LDL in the 2020's: How low is too low?

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Overview

- Unmet need
- Rationale for earlier lipid lowering
- Mendelian randomization and effects of lifelong LDL lowering
- Use of PCSK9 inhibitors
- Appropriate to use more ezetimibe
- What target should we aim for?

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PCSK9 inhibitors and other LDL modifying treatments

- There has been no major advance in the management of elevated LDL since 19th November, 1994 (Ezetimibe 2016)
- Until recently no lipid-modifying therapy has been demonstrated to provide a clinical benefit:
  fibrates, niacin, CETP inhibitors
- Should we focus solely on evermore aggressive LDL reduction (<1.4mmol/L from IMPROVE- IT with ezetimibe)

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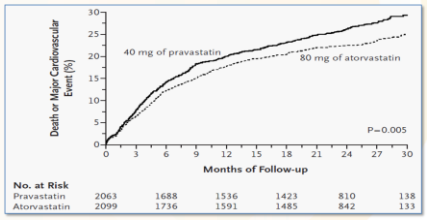
High-dose statins don't abolish risk and there is unmet need – PROVE-IT



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Canon et al. N Engl J Med 2004;350:1495-504

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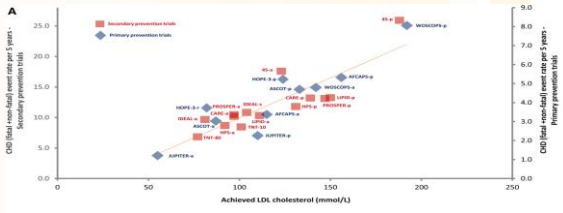
Linear association between achieved low-density lipoprotein cholesterol (LDL-C) level and event rate



Ference BA et al. Eur Heart J 2017;0:1-4

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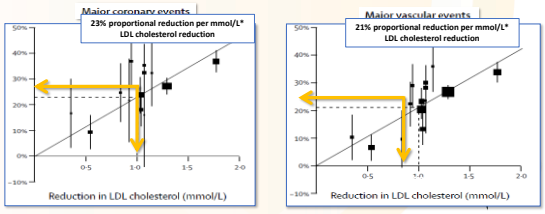
Relation between Proportional Reduction in Incidence of Major Events and Mean Absolute LDL Cholesterol Reduction at 1 Yr

Prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins



CTT Collaboration including White HD; Lancet 2005;366:1267-78

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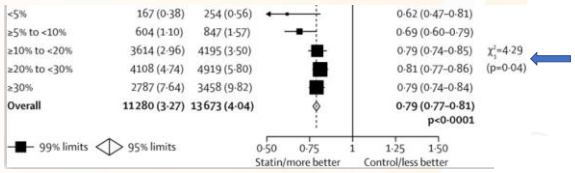
Can absolute risk identify those who will benefit from statins

Baseline Estimated 5-Year Risk: coronary death, MI, stroke revascularisation



CTT Collaboration. Including White HD; Lancet. 2012; 380: 581

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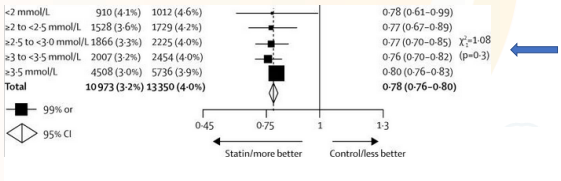
How effective is LDL for identification of those who will benefit from statins

Baseline LDL and coronary death, MI, stroke, revascularisation



CTT Collaboration including White HD; Lancet. 2010;376:1670

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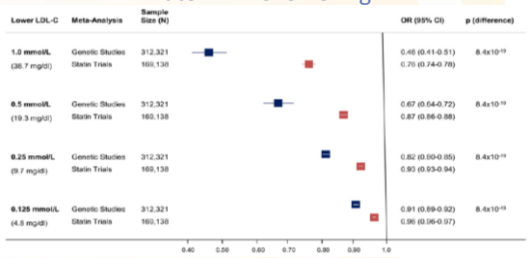
Comparative CHD risk reduction with earlier and later LDL-C lowering



Ference BA et al. Eur Heart J 2017;0:1-4

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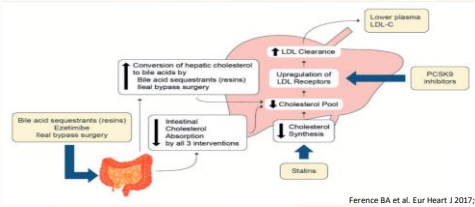
All therapies that lower LDL act by up-regulating LDL receptors and increase LDL clearance



Ference BA et al. Eur Heart J 2017;0:1-4

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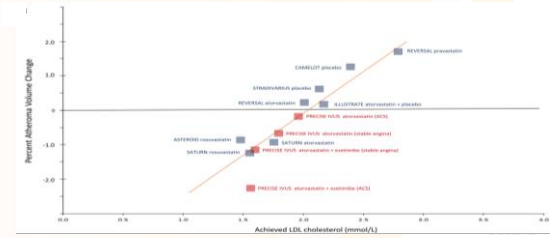
Linear association between achieved low-density lipoprotein cholesterol (LDL-C) level and progression of atherosclerosis



Ference BA et al. Eur Heart J 2017;0:1-4

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The ODYSSEY OUTCOMES Trial: Topline Results Alirocumab in Patients After Acute Coronary Syndrome

Gregory G. Schwartz, Michael Szarek, Deepak L. Bhatt, Vera Bittner, Rafael Diaz, Jay Edelberg, Shaun G. Goodman, Corinne Hanotin, Robert Harrington, J. Wouter Jukema, Guillaume Lecorps, Angèle Moryusef, Robert Pordy, Matthew Roe, Harvey D. White, Andreas Zeiher, **Ph. Gabriel Steg**
On behalf of the ODYSSEY OUTCOMES Investigators and Committees

American College of Cardiology – 67th Scientific Sessions
March 10, 2018

ClinicalTrials.gov: NCT01663402

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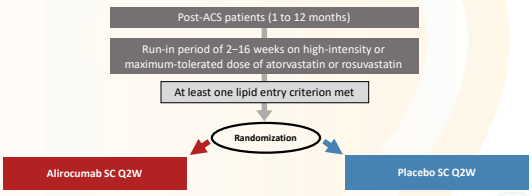
ODYSSEY: Treatment Assignment



Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

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Schwartz GG, et al. Am Heart J 2014;168:682-689.e1

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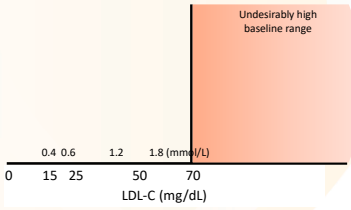
ODYSSEY: A Target Range for LDL-C



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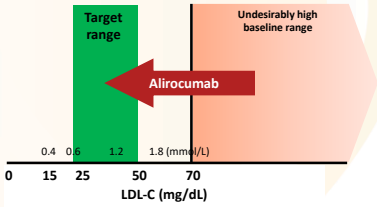

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Schwartz GG, et al. Am Heart J 2014;168:682-689.e1

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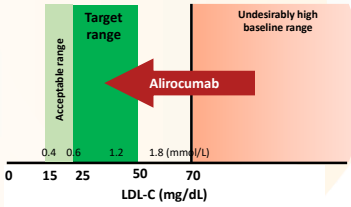
A Target Range for LDL-C



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Schwartz GG, et al. Am Heart J 2014;168:682-689.e1

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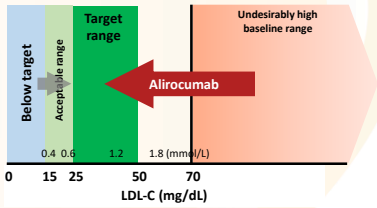
A Target Range for LDL-C

We attempted to maximize the number of patients in the target range and minimize the number below target by blindly titrating alirocumab (75 or 150 mg SC Q2W) or blindly switching to placebo.



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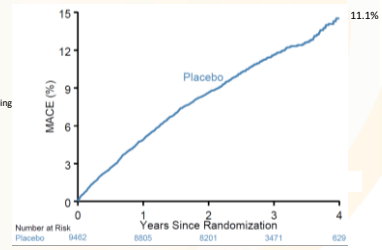
ODYSSEY: Primary Efficacy Endpoint: MACE

MACE: CHD death, non-fatal MI, ischaemic stroke, or unstable angina requiring hospitalization



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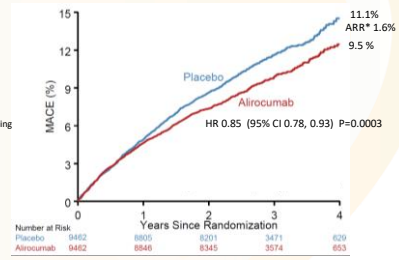

*Based on cumulative incidence

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ODYSSEY: Primary Efficacy and Components

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
MACE	**903 (9.5)**	**1052 (11.1)**	**0.85 (0.78, 0.93)**	**0.0003**
CHD death	205 (2.2)	222 (2.3)	0.92 (0.76, 1.11)	0.38
Non-fatal MI	626 (6.6)	722 (7.6)	0.86 (0.77, 0.96)	0.006
Ischaemic stroke	111 (1.2)	152 (1.6)	0.73 (0.57, 0.93)	0.01
Unstable angina	37 (0.4)	60 (0.6)	0.61 (0.41, 0.92)	0.02

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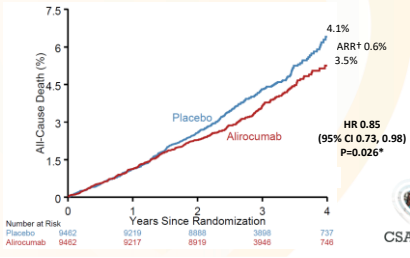
All-Cause Death



*Nominal P-value
†Based on cumulative incidence

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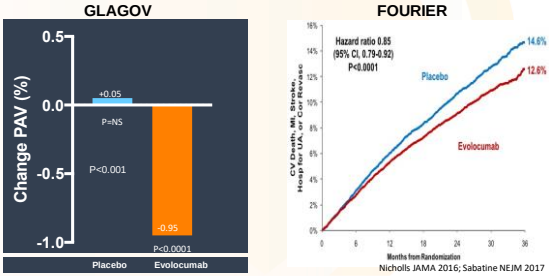
Benefit of Evolocumab on Plaque and Cardiovascular Outcomes



Nicholls JAMA 2016; Sabatine NEJM 2017

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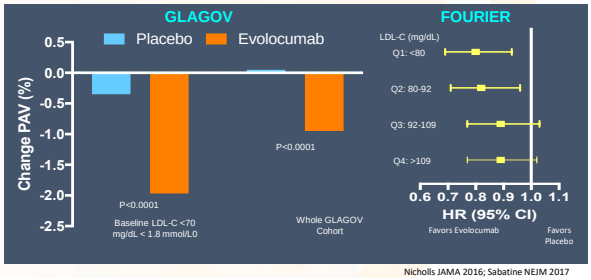
Persistent Benefit of Evolocumab at Low Baseline LDL-C



Nicholls JAMA 2016; Sabatine NEJM 2017

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Reduction of Type 1 and Type 2 Myocardial Infarctions in Patients treated with Alirocumab: Insights from the ODYSSEY Trial

Harvey D White, Ph Gabriel Steg, Michael Szarek, Deepak L Bhatt, Vera A Bittner, Rafael Diaz, Jay M Edelberg, Andrejs Erglis, Shaun G Goodman, Corinne Hanotin, Robert A Harrington, J. Wouter Jukema, Renato D Lopes, Kenneth W Mahaffey, Angele Moryusef, Robert Pordy, Matthew T Roe, Piyamitr Sritara, Pierluigi Tricoci, Andreas M. Zeiher, and Gregory G Schwartz; for the ODYSSEYOUTCOMES Investigators

European Heart Journal (2019) 0, 1–9 doi:10.1093/eurheartj/ehz299
FastTrack Clinical Research

ClinicalTrials.gov: NCT01663402

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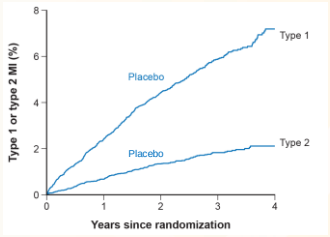
First occurrence of type 1 or 2 MI, and effects of alirocumab over time



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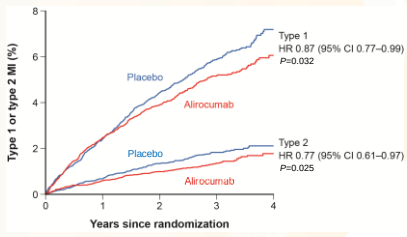
First occurrence of type 1 or 2 MI, and effects of alirocumab over time



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Types of MI and effects of alirocumab

	Alirocumab	Placebo	Treatment HR (95% CI)	P
	Patients, n (%)			
Any MI	639 (6.8)	744 (7.9)	0.85 (0.77–0.95)	0.003
Universal classification				
Type 1	463 (4.9)	528 (5.6)	0.87 (0.77–0.99)	0.032
Type 2	125 (1.3)	162 (1.7)	0.77 (0.61–0.97)	0.025
Type 3	2 (<0.1)	0	–	–
Type 4A	22 (0.2)	28 (0.3)		
Type 4B	50 (0.5)	46 (0.5)	**0.94 (0.72–1.22)**	**0.62**
Type 4C	37 (0.4)	42 (0.4)		
Type 5	2 (<0.1)	3 (<0.1)	–	–

ODYSSEY OUTCOMES

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Conclusions

- In patients with recent ACS and persistent dyslipidemia despite intensive statin therapy, alirocumab reduced occurrence of both type 1 and type 2 MI:
  - Type 1 MI: treatment benefit appeared to increase over time
  - Type 2 MI: first data indicating that a lipid-lowering therapy can attenuate risk
  - Type 4 MI: No effect of alirocumab
- Effect of alirocumab primarily on larger MIs (biomarkers >3 x ULN)

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Optimal Physiologic LDL-C?

A Receptor-Mediated Pathway for Cholesterol Homeostasis

Michael S. Brown and Joseph L. Goldstein

The LDL-receptor studies lend experimental support to the epidemiologists' suggestion that the levels of plasma cholesterol usually seen in Western industrialized societies are inappropriately high (*9*). This support derives from knowledge of the affinity of the LDL receptor for LDL. The receptor binds LDL optimally when the lipoprotein is present at a cholesterol concentration of 2.5 mg/dl (*28*). In view of the 10-to-1 gradient between concentrations of LDL in plasma and interstitial fluid, a level of LDL-cholesterol in plasma of 25 mg/dl would be sufficient to nourish body cells with cholesterol (*118*). This is roughly one-fifth of the level usually seen in Western societies (Fig. 16) (*119*). Several lines of evidence suggest that plasma levels of LDL-cholesterol in the range of 25 to 60 mg/dl (total plasma cholesterol of 110 to 150 mg/dl) might indeed be physiologic for human beings.

Adapted from Nobel Prize Lecture, Stockholm, Sweden, 1985. Science 1986:232:34

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What LDL should we aim for after ACS

- LDL is toxic and should be removed from the body if it is above the physiological range (0.8-1.2 mmol/L)
- If LDL levels were reduced to this range at the age of 30 the average life expectancy would be 105 years (CTT meta-analysis shows a 14% reduction in total mortality for each one mmol reduction in LDL

E Braunwald personal communication 2019

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What LDL-C should we aim for after ACS

- Should it be <1.6 mmol/L based on PROVE-IT
- Should it be <1.4 mmol/L based on IMPROVE-IT
- Should it be <0.8 mmol/L based on FOURIER
- Should it be <0.6 mmol/L based on ideal range target in ODYSSEY
- Should it be <0.6mmol/L based on Brown and Goldstein's physiological range

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What LDL should we aim for after ACS

Lower is better

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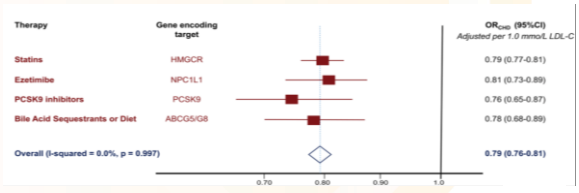
Effects of exposure to lower low-density lipoprotein cholesterol (LDL-C) by mechanism of LDL-C lowering



Ference BA et al. Eur Heart J 2017;0:1-4

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