FOCUS TERAPEUTICI NEL DIABETE MELLITO

Nuove opzioni nelle dislipidemie: Costi e Benefici

Francesco Tassone

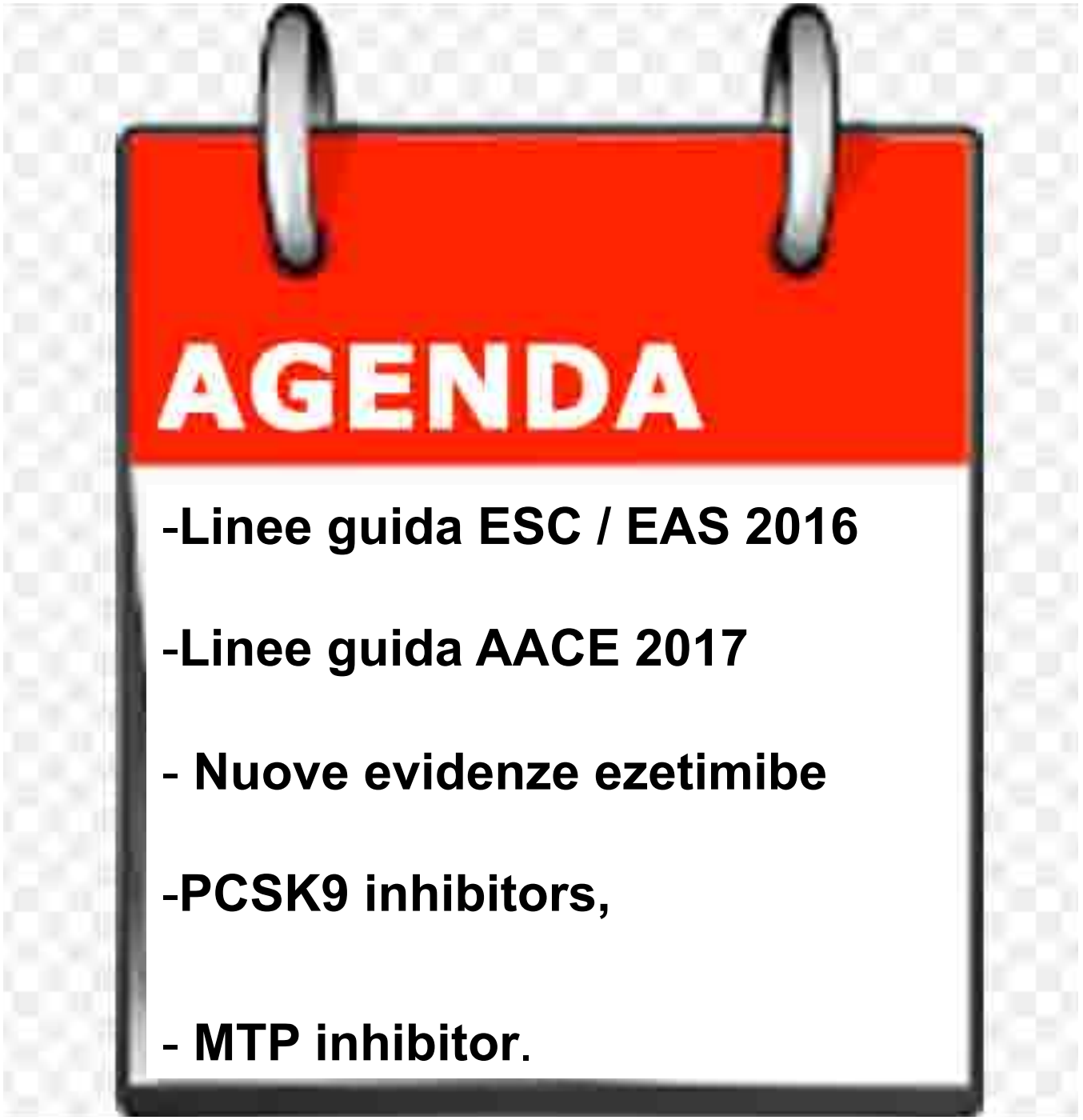
S.C. Endocrinologia, Diabetologia e Metabolismo

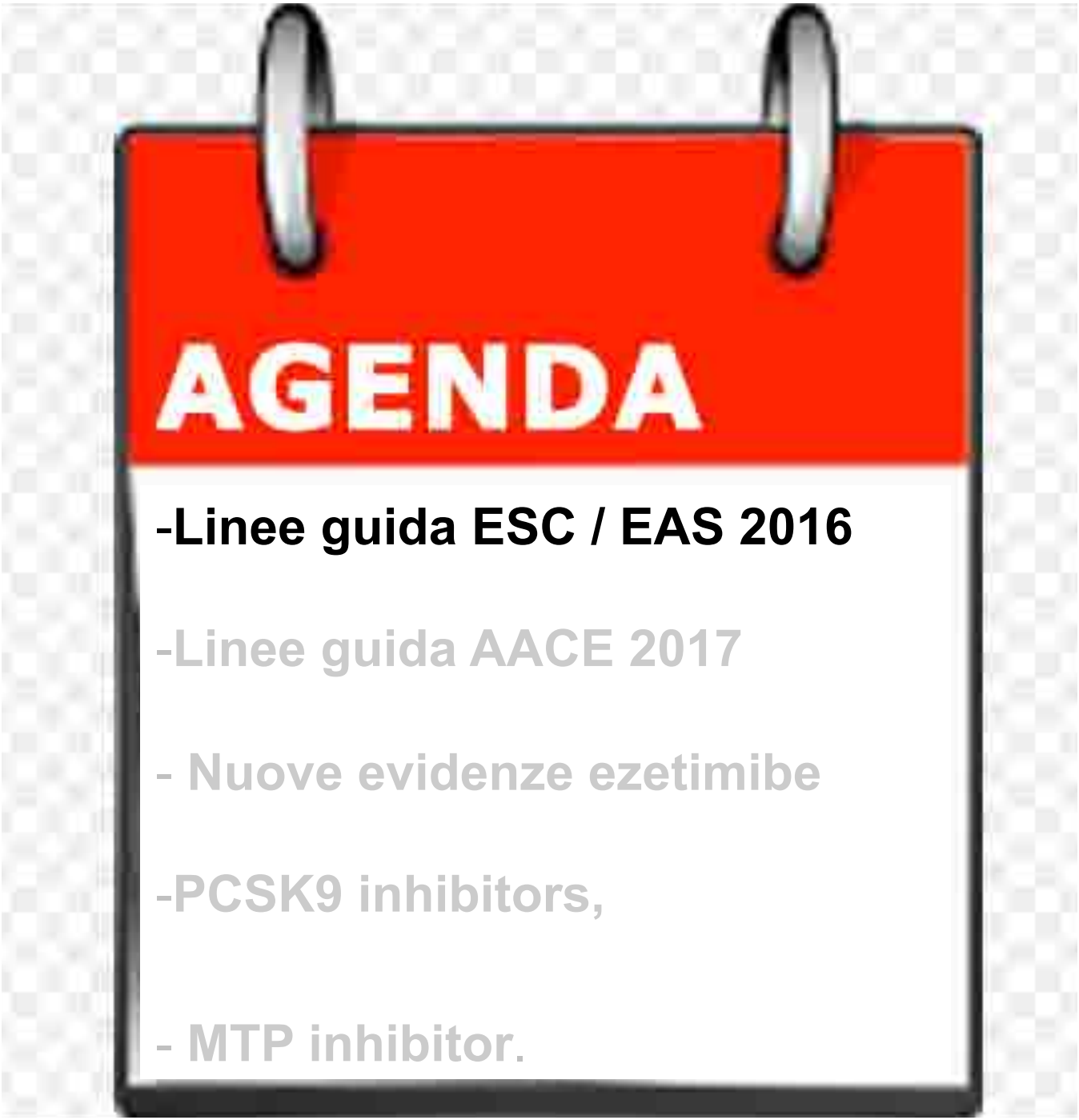
- ASO S Croce e Carle Cuneo

CONFLITTI INTERESSE

-negli ultimi due anni:

-ASTRA ZENECA
- SANOFI
- LILLY.


AGENDA
-Linee guida ESC / EAS 2016
-Linee guida AACE 2017
- Nuove evidenze ezetimibe
-PCSK9 inhibitors,
- MTP inhibitor.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European Heart Journal Advance Access published August 27, 2016

European Heart Journal
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ESC/EAS GUIDELINES

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR)

Authors/Task Force Members: Alberico L. Catapano* (Chairperson) (Italy), Ian Graham* (Chairperson) (Ireland), Guy De Backer (Belgium), Olov Wiklund (Sweden), M. John Chapman (France), Heinz Drexel (Austria), Arno W. Hoes (The Netherlands), Catriona S. Jennings (UK), Ulf Landmesser (Germany), Terje R. Pedersen (Norway), Željko Reiner (Croatia), Gabriele Riccardi (Italy), Marja-Riita Taskinen (Finland), Lale Tokgozoglu (Turkey), W. M. Monique Verschuren (The Netherlands), Charalambos Vlachopoulos (Greece), David A. Wood (UK), Jose Luis Zamorano (Spain)

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Nuove opzioni nelle dislipidemie: Costi e Benefici

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ESC/EAS GUIDELINES

2011

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ENDOCRINE PRACTICE **Rapid Electronic Article in Press**
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DOI:10.4158/EP171764.GL

EXTREME RISK :
LDL TARGET <55
NONHDLC < 80
APOB<70

AACE 2017 Guidelines

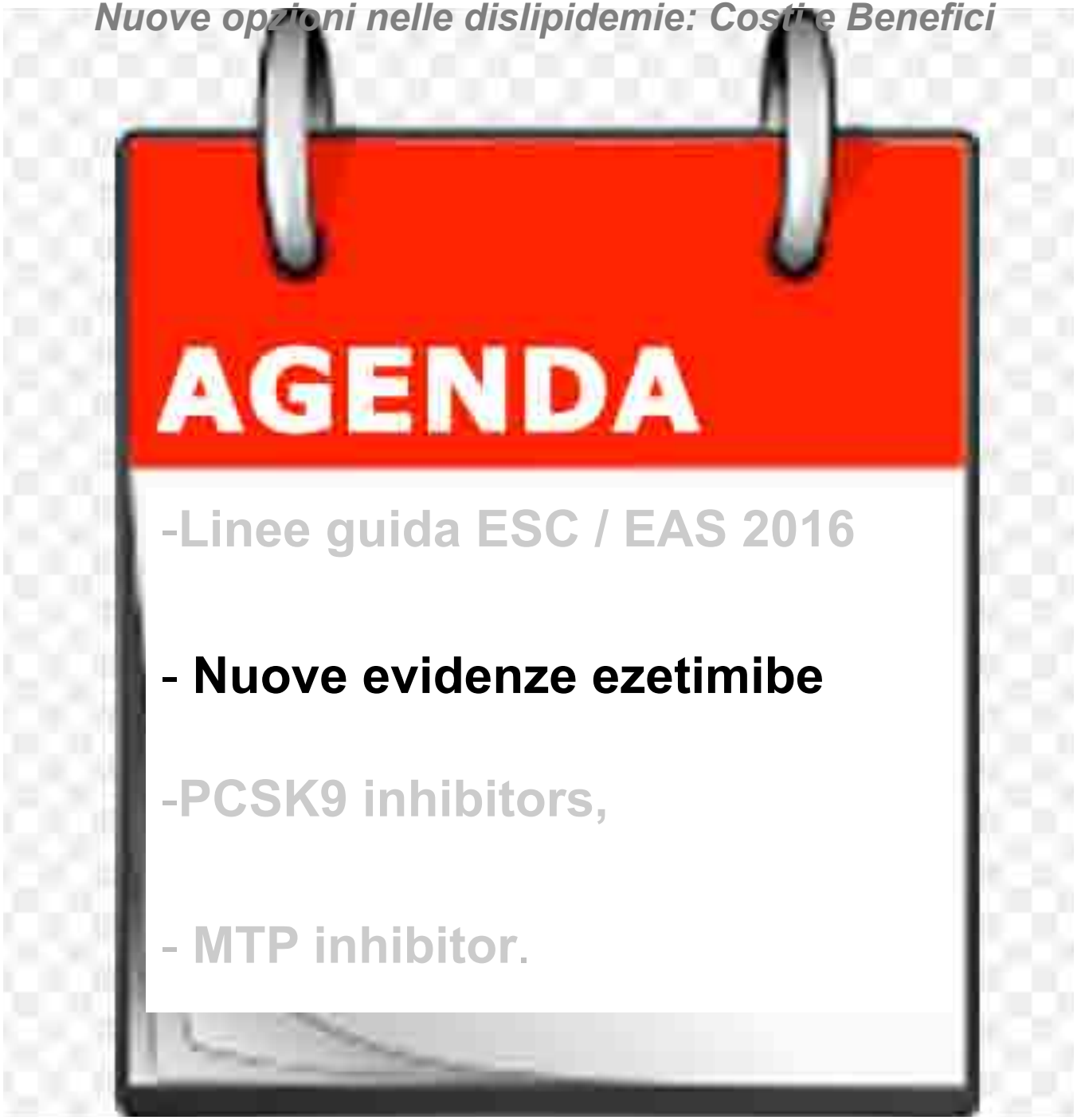
AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF ATHEROSCLEROSIS

EXECUTIVE SUMMARY

Paul S. Jellinger, MD, MACE, Chair[1]; Yehuda Handelsman MD, FACP, FACE Co-Chair[2]; Paul D. Rosenblit, MD, PhD, FNLA, FACE[3], Zachary T. Bloomgarden, MD, MACE[4]; Vivian A. Fonseca, MD, FACE[5]; Alan J. Garber, MD, PhD, FACE[6]; George Grunberger, MD, FACP, FACE[7]; Chris K. Guerin, MD, FNLA, FACE[8]; David S. H. Bell, MD, FACP, FACE[9]; Jeffrey I. Mechanick, MD, FACP, FACE, FACN, ECNU[10]; Rachel Pessah-Pollack, MD, FACE[11]; Kathleen Wyne, MD, PhD, FNLA, FACE[12]; Donald Smith, MD, MPH, FACE[13]; Eliot A. Brinton, MD, FAHA, FNLA[14]; Sergio Fazio, MD, PhD[15] and Michael Davidson, MD, FACC, FACP, FNLA[16].

American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice are systematically developed statements to assist health care professionals in medical decision-making for specific clinical conditions, but are in no way a substitute for a medical professional's independent judgment and should not be considered medical advice.

Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied. These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this


AGENDA
-Linee guida ESC / EAS 2016
- Nuove evidenze ezetimibe
-PCSK9 inhibitors,
- MTP inhibitor.

6.3 Cholesterol absorption inhibitors

6.3.1 Mechanism of action

Ezetimibe is the first lipid-lowering drug that inhibits intestinal uptake of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients. By inhibiting cholesterol absorption at the level of the brush border of the intestine [by interaction with the Niemann-Pick C1-like protein 1 (NPC1L1)], ezetimibe reduces the amount of cholesterol delivered to the liver. In response to reduced cholesterol delivery, the liver reacts by upregulating LDLR expression, which in turn leads to increased clearance of LDL-C from the blood.

6.3.2 Efficacy in clinical studies

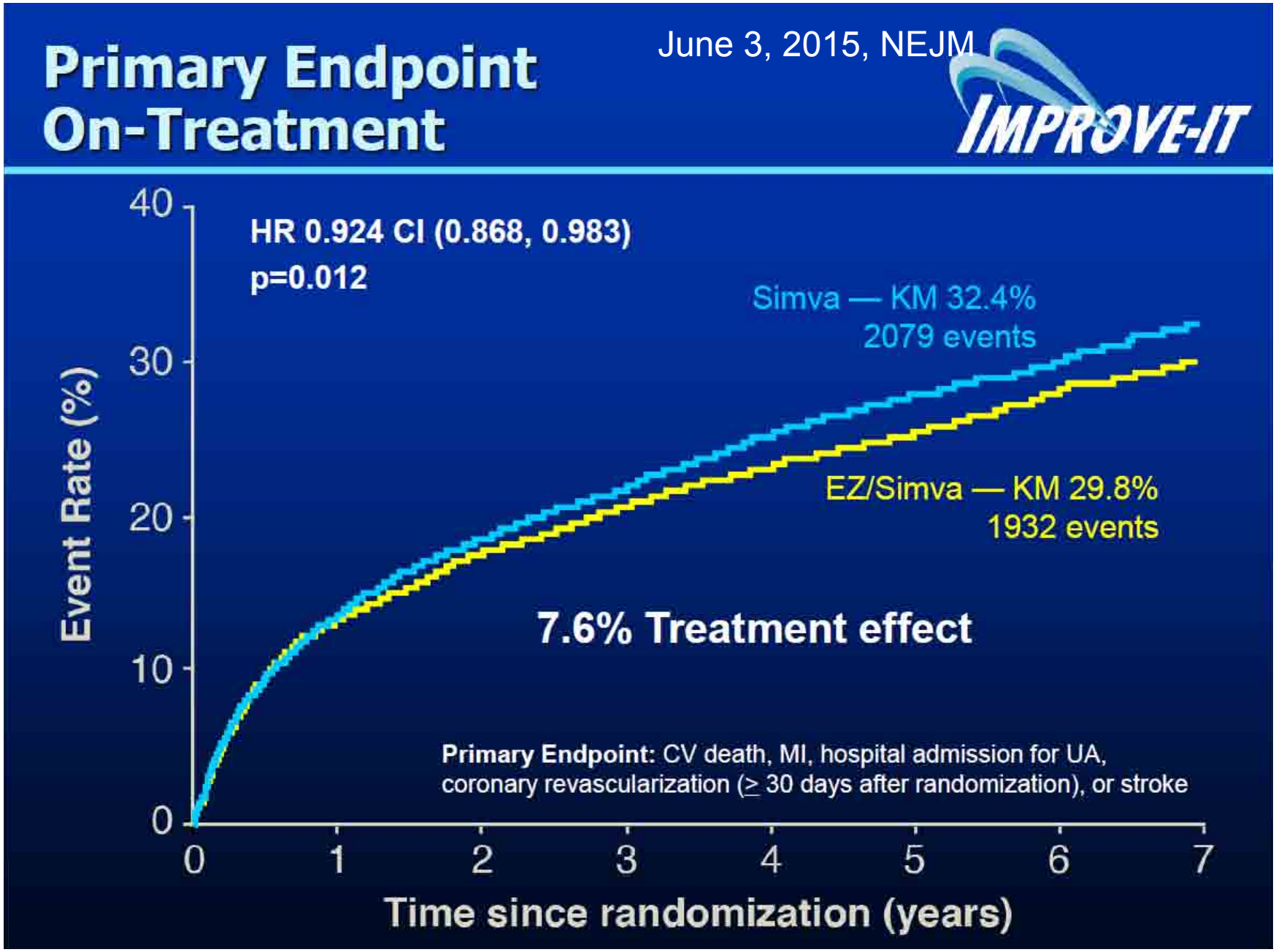
In clinical studies, ezetimibe in monotherapy reduces LDL-C in hypercholesterolaemic patients by 15–22%. Combined therapy with ezetimibe and a statin provides an incremental reduction in LDL-C levels of 15–20%. The efficacy of ezetimibe in association with simvastatin has been addressed in subjects with aortic stenosis in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study[243] and in patients with CKD in the Study of Heart and Renal Protection (SHARP) (see sections 9.7.3 and 9.9.2). In both the SEAS and SHARP trials, a reduction in CV events was demonstrated in the simvastatin–ezetimibe arm vs. placebo.[243,244]

In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) ezetimibe was added to simvastatin (40 mg) in patients after ACS.[63] A total of 18 144 patients were randomized and 5314 patients over 7 years experienced a CVD event; 170 fewer events (32.7 vs. 34.7%) were recorded in the group taking simvastatin plus ezetimibe ($P = 0.016$). The average LDL-C during the study was 1.8 mmol/L in the simvastatin group and 1.4 mmol/L in patients taking ezetimibe plus simvastatin. Also, ischaemic stroke was reduced by 21% in this trial ($P = 0.008$). There was no evidence of harm caused by the further LDL-C reduction. In this group of patients already treated with statins to reach goals, the absolute benefit from added ezetimibe was small, although significant. However, the study supports the proposition that LDL-C lowering by means other than statins is beneficial and can be performed without adverse effects. The beneficial effect of ezetimibe is also supported by genetic studies of mutations in NPC1L1. Naturally occurring mutations that inactivate the protein were found to be associated with reduced plasma LDL-C and reduced risk for CAD.[245]

Taken together with other studies such as the PRECISE-IVUS study,[246] IMPROVE-IT supports the proposal that ezetimibe should be used as second-line therapy in association with statins when the therapeutic goal is not achieved at the maximal tolerated statin dose or in patients intolerant of statins or with contraindications to these drugs.

Table 16 Recommendations for the pharmacological treatment of hypercholesterolaemia

Recommendations	Class [a]	Level [b]	Ref [c]
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal	I	A	62, 64, 68
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C	239, 256, 257
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B	63


Primary Endpoint
On-Treatment
June 3, 2015, NEJM
IMPROVE-IT
HR 0.924 CI (0.868, 0.983)
p=0.012
Simva — KM 32.4%
2079 events
EZ/Simva — KM 29.8%
1932 events
7.6% Treatment effect
Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke
Event Rate (%)
0
10
20
30
40
0
1
2
3
4
5
6
7
Time since randomization (years)

Impact of Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention

The Multicenter Randomized Controlled PRECISE-IVUS Trial

ABSTRACT

BACKGROUND Despite standard statin therapy, a majority of patients retain a high "residual risk" of cardiovascular events.

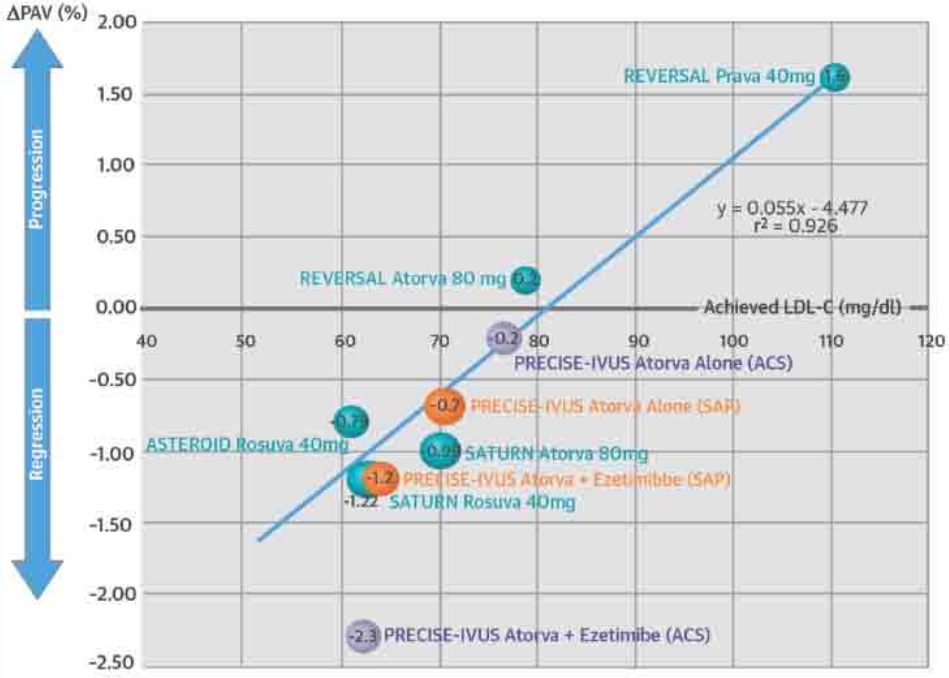
OBJECTIVES The aim of this study was to evaluate the effects of ezetimibe plus atorvastatin versus atorvastatin monotherapy on the lipid profile and coronary atherosclerosis in Japanese patients who underwent percutaneous coronary intervention (PCI).

METHODS This trial was a prospective, randomized, controlled, multicenter study. Eligible patients who underwent PCI were randomly assigned to atorvastatin alone or atorvastatin plus ezetimibe (10 mg) daily. Atorvastatin was uptitrated with a treatment goal of low-density lipoprotein cholesterol (LDL-C) <70 mg/dl. Serial volumetric intravascular ultrasound was performed at baseline and again at 9 to 12 months to quantify the coronary plaque response in 202 patients.

RESULTS The combination of atorvastatin/ezetimibe resulted in lower levels of LDL-C than atorvastatin monotherapy (63.2 ± 16.3 mg/dl vs. 73.3 ± 20.3 mg/dl; $p < 0.001$). For the absolute change in percent atheroma volume (PAV), the mean difference between the 2 groups (-1.538%; 95% confidence interval [CI]: -3.079% to 0.003%) did not exceed the pre-defined noninferiority margin of 3%, but the absolute change in PAV did show superiority for the dual lipid-lowering strategy (-1.4%; 95% CI: -3.4% to -0.1% vs. -0.3%; 95% CI: -1.9% to 0.9% with atorvastatin alone; $p = 0.001$). For PAV, a significantly greater percentage of patients who received atorvastatin/ezetimibe showed coronary plaque regression (78% vs. 58%; $p = 0.004$). Both strategies had acceptable side effect profiles, with a low incidence of laboratory abnormalities and cardiovascular events.

CONCLUSIONS Compared with standard statin monotherapy, the combination of statin plus ezetimibe showed greater coronary plaque regression, which might be attributed to cholesterol absorption inhibition-induced aggressive lipid lowering. (Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound [PRECISE-IVUS]; NCT01043380) (J Am Coll Cardiol 2015;66:495-507) © 2015 by the American College of Cardiology Foundation.

CENTRAL ILLUSTRATION Relationship Between Achieved Low-Density Lipoprotein Cholesterol Levels and the Median Change in Percent Atheroma Volume for Previous Intravascular Ultrasound Trials and the PRECISE-IVUS Trial



Tsujita, K. et al. J Am Coll Cardiol. 2015; 66(5):495-507.

There has been a close correlation between achieved low-density lipoprotein cholesterol (LDL-C) levels and the median change in percent atheroma volume in several intravascular ultrasound trials ($r^2 = 0.926$). Even in the stable angina pectoris cohort of the PRECISE-IVUS (Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound) trial, these plots are located in range with the pre-existing regression line. In contrast, the plot is located far below the line in the atorvastatin/ezetimibe combination arm of the acute coronary syndrome cohort of the PRECISE-IVUS trial, whereas the plot was still in range with the line in the atorvastatin monotherapy arm. ACS = acute coronary syndrome(s); ASTEROID = A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; Atorva = atorvastatin; ΔPAV = absolute change in percent atheroma volume; Prava = pravastatin; REVERSAL = Reversal of Atherosclerosis With Aggressive Lipid-Lowering; SAP = stable angina pectoris; SATURN = Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin.

A SIGNIFICANTLY GREATER % OF PATIENTS ON ATORVA / EZE SHOWED CORONARY PLAQUE REGRESSION (78% VS 58 % ; P = 0.004, PAV= PERCENT ATHEROMA VOLUME)

AJKD

Original Investigation

Cost-effectiveness of Simvastatin plus Ezetimibe for Cardiovascular Prevention in CKD: Results of the Study of Heart and Renal Protection (SHARP)

*Borislava Mihaylova, DPhil,[1] Iryna Schlackow, DPhil,[1] William Herrington, MD,[2] Jingky Lozano-Kühne, PhD,[1] Seamus Kent, MSc,[1] Jonathan Emberson, PhD,[2] Christina Reith, FRCP,[2] Richard Haynes, DM, FRCP,[2] Alan Cass, PhD,[3] Jonathan Craig, PhD,[4] Alastair Gray, PhD,[1] Rory Collins, FRS,[2] Martin J. Landray, PhD, FRCP,[2] and Colin Baigent, FRCP,[2] on behalf of the SHARP Collaborative Group**

Background: Simvastatin, 20 mg, plus ezetimibe, 10 mg, daily (simvastatin plus ezetimibe) reduced major atherosclerotic events in patients with moderate to severe chronic kidney disease (CKD) in the Study of Heart and Renal Protection (SHARP), but its cost-effectiveness is unknown.

Study Design: Cost-effectiveness of simvastatin plus ezetimibe in SHARP, a randomized controlled trial.

Setting & Population: 9,270 patients with CKD randomly assigned to simvastatin plus ezetimibe or placebo; participants in categories by 5-year cardiovascular risk (low, <10%; [illegible] high, ≥20%) and CKD stage (3, 4, 5 not on dialysis, or on dialysis [illegible]

Model, Perspective, & Timeline: Assessment [illegible] projections.

Intervention: Si[illegible] SHARP

Conclusions: Simvastatin plus ezetimibe prevented atherosclerotic events in SHARP, but other less costly statin regimens are likely to be more cost-effective for reducing cardiovascular risk in CKD.

Am J Kidney Dis. 67(4):576-584. © 2016 The Authors. Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

[illegible] in the costs of [illegible]pant categories by cardiovascular [illegible]otic events per 1,000 participants ranged from 10 in [illegible]s in CKD stage 3 to 36 in patients on dialysis therapy. The net cost [illegible]vent avoided with simvastatin plus ezetimibe compared to no LDL-lowering regimen [illegible] £57,060 in patients at low risk to £15,230 in those at high risk (£30,500-£39,600 per QALY); and from £47,280 in CKD stage 3 to £28,180 in patients on dialysis therapy (£13,000-£43,300 per QALY). In scenario analyses, generic high-intensity statin regimens were estimated to yield similar benefits at substantially lower cost.

Limitations: High-intensity statin-alone regimens were not studied in SHARP.

Conclusions: Simvastatin plus ezetimibe prevented atherosclerotic events in SHARP, but other less costly statin regimens are likely to be more cost-effective for reducing cardiovascular risk in CKD.

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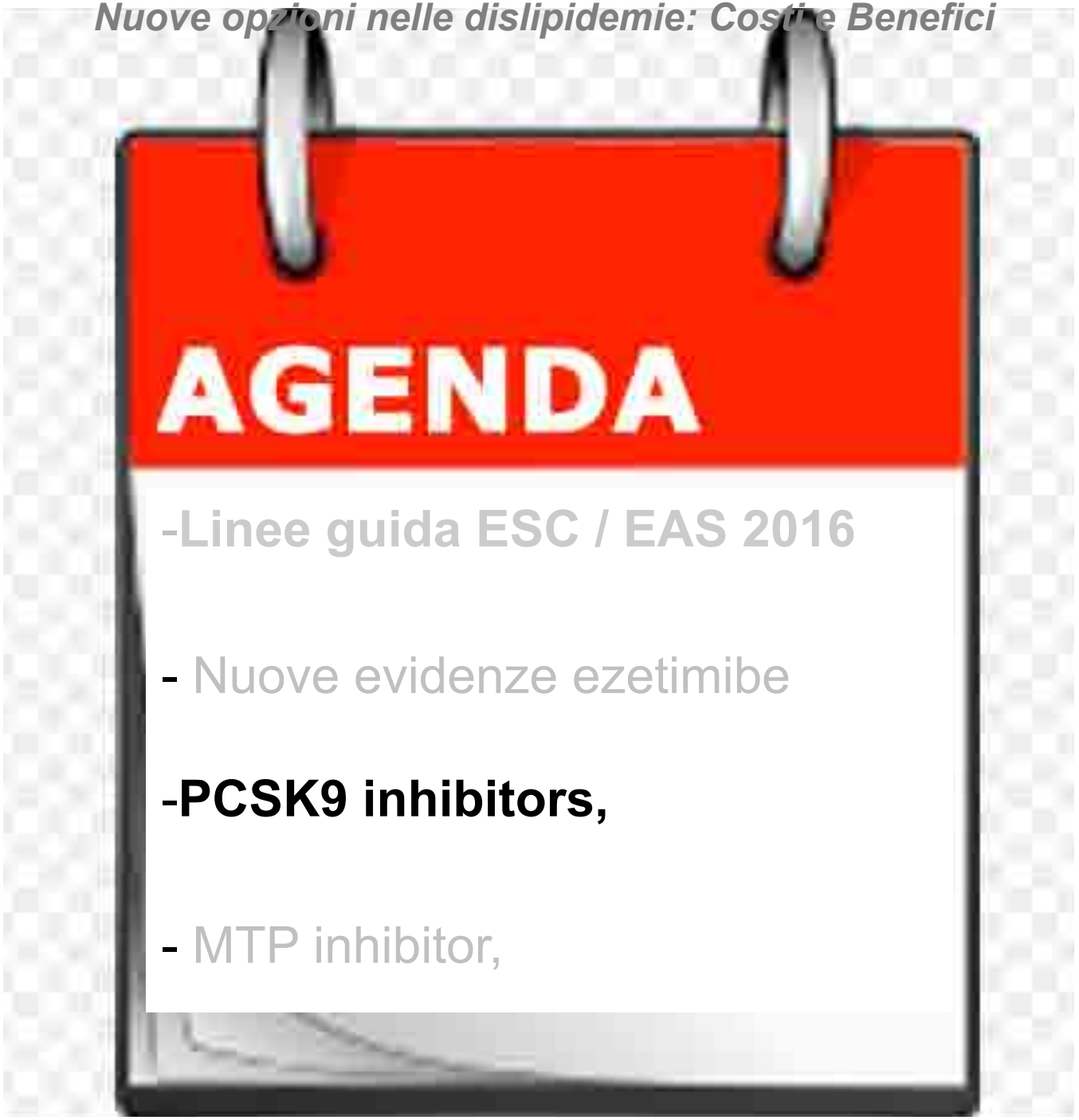

AGENDA
-Linee guida ESC / EAS 2016
- Nuove evidenze ezetimibe
-PCSK9 inhibitors,
- MTP inhibitor,

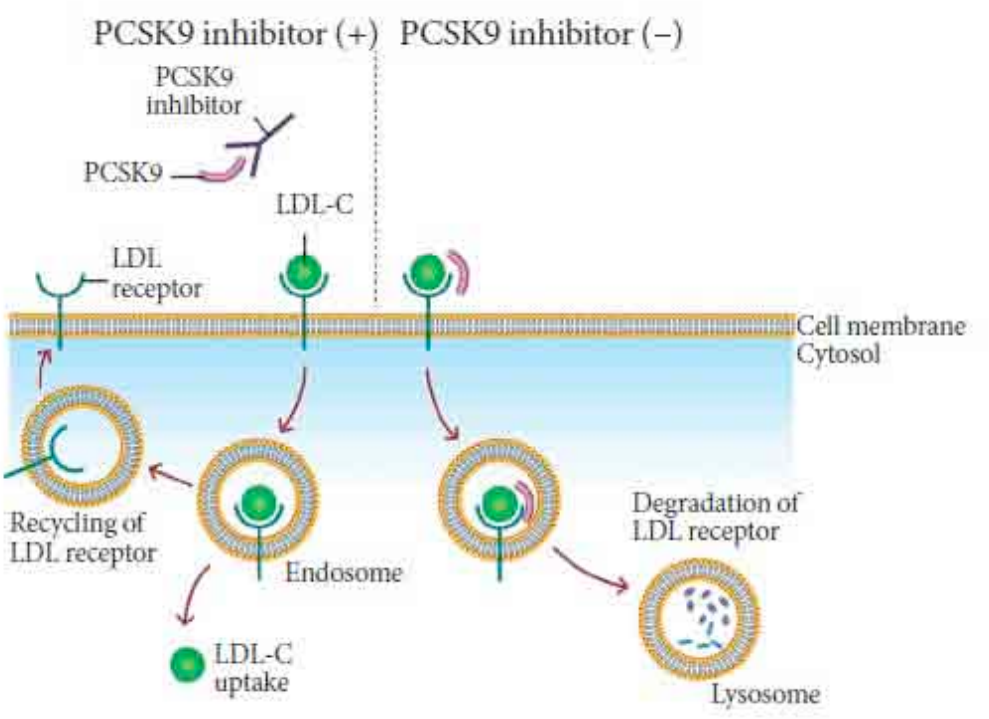
INIBIZIONE DELLA PCSK9

•**PCSK9 (Proprotein Convertase Subtilisin / Kexintype 9)** è una proteina scoperta nel 2003 da un gruppo di ricercatori francesi

•PCSK9 appartiene alla **famiglia delle subtilisine**; è espressa a livello del fegato, dell'intestino tenue e dei reni, ed è presente in circolo. La proteina secreta si **lega ad un sito specifico del recettore per le LDL e viene internalizzata insieme ad esso nelle cellule epatiche,** alterando la via normale seguita dal recettore quando è legato alle lipoproteine. **Come risultato, il recettore non torna a livello della membrana, ma viene degradato**.

•**mutazioni PCSK9 associate con ipercolesterolemia autosomica dominante** in due famiglie francesi in cui erano state precedentemente escluse mutazioni nei geni comunemente candidati e codificanti per il recettore LDL (LDLR) e apoB.

•variazioni genetiche nel gene PCSK9 contribuiscono alla regolazione dei livelli plasmatici di colesterolo LDL, con in particolare rare **varianti con guadagno di funzione (GOF) che portano a ipercolesterolemia**, mentre varianti con **perdita di funzione (LOF) inducono ipocolesterolemia**

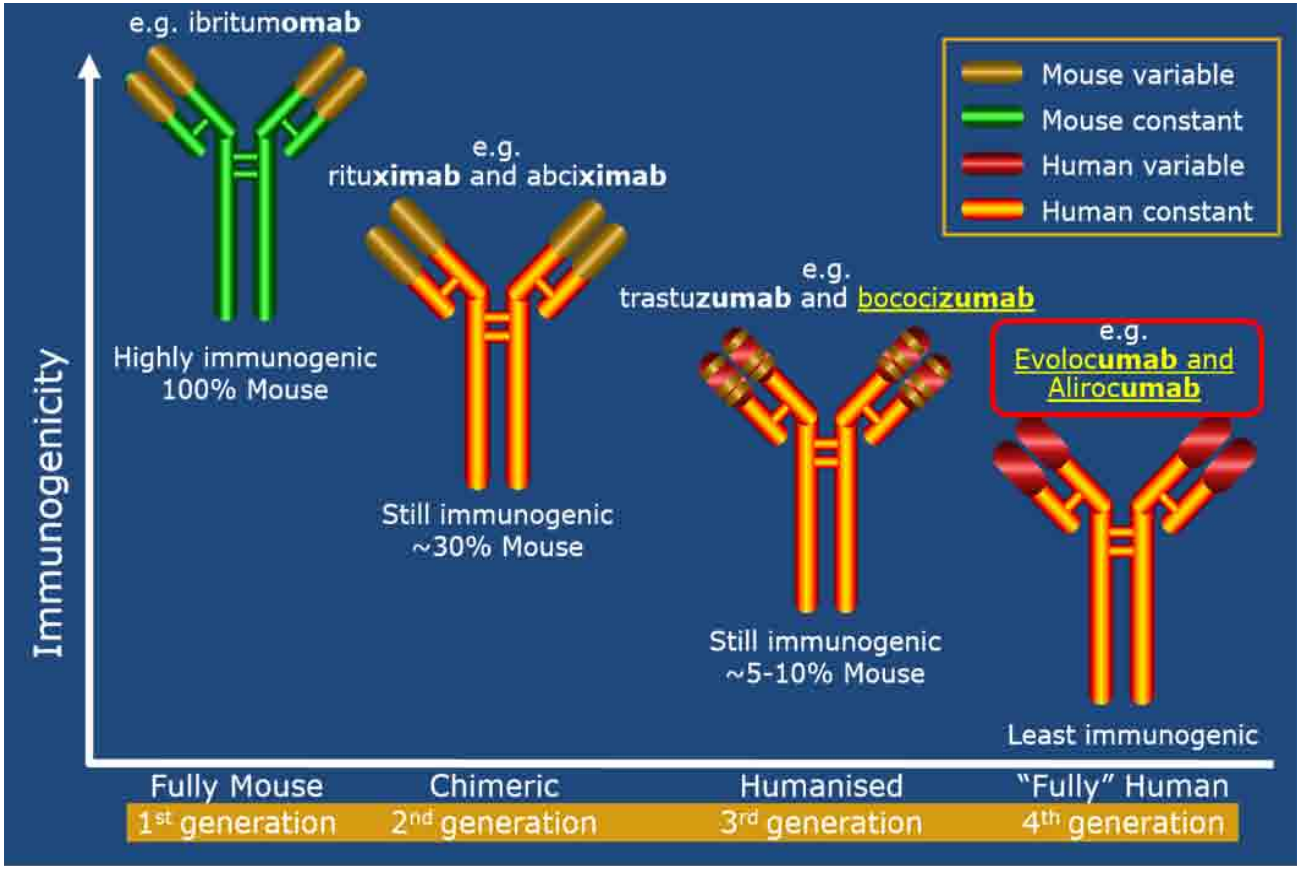


INIBIZIONE DELLA PCSK9

Several approaches to inhibit PCSK9 have been proposed, including

-monoclonal antibody,
- small interfering RNA,
- antisense oligonucleotide,
- mimetic peptides.

Among them, the **fully humanized monoclonal** antibody against PCSK9 showed successful human data by far.



ALIROCUMAB

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 16, 2015 VOL. 372 NO. 16

Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

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ABSTRACT

BACKGROUND

Alirocumab, a monoclonal antibody that inhibits proprotein convertase subtilisin–kexin type 9 (PCSK9), has been shown to reduce low-density lipoprotein (LDL) cholesterol levels in patients who are receiving statin therapy. Larger and longer-term studies are needed to establish safety and efficacy.

METHODS

We conducted a randomized trial involving 2341 patients at high risk for cardiovascular events who had LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or more and were receiving treatment with statins at the maximum tolerated dose (the highest dose associated with an acceptable side-effect profile), with or without other lipid-lowering therapy. Patients were randomly assigned in a 2:1 ratio to receive alirocumab (150 mg) or placebo as a 1-ml subcutaneous injection every 2 weeks for 78 weeks. The primary efficacy end point was the percentage change in calculated LDL cholesterol level from baseline to week 24.

RESULTS

At week 24, the difference between the alirocumab and placebo groups in the mean percentage change from baseline in calculated LDL cholesterol level was −62 percentage points (P<0.001); the treatment effect remained consistent over a period of 78 weeks. The alirocumab group, as compared with the placebo group, had higher rates of injection-site reactions (5.9% vs. 4.2%), myalgia (5.4% vs. 2.9%), neurocognitive events (1.2% vs. 0.5%), and ophthalmologic events (2.9% vs. 1.9%). In a post hoc analysis, the rate of major adverse cardiovascular events (death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) was lower with alirocumab than with placebo (1.7% vs. 3.3%; hazard ratio, 0.52; 95% confidence interval, 0.31 to 0.90; nominal P=0.02).

CONCLUSIONS

Over a period of 78 weeks, alirocumab, when added to statin therapy at the maximum tolerated dose, significantly reduced LDL cholesterol levels. In a post hoc analysis, there was evidence of a reduction in the rate of cardiovascular events with alirocumab. (Funded by Sanofi and Regeneron Pharmaceuticals; ODYSSEY LONG TERM ClinicalTrials.gov number, NCT01507831.)

From the University of Iowa, Iowa City (J.G.R.); Point Médical, Dijon (M.F.), Centre Hospitalier Universitaire de Nantes–Hôpital Nord Laennec, Saint-Herblain (M.K.), University Hospital of Lille, Lille (G. Luc), and Sanofi, Chilly-Mazarin (C.L.) — all in France; Clinique des Maladies Lipidiques de Québec, Quebec, QC, Canada (J.B.); Università di Palermo–Policlinico P. Giaccone, Palermo, Italy (M.A.); the Department of Vascular Medicine, Academic Medical Center, Amsterdam (E.S.S., J.J.P.K.), Lipid Clinic, Oslo University Hospital, Oslo (G. Langslet); University of the Witwatersrand, Johannesburg (F.J.R.); Cardiovascular Center of Sarasota, Sarasota (M.E.S.), and Jacksonville Center for Clinical Research, Jacksonville (M.J.K.) — both in Florida; Westside Medical Associates of Los Angeles, Beverly Hills, CA (N.E.L.); Regeneron Pharmaceuticals, Tarrytown, NY (R.P.), and Sanofi, Bridgewater, NJ (U.C.). Address reprint requests to Dr. Robinson at the Departments of Epidemiology and Medicine, Prevention Intervention Center, College of Public Health, University of Iowa, 145 N. Riverside Dr., S455 CPHH, Iowa City, IA 52242, or at jennifer-g-robinson@uiowa.edu.

*A list of principal investigators in the Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) study is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on March 15, 2015, at NEJM.org.

N Engl J Med 2015;372:1489-99.
DOI: 10.1056/NEJMoa1501031

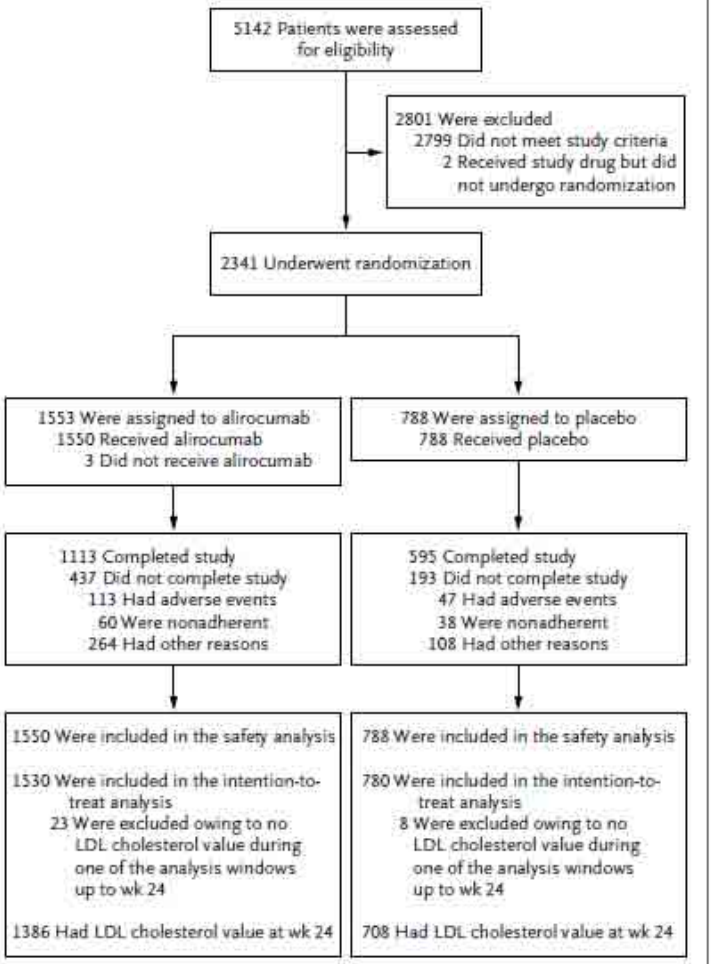
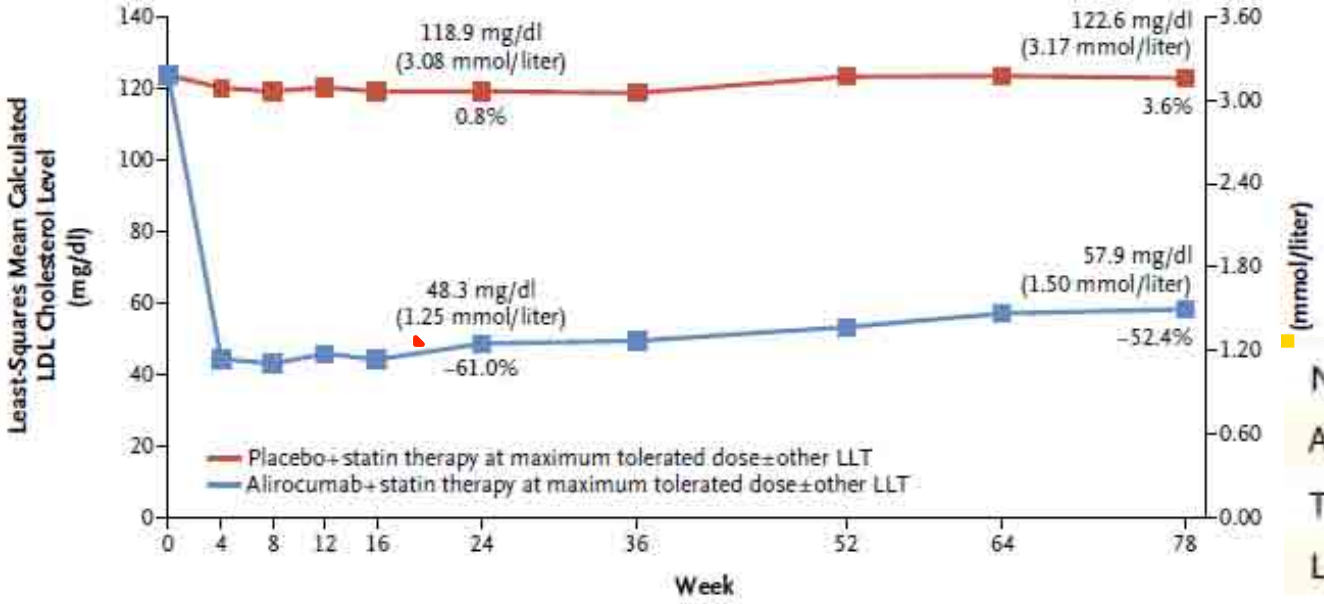


Figure 1. Randomization and Treatment.

The intention-to-treat population included all randomly assigned patients who had both a baseline calculated low-density lipoprotein (LDL) cholesterol value and at least one calculated LDL cholesterol value during one of the analysis windows up to week 24. The three patients in the alirocumab group who underwent randomization but did not receive treatment are included in the intention-to-treat population. Completion of the study was defined, as per the electronic case-report form, in the following way: the last study-drug injection was received (week 76), and the end-of-treatment visit (week 78) occurred within 21 days after the last injection and at least 525 days after randomization.



No. of Patients with Data Available										
Placebo	780	754	747	746	716	708	694	676	659	652
Alirocumab	1530	1473	1458	1436	1412	1386	1359	1349	1324	1269

Non-HDL cholesterol	−51.6±0.6
Apolipoprotein B	−52.8±0.7
Total cholesterol	−37.8±0.5
Lipoprotein(a)¶	−29.3±0.7
Fasting triglycerides¶	−15.6±0.8
HDL cholesterol	4.0±0.4
Apolipoprotein A1	4.0±0.4

Figure 2. Calculated LDL Cholesterol Levels over Time (Intention-to-Treat Analysis).

Calculated LDL cholesterol levels are shown in milligrams per deciliter (left axis) and millimoles per liter (right axis). Values above the data points indicate least-squares mean absolute LDL cholesterol levels, and values below the data points indicate least-squares mean percentage changes from baseline. Values below the chart indicate the number of patients with LDL cholesterol values available for the intention-to-treat analysis at each time point; these include levels measured while the study drug was being taken and, in the case of patients who discontinued the study drug but returned to the clinic for assessments, after the study drug was discontinued. Missing data were accounted for with the use of a mixed-effects model with repeated measures. For statin therapy, the maximum tolerated dose was the highest dose associated with an acceptable side-effect profile. LLT denotes lipid-lowering therapy.

Table 3. Adverse Events of Interest and Laboratory Values: Safety Analysis.*

Event	Alirocumab (N=1550)	Placebo (N=788)	P Value†
Summary of adverse events — no. of patients (%)			
Any adverse event	1255 (81.0)	650 (82.5)	0.40
Serious adverse event	290 (18.7)	154 (19.5)	0.66
Adverse event leading to study-drug discontinuation	111 (7.2)	46 (5.8)	0.26
Adverse event leading to death	8 (0.5)	10 (1.3)	0.08
Cardiovascular adverse events of interest — no. of patients (%)			
Death from coronary heart disease, including death from unknown cause	4 (0.3)	7 (0.9)	0.26
Nonfatal myocardial infarction	14 (0.9)	18 (2.3)	0.01
Fatal or nonfatal ischemic stroke	9 (0.6)	2 (0.3)	0.35
Unstable angina requiring hospitalization	0	1 (0.1)	0.34
Congestive heart failure requiring hospitalization	9 (0.6)	3 (0.4)	0.76
Ischemia-driven coronary revascularization procedure	48 (3.1)	24 (3.0)	1
Positively adjudicated cardiovascular events, including all cardiovascular adverse events listed above	72 (4.6)	40 (5.1)	0.68
Adjudicated major adverse cardiovascular events in post hoc analysis‡	27 (1.7)	26 (3.3)	0.02
Other adverse events of interest			
General allergic reaction — no. of patients (%)	156 (10.1)	75 (9.5)	0.71
Local injection-site reaction — no. of patients (%)	91 (5.9)	33 (4.2)	0.10
Myalgia — no. of patients (%)	84 (5.4)	23 (2.9)	0.006
Neurologic event — no. of patients (%)§	65 (4.2)	35 (4.4)	0.83
Neurocognitive disorder — no. of patients (%)¶	18 (1.2)	4 (0.5)	0.17
Amnesia	5 (0.3)	0	0.17
Memory impairment	4 (0.3)	1 (0.1)	0.67
Confusional state	4 (0.3)	1 (0.1)	0.67
Ophthalmologic event — no. of patients (%)‖	45 (2.9)	15 (1.9)	0.65
Hemolytic anemia — no. of patients	0	0	NC
Diabetes in patients with no history of diabetes — no. of patients/total no. (%)**	18/994 (1.8)	10/509 (2.0)	0.84
Worsening of diabetes in patients with history of diabetes — no. of patients/total no. (%)**	72/556 (12.9)	38/279 (13.6)	0.83
Laboratory values of interest — no. of patients/total no. (%)			
Alanine aminotransferase >3× ULN	28/1533 (1.8)	16/779 (2.1)	0.75
Aspartate aminotransferase >3× ULN	22/1533 (1.4)	18/779 (2.3)	0.13
Creatine kinase >3× ULN	56/1507 (3.7)	38/771 (4.9)	0.18

EVOLOCUMAB

ORIGINAL ARTICLE

Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Stephen D. Wiviott, M.D., Frederick J. Raal, M.B., B.Ch., M.Med., Ph.D., Dirk J. Blom, M.B., Ch.B., M.Med., Ph.D., Jennifer Robinson, M.D., M.P.H., Christie M. Ballantyne, M.D., Ransi Somaratne, M.D., Jason Legg, Ph.D., Scott M. Wasserman, M.D., Robert Scott, M.D., Michael J. Koren, M.D., and Evan A. Stein, M.D., Ph.D., for the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators

ABSTRACT

BACKGROUND

Evolocumab, a monoclonal antibody that inhibits proprotein convertase subtilisin–kexin type 9 (PCSK9), significantly reduced low-density lipoprotein (LDL) cholesterol levels in short-term studies. We conducted two extension studies to obtain longer-term data.

METHODS

In two open-label, randomized trials, we enrolled 4465 patients who had completed 1 of 12 phase 2 or 3 studies ("parent trials") of evolocumab. Regardless of study-group assignments in the parent trials, eligible patients were randomly assigned in a 2:1 ratio to receive either evolocumab (140 mg every 2 weeks or 420 mg monthly) plus standard therapy or standard therapy alone. Patients were followed for a median of 11.1 months with assessment of lipid levels, safety, and (as a prespecified exploratory analysis) adjudicated cardiovascular events including death, myocardial infarction, unstable angina, coronary revascularization, stroke, transient ischemic attack, and heart failure. Data from the two trials were combined.

RESULTS

As compared with standard therapy alone, evolocumab reduced the level of LDL cholesterol by 61%, from a median of 120 mg per deciliter to 48 mg per deciliter ($P<0.001$). Most adverse events occurred with similar frequency in the two groups, although neurocognitive events were reported more frequently in the evolocumab group. The risk of adverse events, including neurocognitive events, did not vary significantly according to the achieved level of LDL cholesterol. The rate of cardiovascular events at 1 year was reduced from 2.18% in the standard-therapy group to 0.95% in the evolocumab group (hazard ratio in the evolocumab group, 0.47; 95% confidence interval, 0.28 to 0.78; $P=0.003$).

CONCLUSIONS

During approximately 1 year of therapy, the use of evolocumab plus standard therapy, as compared with standard therapy alone, significantly reduced LDL cholesterol levels and reduced the incidence of cardiovascular events in a prespecified but exploratory analysis. (Funded by Amgen; OSLER-1 and OSLER-2 ClinicalTrials.gov numbers, NCT01439880 and NCT01854918.)

Table 2. Clinical Characteristics of the Patients at Baseline.*

Characteristic	Evolocumab Group (N=2976)	Standard-Therapy Group (N=1489)
Mean age ±SD — yr	57.8±11.0	58.2±10.9
Male sex — no. (%)	1490 (50.1)	765 (51.4)
White race — no. (%)†	2559 (86.0)	1267 (85.1)
Region		
North America	1402 (47.1)	705 (47.3)
Europe	1205 (40.5)	597 (40.1)
Asia Pacific or South Africa	369 (12.4)	187 (12.6)
Cardiovascular risk factor — no. (%)	2379 (79.9)	1211 (81.3)
Hypertension	1545 (51.9)	777 (52.2)
Diabetes mellitus	382 (12.8)	217 (14.6)
Metabolic syndrome	1035 (34.8)	475 (31.9)
Current cigarette use	465 (15.6)	222 (14.9)
Family history of premature coronary artery disease‡	724 (24.3)	362 (24.3)
Known familial hypercholesterolemia	289 (9.7)	151 (10.1)
Moderately high risk or high risk on NCEP§	1332 (44.8)	693 (46.5)
Coronary artery disease — no. (%)		
Any	589 (19.8)	307 (20.6)
Myocardial infarction	276 (9.3)	141 (9.5)
Percutaneous coronary intervention	325 (10.9)	170 (11.4)
Coronary-artery bypass grafting	185 (6.2)	110 (7.4)
Cerebrovascular or peripheral-artery disease — no. (%)		
Any	266 (8.9)	141 (9.5)
Carotid- or vertebral-artery disease	94 (3.2)	62 (4.2)
Stroke	81 (2.7)	37 (2.5)
Peripheral-artery disease	85 (2.9)	50 (3.4)
Medication use — no. (%)		
Statin¶		
Any	2073 (69.7)	1055 (70.9)
High-intensity	795 (26.7)	415 (27.9)
Moderate-intensity	1034 (34.7)	522 (35.1)
Low-intensity	240 (8.1)	118 (7.9)
Unknown	4 (0.1)	0
Ezetimibe	376 (12.6)	229 (15.4)
Median lipid measure at baseline in parent study (IQR) — mg/dl		
LDL cholesterol	120 (97–148)	121 (97–151)
Total cholesterol	202 (175–234)	205 (174–235)
HDL cholesterol	51 (42–62)	51 (42–62)
Triglycerides	120 (89–165)	119 (89–167)

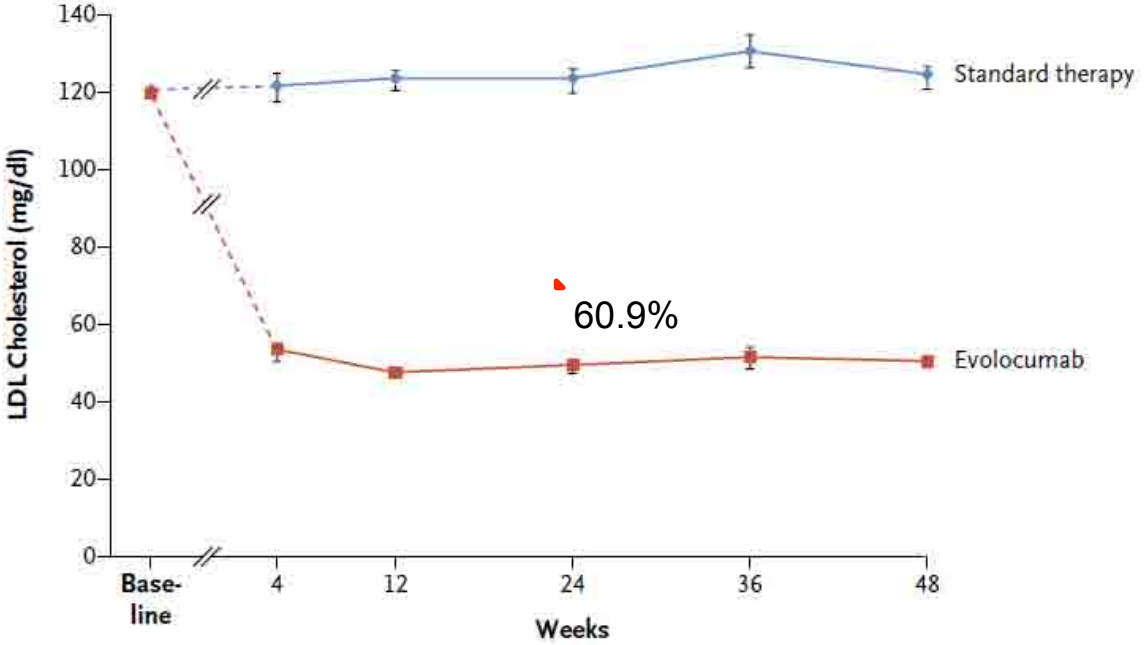
* Baseline characteristics are based on data that were obtained at the start of the parent study; values for statin use and intensity are based on data from the start of the OSLER program. There were no significant differences between the two groups at baseline. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. HDL denotes high-density lipoprotein, and IQR interquartile range.

† Race was self-reported.

‡ A family history of premature coronary artery disease was defined as the presence of coronary artery disease in a first-degree male relative 55 years of age or younger or in a first-degree female relative 65 years of age or younger.

§ According to the criteria of the National Cholesterol Education Program (NCEP), moderately high or high risk is defined as coronary heart disease, coronary heart disease equivalent, or two or more cardiovascular risk factors with an estimated 10-year risk of cardiovascular events of 10% or more.

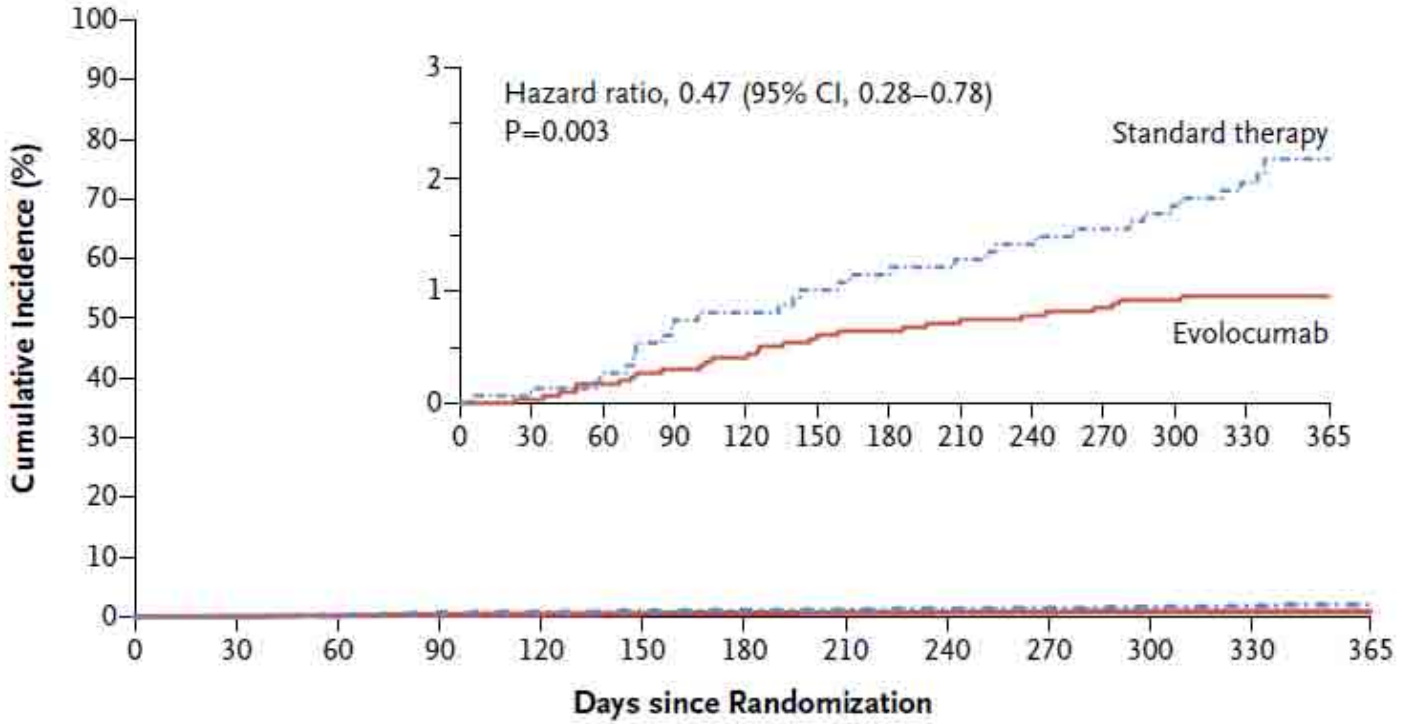
¶ The intensity of statin therapy was defined according to recent guidelines.[4]



No. at Risk						
Standard therapy	1489	394	1388	1376	402	1219
Evolocumab	2976	864	2871	2828	841	2508
Absolute reduction (mg/dl)		60.4	73.4	70.4	72.7	70.5
Percentage reduction		45.3	60.9	58.8	54.0	58.4
P value		<0.001	<0.001	<0.001	<0.001	<0.001

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

LDL cholesterol was measured in both the OSLER-1 and OSLER-2 trials at 12, 24, and 48 weeks and in the OSLER-1 trial at 4 and 36 weeks. Shown are median values with 95% confidence intervals in the two studies. Values for the baseline measurement were obtained before randomization into a parent study. The dashed lines indicate that patients were receiving either evolocumab or placebo during the period from baseline to enrollment into OSLER. In the chart below the graph, the absolute and percentage reductions in the LDL level in the evolocumab group are compared with those in the standard-therapy group and are presented as means. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.



No. at Risk

Standard therapy	1489	1486	1481	1473	1467	1463	1458	1454	1447	1438	1428	1361	407
Evolocumab	2976	2970	2962	2949	2938	2930	2920	2910	2901	2885	2871	2778	843

Figure 2. Cumulative Incidence of Cardiovascular Events.

Included among the cardiovascular events were death, myocardial infarction, unstable angina requiring hospitalization, coronary revascularization, stroke, transient ischemic attack, and hospitalization for heart failure. Cardiovascular events were reported in 29 of 2976 patients in the evolocumab group (Kaplan–Meier 1-year event rate, 0.95%) and in 31 of 1489 patients in the standard-therapy group (Kaplan–Meier 1-year event rate, 2.18%). The inset shows the same data on an expanded y axis. The P value was calculated with the use of a log-rank test.

Table 3. Adverse Events and Laboratory Results.*

Variable	Evolocumab Group (N=2976)	Standard-Therapy Group (N=1489)
	no. (%)	
Adverse events		
Any	2060 (69.2)	965 (64.8)
Serious	222 (7.5)	111 (7.5)
Leading to discontinuation of evolocumab	71 (2.4)	NA
Muscle-related	190 (6.4)	90 (6.0)
Injection-site reaction	129 (4.3)	NA
Neurocognitive event†	27 (0.9)	4 (0.3)
Other‡		
Arthralgia	137 (4.6)	48 (3.2)
Headache	106 (3.6)	32 (2.1)
Limb pain	99 (3.3)	32 (2.1)
Fatigue	83 (2.8)	15 (1.0)
Laboratory results		
Alanine or aspartate aminotransferase >3×ULN at any visit after baseline	31 (1.0)	18 (1.2)
Creatine kinase >5×ULN at any visit after baseline	17 (0.6)	17 (1.1)

* NA denotes not applicable, and ULN upper limit of the normal range.
† Neurocognitive events were delirium (including confusion), cognitive and attention disorders and disturbances, dementia and amnestic conditions, disturbances in thinking and perception, and mental impairment disorders.
‡ Included in this category are adverse events that were reported in at least 1% of patients in the evolocumab group and in more patients in the evolocumab group than in the standard-therapy group by at least 1 percentage point.

A New Class of Antihyperlipidemic

- PCSK9 = **P**roprotein **c**onvertase **s**ubtilisin/**k**exin type **9**
- Two PCSK9 inhibitors approved by FDA, summer 2015
  - Repatha ™ (Evolocumab, Amgen)
  - Praluent® (alirocumab, Sanofi/Regeneron)
- FDA approval based on evidence showing marked reduction (up to 70%) in LDL vs placebo

FDA Indications[2,3]

- Adjunct to diet and maximally tolerated statin therapy in adult patients requiring additional medication and who have:
  - Heterozygous familial hypercholesterolemia
  - Clinical atherosclerotic disease CVD
  - Homozygous familial hypercholesterolemia (additional indication for evolocumab)

4.1 Indicazioni terapeutiche

PRALUENT (Aliro)

Praluent è indicato in adulti con ipercolesterolemia primaria (familiare eterozigote o non familiare) o dislipidemia mista, in aggiunta alla dieta:

- in associazione con una statina o una statina con altre terapie ipolipemizzanti in pazienti non in grado di raggiungere gli obiettivi per il colesterolo LDL (C-LDL) con la dose massima tollerata di statine oppure
- in monoterapia o in associazione con altre terapie ipolipemizzanti in pazienti intolleranti alle statine o per i quali una statina è controindicata.

L'effetto di Praluent su morbilità e mortalità cardiovascolare non è stato ancora determinato.

4.1 Indicazioni terapeutiche

REPATHA (Evolo)

Ipercolesterolemia e dislipidemia mista

Repatha è indicato nei pazienti adulti affetti da ipercolesterolemia primaria (familiare eterozigote e non familiare) o da dislipidemia mista, in aggiunta alla dieta:

- in associazione ad una statina o ad una statina con altre terapie ipolipemizzanti in pazienti che non raggiungono livelli di LDL-C target con la dose massima tollerata di una statina, oppure
- in monoterapia o in associazione ad altre terapie ipolipemizzanti in pazienti intolleranti alle statine o per i quali l'uso di statine è controindicato.

Ipercolesterolemia familiare omozigote

Repatha è indicato in associazione ad altre terapie ipolipemizzanti negli adulti e negli adolescenti di almeno 12 anni di età con ipercolesterolemia familiare omozigote.

L'effetto di Repatha sulla morbilità e sulla mortalità cardiovascolare non è ancora stato determinato.

Efficacy in Clinical Trials

- Evolocumab and alirocumab have similar effects on LDL (no head-to-head trials for direct comparison)[4]
  - Alirocumab: 39% to 62% ↓ LDL
  - Evolocumab: 47% to 56% ↓ LDL
- New meta-analysis[5] evaluated 24 phase 2 or 3 RCTs comparing PCSK9 inhibitor therapy vs placebo:
  - LDL significantly decreased by ~50% with PCSK9 inhibitors (P<.001)

Navarese EP, Kolodziejczak M, Schulze V, et al. Effects of PCSK9 antibodies in adults with hypercholesterolemia: A systematic review and meta-analysis. Ann Intern Med. 2015;163:40-51.

PCSK9 Inhibitors Added to Statin Monotherapy

- Studies found a PCSK9 inhibitor added to statin monotherapy may ↓ LDL by additional 50%-70%[6]
- Meta-analysis:[7] 20 RCTs evaluating PCSK9 inhibitors added to various agents vs placebo found combined therapy with PCSK9 inhibitors[7]:
  - Significantly lowers LDL, total cholesterol, triglycerides, apolipoprotein-B, lipoprotein(a)
  - Increases HDL, apolipoprotein-A1

Li C, Lin L, Zhang W, et al. Efficiency and safety of PCSK9 monoclonal antibody on hypercholesterolemia: a meta-analysis of 20 randomized controlled trials. J Am Heart Assoc. 2015;4:

Dosage and Administration[2,3]

- Alirocumab: SQ injection every 2 weeks at 75 mg[2]
  - May increase to max dose of 150 mg every two weeks
- Evolocumab: SQ injection every 2 weeks at 140 mg[3]
  - May increase to 420 mg once every four weeks
- Contraindications: Hx hypersensitivity reactions to evolocumab, alirocumab
- No dose adjustments needed in mild to moderate hepatic and renal impairment

Annual Cost
May Create Barriers to Access

- Evolocumab: $14,100
- Alirocumab: $14,600
- Companies may provide co-pay incentives and/or offer to cover part of the costs

Descrizione prodotto:	PRALUENT*SC 2PEN 150MG 1ML
Principio attivo:	ALIROCUMAB
Codice prodotto:	044500080
Produttore (Titolare AIC):	SANOFI SpA
Concedibile SSN:	No
Note limitative:	
Ricetta:	CON RICETTA NON RIPETIBILE
Glutine:	
Prezzo al pubblico:	€1272,00

Descrizione prodotto:	PRALUENT*SC 2PEN 75MG 1ML
Principio attivo:	ALIROCUMAB
Codice prodotto:	044500027
Produttore (Titolare AIC):	SANOFI SpA
Concedibile SSN:	No
Note limitative:	
Ricetta:	CON RICETTA NON RIPETIBILE
Glutine:	
Prezzo al pubblico:	€1272,00

Descrizione prodotto:	REPATHA*SC 2PEN 140MG 1ML
Principio attivo:	EVOLOCUMAB
Codice prodotto:	044317030
Produttore (Titolare AIC):	AMGEN DOMPE' SpA
Concedibile SSN:	No
Note limitative:	
Ricetta:	CON RICETTA NON RIPETIBILE
Glutine:	
Prezzo al pubblico:	€1272,48

Circa 1270 euro al mese !!

X 12 = 15000/anno


BREAKING
NEWS

JAMA. 2016 Dec 13;316(22):2373-2384. doi: 10.1001/jama.2016.16951

Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial.

Nicholls SJ[1], Puri R[2], Anderson T[3], Ballantyne CM[4], Cho L[2], Kastelein JJ[5], Koenig W[6], Somaratne R[7], Kassahun H[7], Yang J[7], Wasserm
Podolec J[9], Ophuis AO[10], Cornel JH[11], Borgman M[2], Brennan DM[2], Nissen SE[2].

Author information

13 dicembre 2016

Abstract

IMPORTANCE: Reducing levels of low-density lipoprotein cholesterol (LDL-C) with intensive statin therapy reduces progression of coronary atherosclerosis in proportion to achieved LDL-C levels. Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors produce incremental LDL-C lowering in statin-treated patients; however, the effects of these drugs on coronary atherosclerosis have not been evaluated.

OBJECTIVE: To determine the effects of PCSK9 inhibition with evolocumab on progression of coronary atherosclerosis in statin-treated patients.

DESIGN, SETTING, AND PARTICIPANTS: The GLAGOV multicenter, double-blind, placebo-controlled, randomized clinical trial (enrollment May 3, 2013, to January 12, 2015) conducted at 197 academic and community hospitals in North America, Europe, South America, Asia, Australia, and South Africa and enrolling 968 patients presenting for coronary angiography.

INTERVENTIONS: Participants with angiographic coronary disease were randomized to receive monthly evolocumab (420 mg) (n = 484) or placebo (n = 484) via subcutaneous injection for 76 weeks, in addition to statins.

MAIN OUTCOMES AND MEASURES: The primary efficacy measure was the nominal change in percent atheroma volume (PAV) from baseline to week 78, measured by serial intravascular ultrasonography (IVUS) imaging. Secondary efficacy measures were nominal change in

The primary efficacy parameter, **PAV**, increased 0.05% with placebo and **decreased 0.95% with evolocumab** (difference, -1.0% [95% CI, -1.8% to -0.64%]; P < .001). The secondary efficacy parameter, normalized **TAV, decreased 0.9 mm3 with placebo and 5.8 mm3 with evolocumab** (difference, -4.9 mm3 [95% CI, -7.3 to -2.5]; P < .001). Evolocumab induced plaque regression in a greater percentage of patients than placebo (64.3% vs 47.3%; difference, 17.0% [95% CI, 10.4% to 23.6%]; P < .001 for PAV and 61.5% vs 48.9%; difference, 12.5% [95% CI, 5.9% to 19.2%]; P < .001 for TAV).

Conclusions and Relevance: Among patients with angiographic coronary disease treated with statins, addition of evolocumab, compared with placebo, resulted in a greater decrease in PAV after 76 weeks of treatment. Further studies are needed to assess the effects of PCSK9 inhibition on clinical outcomes.

PLOS ONE

12 gennaio 2017

RESEARCH ARTICLE

Economic Evaluation of PCSK9 Inhibitors in Reducing Cardiovascular Risk from Health System and Private Payer Perspectives

Alejandro Arrieta[1]*, Timothy F. Page[1], Emir Veledar[2,3,4], Khurram Nasir[2,3,4,5]

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Citation: Arrieta A, Page TF, Veledar E, Nasir K (2017) Economic Evaluation of PCSK9 Inhibitors in Reducing Cardiovascular Risk from Health System and Private Payer Perspectives. PLoS ONE 12(1): e0170518. doi:10.1371/journal.pone.0170518

Received: May 20, 2016

Accepted: December 20, 2016

Data Availability Statement: All relevant data are within the paper and its Supporting Information file.

Abstract

...cholesterol levels by ...on the added value to the health care sys- ...benefits. We assess the cost-effectiveness of ...on a decision-analytic model with existing clinical ... compares a lipid-lowering therapy ... treatment only (st... ...spective, ...are presented. At the current ...inhibitors are not cost-effective at an incremental ...per QALY. Moreover, for every dollar invested in PCSK9 ..., the private payer loses $1.98. Our study suggests that the annual treatment price should be set at $4,250 at a societal willingness-to-pay of $100,000 per QALY. However, we estimate the breakeven price for private payer is only $600 per annual treatment. At current prices, our study suggests that PCSK9 inhibitors do not add value to the U.S. health system and their provision is not profitable for private payers. To be the breakthrough drug in the fight against cardiovascular disease, the current price of PCSK9 inhibitors must be reduced by more than 70%.

At the current annual cost of $14,000 to $15,000, PCSK9 inhibitors are not cost-effective at an incremental cost of about $350,000 per QALY.

To be the breakthrough drug in the fight against cardiovascular disease, the current price of PCSK9 inhibitors must be reduced by more than 70%.

Reductions in Atherogenic Lipids and Major Cardiovascular Events

A Pooled Analysis of 10 ODYSSEY Trials Comparing Alirocumab With Control

13 dicembre 2016

Editorial, see p 1944

Kausik K. Ray, MD, MPhil
Henry N. Ginsberg, MD
Michael H. Davidson, MD
Robert Pordy, MD
Laurence Bessac, MD
Pascal Minini, PhD
Robert H. Eckel, MD
Christopher P. Cannon, MD

BACKGROUND: A continuous relationship between reductions in low-density lipoprotein cholesterol (LDL-C) and major adverse cardiovascular events (MACE) has been observed in statin and ezetimibe outcomes trials down to achieved levels of 54 mg/dL. However, it is uncertain whether this relationship extends to LDL-C levels <50 mg/dL. We assessed the relationship between additional LDL-C, non–high-density lipoprotein cholesterol, and apolipoprotein B100 reductions and MACE among patients within the ODYSSEY trials that compared alirocumab with controls (placebo/ezetimibe), mainly as add-on therapy to maximally tolerated statin.

METHODS: Data were pooled from 10 double-blind trials (6699 patient-years of follow-up). Randomization was to alirocumab 75/150 mg every 2 weeks or control for 24 to 104 weeks, added to background statin therapy in 8 trials. This analysis included 4974 patients (3182 taking alirocumab, 1174 taking placebo, 618 taking ezetimibe). In a post hoc analysis, the relationship between average on-t... lipid levels and percent reductions in lipids from baseli... MACE (coronary heart disease death, ... stroke, or unstable ...

CONCLUSIONS: In a post hoc analysis from 10 ODYSSEY trials, greater percentage reductions in LDL-C and lower on-treatment LDL-C were associated with a lower incidence of MACE, including very low levels of LDL-C (<50 mg/dL). These findings require further validation in the ongoing prospective ODYSSEY OUTCOMES trial.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifiers: NCT01507831, NCT01623115, NCT01709500, NCT01617655, NCT01644175, NCT01644188, NCT01644474, NCT01730040, NCT01730053, and NCT01709513.

2 febbraio 2017

Amgen Announces Repatha® (Evolocumab) Significantly Reduced The Risk Of Cardiovascular Events In FOURIER Outcomes Study

Landmark Repatha Cardiovascular Outcomes Study Meets Primary and Key Secondary Endpoint

Detailed Results to be Presented at ACC 66th Annual Scientific Session

THOUSAND OAKS, Calif., Feb. 2, 2017 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the FOURIER trial evaluating whether Repatha® (evolocumab) reduces the risk of cardiovascular events in patients with clinically evident atherosclerotic cardiovascular disease (ASCVD) met its primary composite endpoint (cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, hospitalization for unstable angina or coronary revascularization) and the key secondary composite endpoint (cardiovascular death, non-fatal MI or non-fatal stroke). No new safety issues were observed.

The EBBINGHAUS cognitive function trial conducted in FOURIER patients also achieved its primary endpoint, demonstrating that Repatha was non-inferior to placebo for the effect on cognitive function.

Detailed results from the Repatha FOURIER outcomes trial will be presented at the American College of Cardiology (ACC) 66th Annual Scientific Session Late-Breaking Clinical Trials session in Washington, D.C. on Friday, March 17 at 8 a.m. ET. Detailed results from the Repatha EBBINGHAUS cognitive function trial will be presented at the Late-Breaking Clinical Trials session on Saturday, March 18 at 8 a.m. ET.

Alirocumab : ODISSEY OUTCOMES… risultati fino 2017 / inizio 2018

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ORIGINAL INVESTIGATIONS

Safety of Very Low Low-Density Lipoprotein Cholesterol Levels With Alirocumab

Pooled Data From Randomized Trials

Jennifer G. Robinson, MD, MPH,[a] Robert S. Ros...
William J. Sasiela, PhD,[e] Laur...

CONCLUSIONS LDL-C levels <25 or <15 mg/dl on alirocumab were not associated with an increase in overall treatment-emergent adverse event rates or neurocognitive events, although cataract incidence appeared to be increased in the group achieving LDL-C levels <25 mg/dl. (Pooled analyses of already reported trials; NCT01288443, NCT01288469, NCT01266876, NCT01812707, NCT01507831, NCT01617655, NCT01623115, NCT01709500, NCT01644175, NCT01644188, NCT01730040, NCT01730053, NCT01644474, and NCT01709513)(J Am Coll Cardiol 2017;69:471–82) © 2017 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/).

...least 2 consecutive LDL-C values <25 or ...ong as 104 weeks.

...data from 14 trials were analyzed (double-blind treatment 8 to 104 weeks; n = 3,340 alirocumab, n = 1,894 ...control [placebo or ezetimibe]; representing 4,029 [alirocumab] and 2,114 [control] double-blind patient-years' exposure).

AGENZIA ITALIANA DEL FARMACO

DETERMINA 1 febbraio 2017

Classificazione del medicinale per uso umano «Repatha», ai sensi dell'art. 8, comma 10, della legge 24 dicembre 1993, n. 537. (Determina n. 172/2017). (17A01047)

(GU n.31 del 7-2-2017)

Determina:

Art. 1

Classificazione ai fini della rimborsabilita'

Indicazioni terapeutiche oggetto della negoziazione.

Ipercolesterolemia e dislipidemia mista.

«Repatha» e' indicato nei pazienti adulti affetti da **ipercolesterolemia primaria (familiare eterozigote e non familiare) o da dislipidemia mista, in aggiunta alla dieta: in associazione ad una statina o ad una statina con altre terapie ipolipemizzanti in pazienti che non raggiungono livelli di LDL-C target con la dose massima tollerata di una statina, oppure in monoterapia o in associazione ad altre terapie ipolipemizzanti in pazienti intolleranti alle statine o per i quali l'uso di statine e' controindicato**.

Ipercolesterolemia familiare omozigote.

«Repatha» e' indicato in associazione ad altre terapie ipolipemizzanti negli adulti e negli adolescenti di almeno **dodici anni** di eta' con ipercolesterolemia familiare omozigote.

L'effetto di «Repatha» sulla morbilita' e sulla mortalita ‘ cardiovascolare non e' ancora stato determinato.

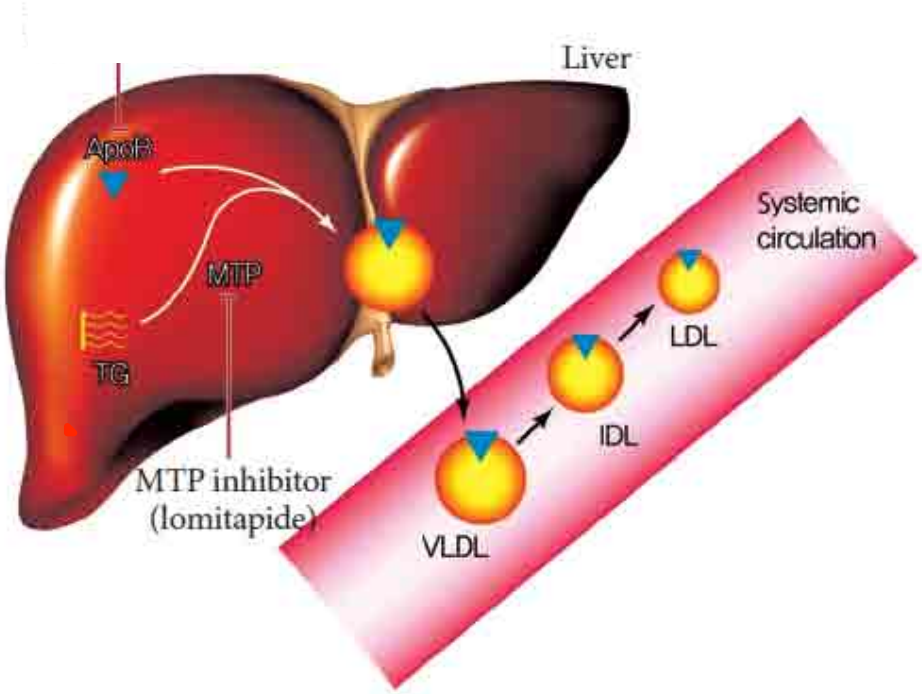
AGENZIA ITALIANA DEL FARMACO

Il medicinale «Repatha» nelle confezioni sotto indicate e ' classificato come segue:
confezione: «140 mg - soluzione iniettabile - uso sottocutaneo
- siringa preriempita (vetro) (sureclick) 1 ml - **1 penna preriempita**
-**classe di rimborsabilita': A;**
prezzo ex factory (IVA esclusa): € 217,34;
prezzo al pubblico (IVA inclusa): € 358,70;
confezione: 140 mg - soluzione iniettabile - uso sottocutaneo -
siringa preriempita (vetro) (sureclick) 1 ml - **2 penne preriempite** -
classe di rimborsabilita': A;
prezzo ex factory (IVA esclusa): € 434,68;
prezzo al pubblico (IVA inclusa): € 717,40.
Ai fini delle prescrizioni a carico del SSN, i centri utilizzatori specificatamente individuati dalle regioni, dovranno compilare la **scheda raccolta dati informatizzata di arruolamento che indica i pazienti eleggibili e la scheda di follow-up, applicando le condizioni negoziali secondo le indicazioni pubblicate sul sito dell'Agenzia, piattaforma web - all'indirizzo https://www.agenziafarmaco.gov.it/registri/ che costituiscono parte integrante della presente determinazione. E' esclusa la prescrizione in modalita' cartacea temporanea.**

Applicazione di uno sconto progressivo in base al meccanismo prezzo/volume, come da condizioni negoziali.
Validita' del contratto: 24 mesi.
Art. 2
Condizioni e modalita' di impiego
Prescrizione del medicinale soggetta a quanto previsto dall'allegato 2 e successive modifiche, alla determinazione 29 ottobre 2004 - PHT Prontuario della distribuzione diretta, pubblicata nel supplemento ordinario alla Gazzetta Ufficiale n. 259 del 4 novembre 2004.
Art. 3
Classificazione ai fini della fornitura
La classificazione ai fini della fornitura del medicinale «Repatha» e' la seguente: medicinali soggetti a prescrizione medica limitativa, vendibili al pubblico su prescrizione di centri ospedalieri e di centri specialistici individuati dalle regioni o su prescrizione di cardiologo, internista (RRL).

- **MTP inhibitor**

LOMITAPIDE : microsomal triglyceride transport protein (MTP) inhibitor



The assembly of very low density lipoprotein (VLDL) requires the loading of triglyceride (TG) to the ApoB in the liver.

MTP works in this process and transfers TG to the ApoB. The secreted VLDL is converted to LDL in the bloodstream.

Lomitapide inhibits the action of MTP inhibiting the assembly of VLDL in the liver, which results in decreased LDL in the bloodstream.

Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study

Marina Cuchel, Emma A Meagher, Hendrik du Toit Theron, Dirk J Blom, A David Marais, Robert A Hegele, Maurizio R Averna, Cesare R Sirtori, Prediman K Shah, Daniel Gaudet, Claudia Stefanutti, Giovanni B Vigna, Anna M E Du Plessis, Kathleen J Propert, William J Sasiela, LeAnne T Bloedon, Daniel J Rader, for the Phase 3 HoFH Lomitapide Study investigators

40mg/die (per os)

Lancet 2013; 381: 40–46

Published Online November 2, 2012 http://dx.doi.org/10.1016/S0140-6736(12)61731-0

See Comment page 7

Institute for Translational Medicine and Therapeutics, Cardiovascular Institute, and Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA (M Cuchel MD, E A Meagher MD, L T Bloedon MS, Prof K J Propert ScD, Prof D J Rader MD); Netcare Private Hospital, Bloemfontein, South Africa (Prof H du Toit Theron MD); Department of Medicine (D J Blom PhD) and Department of Chemical Pathology (Prof A D Marais MD), University of Cape Town, Cape Town, South Africa; Medical Research Council of South Africa, Cape Heart Group, Cape Town, South Africa (D J Blom, A D Marais); Robarts Research Institute and Schulich School of Medicine and Dentistry, University of

Summary

Background Patients with homozygous familial hypercholesterolaemia respond inadequately to existing drugs. We aimed to assess the efficacy and safety of the microsomal triglyceride transfer protein inhibitor lomitapide in adults with this disease.

Methods We did a single-arm, open-label, phase 3 study of lomitapide for treatment of patients with homozygous familial hypercholesterolemia. Current lipid lowering therapy was maintained from 6 weeks before baseline through to at least week 26. Lomitapide dose was escalated on the basis of safety and tolerability from 5 mg to a maximum of 60 mg a day. The primary endpoint was mean percent change in levels of LDL cholesterol from baseline to week 26, after which patients remained on lomitapide through to week 78 for safety assessment. Percent change from baseline to week 26 was assessed with a mixed linear model.

Findings 29 men and women with homozygous familial hypercholesterolaemia, aged 18 years or older, were recruited from 11 centres in four countries (USA, Canada, South Africa, and Italy). 23 of 29 enrolled patients completed both the efficacy phase (26 weeks) and the full study (78 weeks). The median dose of lomitapide was 40 mg a day. LDL cholesterol was reduced by 50% (95% CI −62 to −39) from baseline (mean 8·7 mmol/L [SD 2·9]) to week 26 (4·3 mmol/L [2·5]; p<0·0001). Levels of LDL cholesterol were lower than 2·6 mmol/L in eight patients at 26 weeks. Concentrations of LDL cholesterol remained reduced by 44% (95% CI −57 to −31; p<0·0001) at week 56 and 38% (−52 to −24; p<0·0001) at week 78. Gastrointestinal symptoms were the most common adverse event. Four patients had aminotransaminase levels of more than five times the upper limit of normal, which resolved after dose reduction or temporary interruption of lomitapide. No patient permanently discontinued treatment because of liver abnormalities.

Interpretation Our study suggests that treatment with lomitapide could be a valuable drug in the management of homozygous familial hypercholesterolaemia.

Funding FDA Office of the Orphan Product Development, Aegerion Pharmaceuticals.

▸ Lojuxta 5/10/20 mg

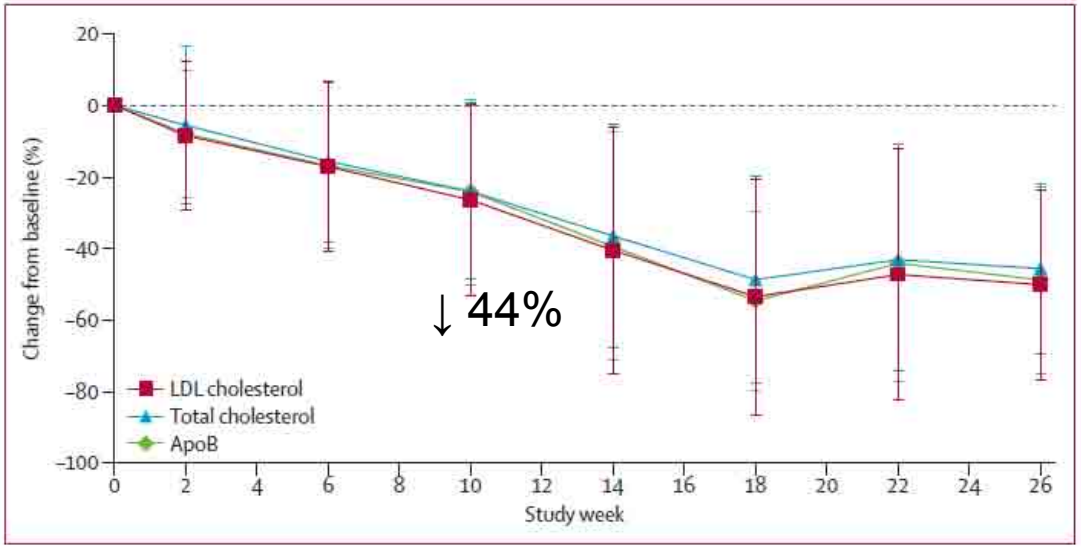
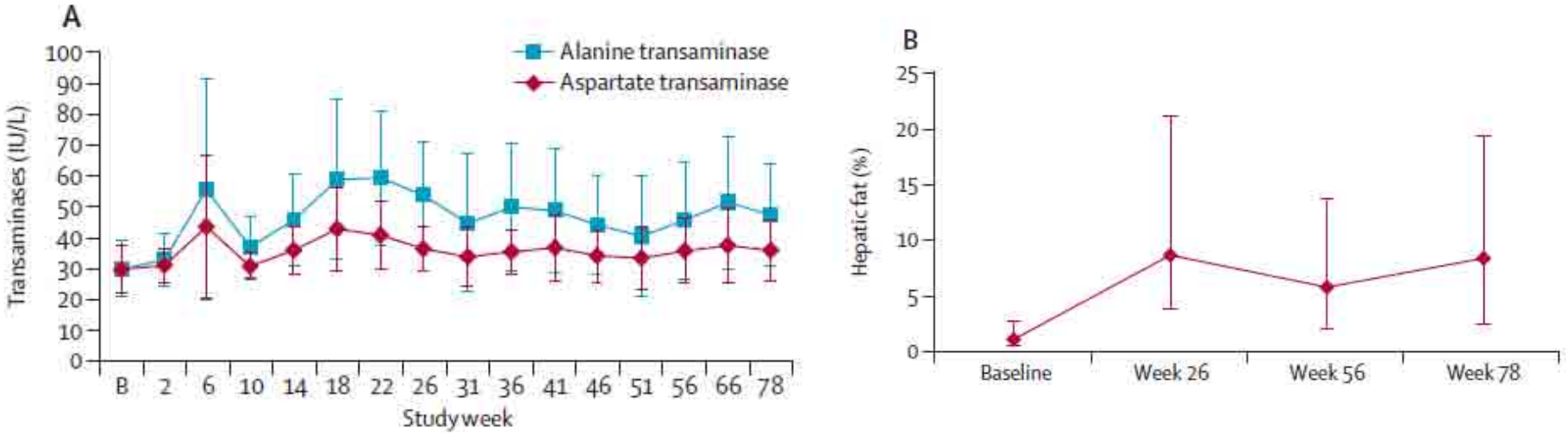


Figure 1: **Mean percent changes in LDL cholesterol, total cholesterol, and ApoB levels from baseline to week 26 (end of efficacy phase)**
Data available at each time point are expressed as mean (SD).



Alanine transaminase and aspartate transaminase levels and percentage of hepatic fat in the liver
Data are mean, 95% CI. Laboratory reference ranges for alanine transaminase levels were 10–40 U/L in men and 10–33 U/L in women; reference ranges for aspartate transaminase levels were 10–43 U/L in men and 10–36 U/L in women (A). Percentage of fat in the liver, as measured by nuclear magnetic resonance spectroscopy at baseline and 26, 56, and 78 weeks of lomitapide treatment (n=20; B).

"Interpretation

We report that lomitapide, when given in addition to currently available lipid-lowering therapy, results in an ***additional 50% reduction in LDL cholesterol****, potentially bringing these high-risk patients closer to target levels.*

The limitations due to the single-arm, open-label design and the safety considerations of potential dose-related transaminase elevations, and ***liver-fat accumulation*** *are counterbalanced and outweighed by the significant LDL cholesterol-lowering eff ects of lomitapide in this severe disorder of unmet medical need.*

Our study suggests that treatment with lomitapide could be a valuable drug in the management of ***homozygous*** *familial hypercholesterolaemia."*

Cuchel M et al , Lancet 2013

Atherosclerosis 240 (2015) 408–414

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journal homepage: www.elsevier.com/locate/atherosclerosis

The lipid-lowering effects of lomitapide are unaffected by adjunctive apheresis in patients with homozygous familial hypercholesterolaemia – A post-hoc analysis of a Phase 3, single-arm, open-label trial

C. Stefanutti [a], D.J. Blom [b], M.R. Averna [c], E.A. Meagher [d], H. dT. Theron [e], A.D. Marais [b], R.A. Hegele [f], C.R. Sirtori [g], P.K. Shah [h], D. Gaudet [i], G.B. Vigna [j], B.S. Sachais [d], S. Di Giacomo [a], A.M.E. du Plessis [k], L.T. Bloedon [l], J. Balser [m], D.J. Rader [d], M. Cuchel [d,*], For the Phase 3 HoFH Lomitapide Study Investigators

"Conclusion: The LDL-C lowering efficacy of lomitapide is unaffected by lipoprotein apheresis."

SOCIETÀ ITALIANA PER LO STUDIO DELLA ARTERIOSCLEROSI

HOMEPAGE LA SOCIETÀ SEZIONI REGIONALI RICERCA E PREMI ISCRIZIONE FONDAZIONE SISA CONTATTACI

Novità *Vedi archivio*

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Lomitapide ottiene l'autorizzazione all'immissione in commercio

Con la pubblicazione della decisione AIFA (Agenzia Italiana del Farmaco) in Gazzetta Ufficiale (G.U. 133 dell'11/6/2015), lomitapide ha ricevuto l'autorizzazione ufficiale per la commercializzazione in Italia, rimborsabile a carico del Servizio Sanitario Nazionale (classe A).

Lomitapide (nome commerciale Lojuxta), della statunitense Aegerion Pharmaceuticals, è approvato per l'uso in pazienti adulti affetti da ipercolesterolemia familiare omozigote (HoFH) come terapia adiuvante di una dieta a basso tenore di grassi e di altri medicinali ipolipemizzanti con o senza aferesi delle lipoproteine a bassa densità (LDL).

La decisione di AIFA segue l'autorizzazione alla commercializzazione in Europa ottenuta a luglio 2013. (Lomitapide disponibile in italia per l'ipercolesterolemia familiare omozigote) Sempre nel 2013, era stata pubblicata in Gazzetta Ufficiale (G.U. 193 del 19/8/2013) la determina AIFA circa l'inserimento del medicinale per uso umano Â«lomitapideÂ» nell'elenco dei medicinali erogabili a totale carico del Servizio Sanitario Nazionale (ai sensi del provvedimento della Commissione Unica del Farmaco concernente l'istituzione dell'elenco dei medicinali innovativi la cui commercializzazione è autorizzata in altri Stati ma non sul territorio nazionale, dei medicinali non ancora autorizzati ma sottoposti a sperimentazione clinica e dei medicinali da impiegare per una indicazione terapeutica diversa da quella autorizzata, da erogarsi a totale carico del Servizio Sanitario Nazionale qualora non esista valida alternativa terapeutica, legge 23 dicembre 1996 n. 648).

Ora lomitapide, come riportato in Gazzetta Ufficiale, è "soggetto a prescrizione medica limitativa, da rinnovare volta per volta, vendibile al pubblico su prescrizione di centri ospedalieri o di specialisti - cardiologo, endocrinologo, internista".

GU 133/2015 con la determina AIFA

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30° Congresso Nazionale

Roma, 20-22 novembre 2016

Abstract deadline: 30 settembre

[continua a leggere]

Nuove opzioni nelle dislipidemie: Costi e Benefici

Descrizione prodotto:	LOJUXTA*FL 28CPS RIGIDE 10MG	Dati regionali
Principio attivo:	LOMITAPIDE MESILATO	
Codice prodotto:	042920025	
Produttore (Titolare AIC):	AEGERION PHARMACEUTICALS	
Concedibile SSN:	Si	
Note limitative:	DISTR DIR ANCHE DA STRUT PUBBL	
Ricetta:	CON RICETTA NON RIPETIBILE	
Glutine:		
Prezzo al pubblico	€31145,15	In commercio

Descrizione prodotto:	LOJUXTA*FL 28CPS RIGIDE 20MG	Dati regionali
Principio attivo:	LOMITAPIDE MESILATO	
Codice prodotto:	042920037	
Produttore (Titolare AIC):	AEGERION PHARMACEUTICALS	
Concedibile SSN:	Si	
Note limitative:	DISTR DIR ANCHE DA STRUT PUBBL	
Ricetta:	CON RICETTA NON RIPETIBILE	
Glutine:		
Prezzo al pubblico	€31145,15	In commercio

31145,15

Descrizione prodotto:	LOJUXTA*FL 28CPS RIGIDE 5MG	Dati regionali
Principio attivo:	LOMITAPIDE MESILATO	
Codice prodotto:	042920013	
Produttore (Titolare AIC):	AEGERION PHARMACEUTICALS	
Concedibile SSN:	Si	
Note limitative:	DISTR DIR ANCHE DA STRUT PUBBL	
Ricetta:	CON RICETTA NON RIPETIBILE	
Glutine:		
Prezzo al pubblico:	€31145,15	In commercio

"CONCLUSIONI / RIASSUMENDO":

.

- L**inee guida ESC / EAS 2016** per il management delle dislipidemie

-Sono uscite le **nuove linee guida AACE 2017** per il management delle dislipidemie !!

-Vengono recepite le nuove evidenze in merito all'**ezetimibe**

-**Inibitori di PCSK9** promettenti studi clinici in aggiunta a statine/altri ipolipemizzanti, con buon profilo di sicurezza, ma siamo in attesa del 'costo definitivo' e delle indicazioni AIFA di rimborsabilità

- **inibitori di MTP** (Lomitapide) promettente risorsa aggiuntiva all'aferesi in HoFH


THANK YOU
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