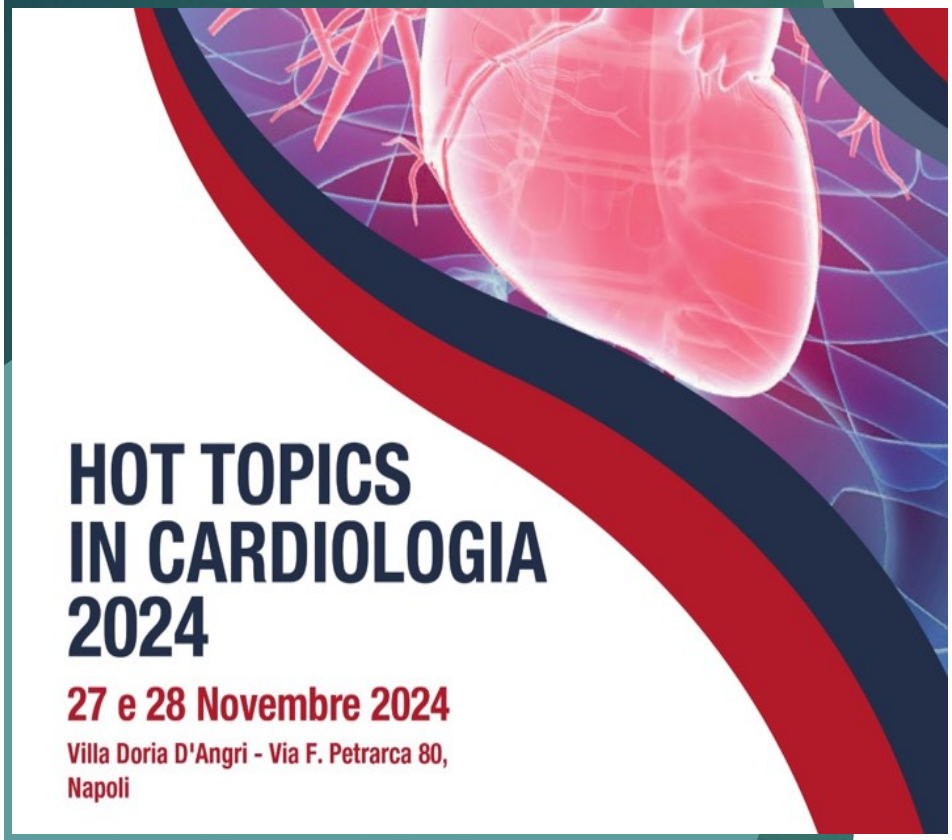


V Sessione:
Cuore e Dislipidemie

- Press Review -

Alessandro Bellis, MD PhD

UTIC con Emodinamica
A.O.R.N. Antonio Cardarelli Napoli

ESC European Society of Cardiology

European Journal of Preventive Cardiology (2024) **31**, 1820–1830
https://doi.org/10.1093/eurjpc/zwae254

FULL RESEARCH PAPER
Lipids & atherosclerosis

In-silico trial emulation to predict the cardiovascular protection of new lipid-lowering drugs: an illustration through the design of the SIRIUS programme

Denis Angoulvant [1]*†, Solène Granjeon-Noriot[2]†, Pierre Amarenco[3], Alexandre Bastien[4], Emmanuelle Bechet[2], Franck Boccara[5], Jean-Pierre Boissel[2], Bertrand Cariou[6], Eulalie Courcelles[2], Alizée Diatchenko[2], Anne Filipovics[4], Riad Kahoul[2], Guillaume Mahé[7], Emmanuel Peyronnet[2], Lolita Portal[4], Solène Porte[2], Yishu Wang[2], and Philippe Gabriel Steg[8]

[1]Cardiology Department, Hôpital Trousseau, CHRU de Tours & Inserm U1327 ISCHEMIA 'Membrane Signalling and Inflammation in Reperfusion Injuries', Université de Tours, 10 boulevard Tonnellé, F37000, Tours, France; [2]Novadiscovery, Lyon, France; [3]Department of Neurology and Stroke Center, APHP, Bichat Hospital, Université Paris-Cité Paris, France and McMaster University, Population Health Research Institute, Hamilton, Ontario, Canada; [4]Novartis, Rueil Malmaison, France; [5]Sorbonne Université, GRC n°22, C2MV-Complications Cardiovasculaires et Métaboliques chez les patients vivant avec le Virus de l'immunodéficience humaine, Inserm UMR_S 938, Centre de Recherche Saint-Antoine, Institut Hospitalo-Universitaire de Cardio-métabolisme et Nutrition (ICAN), Cardiologie, Hôpital Saint Antoine AP-HP, Paris, France; [6]Nantes Université, CHU Nantes, CNRS, Inserm, l'institut du thorax, F-44000 Nantes, France; [7]Vascular Medicine Unit, CHU Rennes, Univ Rennes CIC1414, Rennes, France; and [8]Université Paris-Cité, AP-HP, Hôpital Bichat, and FACT, INSERM U-1148/LVTS, Paris, France

Received 1 May 2024; revised 1 July 2024; accepted 22 July 2024; online publish-ahead-of-print 5 August 2024

See the editorial comment for this article 'Is it time to get SIRIUS about *in silico* modelling of cardiovascular outcomes trials?', by M.P. Bonaca *et al.*, https://doi.org/10.1093/eurjpc/zwae329.

Introduction Inclisiran, an siRNA targeting hepatic PCSK9 mRNA, administered twice-yearly (after initial and 3-month doses), substantially and sustainably reduced LDL-cholesterol (LDL-C) in Phase III trials. Whether lowering LDL-C with inclisiran translates into a reduced risk of major adverse cardiovascular events (MACE) is not yet established. In-silico trials applying a disease computational model to virtual patients receiving new treatments allow to emulate large scale long-term clinical trials. The SIRIUS in-silico trial programme aims to predict the efficacy of inclisiran on CV events in individuals with established atherosclerotic cardiovascular disease (ASCVD).

Methods and results A knowledge-based mechanistic model of ASCVD was built, calibrated, and validated to conduct the SIRIUS programme (NCT05974345) aiming to predict the effect of inclisiran on CV outcomes. The SIRIUS Virtual Population included patients with established ASCVD (previous myocardial infarction (MI), previous ischemic stroke (IS), previous symptomatic lower limb peripheral arterial disease (PAD) defined as either intermittent claudication with ankle-brachial index <0.85, prior peripheral arterial revascularization procedure, or vascular amputation) and fasting LDL-C ≥ 70 mg/dL, despite stable (≥4 weeks) well-tolerated lipid-lowering therapies.

SIRIUS is an in-silico multi-arm trial programme. It follows an idealized crossover design where each virtual patient is its own control, comparing inclisiran to (i) placebo as adjunct to high-intensity statin therapy with or without ezetimibe, (ii) ezetimibe as adjunct to high-intensity statin therapy, (iii) evolocumab as adjunct to high-intensity statin therapy and ezetimibe.

The co-primary efficacy outcomes are based on the time to the first occurrence of any component of 3P-MACE (composite of CV death, nonfatal MI, or nonfatal IS) and time to occurrence of CV death over 5 years.

Perspectives/ conclusion The SIRIUS in-silico trial programme will provide early insights regarding potential effect of inclisiran on MACE in ASCVD patients, several years before the availability of the results from ongoing CV outcomes trials (ORION-4 and VICTORION-2-P).

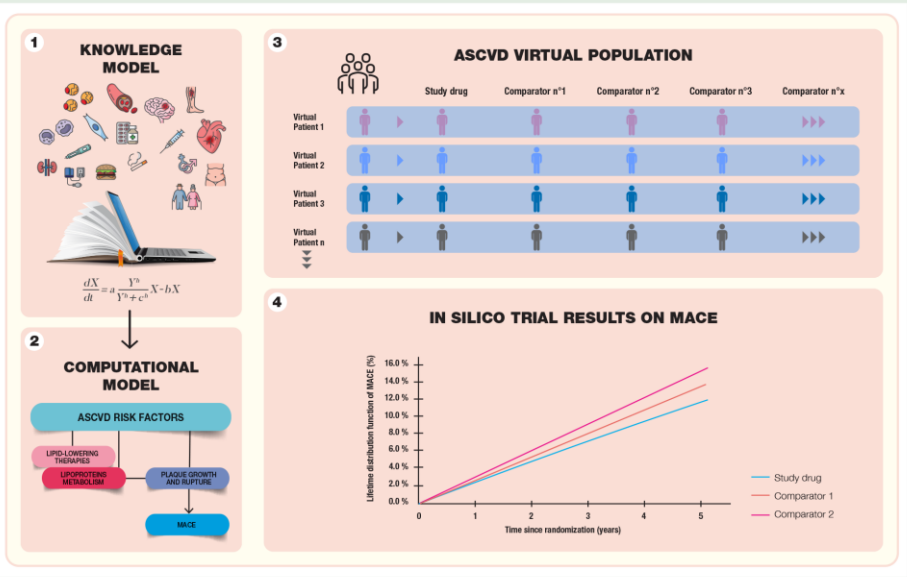
Clinical trial registration Clinicaltrials.gov identifier: NCT05974345

Lay summary The SIRIUS in-silico trial programme is a knowledge-based computer model built to simulate the biological and clinical long-term effects of inclisiran, an siRNA targeting hepatic PCSK9 mRNA, on virtual patients with cardiovascular disease.

Key findings

- The model accurately replicates the biological processes of cardiovascular disease and the impact of lipid-lowering therapies, allowing for the prediction of randomized clinical trials.
- Simulating clinical trials with virtual patients can provide insights into the efficacy and safety of new treatments before the results of randomized clinical trials, potentially speeding up the drug development process.

Graphical Abstract



In-silico modelling applying a disease knowledge-based mechanistic computational model to virtual patients receiving various treatments allow to emulate large-scale long-term in-silico clinical trials. The ASCVD and therapeutics knowledge-based mechanistic model captures, by using mathematical equations, the functional relationships between the biological entities involved in pathophysiology of ASCVD and the mechanisms of action of lipid lowering therapies. **A knowledge model** corresponds to an extensive bibliographical review to collect and organize knowledge on biochemical and cellular processes of interest, pathophysiological mechanisms involved in the development and progression of ASCVD and mechanisms of action of the drugs of interest. The knowledge model is then translated into mathematical equations to obtain **a computational model.** The ASCVD knowledge-based mechanistic model is applied to an ASCVD virtual population which corresponds to a collection of virtual patients generated *in-silico* to capture realistic inter-patient variability. Each virtual patient corresponds to a set of values for each model parameter. The ASCVD model is applied to the ASCVD virtual population (in which each patient is his own control) allowing to emulate multi-arm, large scale and long-term in-silico trials.

Keywords Atherosclerotic cardiovascular disease • Knowledge-based mechanistic model • Lipid lowering therapy • In silico trial • Inclisiran • PCSK9 SiRNA

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 84, NO. 2, 2024

Comparative Cardiovascular Benefits of Bempedoic Acid and Statin Drugs

A. Michael Lincoff, MD,[a] Kausik K. Ray, MD,[b] William J. Sasiela, PhD,[c] Tariq Haddad, MD,[d] Stephen J. Nicholls, MBBS, PhD,[e] Na Li, PhD,[c] Leslie Cho, MD,[a] Denise Mason, BSN,[a] Peter Libby, MD,[f] Shaun G. Goodman, MD, MSc,[g,h] Steven E. Nissen, MD[a]

ABSTRACT

BACKGROUND In the CLEAR (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) Outcomes trial, treatment of statin-intolerant patients with bempedoic acid produced a 21% decrease in low-density lipoprotein cholesterol (LDL-C) relative to placebo and a 13% relative reduction in the risk of major adverse cardiovascular events.

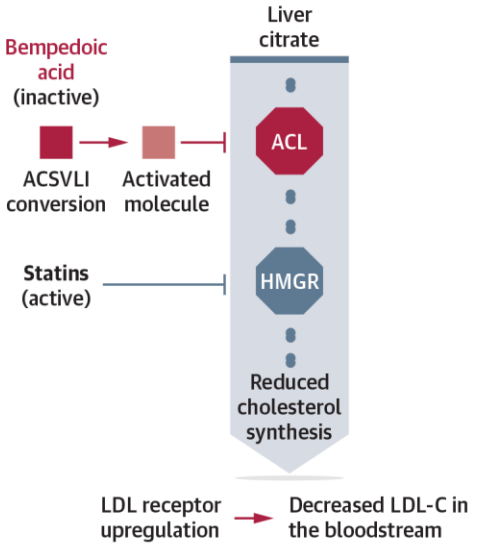
OBJECTIVES This study sought to determine whether the relationship between LDL-C lowering and cardiovascular benefit achieved with bempedoic acid resembles that observed with statins when standardized per unit change in LDL-C.

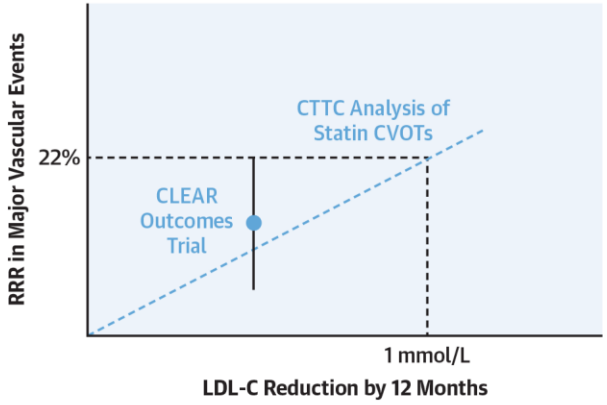
METHODS To compare the treatment effect of bempedoic acid with statins, the methodology of the Cholesterol Treatment Trialists' Collaboration (CTTC) was applied to outcomes among the 13,970 patients enrolled in the CLEAR Outcomes trial. The CTTC endpoint of "major vascular event" was a composite of coronary heart disease death, nonfatal myocardial infarction, fatal or nonfatal stroke, or coronary revascularization. HRs for CTTC-defined endpoints were normalized to 1 mmol/L differences in LDL-C levels between bempedoic acid and placebo groups.

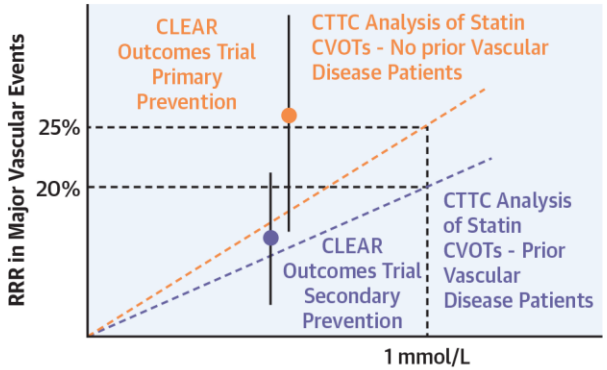
RESULTS A first major vascular event occurred in 703 (10.1%) patients in the bempedoic acid group and 816 (11.7%) patients in the placebo group (HR: 0.85; 95% CI: 0.77-0.94). When normalized per 1 mmol/L reduction in LDL-C, the HR was 0.75 (95% CI: 0.63-0.90), comparable to the rate ratio of 0.78 reported for statins in the CTTC meta-analysis. Normalized risk reductions were similar for bempedoic acid and statins for the endpoints of major coronary events, nonfatal myocardial infarction, and coronary revascularization.

CONCLUSIONS Cardiovascular risk reduction with bempedoic acid is similar to that achieved with statins for a given absolute magnitude of LDL-C lowering. (Evaluation of Major Adverse Cardiovascular Events in Participants With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated with Bempedoic Acid [ETC-1002] or Placebo [CLEAR Outcomes]; NCT02993406). (J Am Coll Cardiol 2024;84:152-162) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

CENTRAL ILLUSTRATION **Reduction in Vascular Events by Bempedoic Acid Compared With Statins**







Lincoff AM, et al. J Am Coll Cardiol. 2024;84(2):152-162.

Relative risk reductions (RRRs) and 95% CIs in major vascular events by bempedoic acid in the CLEAR (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) Outcomes trial by reduction in low-density lipoprotein cholesterol (LDL-C) at 1 year, plotted along the normalized relative risk reduction for statins from the 2010 Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis.
ACL = adenosine triphosphate citrate lyase; ACSVL1 = very long-chain acyl-CoA synthetase; CVOT = cardiovascular outcome trial; HMGR = HMG-CoA reductase; LDL = low-density lipoprotein.

Drugs
https://doi.org/10.1007/s40265-024-02105-5

REVIEW ARTICLE

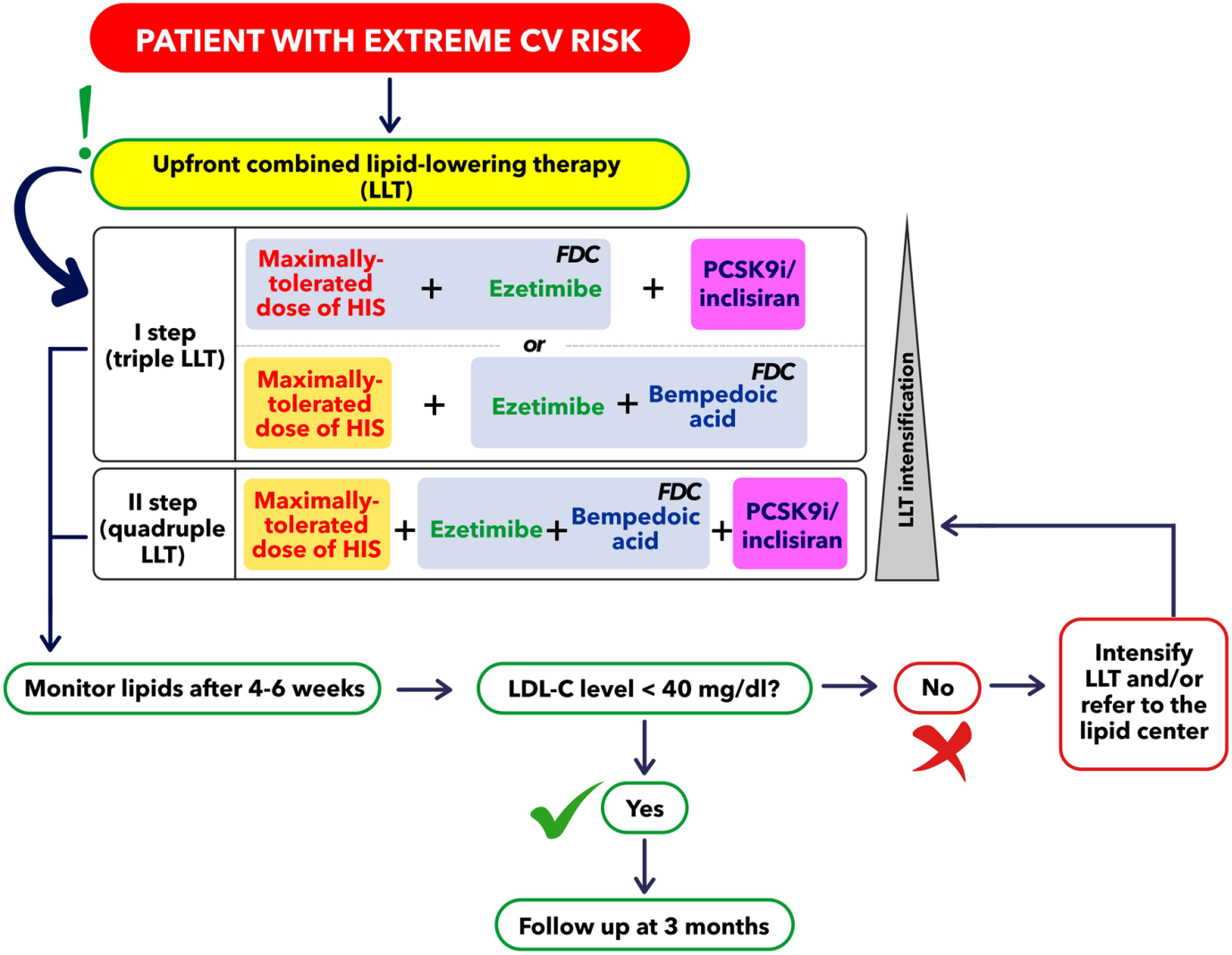
2024 Recommendations on the Optimal Use of Lipid-Lowering Therapy in Established Atherosclerotic Cardiovascular Disease and Following Acute Coronary Syndromes: A Position Paper of the International Lipid Expert Panel (ILEP)

Maciej Banach · Željko Reiner · Stanisław Surma · Gani Bajraktari · Agata Bielecka-Dabrowa · Matjaz Bunc, et al. ***[full author details at the end of the article]***

Accepted: 30 September 2024

Abstract

Atherosclerotic cardiovascular disease (ASCVD) and consequent acute coronary syndromes (ACS) are substantial contributors to morbidity and mortality across Europe. Fortunately, as much as two thirds of this disease's burden is modifiable, in particular by lipid-lowering therapy (LLT). Current guidelines are based on the sound premise that, with respect to low-density lipoprotein cholesterol (LDL-C), "lower is better for longer", and recent data have strongly emphasised the need for also "the earlier the better". In addition to statins, which have been available for several decades, ezetimibe, bempedoic acid (also as fixed dose combinations), and modulators of proprotein convertase subtilisin/kexin type 9 (PCSK9 inhibitors and inclisiran) are additionally very effective approaches to LLT, especially for those at very high and extremely high cardiovascular risk. In real life, however, clinical practice goals are still not met in a substantial proportion of patients (even in 70%). However, with the options we have available, we should render lipid disorders a rare disease. In April 2021, the International Lipid Expert Panel (ILEP) published its first position paper on the optimal use of LLT in post-ACS patients, which complemented the existing guidelines on the management of lipids in patients following ACS, which defined a group of "extremely high-risk" individuals and outlined scenarios where upfront combination therapy should be considered to improve access and adherence to LLT and, consequently, the therapy's effectiveness. These updated recommendations build on the previous work, considering developments in the evidential underpinning of combination LLT, ongoing education on the role of lipid disorder therapy, and changes in the availability of lipid-lowering drugs. Our aim is to provide a guide to address this unmet clinical need, to provide clear practical advice, whilst acknowledging the need for patient-centred care, and accounting for often large differences in the availability of LLTs between countries.


PATIENT WITH EXTREME CV RISK
Upfront combined lipid-lowering therapy (LLT)
I step (triple LLT)
Maximally-tolerated dose of HIS
+
FDC
Ezetimibe
+
PCSK9i/ inclisiran
or
Maximally-tolerated dose of HIS
+
Ezetimibe
+
FDC
Bempedoic acid
II step (quadruple LLT)
Maximally-tolerated dose of HIS
+
Ezetimibe
+
FDC
Bempedoic acid
+
PCSK9i/ inclisiran
LLT intensification
Monitor lipids after 4-6 weeks
LDL-C level < 40 mg/dl?
No
Intensify LLT and/or refer to the lipid center
Yes
Follow up at 3 months

The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Review

J Atheroscler Thromb, 2024; 31: 1479-1495. http://doi.org/10.5551/jat.RV22024

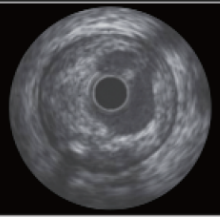
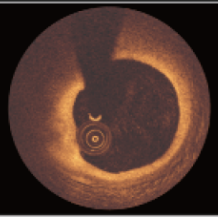
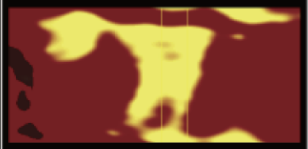
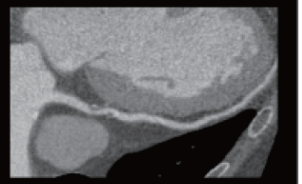
Lipid-lowering Therapy and Coronary Plaque Regression

Yasushi Ueki, Tadashi Itagaki and Koichiro Kuwahara

Department of Cardiovascular Medicine, Shinshu University Hospital, Nagano, Japan

Lipid-lowering therapy plays a central role in reducing cardiovascular events. Over the past few decades, clinical trials utilizing several imaging techniques have consistently shown that lipid-lowering therapy can reduce the coronary plaque burden and improve plaque composition. Although intravascular ultrasound has been the most extensively used modality to assess plaque burden, other invasive modalities, such as optical coherence tomography and near-infrared spectroscopy, provide relevant data on plaque vulnerability, and computed tomography angiography detects both plaque volume and characteristics non-invasively. A large body of evidence supports the notion that reducing low-density lipoprotein cholesterol using statins combined with ezetimibe and proprotein convertase subtillisin/kexin type 9 inhibitors consistently shows improvements in plaque burden and favorable morphological changes. This review summarizes previously obtained data on the impact of lipid-lowering treatment strategies on atherosclerotic plaque regression, as assessed using several imaging modalities.

Key words: Lipid-lowering therapy, Plaque regression, Intravascular ultrasound, Optical coherence tomography, Near-infrared spectroscopy, Computed tomography

Modality	IVUS	OCT	NIRS	CTA
				
General Characteristics				
Energy source	Ultrasound	Near-infrared light	Near-infrared light	X-ray
Resolution (μm)	80-120	10	NA	150-500
Plaque assessment				
Major variables	• PAV • TAV • Remodeling index	• FCT • Macrophage • Lipid arc	• MaxLCBI4mm • LCBI	• PAV • TAV • Plaque composition • High-risk plaque features
Atheroma volume	◎	×	×	○
Cap thickness	×	◎	×	×
Macrophage	×	◎	×	×
Lipid	×	○	◎	○
Calcification	◎	◎	×	○

ESC European Society of Cardiology

European Journal of Preventive Cardiology (2024) **31**, 1863–1875
https://doi.org/10.1093/eurjpc/zwae184

FULL RESEARCH PAPER
Lipids & atherosclerosis

Effects of omega-3 fatty acids on coronary revascularization and cardiovascular events: a meta-analysis

Monica Dinu[1], Francesco Sofi[1,2], Sofia Lotti [1], Barbara Colombini[1], Anna Vittoria Mattioli[3], Alberico L. Catapano[4,5], Manuela Casula [4,5], Andrea Baragetti [4,5], Nathan D. Wong[6], Philippe Gabriel Steg [7], and Giuseppe Ambrosio [8]*

[1]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; [2]Unit of Clinical Nutrition, Careggi University Hospital, Florence, Italy; [3]Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena, Italy; [4]IRCCS MultiMedica, Milan, Italy; [5]Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy; [6]Division of Cardiology, University of California, Irvine, USA; [7]Université Paris-Cité, INSERM U1148, FACT French Alliance for Cardiovascular Trials, AP-HP Hopital Bichat, Paris, France; and [8]Division of Cardiology, Center for Clinical and Translational Research—CERICLET, University of Perugia School of Medicine, Ospedale S. Maria della Misericordia, Via S. Andrea delle Fratte, 06156 Perugia, Italy

Received 14 January 2024; revised 16 April 2024; accepted 18 May 2024; online publish-ahead-of-print 13 June 2024

See the editorial comment for this article 'Navigating omega-3s', by O.R. Sapir *et al.*, https://doi.org/10.1093/eurjpc/zwae261.

Aims Benefits of pharmacologic omega-3 fatty acid administration in cardiovascular prevention are controversial. Particularly, effects on coronary revascularization are unclear; also debated are specific benefits of eicosapentaenoic acid (EPA). We investigated incident coronary revascularizations, myocardial infarction (MI), stroke, heart failure (HF), unstable angina, and cardiovascular death, in subjects randomized to receive EPA or EPA + docosahexaenoic acid (EPA + DHA) vs. control.

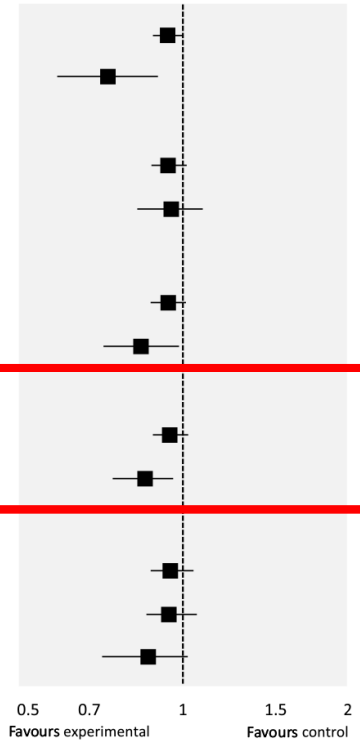
Methods and results Meta-analysis of randomized controlled trials (RCTs) was conducted after MEDLINE, Embase, Scopus, Web of Science, and Cochrane Library search. Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines were followed for abstracting data and assessing data quality and validity. Data were pooled using a random effects model. Eighteen RCTs with 134 144 participants (primary and secondary cardiovascular prevention) receiving DHA + EPA ($n = 52\,498$), EPA alone ($n = 14\,640$), or control/placebo ($n = 67\,006$) were included. Follow-up ranged from 4.5 months to 7.4 years. Overall, compared with controls, omega-3 supplementation reduced the risk of revascularization [0.90, 95% confidence interval (CI) 0.84–0.98; $P = 0.001$; P-heterogeneity = 0.0002; $I^2 = 68\%$], MI (0.89, 95% CI 0.81–0.98; $P = 0.02$; P-heterogeneity = 0.06; $I^2 = 41\%$), and cardiovascular death (0.92, 95% CI 0.85–0.99; $P = 0.02$; P-heterogeneity = 0.13; $I^2 = 33\%$). Lower risk was still observed in trials where most participants (≥60%) were on statin therapy. Compared with DHA + EPA, EPA alone showed a further significant risk reduction of revascularizations (0.76, 95% CI 0.65–0.88; $P = 0.0002$; P-interaction = 0.005) and all outcomes except HF.

Conclusion Omega-3 fatty acid supplementation reduced the risk of cardiovascular events and coronary revascularization, regardless of background statin use. Eicosapentaenoic acid alone produced greater benefits. The role of specific omega-3 molecules in primary vs. secondary prevention and the potential benefits of reduced revascularizations on overall health status and cost savings warrant further research.

Lay summary It is debated whether pharmacologic administration of omega-3 fatty acids reduces cardiac events. In particular, it is unclear whether benefits are actually restricted to the use of eicosapentaenoic acid (EPA), or whether combined administration of EPA + docosahexaenoic acid (DHA) is needed; furthermore, little is known about possible benefits of omega-3 fatty acids in reducing incidence of coronary revascularization procedures. In this meta-analysis of all published evidence of clinical trials comparing EPA alone or EPA + DHA vs. control (134 144 participants), we demonstrate the following:

B

	No. of studies	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio (95% CI)	P	I^2, %	P-het	P-int
Type of intervention											
EPA + DHA	10	3,524	46,569	3,635	46,275		0.95 [0.90, 1.00]	0.06	33%	0.15	0.005
EPA	3	642	14,540	872	14,644		0.76 [0.65, 0.88]	0.0002	44%	0.17	
EPA + DHA dose*											
≤0.9 g/day	7	3,021	39,200	3,106	38,899		0.94 [0.88, 1.01]	0.09	45%	0.09	0.81
>0.9 g/day	3	503	7,369	529	7,376		0.96 [0.82, 1.13]	0.65	17%	0.30	
EPA dose											
≤0.7 g/day	7	3,021	39,200	3,106	38,899		0.94 [0.88, 1.01]	0.09	45%	0.09	0.20
>0.7 g/day	6	1,145	22,009	1,401	22,020		0.84 [0.72, 0.99]	0.04	70%	0.005	
Statin use											
<60% of study population	5	2,110	28,613	2,179	28,585		0.97 [0.91, 1.03]	0.32	18%	0.30	0.07
≥60% of study population	8	2,056	32,596	2,328	32,334		0.86 [0.77, 0.96]	0.007	69%	0.002	
Study population											
Primary CV prevention	3	949	26,912	997	26,944		0.95 [0.85, 1.07]	0.38	42%	0.18	
Secondary CV prevention	6	1,370	8,062	1,407	7,802		0.92 [0.82, 1.04]	0.21	56%	0.04	0.58
Combination **	4	1,847	26,235	2,103	26,173		0.86 [0.73, 1.01]	0.06	84%	0.0002	



*Only studies involving supplementation with combined EPA + DHA were considered in this sub-analysis.
** Combination of primary and secondary CV prevention

Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

Association of Circulating PCSK9 With Ischemia-Reperfusion Injury in Acute ST-Elevation Myocardial Infarction

Christina Tiller, MD, PhD; Magdalena Holzknecht, MD; Ivan Lechner, MD; Fritz Oberhollenzer, MD; Sebastian von der Emde, MD; Thomas Kremser, MD; Can Gollmann-Tepeköylü, MD, PhD; Agnes Mayr, MD; Axel Bauer, MD; Bernhard Metzler, MD; Sebastian J. Reinstadler, MD, PhD; Martin Reindl, MD, PhD

BACKGROUND: Beyond therapeutic implications, PCSK9 (proprotein convertase subtilisin/kexin 9) has emerged as a promising cardiovascular biomarker. The exact role of PCSK9 in the setting of acute ST-elevation myocardial infarction (STEMI) is incompletely understood. We aimed to investigate the association of PCSK9 with ischemia-reperfusion injury, visualized by cardiac magnetic resonance imaging, in patients with STEMI revascularized by primary percutaneous coronary intervention (PCI).

METHODS: In this prespecified substudy from the prospective MARINA-STEMI (NCT04113356) registry, we included 205 patients with STEMI. PCSK9 concentrations were measured from venous blood samples by an immunoassay 24 and 48 hours after PCI. The primary end point was defined as presence of intramyocardial hemorrhage according to cardiac magnetic resonance T2* mapping. Secondary imaging end points were the presence of microvascular obstruction (MVO) and infarct size. The clinical end point was the occurrence of major adverse cardiac events.

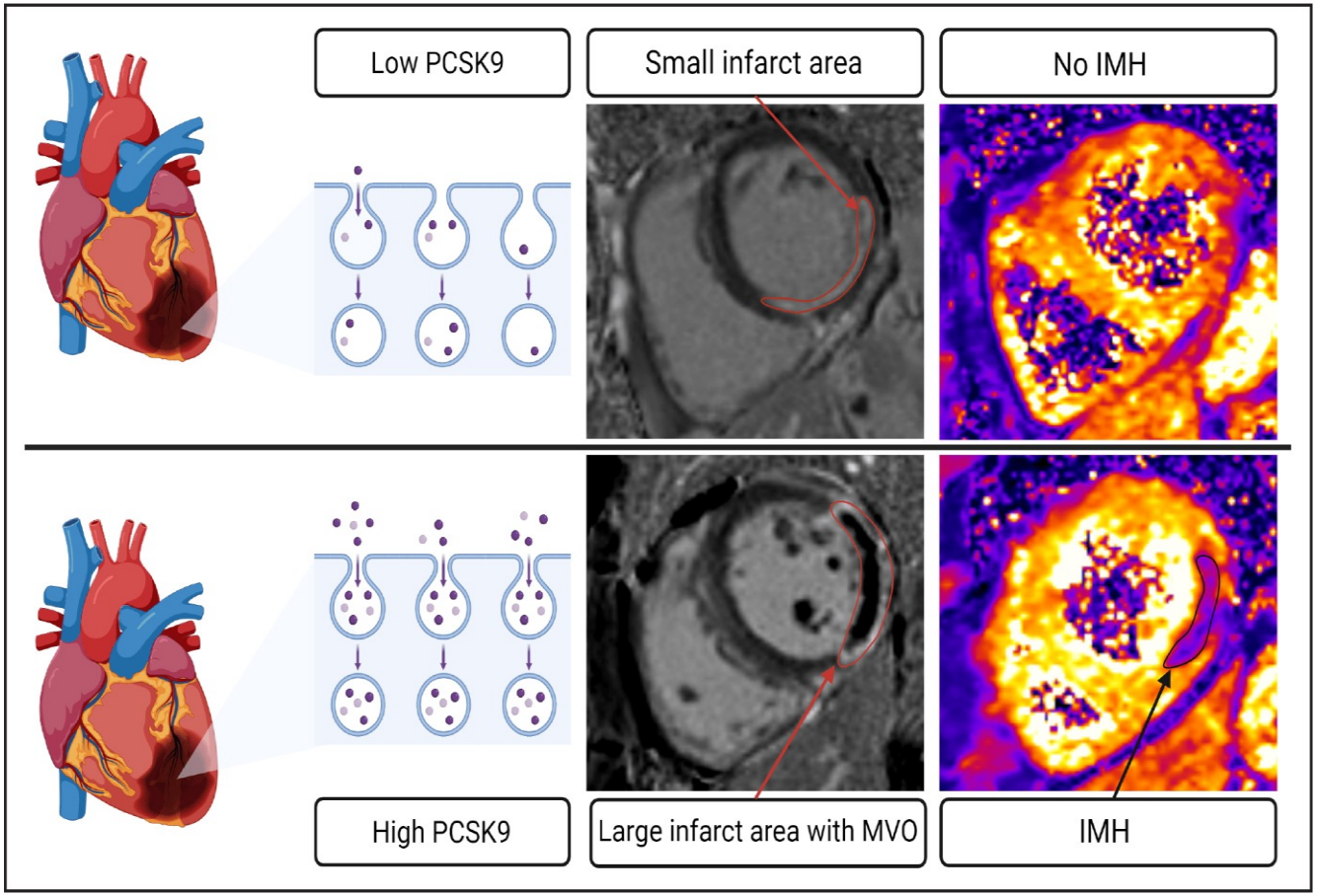
RESULTS: We observed a significant increase in PCSK9 levels from 24 to 48 hours (268–304 ng/mL; $P<0.001$) after PCI. PCSK9 24 hours after PCI did not show any relation to intramyocardial hemorrhage, MVO, and infarct size (all $P>0.05$). PCSK9 concentrations 48 hours post-STEMI were higher in patients with intramyocardial hemorrhage (333 versus 287 ng/mL; $P=0.004$), MVO (320 versus 292 ng/mL; $P=0.020$), and large infarct size (323 versus 296 ng/mL; $P=0.013$). Furthermore, patients with increased PCSK9 levels >361 ng/mL at 48 hours were more likely to experience major adverse cardiac events (15% versus 8%; $P=0.002$) during a median follow-up of 12 months.

CONCLUSIONS: In patients with STEMI, a significant increase in PCSK9 was observed from 24 to 48 hours after PCI. While PCSK9 levels after 24 hours were not related to myocardial or microvascular injury, PCSK9 after 48 hours was significantly associated with intramyocardial hemorrhage, MVO, and infarct size as well as worse subsequent clinical outcomes.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier; NCT04113356.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: animal ■ lipid metabolism ■ risk factors ■ serine protease ■ subtilisin



Tiller C. et al. Circ Cardiovasc Imaging. 2024;17:e016482.

Circulation: Cardiovascular Imaging

EDITORIAL

Is PCSK9 the Key Player in the Ischemia-Reperfusion Match?

Alice Benedetti, MD; Alvise Del Monte, MD

PCSK9 (proprotein convertase subtilisin/kexin type 9) is a serine proteinase mainly synthesized by the liver and represents a potent circulating regulator of the LDL (low-density lipoprotein) metabolism. The main clearance of LDL cholesterol occurs via endocytosis through the LDL receptors on the surface of hepatocytes. PCSK9 binds the extracellular domain of the LDL receptor, inducing its internalization and degradation in the lysosomes rather than recycling it to the plasma membrane.[1] Accordingly, high circulating levels of PCSK9 are associated with a reduced number of LDL receptors and markedly increased levels of circulating LDL cholesterol.[2] As a result, PCSK9 inhibitors are currently used as cholesterol-lowering treatments, determining significant reductions in plasma LDL cholesterol and a lower incidence of cardiovascular mortality and morbidity.[3–6] Beyond the role of PCSK9 in regulating lipid metabolism, other effects have been increasingly recognized. Serum PCSK9 concentration has been associated with the risk of incident cardiovascular disease independently of other established cardiovascular risk factors.[7] Further evidence revealed direct adverse effects of PCSK9 on coronary plaque, including proinflammatory LDL oxidation and plaque composition modification.[8] Moreover, increased plasma levels of PCSK9 have been observed in patients with acute coronary syndrome,[9] and animal models proved that PCSK9 was highly expressed in the myocardium bordering the infarct area.[10] These findings raised new questions about the role of PCSK9 in the pathophysiology of acute coronary syndrome and the potential benefit of PCSK9 inhibition therapy to improve patient outcomes after myocardial infarction.

See Article by Tiller et al

In the current issue, Tiller et al[11] evaluated the association between PCSK9 levels, cardiac magnetic resonance (CMR) evidence of myocardial and microvascular damage, and clinical outcomes in patients with STEMI (ST-segment–elevation myocardial infarction). A population of 205 patients enrolled in the MARINA-STEMI study (Magnetic Resonance Imaging in Acute ST-Elevation Myocardial Infarction) was included in the present analysis.[12] History of previous myocardial infarction or coronary artery intervention and contraindications to CMR were considered exclusion criteria. Levels of circulating PCSK9 were analyzed in venous blood samples drawn at 24 and 48 hours after primary percutaneous coronary intervention. CMR examinations were performed at a median of 3 days after percutaneous coronary intervention, aiming to assess the presence of large infarct size (defined as >19% of left ventricular myocardial mass), microvascular obstruction (MVO), and intramyocardial hemorrhage (IMH). The clinical end point was defined as the occurrence of major adverse cardiac events, a composite outcome of all-cause death, nonfatal re-infarction, and new congestive heart failure. The study results showed a significant increase in PCSK9 levels from 24 to 48 hours after primary percutaneous coronary intervention (268 versus 304 ng/mL; $P<0.001$). Moreover, higher circulating levels of PCSK9 at 48 hours were observed in patients with imaging evidence of IMH (333 versus 287 ng/mL; $P=0.004$), as well as in patients with MVO (320 versus 292 ng/mL; $P=0.02$) and large infarct size (323 versus 296 ng/mL; $P=0.013$). The significant association between PCSK9 and IMH was also validated at multivariable analysis (adjusted odds ratio, 1.68 [95% CI, 1.15–2.45]; $P=0.008$). Notably, these findings were confirmed during follow-up in 175 patients who

Key Words: Editorial ■ cholesterol, LDL ■ magnetic resonance imaging ■ PCSK9 ■ ST elevation myocardial infarction

High Blood Pressure & Cardiovascular Prevention
https://doi.org/10.1007/s40292-024-00676-8

Online ISSN 1179-1985

SHORT COMMUNICATION

PCSK9 Inhibitors: Is the Time Ripe for the "Fast Track" Use Independently on the LDL-C Baseline Values in Acute Coronary Syndrome?

Alessandro Bellis[1] · Ciro Mauro[1] · Emanuele Barbato[2] · Bruno Trimarco[3] · Carmine Morisco[3]

Received: 2 August 2024 / Accepted: 17 September 2024

Abstract

The low-density lipoprotein cholesterol (LDL-C) lowering decreases the risk to develop major adverse cardiovascular events (MACE) in patients with acute coronary syndrome (ACS). Therefore, the "fast track" use of PCSK9 inhibitors (PCSK9i) has been introduced in ACS patients not achieving LDL-C target (70 mg/dl) despite an ongoing lipid lowering therapy with statin at maximum tolerated dosage plus ezetimibe or stain-naïve (LDL-C > 130 mg/dl). PCSK9i "fast track" use has shown to achieve the regression of "non-culprit" atherosclerotic plaques leading to a further MACE decrease. Interestingly, it has been also hypothesized a role of PCSK9i beyond the LDL-C lowering in ACS. PCSK9i have been demonstrated to decrease the inflammation of atherosclerotic plaques and myocardium, inhibit platelet aggregation, and improve the cardiomyocyte survival against the reperfusion injury. All these findings may positively impact on the prognosis and suggest the PCSK9i use in the acute phase of ACS independently on the baseline LDL-C values.

Keywords Acute myocardial infarction · Atherosclerosis · Secondary prevention · Cardiovascullar risk · Lipid lowering therapy


BREAKING NEWS
BREAKING NEWS