

education

FROM THE JOURNALS Edited highlights of weekly research reviews

Digging in the wardrobe: a new look for metformin?

Repurposing drugs is a bit like digging out an old jacket from your wardrobe and finding that it looks good with a new pair of trousers; it's trustworthy, cheap, and offers a novel solution. And so to metformin, the carthorse of diabetes treatment that has reportedly been associated with potential benefits in breast cancer patients in some observational studies. In women with diabetes and breast cancer, the question is whether metformin has a direct antitumour effect in addition to controlling diabetes. If so, then metformin would also be expected to improve survival in non-diabetic women with breast cancer.

However, this useful randomised trial of 3649 women with high risk, non-metastatic, operable breast cancer and no diabetes found that treatment with metformin (850 mg twice daily) for five years compared with placebo did not significantly increase the interval free of invasive disease or overall survival. Analysing the results by hormone receptor status of the cancer did not alter the lack of effect.

• *JAMA* doi:10.1001/jama.2022.6147

Carotid stenosis: surgery or drugs?

Optimal treatment for carotid stenosis has traditionally involved surgical intervention in most cases. But medical treatment has been improving, so which would you opt for now? In this retrospective study of a diverse cohort of nearly 95 000 patients with asymptomatic severe carotid stenosis who didn't have surgery, the rate of ipsilateral carotid-related acute ischaemic stroke was 4.7% over five years, which is lower than historical reports and likely to be more accurate thanks to the robust study design. More information is still needed; this trial couldn't assess the quality of imaging data, use of over-the-counter aspirin, or incidence of transient ischaemic attacks. But it's useful to know the risk of stroke if you choose modern medical management over surgical intervention.

• *JAMA* doi:10.1001/jama.2022.4835

Tranexamic acid: a finger in the dam?

There's a worldwide shortage of blood for transfusions, 40% of which are needed after surgical bleeding. Could giving the antifibrinolytic drug tranexamic acid to all patients at risk of perioperative bleeding and cardiovascular complications, help to reduce that need? This international, randomised trial of 9535 patients found fewer significant bleeds (a composite outcome of life threatening, major, or critical organ bleeding at 30 days) in those given a 1 g intravenous bolus of tranexamic

acid at the start and end of non-cardiac surgery compared with placebo (9.1% v 11.7%). Its good safety profile was borne out in this study, with no significant increase (though inferiority not established) in a composite cardiovascular outcome at 30 days (14.2% v 13.9%). It was a shame that financial pressures and covid-19 contributed to the trial being stopped early, although the researchers still recruited 95% of the planned sample size.

• *N Engl J Med* doi:10.1056/NEJMoa2201171

Hard day's night?

A tired surgeon is a worrying prospect, but any association between fatigue and patient outcomes has been hard to study reliably. This important cross-sectional study of outcomes of nearly half a million daytime operations across 50 hospitals in the US and Netherlands found that there was no significant association between surgeons who had operated the previous night and those that hadn't in terms of the incidence of in-hospital death or major complications such as sepsis, pneumonia, myocardial infarction, thrombosis, or stroke (5.89% v 5.87% after adjusting for confounders). This lack of association held true overall and for those patients at highest risk of death or major surgical complications. The results are certainly reassuring, but intuitively I'd rather be operated on by someone who has had a good night's sleep rather than one who's been working all night.

• *JAMA Intern Med* doi:10.1001/jamainternmed.2022.1563

Crohn's news

There's encouraging news for people with moderate to severely active Crohn's disease from two randomised trials which showed that risankizumab, a novel humanised monoclonal antibody targeting interleukin 23A, was well tolerated and effective in inducing and maintaining remission. D'Haens and colleagues reported results of two phase 3 trial induction studies (ADVANCE and MOTIVATE), which found 600 mg and 1200 mg doses of intravenous risankizumab achieved early symptom control by week 4 and endoscopic improvement at week 12 compared with placebo.

Ferrante and colleagues reported similarly positive results from the FORTIFY phase 3 trials using subcutaneous risankizumab for a year while withdrawing other maintenance drugs in those who responded to 12 weeks of intravenous risankizumab. The co-primary endpoints of clinical remission and robust evidence of endoscopic response made the results more compelling.

• *Lancet* doi:10.1016/S0140-6736(22)00467-6

• *Lancet* doi:10.1016/S0140-6736(22)00466-4

Ann Robinson, NHS GP and health writer and broadcaster

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Self-testing kit for STIs increases diagnoses while reducing costs

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The study

Swab-yourself trial with economic monitoring and testing for infections collectively (SYSTEMATIC): Part 2

Wilson JD, Wallace HE, Loftus-Keeling M, et al

Clin Infect Dis 2020;73:3183-93

Why was this study needed?

Most people with chlamydia have no symptoms. Many with gonorrhoea also lack symptoms.

Standard tests take urine samples or swabs of the vagina or penis. Most national and international guidelines recommend also testing the rectum and throat (triple site screening) only for groups at high risk, which include:

- men who have sex with men
- women who have received anal sex
- women who have given oral sex.

But triple site samples cost three times as much to analyse as single swabs.

A solution would be for people to take their own samples from the three areas of their body and place them together in one container. Pooled triple site samples should cost no more to analyse than a single sample. This systematic study aimed to work out whether triple site pooling is a reliable way of diagnosing gonorrhoea and chlamydia.

What did the study do?

The Systematic trial included 1284 women and 509 men who have sex with men. All attended a sexual health clinic in Leeds. Some 116 (9%) tested positive for gonorrhoea; 276 (15%) for chlamydia.

The first part of the trial found that self-taken swabs of throat and rectum gave diagnoses as accurately as swabs taken by clinicians. The study also found that it was cheaper for people to take their own swabs at home than for clinicians to take the swabs in a clinic.

It also found that many infections would have been missed by a single

swab of the vagina or urine test. Single swabs missed 100 gonorrhoea and chlamydia infections out of a total of 392.

The second part of the systematic trial looked at the effect of pooling triple site samples into one container for a single analysis. Samples were taken from throat and rectum for each individual. Plus, in women, from the vagina; and in men who have sex with men, from the urine. Self-taken samples were pooled (three per person); swabs taken by clinicians were analysed in three separate tests.

What did it find?

- Gonorrhoea was detected equally well by pooled and single swabs, both in women and in men who have sex with men (both approaches picked up 98% of infections)
- Chlamydia was slightly less likely to be picked up in pooled swabs than in three separate tests (3% lower for women; 5% lower for

men who have sex with men) and 13 infections were missed.

Although the detection rate for chlamydia was lower with pooled samples, it still picked up more than 90% of infections, which is the recommended minimum. The researchers say the reduction in sensitivity for men who have sex with men could be due to urine diluting the sample.

Why is this important?

The trial found that many infections are missed by the current single site test. The researchers would like triple site, pooled samples to be offered to all women and men who have sex with men. This would vastly reduce the number of missed infections.

Pooled samples could introduce significant cost savings. This matters because, even in high income countries, publicly funded health systems struggle to fund individually tested triple site swabs.

This research demonstrates that sexual health services can save money by pooling triple site samples from men who have sex with men while introducing routine triple site testing for all women.

Research from the study shows that the sampling could be done either by a clinician or as a self-test. This would not make a difference to the accuracy of the test.

What's next?

Since the trial, the authors have surveyed men who have sex with men to ask how they felt about accepting more missed chlamydia infections at large cost savings to the NHS. They found that most (more than 90%) would be happy with a test that detected 97% of infections.

The current test does not quite reach that threshold. Researchers

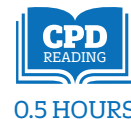
in the trial are now exploring different pooling techniques, which could increase the detection of chlamydia in men who have sex with men. The research team plans to use a smaller volume of urine, plus a swab of the urethra entrance, to avoid dilution of the sample.

Some clinics have already introduced pooled triple site samples taken by the individual.

Competing interests: *The BMJ* has judged that there are no disqualifying financial ties to commercial companies. Further details of other interests, disclaimers, and permissions can be found on bmj.com

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



Full author details on [bmj.com](https://www.bmj.com)

Correspondence to: N Delvaux nicolas.delvaux@kuleuven.be; S Lishheyu gmail.com

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?

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.

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. Our patient partnership liaisons hosted small meetings with patient partners 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 recommendations. They also contributed to the identification of practical issues related to the decision of choosing lipid-lowering drugs. We thank them for their great contribution.

The evidence

A linked systematic review and network meta-analysis (14 trials including 83 660 participants) of benefits found that PCSK9 inhibitors or ezetimibe probably reduce myocardial infarctions and stroke in patients with very high and high cardiovascular risk, with no impact on mortality (moderate to high certainty evidence), but not in those with moderate and low cardiovascular risk. PCSK9 inhibitors may have similar effects to ezetimibe on reducing non-fatal myocardial infarction or stroke (low certainty evidence). These relative benefits were consistent, but their absolute magnitude varied based on cardiovascular risk in individual patients. Two systematic reviews on harms found no important adverse events for these drugs (moderate to high certainty evidence). PCSK9 inhibitors require injections that sometimes result in injection site reactions (best estimate 15 more per 1000 in a 5 year timeframe), representing a burden and harm that may matter to patients. The MATCH-IT decision support tool allows you to interact with the evidence and your patients across the alternative options: <https://magicevidence.org/match-it/210609dist-lipid-lowering-drugs/>.

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 using local reliable risk calculators. 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.

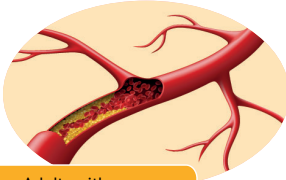
Because of the anticipated large variability of patients' values and preferences, well informed choices warrant shared decision making. Interactive evidence summaries and decision aids linked to the recommendations can facilitate such shared decisions. The strong recommendations against adding another 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 intolerant to statins and 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.

Visual summary of recommendation

Population

This recommendation applies only to people with these characteristics:



Adults with elevated low-density lipoprotein (LDL) cholesterol
 Over 70 mg/dL
 Over 1.8 mmol/L
 Using high dose statins or intolerant to statins



Wanting to reduce the risk of major cardiovascular events

Different recommendations apply to people with the characteristics shown below:

MACE	People using high dose statins	People intolerant to statins
Risk of experiencing a major adverse cardiovascular event within 5 years		
Low <5%	Recommendation 1	Recommendation 5
Moderate 5-15%	Recommendation 2	Recommendation 6
High 15-20%	Recommendation 3	Recommendation 7
Very high >20%	Recommendation 4	Recommendation 8

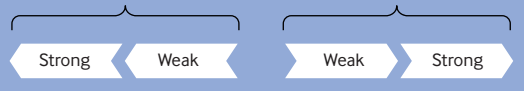
See an interactive version of this graphic online
<https://bit.ly/bmj-rr-lipids>

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

Recommendations

Favours intervention to the left Favours intervention to the right



	People considering cardiovascular risk reduction	People adding a second lipid-lowering drug	People considering further cardiovascular risk reduction
1	Statin alone Strong ← Weak	Adding a second lipid-lowering drug Weak → Strong	
2	Statin alone Strong ← Weak	Adding a second lipid-lowering drug Weak → Strong	Ezetimibe plus statins Strong ← Weak
3	Statin alone Strong ← Weak	Adding a second lipid-lowering drug Weak → Strong	Ezetimibe plus statins Strong ← Weak
4	Statin alone Strong ← Weak	Adding a second lipid-lowering drug Weak → Strong	Ezetimibe plus statins Strong ← Weak
5	No lipid-lowering drug Strong ← Weak	Ezetimibe or PCSK9 inhibitors Weak → Strong	
6	No lipid-lowering drug Strong ← Weak	Ezetimibe or PCSK9 inhibitors Weak → Strong	Ezetimibe Strong ← Weak
7	No lipid-lowering drug Strong ← Weak	Ezetimibe or PCSK9 inhibitors Weak → Strong	Ezetimibe Strong ← Weak
8	No lipid-lowering drug Strong ← Weak	Ezetimibe or PCSK9 inhibitors Weak → Strong	Ezetimibe Strong ← Weak

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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-protein 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. But the newer lipid-lowering drugs, particularly PCSK9 inhibitors, are expensive. Moreover, PCSK9 inhibitors are provided via subcutaneous injections, which can be inconvenient.

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,^{11 12} 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:

- Firstly, should patients add another lipid-lowering agent to current therapy?
- Secondly, if patients choose to add another drug, which drug should they choose (ezetimibe or a PCSK9 inhibitor)?
- Thirdly, 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/210609dist-lipid-lowering-drugs/>).

Current practice

Clinical practice guidelines differ in their recommendations. Guidelines suggest different LDL targets, and only a minority provide clear and actionable recommendations with a defined strength. The European Society of Cardiology (ESC) guidelines suggest 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).^{3 4} Physicians are increasingly considering other lipid-lowering drugs solely to achieve LDL cholesterol treatment goals rather than for important reduction of absolute cardiovascular risk.

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. The table shows the characteristics of patients and studies, also available in the systematic review.¹³

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 events 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 rely on indirect evidence.

Characteristics of eligible studies and participants			
Characteristics	Comparison		
	PCSK9 inhibitors v control	Ezetimibe v control	PCSK9 inhibitors v ezetimibe
Trials			
No of trials	10	3	1
Median (range) sample size	1590 (517 to 27 564)	2759 (1721 to 3769)	720
Median follow-up (years)	1.5	4.1	0.9
Participants			
Median or mean (range) age (years)	60.3 (56 to 66.1)	73 (65.5 to 80.6)	61.5
Median or mean (range) percentage female	35 (25 to 49)	49 (24 to 74)	26
Mean (range) baseline LDL cholesterol	92 to 128 mg/dL (2.4 to 3.3 mmol/L)	93.8 to 161 mg/dL (2.4 to 4.2 mmol/L)	106 mg/dL (2.7 mmol/L)

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 duration 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://magicevidence.org/match-it/210609dist-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 preferences

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.

PCSK9 inhibitors and ezetimibe would provide important benefits for adults in the high and very high risk group

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 not 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).

This guideline represents a shift from the traditional focus on lipid level goals to a focus on reducing an individual's overall cardiovascular risk

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.

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. 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.

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 interactions²² 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.²³

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, the 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.

Uncertainty

There are several limitations in the evidence underlying this guideline, resulting in uncertainties and key research questions. Firstly, there is almost no direct evidence on major adverse cardiovascular events 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.

Secondly, we know little about the values and preferences of adults considering lipid-lowering drugs. 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.

Thirdly, 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.

Competing interests: See bmj.com.

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Find the full version with references at doi: [10.1136/bmj-2021-069066](https://doi.org/10.1136/bmj-2021-069066)

EDUCATION INTO PRACTICE

- How will you identify patients who might require a change in their lipid medication regimen 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?

PCSK9 inhibitors and ezetimibe with or without statin therapy for cardiovascular risk reduction

Khan Su, Yedlapati SA, Lone AN, et al

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Find this at doi: 10.1136/bmj-2021-069116

Study question What are the effects of ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors on cardiovascular outcomes in adults who are taking maximally tolerated statin therapy or are statin intolerant and are seeking further cardiovascular risk reduction?

Methods A frequentist fixed effects network meta-analysis was performed and estimated relative risks (RR) and absolute risks per 1000 patients treated for five years for non-fatal myocardial infarction (MI), non-fatal stroke, all cause mortality, and cardiovascular mortality.

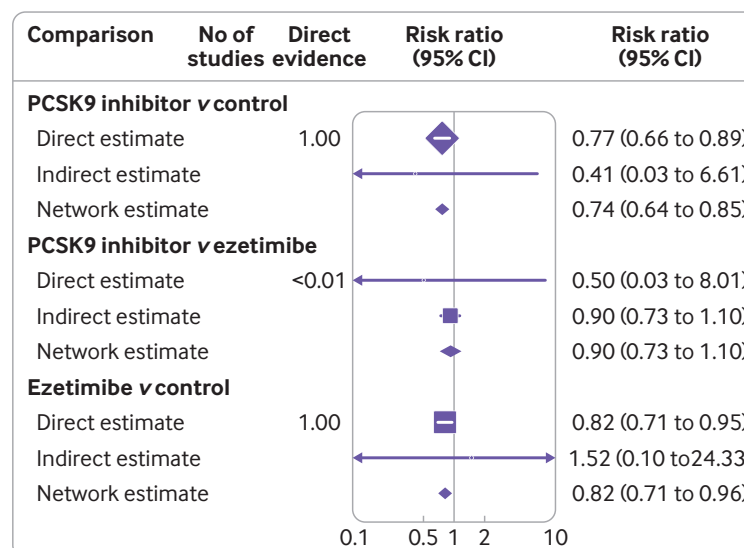
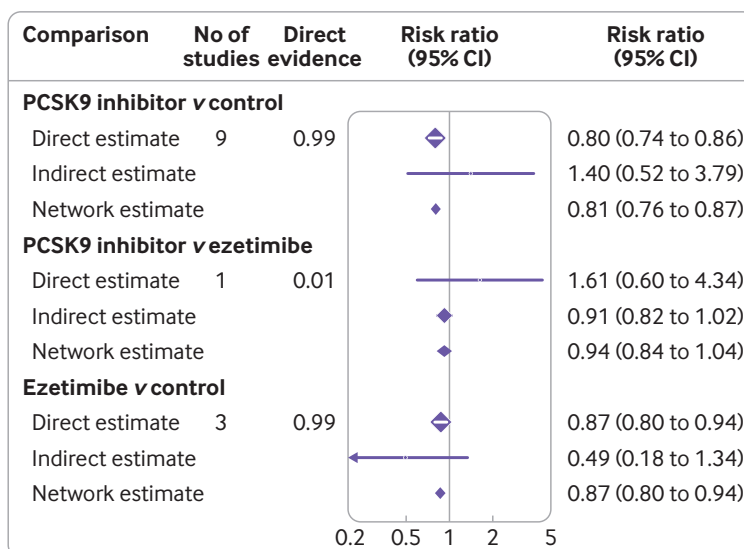
Study answer and limitations Adding ezetimibe to statins reduced non-fatal MI (RR 0.87 (95% confidence interval 0.80 to 0.94)) and stroke (RR 0.82 (0.71 to 0.96)), as did adding PCSK9 inhibitors to statins (RR 0.81 (0.76 to 0.87) and 0.74 (0.64 to 0.85) respectively). When categorised by cardiovascular risk, ezetimibe or PCSK9 inhibitors may reduce non-fatal MI and stroke in adults at very high or high cardiovascular risk, but not in those at moderate or low cardiovascular risk. Ezetimibe or PCSK9 inhibitors had no significant effect on mortality. Limitations include no direct evidence on any cardiovascular endpoint for statin intolerant patients and very little direct evidence in moderate and low risk individuals.

What this study adds Ezetimibe or PCSK9 inhibitors may reduce non-fatal myocardial infarction and stroke in adults at very high or high cardiovascular risk who are already receiving maximally tolerated statin therapy or are statin-intolerant, but not in those at moderate or low cardiovascular risk.

Funding, competing interests, and data sharing

This study did not receive any funding.

See full paper on bmj.com for individual author funding and competing interests. All data are available on request.



Forest plot showing node-split analysis for non-fatal myocardial infarction (top) and non-fatal stroke (bottom). Number of studies represents number of component trials in each comparison. Direct evidence reports proportion of direct evidence in summary estimates

ENDGAMES

CASE REVIEW

Recurrent cough, fever, dyspnoea, and chest pain

A man in his 30s was admitted to the respiratory and critical care ward with a >2 month history of recurrent cough, fever, dyspnoea on exertion, and pleuritic pain in the left hemithorax but no haemoptysis.

Two months earlier, chest radiography had shown pulmonary infiltrates, and antibiotic treatment was unsuccessful. One month earlier, pulmonary embolism (PE) was diagnosed after blood gas analysis showed hypoxaemia, and chest computed tomography pulmonary angiography (CTPA) showed multiple filling defects affecting the main pulmonary artery (MPA), right pulmonary artery (RPA), and left pulmonary artery (LPA). At that time he was treated with rivaroxaban and discharged.

At this latest presentation, his respiration rate was 21 breaths/min and oxygen saturation was 97% on room air. Routine blood tests, blood gas analysis, testing for troponin I, B-type natriuretic peptide, prothrombin time, and thrombophilia screening were normal. D-dimer levels and compression ultrasonography were also normal. Echocardiography showed mild pulmonary hypertension. CTPA (fig 1) showed an increase in the diameter of the MPA and multiple filling defects that were still affecting the MPA, RPA, and LPA (those in the RPA more extensive than previously). In accordance with National Institute for Health and Care Excellence (NICE) guidance, the patient also underwent positron emission tomography and computed tomography (PET-CT) (fig 2).

- 1 What are the differential diagnoses of this clinical presentation?
- 2 What is the most likely diagnosis?
- 3 When does NICE recommend PET-CT imaging for suspected venous thromboembolic disease?

Submitted by Xuanna Zhao, Yu Jie Huang, Bin Wu, and Dong Wu

Patient consent obtained.

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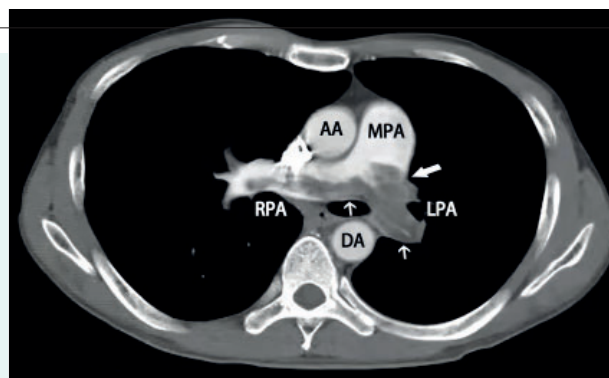


Fig 1 | Chest CTPA showing an increase in diameter of the main pulmonary artery (MPA) and lobulated filling defects extending from the bifurcation to the right pulmonary artery (RPA) and left pulmonary artery (LPA) (thick white arrow). AA=ascending aorta; DA=descending aorta

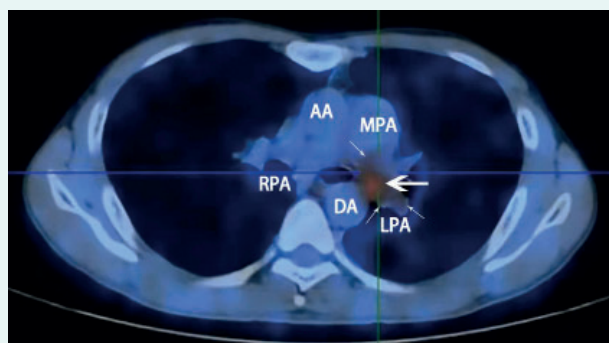


Fig 2 | Integration of 18F-fluorodeoxyglucose positron emission tomography and computed tomography showing multiple low density soft tissue shadows in the MPA, RPA, and LPA, with increasing non-homogenous fluorodeoxyglucose uptake (maximum standardised uptake value, 4.4) (thick white arrow), especially in the LPA and MPA (three thin arrows)

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PATIENT OUTCOME
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LEARNING POINT
• Consider PE mimics in patients with persistent vascular filling defects despite adequate anticoagulation, or in patients with a protracted clinical presentation.

3 When does NICE recommend PET-CT imaging for suspected venous thromboembolic disease?
To exclude co-existing disease or malignancy in patients receiving a diagnosis of unprovoked venous thromboembolism (VTE). Unprovoked VTE is defined as deep vein thrombosis or PE in a patient with no major clinical risk factors such as oral contraceptive, hormone replacement therapy, active cancer, thrombophilia, or a family history of VTE.

2 What is the most likely diagnosis?
CTPA indicating a form of vascular occlusion, these tumours can mimic and are easily misdiagnosed as PE.

1 What are the differential diagnoses?
New PE, recurrent or unresolved PE refractory to anticoagulation, and PE mimics, such as pulmonary artery tumours, pulmonary IgG4-related disease, Takayasu arteritis, Behçet's disease, and Hughes-Stovin syndrome.

CASE REVIEW Recurrent cough, fever, dyspnoea, and chest pain

answers



You can record CPD points for reading any article. We suggest half an hour to read and reflect on each.



Articles with a "learning module" logo have a linked BMJ Learning module at <http://learning.bmj.com>.

Multiloculated tuberculoma

This is a magnetic resonance image (MRI) showing a multiloculated tuberculoma in the left cerebellar hemisphere of a man in his 30s (arrow).

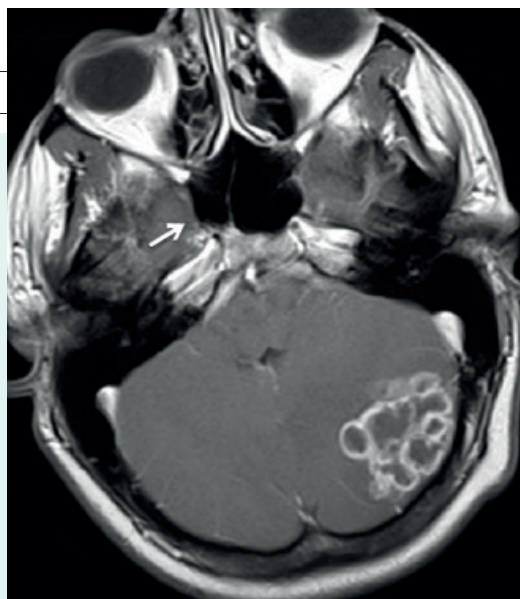
He presented with a three week history of severe headache and two months of weight loss and night sweats. He reported no cough or fever. He had migrated from Eritrea, where tuberculosis is endemic.

On examination he had brisk reflexes globally, dysmetria on finger nose finger testing, a narrow based gait, and was unsteady on heel to toe walking. MRI showed a well defined loculated lesion in the left cerebellar hemisphere causing effacement of the fourth ventricle and hydrocephalus.

Further imaging of his abdomen and chest identified multifocal fluid collections involving the prostate and seminal vesicles but no abnormality in the lungs. Tests for HIV and *Toxoplasma gondii* gave negative results. Bladder fluid obtained by aspiration was positive for tuberculosis on polymerase chain reaction test. Multifocal extra pulmonary tuberculosis was diagnosed.

Although tuberculoma accounts for a substantial proportion of intracranial space occupying lesions worldwide, diagnosis is often delayed because of difficulty obtaining appropriate tissue or fluid samples for confirmation. Tuberculoma should be considered in patients diagnosed with space occupying lesions from countries where tuberculosis is endemic.

If you would like to write a Minerva picture case, please see our author guidelines at <http://bit.ly/29HCBAL> and submit online at <http://bit.ly/29yyGSx>



Tarekegn Geberhiwot (tarekegn.hiwot@uhb.nhs.uk)
Andrew Toogood; Vijay Sawlani, University of Birmingham, UK
Patient consent obtained.

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Memory in older women

Women who are 80 and older and retain exceptionally good episodic memory (a group sometimes called “super agers”) are likely to have eaten a Mediterranean-type diet and to have been physically active in middle age. That’s the finding of a case-control investigation nested within the Nurses’ Health Study. By contrast, lifestyle behaviours at older ages differed little between those with good and those with less good memories (*Age Ageing* doi:10.1093/ageing/afac102).

Mouse memory

On the subject of memory, a recent report concludes that cerebrospinal fluid taken from young mice and infused into the lateral ventricle of ageing mice boosts oligodendrocyte progenitor cell proliferation in the hippocampus and improves performance on a test of memory function. A fibroblast growth factor seems to be the key molecule mediating this effect (<https://www.nature.com/articles/d41586-022-01282-1>).

Unscrambling eggs

Once the cornerstone of any nutritious breakfast, the reputation of eggs is in decline. A meta-analysis of longitudinal studies concludes that higher egg consumption is associated with an increased all cause and cardiovascular

mortality. Of course, people who eat more eggs are likely to eat less of some other foods. If consumption of these foods is also linked to mortality, it’s hard to be sure that eggs are the real culprit (*Circulation* doi:10.1161/CIRCULATIONAHA.121.057642).

Outdoor play

Hardly a week goes by without this column mentioning an investigation showing the benefits of physical activity for longevity, cognition, or mood. Physical activity may be even more important for the health of growing children. A survey of childcare settings and “head start” programmes in the US finds that it doesn’t get enough attention. Only 50% of classrooms met national guidelines recommending 60 to 90 minutes of physical activity a day (*Pediatrics* doi:10.1542/peds.2020-048850).

Stopping smoking in pregnancy

Although nicotine patches are commonly offered to pregnant women who smoke to help them quit, success rates are low. A randomised trial finds that electronic cigarettes aren’t much better. Verified stopping rates were 6.8% in those allocated to e-cigarettes versus 4.4% in those using patches. Low birthweight was less frequent in the offspring of mothers using e-cigarettes (*Nat Med* doi:10.1038/s41591-022-01808-0).

Only 50% of US childcare settings meet guidelines on daily physical activity

Function of the cuneate nucleus

The cuneate nucleus in the lower part of the brainstem was thought to be a relay station for ascending dorsal column afferents from the upper limb. Recent research has shown that it has a gatekeeping function. Descending pathways from the cortex control how much neural traffic the cuneate nucleus allows to pass, thus filtering out sensory information when it’s of low importance (<https://www.scientificamerican.com/article/how-the-brain-tells-apart-important-and-unimportant-sensations>).

Poor pregnancy outcomes in women with type 2 diabetes

The number of pregnancies complicated by pre-existing type 2 diabetes is increasing. An observational study in the US reports shockingly high rates of poor outcomes. Pregnancy loss occurred in a quarter of pregnancies, and preterm birth occurred in a third. More than a third of the pregnancies were complicated by chronic hypertension. Among the offspring, 8% were small for gestational age, 27% large for gestational age, and 18% in the macrosomic range (*Diabetes Care* doi:10.2337/dc21-1071).

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