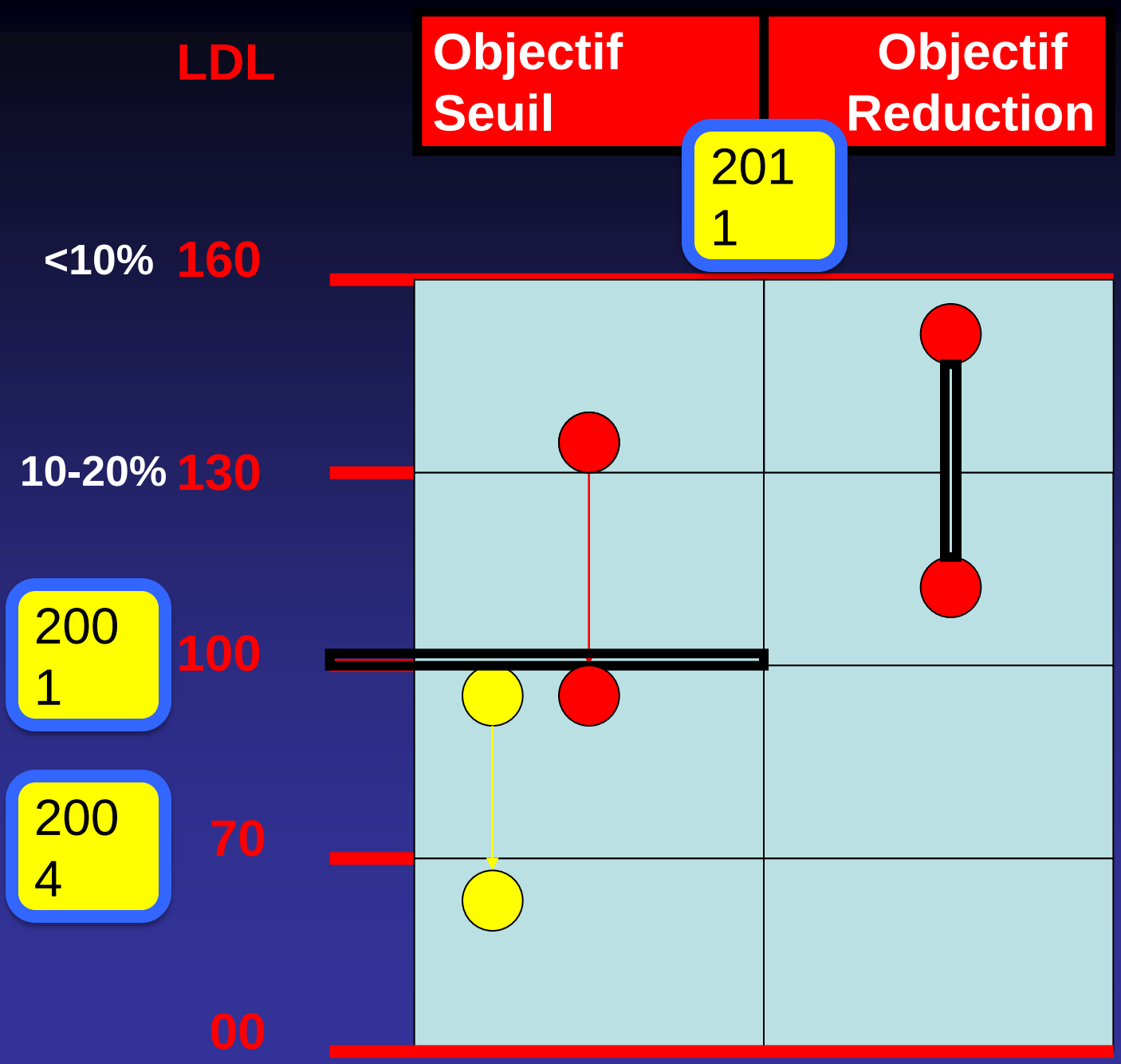
Cholesterol Drugs at the Crossroads

A La croisée des chemins

Alami M, MD. Casablanca, Morocco

Casablanca, April 02, 2015



NCEP Report. Circulation, July 13, 2004

1

ESC 2011 Lessons

WHICH

Table 8 Recommendations for treatment targets for LDL-C

Recommendations	Class[a]	Level[b]	Ref[c]
In patients at VERY HIGH CV risk (established CVD, type 2 diabetes, type 1 diabetes with target organ damage, moderate to severe CKD or a SCORE level ≥10%) the LDL-C goal is <1.8 mmol/L (less than ~70 mg/dL) and/or ≥50% LDL-C reduction when target level cannot be reached.	I	A	15, 32, 33
In patients at HIGH CV risk (markedly elevated single risk factors, a SCORE level ≥5 to <10%) an LDL-C goal <2.5 mmol/L (less than ~100 mg/dL) should be considered.	IIa	A	15, 16, 17
In subjects at MODERATE risk (SCORE level >1 to ≤5%) an LDL-C goal <3.0 mmol/L (less than ~115 mg/dL) should be considered.	IIa	C	-

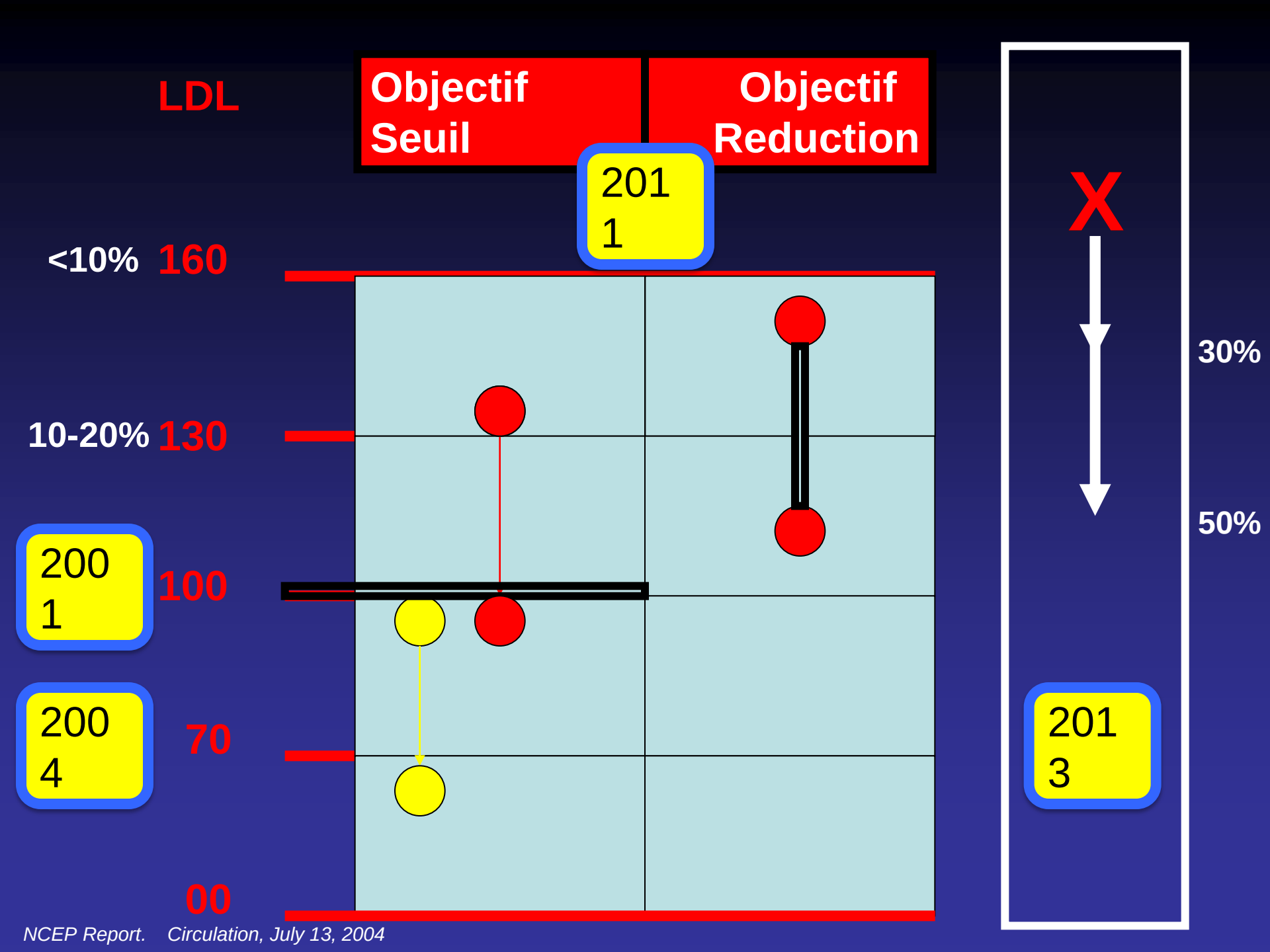
HOW

Table 14 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 target level.	I	A	15, 16, 17
In the case of statin intolerance, bile acid sequestrants or nicotinic acid should be considered.	IIa	B	108, 120
A cholesterol absorption inhibitor, alone or in combination with bile acid sequestrants or nicotinic acid, may also be considered in the case of statin intolerance.	IIb	C	-
If target level is not reached, statin combination with a cholesterol absorption inhibitor or bile acid sequestrant or nicotinic acid may be considered.	IIb	C	-

2

AHA/ACC 2013 Lessons



NCEP Report. Circulation, July 13, 2004

WHICH
HOW

How Intense Should Statin Therapy Be?
Could Not Find Evidence to Support Specific LDL Treatment Targets

- **Don't treat to specific targets*:** Treating to targets results in under- and overtreatment*; use appropriate-intensity treatment

WHO

Cholesterol Treatment to Reduce Atherosclerotic Risk
Attempt to Identify 4 Statin Groups

1. Does the patient have a history of heart disease or stroke? Are they using secondary prevention? (Use 2011 AHA/ACC secondary prevention guidelines)
2. Is LDL > 190 mg/dL? They have FH.


3
ICE 2014
Lessons

NICE Guidelines 2014

Secondary prevention

1.3.20 Start statin treatment in people with CVD with atorvastatin 80 mg[6]. Use a lower dose of atorvastatin if any of the following apply:

- potential drug interactions
- high risk of adverse effects
- patient preference. **[new 2014]**

1.3.21 Do not delay statin treatment in secondary prevention to manage modifiable risk factors. **[2014]**

1.3.22 If a person has acute coronary syndrome, do not delay statin treatment. Take a lipid sample on admission and about 3 months after the start of treatment. **[2008, amended 2014]**

NICE Guidelines 2014

Primary prevention for people with type 2 diabetes

1.3.26 Offer atorvastatin 20 mg for the primary prevention of CVD to people with type 2 diabetes who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. **[new 2014]** [This recommendation updates and replaces recommendations 1.10.1.2, 1.10.1.3, and 1.10.1.5 from Type 2 diabetes (NICE clinical guideline 87).]

People with CKD

1.3.27 Offer atorvastatin 20 mg for the primary or secondary prevention of CVD to people with CKD[r].

- Increase thedose if a greater than 40% reduction in non-HDL cholesterol is not achieved (see recommendation 1.3.28) and eGFR is 30 ml/min/1.73 m^2 or more.
- Agree the use of higher doses with a renal specialist if eGFR is less than 30 ml/min/ 1.73 m^2. **[new 2014]**

4

Today

Poor response to statins predicts growth in plaque

BY KARI OAKES in Cardiology on February 26th, 2015

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FROM ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY

For about one in five patients with known atherosclerotic coronary artery disease, standard-dose therapy with statins did not result in significant lowering of LDL cholesterol.

Furthermore, the results of this large pooled data sample showed that for statin hyporesponders, statin therapy did not prevent progression of intravascular plaque volume as measured by grayscale intravascular ultrasound.

Atheroma Progression in Hyporesponders to Statin Therapy
Yu Kataoka, Julie St. John, Kathy Wolski, Kiyoko Uno, Rishi Puri, E. Murat Tuzcu, Steven E. Nissen, and Stephen J. Nicholls
Arterioscler Thromb Vasc Biol 2015; first published on February 26 2015 as doi:10.1161/ATVBAHA.114.304477

NIACIN

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 15, 2011 VOL. 365 NO. 24

Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy

The AIM-HIGH Investigators*

CONCLUSIONS

Among patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of less than 70 mg per deciliter (1.81 mmol per liter), there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up period, despite significant improvements in HDL cholesterol and triglyceride levels. (Funded by the National Heart, Lung, and Blood Institute and Abbott Laboratories; AIM-HIGH ClinicalTrials.gov number, NCT00120289.)

EZETIMIBE

18.000 pts within 10d of ACS

LDL<0.95

Even lower is better

Benefit of a LDL Lowering with a Non Statin

RRR= 6.4%

CETP inhibitor Anacetrapib

Articles

Anacetrapib as lipid-modifying therapy in patients with heterozygous familial hypercholesterolaemia (REALIZE): a randomised, double-blind, placebo-controlled, phase 3 study

Prof John J P Kastelein, MD, Joost Besseling, MD, Sukrut Shah, PhD, Jean Bergeron, MD, Gisle Langslet, MD, G Kees Hovingh, MD, Naab Al-Saady, MD, Michiel Koeijvoets, BSc, John Hunter, MS, Amy O Johnson-Levonas, PhD, Jennifer Fable, PharmD, Aditi Sapre, PhD, Yale Mitchel, MD

Published Online: 02 March 2015

LDL

40%

HDL

x2

PCSK9 inhibitors

ALIROCUMAB
75-150/2weeks

EZETIMIBE
10mg

ATORVASTATIN
20mg

Better Tolerance

Impressive Reduction in LDL

60% LDL Reduction

PCSK9 inhibitors

STATIN (max tolerated dose)

ALIROCUMAB

PLACEBO

LDL 60%

CV events 54%

25

No MAE

Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Jennifer G. Robinson, M.D., M.P.H., Michel Farnier, M.D., Ph.D., Michel Krempf, M.D., Jean Bergeron, M.D., Gérald Luc, M.D., Maurizio Averna, M.D., Erik S. Stroes, M.D., Ph.D., Gisle Langslet, M.D., Frederick J. Raal, M.D., Ph.D., Mahfouz El Shahawy, M.D., Michael J. Koren, M.D., Norman E. Lepor, M.D., Christelle Lorenzato, M.Sc., Robert Pordy, M.D., Umesh Chaudhari, M.D., and John J.P. Kastelein, M.D., Ph.D., for the ODYSSEY LONG TERM Investigators*

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 CPBH, 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 Supple-

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

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

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; $P=0.003$).

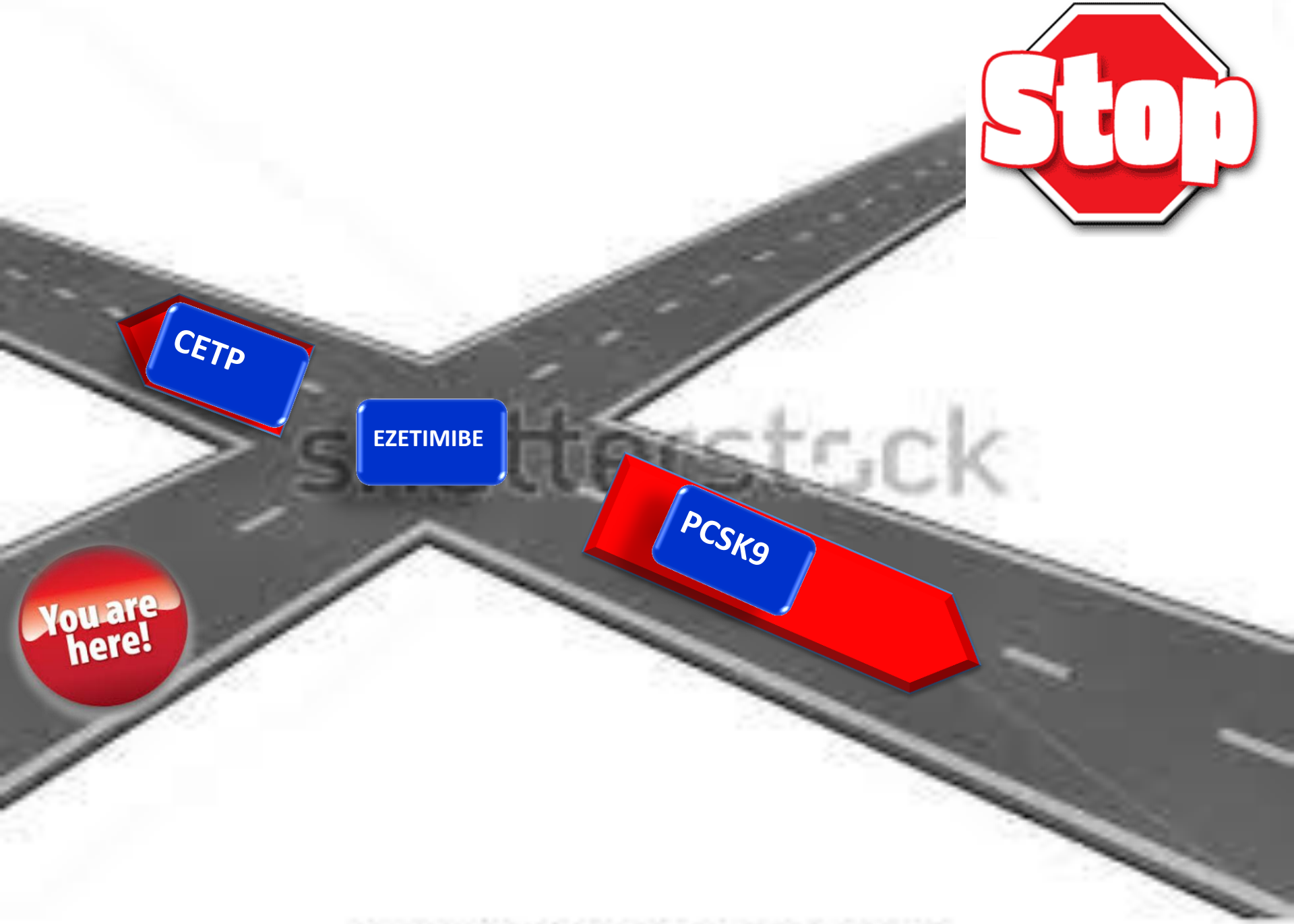
CONCLUSIONS

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.)

From the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, and the Department of Medicine, Harvard Medical School, Boston (M.S.S., R.P.G., S.D.W.); the Carbohydrate and Lipid Metabolism Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg (F.J.R.), and the Division of Lipidology, Department of Medicine, University of Cape Town, Cape Town (D.J.B.) — both in South Africa; the Departments of Epidemiology and Medicine, College of Public Health, University of Iowa, Iowa City (J.R.); the Sections of Cardiovascular Research and Cardiology, Department of Medicine, Baylor College of Medicine, and the Center for Cardiovascular Disease Prevention, Houston Methodist DeBakey Heart and Vascular Center, Houston (C.M.B.); Amgen, Thousand Oaks, CA (R. Somaratne, J.L., S.M.W., R. Scott); Jacksonville Center for Clinical Research, Jacksonville, FL (M.J.K.); and the Metabolic and Atherosclerosis Research Center, Cincinnati (E.A.S.). Address reprint requests to Dr. Sabatine at the TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at msabatine@partners.org; or to Dr. Stein at the Metabolic and Atherosclerosis Research Center, 5355 Medpace Way, Cincinnati, OH 45275, or at steinmyl@aol.com.

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

DOI: 10.1056/NEJMoa1500858


Stop
CETP
EZETIMIBE
PCSK9
You are here!

5 omorrow

CETP inhibitor Anacetrapib