SABATO 9 OTTOBRE

Impiego degli inibitori PCSK9 nel trattamento dell'ipercolesterolemia familiare

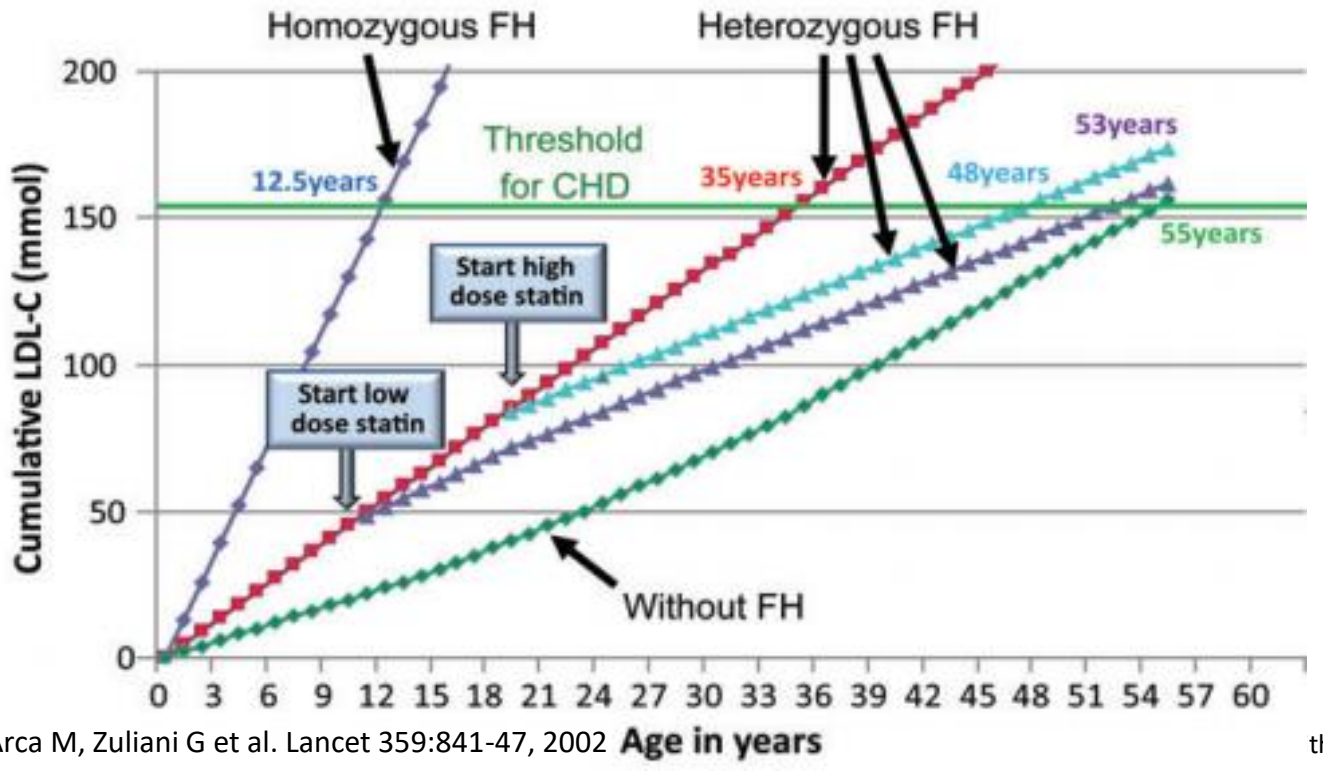
Alberto Zambon, *Padova*

A Zambon - Faculty Disclosure

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Alfasigma	x							
Amgen	x							
Eli Lilly	x							
AKCEA		x						
Abbott - Mylan	x	x						
Daiichi Sankyo	x							
Servier	x							
Sanofi	x							
Amryt	x							
Amarin	x	x						
Novartis		x						

Introduction – Familial Hypercholesterolemia

- **Homozygous FH** (HoFH) is a rare and life-threatening disease (estimated rate of 1/160.000-320.000), while the **frequency of Heterozygous FH (HeFH) can be estimated to be between 1/200 and 1/250** in the general population, putting the total number of cases in Italy at 250-300.000
- 15-16.000 le persone con HeFH attualmente diagnosticate - Solo 4-6% delle persone HeFH
- **4 HeFH su 5 non a target per LDL-C** anche se la maggioranza in statine ad elevata efficacia ad alto dosaggio (±ezetimibe)
- Although **early diagnosis and treatment** from childhood are crucial to reduce cardiovascular events and premature death, FH still remains *underdiagnosed* and *undertreated* in general population



*Arca M, Zuliani G et al. Lancet 359:841-47, 2002

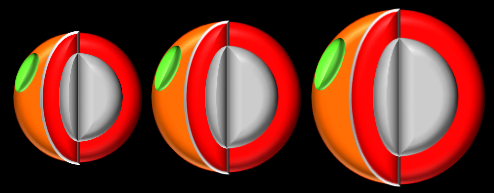
Cumulative LDL-c burden of a 55y non-FH subject is 160 mmol.

In an untreated FH subject, this is attained by age 35 years, but is delayed in FH patients treated from age 18 years (48 y), and further delayed in those treated from age 10 years (53 y).

thout familial hypercholesterolaemia as afunction of the age of initiation of statin therapy. Data derived from Huijgen et al. and Starr et al.

Ipercolesterolemia Familiare (FH): Sotto-diagnosticata e sottotrattata

LDL-C



FH Target #1 in tutte le Linee Guida

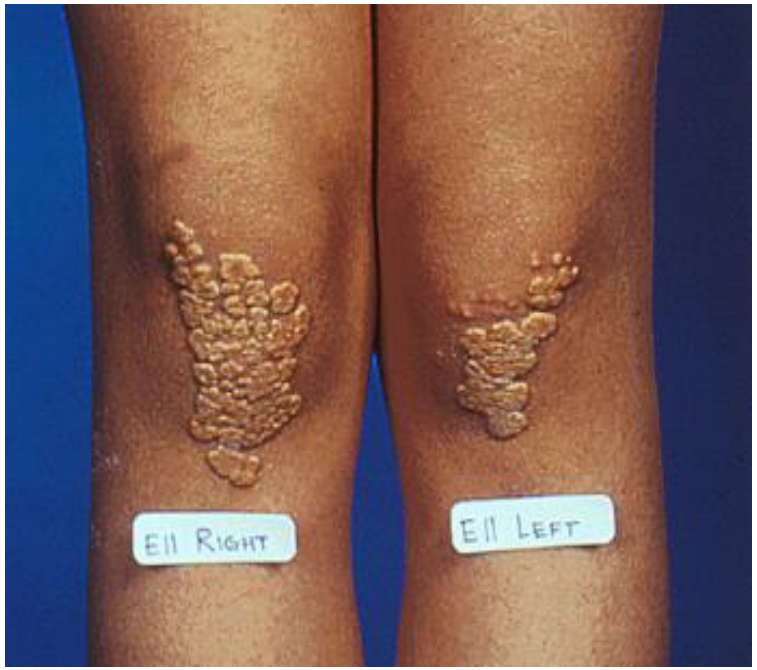
Colesterolo Plasmatico	Forme PRIMITIVE	
300-580 mg/dl	**Ipercolesterolemia Familiare Eterozigote***	nche in assenza di CVD s. SCORE)
480-1000 mg/dl	**Ipercolesterolemia Familiare Omozigote***	

***Ipercolesterolemia Familiare (FH) monogenica**

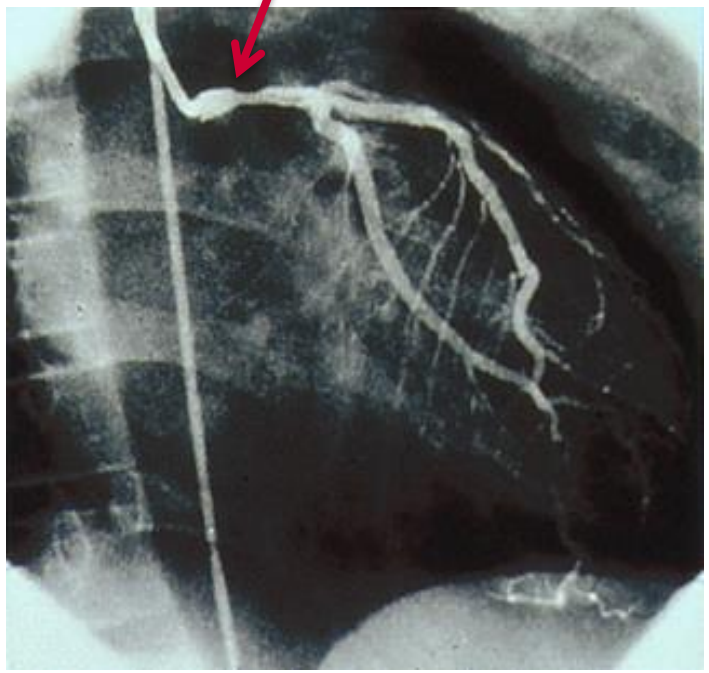
Heart Journal (2019)

TIPICA PRESENTAZIONE CLINICA DI UN PAZIENTE CON HoFH

- Femmina di 28 anni
- Xantomi cutanei dall'età di 3 anni
- Coronaropatia Ostruttiva con CABG* a 12 anni
- LDL colesterolo = 780 mg/dL



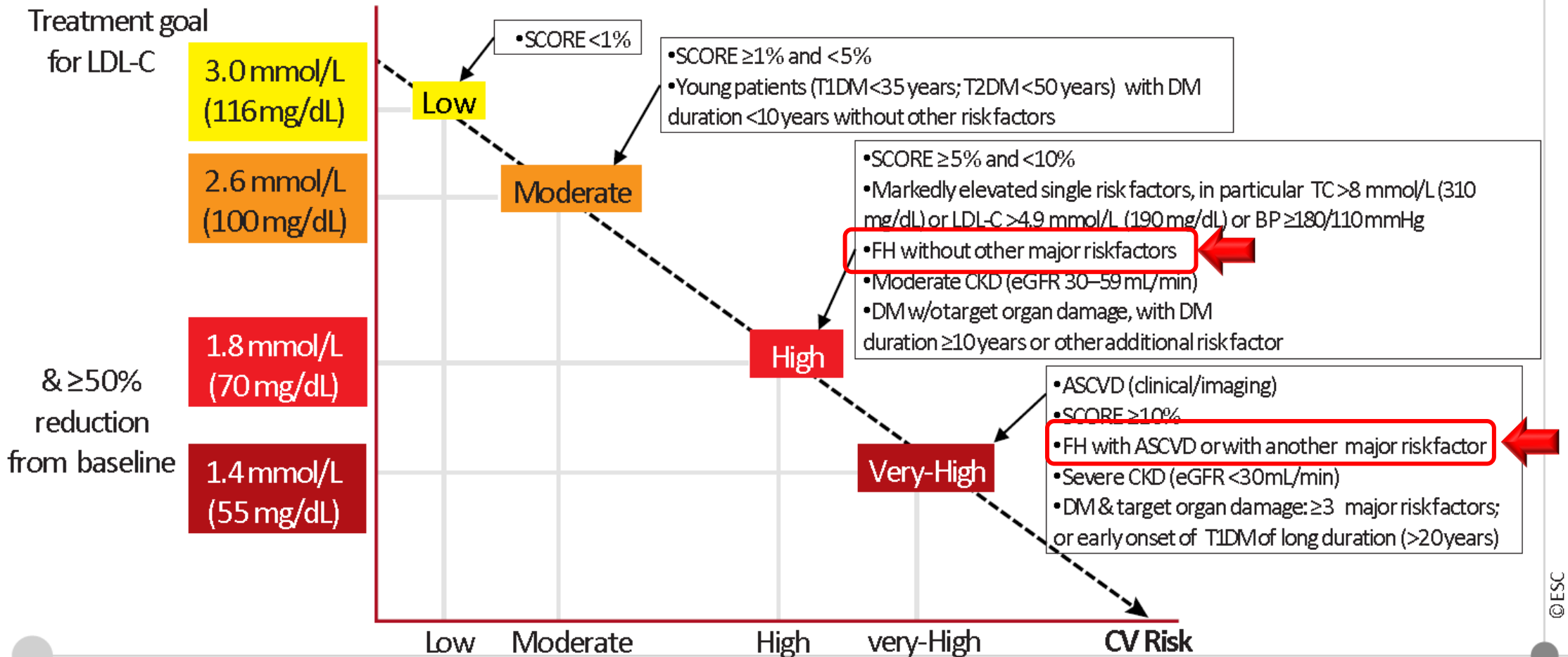
3 anni



12 anni

* CABG = Coronary Artery Bypass Graft

Treatment goals for low-density lipoprotein cholesterol (LDL-C) across categories of total cardiovascular disease risk



www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

NUOVE TERAPIE IPOLIPEMIZZANTI PER I PAZIENTI CON IPERCOLESTEROLEMIA FAMILIARE

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Position Paper SISA 2016 (Modificata secondo linee guida EAS 2019)

In tutti i Pazienti, il prima possibile:
Raccomandazioni dietetiche e stile di vita (es. fumo)
Statine (atorva o rosuvastatina) alla **massima dose** tollerata
Aggiungere **Ezetimibe**

Pazienti Intolleranti alle statina

Se LDL-C >100 mg/dl

PCSK9 Inibitori
al massimo dosaggio

Se LDL-C>100 mg/dl e malattia vascolare progressiva

LDL-Aferesi
Settimanale/bisettimanale
Lomitapide

Monitorare lo stato di salute del pziente (test funzionalità epatica, status vascolare)

Target C-LDL:
<70 mg/dl (adulti)
<135 mg/dl (bambini)
<55 mg/dl (adulti con CVD presente o altro fattore di rischio maggiore)

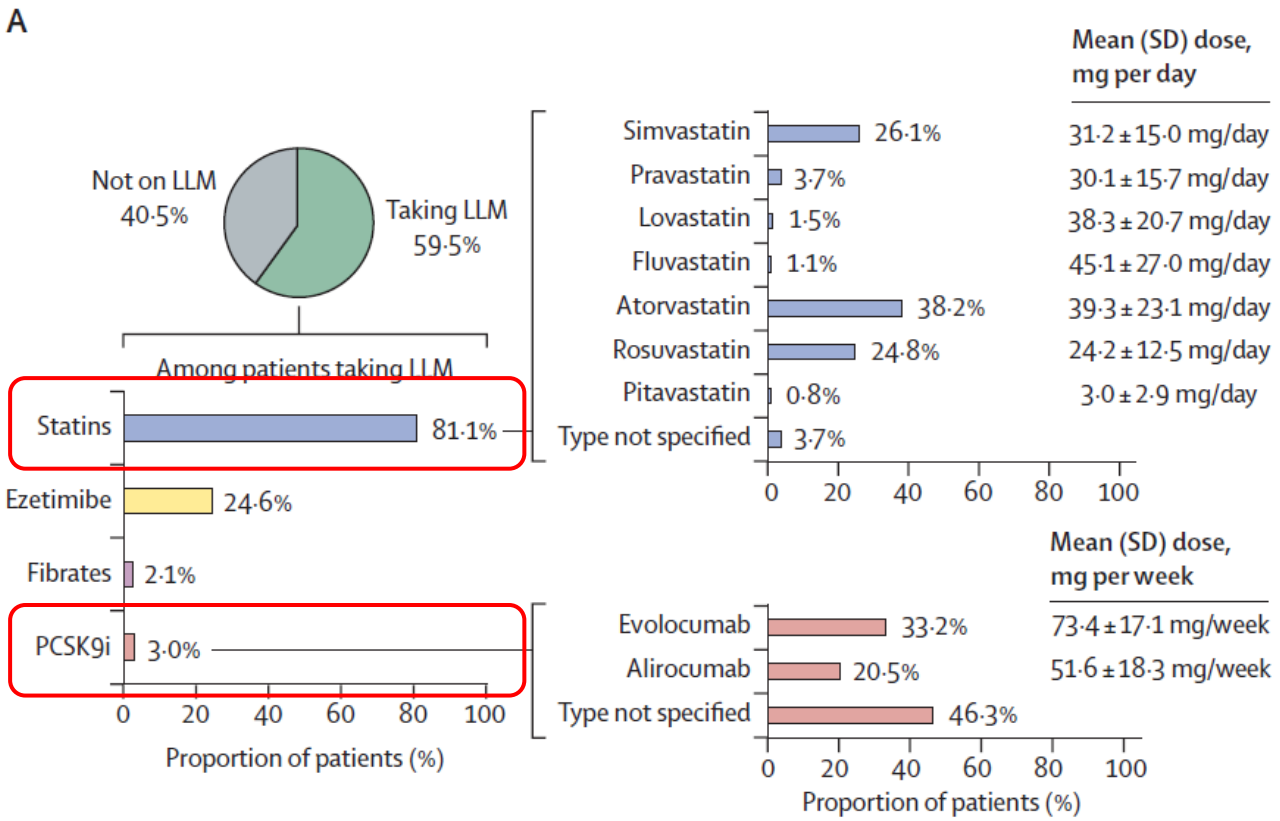
Global perspective of familial hypercholesterolaemia: a cross-sectional study from the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC)

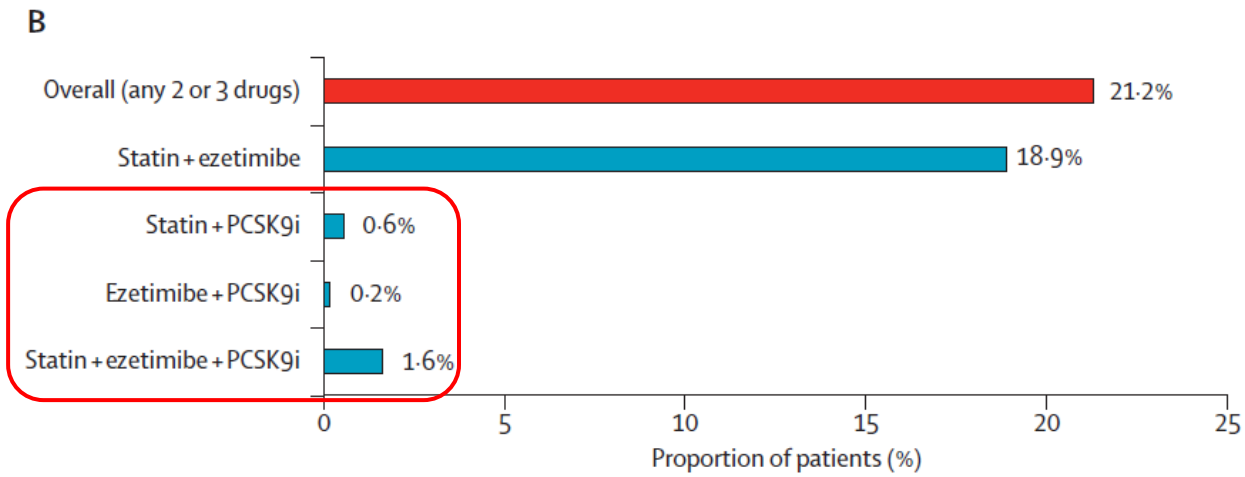
Published Online
September 7, 2021
https://doi.org/10.1016/
S0140-6736(21)01122-3
See Online/Comment

EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC)*

42 167 adults from 56 countries were included in the study.

Class and type of LLM (A) and combination therapy among participants taking statins, ezetimibe, or PCSK9i (B)





LLM=lipid-lowering medication. PCSK9i=proprotein convertase subtilisin–kexin type 9 inhibitors.

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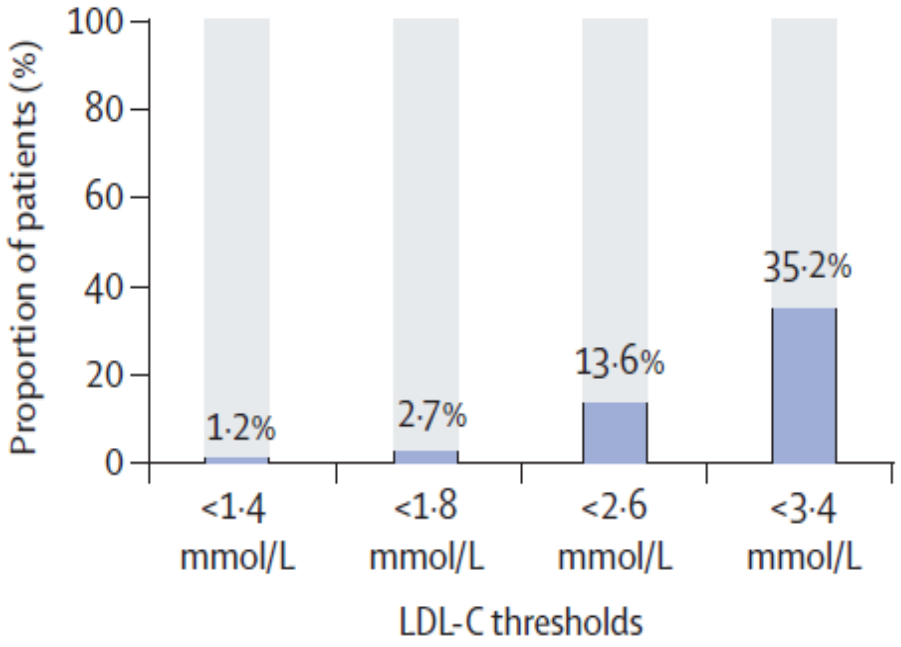
A



Guideline-recommended LDL cholesterol concentrations are infrequently achieved with single-drug therapy

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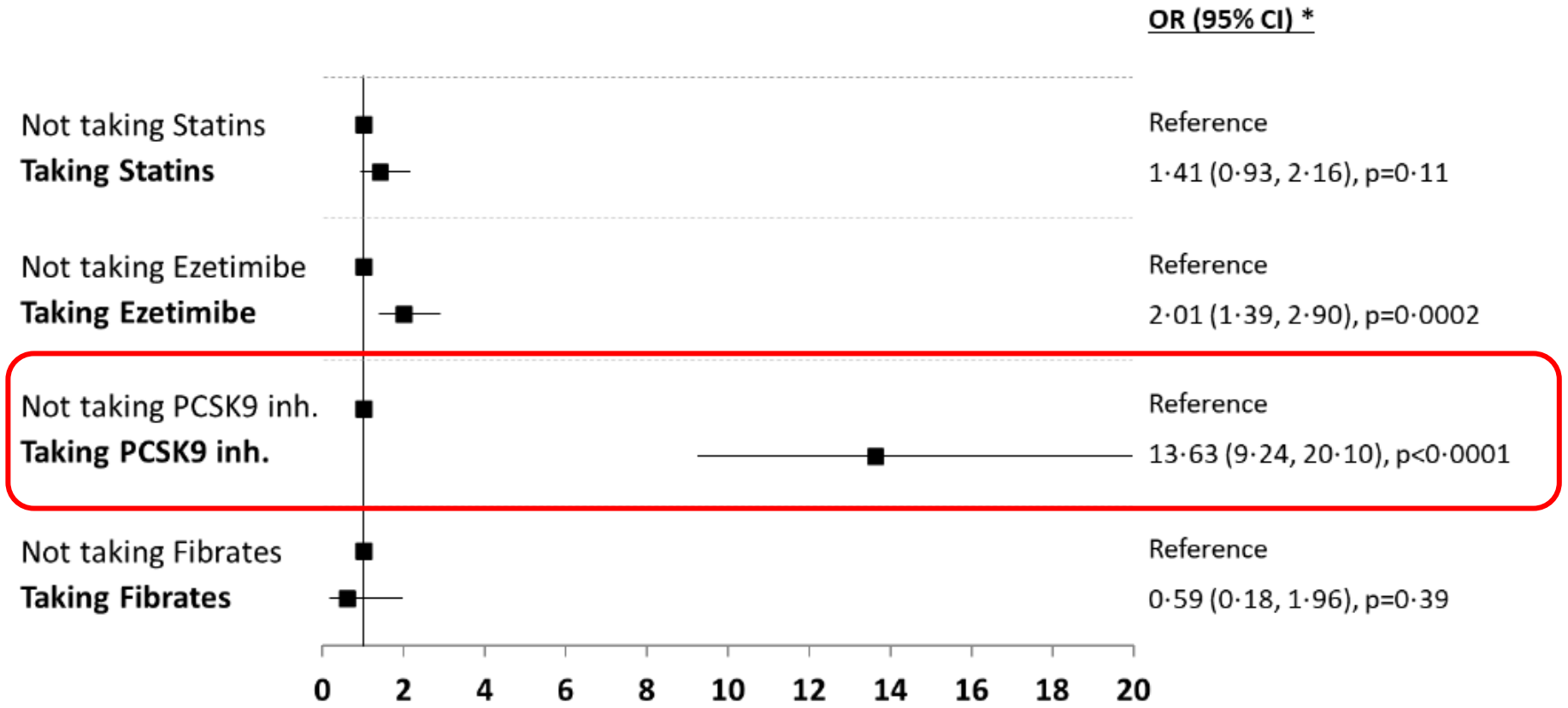
Association of type of lipid-lowering medication taking with having an LDL-C <1.4 mmol/L



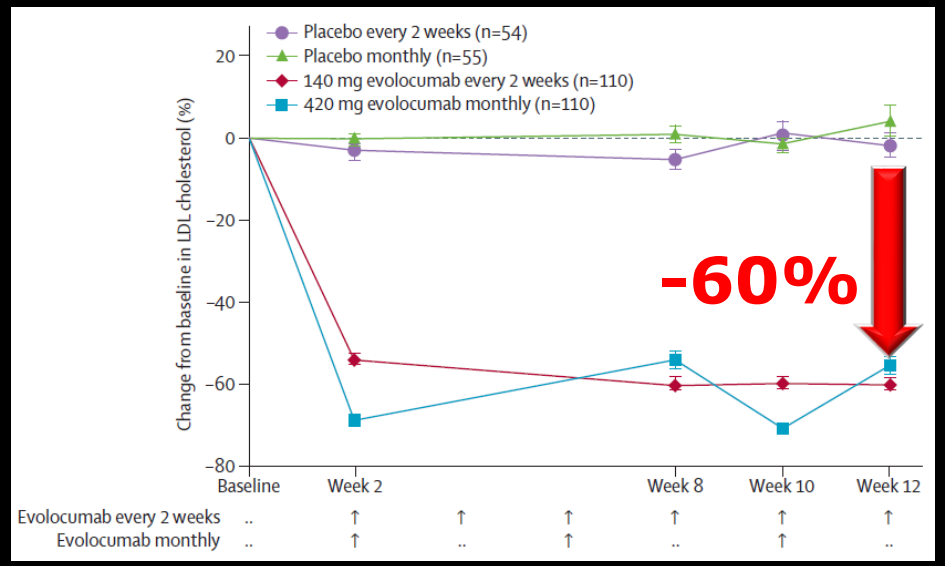
X13.6

PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial

Frederick J Raal, Evan A Stein, Robert Dufour, Traci Turner, Fernando Civeira, Lesley Burgess, Gisle Langslet, Russell Scott, Anders G Olsson, David Sullivan, G Kees Hovingh, Bertrand Cariou, Ioanna Gouni-Berthold, Ransi Somaratne, Ian Bridges, Rob Scott, Scott M Wasserman, Daniel Gaudet, for the RUTHERFORD-2 Investigators*

- **329 patients** with heterozygous familial hypercholesterolaemia
- **LDL-C≥ 100 mg/dl**
- **Evolocumab 140 mg every 2 weeks**
- **Evolocumab 420 mg monthly**

Mean % change from baseline in LDL-C



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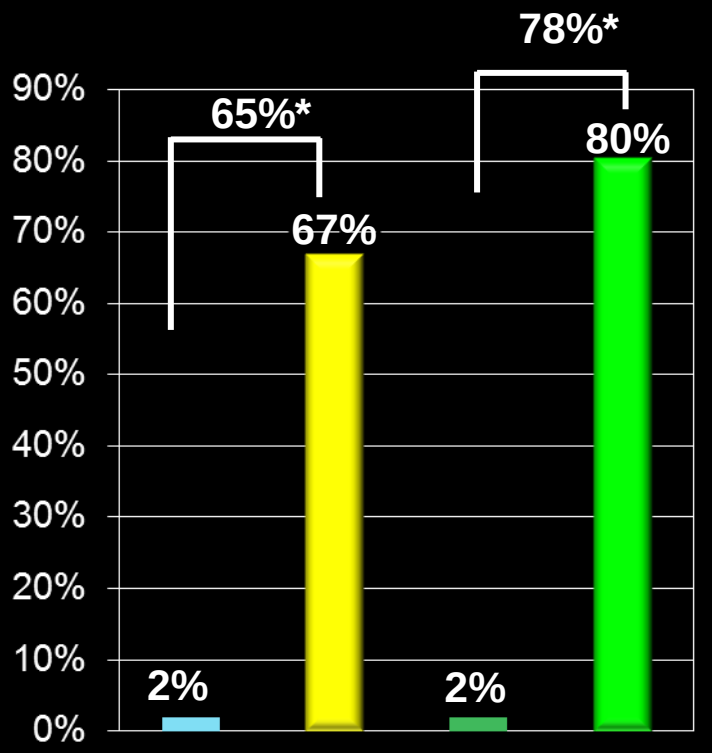
LDL-C Goal Achievement < 70 mg/dL
Weeks 10 and 12



Placebo Q2W (N = 54) **Evolocumab 140 mg Q2W (N = 110)**
Placebo QM (N = 55) **Evolocumab 420 mg QM (N = 110)**

*P<0.0001 evolocumab treatment difference vs placebo

The Lancet, 385:331-340, 2015

Efficacy and Safety of the PCSK9 Monoclonal Antibody Alirocumab versus Placebo in 1257 Patients with Heterozygous Familial Hypercholesterolaemia: Analyses up to 78 Weeks from Four ODYSSEY Trials - ESC 2015

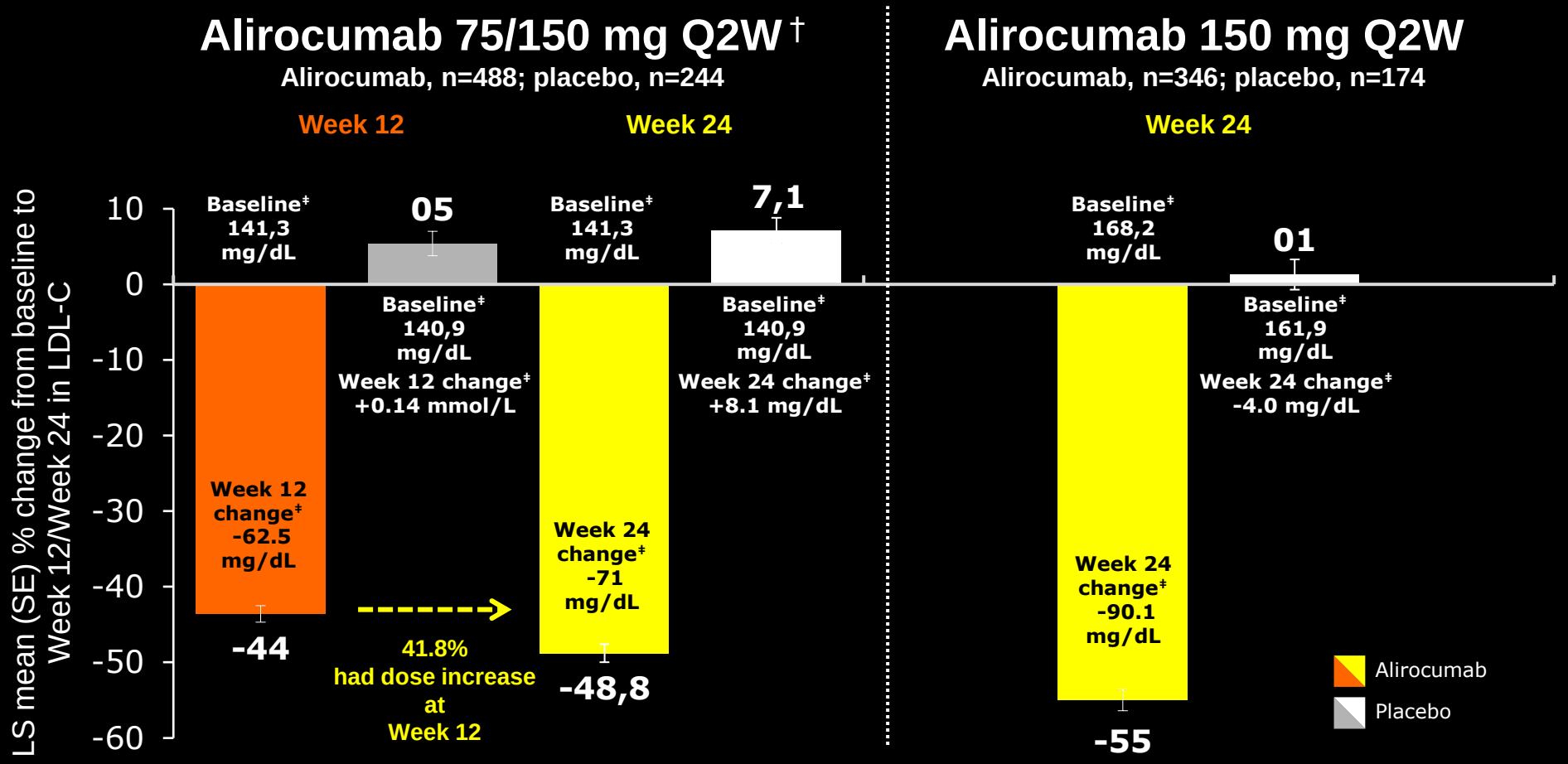
John J.P. Kastelein[1], Michel Farnier[2], G. Kees Hovingh[1], Gisle Langslet[3], Marie T. Baccara-Dinet[4], Daniel A. Gipe[5], Umesh Chaudhari[6], Jian Zhao[7], Christelle Lorenzato[8], Henry N. Ginsberg[9]

[1]Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [2]Lipid Clinic, Point Médical, Dijon, France; [3]Lipid Clinic, Oslo University Hospital, Oslo, Norway; [4]Sanofi, Montpellier, France; [5]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [6]Sanofi, Bridgewater, NJ, USA; [7]Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA; [8]Sanofi, Paris, France; [9]Columbia University, New York, NY, USA

This study was funded by Sanofi and Regeneron Pharmaceuticals, Inc.

Kastelein JJP, J Clin Lipidol Mar - Apr;11(2):507-514, 2017

LDL-C Reduction with Alirocumab in Both Pooled Study Groups (ITT)



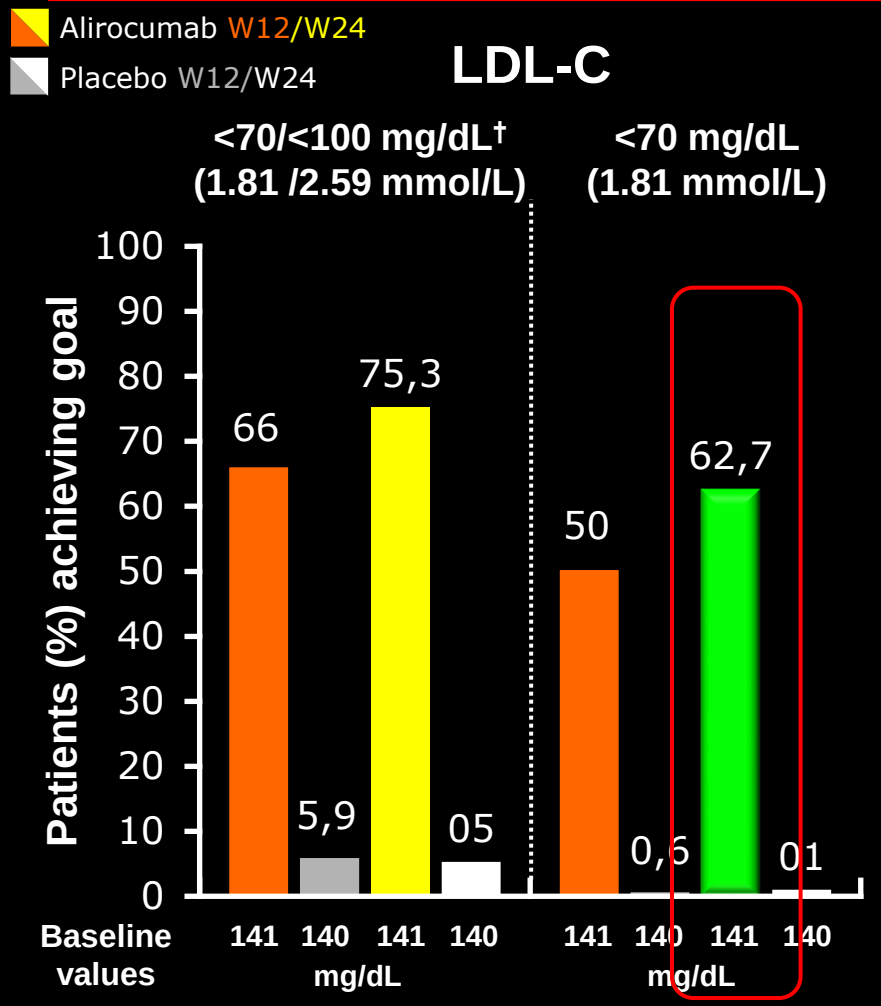
All % changes *P*<0.0001 versus placebo

†75 mg Q2W increased to 150 mg Q2W at Week 12 if LDL-C levels at Week 8 were ≥1.81 mmol/L [70 mg/dL].
‡Baseline values are means; Week 12 and Week 24 are LS means taken from mixed-effect model with repeated measures analysis.
LS, least squares; SE, standard error.
Figure shows ITT analysis performed on ITT population.

Kastelein JJP, J Clin Lipidol Mar - Apr;11(2):507-514, 2017

Goal Attainment (ITT)

Pool of FH I and II Studies
(Alirocumab 75/150 mg Q2W)

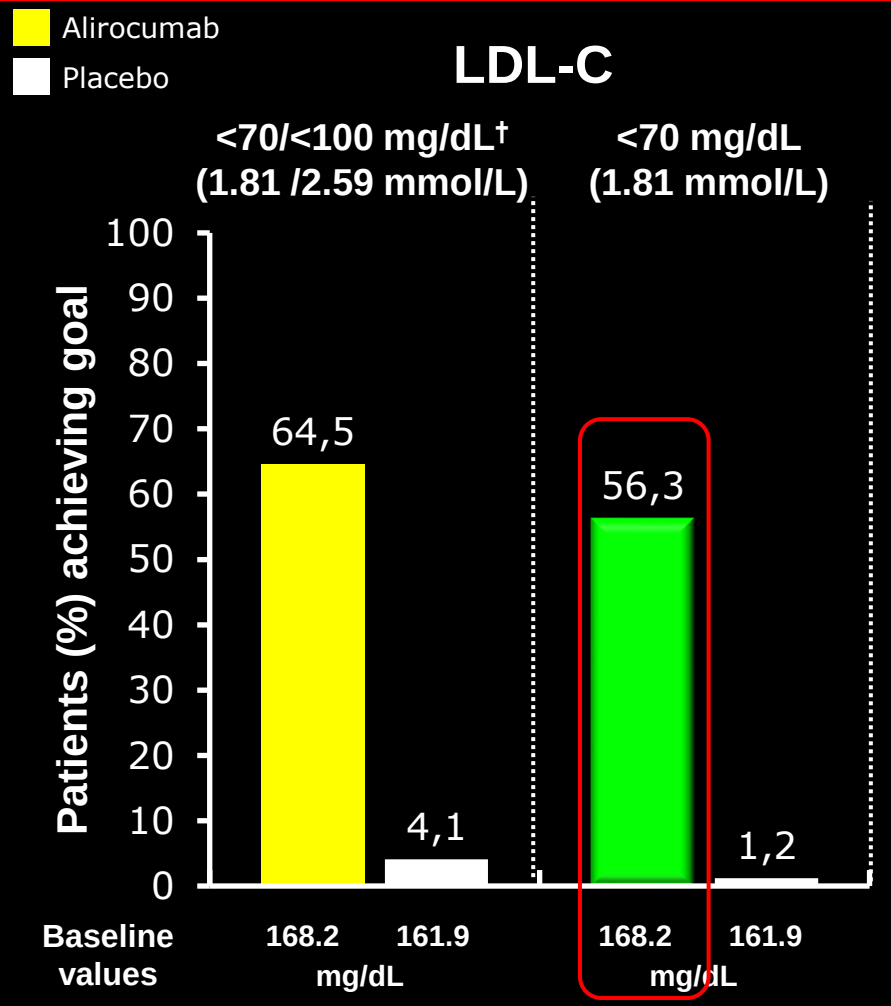


All *P*<0.0001 versus placebo

Alirocumab dose 75 mg Q2W increased to 150 mg Q2W in 41.8% of patients at Week 12 as their LDL-C levels at Week 8 were ≥1.81 mmol/L [70 mg/dL];
†Depending on CV risk;
Figure shows ITT analysis performed on ITT population.

Goal Attainment (ITT)

Pool of LONG TERM (HeFH) and HIGH FH
(Alirocumab 150 mg Q2W)



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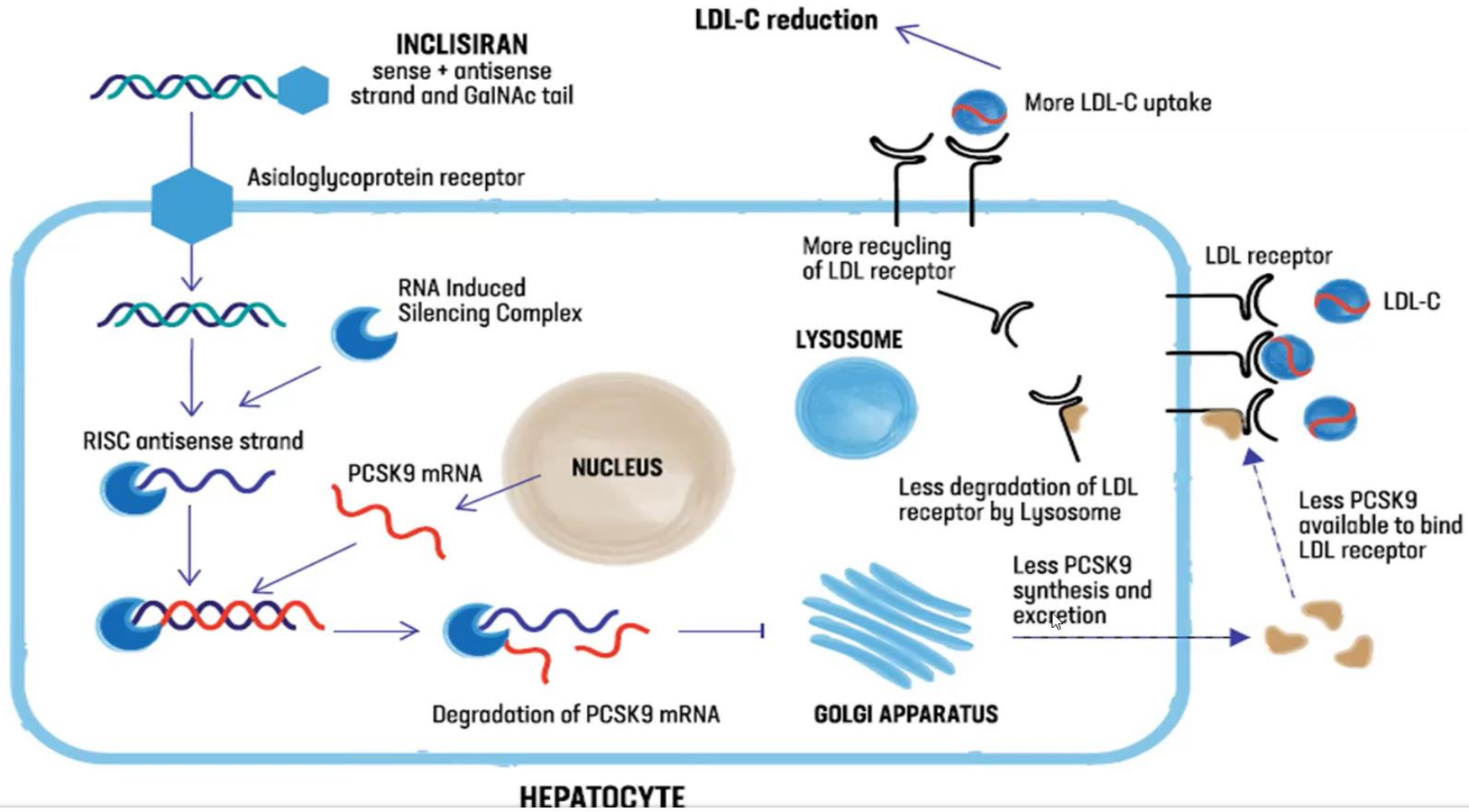
PCSK9 Pharmacological inhibition

Inclisiran: Mechanism of action



Sinning et al. Current Cardiology Reports 2020; 22:176

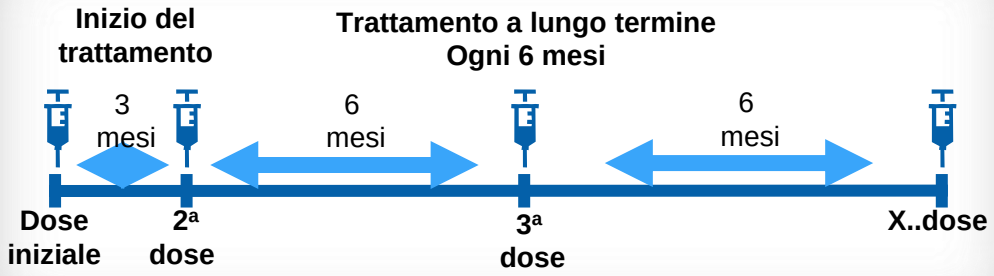
Trattamento con inclisiran

Dosaggio e somministrazione

Formulazione[1,2]

- Siringa preriempita
- Ogni siringa preriempita contiene inclisiran sodico equivalente a 284 mg di inclisiran in 1,5 mL di soluzione
- Conservazione a temperatura ambiente

Regime posologico[1,2]



Sviluppo[1]

programma di sviluppo ORION per determinarne l'efficacia, la sicurezza e la tollerabilità

Somministrazione[1,2]

Uso sottocutaneo.

Inclisiran è somministrato tramite iniezione sottocutanea nell'addome; siti di iniezione alternativi comprendono il braccio o la coscia.

Ogni dose da 284 mg viene somministrata utilizzando una singola siringa preriempita.

Ogni siringa preriempita è solo monouso.

Inclisiran è destinato alla somministrazione da parte di un operatore sanitario.

1. Leqvio | European Medicines Agency (europa.eu EPAR Inclisiran/Leqvio 2. Smpc Incliriran/Leqvio

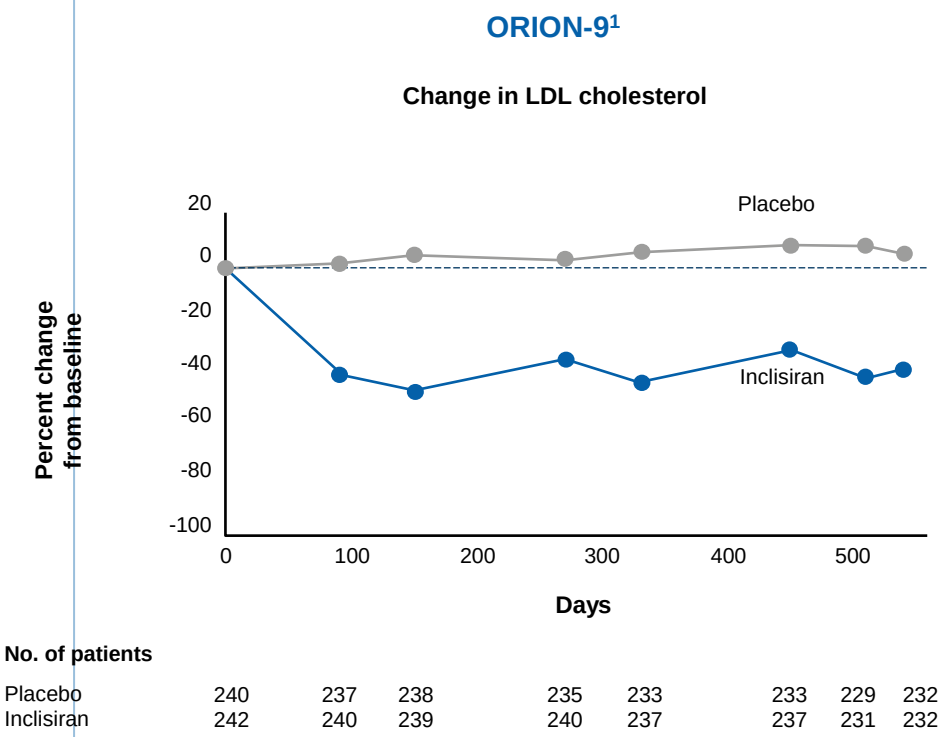
*Equivale a 284 mg di inclisiran

Studi ORION 9
Caratteristiche al basale dei pazienti arruolati[1]

Characteristic	ORION-9[1]
Population	**HeFH (n=482)**
ASCVD status (%)	27.4%
Average age (yr)	56
Gender (male)	47.1%
LDL-C	4.0 mmol/L (153.1 mg/dL)
Statin use (%)	90.5%
High intensity statin use (%)	73.9%
Ezetimibe use	52.9%
Diabetes mellitus	10%

Studi ORION 9
Inclisiran fornisce un'efficace e prolungata riduzione delle LDL-C per 18 .

Variazione percentuale LDL nel tempo (over time)



Between group difference

-47.9%
(*P*<0.001)

% of target-reached patients (LDL-C <70 mg/dl)[3]

ASCVD
Inclisiran: 62,5% of the patients
Placebo: 1,4% of the patients

1. Raal FJ, et al. N Engl J Med. 2020;382(16):1520-1530. .

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PCSK9 Inibitori
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INCLISIRAN*

SNODO TERAPEUTICO CHIAVE

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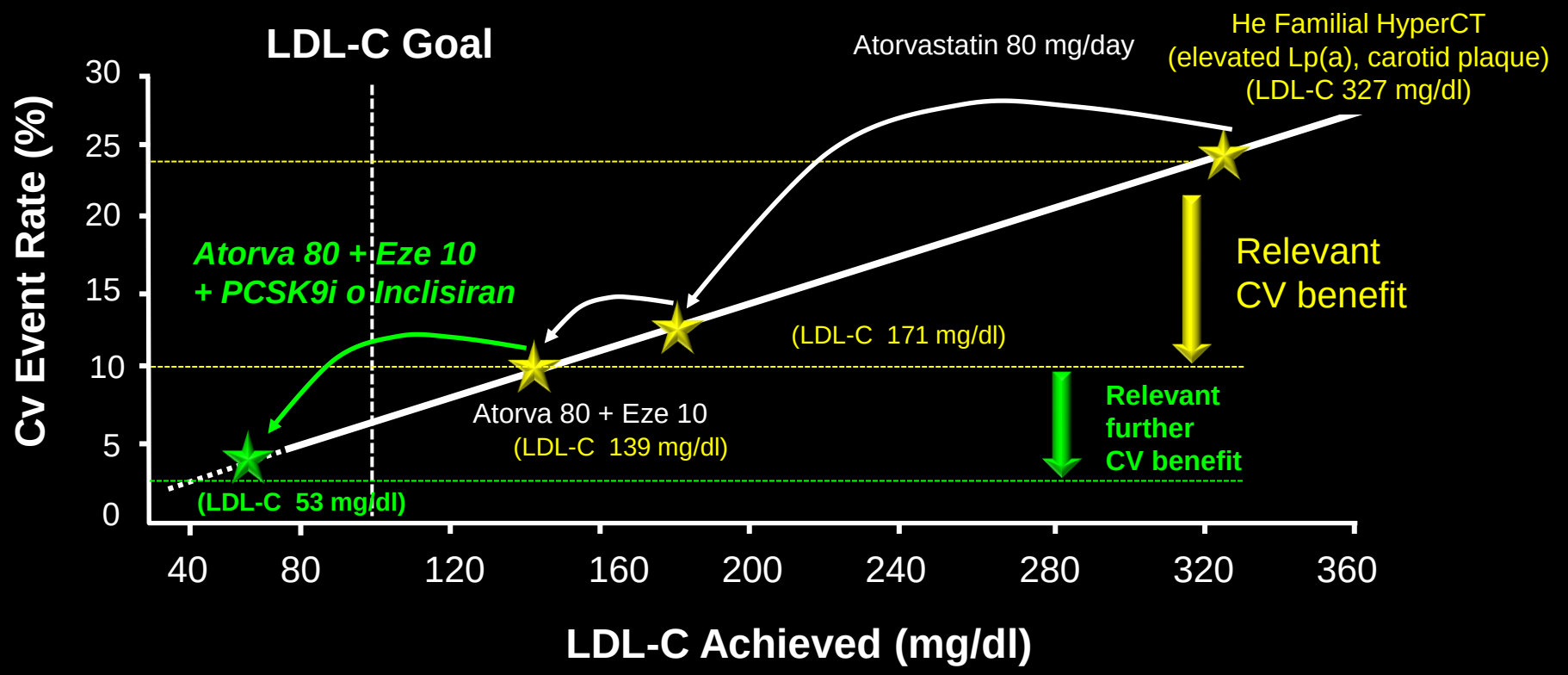
Settimanale/bisettimanale
Lomitapide

Monitorare lo stato di salute del pziente (test funzionalità epatica, status vascolare)

*Verosimilmente disponibile nel 2022

PCSK9 Inhibitors Are GAME CHANGER in the Prevention of (Premature) CV Event in Patients with Familial Hypercholesterolemia



PCSK9 Inhibition is a GAME CHANGER For Familial Hypercholesterolemia!!

* *LDL-C g* *as.*

Reiner Z et al. Eur Heart J 2011;32:1769-818

Ipercolesterolemia Familiare

E’ necessario e opportuno uno spostamento dell’attenzione nei riguardi dell’approccio terapeutico dei pazienti HeFH e HoFH:

Si scrive: terapia ipocolesterolemizzante

Si legge: **anni (molti) di vita guadagnati e qualità di vita migliorata**