Cost effective patient management to reduce mortality

Speaker: Hani Mohamed Sabbour (UAE)

Moderator: Abdulmajeed Al Zubaidi (UAE)

Educational objective: Identify high risk patients including who could and have the most benefit from newer therapies, especially PCSK9 inhibitors and EPA

2020 MIDDLE EAST SUMMIT ON RESIDUAL CARDIOVASCULAR RISK

INTERNATIONAL ATHEROSCLEROSIS SOCIETY

Which of the following patients should receive a combination of statin, ezetimibe and a PCKS9 inhibitor?

Select all that apply

A. Very-high-risk patients without FH
B. Very-high-risk patients with FH
C. Very-high-risk patients with FH unable to achieve target with statin+ezetimibe therapy
D. Very-high-risk patients without FH unable to achieve target with statin+ezetimibe therapy

Disclosures

Hani Mohamed Sabbour

- Speakers Bureau: AZ, Abbott, Aegerion, Amgen, Merck, Sanofi

Abdulmajeed Al Zubaidi

- None

Cost-benefit management in DM and high-risk patients reducing LDL and residual cardiovascular events

HANI SABBOUR MD FACC FHRS

FEBRUARY 21TH 2020

2020 MIDDLE EAST
SUMMIT ON RESIDUAL
CARDIOVASCULAR RISK

INTERNATIONAL
ATHEROSCLEROSIS
SOCIETY

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CV risk categories in patients with diabetes in the new 2019 ESC guidelines

The 2019 ESC guidelines[1a] build upon the SCORE risk from the 2016 European Guidelines on CVD prevention in clinical practice[2] to stratify CV risk in patients with diabetes and pre-diabetes

Very high risk

Patients with DM and established CVD
or other target organ damage[b]
or three or more major risk factors[c]
or early onset T1D of long duration (>20 years)

High risk

Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor

Moderate risk

Young patients (T1D aged <35 years or T2D aged <50 years) with DM duration <10 years, without other risk factors

[a]Modified from the 2016 European guidelines on cardiovascular disease prevention in clinical practice[2]
[b]Proteinuria, renal impairment defined as eGFR ≥30 mL/min/1.73 m^2, left ventricular hypertrophy or retinopathy
[c]Age, hypertension, dyslipidaemia, smoking, obesity
CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; SCORE, Systematic Coronary Risk Estimation; T1D, type 1 diabetes; T2D, type 2 diabetes

1. Cosentino F et al. *Eur Heart J* 2019;00:1–69; 2. Piepoli MF et al. *Eur Heart J* 2016;37:2315–2381

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HOPE trial: Independent predictive variables for combined endpoints of CV death, MI, and stroke

Variable	Hazard ratio
Microalbuminuria	1.59
Creatinine >1.4 mg/dL	1.40
CAD	1.51
PVD	1.49
Diabetes Mellitus	1.42
Male	1.20
Age	1.03
Waist-Hip Ratio	1.13

Mann JFE, et al. Ann Intern Med. 2001;134(8):629-636.

The dual significance of proteinuria

- Proteinuria (albuminuria) results from injury to glomerular circulation
  - Increased proteinuria (albuminuria) is associated with progressive kidney disease
- In diabetes and hypertension, proteinuria (albuminuria) is also an indicator of injury in the systemic circulation
  - Proteinuria (albuminuria) is associated with increased cardiovascular risk

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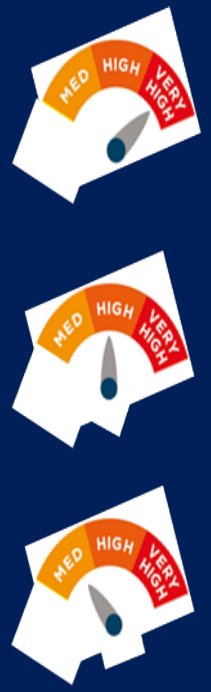

Very high risk

PATIENTS WITH BOTH DM AND CVD ARE AT THE HIGHEST LEVEL OF RISK
(EXTREME) HIGH RISK AS MENTIONED IN AACE DEFINITON

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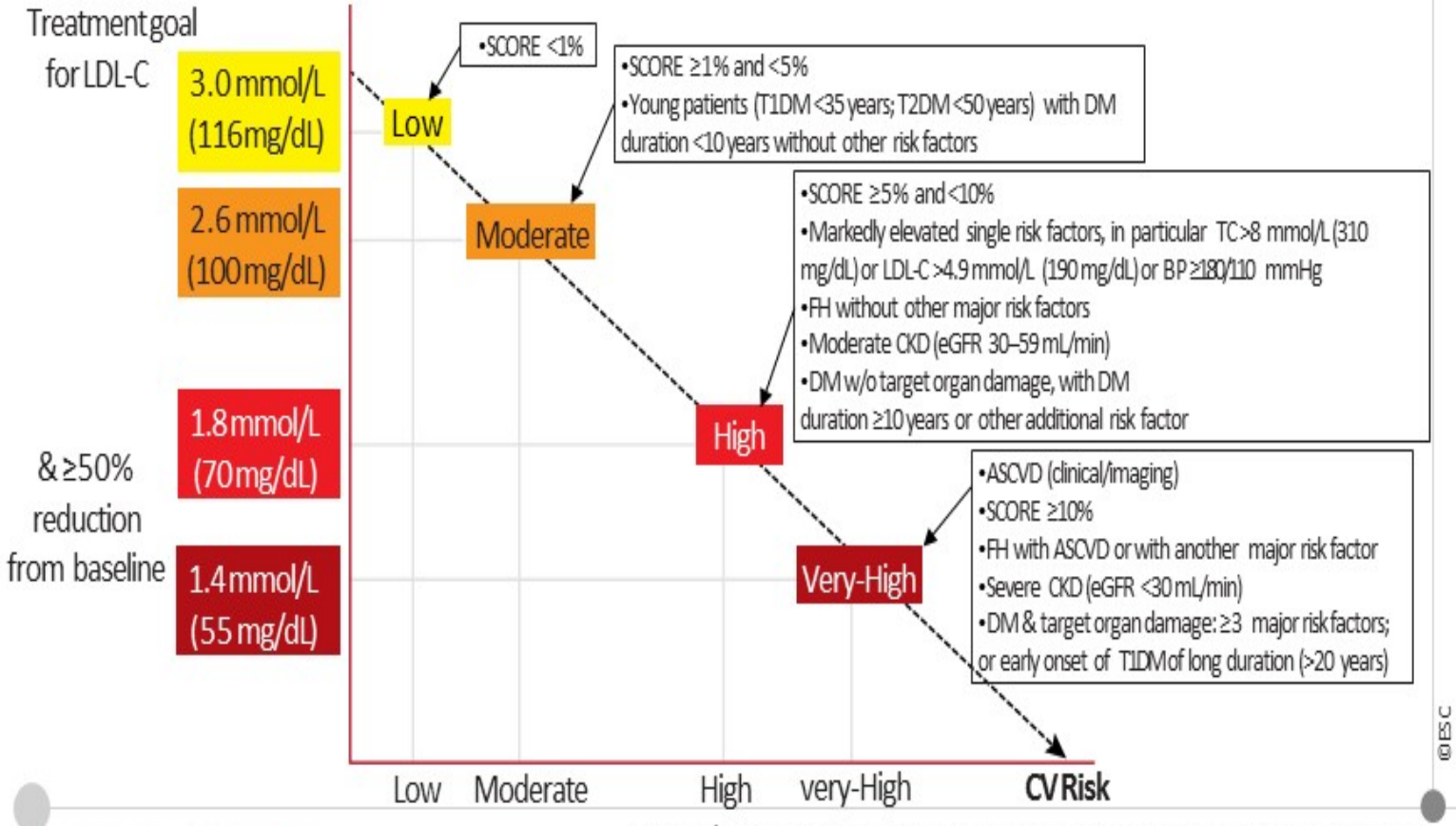
Central Illustration Upper panel Treatment goals for low-density lipoprotein cholesterol (LDL-C) across categories of total cardiovascular disease risk

EAS ESC European Society of Cardiology



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2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Recommendations for the management of dyslipidaemia with lipid-lowering drugs (1)

ESC European Society

New target 1.4 / 55 is derived from IMPROVE IT

Recommendations		
Targets		
In patients with T2DM at moderate CV risk, an LDL-C target of <2.6 mmol/L (<100 mg/dL) is recommended.	I	A
In patients with T2DM at high CV risk, an LDL-C target of <1.8 mmol/L (<70 mg/dL) and LDL-C reduction of at least 50% is recommended.	I	A
In patients with T2DM at very high CV risk, an LDL-C target of <1.4 mmol/L (<55 mg/dL) and LDL-C reduction of at least 50% is	I	B
In patients with T2DM, a secondary goal of a non–HDL-C target of <2.2 mmol/L (<85 mg/dL) in very high CV risk patients, and <2.6 mmol/L (<100 mg/dL) in high CV risk patients, is recommended.	I	B

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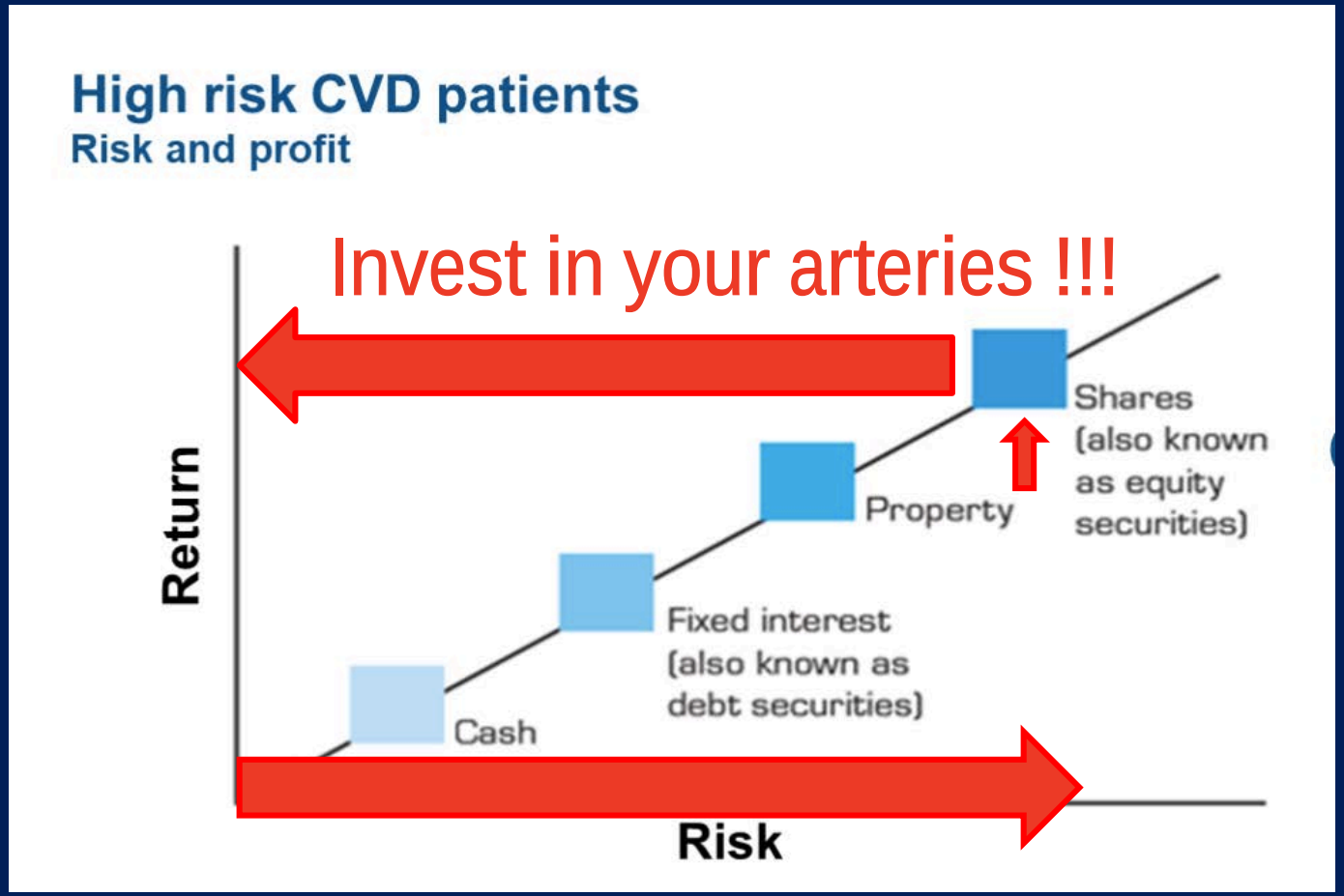
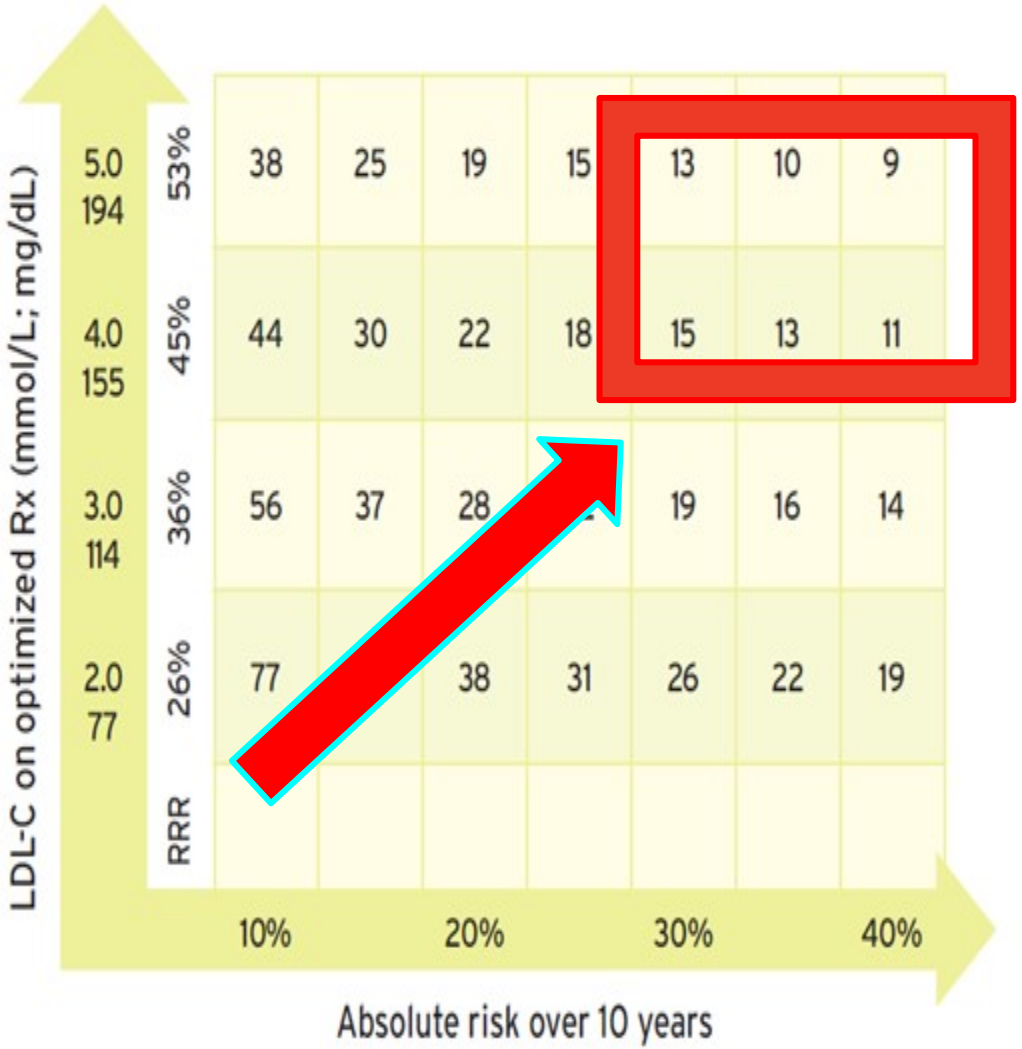
ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

Early and intensive investment in the highest risk patients gives the greatest profit & reward of lives saved



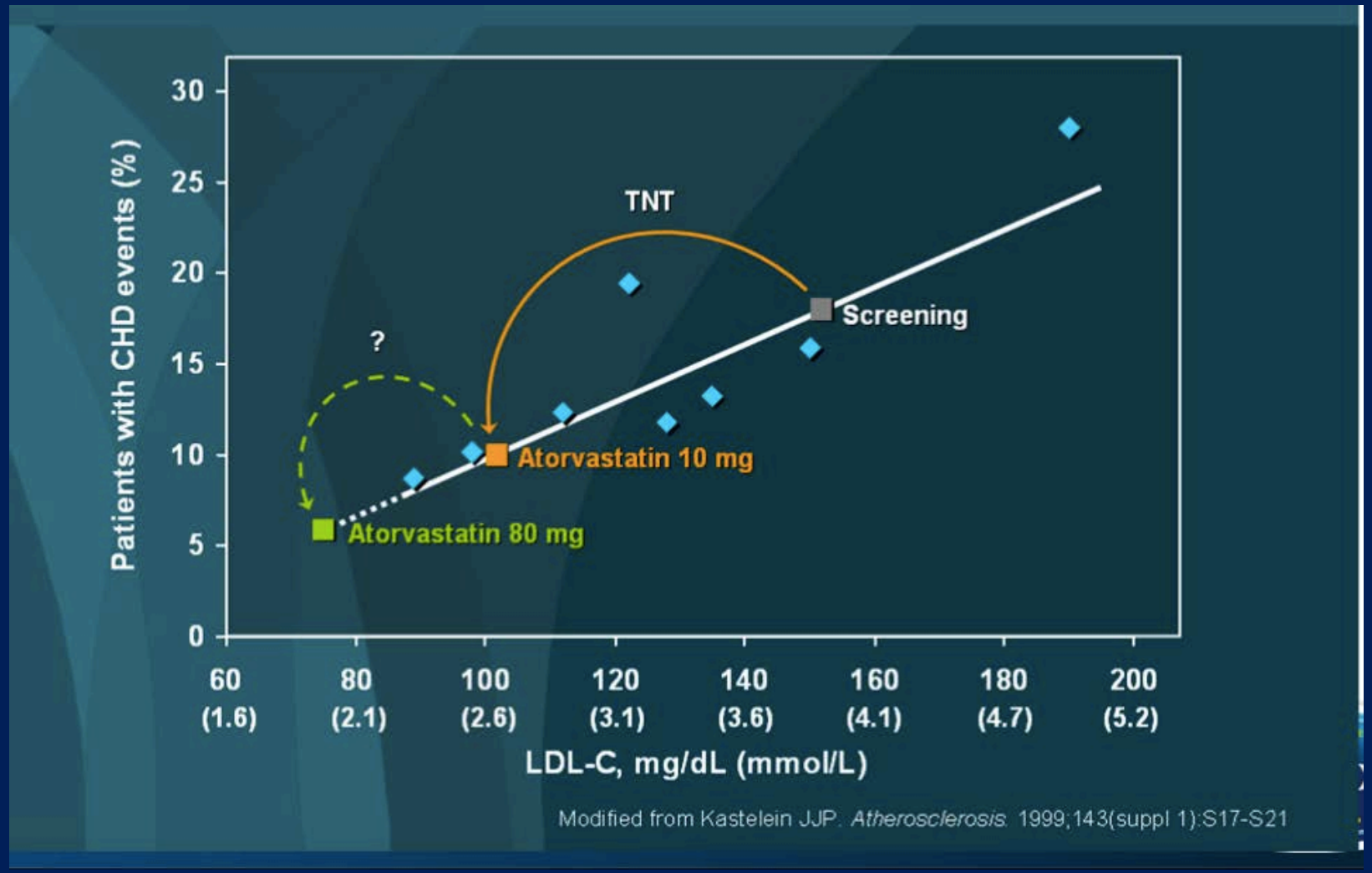
EAS ESC
European Society of Cardiology



NNT (>5 years) as function of estimated 10-year risk of ACVE, starting LDL-C (on optimized statin/ezetimibe therapy), and average relative risk reduction associated with LDL-C drop of 60%

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 - doi: 10.1093/eurheartj/ehz455)

CTTC analysis every 39 MG/DLDROP of LDL = linear decrease in risk



Why do we need a novel therapy

- Patients on maximal statins still suffer from cv events, fatal and non fatal
- Maximizing dose or doubling statin only lowers 6 percent more LDL
- Combination and synergy strategy is therefore essential
- TNT (atorva 80) LDL 60 but event rates still >7% = residual risk

These patients are very common in the UAE!!

TEN YEAR RISK OF 30-40% IN SPITE OF STATIN THERAPY

WE SEE THEM EVERY DAY !!!

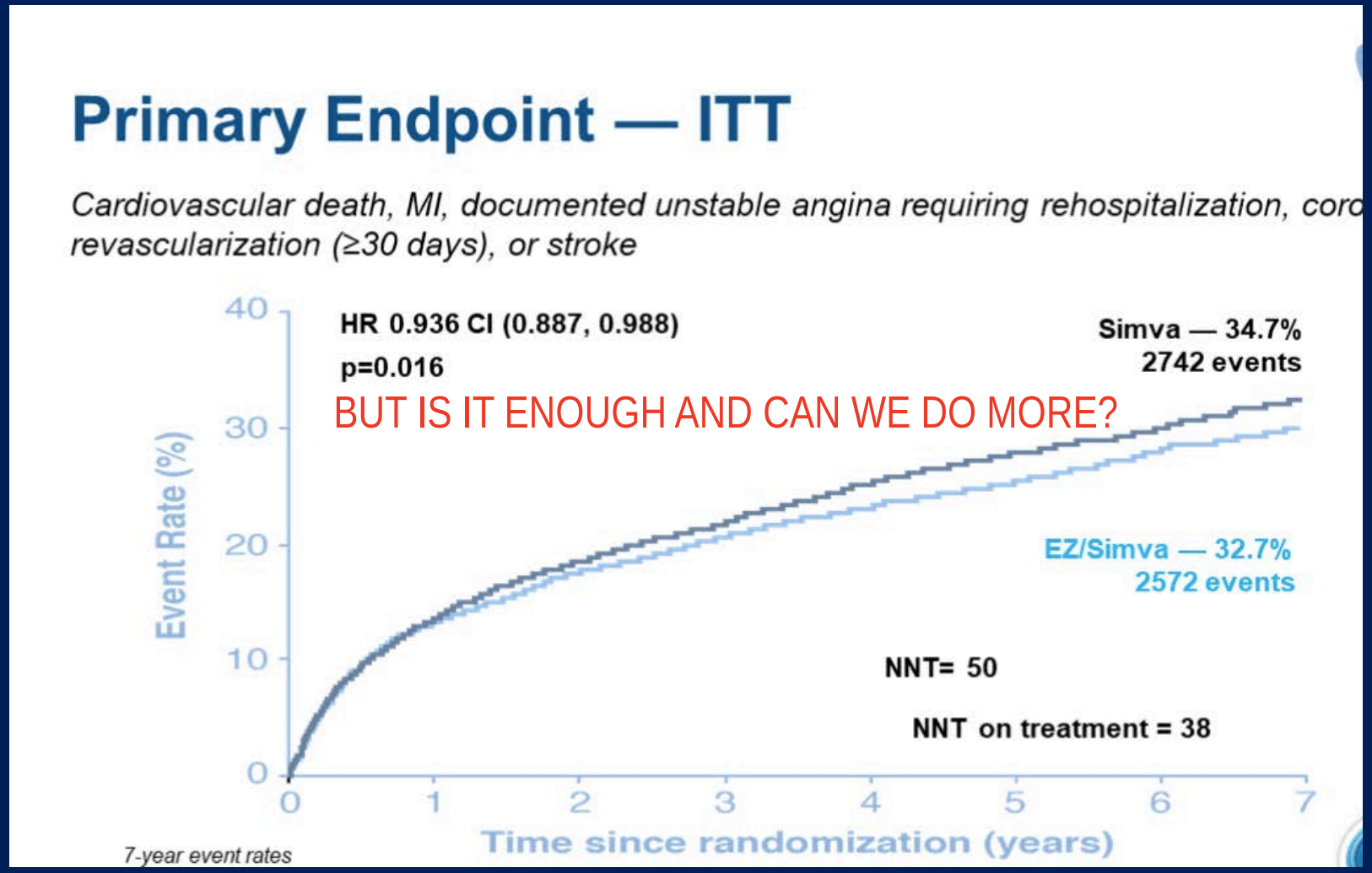
Table I Categories of 'highest risk' for ASCVD (around or above a benchmark of 30% 10-year risk) on statin therapy, based on published trial data

Category	Projected 10-year risk on moderate- or high-intensity statin therapy (%)
Clinical ASCVD + diabetes	28–38
No CKD	26–29
With CKD	28–43
Clinical ASCVD + CKD	34–35
Recent acute coronary syndrome (<3 months)	32
CHD and poorly controlled risk factors	28–41
CHD and peripheral vascular disease	43–55
CHD and age ≥65 years	21–54
Stroke/transient ischaemic attack and male	31
CHD and familial hypercholesterolaemia (baseline LDL-C ≥190 mg/dL)	41

ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CKD, chronic kidney disease.
Adapted from Robinson *et al.*[22]

Annemans et al. Eur Heart J 2018;39:2546–2550

Improve IT (2014): lower LDL is better



Cannon et al. N Engl J Med 2015;372:2387–2397

Recommendations for pharmacological low-density lipoprotein cholesterol lowering (1)

EAS ESC European Society of Cardiology

	Class	Level
It is recommended to prescribe a high-intensity statin up to the highest tolerated dose to reach the goals[c] set for the specific level of risk.	I	A
If the goals[c] are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.	I	B
For primary prevention patients at very-high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered.	IIb	C

[c] For definitions see Full Text.

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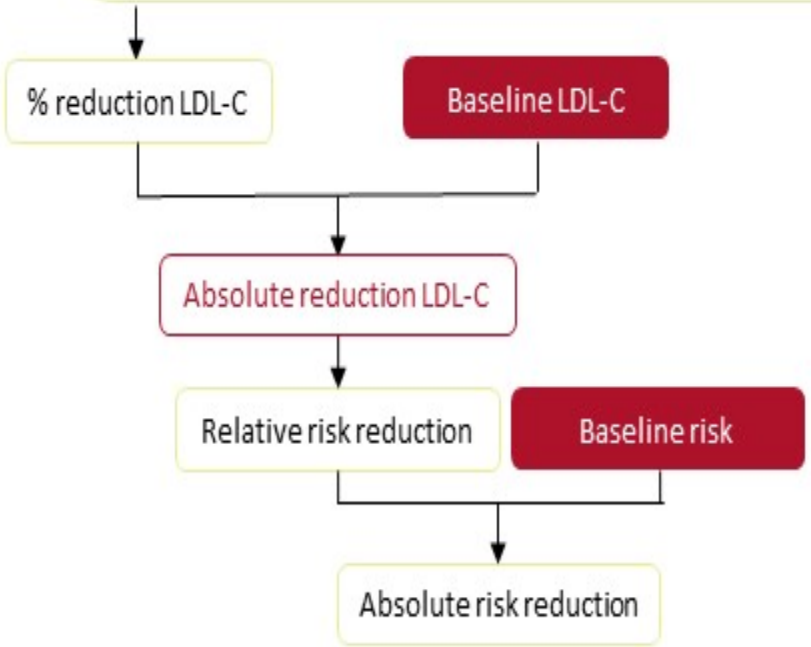
Intensity of lipid lowering treatment

Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%

PCSK9I INTENSITY 75-85%



Expected clinical benefit of low-density lipoprotein cholesterol lowering therapies

LDL-C = low-density lipoprotein cholesterol;
PCSK9 = proprotein convertase subtilisin/kexin type 9.

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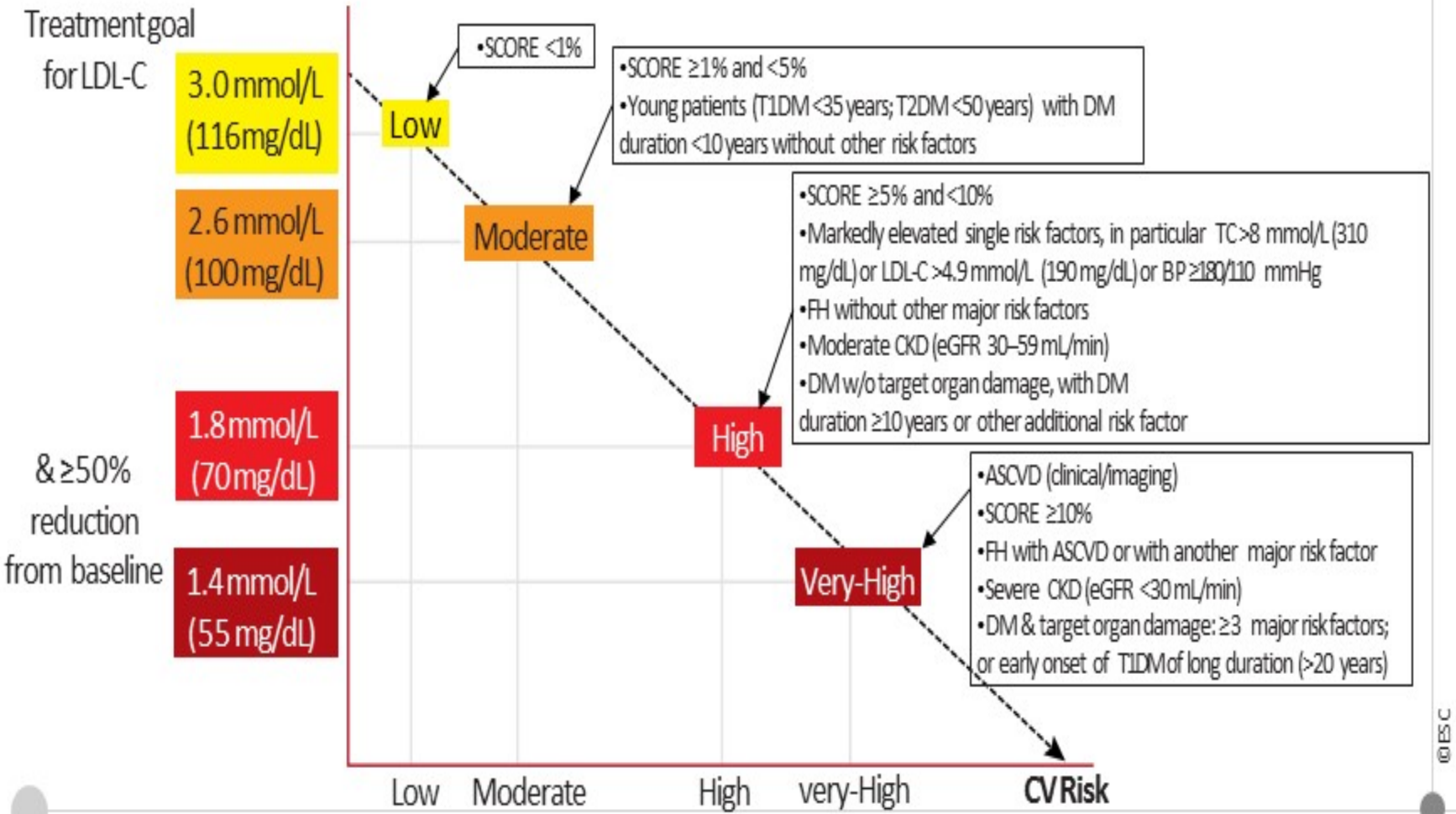

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Recommendations for the management of dyslipidaemia with lipid-lowering drugs (2)

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Recommendations	Class	Level
Treatment		
Statins are recommended as the first-choice lipid-lowering treatment in patients with DM and high LDL-C levels: administration of statins is defined based on the CV risk profile of the patient and the recommended LDL-C (or non–HDL-C) target levels.	I	A
If the target LDL-C is not reached, combination therapy with ezetimibe is recommended.	I	B
In patients at very high CV risk, with persistent high LDL-C despite treatment with maximum tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor is recommended.	I	A

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ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

Central Illustration Lower panel: Treatment algorithm for pharmacological LDL-C lowering (1)

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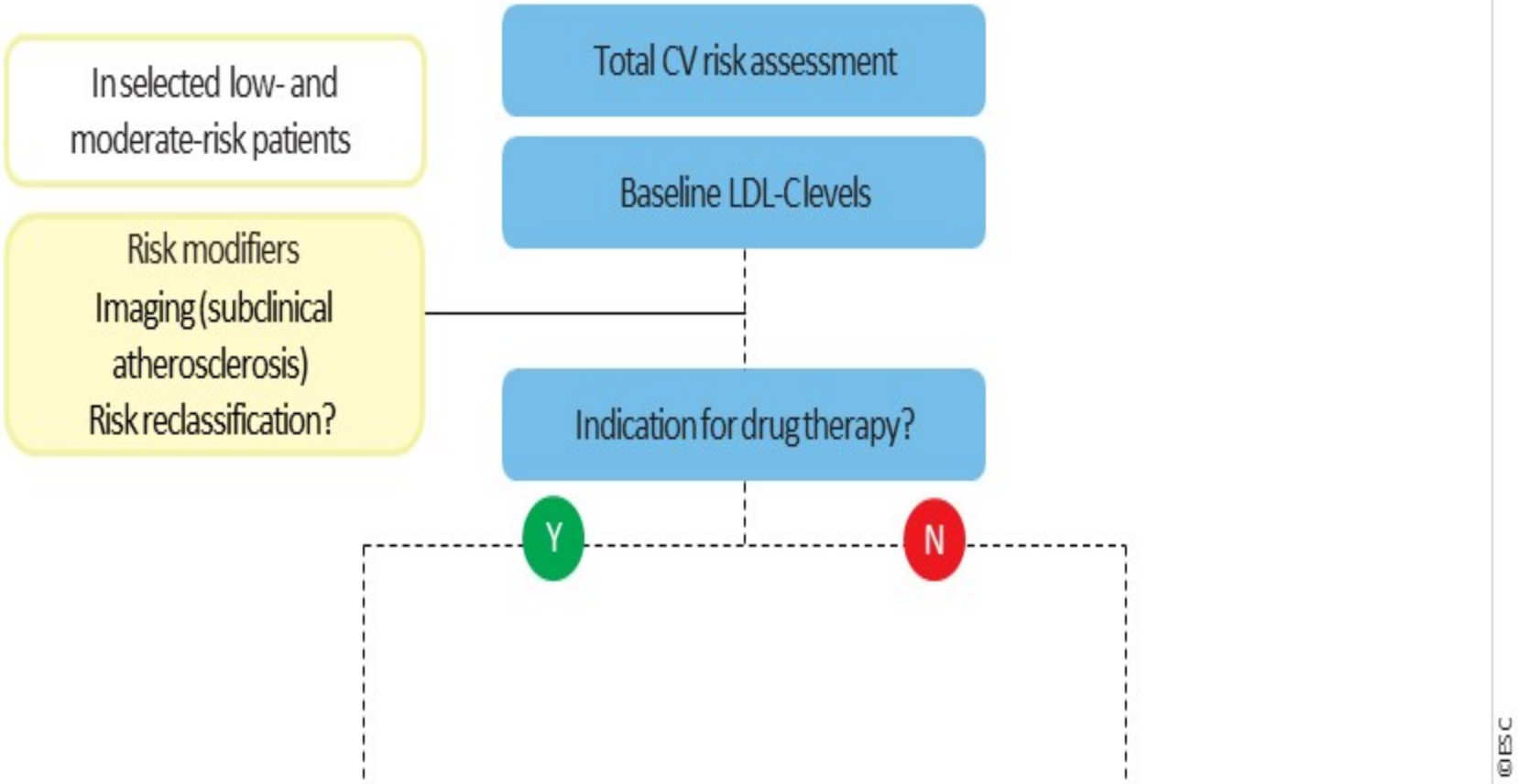

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Central Illustration Lower panel: Treatment algorithm for pharmacological LDL-C lowering (2)

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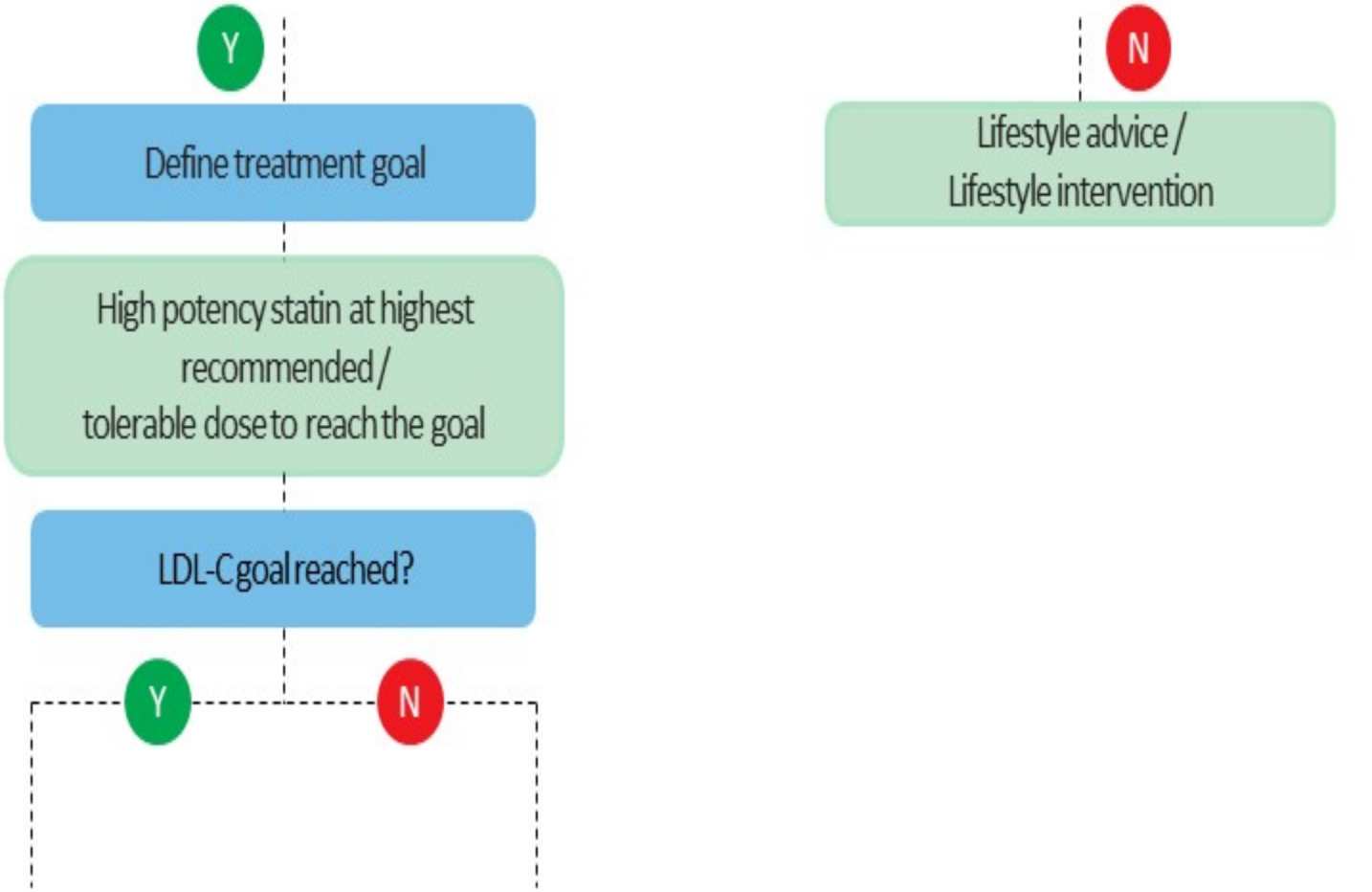

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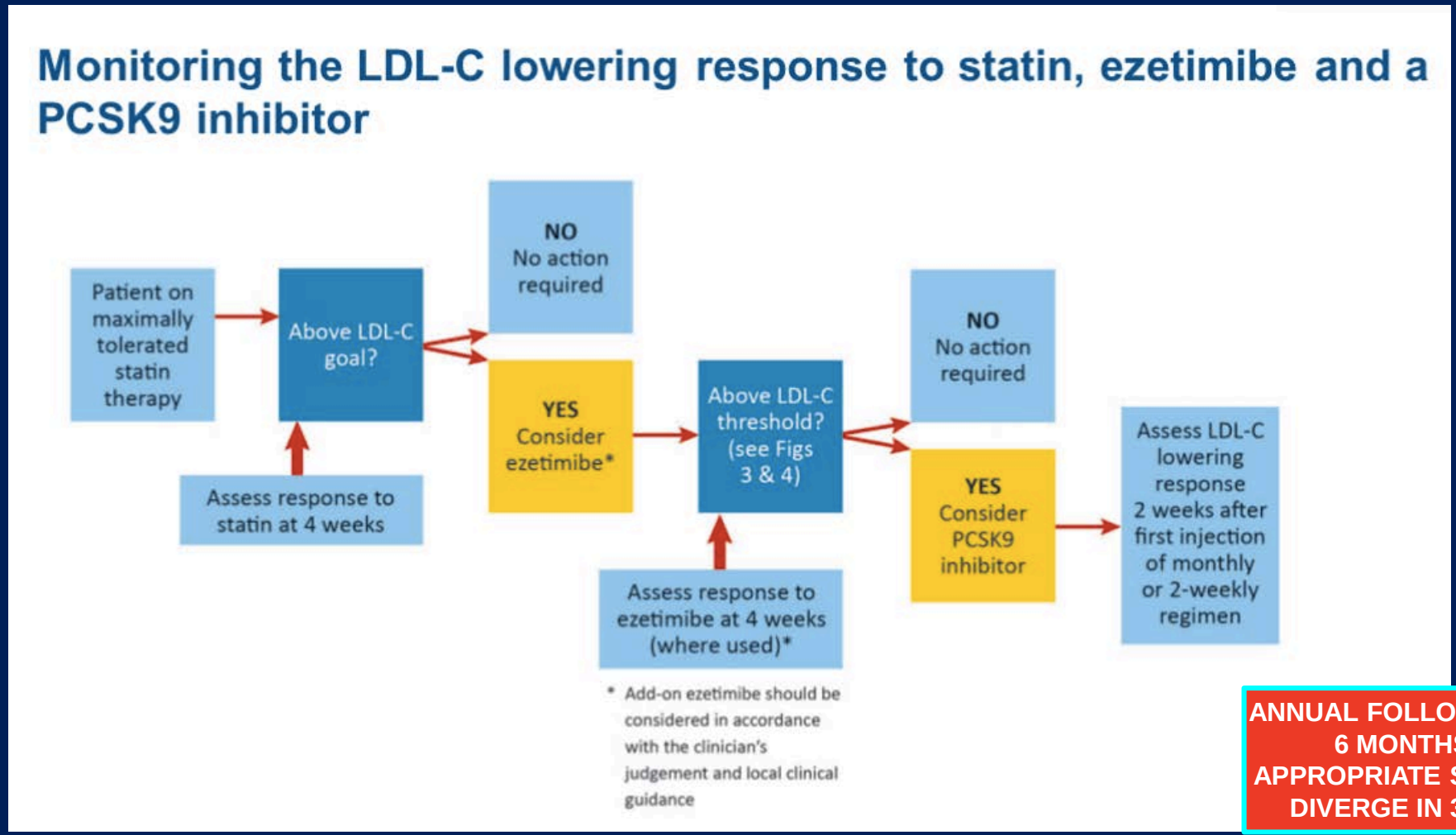
2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Monitoring response to any lipid-lowering therapy four week rule

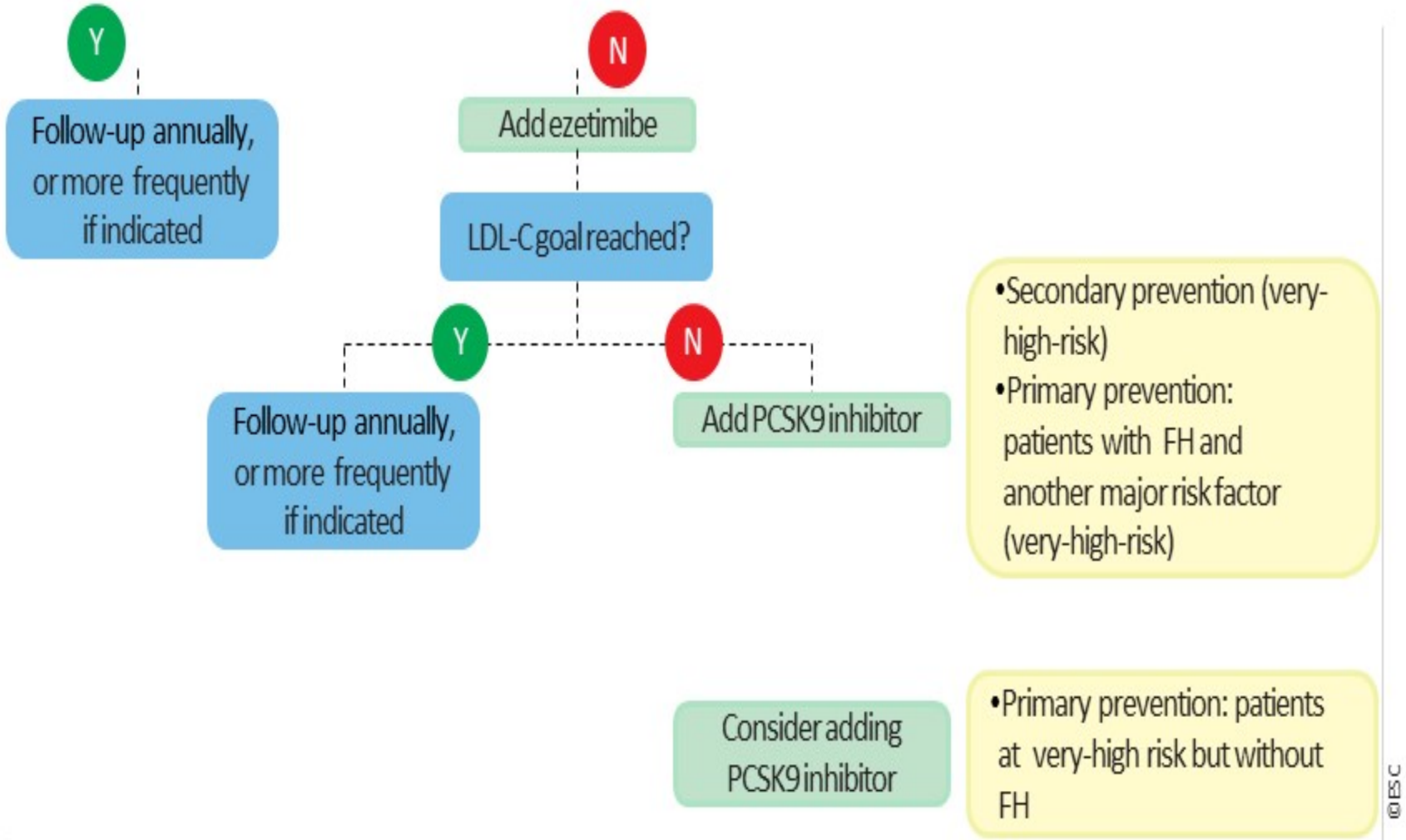


ANNUAL FOLLOW UP OR EVEN 6 MONTHS IS NOT APPROPRIATE SINCE CURVES DIVERGE IN 3 MONTHS !!

European Heart Journal 2018;39:1131–1143

Central Illustration Lower panel: Treatment algorithm for pharmacological LDL-C lowering (3)

EAS ESC European Society of Cardiology



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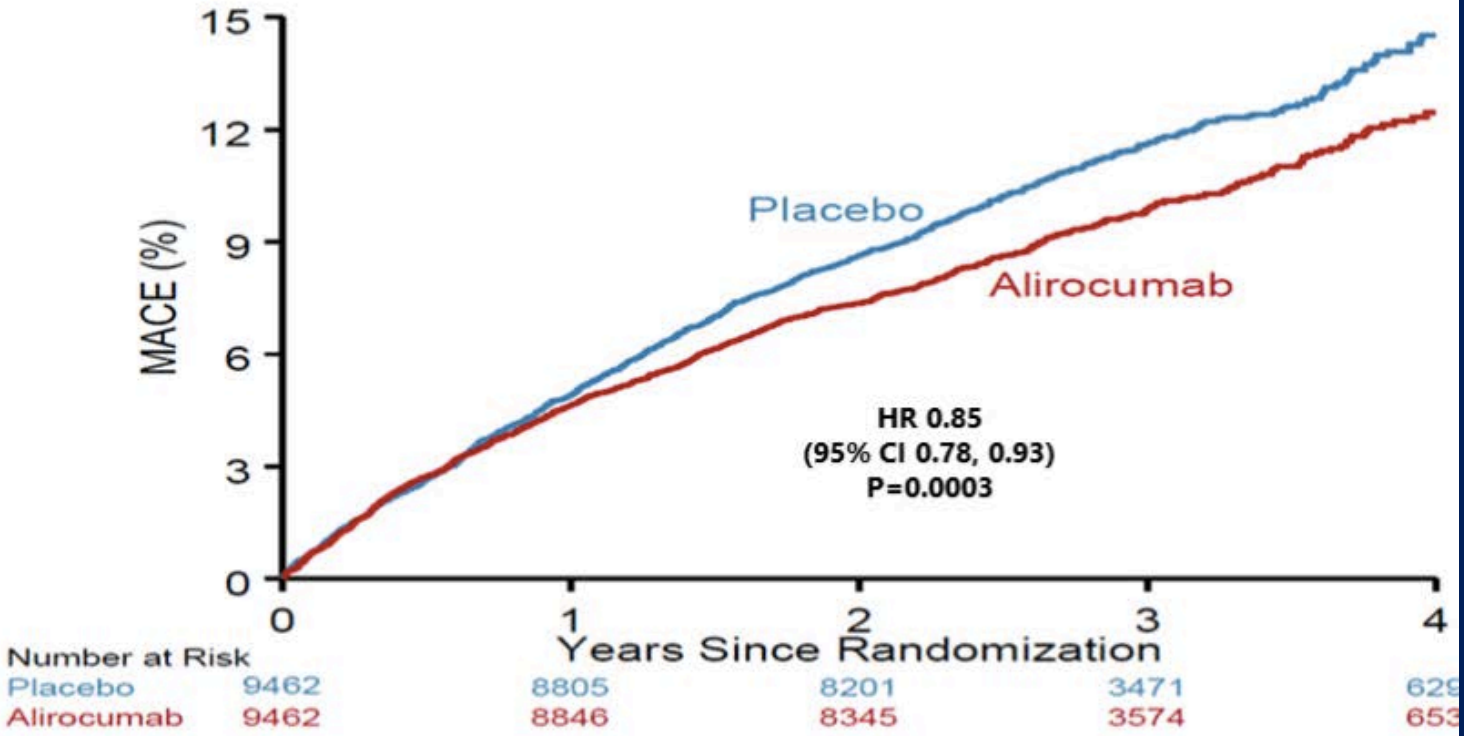
2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Odyssey alirocumab

Primary Efficacy Endpoint: MACE

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



*Based on cumulative incidence
Presented by STEG et al. ACC 2018

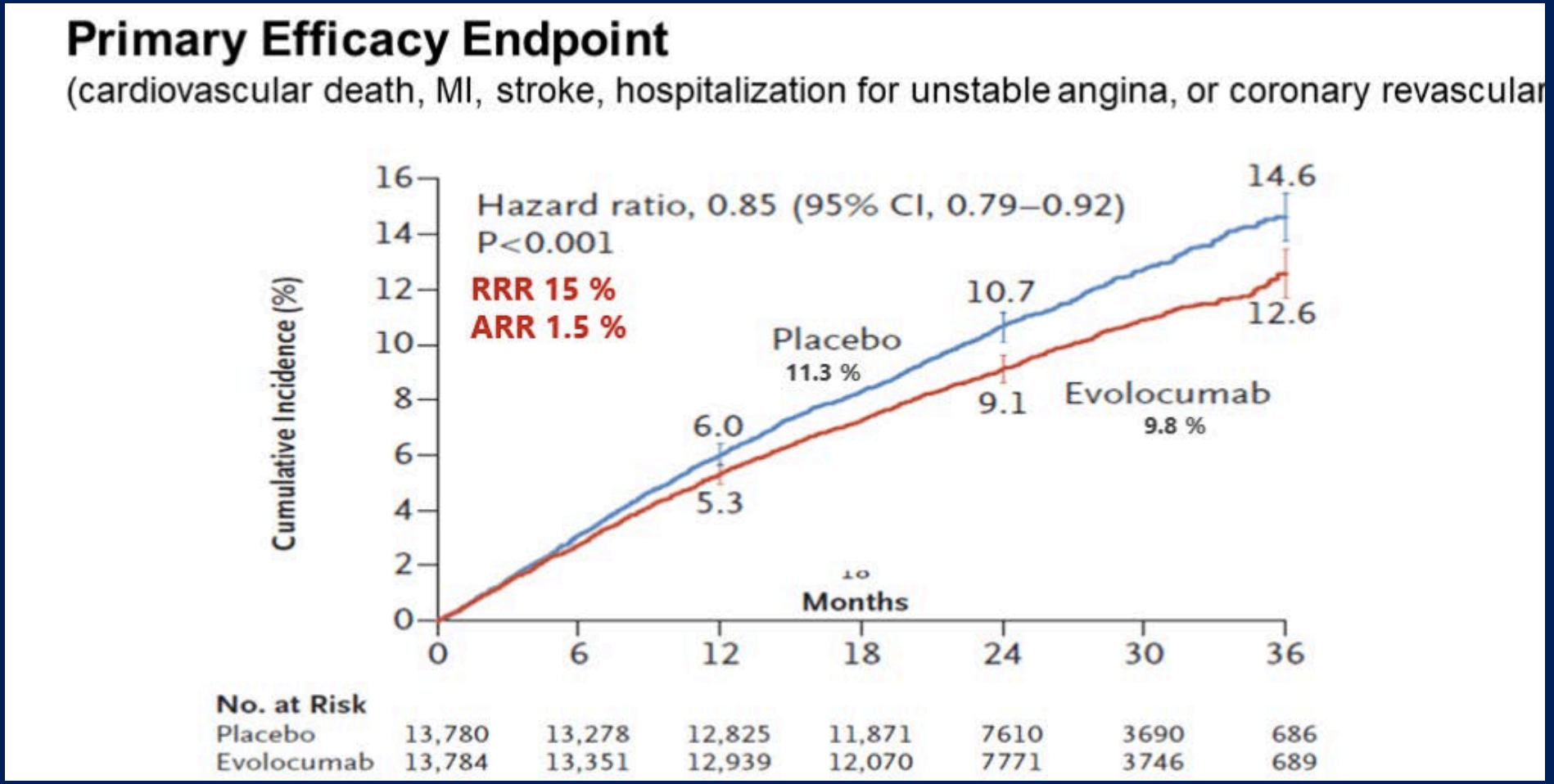
PCSK9 inhibition: What we know

- PCSK9 GOF = high LDL-C
- PCSK9 SNPs predict LDL-C and CVD
- PCSK9i is beneficial, both in terms of LDL-C as well as on CVD endpoints
- Residual risk in statin treated patients

FOURIER trial

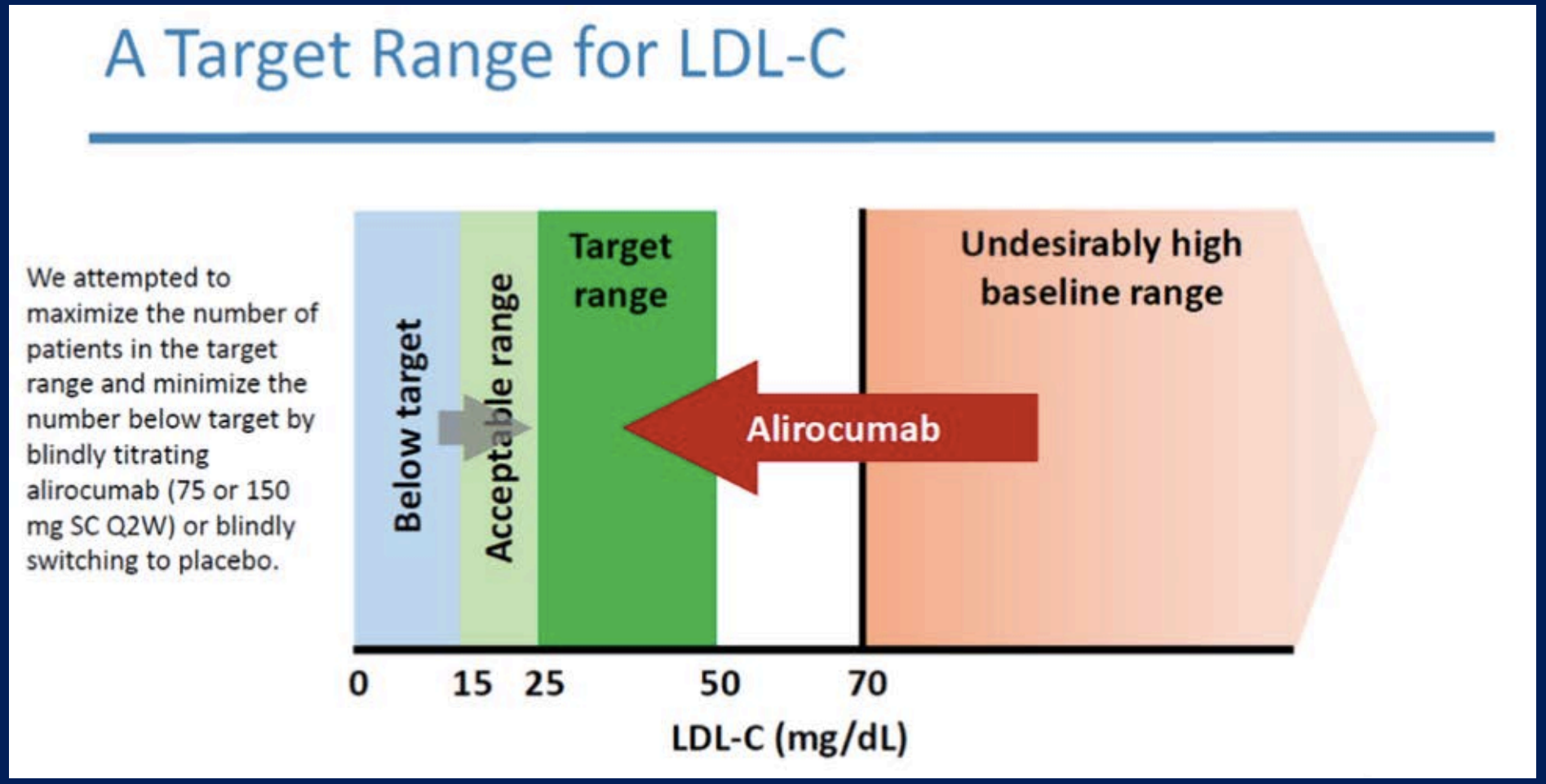
- 27,564 stable patients with established CV disease [prior MI (81%), prior stroke (19%), or symptomatic PAD (13%)]
- 69% on high-intensity statins
- LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL
- Randomized to evolocumab Q2W (or Q4W) vs placebo
- Median follow-up 2.2 years

FOURIER trial



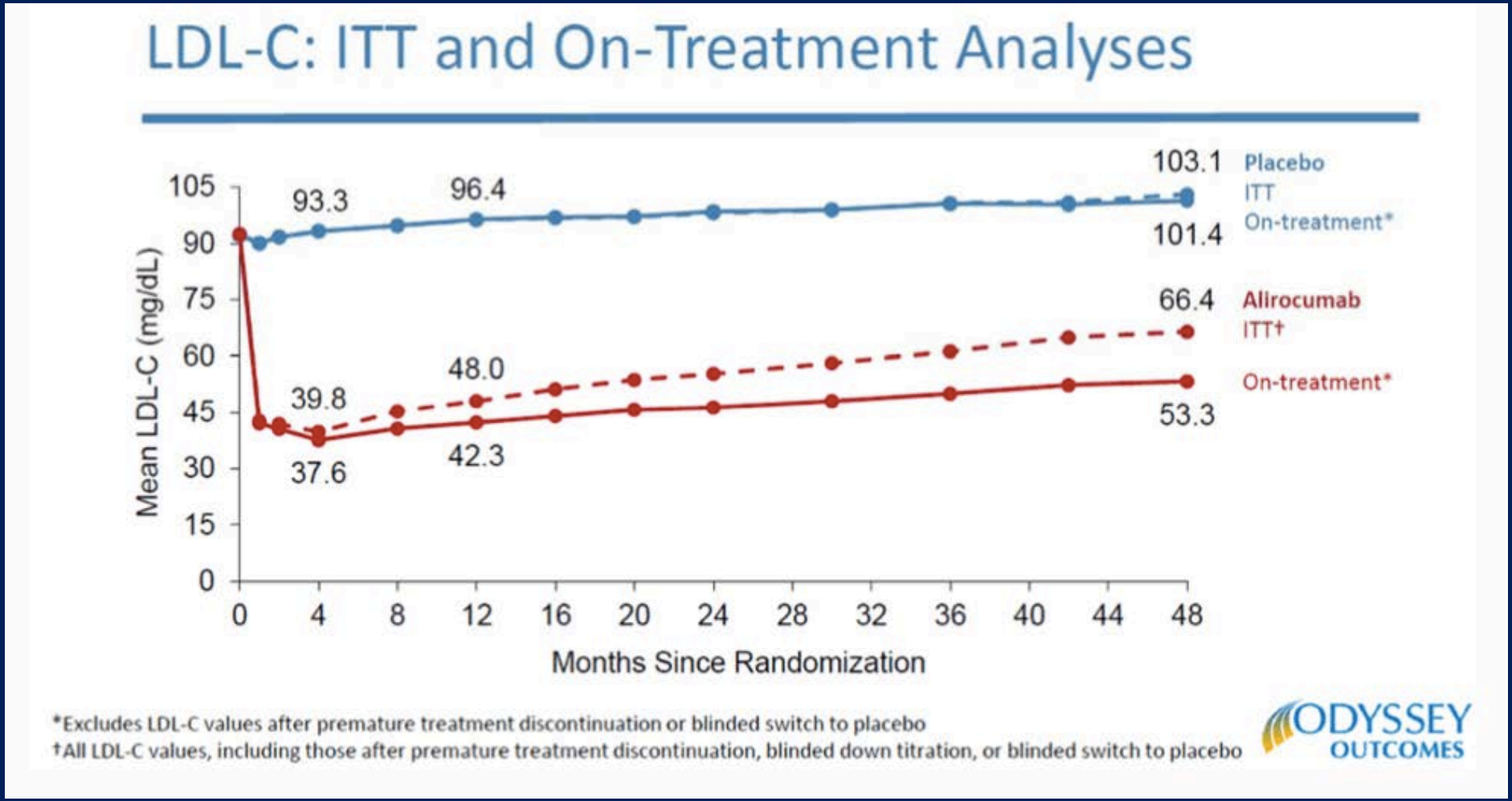
ARR, absolution risk reduction; RRR, relative risk reduction
Sabatine et al. N Engl J Med 2017;376:1713–1722

FOURIER did not limit the LDL lowering and there was no target range unlike odyssey

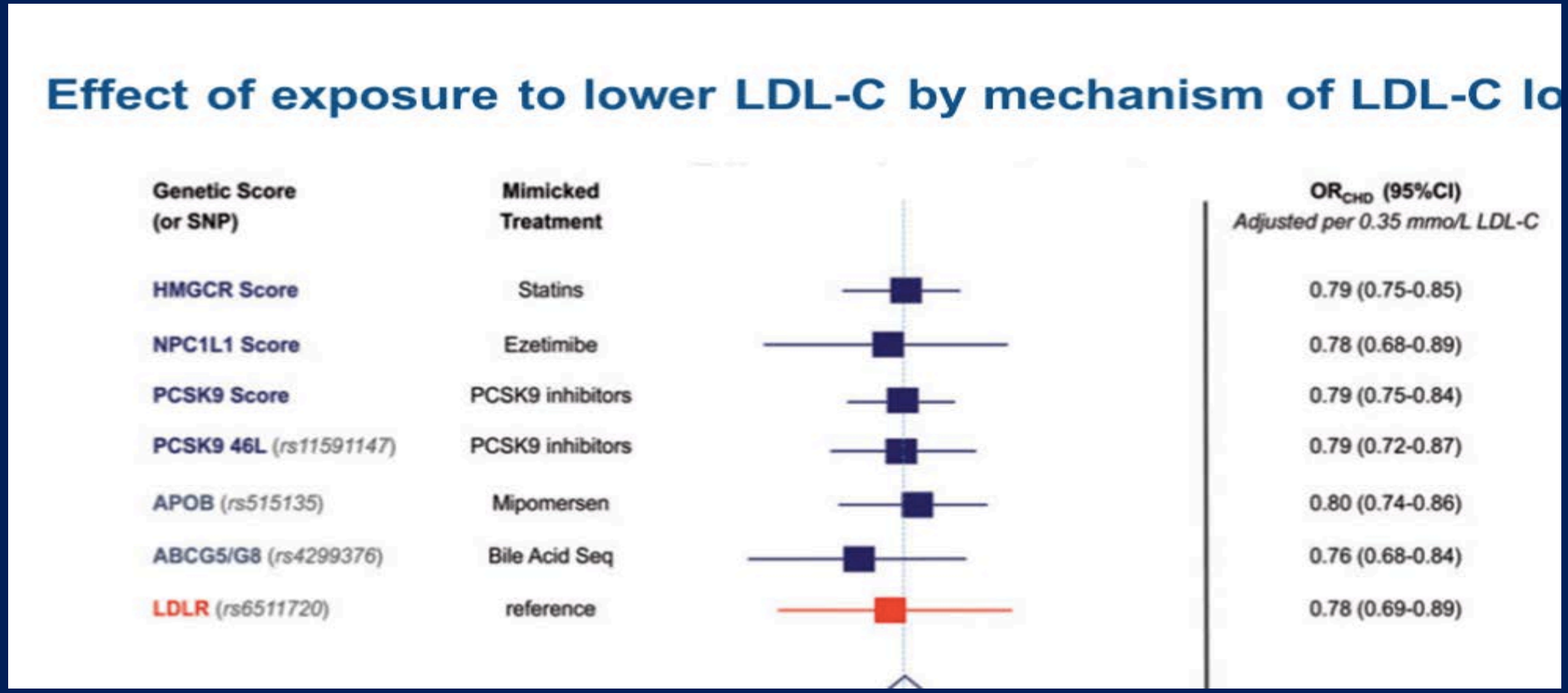


Schwartz GG et al. Am Heart J 2014;168:682–689.e1

Increase in LDL over time due to down titration



LDL is bad and the lower the LDL better it doesn't matter how it is lowered !!!



Genetically lower or pharmacologically lower LDL = better outcome

Effect of exposure to lower LDL-C by mechanism of LDL-C lowering

Magnitude of the benefit from LDL-C lowering is:

- independent of the means by which it is achieved
- *proportionate to the absolute decrease in LDL-C*
- *dependent of the absolute risk for recurrent cardiovascular events*

Ference et al. Eur Heart J 2017;38:2459–2472

Major learnings from RCTS on LDL lowering

Highest risk, Highest benefit

ESC European Society of Cardiology

European Heart Journal (2018) 39, 2546–2550
doi:10.1093/eurheartj/ehx710

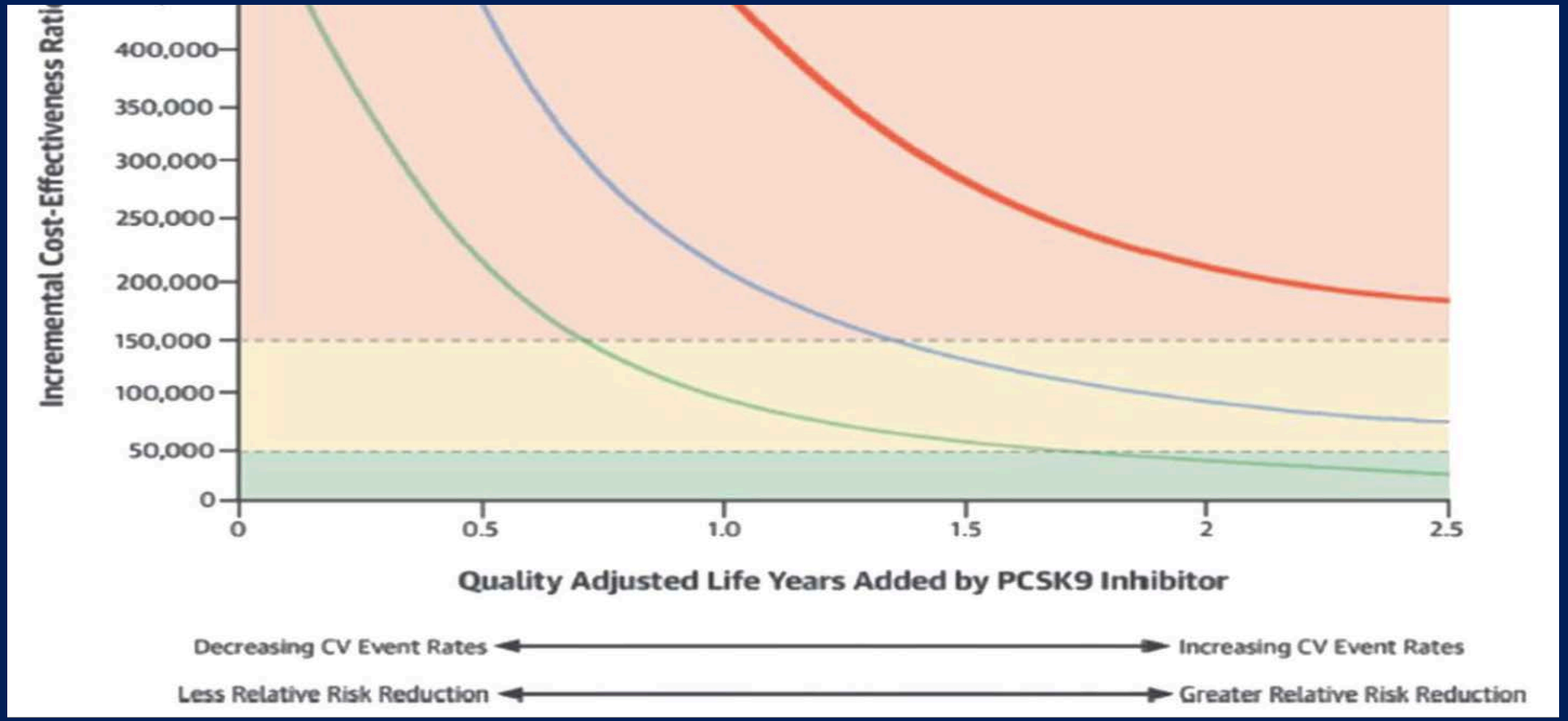
CURRENT OPINION
Lipids

'Highest risk–highest benefit' strategy: a pragmatic, cost-effective approach to targeting use of PCSK9 inhibitor therapies

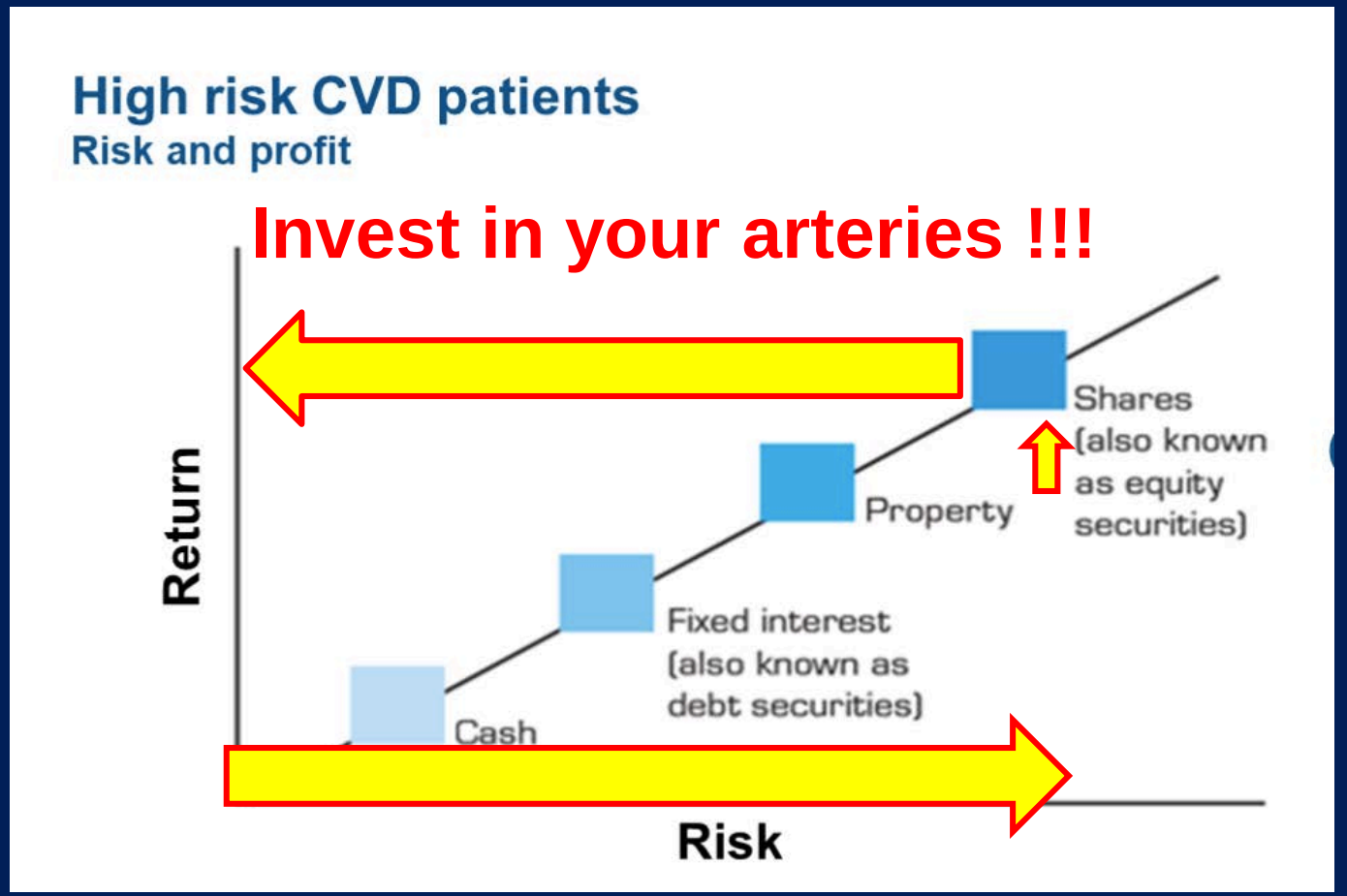
Lieven Annemans[1]*†, Chris J. Packard[2†], Andrew Briggs[3], and Kausik K. Ray[4]

- How identify the patients at the highest risk for recurrent ASCVD ?
- LDL-C on statin, score of risk in secondary prevention, clinical categories

Highest risk highest benefit



Intensive investment in the highest risk patients gives the greatest profit & reward of lives saved



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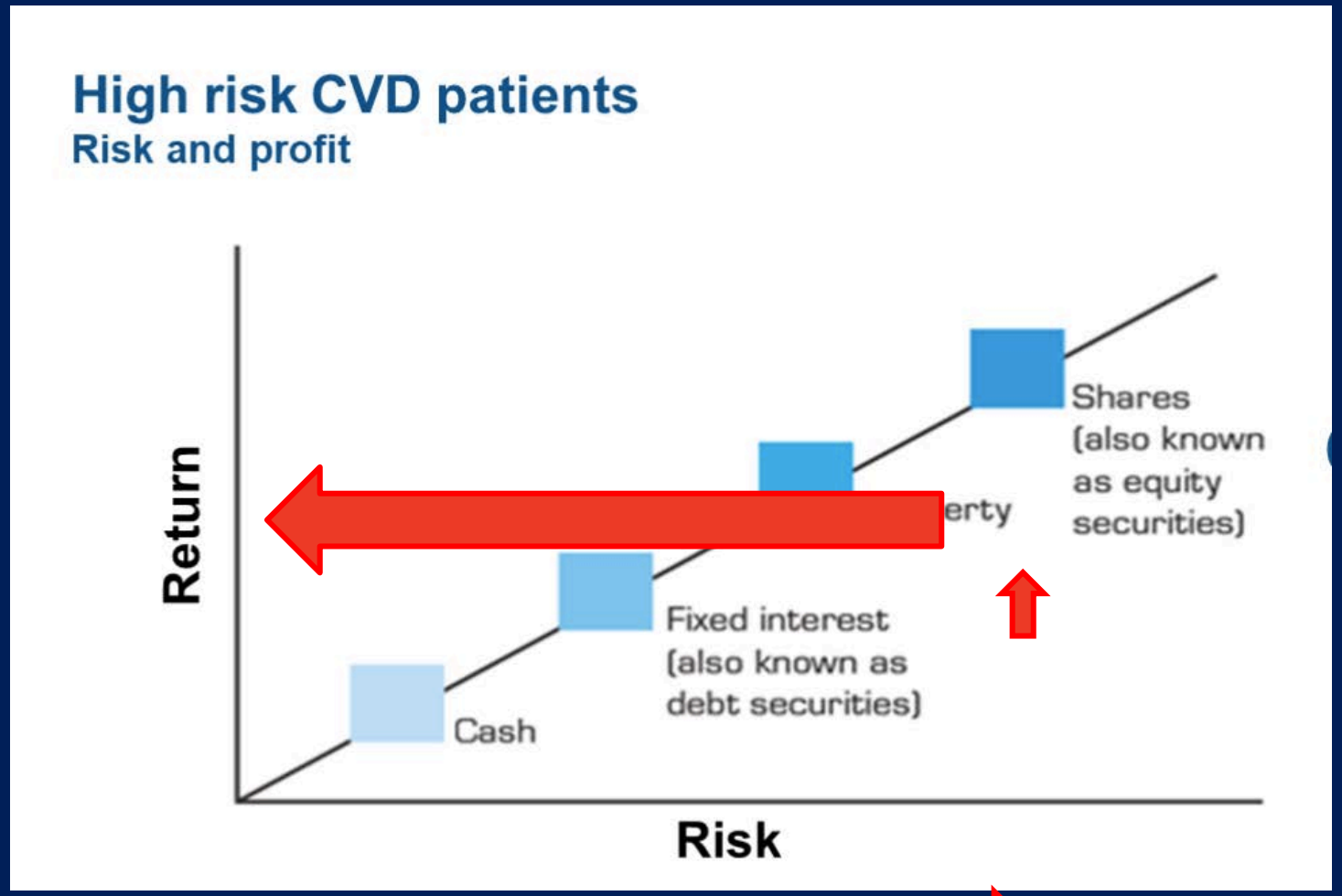
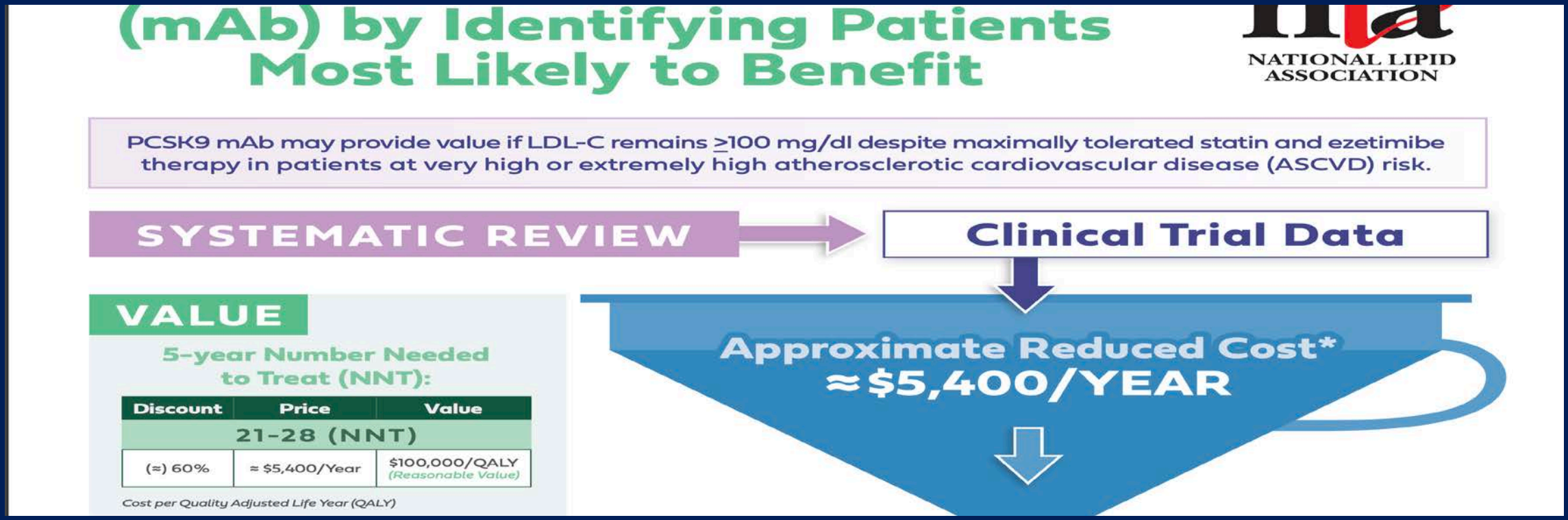
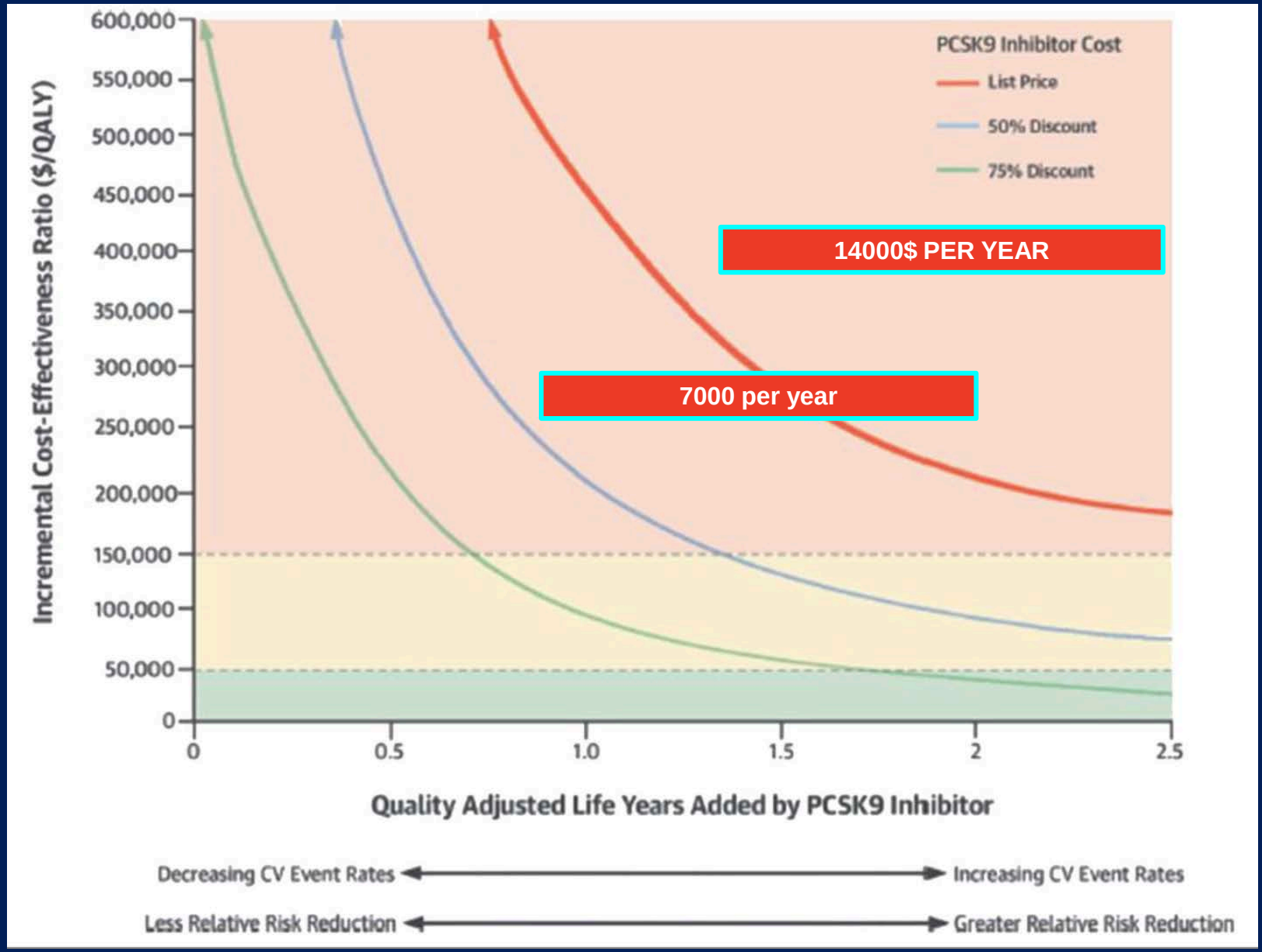


Common reasons for denial of a PCSK9 inhibitor

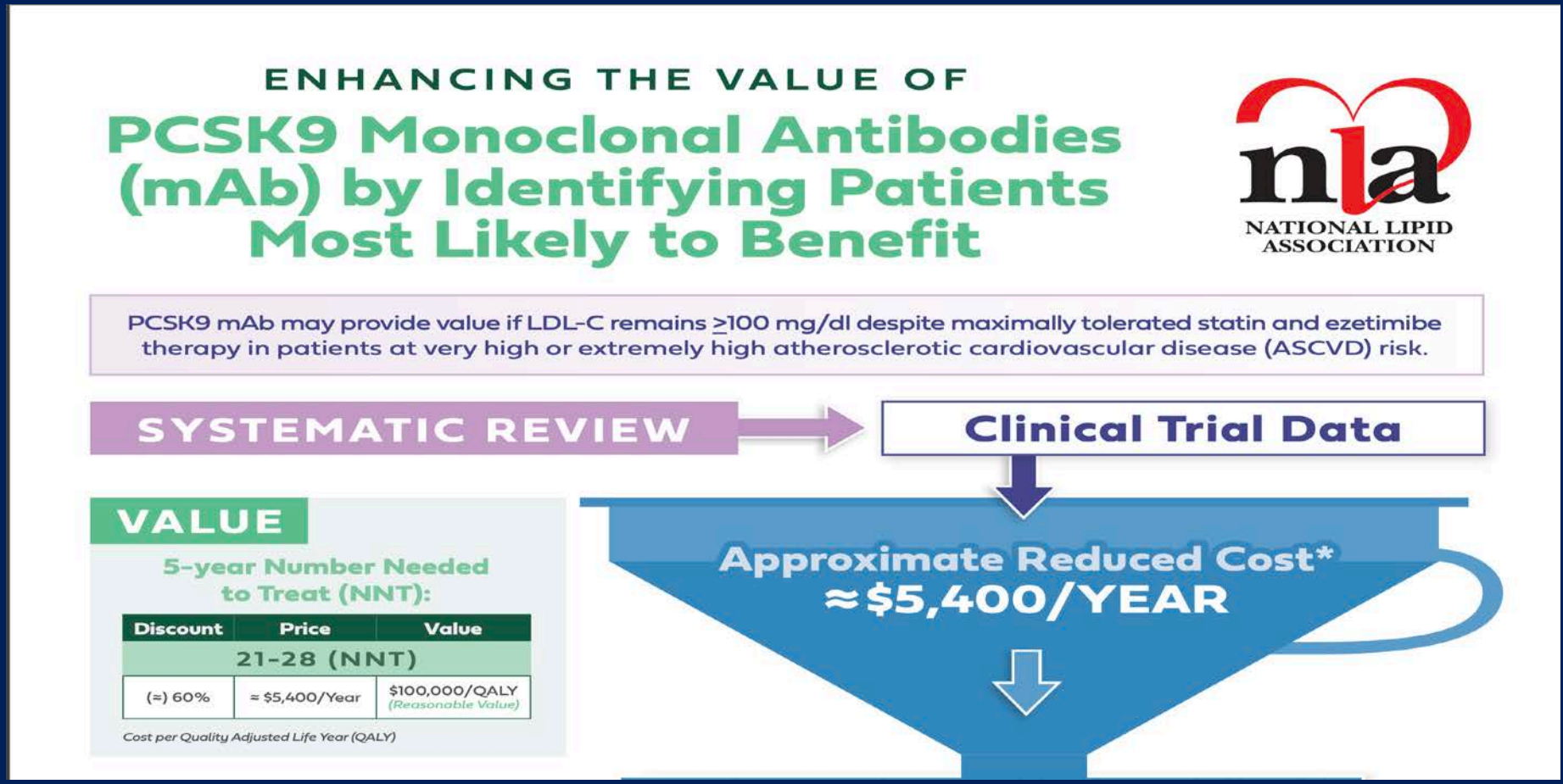



Incremental Cost-Effectiveness Ratio ($/QALY)
600,000
550,000
500,000
450,000
400,000
350,000
300,000
250,000
200,000
150,000
100,000
50,000
0
0
0.5
1.0
1.5
2
2.5
Quality Adjusted Life Years Added by PCSK9 Inhibitor
PCSK9 Inhibitor Cost
List Price
50% Discount
75% Discount
14000$ PER YEAR
7000 per year
Decreasing CV Event Rates
Increasing CV Event Rates
Less Relative Risk Reduction
Greater Relative Risk Reduction

Cost-effectiveness analysis for PCSK9 inhibitors

- Conceptual relationship between the clinical effectiveness of PCSK9 inhibitor therapy, measured in QALYs added compared with statin therapy, on the horizontal axis, and their clinical value, measured in dollars per QALY added, on the vertical axis.
- The top curve indicates the relationship at full U.S list price of PCSK9 inhibitor therapy ($14,000/y), the middle curve indicates the relationship if the price were reduced by 50% (i.e., to $7,000/y), and the bottom curve indicates the relationship if the price were reduced by 75% (i.e., to $3,500/y).

NLA statement on cost effectiveness at current US cost



Patients with heterozygous familial hypercholesterolemia (HeFH) or severe hypercholesterolemia (SH)

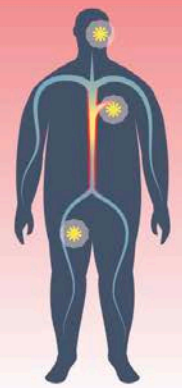
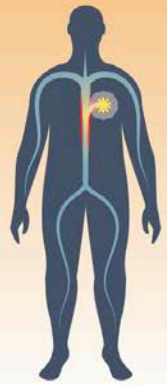
On Maximally Tolerated Statin & Ezetimibe Therapy		
	High Value <$50,000/QALY	Reasonable Value <$100,000/QALY
5-year NNT	≤14	≤28
Secondary Prevention		
HeFH or SH >220 mg/dl with clinical ASCVD *(ASCVD risk likely similar when coronary artery calcium >100 Agatston units)*	LDL-C ≥100 mg/dl	LDL-C ≥70 mg/dl
Primary Prevention		
HeFH or SH >220 mg/dl *with risk factor(s)**	LDL-C ≥190 mg/dl	LDL-C ≥100 mg/dl

Patients with ASCVD on Maximally Tolerated Statin +/- Ezetimibe Therapy

	High Value <$50,000/QALY	Reasonable Value <$100,000/QALY
5-year NNT	≤10	≤21
10-year ASCVD risk		
≥40%	LDL-C >130 mg/dl	LDL-C ≥70 mg/dl
30-39%	LDL-C ≥190 mg/dl	LDL-C >100 mg/dl
20-29%	N/A	LDL-C ≥130 mg/dl

High, Very High and Extremely High-Risk Patients

On Maximally Tolerated Statin +/- Ezetimibe

Extreme High Risk >40% 10y ASCVD risk	Very High Risk 30-39% 10y ASCVD risk	High Risk 20-29% 10y ASCVD risk
		
LDL-C ≥70 mg/dl	**LDL-C ≥100 mg/dl**	**LDL-C ≥130 mg/dl**
• Extensive or active burden of ASCVD, usually with extremely high risk and poorly controlled cardiometabolic risk factors. • Less extensive ASCVD and extremely high risk cardiometabolic risk factors	• Less extensive ASCVD and poorly controlled cardiometabolic risk factors	• Less extensive ASCVD and well controlled cardiometabolic risk factors • Primary prevention HeFH or SH LDL-C>220 mg/dl and poorly controlled cardiometabolic risk factors

Robinson, Jennifer G., et al. "Enhancing the Value of PCSK9 Monoclonal Antibodies by Identifying Patients Most Likely to Benefit." Journal of Clinical Lipidology, 16 May 2019, doi:10.1016/j.jacl.2019.05.005.

FH & severe FH LDL cutoff on top of statin and EZE

Patients with heterozygous familial hypercholesterolemia (HeFH) or severe hypercholesterolemia (SH)

On Maximally Tolerated Statin & Ezetimibe Therapy		
	High Value *<$50,000/QALY*	Reasonable Value *<$100,000/QALY*
5-year NNT	≤14	≤28
Secondary Prevention		
HeFH 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		
HeFH or SH >220 mg/dl *with risk factor(s)**	LDL-C ≥190 mg/dl	LDL-C ≥100 mg/dl

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

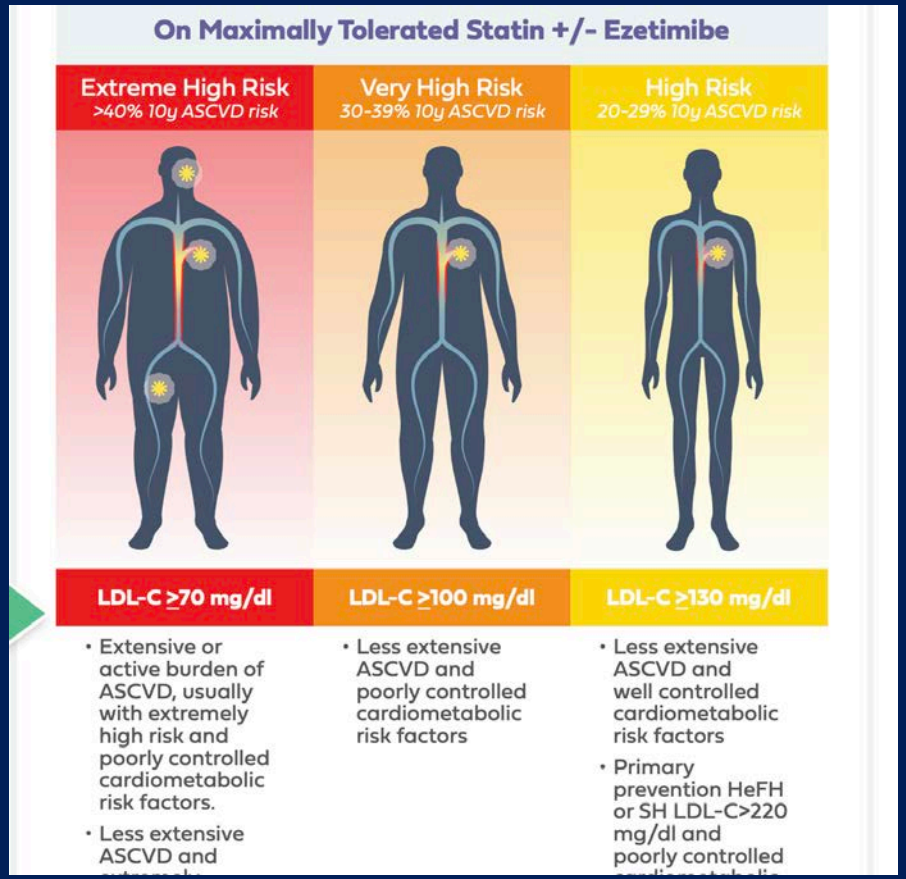
RESIDUAL LDLLEEVEL ON STATIN AND EZE

Patients with ASCVD on Maximally Tolerated Statin +/- Ezetimibe Therapy

	High Value <$50,000/QALY	Reasonable Value <$100,000/QALY
5-year NNT	≤10	≤21
10-year ASCVD risk		
≥40%	LDL-C >130 mg/dl	LDL-C ≥70 mg/dl
30-39%	LDL-C ≥190 mg/dl	LDL-C >100 mg/dl
20-29%	N/A	LDL-C ≥130 mg/dl

Robinson, Jennifer G., et al. "Enhancing the Value of PCSK9 Monoclonal Antibodies by Identifying Patients Most Likely to Benefit." Journal of Clinical Lipidology, 16 May 2019, doi:10.1016/j.jacl.2019.05.005.

CLINICAL PROFILE AND RISK



Patients with ASCVD on Maximally Tolerated Statin +/- Ezetimibe Therapy

	High Value <$50,000/QALY	Reasonable Value <$100,000/QALY
5-year NNT	≤10	≤21
10-year ASCVD risk		
≥40%	LDL-C >130 mg/dl	LDL-C ≥70 mg/dl
30-39%	LDL-C ≥190 mg/dl	LDL-C >100 mg/dl
20-29%	N/A	LDL-C ≥130 mg/dl

LDL-C ≥70 mg/dl	LDL-C ≥100 mg/dl	LDL-C ≥130 mg/dl
• Extensive or active burden of ASCVD, usually with extremely high risk and poorly controlled cardiometabolic risk factors. • Less extensive ASCVD and extremely high risk cardiometabolic risk factors	• Less extensive ASCVD and poorly controlled cardiometabolic risk factors	• Less extensive ASCVD and well controlled cardiometabolic risk factors • Primary prevention HeFH or SH LDL-C>220 mg/dl and poorly controlled cardiometabolic risk factors

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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	
1. Polyvascular clinical ASCVD (coronary heart disease†, ischemic stroke, and symptomatic peripheral arterial disease) 2. Symptomatic peripheral arterial disease** in 3. addition to a coronary heart disease† or ischemic stroke 4. 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 5. Recurrent myocardial infarction within 2 years	1. Heterozygous familial hypercholesterolemia with 2. clinical ASCVD (or coronary artery calcium >100) 3. History of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease** with at least one of: 1. Diabetes 2. LDL-C >100 mg/dl 3. Less than high intensity statin therapy 4. High sensitivity C-reactive protein >3 mg/L 4. 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

ON STATIN THERAPY	
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