2017 Update of ESC/EAS Task Force on Practical Clinical Guidance for PCSK9 inhibition in Patients with Atherosclerotic Cardiovascular Disease or in Familial Hypercholesterolaemia

Landmesser U et al. Eur Heart J 2017; https://doi.org/10.1093/eurheartj/ehx549

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CURRENT OPINION

2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia

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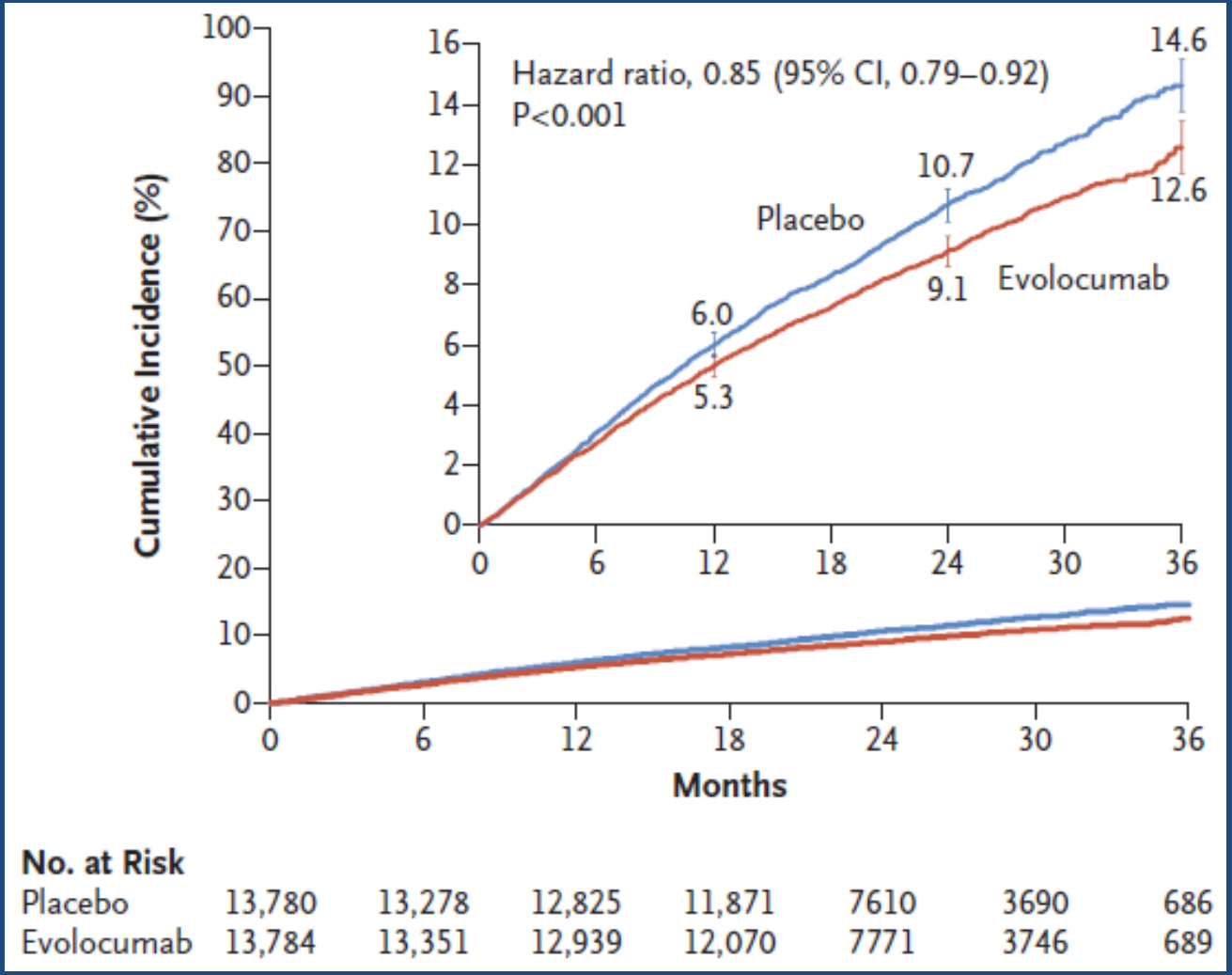
Cardiovascular Outcomes Studies with PCSK9 Inhibitors: What Have We Learned?

FOURIER: Impact of LDL-C Lowering on Primary End Point*

***Composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization)**



Patients with stable ASCVD

LDL-C at baseline:
2.4 mmol/L (92 mg/dL)

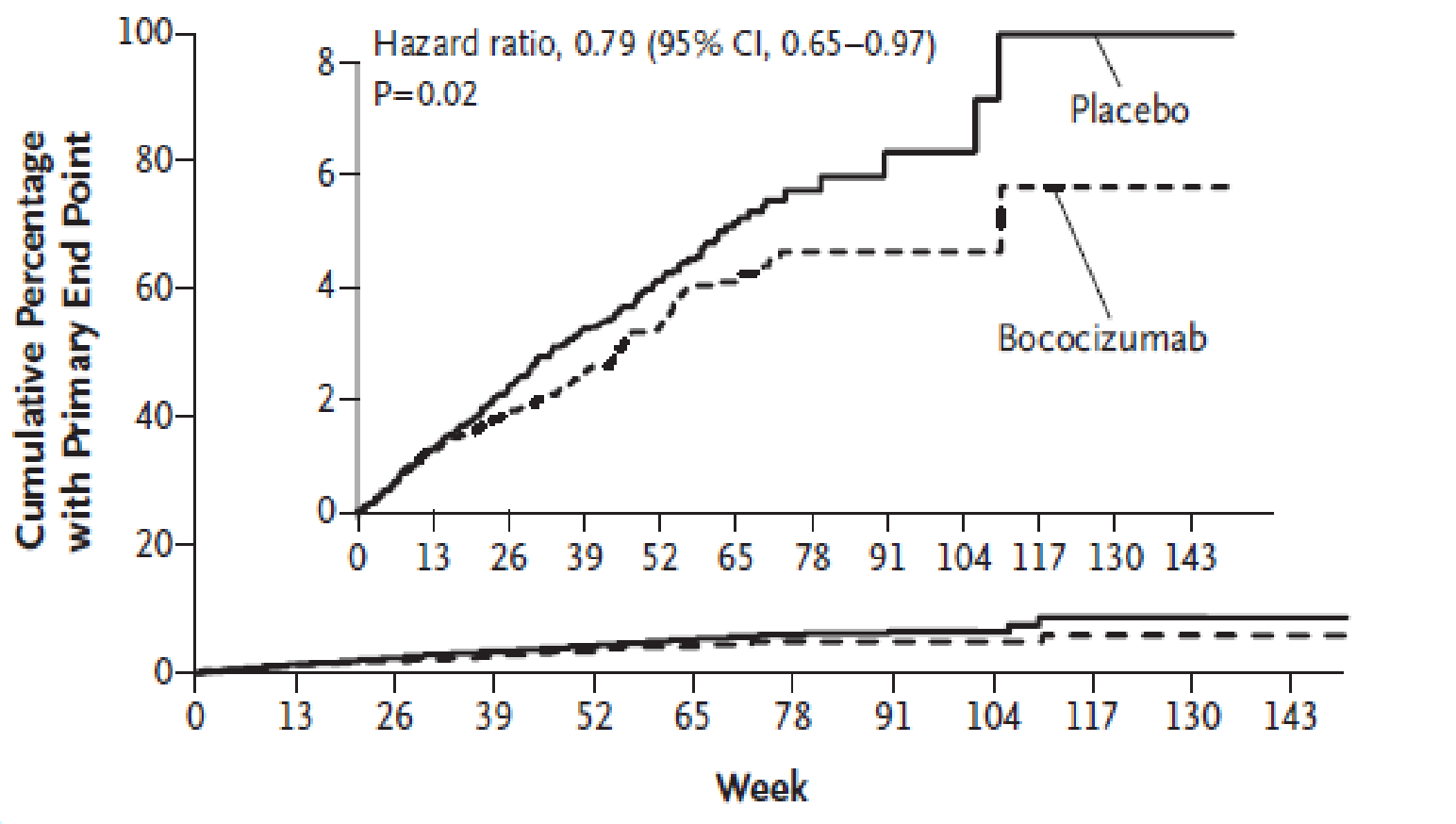
LDL-C with evolocumab:
0.78 mmol/L (30 mg/dL)

Reduction in LDL-C 59% (1.5 mmol/l)

Sabatine M et al NEJM 2017; 376:1713-22.

The SPIRE 2 Cardiovascular Outcomes Trial: Impact of LDL-C Lowering on Primary Pre-specified Endpoint*

*Composite of nonfatal MI, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death



Patients with stable ASCVD; history of diabetes, CKD, PAD or additional risk indicators; or history of familial hypercholesterolaemia (7.3%)

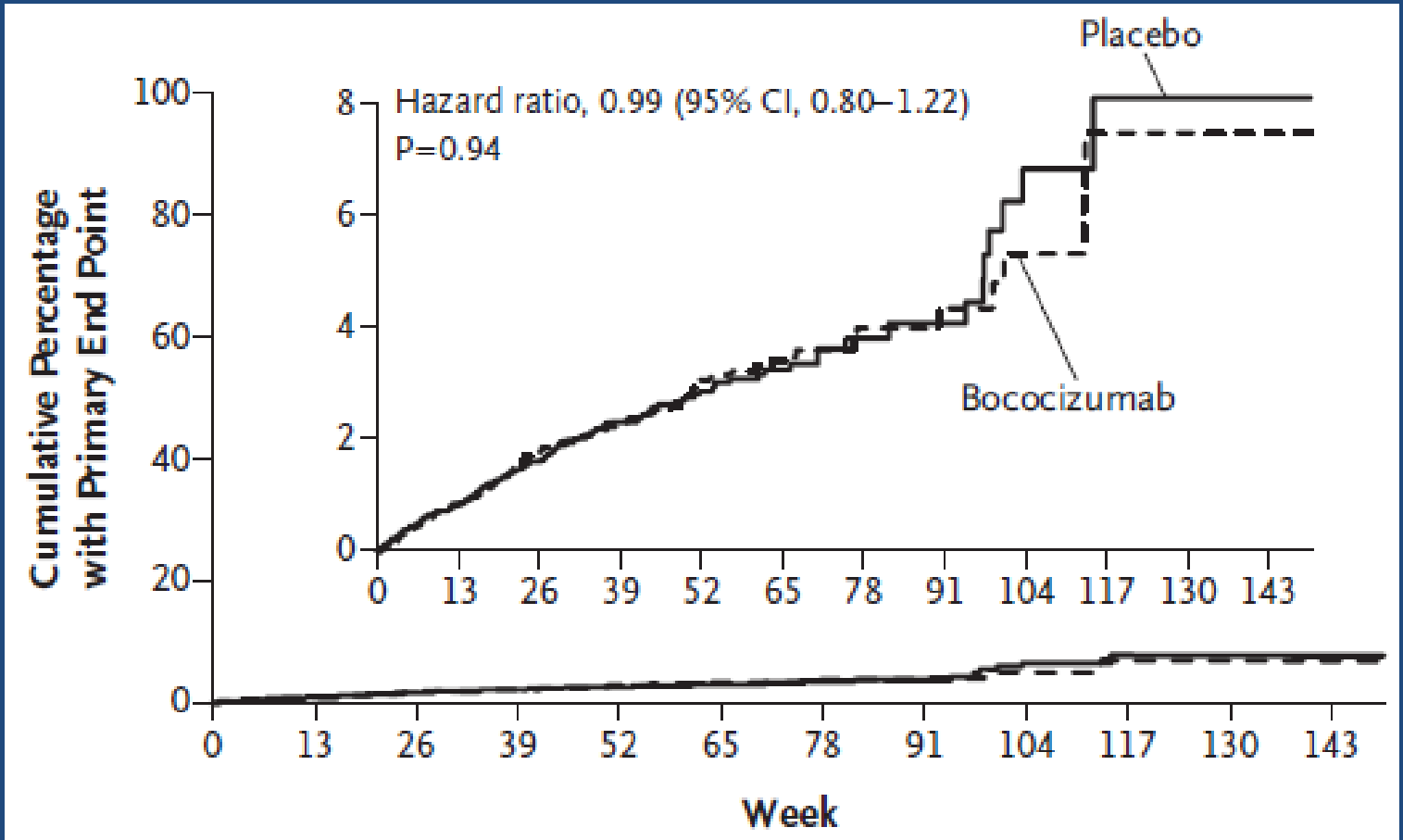
LDL-C at baseline:
3.5 mmol/L (134 mg/dL)

Reduction in LDL-C 56.8% (14 wk)
Duration of follow-up: 12 months

Ridker PM, et al. N Engl J Med 2017;376:527-39

The SPIRE 1 Cardiovascular Outcomes Trial: Impact on LDL-C Lowering on Primary Pre-specified Endpoint*

*** Composite of n**onfatal MI, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death



Patients with stable ASCVD; history of diabetes, CKD, PAD or additional risk indicators; or history of familial hypercholesterolaemia (1.8%)
LDL-C at baseline:
2.4 mmol/L (94 mg/dL)

Reduction in LDL-C 60.5% (14 wk)
Duration of follow-up: 7 months

Ridker PM, et al. N Engl J Med 2017;376:1527-39.

Reasons for Termination of Bococizumab

Box 1 Key reasons for termination of bococizumab

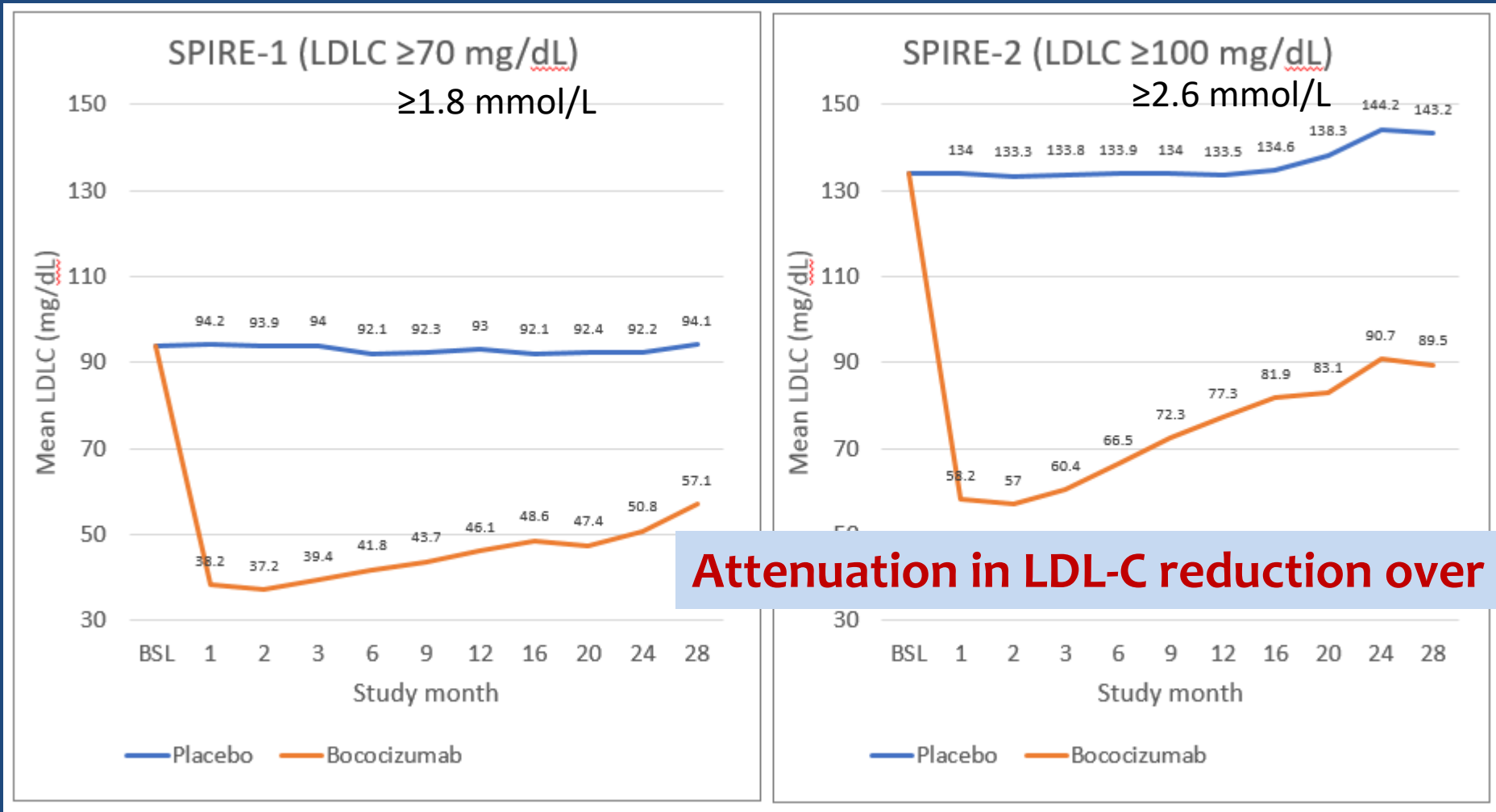
The development of bococizumab was discontinued by Pfizer in late 2016.[a] The key reasons for this were a high level of immunogenicity and wide variability in the low-density lipoprotein cholesterol (LDL-C) lowering response.

- *Immunogenicity*: In statin-treated patients, PCSK9 inhibition with bococizumab reduced LDL-C levels by 55–60% in the short-term, but this effect was attenuated over time in 10–15% of patients due to the development of antidrug antibodies. It is important to note that this effect was specific to bococizumab, a partially humanized monoclonal antibody, which is characterized by substitution of rodent DNA sequences for <5% of human DNA sequences. It is thought that this substitution may have directly affected the immunogenicity of the antibody. This effect has not been reported for either evolocumab or alirocumab, which are fully human monoclonal antibodies. This immunogenicity may also explain the higher rate of injection site reactions (~10%) observed with bococizumab compared with either alirocumab or evolocumab (<5%).
- *Variability in LDL-C lowering response*: Irrespective of the presence or absence of antidrug antibodies, there was wide individual variability in the LDL-C lowering response with bococizumab; about 1 in 10 showed no reduction in LDL-C levels.

[a]Press release Tuesday, 1 November 2016. Pfizer Discontinues Global Development of Bococizumab, Its Investigational PCSK9 Inhibitor.

Landmesser U et al. Eur Heart J 2017; https://doi.org/10.1093/eurheartj/ehx549

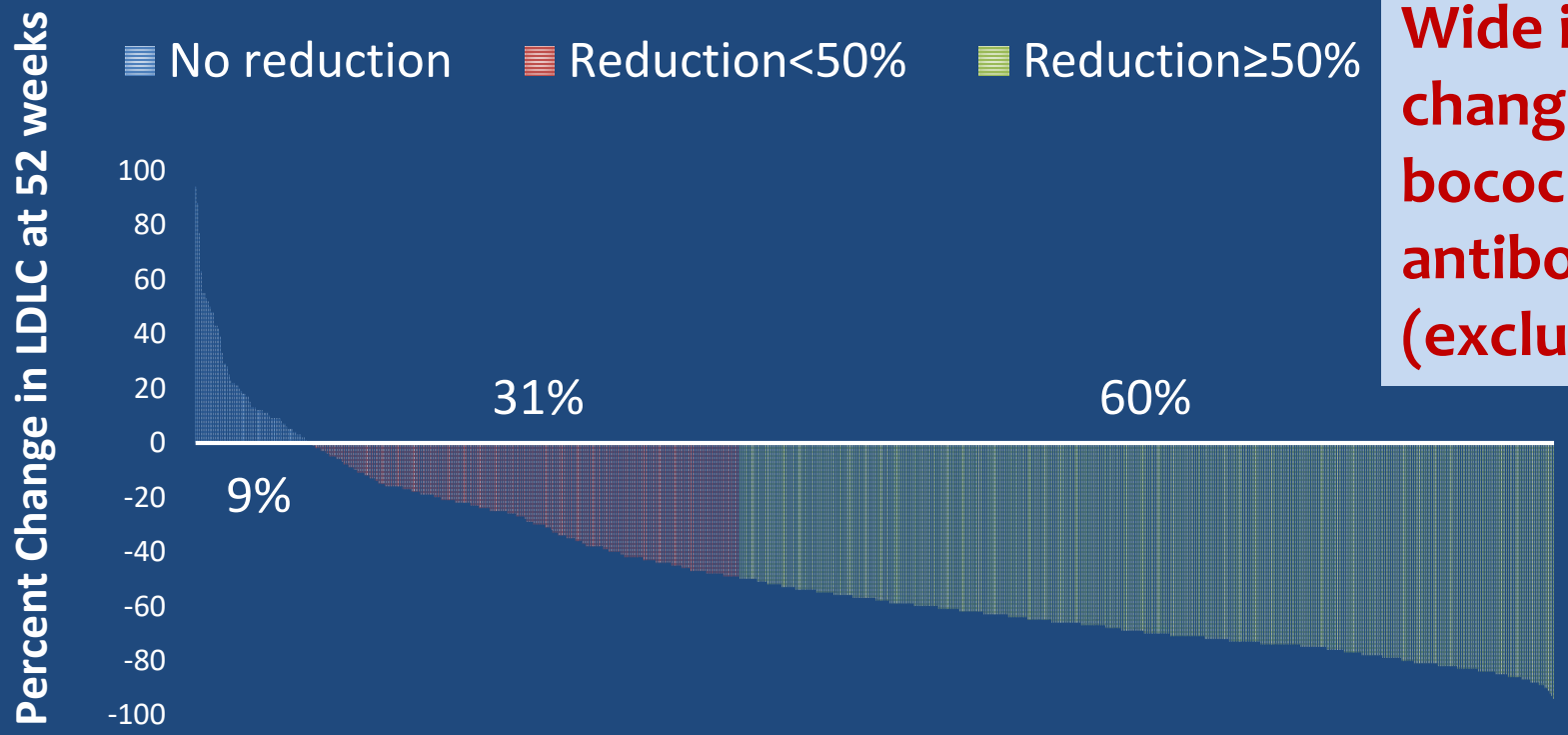
The SPIRE 1 and SPIRE 2 Cardiovascular Outcomes Trials: Confirmation of Attenuation in LDL-C Reduction Over Time



Attenuation in LDL-C reduction over 52 weeks

Ridker PM et al. N Engl J Med 2017;376:1517-26

The SPIRE 1 and SPIRE 2 Cardiovascular Outcomes Trials: Confirmation of Wide Individual Variability in Percent LDLC Reduction



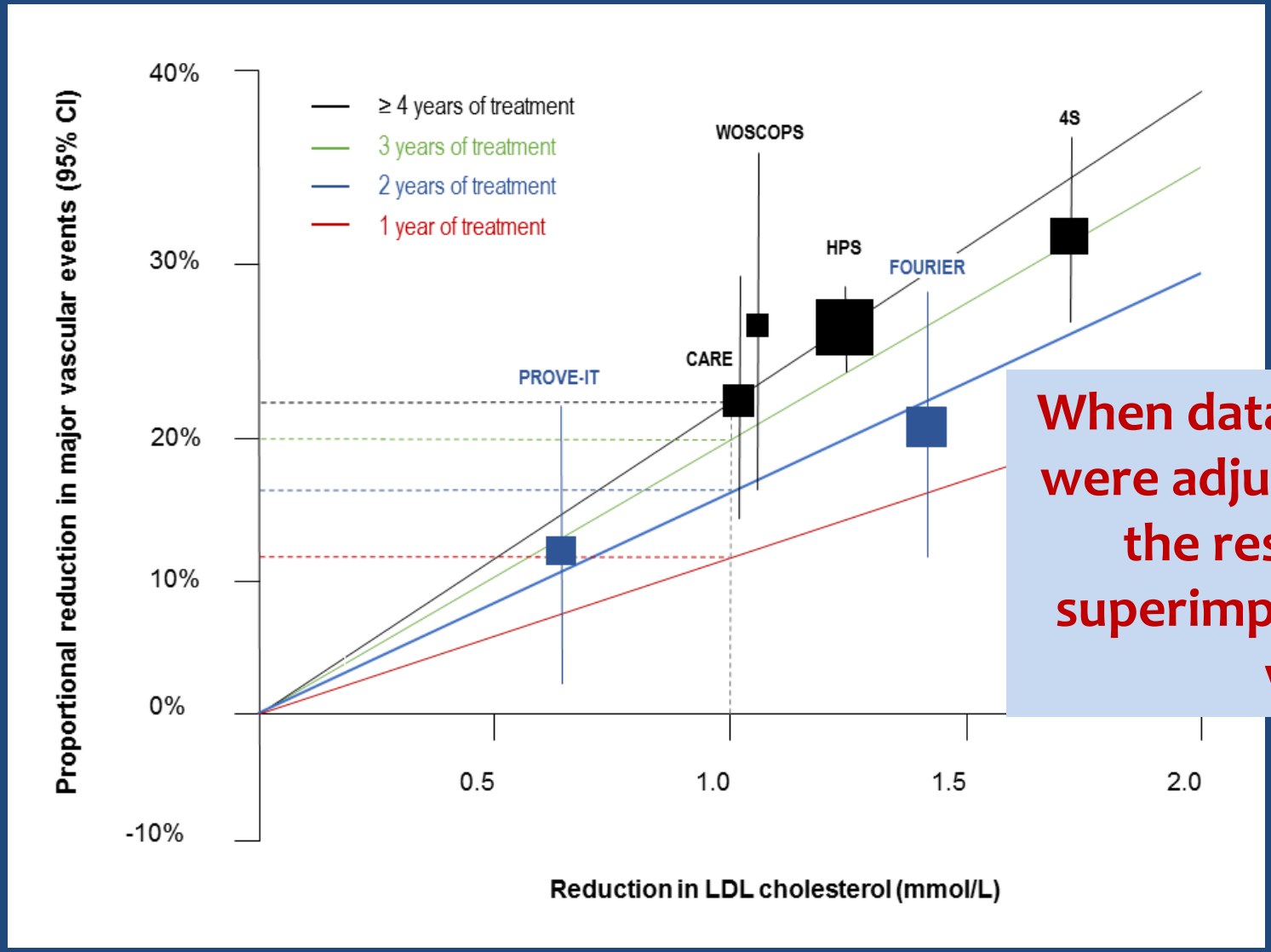
Wide individual variation in percent change in LDL-C at 52 weeks with bococizumab, even in antidrug antibody negative patients (excluding noncompliant patients)

Ridker PM et al. N Engl J Med 2017;376:1517-26

What Have We Learned from Cardiovascular Outcomes Studies with PCSK9 Inhibitors?

- In very high-risk patients, the addition of a PCSK9 inhibitor to intensive statin therapy substantially reduces LDL-C levels (>50%) and this translates to reduction in cardiovascular events.
- Nonfatal MI is the key driver of this benefit
- There is no evidence for a lower LDL-C threshold for cardiovascular benefit
- PCSK9 inhibition appears to be safe and well tolerated over the duration of trials, although long-term surveillance is clearly needed

Cardiovascular Benefit with PCSK9 Inhibition per mmol/L LDL-C Reduction



When data from the CTT Collaboration were adjusted for duration of therapy, the results from FOURIER were superimposable with those observed with statin therapy

Landmesser U et al. Eur Heart J 2017; https://doi.org/10.1093/eurheartj/ehx549

Key Messages: 2017 ESC/EAS Clinical Guidance on the Use of PCSK9 Inhibitors

Priority Patient Groups for PCSK9 Inhibition

- **Patients with clinical ASCVD and substantially elevated LDL-C levels.**

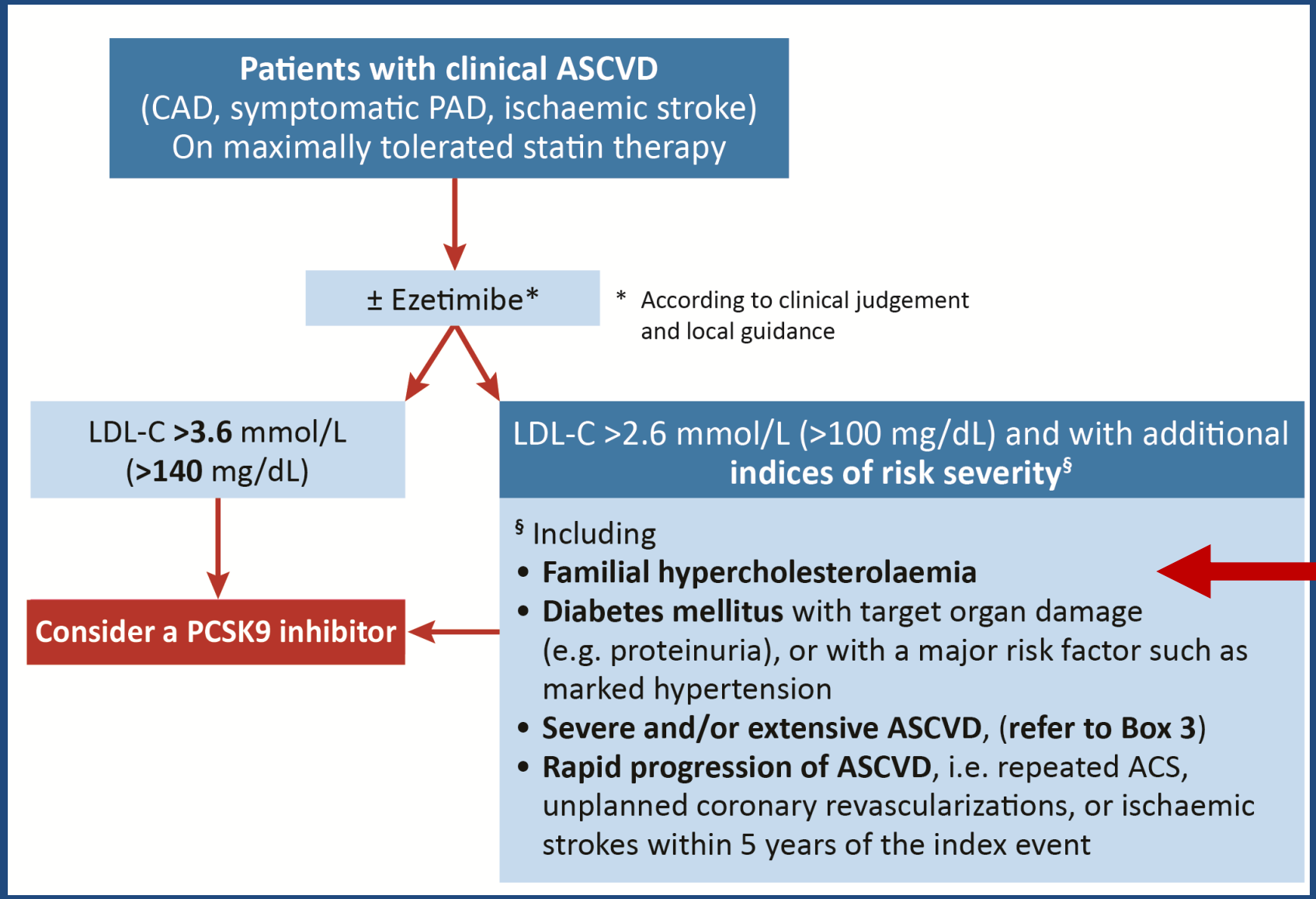
Patients should be on maximally tolerated statin therapy (ideally with concomitant ezetimibe), or unable to tolerate three or more statins.

- **Familial hypercholesterolaemia (FH) patients without clinical ASCVD but with substantially elevated LDL-C levels**

Patients should be on maximally tolerated statin therapy plus ezetimibe

Landmesser U et al. Eur Heart J 2017; https://doi.org/10.1093/eurheartj/ehx549

Patients with Clinical ASCVD : When to Consider a PCSK9 Inhibitor



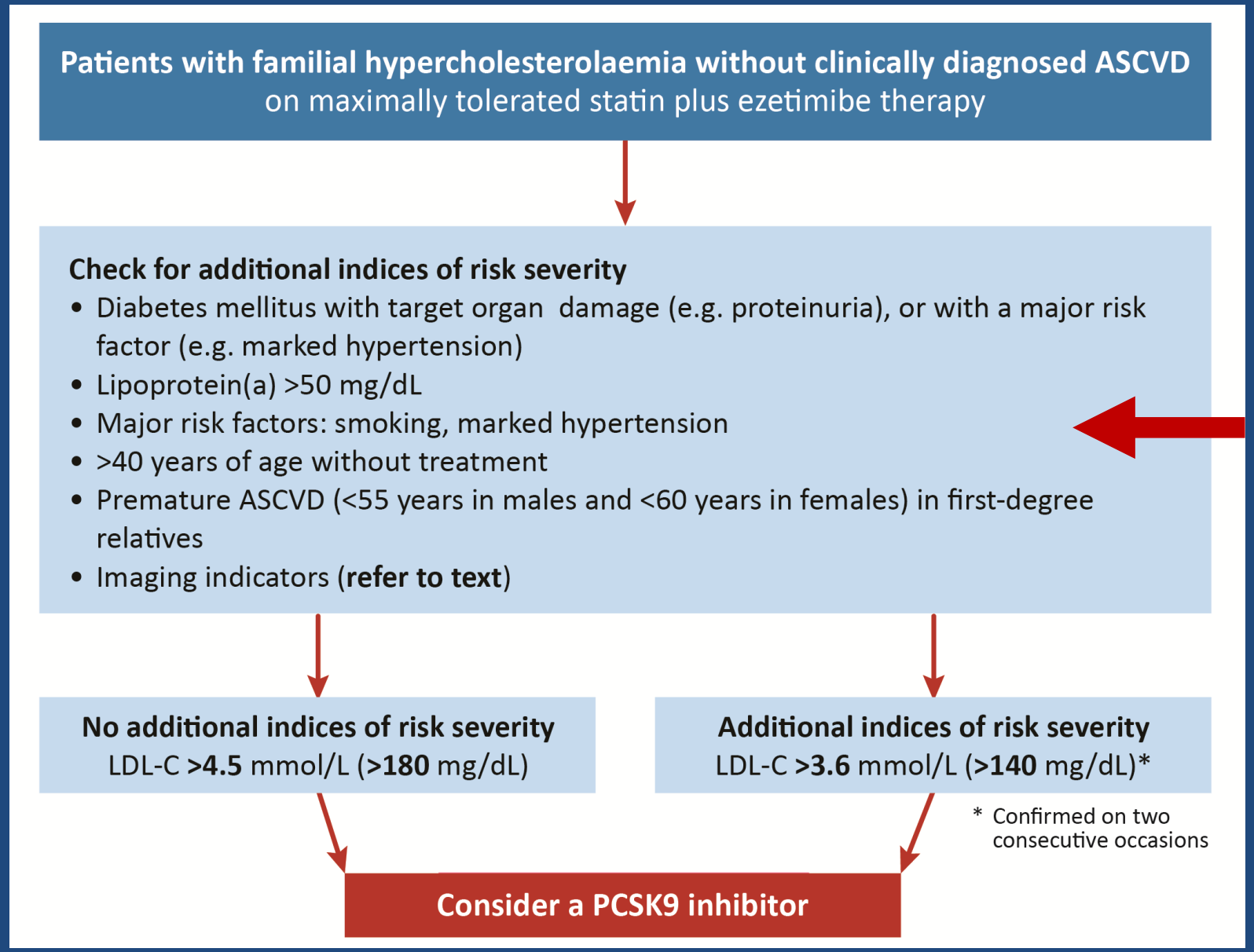
Two LDL-C thresholds:

>3.6 mmol/L (>140 mg/dL)

>2.6 mmol/L (>100 mg/dL) with additional indices of risk severity

Landmesser U et al. Eur Heart J 2017; https://doi.org/10.1093/eurheartj/ehx549

FH Patients without ASCVD : When to Consider a PCSK9 Inhibitor



Two LDL-C thresholds:

>4.5 mmol/L (>180 mg/dL)

>3.6 mmol/L (>140 mg/dL) with additional indices of risk severity

Landmesser U et al. Eur Heart J 2017; https://doi.org/10.1093/eurheartj/ehx549

LDL-C Thresholds for Considering a PCSK9 Inhibitor

Patients with clinical ASCVD	LDL-C threshold
• On maximally tolerated statin (with or without ezetimibe) or with statin intolerance	>3.6 mmol/L (140 mg/dL)
• With additional indices of risk severity	>2.6 mmol/L or 100 mg/dL

Indices of risk severity: FH, diabetes mellitus with target organ damage or with a major risk factor such as marked hypertension; severe or extensive ASCVD; or rapid progression of ASCVD (repeated acute coronary syndrome, unplanned coronary revascularizations or ischaemic stroke within 5 years of the event).

Familial hypercholesterolaemia patients without clinical ASCVD	LDL-C threshold
• On maximally tolerated statin plus ezetimibe	>4.5 mmol/L (180 mg/dL)
• With additional indices of risk severity (see below)	>3.6 mmol/L (140 mg/dL)

Indices of risk severity: Diabetes mellitus with target organ damage or with a major risk factor such as marked hypertension; lipoprotein(a) >50 mg/dl; major risk factors such as smoking, marked hypertension; >40 years without treatment; premature ASCVD (<55 years in males and <60 years in females) in first degree relatives; and imaging indicators of increased risk.

Landmesser U et al. Eur Heart J 2017; https://doi.org/10.1093/eurheartj/ehx549

Use of Imaging in Risk Assessment

- Simple non-invasive measures (e.g. carotid intima media thickness or ankle brachial pressure index) for assessment of generalized large vessel atherosclerosis
- Carotid artery scanning (usually ultrasound) for diagnosis of carotid artery plaque
- Coronary calcium score; a score >400 reflects significant and possibly high-risk coronary artery disease
- Coronary computed tomography angiography for assessment of high-risk markers (global or focal)

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Markers of High Risk with Coronary Computed Tomography Angiography

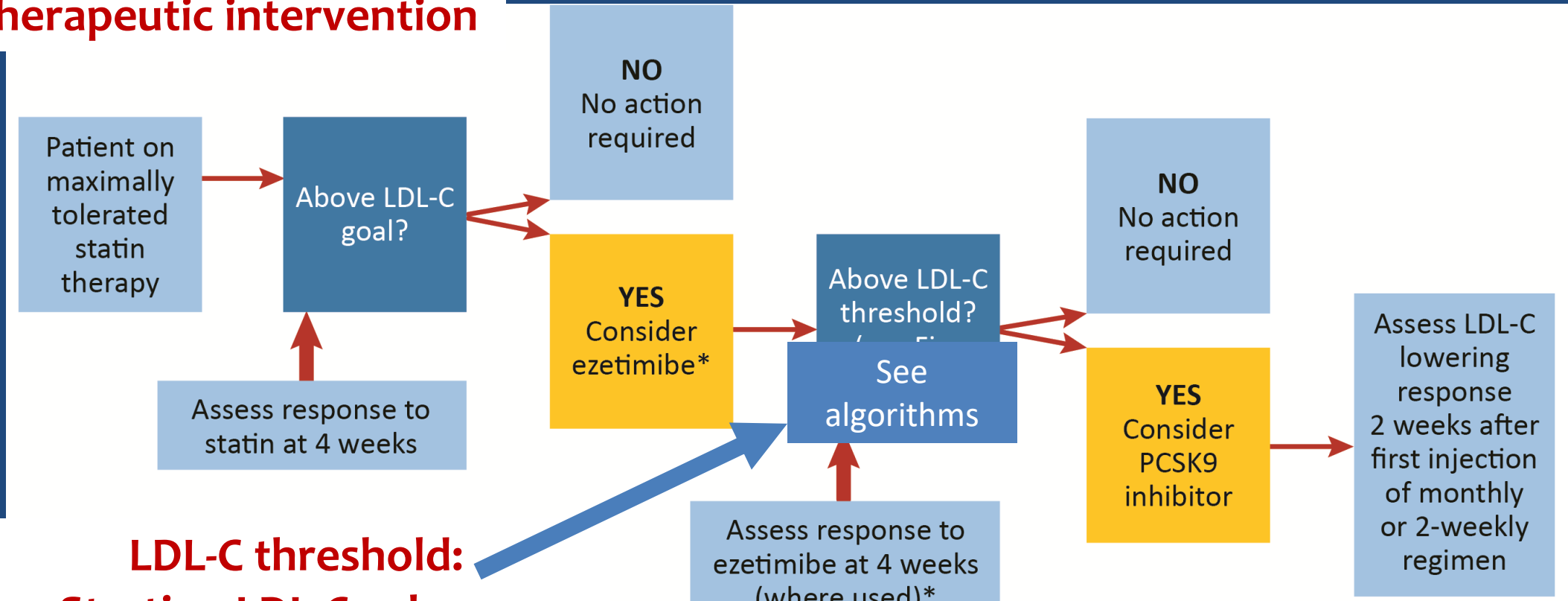
- **Global high risk markers**
  - left main disease
  - proximal left anterior descending artery (LAD) disease
  - 3-vessel disease

- **Focal high-risk markers**
  - stenosis severity >50% luminal obstruction
  - mixed or non-calcified lesions
    (these reflect earlier, unstable atherosclerosis)

Landmesser U et al. Eur Heart J 2017; https://doi.org/10.1093/eurheartj/ehx549

Monitoring the LDL-C Lowering Response

LDL-C goal: Aim of therapeutic intervention



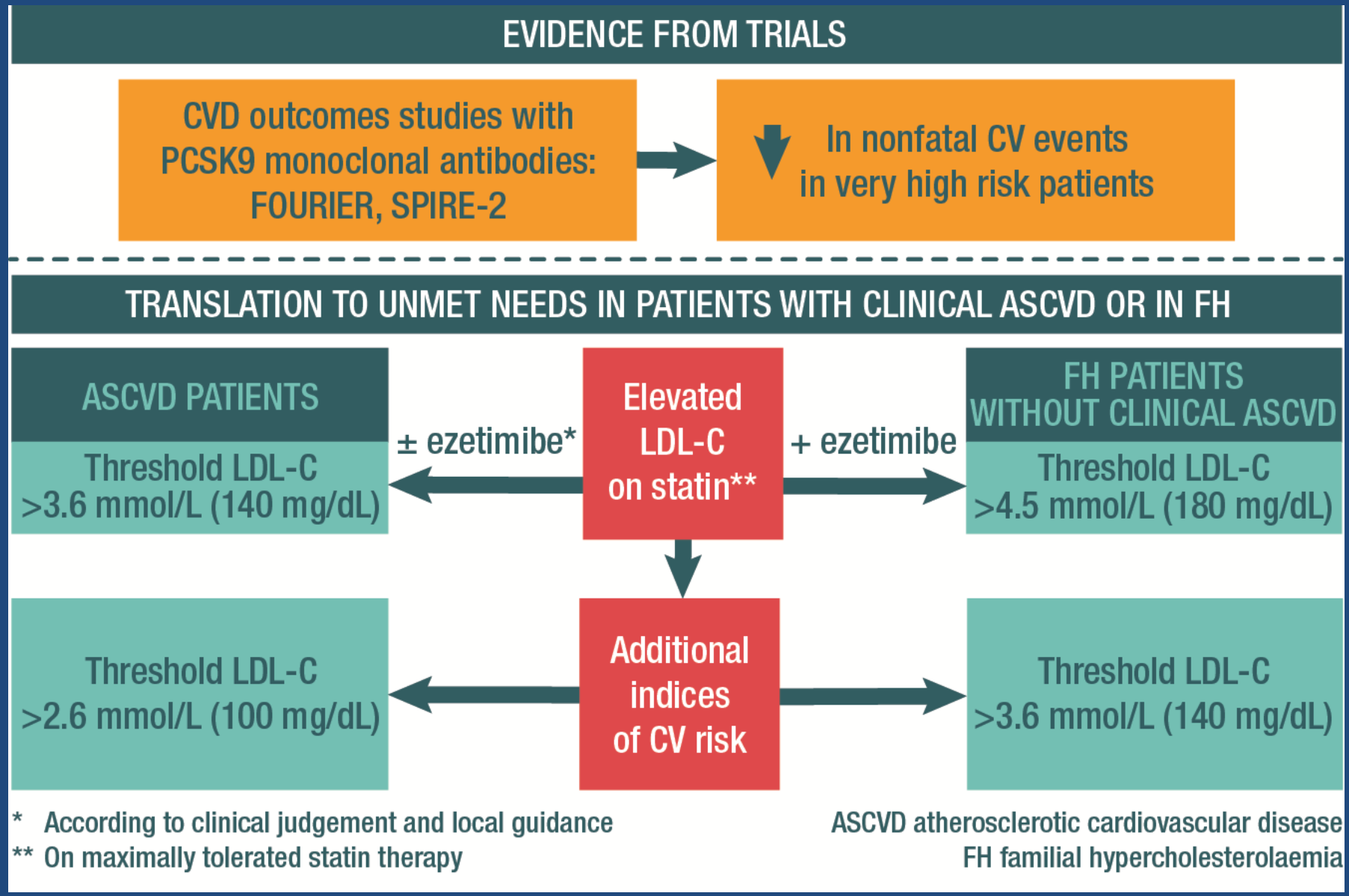
LDL-C threshold: Starting LDL-C value on which treatment decisions for a PCSK9 inhibitor are based

* Add-on ezetimibe should be considered in accordance with the clinician's judgement and local clinical guidance

Check before next injection if using a 2-weekly regimen

Landmesser U et al. Eur Heart J 2017; https://doi.org/10.1093/eurheartj/ehx549

Use of PCSK9 inhibitors: Translating Clinical Trial Evidence to Practice



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PCSK9 Inhibitors: Unanswered Questions

PCSK9 Inhibitors: What More Do We Need to Know?

- Inter-individual variability in LDL-C lowering response to alirocumab and evolocumab
- Impact in patients with recent (<1 month) cardiovascular events
- Impact in other very high risk groups, notably those with CKD (not requiring dialysis)
- Long-term efficacy and safety in clinical use
- Long-term safety of very low LDL-C levels, including risk for diabetes
- Long-term impact on cardiovascular mortality
- Impact of very low LDL-C levels on plaque composition and stability
- Cost-effectiveness of PCSK9 inhibition added to maximally tolerated statin therapy with or without ezetimibe

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