RAPID RECOMMENDATIONS

PCSK9 inhibitors and ezetimibe for the reduction of cardiovascular events: a clinical practice guideline with risk-stratified recommendations

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ABSTRACT

CLINICAL QUESTION
In adults with low density lipoprotein (LDL) cholesterol levels ≥1.8 mmol/L (≥70 mg/dL) who are already taking the maximum dose of statins or are intolerant to statins, should another lipid-lowering drug be added, either a proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitor or ezetimibe, to reduce the risk of major cardiovascular events? If so, which drug is preferred? Having decided to use one, should we add the other lipid-lowering drug?

CURRENT PRACTICE
Most guidelines emphasise LDL cholesterol targets in their recommendations for prescribing PCSK9 inhibitors and/or ezetimibe in adults at high risk of experiencing a major adverse cardiovascular event. However, to achieve these goals in very high risk patients with statins alone is almost impossible, so physicians are increasingly considering other lipid-lowering drugs solely for achieving LDL cholesterol treatment goals rather than for achieving important absolute cardiovascular risk reduction. Most guidelines do not systematically assess the cardiovascular benefits of adding PCSK9 inhibitors and/or ezetimibe for all risk groups across primary and secondary prevention, nor do they report, in accordance with explicit judgments of assumed patients’ values and preferences, absolute benefits and harms and potential treatment burdens.

RECOMMENDATIONS
The guideline panel provided mostly weak recommendations, which means we rely on shared decision making when applying these recommendations. For adults already using statins, the panel suggests adding a second lipid-lowering drug in people at very high and high cardiovascular risk but recommends against adding it in people at low cardiovascular risk. For adults who are intolerant to statins, the panel recommends using a lipid-lowering drug in people at very high and high cardiovascular risk but against adding it in those at low cardiovascular risk. When choosing to add another lipid-lowering drug, the panel suggests ezetimibe in preference to PCSK9 inhibitors. The panel suggests further adding a PCSK9 inhibitor to ezetimibe for adults already taking statins at very high risk and those at very high and high risk who are intolerant to statins.
UNDERSTANDING THE RECOMMENDATIONS

The stratification into four cardiovascular risk groups means that, to use the recommendations, physicians need to identify their patient’s risk first. We therefore suggest, specific to various geographical regions, using some reliable risk calculators that estimate patients’ cardiovascular risk based on a mix of known risk factors. The largely weak recommendations concerning the addition of ezetimibe or PCSK9 inhibitors reflect what the panel considered to be a close balance between small reductions in stroke and myocardial infarctions weighed against the burdens and limited harms.

Because of the anticipated large variability of patients’ values and preferences, well informed choices warrant shared decision making. Interactive evidence summaries and decision aids linked to the recommendations can facilitate such shared decisions. The strong recommendations against adding another drug in people at low cardiovascular risk reflect what the panel considered to be a burden without important benefits. The strong recommendation for adding either ezetimibe or PCSK9 inhibitors in people at high and very high cardiovascular risk reflect a clear benefit.

The panel recognised the key uncertainty in the evidence concerning patient values and preferences, namely that what most people consider important reductions in cardiovascular risks, weighed against burdens and harms, remains unclear. Finally, availability and costs will influence decisions when healthcare systems, clinicians, or people consider adding ezetimibe or PCSK9 inhibitors.

Introduction

Prevention of cardiovascular events by managing modifiable risk factors including elevated low-density lipoprotein (LDL) cholesterol represents an essential, cost effective approach to reduce the global cardiovascular disease burden.1 Anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (PCSK9 inhibitors) and ezetimibe are newer effective lipid-lowering drugs increasingly given to patients at high cardiovascular risk to meet specific LDL cholesterol targets.

In addition to lifestyle interventions, statins are now the primary treatment to reduce numbers of cardiovascular events in people at increased risk.2 Current guidelines for treating patients at high cardiovascular risk generally recommend the maximally tolerated dose of statins and other possible drugs to meet absolute levels or relative reduction of LDL cholesterol or non-HDL cholesterol (box 1). But the newer lipid-lowering drugs, particularly PCSK9 inhibitors, are expensive. Moreover, PCSK9 inhibitors are provided via subcutaneous injections which can be inconvenient.

Box 1: Major guideline recommendations for lipid-lowering agents (PCSK9 inhibitors and ezetimibe) in adults at high or very high cardiovascular risk

American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines updated 20194

- In patients with very high cardiovascular risk, it is reasonable to add ezetimibe to maximally tolerated statin therapy when LDL cholesterol level remains ≥70 mg/dL (1.8 mmol/L)
- If the LDL cholesterol level on maximally tolerated statin and ezetimibe therapy remains ≥100 mg/dL (2.6 mmol/L), adding a PCSK9 inhibitor is reasonable
- For patients with severe primary hypercholesterolemia, the recommendations are similar, but with different LDL cholesterol targets
  - Class of recommendation I to IIa, level of evidence A to B-NR

Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult 20215

- For all secondary prevention patients with cardiovascular diseases in whom LDL cholesterol remains ≥70 mg/dL (1.8 mmol/L) on maximally tolerated statin dose, intensification of lipid-lowering therapy with ezetimibe and/or PCSK9 inhibitor therapy is recommended
- If ezetimibe is used initially and LDL remains ≥70 mg/dL (1.8 mmol/L), PCSK9 inhibitor therapy is recommended
  - Strong recommendation, high quality evidence

National Institute for Health and Care Excellence (NICE) 20196

- Among high risk patients with primary hypercholesterolaemia and mixed dyslipidaemia who are intolerant to statins or who fail to meet target LDL cholesterol levels (135 mg/dL (3.5 mmol/L) for very high cardiovascular risk), despite statin (and ezetimibe) therapy, use of a PCSK9 inhibitor (evolocumab or alirocumab) is approved
  - Unclear strength of recommendation, unclear quality of evidence

NHS England Lipids Management Pathway 20217

- For primary prevention, if the maximum tolerated dose of statin does not achieve non-HDL cholesterol reduction over 40% of baseline value after 3 months consider adding ezetimibe
- For adults with a very high risk of cardiovascular risk, or if therapy is not tolerated, or LDL cholesterol remains high after adding ezetimibe and statins, consider adding PCSK9 inhibitors
  - Unclear strength of recommendation, unclear quality of evidence

Kaiser Permanente National Cholesterol and Cardiovascular Risk Clinician Guide 20188

- For individuals with clinical atherosclerotic cardiovascular diseases and with persistently elevated blood lipids (such as LDL 130 mg/dL (3.4 mmol/L) despite taking the maximum tolerated oral lipid-lowering therapy (statin, ezetimibe, ± bile acid sequestrant), consider discussing adding a PCSK9 inhibitor with a lipid specialist
  - Unclear strength of recommendation, unclear quality of evidence

SIGN: Risk estimation and the prevention of cardiovascular disease 20179

- PCSK9 inhibitors should be considered in patients at high risk of vascular events with cholesterol levels remaining above target levels (135 mg/dL (3.5 mmol/L) for secondary prevention population) despite other tolerated lipid-lowering therapy
  - Unclear strength of recommendation, unclear quality of evidence

Guidelines, however, offer differing LDL cholesterol treatment targets, leaving clinicians unclear how to choose the newer expensive lipid-lowering drugs. Furthermore, concerns regarding too much medicine or overtreatment highlight the need for
trustworthy guidelines that balance absolute benefits and harms to determine, for patients and society, the advisability of adding other lipid-lowering drugs to statins. The guideline panel made recommendations for adults who are receiving high doses of or are intolerant to statins with LDL cholesterol levels over 70 mg/dL (1.8 mmol/L) and considering newer lipid-lowering drugs to reduce cardiovascular risk. These recommendations address adults with and those without established cardiovascular disease (that is, primary and secondary prevention populations). The panel included PCSK9 inhibitors, ezetimibe, and a combination of both as add-on therapy to statins. This guideline differs from others in that, after specifying a minimal LDL cholesterol level below which further lipid lowering is not appropriate, recommendations are based exclusively on the absolute benefits of these drugs on cardiovascular outcomes rather than meeting targets for LDL cholesterol level.

Although systematic reviews of randomised trials show similar relative risk reductions in cardiovascular events for PCSK9 inhibitors or ezetimibe, the absolute benefits of these drugs depend on cardiovascular risk in individual patients. Their comparative effectiveness—with absolute benefits carefully weighed against burdens and harms—should therefore inform clinicians and their patients whether and when they should consider adding ezetimibe or a PCSK9 inhibitor to reduce cardiovascular risk. Given the complexity of multiple available treatment options, we used the following question order, thought to be representative of decisions patients and their clinicians will face:

- First, should patients add another lipid-lowering agent to current therapy?
- Second, if patients choose to add another drug, which drug should they choose (ezetimibe or a PCSK9 inhibitor)?
- Third, for those who have chosen to add one of these two drugs, should they further add the other lipid-lowering drug?

The infographic provides an overview of the risk-stratified recommendations, with evidence summaries of the benefits and harms of ezetimibe and PCSK9 inhibitors, as well as other key issues, including the burden of treatment. The MATCH-IT tool provides an interactive view of the alternative treatment options and outcomes and is also designed for shared decision making with patients (https://magicevidence.org/match-it/220504dist-lipid-lowering-drugs/).

Box 2 shows all evidence linked in this Rapid Recommendation package. Any new evidence that emerges after the initial publication of these recommendations will be listed in table 3 at the end of this article.

**Box 2: Linked resources in this BMJ Rapid Recommendations cluster**

- Summary of the results from the Rapid Recommendation process

- Review and network meta-analysis of all available randomised trials that assessed effects of PCSK9 inhibitors and ezetimibe with or without statin therapy for cardiovascular risk reduction

- Harm reviews


- Expanded version of results with multi-layered recommendations, evidence summaries and decision aids for use on all devices

**Current practice**

Clinical practice guidelines differ in their recommendations. Box 1 shows recommendations for adults at high or very high cardiovascular risk who have not achieved target LDL cholesterol levels despite the maximum tolerated dose of statin. Guidelines suggest different LDL targets, and only a minority provide clear and actionable recommendations with a defined strength; instead, several use wording such as “adding a PCSK9 inhibitor is reasonable” or “consider discussing adding PCSK9 inhibitor with a lipid specialist.” Examples of varying thresholds include the European Society of Cardiology (ESC) guidelines offering an aggressive LDL cholesterol target of 55 mg/dL (1.4 mmol/L) for patients with very high cardiovascular risk, while the American College of Cardiology/American Heart Association (AHA/ACC) guidelines set a less aggressive LDL cholesterol target of 70 mg/dL (1.8 mmol/L). To achieve these goals in very high risk patients with statins alone is almost impossible, so physicians are increasingly considering other lipid-lowering drugs solely to achieve LDL cholesterol treatment goals rather than for important reduction of absolute cardiovascular risk.
How this recommendations was created

The guideline panel

Our international panel included three patient partners (including those using and those intolerant to statins), cardiologists, general practitioners, general internists, methodologists, endocrinologists, and one geriatrician.

No panel member reported financial conflicts of interest. Intellectual and professional conflicts were minimised and managed (see appendix 1 on bmj.com for details of panel members and their competing interests). The panel met online to discuss the scope of the recommendations and the patient-important outcomes that they considered most important. What research did the guideline panel propose and review?

Visual summary of recommendation

<table>
<thead>
<tr>
<th>Population</th>
<th>Different recommendations apply to people with the characteristics shown below:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults with elevated low-density lipoprotein (LDL) cholesterol</td>
<td></td>
</tr>
<tr>
<td>Over 70 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Over 1.8 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Using high dose statins or intolerant to statins</td>
<td></td>
</tr>
<tr>
<td>Wanting to reduce the risk of major cardiovascular events</td>
<td></td>
</tr>
</tbody>
</table>

MACE

Risk of experiencing a major adverse cardiovascular event within 5 years

<table>
<thead>
<tr>
<th>People using high dose statins</th>
<th>People intolerant to statins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low 5%</td>
<td>Recommendation 1</td>
</tr>
<tr>
<td>Moderate 5-15%</td>
<td>Recommendation 2</td>
</tr>
<tr>
<td>High 15-20%</td>
<td>Recommendation 3</td>
</tr>
<tr>
<td>Very high &gt;20%</td>
<td>Recommendation 4</td>
</tr>
</tbody>
</table>

Values and preferences

The patient’s values and preferences probably vary widely. These recommendations reflect a belief that most patients value a modest reduction (about 10 per 1000) in myocardial infarction or stroke over 5 years. However, some patients may value smaller reductions in these major events.

See an interactive version of this graphic online


Recommendations

<table>
<thead>
<tr>
<th>People considering cardiovascular risk reduction</th>
<th>Favours intervention to the left</th>
<th>Favours intervention to the right</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins alone</td>
<td>Strong</td>
<td>Weak</td>
</tr>
<tr>
<td>Adding a second lipid-lowering drug</td>
<td>Weak</td>
<td>Strong</td>
</tr>
</tbody>
</table>

| People adding a second lipid-lowering drug       | Ezetimibe plus statins           | PCSK9 inhibitors plus statins     |
|                                                | Strong                           | Weak                              |
|                                                | Strong                           | Weak                              |

<table>
<thead>
<tr>
<th>People considering further cardiovascular risk reduction</th>
<th>Ezetimibe plus PCSK9 inhibitors plus statins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins alone</td>
<td>Strong</td>
</tr>
<tr>
<td>Adding a second lipid-lowering drug</td>
<td>Weak</td>
</tr>
<tr>
<td>Ezetimibe plus statins</td>
<td>Strong</td>
</tr>
<tr>
<td>PCSK9 inhibitors plus statins</td>
<td>Weak</td>
</tr>
</tbody>
</table>

| People starting a lipid-lowering drug                  | Ezetimibe                                  | PCSK9 inhibitors                  |
|--------------------------------------------------------|--------------------------------------------|
| Statins alone                                            | Strong                                     |
| Ezetimibe                                               | Weak                                       |
| PCSK9 inhibitors                                        | Strong                                     |

<table>
<thead>
<tr>
<th>People considering further cardiovascular risk reduction</th>
<th>Ezetimibe plus PCSK9 inhibitors plus statins</th>
</tr>
</thead>
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<tr>
<td>Statins alone</td>
<td>Strong</td>
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<tr>
<td>Ezetimibe</td>
<td>Weak</td>
</tr>
<tr>
<td>PCSK9 inhibitors plus statins</td>
<td>Strong</td>
</tr>
</tbody>
</table>

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In addition to the primary role of lifestyle interventions, statins are now the primary treatment to reduce cardiovascular events. The panel decided that patients and clinicians should consider new lipid-lowering drugs (either a PCSK9 inhibitor or ezetimibe) after statins. The panel proposed a systematic review and network meta-analysis of randomised controlled trials on the comparative effectiveness of PCSK9 inhibitors or ezetimibe versus no PCSK9 inhibitors or ezetimibe on cardiovascular benefits.13

Only trials following patients for ≥6 months and including ≥500 patients were included. The panel also proposed two systematic reviews with pairwise meta-analysis of randomised controlled trials to inform adverse outcomes of adding PCSK9 inhibitors or ezetimibe to current lipid-lowering interventions.14 15

**What outcomes did the guideline panel consider important?**

The panel considered all-cause mortality, cardiovascular mortality, non-fatal stroke, and non-fatal myocardial infarction over five years to be the critical outcomes; most eligible trials followed patients for less than 3 years. The panel considered burden of treatment to be a factor of key importance for patients.29 The panel selected known adverse effects including injection site reactions leading to discontinuation, myalgia or muscular pain, and new-onset diabetes as important adverse outcomes.

**Values and preferences**

The panel conducted a preliminary search for patients’ values and preferences regarding lipid-lowering drugs but did not find any direct research evidence to inform their judgments. Panel members completed a survey eliciting their views on the benefits that patients would consider important. The panel’s judgments on patients’ values and preferences showed large variability, likely reflecting varying individual patient thresholds. The panel chose the medians of the survey results for each outcome as the best estimate of the minimal important difference (MID): a reduction of 8 per 1000 for mortality, 10 per 1000 for non-fatal stroke, and 12 per 1000 for non-fatal myocardial infarction over 5 years. We used the MID to rate the imprecision of the results, and the panel considered these thresholds when discussing the final recommendations.

**Risk stratification**

The panel defined groups of patients at varying risk of cardiovascular events. Box 3 outlines how the panel defined risk categories. For primary prevention, the panel used the risk prediction model and calculator (PREDICT),18 defining adults to be at low, intermediate, and high risk for cardiovascular events over 5 years. For secondary prevention, all patients are defined as very high risk.

**How did the guideline panel formulate the recommendations?**

The panel met by videoconferences to discuss the evidence and to formulate recommendations. The panel followed the BMJ Rapid Recommendations procedures for creating a trustworthy recommendation, using GRADE30 and MAGICapp (www.magicapp.org) to critically appraise the evidence and create recommendations. Since this is an international guideline, the panel took an individual patient perspective, rather than a societal, public health, or health payer perspective, which largely vary among countries.

The panel focused on cardiovascular risk and absolute benefits weighed against harms and burdens or practical issues. With an individual patient perspective, what patients would find to be important cardiovascular benefits is key and hinges on their values and preferences.

In moving from evidence to recommendations, the panel reviewed evidence summaries for multiple and pairwise comparisons, considered the certainty (quality) of the evidence for each important outcome; the balance of benefits and harms of adding a PCSK9 inhibitor, ezetimibe, and possible combinations; expected variations in patients’ values and preferences (informed by the survey); and the burden of treatment in the form of practical issues. The panel did not directly consider the cost of medications but recognised that cost is important from a health systems perspective and that clinicians and patients may have to deal with cost issues. The co-chairs, aiming to reach consensus, facilitated discussions and, when needed, conducted preliminary votes. Following GRADE guidance, recommendations can be strong or weak (conditional), and for or against a specific course of action.31 The panel succeeded in achieving consensus on all recommendations.

**The evidence**

**Benefits of PCSK9 inhibitors and ezetimibe**

The systematic review with network meta-analysis included 14 RCTs (93% were industry funded) including 83 660 individuals with or without established cardiovascular diseases. Table 1 shows the characteristics of patients and studies, also available in the systematic review.13

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PCSK9 inhibitors v control</th>
<th>Ezetimibe v control</th>
<th>PCSK9 inhibitors v ezetimibe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials</td>
<td>10</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Median (range) sample size (patients)</td>
<td>1590 (517 to 27 564)</td>
<td>2759 (172 to 3769)</td>
<td>720</td>
</tr>
<tr>
<td>Median follow-up (years)</td>
<td>1.5</td>
<td>4.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median or mean (range) age (years)</td>
<td>60.3 (56 to 66.1)</td>
<td>73 (65.5 to 80.6)</td>
<td>61.5</td>
</tr>
<tr>
<td>Median or mean (range) percentage female</td>
<td>35 (25 to 49)</td>
<td>49 (24 to 74)</td>
<td>26</td>
</tr>
<tr>
<td>Mean (range) baseline LDL cholesterol (mg/dL)</td>
<td>92 to 128 (2.4 to 3.3 mmom/L)</td>
<td>93.8 to 161 (2.4 to 4.2 mmom/L)</td>
<td>106 (2.7 mmom/L)</td>
</tr>
</tbody>
</table>

PCSK9 inhibitors or ezetimibe have no impact on all-cause mortality or cardiovascular mortality; this is true for all risk groups (moderate to high certainty evidence). Both PCSK9 inhibitors and ezetimibe can reduce non-fatal myocardial infarctions and stroke (moderate to high certainty evidence). PCSK9 inhibitors may have similar effects to ezetimibe on reducing non-fatal myocardial infarction or stroke (low certainty evidence). Further adding a PCSK9 inhibitor may reduce non-fatal myocardial infarction or stroke among those at very high risk (low certainty evidence).

Although we planned to conduct subgroup analyses according to certain variables—primary versus secondary prevention, follow-up duration (<1 year versus ≥1 year), low or high risk of bias, presence or absence of familial hypercholesterolemia—limited data in the current evidence restricted our ability to do so.

Available evidence included insufficient direct comparisons on the risk of major adverse cardiovascular event to inform the choice between PCSK9 inhibitors versus ezetimibe and the addition of one drug versus the other; therefore these recommendations were informed almost exclusively by indirect evidence.

The review team
did not find incoherence in direct and indirect comparisons of PCSK9 inhibitors with ezetimibe. Moreover, most eligible trials enrolled patients with high or very high cardiovascular risk, a further source of indirectness regarding people at low or moderate risk. Most of the RCTs examined the effectiveness of PCSK9 inhibitors with less than three years’ follow-up, so recommendations beyond that point carry this final source of indirectness.

Harms of ezetimibe and PCSK9 inhibitors

A systematic review of potential harms from ezetimibe (47 randomised trials, 28,244 participants) with 36 weeks’ median follow-up duration found moderate to high certainty evidence for no increase in any adverse events leading to discontinuation, cancer, fracture, neurocognitive events, or new-onset diabetes.14

Another systematic review of potential harms from PCSK9 inhibitors (32 trials of 65,861 participants) with 52 weeks median follow-up found high certainty evidence for an increase in injection-site reactions leading to discontinuation (15 per 1000 over five years). PCSK9 inhibitors were not associated with any other adverse events leading to discontinuation (low certainty), myalgia or muscular pain leading to discontinuation (moderate certainty), neurocognitive events (high certainty), or new-onset diabetes (high certainty).15

Absolute effects on benefits and harms

While harms and burdens from adding a PCSK9 inhibitor or ezetimibe are similar across different risk groups, the absolute magnitude of benefits from adding these drugs is highly dependent on individual baseline risk (see infographic) and the MATCH-IT tool (https://magic.evidence.org/match-it/220504/dist-lipid-lowering-drugs/). The addition of ezetimibe or a PCSK9 inhibitor to current therapy generally results in fairly similar absolute benefits and absence of serious adverse events.

Values and preference

In the absence of empirical evidence to guide decisions on what constituted important benefits to patients, the panel used inferred values and preferences documented in a survey of the panel (see “How this recommendation was created”). Using the identified thresholds for important benefit from this survey (such as 10 fewer strokes per 1000 patients treated for 5 years), the panel perceived PCSK9 inhibitors and ezetimibe both would provide important benefits for adults in the high and very high risk group, but would be of little benefit for adults in the low risk group. Having prescribed either drug in addition to current therapy, adding the second drug would provide small but important benefits for adults at high and very high risk, trivial benefits for adults with moderate risk, and little or no benefit for adults with low risk.

Understanding the recommendations

Recommendations

The guideline panel provided mostly weak recommendations as follows:

- For adults taking high dose statins, with LDL cholesterol >70 mg/dL (1.8 mmol/L)
  - Low risk (<5% five year risk of major adverse cardiovascular event (MACE)): We recommend not adding a second lipid-lowering drug (strong recommendation)
  - Moderate risk (5-15% five year risk of MACE): We suggest not adding a second lipid-lowering drug; but for those who are considering adding a second lipid-lowering drug, we suggest adding ezetimibe first (weak recommendation); we recommend not adding a PCSK9 inhibitor to ezetimibe (strong recommendation)
- High risk (15-20% five year risk of MACE): We suggest adding a second lipid-lowering drug, preferably ezetimibe first; we suggest adding a PCSK9 inhibitor to ezetimibe (weak recommendation).
- Very high risk (>20% five year risk of MACE): We suggest adding a second lipid-lowering drug, preferably ezetimibe first; we suggest adding a PCSK9 inhibitor to ezetimibe (weak recommendation).
  - For adults intolerant to statins with LDL cholesterol >70 mg/dL (1.8 mmol/L)
  - Low risk (<5% five year risk of MACE): We recommend not using a lipid-lowering drug (strong recommendation)
  - Moderate risk (5-15% five year risk of MACE): We suggest not using a lipid-lowering drug; but for those who are considering using a lipid-lowering drug, we suggest adding ezetimibe first (weak recommendation); we recommend not adding a PCSK9 inhibitor to ezetimibe (strong recommendation)
  - High risk (15-20% five year risk of MACE) and very high risk (>20% five year risk of MACE): We recommend using a lipid-lowering drug (strong recommendation), preferably ezetimibe first; we suggest adding a PCSK9 inhibitor to ezetimibe (weak recommendation).

To whom do they apply?

The recommendations apply to adults with LDL cholesterol >70 mg/dL (1.8 mmol/L) considering further reduction in risk of CV events who are already taking statins or are intolerant to statins. Please note that people who previously reported severe muscle symptoms when taking statins (may be labelled as intolerant to statins) should first consider restarting statins at a low dose to reduce their cardiovascular risk, as many could have a nocebo effect or combined effect.16 17

This guideline represents a shift from the traditional focus on lipid level goals to a focus on reducing an individual’s overall cardiovascular risk. Clinicians need to identify patients’ individual cardiovascular risks to apply these risk-stratified recommendations. The use of these recommendations therefore warrants explicit judgments of individual baseline cardiovascular risk, using credible risk calculators applicable to specific geographic regions. Most risk prediction tools use a cardiovascular risk over a period of 10 years, but this is not consistent with many trials on interventions for cardiovascular risk, which rarely extend beyond five years. The panel chose the most widely applicable calculator (PREDICT) to estimate patients’ risk, of mortality, non-fatal myocardial infarction, and non-fatal stroke over five years, in part because PREDICT provides risk estimates for both primary and secondary prevention populations (appendix 2). Box 3 presents our approach to risk stratification, with key characteristics to consider displayed in the infographic.

Box 3: Risk stratification approach and baseline risk estimation for the guideline

The panel estimated baseline risks for individual outcomes (mortality, non-fatal myocardial infarction, and non-fatal stroke) over a five year timeframe. We used medians of the risk within each risk category from the PREDICT cohort18 as the baseline risk estimates. The PREDICT cohort
includes five ethnic populations (European, Maori, Pacific, Indian, Chinese or other Asian) and 11 risk attributes.

**Primary prevention population (patients typically seen in primary care)**
- **Low risk**—Patients with 1-2 cardiovascular risk factors (5% five year risk of major adverse cardiovascular event (MACE), median 2%)
- **Moderate risk**—Patients with 3-4 cardiovascular risk factors (5-15% five year risk of MACE, median 7%)
- **High risk**—Patients with ≥5 cardiovascular risk factors or hereditary or familial lipid disorder (15-20% five year risk of MACE, median 18%).

**Secondary prevention population (patients typically seen in specialist health care)**
- **Very high risk**—Patients with established cardiovascular diseases (>20% five year risk of MACE, median 24%).

**Assumptions**
- Statins reduce cardiovascular risk. We used the relative risk reductions from a previously published systematic review for adding statins to no drug treatment (without statins).
- MACE is a composite outcome, but the panel was interested in the effects on individual components. To unravel MACE, we used a set of assumptions supported by previous studies reporting the general distributions for different events. Non-fatal myocardial infarction and stroke will occur nine times more often than cardiovascular deaths. Non-fatal myocardial infarction will occur 1.3 more often than non-fatal stroke, and all-cause mortality will occur 1.5 times more often than cardiovascular mortality. This method did not, however, take account of the proportions of the individual outcomes in MACE being age and sex dependent. We chose fixed proportions to avoid unmanageable complexity (see appendix 2 on bmj.com).

**Values and preferences variability**
The panel recognised that values and preferences probably vary widely across patients. Our recommendations reflect a belief that most patients value a modest reduction in myocardial infarction or stroke over five years, including absolute reductions in the order of 10 per 1000. However, some patients may value smaller reductions in these major events. The main burden of treatment with PCSK9 inhibitors is injections and risk of local skin reactions. The panel’s recommendations are based on the members’ inference that patients consider the burden of regular medication, including periodic injections, would be outweighed by an important reduction in major events.

The panel made one strong recommendation based on low quality evidence; for adults already receiving high dose statins at moderate cardiovascular risk, we recommend against adding a PCSK9 inhibitor to ezetimibe and statins. For this recommendation, the panel placed a high priority on avoiding the burden of injections and minimising the use of polypharmacy and the possibility of drug-drug interactions when there are no clear benefits on major adverse cardiovascular events.

**Shared decision making, including practical issues**
Shared decision making is particularly important when recommendations are weak and values and preferences are likely to vary substantially. When adding PCSK9 inhibitors or ezetimibe, the previous lipid-lowering drug (maximally tolerated statins) would remain unchanged. Many people may prefer oral medicines to injectable drugs. Implementing injection medications may introduce various barriers and need effective communication with patients. Table 2 shows the practical issues regarding adding a PCSK9 inhibitor or ezetimibe or statins alone.
Table 2 | Practical issues about use of PCSK9 inhibitors and ezetimibe in adults

<table>
<thead>
<tr>
<th>PCSK9 inhibitors</th>
<th>Ezetimibe</th>
<th>Statins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication routine</td>
<td>Administered every 2 weeks or monthly by subcutaneous injection (inclisiran can be given every 6 months)</td>
<td>Tablets taken once daily at any time of day. Ezetimibe–statin combination pills are available</td>
</tr>
<tr>
<td>Test and visit</td>
<td></td>
<td>Regular blood samples or visits after starting a new medication to monitor adherence and potential harms are encouraged</td>
</tr>
<tr>
<td>Recovery and adaptation</td>
<td></td>
<td>Most people need to take these medications for the rest of their lives.</td>
</tr>
<tr>
<td>Adverse effects, interactions, and antidote</td>
<td>Injection site reactions are usually mild, including pain, erythema or allergic effects. Muscle toxicity or hepatic dysfunction seem uncommon. The overall incidence of side effects is similar to placebo. Long-term (&gt;3 years) safety issues need further investigation</td>
<td>Adverse reactions are mild and transient, including gastrointestinal events, myalgia or muscular pain, hepatic dysfunction, headache, and fatigue. The overall incidence of side effects is similar to placebo.</td>
</tr>
<tr>
<td>Physical wellbeing</td>
<td>All drugs have no or little effect on body weight.</td>
<td></td>
</tr>
<tr>
<td>Emotional wellbeing</td>
<td>Emotional stress can occur from starting or adding new injection medication and be related to side effects, especially for long-term safety issues.</td>
<td>Emotional stress can occur from adding new oral medication related to side effects</td>
</tr>
<tr>
<td>Pregnancy and nursing</td>
<td>All lipid-lowering drugs should be avoided during pregnancy and nursing or in women who may become pregnant. Lifestyle interventions can be considered during pregnancy and nursing as general management for dyslipidaemias.</td>
<td>Ezetimibe is more expensive than statins but much cheaper than PCSK9 inhibitors and easy to access. Statins are generally inexpensive and easy to access</td>
</tr>
<tr>
<td>Costs and access</td>
<td>Costs vary between specific agents and depend on health insurance and policy. Even though the cost will hugely affect the individual or society’s decision, we put the cost aside when we make our recommendations. PCSK9 inhibitors are the most expensive drugs among the drugs and not easy to access.</td>
<td>Ezetimibe is more expensive than statins but much cheaper than PCSK9 inhibitors and easy to access. Statins are generally inexpensive and easy to access</td>
</tr>
<tr>
<td>Food and drinks</td>
<td>A diet to maintain a healthy weight (such as Mediterranean diet) is advised as general management for patients with dyslipidaemias.</td>
<td>Drugs should be stored in a dry environment below 30°C and avoid sunshine</td>
</tr>
<tr>
<td>Storage and transportation before use</td>
<td>PCSK9 inhibitors should be stored and transported at 2-8°C and avoid sunshine and freezing.</td>
<td></td>
</tr>
<tr>
<td>Exercise and activities</td>
<td>Exercise and activities are advised as a general management for patients with dyslipidaemias.</td>
<td>Exercise and activities are advised as a general management for patients with dyslipidaemias</td>
</tr>
<tr>
<td>Travel time and driving</td>
<td>Patients may need special equipment to transport their drugs and injection equipment when undertaking long travel.</td>
<td>No influence</td>
</tr>
</tbody>
</table>

Costs and availability

Both ezetimibe and statins are generically available worldwide. Ezetimibe is more expensive than statins but much cheaper than PCSK9 inhibitors. PCSK9 inhibitors are delivered by injection and require special equipment when using or travelling. Two PCSK9 inhibitors (alirocumab, evolocumab) have been approved and are available in Europe, US, and Canada, with inclisiran so far approved only in Europe. Because of cost, storage and transportation requirements, and local health policy, they are unavailable in many other countries or areas, especially middle or low-income countries. Our recommendations do not consider medication costs. However, the panel recognises that, for patients who have to bear the costs of medication, the cost may prove decisive.

Costs of PCSK9 inhibitors are potentially prohibitive, and a key factor in a healthcare systems perspective. A related cost-effectiveness analysis reported variable results: some, but not all, studies suggest that the addition of evolocumab or alirocumab to maximally tolerated statin therapy, with or without ezetimibe, with current pricing, may meet accepted cost-effectiveness thresholds in the US among patients at very high risk of atherosclerotic cardiovascular diseases. Although the guideline panel, in making recommendations from the perspective of patients, did not directly consider the cost of medication, our recommendations are in line with the preference with the cost-effectiveness concerns and drug availability, favouring ezetimibe over PCSK9 inhibitors in people needing another lipid-lowering drug. Clinicians and patients need to consider the cost based on the local scenario.

Uncertainty

There are several limitations in the evidence underlying this guideline, resulting in uncertainties and key research questions. First, there is almost no direct evidence on major adverse cardiovascular event to inform comparisons between PCSK9 inhibitors and ezetimibe, and the addition of one of these drugs to the other. There is also little direct evidence in moderate or low risk individuals and long term effects (over 3 years) or safety issues for adding PCSK9 inhibitors. These limitations in the evidence explain in part the panel’s reluctance to recommend adding the two drugs to patients at low or moderate cardiovascular risk.

Second, we know little about the values and preferences of adults considering lipid-lowering drugs: our survey leaves great uncertainty about the true distribution of values and preferences and highlights the need for further research. For example, formal
qualitative or quantitative studies could provide insight into patients’ values and preferences, and particularly into the minimal important difference on important cardiovascular outcomes in the context of different cultures and health systems.

Third, the long term (over three years) side effects of adding a PCSK9 inhibitor are unclear. Long term drug surveillance and monitoring of adverse reactions will provide further evidence on this issue. Furthermore, the PREDICT tool was developed based on cohorts from New Zealand, and thus other populations may have somewhat different levels or determinants of risk than PREDICT.

**Tips on calculating cardiovascular risk**

We suggest that patients and clinicians use the most reliable risk calculator that suits the local population to estimate patients’ cardiovascular risk. **Box 4** lists validated risk calculators in the published literature. If such calculators are unavailable or unfeasible, we suggest the following strategy to identify individual cardiovascular risk: for primary prevention, clinicians need to calculate patients’ cardiovascular risk based on risk factors of cardiovascular disease, including but not limited to older age (>50 years old), male, tobacco use, diabetes, family history of cardiovascular disease, high blood pressure, elevated total cholesterol, and reduced high-density lipoprotein-cholesterol. For secondary prevention populations, clinicians can identify patients with established cardiovascular disease.

**Box 4: Validated risk calculators in literature for reference.**

- Framingham Risk Score-Cardiovascular Disease: https://framinghamheartstudy.org/fhs-risk-functions/
- QRISK: https://www.qrisk.org/
- China-PAR: https://www.cvdrisk.com.cn/ASCVD/Eval
- PREDICT: https://cvdrisk.mohio.co.nz/

Note: Most risk calculators calculate cardiovascular risk over 10 years, whereas our recommendations are based on five year cardiovascular risk (appendix 2). Clinicians can estimate five year risk by dividing 10 year calculator estimates in half, if we assume that the risks are distributed evenly. These tools may overestimate risk as they were developed when baseline cardiovascular risks were higher than is currently the case.

Baseline cardiovascular risk may vary across countries and ethnicities. Although we suggest using reliable risk calculators validated in specific geographic settings, these tools cannot take account of all cardiovascular risk factors, and clinicians therefore need to use such tools with caution, supplemented by their clinical expertise. New emerging biomarkers such as lipoprotein(a) and coronary artery calcium score might be helpful for further risk stratification.

**Updates to this article**

Table 3 shows evidence that has emerged since the publication of this article. As new evidence is published, a group will assess the new evidence and make a judgment on the desirability of altering the recommendation.

**Table 3 | New evidence which has emerged after the initial publication of this article**

<table>
<thead>
<tr>
<th>Date</th>
<th>New evidence</th>
<th>Citation</th>
<th>Findings</th>
<th>Implications for recommendation</th>
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</thead>
<tbody>
<tr>
<td></td>
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</table>

There are currently no updates to the article. The MAGIC workgroup will monitor related evidence. The steering group will start updating the recommendations when potential practice-changing evidence emerges.

**Education into practice**

- How will you identify patients who might require a change in their lipid medication regime based on these recommendations?
- How will you help individuals to make a choice about PCSK9 inhibitors or ezetimibe after they reach the maximum dose of statins or are intolerant to statins?
- What cardiovascular risk calculator is most appropriate to use locally for your population in order to implement these recommendations?

**How patients were involved in the creation of this article**

Three patients who have taken lipid-lowering drugs (including one patient with intolerance to statins) were full panel members. Before the formal discussion with the whole panel, our patient partnership liaisons (Geerttruida Bekkering and Lyubov Lytvyn) hosted small meetings with patient partners only to discuss the guideline process and the evidence. During the survey and the meeting, the steering group and meeting chairs emphasised patient partners’ voices for consideration.

The three patient partners helped the panel identify important outcomes and rated outcomes, led the discussion on values and preferences, and participated in the teleconferences and email discussions on the evidence and recommendation. They also contributed to the identification of practical issues related to the decision of choosing lipid-lowering drugs and met all authorship criteria for the present guideline. We thank them for their great contribution.

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Disclaimer: Participation in the panel and authorship of this manuscript does not constitute organisational endorsement of the recommendations.

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We thank panel member Hans Van Brabant for his contribution in identifying critical outcomes and finalising clinical questions for the guideline. We learnt of his passing with great sadness.


Appendix 1: Full list of authors and summary of their competing interests

Appendix 2: Rationale for choice of risk stratification