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Protocol for Systematic Review and Meta-Analysis on Randomized Clinical Trials on the Efficacy and Safety of Pitavastatin

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ABSTRACT

Background: Pitavastatin is a novel statin that possesses some advantages over conventional statin.

Aim of the review: The subjects with primary or secondary cardiac events (**population**) receiving pitavastatin (**intervention**) will be compared to placebo or other statin members (**comparators**), for the non-inferiority or superiority in terms of effects on low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and/or major cardiac events (**outcome**).

Methods: The protocol has been developed based on the **PRISMA-P** checklist by using (**PICO** [**population**, **intervention**, **comparators**, **and outcome**]) items, for adult subjects who have received pitavastatin in randomized clinical trials. We will search for databases such as Google Scholar, PubMed, and the Cochrane using specific MESH terms**.** The RevMan will be used to quantify the synthesis of data (I^2 index, tau squared, and the Q-test *P*-value) for studies heterogeneity.

Results: Our current systematic review will provide highly relevant findings about the role of pitavastatin in the primary and secondary prevention of CVDs compared to the other statin. This will permit the prescribers to make informed decisions about the most efficacious and safest statin for their clients. The current study findings will contribute to inform evidence-based clinical practices and guidelines for policies and planning prevention strategies. The work will provide evidence by synthesis of well-designed and robust RCT-s conducted on one of the most efficacious and safest statins.

Conclusion: The current protocol will report the difference in efficacy of pitavastatin (intervention) compared to placebo or other statin members (comparators). Moreover, the protocol will assess the difference on the safety profile between the intervention and the comparators.

Keywords: Dyslipidemia; efficacy; low-density lipoprotein cholesterol (LDL-C); pitavastatin; randomized clinical trial; safety; systematic review

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Impact of findings on practice

- Cardiologists and internists may offer pitavastatin as suitable first-line treatment option for subjects, with renal and hepatic impairments, those with multiple medications, and elderly provided improved safety and efficacy profiles.
- The clinical practitioner may offer pitavastatin management choice for those with acute coronary syndrome, or diabetes and/or metabolic syndrome.
- Initial use of pitavastatin should be accompanied with screening and monitoring for new-onset diabetes.
- Individualized statin pharmacotherapy is warranted for improved clinical outcomes.

INTRODUCTION

The effect of pitavastatin is evident on minimizing the level of low-density lipoprotein cholesterol (LDL-C) and total triglycerides while increasing the levels of high-density lipoprotein cholesterol (HDL-C). These effects contribute to lowering the clinical risk factor for cardiovascular diseases (CVDs), [1-3]. The food and Drug Administration (FDA) compelling indication of pitavastatin is labelled for primary hypercholesterolemia, (heterozygous familial hypercholesterolemia, and mixed hyperlipidemia).

The **TOHO-LIP** trial has shown that pitavastatin reduces major adverse cardiac events (MACE) as compared to atorvastatin (MACE, [2.9% versus 8.1%, hazard ratio (HR), 0.366; 95% confidence interval (CI) 0.170-0.787;] *P* = .01) respectively. Furthermore, pitavastatin as compared to atorvastatin has exhibited improvement in coronary revascularization for stable angina (4.5% versus 12.9%, HR = 0.350; 95% CI 0.189-0.645, *P* = .001) respectively, [4]. The multicenter randomized head-to-head **PATROL** trial of 302 subjects randomized to either pitavastatin or rosuvastatin or atorvastatin, has shown no differences in adverse events (40-45% reduction in LDL). However, pitavastatin has demonstrated better safety profile regarding reduction on glycated hemoglobin (HbA1c), [5].

The pitavastatin risk for the new-onset diabetes has been reduced by 18% as shown in the **J-PERDICT** trial (Japan Prevention Trial of Diabetes by Pitavastatin in Patients with Impaired Glucose Tolerance), [6]. Furthermore, pitavastatin has demonstrated reduced levels of HbA1c (8.1% at baseline to 7.4% at 6 months) in the **LIVES** (LIVALO Effectiveness and Safety) trial of the Japanese long-term prospective post-marketing surveillance, [7].

Pitavastatin has shown greater improvement in endothelial function, [8] and better glycemic control, which can be attributed to its different chemical entity and variable pharmacokinetic profile, [9-11].

Rationale

The new pitavastatin appears to have high efficacy in lipid lowering, less adverse effects and less occurrence of new-onset diabetes. Pitavastatin is a novel statin that possesses some advantages over the conventional statin in the primary and secondary prevention of cardiovascular events. Subjects with acute coronary syndrome (ACS), metabolic syndrome and/or diabetes appear to be suitable candidates for pitavastatin pharmacotherapy. There is recent evidence to prove that pitavastatin exerts neutral or favorable effects on diabetes.

Therefore, it is prudent to individualize the selection of statin especially in subjects with diabetes and/or with ACS. There is a need for exploring the clinical therapeutic option for the use of pitavastatin in a diverse population (diabetes) and in sub population (coexisting ACS).

Objectives

1. In subjects (**participants**) with any type/stage of dyslipidemia: - does the use of pitavastatin (**intervention**) as compared to placebo or other statin members (**comparators**) prove non-inferiority or superiority over placebo/comparators in terms of reduction of LDL-C (**outcome**)?
2. Does the use of pitavastatin therapy prove better safety profile over placebo/comparators in subjects with any type/stage of dyslipidemia?
3. Is there any differences aligned between pitavastatin and the other statin members (atorvastatin, pravastatin, rosuvastatin, simvastatin) based on efficacy, precautions and safety profile and/or dyslipidemia type (i.e., based on

Frederickson classification of dyslipidemia and/or primary versus secondary dyslipidemia)?

Aim of the review

The purpose of the protocol of the current systematic review and meta-analysis is to assess the efficacy and safety of pitavastatin, compare and explore the efficacy and safety of pitavastatin versus other statin class members (atorvastatin, pravastatin, rosuvastatin, simvastatin) in terms of reduction in LDL-C and/or MACE.

Ethics approval

Ethics approval is not required in the current systematic review and meta-analysis.

METHODS

The current protocol has followed Cochrane library instructions in its developing. We have developed a protocol for the current systematic review and meta-analysis on the efficacy and safety profiles of pitavastatin with the primary endpoint of improvement in LDL-C levels and/or MACE. The developed protocol was based on the PRISMA-P checklist http://www.prisma statement.org/Extensions/Protocols.aspx, [12]. The developed protocol has been registered (CRD42020199668) on the International Prospective Register of Systematic Reviews (PROSPERO) website, [https://www.crd.york.ac.uk/prospero/#myprospero].

Eligibility criteria

We will conduct a systematic review and meta-analysis (participants, interventions, comparisons and outcomes [**PICO**]) on phase II and phase III RCT-s for subjects with primary or secondary cardiac events who have received pitavastatin.

The types of participants are **s**ubjects diagnosed with dyslipidemia (**population**) any type and receiving pitavastatin (**interventions)** versus placebo or comparator **(comparisons)** with the primary efficacy endpoint of minimization of LDL-C and/or MACE, cardiovascular death, myocardial infarction (fatal/nonfatal), and stroke (fatal/nonfatal) and/or their composite (**outcomes**). The secondary safety endpoint will be the development of adverse events. The **measure of effect** will be expressed as relative risks, odds ratios, hazard ratio, risk difference, and/or 'number needed to treat, [**Figure 1**].

Figure 1: Characteristics of included articles

Method: Randomized controlled trial with placebo and/or active comparator

Participants: Subjects with or without dyslipidemia; population size and the number of randomized patients in each arm of the trial; proportion of males versus females; age range (mean ± SD); BMI (mean ± SD); baseline laboratory values of LDL-C, HDL-C, TC, and TG.
baseline clinical characteristics of subjects recruited.

Interventions: 1 mg, 2 mg or 4 mg pitavastatin versus the comparator (doses of other statins like atorvastatin, pravastatin, rosuvastatin, and simvastatin).

Outcomes: 1. The primary outcome measure will be the clinical improvement in LDL-C and/or MACE at the end of treatment in the ITT population.
2. The differences in treatment (effect size) between the intervention drug (pitavastatin) and placebo/comparators (atorvastatin, pravastatin, rosuvastatin, simvastatin) as non-inferiority or superiority will be reported.
3. The measures of effect will be the reduction in LDL-C and/or increase in HDL-C, and/or minimization of MACE, from baseline to end-point of the trial.

- **The magnitude of difference between pitavastatin and the placebo or the comparator will be of high priority.**

5. Secondary outcomes: treatment emergent adverse events like musculoskeletal disorders (due to which some patients have discontinued the treatment and/or withdrawn from the trial).

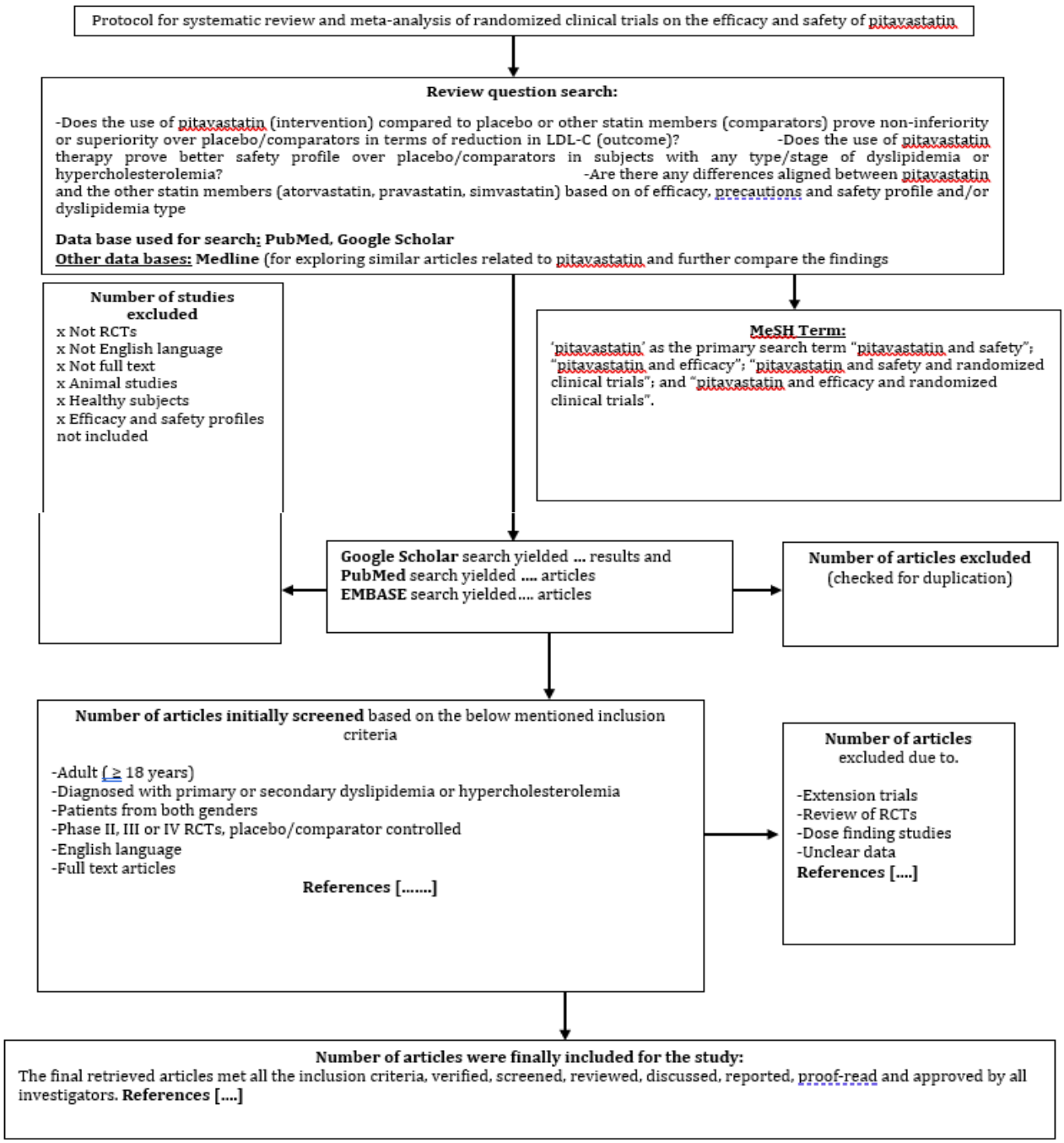
Notes: Acknowledgements of financial sources or funding grants, conflicts of interest.

Key Words: - LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides; MACE: major cardiac events.

The **inclusion criteria** will be the following: subjects diagnosed with primary or secondary dyslipidemia (all types), adult ≥18 years, both genders, hospitalized and non-hospitalized, RCT design (phase II RCT or phase III RCT,) with placebo/comparator, subjects receiving intervention drug pitavastatin; trials published in English language, full-text articles, primary outcomes reported status of LDL-C and/or MACE, conducted on humans within the last years (2005-2020).

We will **exclude** non RCT, trials with primary outcome other than the efficacy of pitavastatin on LDL-C and/or MACE, RCT with post-analysis studies, dose-finding RCT-s, retrospective trials, trial on pediatric population, unpublished trials, and trials that have been conducted on pregnant subjects and transplant subjects. We will conduct the search for published RCT (full text) on the English language reporting the efficacy and safety of pitavastatin. The current systematic review will be on RCT-s phase II and phase III subjects with primary or secondary dyslipidemia (all types). The **setting** will be out/in patients (hospitalized or not hospitalized). Trials will be retrieved are those published or conducted during

the period from 2005 to 2020. The **search methods** for trials retrieved will be conducted via Google Scholar, PubMed, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL), for published RCTs involving subjects with dyslipidemia receiving pitavastatin versus placebo, or comparators (atorvastatin, pravastatin, rosuvastatin, simvastatin). The database will be retrieved between the years 2005 to 2020 with the Medical Subject Headings (MeSH) search terms: 'pitavastatin' as the primary search term "pitavastatin and safety"; "pitavastatin and efficacy"; "pitavastatin and safety and randomized clinical trials"; and "pitavastatin and efficacy and randomized clinical trials". The **selection criteria** will be pitavastatin alone compared to placebo or **an**other statin. The selected trials citations will be imported into systematic review managers/software (COVIDENCE https://www.covidence.org). In addition, we will use manual search for citations with the same MeSH terms and conditions. All data will be collated by using the predefined Cochrane library approved structured modified forms. The draft of the search strategy to be used for one electronic database including planned limits is shown in, [**Figure 2 diagram flow chart**].



The data collection and analysis (data management) will be via access of full articles, screening and retrieving content with the predefined checklist (Cochrane templates) developed and modified specifically to ensure the strict inclusion criteria. We will follow the checklist

that has been adapted for use with protocol submissions to *Systematic Reviews* from Moher D et al, [13].

The selection process of the trials will be conducted by all the authors based on the inclusion and exclusion criteria. The methods that will be used for identifying the published trials in the official websites will be structured, predefined and specific MeSH terms for identifying eligible trials for inclusion in the current systematic review and meta-analysis. We will follow a strict checklist with pre-specified inclusion and exclusion criteria to ensure that the identified trials are as per the current systematic review methodology. The authors (A Sadeq, AAE, NALMAZ, FHF, JD, AIF) will double check the process and repeat the search terms individually and will compare the attempts, whereby, discrepancies will be resolved with discussions in reporting. The selected trials will be further reviewed by (MAISK, KG, IMA, AAL, ABA, AEL), will be double checked by other different authors (SMES, IYK, SMM, DN, NAK, HA and A Adel) and verified by repeating the process mentioned-above. The final double checking and verification will ensure that the selected trials precisely met the final relevant information and primary outcome needed for the current systematic review and meta-analysis (, IYK, SMM, DN, NAK, AA, A Adel). The type of dyslipidemia, trial duration, follow-up duration and primary end point (outcomes measures) will be shown in the supplementary material. The trials registration, DOI and author details, of the respective included RCT will be presented in the supplementary material. The safety outcomes (adverse events [AEs]) for the trials included in the current systematic review will be presented in the tables.

The data extraction and synthesis will be via the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, which will be used to abstract data and assess quality and validity. Data extraction (selection and coding) will be performed on the relevant variables from the original RCT and supplementary materials. The data extraction will contain trial registration, study country, number of involved countries (trial centers), type of ACS, trial duration, follow-up duration, the efficacy data, primary endpoint (outcomes measures), the safety outcomes (adverse events) for the included trials. The above data will be collated with structured forms, verified, reviewed, double-checked, independently confirmed, and recorded in the final format in excel sheets and conveyed to the RevMan 5.4 databases.

Data items will be defined for all variables for which data will be sought (e.g., PICO items, funding sources), any pre planned data assumptions and simplifications. **PICO** items: We will conduct a systematic review and meta-analysis (participants, interventions, comparisons and outcomes [PICO]) on phase II and phase III RCT-s for subjects with primary or secondary dyslipidemia who have received pitavastatin. Subjects both gender with or without dyslipidemia any type (**participants**) and receiving pitavastatin (**intervention**) for primary or secondary prevention of cardiovascular events randomized versus placebo or comparator (**comparison**). The primary efficacy endpoint will be the minimization of LDL-C and/or major cardiovascular events (MACE), cardiovascular death, myocardial infarction (fatal/nonfatal), and stroke (fatal/nonfatal) and/or their composite (**outcomes**).

Outcome measures

The primary outcome measure will be the clinical improvement in LDL-C and/or MACE at the end of treatment in the ITT population. The differences in treatment (effect size) between the intervention drug (pitavastatin) and placebo/comparators (atorvastatin, pravastatin, rosuvastatin, simvastatin) as non-inferiority or superiority will be reported. The **measures of effect** will be the reduction on LDL-C and/or increase in HDL-C, and/or minimization of MACE. The magnitude of difference between pitavastatin and the placebo or the comparator will be of high priority, [**Figure 3**].

Figure 3: The protocol summary of primary outcomes

1. The percentage change in fasting serum LDL-C concentrations from baseline.
2. A composite of cardiovascular death, sudden death of unknown origin, nonfatal acute myocardial infarction, nonfatal ischemic stroke, transient ischemic attack (MACE 3).
3. A composite of cardiovascular death, sudden death of unknown origin, nonfatal acute myocardial infarction, nonfatal ischemic stroke, transient ischemic attack, or heart failure that required emergency hospitalization (MACE 4).
4. The percent changes in HDL-C and adiponectin levels relative to the baseline values.
5. Percent change from baseline in non-HDL-C level.

The risk of bias in individual studies (**quality of RCT-s and assessment of risk of bias)**

In order to minimize and avoid bias in the selection of RCT-s (both at study level and outcome), the quality of the RCT-s will be judged by the five-point scale as per Jadad et al, [14].

The risk of bias in selected trials will be via confirming the following points: the randomization technique, description of the blinding method, completeness of follow up, reporting discontinuation, loss to follow-up, and failure to adhere to the intent to treat (ITT) principle; performing analyses considering all subjects; there is no selective outcome reporting and no use of any invalidated outcome measures. The risk of bias tool, version 2.0 (Cochrane) will be used for the risk of bias assessment.

Data Synthesis

The data synthesis will be quantitative, descriptive data will be presented, and inferential statistics and meta-analysis will be performed. The **exploration of variation in effects** (quantitative synthesis), i.e. (heterogeneity) in the RCTs included in the current systematic review and

meta-analysis will be comprised of a set of clinical covariates (clinical heterogeneity) from the relevant population level (matched groups of dyslipidemia, such as primary versus secondary), the intervention level (intervention vs. comparator), outcomes level (ITT: clinical success, superiority/inferiority and statistical magnitude of difference) and planned summary measure. We will perform our meta-analyses using the RevMan 5.4. The RevMan will be used to combine data from studies and explore the consistency between trials. We will use the random effects model with the Mantel-Haenszel (MH) method for each clinical endpoint. We will calculate the pooled estimates of odds ratio (OR) with 95% confidence interval (CI). We will use the I^2 index, tau squared, and the Q-test *P* value to examine heterogeneity among individual study effect sizes. In order to reduce the risk of bias, we will undertake independent pooling of data from RCT-s and we will prepare funnel plots and Egger's linear regression test of funnel plot asymmetry to assess the publication bias. We will display the pooled estimates with a 95% CI. The P values are considered statistically significant at less than 0.05. We will also perform a sensitivity analysis to reveal inconsistency. The forest plots will be generated to show the relative effect size of the intervening comparator for each clinical outcome. We will use meta-regression techniques to reveal heterogeneity.

The proposed additional analyses: we will conduct meta-analysis in the current systematic review as well as reporting the sensitivity analysis. However, we also plan a structured synthesis of data and comparison between the inferences in the respective trials (e.g., per-protocol analysis, sensitivity and/or subgroup analyses and/or meta-regression). Data will be pooled using random-effects models.

The meta-bias: The publication bias is defined as the failure to publish the results of a study on the basis of the direction or strength of the study findings. In the current systematic review and meta-analysis, we will use a funnel plot to check for the existence of publication bias or systematic heterogeneity in the studies taken for analysis. We will use Egger's regression for quantifying funnel plot asymmetry or Rosenthal's fail-safe number or "fail-safe N method". We will plan to avoid selective reporting within trials by not excluding non-significant study outcomes and by describing structured search criteria based on published methodologies.

Confidence in cumulative evidence: we will assess the strength of evidence of the final results in a GRADE Evidence Profile (GEP). This GEP will contain the PICO question, the type and number of trials included the number of participants in the trials, the effect sizes and their confidence intervals and the grading of the quality of the evidence and its starting level and reasons for upgrading or downgrading the quality. The quality of evidence for all outcomes for the included trials will be judged using an adaptation of the GRADE methodology assessment, [15-17], and assessed across the domains of risk of bias (consistency, directness, precision and publication bias). The full electronic search strategy in the database, limits of search used, check of duplication as per the PRISMA guidelines, will be shown in; [Figure-diagram 1]. The PRISMA chart and the complete PRISMA-P form will be provided in the supplementary material, **Appendix I**.

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	✓		1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such			5
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	YES		Prospero CRD42020199668
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	✓		1-4
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	✓		4-5
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		No	-

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Support					
Sources	5a	Indicate sources of financial or other support for the review	✓		5
Sponsor	5b	Provide name for the review funder and/or sponsor	✓		5
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	✓		5
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	✓		8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	✓		9
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	✓		10
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	✓		11
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	✓		12
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	✓		11-13
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	✓		12
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	✓		12
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	✓		13
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	✓		13
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	✓		14

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	✓		14
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	✓		14-15
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	✓		15
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned			15
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	✓		15
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	✓		15-16

The operational definitions

Secondary prevention: This is the long-term treatment to prevent recurrent cardiac morbidity and mortality, and to improve quality of life in people who had either MI or ACS, or who are at high risk of ischemic cardiac events for other reasons, such as severe coronary artery stenosis or prior coronary surgical procedures.

MACE: Major adverse cardiovascular events (cardiac death, non-fatal and fatal MI and stroke) sometimes termed major adverse cardiac clinical events (MACCE), which is a composite of total death, MI, coronary revascularization, and stroke.

DISCUSSION

The high level of cholesterol is a potentially modifiable risk factor that contributes to the risk of developing heart attack (MI) and other MACE. The increasing morbidity and mortality from CVDs can be minimized with the continued use of statin for primary prevention. The selection of the most efficacious statin remains a challenge for most clinical practices, particularly in subjects with ACS and/or diabetes.

The work will provide evidence by synthesis of well-designed and robust RCT-s conducted on one of the most efficacious and safest statins. We intend to minimize the publication bias and reporting bias with the use of published technical methods as mentioned-previously in the protocol. We intend to share our findings with the academia and cardiology societies worldwide.

In a recent non-inferiority multicenter phase 3 parallel RCT pitavastatin 2 mg was compared to atorvastatin 10 mg in subjects (664) with hypercholesterolemia at high risk for atherosclerotic cardiovascular disease (has one or more of atherosclerotic disease risk factors). Pitavastatin 2 mg/day has significantly reduced the primary end point (a composite of cardiovascular death, sudden death of unknown origin, nonfatal acute myocardial infarction, nonfatal ischemic stroke, transient ischemic attack, or heart failure that required emergency hospitalization (MACE 4) which have had occurred less frequently in the pitavastatin group with 9 subjects (2.9%) than 25 subjects (8.1%) in the atorvastatin group. Furthermore, pitavastatin has **significantly reduced** the secondary composite end point (composite of the primary end point event plus clinically indicated coronary revascularization for stable angina), occurring in 14 subjects (4.5%) in the pitavastatin group and 40 subjects (12.9%) in the atorvastatin group, [18].

In a superiority double-blind, double-dummy, active controlled phase 4 RCT, 252 subjects diagnosed with dyslipidemia (fasting serum LDL-C of 130-220 mg/dL and TG ≤ 400 mg/dL) pitavastatin 4 mg was compared to pravastatin 40 mg. The reduction in LDL-C was significantly greater in the pitavastatin 4 mg group by 31.1%, than in the pravastatin 40mg group by 20.9% at 12 weeks of therapy. After weeks 12 and 52 of therapy, the reductions in non-HDL-C and Apo-B were significantly greater with pitavastatin than with pravastatin. The other secondary lipid parameters were in favor for the pitavastatin group rather than pravastatin group, [19].

Another earlier multicenter work was conducted on 2014 as phase IV double -blind double-dummy active-control superiority RCT trial of 328 subjects diagnosed with primary hyperlipidemia or mixed dyslipidemia. The trail has revealed superiority median percent change from baseline to end-point, LDL-C levels were reduced by -38.1% for pitavastatin 4mg and by -26.4% for pravastatin 40mg. The ApoB, TC, and non–HDL-C, the median reductions from baseline to the week 12 endpoint were significant for each agent. TG were significantly reduced from baseline for pitavastatin (–16.3%) and pravastatin (–12.7%), [20].

Our current systematic review and meta-analysis will provide highly relevant findings to determine the optimal statin for primary and secondary prevention of CVDs. This will permit the prescribers to make informed decisions

about the most efficacious and safest statin for their clients. The expected findings will contribute to inform evidence-based clinical practices and guidelines for policies and planning prevention strategies. Furthermore, the findings will help to inform researcher and expand the future subsequent research, and evaluation of additional population interventions.

CONCLUSION

Pitavastatin has important role in the management of hypercholesterolemia with high safety profile and potent lowering effects on LDL-C. The current protocol will report the difference in efficacy of pitavastatin (intervention) compared to placebo or other statin members (comparators). Moreover, the protocol will assess the difference on the safety profile between the intervention and the comparators. The choice of statin should be based on the assessment of the individual risk.

Authors' contributions

We declare that A Sadeq, AAE, NALMAZ, FHF, JD, AIF, MAISK, KG, IMA, AAL, ABA, AEL, SMES, IYK, SMM, DN, NAK, AA and A Adel, contributions to the conception, design of the protocol, drafted the work, revised it critically for important intellectual content, approved the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST

The authors would like to acknowledge no conflict of interest.

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