For a 2017 optimally treated patient with coronary heart disease

Do new trials published recently suggest that we should add additional drugs or lifestyle modification? And what in whom?

Current treatment:
- Non-smoking
- Exercise
- Low-fat diet
- Statin max dose
- Aspirin
- ACE-inhibitor
- +/- Beta-blocker

Additional non-optimal risk factors:
- High LDL cholesterol
- High C-reactive protein
- Diabetes
- Atherothrombosis risk

You could consider for a patient based on individual decision:
- Ezetimibe and/or PCSK9 inhibitor
- Interleukin-1β inhibitor (if available)
- Sodium/glucose cotransporter 2 inhibitor or glucagon like peptide 1 receptor agonist
- Long-term dual antiplatelet therapy or low-dose factor Xa antagonist with aspirin
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From: 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
Eur Heart J. Published online October 16, 2017. doi:10.1093/eurheartj/ehx549
Eur Heart J | Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2017. For permissions, please email: journals.permissions@oup.com.
Décès d'origine cardiovasculaire, infarctus, AVC, insuffisance cardiaque, revascularisation

\[ HR = 0.75; IC_{95} : 0.64-0.88; p = 0.0004 \]

Patients, n
- Placebo: 6344, 6192, 5970, 2073
- Rosuvastatine: 6361, 6241, 6039, 2122
Décès d’origine cardiovasculaire, infarctus, AVC, Insuffisance cardiaque, revascularisation

HR = 0,72 ; IC\textsubscript{95} : 0,57-0,89 ; p = 0,0030
Réduction du risque relatif selon le traitement et la tension artérielle

Population globale

- Traitement combiné
- Rosuvastatine seul
- Candesartan + HCTZ seul

TA élevée (tertile supérieur)

- Traitement combiné: 40
- Rosuvastatine seul: 20
- Candesartan + HCTZ seul: 24

TA normale (tertile bas ou intermédiaire)

- Traitement combiné: 19
- Rosuvastatine seul: 31
- Candesartan + HCTZ seul: -8

La Lettre du Cardiologue

ACC 2016 - D’après Yusuf S et al. Late Breaking Session I, actualisé
**Background**

**PCSK9: Proprotein convertase subtilisin/kexin type 9**
- Chaperones LDL-R to destruction → increase circulating LDL-C
- Loss-of-function genetic variants → increase LDL-R → reduce LDL-C and reduce risk of MI

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**Evolocumab and Alirocumab**
- Human anti-PCSK9 mAb
- 50% to 60% reduce LDL-C\(^a\)
- Safe and well-tolerated in Phase 2 and 3 studies\(^b\)

---


PCSK9 blocks LDLR-Recycling

More LDL-Receptor
Less LDL-C

modifiziert nach Cohen JC, Hobbs HH. Science 2013 (6133):689-90
FOURIER Trial Design

27,564 high-risk, stable patients with established CVD (prior MI, prior stroke, or symptomatic PAD)

Screening, lipid stabilization, and placebo run-in
High- or moderate-intensity statin therapy (± ezetimibe)

LDL-C ≥ 70 mg/dL or non–HDL-C ≥ 100 mg/dL

Evolocumab SC 140 mg every 2 weeks or 420 mg every month
Randomized, double blind
Placebo SC Every 2 weeks or every month

Follow-up every 12 weeks

LDL-C Levels

<table>
<thead>
<tr>
<th>LDL Cholesterol</th>
<th>Evolocumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 70 mg/dL</td>
<td>87%</td>
<td>18%</td>
</tr>
<tr>
<td>≤ 40 mg/dL</td>
<td>67%</td>
<td>0.5%</td>
</tr>
<tr>
<td>≤ 25 mg/dL</td>
<td>42%</td>
<td>&lt; 0.1%</td>
</tr>
</tbody>
</table>
**FOURIER**

**LDL-C Reduction**

- Placebo:
  - 59% mean reduction (95% CI: 58, 60); $P < .00001$
  - Absolute reduction: 56 mg/dL (95% CI: 55, 57)

- Evolocumab:
  - Median 30 mg/dL, IQR 19-46 mg/dL

Time, wk

Primary Endpoint

![Graph showing cumulative incidence over months for Placebo and Evolocumab with hazard ratio, 0.85 (95% CI, 0.79–0.92) and P<0.001.]

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>13,780</td>
<td>13,351</td>
</tr>
<tr>
<td></td>
<td>13,278</td>
<td>13,784</td>
</tr>
<tr>
<td></td>
<td>12,825</td>
<td>12,351</td>
</tr>
<tr>
<td></td>
<td>11,871</td>
<td>12,070</td>
</tr>
<tr>
<td></td>
<td>7610</td>
<td>3690</td>
</tr>
<tr>
<td></td>
<td>3690</td>
<td>686</td>
</tr>
</tbody>
</table>
Key Secondary Efficacy Endpoint

![Graph showing cumulative incidence and hazard ratio with placebo and Evolocumab groups.]

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Placebo</th>
<th>Placebo</th>
<th>Evolocumab</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>0</td>
<td>6</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>13,780</td>
<td>13,449</td>
<td>13,142</td>
<td>12,288</td>
</tr>
<tr>
<td></td>
<td>13,784</td>
<td>13,501</td>
<td>13,241</td>
<td>12,456</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.80 (95% CI, 0.73–0.88) $P<0.001$
FOURIER: Results

Primary Outcome
CV Death, MI, Stroke, Revascularization, or Hospitalization for UA

- Evolocumab
- Placebo

Hazard ratio 0.85 (95% CI, 0.79-0.92)
P < .0001

Secondary Outcome
CV Death, MI, or Stroke

- Evolocumab
- Placebo

Hazard ratio 0.80 (95% CI, 0.73-0.88)
P < .0001

FOURIER subanalysis PAD

CV Death, MI or stroke in patients with and without PAD

- Placebo: N=3,642
- Evolocumab

RRR: 27%
HR: 0.73 (0.68; 0.81)
P=0.0040

PAD: N=23,522
RRR: 3.5%
HR: 0.81 (0.73; 0.90)
P=0.001
NNT=38,29

No PAD
RRR: 1.4%
HR: 0.86 (0.77; 0.96)
P=0.011
NNT=59,72

Bonaca M | LBS-o2
Bonaca M et al, Circulation 2017;137. DOI: 10.1161/CIRCULATIONAHA.117.032235
FOURIER subanalysis PAD

Major adverse limb events

Placebo
Evolocumab

All patients
N=27,564
42% RRR
HR 0.58
(0.38; 0.88)
P=0.0053

Outcome | HR | 95%CI  
--- | --- | ---  
MALE | 0.58 | (0.38; 0.88)  
ALI or major amputation | 0.52 | 0.31; 0.89  
ALI | 0.55 | 0.31; 0.97  
Major amputation | 0.57 | 0.17; 1.95  
Urgent revascularization | 0.69 | 0.38; 1.26  

Bonaca M | LBS-o2
Bonaca M et al, Circulation 2017;137. DOI: 10.1161/CIRCULATIONAHA.117.032235

Congress Update | Cardiovascular | AHA 2017
FOURIER subanalysis history of MI – results

Benefit of EvoMab based on time from qualifying MI

- Qualifying MI < 2 years ago:
  - 24% RRR
  - HR 0.76 (95% CI 0.64; 0.89)
  - NNT 35
  - P < 0.001

- Qualifying MI ≥ 2 years ago:
  - 13% RRR
  - HR 0.87 (95% CI 0.76; 0.99)
  - NNT 35
  - P < 0.04

Benefit of EvoMab based on multivessel disease

- Multivessel disease:
  - 30% RRR
  - HR 0.70 (95% CI 0.58; 0.84)
  - NNT 29
  - P < 0.001

- No multivessel disease:
  - 11% RRR
  - HR 0.89 (95% CI 0.75; 1.00)
  - NNT 78
  - P < 0.055

Placebo vs. Evolocumab

CV death, MI, or stroke

P interaction = 0.18

P interaction = 0.03
## Safety: Adverse Events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Evolocumab (N=13,769)</th>
<th>Placebo (N=13,756)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events — no. of patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>10,664 (77.4)</td>
<td>10,644 (77.4)</td>
</tr>
<tr>
<td>Serious</td>
<td>3410 (24.8)</td>
<td>3404 (24.7)</td>
</tr>
<tr>
<td>Thought to be related to the study agent and leading to discontinuation of study regimen</td>
<td>226 (1.6)</td>
<td>201 (1.5)</td>
</tr>
<tr>
<td>Injection-site reaction*</td>
<td>296 (2.1)</td>
<td>219 (1.6)</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>420 (3.1)</td>
<td>393 (2.9)</td>
</tr>
<tr>
<td>Muscle-related event</td>
<td>682 (5.0)</td>
<td>656 (4.8)</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>8 (0.1)</td>
<td>11 (0.1)</td>
</tr>
<tr>
<td>Cataract</td>
<td>228 (1.7)</td>
<td>242 (1.8)</td>
</tr>
<tr>
<td>Adjudicated case of new-onset diabetes†</td>
<td>677 (8.1)</td>
<td>644 (7.7)</td>
</tr>
<tr>
<td>Neurocognitive event</td>
<td>217 (1.6)</td>
<td>202 (1.5)</td>
</tr>
<tr>
<td>Laboratory results — no. of patients/total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminotransferase level &gt;3 times the upper limit of the normal range</td>
<td>240/13,543 (1.8)</td>
<td>242/13,523 (1.8)</td>
</tr>
<tr>
<td>Creatine kinase level &gt;5 times the upper limit of the normal range</td>
<td>95/13,543 (0.7)</td>
<td>99/13,523 (0.7)</td>
</tr>
</tbody>
</table>

* The between-group difference was nominally significant (P<0.001).
† The total numbers of patients were 8337 in the evolocumab group and 8339 in the placebo group, because patients with prevalent diabetes at the start of the trial were excluded.
FOURIER: Lower CV Event Rates With Lower LDL-C Levels, as Low as 20 mg/dL (~0.5 mmol/L)

*Relationship between the achieved LDL-C concentration at 4 weeks and the risk of CV death, MI, or stroke. Reprinted from *Lancet*, 390 Giugliano RP et al, Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. 1962-1971, Copyright 2017, with permission from Elsevier.*
Proportional Reductions in Risks of MVEs* per mmol/L Reduction in LDL-C During Each Year of Scheduled Statin Treatment

<table>
<thead>
<tr>
<th>Total Number of MVEs</th>
<th>99% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 year</td>
<td>4680</td>
<td></td>
</tr>
<tr>
<td>1-2 years</td>
<td>3580</td>
<td></td>
</tr>
<tr>
<td>2-3 years</td>
<td>3124</td>
<td></td>
</tr>
<tr>
<td>3-4 years</td>
<td>2483</td>
<td></td>
</tr>
<tr>
<td>4-5 years</td>
<td>1819</td>
<td></td>
</tr>
<tr>
<td>≥ 5 years</td>
<td>1018</td>
<td></td>
</tr>
<tr>
<td>All years</td>
<td>16704</td>
<td></td>
</tr>
<tr>
<td>Years 1 - ≥ 5</td>
<td>12024</td>
<td></td>
</tr>
</tbody>
</table>

FOURIER RRR Standardized to 1 mmol/L

- 0.92
- 0.87

FOURIER Primary Endpoint:
Overall RRR is 15%; RRR was 12% in the first year and 19% beyond the first year

Adapted From CTT Collaboration. The median duration across the studies included in the CTT meta-analysis was 4.9 years.
*MVEs (major vascular events) defined as coronary deaths, MIs, strokes, and coronary revascularizations.
Study Conclusions

• When added to statin therapy, evolocumab lowered LDL cholesterol levels by 59% from baseline compared to placebo, from a median of 92 mg/dL to 30 mg/dL

• ↓ risk of the primary composite endpoint by 15% and ↓ risk of the key secondary endpoint by 20%

• Magnitude of risk reduction shown to increase over time

• No effect of additional LDL-C lowering on cardiovascular death or all-cause mortality

• Injection-site reactions were significantly higher in the evolocumab group compared to the placebo group
Evolocumab reduces LDL-C and percent atheroma volume

GLAGOV Trial Schematic

968 patients with angiographic CAD, stable statin dose and LDL-C ≥80 mg/dL OR 60-80 mg/dL and 1 major or 3 minor risk factors

Screening, placebo run-in period
- Coronary angiogram
- Baseline IVUS
- Virtual histology

Up to 4 week lipid stabilization period

Max 6 weeks

Placebo SC monthly

Evolocumab 420 mg SC monthly

End of Study
Evolocumab added to statin induces plaque regression but does not change plaque composition.
The SPIRE-2 Cardiovascular Outcomes Trial:
Baseline LDL-C ≥ 100 mg/dL Primary Prespecified Endpoint

Hazard ratio, 0.79 (95% CI, 0.65–0.97)
P=0.02

Placebo

Bococizumab

Baseline LDL-C 133 mg/dL
Placebo Event Rate 4.19/100-person y
Median Follow-up 12 months

Cumulative Percentage with Primary End Point

No. at Risk
Placebo 5309 5220 5130 4214 2319 1174 419 216 116 49 14 4
Bococizumab 5312 5223 5161 4250 2346 1202 431 221 118 49 13 2

*Nonfatal MI, nonfatal stroke, hospitalization for UA requiring urgent revascularization, or CV death.
ODYSSEY OUTCOMES: Study Design

A randomized, double-blind, placebo-controlled study

Patients with recent ACS on maximally tolerated statin ± other LLT†
Not at predefined target (i.e., LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL or apolipoprotein B ≥ 80 mg/dL)

n=9000

Double-blind treatment period

Alirocumab 75 mg or 150 mg* every 2 weeks adjusted in blinded fashion to achieve 15 ≤ LDL-C < 50 mg/dL

n=9000

Placebo SC every 2 weeks

Diet (NCEP-ATP III TLC or equivalent) and stable statin dose ± stable dose of other LLT

Randomization
Month

2
4
6
8
12
16
20
24
30
36
60
64

Dose was uptitrated to 150 mg every 2 weeks at month 2 if LDL-C ≥ 50 mg/dL (1.29 mmol/L) at month 1 visit.

After 36 months follow-up visits occur every 6 months

Double-blind treatment ended

* Dose titrated up to 150 mg every 2 weeks at month 2 if LDL-C ≥ 50 mg/dL (1.29 mmol/L) at month 1 visit.
† Atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg OR maximally tolerated dose of statin (can be 0 mg).
If LDL-C < 25 mg/dL on any 2 consecutive measurements on alirocumab 150 mg, the dose is reduced to 75 mg.
If LDL-C < 15 mg/dL on 2 consecutive measurements with alirocumab 75 mg, active treatment is discontinued at the next study visit and substituted with placebo.
## ODYSSEY OUTCOMES and FOURIER
### Demographics: Patient Histories

<table>
<thead>
<tr>
<th></th>
<th>ODYSSEY OUTCOMES [a] (n=18,312)</th>
<th>FOURIER [b] (n=27,564)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>58.6</td>
<td>62.5</td>
</tr>
<tr>
<td>Male, %</td>
<td>74.8</td>
<td>75.4</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>63.3</td>
<td>80.0</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>28.9</td>
<td>33.9</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>23.9</td>
<td>28.2</td>
</tr>
<tr>
<td>History of MI, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mean time from index event 3.6 months, 75% &lt; 4 months) including 35% prior CAD + 20% with recurrent event</td>
<td>100% ACS</td>
<td>81.1 (31% MI &lt; 1 y)</td>
</tr>
<tr>
<td>History of stroke, %</td>
<td>2.9</td>
<td>19.3</td>
</tr>
<tr>
<td>History of PAD, %</td>
<td>3.7</td>
<td>13.2</td>
</tr>
</tbody>
</table>

---

## ODISSEY OUTCOMES and FOURIER
Demographics: LLTs and Lipids

<table>
<thead>
<tr>
<th></th>
<th>ODYSSEY OUTCOMES(^{[a]}) (n=18,312)</th>
<th>FOURIER(^{[b]}) (n=27,564)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LLTs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-intensity stain, %</td>
<td>89.5</td>
<td>69.2</td>
</tr>
<tr>
<td>Moderate-/low-intensity statin, %</td>
<td>7.8</td>
<td>30.7</td>
</tr>
<tr>
<td>Ezetimibe, %</td>
<td>2.9</td>
<td>5.1</td>
</tr>
<tr>
<td><strong>Lipid parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median LDL-C, mg/dL</td>
<td>86.5</td>
<td>91.5</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>160.0</td>
<td>167.0</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>42.5</td>
<td>44.0</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>129.2</td>
<td>133.0</td>
</tr>
</tbody>
</table>

Reprinted from *Am Heart J.*, Rationale and design of the Further cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk trial. 94-101. Copyright 2017, with permission from Elsevier

# ODYSSSEY OUTCOMES and FOURIER: Primary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>ODYSSSEY OUTCOMES[a]</th>
<th>FOURIER[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD death</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>MI</td>
<td>X (nonfatal)</td>
<td>X</td>
</tr>
<tr>
<td>Stroke</td>
<td>X (fatal/nonfatal)</td>
<td>X (ischemic and hemorrhagic)</td>
</tr>
<tr>
<td>UA requiring hospitalization</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

**CHD Death per ODYSSSEY CVOT Protocol**
- Any death with a clear relationship to underlying CHD
  - Death secondary to acute MI
  - Sudden death, heart failure, etc

**CV Death per ACC/AHA Clinical Data Standard 2014**
- Death resulting from an acute MI, sudden cardiac death, death due to heart failure, death due to stroke, death due to CV procedures, death due to CV hemorrhage, and death due to other CV causes

Reprinted from *Am Heart J.*, Rationale and design of the Further cardiovascular OUTcomes Research with PCSK9 Inhibition in subjects with Elevated Risk trial. 94-101. Copyright 2017, with permission from Elsevier

PCSK9 CVOTs: Key Scientific Points

- FOURIER results further support the LDL-C hypothesis (i.e., lowering LDL-C reduces CV events)
  - RRR is 15% for 1\textsuperscript{st} endpoint and 20% for 2\textsuperscript{nd} endpoint
- A potential limitation of FOURIER is the shorter duration of follow-up (median of 2.2 years); ODYSSEY OUTCOMES will have longer estimated mean double-blind follow-up of \sim3 years and a maximum of 5 years at trial completion
- Elements of the ODYSSEY OUTCOMES trial are different from FOURIER, including:
  - A longer follow-up
  - A higher risk patient population
  - Treat-to-goal approach
  - Higher proportion of patients on high-intensity statin
  - Inclusion of CHD death as a component of the primary composite endpoint
- PCSK9 inhibition is an exciting new therapy—we need to get it to the right patients in clinical practice
From: Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies
Eur Heart J | Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2017. For permissions, please email: journals.permissions@oup.com.
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Randomized trials of CETP inhibitors in statin treated patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>CETP Inhibitor</th>
<th>LDL-C Effect</th>
<th>HDL-C Effect</th>
<th>Remnants Effect</th>
<th>ApoB Effect</th>
<th>SBP Effect</th>
<th>ASCVD Effect</th>
<th>Mortality Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILLUMINATE</td>
<td>Torcetrapib</td>
<td>↓ 25%</td>
<td>↑ 72%</td>
<td>↑ 9%</td>
<td>↓ 4%</td>
<td></td>
<td>↑ 25%</td>
<td>↑ 58%</td>
</tr>
<tr>
<td>dal-OUTCOMES</td>
<td>Dalcetrapib</td>
<td>↑ 132%</td>
<td>↑ 28%</td>
<td>No effect</td>
<td></td>
<td></td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>ACCELERATE</td>
<td>Evacetrapib</td>
<td>↓ 6%</td>
<td>↑ 132%</td>
<td>No effect</td>
<td></td>
<td></td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>REVEAL</td>
<td>Anacetrapib</td>
<td>↓ 7%</td>
<td>↑ 104%</td>
<td>No effect</td>
<td></td>
<td></td>
<td>No effect</td>
<td>No effect</td>
</tr>
</tbody>
</table>

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LDL REDUCTION – CETP INHIBITION

REVEAL: Randomized placebo-controlled trial of anacetrapib added to statin in 30,449 patients with atherosclerotic vascular disease

Effects of anacetrapib on lipids at trial midpoint

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Absolute difference</th>
<th>SI units</th>
<th>Proportional difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL cholesterol</td>
<td>+43</td>
<td>+1.1 mmol/L</td>
<td>104%</td>
</tr>
<tr>
<td>Apolipoprotein AI</td>
<td>+42</td>
<td>+0.4 g/L</td>
<td>36%</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Direct (Genzyme)</td>
<td>-26</td>
<td>-0.7 mmol/L</td>
<td>-41%</td>
</tr>
<tr>
<td>- Beta-quantification*</td>
<td>-11</td>
<td>-0.3 mmol/L</td>
<td>-17%</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>-12</td>
<td>-0.1 g/L</td>
<td>-18%</td>
</tr>
</tbody>
</table>

Proportional reduction in Coronary death or MI vs. absolute reduction in non-HDL cholesterol (derived from published CTT meta-analysis)

- Statin vs. control >50 mg/dL (4 trials)
- More vs. less 22 mg/dL (17 trials)
- Statin vs. control <50 mg/dL (5 trials)

No excess of mortality, cancer or other serious adverse events
Small increase in blood pressure and small reduction in kidney function

M. Landray (Oxford, UK) 4728
2013 ACC/AHA Guidelines

STATINS are FIRST-LINE for CVD prevention

Journal of the American College of Cardiology

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults
Neil J. Stone, MD, MACP, FAHA, FACC; Jennifer G. Robinson, MD, MPH, FAHA; Alice H. Lichtenstein, DSC, FAHA; C. Noel Bairey Merz, MD, FAHA, FACC; Conrad B. Blum, MD, FAHA; Robert H. Eckel, MD, FAHA; Anne C. Goldberg, MD, FACP, FAHA; David Gordon, MD; Daniel Levy, MD; Donald M. Lloyd-Jones, MD, SCM, FACC, FAHA; Patrick McBride, MD, MPH, FAHA; J. Sanford Schwartz, MD; Susan T. Shero, MS, RN; Sidney C. Smith, JR, MD, FACC, FAHA; Karol Watson, MD, PhD, FACC, FAHA; Peter W. F. Wilson, MD, FAHA

2013 ACC/AHA Cholesterol Guideline
NET BENEFIT APPROACH
Strong evidence of net ASCVD risk reduction benefit

Use statins in 4 patient groups:

- Clinical ASCVD
- LDL-C >190 mg/dL
- Diabetes age 40 to 75 years
- >7.5% 10-year ASCVD (hard event) risk

### 2017 AACE Guidelines for the Management of Dyslipidemia

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Risk Factors/10-Year Risk</th>
<th>Treatment Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extreme risk</strong></td>
<td>• Progressive ASCVD including unstable angina in patients after achieving an LDL-C &lt; 70 mg/dL&lt;br&gt;• Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeF&lt;br&gt;• History of premature ASCVD (&lt; 55 male, &lt; 65 female)</td>
<td>LDL-C, mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-HDL-C, mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apo B, mg/dL</td>
</tr>
<tr>
<td><strong>Very high risk</strong></td>
<td>• Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk &gt; 20%&lt;br&gt;• Diabetes or CKD 3/4 with 1 or more risk factor(s)&lt;br&gt;• HeFH</td>
<td>LDL-C, mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-HDL-C, mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apo B, mg/dL</td>
</tr>
</tbody>
</table>

2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway: Nonstatin Therapies for ASCVD

≥ 21 years old, clinical ASCVD + comorbidities, on statin

≥ 50% LDL-C reduction (or LDL-C < 70, non-HDL-C <100 mg/dL) on MTD statin

YES

NO

Address factors related to adherence, lifestyle, and statin tolerance

≥ 50% LDL-C reduction (or LDL-C < 70, non-HDL-C <100 mg/dL) on MTD statin

YES

NO

Clinician-patient discussion on treatment factors, and patient preferences

Decision for no additional medication

Optional non-statin therapy

Consider ezetimibe or PCSK9 inhibitor; add other second agent if needed

# 2016 ESC/EAS Guidelines for the Management of Dyslipidemias

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Definition</th>
<th>LDL-C Goal</th>
</tr>
</thead>
</table>
| Very high     | • Documented CVD  
• T2D with target organ damage or a major risk factor  
• 10-year risk ≥ 10% for fatal CVD | < 70 mg/dL  
Or ≥ 50% reduction if LDL-C 70-135 mg/dL |
| High          | • Cholesterol > 310 mg/dL or BP ≥ 180/110 mmHg  
• Most people with T2D  
• Moderate CKD  
• 10-year risk ≥ 5% for fatal CVD | < 100 mg/dL  
Or ≥ 50% reduction if LDL-C 100-200 mg/dL |
| Moderate      | 10-year risk ≥ 1% - < 5% for fatal CVD | < 115 mg/dL |
| Low           | 10-year risk < 1% for fatal CVD | < 115 mg/dL |

Patients with clinical ASCVD (CAD, symptomatic PAD, ischaemic stroke) On maximally tolerated statin therapy

± Ezetimibe*

* According to clinical judgement and local guidance

LDL-C > 3.6 mmol/L (>140 mg/dL)
Consider a PCSK9 inhibitor

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

§ Including

- Familial hypercholesterolaemia
- Diabetes mellitus with target organ damage (e.g. proteinuria), or with a major risk factor such as marked hypertension
- Severe and/or extensive ASCV (e.g. severe polyvascular disease, extensive coronary disease - refer to Box 3)
- Rapid progression of ASCVD, i.e. repeated ACS, unplanned coronary revascularizations, or ischaemic strokes within 5 years of the index event

From: 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
Eur Heart J. Published online October 16, 2017. doi:10.1093/eurheartj/ehx549
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Patients with familial hypercholesterolaemia without clinically diagnosed ASCVD on maximally tolerated statin plus ezetimibe therapy

Check for additional indices of risk severity
- Diabetes mellitus with target organ damage (e.g. proteinuria), or with a major risk factor (e.g. marked hypertension)
- Lipoprotein(a) >50 mg/dL
- Major risk factors: smoking, marked hypertension
- >40 years of age without treatment
- Premature ASCVD (<55 years in males and <60 years in females) in first-degree relatives
- Imaging indicators (refer to text)

No additional indices of risk severity
- LDL-C >4.5 mmol/L (>180 mg/dL)

Additional indices of risk severity
- LDL-C >3.6 mmol/L (>140 mg/dL)*

* Confirmed on two consecutive occasions

Consider a PCSK9 inhibitor

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