

Inibitori di PCSK9

Prof. Alberto Corsini

Università degli Studi di Milano

Inibitori PCSK9

- Razionale
- Farmacologia
- Efficacia
- Sicurezza
- Dati del mondo reale

**Perche' PCSK9 come bersaglio
farmacologico?**

**Perche' un anticorpo
monoclonale?**

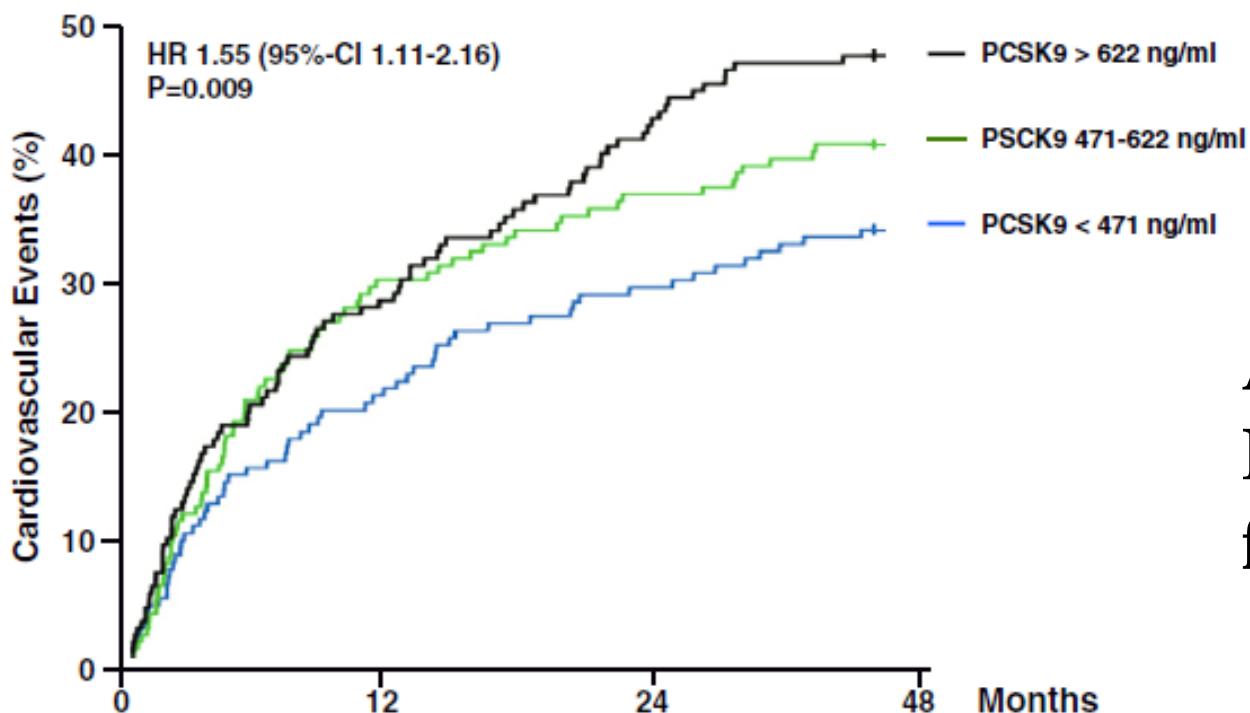
Proprotein convertase subtilisin/kexin 9 (PCSK9)

- **Biochimica/fisiologia**
- Epidemiologia
- Genetica
- Farmacologia



Risk prediction with proprotein convertase subtilisin/kexin type 9 (PCSK9) in patients with stable coronary disease on statin treatment

Christian Werner ^a, Michael M. Hoffmann ^b, Karl Winkler ^b, Michael Böhm ^a, Ulrich Laufs ^{a,*}



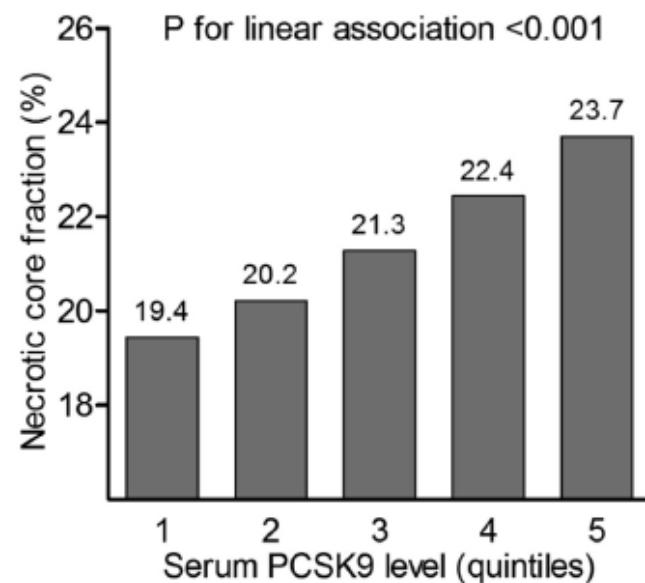
**Association of
PCSK9 with event-
free survival**



PCSK9 in relation to coronary plaque inflammation: Results of the ATHEROREMO-IVUS study

Jin M. Cheng ¹, Rohit M. Oemrawsingh ¹, Hector M. Garcia-Garcia, Eric Boersma,
Robert-Jan van Geuns, Patrick W. Serruys, Isabella Kardys, K. Martijn Akkerhuis*

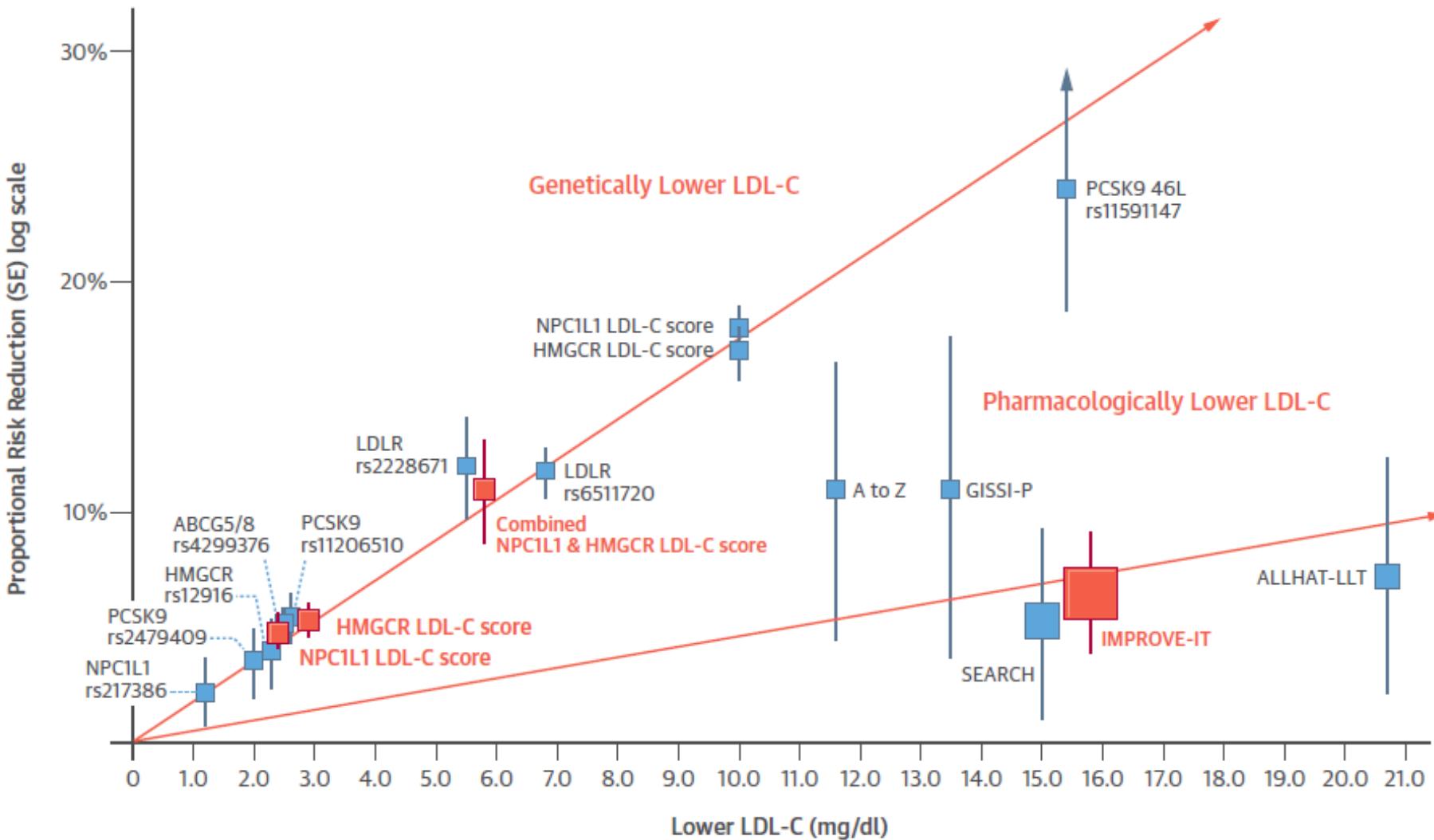
Erasmus MC, Department of Cardiology, Rotterdam, The Netherlands



| Quintile boundaries ($\mu\text{g/L}$) | | | | | |
|---|-----|-----|-----|-----|-----|
| Lower | 91 | 203 | 246 | 296 | 351 |
| Upper | 203 | 246 | 296 | 351 | 804 |

Fig. 2. Association between serum PCSK9 level and fraction of coronary plaque that consists of necrotic core tissue. PCSK9, proprotein convertase subtilisin/kexin type 9.

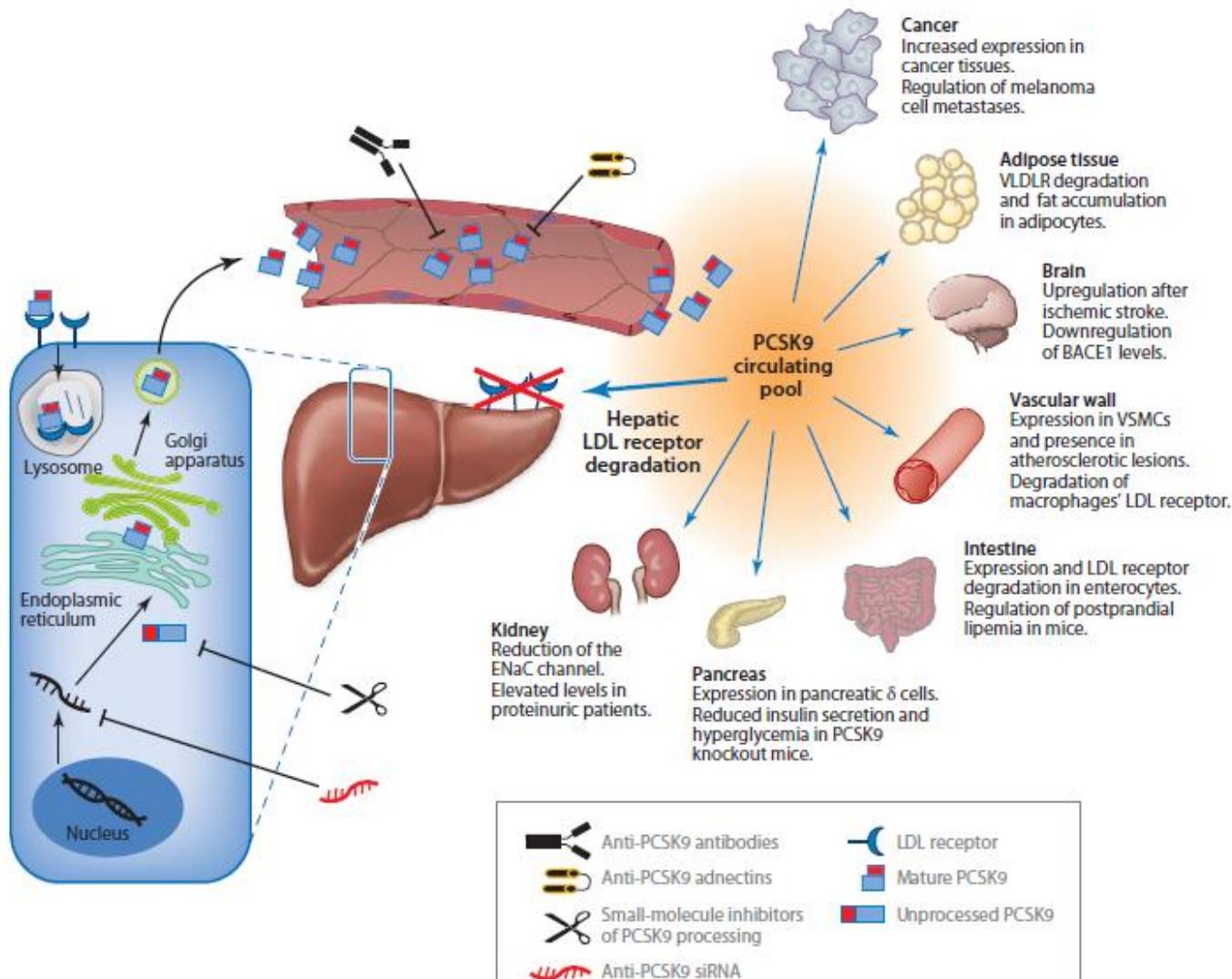
Linear Association Between Genetically and Pharmacologically Mediated Lower LDL and Risk of Coronary Heart Disease



**Perche' PCSK9 come bersaglio
farmacologico?**

**Perche' un anticorpo
monoclonale?**

PCSK9: ruolo fisiologico e modulazione farmacologica



Anti-PCSK9 Therapeutic Approaches

| Mechanism of Action | Class | Agent | Company | Phase |
|---------------------|-------------------------------|--------------------------------|-------------------------------|------------------------|
| PCSK9 binding | | | | |
| | Human monoclonal antibody | Altrocumab (REGN727/SAR236553) | Regeneron/Sanofi | Approved in USA and EU |
| | Human monoclonal antibody | Evolocumab (AMG145) | Amgen | Approved In USA and EU |
| | Humanized monoclonal antibody | Bococizumab (PF-04950615) | Pfizer | 3 |
| | Human monoclonal antibody | LY3015014 | Eli Lilly | 2 |
| | Modified binding protein | Adnectin (BMS962476) | BMS/Adnexus | I |
| | Small-molecule Inhibitor | SX-PCK9 | Serometrix | Preclinical |
| PCSK9 synthesis | | | | |
| | RNA Interference | ALN-PCSsc | Alnylam/The Medicines Company | I |

PCSK9, proprotein convertase subtilisin/kexin type 9.

Ito MK et al J Clin Pharmacol. 2016 May 16

Inibitori PCSK9

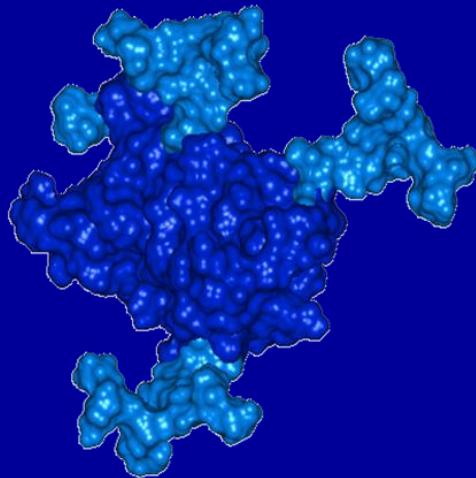
- Razionale
- **Farmacologia**
- Efficacia
- Sicurezza
- Dati del mondo reale

Proteins

Molecular Size and 3-D Structure and Complexity

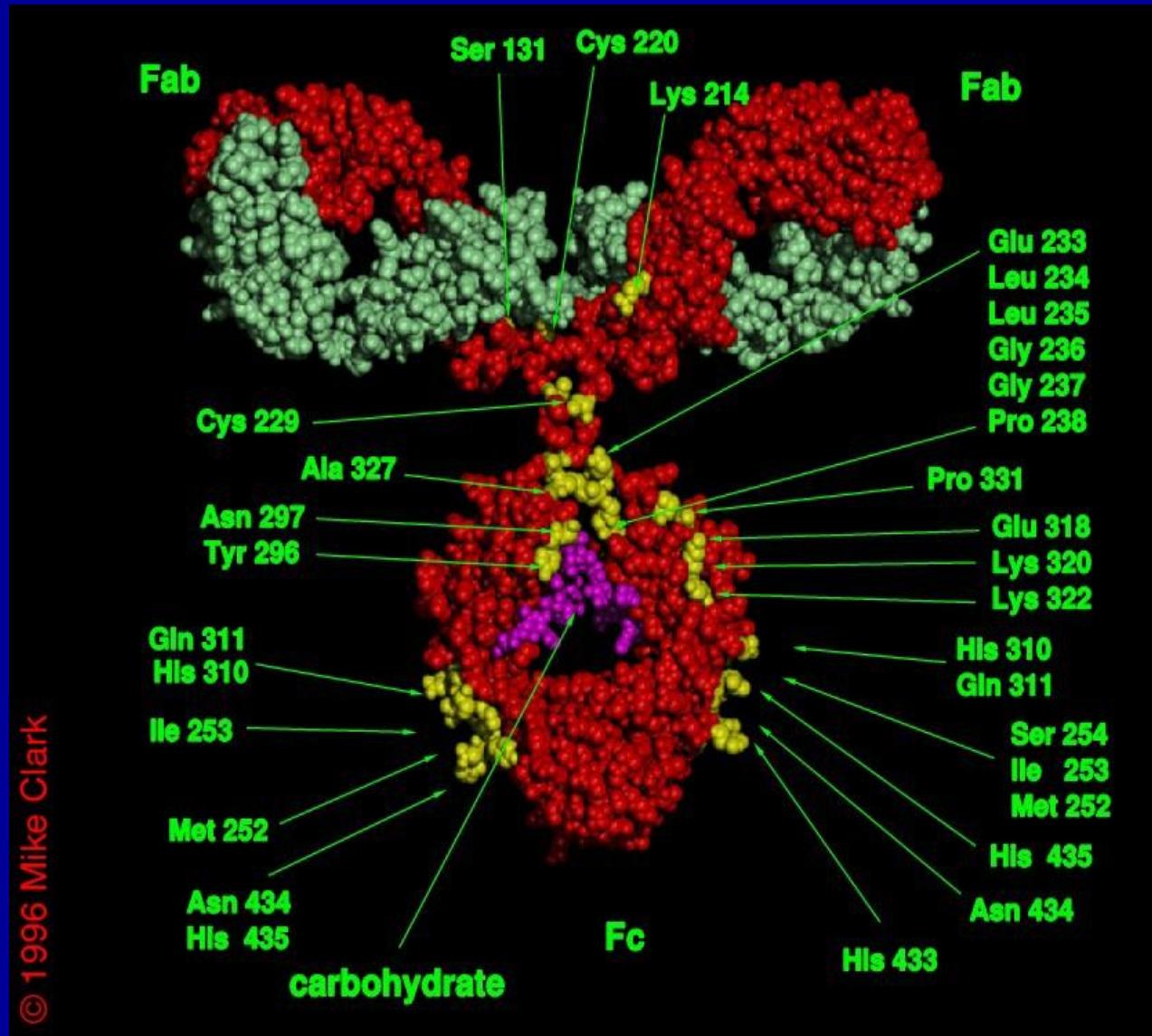


Aspirin



Erythropoietin

Antibody (IgG) molecule

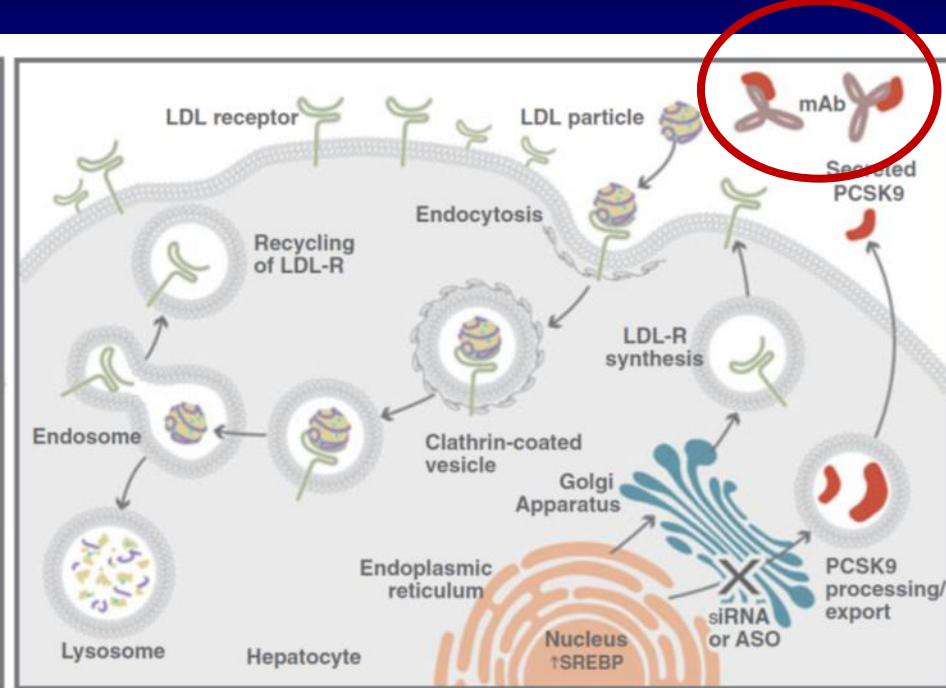
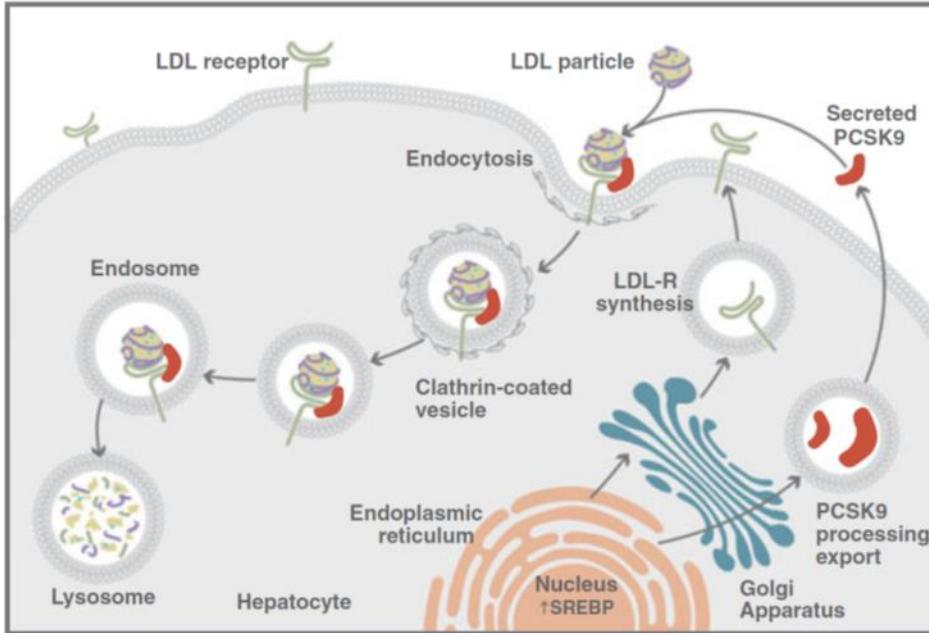


Evolocumab è un anticorpo monoclonale umano di tipo IgG2 prodotto in cellule ovariche di criceto cinese (CHO) mediante tecnologia del DNA ricombinante

Evolocumab RCP

| | Small Molecule | Monoclonal Antibody |
|---------------------------|-----------------------|----------------------------------|
| Size | ~ 0.5 kDa | ~ 150 kDa |
| Structure | Chemical entity | Immunoglobulin |
| Target | Intracellular, CNS | Extracellular |
| Target Specificity | Low(er) | High |
| Metabolism | Hepatic/renal | RES, target-mediated disposition |
| Administration | PO | SC or IV |
| Crossing BBB | Potentially yes | No |

Interaction of PCSK9 and the LDL receptor

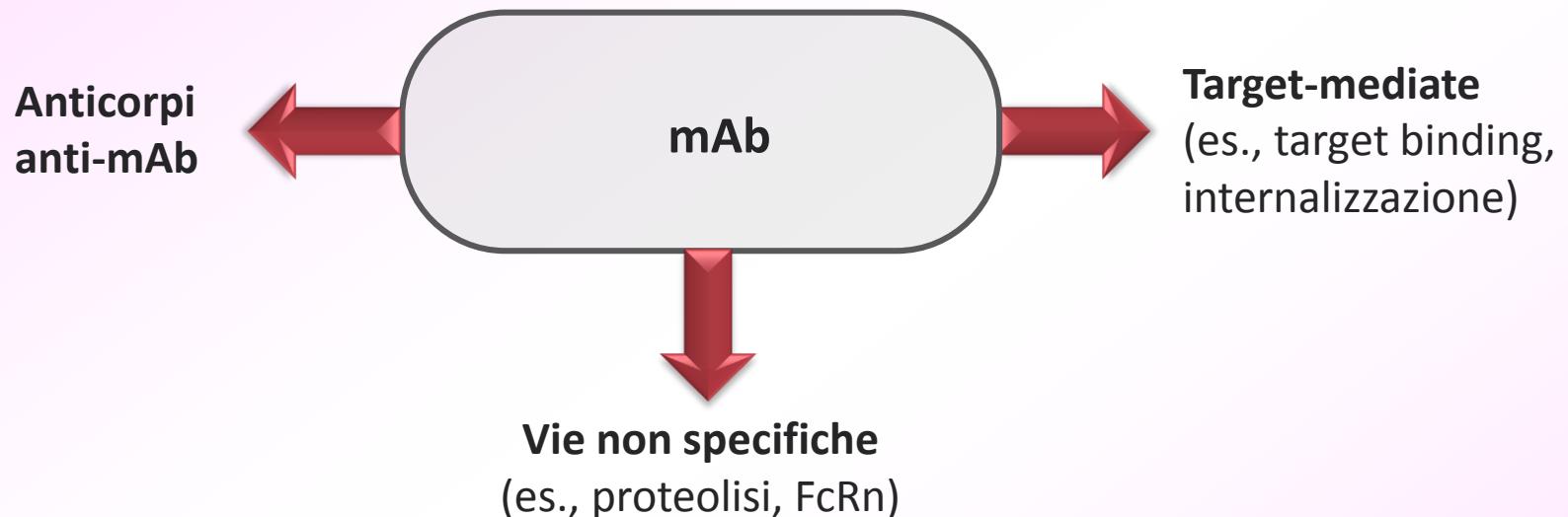


Stein EA and Swerdlow GD Curr Atheroscler Rep (2013) 15:310

Alirocumab: Pharmacokinetic properties

- Linear / Non linear pharmacokinetics (by PCSK9 and RES)
- Bioavailability about 85%
- Tmax 3-7 days
- Vss 3.5 Lt
- T1/2 consistent with other IgG1 Mab (i.e. 3 weeks)
- The half-life of alirocumab at steady state was 17 to 20 days in patients receiving alirocumab as monotherapy at subcutaneous doses of either 75 mg Q2W or 150 mg Q2W
- When co-administered with a statin, the median apparent half-life of alirocumab was 12 days.

VIE DI ELIMINAZIONE DEGLI ANTICORPI MONOCLONALI



- Riduzione e/o stabilizzazione del tumore a seguito della terapia
- Riduzione espressione antigene → Riduzione clearance

ELIMINAZIONE DEGLI ANTICORPI MONOCLONALI

- Differente affinità della frazione C dell'anticorpo monoclonale al recettore neonatale (FcRn)
 - ▶ I'emivita aumenta a seconda che siano murini (2-3 giorni), chimerici (8-10 giorni) o umanizzati (20-23 giorni)
- L'effetto dell'età, del genere, della funzionalità renale ed epatica sulla farmacocinetica degli anticorpi monoclonali è controversa
 - Le differenze tra pazienti, in termini farmacocinetici, sono generalmente modeste
- Auto-antibodies (e.g. rheumatoid factors)
 - ▶ esposizione al farmaco consistente nelle diverse tipologie di pazienti

4.2 Posology and method of administration

Posology

The usual starting dose for Praluent is 75 mg administered subcutaneously once every 2 weeks. Patients requiring larger LDL-C reduction (>60%) may be started on 150 mg administered subcutaneously once every 2 weeks.

The dose of Praluent can be individualised based on patient characteristics such as baseline LDL-C level, goal of therapy, and response. Lipid levels can be assessed 4 weeks after treatment initiation or titration, when steady-state LDL-C is usually achieved, and dose adjusted accordingly (up-titration or down-titration). Patients should be treated with the lowest dose necessary to achieve the desired LDL-C reduction.

Special populations

Paediatric population

The safety and efficacy of Praluent in children and adolescents less than 18 years of age have not been established. No data are available.

Elderly

No dose adjustment is needed for elderly patients.

Hepatic impairment

No dose adjustment is needed for patients with mild or moderate hepatic impairment. No data are available in patients with severe hepatic impairment.

Renal impairment

No dose adjustment is needed for patients with mild or moderate renal impairment. Limited data are available in patients with severe renal impairment (see section 5.2).

Body weight

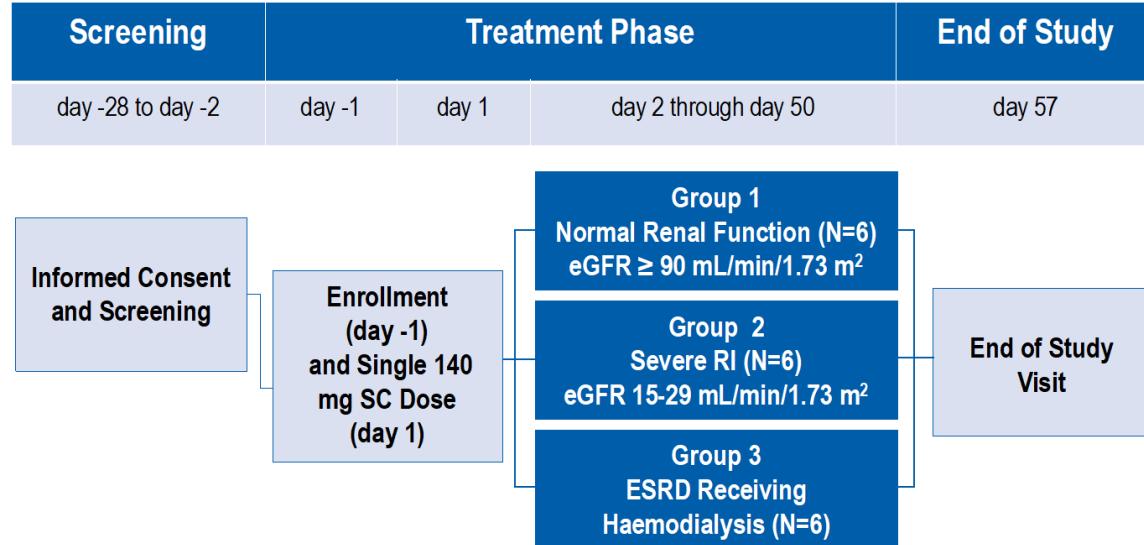
No dose adjustment is needed in patients based on weight.

Influence of Renal Function on Evolocumab Exposure, Pharmacodynamics, and Safety

Clinical Pharmacology
in Drug Development
2019;00(0) 1–9
© 2019 The Authors. *Clinical Pharmacology in Drug Development*
Published by Wiley Periodicals, Inc. on
behalf of The American College of
Clinical Pharmacology
DOI: 10.1002/cpdd.650

Edward Lee¹, John P. Gibbs^{1,*}, Maurice G. Emery^{1,*}, Geoffrey Block²,
Scott M. Wasserman¹, Lisa Hamilton^{3,*}, Sreeneeranji Kasichayanula^{1,*},
Patrick Hanafin^{1,*}, Ransi Somaratne^{1,*}, and Ogo Egbuna^{1,*}

Figure 1. Study Design and Treatment Schema



The Modification of Diet in Renal Disease (MDRD) study equation was used to estimate GFR. eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; RI, renal impairment; SC, subcutaneous

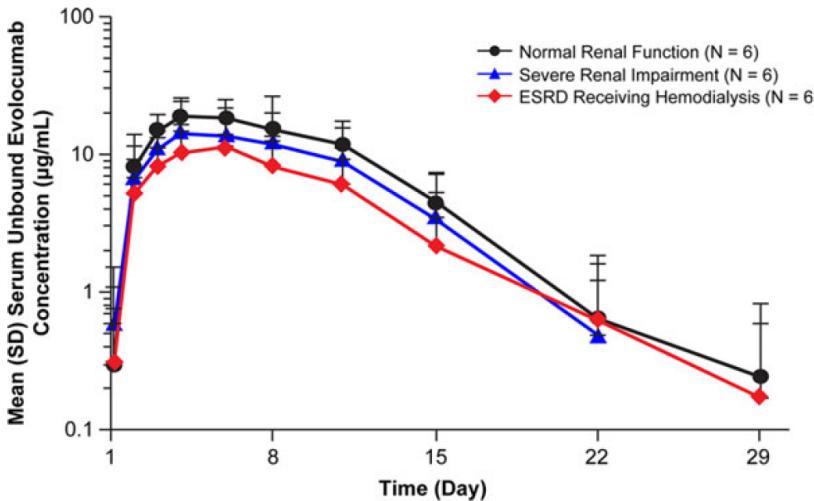


Figure 1. Mean \pm standard deviation serum unbound evolocumab concentration-time profiles from normal renal function, severe renal impairment, or ESRD receiving hemodialysis patients after a single 140-mg subcutaneous dose of evolocumab, depicted as a log-linear plot. The lower limit of quantification was 0.8 $\mu\text{g}/\text{mL}$. ESRD, end-stage renal disease; SD, standard deviation.

These results support the use of evolocumab without dose adjustment in patients who have severe RI or ESRD.

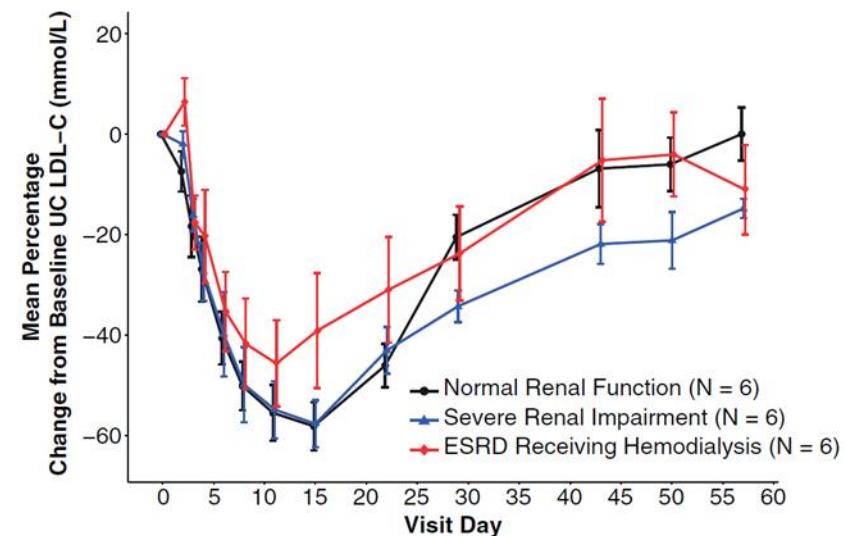


Figure 4. Mean percent change \pm standard error from baseline of UC LDL-C (mg/dL) over time by degree of renal impairment. ESRD, end-stage renal disease; LDL-C, low-density lipoprotein cholesterol; UC, ultracentrifugation.

Evaluation of Evolocumab (AMG 145), a Fully Human Anti-PCSK9 IgG2 Monoclonal Antibody, in Subjects With Hepatic Impairment

The Journal of Clinical Pharmacology
2017, 57(4) 513–523
© 2016, The Authors. *The Journal of Clinical Pharmacology* published by
Wiley Periodicals, Inc. on behalf of
American College of Clinical Pharmacology
DOI: 10.1002/jcpb.832

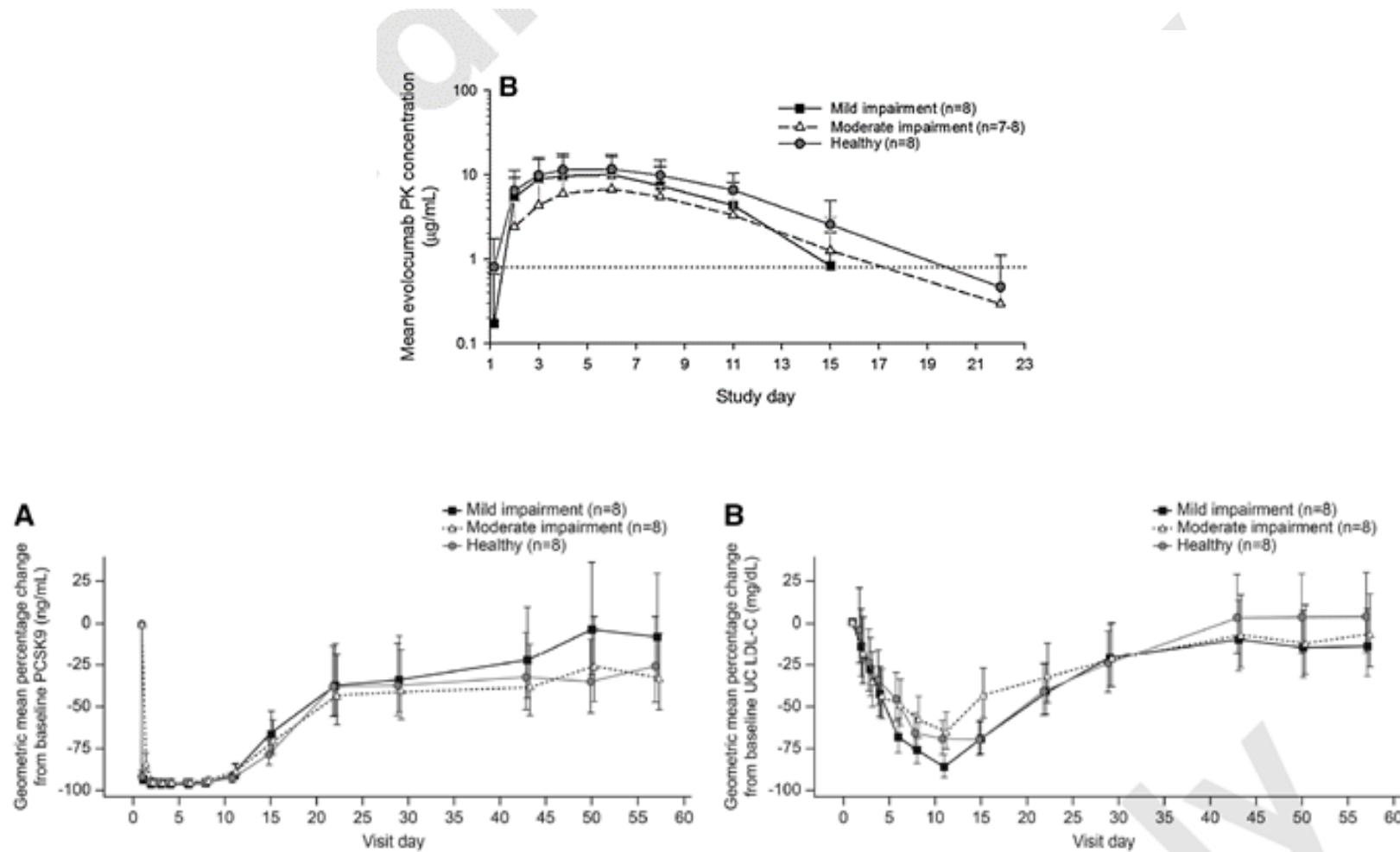
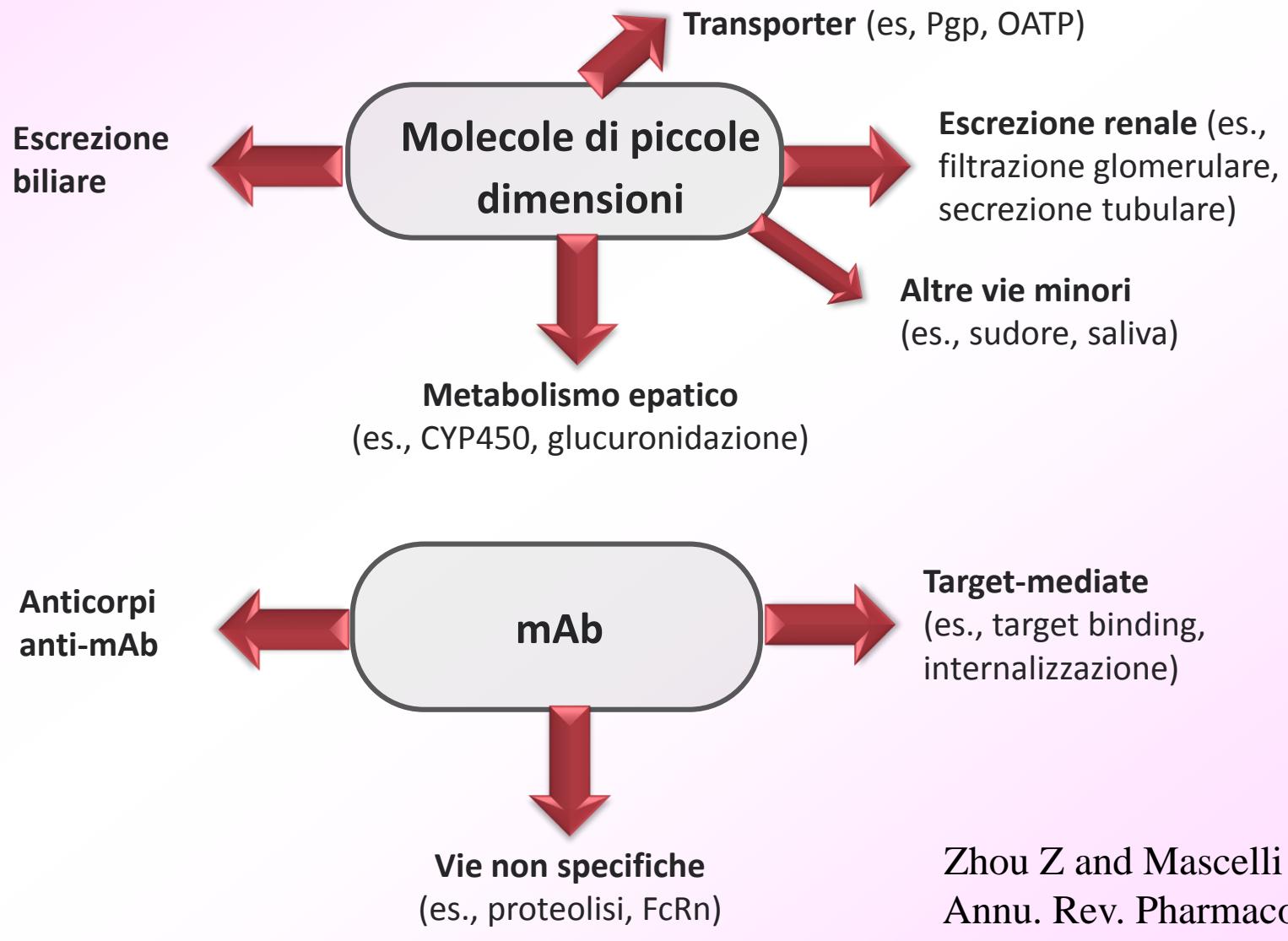


Figure 3. Geometric mean percentage ($\pm 95\%$ confidence intervals) changes from baseline in (A) proprotein convertase subtilisin kexin type 9 (PCSK9) and (B) ultracentrifugation (UC) low-density lipoprotein cholesterol (LDL-C) by degree of hepatic impairment.

ELIMINAZIONE DEGLI ANTICORPI MONOCLONALI

- Non vengono metabolizzati attraverso la catalisi indotta dai citocromi
 - Non vanno incontro a processi di coniugazione
 - Non sono riconosciuti dai trasportatori
-  Fortemente ridotto il rischio di interazione con altri farmaci

VIE DI ELIMINAZIONE DEGLI ANTICORPI MONOCLONALI



4.5 Interazioni con altri medicinali ed altre forme di interazione

Effetti di alirocumab su altri medicinali

Dato che alirocumab è un farmaco biologico, non si prevedono effetti farmacocinetici di alirocumab su altri medicinali e nessun effetto sugli enzimi del citocromo P450.

Effetti di altri medicinali su alirocumab

È noto che le statine e altre terapie che modificano il profilo lipidico aumentano la produzione di PCSK9, la proteina su cui agisce alirocumab. Ciò provoca un aumento della clearance target-mediata e una ridotta esposizione sistemica ad alirocumab. Rispetto ad alirocumab in monoterapia, l'esposizione ad alirocumab è inferiore di circa il 40%, il 15% e il 35% se il farmaco viene usato in concomitanza rispettivamente con statine, ezetimibe e fenofibrato. Tuttavia, la riduzione del C-LDL viene mantenuta durante l'intervallo tra le dosi quando alirocumab viene somministrato ogni due settimane.

Alirocumab RCP



Review

Pharmacokinetics interactions of monoclonal antibodies



Nicola Ferri^{a,*}, Stefano Bellosta^b, Ludovico Baldessin^d, Donatella Boccia^d, Giorgi Racagni^c, Alberto Corsini^c

Examples of mAb-small molecule drug interactions.

| mAbs | Small molecule drug | Effect observed |
|-------------|---------------------------------|---|
| Adalimumab | Methotrexate | Reduced clearance of Adalimumab after single and multiple dosing by 29% and 44%, respectively |
| Alirocumab | Statins, Ezetimibe, Fenofibrate | Exposure of Alirocumab reduced by about 40%, 15%, and 35% when administered concomitantly with Statins, Ezetimibe, and Fenofibrate, respectively No dose adjustment needed |
| Cetuximab | Irinotecan | Reduced SN-38 glucuronide plasma concentration by 31% |
| Canakinumab | Drugs metabolized by CYP3A4 | Increased clearance of drugs metabolized by CYP3A4 |
| Daclizumab | Mycophenolate mofetil | Reduced plasma concentration, Cmax, and AUC ₀₋₈ of Mycophenolic acid glucuronide at weeks 4 and 8 |
| Evolocumab | Statins | Increased clearance of Evolocumab by 20%. No dose adjustment needed |



Imaging of Coronary Plaques in Subjects Treated With Evolocumab

Fourier Open-label Extension Study in Subjects With Clinically Evident Cardiovascular Disease in Selected European Countries

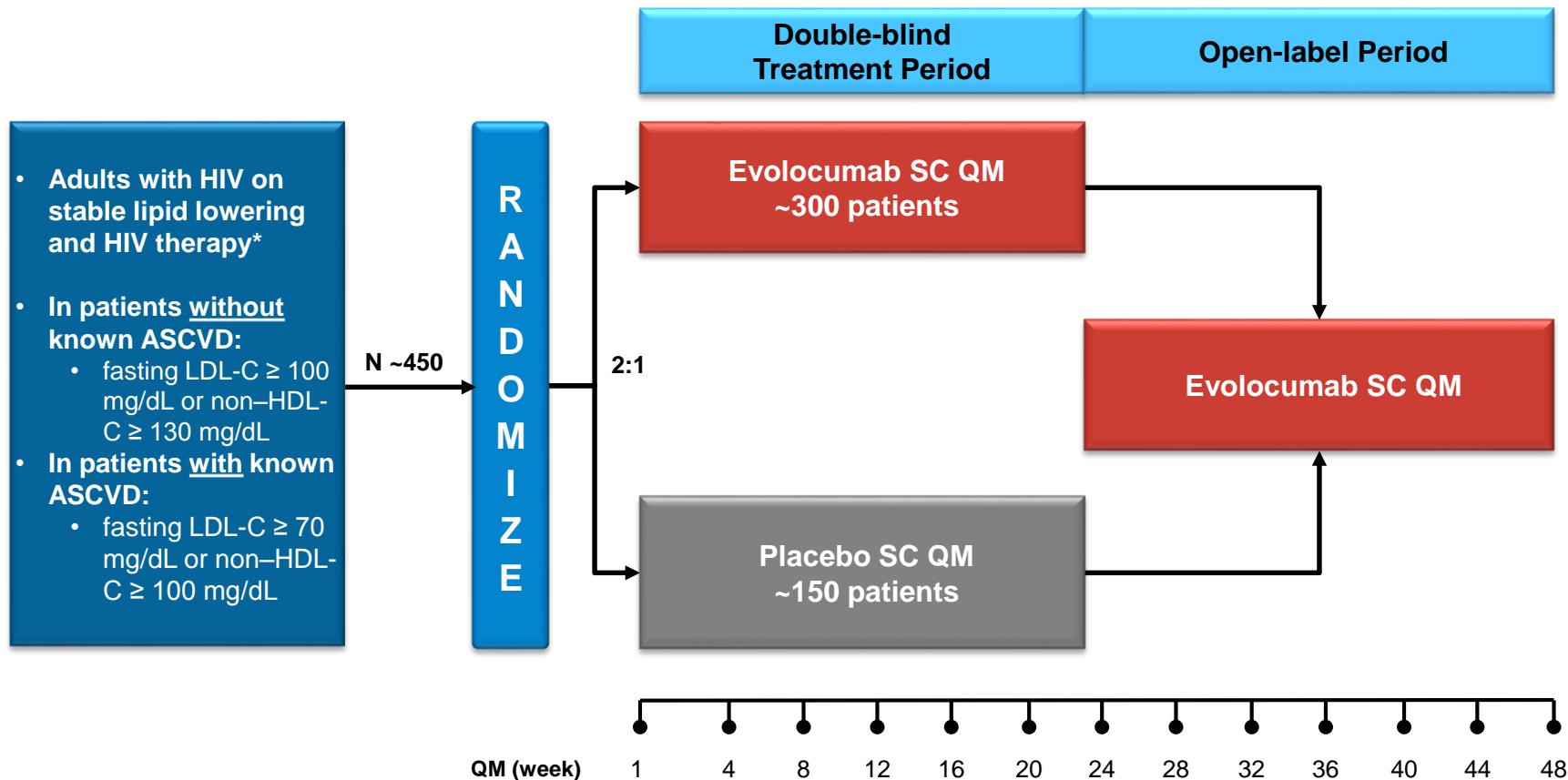
Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk Open-label Extension

Safety, Tolerability & Efficacy on LDL-C of Evolocumab in Subjects With HIV & Hyperlipidemia/Mixed Dyslipidemia

Open Label Study to Evaluate Safety, Tolerability and Efficacy of Evolocumab (AMG 145) in Pediatric Subjects (10 to 17 Years of Age) With Heterozygous Familial Hypercholesterolemia (HeFH) or Homozygous Familial Hypercholesterolemia (HoFH). (HAUSER-OLE)

BEIJERINCK in HIV patients

Study Design and Treatment Schema



*Stable lipid-lowering therapy is defined as no change for \geq 4 weeks prior to randomization and not expected to change during the study. Stable HIV therapy is defined as no change for \geq 6 months prior to randomization.

ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol; QM = once monthly; SC = subcutaneous.

ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT02833844?term=NCT02833844&rank=1>. Accessed May 4, 2017.

Inibitori PCSK9

- Razionale
- Farmacologia
- **Efficacia**
- Sicurezza
- Dati del mondo reale

ALIROCUMAB lowers LDL-C by 50-60% in several conditions:

1

Monotherapy

2

Add-on to statin therapy

3

Add-on to non statin therapy
Statin intolerance

4

FH patients

5

CHD patients

6

High risk patients (e.g. Diabetes)

Table 3. Effect of evolocumab compared with placebo on lipid parameters in the Phase III trials.

| Background | Without statin | | | | With statin ± ezetimibe | | Risk-based therapy | HoFH with statin ± ezetimibe |
|---|----------------|-----------|------------|-----------|-------------------------|-----------|----------------------|------------------------------|
| Study | MENDEL-2 | | LAPLACE-2 | | RUTHERFORD-2 | | DESCARTES | TESLA Part B |
| Treatment | 140 mg Q2W | 420 mg QM | 140 mg Q2W | 420 mg QM | 140 mg Q2W | 420 mg QM | 420 mg QM | 420 mg QM |
| <i>Least square mean percent change from baseline versus placebo at week 12</i> | | | | | | | | |
| LDL-C calc | -59% | -57% | -73% | -64% | -61% | -60% | -58/59% [†] | -32% |
| <i>Least square mean percent change from baseline versus placebo at mean of weeks 10 and 12</i> | | | | | | | | |
| LDL-C calc | -57% | -60% | -72% | -69% | -61% | -66% | NA | -31% [‡] |
| TC | -35% | -37% | -41% | -40% | -42% | -44% | -33% | |
| Non-HDL-C | -49% | -53% | -60% | -60% | -56% | -60% | -50% | |
| ApoB | -47% | -51% | -56% | -56% | -49% | -55% | -44% | -23% [‡] |
| Lp(a) | -25% | -26% | -30% | -27% | -31% | -31% | -22% | -11% [‡] |
| TG | 0% | -22% | -17% | -23% | -22% | -17% | -12% | -3.3% [‡] |
| VLDL-C | 0% | -22% | -18% | -22% | -23% | -16% | 29% | |
| HDL-C | 6% | 9% | 6% | 8% | 8% | 9% | 5% | 1.3% [‡] |
| ApoA1 | 3% | 5% | 3% | 5% | 7% | 5% | 3% | |

[†]LDL-C percent change from baseline to week 12/52 relative to placebo; week 12 value is based on preparative ultracentrifugation.

[‡]LDL-C percent change from baseline to mean of weeks 6 and 12; week 10 values not available.

References [36,38–41].

PCSK9 loss-of-function variants and Lp(a) phenotypes among black US adults

Table 2. Differences in median lipoprotein(a) protein concentration comparing participants with versus without PCSK9 loss-of-function variants.

| | | PCSK9 loss-of-function variants | | |
|---------------|--|---------------------------------|--------------------|---------|
| | | No | Yes | p-value |
| Lp(a), nmol/L | Median (25 th , 75 th percentile) | 80.4 (39.7, 138.4) | 63.2 (30.4, 119.6) | 0.016 |

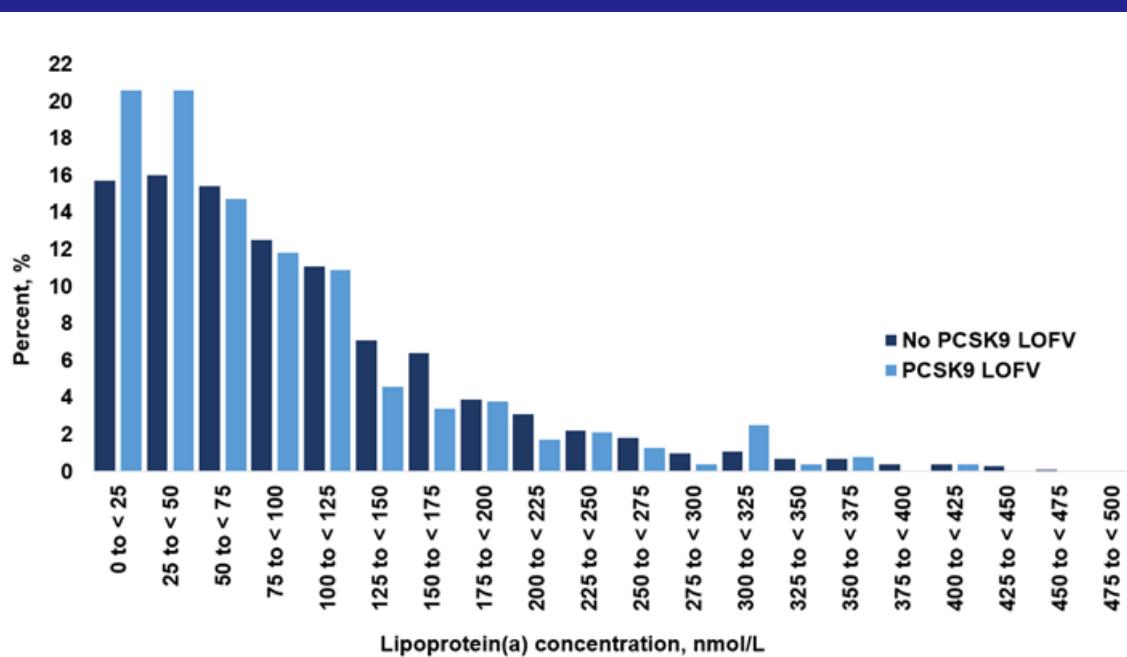
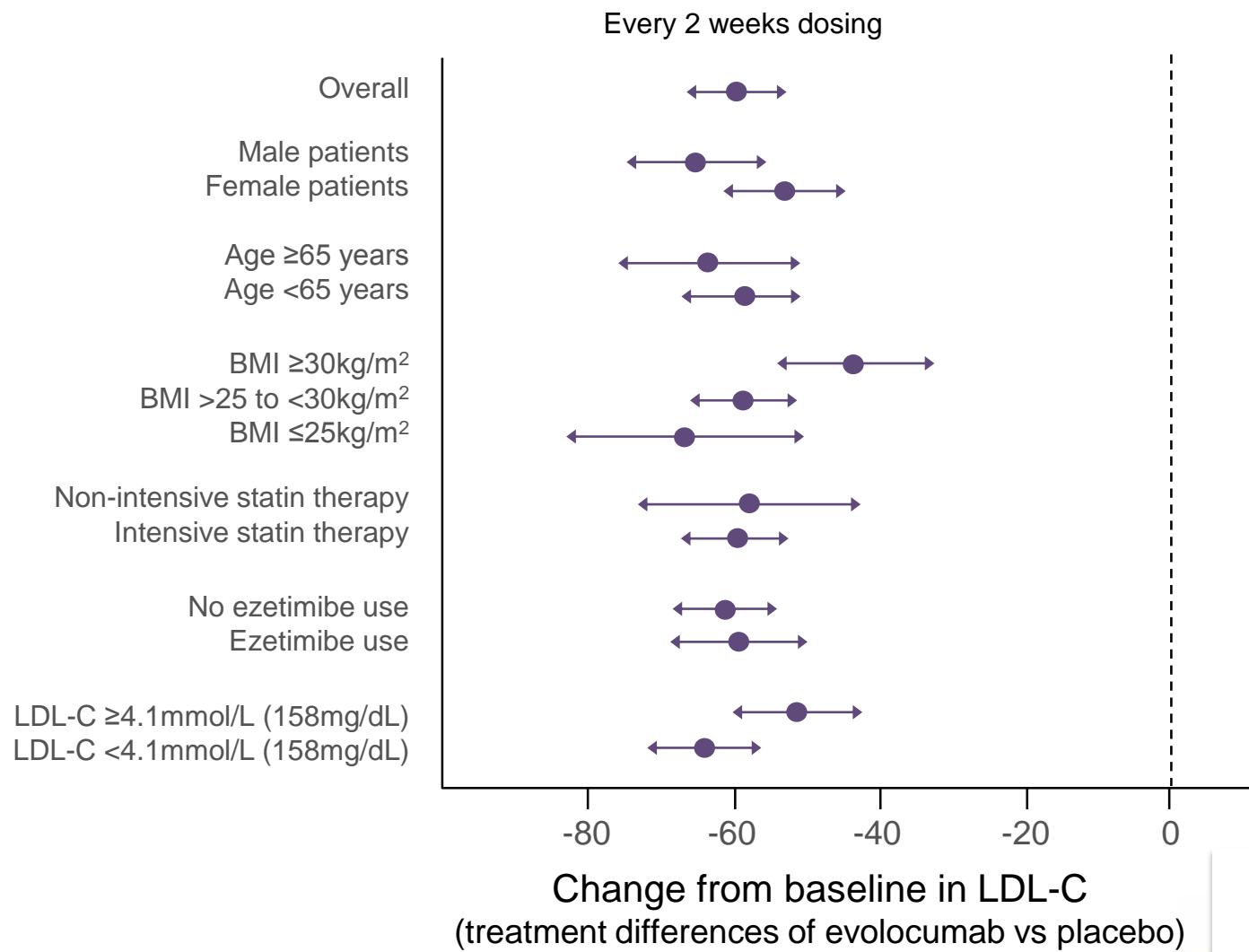


Figure 1. Distribution of lipoprotein(a) protein concentration among participants with and without PCSK9

Evolocumab significantly reduces LDL-C irrespective of baseline characteristics

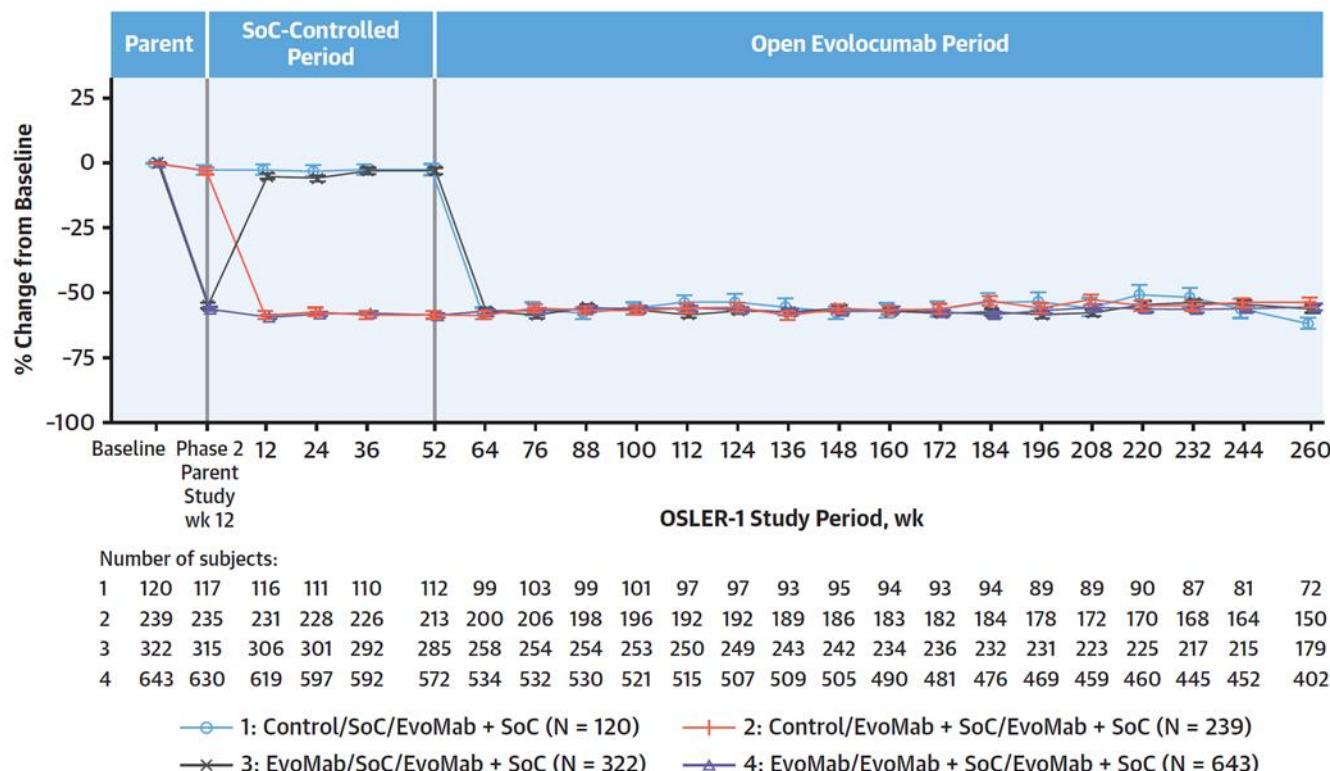




Long-Term Efficacy and Safety of Evolocumab in Patients With Hypercholesterolemia

Michael J. Koren, MD,^a Marc S. Sabatine, MD, MPH,^b Robert P. Giugliano, MD, SM,^b Gisle Langslet, MD, PhD,^c Stephen D. Wiviott, MD,^b Andrea Ruzza, MD, PhD,^d Yuhui Ma, PhD,^d Andrew W. Hamer, MD,^d Scott M. Wasserman, MD,^d Frederick J. Raal, MBBS, MMED, PhD^e

FIGURE 2 Effects of Evolocumab on LDL-C Levels Over 5 Years



Calculated LDL-C percentage change (mean \pm SE) from the phase 2, parent-study baseline to week 260 of OSLER-1 study. The error bars represent SEs. Plot is based on observed data with no imputation for missing values. The mean baseline LDL-C level was 140 mg/dl (3.62 mmol/l). The mean week 260 on-treatment LDL-C level was 61 mg/dl (1.47 mmol/l). The key shows parent study assignment/year 1 assignment/long-term open-label assignment. To convert LDL-C to millimoles per liter, multiply by 0.0259. LDL-C = low-density lipoprotein cholesterol; other abbreviations as in Figure 1.

REVIEW ARTICLE



Lipid lowering drugs and inflammatory changes: an impact on cardiovascular outcomes?

M. Ruscica^{a*} , N. Ferri^{b*} , C. Macchi^a , A. Corsini^a and C. R. Sirtori^c

^aDipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano, Milan, Italy; ^bDipartimento di Scienze del Farmaco, Università degli Studi di Padova, Padova, Italy; ^cCentro Dislipidemie, A.S.T. Grande Ospedale Metropolitano Niguarda, Milan, Italy

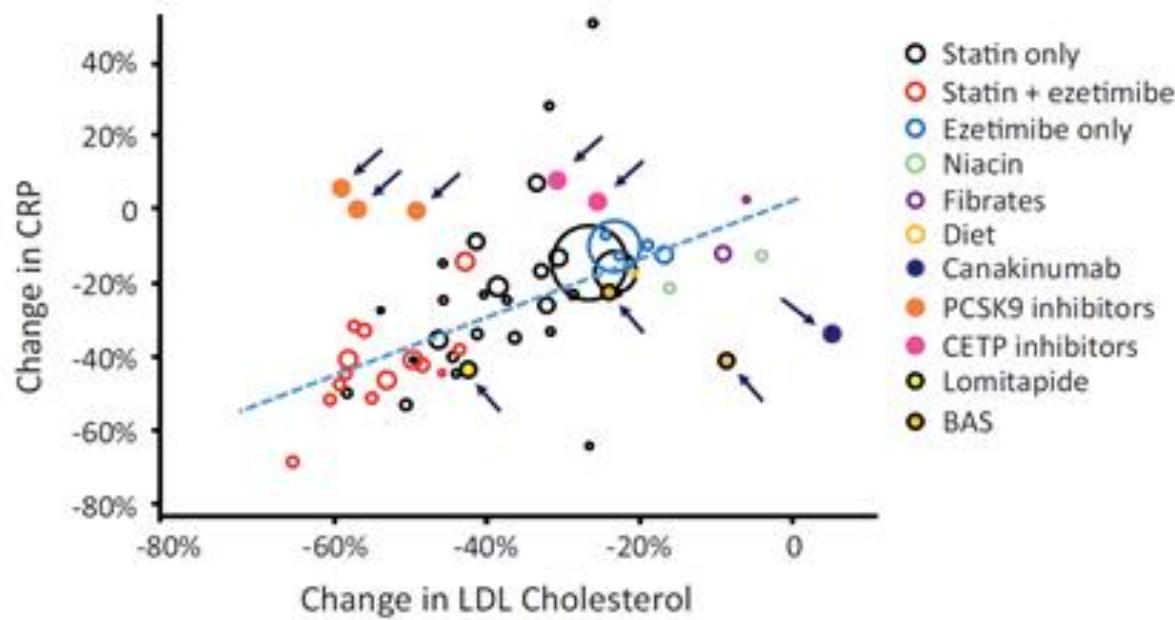


Figure 1. Pharmacological changes of LDL-C and CRP. Modified from Kinlay S et al. [6]. CETP: Cholesterol ester transfer protein; PCSK9: Proprotein convertase subtilisin/kexin 9.



Imaging of Coronary Plaques in Subjects Treated With Evolocumab

Fourier Open-label Extension Study in Subjects With Clinically Evident Cardiovascular Disease in Selected European Countries

Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk Open-label Extension

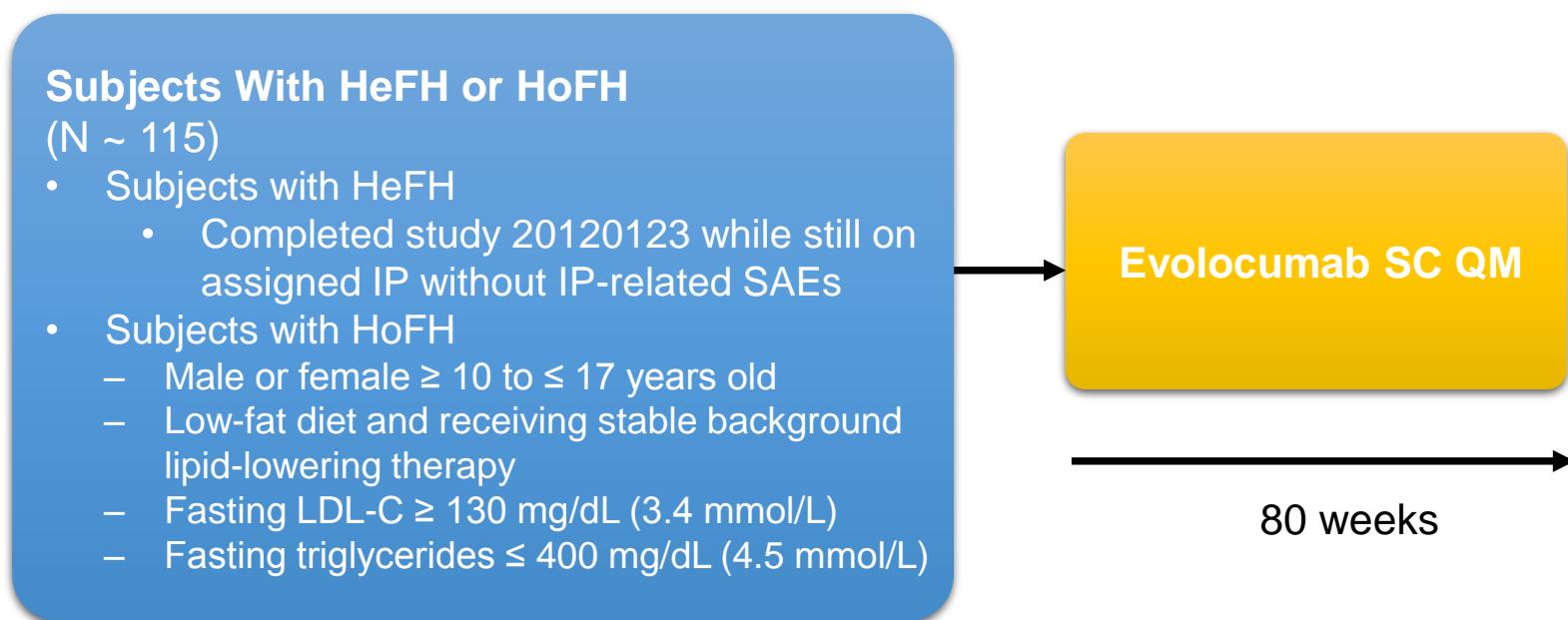
Safety, Tolerability & Efficacy on LDL-C of Evolocumab in Subjects With HIV & Hyperlipidemia/Mixed Dyslipidemia

Open Label Study to Evaluate Safety, Tolerability and Efficacy of Evolocumab (AMG 145) in Pediatric Subjects (10 to 17 Years of Age) With Heterozygous Familial Hypercholesterolemia (HeFH) or Homozygous Familial Hypercholesterolemia (HoFH). (HAUSER-OLE)

HAUSER OLE in paediatric patients

Study Design and Treatment Schema

PHASE 3 STUDY DESIGN:

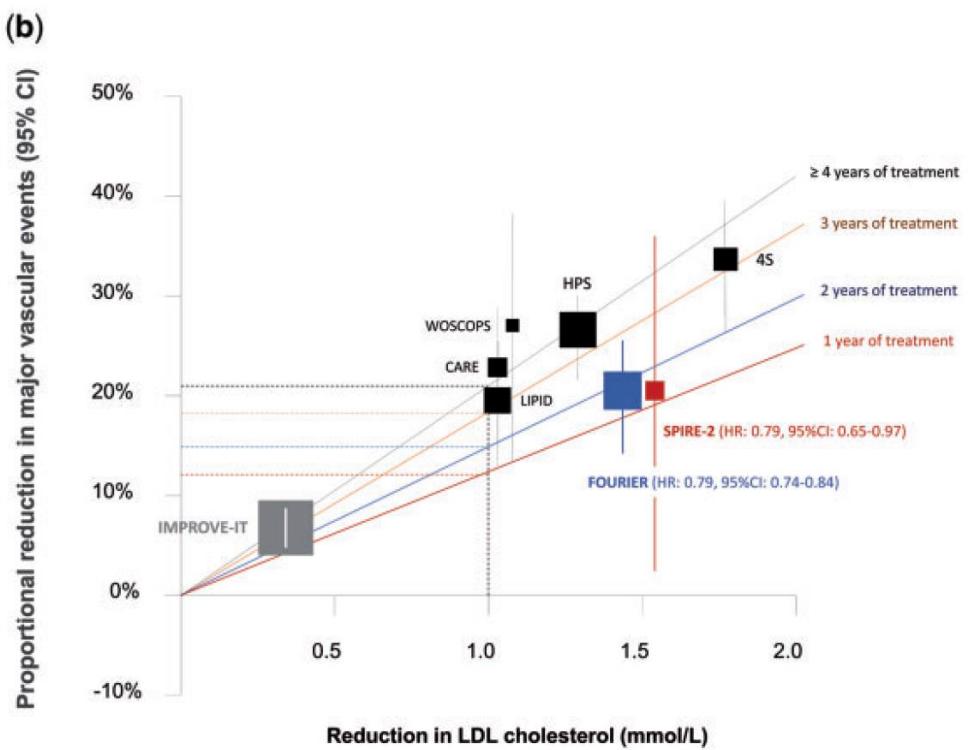
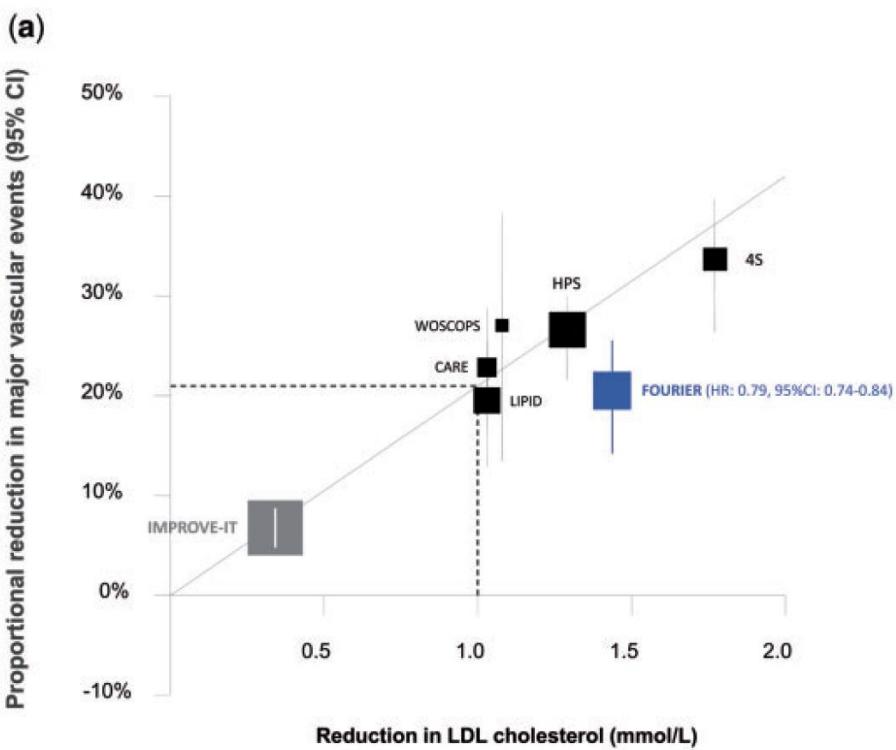


HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; IP = investigational product; LDL-C = low-density lipoprotein cholesterol; QM = once monthly; SC = subcutaneous; SAE = serious adverse event

ClinicalTrials.gov. clinicaltrials.gov/ct2/show/NCT02624869?term=NCT02624869&rank=1. Accessed December 14, 2017.

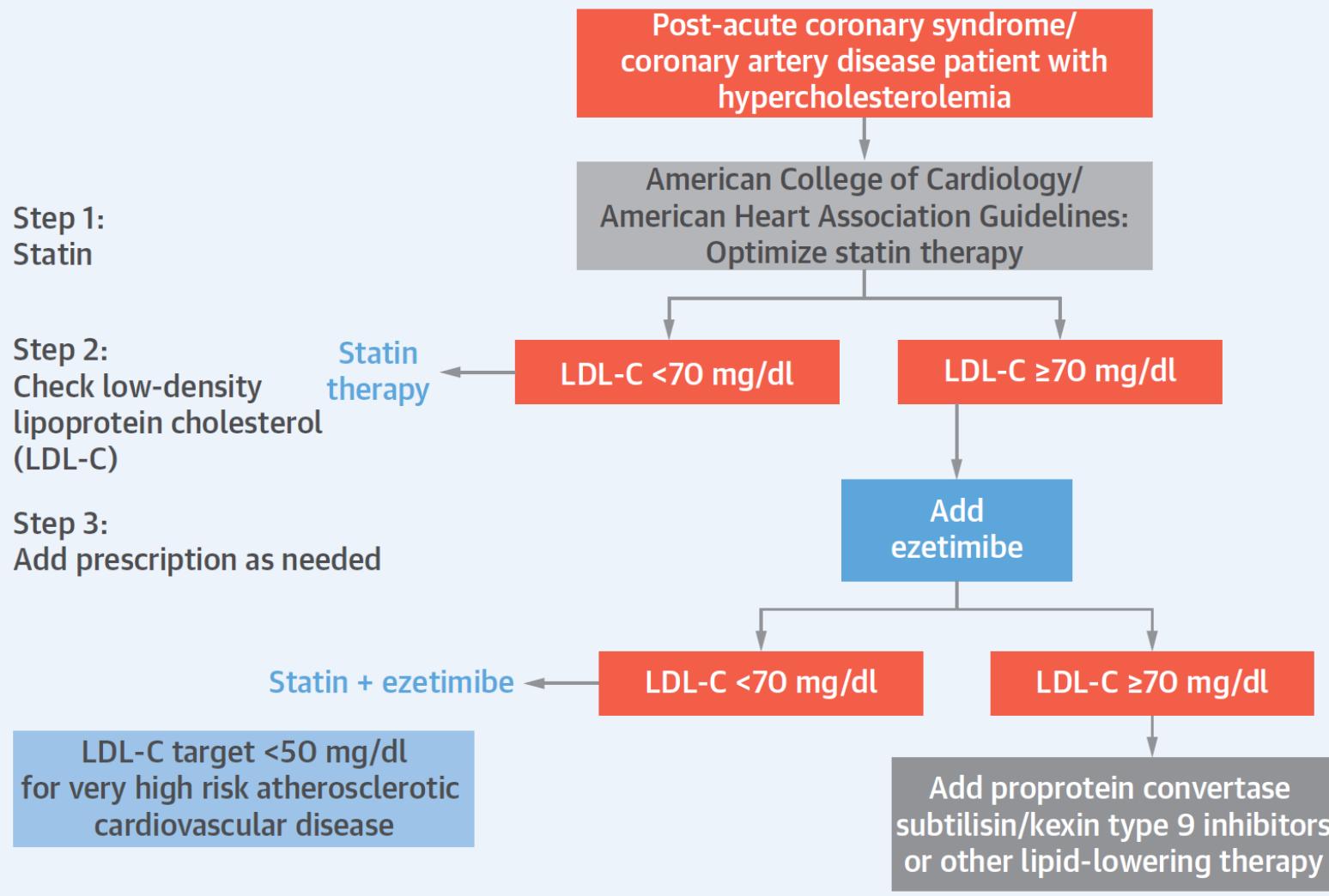
| | FOURIER | ODYSSEY OUTCOMES |
|-------------------------|--|--|
| Population | Stable ASCVD | Recent ACS |
| Qualifying LDL-C, mg/dL | ≥70 | ≥70 |
| Primary endpoint | <u>5-point MACE:</u> CV death, MI, CVA, UA, coronary revasc. | <u>4-point MACE:</u> CHD death, MI, CVA, UA |
| Follow up | 26 months | 34 months |
| Age (median, years) | 63 | 58 |
| ACS <1 year | 20% | 100% |
| High-intensity statin | 69% | 89% |
| No statin | 0.2% | 2.5% |

Effect of statins and PCSK9 inhibitors on the risk of CVD for various durations of total treatment



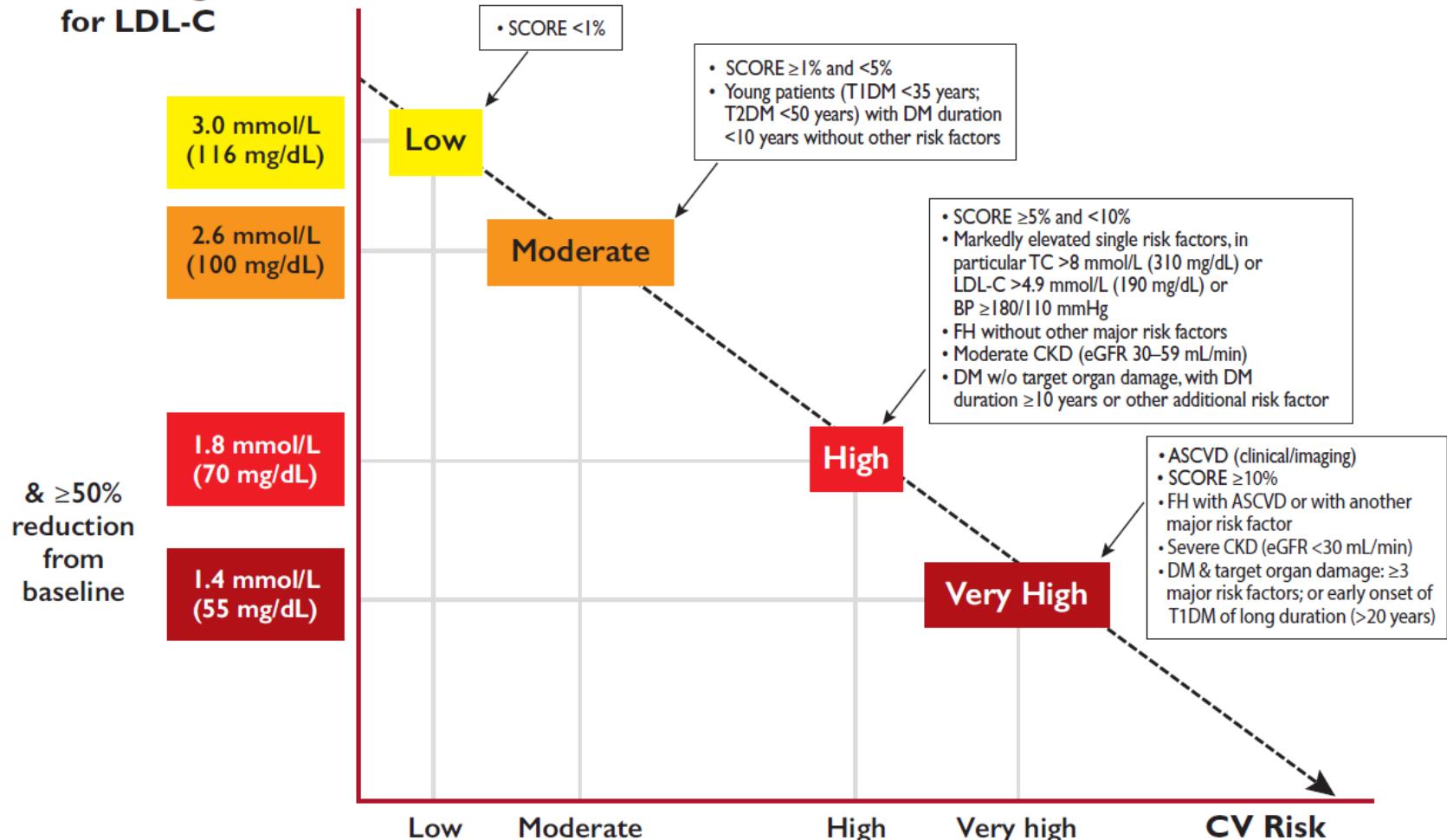
CENTRAL ILLUSTRATION Clinical Algorithm for Managing Low-Density Lipoprotein Cholesterol

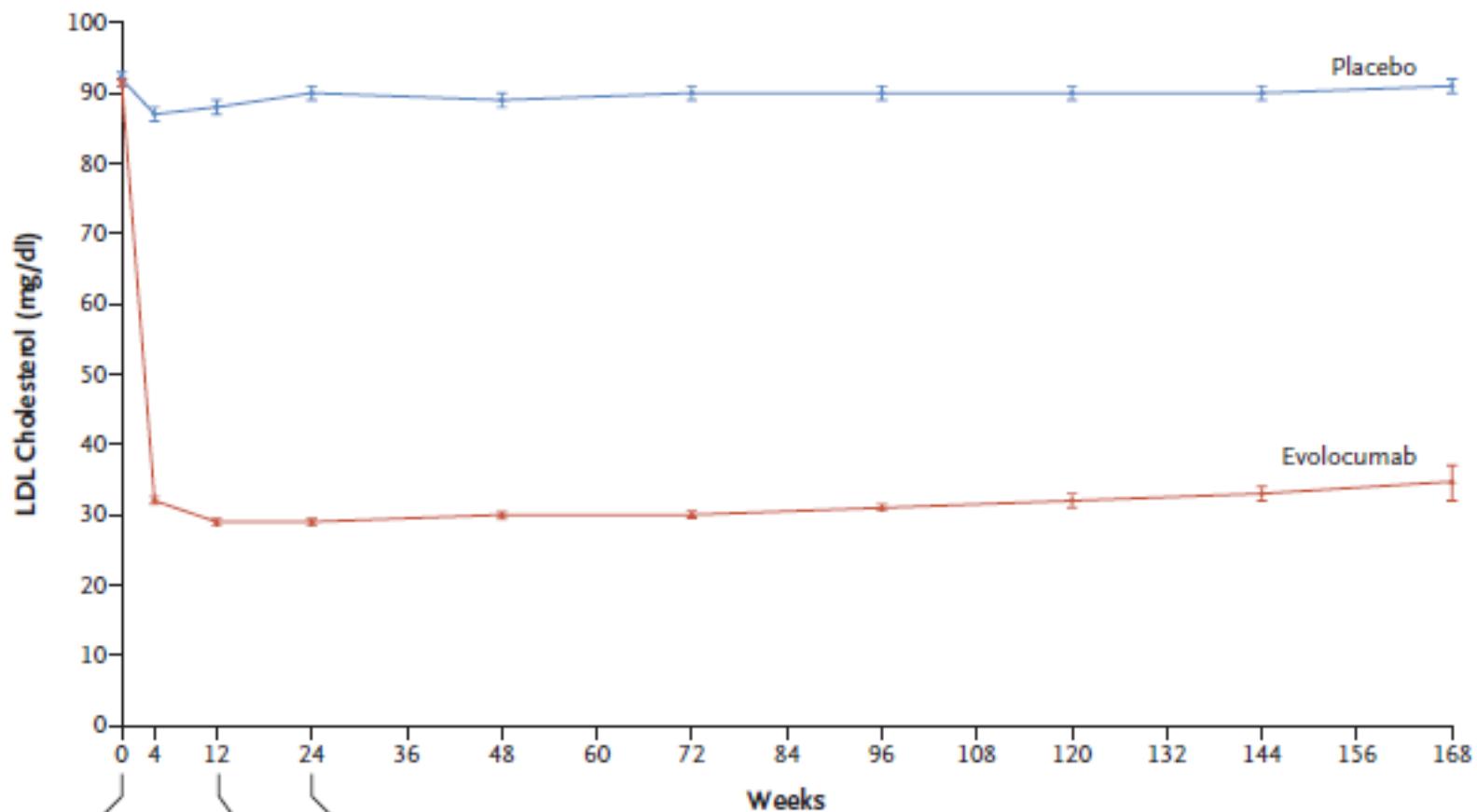
Treatment algorithm for hypercholesterolemia



Treatment goals for LDL-C across categories of total CVD risk

B Treatment goal for LDL-C





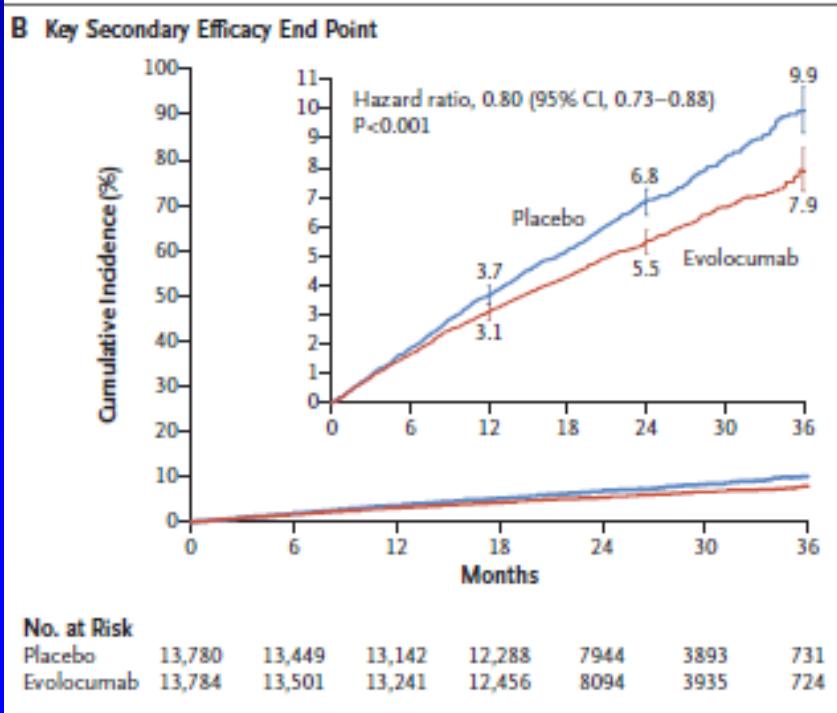
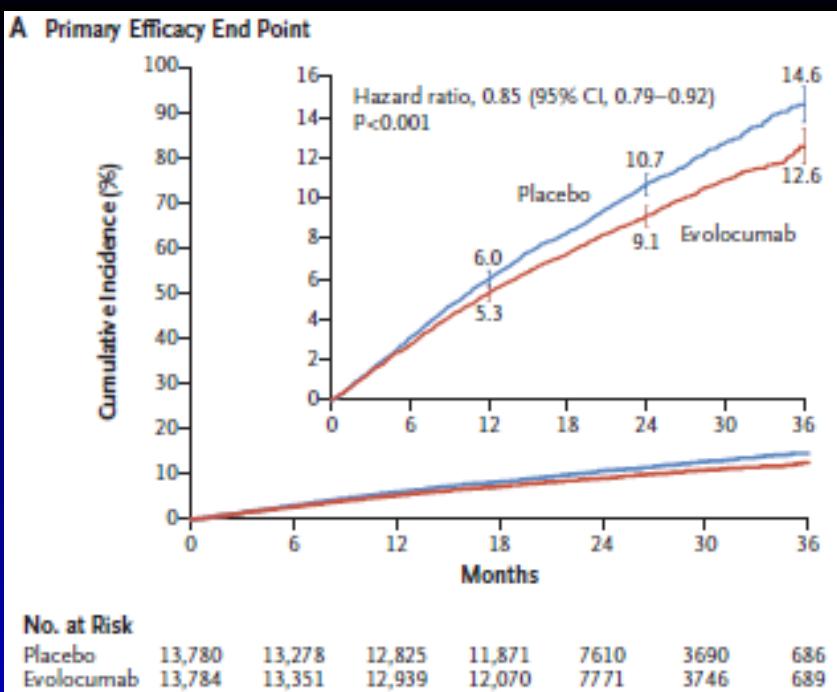
No. at Risk

| | | | | | | | | | | |
|-----------------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Placebo | 13,779 | 13,251 | 13,151 | 12,954 | 12,596 | 12,311 | 10,812 | 6926 | 3352 | 790 |
| Evolocumab | 13,784 | 13,288 | 13,144 | 12,964 | 12,645 | 12,359 | 10,902 | 6958 | 3323 | 768 |
| Absolute difference (mg/dl) | | 54 | 58 | 57 | 56 | 55 | 54 | 52 | 53 | 50 |
| Percentage difference | | 57 | 61 | 61 | 59 | 58 | 57 | 55 | 56 | 54 |
| P value | | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

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

March 17, 2017, at NEJM.org.

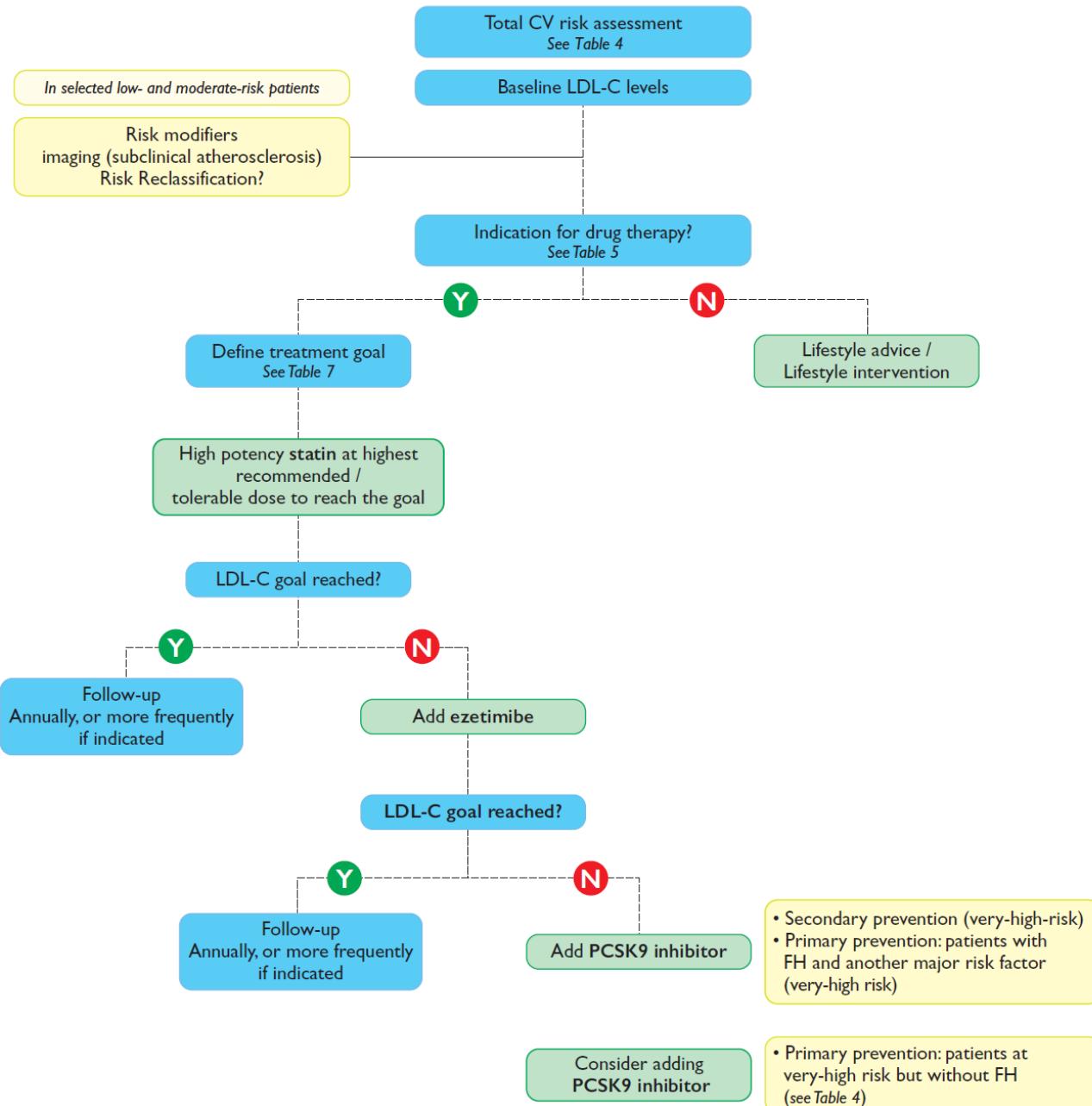
Cumulative Incidence of Cardiovascular Events



Sabatine MS et al N
Engl J Med. 2017
376(18):1713-1722

Treatment algorithm for pharmacological LDL-C lowering

A



Recommendations for pharmacological low-density lipoprotein cholesterol lowering

| Recommendations | Class ^a | Level ^b |
|---|--------------------|--------------------|
| It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk. ^{32,34,38} | I | A |
| If the goals ^c are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended. ³³ | I | B |
| For primary prevention patients at very-high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered. | IIb | C |
| For secondary prevention, patients at very-high risk not achieving their goal ^c on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended. ^{119,120} | I | A |
| For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal ^c on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended. | I | C |
| If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered. ^{197,265,353} | IIa | C |
| If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may also be considered. ^{197,265,353} | IIb | C |
| If the goal ^c is not achieved, statin combination with a bile acid sequestrant may be considered. | IIb | C |

ASCVD = atherosclerotic cardiovascular disease; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.

^aClass of recommendation.

^bLevel of evidence.

^cFor definitions see Table 7.



Atherosclerosis

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

Review article

PCSK9 inhibition and inflammation: A narrative review

Massimiliano Ruscica^{a,*}, Lale Tokgözoglu^b, Alberto Corsini^{a,c}, Cesare R. Sirtori^d

M. Ruscica, et al.

Atherosclerosis 288 (2019) 146–155

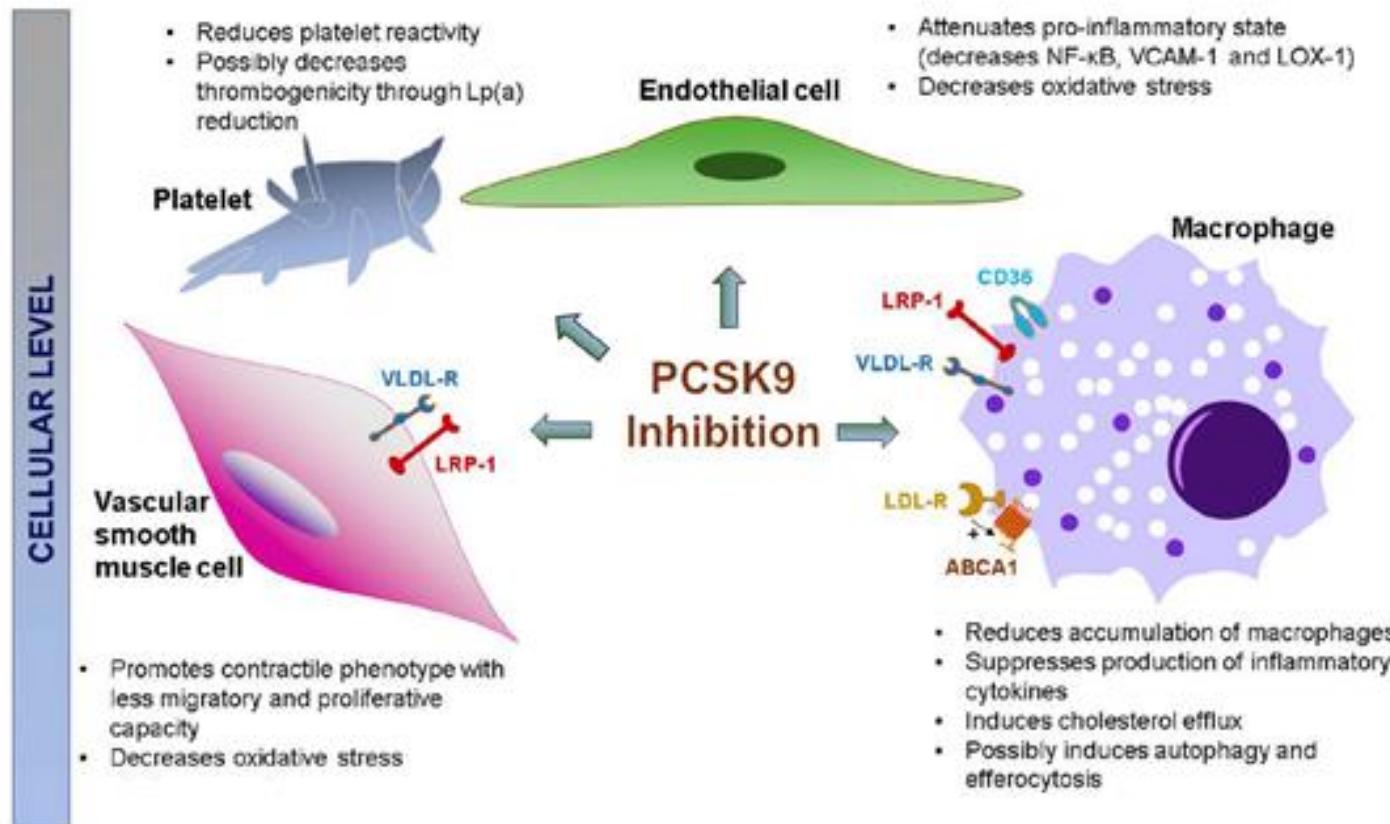
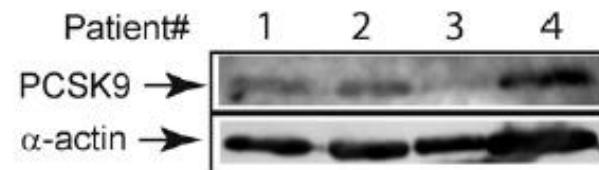


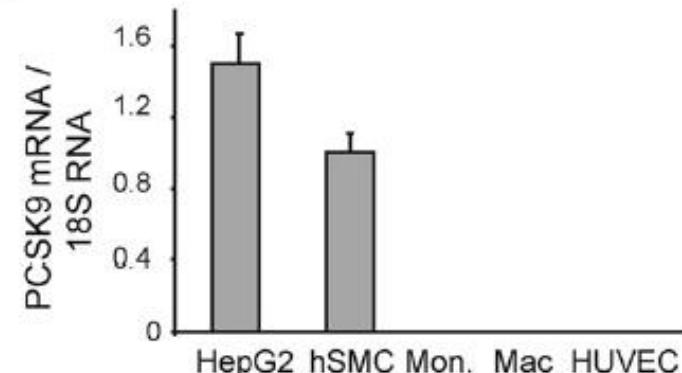
Fig. 1. Possible pleiotropic effects of PCSK9 inhibition in atherosclerosis.
Reproduced with permission from Nature Springer [148].

PCSK9 is expressed in human SMCs and in atherosclerotic plaques

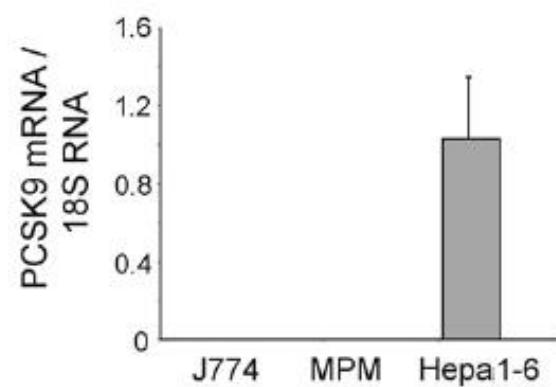
A



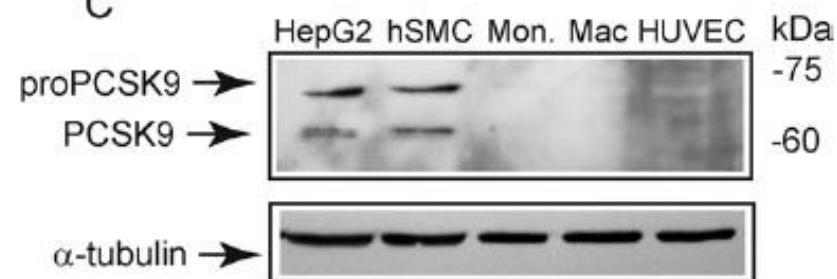
B



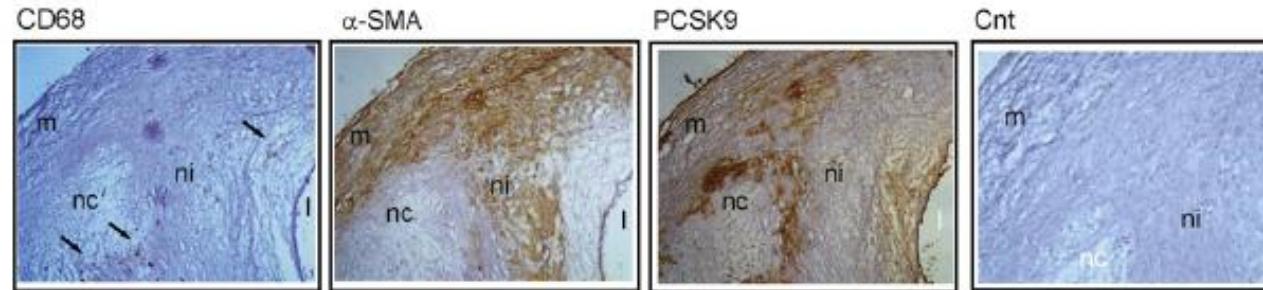
D



C



E



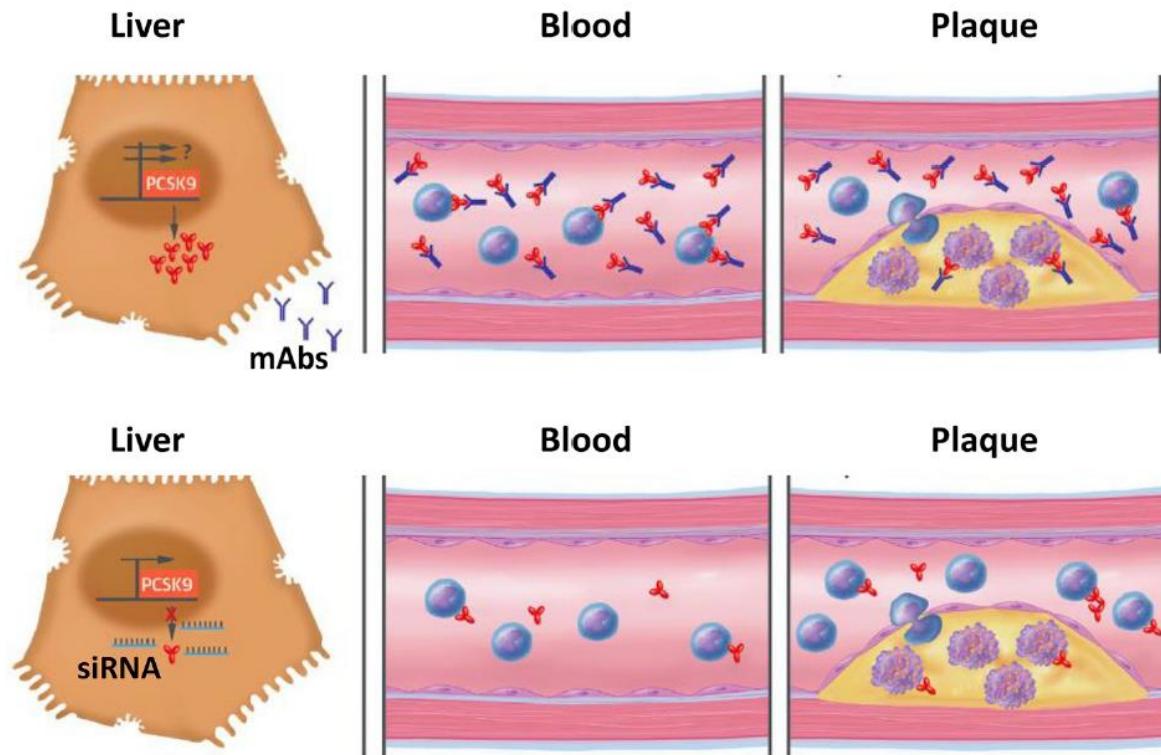
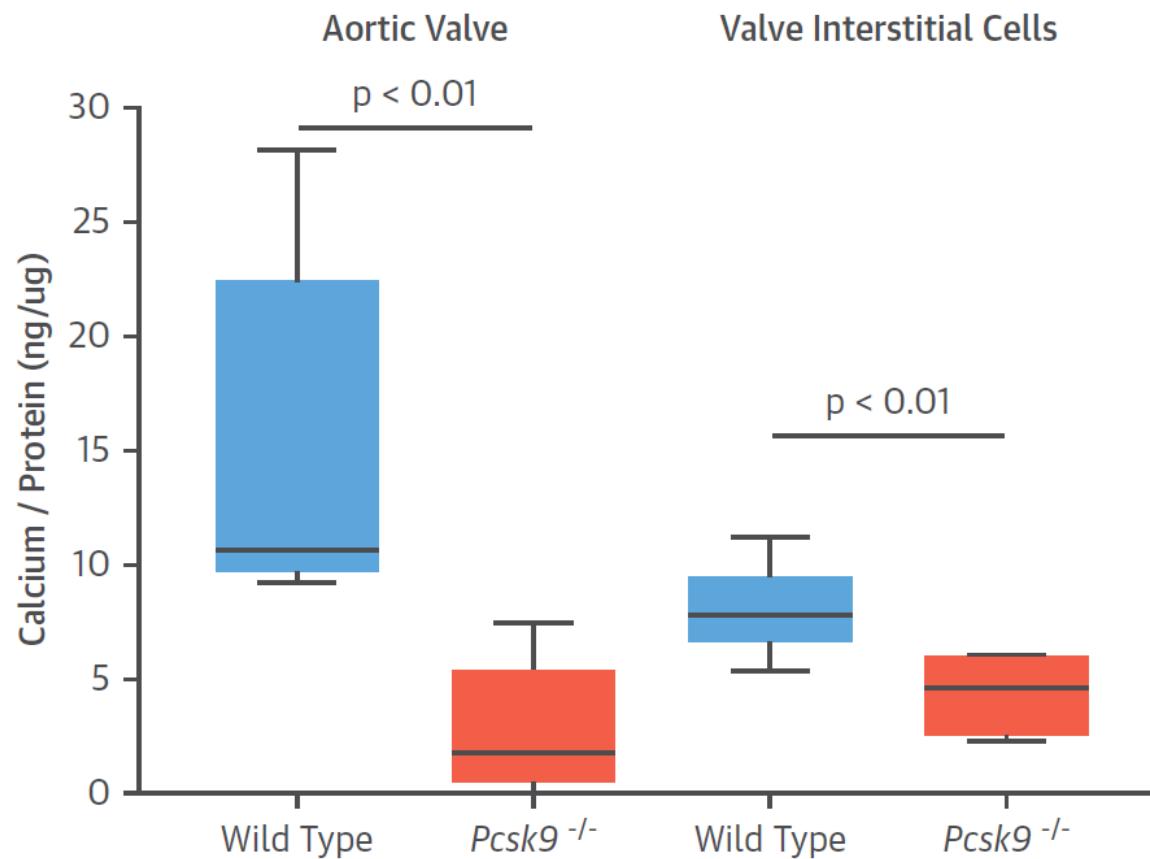


Fig. 2. Presence of PCSK9 in the atheroma upon inhibition by monoclonal antibodies or siRNA (inclisiran).

(Upper panel) Monoclonal antibodies bind PCSK9 leading to its circulation in immune complexes either free or bound to LDL. These complexes may enter atheromas. (Lower panel) siRNA does not affect the local production of PCSK9 by macrophages and smooth muscle cells in the atheroma, but it reduces the amount of circulating PCSK9 penetrating plaques. mAbs, monoclonal antibodies; siRNA, silencing RNA. Modified with permission from Elsevier [111].

FIGURE 1 PCSK9 and Calcification



Total calcium content in aortic valve leaflets and in valve interstitial cells from *Pcsk9*^{-/-} and wild-type mice. The **central line** illustrates the median, and **box limits** indicate the 25th and 75th percentiles.



Evaluation of plasma PCSK9 concentrations, transcript of LDL receptor, as well as the total number of monocyte LDL receptors in acute coronary syndrome patients

Paweł Burchardt^{1, 2}, Janusz Rzeźniczak², Joanna Dudziak², Anna Dżumak³, Tomasz Marchlewski², Teresa Ganowicz-Kaatz², Monika Popiak², Marek Słomczyński², Marcin Jezierski², Witold Laskowski², Tomasz Luczak², Robert Plewa^{3, 4}

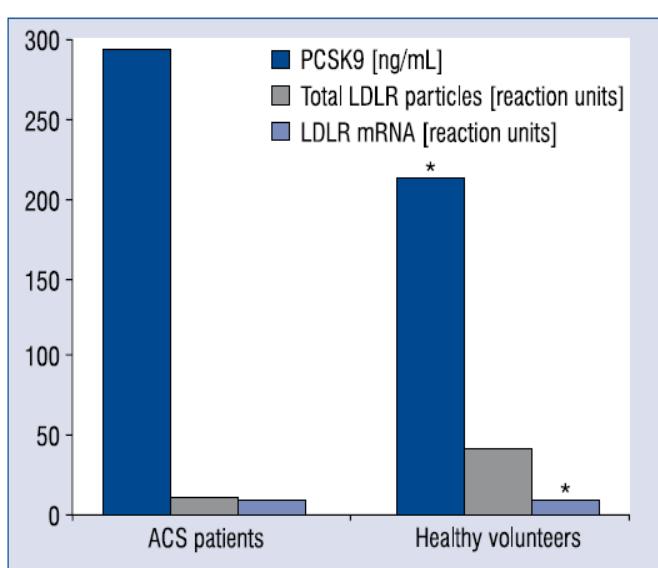


Figure 1. Comparison of acute coronary syndrome (ACS) vs. healthy volunteers according to value of PCSK9, LDLRs mRNA, and total monocytes LDLR amount (measured as an average fluorescence of anti-LDLR antibodies (see text); *p < 0.05.

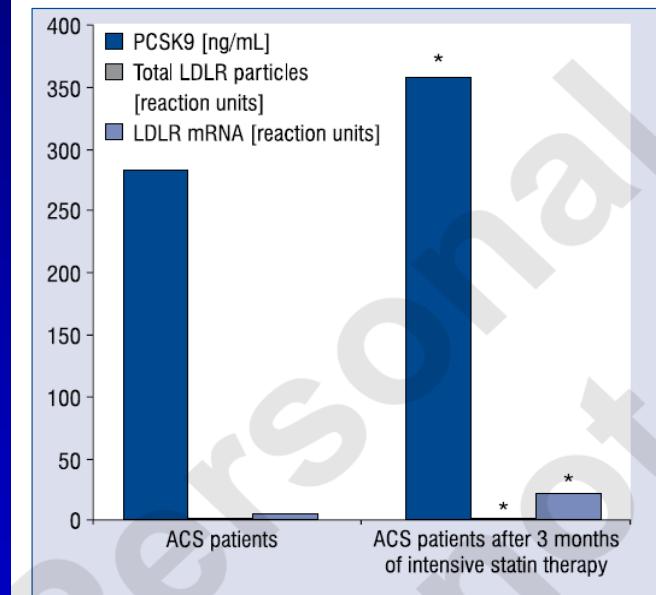


Figure 2. Comparison of the same patients during acute coronary syndrome (ACS) vs. 3-month period of intensive statin therapy (initiated during ACS) according to value of PCSK9, LDLRs mRNA, and total monocytes LDLR amount (measured as an average fluorescence of anti-LDLR antibodies (see text); *p < 0.05.

Original article

Circulating PCSK9 levels in acute coronary syndrome:
Results from the PC-SCA-9 prospective study

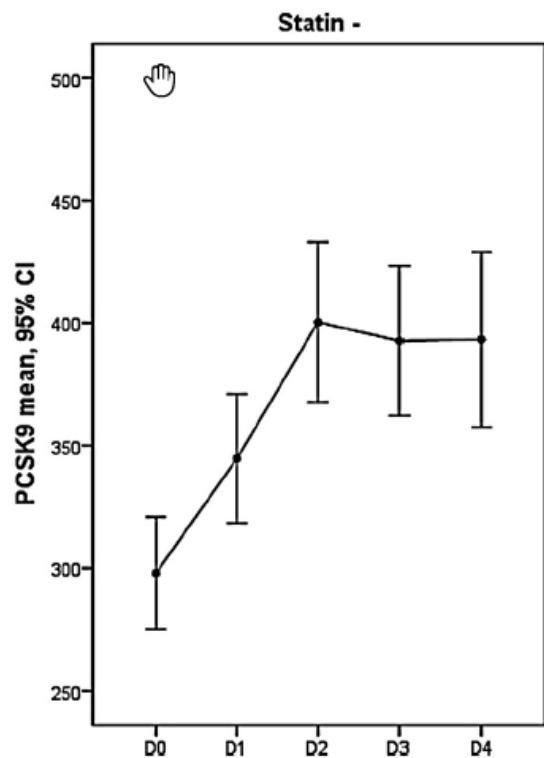
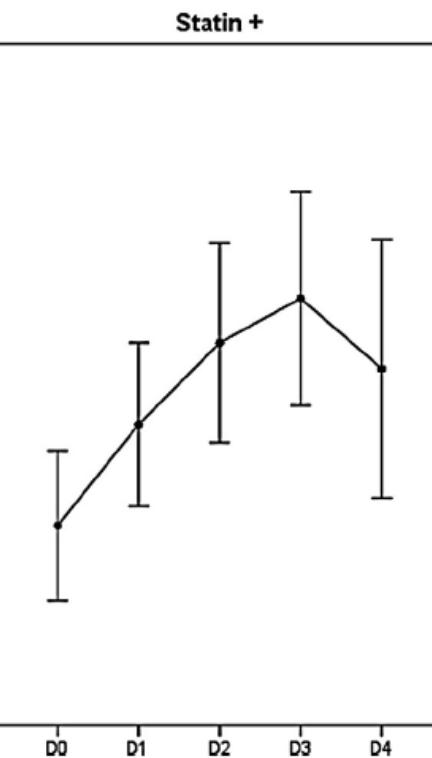
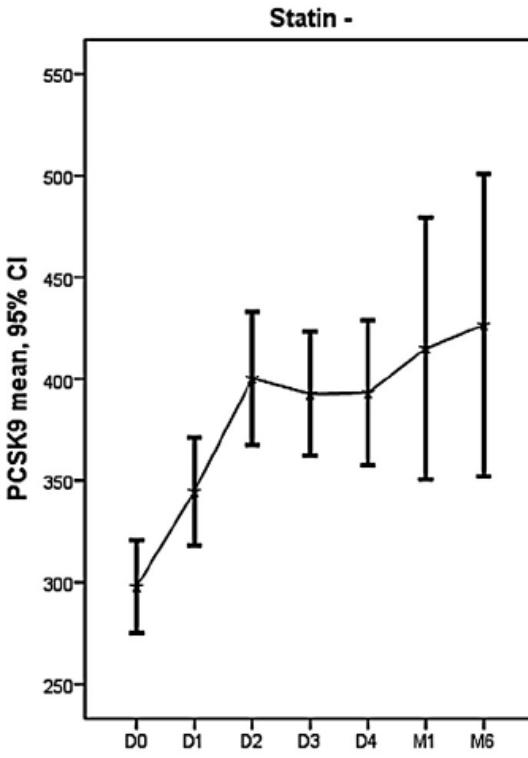
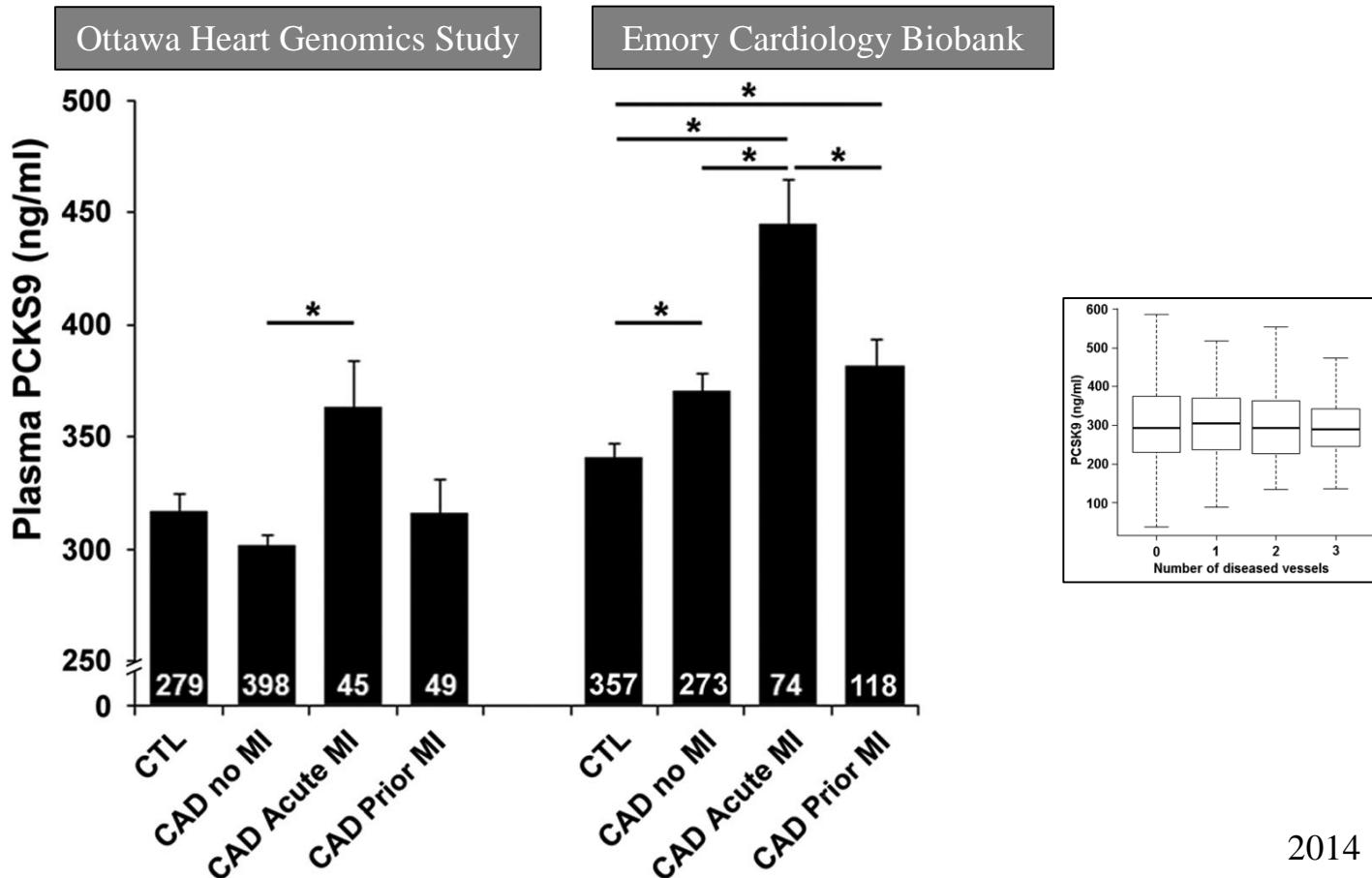
B. Cariou ^{a,b,c,*}, P. Guérin ^d, C. Le May ^c, V. Letocart ^d, L. Arnaud ^c, B. Guyomarch ^{b,c},
M. Pichelin ^{a,b,c}, V. Probst ^{b,d}
A

B

C


Fig. 2. Kinetics of plasma proprotein convertase subtilisin/kexin type 9 (PCSK9) concentrations in acute coronary syndrome (ACS) patients during hospitalization at our cardiology intensive care unit (ICU) who were (A) statin-naïve (statin-) and (B) taking statins (statin+) on admission [Day 0 (D0)], and (C) a subgroup ($n = 27$) followed for 6 months.

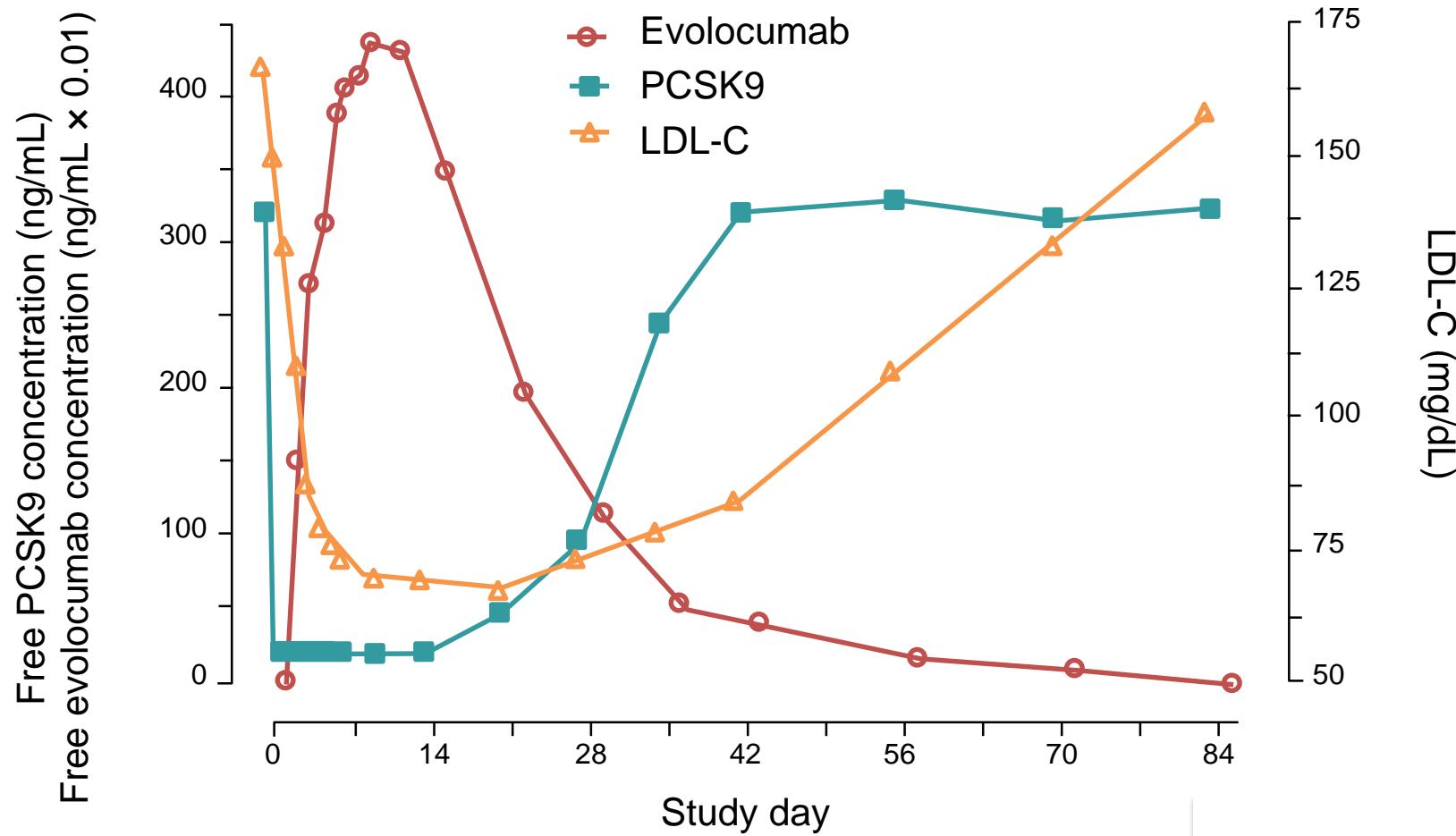
Plasma PCSK9 Levels Are Elevated with Acute Myocardial Infarction in Two Independent Retrospective Angiographic Studies

Naif A. M. Almontashiri^{1,2,3}, Ragnar O. Vilmundarson^{1,2}, Nima Ghasemzadeh⁴, Sonny Dandona⁵, Robert Roberts^{1,6}, Arshed A. Quyyumi⁵, Hsiao-Huei Chen^{6,7*}, Alexandre F. R. Stewart^{1,2,6*}



2014

Evolocumab produces rapid suppression of PCSK9 and LDL-C levels





A Trial of Alirocumab and Plaque Regression in Peripheral Arterial Disease

Alirocumab and Reverse Cholesterol Transport

Alirocumab in Patients With Acute Myocardial Infarction

An 8-Week Dose-Finding Study to Evaluate the Efficacy and Safety of Alirocumab in Children and Adolescents With Heterozygous Familial Hypercholesterolemia (ODYSSEY KIDS)

The Alirocumab for Stopping Atherosclerosis Progression in Saphenous Vein Grafts (ASAP-SVG) Pilot Trial (ASAP-SVG)

Alirocumab in Patients on a Stable Dialysis Regimen



U.S. National Library of Medicine

ClinicalTrials.gov

EVOlucumab for Early Reduction of LDL-cholesterol Levels in Patients With Acute Coronary Syndromes (EVOPACS) (EVOPACS)

Evolocumab in Acute Coronary Syndrome (EVACS)

Imaging of Coronary Plaques in Subjects Treated With Evolocumab

Vascular Effects of Alirocumab in Acute MI-Patients (PACMAN-AMI)

Effects of Acute, Rapid Lowering of LDL Cholesterol With Alirocumab in Patients With STEMI Undergoing Primary PCI (EPIC STEMI)

Alirocumab in Patients With Acute Myocardial Infarction

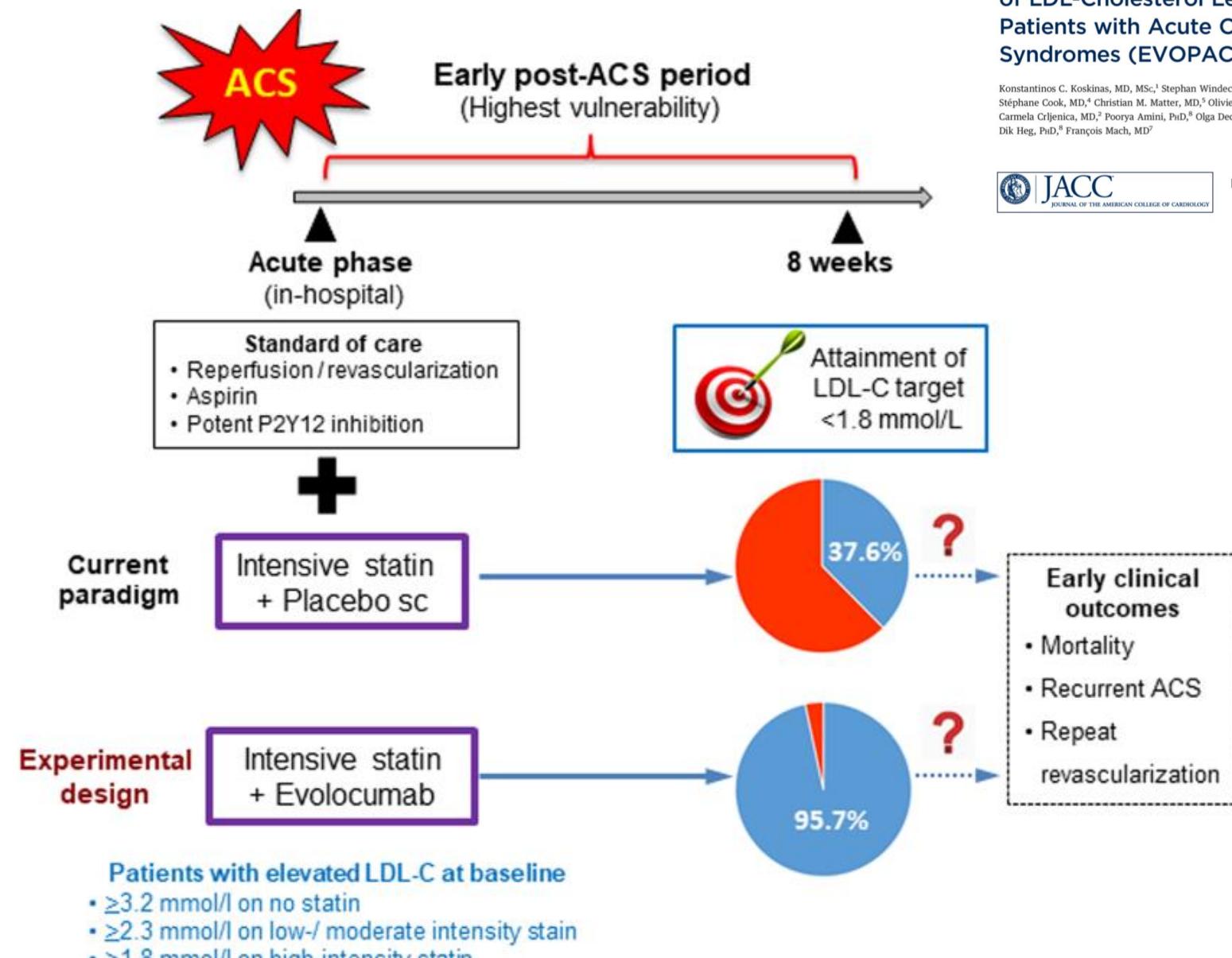
Early Alirocumab to Reduce LDL-C in Myocardial Infarction (EARLY)

Evolocumab for Early Reduction of LDL-Cholesterol Levels in Patients with Acute Coronary Syndromes (EVOPACS)

Konstantinos C. Koskinas, MD, MSc,¹ Stephan Windecker, MD,¹ Giovanni Pedrazzini, MD,² Christian Mueller, MD,³ Stéphane Cook, MD,⁴ Christian M. Matter, MD,⁵ Olivier Muller, MD,⁶ Jonas Häner, MD,¹ Baris Gencer, MD,⁷ Carmela Crjenica, MD,² Poorya Amini, PhD,⁸ Olga Deckarm, MD,¹ Juan F. Iglesias, MD,⁷ Lorenz Räber, MD, PhD,¹ Dik Heg, PhD,⁸ François Mach, MD¹



Manuscript published online August 31, 2019
<https://doi.org/10.1016/j.jacc.2019.08.010>



Evolocumab for Early Reduction of LDL-Cholesterol Levels in Patients with Acute Coronary Syndromes (EVOPACS)

Konstantinos C. Koskinas, MD, MSc,¹ Stephan Windecker, MD,¹ Giovanni Pedrazzini, MD,² Christian Mueller, MD,³ Stéphane Cook, MD,⁴ Christian M. Matter, MD,⁵ Olivier Muller, MD,⁶ Jonas Häner, MD,¹ Baris Gencer, MD,⁷ Carmela Crlejenica, MD,² Poorya Amini, PhD,⁸ Olga Deckarm, MD,¹ Juan F. Iglesias, MD,⁷ Lorenz Räber, MD, PhD,¹ Dik Heg, PhD,⁸ François Mach, MD¹



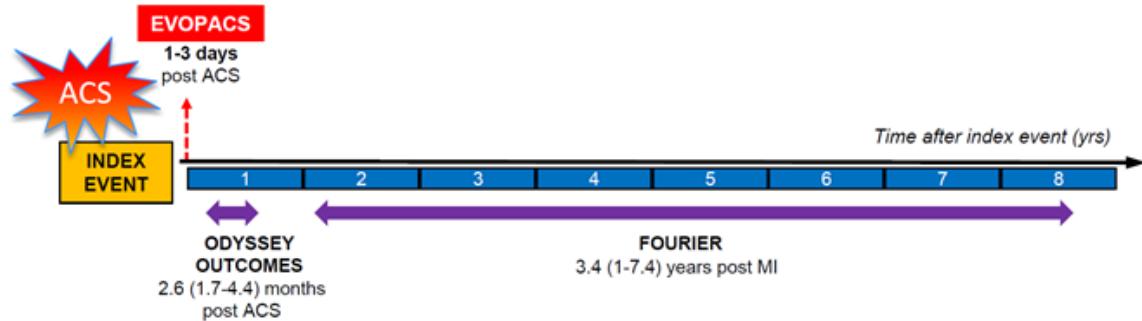
Manuscript published online August 31, 2019

<https://doi.org/10.1016/j.jacc.2019.08.010>

Together with
ESC Congress World Congress
Paris 2019 of Cardiology

Study Hypothesis

- PCSK9 inhibition with evolocumab, administered in the **early phase of ACS**, is well tolerated and results in greater reduction of LDL-C levels at 8 weeks compared with placebo in patients receiving with high-intensity statin treatment

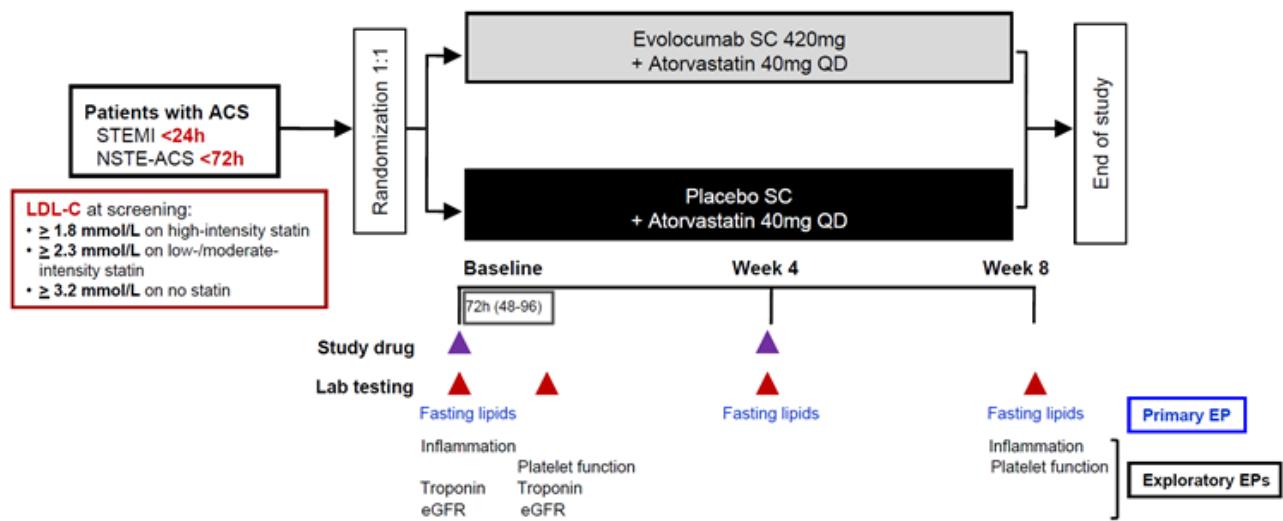


Study Endpoints

- Primary EP: % Change in LDL-C from baseline to 8 weeks
- Secondary EP: Safety and tolerability
- Exploratory EPs:
 - hs-CRP and other inflammatory biomarkers
 - Platelet reactivity
 - Contrast-induced acute kidney injury
 - Post-PCI myocardial injury

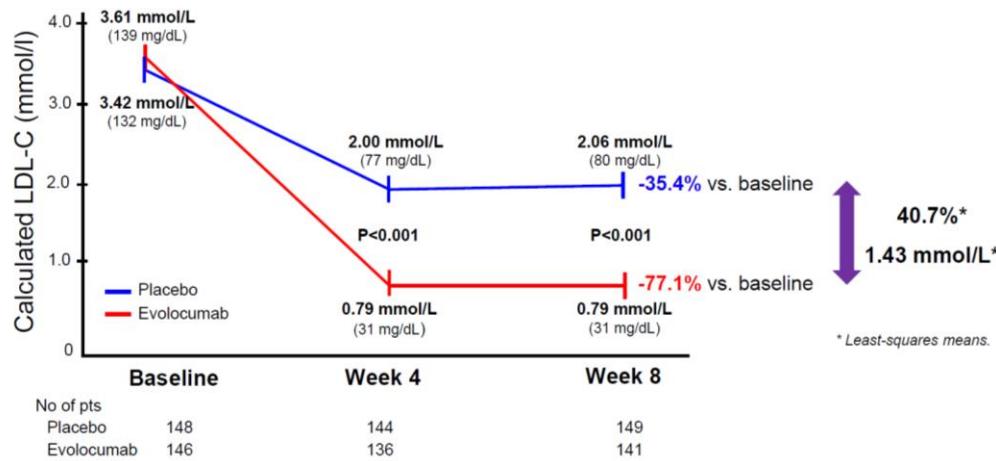
Together with
ESC Congress
Paris 2019 World Congress
of Cardiology

Study Design



Primary endpoint: % Change in LDL-C at 8 wks

EVOPACS



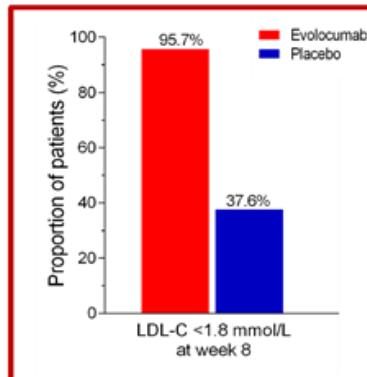
Together with
ESC Congress
Paris 2019

World Congress
of Cardiology

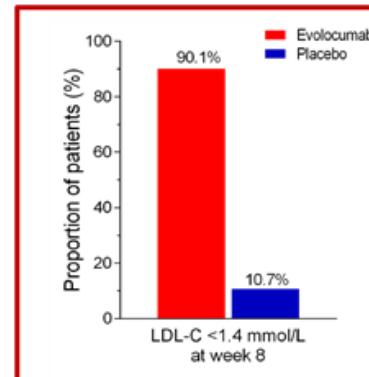
EVOPACS

Achievement of LDL-C Treatment Targets

LDL-C target <1.8 mmol/L
(<70 mg/dL)



LDL-C target <1.4 mmol/L
(<55 mg/dL)



Together with
ESC Congress
Paris 2019

World Congress
of Cardiology

ESC/EAS 2019 Dyslipidemia Guidelines
Mach F, et al. Eur Heart J 2019; In Press

Inibitori PCSK9

- Razionale
- Farmacologia
- Efficacia
- **Sicurezza**
- Dati del mondo reale

Table 3. Adverse Events and Laboratory Test Results.

| Outcome | Evolocumab (N = 13,769) | Placebo (N = 13,756) |
|--|----------------------------|-------------------------|
| Adverse events — no. of patients (%) | | |
| Any | 10,664 (77.4) | 10,644 (77.4) |
| Serious | 3410 (24.8) | 3404 (24.7) |
| Thought to be related to the study agent and leading to discontinuation of study regimen | 226 (1.6) | 201 (1.5) |
| Injection-site reaction* | 296 (2.1) | 219 (1.6) |
| Allergic reaction | 420 (3.1) | 393 (2.9) |
| Muscle-related event | 682 (5.0) | 656 (4.8) |
| Rhabdomyolysis | 8 (0.1) | 11 (0.1) |
| Cataract | 228 (1.7) | 242 (1.8) |
| Adjudicated case of new-onset diabetes† | 677 (8.1) | 644 (7.7) |
| Neurocognitive event | 217 (1.6) | 202 (1.5) |
| Laboratory results — no. of patients/total no. (%) | | |
| Aminotransferase level >3 times the upper limit of the normal range | 240/13,543 (1.8) | 242/13,523 (1.8) |
| Creatine kinase level >5 times the upper limit of the normal range | 95/13,543 (0.7) | 99/13,523 (0.7) |

European Heart Journal Supplements (2019) **21** (Supplement B), B48-B49

The Heart of the Matter

doi:10.1093/eurheartj/suz007



European Society
of Cardiology

Statin-associated muscle symptoms: is Proprotein convertase subtilisin/kexin type 9 inhibitors a therapeutic option?

Alberto Corsini^{1,2}



Intolleranza alle statine*: criteri di eleggibilità

Indicazioni autorizzate e rimborsate SSN (decisione CTS):

- ◆ Impossibilità a tollerare almeno 2 statine di cui una alla dose iniziale (rosuvastatina 5 mg/die, atorvastatina 10 mg/die, simvastatina 10 mg/die, lovastatina 20 mg/die, pravastatina 40 mg/die, fluvastatina 40 mg/die) ed una seconda statina ad una qualsiasi dose
- ◆ Associazione con uno o più eventi avversi correlati all'uso di statine confermati e non tollerabili oppure associazione con significative alterazioni dei biomarkers (CPK >10 x ULN, eseguito in assenza di sforzi muscolari)
- ◆ Risoluzione o netto miglioramento della sintomatologia, normalizzazione o netta riduzione dei biomarkers alla sospensione/riduzione della dose di statina
Sintomatologia/innalzamento dei biomarkers non attribuibile ad altre cause (interazioni farmacologiche o condizioni cliniche note che possono aumentare il rischio di intolleranza alle statine)

Ai fini dell'eleggibilità è necessario inserire 3 determinazioni, del profilo lipidico a distanza di almeno 3 mesi l'una dall'altra. Ai fini dell'eleggibilità tutti e tre i valori di colesterolo LDL devono essere al di sopra del target specifico



Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance

The GAUSS-3 Randomized Clinical Trial

Table 4. Most Common Adverse Events During Phase B of the GAUSS-3 Trial

| Adverse Event | No. (%) of Patients | |
|---------------------------------------|-----------------------|-------------------------|
| | Ezetimibe (n = 73) | Evolocumab (n = 145) |
| Total muscle-related events | 21 (28.8) | 30 (20.7) |
| Myalgia | 16 (21.9) | 20 (13.8) |
| Creatine kinase increase ^a | 1 (1.4) | 4 (2.8) |
| Musculoskeletal pain | 1 (1.4) | 5 (3.4) |
| Muscle weakness | 0 | 3 (2.1) |
| Nasopharyngitis | 2 (2.7) | 14 (9.7) |
| Arthralgia | 1 (1.4) | 13 (9.0) |
| Pain in extremity | 1 (1.4) | 13 (9.0) |
| Muscle spasms | 5 (6.8) | 13 (9.0) |
| Fatigue | 5 (6.8) | 12 (8.3) |
| Headache | 7 (9.6) | 10 (6.9) |
| Back pain | 6 (8.2) | 10 (6.9) |
| Injection site reactions | 2 (2.7) | 7 (4.8) |
| Influenza | 1 (1.4) | 7 (4.8) |
| Diarrhea | 4 (5.5) | 6 (4.1) |
| Urinary tract infection | 4 (5.5) | 5 (3.4) |
| Nausea | 3 (4.1) | 5 (3.4) |
| Rash | 3 (4.1) | 5 (3.4) |
| Fall | 1 (1.4) | 5 (3.4) |
| Gastroesophageal reflux disease | 0 | 5 (3.4) |
| Insomnia | 0 | 5 (3.4) |

Figure 3. Mean Percent Change in Low-Density Lipoprotein Cholesterol Level During Randomized Treatment With Ezetimibe or Evolocumab, GAUSS-3 Trial

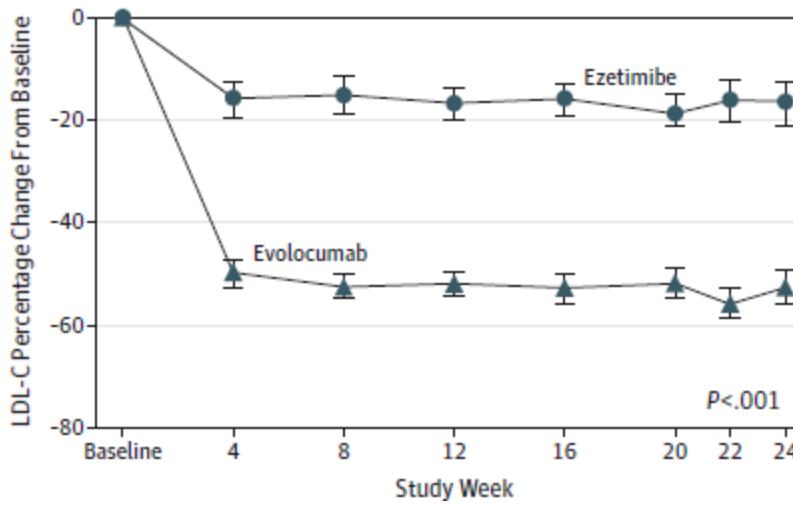


Table 3. Adverse Events and Laboratory Test Results.

| Outcome | Evolocumab (N=13,769) | Placebo (N=13,756) |
|--|--------------------------|-----------------------|
| Adverse events — no. of patients (%) | | |
| Any | 10,664 (77.4) | 10,644 (77.4) |
| Serious | 3410 (24.8) | 3404 (24.7) |
| Thought to be related to the study agent and leading to discontinuation of study regimen | 226 (1.6) | 201 (1.5) |
| Injection-site reaction* | 296 (2.1) | 219 (1.6) |
| Allergic reaction | 420 (3.1) | 393 (2.9) |
| Muscle-related event | 682 (5.0) | 656 (4.8) |
| Rhabdomyolysis | 8 (0.1) | 11 (0.1) |
| Cataract | 228 (1.7) | 242 (1.8) |
| Adjudicated case of new-onset diabetes† | 677 (8.1) | 644 (7.7) |
| Neurocognitive event | 217 (1.6) | 202 (1.5) |
| Laboratory results — no. of patients/total no. (%) | | |
| Aminotransferase level >3 times the upper limit of the normal range | 240/13,543 (1.8) | 242/13,523 (1.8) |
| Creatine kinase level >5 times the upper limit of the normal range | 95/13,543 (0.7) | 99/13,523 (0.7) |

Efficacy and safety of evolocumab in individuals with type 2 diabetes mellitus: primary results of the randomised controlled BANTING study

Robert S. Rosenson¹ & Martha L. Daviglus² & Yehuda Handelsman³ & Paolo Pozzilli⁴ & Harold Bays⁵ & Maria Laura Monsalvo⁶ & Mary Elliott-Davey⁷ & Ransi Somaratne⁶ & Peter Reaven⁸

Table 2 Efficacy results at week 12 and at the mean of weeks 10 and 12

| Variable | Week 12 | | Mean of weeks 10 and 12 | |
|--|--------------------------|------------------------------|--------------------------|-------------------------|
| | Placebo (n = 141) | Evolocumab (n = 280) | Placebo (n = 141) | Evolocumab (n = 280) |
| LDL-C | | | | |
| Change from baseline, %, mean (SEM) ^a | -1.1 (1.9) | -54.3 (1.4) | -0.8 (1.8) | -65.0 (1.3) |
| Treatment difference, mean (SEM) ^b | -53.1 (2.3) [†] | | -64.1 (2.1) [†] | |
| Achievement of <1.81 mmol/l, n (%) | 20 (15.4) | 213 (84.5) | 20 (14.8) | 253 (92.7) |
| Achievement of ≥50% reduction, n (%) | 1 (0.8) | 165 (65.5) | 1 (0.7) | 221 (84.2) |
| Change from baseline in other lipids, %, mean (SEM) ^a | | | | |
| Non-HDL-C | -0.6 (1.8) | -46.9 (1.3) | -0.1 (1.6) | -56.6 (1.2) |
| ApoB | 1.8 (1.7) | -40.3 (1.3) | 2.3 (1.6) | -50.2 (1.2) |
| Total cholesterol | -1.2 (1.4) | -35.0 (1.0) | -1.1 (1.2) | -42.2 (0.9) |
| Lp(a) | 7.4 (3.1) | -25.2 (2.3) | 9.6 (3.3) | -30.9 (2.4) |
| Triacylglycerol | 4.8 (3.4) | -8.9 (2.5) | 6.6 (2.9) | -12.6 (2.2) |
| HDL-C | -1.4 (1.4) | 6.0 (1.0) | -2.6 (1.3) | 7.2 (0.9) |
| VLDL-C | 3.0 (2.9) | -10.3 (2.2) | 3.4 (2.6) | -13.6 (1.9) |
| Change from baseline in glycaemic measure, median (Q1, Q3) | | | | |
| HbA _{1c} , % | 0.1 (-0.2, 0.5) | 0.1 (-0.2, 0.5) [‡] | N/A | N/A |
| HbA _{1c} , mmol/mol | 1.1 (-2.2, 5.5) | 1.1 (-2.2, 5.5) | | |
| Fasting serum glucose, mmol/l | 0.2 (-0.8, 1.6) | 0.3 (-0.8, 1.7) [§] | N/A | N/A |

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

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

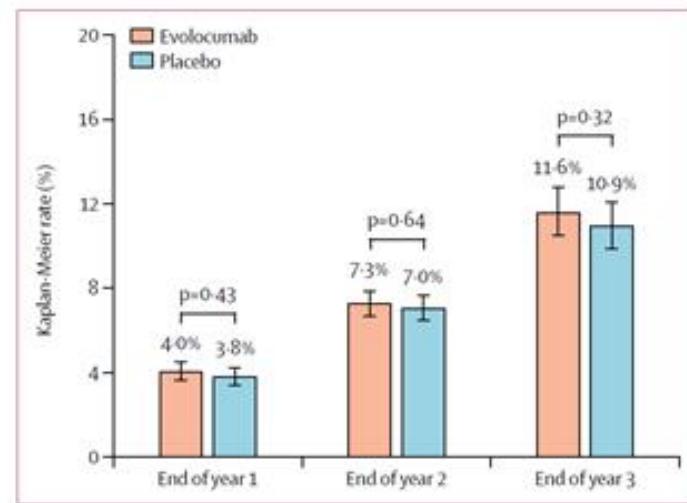
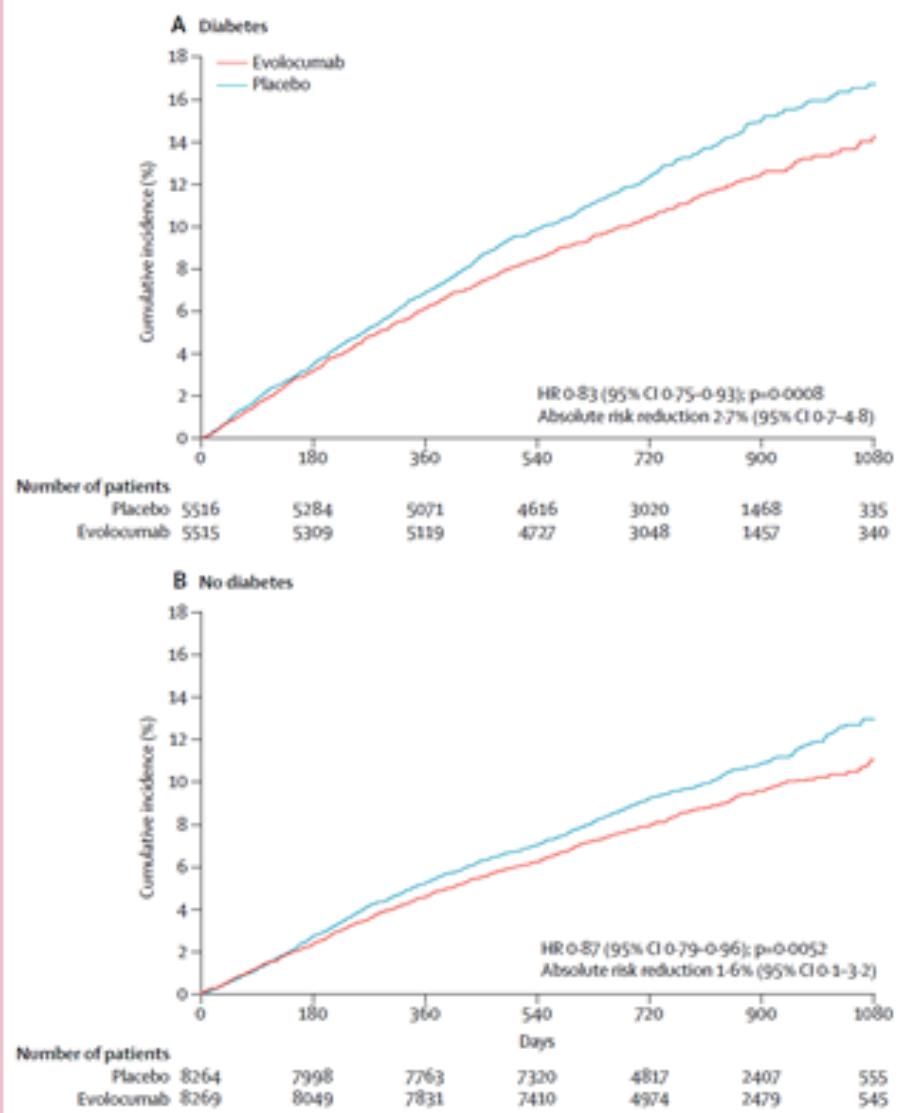


Figure 4: New-onset diabetes

Data are the cumulative incidence of new-onset diabetes at the end of 1, 2, and 3 years of follow-up in the evolocumab and placebo treatment groups, among patients without diabetes at baseline. Error bars are 95% CIs.

Table 3. Adverse Events and Laboratory Test Results.

| Outcome | Evolocumab (N = 13,769) | Placebo (N = 13,756) |
|--|----------------------------|-------------------------|
| Adverse events — no. of patients (%) | | |
| Any | 10,664 (77.4) | 10,644 (77.4) |
| Serious | 3410 (24.8) | 3404 (24.7) |
| Thought to be related to the study agent and leading to discontinuation of study regimen | 226 (1.6) | 201 (1.5) |
| Injection-site reaction* | 296 (2.1) | 219 (1.6) |
| Allergic reaction | 420 (3.1) | 393 (2.9) |
| Muscle-related event | 682 (5.0) | 656 (4.8) |
| Rhabdomyolysis | 8 (0.1) | 11 (0.1) |
| Cataract | 228 (1.7) | 242 (1.8) |
| Adjudicated case of new-onset diabetes† | 677 (8.1) | 644 (7.7) |
| Neurocognitive event | 217 (1.6) | 202 (1.5) |
| Laboratory results — no. of patients/total no. (%) | | |
| Aminotransferase level >3 times the upper limit of the normal range | 240/13,543 (1.8) | 242/13,523 (1.8) |
| Creatine kinase level >5 times the upper limit of the normal range | 95/13,543 (0.7) | 99/13,523 (0.7) |

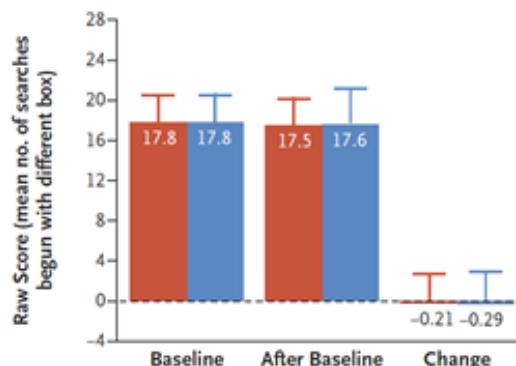
ORIGINAL ARTICLE

Cognitive Function in a Randomized Trial of Evolocumab

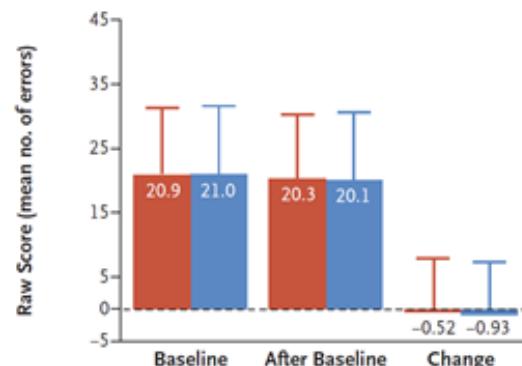
Robert P. Giugliano, M.D., François Mach, M.D., Kenton Zavitz, Ph.D., Christopher Kurtz, M.D., Kyungah Im, Ph.D., Estella Kanevsky, M.S., Jingjing Schneider, Ph.D., Huei Wang, Ph.D., Anthony Keech, M.D., Terje R. Pedersen, M.D., Marc S. Sabatine, M.D., M.P.H., Peter S. Sever, Ph.D., F.R.C.P., Jennifer G. Robinson, M.D., M.P.H., Narimon Honarpour, M.D., Ph.D., Scott M. Wasserman, M.D., and Brian R. Ott, M.D., for the EBBINGHAUS Investigators*

Evolocumab group Placebo group

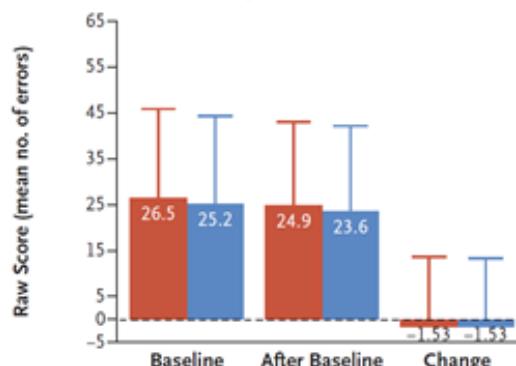
A Spatial Working Memory Strategy Index of Executive Function



B Spatial Working Memory Between Errors



C Paired Associated Learning



D Median 5-Choice Reaction Time

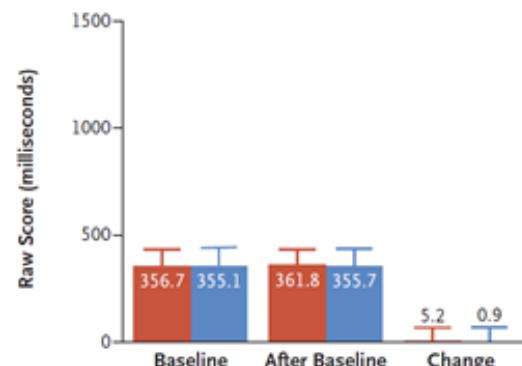


Figure 1. Primary and Secondary Cambridge Neuropsychological Test Automated Battery (CANTAB) End Points.

Inibitori PCSK9

- Razionale
- Farmacologia
- Efficacia
- Sicurezza
- **Dati del mondo reale**



PCSK9 inhibitors in clinical practice: Delivering on the promise?

Robert M. Stoekenbroek ¹, Merel L. Hartgers ¹, Roger Rutte, Douwe D. de Wijer,
Erik S.G. Stroes, G. Kees Hovingh*



Department of Vascular Medicine, Academic Medical Center, 1100DD Amsterdam, The Netherlands

Table 1

Baseline characteristics.

| | N = 238 |
|---|------------|
| Age, years (SD) | 58 (11) |
| Male, n (%) | 139 (58.4) |
| White, n (%) | 232 (97.5) |
| Previous CVD, n (%) | 149 (62.6) |
| FH, n (%) | 160 (67.2) |
| Statin intolerance ^a , n (%) | 102 (42.9) |
| Smoking | |
| Current, n (%) | 31 (16.5) |
| Former, n (%) | 66 (35.1) |
| Never, n (%) | 91 (48.4) |
| Unknown, n (%) | 50 |
| BMI, kg/m ² (SD) | 27.6 (4.6) |
| Hypertension, n (%) | 97 (40.8) |
| Type 2 diabetes, n (%) | 40 (16.8) |
| Concomitant lipid-lowering therapy | |
| Statins, n (%) | 133 (55.9) |
| Ezetimibe, n (%) | 217 (91.2) |
| Fibrates, n (%) | 8 (3.4) |
| Bile acid sequestrants, n (%) | 8 (3.4) |

SD, standard deviation; n, number; BMI, body mass index; CVD, cardiovascular disease.

^a Unable to tolerate at least three different statins due to muscle symptoms.

Table 2

PCSK9 inhibitor treatment.

| | N = 238 |
|---|------------|
| Prior study participation, n (%) | 99 (41.6) |
| Initial treatment | |
| Evolocumab 140 mg/2 weeks, n (%) | 118 (52.0) |
| Evolocumab 420 mg/months, n (%) | 3 (1.3) |
| Alirocumab 75 mg/2 weeks, n (%) | 42 (18.5) |
| Alirocumab 150 mg/2 weeks, n (%) | 64 (28.2) |
| Unknown ^a | 11 (4.6) |
| Change in PCSK9 inhibitor treatment, n (%) | 8 (3.4) |
| Discontinued PCSK9 inhibitor treatment, n (%) | 6 (2.5) |

SD, standard deviation; n, number.

^a Study allocation not yet unblinded.

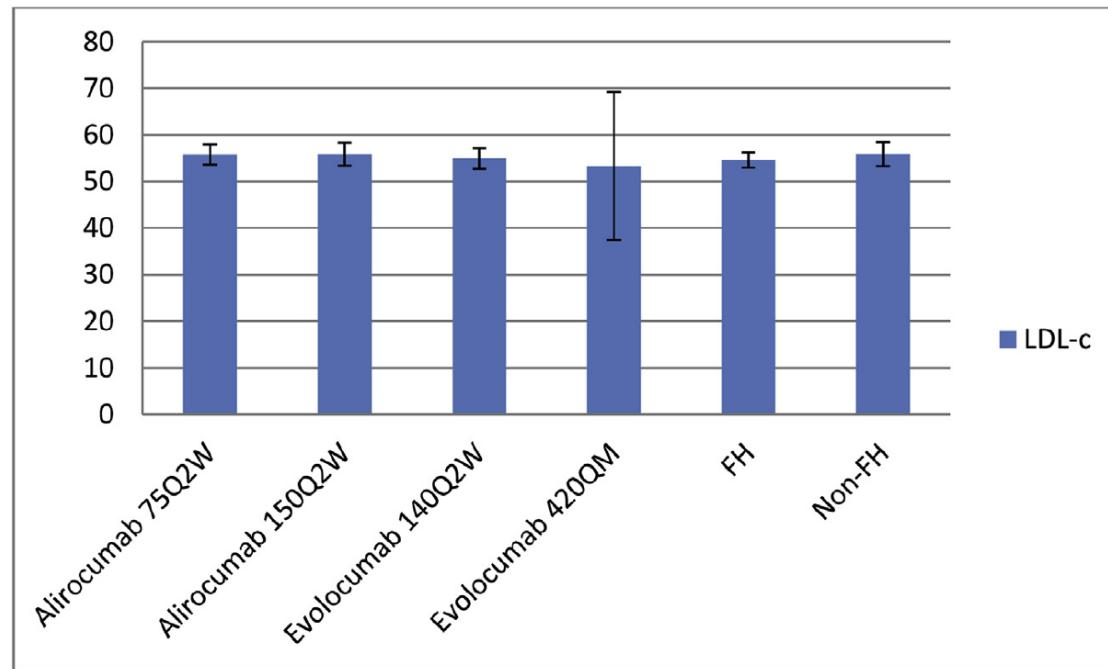


Fig. 1. Percentage reductions and standard errors in LDL-cholesterol for the different dosing regimens and for patients with or without FH, from baseline to the last available lipid measurement.

Efficacy outcomes.

| | Baseline | Baseline (ezetimibe corrected) | Last measurement | %-change (95% CI) | %-change (ezetimibe corrected; 95% CI) |
|-----------------------------|------------------|--------------------------------|------------------|-------------------|--|
| Total cholesterol, mmol/L | 6.46 (5.26–7.96) | 6.28 (4.91–7.58) | 3.82 (3.03–4.77) | −38.9 (36.7–41.0) | −35.4 (33.1–37.7) |
| LDL cholesterol, mmol/L | 4.37 (3.36–5.72) | 4.07 (3.02–5.29) | 1.71 (1.09–2.52) | −58.3 (55.7–60.9) | −55.0 (52.3–57.7) |
| Non-HDL cholesterol, mmol/L | 4.99 (4.11–6.54) | 4.82 (3.56–6.18) | 2.39 (1.68–3.13) | −52.0 (49.4–54.6) | −48.1 (45.3–51.0) |
| HDL cholesterol, mmol/L | 1.29 (1.06–1.54) | 1.30 (1.07–1.54) | 1.42 (1.18–1.70) | +13.2 (8.9–17.5) | +12.3 (8.1–16.6) |
| Triglycerides, mmol/L | 1.50 (0.99–2.05) | 1.42 (0.98–1.98) | 1.20 (0.84–1.76) | −10.2 (4.0–16.3) | −7.0 (0.7–13.3) |

Absolute values are medians and interquartile ranges, reductions are means and 95% confidence intervals.

SD, standard deviation; n, number; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IQR, interquartile range.

Fig. 1. Percentage reductions and standard errors in LDL-cholesterol for the different dosing regimens and for patients with or without FH, from baseline to the last available lipid measurement.

Table 4
Discontinuation rate and side effects.

| | |
|--|-----------|
| Discontinuation total, n (%) | 6 (2.5) |
| Discontinuation due to side effects, n (%) | 6 (2.5) |
| Skipping doses, n (%) | 11 (4.6) |
| Side effects | |
| Any, n (%) | 37 (15.5) |
| Muscle symptoms, n (%) | 9 (3.8) |
| Injection-site reactions, n (%) | 8 (3.4) |
| Flu-like symptoms/nasopharyngitis, n (%) | 6 (2.6) |
| Joint pain, n (%) | 2 (0.8) |
| Fatigue, n (%) | 2 (0.8) |
| Headache/neurological, n (%) | 2 (0.8) |
| Other, n (%) | 8 (3.4) |
| Non-response, n (%) | 3 (1.3) |
| <25% LDL-cholesterol reduction, n (%) | 15 (6.5) |

Conclusions: The observed lipid reductions and side effects profile of PCSK9 inhibitors in a routine care setting were comparable to observations in clinical trials.

Inibitori di PCSK9: Take home message

- Le evidenze attuali documentano numerosi aspetti condivisi dagli inibitori di PCSK9:
- Meccanismo d'azione
- il profilo farmacologico
- l'efficacia nelle dislipidemie
- I benefici clinici inclusa la riduzione della mortalità totale
- tollerabilità e sicurezza

Combined lipid-lowering therapy

| Drug class | LDL-C Decrease (%) | Non-HDL-C Decrease (%) | HDL-C Increase (%) | TG Decrease (%) |
|-----------------|-----------------------|---------------------------|-----------------------|--------------------|
| Statin | +++ | +++ | + | ++ |
| Ezetimibe | ++ | ++ | + | + |
| Feno | + | + | ++ | ++++ |
| PCSK9 inhibitor | ++++ | ++++ | + | + |