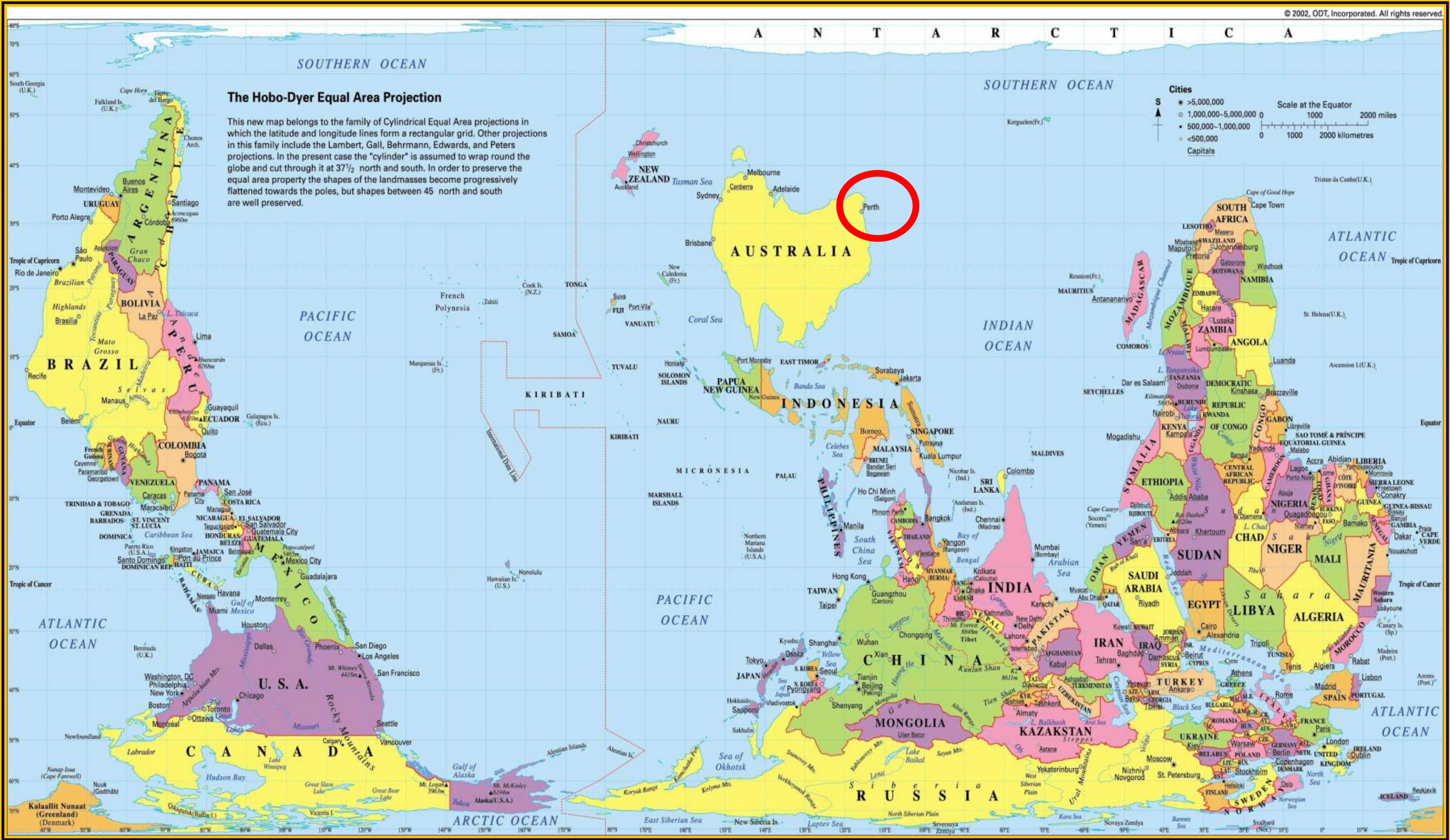
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ANTARCTICA
SOUTHERN OCEAN
The Hobo-Dyer Equal Area Projection
This new map belongs to the family of Cylindrical Equal Area projections in which the latitude and longitude lines form a rectangular grid. Other projections in this family include the Lambert, Gall, Behrmann, Edwards, and Peters projections. In the present case the "cylinder" is assumed to wrap round the globe and cut through it at 37½ north and south. In order to preserve the equal area property the shapes of the landmasses become progressively flattened towards the poles, but shapes between 45 north and south are well preserved.
Cities
>5,000,000
1,000,000–5,000,000
500,000–1,000,000
<500,000
Capitals
Scale at the Equator
0 1000 2000 miles
0 1000 2000 kilometres
AUSTRALIA
Perth
Adelaide
Melbourne
Sydney
Brisbane
NEW ZEALAND
Tasman Sea
Coral Sea
PAPUA NEW GUINEA
INDONESIA
MALAYSIA
PHILIPPINES
INDIAN OCEAN
PACIFIC OCEAN
ATLANTIC OCEAN
ARCTIC OCEAN
BRAZIL
ARGENTINA
CHILE
PERU
BOLIVIA
COLOMBIA
VENEZUELA
MEXICO
U. S. A.
CANADA
SOUTH AFRICA
ANGOLA
ZAMBIA
SUDAN
CHAD
NIGER
MALI
LIBYA
ALGERIA
EGYPT
SAUDI ARABIA
IRAN
INDIA
CHINA
MONGOLIA
KAZAKSTAN
RUSSIA
TURKEY
JAPAN
KIRIBATI
MICRONESIA
Tropic of Capricorn
Equator
Tropic of Cancer

Gerald F Watts: Disclosures

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other*
Amgen	X	X	X					
Kowa	X							
MSD	X							
Sanofi	X	X	X					
Regeneron		X	X					
Gemphire		X						
Pfizer			X					

PCSK9 mAbs 2018

Gerald F Watts

Cardiometabolic Service, Royal Perth Hospital,

School of Medicine, University of Western Australia

SITeCS, Naples, November 17th, 2018

Outline of Presentation

- Background & Context
- Clinical Outcome Trials
- Contemporary Guidelines
- Clinical Use & Challenges

PCSK9 inhibition meets several challenges in ASCVD prevention

- Residual risk on statins
- Non-adherence to orals
- Statin intolerance
- High LDL (FH)
- High Lp(a)

Determinants of CV Benefit

- Background absolute CV risk
- Baseline LDL-C concentration
- Magnitude of LDL-C reduction
- Duration of LDL-C reduction

Ference et al Eur Heart Jl 2017

PCSK9 is encoded by a gene associated with LDL-C and CAD

Gain of function → High LDL
Premature heart disease

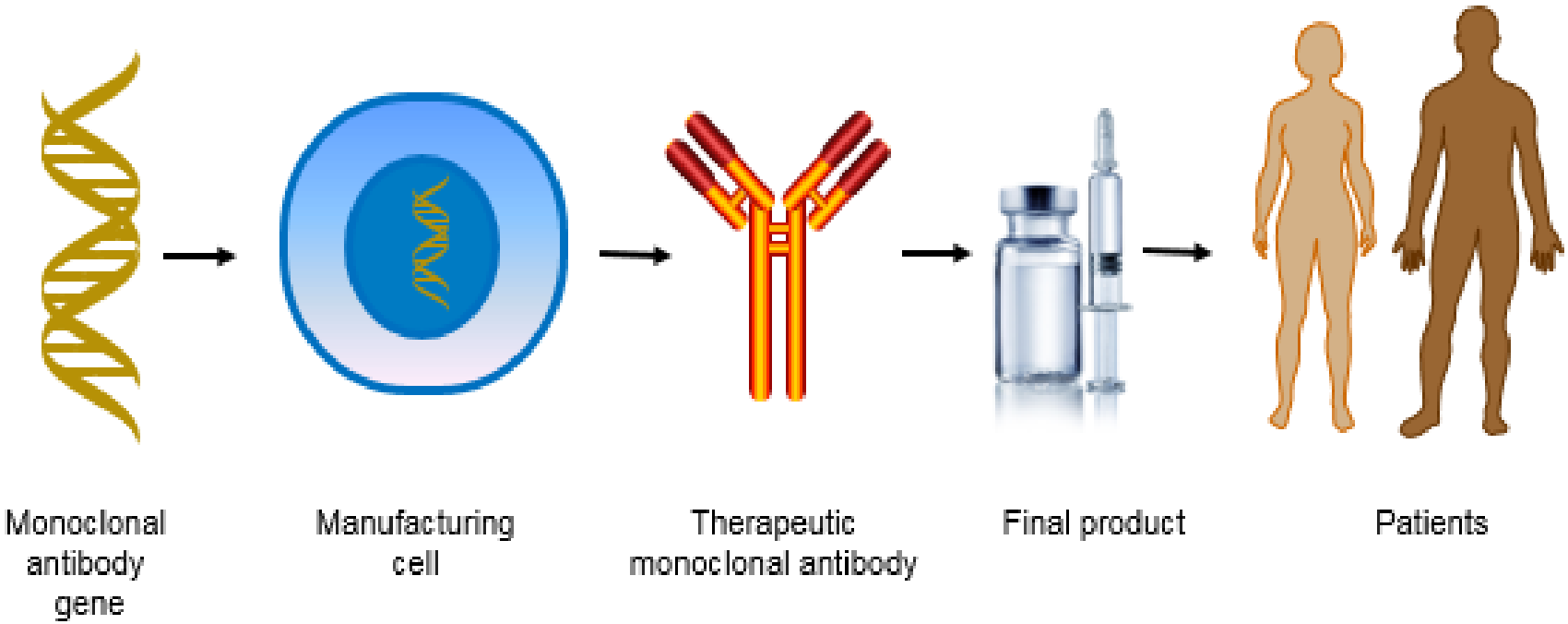
Loss of function → Low LDL
Prevention of heart disease

Abifadel M, et al. Nat Genet 2003;34:154-156.
Cohen J, et al. N Engl J Med 2006; 354:1264–1272.
Page MM, et al. Clinical Science 2015;129:63-79.

Anti-PCSK9 Therapeutic Agents

- **Inhibition of PCSK9 binding to LDLR**
  - **Monoclonal antibodies (mAb)**
  - **Small peptide molecules**
  - **Adnectins**
  - **Vaccines**
- **Inhibition of PCSK9 synthesis (gene silencing)**
  - **Antisense oligonucleotides**
  - **Small interfering RNA**
- **Inhibition of PCSK9 autocatalytic processing**
  - **Small molecule inhibitors**

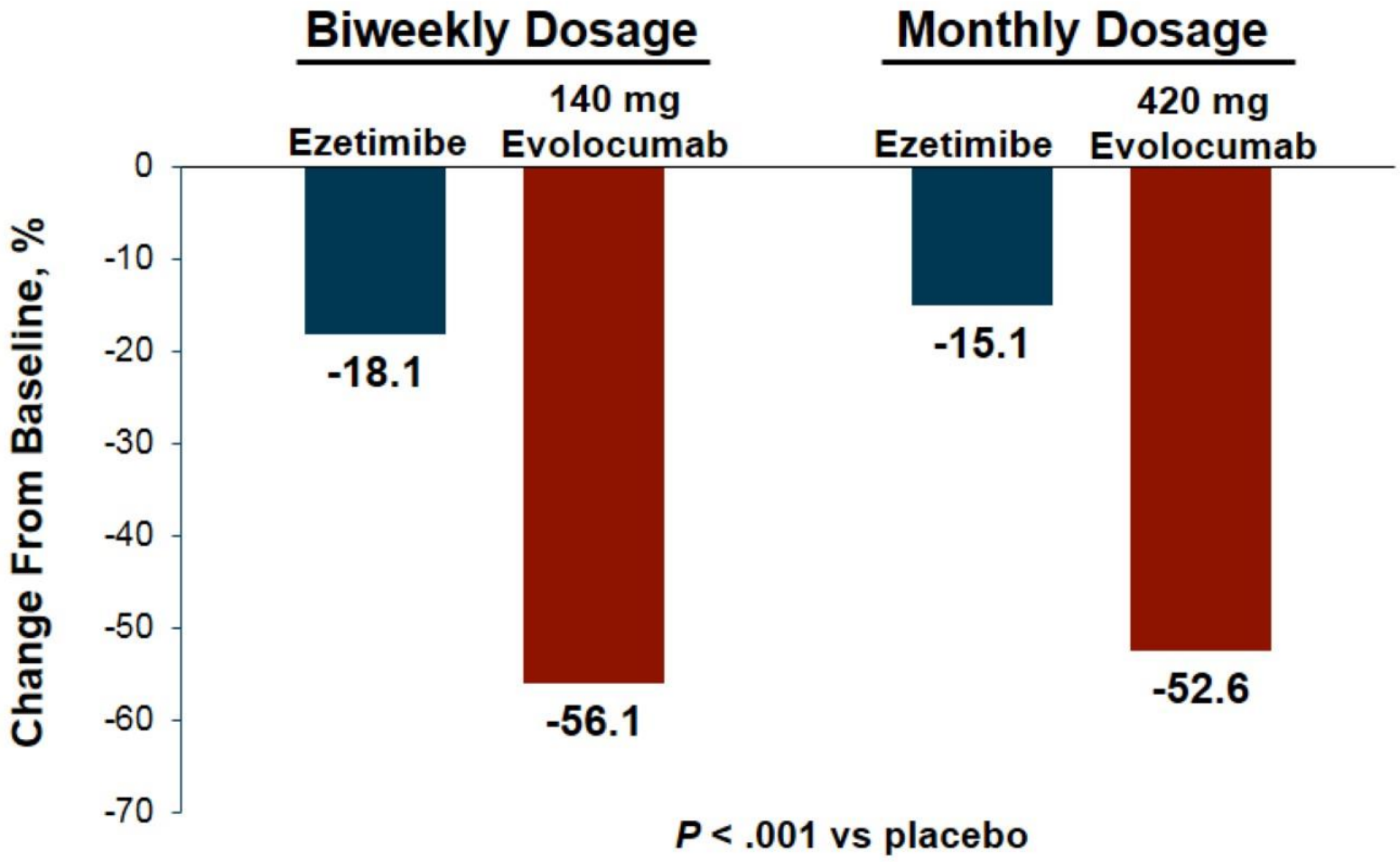
Monoclonal Antibodies



Evolocumab **Alirocumab**

GAUSS-2 Study of Evolocumab in Statin-Intolerant Patients

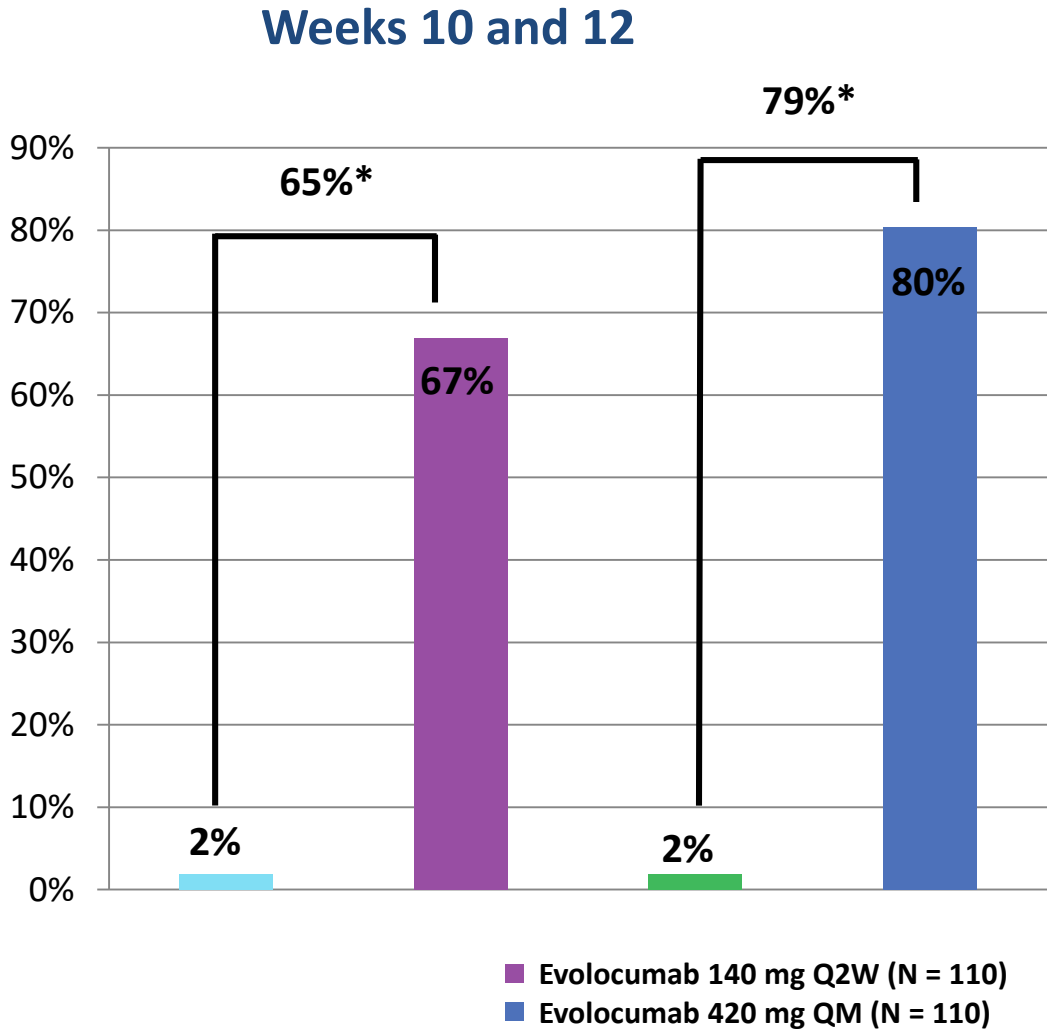
% Change in LDL-C From Baseline at Week 12



Stroes E, et al. *J Am Coll Cardiol*. 2014;63:2541-2548.

RUTHERFORD-2: Trial in heterozygous FH

With Evolocumab the majority of patients achieved LDL-C goal < 1.8 mmol/L regardless of background statin therapy



*P<0.0001 evolocumab treatment difference vs placebo

Raal FJ, et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61399-4 and supplementary material.

PCSK9 mAb CV Outcome Trials

Evolocumab : FOURIER[1]
N = 27,564

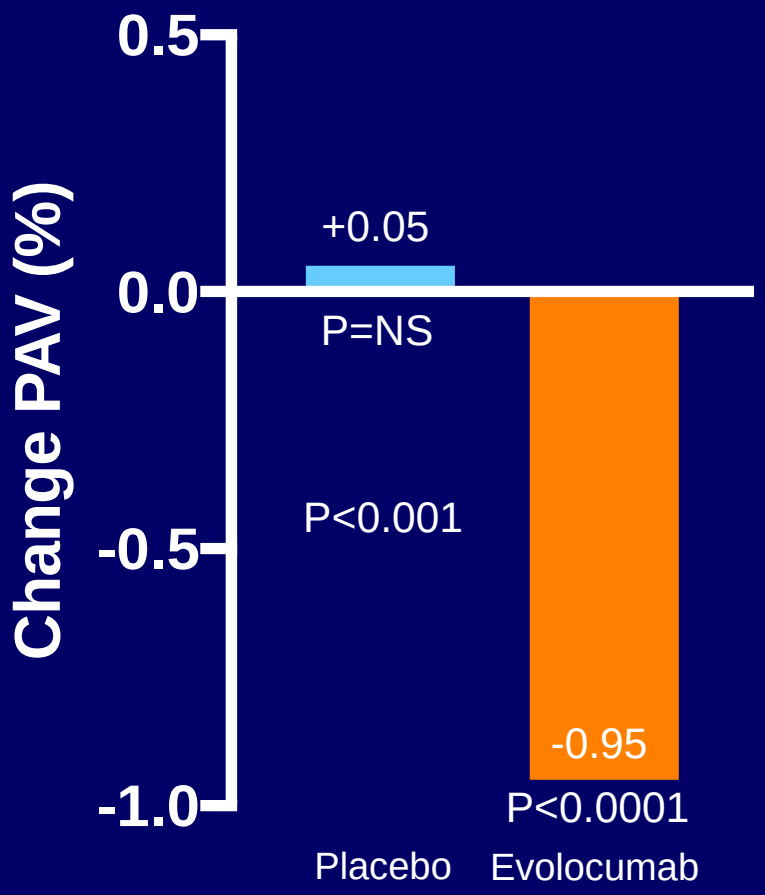
*Non-haemorrhagic stroke.

Alirocumab :
ODYSSEY OUTCOMES[2]
N ~ 18,000

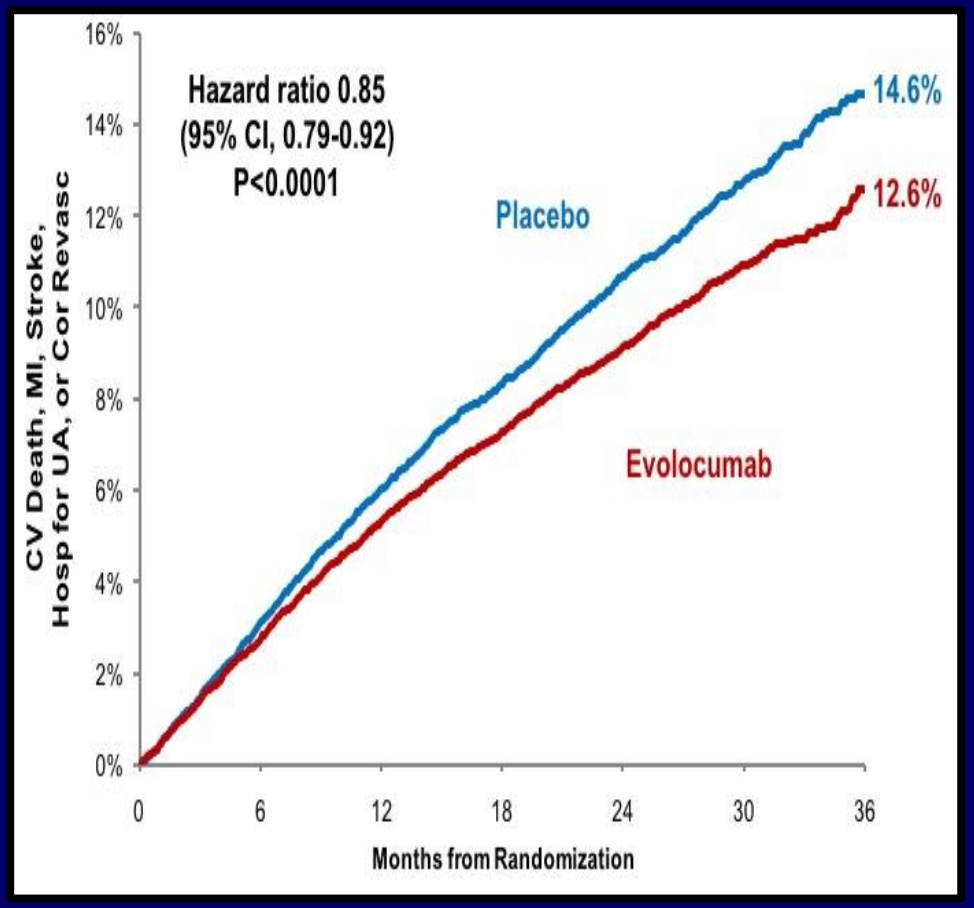
1. Sabatine MS, et al. Am Heart J 2016;173:94–101.
2. Schwartz GG, et al. Am Heart J 2014;168:682–9.

Benefit of Evolocumab on Plaque and Cardiovascular Outcomes

GLAGOV



FOURIER



Nicholls JAMA 2016.
Sabatine NEJM 2017.

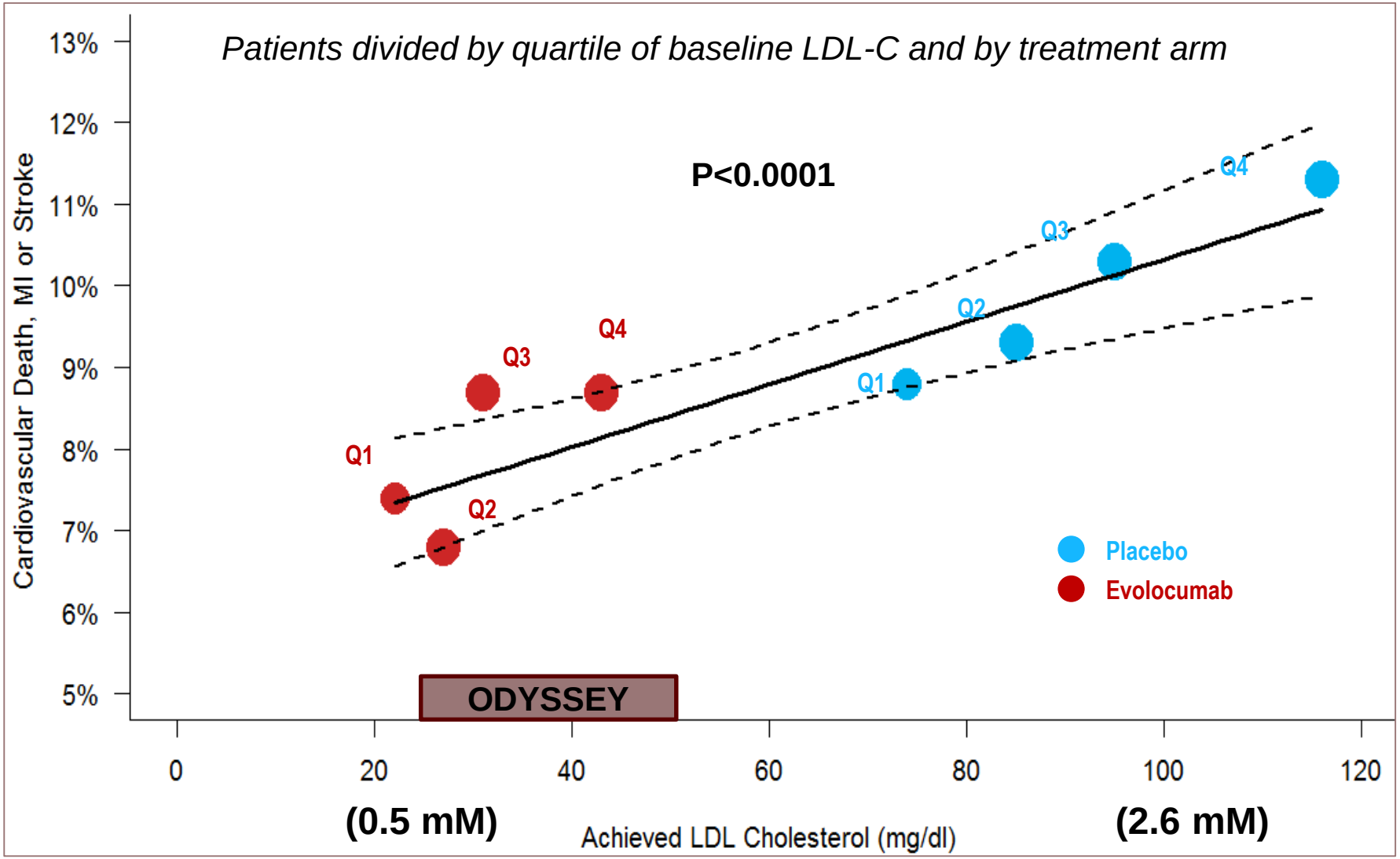
Conclusions

- LDL-C can now be reduced to unprecedented low levels with statin + PCSK9i (<< 1 mmol/L)
- A strong progressive relationship of achieved LDL-C and CV events seen, down to LDL <0.26 mmol/L (<10 mg/dL)
- No excess in safety events with very low achieved LDL-C <0.5 mmol/L (<20 mg/dL) at 2.2 years

These data suggest that we should target considerably lower LDL-C than is currently recommended for our patients with atherosclerotic CV disease

Sabatine and Giugliano JAMA Cardiol 2017; 2: 935-6

Lower LDL-C is Better



Lower Numbers Needed to Treat

- Diabetes Mellitus…….. 37
- Recent/multiple MIs…. 35
- Multivessel CAD…….. 29
- Peripheral AD…….. 16

Sabatine et al Lancet Diabetes Endocrinol 2017; 5: 941-50
Bonaca et al Circulation 2018 ;137:338-350

High CRP and Lp(a)

The NEW ENGLAND JOURNAL of MEDICINE

DOI: 10.1056/NEJMoa1801174

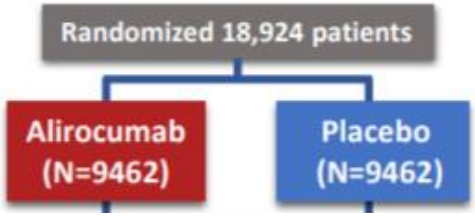
ORIGINAL ARTICLE

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

G.G. Schwartz, P.G. Steg, M. Szarek, D.L. Bhatt, V.A. Bittner, R. Diaz, J.M. Edelberg, S.G. Goodman, C. Hanotin, R.A. Harrington, J.W. Jukema, G. Lecorps, K.W. Mahaffey, A. Moryusef, R. Pordy, K. Quintero, M.T. Roe, W.J. Sasiela, J.-F. Tamby, P. Tricoci, H.D. White, and A.M. Zeiher, for the ODYSSEY OUTCOMES Committees and Investigators*

ODYSSEY OUTCOMES

Patient Disposition

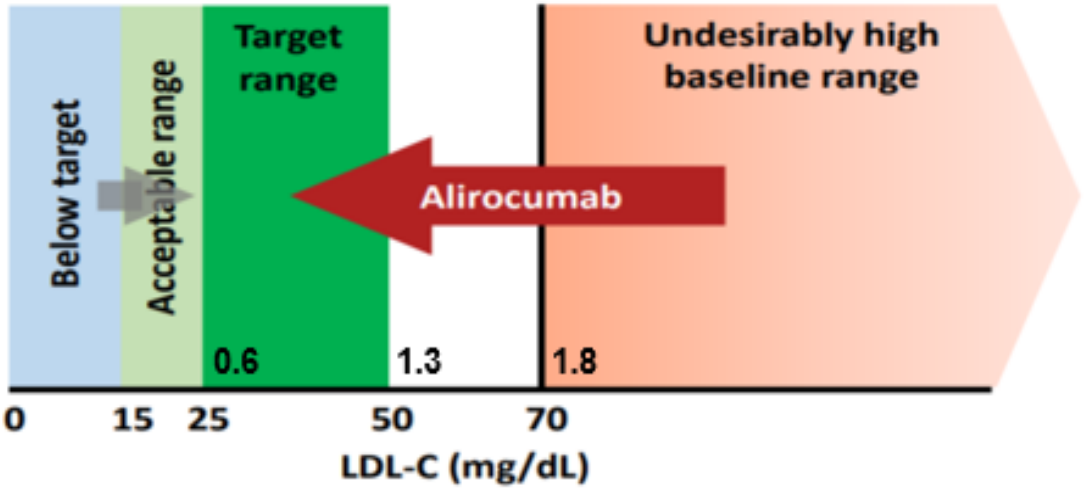


A Target Range for LDL-C

- Premature t
- Blinded swit LDL-C values
- Patients lost

*Ascertainmer and all-cause d

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.

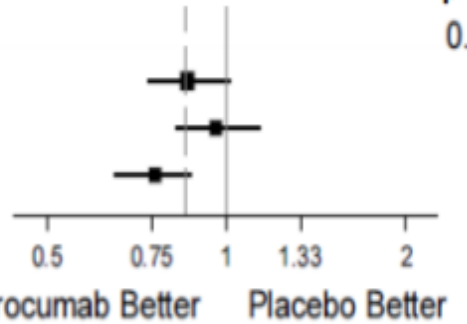


SEY
OMES

ODYSSEY OUTCOMES

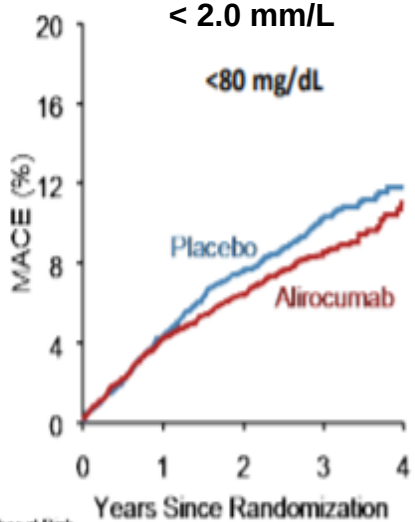
Primary Efficacy in Main Prespecified Subgroups

Subgroup	Patients	Incidence (%) Alirocumab	Placebo	HR (95% CI)	p-value*
LDL (mg/dL)					0.09
<80	7164	8.3	9.5	0.86 (0.74, 1.01)	
80 - <100	6128	9.2	9.5	0.96 (0.82, 1.14)	
≥100	5629	11.5	14.9	0.76 (0.65, 0.87)	



*P-values for interaction

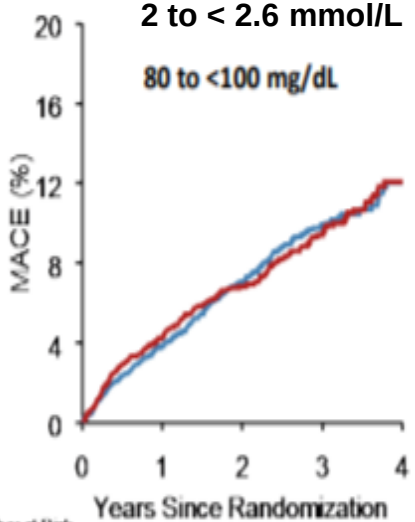
< 2.0 mm/L



Number at Risk

Placebo	3583	3347	3122	1290	256
Alirocumab	3581	3365	3183	1327	233

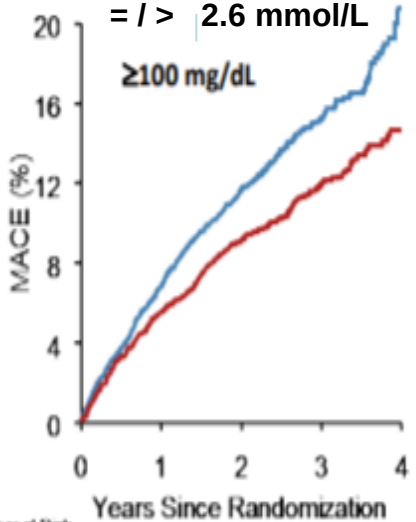
2 to < 2.6 mmol/L



Number at Risk

Placebo	3062	2889	2708	1195	195
Alirocumab	3066	2880	2732	1194	213

= / > 2.6 mmol/L



Number at Risk

Placebo	2815	2568	2371	986	178
Alirocumab	2814	2602	2431	1053	207

ODYSSEY OUTCOMES

ODYSSEY OUTCOMES

Conclusions

The total number of nonfatal cardiovascular events and deaths prevented with alirocumab was twice the number of first events prevented.

Consequently, total event reduction may be is a more comprehensive metric to capture the totality of alirocumab clinical efficacy after ACS.

Szarek M et al J Am Coll Cardiol. 2018 Oct 27th

ODYSSEY OUTCOMES

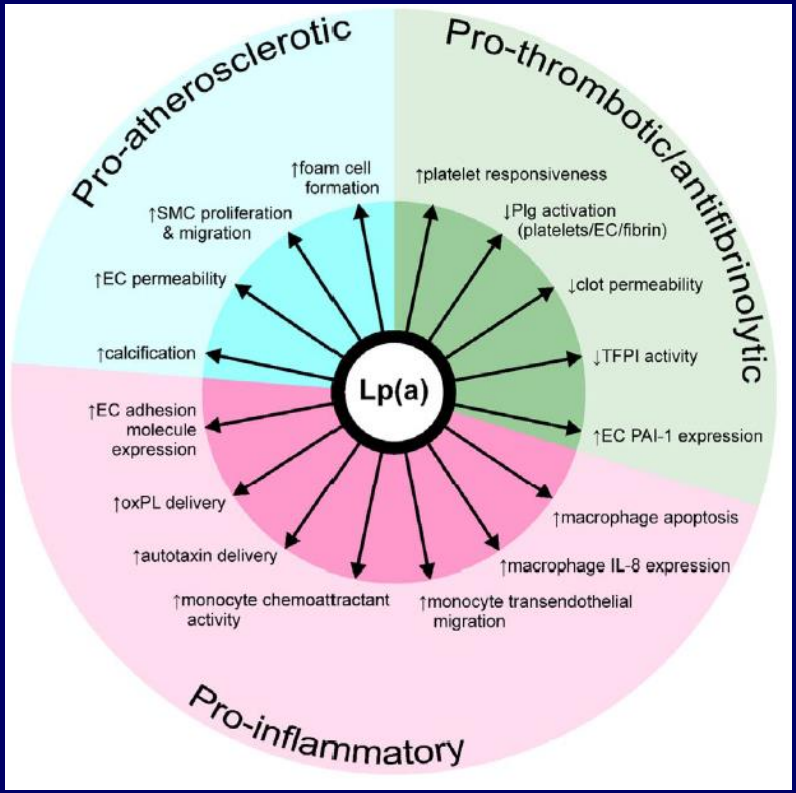
Clinical Perspective

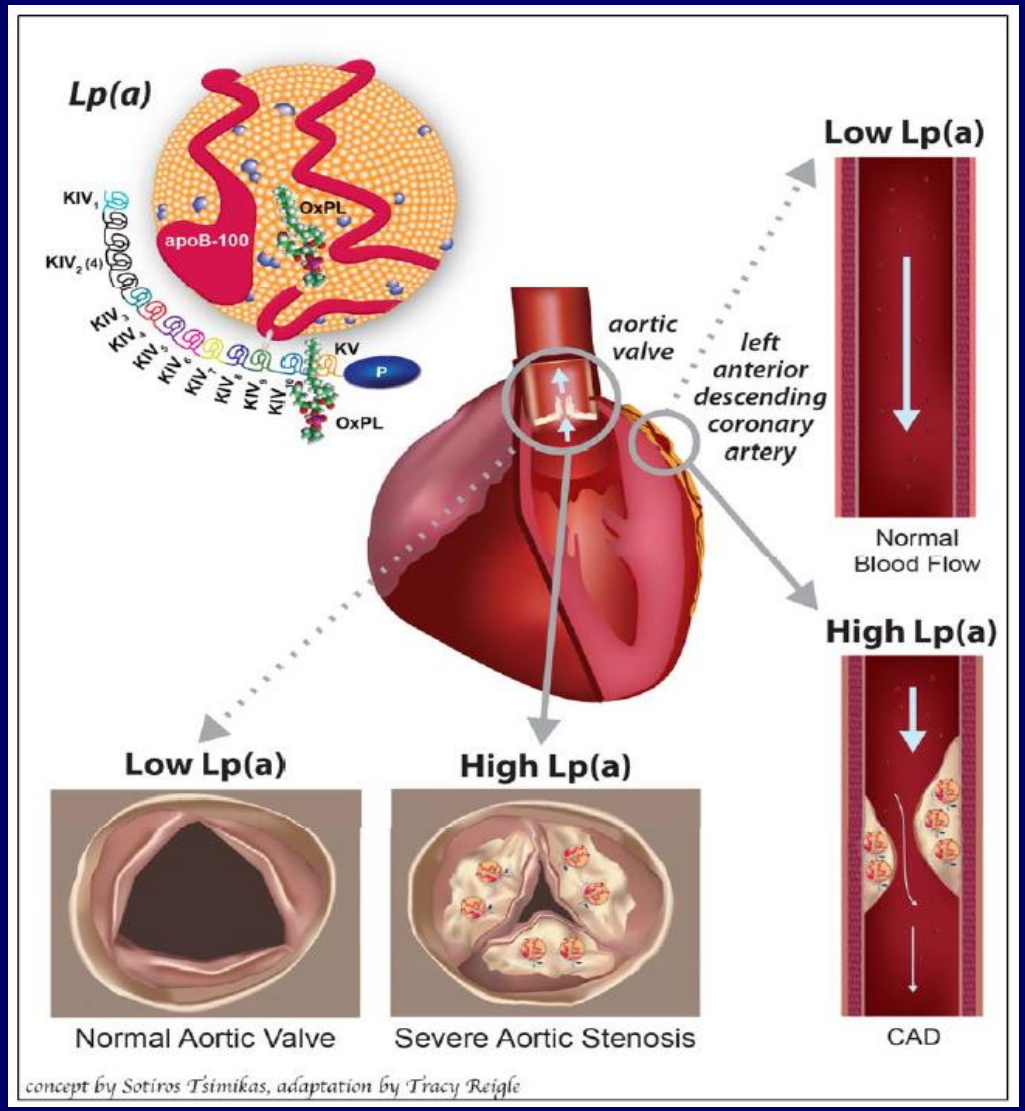
- In this nearly 19,000-patient placebo-controlled trial, including many patients treated for ≥3 years, there was no safety signal with alirocumab other than injection site reactions
- Among patients with ACS and baseline LDL-C ≥100 mg/dL, alirocumab reduced MACE by 24% (ARR 3.4%) and all-cause death by 29% (ARR 1.7%) compared with placebo
  - ➢These are the patients who may benefit most from treatment

ARR, absolute risk reduction

ODYSSEY OUTCOMES

Lp(a)





Ellis et al Progress Lipid Res 2017

ODYSSEY OUTCOMES: Lp(a)

Conclusions

1. Baseline Lp(a) is an independent predictor of MACE and non-fatal MI among patients with recent ACS, independent of treatment with alirocumab and baseline LDL-C.
2. Lp(a) lowering by alirocumab is associated with a reduced risk of MACE and non-fatal MI, independent of baseline LDL-C and concurrent LDL-C lowering.

Bittner et al ISA, Toronto, 2018

Trial-Based Economic Analysis

Bhatt et al, AHA 18

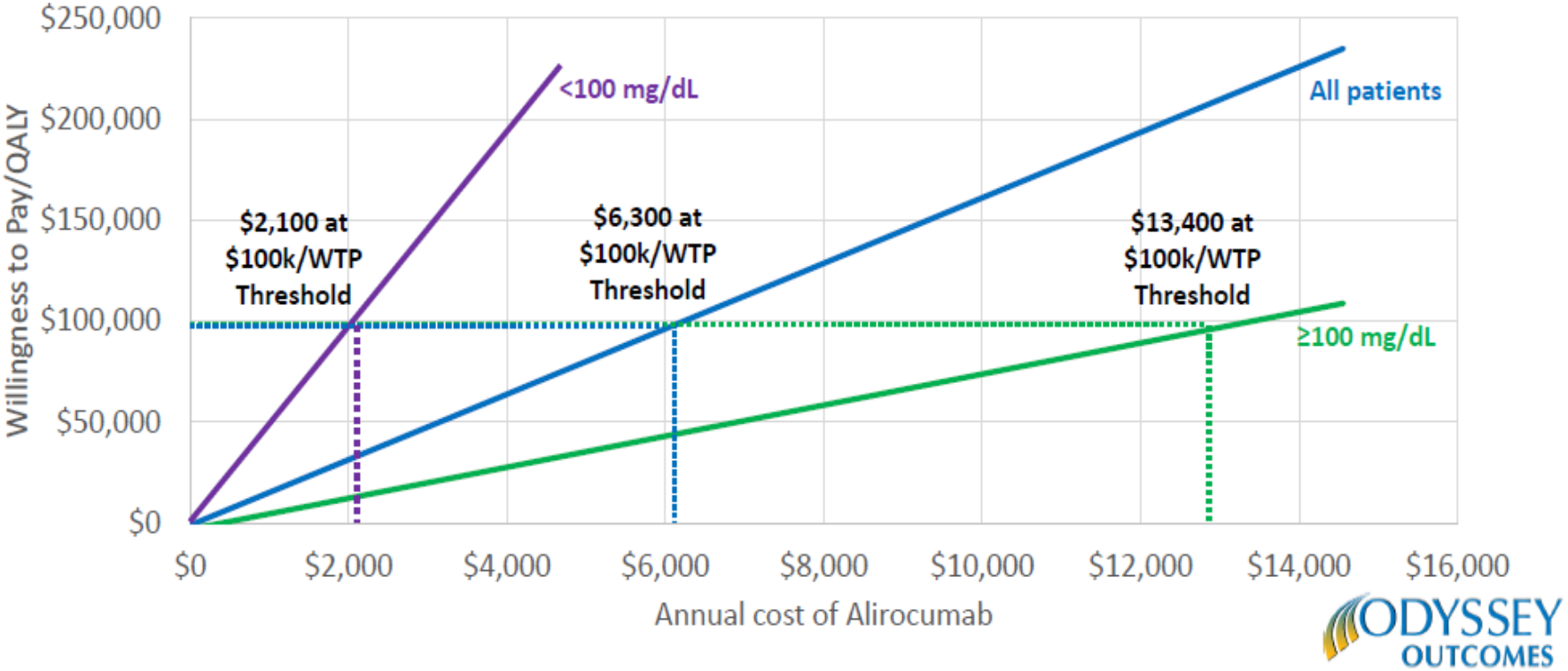
Conclusion

- In the overall ODYSSEY OUTCOMES population, alirocumab was cost effective at a price up to **$6,319** per year at the $100,000 willingness to pay threshold
- The higher the baseline LDL-C, the higher the value of alirocumab appeared to be
- Based on both absolute clinical benefit and cost-effectiveness, alirocumab may offer good value in patients with a history of ACS and LDL-C ≥100 mg/dL despite maximally tolerated statin therapy

Bhatt D et al AHA, Chicago, Nov 2018

Varying the Cost of Alirocumab

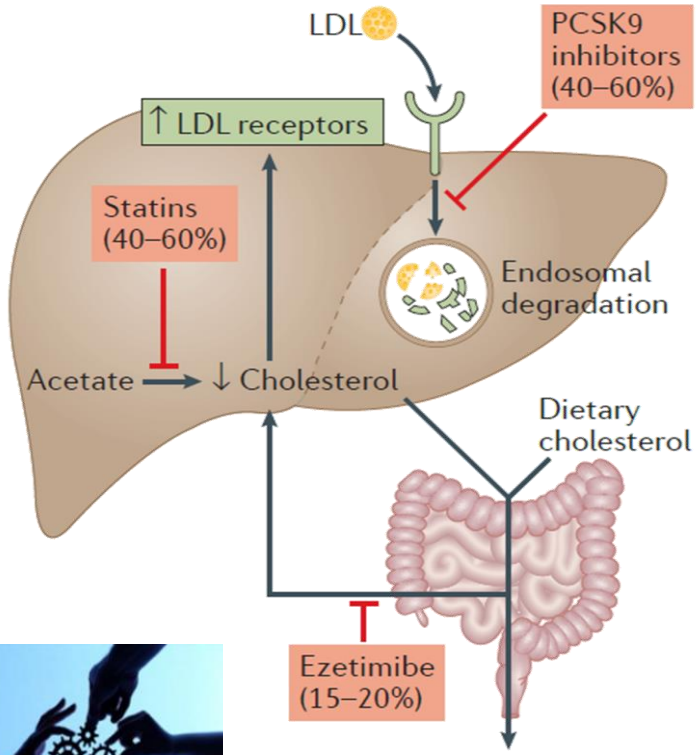
At any level of willingness to pay, cost-effectiveness is lesser in patients with baseline LDL-C values <100 mg/dL relative to the overall ITT population



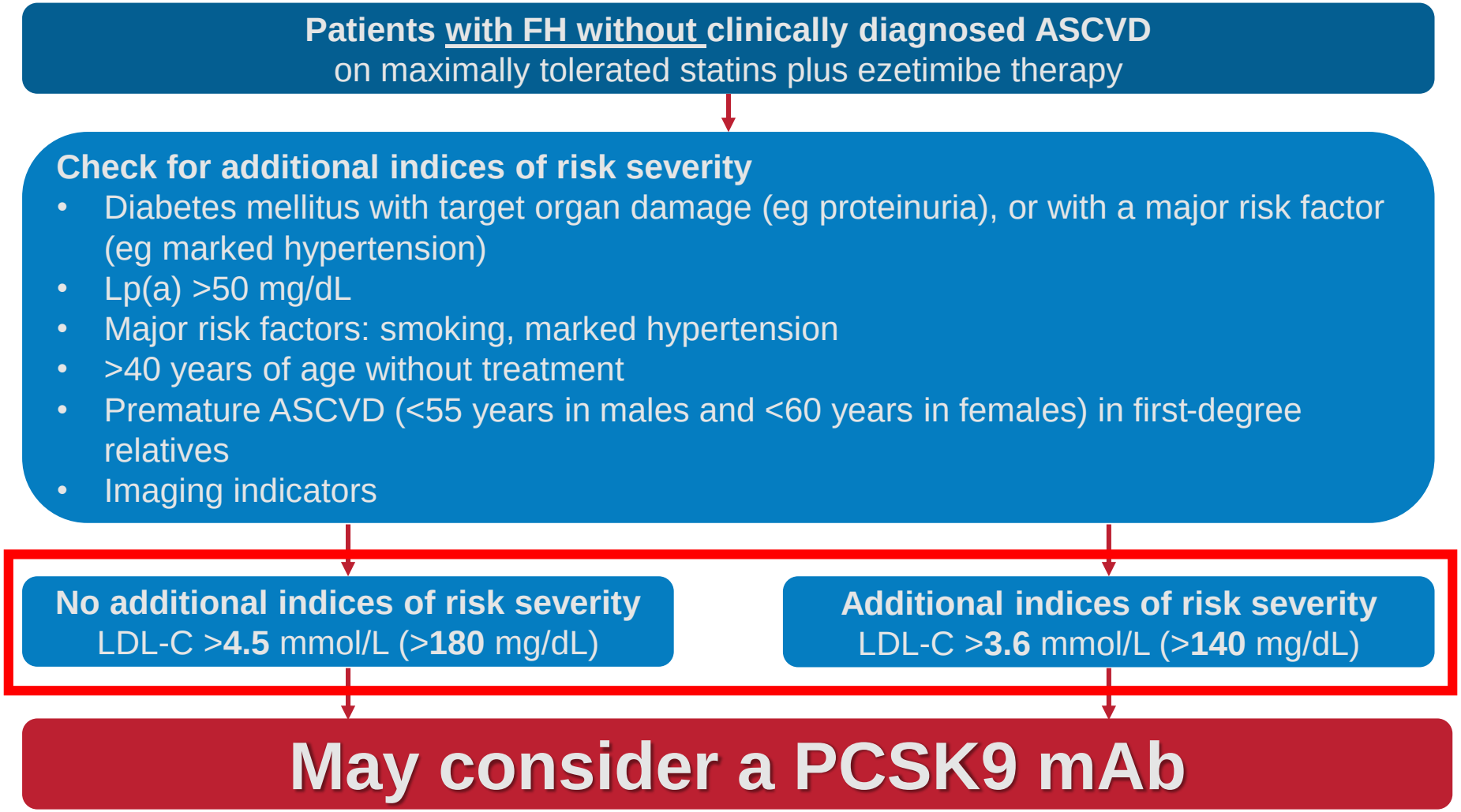
Bhatt D et al AHA, Chicago, Nov 2018

Multiple recommendations on use of PCSK9 monoclonal antibodies

- **American Heart Association/American College of Cardiology**
  - Grundy SM et al *Circulation 2018 Nov 3rd*
- **American Heart Association**
  - Gidding SS *et al. Circulation* 2015;132:167–92.
- **American College of Cardiology**
  - Lloyd-Jones DM *et al. J Am Coll Cardiol* 2017;70:1785–822.
- **International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel**
  - Santos RD *et al. Lancet Diabetes Endocrinol* 2016;4:850–61.
- **European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS) Task Force**
  - Landmesser U *et al. Eur Heart J* 2017;[Epub ahead of print]
- **European Society of Cardiology**
  - Catapano AL *et al. Eur Heart J* 2016;37:2999–3058.
- **American Association of Clinical Endocrinologists / American College of Endocrinology**
  - Jellinger PS *et al Endocr Pract* 2017;23(Suppl 2):1–87.
- **National Lipid Association**
  - Orringer CE *et al. Clin Lipidol* 2017;11:880–90.



EAS/ESC Taskforce on PCSK9 mAbs



Landmesser U et al Eur Heart J 2018;39:1131-1143

EAS/ESC Taskforce on PCSK9 mAbs

Patients <u>with</u> clinically diagnosed ASCVD (CAD, symptomatic PAD, ischaemic stroke) on maximally tolerated statin therapy

± Ezetemibe

LDL-C >**2.6** mmol/L (>**100** mg/dL) and **with additional indices of risk severity**

Including

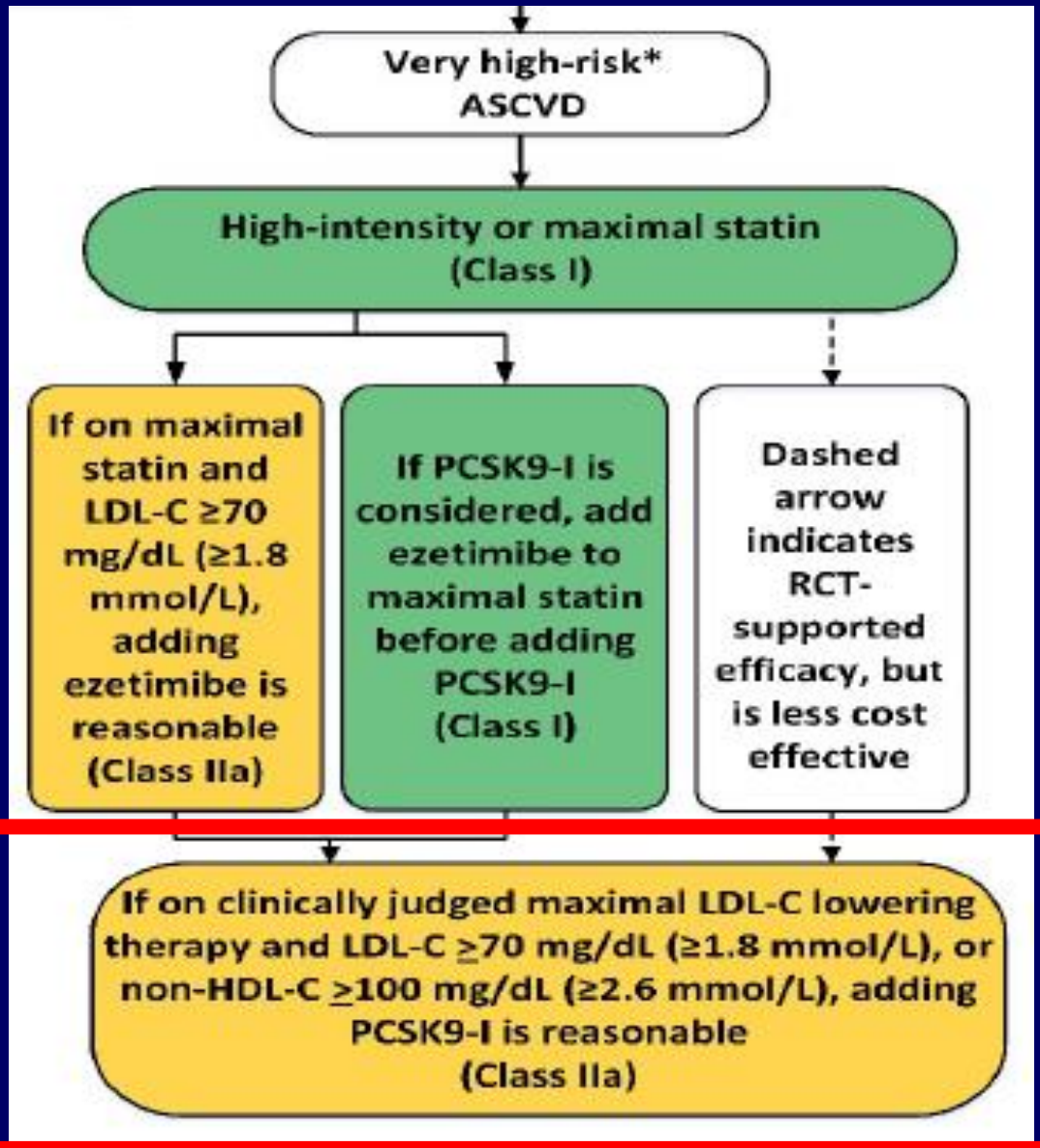
- **Familial hypercholesterolemia**
- **Diabetes mellitus** with target organ damage (eg proteinuria) or with a major risk factor such as marked hypertension
- **Severe and/or extensive ASCV (eg severe polyvascular disease, extensive coronary disease**
- Rapid progression of ASCVD ie repeated ACS, unplanned coronary revascularizations or ischaemic strokes within 5 years of index event

LDL-C >**3.6** mmol/L (>**140** mg/dL)

Should consider a PCSK9 mAb

Landmesser U et al Eur Heart J 2018;39:1131-1143

AHA/ACC Cholesterol Guidelines



Grundy SM et al Circulation 2018 Nov 10 th

Table 4. Very High-Risk* of Future ASCVD Events

Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation (S4.1-39))
High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2) (S4.1-15, S4.1-17)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

*Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

Grundy SM et al Circulation 2018 Nov 10th

4.2. Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])

COR	LOE	Recommendations
IIb	B-R	4. In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered (S4.2-9, S4.2-13–S4.2-15).
IIb	C-LD	5. In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL (≥5.7 mmol/L) or higher and who achieve an on-treatment LDL-C level of 130 mg/dL (≥3.4 mmol/L) or higher while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered (S4.2-13–S4.2-17)
Value Statement: Uncertain Value (B-NR)		6. Among patients with FH without evidence of clinical ASCVD taking maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at mid-2018 U.S. list prices.

AMERICAN COLLEGE of CARDIOLOGY

Grundy SM et al Circulation 2018 Nov 10 th

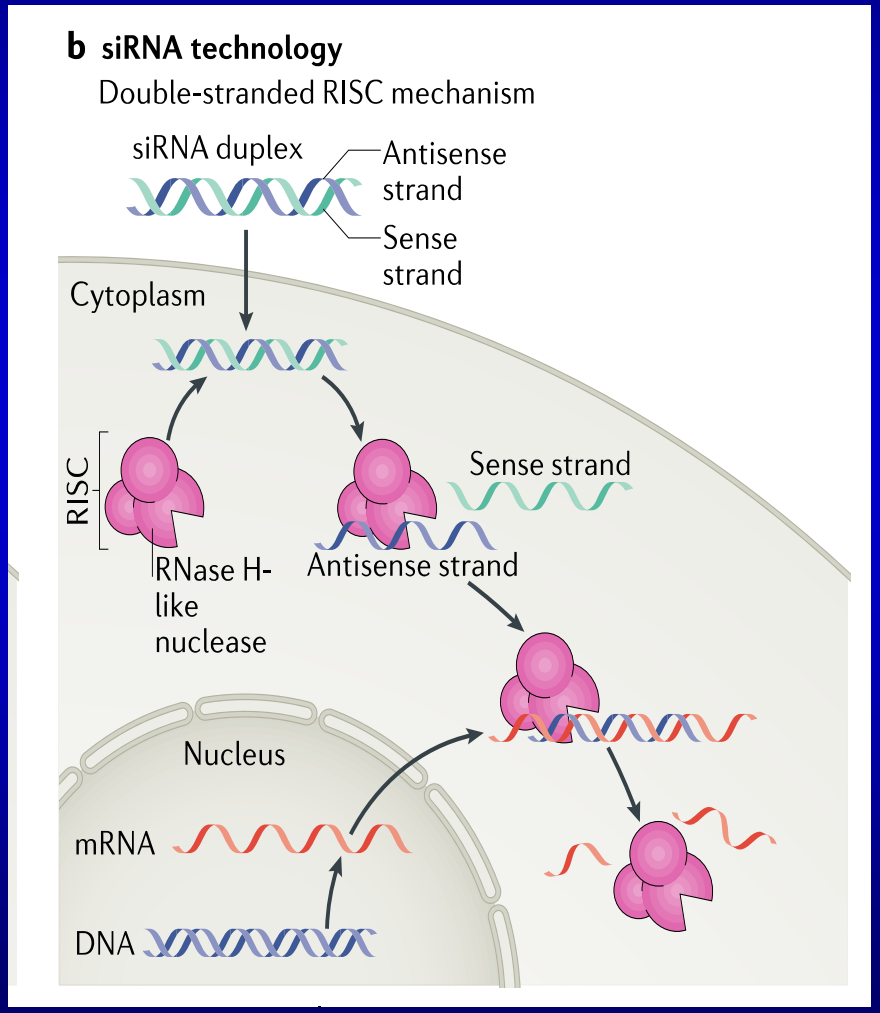
American Heart Association.

LDL-cholesterol (mmol/L) thresholds for considering adding PCSK9 mAb to max tolerated statin + ezetimibe

Patient Group	AHA/ACC 2018	ESC/EAS 2017
Higher risk ASCVD	≥1.8	>2.6
Lower risk ASCVD	-	>3.6
FH without ASCVD	≥2.6	>3.6-4.5*

* Depending on CV risk

Inclisiran: siRNA aimed at PCSK9



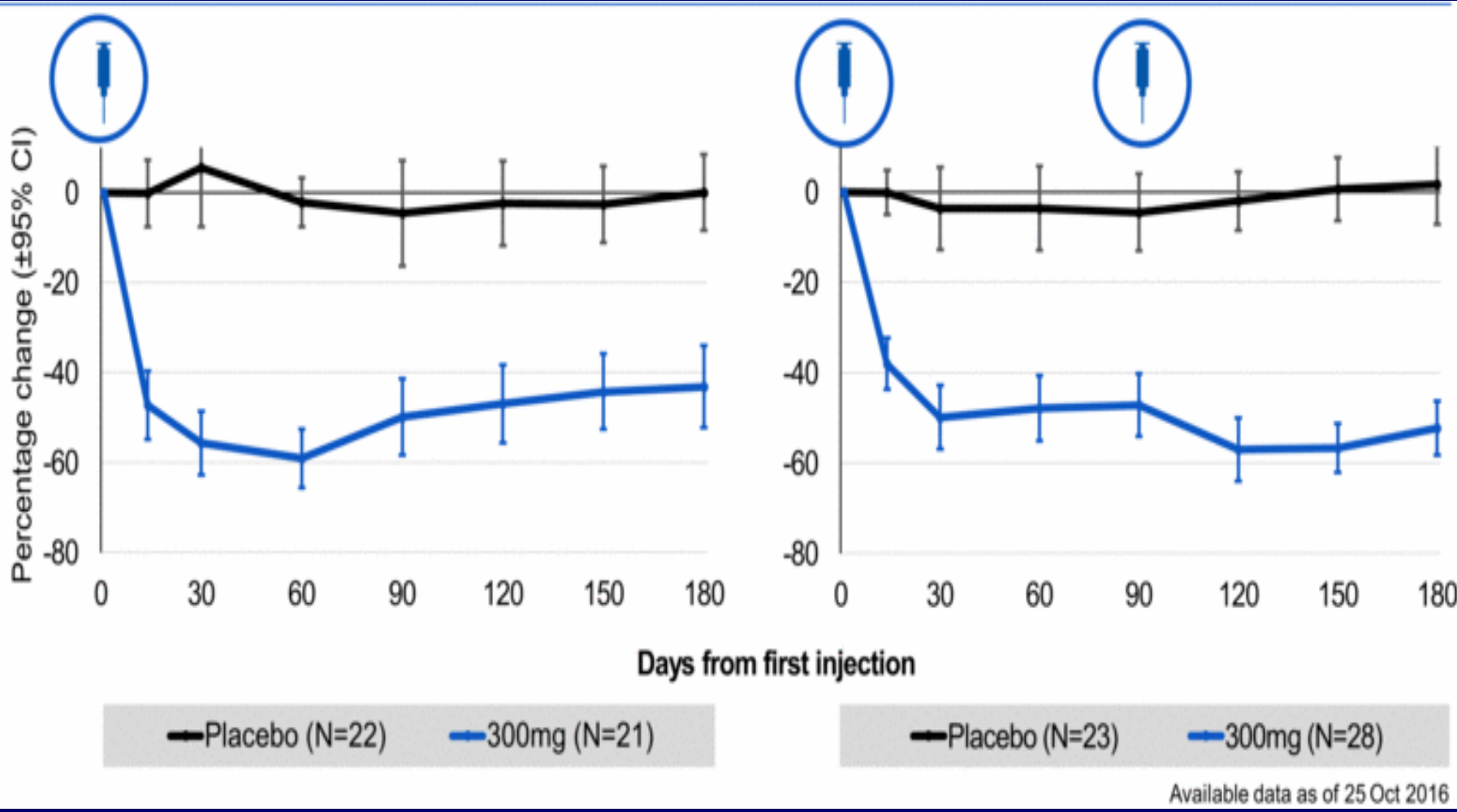
Strengths

- Lowers LDL-C comparably to mAb PCSK9 inhibitors
- Convenient two to three times yearly dosing
- Decreased variability in patient to patient LDL-C reduction compared to statins and mAb PCSK9 inhibitors

Opportunities

- Potential to gain market share by launching at a discounted price as compared to mAb PSCK9 inhibitors

One dose and two doses of Inclisiran up to day 180
Efficacy of 300 mg vs. placebo on LDLc

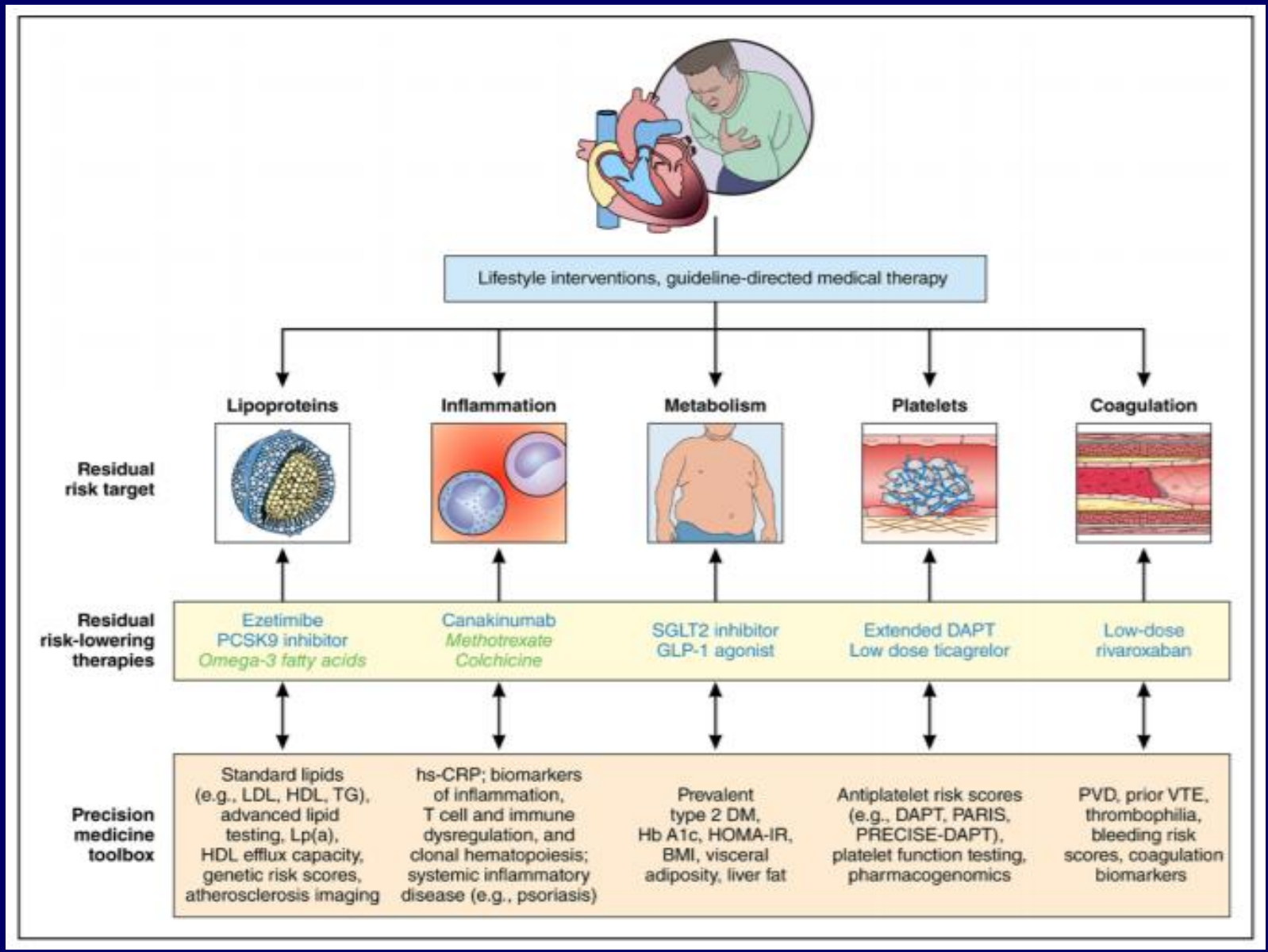


Ray et al NEJM 2017;376:1430-40.

Use and Challenges of PCSK9 mAbs

- FH Syndromes: NOW, but HoFH can be issue
- Post-ACS, stable secondary prevention: emerging indications
- Challenge of other new therapies: DAPT, Asp+ NOAC; n3-PUFAs; SGLT2is; anti-inflam; Inclisiran
- Primary prevention: need large RCTs
- Cost-benefit and safety issues

Framework for Targeting ASCVD Residual Risk



Patel et al Circulation 2018;137:2551–2553