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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Does the addition of ezetimibe to statins reduce cardiovascular risk?

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Abstract

Statins are the mainstay of lipid-lowering therapy nowadays, since they reduce cardiovascular risk when used as primary or secondary prevention. However, only one third of the patients reach the goals established in several guidelines, and even if they do, they keep a risk higher than healthy controls. One of the new lipid-lowering agents is ezetimibe. Searching in Epistemonikos database, which is maintained by screening multiple databases, we identified nine systematic reviews comprising 67 trials overall. We combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded adding ezetimibe to statins probably results in little or no difference in overall mortality. It might lead to a small reduction in the risk of myocardial infarction and stroke, but the certainty of the evidence is low.

Problem

Cardiovascular disease is the leading cause of death in adults. Higher LDL cholesterol levels are associated to an increase in the risk of coronary artery disease. This risk decreases with lower LDL levels until approximately 80 mg/dl (2.1 mmol/l) [1]. Therefore, multiple clinical guidelines have set LDL goals, which in many cases require intensive treatment [1]. Even though high dose statin regimen constitutes an option, many patients do not achieve the goals. In addition, even when they do, their cardiovascular risk remains higher than the general population, an effect called residual risk. New alternatives have emerged, such as ezetimibe, a cholesterol absorption inhibitor that blocks the intestinal absorption of dietary and biliary cholesterol and related plant sterols without affecting the uptake of triglycerides or fat-soluble vitamins. Considering its mechanism differs from statins, which reduce cholesterol synthesis, they might be a good choice for combination treatment. However, it remains unclear if adding ezetimibe to statin treatment has benefits, especially in reducing long-term cardiovascular risk.

Methods

We used Epistemonikos database, which is maintained by screening multiple databases, to identify systematic reviews and their included primary studies. With this information, we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages
- The addition of ezetimibe to statins probably leads to little or no difference in overall mortality.
- The addition of ezetimibe to statins might lead to a small reduction in the risk of myocardial infarction and stroke, but the certainty of the evidence is low.
- The addition of ezetimibe to statins does not increase serious adverse events.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found nine systematic reviews [2],[3],[4],[5],[6],[7],[8],[9],[10] that include 67 randomized controlled trials on ezetimibe and hypercholesterolemia, reported in 69 references [11],[12],[13],[14],[15], [16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29], [30],[31],[32],[33],[34],[35],[36],[37],[38],[39],[40],[41],[42],[43], [44],[45],[46],[47],[48],[49],[50],[51],[52],[53],[54],[55],[56],[57], [58],[59],[60],[61],[62],[63],[64],[65],[66],[67],[68],[69],[70],[71], [72],[73],[74],[75],[76],[77],[78],[79]. This summary analyzes the 37 trials that compared the addition of ezetimibe to statins versus same dose of statins used as monotherapy, which constitutes the most relevant clinical question [12],[17],[18],[19],[23],[24],[26],[27],[28],[29],[31], [34],[35],[36],[37],[40],[42],[43],[46],[48],[49],[50],[52],[53],[54], [58],[65],[66], [67],[68],[69],[71],[73],[74],[76],[77],[78].
What types of patients were included	Nine trials included patients with coronary artery disease [26],[27], [37], [42], [48],[53],[54],[71],[74]; two of them included participants with LDL levels below 160 mg/dl [42],[71]. One trial included patients with hypercholesterolemia and high cardiovascular risk [58], one trial was conducted on patients with acute coronary syndrome [29], one trial on patients with acute myocardial infarction [69], one trial included diabetic patients with hypercholesterolemia [17], two trials included patients with peripheral artery disease [50],[76]; two trials included patients with chronic kidney disease [31],[73] and 18 trials included patients with primary hypercholesterolemia [12],[18],[19],[23],[24],[28],[34],[35], [36],[40],[43],[46],[65],[66],[67],[68],[77],[78]. One trial included African-American participants only [18]. One trial included homozygous familial hypercholesterolemia [52]; and one trial was conducted on healthy subjects [49].
What types of interventions were included	Five trials compared the effects of atorvastatin and ezetimibe versus atorvastatin plus placebo [26],[42],[66],[67],[74]; 22 trials simvastatin plus ezetimibe versus simvastatin plus placebo [17],[18],[19],[23],[28], [29],[31],[35],[37],[40],[43],[46],[49],[53],[54],[68],[69],[71],[73], [76],[77],[78]; one trial atorvastatin and simvastatin associated with ezetimibe versus both statins plus placebo separately [52]; one trial simvastatin plus ezetimibe versus atorvastatin plus placebo [65]; six trials compared pravastatin, lovastatin, fluvastatin or several statins in the same trial associated with ezetimibe versus statin monotherapy [12],[24],[34], [36],[48],[58]; and two trials compared rosuvastatin plus ezetimibe versus rosuvastatin plus placebo [27],[50].
What types of outcomes were measured	Even though the primary studies reported outcomes in different ways, the systematic reviews identified grouped them as follows: • Overall mortality • Cardiovascular mortality • Cardiovascular events (nonfatal acute myocardial infarction, nonfatal stroke, high risk unstable angina and coronary revascularization) • Acute myocardial infarction • Stroke • Coronary revascularization • Serious adverse events (life threatening events, events that require hospitalization, congenital anomalies or permanent damage) • Cancer incidence

Summary of findings

The information about the effects of ezetimibe associated to statins is based on 37 randomized controlled trials [12],[17],[18],[19],[23],[24],[26],[27],[28],[29],[31],[34],[35],[36],[37],[40],[42],[43],[46],[48],[49],[50],[52],[53],[54],[58],[65],[66],[67],[68],[69],[71],[73],[74],[76],[77],[78]. Only nine trials reported overall mortality [29],[31],[42],[43],[50],[66],[73],[74],[76], seven reported nonfatal myocardial infarction [27],[29],[43],[50],[73],[74],[76], six informed nonfatal stroke [31],[43],[50],[73],[74],[76], three reported coronary revascularization [27],[29],[74] and 17 analyzed serious adverse events [17],[23],[24],[27],[29],[30],[31],[37],[42],[46],[53],[54],[64],[66],[71],[73],[78]. The summary of findings is the following:

- The addition of ezetimibe to statins probably leads to little or no difference in overall mortality. The certainty of the evidence is moderate.
- The addition of ezetimibe to statins might lead to a small reduction in the risk of myocardial infarction, but the certainty of the evidence is low.
- The addition of ezetimibe to statins might lead to a small reduction in the risk of stroke, but the certainty of the evidence is low.
- The addition of ezetimibe to statins does not increase serious adverse events. The certainty of the evidence is high.

Ezetimibe addition to statin treatment				
Patients	Moderate or high cardiovascular risk, known coronary artery disease and/or hypercholesterolemia			
Intervention	Ezetimibe + statins			
Comparison	Placebo + statins (in the same dose)			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT ezetimibe	**WITH Ezetimibe**		
	Difference: patients per 1000			
Overall mortality	160 per 1000	160 per 1000	RR 1.00 (0.95 to 1.06)	⨁⨁⨁◯[1] Moderate
	Difference: no difference (Margin of error: 10 less to 6 more)			
Acute myocardial infarction	179 per 1000	167 per 1000	RR 0.93 (0.88 to 0.97)	⨁⨁◯◯[1,2] Low
	Difference: 12 less per 1000 (Margin of error: 5 to 21 less)			
Stroke	41 per 1000	34 per 1000	RR 0.84 (0.69 to 1.02)	⨁⨁◯◯[1,2] Low
	Difference 7 less per 1000 (Margin of error: 13 less to 1 more)			
Serious adverse events	315 per 1000	318 per 1000	RR 1.01 (0.97 to 1.04)	⨁⨁⨁⨁ High
	Difference: 3 more per 1000 (Margin of error: 9 less to 13 more)			

RR= Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

* The risk **WITHOUT ezetimibe** is based on the risk in the control group of the trials. The risk **WITH ezetimibe** (and its margin of error) is calculated from relative effect (and its margin of error).

[1] The certainty of the evidence was reduced because of risk of bias.
[2] The certainty of evidence was reduced because of lack of precision. The confidence interval includes the possibility that there is no clinically relevant effect.

About the certainty of the evidence (GRADE)*

⨁⨁⨁⨁
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⨁⨁⨁◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⨁⨁◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⨁◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- Most data comes from trials with patients with LDL levels ≤ 140 mg/dl, with chronic kidney disease or with recent acute coronary syndrome.
- It is reasonable to expect a similar effect in patients with a lower cardiovascular risk, however, would ezetimibe effect be true, the benefits on these patients would be even less, due to their lower baseline risk.

About the outcomes included in this summary

- The outcomes included are those most relevant for decision making.
- It is important to note the LDL cholesterol level achieved is not a patient reported outcome, but a surrogate outcome. These results must be used only when there is no information on more important outcomes available.
- Other outcome commonly used by the main guidelines is revascularization. This was not included because of its minor relative importance when being compared to the others. However, no effect on this outcome was observed (RR 0.96; 95% CI 0.90 to 1.01; high certainty of the evidence).

Balance between benefits and risks, and certainty of the evidence

- This treatment probably has no effect on mortality, and it might have a small effect on cardiovascular events, but this is based on low-certainty evidence. On the other hand, it has no serious adverse effects.

What would patients and their doctors think about this intervention

- Given this intervention has a small and uncertain benefit, but without any adverse effects, and at a relatively high cost, there will probably be a high degree of variability in the decisions made by patients and their physicians, depending on how they value these factors.

Resource considerations

- Considering ezetimibe is a high cost drug and has a small magnitude of benefit, it is unlikely that it is a cost effective alternative, although a formal evaluation on this matter would be desirable on settings where its use is being considered.

Differences between this summary and other sources

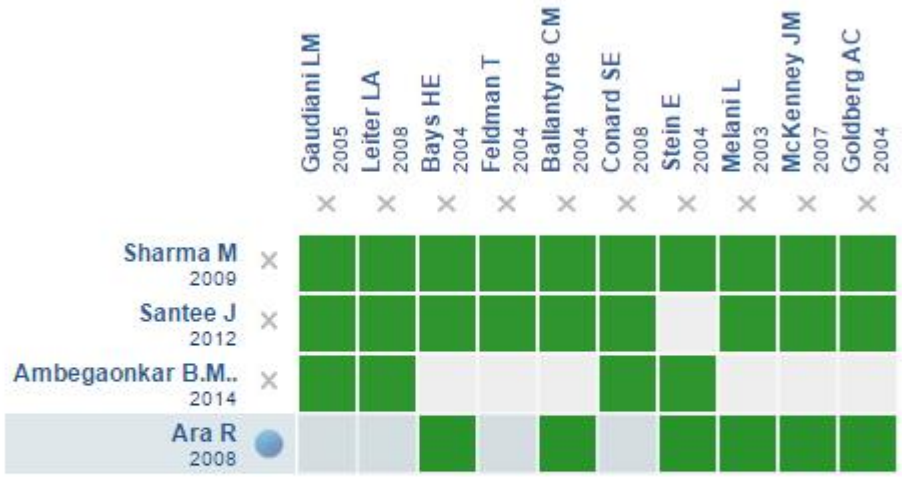
- This summary partially agrees with the different systematic reviews, who differ between themselves. For example, one of the reviews concludes that even with a small effect, because of the importance of the outcomes analyzed, these must be important to patients [3], meanwhile others suggest there is no relevant benefit in comparison to statins as a monotherapy [5].
- The 2015 European Society of Cardiology guidelines recommend the use of ezetimibe in patients with LDL levels above ≥70mg/dl despite maximally tolerated dose of statin therapy [80]. This recommendation does not differ from this summary, as it recommends ezetimibe exclusively if statin treatment fails, acknowledging the small reduction in cardiovascular events and the scant difference in mortality.

Could this evidence change in the future?

- The probability of future evidence changing the conclusions of this summary for some of the outcomes that are critical for decision making is high, because of the level of uncertainty.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version**: Ezetimibe for hypercholesterolaemia

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

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