National Lipid Association Statement

Enhancing the Value of PCSK9 Monoclonal Antibodies by Identifying Patients Most Likely to Benefit

Jennifer G Robinson MD MPH

Director, Preventive Intervention Center

Departments of Epidemiology and Internal Medicine, Division of Cardiology

University of Iowa

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Jennifer G Robinson MD MPH FAHA
Manju Benguluru Jayanna MBBS
Alan S Brown MD FACC FNLA
Karen Aspry MD MS FACC FNLA FAHA
Carl Orringer MD FLNA
Edward A Gill MD FNLA FASE FACP FACC FAHA
Anne Goldberg MD FACP FNLA
Laney K. Jones PharmD MPH
Kevin Maki, PhD
Dave L. Dixon, PharmD
Joseph Saseen PharmD FNLA
Daniel Soffer MD FNLA FACP

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Disclosures

Jennifer G Robinson MD MPH has received research grants to Institution from Acasti, Amarin, Amgen, Astra-Zeneca, Esai, Esperion, Merck, Pfizer, Regeneron, Sanofi, Takeda and served as a consultant for Amgen, Merck, Novartis, Novo Nordisk, Pfizer, Regeneron and Sanofi.

Manju Bengularu Jayanna MBBS None.

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Daniel Soffer MD FNLA FACP has received grants to institution from AstraZeneca, Novartis, Regeneron, Akcea Therapeutics, NIH and Regenxbio, served as consultant for Amgen Inc, Akcea Therapeutics, Regeneron, Medicure and as a speaker for Sanofi and Akcea Therapeutics.

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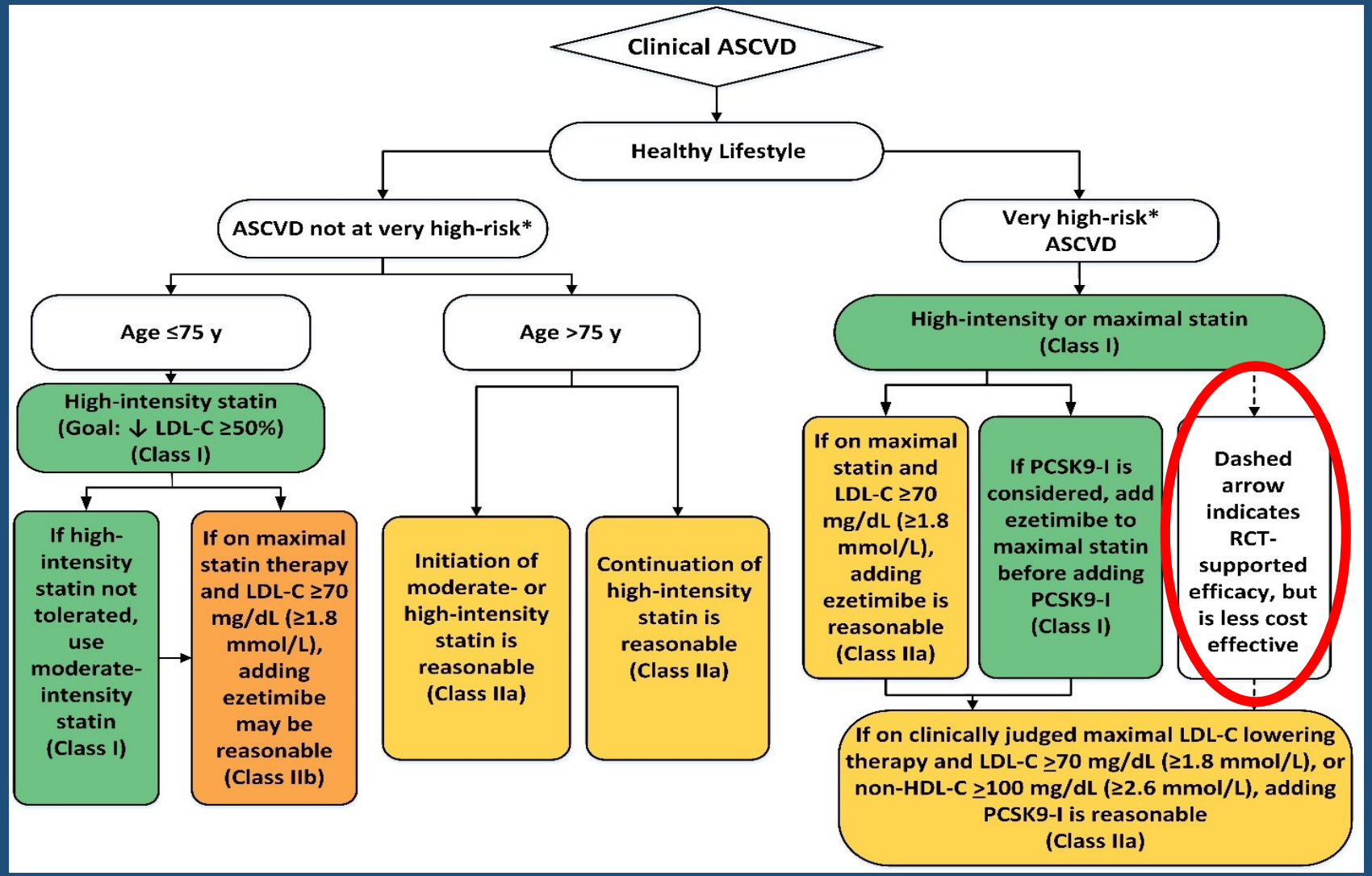
Purpose:

- Update for clinical decision-making based on new information
  - PCSK9 mAb discounting
  - Potential for net ASCVD risk reduction benefit from added LDL-C lowering therapy
    - Systematic review to identify heterogeneity in benefits observed in subgroup analyses

2018 AHA/ACC/Multispecialty Cholesterol Guideline



Grundy SM, et al. *J Am Coll Cardiol.* 2018. [Epub ahead of print]

Value Statement: Low Value (LOE: B-NR)	**6. At mid-2018 list prices, PCSK9 inhibitors have a low cost value (>$150,000 per QALY) compared to good cost value (<$50,000 per QALY) (Section 7 provides a full discussion of the dynamic interaction of different prices and clinical benefit) (S4.1-21–S4.1-23).**

Since 2018 ACC/AHA Guideline …

2015: Alirocumab & evolocumab approved—initial list price > $14,000/year[1]

July 1, 2018: Sanofi and Regeneron will lower the net price ($4,500 to $8,000 per year) for higher-risk patients with LDL ≥ 100 mg/dL despite intensive statin therapy[2]

October 24, 2018: Amgen discounts evolocumab ≈60% to $**5,850**/year[3]

February 11, 2019: Regeneron/Sanofi discounts alirocumab ≈60% to $**5,850**/year[4]

1. PR Newswire. www.prnewswire.com/news-releases/regeneron-and-sanofi-announce-fda-approval-of-praluent-alirocumab-injection-the-first-pcsk9-inhibitor-in-the-us-for-the-treatment-of-high-ldl-cholesterol-in-adult-patients-300118572.html.
2. *MedPage Today.* www.medpagetoday.com/cardiology/dyslipidemia/72638.
3. *MedPage Today.* www.medpagetoday.com/cardiology/dyslipidemia/75917.
4. Reuters. www.reuters.com/article/us-sanofi-fr-regeneron-cholesterol/sanofi-and-regeneron-cut-list-price-of-cholesterol-drug-by-60-percent-idUSKCN1Q019M.

NNT to Inform Nonstatin Decision Making

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Determining When to Add Nonstatin Therapy

A Quantitative Approach

Jennifer G. Robinson, MD, MPH,[a] Roeland Huijgen, MD, PhD,[b] Kausik Ray, MBChB, MD, MPhil,[c] Jane Persons, PhD,[a] John J.P. Kastelein, MD, PhD,[b] Michael J. Pencina, PhD[d]

ABSTRACT

BACKGROUND Costs and uncertainty about the benefits of nonstatin therapies limit their use.

OBJECTIVES The authors sought to identify patients who might benefit from the addition of a nonstatin to background statin therapy.

METHODS We performed systematic reviews of subgroup analyses from randomized trials and observational studies with statin-treated participants to determine estimated 10-year absolute risk of atherosclerotic cardiovascular disease (ASCVD) and to define high-risk and very high-risk patients. We used the relative risk reductions for the addition of a nonstatin to lower low-density lipoprotein (LDL-C) used to determine the number needed to treat (NNT) to prevent 1 ASCVD event over 5 years for each patient group and to allow comparisons with 5-year cost analyses.

RESULTS The 10-year ASCVD risk is at least 30% (very high risk) for statin-treated participants with clinical ASCVD and comorbidities, and 20% to 29% (high risk) for those with ASCVD without comorbidities or who have heterozygous familial hypercholesterolemia. Adding ezetimibe to reduce low-density LDL-C by 20% would provide a 5-year NNT ≤50 for very high-risk patients with LDL-C ≥130 mg/dl or for high-risk patients with LDL-C ≥190 mg/dl, and an NNT ≤30 for very high-risk patients with LDL-C ≥160 mg/dl. Adding a PCSK9 monoclonal antibody to lower LDL-C by at least 50% would provide an NNT ≤50 for very high-risk and high-risk patients with LDL-C ≥70 mg/dl, and an NNT ≤30 for very high-risk and high-risk patients with an LDL-C ≥130 mg/dl.

CONCLUSIONS Adding ezetimibe or PCSK9 monoclonal antibodies to maximally tolerated statin therapy may be cost effective in very high-risk and high-risk patients, depending on baseline LDL-C levels.
(J Am Coll Cardiol 2016;68:2412–21) © 2016 by the American College of Cardiology Foundation.

Determine potential for NET BENEFIT from adding additional LDL-C lowering for additional CVD risk reduction

Number Needed to Treat to prevent one event

$$NNT = \frac{1}{ARR}$$

Absolute Risk Reduction = Absolute CVD risk X Relative risk reduction from therapy

Robinson JG, et al. *J Am Coll Cardiol*. 2016;68:2412-21.

Extremely high risk ≥40% 10-year ASCVD risk

Systematic review subgroups of RCTS Moderate vs high intensity statins, PCSK9 mAbs

ON STATIN THERAPY	
Burden and activity of clinical ASCVD	**Adverse or poorly controlled cardiometabolic risk factors**
EXTREMELY HIGH ATHEROSCLEROTIC BURDEN	**EXTREMELY HIGH RISK FACTORS**
Majority had at least 1 additional adverse or poorly controlled cardiometabolic risk factor	

• Polyvascular clinical ASCVD (coronary heart disease†, ischemic stroke, and symptomatic peripheral arterial disease)
• Symptomatic peripheral arterial disease** in addition to a coronary heart disease† or ischemic stroke
• A clinical ASCVD event (coronary heart disease†, stroke, or symptomatic peripheral arterial disease**) with multi-vessel coronary artery disease defined as ≥40% stenosis in ≥2 large vessels
• Recurrent myocardial infarction within 2 years
	• Heterozygous familial hypercholesterolemia with clinical ASCVD (or coronary artery calcium >100)
	• History of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease** with at least one of:
	  ○ Diabetes
	  ○ LDL-C >100 mg/dl
	  ○ Less than high intensity statin therapy
	  ○ High sensitivity C-reactive protein >3 mg/L
	• Poorly controlled hypertension and clinical ASCVD

† Clinically evident coronary heart disease includes myocardial infarction, history of angina with objective evidence of coronary artery disease (electrocardigraphic, positive stress test, wall motion abnormality on ultrasound, coronary angiographic evidence of significant atherosclerotic lesions), or prior revascularization including coronary artery bypass grafting or percutaneous coronary intervention)

Very high risk 30-39% 10-year ASCVD risk

Systematic review subgroups of RCTS Moderate vs high intensity statins, PCSK9 mAbs

ON STATIN THERAPY	
Burden and activity of clinical ASCVD	**Adverse or poorly controlled cardiometabolic risk factors**
VERY HIGH ATHEROSCLEROTIC BURDEN	**VERY HIGH RISK FACTORS**
Majority had at least 1 additional adverse or poorly controlled cardiometabolic risk factor	
• Recent acute coronary syndrome (only if no subsequent event within 2 years) • Coronary heart disease† and ischemic stroke without symptomatic peripheral arterial disease** • Coronary artery bypass grafting	Clinical ASCVD and one or more of: • Age ≥65 years • Chronic kidney disease • Lipoprotein(a) ≥37 nmol/L • High sensitivity C-reactive protein 1-3 mg/L • Metabolic syndrome with a history of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease** • Smoking

High risk 20-29% 10-year ASCVD risk

Systematic review subgroups of RCTS Moderate vs high intensity statins, PCSK9 mAbs

ON STATIN THERAPY	
Burden and activity of clinical ASCVD	
HIGH ATHEROSCLEROTIC BURDEN	**WELL-CONTROLLED RISK FACTORS**
<u>High burden (20-29% 10-year ASCVD risk)</u> • Coronary heart disease† only • Ischemic stroke only • Symptomatic peripheral arterial disease only** • Acute coronary syndrome with no subsequent ASCVD event after 2 years	

Did not find heart failure subgroups as in 2018 AHA/ACC Cholesterol Guideline “Very high ASCVD risk” group; Patients with NYHA Class 3 & 4 heart failure excluded from RCTs

5-year NNTs, Acquisition Costs, and Quality Adjusted Life-years (QALY)

5-year NNT 10-14	**No discount ($14,000/year) /≈ $150,000 QALY (Poor value)**
5-year NNT 21-28	Discount ≈ 50% (≈ $7700/year) /$150,000 QALY (Low value) **Discount ≈ 60% (≈ $5400/year) /$100,000 QALY (Reasonable value)** Discount ≈ 77% (≈ $3200/year) /$50,000 QALY (High value) Discount ≈ 85% (≈ $2200/year) to avoid exceeding growth targets US healthcare costs

US dollars; Based on ICER JAMA Int Med 2016; 176: 107-108 in Robinson JG, et al. J Am Coll Cardiol 2016; 68: 2412-2421

Extremely high risk (45% 10-year ASCVD risk)

PCSK9 mAb – about $5400 year acquisition cost

5-year NNT: 21-28=Reasonable value $100,00/QALY 10-14 =High value $50,000/QALY

Initial LDL-C	Ezetimibe LDL-C ↓20%	PCSK9 mAb LDL-C ↓50%	PCSK9 mAb LDL-C ↓65%
190 mg/dL (4.9 mmol/L)	21	8	6
160 mg/dL (4.1 mmol/L)	24	10	7
130 mg/dL (3.4 mmol/L)	30	12	9
100 mg/dL (2.6 mmol/L)	39	16	12
70 mg/dL (1.8 mmol/L)	56	28	22

Reasonable NNT thresholds for **physicians NNT < 50** and **patients NNT <30** (Steel N. *BMJ.* 2000; 320:1446-1447

Very high risk (30 10-year ASCVD risk)

PCSK9 mAb – about $5400 year acquisition cost

5-year NNT: 21-28=Reasonable value $100,00/QALY 10-14 =High value $50,000/QALY

Initial LDL-C	Ezetimibe LDL-C ↓20%	PCSK9 mAb LDL-C ↓50%	PCSK9 mAb LDL-C ↓65%
190 mg/dL (4.9 mmol/L)	32	13	10
160 mg/dL (4.1 mmol/L)	38	15	12
130 mg/dL (3.4 mmol/L)	47	19	15
100 mg/dL (2.6 mmol/L)	61	25	19
70 mg/dL (1.8 mmol/L)	88	43*	33*

Reasonable NNT thresholds for **physicians NNT < 50** and **patients NNT <30** (Steel N. *BMJ.* 2000; 320:1446-1447

High risk ASCVD (20% 10-year ASCVD risk)

PCSK9 mAb – about $5400 year acquisition cost

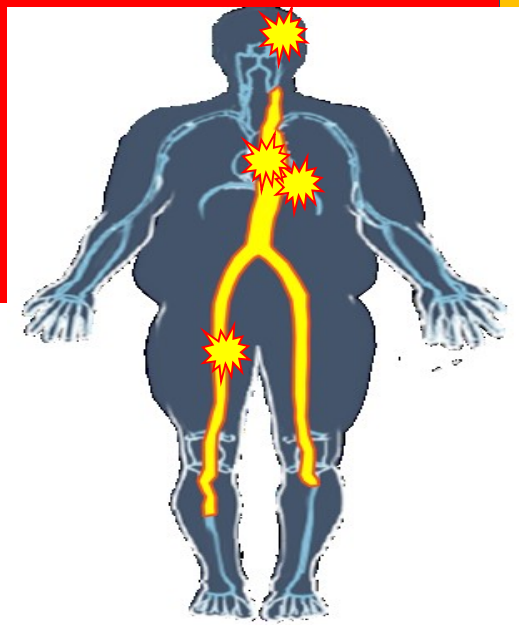
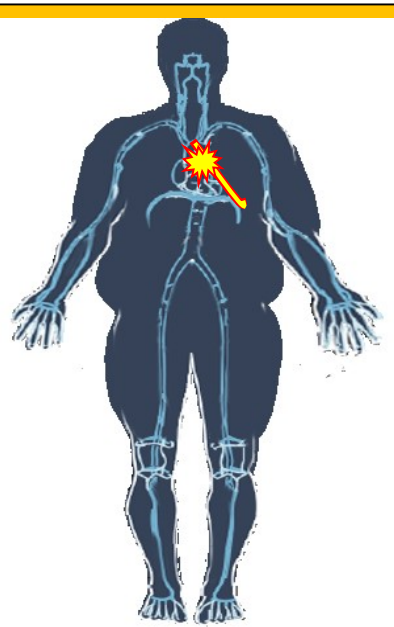
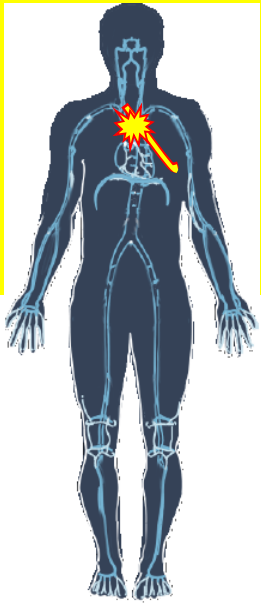
5-year NNT: 21-28=Reasonable value $100,00/QALY 10-14 =High value $50,000/QALY

Initial LDL-C	Ezetimibe LDL-C ↓20%	PCSK9 mAb LDL-C ↓50%	PCSK9 mAb LDL-C ↓65%
190 mg/dL (4.9 mmol/L)	48	19	15
160 mg/dL (4.1 mmol/L)	57	23	18
130 mg/dL (3.4 mmol/L)	71	28	22
100 mg/dL (2.6 mmol/L)	92	37	28
70 mg/dL (1.8 mmol/L)	131	65*	50*

Reasonable NNT thresholds for **physicians NNT < 50** and **patients NNT <30** (Steel N. *BMJ.* 2000; 320:1446-1447

NLA Statement: REASONABLE - HIGH VALUE FROM ADDING PCSK9 mAb

ON MAXIMALLY TOLERATED STATIN THERAPY (±ezetimibe)

Extremely High Risk ≥40% 10-year ASCVD risk	Very High Risk 30-39% 10-y ASCVD risk	High Risk 20-29% 10-year ASCVD risk
		
Extensive or active burden of ASCVD Usually with poorly controlled cardiometabolic risk factors	**Less extensive ASCVD & Poorly controlled cardiometabolic risk factors**	**Less extensive ASCVD & Well controlled risk factors**
Less extensive ASCVD & Extremely high risk cardiometabolic risk factors		**Primary prevention HeFH/SGH LDL-C≥220 mg/dl & Poorly controlled cardiometabolic risk factors**
LDL-C ≥70 mg/dl	**LDL-C ≥100 mg/dl**	**LDL-C ≥130 mg/dl**

Robinson JG, et al. J Clin Lipidol 2019; online ahead of print

2018 AHA/ACC/Multispecialty Cholesterol Guideline

Severe Hypercholesterolemia LDL-C ≥190 mg/dl

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.

Grundy SM, et al. *J Am Coll Cardiol.* 2018. [Epub ahead of print]

HeFH & SH ≥220 mg/dl

- Severe hypercholesterolemia LDL-C ≥190 mg/dl without HeFH
  - 5-fold higher lifetime ASCVD risk
- Heterozygous Familial Hypercholesterolemia (HeFH)
  - 20-fold higher lifetime ASCVD risk
  - Highest ASCVD risk – CAC ≥100 or risk factors
- Primary severe hypercholesterolemia LDL-C ≥220 mg/dL (SH ≥220 mg/dL)
  - At very high ASCVD risk – similar to HeFH

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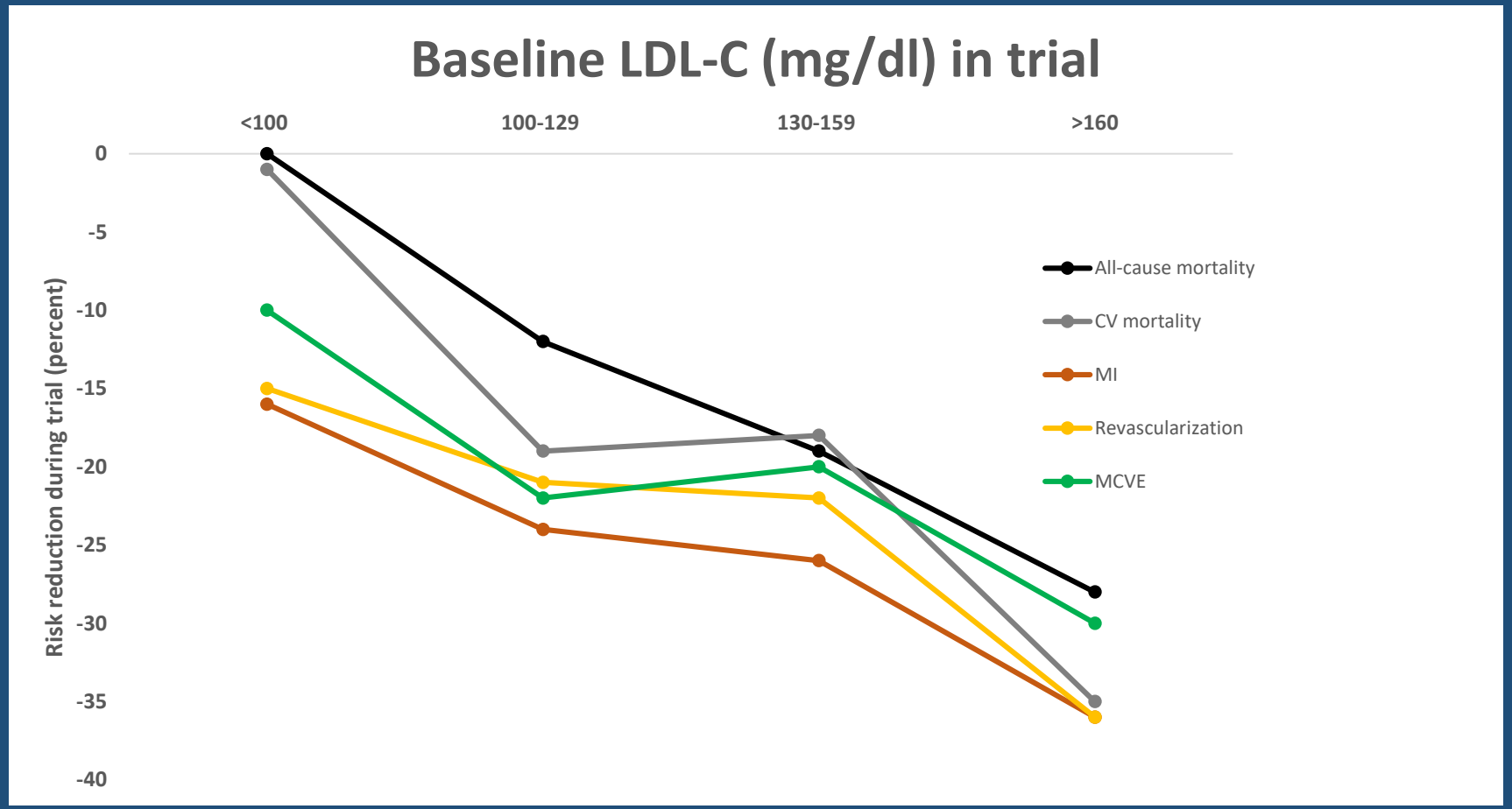
ON MAXIMALLY TOLERATED STATIN & EZETIMIBE THERAPY		
	High value (<$50,000/QALY)	**Reasonable value** (<$100,000/QALY)
5-year NNT	14	28
SECONDARY PREVENTION		
FH or SH ≥220 mg/dl with clinical ASCVD (ASCVD risk likely similar when coronary artery calcium >100 Agatston units)	LDL-C ≥100 mg/dl	LDL-C ≥70 mg/dl
PRIMARY PREVENTION		
FH or SH ≥220 mg/dl with risk factor(s)*	LDL-C ≥190 mg/dl)	LDL-C >100 mg/dl

* Age >35 years, male sex, obesity, hypertension, smoking, lipoprotein (a) <50 mg/dl, low HDL-C <35 mg/dl

Greater mortality/ASCVD risk reduction when LDL ≥100 mg/dl



Total mortality

Additional **10%** RRR per 40 mg/dl higher baseline LDL-C

CV mortality

Additional **14%** RRR per 40 mg/dl higher baseline LDL-C

From Navarese EP, Robinson JG (co-primary authors). JAMA 2018; 319: 1566-1579

NLA Statement: REASONABLE - HIGH VALUE FROM ADDING PCSK9 mAb

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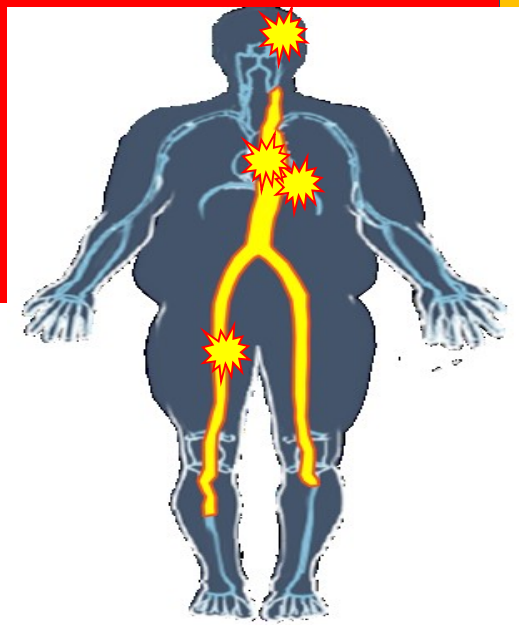	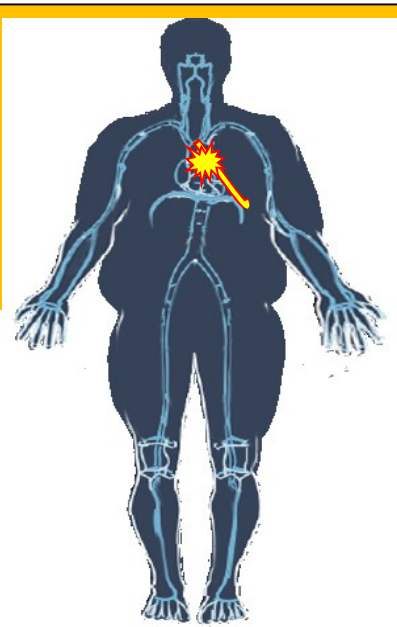	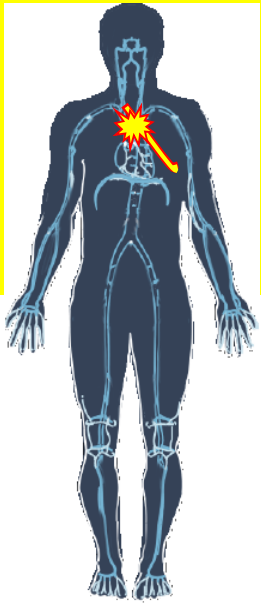
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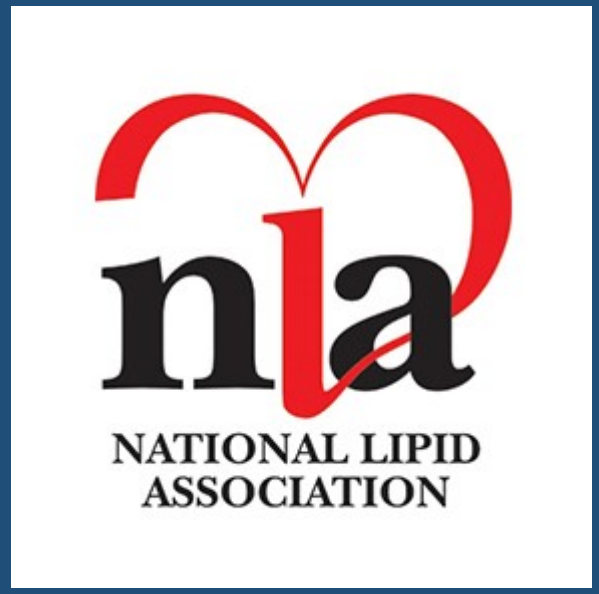
LDL-C ≥70 mg/dl	**LDL-C ≥100 mg/dl**	**LDL-C ≥130 mg/dl**

Robinson JG, et al. J Clin Lipidol 2019; online ahead of print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