Quality assessment and comparative analysis on the recommendations of current guidelines on screening and diagnosis of peripheral arterial disease: a systematic review

Oliseneku Damien Uyagu, Cosmas Ofoegbu, Joseph Ikhide, Emeka Chukwuka, Okezie Enwere, Omokhara Ogierakhi, Alex Adelosoye

ABSTRACT

Objectives There are several clinical practice guidelines available for peripheral artery disease (PAD). The paucity of strong evidence is known to give room for variations in recommendations across guidelines, with attendant confusion among clinicians in clinical practice. This study aims to conduct a quality assessment and comparative analysis on PAD screening and diagnostic recommendations in PAD management.

Selection Clinical practice guidelines written after 2010 and on or before 2020 were targeted. An exhaustive search was conducted through the major medical databases and websites of specialist international organisations of interest, and selection was made using our inclusion/exclusion criteria.

Setting Global. All guidelines written in English were included in this study.

Selected guidelines Nine guidelines were selected.

Outcomes The primary outcomes were the guidelines' quality and variations in screening and diagnostic recommendations in the selected guidelines.

Results Regarding quality, the guidelines had the lowest scores across the applicability and stakeholder involvement domains with means (SD) of 62 (9.9) and 65.3 (13), respectively. The highest score was clarity of presentation, with a mean (SD) of 86.8 (5.1). Also, the trend showed guideline quality scores improved over time. The guidelines unanimously offered to screen ‘high-risk’ patients, although there were some discrepancies in the appropriate age range and unavailability of strong evidence backing this recommendation. The guidelines harmoniously adopted the Ankle-Brachial Index as the initial diagnostic investigation of choice. However, concerning further diagnostic investigations and imaging, we found several discrepancies among the recommendations in the absence of strong evidence.

Conclusion Though the quality of the guidelines is shown to be improving over time, they perform poorly in stakeholder involvement and applicability domains, which could be influencing interest in research revolving around screening and diagnostic recommendations. Involving primary care providers and the public can be a possible solution.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This review, unlike previous studies, focused on recent peripheral arterial diseases (PAD) guidelines written after 2010 and reflects a synthesis of the current state of guideline quality and the most recent recommendations in PAD management regarding screening and diagnosis.

⇒ Complex data has been aggregated, comparatively assessed using thematic analysis and the results presented in concise and straightforward forms using texts, charts, and tables.

⇒ By using rigorous systematic review methodology and a mixed qualitative and quantitative approach to the data analysis, this study has revealed the current areas of strengths and weaknesses of the quality of the PAD guidelines.

⇒ Qualitative analyses are inherently challenging to process, especially when dealing with clinical practice guidelines (CPGs) that contain large amounts of information; the process was cumbersome and time-consuming with the inevitable loss of data during the thematic classification process.

⇒ The search strategies were executed exclusively in English language labouring under the auspices that the major PAD CPGs will have an English language translation, so it is possible that some guidelines written within the study time frame were not captured due to this limitation.

INTRODUCTION

Atherosclerotic disease is an umbrella term for the world’s leading cause of mortality and morbidity.1 Peripheral artery disease (PAD) is a major component of this group of disorders after cerebrovascular and coronary artery disease, sharing the same risk factors as other atherosclerotic conditions.2 Interestingly, according to data from the REACH (Reduction of Atherothrombosis for Continued Health) registry, it was observed that individuals with PAD do not achieve risk factor
control as frequently as those with coronary artery disease (CAD) and cerebrovascular disease (CVD). In addition, they had higher levels of mortality comparatively. The apparent explanation is that PAD is the most underdiagnosed and poorly treated atherosclerotic disease. PAD is a chronic medical disease with an asymptomatic phase of variable duration, with some individuals progressing into the symptomatic phase. Optimal management mainly involves early identification of the condition (screening and diagnosis), optimal medical management, which requires risk factor modification (through pharmacological and non-pharmacological methods), supervised exercise therapy and sometimes revascularisation.

Clinical practice guidelines (CPGs) have methodically developed statements to guide physicians and patients in making safe healthcare decisions based on the best available evidence. Currently, there are some CPGs outlining recommendations regarding the core aspects of management. A few partial reviews have been conducted on aspects of PAD guidelines in the past. Our study encompasses all aspects of PAD. Management from screening and diagnosis, through medical management to revascularisation and follow-up. Due to the volume of findings, the paper has been split into three papers, which is the first of the series. This paper encompasses the quality assessment and critical analysis of recommendations across screening and diagnostic recommendations. Also, we have limited the publication date range for the CPGs from after the year 2010 until 2020 to get the most recent information on PAD management recommendations, unlike the previous reviews, which scanned guidelines over a wide range of time. As such, the risk of evaluating outdated information is avoided.

As outlined in our published protocol, this paper aims to elucidate with diligent analysis, evaluation and crisp data presentation of the quality of the current guidelines on PAD, with recommendations on their suitability for use in clinical practice. In addition, we intend to review the long-standing debate on screening and diagnostic recommendations to ascertain the level of variation between authoring organisations. We expect that there should be greater levels of harmony with new evidence compared with older guideline reviews. Also, areas of interest where recommendations vary due to low-level evidence will be elucidated.

MATERIALS AND METHODS

A systematic search was conducted, and eligible guidelines were selected based on the attributes listed in the PICAR (Population, Intervention, Comparator, Attribute, Recommendation Characteristics) statement of our published protocol (available in online supplemental appendix 1). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement were used as a reference to report items and results in this study.

Patient and public involvement statement

Patients who are members of the Peripheral Arterial Diseases Support Group (https://www.facebook.com/groups/pad.pvd.support/members) were involved in this study’s design (in modelling the research objectives). The Way to My Heart.org (https://www.thewaytoomyheart.org/) founded this support group. The patient public involvement is coordinated through the group’s leaders/founders (also, patients are actively involved in providing support to their fellow patients), who are advisory members to the research team. They have identified this research as a priority area for clinicians who care for patients with PAD. The group members have been informed of this study’s results through their leadership. The support group will also participate in publicising the study after publication.

Search strategy

A systematic search was performed to identify relevant CPGs on PAD. One reviewer (ODU) conducted the search and extraction in line with the inclusion and exclusion criteria, and this was independently verified by a second reviewer (CO). A third reviewer (JI) was called in to resolve differing results. We developed a concept table to generate appropriate search terms (Medical Subject Headings, free-text vocabulary, key words) depending on the database’s peculiarities. Databases searched included Scopus (which includes Embase and MEDLINE), TRIP and Cochrane. The search also included guideline developer websites such as NICE, SIGN, NIH, GIN and websites for national academic societies. Details of the search strategies can be found in online supplemental appendix 2 and the protocol.

Selection of guidelines

In line with our protocol, guidelines that met the following inclusion criteria were selected.

1. The guideline is a CPG developed for people with PAD.
2. The guideline covers recommendations regarding screening, non-pharmacological and pharmacological interventions, surgical and follow-up management.
3. The guidelines were written after 2010 and in or before 2020.
4. The guideline is the most recent version.
5. The guideline is available online.
6. Related or international academic organisations wrote the guideline.

Our exclusion criteria were.

1. The topic is only mentioned in the guideline.
2. The guideline is limited to a specific aspect of PAD management, such as screening, pharmacological management, etc.
Outcomes
The primary outcome sought in this study were; Guideline Quality and Guideline recommendations on screening and diagnostic methods. Secondary outcome data included guideline characteristics; year of writing, funding source, writing language, location and website/source.

Quality assessment
In this study, the updated AGREE-II instrument was used to assess the quality of the selected guidelines. The AGREE-II instrument is a 23-item tool with international certification that evaluates the six methodological quality domains of a guideline, including scope and purpose, stakeholder involvement, the rigour of development, clarity of presentation and applicability and editorial independence. As was written in the protocol, the assessment was conducted by four reviewers (as recommended by the tool’s developers to minimise bias) using the instrument to assess all selected guidelines. The reviewers scored each guideline across each domain on a Likert scale of 1 through 7 (from strongly disagree to strongly agree). In addition, the reviewers gave an overall score of the guidelines on a similar Likert scale. As such, each guideline has two sets of scores: (a) the domain scores and (b) the overall score for the guideline. The details for the scoring system of the AGREE instrument are outlined in the protocol.

The overall quality assessment was arrived at using the domain scores in line with the study protocol. Guidelines with four or more domains scored over 60% would be regarded as ‘strongly recommended for use in practice’; if scores of most domains (four or more) ranged from 30% to 60%, the guideline was considered ‘recommended for use with some modification’. Those with domain scores (four or more) less than 30% were regarded as ‘not recommended for use in practice’. The overall guideline scores were used as a supporting statistic only and did not directly contribute to the grading of guideline quality. The data set for the quality appraisal is readily available in a public database.

Guideline recommendations
The recommendations were extracted into a matrix in Microsoft Excel sheets. Then thematic analysis was used to organise the recommendations into themes which allowed us to summarise the information into tables for comparison. The strength of recommendations and level of evidence was extracted and displayed in the tables for each recommendation. Each guideline used its grading method, which we harmonised using our grading system for the purpose of comparison for this study (tables 1 and 2).

One reviewer performed extractions and then reviewed for completeness and consistency by another reviewer, after which comparisons were made across the guidelines.

RESULTS
Search results
The initial search identified 3149 citations. The flowchart (figure 1) shows how we systematically eliminated the guidelines by removing duplicates, previous versions and guidelines written outside the date range, screening the title and abstracts for citations not related to the topic, removing those which were not CPGs and finally eliminating those which targeted aspects of PAD. Management of special populations. In the end, we had nine CPGs, which were included in this study for analysis.

Table 1 Harmonising recommendation strength grading system across the guidelines

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<tbody>
<tr>
<td>For</td>
<td>Class I</td>
<td>Adopted ESC model</td>
<td>Class I</td>
<td>A</td>
<td>Class I</td>
<td>Grade 1</td>
<td>Class I</td>
<td>Class I</td>
<td>Adoptions AHA 2016</td>
</tr>
<tr>
<td>Strong; A</td>
<td>Strong words (offer, measure, advice etc).</td>
<td>Class Ia</td>
<td>Class Ia</td>
<td>Class Ia</td>
<td>Class Ia</td>
<td>Class Ia</td>
<td>Class Ia</td>
<td>Class Ia</td>
<td>Class Ia</td>
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<tr>
<td>Moderate; B</td>
<td>Less confident words, eg, ‘Consider’.</td>
<td>Class Iib</td>
<td>Class Iib</td>
<td>Class Iib</td>
<td>Class Iib</td>
<td>Good practice statement</td>
<td>Good practice statement</td>
<td>Good practice statement</td>
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<tr>
<td>Weak; C</td>
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<tr>
<td>Ungraded; D</td>
<td>Consensus recommendation, insufficient evidence</td>
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<tr>
<td>Against</td>
<td>Class III</td>
<td>No benefit</td>
<td>Class III</td>
<td>Class III</td>
<td>Class III</td>
<td>Class III</td>
<td>Class III</td>
<td>Class III</td>
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<tr>
<td>No benefit; N</td>
<td>Harm; H</td>
<td>Do not offer</td>
<td>Class III</td>
<td>Class III</td>
<td>Class III</td>
<td>Class III</td>
<td>Class III</td>
<td>Class III</td>
<td>Class III</td>
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</table>

Guideline characteristics

The guidelines included are presented in table 3. They were written after 2010 and before or in 2020. Most of the guidelines (eight) were written in English, except the German guideline, which was written in German. The extended German guideline was translated into English for analysis, while a short version was already translated into English. Two guidelines did not state their source of funding (Vascular Society of Southern Africa (VASSA) and Central European Vascular Forum (CEVF)). The overall AGREE score on guideline quality ranged from 68 to 84.

Guideline appraisal

The standardised scores for each guideline were calculated according to the formula provided by the AGREE tool developers. The scores were displayed with a radar chart which allowed for easy comparison of all the guidelines included in this study across domains in figure 2. To give a general overview of the domains, Scope and Purpose; range 60–90, with a mean (SD) of 78.4 (11.4), Stakeholder Involvement; range 50–88, with a mean (SD) of 65.3 (13), Rigour of Development; range 43–82, with a mean (SD) of 70 (11.7), Clarity; range 75–94, with a mean (SD) of 86.8 (5.1), Applicability; range 46–77 with a mean (SD) of 62 (9.9), Editorial Independence; range 44–94 with a mean (SD) of 76.2 (18.6) and Overall quality; range 68–86 with a mean (SD) of 78.5 (7.2).

The domains with the highest score were Clarity of presentation, Scope and purpose and Editorial independence in order of decreasing magnitude. In contrast, Applicability and Stakeholder Involvement tied domains with the lowest scores. Seven guidelines met the criteria for high-quality guidelines, while two, the CEVF and South African guidelines, were recommended for use with some modification as moderate quality guidelines.

Another area of interest was to see the performance of the guidelines over time. The line chart in figure 3 shows...
the composite scores across domains for each guideline plotted over time. We can see clearly that the general trend shows the guidelines increasing in quality from 2012 through 2020.

Guideline recommendations

Screening recommendations

All included guidelines unanimously recommend screening high-risk groups, as seen in Table 4 (expanded table available in online supplemental appendix 3). Recommendations against screening groups not at risk were given by the American College of Cardiology/American Heart Association (ACC/AHA) guideline and the Asian Consensus. The strength of recommendations was predominantly strong (except for the AHA guideline and Asian Consensus Statement). The evidence levels for this recommendation were predominantly moderate except for the German S3 guideline, which relied on strong evidence and European Society of Cardiology (ESC), which used weak evidence.

In those with no additional risk factors, the age range for screening recommendations with the more recent guideline written after 2016 (AHA/ACC, ESC and the Asian Consensus paper) suggest screening adults over 65 years of age, while the older guidelines (VASSA and CEVF) suggest screening for those over 70 years.

The guidelines made unanimous recommendations for using Ankle Brachial Index (ABI) as the screening tool, with the older guidelines recommending further testing in the face of normal ABI in high-risk groups. Only the CEVF guideline suggested a screening interval of 2–3 years in high-risk groups regarding a screening interval. Risk factor modification for high-risk groups is recommended by four guidelines.

Table 3  Characteristics of included guidelines

<table>
<thead>
<tr>
<th>CPG</th>
<th>Developing Organisation</th>
<th>Country</th>
<th>Language of publication</th>
<th>Date of search</th>
<th>Date of release</th>
<th>Publication site</th>
<th>Funding</th>
<th>Overall AGREE score</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3 2016</td>
<td>One academic society</td>
<td>Germany</td>
<td>German</td>
<td>2020</td>
<td>2016</td>
<td><a href="https://www.aerzteblatt.de/int/archive/183158/The-diagnosis-and-treatment-of-Peripheral-arterial-vascular-disease">https://www.aerzteblatt.de/int/archive/183158/The-diagnosis-and-treatment-of-Peripheral-arterial-vascular-disease</a></td>
<td>German Society for Angiology</td>
<td>82</td>
</tr>
</tbody>
</table>

Asian Consensus 2020

<table>
<thead>
<tr>
<th>Country</th>
<th>Language of publication</th>
<th>Date of search</th>
<th>Date of release</th>
<th>Publication site</th>
<th>Funding</th>
<th>Overall AGREE score</th>
</tr>
</thead>
</table>
Regarding imaging, six guidelines recommended Doppler ultrasound scan (DUS) as the first-line imaging modality, with four making a strong recommendation. There was wide variation in the level of evidence used in making this recommendation. While contrast-enhanced magnetic resonance angiography (CE-MRA) and CT angiography (CTA) were unanimously recommended as additional imaging, there was variation in the circumstances in which they are to be used. Evidence levels for the recommendations for these imaging modalities ranged between middle and low. Three guidelines noted digital subtraction angiography (DSA) as the gold standard for imaging in PAD. Five guidelines unanimously agreed that this modality should be reserved for cases where the arterial networks could not be adequately visualised with the other modalities.

**DISCUSSION**

Overall, nine guidelines were identified and analysed in this study. In line with the study objectives, the quality of the guidelines was appraised using the AGREE tool, with the results summarised in table 3 and figures 1 and 2. This study found low scores across the applicability and stakeholder involvement domains. The low scores in applicability can be explained by the fact that most of the analysed guidelines did not mention monitoring or auditing criteria. Also, there was an ambiguous representation of the facilitators and barriers to implementing the guideline recommendations. Furthermore, aside from the CEVF guidelines, we observed that general practitioners (GPs), patients and public involvement were poorly represented in the guideline development committees, resulting in low stakeholder involvement scores. This is particularly of interest, given that PAD is a largely underdiagnosed and highly prevalent condition, especially among patients seen in primary care where they can and should be identified.22 Improved GP and public involvement will improve the adoption of guideline recommendations, ultimately translating into improved patient care through early identification, which will impact a public health scale
<table>
<thead>
<tr>
<th>CPG</th>
<th>ABI</th>
<th>Further testing</th>
<th>Imaging</th>
<th>Screening for AAA.</th>
<th>Screening for CAD</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>DUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NICE 2012</td>
<td>For</td>
<td>A 2</td>
<td>Against 4</td>
<td>First line A 1–3</td>
<td>Second line A 1–2</td>
</tr>
<tr>
<td>VASSA 2012</td>
<td>For</td>
<td>CR</td>
<td>For 4</td>
<td>First line 4</td>
<td>For* A 2</td>
</tr>
<tr>
<td>CEVF 2013</td>
<td>For</td>
<td>A 2</td>
<td>For 4</td>
<td>For 4</td>
<td>For</td>
</tr>
<tr>
<td>S3 2016</td>
<td>For</td>
<td>A 2</td>
<td>For 4</td>
<td>First line A 1</td>
<td>For</td>
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<tr>
<td>ESC 2017</td>
<td>For</td>
<td>A 3</td>
<td>For 4</td>
<td>First line A 3</td>
<td>For A 3</td>
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<td>For</td>
<td>A 2–3</td>
<td>For I–IIb 2–3</td>
<td>First line A 2</td>
<td>For A 2</td>
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<tr>
<td>Asian Consensus 2020</td>
<td>For</td>
<td>A–B 2–3</td>
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given the high prevalence of people living with PAD. A 2016 estimate placed age-standardised rates at 1930 (95% CI: 1702 - 2202) per 100,000 for women and 1658 (95% UI: 1457 to 1900) per 100,000 for men. Furthermore, we noticed an improvement in the guidelines across time in all domains in our study (figure 3), and this effect was present when we compared scores in this study to those done previously. The rigour of development scores particularly exemplifies this. The line chart in figure 3 clearly shows the rigour improving in the guidelines as they get more recent, just as observed in previous PAD guideline quality assessments. Unsurprisingly, we noticed better scores across the domains in this review compared with the previous studies. Hence we can confidently say that the PAD guidelines are improving over time which is encouraging.

With regards to the recommendations on screening, we observed increased harmony across the guidelines of interest (over the study period) as opposed to the heterogeneity in the recommendations found in previous reviews, which included much older guidelines. Despite the underlying deficiency in high-quality evidence, that is, randomised controlled trials (RCTs) specifically designed to compare screening versus non-screening for PAD are still lacking across the guidelines. However, there is a general harmony in the recommendation to screen ‘high risk’ patients. The best evidence supporting screening comes from the VIVA study, where combined screening for aortic abdominal aneurysm (AAA), PAD and hypertension was offered to men aged 65–74. The PAD research community continues to anticipate an RCT to address this topic confidently. In addressing the high-risk group, there was some conflict regarding age and general silence on the contribution of gender, which is well known to influence cardiovascular risk. Furthermore, in this study, we observed that just one guideline proffered a recommendation on screening intervals for PAD, further highlighting the gaps created by the absence of clear evidence.

In this paper, we also reviewed the recommendations for diagnosing ABI. We found no discrepancy in using ABI in conjunction with clinical history and physical examination for the initial diagnosis of PAD, as solid evidence exists for this recommendation. However, there is ample evidence to show that there are occasions when ABI readings are difficult to rely on, for example, in conditions associated with hardened arteries such as diabetes. In such settings, other methods were made across the guidelines for using such methods as Exercise ABI, Toe-Brachial Index (TBI), TaP02, pulse waveform, SPP, among others. There is sparse evidence backing these recommendations with attendant variations in the circumstances in which they should be used. Six guidelines strongly support the use of TBI in situations where there may be arterial hardening, such as diabetes, based on moderate-level evidence. Additionally, we noticed the more recent guidelines (written after 2016) relied on weak-to-moderate level evidence as opposed to the older ones, which relied more on consensus. So, while more evidence is finding its way into the guidelines clarifying this topic, we look forward to more extensive studies being conducted to enhance clarity. Furthermore, as with the recommendations on screening, these areas are of research interest to primary care physicians who are poorly represented in the PAD guideline writing groups could explain the apparent lack of interest in these topics.

The guidelines agreed that imaging is reserved for patients with confirmed PAD via initial testing methods, for whom revascularisation is being considered. The available imaging techniques suggested in the guidelines were uniform, including DUS, CTA, CE-MRA and DSA. It is widely acknowledged that place of practice, availability of enabling equipment, local policies and healthcare funding modalities offer some variation in the sequence/ circumstances in which each modality should be chosen. For these reasons, rather than based on solid evidence, the majority (six guidelines) recommended that DUS be used as the first-line imaging of choice because it is readily available and offers the least risk to the patients (table 5). Conversely, most guidelines also agreed that DSA should be reserved for cases where the arterial architecture remains ambiguous despite imaging with the other modalities due to elevated risk levels associated with its use.

And finally, regarding screening for other arterial diseases in other vascular beds, most of the guidelines were silent. Perhaps there appears to be no additional benefit to be obtained from this. Three guidelines, CEVF, AHA and the Asian Consensus, did make recommendations. All three guidelines recommended screening for AAA via ultrasound scan, two of them, AHA and the Asian Consensus, relied on evidence that shows that PAD is a strong independent risk factor for AAA. However, the CEVF guideline recommends screening for CAD based on consensus recommendations. In contrast, the AHA and Asian Consensus cautioned against screening for arterial disease in other vascular beds, stating that current evidence does not justify the benefit, especially since patients with PAD should be placed on best medical therapy (BMT). Current evidence has established that people living with PAD have higher rates of atherosclerotic arterial disease in other arterial beds (CAD, CVD, renal artery disease). So long as there is no need for vascu-larisation, the treatment for all these conditions remains BMT, including risk factor optimisation that the patient with PAD already benefits from. Justifying screening for these conditions will require evidence showing that revas-cularising asymptomatic forms of these diseases will result in better mortality and morbidity rates, which is currently unavailable.

There were some obvious limitations to this study. First, this review used thematic qualitative analysis in synthesising guideline recommendations for comparison. Given the large volume of information contained in the guidelines, some loss of vital information was inevitable during data analysis. Extensive efforts were made to minimise
these losses by using consistent rigorous and systematic approaches while organising the data into themes for comparison. Second, during the literature search for relevant CPGs, we exclusively conducted our search strategies in English. As such, it is not impossible that some relevant guidelines written during this period were not captured in this study.

CONCLUSION
The quality of PAD guidelines have been improving consistently over time. Nonetheless, future guideline writers/updates should consider focusing on the guideline applicability and stakeholder involvement domains. There is less variation in screening recommendations in the recent guidelines, but a dearth of evidence persists, which could be solved with better stakeholder involvement among guideline writing committees. Finally, more research is needed to provide better evidence and thus improve guideline recommendations on imaging options for PAD.

ETHICS APPROVAL STATEMENT
Being a systematic review that does not involve human subjects or other sensitive data, there was no need to seek ethical approval.

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ODU was responsible for the initial concept, design and is responsible for the overall content as guarantor of the study. All authors, ODU, CO, JI, OE, EC, AA and OO, participated in the concept and design, extraction, analysis and interpretation of the data, critical revision of the manuscript and approval of the final version to be published.

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Supplemental material
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