)
Weight — kg	85.0±17.3	85.[illegible]±17.4
Region		
North America	2,287 (16.6)	2,284 ([illegible].6)
Europe	8,666 (62.9)	8,669 ([illegible].9)
Latin America	913 (6.6)	910 (6.6)
Asia Pacific and South Africa	1,918 (13.9)	1,917 (13.9)
Type of atherosclerosis‡		
Myocardial infarction — no. (%)	11,145 (80.9)	11,206 (81.3)
Median time from most recent previous myocardial infarction (IQR) — yr	3.4 (1.0–7.4)	3.3 (0.9–7.7)
Nonhemorrhagic stroke	2686 (19.5)	2651 (19.2)
Median time from most recent previous stroke (IQR) — yr	3.2 (1.1–7.1)	3.3 (1.1–7.3)
Peripheral artery disease — no. (%)	1,858 (13.5)	1,784 (12.9)
Cardiovascular risk factors		
Hypertension — no./total no. (%)	11,045/13,784 (80.1)	11,039/13,779 (80.1)
Diabetes mellitus — no. (%)	5,054 (36.7)	5,027 (36.5)
Current cigarette use — no./total no. (%)	3854/13,783 (28.0)	3923/13,779 (28.5)
Statin use — no. (%)§		
High intensity	9,585 (69.5)	9,518 (69.1)
Moderate intensity	4,161 (30.2)	4,231 (30.7)
Low intensity, unknown intensity, or no data	38 (0.3)	31 (0.2)
Ezetimibe — no. (%)	726 (5.3)	714 (5.2)
Other cardiovascular medications — no./total no. (%)		
Aspirin, $P2Y_{12}$ inhibitor, or both	12,766/13,772 (92.7)	12,666/13,767 (92.0)
Beta-blocker	10,441/13,772 (75.8)	10,374/13,767 (75.4)
ACE inhibitor or ARB, aldosterone antagonist, or both	10,803/13,772 (78.4)	10,730/13,767 (77.9)
Median lipid measures (IQR)		
LDL cholesterol — mg/dl	92 (80–109)	92 (80–109)
Total cholesterol — mg/dl	168 (151–188)	168 (151–189)
HDL cholesterol — mg/dl	44 (37–53)	44 (37–53)
Triglycerides — mg/dl	134 (101–183)	133 (99–181)
Lipoprotein(a) — nmol/liter	37 (13–166)	37 (13–164)

The NEW ENGLAND JOURNAL of MEDICINE

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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*

TRIAL POPULATION

Patients were eligible for participation in the trial if they were between 40 and 85 years of age and had clinically evident atherosclerotic cardiovascular disease, defined as a history of myocardial infarction, nonhemorrhagic stroke, or symptomatic peripheral artery disease, as well as additional characteristics that placed them at higher cardiovascular risk. (Full eligibility criteria are provided in the Supplementary Appendix.) Patients had to have a fasting LDL cholesterol level of 70 mg per deciliter (1.8 mmol per liter) or higher or a non–high-density lipoprotein (HDL) cholesterol level of 100 mg per deciliter (2.6 mmol per liter) or higher while they were taking an optimized regimen of lipid-lowering therapy, which was defined as preferably a high-intensity statin but must have been at least atorvastatin at a dose of 20 mg daily or its equivalent, with or without ezetimibe. Written informed consent was obtained from all the patients.

Sabatine MS, et al; FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017 May 4;376(18):1713-1722. doi: 10.1056/NEJMoa1615664. Epub 2017 Mar 17. PMID: 28304224.

PCSK9i (2)

Table 2. Primary and Secondary End Points.

Outcome	Evolocumab (N=13,784)	Placebo (N=13,780)	Hazard Ratio (95% CI)	P Value*
	no. of patients (%)			
Primary end point: cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization	1344 (9.8)	1563 (11.3)	0.85 (0.79–0.92)	<0.001
Key secondary end point: cardiovascular death, myocardial infarction, or stroke	816 (5.9)	1013 (7.4)	0.80 (0.73–0.88)	<0.001
Other end points				
Cardiovascular death	251 (1.8)	240 (1.7)	1.05 (0.88–1.25)	0.62
Due to acute myocardial infarction	25 (0.18)	30 (0.22)	0.84 (0.49–1.42)	
Due to stroke	31 (0.22)	33 (0.24)	0.94 (0.58–1.54)	
Other cardiovascular death	195 (1.4)	177 (1.3)	1.10 (0.90–1.35)	
Death from any cause	444 (3.2)	426 (3.1)	1.04 (0.91–1.19)	0.54
Myocardial infarction	468 (3.4)	639 (4.6)	0.73 (0.65–0.82)	<0.001
Hospitalization for unstable angina	236 (1.7)	239 (1.7)	0.99 (0.82–1.18)	0.89
Stroke	207 (1.5)	262 (1.9)	0.79 (0.66–0.95)	0.01
Ischemic	171 (1.2)	226 (1.6)	0.75 (0.62–0.92)	
Hemorrhagic	29 (0.21)	25 (0.18)	1.16 (0.68–1.98)	
Unknown	13 (0.09)	14 (0.10)	0.93 (0.44–1.97)	
Coronary revascularization	759 (5.5)	965 (7.0)	0.78 (0.71–0.86)	<0.001
Urgent	403 (2.9)	547 (4.0)	0.73 (0.64–0.83)	
Elective	420 (3.0)	504 (3.7)	0.83 (0.73–0.95)	
Cardiovascular death or hospitalization for worsening heart failure	402 (2.9)	408 (3.0)	0.98 (0.86–1.13)	0.82
Ischemic stroke or transient ischemic attack	229 (1.7)	295 (2.1)	0.77 (0.65–0.92)	0.003
CTTC composite end point†	1271 (9.2)	1512 (11.0)	0.83 (0.77–0.90)	<0.001

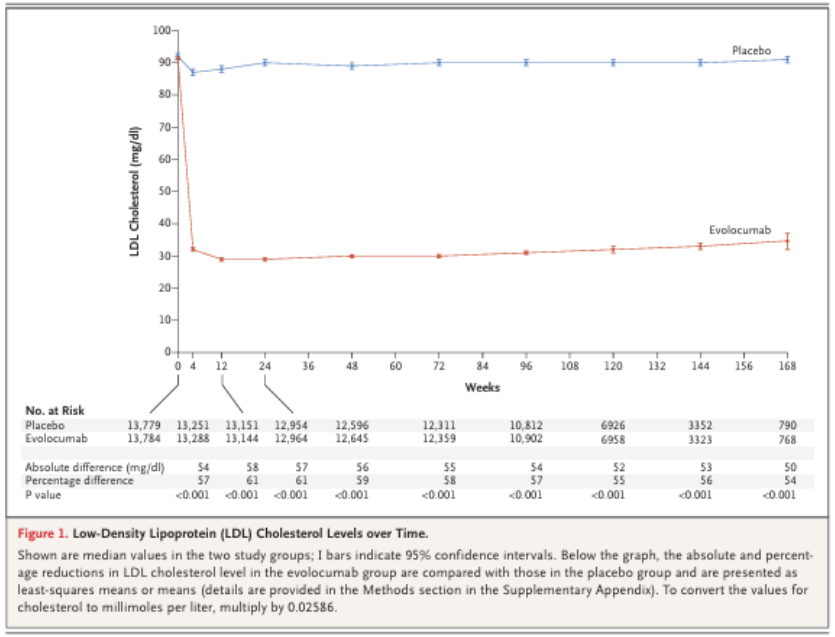
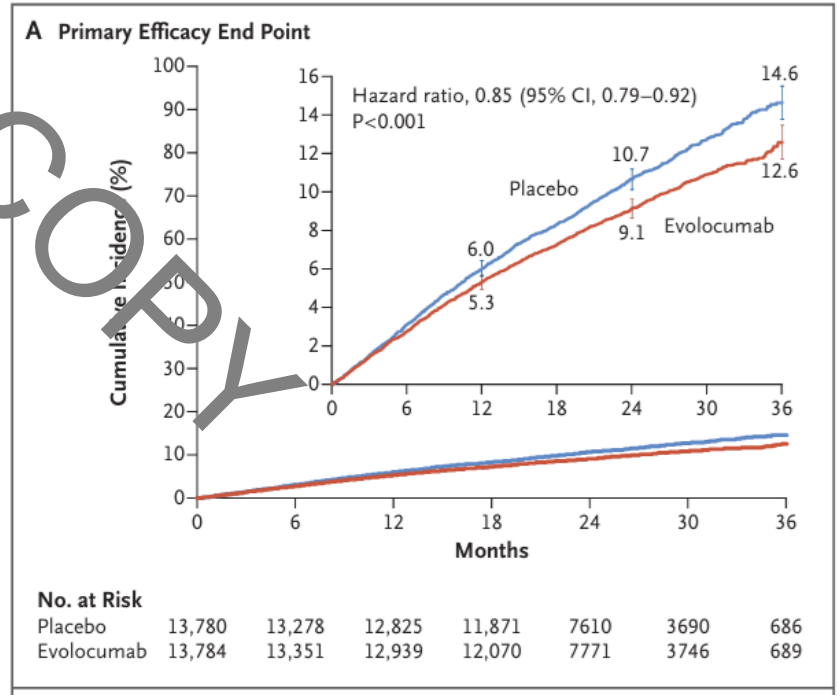


Figure 1. Low-Density Lipoprotein (LDL) Cholesterol Levels over Time.

Shown are median values in the two study groups; I bars indicate 95% confidence intervals. Below the graph, the absolute and percentage reductions in LDL cholesterol level in the evolocumab group are compared with those in the placebo group and are presented as least-squares means or means (details are provided in the Methods section in the Supplementary Appendix). To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.



Sabatine MS, et al; FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017 May 4;376(18):1713-1722. doi: 10.1056/NEJMoa1615664. Epub 2017 Mar 17. PMID: 28304224.

PCSK9i (3)

Table 3. Adverse Events and Laboratory Test Results.

Outcome	Evolocumab (N = 13,769)	Placebo (N = 13,756)
Adverse events — no. of patients (%)		
Any	10,664 (77.4)	10,644 (77.4)
Serious	3410 (24.8)	3404 (24.7)
Thought to be related to the study agent and leading to discontinuation of study regimen	226 (1.6)	201 (1.5)
Injection-site reaction*	296 (2.1)	219 (1.6)
Allergic reaction	420 (3.1)	393 (2.9)
Muscle-related event	682 (5.0)	656 (4.8)
Rhabdomyolysis	(0.1)	11 (0.1)
Cataract		242 (1.8)
Adjudicated case of new-onset diabetes†		644 (7.7)
Neurocognitive event	217 (1.6)	202 (1.5)
Laboratory results — no. of patients/total no. (%)		
Aminotransferase level >3 times the upper limit of the normal range	240/13,543 (1.8)	242/13,523 (1.8)
Creatine kinase level >5 times the upper limit of the normal range	95/13,543 (0.7)	99/13,523 (0.7)

Sabatine MS, et al; FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017 May 4;376(18):1713-1722. doi: 10.1056/NEJMoa1615664. Epub 2017 Mar 17. PMID: 28304224.

Advice

following resubmission:

evolocumab (Repatha®) is accepted for restricted use within NHS Scotland.

Indication under review: in adults with primary hypercholesterolaemia (heterozygous familial hypercholesterolaemia and non-familial) or mixed dyslipidaemia, as an adjunct to diet:
• in combination with a statin or statin with other lipid lowering therapies in patients unable to reach low density lipoprotein-cholesterol (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 contraindicated.

SMC restriction: for specialist use only, when administered at a dose of 140mg every two weeks, in patients at high cardiovascular risk as follows:
• patients with heterozygous familial hypercholesterolaemia (HeFH) and LDL-C ≥5.0mmol/L for primary prevention of cardiovascular events or,
• patients with HeFH and LDL-C ≥3.5mmol/L for secondary prevention of cardiovascular events or,
• patients at high risk due to previous cardiovascular events and LDL-C ≥4.0mmol/L or
• patients with recurrent/polyvascular disease and LDL-C ≥3.5mmol/L

https://scottishmedicines.org.uk/medicines-advice/evolocumab-repatha-resubmission-114816/

Bempedoic Acid (1)

The NEW ENGLAND JOURNAL of MEDICINE

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Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

S.E. Nissen, A.M. Lincoff, D. Brennan, K.K. Ray, D. Mason, J.J.P. Kastelein, P.D. Thompson, P. Libby, L. Cho, J. Plutzky, H.E. Bays, P.M. Moriarty, V. Menon, D.E. Grobbee, M.J. Louie, C.-F. Chen, N. Li, L.A. Bloedon, P. Robinson, M. Horner, W.J. Sasiela, J. McCluskey, D. Davey, P. Fajardo-Campos, P. Petrovic, J. Fedacko, W. Zmuda, Y. Lukyanov, and S.J. Nicholls, for the CLEAR Outcomes Investigators*

TRIAL POPULATION

Patients 18 to 85 years of age were eligible if they met either of two criteria for increased cardiovascular risk — a previous cardiovascular event (secondary-prevention patients) or clinical features that placed them at high risk for a cardiovascular event (primary-prevention patients).[13]

Table 1. Demographic and Baseline Patient Characteristics in the Intention-to-Treat Population.*

Characteristic	Bempedoic Acid (N=6992)	Placebo (N=6978)
Age		
Mean — yr	65.5±9.0	65.5±8.9
Distribution — no. (%)		
<65 yr	2859 (40.9)	2907 (41.7)
≥65 to <75 yr	3070 (43.9)	3027 (43.4)
≥75 yr	1063 (15.2)	1044 (15.0)
Female sex — no. (%)	3361 (48.1)	3379 (48.4)
White race — no. (%)†	6397 (91.5)	6335 (90.8)
Hispanic or Latinx — no. (%)†	1190 (17.0)	1143 (16.4)
Body-mass index‡	29.9±5.2	30.0±5.2
LDL cholesterol		
Mean value — mg/dl	139.0±34.9	139.0±35.2
Distribution — no. (%)		
<130 mg/dl	3074 (44.0)	3089 (44.3)
≥130 to <160 mg/dl	2213 (31.7)	2250 (32.2)
≥160 mg/dl	1705 (24.4)	1639 (23.5)
HDL cholesterol — mg/dl	49.6±13.3	49.4±13.3
Non-HDL cholesterol — mg/dl	173.8±39.5	173.9±40.2
Total cholesterol — mg/dl	223.5±40.6	223.3±41.1
Median triglycerides (IQR) — mg/dl	159.5 (118.0–216.5)	158.5 (118.0–215.0)
Median high-sensitivity CRP (IQR) — mg/liter	2.3 (1.2–4.5)	2.3 (1.2–4.5)
Estimated GFR — no. (%)		
≥90 ml/min/1.73 m²	1216 (17.4)	1233 (17.7)
≥60 to <90 ml/min/1.73 m²	4322 (61.8)	4282 (61.4)
≥30 to <60 ml/min/1.73 m²	1437 (20.6)	1444 (20.7)
Cardiovascular risk category — no. (%)		
Primary prevention	2100 (30.0)	2106 (30.2)
Secondary prevention	4892 (70.0)	4872 (69.8)
Coronary artery disease	3574 (51.1)	3536 (50.7)
Peripheral arterial disease	794 (11.4)	830 (11.9)
Cerebrovascular atherosclerotic disease	1027 (14.7)	1040 (14.9)
Glycemic status — no. (%)		
Diabetes§	3144 (45.0)	3229 (46.3)
Inadequately controlled diabetes¶	1356 (19.4)	1369 (19.6)
Statin use — no. (%)	1601 (22.9)	1573 (22.5)
Ezetimibe use — no. (%)	803 (11.5)	809 (11.6)

Nissen SE, et al; CLEAR Outcomes Investigators. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. N Engl J Med. 2023 Apr 13;388(15):1353-1364. doi: 10.1056/NEJMoa2215024. Epub 2023 Mar 4. PMID: 36876740.

Bempedoic Acid (2)

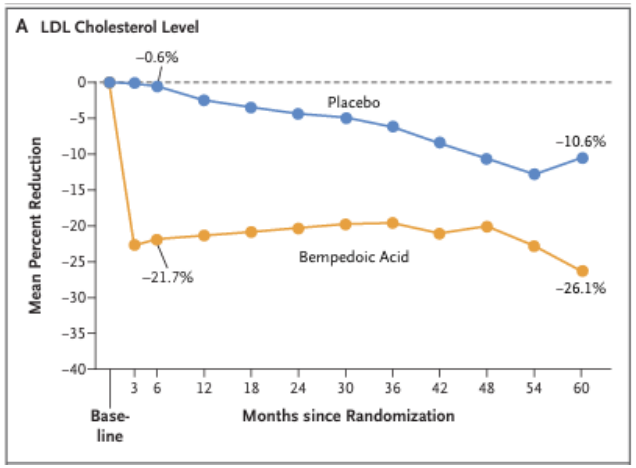
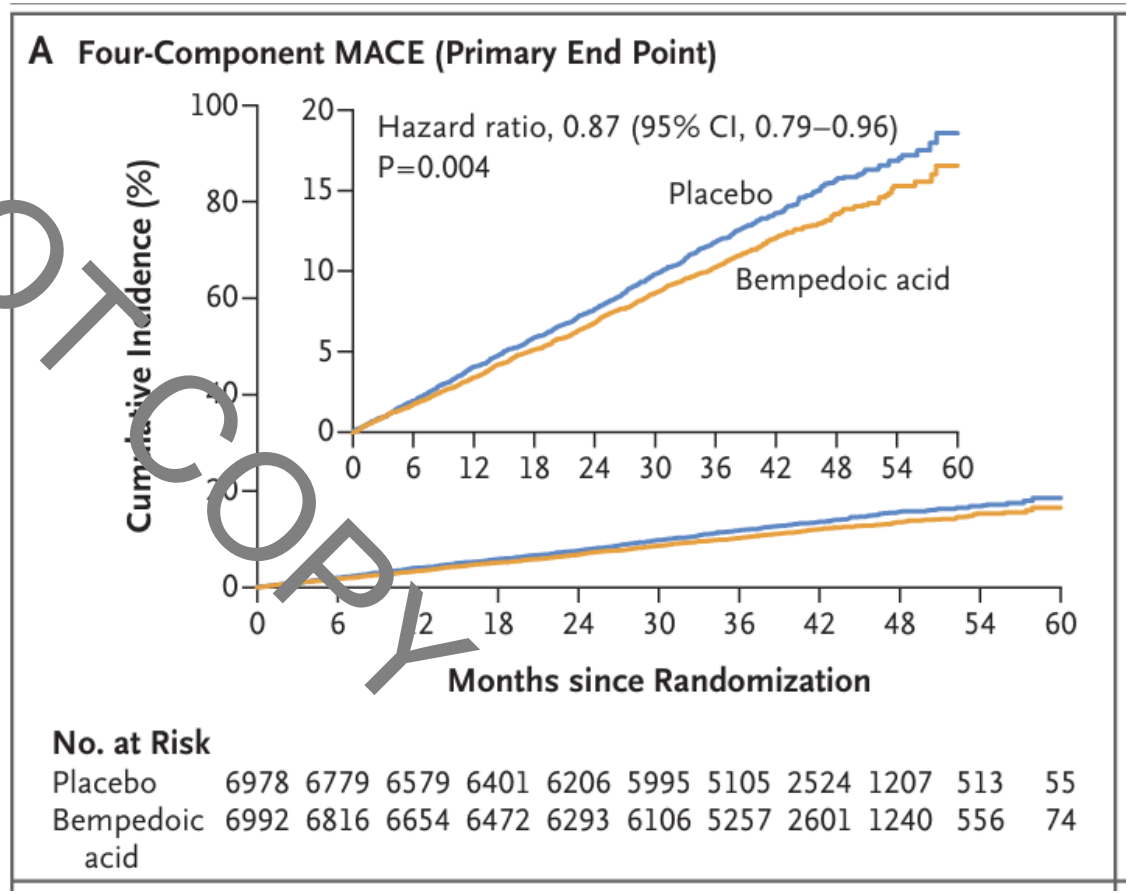


Table 2. Efficacy End Points in the Intention-to-Treat Population.*

Outcome	Bempedoic Acid (N=6992)	Placebo (N=6978)	Difference (95% CI)*	P Value†
Primary efficacy end point				
Four-component MACE — no. (%)‡	819 (11.7)	927 (13.3)	0.87 (0.79 to 0.96)	0.004
Key secondary efficacy end points				
Three-component MACE — no. (%)§	575 (8.2)	663 (9.5)	0.85 (0.76 to 0.96)	0.006
Fatal or nonfatal myocardial infarction — no. (%)	261 (3.7)	334 (4.8)	0.77 (0.66 to 0.91)	0.002
Coronary revascularization — no. (%)	435 (6.2)	529 (7.6)	0.81 (0.72 to 0.92)	0.001
Fatal or nonfatal stroke — no. (%)	135 (1.9)	158 (2.3)	0.85 (0.67 to 1.07)	0.16
Death from cardiovascular causes — no. (%)	269 (3.8)	257 (3.7)	1.04 (0.88 to 1.24)	
Death from any cause — no. (%)	434 (6.2)	420 (6.0)	1.03 (0.90 to 1.18)	
Additional secondary end points				
Death from any cause, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization — no. (%)	962 (13.8)	1062 (15.2)	0.89 (0.82 to 0.97)	
Five-component MACE — no. (%)¶	831 (11.9)	952 (13.6)	0.86 (0.78 to 0.94)	
Hospitalization for unstable angina — no. (%)	91 (1.3)	137 (2.0)	0.66 (0.50 to 0.86)	
New-onset type 2 diabetes mellitus — no./total no. (%)‖	429/3848 (11.1)	433/3749 (11.5)	0.95 (0.83 to 1.09)	
Change from baseline in secondary lipid and biomarker efficacy end points				
Mean percent change in mean LDL cholesterol level at 6 mo (95% CI)**	−21.1 (−21.6 to −20.5)	−0.8 (−1.4 to −0.2)	−20.3 (−21.1 to −19.5)	
Median percent change in high-sensitivity CRP level at 6 mo (95% CI)	−22.2 (−23.5 to −20.8)	2.4 (0.0 to 4.2)	−21.6 (−23.7 to −19.6)	
Mean percentage-point change in glycated hemoglobin level at 12 mo in patients with inadequately controlled type 2 diabetes mellitus (95% CI)**††	−0.04 (−0.12 to 0.03)	−0.01 (−0.09 to 0.06)	−0.03 (−0.14 to 0.08)	



Nissen SE, et al; CLEAR Outcomes Investigators. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. N Engl J Med. 2023 Apr 13;388(15):1353-1364. doi: 10.1056/NEJMoa2215024. Epub 2023 Mar 4. PMID: 36876740.

Bempedoic Acid (3)

Table 3. Investigator-Reported Adverse Events and Laboratory Safety-Related Findings in the Safety Population.*

Event	Bempedoic Acid (N=7001)	Placebo (N=6964)
Any adverse event that started or worsened after the first dose of a trial agent — no. (%)	6040 (86.3)	5919 (85.0)
Serious adverse event that started or worsened after the first dose of a trial agent — no. (%)	1767 (25.2)	1733 (24.9)
Adverse event leading to discontinuation of the trial regimen — no. (%)	759 (10.8)	722 (10.4)
Prespecified adverse events of special interest		
Myalgia — no. (%)	393 (5.6)	471 (6.8)
Discontinuation of the trial regimen because of myalgia — no. (%)	124 (1.8)	129 (1.9)
New-onset diabetes in patients without diabetes at baseline — no./total no. (%)	621/3856 (16.1)	640/3740 (17.1)
New-onset diabetes in patients with prediabetes at baseline — no./total no. (%)†	569/2913 (19.5)	586/2877 (20.4)
New-onset diabetes in patients with normoglycemia at baseline — no./total no. (%)†	52/938 (5.5)	54/863 (6.3)
Worsening hyperglycemia — no./total no. (%)‡	713/3145 (22.7)	746/3224 (23.1)
Hypoglycemia — no. (%)	304 (4.3)	267 (3.8)
Metabolic acidosis — no. (%)	13 (0.2)	14 (0.2)
Elevated hepatic-enzyme level — no. (%)	317 (4.5)	279 (4.0)
Renal impairment — no. (%)	802 (11.5)	598 (8.6)
Neurocognitive disorders — no. (%)	58 (0.8)	69 (1.0)
Atrial fibrillation — no. (%)	229 (3.3)	246 (3.5)
Adjudicated tendon rupture — no. (%)	86 (1.2)	66 (0.9)
Tendinopathies — no. (%)	118 (1.7)	128 (1.8)
Malignant conditions — no. (%)	321 (4.6)	341 (4.9)
Other adverse events — no. (%)		
Hyperuricemia	763 (10.9)	393 (5.6)
Gout	215 (3.1)	143 (2.1)
Cholelithiasis	152 (2.2)	81 (1.2)

Nissen SE, et al; CLEAR Outcomes Investigators. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. N Engl J Med. 2023 Apr 13;388(15):1353-1364. doi: 10.1056/NEJMoa2215024. Epub 2023 Mar 4. PMID: 36876740.

Bempedoic Acid (4)

Indication under review: in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

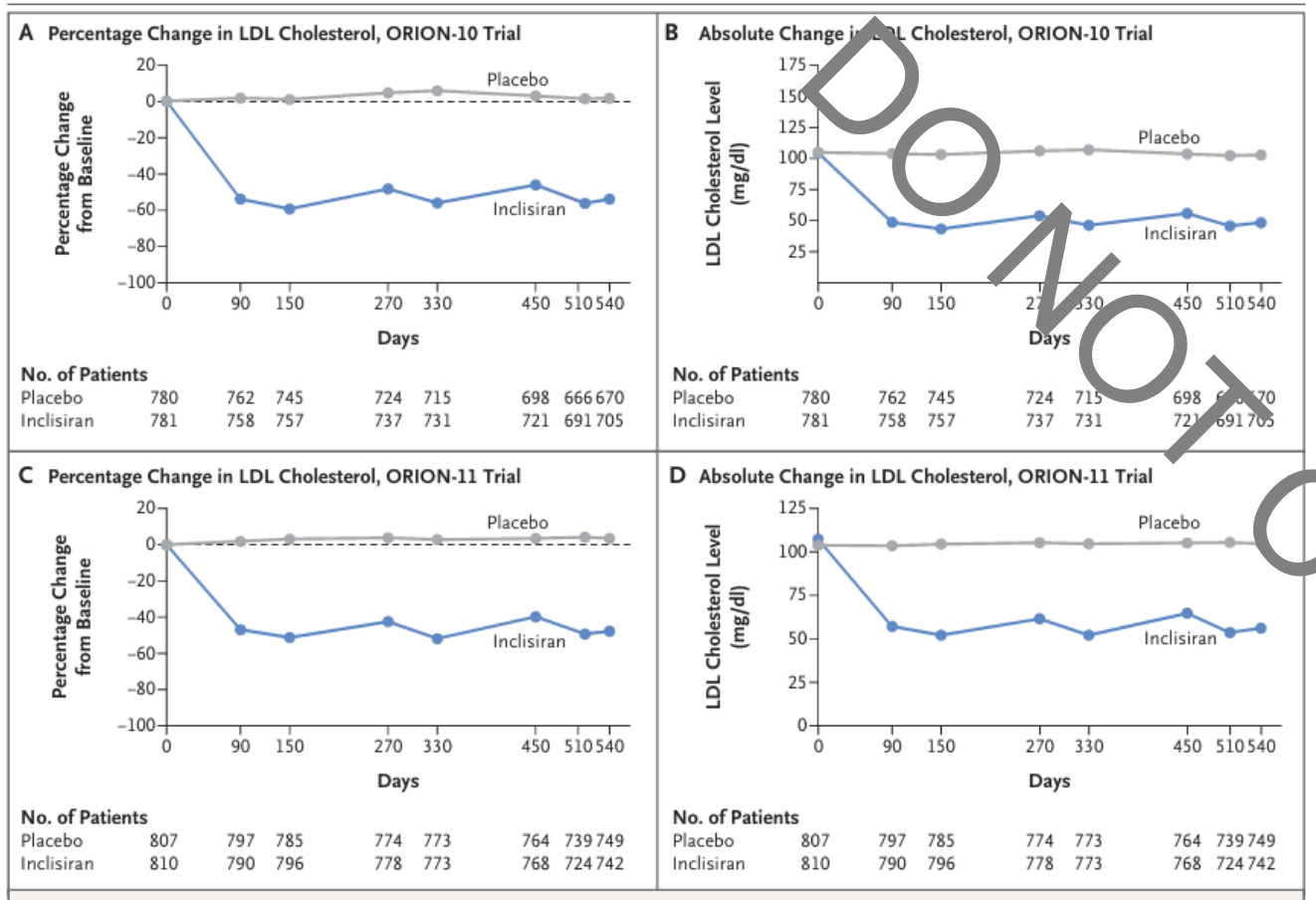
- in combination with a statin in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin in addition to ezetimibe
- alone in patients who are either statin-intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals with ezetimibe alone
- in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin.

SMC restriction: for use in patients who are:

- statin intolerant or for whom a statin is contra-indicated
- where ezetimibe alone does not appropriately control LDL-C
- where proprotein convertase subtilisin/ kexin type 9 (PCSK9) inhibitors are not appropriate

https://scottishmedicines.org.uk/medicines-advice/bempedoic-acidezetimibe-nustendi-abb-smc2406/

Inclisiran



- Injection every 6 months (need to be administered by healthcare professional)
- No outcome data yet (due late-2026 / early-2027)
- Typically reserved for Lipid Clinic only for patients who do not tolerate or do not respond to PSCK9i

Ray KK, el at; ORION-10 and ORION-11 Investigators. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. N Engl J Med. 2020 Apr 16;382(16):1507-1519. doi: 10.1056/NEJMoa1912387. Epub 2020 Mar 18. PMID: 32187462.

Icosapent Ethyl (Vazkepa)

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Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

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BACKGROUND

Patients with elevated triglyceride levels are at increased risk for ischemic events. Icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, lowers triglyceride levels, but data are needed to determine its effects on ischemic events.

METHODS

We performed a multicenter, randomized, double-blind, placebo-controlled trial involving patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135 to 499 mg per deciliter (1.52 to 5.63 mmol per liter) and a low-density lipoprotein cholesterol level of 41 to 100 mg per deciliter (1.06 to 2.59 mmol per liter). The patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total daily dose, 4 g) or placebo. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The key secondary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

RESULTS

A total of 8179 patients were enrolled (70.7% for secondary prevention of cardiovascular events) and were followed for a median of 4.9 years. A primary end-point event occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22.0% of the patients in the placebo group (hazard ratio, 0.75; 95% confidence interval [CI], 0.68 to 0.83; P<0.001); the corresponding rates of the key secondary end point were 11.2% and 14.8% (hazard ratio, 0.74; 95% CI, 0.65 to 0.83; P<0.001). The rates of additional ischemic end points, as assessed according to a prespecified hierarchical schema, were significantly lower in the icosapent ethyl group than in the placebo group, including the rate of cardiovascular death (4.3% vs. 5.2%; hazard ratio, 0.80; 95% CI, 0.66 to 0.98; P=0.03). A larger percentage of patients in the icosapent ethyl group than in the placebo group were hospitalized for atrial fibrillation or flutter (3.1% vs. 2.1%; P=0.004). Serious bleeding events occurred in 2.7% of the patients in the icosapent ethyl group and in 2.1% in the placebo group (P=0.06).

CONCLUSIONS

Among patients with elevated triglyceride levels despite the use of statins, the risk of ischemic events, including cardiovascular death, was significantly lower among those who received 2 g of icosapent ethyl twice daily than among those who received placebo. (Funded by Amarin Pharma; REDUCE-IT ClinicalTrials.gov number, NCT01492361.)

- Probably not for routine use in patients following ACS, due to increased risk of AF and potentially bleeds

Bhatt DL, et al; REDUCE-IT Investigators. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med. 2019 Jan 3;380(1):11-22. doi: 10.1056/NEJMoa1812792. Epub 2018 Nov 10. PMID: 30415628.

Thanks!

Questions?