PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Strategies for Enhancing the Initiation of Cholesterol Lowering Medication Among Patients at High Cardiovascular Disease Risk: A Qualitative Descriptive Exploration of Patient and General Practitioners' Perspectives on a Facilitated Relay Intervention in Alberta, Canada
AUTHORS	Campbell, David; Lee, Rachelle; McBrien, Kerry; Anderson, Todd; Quan, Hude; Leung, Alexander; Chen, Guanmin; Lu, Mingshan; Naugler, Christopher; Butalia, Sonia

VERSION 1 – REVIEW

REVIEWER	hayden B Bosworth 2002
REVIEW RETURNED	12-Apr-2020

GENERAL COMMENTS	Strategies for Enhancing Cholesterol Lowering Medication Use Among Patients at High Cardiovascular Disease Risk: Patient and General Practitioners' Perspectives on a Facilitated Relay Intervention 14 patients at high risk – high risk is not operationalized. Findings are preliminary and confirmatory. It is not clear what the study adds to the literature Introduction. Lines 62-64 – mention of other conditions could be looked to as models for closing the gap with improving adherence to CVD related treatment; however, the three references are somewhat out dated and more recent data would suggest that there continues to be a significant gap. While facilitated relay is a quality improvement strategy whereby information about individual patients is sent directly to healthcare providers through a means other than the usual clinical care, this strategy generally only works in a capitated system not focused on fee for service given care may not be reimbursed. Related, the time between testing and communicating back to the patient is important to consider. There seems to be a disconnect between what is reported in the abstract and the overall goal of the paper as described in the introduction. The abstract refers to 'examining the perspectives of patients and general practitioners (GPs) regarding interventions to increase cholesterol lowering medication (or statin) use', yet the focus of the paper appears to be evaluating a specific intervention focused on lab-based facilitated relay intervention.

	Results It is somewhat surprising that the physicians did not appear to comment on such issues as cost, reimbursement, time to follow up on cholesterol levels, whose clinical responsibility it is to treat cholesterol, competing needs/priorities – issues that have been indicated previously as factors that impact physicians ability to treat cholesterol and CVD risk in general. With two focus groups, there are concerns that saturation may not have been reached among the patient groups. In general, the paper focuses on reviewing a potential intervention and the larger contribution to the literature on how to improve cholesterol treatment was not clear.

REVIEWER	Shannon Armstrong The Medicines Company, USA
REVIEW RETURNED	11-May-2020

GENERAL COMMENTS	This paper addresses the issue of statin underuse in a high risk population, a situation which leads to unacceptable excess mortality. As such it is addressing an important healthcare issue. The authors use a qualitative method to elicit feedback from key stakeholders- GPs and patients - on potential interventions and specifically an intervention they have devised based on facilitated relay. This manuscript could benefit from a reorganization as details of the studies methods appear spread across introduction, methods and results. A few suggestions to strengthen this manuscript: the introduction sorely lack any justification for the proposed facilitated relay intervention. Please include a paragraph on what is known about statin underuse. Both the USAGE survey and REGARDS study provide some insight to these questions. You state that facilitated relay has been shown to improve CV risk factors, and some exploration of the issues will help to establish a rationale for facilitated relay intervention. The introduction should also convey more urgency around this issue of statin underuse. As it is written, it does not indicate that this issue is deserving of any time and attention. You might also provide a brief description of the guideline recommendation for this group, since the conflicting guidelines come up as a topic of concern for GPs in your results. Methods: I have some concerns about your recruitment methods. I understand the difficulty in recruiting participants. You state that GPs were sampled using a snowball method and then purposively to get a balance of age and gender. Looking at your descriptive statistics, GPs tend to skew heavily younger and female and urban. Perhaps this is intentional and reflects the actual demographics of GPs in your area? Also, how do these GPs compare to ones who tend to underprescribe statins? Your discussion guide indicates some of these questions were raised- can they be incorporated into the descriptive statistics table? For example, how often are you testing cholesterol? Your intervention relies on reporting the results of a cholesterol tests - if your GPs aren't ordering the tests, your intervention may have a problem before it gets started. With regards to patient recruiting, you say you recruit patients "who may potentially" be recipients. Why? What additional screening criteria did you apply in securing your patient panel? It is not clear that any effort was made to recruit patients who fit the "high risk" criteria, except advertising in areas of the healthcenter which treat

	such patients. Details on screening would be useful to include. Under data collection, you state that interview guides were developed based on literature review. Relevant citations here of any papers useful in shaping your thinking should be included. More info should be included in both the paper and appendix on the intervention itself. The physician letter is included, the patient communication should also be included. Consider a schematic of the intervention. For example, patient receive cholesterol test- what result triggers the intervention? how long before a communication is sent? when does the patient receive? when does the GP receive? As the focus of this paper is the facilitated relay intervention, this should be clearly described. Data analysis methods are appropriate and well described. Results: More details on recruitment should be included. X# were contacted, X# agreed to participate, x# were schedule for interviews, saturation was reached at 17 interviewing. Similarly, more details on patient recruitment. In your Table 1b, "none/high cholesterol" should be split as these are very different. If 23% of your patient sample has no clinical reason to be included, that would limit the relevance of the results of patient focus groups. Also, for statin use, consider IDing what # had been prescribed but stopped or never started, as these would be the group most likely to be targeted by an intervention. DISCUSSION: There is a large body of literature on interventions targeted to physicians/patients or both on statin use. Only a very few are mentioned here. Jenstrom-Karlsson et al, have written a nice review of patient centered interventions which might be useful. As have Van Driel at el for the Cochrane Collaboration. An understand of how this intervention compares to other interventions that have been tried will be important.

REVIEWER	Jesper Bo Nielsen University of Southern Denmark, Denmark
REVIEW RETURNED	28-Aug-2020

GENERAL COMMENTS	BMJ Open – Strategies for enhancing cholesterol lowering medication use among . . . . General remarks: Reading the interview guides and reading the citations presents to me a different story than the one presented as the objective by the authors. The authors have an objective related to interventions to increase the use of medication. However, what appears more obvious (to me) as the main theme in the interview guide and the citations from the GPs is a better support in deciding who to treat. The GPs are asking for support to do rational pharmacotherapy – and this is not the same as increasing the use of medications. I think the authors may not have framed their story correctly in their title and objectives. The authors which to increase medication with statins. However, the benefit of statins for primary prevention and for elderly persons with limited remaining life expectancy have been questioned (e.g. Kristensen et al. BMJ Open 2015 plus papers on deprescribing). The present study appears to focus on the fraction of patients in need of secondary prevention through use of statins. This needs to be clearer early in the manuscript and reflected also in discussion and conclusion. The intervention tested in the present manuscript is one among several ways to try to affect adherence. A recent publication in BMJ

	(Ivers et al. BMJ 2020) tested an intervention through a pragmatic randomized controlled trial with some similarity to the present intervention, and also in a Canadian setting. The authors should have a look at that paper and include reflections on how the findings from Ivers et al. relate to their own. The authors discuss how to inform and discuss use of statins with their patients. I would like to see reflections on how they would suggest describing the quantitative benefit of statin treatment to patients as well as GPs. The inclusion of patient in the decision process is often seen as a way to increase adherence to clinical decisions (shared decision making) How do the authors see their observations in this context? I would like to see each quotation in the text identified (e.g. by a separate number for each informant). Specifics: Page 3, line 42: The authors present the recruitment of patients from a group with specific interests as a limitation. The authors should expand a little on which implication they see from this limitation. Page 3, line 43: Which context/setting-specific characteristics made you write this statement? Page 3, line 70: Please clarify what is meant by 'our setting' Page 7, line 24-28: Do the authors find the evidence for use of statins equally good for all four groups at all ages (e.g. diabetes only)? Page 7, line 199-202: this is interesting reading and has nothing to do with strategies to enhance use of statins but basically having support in offering statins to those for which evidence of effect exists. Page 8, table title: the title states 'General suggestions by GPs and patients to increase statin use', but the citations have very little to do with increasing the use. It about a better and evidence-based way of offering treatment.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

14 patients at high risk – high risk is not operationalized.

Thank you for this excellent point and now high risk has been operationalized.

> We recruited patients who may potentially be recipients of the intervention. Specifically, we were interested in recruiting those at high risk of cardiovascular disease, or with a prior history of vascular disease (myocardial infarction, stroke or peripheral vascular disease), diabetes, or chronic kidney disease.

Findings are preliminary and confirmatory. It is not clear what the study adds to the literature

Thank you for your comment. Previous work has shown that the initiation of cholesterol lowering therapy is low in whom they are indicated. We feel that clinicians, researchers and healthcare systems who are interested in employing new strategies, including facilitated relay, will find our results to be important to planning their strategies and interventions. For an intervention to have the potential to maximally improve outcomes, it was important to have the input of key stakeholders prior to the

application of any intervention. This allows for the development of more comprehensive programs and strategies, rather than one that relies on prescriber feedback alone. In contrast to other studies, we have purposely used qualitative methods which allows us to explore in detail different strategies as well as included both patients and prescribers, enhancing stakeholder input. We feel that researchers and healthcare systems who are interested in employing facilitated relay will find our results to be important to planning their intervention.

Introduction.
Lines 62-64 – mention of other conditions could be looked to as models for closing the gap with improving adherence to CVD related treatment; however, the three references are somewhat out dated and more recent data would suggest that there continues to be a significant gap.

Thank you for raising this important point, I have included it in the introduction, including some more recent references:

> Despite the establishment and promotion of facilitated relay and other quality improvement strategies, there remain significant treatment gaps in hypertension (15) and other chronic conditions (16). Furthermore, while facilitated relay has been shown to be effective in improving a number of cardiovascular risk factors (12, 17), it remains among the least commonly used quality improvement strategies (18) and has not been explored in the management of dyslipidemia.

While facilitated relay is a quality improvement strategy whereby information about individual patients is sent directly to healthcare providers through a means other than the usual clinical care, this strategy generally only works in a capitated system not focused on fee for service given care may not be reimbursed. Related, the time between testing and communicating back to the patient is important to consider.

Thank you for this comment. In our literature search, we found that the utility of this strategy has been demonstrated in a wide variety of healthcare systems with varied payment models: https://pubmed.ncbi.nlm.nih.gov/26330299/

Certainly, alternative models of provider payments is a separate quality improvement strategy and may incentivize providers to provide guideline concordant care, as I understand, these are complimentary, and the success of facilitated relay does not depend on co-intervention of payment changes.

There seems to be a disconnect between what is reported in the abstract and the overall goal of the paper as described in the introduction. The abstract refers to 'examining the perspectives of patients and general practitioners (GPs) regarding interventions to increase cholesterol lowering medication (or statin) use', yet the focus of the paper appears to be evaluating a specific intervention focused on lab-based facilitated relay intervention.

Thank you for this comment. In the abstract (i.e. objective, main outcomes measures, results, conclusions) and the methods section of the paper (i.e. data collection section, interview guides) we aimed to examine interventions in general, as well our specific proposed facilitated relay intervention. For example, in our data collection section we state:

> Interview and focus group guides were designed so that they initially asked study participants what they thought would be effective strategies or interventions to improve statin use (i.e.

> prescribing, patient use and adherence). After they had given their unprompted views, participants were then given a brief explanation of facilitated relay, the proposed intervention, and shown a copy of the proposed intervention letter (Appendix C) and asked for their feedback.

This is also how the results section is structured, where the first section is *General Suggestions for Potential Interventions,* which is followed by *Feedback on the Proposed Facilitated Relay Intervention.* We also feel that our re-organization of our methods, a comment provided by another reviewer (#2), improves the clarity of this paper.

Results

It is somewhat surprising that the physicians did not appear to comment on such issues as cost, reimbursement, time to follow up on cholesterol levels, whose clinical responsibility it is to treat cholesterol, competing needs/priorities – issues that have been indicated previously as factors that impact physicians ability to treat cholesterol and CVD risk in general.

Thank you for this comment. These issues, general barriers to the management of cholesterol and CVD risk factors, were all discussed in the interviews. However, they are not presented in this manuscript, as the focus of this manuscript was specifically the responses to the questions about interventions that could address some of these barriers.

The data from the generic barriers/facilitators to statin prescription questions have been reported separately: https://www.sciencedirect.com/science/article/pii/S2589790X20300962 , in a manuscript that is cited several times in the present manuscript.

We have made the decision not to re-report these findings in this manuscript to allow us the space to adequately describe the results particularly pertinent to interventions to address these issues.

With two focus groups, there are concerns that saturation may not have been reached among the patient groups.

Thank you and the reviewer is absolutely correct, we had pre-defined that we would conduct two focus groups among patients, and it is quite possible that saturation was not achieved. We have added to the strengths and limitations section after the abstract and cited this directly as a limitation to this work:

> There are limitations to this study. Firstly, as in most qualitative studies, the number of participants was relatively small. This limitation is mitigated by the fact that physician interviews proceeded until the point of saturation. Patient data were not collected in this manner, and these themes may not be fully saturated and we appreciate this as a limitation.

In general, the paper focuses on reviewing a potential intervention and the larger contribution to the literature on how to improve cholesterol treatment was not clear.

Because statin underuse is so widespread and likely results in a significant burden of avoidable morbidity and mortality, we know we are not the only group considering ways to enhance the prescription, initiation, and adherence with these therapies via quality improvement techniques. While part of our study gathered feedback upon our specific intervention, we believe that the findings represented in our study will be of use to many others who are working on devising interventions and quality improvement strategies to enhance the uptake of preventive medications including statins. We have added a line to the conclusion to drive home this point raised by the reviewer:

Our study sought perspectives of both healthcare providers and patients, which will be incorporated into intervention design to maximize acceptability. Insights gained from qualitative data will be used to improve the likelihood of success and achieve the desired clinical impact. The insights about these interventions are also likely to be of interest to many researchers and clinicians who are considering and designing provider- and/or patient-facing interventions to improve the uptake of preventive medications.

Reviewer: 2

This paper addresses the issue of statin underuse in a high risk population, a situation which leads to unacceptable excess mortality. As such it is addressing an important healthcare issue. The authors use a qualitative method to elicit feedback from key stakeholders- GPs and patients - on potential interventions and specifically an intervention they have devised based on facilitated relay. This manuscript could benefit from a reorganization as details of the studies methods appear spread across introduction, methods and results.

Thank you for this important suggestion. We have done as recommended by the reviewer and made it more clear how the study was conducted, pulling all these details together in the methods section. We now feel that it is much clearer for a reader, and thank the reviewer for this comment.

In particular, we created a new section in the methods where we describe the intervention (including a new figure to illustrate this), and have consolidated all the information about our data collection into the appropriate section in the methods.

A few suggestions to strengthen this manuscript:
the introduction sorely lack any justification for the proposed facilitated relay intervention. Please include a paragraph on what is known about statin underuse. Both the USAGE survey and REGARDS study provide some insight to these questions. You state that facilitated relay has been shown to improve CV risk factors, and some exploration of the issues will help to establish a rationale for facilitated relay intervention.

Thank you very much for this excellent suggestion. I have added the following paragraph – including the suggested references to the introduction, which I think sets up the justification for a facilitated relay strategy much better than was evident in the previous version:

> Physicians and patients face numerous barriers when it comes to prescribing and adhering to statin therapy, from the providers perspective this includes lack of knowledge, conflicting clinical guidelines, lack of systems to identify patients who should be taking statins (11). On the other hand, patients often experience or fear side effects or are simply averse to taking additional medications (11). Furthermore, patients that face social disadvantages such as low income, lack of health insurance, and minority race are more likely to not use statins (12). A large US-based survey found that side effects were common and that many former statin users were unsatisfied with the explanation provided by their prescriber about the importance of the medication (13). Providers need resources to help them provide this counselling to patients and to arm them with strategies to mitigate common statin side effects, like muscle pain (14).
>
> There are clearly many challenges that lead to the observed clinical treatment gap for patients who have indications for statin treatment. However, some studies have shown that such treatment gaps, in related conditions like hypertension, can be closed using quality improvement strategies (15-17). Integrated quality improvement strategies that target both

patients and healthcare providers are more likely to achieve quality indicators than strategies which only target one aspect in isolation(16). One such strategy is facilitated relay.

The introduction should also convey more urgency around this issue of statin underuse. As it is written, it does not indicate that this issue is deserving of any time and attention.

Thank you for this excellent suggestion that will improve our manuscript. We have added the following to the end of the introductory paragraph:

> The lack of statin treatment for patients with indicated conditions results in significant excess morbidity and mortality. In Canada, specifically, if all patients with indications for statins were treated, this would result in nearly 40,000 cardiovascular events avoided (11). In the United States, 13% of cardiovascular deaths could be averted with perfect statin adherence among patients at high cardiovascular risk (12).

You might also provide a brief description of the guideline recommendation for this group, since the conflicting guidelines come up as a topic of concern for GPs in your results.

Thank you for this excellent suggestion, I can certainly understand how this would be unclear for someone not from our region and unfamiliar with our prevalent guidelines. In order to clarify this, we have added the following as a footnote to Table 2, connected with an asterisk:

> * Specialist guidelines, the 2016 Canadian Cardiovascular Society guideline (7) advocates that patients at high risk be treated with statin therapy to achieve a target LDL-c level of < 2.0 mmol/L. GP Guidelines, the 2015 TOP Alberta Guideline (46) encourages GPs to treat high risk patients with moderate-to-high intensity statins and should not repeat lipid levels, or attempt to treat to a fixed target.

This issue is also referenced in our General Practitioner Education section of the results:

> Whether providers should be treating patients to a specific cholesterol level was a major source of confusion. They frequently referenced receiving conflicting advice, including a contradiction in clinical practice guidelines(49), some of which advocate for a ‘fire and forget’ approach(9, 50), while Canadian(8) and European(51) specialist guidelines recommend a ‘treat-to-target’ approach(8).

Methods: I have some concerns about your recruitment methods. I understand the difficulty in recruiting participants. You state that GPs were sampled using a snowball method and then purposively to get a balance of age and gender. Looking at your descriptive statistics, GPs tend to skew heavily younger and female and urban. Perhaps this is intentional and reflects the actual demographics of GPs in your area?

Thank you for raising this issue regarding sampling. We did indeed use a principal snowball sampling methodology. We then applied sampling strata to ensure that we had representation in our sample from a variety of demographic groups. Note that our objective was never to be ‘balanced’ or ‘representative’ of the GP population in our area, as these are traditionally sampling principles related to quantitative research, rather than qualitative research, where simply having representation with demographic groups is the objective.

Also, how do these GPs compare to ones who tend to underprescribe statins? Your discussion guide indicates some of these questions were raised- can they be incorporated into the descriptive statistics table? For example, how often are you testing cholesterol? Your intervention relies on reporting the results of a cholesterol tests - if your GPs aren't ordering the tests, your intervention may have a problem before it gets started.

Thank you for this suggestion, it is certainly helpful to include these practice characteristics in our descriptive table. We know how many patients each provider has that are at high risk of cardiovascular disease. At your suggestion, we have also extracted, from the qualitative records the proportion of a physician's patients who are at high cardiovascular risk, and the proportion of those who have a current lipid profile on file. Unfortunately, this was pulled from the interview transcripts and therefore it was not asked (or answered) uniformly for every participant. This data has now been presented in Table 1 as requested:

Proportion of patients who would be considered high risk on the basis of cardiovascular risk factors (n=14)	Mean: 32% Range 10-75%
Proportion of high-risk patients who have a current LDL-level on file (n=9)	Mean: 82% Range 70-90%

With regards to patient recruiting, you say you recruit patients "who may potentially" be recipients. Why? What additional screening criteria did you apply in securing your patient panel? It is not clear that any effort was made to recruit patients who fit the "high risk" criteria, except advertising in areas of the health center which treat such patients. Details on screening would be useful to include.

Thank you for pointing out that this was unclear in our manuscript. Please note that we have made changes to make the study population clearer:

> We recruited patients who would qualify as recipients of the proposed intervention. Specifically, we were interested in recruiting those at high risk of cardiovascular disease, who self-reported a prior history of high cholesterol, preferably with co-existing vascular disease (myocardial infarction, stroke or peripheral vascular disease), diabetes, or chronic kidney disease.

Under data collection, you state that interview guides were developed based on literature review. Relevant citations here of any papers useful in shaping your thinking should be included.

Thank you for pointing out this oversight on our part. We have included references to the papers that shaped our thinking in the development of the question guides:

> Both focus groups and interviews were guided by question guides (Appendix A & B) which were developed based on a review of the literature (35, 36) and discussion with the research team

More info should be included in both the paper and appendix on the intervention itself. The physician letter is included, the patient communication should also be included. Consider a schematic of the intervention. For example, patient receive cholesterol test- what result triggers the intervention? how long before a communication is sent? when does the patient receive? when does the GP receive? As the focus of this paper is the facilitated relay intervention, this should be clearly described.

This is an excellent point raised by the reviewer. In order to clarify the intervention, we have It is important to note that at the stage when this data was being collected, the intervention was purely proposed/hypothetical. Therefore, some of the details requested (i.e. time before communication is sent, etc…) is still in development so it was not presented to participants, including the actual patient communication. We presented the physician letter, which was co-designed by several physicians, and asked them to comment on it and provide feedback on how the patient-facing communication should be different from what they were shown. Our hope was to use this experience to co-design the patient intervention with patient partners, rather than to have one pre-conceived by researchers and physicians. We have added a brief note to clarify that it was the physician letter that they were shown:

> After they had given their unprompted views, participants were then given a brief explanation of facilitated relay, the specifics of the proposed intervention (Figure 1), and they were shown a copy of the proposed intervention letter for GPs (Appendix C).

However, the reviewer's point is an important one. Our intervention, even though only proposed, was not clearly enough described to allow a reader to understand what we were receiving feedback on. In order to clarify this point, we have added the following to the background section, including a figure to help clarify the point:

> **Proposed Intervention**
>
> We drew from behaviour change theory to develop a facilitated relay intervention to increase statin prescriptions (33-35) (Figure 1). Our proposed intervention partners with our province's single laboratory system to identify individuals who have elevated cholesterol levels, statin-indicated conditions, and who are not currently filling prescriptions for statins. Our lab system has access to province-wide administrative databases, including labs, pharmacy dispensations, and hospitalization data. For every elevated LDL-cholesterol level, the lab would have an algorithm that would check the patients' records for evidence of statin-indicated conditions (administrative markers of myocardial infarction, stroke, diabetes, or chronic kidney disease), and would then identify if they have recently filled a statin prescription. This is possible because of province-wide, linkable databases. For patients who are not filling statins, but who should be, their GP who had ordered the cholesterol levels and the patient, will then each receive a letter outlining the indication for treatment and the potential to benefit from statin therapy. The patient letter will encourage them to speak to their GP, and the GP letter will encourage them to make an appointment to discuss directly with the patient - both with the objective to initiate or renew statin prescriptions.

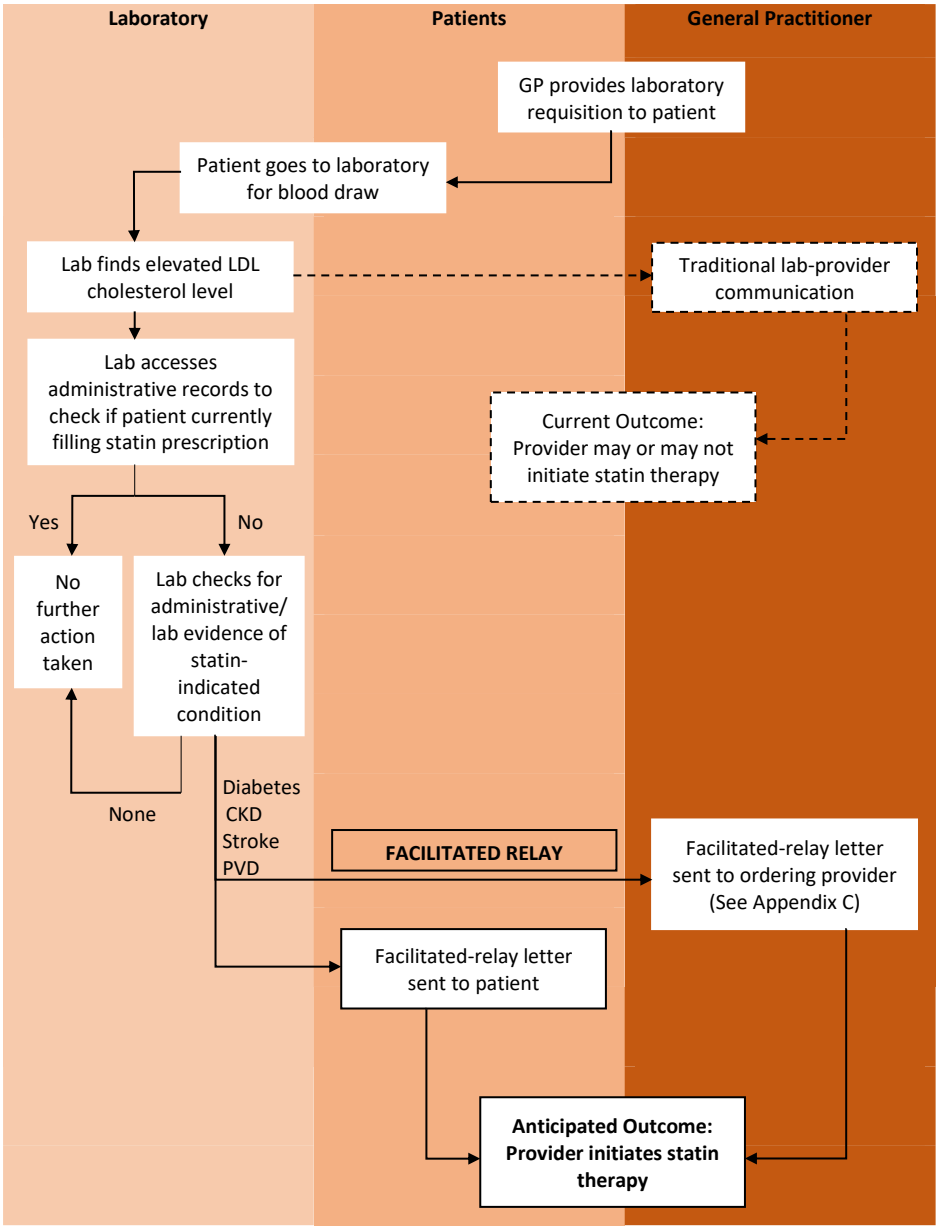

Figure 1: Laboratory-Based Facilitated-Relay Intervention
Dashed lines: traditional interface between lab and ordering provider

Data analysis methods are appropriate and well described.

Thank you.

Results:
More details on recruitment should be included. X# were contacted, X# agreed to participate, x# were schedule for interviews, saturation was reached at 17 interviewing.

Excellent point, thank you very much for this suggestion. We have provided the details requested:

> We initially reached out to 27 GPs to invite them to participate, 4 declined to participate, 3 didn't respond to the invitation, 19 were scheduled for interviews, with 2 cancelling. We reached saturation after having completed 17 individual GP interviews (Table 1a).

Similarly, more details on patient recruitment. In your Table 1b, "none/high cholesterol" should be split as these are very different. If 23% of your patient sample has no clinical reason to be included, that would limit the relevance of the results of patient focus groups.

My apologies for this confusing nomenclature. “None” referred to no other indications for statin therapy, other than high cholesterol levels. We have deleted “none” from the table, making it more clear that this 23% did have indication for statin therapy, but that it was on the basis of elevated cholesterol levels alone, rather than being indicated by a coexistent condition.

Also, for statin use, consider IDing what # had been prescribed but stopped or never started, as these would be the group most likely to be targeted by an intervention.

This would have been helpful, indeed. Unfortunately, this was not specified on our baseline questionnaire so we cannot provide this information. However, we would envision that the intervention proposed would apply equally to those who have never started on a statin as well as those in whom statins had previously been tried but are not currently being used, so we do not see this as a major limitation.

DISCUSSION:
There is a large body of literature on interventions targeted to physicians/patients or both on statin use. Only a very few are mentioned here. Jenstrom-Karlsson et al, have written a nice review of patient centered interventions which might be useful. As have Van Driel at el for the Cochrane Collaboration. An understand of how this intervention compares to other interventions that have been tried will be important.

Thank you for this important comment. Indeed, this section of our discussion was somewhat thin and we appreciate the chance to improve upon it. We have added the following, including the suggested references, which were very helpful:

> A number of interventions have been attempted to address the problem of statin underuse. A number of patient-centered approaches have been tried with varying success (23). While active forms of education, like cognitive education and behavioural counselling seem to work (51), more passive forms of education are often unsuccessful at changing behaviour, as in the recent ISLAND trial which found their intervention, comprised of a mail and phone education strategy to encourage patients to take prescribed medication, had no impact on adherence (52). Others have found that multifaceted interventions focusing on enhancing care provision through team-based care may be effective at increasing statin adherence (53).
>
> However, when trying to target the problem of low statin prescribing, patient-facing interventions are not likely to work. An alternate approach is to facilitate GPs ability to identify and prescribe statins, to those in whom they are appropriate (54), through audit and feedback or facilitated relay.

Reviewer: 3

The authors which to increase medication with statins. However, the benefit of statins for primary prevention and for elderly persons with limited remaining life expectancy have been questioned (e.g. Kristensen et al. BMJ Open 2015 plus papers on deprescribing). The present study appears to focus on the fraction of patients in need of secondary prevention through

use of statins. This needs to be clearer early in the manuscript and reflected also in discussion and conclusion.

Thank you for this comment and we agree that there is certainly a stronger evidence base for the use of statins in secondary prevention settings than in primary prevention. However, randomized clinical trials have identified that there are certain groups of "primary prevention" patients, for example middle aged people with type 2 diabetes or those with chronic kidney disease, in whom statins are beneficial. In our national, evidence-based guidelines, these are referred to as "statin-indicated conditions", and include patients with diabetes, chronic kidney disease as well as secondary prevention groups (i.e. those with pre-existing vascular disease). We have reworked the introductory paragraph of the paper to acknowledge this tension, by adding:

> Vascular disease, including coronary artery disease, peripheral artery disease, and cerebrovascular disease, remains among the leading causes of mortality worldwide (4). A class of medications, HMG-CoA Reductase Inhibitors, commonly known as statins, have been proven to be effective for lowering the risk of vascular events (5). Individuals who have previously had vascular disease (i.e. secondary prevention) derive a greater absolute risk reduction from statins than those who have never had vascular disease (i.e. primary prevention) (6). There are some individuals who have never had vascular disease, such as those with diabetes or chronic kidney disease, who also have been shown in randomized controlled trials to benefit from therapy (7-9).

We have also added the following to the discussion:

> While statins have a more limited role in certain populations (low risk and those with limited life expectancy) (49, 50), they are important for the prevention of cardiovascular disease in patients who have previous atherosclerotic disease and in those with diabetes and kidney disease (7-9).

In the conclusions we specify that our findings are specifically about increasing statin use among those at high risk of cardiovascular disease:

> Statin therapy has been demonstrated to effectively lower cholesterol and reduce the risk of cardiovascular events and death in individuals at high risk of cardiovascular disease.

The intervention tested in the present manuscript is one among several ways to try to affect adherence. A recent publication in BMJ (Ivers et al. BMJ 2020) tested an intervention through a pragmatic randomized controlled trial with some similarity to the present intervention, and also in a Canadian setting. The authors should have a look at that paper and include reflections on how the findings from Ivers et al. relate to their own.

Thank you for the suggestion. We feel that the intervention in the ISLAND trial is different from what we are proposing here. However, it is a good point that this could be mentioned as an alternative approach, we have included the following in our discussion section:

> A number of interventions have been attempted to address the problem of statin underuse. A number of patient-centered approaches have been tried with varying success (23). While active forms of education, like cognitive education and behavioural counselling seem to work (51), more passive forms of education are often unsuccessful at changing behaviour, as in the recent ISLAND trial which found their intervention, comprised of a mail and phone education strategy to encourage patients to take prescribed medication, had no impact on adherence (52). Others have found that multifaceted interventions focusing on enhancing care provision through team-based care may be effective at increasing statin adherence (53).

> However, when trying to target the problem of low statin prescribing, patient-facing interventions are not likely to work. An alternate approach is to facilitate GPs ability to identify and prescribe statins, to those in whom they are appropriate (54), through audit and feedback or facilitated relay.

The authors discuss how to inform and discuss use of statins with their patients. I would like to see reflections on how they would suggest describing the quantitative benefit of statin treatment to patients as well as GPs.

Thank you for you comment as importantly as much as we aim to address underuse, there is appreciably also overuse of statins. We have included a comment on this:

> Finally, we also appreciate that as much as there is underuse of statins, there is also overuse, for example, in people with short life expectancy. Perhaps interventions to increase initiation may also include a component that conveys statin benefits are measured in years rather than months.

The inclusion of patient in the decision process is often seen as a way to increase adherence to clinical decisions (shared decision making) How do the authors see their observations in this context?

We fully agree with the reviewer, which is, in fact why we have proposed a dual-pronged approach to our facilitated relay intervention, with letters going to both patients and providers so that both were informed and on a more level playing field for discussions about whether or not to initiate statin therapy. To address this more directly, we have added the following to the description of the intervention:

> We felt that it was important to include patients in the facilitated relay to empower them in discussions with their GP and to enable shared decision-making (36), which has been demonstrated to improve adherence with statins (37).

We also added this to the discussion section:

> Patients also suggested that providing themselves with laboratory test results and information on treatment options may result in better medical care, generally supporting our hypothesis that facilitating shared decision making was a key element of a novel intervention.

I would like to see each quotation in the text identified (e.g. by a separate number for each informant).

Thank you for this important comment. We have indeed added informant numbers associated with each quotation.

Page 3, line 42: The authors present the recruitment of patients from a group with specific interests as a limitation. The authors should expand a little on which implication they see from this limitation.

Thanks for this. We have added the following to the strengths and weaknesses section (after abstract and in the discussion section):

- The patient sample we recruited may not be representative of the broader population, as many of them had previously stated an interest in quality improvement and research – and therefore may be attuned to the importance of preventive therapies more than other members of the general public.

Page 3, line 43: Which context/setting-specific characteristics made you write this statement?

This statement was not written in response to any particular contextual factor, but simply to acknowledge that a limitation of in-depth qualitative research is that participants' responses/perspectives are dependent upon setting, such that findings from one jurisdiction may not be directly transferrable to another.

Page 3, line 70: Please clarify what is meant by 'our setting'

Thank you, this vague statement has been deleted in favour of stating:

> Despite the establishment and promotion of facilitated relay and other quality improvement strategies, there remain significant treatment gaps in hypertension (21) and other chronic conditions (22). Furthermore, while facilitated relay has been shown to be effective in improving a number of cardiovascular risk factors (18, 23), it remains among the least commonly used quality improvement strategies (24) and has not been explored in the management of dyslipidemia.

Page 7, line 24-28: Do the authors find the evidence for use of statins equally good for all four groups at all ages (e.g. diabetes only)?

Thank you for your comment and we believe the reviewer is referring to the 4 groups in Table 1b (None/High cholesterol only; Diabetes only; Myocardial infarct (MI) only; Diabetes & MI). Evidence for all four groups at all ages is not equal and we did not intend to imply this. This was simply a tabulation of a brief demographic questionnaire used at the beginning of our focus groups in which patients self-reported their condition(s). We have revised the title of Table 1b to "Descriptive statistics for patient participants based on self-report".

Reading the interview guides and reading the citations presents to me a different story than the one presented as the objective by the authors. The authors have an objective related to interventions to increase the use of medication. However, what appears more obvious (to me) as the main theme in the interview guide and the citations from the GPs is a better support in deciding who to treat. The GPs are asking for support to do rational pharmacotherapy – and this is not the same as increasing the use of medications. I think the authors may not have framed their story correctly in their title and objectives.

Page 8, table title: the title states 'General suggestions by GPs and patients to increase statin use', but the citations have very little to do with increasing the use. It about a better and evidence-based way of offering treatment.

Page 7, line 199-202: this is interesting reading and has nothing to do with strategies to enhance use of statins but basically having support in offering statins to those for which

We have grouped these reviewer comments together as we believe that they all reflect an important point in highlighting that there is some confusion around the language used throughout the paper.

We had intended "use" as an umbrella term getting at both the prescription/initiation of statins and adherence to statins once they are prescribed. This term would have both implications for both providers (who have been documented to fail to prescribe statins to those in whom they are indicated), and patients (who may choose to adhere, or not to prescribed statin therapy).

It is an important point raised by the reviewer, and we have attempted to clarify this by changing "USE" to initiation throughout.

With the intent of addressing this comment, we have changed the title to:

> **Strategies for Enhancing the Initiation of Cholesterol Lowering Medication ~~Use~~ Among Patients at High Cardiovascular Disease Risk: A Qualitative Descriptive Exploration of Patient and General Practitioners' Perspectives on a Facilitated Relay Intervention in Alberta, Canada**

We have also added the following into the description of the study design:

> We conducted a qualitative descriptive study (29) to explore patients' and general practitioners' perspectives on interventions to increase initiation of statins for cardiovascular risk reduction and treatment of high.

Thank you, I think that this is clarified by the change made above, but to be even more transparent, we have changed the title of Table 2 to read:

> **Table 2.** General suggestions by general practitioners and patients to increase initiation of statins

Additionally, we made similar changes throughout the manuscript to reflect the suggestions recommended by Reviewer 3 around the terminology used.

VERSION 2 – REVIEW

REVIEWER	Jesper Bo Nielsen University of Southern Denmark, Denmark
REVIEW RETURNED	24-Sep-2020

GENERAL COMMENTS	This manuscript has clearly been improved. Now clarifying the focus on initiating treatment and including information that overuse in specific groups gives a more balanced manuscript. Two minor points: Line 217 Here the authors describe that 27 GPs were invited and 7 declined or did not respond. That leaves 20 GPs, but why did the authors schedule interviews with only 19 GPs? Table 1a A new title is needed as patient statistics are now included in the revised manuscript (or should these data perhaps go to Table 1b??). To that end, please clarify what 'mean' means and how the percentages for mean and range have been reached.

VERSION 2 – AUTHOR RESPONSE

Thank you very much, I have addressed the two minor issues raised by the reviewer in the updated version of the manuscript.