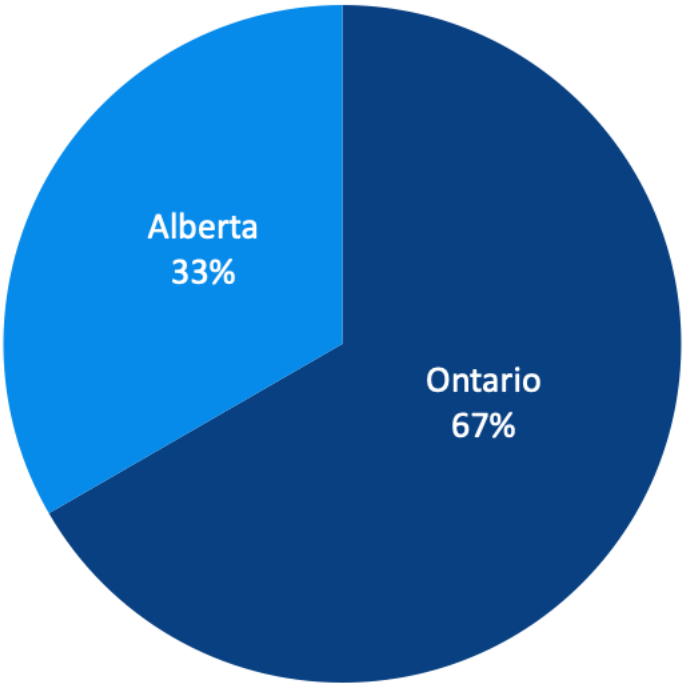
Peer review of PEER Umbrella systematic review of systematic reviews: lipid-lowering therapies for cardiovascular disease prevention and management in primary care

Response Statistics

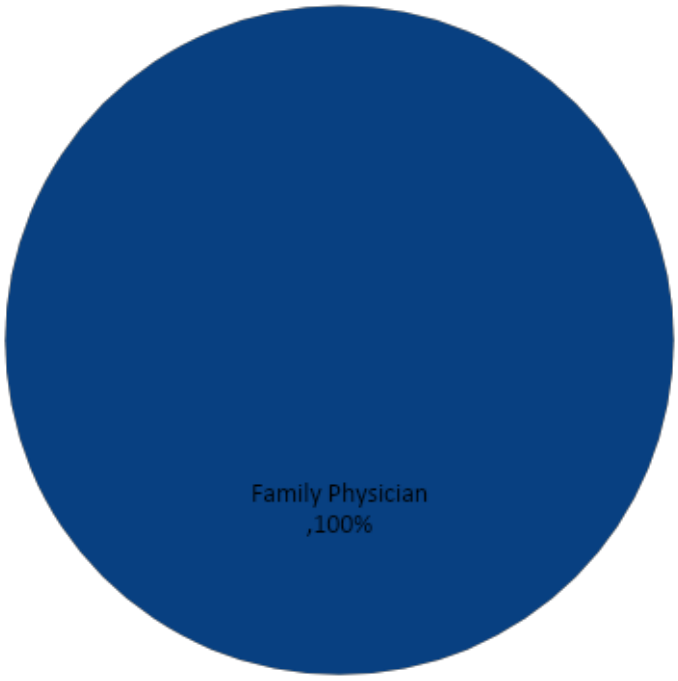
Completed reviews: 6 (note: 1 did not complete survey but submitted word document with comments)

1. Province



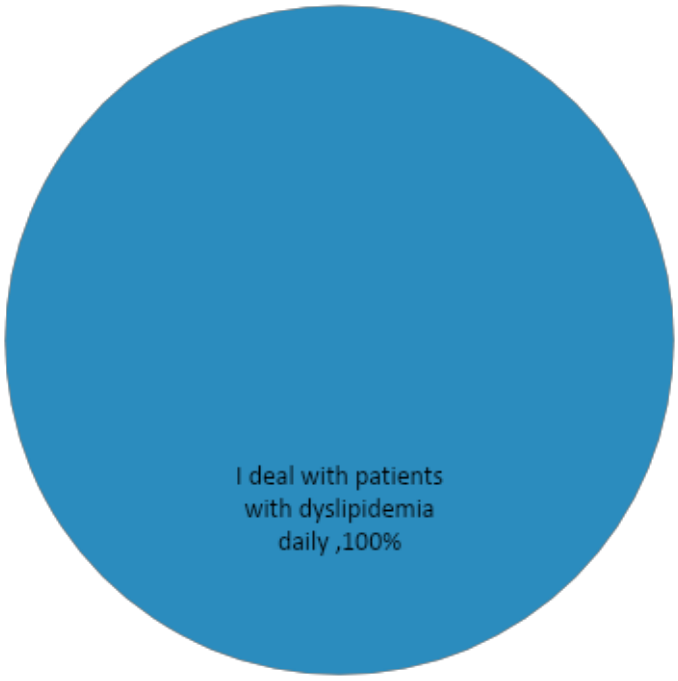
Province	Count	Percent
Alberta	2	33%
Ontario	4	67%
Total	6	100%

2. Occupation



Value	Percent	Count
Family physician	100%	6
Total	100%	6

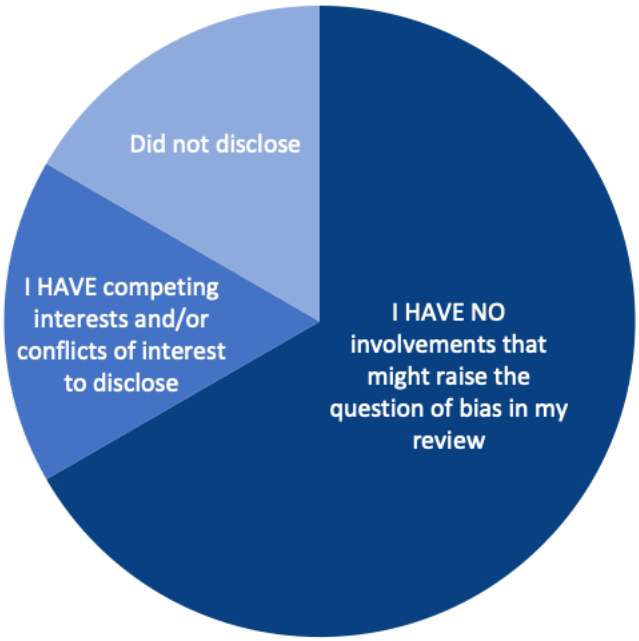
3. My level of familiarity with treating dyslipidemia can best be described as:



Value	Percent	Count
I deal with patients with dyslipidemia daily	100%	5
Total	100%	5

3. Level of familiarity with treating dyslipidemia

4. Competing interests or conflict of interest declaration



Value	Percent	Count
I HAVE NO involvements that might raise the question of bias in my review	66%	4
I HAVE competing interests and/or conflicts of interest to disclose	17%	1
Did not disclose	17%	1
Total	100%	6

5. Enter conflict of interest details here:

ID	Response
1	I serve as the Chief Medical Officer at Currant Care Inc., which has a patent on a health technology wearable along with other health care technologies. No relation to the contents of the review but may be classified as medical device so placing it here for COI disclosure.

6. Overall strengths of the systematic review:

ID	Response
1	Quite comprehensive and helpful for most practicing physicians.
2	A lot of data and results are clear and easy to interpret in general.
3	This is a review of systematic reviews assessed from a primary care perspective. The study was registered on PROSPERO. The team consists of mostly family physicians which is great.
4	Fantastic work - what a comprehensive, thoughtful look at an important topic! Congratulations to the team for all the work that went into this. I hope my comments are helpful as you revise this document.
5	This being so large and all-encompassing gives us a sense nothing could have been missed. It has a high sensitivity (i.e., there is assurance that if no evidence was found, there truly is no evidence). It has important messages for primary care. It was conducted in thorough and up to date methods. The approach is well-described and fairly easy to understand. The sub-analyses are really useful, the tables are clear and simple and easy to understand. We don't think your limited data on primary prevention is a study limitation (which is where you put it): it is a study strength shedding important light on a scientific limitation. This finding is really important to primary care.

7. Overall weaknesses of the systematic review

ID	Response	Comments
1	Lack of primary prevention data will limit usefulness outside of the people who are already seeing a cardiologist and this did not address the difficult relationship between primary care physicians and specialists, given the broad scope of the systematic review a comment would be helpful to empower family physicians.	Guideline will address these concerns.
2	I would add a bit more to the conclusion regarding data found for primary vs secondary prevention so that is clearer to the reader.	Drugs with evidence tend to have a similar relative effect in primary and in secondary prevention; however, we do not have data to confirm that because of i) the limited available evidence specific to primary prevention, and ii) our methodology, which sometimes prevented us from using certain subgroup analyses (because they were not available in the systematic reviews).
3	*Major comments* This 'review of reviews' generates a median relative risk estimate which is non-weighted. This generates a statistic which overrepresents RCTs done earlier in the study period and does not consider the number of participants in each RCT. This statistic is certainly inferior to a direct meta-analysis of the available RCT's with a resulting aggregate relative risk calculation. Bringing to attention of primary care providers the most recent aggregate effectiveness statistic from meta-analyses on each intervention is certainly helpful. Creating an aggregate statistic inferior to this I do not feel has anything to offer. I do not feel that this manuscript brings a new perspective to the body of literature. I suggest that the authors focus on a review of the most up to date literature and refrain from producing an aggregate statistic. *Minor comments* The authors only selected meta-analyses to include over the past 5 years. It is unclear why this time period was chosen. The authors refer to an online calculator as opposed to including the formula in the manuscript. I would suggest including the formula instead. It is unclear to me what this manuscript has to offer over and above just highlighting the most recent meta-analyses on each intervention.	We agree with the comments about the limitations of a systematic review of systematic reviews. Limiting our search to the last 5 years probably protected us to some extent from giving too much weight to older trials. Using median and IQR gives an overall idea of the results and their consistency in the systematic reviews. More information added in the discussion section. Formula for converting ORs to RRs added.
4	For me, I think would help most is using standard terminology around effectiveness throughout. Each section ends with a 'discussion' about the results, and there are different phrases and words (e.g., 'net clinical benefit') used to describe the results. If you could land on a set of	Changes made to be more consistent in the discussion sections.

ID	Response	Comments
	common phrases, that would really help compare the sections and then you can use those phrases at the end.	
5	This gives the impression that huge amounts of data (individuals, RCTs, specific drugs, comparisons with placebo vs with another active agent, period of follow-up, and positive and negative outcomes) are embedded within. The truth is mainly in the appendices. It is hard to comprehend how putting so many different lengths of follow-up, types of drugs (how many different statins are actually included?), types of outcome measures, and rigor of RCT and SR methods, might have an effect on your umbrella results. There is certainly power in the final conclusions you can make, but can you help us to understand what has been lost about "the particular" in this? What is being glossed over? What cannot be used for shared decision-making (like translating an RR of 0.9 from this to care)?	Guideline will translate data into something more useful.
	The distinction of treating for primary vs secondary prevention in clinically important, pleased it has a table, but this should make its way all the way to the abstract. Even a general statement of difference in outcomes would be useful.	Focused on primary and overall (not secondary) as that was the focus of our SR. Precisions added when describing primary cardiovascular prevention.
	Under data synthesis strategy not specified what statistics were used to define significance. Exclusion criteria were reiterated twice in lines 82 - 87 and felt unclear. Data synthesis strategy description was somewhat redundant when describing how outcomes were reported depending on numbers of systematic reviews for each intervention.	Precisions added and redundancy removed.
	Line 503 - half sentence about omega fatty acids, then full sentence later in conclusion (missing part of a sentence?)	Fixed.
	Cannot find a clear rule for how many significant SRs were required to determine overall significance of the group of SRs. E.g., in Table 1 it appears that overall analysis determined to be significant if half were (Wouldn't it be reasonable to conclude with 4/8 that there remains significant doubt?)	Precisions added in the method section and under tables when indicated.
	I do not have appendix 7 re: GRADE but a bit of summary at least in the text would help us to know whether GRADE and AMSTAR was reassuring or non-reassuring.	See Appendix 2 and 7.
	Not clear how a MACE that included CV death, vs one that does not, is being reported in tables or in text. If some SRs include CV death, then are those not included in the analysis of CV death by itself?	MACE includes CV mortality or all-cause mortality, in addition to various outcomes. We focused on three-point MACE when possible. When not available and different MACE definitions were used, we considered downgrading it for indirectness in GRADE.

7. Overall weaknesses of the systematic review

ID	Response	Comments
	Can you help us to understand what the effect is on the end results if some RCTs are included in more than one SR (or maybe in all of the SRs)? What does it mean to have this repeated over and over?	There is a risk of overrepresentation of some RCTs. Information about that risk was added.
6	I have read this systematic review of systematic reviews. It is satisfactory in a mechanistic way in that you effectively describe and report on what they contain. However, I have concerns that the very nature of this process leaves doubts.	
	1. The nature of review of reviews means that the original data of the trials are redigested by different groups. There is no selection on the quality of the systematic reviews, and which ones have excluded particular trials for marginal quality. Thus, presumably the highest quality trials have been incorporated in all reviews and perhaps dominate the results more than those low-quality trials that were only included in a few. It would be better to have excluded poor quality reviews.	We agree with the comment. It is a limitation of SR of SRs. Information on this limitation was added in the discussion section.
	2. It is valuable to identify the target groups: primary prevention, secondary prevention, specific sub-groups since family physicians see all of these and must respond to their needs and discuss the recommendations cardiologists make. You state statins have similar effects for primary and secondary prevention: presumably relative risk reductions. It would help to phrase these also as absolute risks.	Guideline will address this comment as it will include a calculator to estimate the absolute cardiovascular risk of an individual and the absolute effect of each intervention for this particular individual.
	3. Nearly all the trials are sponsored by drug companies. They have a vested interest in NOT measuring harms. Sometimes the design is such that those who get side effects in an initial period are not eligible for long-term participation. Besides while lipid trials tend to be long-term, they are still limited in duration, compared to the lifelong treatments we routinely use. So, the data on side effects and withdrawals is likely to represent underestimates of the true proportions in normal practice.	Information was added in the limitations section.
	4. Are there any non-industry funded trials? If so, do they show any different results?	Likely almost no non-industry funded trials and no specific analysis were made to see if the source of funding had any influence on the results.
	5. The original data for the lipid trials is held by a repository at U of Oxford under the following policy: "Individual patient data from each contributing trial have been provided to the CTT Collaboration on the understanding that they would be used only for the purpose of the CTT meta-analyses and would not be released to others. Requests for such data should be made directly to the data custodians of each trial.	This situation was not addressed in our SR.

7. Overall weaknesses of the systematic review

ID	Response	Comments
	CTT Collaborators and other bona fide researchers are welcome, however, to suggest analyses in writing to the Secretariat. Where proposals are thought to be feasible and of potential interest, the Secretariat will conduct such analyses or, where appropriate, seek the views of the Collaboration on whether the analyses should be performed. If so, then the proposing scientist(s) will be invited to collaborate with the Secretariat in conducting and interpreting the analyses, and will be members of the Writing Committee in any papers describing the results of analyses." As a consequence, there is residual doubt about the true effects: what are they hiding?	

7. Overall weaknesses of the systematic review

8. Feedback or comments on the abstract or introduction

ID	Response	Comments
4	Data only from 2017-2022 - unclear to me as a reader why you limited to that.	Inclusion was limited to the last 5 years to limit the amount of data and the overrepresentation of older trials.
	Suggest defining MACE in the abstract because you are describing a difference in the effectiveness of interventions for MACE vs. MI/death and I think this is a bit confusing without that being explicit.	Defined in the method section.
	Line 39: don't know what EPA supplements refers to (define this abbreviation earlier on)	Definition added.
	It is now obvious to me at line 45 that you really need to tell the reader what is included in MACE for them to be able to understand the difference between this and other outcomes.	Defined in the method section.
	Line 53: worth saying "medications"? because you are focused on medications, not 'interventions' more generally.	Changed.
	In general, I think the introduction needs a bit more detail (depends of course on where you are submitting it for publication) - some more about the epidemiology of dyslipidemia, the relationship between it and heart disease.	No addition made as we are limited in the number of words we can use.
5	Abstract mentions that the study looked at benefits and harms of various lipid lowering agents but only outlines benefits in results quoted in the abstract Would be good to have even a small distinction here about primary vs secondary prevention.	Limited by the length of the abstract.
	For clarity, may have been better to list the agents in the same order throughout the abstract - intro arranges them alphabetically, but results go from strongest evidence base to least evidence base.	Order changed.
	Definitely a very brief intro here. Since we don't often see umbrella reviews, some comment about why this is helpful and what the pros and cons are could be useful.	Some information added in the discussion section.
	Also maybe anything about how we in primary care are experiencing the abundance of literature on lipid treatment, and that it is generally filtered through specialist lens which may not always be helpful to us.	The guideline will address some of these comments.

9. Feedback or comments on the methods

ID	Response	Comments
4	I'm still not clear from background and methods why you chose the dates you did - I think there is probably a simple explanation but it's missing right now.	Addressed above and information added in the SR.
	Line 78: why are these 'special populations of interest'? (I know it's because they have increased CVD risk but I think this needs to be specified)	Information added.
	Line 91: was a librarian included in the review?	A librarian was not included in the review as it was an update of a previously published systematic review.
	Line 102: you really need to sort out the outcomes, I'm finding this really confusing. I think the way to go about this is to say 'our primary outcome was MACE, then our secondary outcomes were y, z. MACE was usually defined as x. However, this term is used variably across studies, referring to some combination of the following outcomes: a, b, c. We therefore decided to report this outcome in the following way…' (and then describe how you handled it)	Changes made to the relevant section.
	Line 104: tell the reader what are the adverse events you included.	Specific adverse events were not pre-planned in our protocol. We collected what we found in the systematic reviews.
	Overall, I think the methods needs a bit more detail to prepare the reader for the results.	
	Line 112: give authors' initials who did this – also it is not quite clear what you mean by "titles and abstracts", suggest being a bit more descriptive about this process.	Our group included too many people to add each one's initials. Titles and abstract screening is part of the Methodological Expectations of Cochrane Intervention Reviews (MECIR) criteria which are cited in this section so we do note think it's needed to add something here.
	Line 132: sorry for being this person, but it's "data were" not "data is"…!	Changed.
	Line 137: define primary and secondary prevention subgroups.	Precisions added.

10. Feedback or comments on the overall results

ID	Response	Comments
4	Line 151: note that AMSTAR is not supposed to be used to 'generate a score' https://amstar.ca/Amstar-2.php - you should report confidence in the review instead – depends how knowledgeable of a reviewer you get when you submit, but the way it is presented now might be a problem for a systematic review methodologist	Changed.
	Line 158: 'primary efficacy results' refers to your primary outcome? If so, just say 'full details of the primary outcome are in table 1' because it's unclear what 'primary efficacy results' refers to – I don't think this term was defined earlier?	Changed.

11. Feedback or comments on statins

ID	Response	Comments
1	Very helpful update regarding liver/renal/diabetes. Some clarity regarding previously reported progression from pre-diabetes to diabetes.	10% increase in incidence of DM. 2015 guideline states: 1 in 250 for low potency and 1 in 125 for high potency statins. Guideline will include numbers.
2	Could the data be further broken down into low vs high dose statins? Or, is the summary basically that just being on a statin at all is beneficial?	We did not break down into low vs high our SR of SRs. The guideline will address statin intensity.
4	Line 179 onwards: this comes out of nowhere for me, because you haven't told me as a reader in 'methods', which harms you included. I think you should be much more explicit in methods about the outcomes and harms you are including in this section.	Changed.
	I don't understand '2 SRs statistically significant' – does it add any information to include this? For me it would be more readable to only report the RR and IQR throughout – we're reading this for the results of your pooling of data, not to see how many included SRs were 'statistically significant'.	Number of statistically significant results is important to assess the overall result. There could be an outcome with X SRs all reporting a positive but non-statistically significant result, which should be interpreted with caution.
5	30 SRs. How many RCTs? How many different drugs? I.e., are the 30 SRs all looking at exactly the same individuals? Or not?	Information on each SR is available in the appendix. # RCTs already included.
	The distinction between amount of evidence showing benefit on all-cause mortality in either primary or secondary prevention is incredibly confusing. We see in statin results efficacy section that the aggregate of primary and secondary studies is on balance showing benefit (6/8 SR) and this agrees with Table 1. We see in Table 2 that only half of the primary prevention SRs show benefit for all-cause mortality (which by the way somehow gets the colour green, how was that decided?). We are not sure if the 8 SR in table 1 are the same as the 8 SR in Table 2 (must be some are same and some are different).	Information added in the method section.
	And finally, in "discussion" of statins, we see some brand-new numbers not found anywhere else saying 3 of 10 SR are significant for all-cause mortality. Where did that come from?	Secondary prevention table available in the appendix. Information added in the discussion section for statins.
	Conclusion by authors was that benefits outweigh risks, but that is really a shared decision-making statement appropriate for the guideline and not the SR we feel. (I still am not going to take a statin!)	Guideline will address.

12. Feedback or comments on ezetimibe

ID	Response	Comments
2	I would suggest emphasizing more that the data showing positives was from ezetimibe & statin, but no significant benefit from ezetimibe alone.	Reported in the discussion section of ezetimibe.
4	Line 229: unless I'm missing something, you should decide whether a fixed-effects or random-effects approach is most appropriate here and go with that (I would suggest random-effects). It's generally not justifiable to 'do both' and then report the difference, unless there is a specific reason.	We did SR of SRs not our own SR. We used the analysis found in the SRs.
	Line 251: why not include these in the review, instead of only mentioning them in the discussion?	This was according to our methodology.

13. Feedback or comments on PCSK9 inhibitors

ID	Response	Comments
4	Line 285: the fact you are describing 'injection site reactions' needs introduction earlier on – see my previous suggestions about being more explicit in 'methods' about outcomes.	Addressed previously.
	Line 291: I would suspect that most of the RCTs included in the SRs in your review are 'industry-funded', yet you only mention it here. I think if you don't have these data for all of the included RCTs, I would not raise this here – you could be more general about it in the overall discussion, but its presentation here suggests that you were focusing on this.	Changed.
5	Good that noted limitations (industry funded trials looking at 2ary prevention with max dose statin) → may not be valid aka answering the question as whether helpful as an individual agent.	
	Many trials focused on familial hypercholesterolemia *BUT this was supposed to be an exclusion criteria? Should clarify if was excluded.	SRs excluded only if focused on familial hypercholesterolemia.

14. Feedback or comments on fibrates

ID	Response	Comments
2	I like how the abstract emphasized no benefit when added to a statin.	

15. Feedback or comments on bile acid sequestrants

ID	Response	Comments
4	Line 356: tell us a bit more about what harms you were looking for, in this population.	We used what was reported in the papers and were not looking for specific AEs.

16. Feedback or comments on niacin

ID	Response	Comments
2	In the discussion section I would add a line regarding the high adverse effect rate from the data you reported.	Added.

17. Feedback or comments on omega-3 supplements

ID	Response	Comments
1	Hardest-to-read section given the lack of clarity about effects.	
4	Line 442: this has made me realize that every 'discussion' section ends in a slightly different way. Could you come up with some standard terminology (e.g., here you use 'net clinical benefit', other sections say it slightly differently) so that as the reader moves through, they can clearly understand your interpretation of the results?	Changed.

18. Overall feedback or comments on conclusion

ID	Response	Comments
1	The conclusion may benefit from some form of the line from the discussion - "Our review did not find statistically significant primary prevention benefits for BAS, ezetimibe, niacin, omega-3s, EPA ethyl ester or PCSK9 inhibitor". This will arm physicians with a clear answer when asked about this. Especially in patients with whom the ??	Added.
4	Line 482 and throughout: you often say "systematics reviews" (needs a quick ctrl f and replace!)	Fixed.
	Can you give a summary of how many RCTs were included within all the reviews, and how many of those were for primary prevention? This is an important point but right now a bit too qualitatively described for me to wrap my head around.	Included in write up and appendix table.
	Line 497: you'll need a reference or some #s to back this up, otherwise I would suggest taking it out – reviewers will balk at this without proof (although I'm sure it's true, as it is for most drug trials… drugs are expensive and only drug companies are willing to invest in this sort of thing, for the most part).	Reference added.
	Line 502: suggest re-writing this, there are some typos and it's a bit confusing – goes back to the point about using standard terminology throughout around benefit and harm.	Changed.

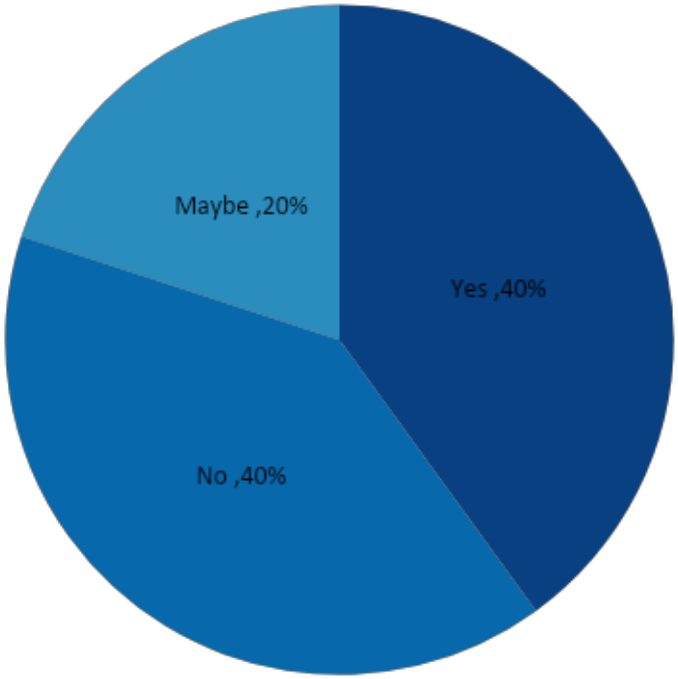
19. Feedback or comments on tables and figures

ID	Response	Comments
2	I like how the significant boxes are highlighted - helps the reader who is quickly scanning the document.	
5	Generally excellent amount of detail and easy to read.	
6	The tables of effects and side effects are difficult to interpret: a column of absolute risks would be helpful.	Not appropriate for our review. Guideline will address.
	Side effects are best measured in long term cohort studies, with reports from adverse drug event registries, not trials.	
	Readers would like to know is there an upper age limit for effectiveness of these drugs: at least a comment on their value by age would be useful, if that is possible.	Guideline will address.

20. Other comments, suggestions, or edits?

ID	Response	Comments
4	Thanks for the opportunity to review this.	

21. Would you be interested in being a peer reviewer for the PEER Lipid Guideline once completed in May or June 2023?



Value	Count	Percent
Yes	2	40%
No	2	40%
Maybe	1	10%
Total	5	100%

21. PEER 2023 Lipid Guideline peer review interest

22. Acknowledgements

PEER would like to thank all the people who contributed to the peer review for this systematic review of systematic reviews. The following are the names of the reviewers who gave permission for their names to be published.

Name	Profession	Location
Jim Dickinson	Family physician	Alberta
Geneil Dufresne	Family physician	Alberta
Dale Guenter	Family physician	Ontario
Ruben Hummelen	Family physician	Ontario
Braden O'Neill	Family physician	Ontario
Jobin Varughese	Family physician	Ontario