Adding PCSK9i to Statins

Insights from GLACOV Trial

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Outline

- **Beside statins, do we need a new lipid lowering drug?**
- **Background on PCSK9 and PCSK9 mab**
- **Answer some questions**
- **GLACOV trial**

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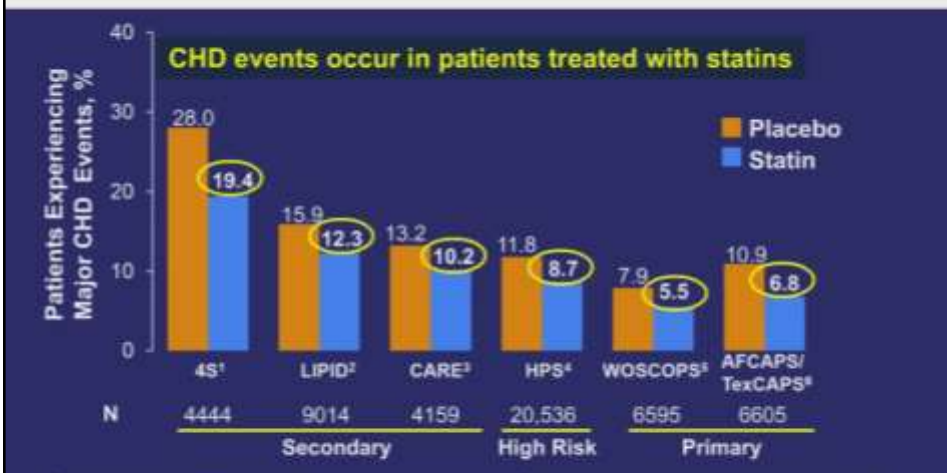
Statins

Risk reduction per 39-mg/dL LDL-C reduction while on statin therapy

	Risk reduction
MACE	24%
Coronary revascularization	24%
Stroke	15%
Death	10%

Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomized trial. Lancet 2010;376:1670–1681

Residual CVD Risk in Major Statin Trials



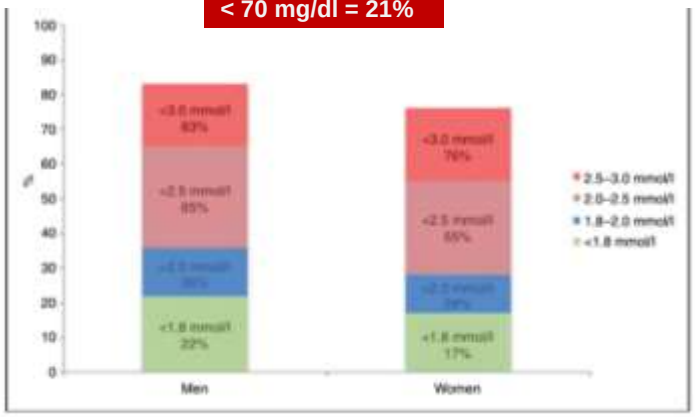
[1]4S Group. *Lancet*. 1994;344:1383-9.
[2]LIPID Study Group. *N Engl J Med*. 1998;339:1349-57.
[3]Sacks FM et al. *N Engl J Med*. 1996;335:1001-9.
[4]HPS Collaborative Group. *Lancet*. 2002;360:7-22.
[5]Shepherd J et al. *N Engl J Med*. 1995;333:1301-7.
[6] Downs JR et al. *JAMA*. 1998;279:1615-22.

4S=Scandinavian Simvastatin Survival Study; AFCAPS= Air Force Coronary Atherosclerosis Prevention Study (CAPS); CARE=Cholesterol and Recurrent Events; HPS=Heart Protection Study; LIPID= Long-term intervention with pravastatin in ischemic disease; TexCAPS=Texas CAPS; WOSCOPS=West of Scotland Coronary Prevention Study.

LDL-C goal achievement

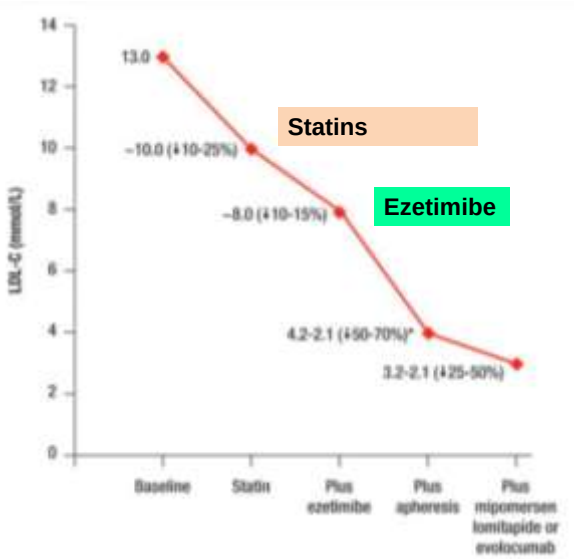
EUROASPIRE IV
CAD patients from 24 European countries

< 100 mg/dl = 58%
< 70 mg/dl = 21%



European Journal of Preventive Cardiology 2016, Vol. 23(6) 636–648

FH



Clin Res Cardiol Suppl 2012;7:7– 14

Improvement in LDL-cholesterol levels of patients with familial hypercholesterolemia: Can we do better? Analysis of results obtained during the past two decades in 1669 French subjects

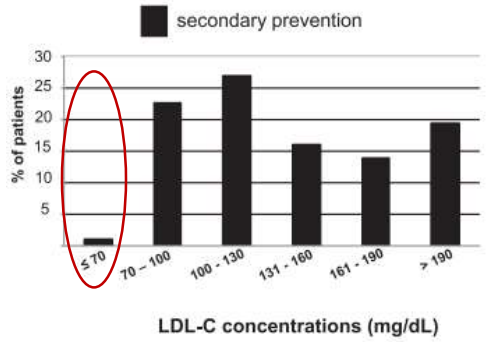
616 HeFH patients treated after 2005

- Goal of LDL –C < 100 mg/dl:
  - On maximum therapy (potent statin + other agent) : **18.8%**
- Goal of LDL-C < 100 and/or > 50% reduction: 33.5%

Atherosclerosis 234 (2014) 136e141

Improvement in LDL-cholesterol levels of patients with familial hypercholesterolemia: Can we do better? Analysis of results obtained during the past two decades in 1669 French subjects

616 HeFH patients treated after 2005



Atherosclerosis 234 (2014) 136e141

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- Beside statins, do we need new lipid lowering drug?
- **Background on PCSK9 mab**
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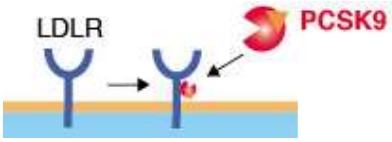
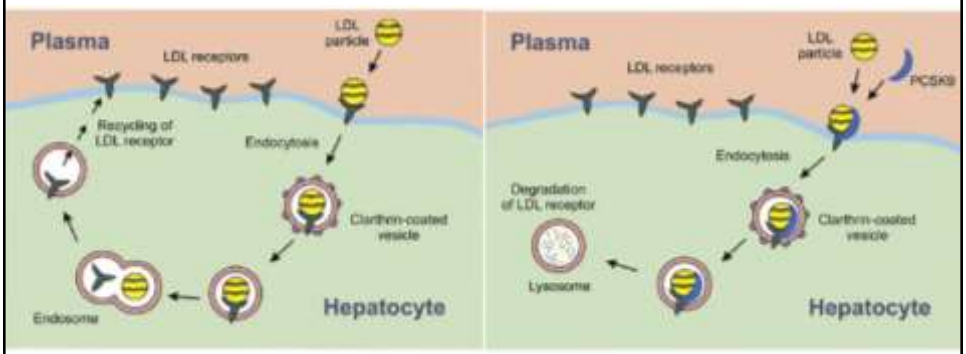
PCSK9

- A serine protease enzyme
- Produced mainly in hepatocytes
- Secreted in the plasma
- Binds to the extracellular domain of LDL-R



PCSK9



Recycled back

PCSK9 gene mutations

Gain of function mutation
FH (1%)

PCSK9 mabs

Table 2 PCSK9 Inhibitors in Late-Stage Development

Generic (trade) name/manufacturer	Clinical trials	Phase 3 clinical trial data available	FDA approval date	MAb type	Route	Dose
Evolocumab (Repatha) Amgen	OSLER PROFICIO; DESCARTES; MENDEL; GAUSS; RUTHERFORD; TESLA; FOURIER; LAPLACE; TAUSSIG; GLAGOV	Yes	Approved August 27, 2015	Fully human MAb	SC	140 mg every 2 weeks or 420 mg monthly
Alirocumab (Praluent) Sanofi-Aventis/ Regeneron	ODYSSEY series	Yes	Approved July 24, 2015	Fully human MAb	SC	75 mg every 2 weeks or 150 mg every 4 weeks

PCSK9 i: Studies

Table 4.1. Other Phase III studies that evaluated PCSK9 inhibitors

Drug (study)	Patient population	N, duration	Effect on LDL-C
Evolocumab (TESLA-B)[3]	Homozygous FH	49, 12 w	Δ −30.9% *vs.* placebo
Evolocumab (RUTHERFORD-2)[4]	Heterozygous FH	331, 12 w	Δ −59% to −66% *vs.* placebo for 2-weekly or monthly administration
Evolocumab (LAPLACE-2)[5]	HC	2,067, 12 w	Δ −63% to −75% *vs.* placebo for 2-weekly or monthly administration with moderate- or high-intensity statin
Evolocumab (GAUSS-2)[6]	Statin-intolerant	307, 12 w	Δ −63% to −75% *vs.* placebo, Δ −37% to −39% *vs.* ezetimibe, each for 2-weekly or monthly administration
Evolocumab (MENDEL-2)[7]	HC not previously on drug treatment	614, 12 w	Δ −55% to −57% *vs.* placebo, Δ −38% to −40% *vs.* ezetimibe, each for 2-weekly or monthly administration
Alirocumab (ODYSSEY-COMBO II)[8]	High CV risk on maximal statin therapy	707, 104 w	Δ −51% *vs.* baseline, Δ −30% *vs.* ezetimibe (each at week 24)
Alirocumab (ODYSSEY-FH I)[9]	Heterozygous FH on maximal statin ± other lipid-modifying therapy	486, 78 w	Δ −58% *vs.* ezetimibe
Alirocumab (ODYSSEY-FH II)[9]	Heterozygous FH on maximal statin ± other lipid-modifying therapy	249, 78 w	Δ −51% *vs.* ezetimibe

PCSK9 i: Effect on lipogram

	% Δ
LDL-C	↓ 40's-70's
Lp(a)	↓20-30%
HDL	↑ 5-10%
VLDL	↓5-20

PCSK9i: Indications

High risk patients:

- FH
- High CV risk

✓ Failed to achieve LDL-C target
✓ Adjunct to diet + maxim tolerated **statins**

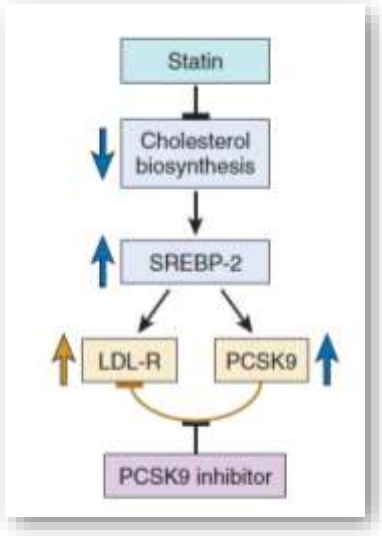
- **Statin intolerance**

Statins + PCSK9 i

Source: McKenney JM. Understanding PCSK9 and anti-PCSK9 therapies. J Clin Lipidol. 2015;9:170-86.

Int J Biol Sci. 2012;8(3):310-327

Statins increases PCSK9 levels



Int J Biol Sci. 2012;8(3):310-327

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- Beside statins, do we need new lipid lowering drug?
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- **Answer some questions**
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Uncertainties

- How safe is the chronic exposure to mabs?

Uncertainties

- How safe is the chronic exposure to mabs?
- How safe are the very low LDL-C levels achieved by PCSK9i?

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

Pooled Data From Randomized Trials

14 Trial; 3182 patients; median exposure = 78 weeks

	LDL-C ≥25 mg/dl (n = 2,371)	LDL-C <25 mg/dl (n = 811)	HR (95% CI) for LDL-C <25 vs. ≥25 mg/dl
Neurological events	4.4 (104)	2.5 (20)	0.53 (0.30–0.93)
Neurocognitive disorders	1.1 (25)	0.6 (5)	0.38 (0.13–1.09)
Musculoskeletal events	17.0 (403)	14.2 (115)	0.75 (0.59–0.97)
Diabetes mellitus or diabetic complications event (regardless of baseline status)	4.0 (94)	6.0 (49)	1.09 (0.72–1.65)
Diabetes mellitus or diabetic complication event (patients with diabetes at baseline)	9.2 (62)	12.0 (37)	1.05 (0.66–1.68)
Ophthalmologic events	2.0 (47)	1.6 (13)	0.64 (0.31–1.31)
Cataracts	0.8 (19)	2.6 (21)	3.4 (1.58–7.35)*
Hepatic disorders	3.0 (72)	2.0 (16)	1.01 (0.54–1.88)

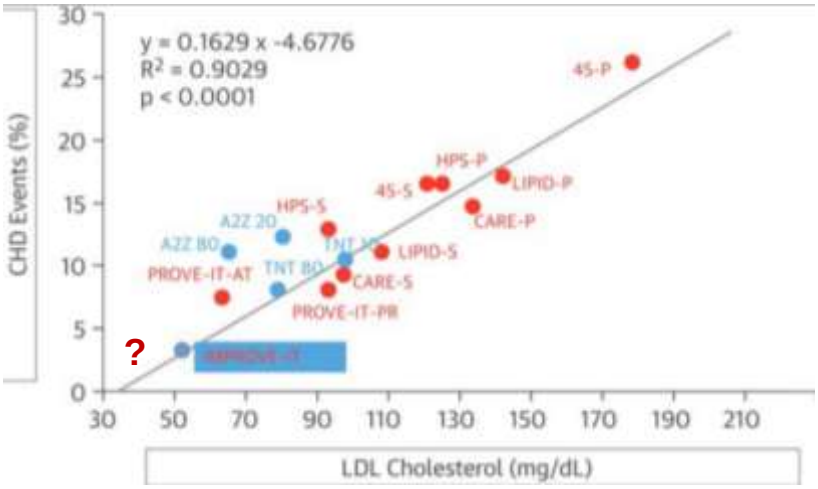
Values are % (n). *p = 0.0018. All other comparisons were not significant. For definitions of these categories, see

J Am Coll Cardiol 2017;69:471–82

Uncertainties

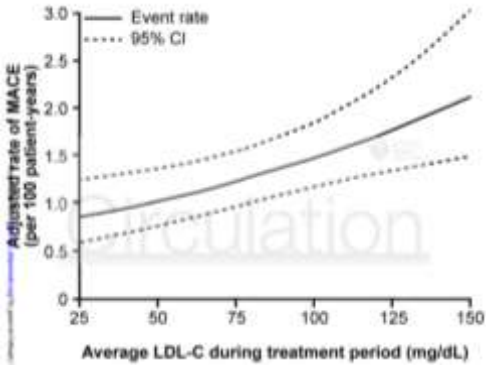
- How safe is the chronic exposure to mabs?
- How safe are the very low LDL-C levels achieved by PCSK9i?
- Are lower LDL-C levels associated with better CV outcomes?

The lower the LDL-C the better



The lower the LDL-C the better

A Pooled Analysis of 10 ODYSSEY Trials (4974 patients)



For each 39 mg/dL lower achieved LDL-C, MACE incidence fell by 24%

Circulation 2016; DOI: 10.1161/CIRCULATIONAHA.116.024604.

PCSK9i: CV outcome

2,341 patients treated with alirocumab for at least 52 weeks

Table 4.2. Cardiovascular events in the ODYSSEY LONG TERM study with alirocumab in patients at high cardiovascular risk receiving a statin[13]

	Alirocumab (n=1,550)	Placebo (n=788)	p
Non-fatal myocardial infarction	0.9	2.3	0.01
Death from coronary heart disease[b]	0.3	0.9	0.26
Fatal or non-fatal ischaemic stroke	0.6	0.3	0.35
Hospitalisation for CHF	0.6	0.4	0.76
Coronary revascularisation due to ischaemia	3.1	3.0	1
All positively adjudicated cardiovascular events[c]	0.46	0.51	0.68
Adjudicated major adverse cardiac events[a] (%)	1.7	3.3	0.02

RRR = 48%

Engl J Med 2015;372:1489-99

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

Treatment with a PCSK9 antibody should be considered in FH patients with CVD or with other factors putting them at very high-risk for CHD, such as other CV risk factors, family history, high Lp(a) or statin intolerance.	IIa	C
In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	IIb	C

European Heart Journal (2016) 37, 2999–3058

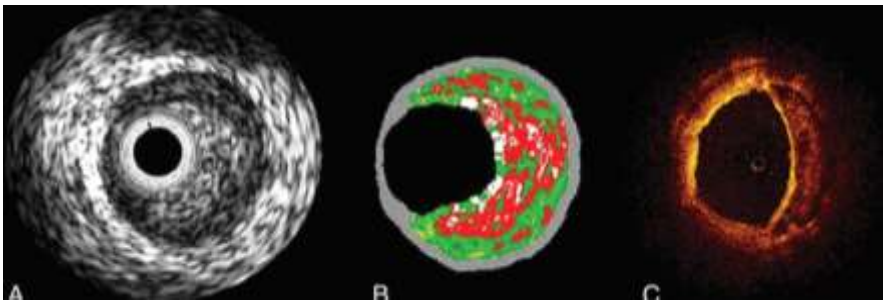
PCSK9i: Long term CV events

Name of study	Monoclonal antibody	Patient population	Study objectives and follow-up period
FOURIER	Evolocumab	Clinical CVD, high risk of recurrent CVD event, and LDL-C level ≥70 mg/dL or non-HDL-C ≥100 mg/dL (no specification regarding statin therapy)	To assess the effect of evolocumab every 2 or 4 weeks plus a statin vs. placebo plus a statin on major CVD events (CVD death, nonfatal myocardial infarction, unstable angina requiring hospitalization, stroke, or coronary revascularization), at 5 years
ODYSSEY OUTCOMES	Alirocumab	Recent (in the past 4–16 weeks) acute coronary syndrome event requiring hospitalization	To compare the effect of alirocumab vs. placebo on CVD events (cardiovascular death, nonfatal myocardial infarction, fatal and non-fatal ischaemic stroke, and unstable angina requiring hospitalization), for up to 64 months

Uncertainties

- How safe is the chronic exposure to mabs?
- How safe are the very low LDL-C levels achieved by PCSK9i?
- Are lower LDL-C levels associated with better CV outcomes?
- What is the effect of PCSK9i on coronary plaques progression?

Plaque Progression



Plaque progression and CV outcome

6 IVUS studies with > 4000 pts; FU: 21 months

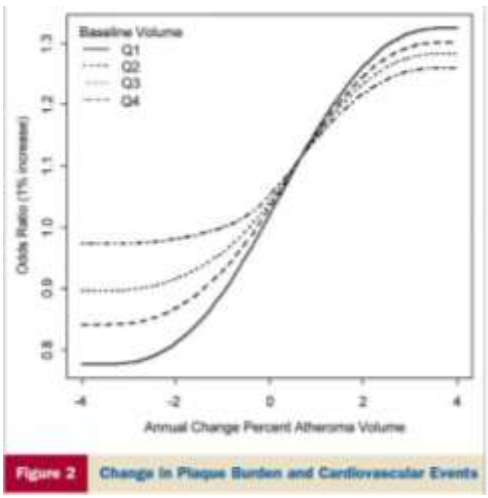


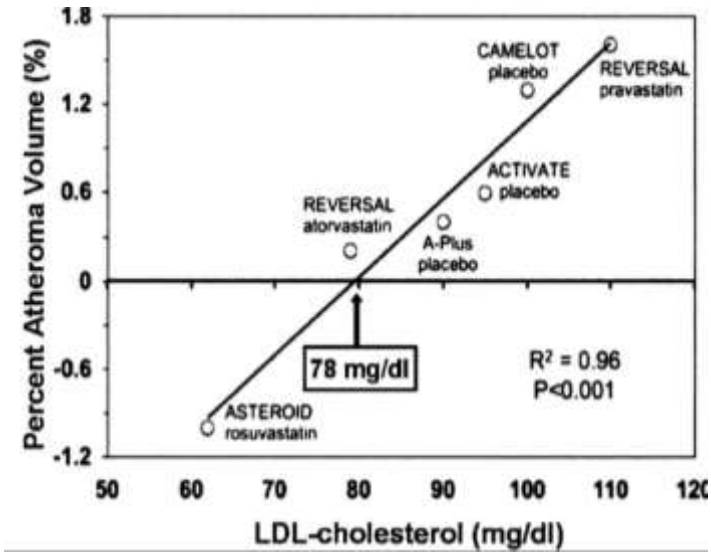
Figure 2 Change in Plaque Burden and Cardiovascular Events

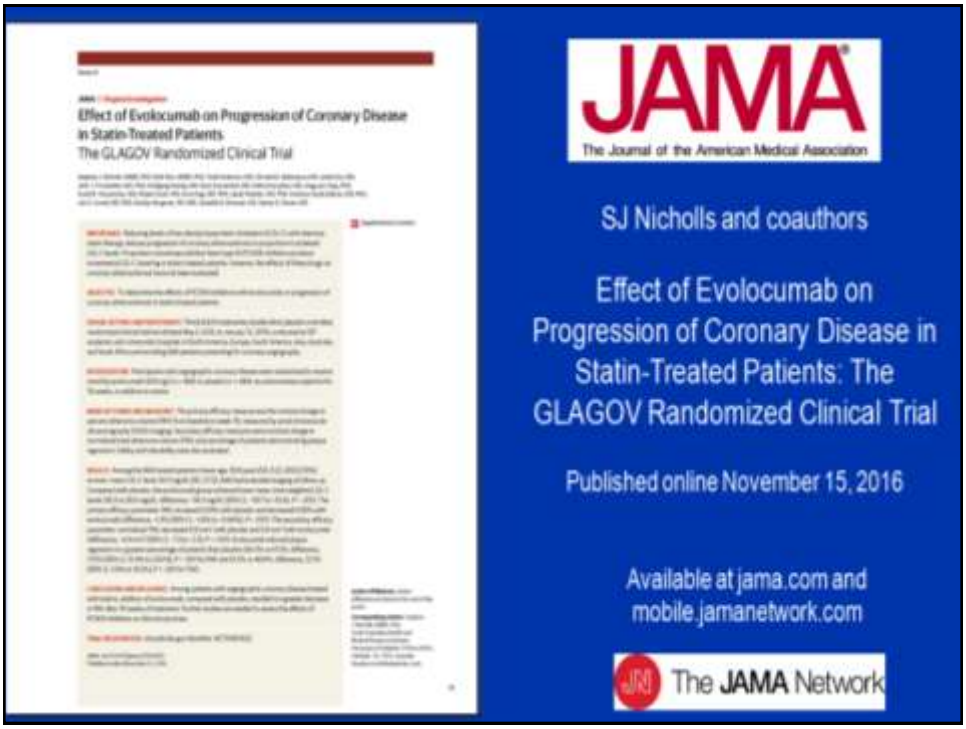
Patients with MACE:
0.95% ↑ in plaque volume

Patients without MACE:
0.46% ↑ in plaque volume

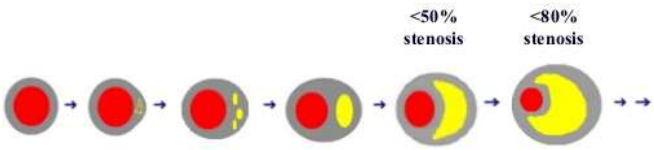
J Am Coll Cardiol 2010;55:2399–407

The lower the LDL , the slower the Plaque Progression





Seymour Glagov
1925-2008



Luminal area is not endangered until more than 40% of internal elastic lamina is destructed and occupied by plaque

968 patients at 197 global centers with symptomatic CAD and other high risk features. Coronary angiography showing 20-50% stenosis in a target vessel

Stable, optimized statin dose for 4 weeks with LDL-C >80 mg/dL or 60-80 mg with additional high risk features

Intravascular ultrasound via motorized pullback at 0.5 mm/sec through >40 mm segment

Statin monotherapy

18 months treatment

Statin plus monthly SC evolocumab 420 mg

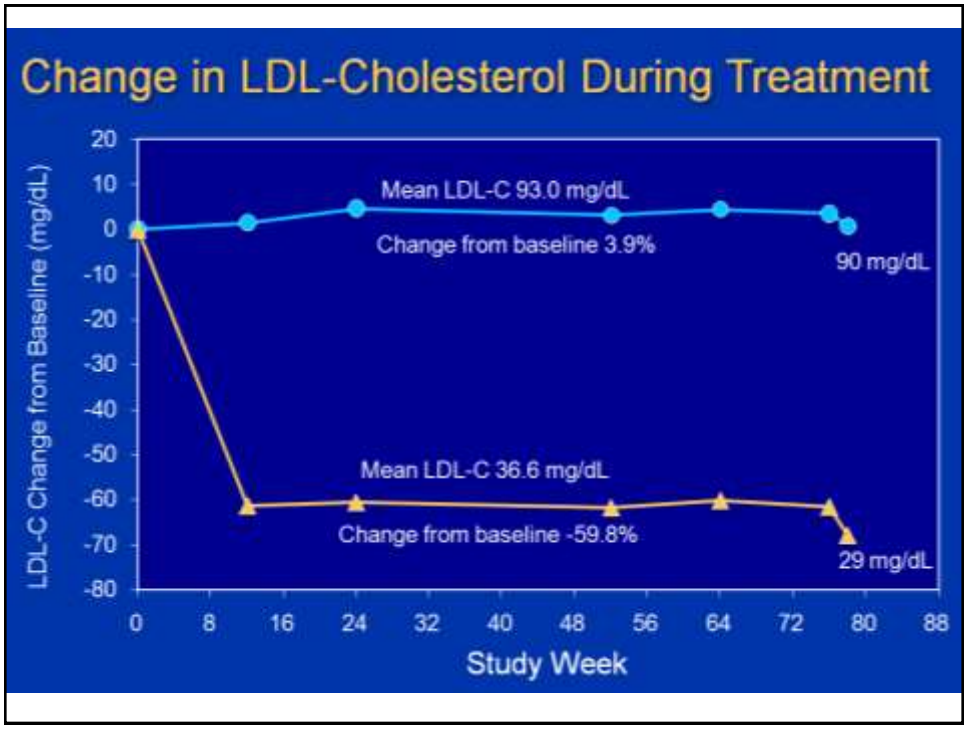
61 patients did not complete

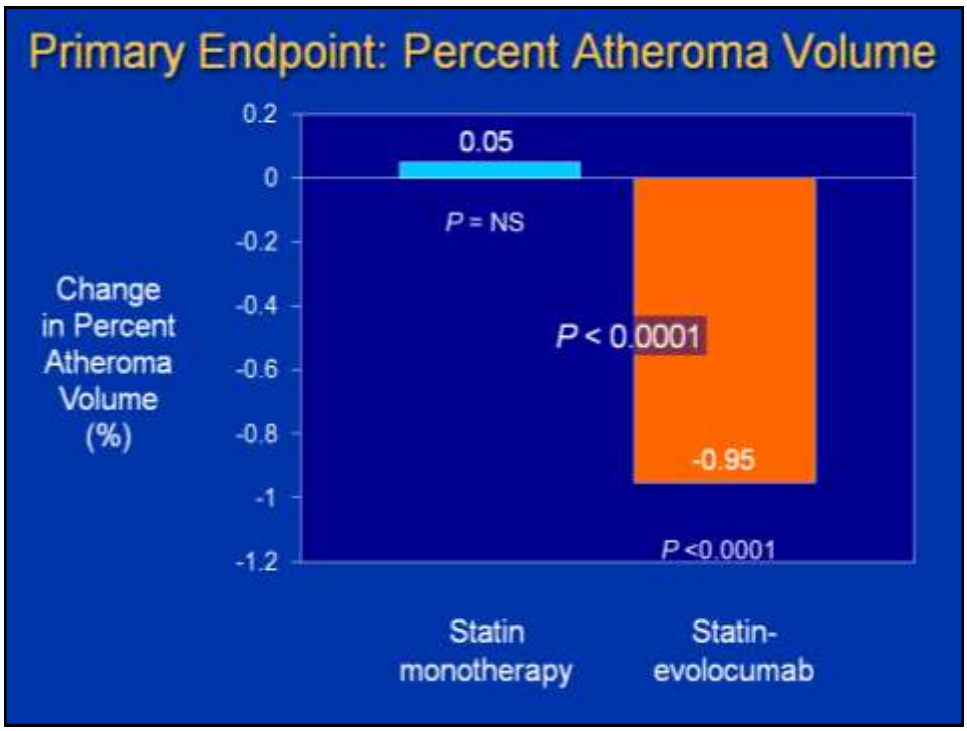
61 patients did not complete

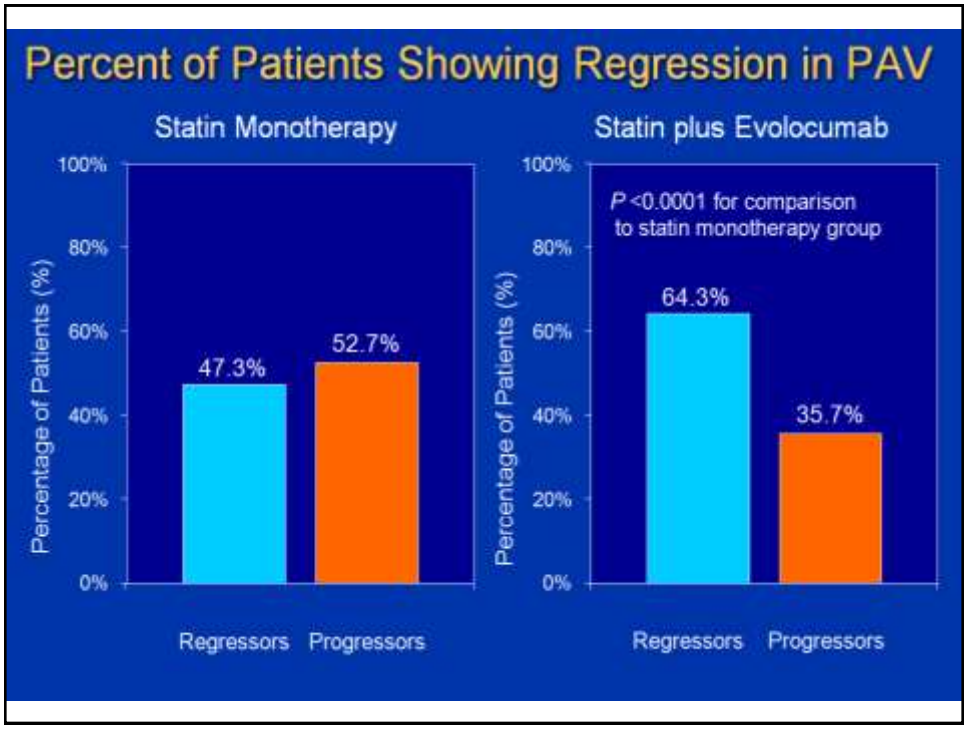
423 statin completers

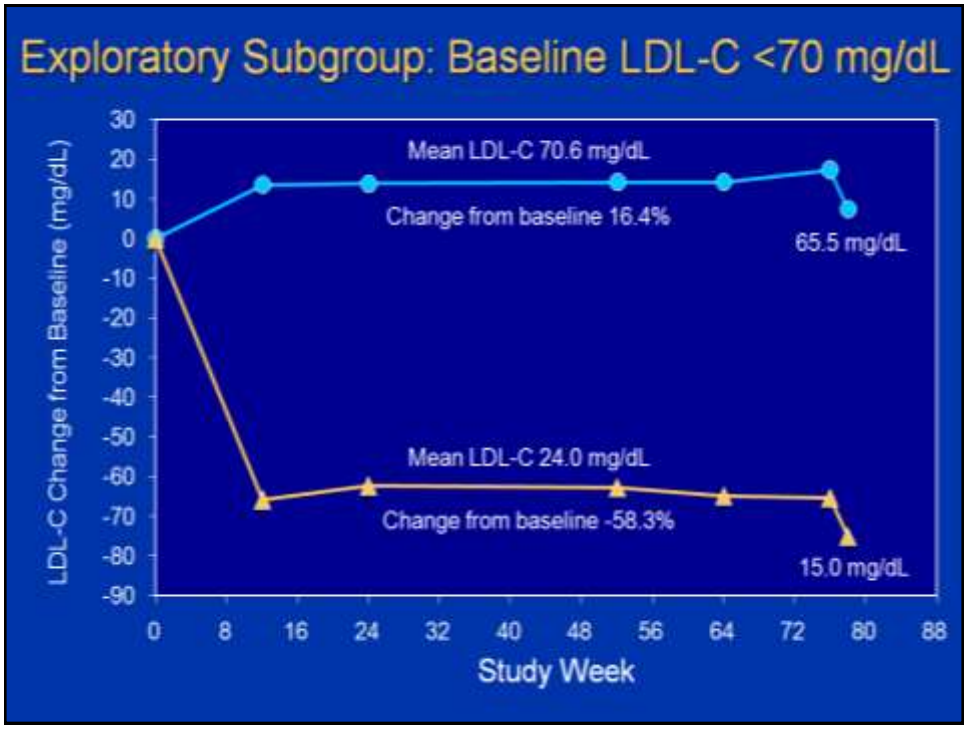
423 evolocumab completers

Follow-up IVUS of originally imaged "target" vessel (n=846)

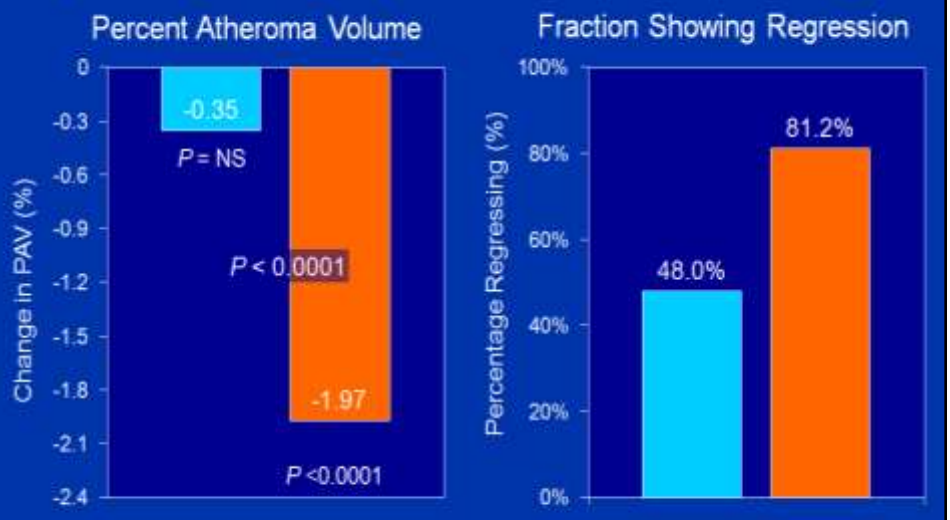

Change in LDL-Cholesterol During Treatment
LDL-C Change from Baseline (mg/dL)
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
Mean LDL-C 93.0 mg/dL
Change from baseline 3.9%
90 mg/dL
Mean LDL-C 36.6 mg/dL
Change from baseline -59.8%
29 mg/dL
0
8
16
24
32
40
48
56
64
72
80
88
Study Week


Primary Endpoint: Percent Atheroma Volume
Change in Percent Atheroma Volume (%)
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
0.05
P = NS
P < 0.0001
-0.95
P <0.0001
Statin monotherapy
Statin-evolocumab


Percent of Patients Showing Regression in PAV
Statin Monotherapy
Statin plus Evolocumab
Percentage of Patients (%)
100%
80%
60%
40%
20%
0%
47.3%
52.7%
Regressors
Progressors
P <0.0001 for comparison to statin monotherapy group
64.3%
35.7%


Exploratory Subgroup: Baseline LDL-C <70 mg/dL
LDL-C Change from Baseline (mg/dL)
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
Mean LDL-C 70.6 mg/dL
Change from baseline 16.4%
65.5 mg/dL
Mean LDL-C 24.0 mg/dL
Change from baseline -58.3%
15.0 mg/dL
0
8
16
24
32
40
48
56
64
72
80
88
Study Week

Exploratory Subgroup: Baseline LDL-C <70 mg/dL



Adverse Clinical Events and Safety Findings

Event	Placebo (N=484)	Evolocumab (N=484)
Death	0.8%	0.6%
Nonfatal MI	2.9%	2.1%
Nonfatal Stroke	0.6%	0.4%
Hosp. for Unstable Angina	0.8%	0.6%
Coronary Revascularization	13.6%	10.3%
First Major Cardiovascular Event	15.3%	12.2%
Injection site reactions	0%	0.4%
Anti-evolocumab binding antibody	NA	0.2%
Neutralizing antibodies	NA	0%
Neurocognitive events	1.2%	1.4%
New onset diabetes	3.7%	3.6%
Myalgia	5.8%	7.0%

GLACOV: insights

- Produced plaque regression (+++)
- Benefits were even observed in patients with baseline LDL-C <70 mg/dL (the lowest levels recommended by l guidelines)
- Benefit occurred at LDL-C levels as low as 20 mg/dL
- No safety issues were identified

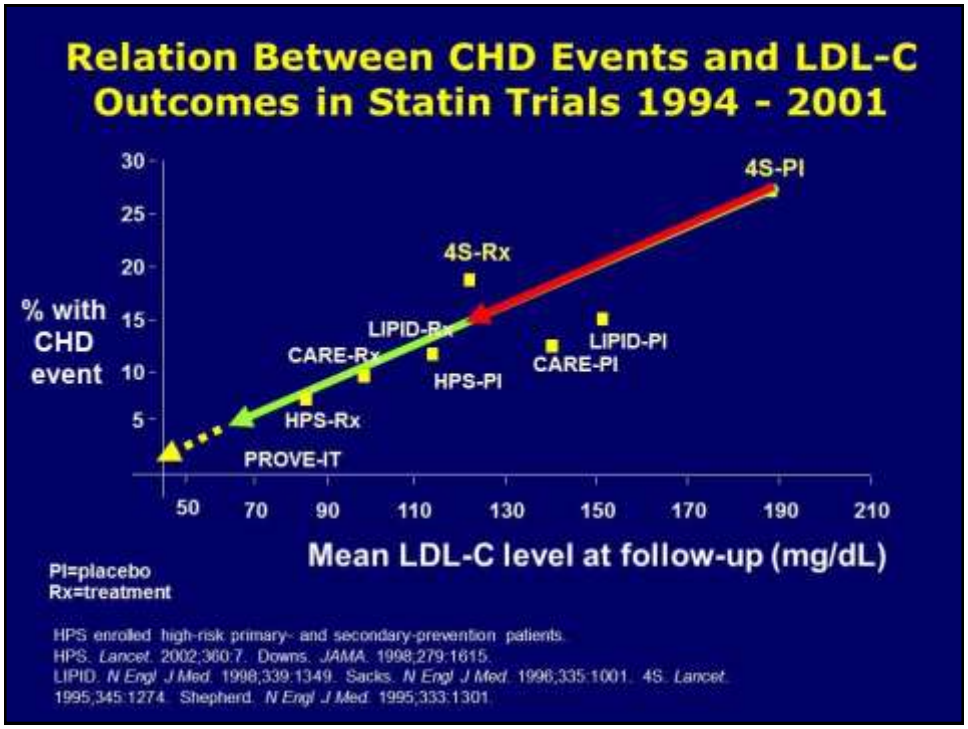
GLACOV: insights

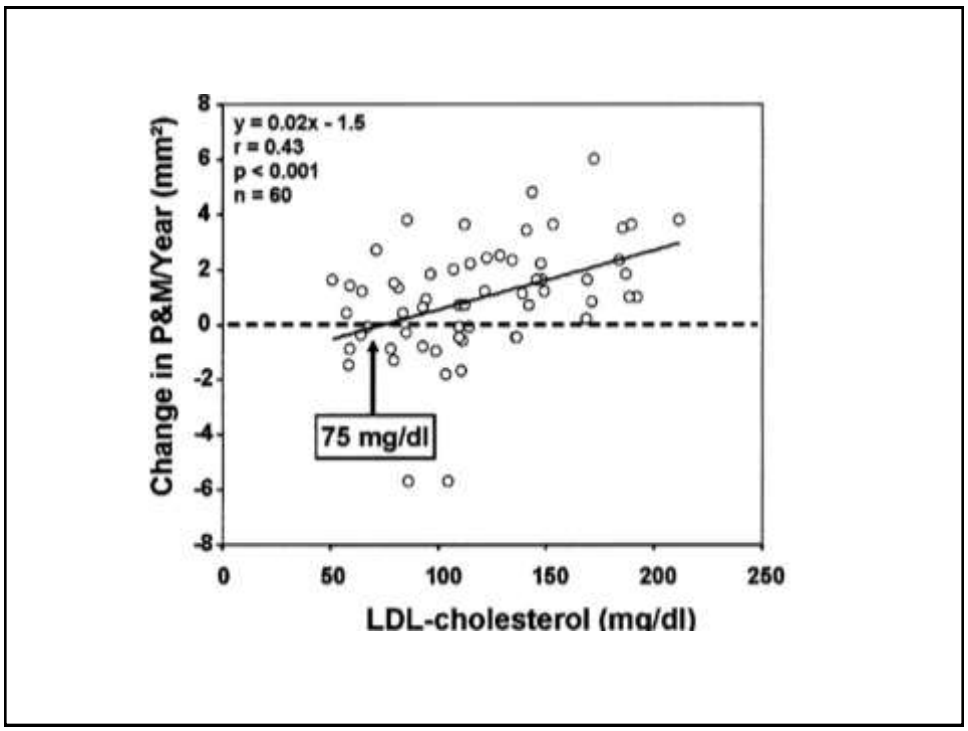
- **Plaque regression does not guarantee a reduction in the rate of clinical events**
- **This was a trial about plaque quantity (not quality):** regression does not necessary mean plaque stabilization
- **Imaging of plaque to detect progression / regression may guide therapy in very high risk patient (FH)**

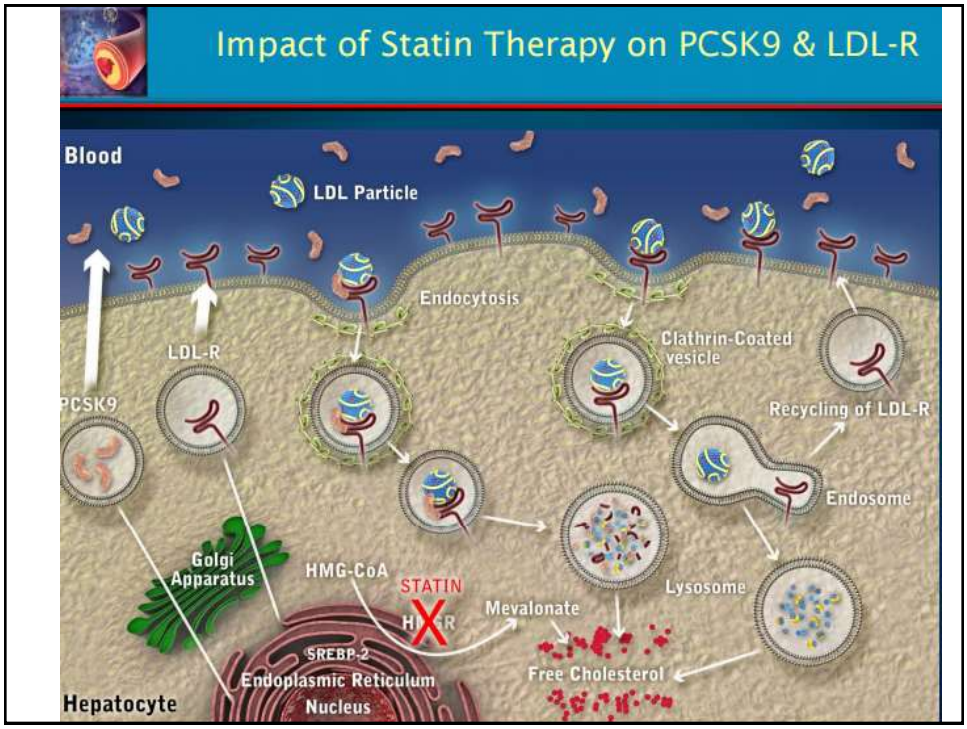
Plaque Regression

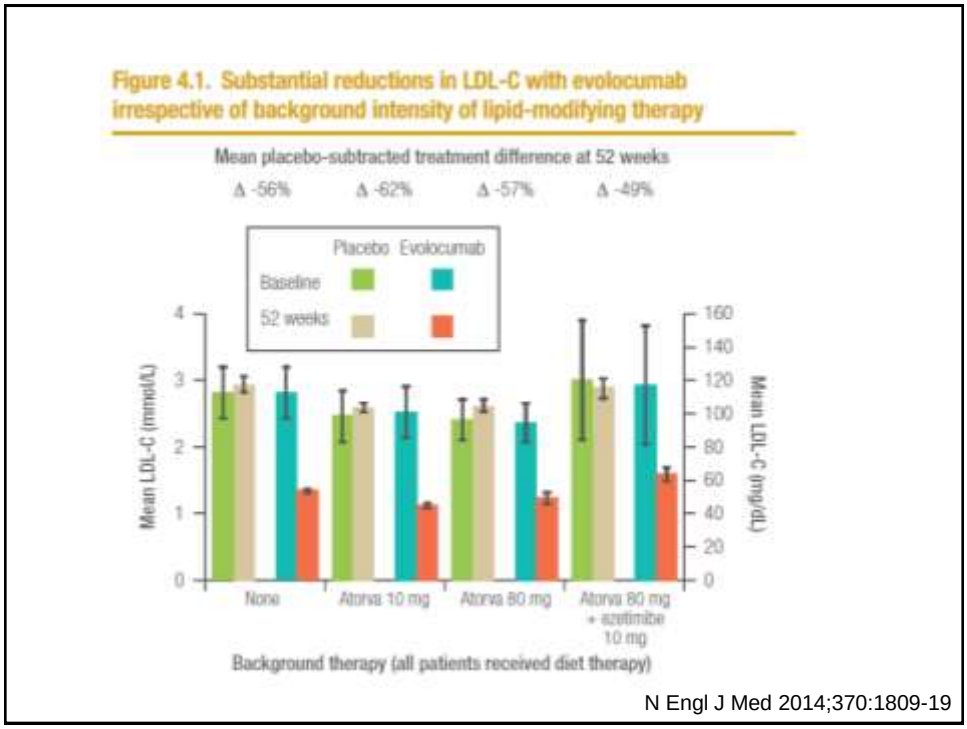
Flow

- Background
- Still, unanswered questions
- long term
- Plaque regression: surrogate or real endpoint


Relation Between CHD Events and LDL-C Outcomes in Statin Trials 1994 - 2001
% with CHD event
30
25
20
15
10
5
4S-PI
4S-Rx
LIPID-Rx
CARE-Rx
HPS-PI
LIPID-PI
CARE-PI
HPS-Rx
PROVE-IT
50
70
90
110
130
150
170
190
210
Mean LDL-C level at follow-up (mg/dL)
PI=placebo
Rx=treatment
HPS enrolled high-risk primary- and secondary-prevention patients.
HPS. Lancet. 2002;360:7. Downs. JAMA. 1998;279:1615.
LIPID. N Engl J Med. 1998;339:1349. Sacks. N Engl J Med. 1996;335:1001. 4S. Lancet. 1995;345:1274. Shepherd. N Engl J Med. 1995;333:1301


y = 0.02x - 1.5
r = 0.43
p < 0.001
n = 60
Change in P&M/Year (mm²)
8
6
4
2
0
-2
-4
-6
-8
75 mg/dl
0
50
100
150
200
250
LDL-cholesterol (mg/dl)





N Engl J Med 2014;370:1809-19