

# Cholesterol; what are the future lipid targets?

*“lipidologist out-of-business in 5-10 years”?*

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# Disclosure

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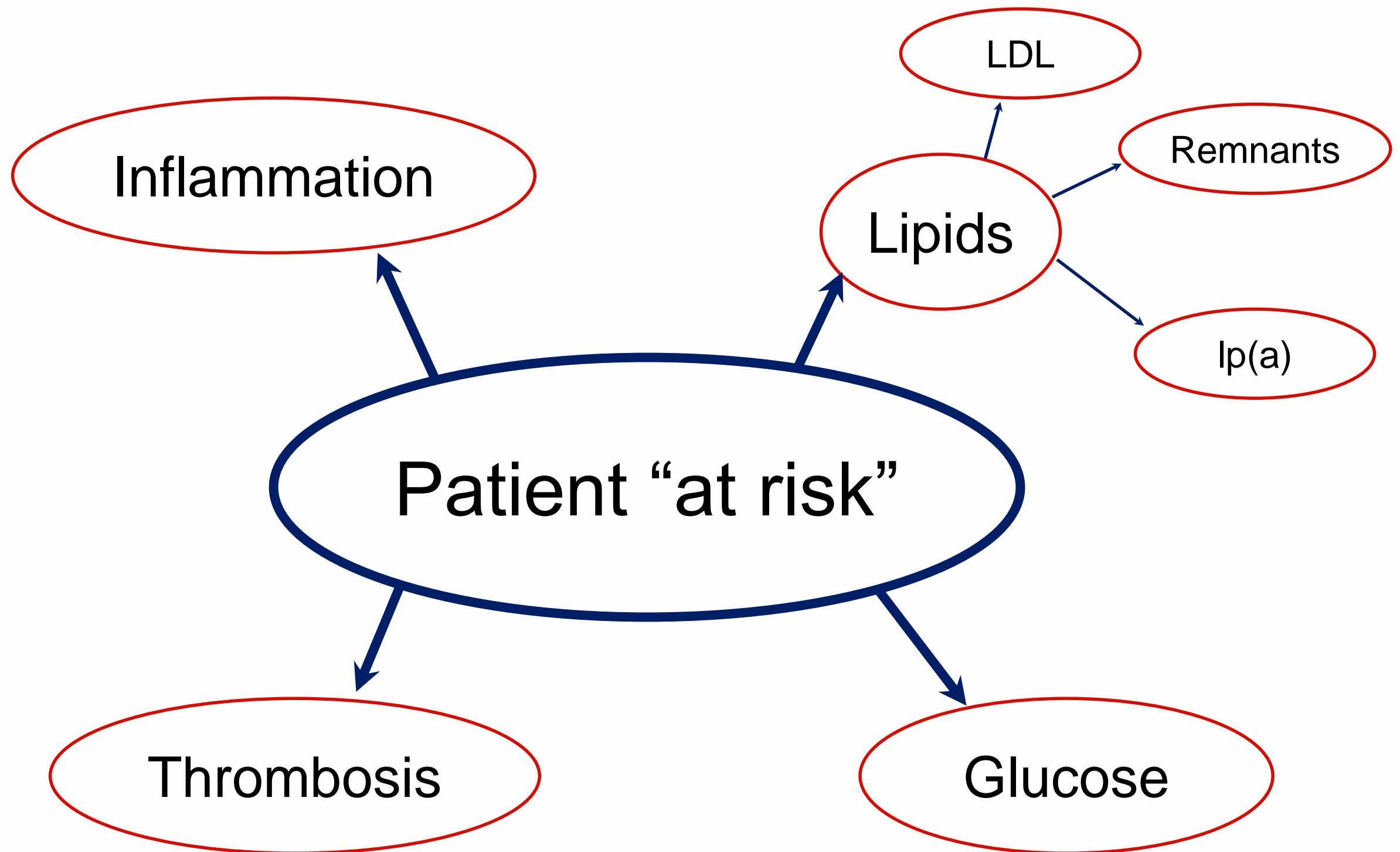
- Consultant and/or speaker for pharmaceutical companies that develop molecules that influence lipoprotein metabolism, including Regeneron, Pfizer, MSD, Sanofi, Amgen
  - PI for clinical trials in dyslipidemia conducted with i.e. Amgen, Sanofi, Eli Lilly, Novartis, Kowa, Genzyme, Cerenis, Pfizer, Dezima, Astra Zeneca
- Research grants: ZonMW, EU, Amgen, Sanofi, AstraZeneca Aegerion, Synageva

The department and/or Vascular Research Foundation receives the honoraria and investigator fees.

No shares or Stock, No ownership

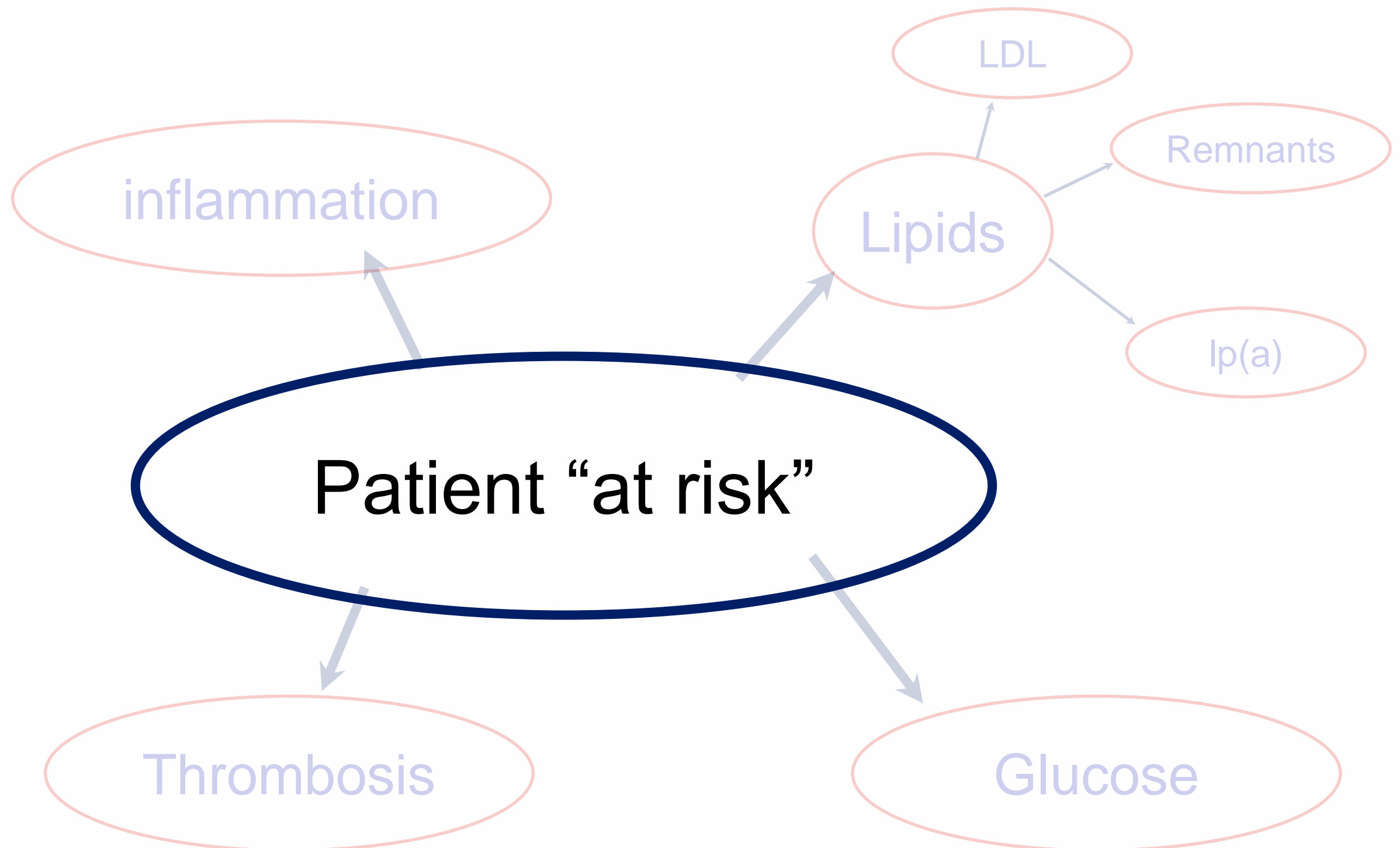
# CVRM in the years to come.....

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# CVRM in the years to come.....

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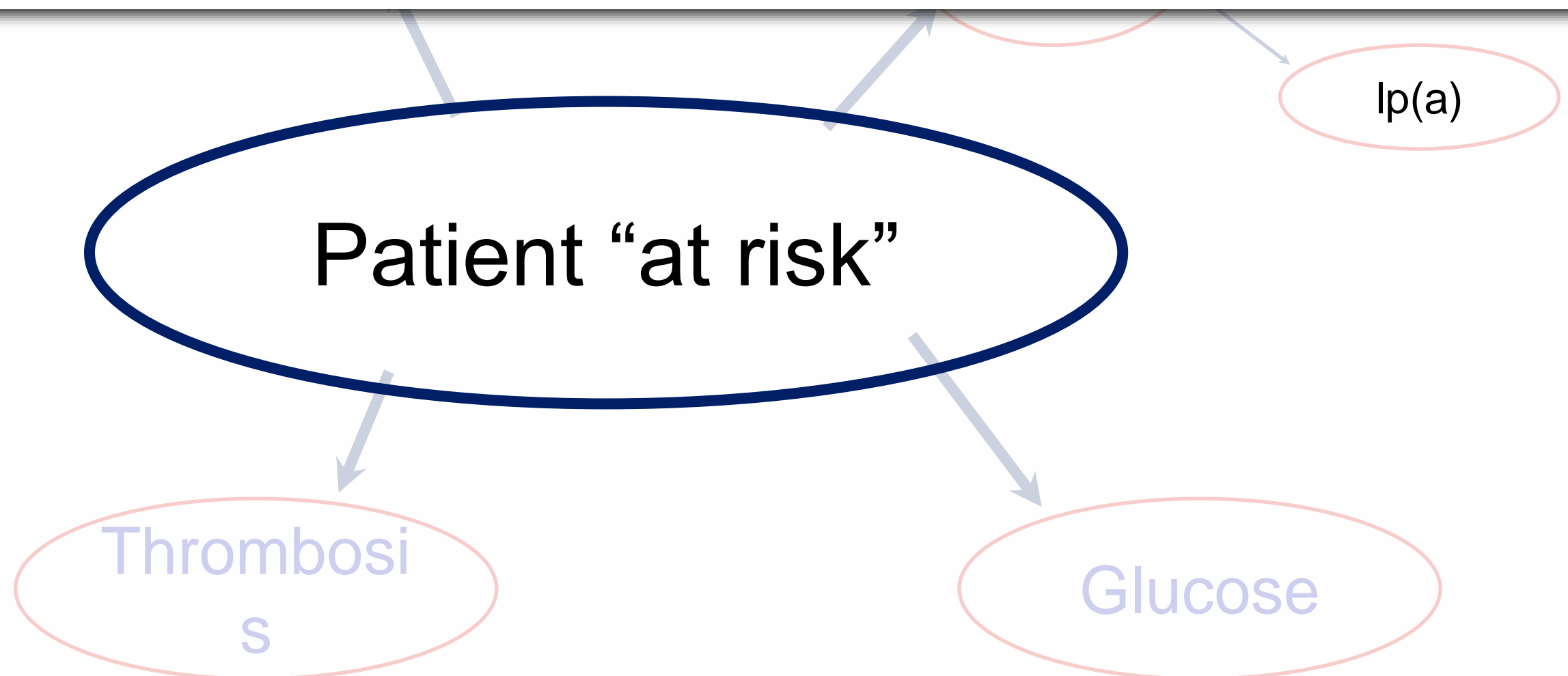
# CVRM in the years to come.....

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Circulation. 2016 Nov 8;134(19):1419-1429. Epub 2016 Sep 28.

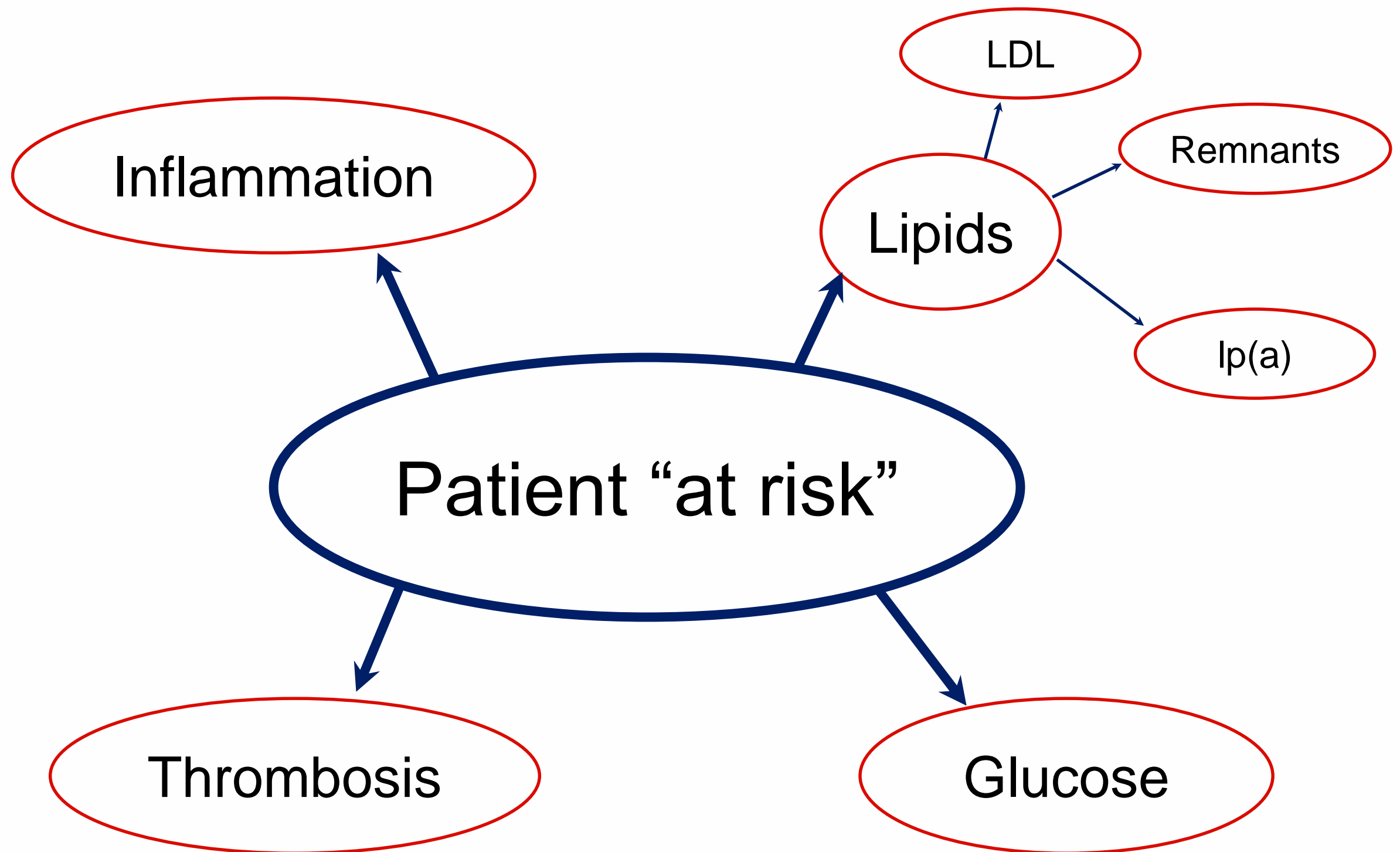
## **Distribution of Estimated 10-Year Risk of Recurrent Vascular Events and Residual Risk in a Secondary Prevention Population.**

Kaasenbrood L<sup>1</sup>, Boekholdt SM<sup>1</sup>, van der Graaf Y<sup>1</sup>, Ray KK<sup>1</sup>, Peters RJ<sup>1</sup>, Kastelein JJ<sup>1</sup>, Amarencu P<sup>1</sup>, LaRosa JC<sup>1</sup>, Cramer MJ<sup>1</sup>, Westerink J<sup>1</sup>, Kappelle LJ<sup>1</sup>, de Borst GJ<sup>1</sup>, Visseren FL<sup>2</sup>.



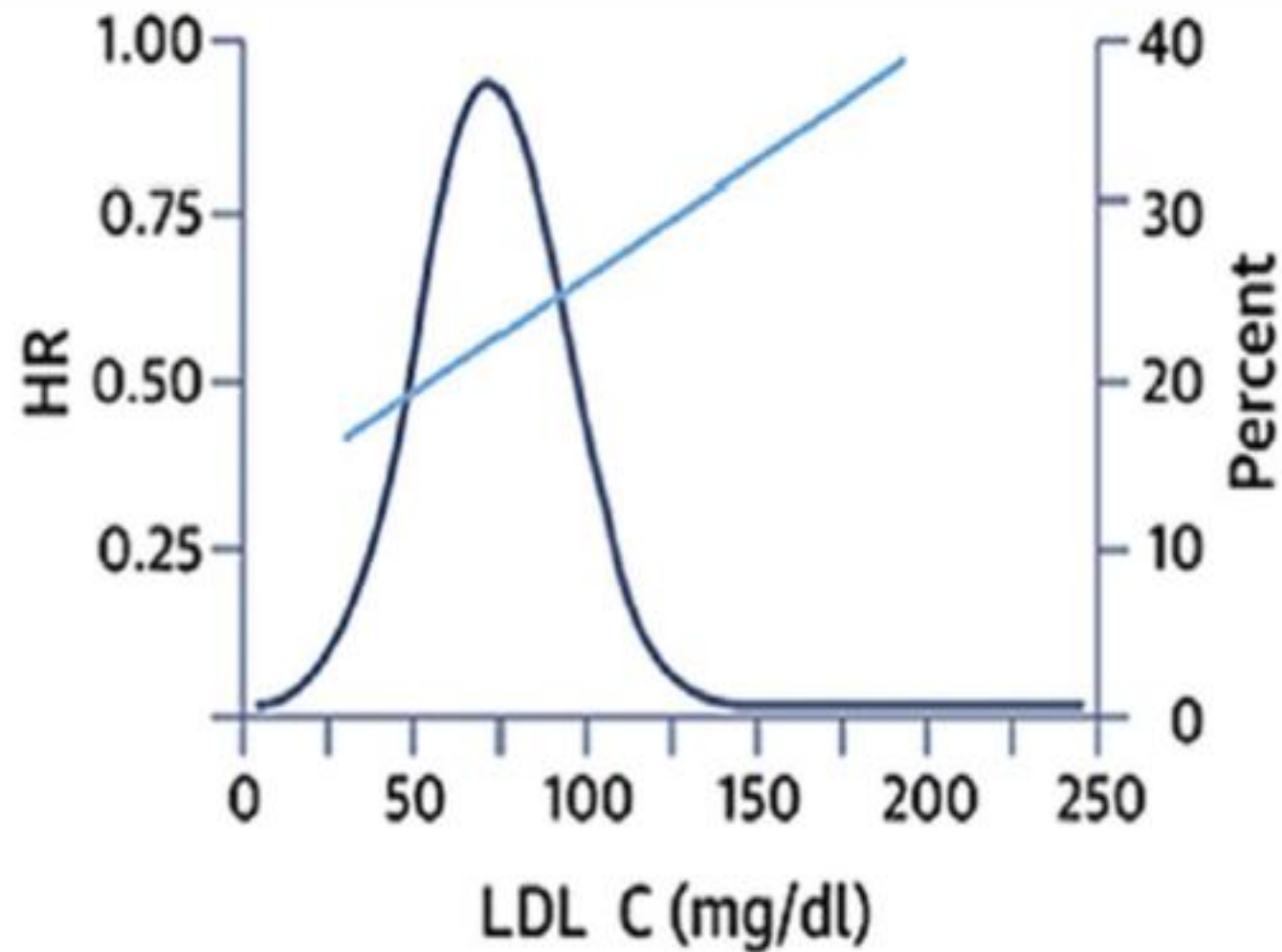
# CVRM in the years to come.....

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# Achieved LDL-C matters

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# Milestones towards acceptance of the LDL-C hypothesis

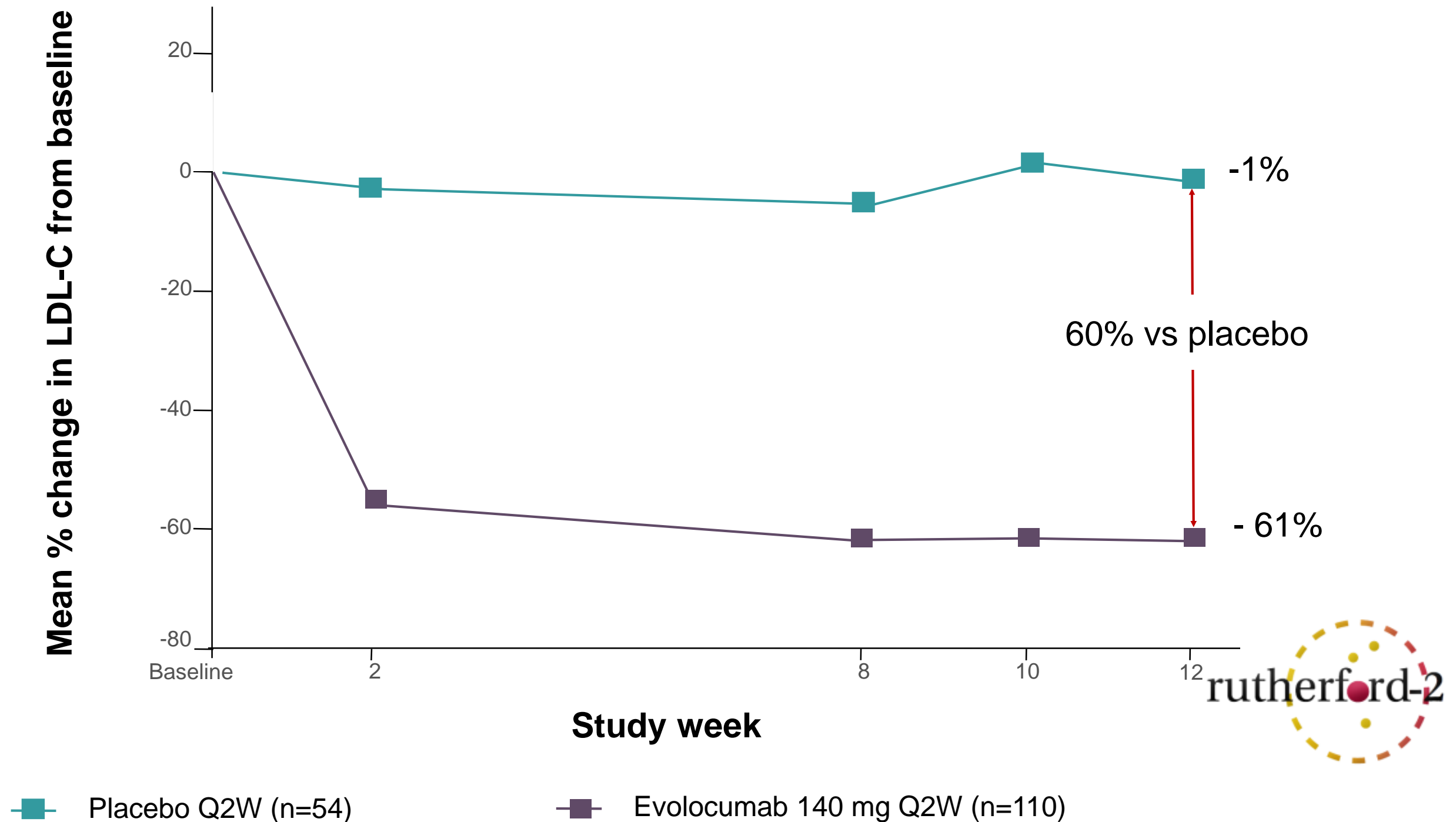
Anitschkow, the cholesterol-fed rabbit model	1913
Muller, familial hypercholesterolemia, xanthomatosis	1939
Gofman, lipoproteins in plasma correlate with CHD risk	1949
Framingham Study, CHD risk is highest in groups with highest blood cholesterol levels	1961
Nobel Prize to Konrad Bloch for elucidating cholesterol biosynthesis pathway	1964
Goldstein and Brown, the LDL receptor and regulation of cholesterol and lipoprotein metabolism	1974
Endo, discovery of the first effective statin drug (statins not marketed until 1987)	1976
Merck, discovery of mevinolin (lovastatin), later to become the first statin to reach the market	1980
Innerarity, discovery of ApoB implication in FH	1985
The statin era: (4S) showing that treatment with simvastatin reduces coronary heart disease mortality	1994
Abifadel, discovery of PCSK9 implication in FH	2003
Improve-it, adding Ezetimibe: beneficial effect on CVD	2015
PCSK9 ab outcome trials...effect on CVD	2017



A CENTURY

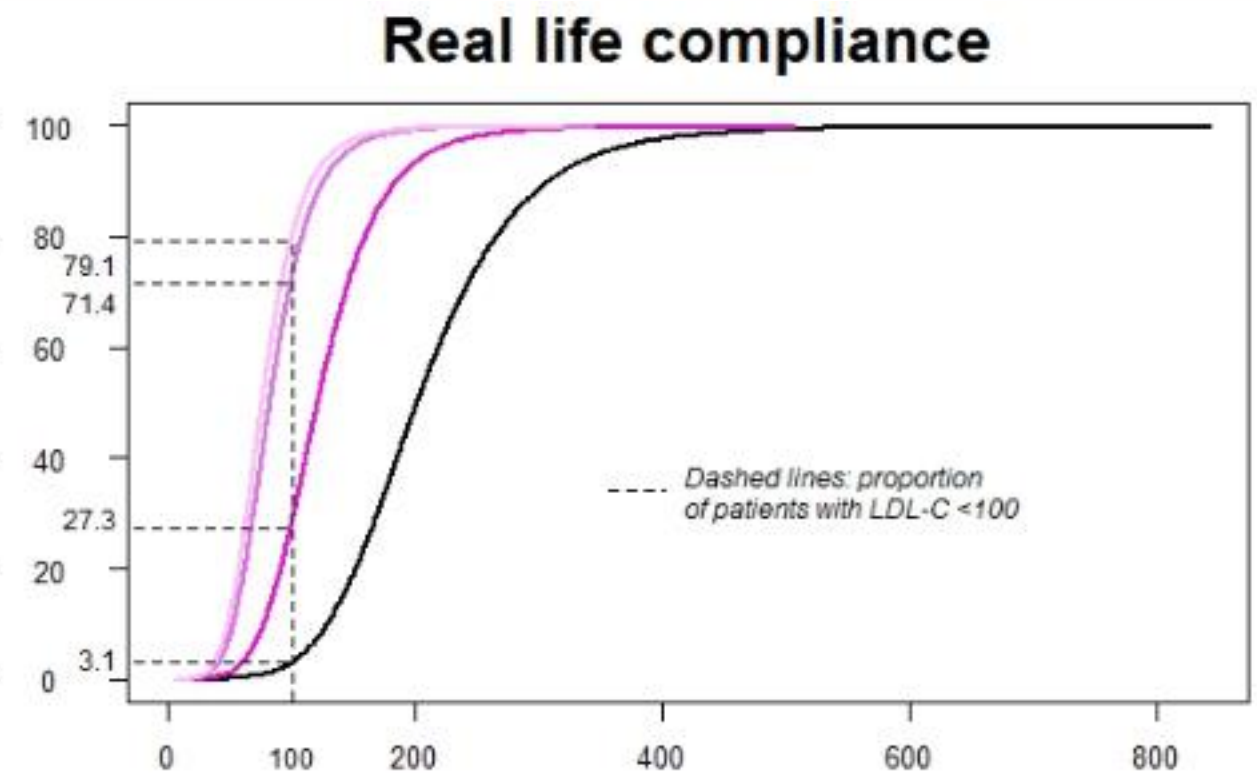
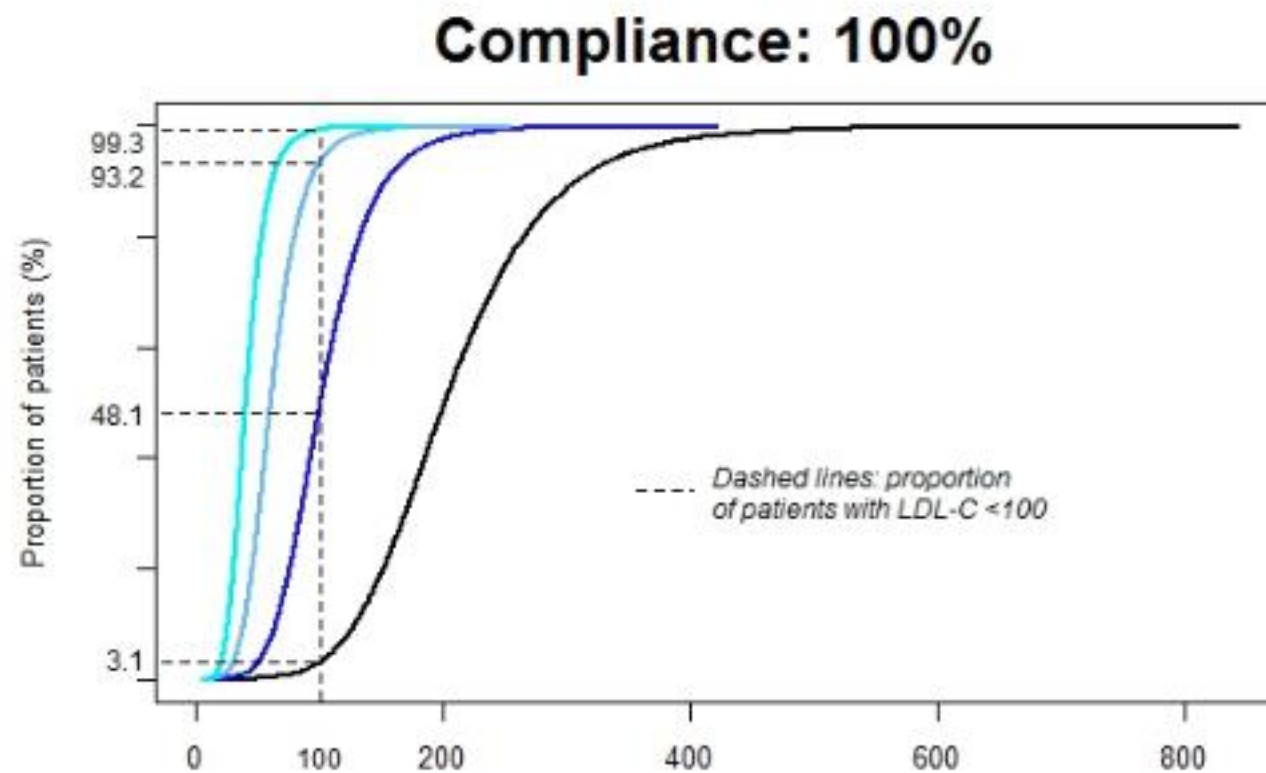


# Evolocumab significantly reduces LDL-C in patients with heterozygous FH

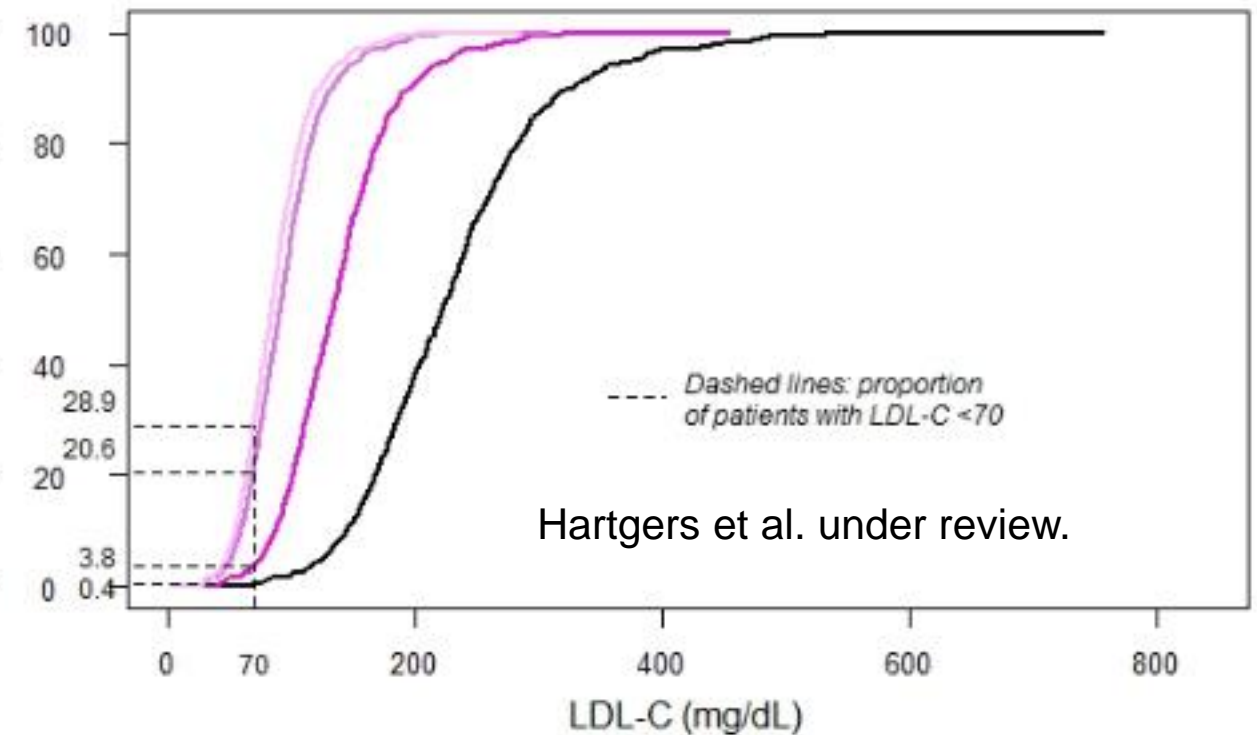
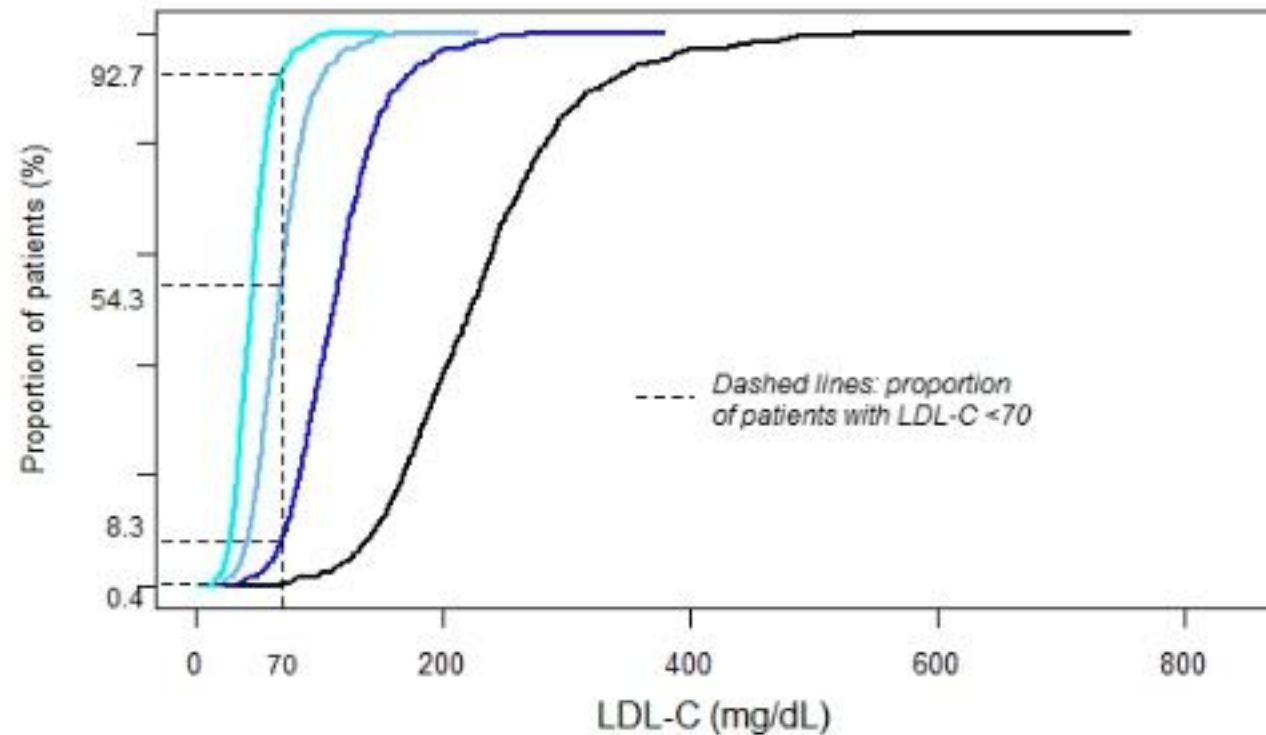


# PCSK9i in heFH

Without CHD



With CHD



Hartgers et al. under review.

- Off treatment
- Reduction of 50% (maximal current therapy)
- Reduction of 50% and 40% (maximal current therapy and CETP inhibition)
- Reduction of 50% and 60% (maximal current therapy and PCSK9 inhibition)

- Reduction of 40% (maximal current therapy)
- Reduction of 40% and 32% (maximal current therapy and CETP inhibition)
- Reduction of 40% and 37.2% (maximal current therapy and PCSK9 inhibition)

## Cost-Effectiveness of Evolocumab in Patients With High Cardiovascular Risk in Spain


Guillermo Villa, PhD<sup>1</sup>; Mickael Lothgren, PhD<sup>1</sup>; Lucie Kutikova, PhD<sup>2</sup>; Peter Lindgren, PhD<sup>3,4</sup>; Shravanthi R. Gandra, PhD<sup>5</sup>; Gregg C. Fonarow, MD<sup>6</sup>; Francesc Sorio, MSc<sup>7</sup>; Lluís Masana, MD, PhD<sup>8,9</sup>; Antoni Bayes-Genis, MD, PhD<sup>10</sup>; and Ben van Hout, PhD<sup>11</sup>

“Evolocumab plus to SoC may provide a cost-effective option for LDL-C lowering in FH and SP patients in Spain.”

assumptions: RR heFH 13, on Rx 10  
10 year event risk 50%  
lifetime risk 95%

**REVIEWS**

# **PCSK9 inhibitor access barriers—issues and recommendations: Improving the access process for patients, clinicians and payers**

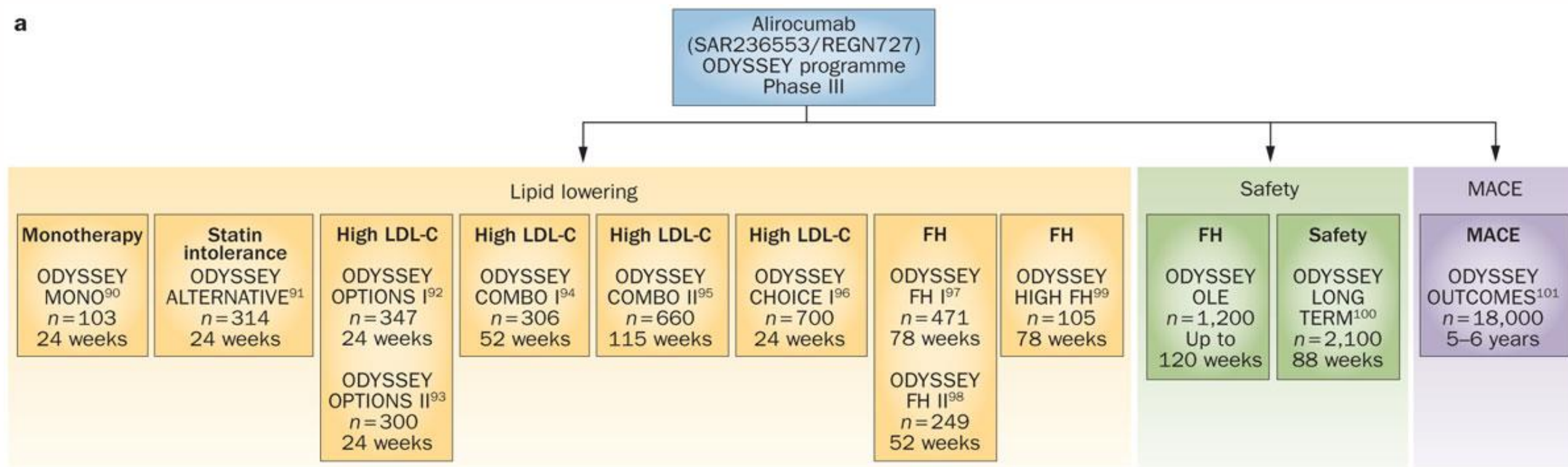
Seth J. Baum<sup>1</sup>  | Peter P. Toth<sup>2</sup> | James A. Underberg<sup>3</sup> | Paul Jellinger<sup>4</sup> | Joyce Ross<sup>5</sup> |  
Katherine Wilemon<sup>6</sup>

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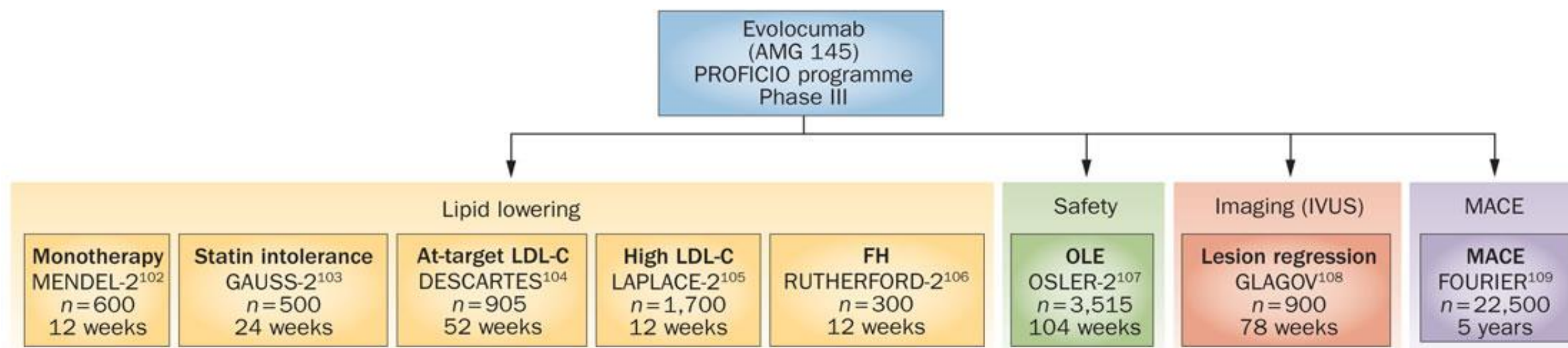
80 -90 % denial



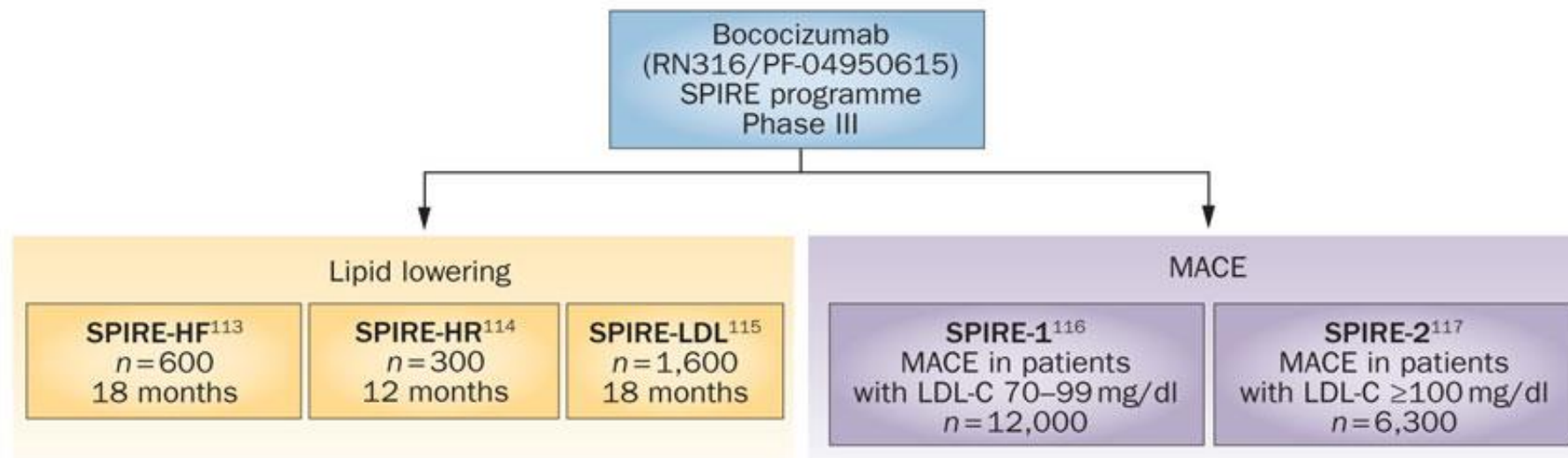
**a**



**b**



**c**



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ESTABLISHED IN 1812

MAY 4, 2017

VOL. 376 NO. 18

## **Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease**

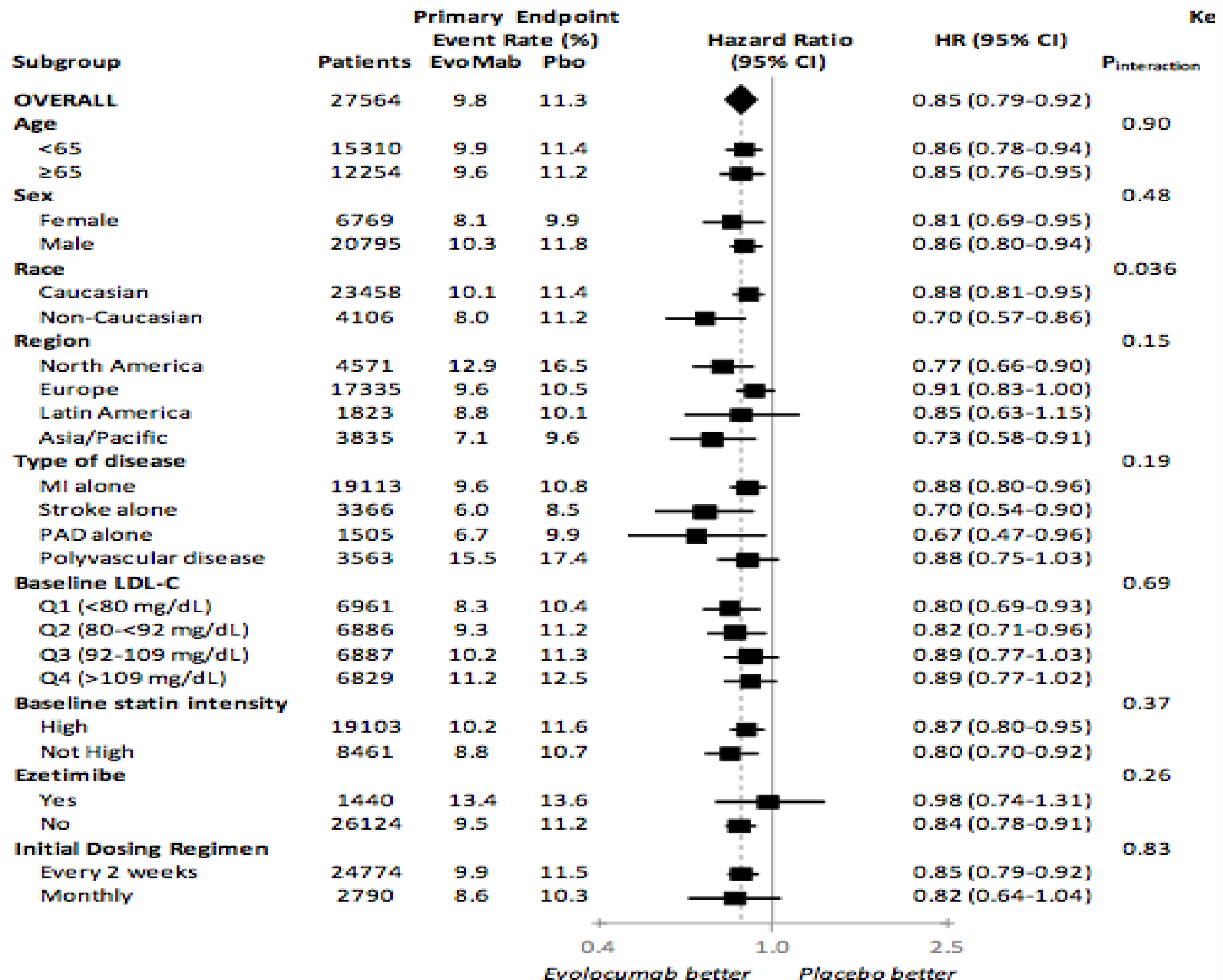
Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D.,  
Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A.,  
Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P.,  
and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators\*

PCSK9i; one size fits all??

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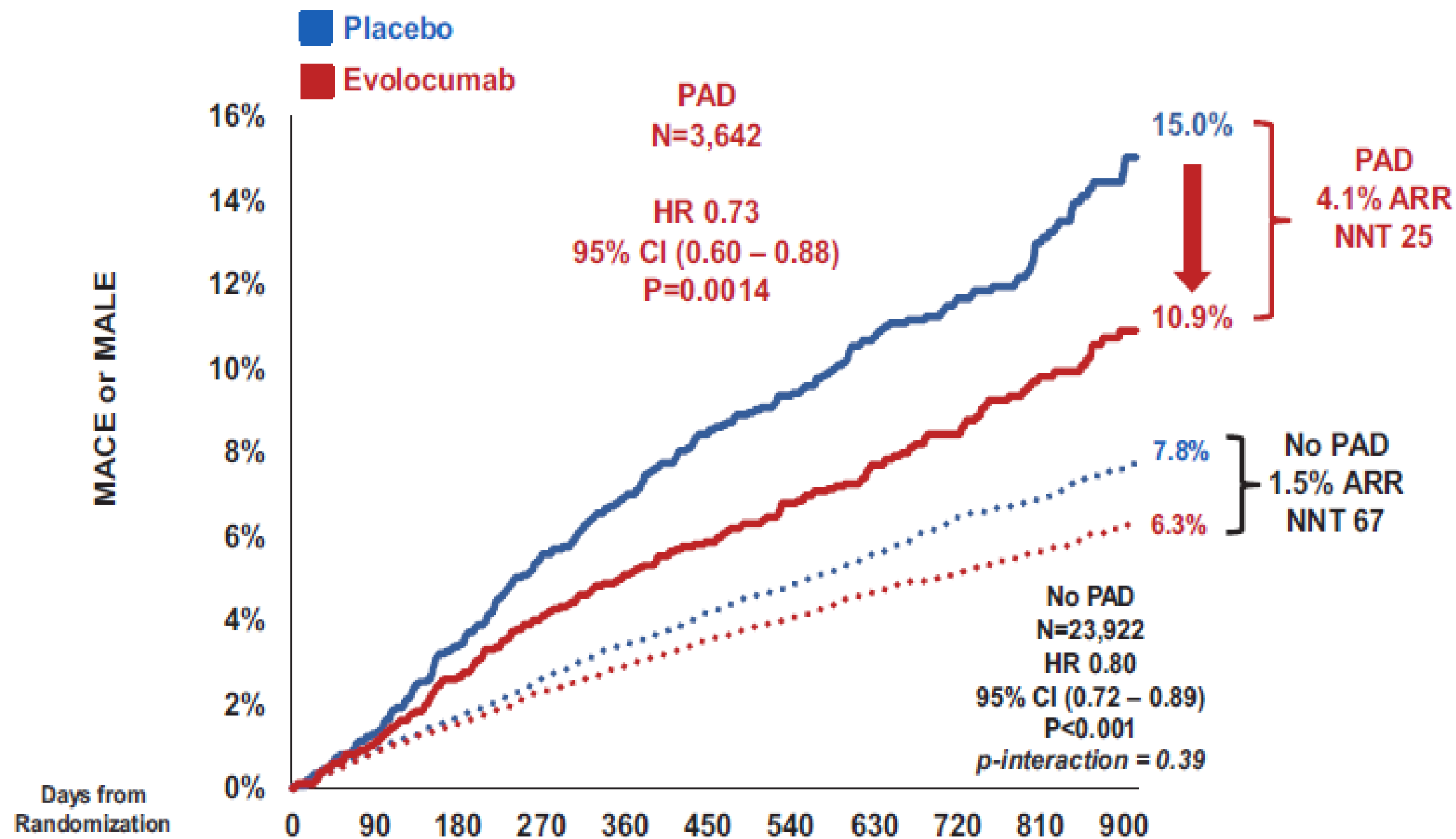
# Post hoc

**Supplementary Figure S5 – Efficacy in Key Subgroups**





# MACE or MALE in Patients with and without PAD



Number at risk

Placebo PAD	1784	1753	1711	1665	1630	1601	1555	1305	994	712	438
Evolocumab PAD	1858	1832	1798	1764	1741	1721	1671	1412	1078	765	471
Placebo no PAD	11996	11859	11727	11600	11486	11367	10758	9089	7160	5424	3630
Evolocumab no PAD	11926	11802	11698	11582	11488	11394	10825	9133	7254	5471	3647

	<b>N</b>	<b>Cumulative incidence of CV death, MI, or stroke</b>	<b>ARR</b>	<b>NNT</b>
<b>Overall patients with prior MI</b>	N= 22,351	--	--	--
<b>Time from Qualifying MI</b>	<b>&lt; 2 y ago</b> N=8,402	10.8%	2.9%	<b>35</b>
	<b>≥ 2 y ago</b> N=13,918	9.3%	1.0%	<b>101</b>
<b>Number of Prior MIs</b>	<b>≥ 2</b> N=5,285	15.0%	2.6%	<b>38</b>
	<b>1</b> N=17,047	8.2%	1.7%	<b>60</b>
<b>Residual Multivessel CAD</b>	<b>MVD</b> N=5,618	12.6%	3.4%	<b>29</b>
	<b>No MVD</b> N=16,715	8.9%	1.3%	<b>78</b>

Marc Sabatine AHA Anaheim 2017



# What about DM and weight gain?



## Anti-PCSK9 antibodies — beneficial or inducers of diabetes?

*Rutger Verbeek and G. Kees Hovingh*

A recent study has shown that evolocumab, an injectable monoclonal antibody directed against proprotein convertase subtilisin/kexin type 9 (PCSK9), robustly reduces levels of LDL cholesterol and decreases the risk of cardiovascular disease in patients with and without diabetes mellitus. When given on top of statins, evolocumab does not induce diabetes mellitus.

*Refers to Sabatine, M. S. et al. 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. Lancet Diabetes Endocrinol. [http://dx.doi.org/10.1016/S2213-8587\(17\)30313-3](http://dx.doi.org/10.1016/S2213-8587(17)30313-3) (2017)*

## **Effect of the Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitor Evolocumab on Glycemia, Body Weight, and New-Onset Diabetes Mellitus.**

Sattar N<sup>1</sup>, Toth PP<sup>2</sup>, Blom DJ<sup>3</sup>, Koren MJ<sup>4</sup>, Soran H<sup>5</sup>, Uhart M<sup>6</sup>, Elliott M<sup>7</sup>, Cyrille M<sup>6</sup>, Somaratne R<sup>6</sup>, Preiss D<sup>8</sup>.

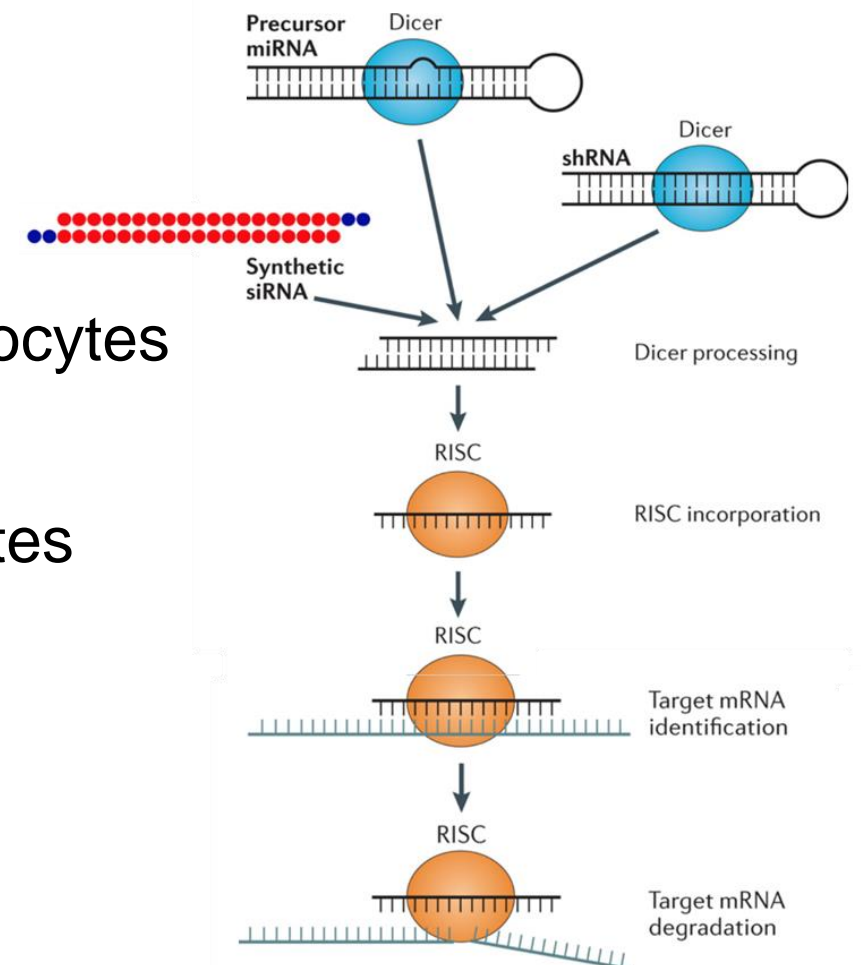
PCSK9 antibodies; anything else?

# **Effect of an RNA interference drug on the synthesis of proprotein convertase subtilisin/kexin type 9 (PCSK9) and the concentration of serum LDL cholesterol in healthy volunteers: a randomised, single-blind, placebo-controlled, phase 1 trial**

*Kevin Fitzgerald, Maria Frank-Kamenetsky, Svetlana Shulga-Morskaya, Abigail Liebow, Brian R Bettencourt, Jessica E Sutherland, Renta M Hutabarat, Valerie A Clausen, Verena Karsten, Jeffrey Cehelsky, Saraswathy V Nochur, Victor Kotelianski, Jay Horton, Timothy Mant, Joseph Chiesa, James Ritter, Malathy Munisamy, Akshay K Vaishnaw, Jared A Gollob, Amy Simon*

# Background of Inclisiran

- Inclisiran – 3<sup>rd</sup> generation chemically synthesized siRNA
- Enhanced stabilization chemistry results in long duration of action
- Inclisiran catalytic process to ↓ PCSK9 levels
- GalNAc linker - targeted and rapid uptake by hepatocytes
- Antisense strand incorporated in RISC
- Prevents degradation of LDL receptors in hepatocytes
- Unique PK & PD profile (SC administration)
  - Peak plasma concentrations after 4 hrs
  - Clinical dose not detected in plasma after 24 hrs
  - Long PD effect after single injection (> 6 months)

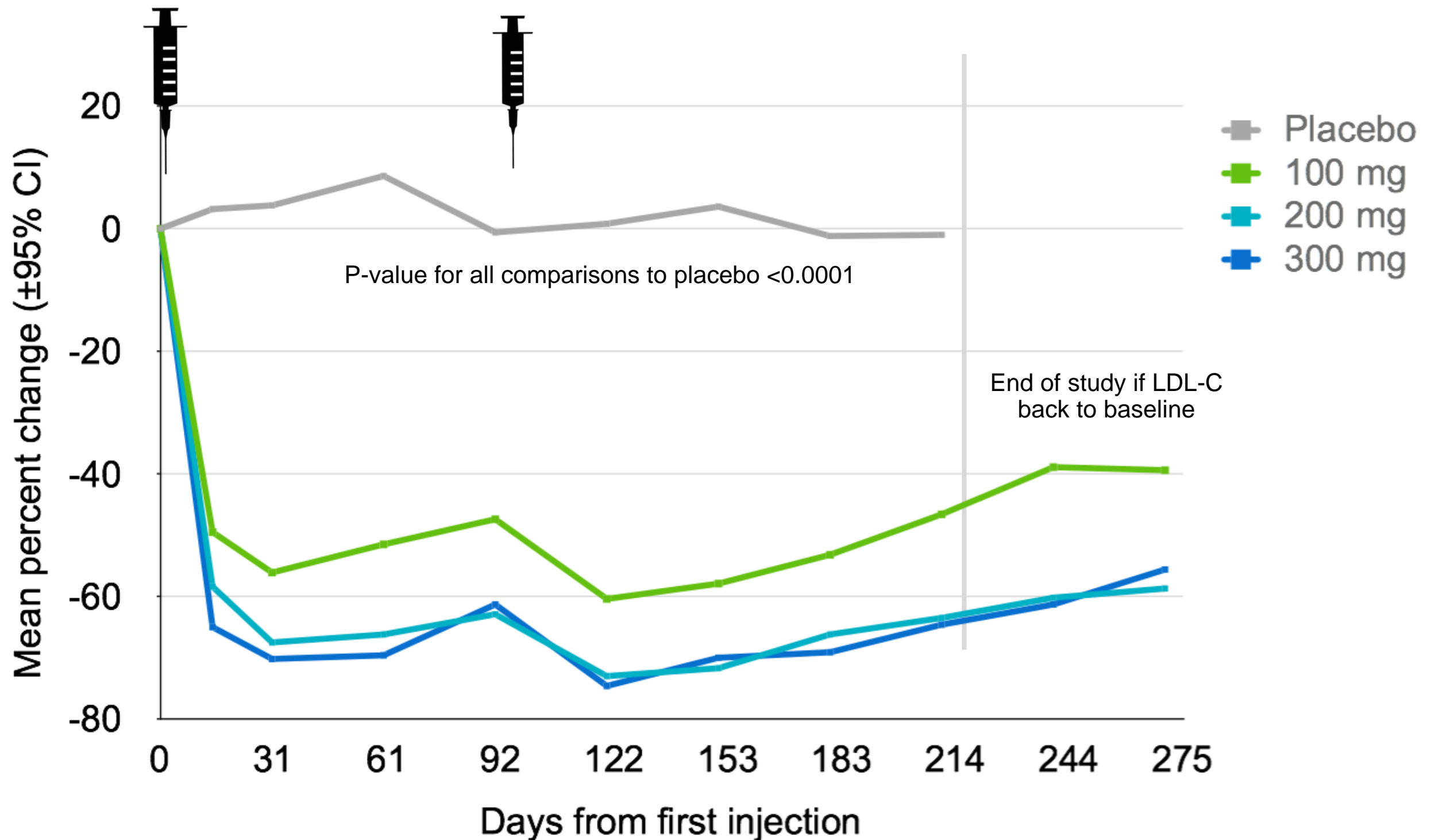


# No safety concerns

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- No thrombocytopenia
  - No neuropathy
  - No immunogenicity (no anti-drug antibodies)
  - No pro-inflammatory symptoms or elevated markers
-

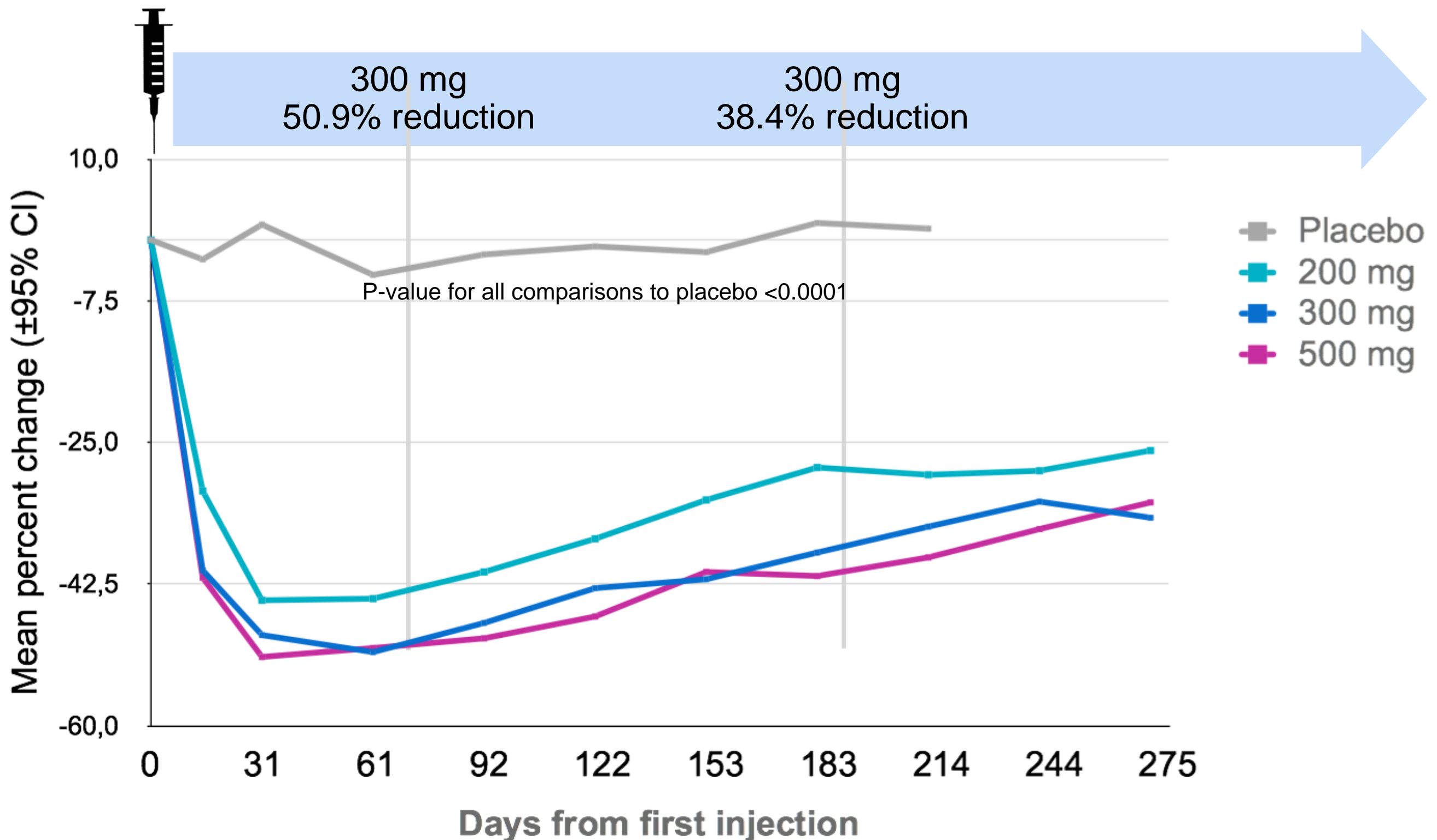
# Efficacy: Two dose starting regimen: PCSK9 level



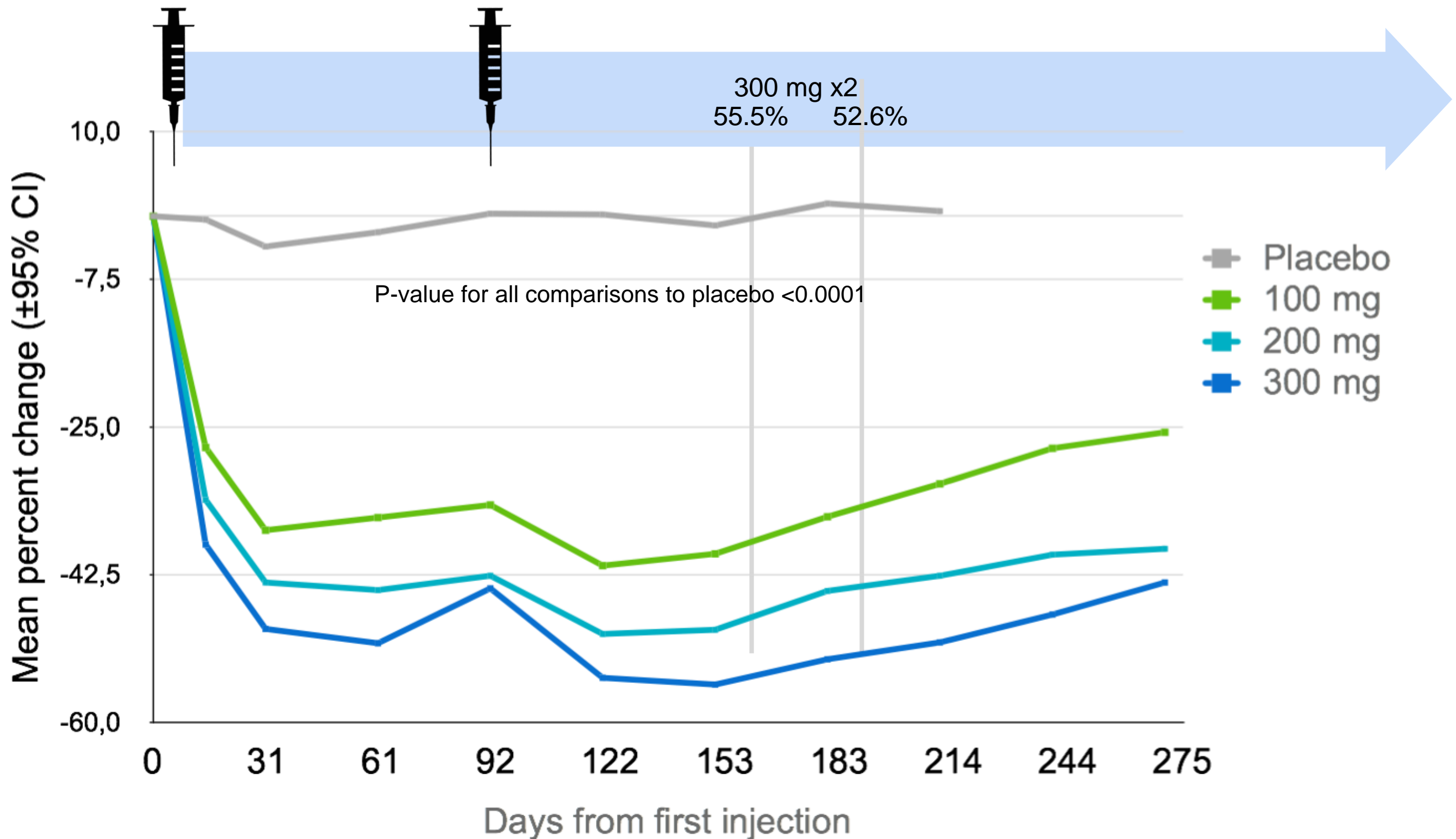


# Efficacy: One dose starting regimen

## LDL-C reductions – 300 mg optimal



# Efficacy: Two dose starting regimen



# Phase II ORION-1 Study: Conclusions

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No safety concerns

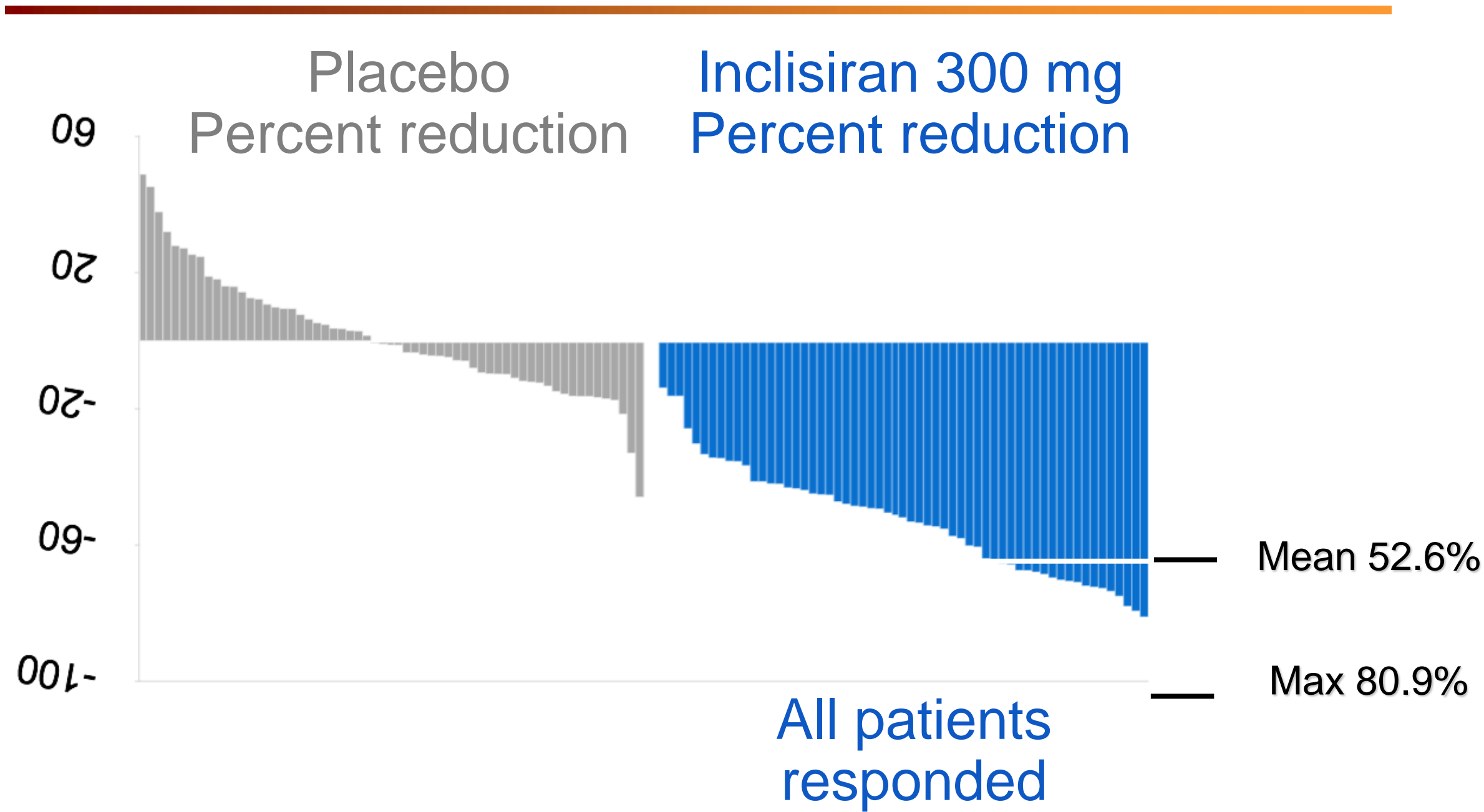
- Low incidence of injection site reactions
- No LFT elevations related to drug
- No evidence of anti-drug antibodies

Optimal dosage 300 mg given twice as starting regimen then Q6 monthly

- All patients had significant LDL-C lowering
  - At 6 months, mean LDL-C ↓ of 52.6% (64 mg/dL), and up to 81% (122 mg/dL)
-

# Efficacy: Two dose starting regimen

## Individual patient responses (%) at day 180



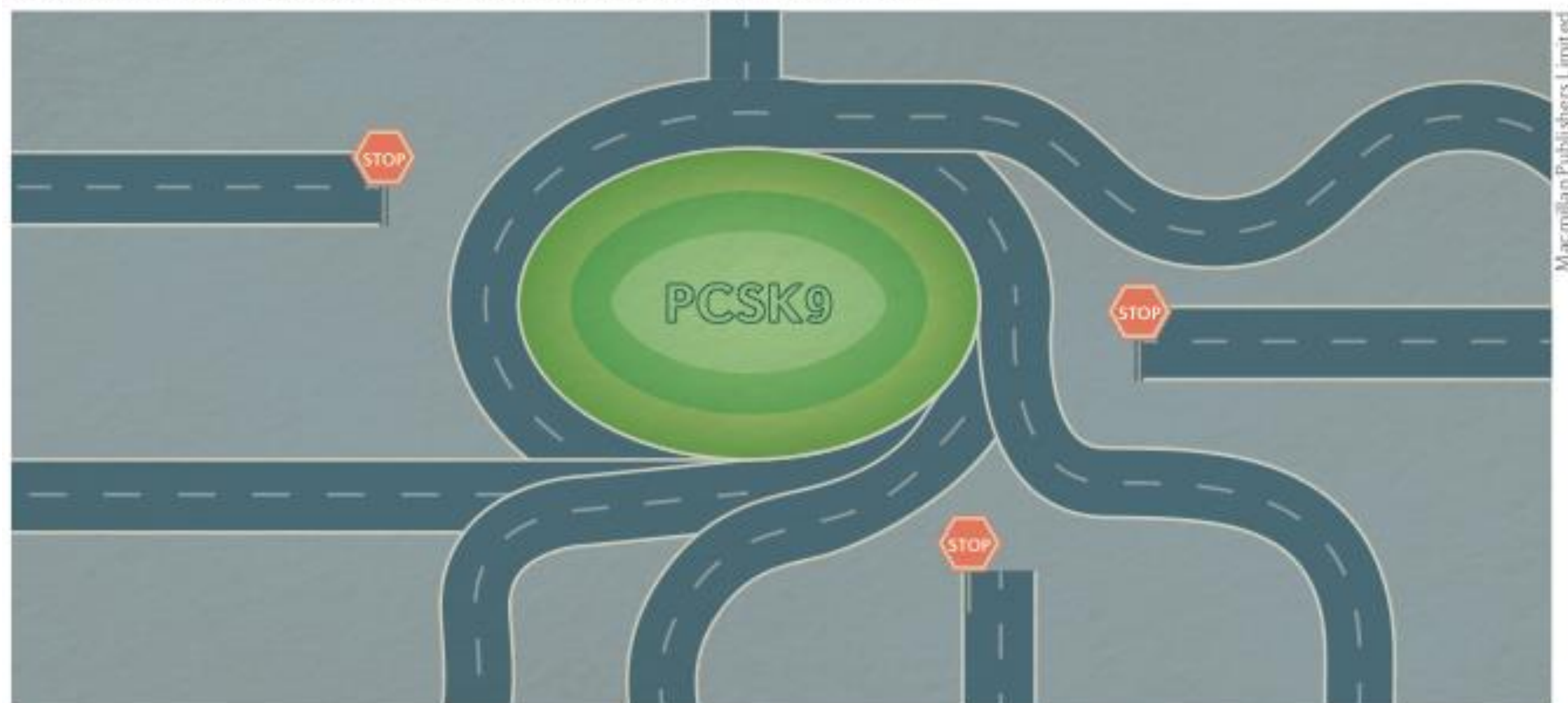


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ORIGINAL ARTICLE

# Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol

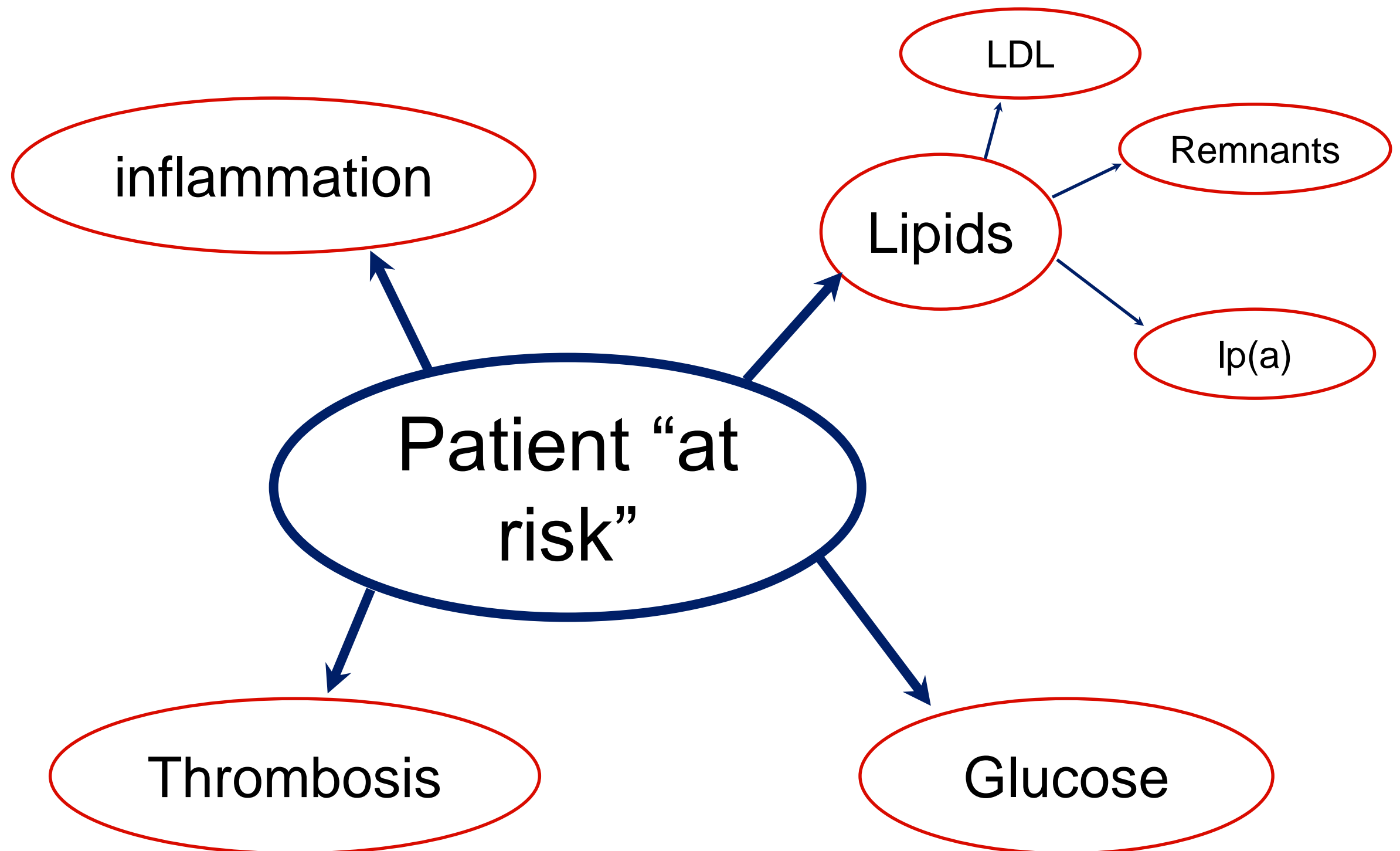
Kausik K. Ray, M.D., Ulf Landmesser, M.D., Lawrence A. Leiter, M.D.,  
David Kallend, M.D., Robert Dufour, M.D., Mahir Karakas, M.D., Tim Hall, M.D.,  
Roland P.T. Troquay, M.D., Traci Turner, M.D., Frank L.J. Visseren, M.D.,  
Peter Wijngaard, Ph.D., R. Scott Wright, M.D., and John J.P. Kastelein, M.D., Ph.D.



Drug	Sponsor	Modality	Status
Alirocumab and evolocumab	Regeneron/Sanofi and Amgen	Monoclonal antibody	Approved
Inclisiran	Alnylam/The Medicines Company	RNA interference	Phase III planned
MEDI4166	AstraZeneca	PCSK9 antibody fused to GLP1 peptide	Phase I/II
AT04A and AT06A	Affiris	Vaccine	Phase I
DS-9001	Daiichi Sankyo/Pieris Pharmaceuticals	Anticalin (antibody mimetic)	Phase I
CRISPR-based approach	Academic project and AstraZeneca	CRISPR	Preclinical
PF-06446846	Pfizer	Small molecule	Discontinued
BMS-PCSK9Rx and SPC5001	BMS/Ionis Pharmaceuticals and Santaris Pharma/Roche	Antisense	Discontinued
BMS-962476	BMS	Adnectin (antibody mimetic)	Discontinued

# CVRM in the years to come.....

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# ANGPTL3 ?

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BRIEF REPORT

## Exome Sequencing, *ANGPTL3* Mutations, and Familial Combined Hypolipidemia

Kiran Musunuru, M.D., Ph.D., M.P.H., James P. Pirruccello, B.S., Ron Do, M.S., Gina M. Peloso, M.S., Candace Guiducci, B.S., Carrie Sougnez, B.S., Kiran V. Garimella, M.S., Sheila Fisher, M.L.A., Justin Abreu, M.S., Andrew J. Barry, B.S., Tim Fennell, B.S., Eric Banks, Ph.D., Lauren Ambrogio, B.S., Kristian Cibulskis, B.S., Andrew Kernysky, Ph.D., Elena Gonzalez, B.S., Nicholas Rudzicz, M.S., James C. Engert, Ph.D., Mark A. DePristo, Ph.D., Mark J. Daly, Ph.D., Jonathan C. Cohen, Ph.D., Helen H. Hobbs, M.D., David Altshuler, M.D., Ph.D., Gustav Schonfeld, M.D., Stacey B. Gabriel, Ph.D., Pin Yue, Ph.D., and Sekar Kathiresan, M.D.

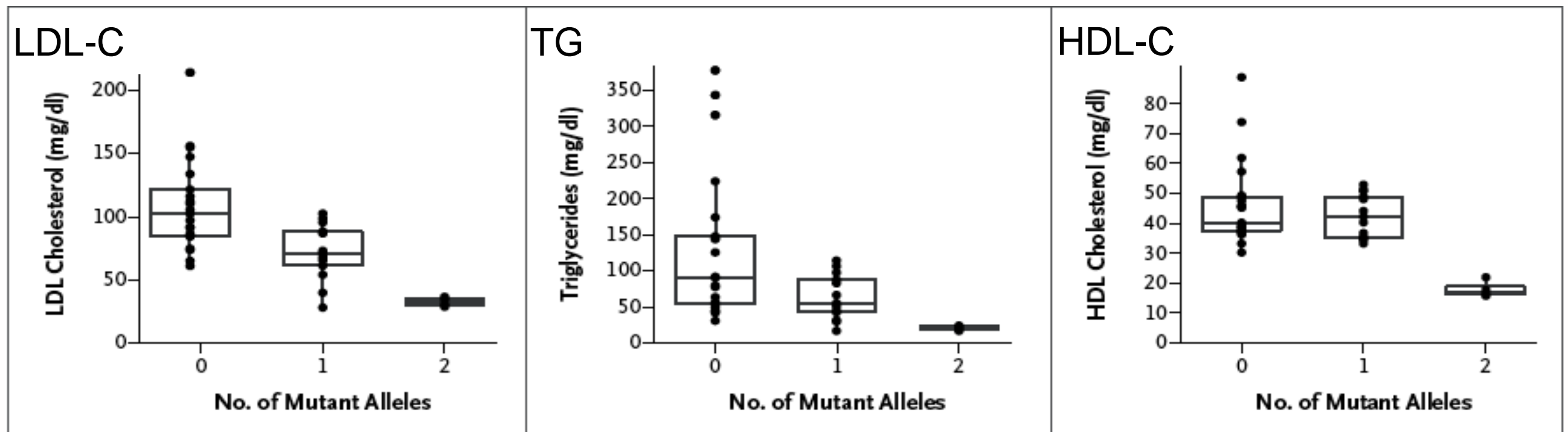
### SUMMARY

From the Cardiovascular Research Center (K.M., J.P.P., R.D., S.K.), Center for Human Genetic Research (K.M., J.P.P., R.D., M.J.D., D.A., S.K.), and Department of Molecular Biology (D.A.), Massachusetts General Hospital; Departments of Medicine (K.M., M.J.D., D.A., S.K.) and Genetics (D.A.), Harvard Medical School; and Department of Biostatistics, Boston University School of Public Health (G.M.P.) — all in Boston; Program in Medical and Population Genetics, Broad Institute, Cambridge, MA (K.M., J.P.P., R.D., C.G., C.S., K.V.G., S.F., J.A., A.J.B., T.F., E.B., L.A., K.C., A.K., E.G., M.A.D., M.J.D., D.A., S.B.G., S.K.); Johns Hopkins University School of Medicine, Baltimore

We sequenced all protein-coding regions of the genome (the “exome”) in two family members with combined hypolipidemia, marked by extremely low plasma levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. These two participants were compound heterozygotes for two distinct nonsense mutations in *ANGPTL3* (encoding the angiopoietin-like 3 protein). *ANGPTL3* has been reported to inhibit lipoprotein lipase and endothelial lipase, thereby increasing plasma triglyceride and HDL cholesterol levels in rodents. Our finding of *ANGPTL3* mutations highlights a role for the gene in LDL cholesterol metabolism in humans and shows the usefulness of exome sequencing for identification of novel genetic causes of inherited disorders. (Funded by the National Human Genome Research Institute and others.)

# Genetic Inactivation of ANGPTL3 Reduces Plasma LDL-C, Triglyceride and HDL-C in Humans

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Examination of Subjects with LoF Mutations in ANGPTL3.  
Musurunu, et. al NEJM 2010

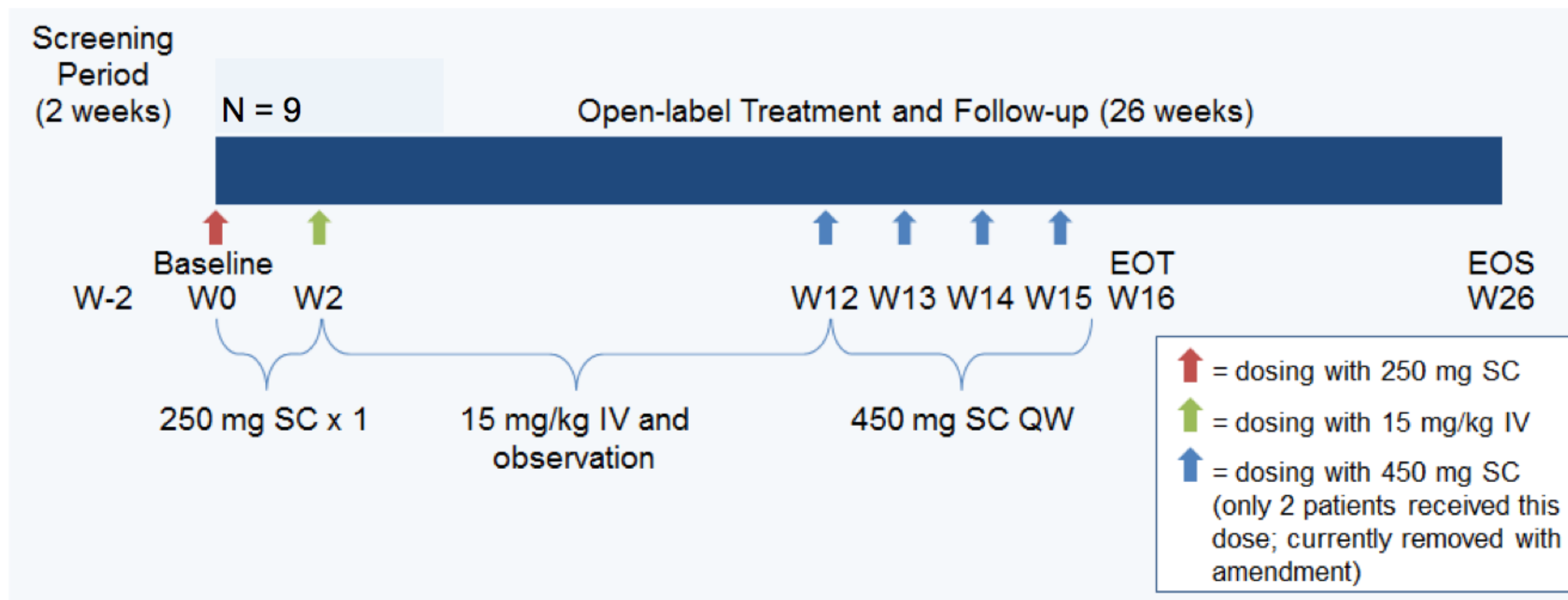
## **ANGPTL3 Deficiency and Protection Against Coronary Artery Disease.**

Stitzel NO<sup>1</sup>, Khera AV<sup>2</sup>, Wang X<sup>3</sup>, Bierhals AJ<sup>4</sup>, Vourakis AC<sup>5</sup>, Sperry AE<sup>5</sup>, Natarajan P<sup>2</sup>, Klarin D<sup>6</sup>, Emdin CA<sup>2</sup>, Zekavat SM<sup>7</sup>, Nomura A<sup>2</sup>, Erdmann J<sup>8</sup>, Schunkert H<sup>9</sup>, Samani NJ<sup>10</sup>, Kraus WE<sup>11</sup>, Shah SH<sup>11</sup>, Yu B<sup>12</sup>, Boerwinkle E<sup>12</sup>, Rader DJ<sup>13</sup>, Gupta N<sup>7</sup>, Frossard PM<sup>14</sup>, Rasheed A<sup>14</sup>, Danesh J<sup>15</sup>, Lander ES<sup>7</sup>, Gabriel S<sup>7</sup>, Saleheen D<sup>16</sup>, Musunuru K<sup>17</sup>, Kathiresan S<sup>18</sup>, PROMIS and Myocardial Infarction Genetics Consortium Investigators.

21,980 people with CAD and 158,200 control subjects  
heterozygous carriers of ANGPTL3 LOF mutations:  
17% TG reduction and 12% LDL-C reduction.

Carrier status was associated with a 34% reduction in  
odds of CAD (odds ratio: 0.66; 95% confidence  
interval: 0.44 to 0.98;  $p = 0.04$ ).

# Study Design



Current LLT was maintained from at least 4 weeks before screening, and through the 26-week treatment and observation period

Variable	Mean±SD % change	Mean±SD or median (Q1, Q3) absolute change
LDL-C	−49 ± 23	−4.1 ± 2.3 mmol/L
Non-HDL cholesterol	−49 ± 22	−4.3 ± 2.4 mmol/L
Apolipoprotein A1	−39 ± 9	−43 ± 17 mg/dL
Apolipoprotein B	−46 ± 18	−1.0 ± 0.6 mmol/L
Total cholesterol	−47 ± 19	−4.7 ± 2.3 mmol/L
Lipoprotein(a)	−19 (−27, 1)	−27 (−29, 1) nmol/L
HDL-cholesterol	−36 ± 16	−0.4 ± 0.3 mmol/L
Triglycerides	−47 (−57, −38)	−0.3 (−0.2, −0.6) mmol/L

Data given as mean ± SD or median (Q1, Q3)

# ANGPTL3?

## [Genetic and Pharmacologic Inactivation of \*\*ANGPTL3\*\* and Cardiovascular Disease.](#)

Dewey FE, Gusarova V, Dunbar RL, O'Dushlaine C, Schurmann C, Gottesman O, McCarthy S, Van Hout CV, Bruse S, Dansky HM, Leader JB, Murray MF, Ritchie MD, Kirchner HL, Habegger L, Lopez A, Penn J, Zhao A, Shao W, Stahl N, Murphy AJ, Hamon S, Bouzelmat A, Zhang R, Shumel B, Pordy R, Gipe D, Herman GA, Sheu WHH, Lee IT, Liang KW, Guo X, Rotter JI, Chen YI, Kraus WE, Shah SH, Damrauer S, Small A, Rader DJ, Wulff AB, Nordestgaard BG, Tybjaerg-Hansen A, van den Hoek AM, Princen HMG, Ledbetter DH, Carey DJ, Overton JD, Reid JG, Sasiela WJ, Banerjee P, Shuldiner AR, Borecki IB, Teslovich TM, Yancopoulos GD, Mellis SJ, Gromada J, Baras A.

N Engl J Med. 2017 Jul 20;377(3):211-221. doi: 10.1056/NEJMoa1612790. Epub 2017 May 24.

PMID: 28538136

[Similar articles](#)

## [Cardiovascular and Metabolic Effects of \*\*ANGPTL3\*\* Antisense Oligonucleotides.](#)

Graham MJ, Lee RG, Brandt TA, Tai LJ, Fu W, Peralta R, Yu R, Hurh E, Paz E, McEvoy BW, Baker BF, Pham NC, Digenio A, Hughes SG, Geary RS, Witztum JL, Crooke RM, Tsimikas S.

N Engl J Med. 2017 Jul 20;377(3):222-232. doi: 10.1056/NEJMoa1701329. Epub 2017 May 24.

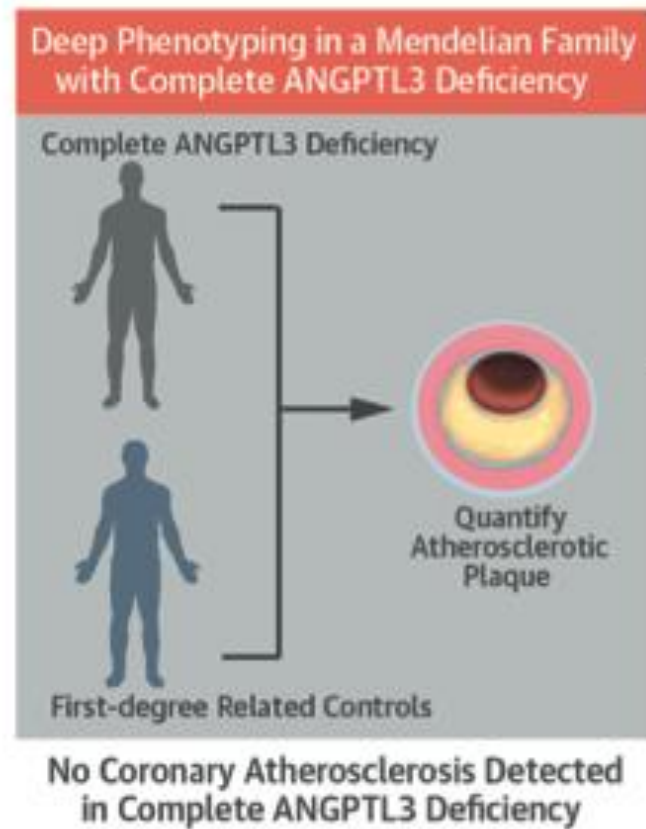
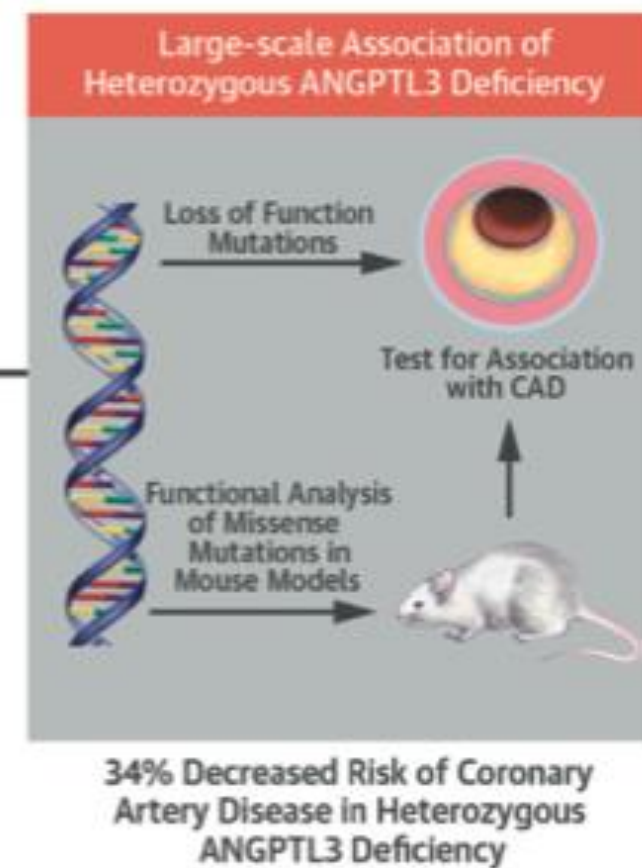
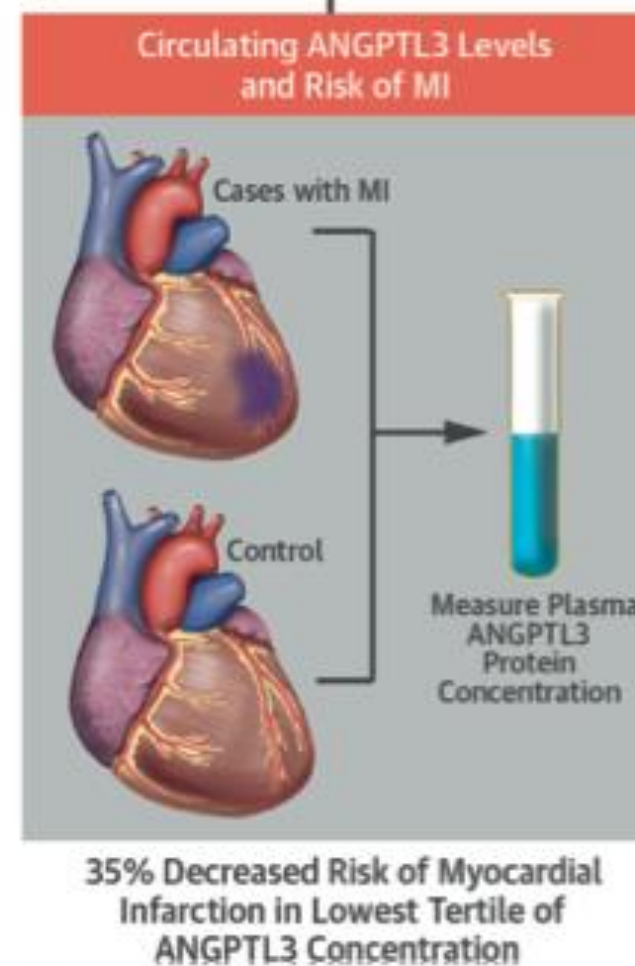
PMID: 28538111

[Similar articles](#)

## [\*\*ANGPTL3\*\* Inhibition in Homozygous Familial Hypercholesterolemia.](#)

Gaudet D, Gipe DA, Pordy R, Ahmad Z, Cuchel M, Shah PK, Chyu KY, Sasiela WJ, Chan KC, Brisson D, Khoury E, Banerjee P, Gusarova V, Gromada J, Stahl N, Yancopoulos GD, Hovingh GK.

N Engl J Med. 2017 Jul 20;377(3):296-297. doi: 10.1056/NEJMc1705994. No abstract available.

**A****B****C**

**3 Lines of Evidence:  
ANGPTL3 Deficiency  
Protects Against CAD**





# Cardiovascular endocrinology: Is *ANGPTL3* the next *PCSK9*?

Kiran Musunuru & Sekar Kathiresan

[Affiliations](#) | [Corresponding author](#)

*Nature Reviews Endocrinology* (2017) | doi:10.1038/nrendo.2017.88

Published online 14 July 2017

# Lp(a)

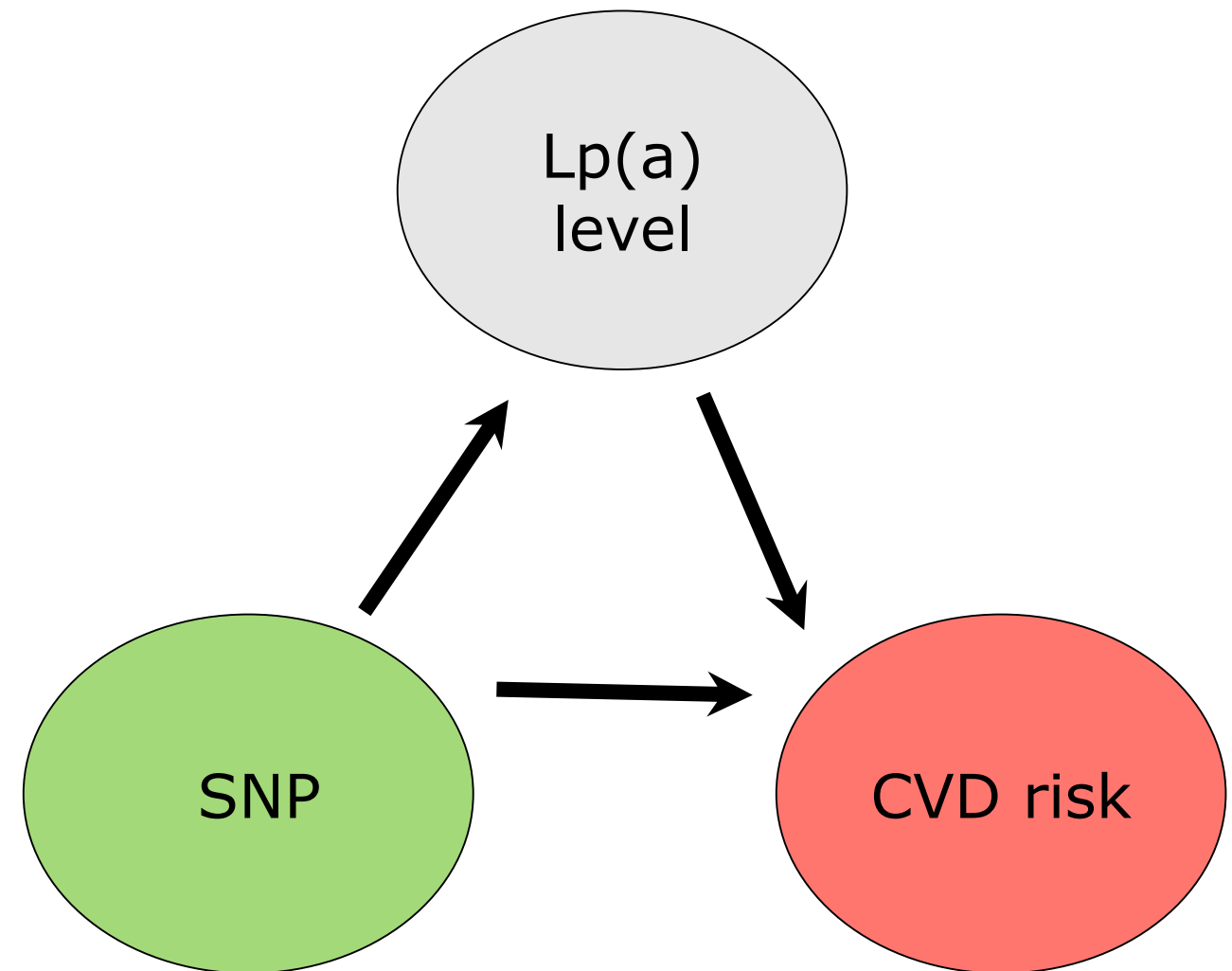
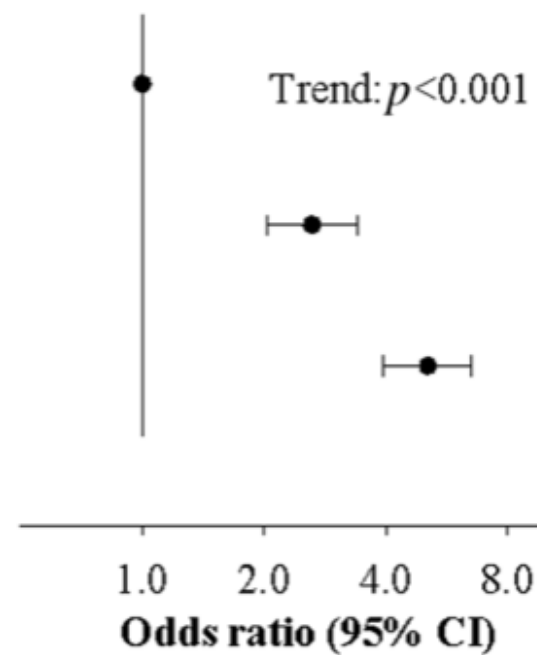
Coronary (CIHDS): case-control

Lp(a) (mg/dL)	Controls (N)	Cases (N)
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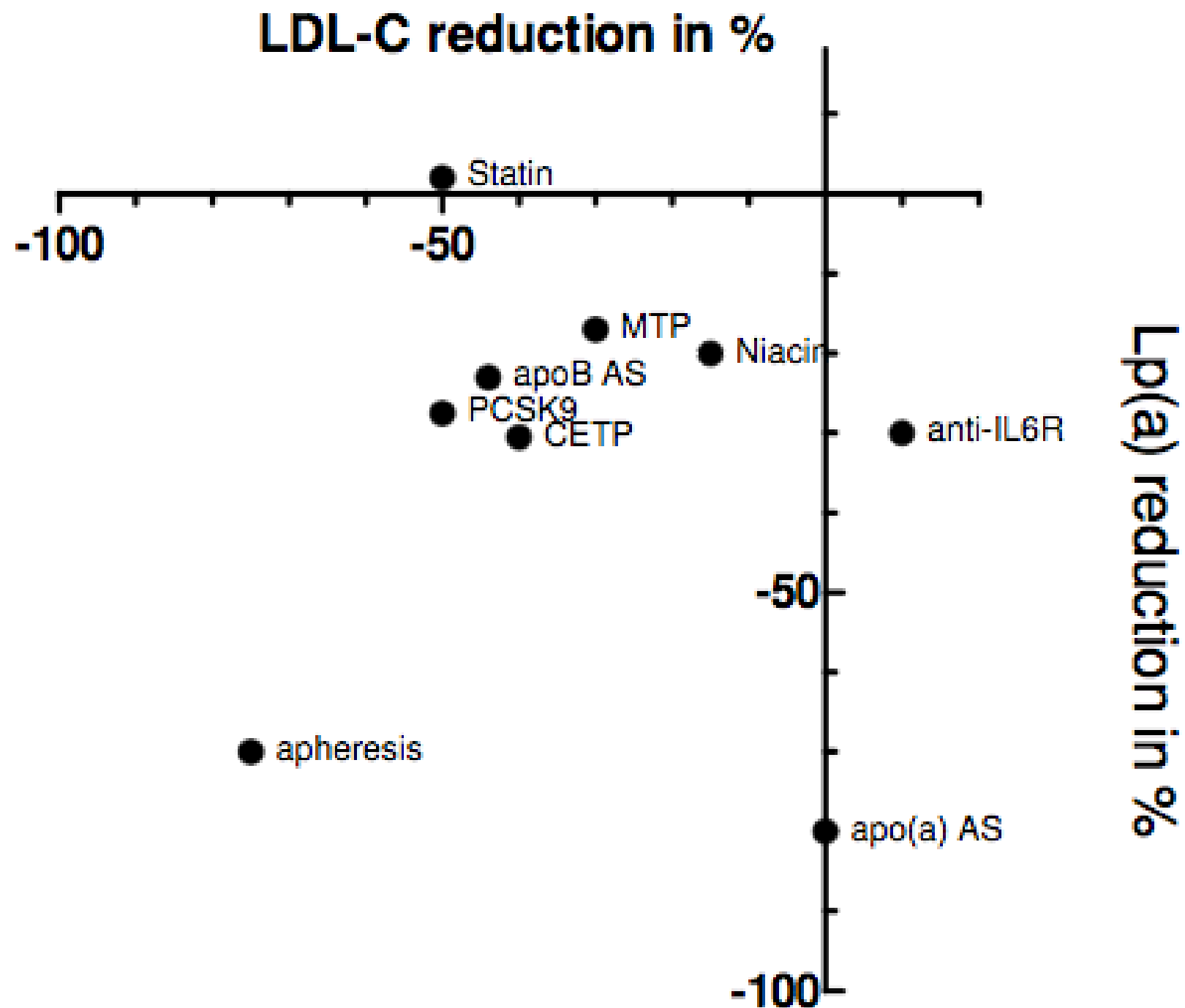
3 (1-7)	576	113
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20 (15-27)	455	234
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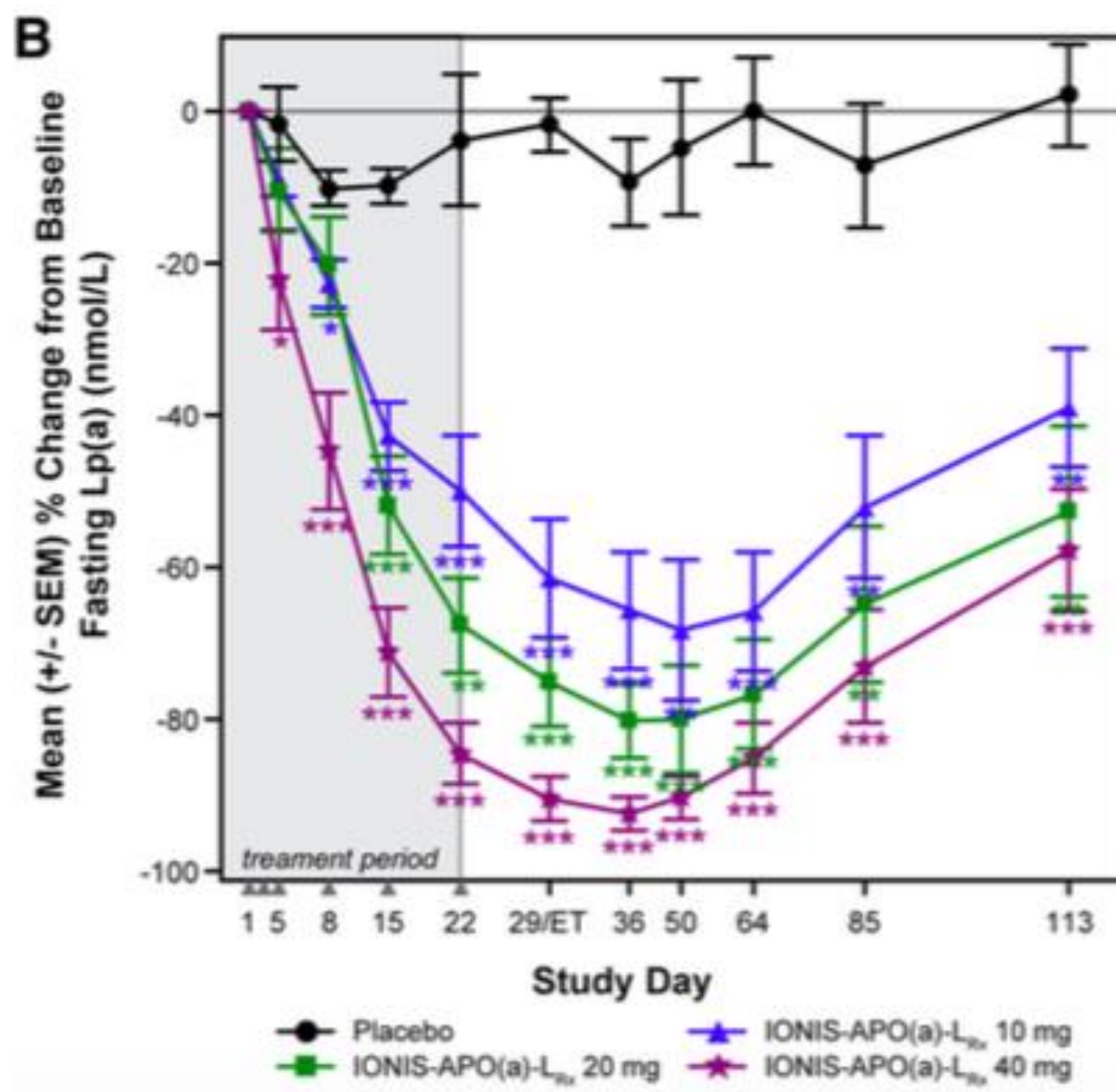
72 (48-119)	347	342
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# Effect of current therapies on Lp(a)



# Antisense Rx; low dose, impressive and longlasting Lp(a) lowering



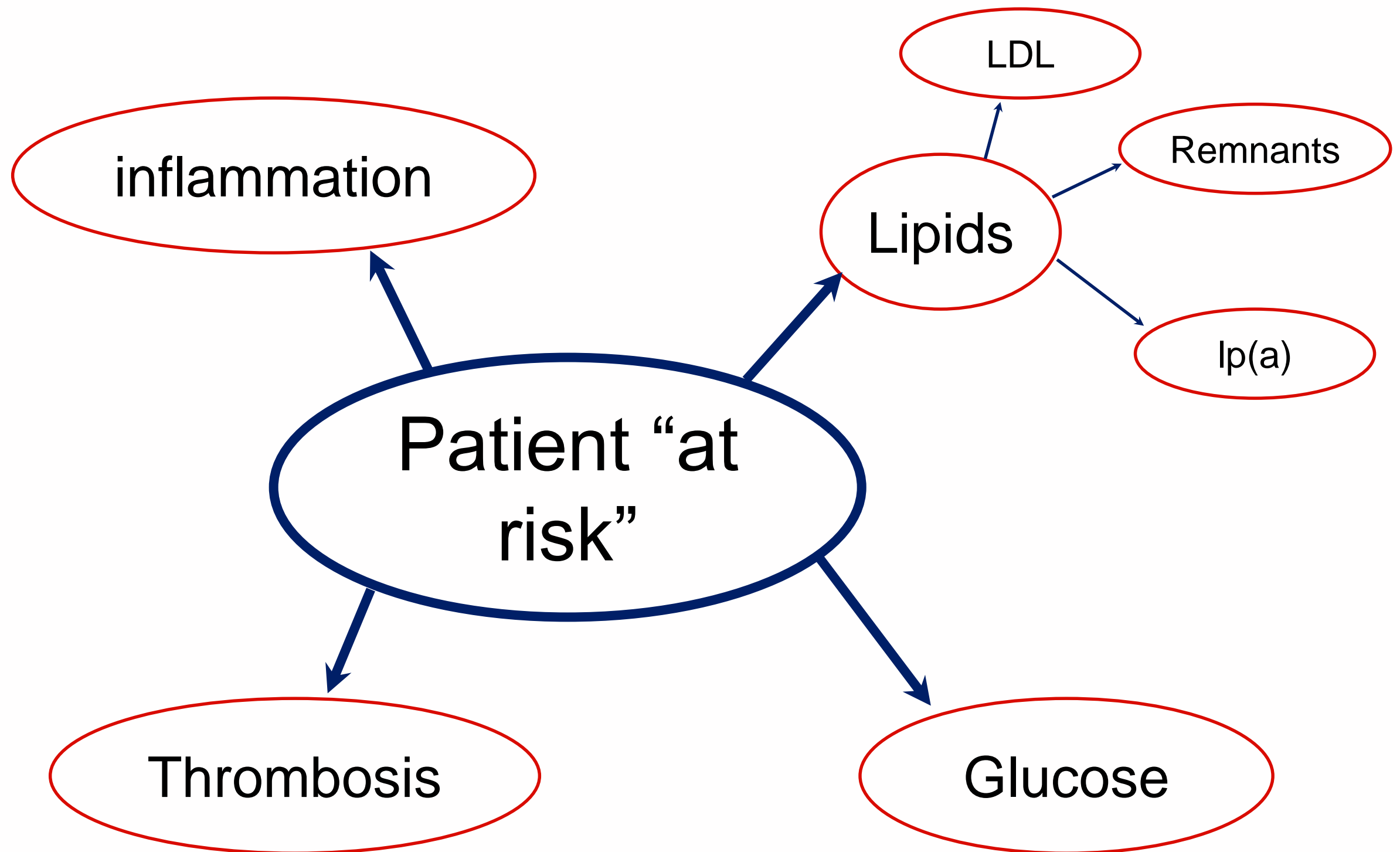
Viney N, Capelleveen J, -- Stroes E, Tsimikas S, Lancet (2016)

PCSK9, ANGPTL3 and  $l_p(a)$  and so much more....



# CVRM in the years to come.....

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# Guideline

Daily Clinic

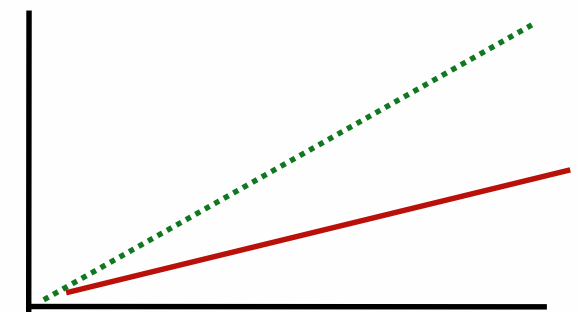
Gaps identified  
in clinic

Level of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

## Evidence rating

Evidence from clinical trials  
(and observational) studies



# Guideline

Level of evidence

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## Evidence rating

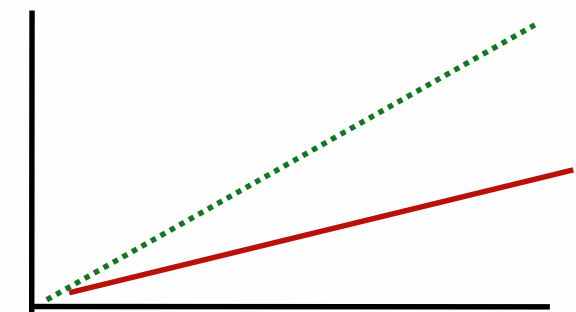
Daily Clinic

Collaborative Strategy, nationwide?

Gaps identified  
in clinic

Evidence from clinical trials  
(and observational) studies

How to deal with the results of  
CANTOS, Compass, Empareg and  
FOURIER





# Cholesterol; what are the future lipid targets?

*“lipidologist out-of-business in 5-10 years”?*

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You Bet!