Current and future management of hyperlipidaemia and atherosclerosis: From statins to combination therapy

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Expert panel

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Agenda

What is the impact of statins on lipidaemia and what are their limitations?

Presentation: Alberico Catapano
Panel discussion: Jacques Genest and Kausik Ray, moderated by Alberico Catapano

When is monotherapy with statins no longer sufficient?

Presentation: Alberico Catapano
Panel discussion: Jacques Genest and Kausik Ray, moderated by Alberico Catapano

What are the advantages of combination therapy and when should it be considered?

Presentation: Alberico Catapano
Panel discussion: Jacques Genest and Kausik Ray, moderated by Alberico Catapano

Statins are the cornerstone of lipid-lowering therapy, in addition to healthy lifestyle interventions

Atorvastatin, rosuvastatin, simvastatin are the primary statin medications used in clinical practice

High-, moderate-, and low-intensity statin therapy*[1]

	High intensity (≥50% LDL-C lowering†)	Moderate intensity (30–49% LDL-C lowering†)	Low intensity (<30% LDL-C lowering†)
Primary statins used in clinical practice	**Atorvastatin (40 mg‡) 80 mg** **Rosuvastatin 20 mg (40 mg)**	**Atorvastatin 10 mg** (20 mg) **Rosuvastatin** (5 mg) **10 mg** **Simvastatin 20–40 mg§**	Simvastatin 10 mg
Other statins		**Pravastatin 40 mg** (80 mg) **Lovastatin 40 mg** (80 mg) Fluvastatin XL 80 mg **Fluvastatin 40 mg BID** Pitavastatin 1–4 mg	**Pravastatin 10–20 mg** **Lovastatin 20 mg** Fluvastatin 20–40 mg

Boldface type indicates specific statins and doses evaluated in RCTs[2–4] and the Cholesterol Treatment Trialists' 2010 meta-analysis.[5] All these RCTs demonstrated a reduction in major CV events.

% LDL-C reductions with the primary statin medications used in clinical practice were estimated using the median reduction in LDL-C from the VOYAGER database.[6] Reductions in LDL-C for other statin medications were identified according to FDA-approved product labelling in adults with hyperlipidaemia, primary hypercholesterolaemia, and mixed dyslipidaemia.

*% reductions are estimates from data across large populations. Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. †LDL-C lowering that should occur with the dosage listed below each intensity. ‡Evidence from one RCT only: down titration if unable to tolerate atorvastatin 80 mg in the IDEAL study.[2] §Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.

BID, twice daily; CV, cardiovascular; FDA, US Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial; XL, extended release.

1. Grundy S, et al. *J Am Coll Cardiol.* 2019;73:3168–209. 2. Pedersen TR, et al. *JAMA.* 2005;294:2437–45. 3. Ridker PM, et al. *N Engl J Med.* 2008;359:2195–207. 4. Yusuf S, et al. *N Engl J Med.* 2016;374:2021–31. 5. Baigent C, et al. *Lancet.* 2010;376:1670–81. 6. Karlson BW, et al. *Eur Heart J Cardiovasc Pharmacother.* 2016;2:212–7.

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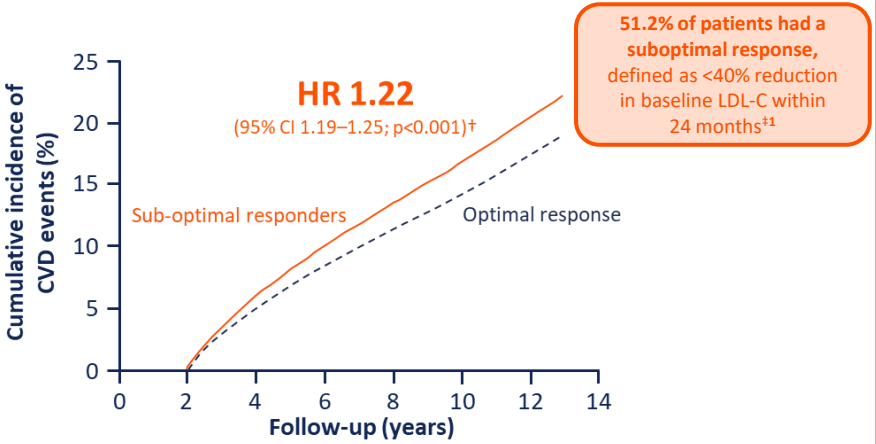
Sub-optimal responses and intolerance to statins are common

>50% patients have a sub-optimal LDL-C response and increased risk of future CVD*[1]; up to 30% are intolerant[2]

Cumulative incidence of CVD events in patients with sub-optimal vs optimal LDL-C response to statin therapy[1]



51.2% of patients had a suboptimal response, defined as <40% reduction in baseline LDL-C within 24 months‡[1]

Adapted from Akyea RK, et al. *Heart.* 2019.[1]

Discontinuation and nonadherence to statins remains a gap in the prevention of CVD[3]

- The major reason for statin discontinuation is **toxicity or intolerance**, largely due to development of **statin-associated muscle symptoms (SAMS)**[3]
  - Intolerance due to SAMS occurs in up to **30%** of patients[2]
- More than **72%** of all statin AEs are muscle related[3]
  - E.g. myalgia, myopathy, myositis with elevated CK, or rhabdomyolysis
- Other AEs include new-onset T2D, neurological and neurocognitive effects, hepatotoxicity and renal toxicity[3]

*Prospective cohort study of 165,411 primary care patients, from the UK Clinical Practice Research Datalink, who were free of CVD before statin initiation, and had at least one pre-treatment LDL-C within 12 months before, and one post-treatment LDL-C within 24 months after, statin initiation. †Adjusted for age and baseline LDL-C level. ‡Based on current national guidelines.

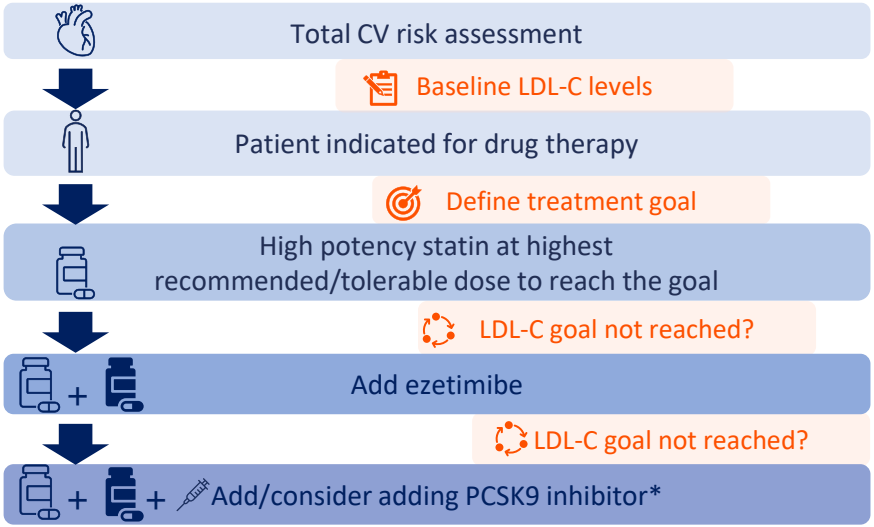
AE, adverse event; CI, confidence interval; CK, creatinine kinase; CVD, cardiovascular disease; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; T2D, type 2 diabetes.

1. Akyea RK, et al. *Heart.* 2019;105:975–81. 2. Laufs U, et al. *Curr Opin Lipidol.* 2015;26:492–501. 3. Ward NC, et al. *Circ Res.* 2019;124:328–50.

If LDL-C goals are not achieved with maximally tolerated statin, combination with ezetimibe is recommended

Although LDL-C goals are attained with monotherapy in many patients, a significant proportion of patients at high risk or with very high LDL-C levels need additional treatment

Treatment algorithm for pharmacological LDL-C lowering



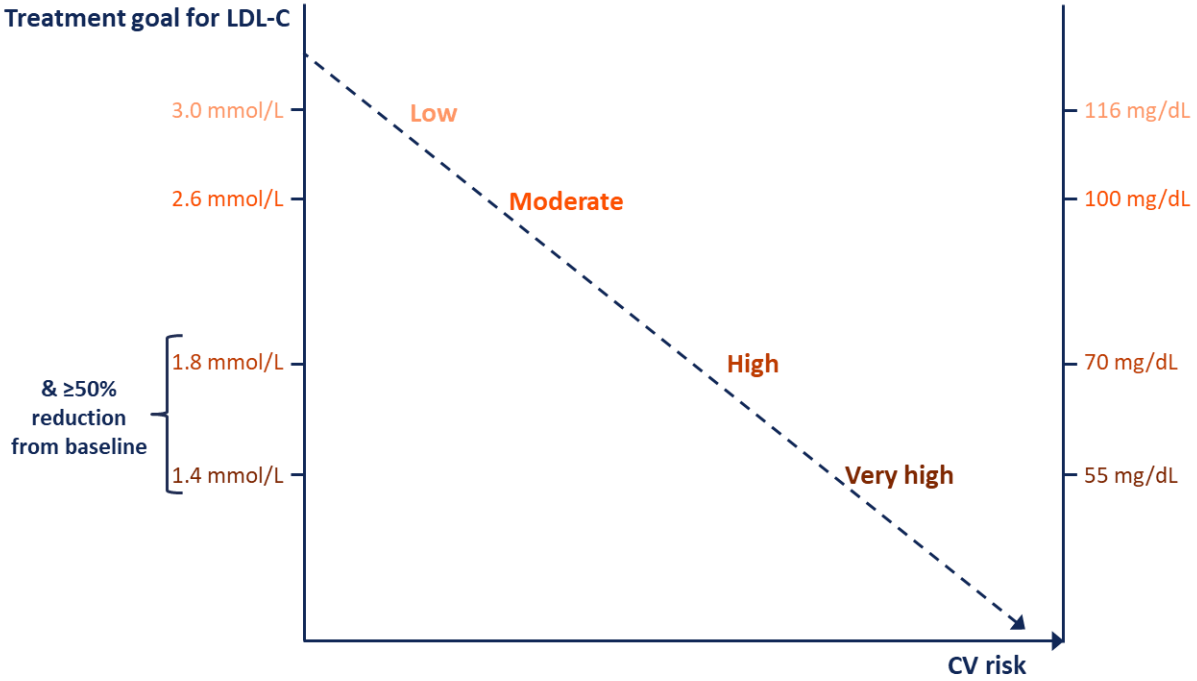
Intensity of lipid-lowering treatment	
Treatment	Average LDL-C reduction
High intensity statin	~50%
High intensity statin + ezetimibe	~65%
PCSK9 inhibitor + high intensity statin + ezetimibe	~85%

*Add PCSK9 inhibitor for: secondary prevention (very-high risk); primary prevention: patients with FH and another major risk factor (very-high risk). Consider adding PCSK9 inhibitor for primary prevention: patients at very-high risk, but without FH.

CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; FH, familial hypercholesterolaemia; PCSK9, proprotein convertase subtilisin/kexin type 9.

Mach F, et al. *Eur Heart J.* 2020;41:111–88.

Treatment goals for LDL-C across categories of total CVD risk



Low

- SCORE <1%

Moderate

- SCORE ≥1% and <5%
- Young patients (T1D <35 years; T2D <50 years); diabetes duration <10 years, no other risk factors

High

- SCORE ≥5% and <10%
- Markedly elevated single risk factors, e.g. TC >8 mmol/L (310 mg/dL); LDL-C >4.9 mmol/L (190 mg/dL); BP ≥180/110 mmHg
- FH, no other major risk factors
- Moderate CKD (eGFR 30–59 mL/min)
- Diabetes; no target organ damage; duration ≥10 years or other risk factor

Very high

- ASCVD (clinical/imaging)
- SCORE ≥10%
- FH with ASCVD or another major risk factor
- Severe CKD (eGFR <30 mL/min)
- T1D/T2D and target organ damage: ≥3 major risk factors; or early onset of T1D of >20-years duration

ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; SCORE, Systematic Coronary Risk Estimation; T1D, type 1 diabetes; T2D, type 2 diabetes; TC, total cholesterol.

Adapted from Mach F, et al. *Eur Heart J.* 2020;41:111–88.

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