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Systematic Review

Methodological quality and clinical recommendations of guidelines on the management of dyslipidaemias for cardiovascular disease risk reduction: a systematic review and an appraisal through AGREE II and AGREE REX tools

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Abstract

Background: Clinical practice guidelines (CPGs) are statements to assist practitioners and stakeholders in decisions about healthcare. Low methodological quality guidelines may prejudice decision-making and negatively affect clinical outcomes in non-communicable diseases, such as cardiovascular diseases worsted by poor lipid management. We appraised the quality of CPGs on dyslipidemia management and synthesized the most updated pharmacological recommendations.

Methods: A systematic review following international recommendations was performed. Searches to retrieve CPG on pharmacological treatments in adults with dyslipidaemia were conducted in PubMed, Scopus, and Trip databases. Eligible articles were assessed using AGREE II (methodological quality) and AGREE-REX (recommendation excellence) tools. Descriptive statistics were used to summarize data. The most updated guidelines (published after 2019) had their recommendations qualitatively synthesized in an exploratory analysis.

Results: Overall, 66 guidelines authored by professional societies (75%) and targeting clinicians as primary users were selected. The AGREE II domains *Scope and Purpose* (89%) and *Clarity of Presentation* (97%), and the AGREE-REX item *Clinical Applicability* (77.0%) obtained the highest values. Conversely, guidelines were methodologically poorly performed/documented (46%) and scarcely provided data on the implementability of practical recommendations (38%). Recommendations on pharmacological treatments are overall similar, with slight differences concerning the use of supplements and the availability of drugs.

Conclusion: High-quality dyslipidaemia CPG, especially outside North America and Europe, and strictly addressing evidence synthesis, appraisal, and recommendations are needed, especially to guide primary care decisions. CPG developers should consider stakeholders' values and preferences and adapt existing statements to individual populations and healthcare systems to ensure successful implementation interventions.

Key words: practice guidelines as topic/standards; humans; adult; dyslipidemias; quality of health care; quality assurance, health care

Background

Highly prevalent non-communicable diseases (e.g. heart disease, stroke, diabetes, chronic lung disease) are responsible for most global deaths (73.6% in 2019) [1]. These diseases are often driven by multiple risk factors such as smoking, high blood pressure, obesity, or family history, and are aggravated by an imbalance in LDL-cholesterol (LDL-c) lipoproteins and triglyceride (TG) levels [2–8], defined as dyslipidaemia [7–9]. Actions addressed at preventing and treating dyslipidaemia and other risk factors are critical, especially in primary care, since severe or untreated lipid disorders can lead to end-organ diseases, which include cardiovascular diseases (CVDs; e.g. stroke, coronary artery disease (CAD), peripheral arterial disease), acute pancreatitis, and hepatosplenomegaly [10, 11].

Access to high-quality and updated scientific evidence can underpin clinical recommendations towards more effective, safe, and affordable health services [12]. Clinical practice guidelines (CPGs) include systematically developed statements built upon evidence-based principles that aim to assist

Key messages

- Practice guidelines for dyslipidaemia: methodological weaknesses.
- Guidelines' quality varies across continents, but not over time.
- Dyslipidaemias' management: focus on preventing cardiovascular events.
- Primary care approach: statins; caution advised for Asians.
- Literature gaps: scaling treatment and statin intolerance.
- Discrepancies among guidelines on dietary supplement use.

practitioners and other stakeholders in making decisions about appropriate care within a specific clinical scenario [12–14]. To ensure the methodological quality of CPGs and steer practice recommendations, validated and widely recognized tools such as AGREE II and AGREE REX have been developed [15–19]. Yet, limited research has evaluated the quality of lipids disorders management recommendations, either by primarily focussing on coronary heart disease (data from 2009 to 2019) [20] or by restricting the appraisal to specific guidelines as from the 2019 European Society of Cardiology and the European Atherosclerosis Society (ESC/EAS) [21]. Our goal was to critically appraise the methodological quality of CPGs in managing dyslipidaemias for cardiovascular risk reduction and stand out differences and opportunities to improve their development. Moreover, we aimed to exploratorily compare the practical pharmacological recommendations of the most updated guidelines.

Methods

This systematic review followed Joanna Briggs and Cochrane's recommendations [22, 23] and was reported following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [24–26] (PROSPERO CRD42023481886). Two authors independently conducted the study selection and data extraction processes, and a third author resolved potential discrepancies.

Search strategy and CPG selection

A systematic search was performed in the PubMed, Scopus, and Trip databases (December 2023) using terms related to 'clinical guidelines' and 'dyslipidaemia' (search strategies at Supplementary material) without timeframe or language limits. A manual search of the reference lists from the included studies was also performed. Documents related to the eligible CPGs (e.g. Supplementary material, Development guidance) were manually obtained from the sources described in the guidelines.

Studies were included if they met all eligibility criteria: referred to a CPG comprising clinical practice recommendations related to pharmacological treatments (i.e. drugs in any dose, regimen, or combinations) for adult patients with dyslipidemias (i.e. any health-related condition with changes in lipid parameters regardless of other comorbidities) aiming at disease control or cure. The document should comprise a statement from an expert panel, including evidence-based treatment recommendations. Only documents available online and authored by professional societies or governmental organizations were considered for eligibility.

During the screening phase, articles were excluded if deemed irrelevant to the study objectives. In the full-text eligibility phase, reports targeting specific population subgroups (e.g. women, elderly patients) or a single type of dyslipidaemia imbalance were excluded. Articles in languages other than English, German, French, Spanish, and Portuguese were excluded.

Data extraction

Information (i.e. authors, affiliations, geographic location, publication year, and evidence grading tools) from eligible CPGs was extracted using Microsoft Excel 365 spreadsheets. Clinical practical recommendations were extracted from guidelines published between 2019 and 2023 (the past 5 years). The recommendations were expressed using a standardized matrix with a traffic light plot to correlate the type of evidence with recommendation strength. The level of evidence follows the evidence-based medicine pyramid. The recommendations' classification was established by the authors according to the contents described by the assessment tools (see further details in Supplementary material).

Guidelines appraisal

The included guidelines were appraised by two authors independently using both AGREE-II and AGREE-REX instruments [16, 27]. Ratings on a 7-point scale were employed, with one indicating poor fulfilment of the criteria and seven indicating complete disclosure of all requirements. The domains, criteria details, suggested criteria for each item, and scoring methodology are described in the user manual [13, 28, 29]. The overall assessment for each instrument was derived by computing the mean across their respective domains.

Data analyses and synthesis

Descriptive statistics were used to summarize the data. For dichotomous variables, absolute and relative frequencies were reported, while continuous variables were represented using the mean, standard deviation (SD), or median, interquartile range [IQR], and minimum–maximum values. Student's *t*-test was used to compare scores between the two groups. Cohen's d and η^2 values and 95% confidence intervals were employed as effect size measures to evaluate the magnitude of differences [30]. A bivariate analysis was conducted with overall and domain scores against the type of party involved in the guideline generation (professional or governmental body), publication date, and CPG's geographical origin. Analyses were performed in IBM SPSS Statistics v.28 (significance level set at 0.05).

Results

A total of 11 200 records were retrieved after duplicate removal, of which 112, corresponding to 66 unique CPGs, were included for synthesis (see details in Supplementary material).

These guidelines were published between 1988 and 2023 (median 2017; IQR 2013–2020). Most documents were from North America (n = 22; 33%), followed by Asia (n = 18; 27%) and Europe (n = 11; 17%), being predominantly authored by professional societies (n = 47; 71%) or governmental entities (n = 13, 20%). In 44% of cases (n = 29), no declaration of CPG funding was found, while 40% (n = 26) were sponsored by pharmaceutical industries. Ten guidelines (nine from professional societies and one from a government institution) did not report a conflict of interest (COI).

All guidelines were centred on the prevention of CVD through the management of dyslipidaemias (a major modifiable risk factor). They declared an evidence-based methodological approach with recommendations formulated by an expert panel. Almost half of the CPGs (n = 30; 46%) used tools from their respective organizations to appraise the evidence and strength of the recommendations, such as those from the ESC/EAS and the American Heart Association (AHA). Twelve guidelines (18%) used the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) tool (Table 1).

Quality appraisal of the eligible practice guidelines

The overall results from the methodological appraisal of the CPGs are depicted in Table 1. Scores were 72% (SD 11) and 52% (SD 15) for the AGREE II and AGREE REX tools, respectively, indicating moderate quality. In AGREE II, the highest scores were achieved in Domain 4 (Clarity of Presentation) (97%; SD 7), followed by Domain 1 (Scope and Purpose) (89%; SD 14). Domains 6 (Editorial Independence), 5 (Applicability), and 2 (Stakeholder Involvement) had moderate scores of 69% (SD 22), 66% (SD 22), and 63% (SD 14), respectively. The items with the lowest scores were: 5 (‘*The views and preferences of the target population have been sought*’), 20 (‘*The potential resource implications of applying the recommendations have been considered*’), and 23 *(‘Competing interests of guideline development group members have been recorded and addressed’)*—medians of 3 (IQR 1–4), 3 (IQR 2–4), and 4 (IQR 2–6), respectively. Domain 3 (Rigour of Development) performed worst (46%; SD 20), with lowest rates for items 7 (‘*Systematic methods were used to search for evidence*’), 13 (‘*The guideline has been externally reviewed by experts prior to its publication*’), and 14 (‘*A procedure for updating the guideline is provided*’) with medians of 1 (IQR 1–4), 2 (IQR 1–4) and 2 (IQR 1–4), respectively. For AGREE REX, the highest scores were observed for Domain 1 (Clinical Applicability)—77% (SD 15)—while Domains 2 (Values and Preferences) and 3 (Implementability) scored 41% (SD 17) and 38% (SD 17), respectively. AGREE REX’s items 7 (Values and Preferences of Guideline Developers) and 8 (Purpose) scored the lowest (median 2; IQR 1–3).

No significant differences in guidelines’ quality were observed over the years. Yet, significant differences in favour of government-created guidelines vs. professional societies were observed for AGREE II overall assessment (P = 0.03) and Domains 2 (P < 0.01) and 3 (P = 0.05) (Fig. 1). CPG quality also varied according to their geographical origin, with guidelines from Europe outscoring Asia (both AGREE II overall score [P = 0.01] and AGREE II Domain 5 [P < 0.01]), Africa (AGREE II Domain 3 [P = 0.02], and AGREE REX Domain 1 [P = 0.04]), and North America (AGREE II Domain 5; P = 0.04) (Fig. 2).

Recommendations synthesis

A total of 20 guidelines were published in the past 5 years (2019–2023) and, thus, had their overall recommendations on pharmacological interventions for adults with dyslipidaemia summarized in Supplementary Tables 10 and 11. Two CPGs (BC 2021 and PEER 2023) gathered recommendations from other guidelines [31–33].

Overall, clinical recommendations, mostly targeted at reducing LDL and TG, were designed to assist clinicians in selecting the optimal course of care with their patients. They recommend that individuals are classified according to their CVD risk, yet different methods (e.g. QRISK3 algorithm [34], Chin-Shan [35], SCORE [36]) can be used. As patients with obesity, diabetes, chronic kidney disease (CKD), or with a history of CVD are more likely to experience cardiovascular events, they should be classified as having high, very high, or ultra-high risk for these events [34].

The first clinical approach to manage dyslipidaemia in primary care is to advise patients on healthier lifestyle choices (e.g. physical activities, balanced diet) before considering pharmacological interventions; simultaneously, secondary causes of lipid imbalance and patients’ comorbidities should be investigated. If treatment goals are not achieved, statins are the first-line approach to reduce high LDL-c or TG. Two treatment approaches are usually recommended by the guidelines: (i) prescribing moderate or high-intensity statins for all individuals with proven dyslipidaemias; (ii) calculating CVD risk score and estimating an LDL-c target. For patients at high or very high risk, a 50% reduction of LDL-c baseline or levels below 40 and 50 mg/dl is expected [31]. In low-to-moderate risk cases, it is recommended to achieve a reduction in LDL-c ranging from 30% to 50%, or a target threshold of 100 mg/dl or lower.

Yet, the use of statins may differ according to the clinical scenario. The CPGs correlate the intensity and dose of statins with the patient’s risk of developing CVD and their individual tolerance to the drug. Caution is advised when prescribing statins for primary prevention in Asians, since limited evidence is available for this population [37]. If the level of LDL-c still does not achieve the target value, other medications can be used, such as ezetimibe and PCSK9 inhibitors [31, 34, 38]. In patients with persistently elevated TG, the consideration of fibrates or icosapent ethyl may be warranted, provided their benefits outweigh potential side effects [32, 39]. Evidence gaps on scaling treatment process and statins intolerance still exist, which may be particularly concerning in subgroups of patients with elevated risk of cardiovascular events.

Discussion

This systematic review appraised 66 CPGs on pharmacological treatments for dyslipidaemia using AGREE II and AGREE REX tools, which correlate the credibility of guidelines and the validity of their recommendations to be used in clinical practice [40–44]. The primary management of dyslipidaemia, typically performed by primary care practitioners, extends beyond the reduction of lipid levels. It underpins CVD prevention efforts for both healthy individuals and those with comorbidities (e.g. elderly, patients with diabetes, CKD) while also helping to mitigate the risk of developing non-alcoholic fatty liver or pancreatitis in some patients [45–47]. Hence, guidelines narrowly focussing on lipid management as a risk

Table 1. Characteristics of the 66 included guidelines for dyslipidaemia management for CVD prevention (1988–2023) and results for AGREE II and AGREE REX domains.

Guideline	Goals (prevention of; management of)	Country—geographic location	Year	Recommendation tool	Organization	Fund	AII_ score	AII_ D1	AII_ D2	AII_ D3	AII_ D4	AII_ D5	AII_ D6	R_ score	R_ D1	R_ D2	R_ D3
AACE 2012	CVD; ODD	USA—North America	2012	Adapted	PS	NR	78	100	67	46	100	58	100	59	94	36	47
AACE 2017	CVD; ODD	USA—North America	2017	Organizers authorship	PS	AA	81	100	79	60	100	59	85	45	78	22	35
AACE 2020	CVD; ODD	USA—North America	2020	Not reported	PS	NR	51	69	65	25	69	38	40	67	93	46	62
AHA/ACC 2013	CVD	USA—North America	2013	Adapted	PS	NR	64	75	58	52	100	58	40	78	100	75	60
AHA/ACC 2018	CVD	USA—North America	2018	Organizers authorship	PS	OF	73	100	69	62	100	68	40	61	100	43	42
APSC 2021	CVD	Asian Pacific—Asia	2021	Grade	PS	PEG	67	100	50	41	100	48	65	33	64	19	15
BC 2014	CVD	Canada—North America	2014	Not reported	G	PS; G	53	69	39	22	83	57	50	49	70	45	33
BC 2021	CVD	Canada—North America	2021	Not reported	G	PS; G	53	69	39	20	83	57	50	39	83	17	18
BRAZIL 2019	CVD; P; ODD	Brazil—South America	2019	Grade	G	G	82	100	78	75	100	57	83	32	89	6	0
C-CHANGE 2011	CVD	Canada—North America	2011	*	PS and G	G	70	75	67	26	97	73	80	74	90	66	65
C-CHANGE 2014	CVD	Canada—North America	2014	*	PS and G	G	71	69	78	40	97	73	68	37	54	29	28
C-CHANGE 2018	CVD	Canada—North America	2018	*	PS and G	G	83	75	86	54	97	83	100	43	62	36	32
C-CHANGE 2022	CVD	Canada—North America	2022	*	PS and G	G	85	75	94	63	100	80	100	79	97	90	52
CCS 2006	CVD	Canada—North America	2006	Adapted	PS	OF	72	100	58	41	97	63	73	40	64	31	25
CCS 2009	CVD	Canada—North America	2009	Organizers authorship	PS	OF	83	100	65	64	100	72	100	54	77	40	47
CCS 2012	CVD	Canada—North America	2013	Grade	PS	NR	87	94	76	63	100	89	100	80	94	64	83
CCS 2016	CVD	Canada—North America	2016	Grade	PS	OF	65	75	56	48	97	44	73	71	100	61	52
CCS 2021	CVD	Canada—North America	2021	Grade	PS	OF	82	100	72	55	100	75	90	43	62	32	33
CHINA 2016	CVD; ODD	China—Asia	2018	Adapted	PS	PS; G	68	94	68	47	100	59	40	44	70	32	28
CHINA 2023	CVD	China—Asia	2023	Adapted	PS	PS; G	63	75	72	46	94	37	53	49	71	40	37

Table 1. Continued

Guideline	Goals (prevention of; management of)	Country—geographic location	Year	Recommendation tool	Organization	Fund	AII_ score	AII_ D1	AII_ D2	AII_ D3	AII_ D4	AII_ D5	AII_ D6	R_ score	R_ D1	R_ D2	R_ D3
EAS 1988	CVD	Europe	1988	Not reported	PS	NR	58	100	58	16	100	51	25	33	64	19	15
EGYPT 2020	CVD; ODD	Egypt—Africa	2020	Not reported	PS	NR	69	100	50	18	100	67	78	37	64	22	25
ESC 2021	CVD	Europe	2021	Organizers authorship	PS	PS	77	100	61	33	100	72	95	49	77	26	43
ESC/EAS 2011	CVD	Europe	2011	Organizers authorship	PS	PS	73	94	54	43	100	72	75	58	80	43	52
ESC/EAS 2016	CVD	Europe	2016	Organizers authorship	PS	PS	84	100	60	51	100	93	100	67	86	55	62
ESC/EAS 2019	CVD	Europe	2019	Organizers authorship	PS	PS	68	72	39	47	100	58	90	37	68	22	20
IAS 2014	CVD	International	2014	Not reported	PS	NR	70	64	61	40	100	81	75	52	84	32	38
INDIA 2018	CVD	India—Asia	2018	Organizers authorship	PS	NR	49	100	63	16	56	38	20	31	47	25	20
JAS 2007	CVD	Japan—Asia	2007	Not reported	PS	NR	72	100	56	40	100	86	50	51	77	50	25
JAS 2012	CVD	Japan—Asia	2012	Not reported	PS	NR	53	69	39	24	92	37	58	36	58	26	23
JAS 2017	CVD	Japan—Asia	2017	Organizers authorship	PS	NR	69	64	56	58	100	68	70	30	64	17	8
KSO-LA 2016	CVD; ODD	South Korea—Asia	2016	Adapted	PS	NR	66	100	64	26	100	69	35	45	66	34	35
KSO-LA 2018	CVD	South Korea—Asia	2018	Organizers authorship	PS	NR	71	83	44	45	100	79	75	43	74	25	30
MALAYSIA 2017	CVD	Malaysia—Asia	2017	Adapted	PS and G	PEG	87	100	75	86	100	82	83	57	91	33	47
MHS 2013	CVD	Mexico—North America	2013	Organizers authorship	G	NR	65	78	68	40	86	71	45	41	64	34	25
MIDDLE EAST 2016	CVD	Middle East—Asia	2016	Not reported	PS	PTH	55	75	42	35	97	48	35	42	62	25	40
MIDDLE EAST2021	CVD	Middle East—Asia	2021	Organizers authorship	PS	PTH	67	100	56	28	100	33	85	40	70	32	18
MSPS 2015	CVD	Colombia—South America	2015	Grade	G	G	90	100	90	71	100	81	100	83	93	76	78
NHFA CSANZ 2001	CVD	New Zealand and Australia—Oceania	2001	Not reported	PS	NR	71	92	58	45	100	82	50	67	91	57	53
NHFA/CSANZ 2005	CVD	New Zealand and Australia—Oceania	2005	Adapted	PS	NR	66	92	49	35	100	83	40	49	76	38	35
NICE 2008 (revised in 2010)	CVD	United Kingdom—Europe	2010	Organizers authorship	G	G	88	100	96	82	94	88	70	64	89	64	38

Table 1. Continued

Guideline	Goals (prevention of; management of)	Country—geographic location	Year	Recommendation tool	Organization	Fund	AII_ score	AII_ D1	AII_ D2	AII_ D3	AII_ D4	AII_ D5	AII_ D6	R_ score	R_ D1	R_ D2	R_ D3
NICE 2014	CVD	United Kingdom—Europe	2014	Grade	G	G	99	100	100	97	100	100	100	72	94	63	60
NICE 2023	CVD	United Kingdom—Europe	2023	Grade	G	G	100	100	100	98	100	100	100	95	100	91	95
NLA 2015	CVD	USA—North America	2014	Adapted	PS	NR	76	75	64	43	100	75	100	34	21	42	38
PEER 2015	CVD	Canada—North America	2015	Adapted	PS	PF	66	75	67	46	97	48	65	66	94	61	42
PEER 2023	CVD	Canada—North America	2023	Grade	PS	OF (PS)	73	75	60	74	100	67	63	62	77	58	52
PHILIPPINES 2015	CVD	Philippines—Asia	2015	Grade	PS and G	NR	68	100	63	35	100	55	55	66	81	61	57
PHILIPPINES 2020	CVD	Philippines—Asia	2020	Grade	PS	OF (PS)	79	100	64	55	100	58	95	49	73	36	37
PoLA/CFPiP/PCS 2017	CVD; ODD	Poland—Europe	2016	Organizers authorship	PS	NR	77	100	50	51	100	88	75	56	89	44	35
PoLA/CFPiP/PCS 2021	CVD; ODD	Poland—Europe	2021	Organizers authorship	PS	NR	78	100	67	37	100	82	80	61	82	51	48
QATAR 2020	CVD; ODD	Qatar—Asia	2020	Organizers authorship	G	G	67	92	78	42	100	41	50	61	94	51	38
SAH/LASSA 2000	CVD	South Africa—Africa	2000	Organizers authorship	PS	PEG; PF	67	100	67	18	100	53	63	39	59	31	25
SAH/LASSA 2012	CVD	South Africa—Africa	2013	Organizers authorship	PS	NR	59	83	58	14	100	61	40	38	53	38	25
SAH/LASSA 2015	CVD	South Africa—Africa	2015	Organizers authorship	PS	NR	58	100	39	17	100	64	25	40	54	38	30
SAH/LASSA 2018	CVD	South Afica—Africa	2018	Organizers authorship	PS	PF	68	72	39	47	100	58	90	42	61	34	30
SAUDI 2022	CVD	Saudi Arabia—Asia	2022	Organizers authorship	G	DNF	72	69	71	53	100	69	70	55	80	49	37
SBC 2001	CVD	Brazil—South America	2001	Organizers authorship	PS	NR	75	100	72	50	100	66	63	58	94	44	35
SBC 2007	CVD	Brazil—South America	2007	Organizers authorship	PS	NR	63	100	39	35	100	54	50	43	68	32	28
SBC 2013	CVD	Brazil—South America	2013	Organizers authorship	PS	NR	75	100	50	52	97	63	88	48	94	28	20
SBC 2017	CVD	Brazil—South America	2017	Organizers authorship	PS	NR	74	100	50	38	100	71	83	56	83	42	43

Table 1. Continued

Guideline	Goals (prevention of; management of)	Country—geographic location	Year	Recommendation tool	Organization	Fund	AII_ score	AII_ D1	AII_ D2	AII_ D3	AII_ D4	AII_ D5	AII_ D6	R_ score	R_ D1	R_ D2	R_ D3
SBC 2019	CVD	Brazil—South America	2019	Organizers authorship	PS	NR	59	69	28	30	100	53	75	34	77	16	10
SIGN 149	CVD	Scotland—Europe	2017	Organizers authorship	G	G; PF	92	100	90	79	100	97	88	55	80	40	47
SINGAPORE 2016	CVD	Singapore—Asia	2017	Organizers authorship	G	NR	72	100	71	37	97	79	50	48	77	31	35
SMC 2022	CVD	Mexico—North America	2022	Organizers authorship	PS	PF	78	100	78	81	100	37	75	55	74	47	45
TAIWAN 2022	CVD	Taiwan—Asia	2022	Organizers authorship	PS	NR	52	56	39	12	100	33	70	34	66	22	15
US VA/DOD 2020	CVD	USA—North America	2020	Grade	G	G	81	100	88	60	100	71	70	63	91	53	45
					Mean		72	89	63	46	97	66	69	52	77	41	38
					Standard deviation		11.2	13.5	16.3	19.8	7.2	16.7	22.0	14.6	15.3	17.3	17.4

Results expressed as mean (%) and standard deviation.
Note: AII—AGREE II overall assessment (mean of the six domains); AGREE II domains: AII D1—scope and purpose, AII D2—stakeholder involvement, AII D3—rigour of development, AII D4—clarity of presentation, AII D5—applicability, AII D6—editorial independence; AR—AGREE Rex overall assessment (mean of the three domains); AGREE REX domains: AR D1—clinical applicability, AR D2—values and preferences, AR D3—implementability.
Red squares: score ≤ 25%; yellow squares: 25% < score ≤ 50%; blue squares: 50% < score ≤ 75%; green squares: scores > 75%. Abbreviations: AA—financial support for administrative activities and logistics; CVD—cardiovascular diseases; DNF—declared "no funding received"; G—governmental; NR—not reported; ODD—other dyslipidaemic disorders; OF—own (organizational) funds; P—pancreatitis; PEG—private educational grants; PF—private funds; PS—professional society; PTH—private travel honoraria.

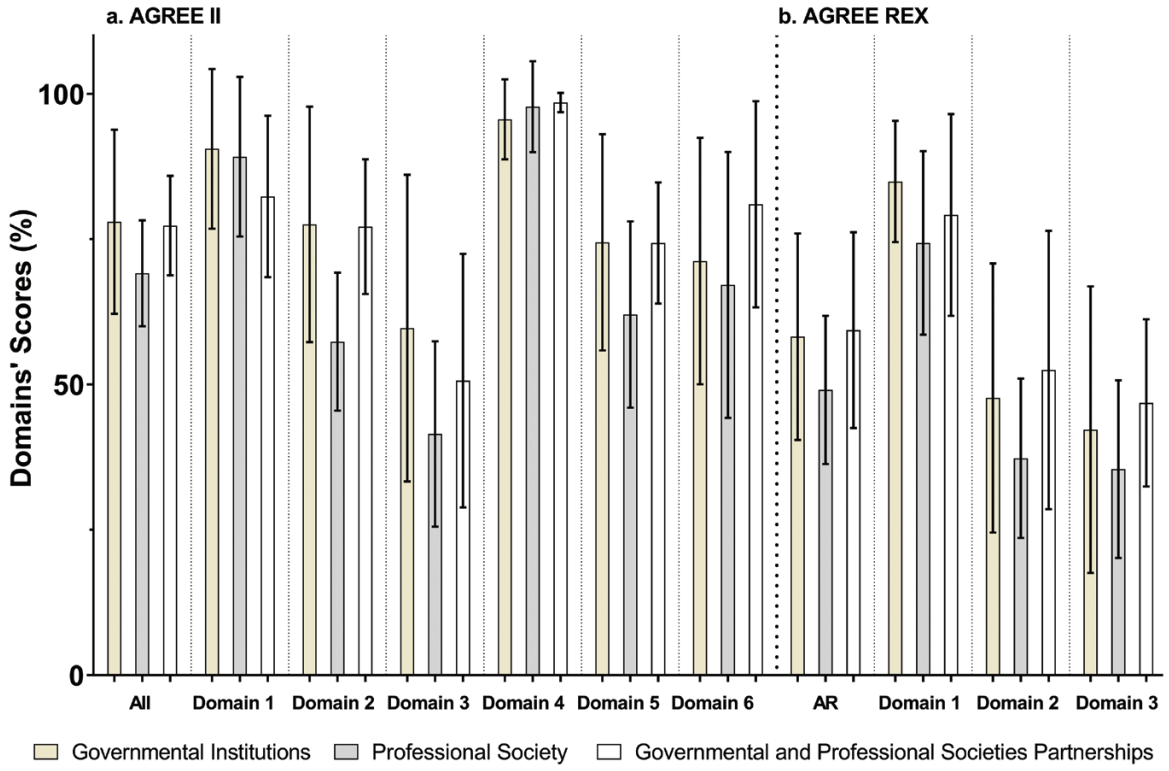

Figure 1. Comparison of AGREE II and AGREE REX domains' scores of the sixty-six CPGs (1988–2023) published by governmental organizations, professional societies or mixed developers. Results expressed as mean (%) and standard deviation. Note: AII—AGREE II overall assessment (mean of the AII six domains); AGREE II Domains: AII D1—Scope and Purpose, AII D2—Stakeholder Involvement, AII D3—Rigour of Development, AII D4—Clarity of Presentation, AII D5—Applicability, AII D6—Editorial Independence; AR—AGREE Rex overall assessment (mean of the AR three domains); AGREE REX domains: AR D1—Clinical Applicability, AR D2—Values and Preferences, AR D3—Implementability.

factor, without considering broader variables (e.g. smoking, genetic predispositions) may have limited practical value in primary care as they may not fully address the complexities of patients. Practical recommendations, including on patients' screening, methods to score cardiovascular risk assessment, diagnostic tools, and therapeutics, must uphold high standards for quality, accessibility, applicability, and feasibility for implementation in primary care settings [48].

Although around one-third of CPGs on dyslipidaemia was recently published, we found no significant improvements in their quality over time. Guidelines presented an overall moderate quality, with higher scores on AGREE II domains 1 (Scope and purpose) and 4 (Clarity of presentation) and on AGREE REX domain 1 (Clinical applicability), which is consistent with findings from studies on other clinical conditions [49–62]. Although these results suggest that guidelines are well written and are clinically relevant for stakeholders, several methodological issues were identified in Domain 3 of AGREE II (rigour of development) and Domain 2 of AGREE-REX (Values and Preferences). Most documents omitted information on the methods used for evidence gathering and recommendation development, CPG's strengths and limitations, external reviewers, and updating procedures. The use of evidence-to-decision frameworks in these cases could provide better documents with more transparent recommendations [63, 64].

Governmental guidelines often exhibit greater rigour than those from professional societies [59, 65, 66], being also less susceptible to COI and sponsors' influence—as confirmed by our study [67]. Some strategies to reduce COI included ensuring equal attention to both intellectual and financial conflicts, with explicit criteria provided for both; assigning methodologists without COI to oversee each chapter; limiting the formulation of recommendations to a panel of members with no relevant a priori bias [67, 68].

North America, Asia, and Europe published more guidelines, which is in accordance with the publication patterns worldwide [20, 59]. Yet, population characteristics reinforce the importance of local CPGs, especially in metabolic diseases [69–71] (e.g. dyslipidaemia is less prevalent in China but has a higher probability in South Asians, Hispanics, and black Americans [72, 73]; the metabolism of statins have differences between Asian and Western populations [74–76]). Europe presented the CPGs with higher quality, similar to previous studies on respiratory and CVD guidelines [77–81]. This can be due to the methods for developing, writing, and reporting practice guidelines in each country and the availability of resources. When tailoring recommendations to a specific population, it is paramount to integrate behavioural and social factors into the process, ensuring the engagement of stakeholders (AGREE II Domain 2), their values and preferences (AGREE-REX Domain 2), and other implementability features (AGREE-REX Domain 3) [82, 83]. CPGs are often written for specialized societies without significant input from primary care physicians, which may result in impractical or resource-intensive recommendations [84]. To increase stakeholders' involvement in the creation of guidelines, strategies such as training non-technical peers and performing focus groups and interviews with community leaders are highly recommended [85–91]. Moreover, employing standardized

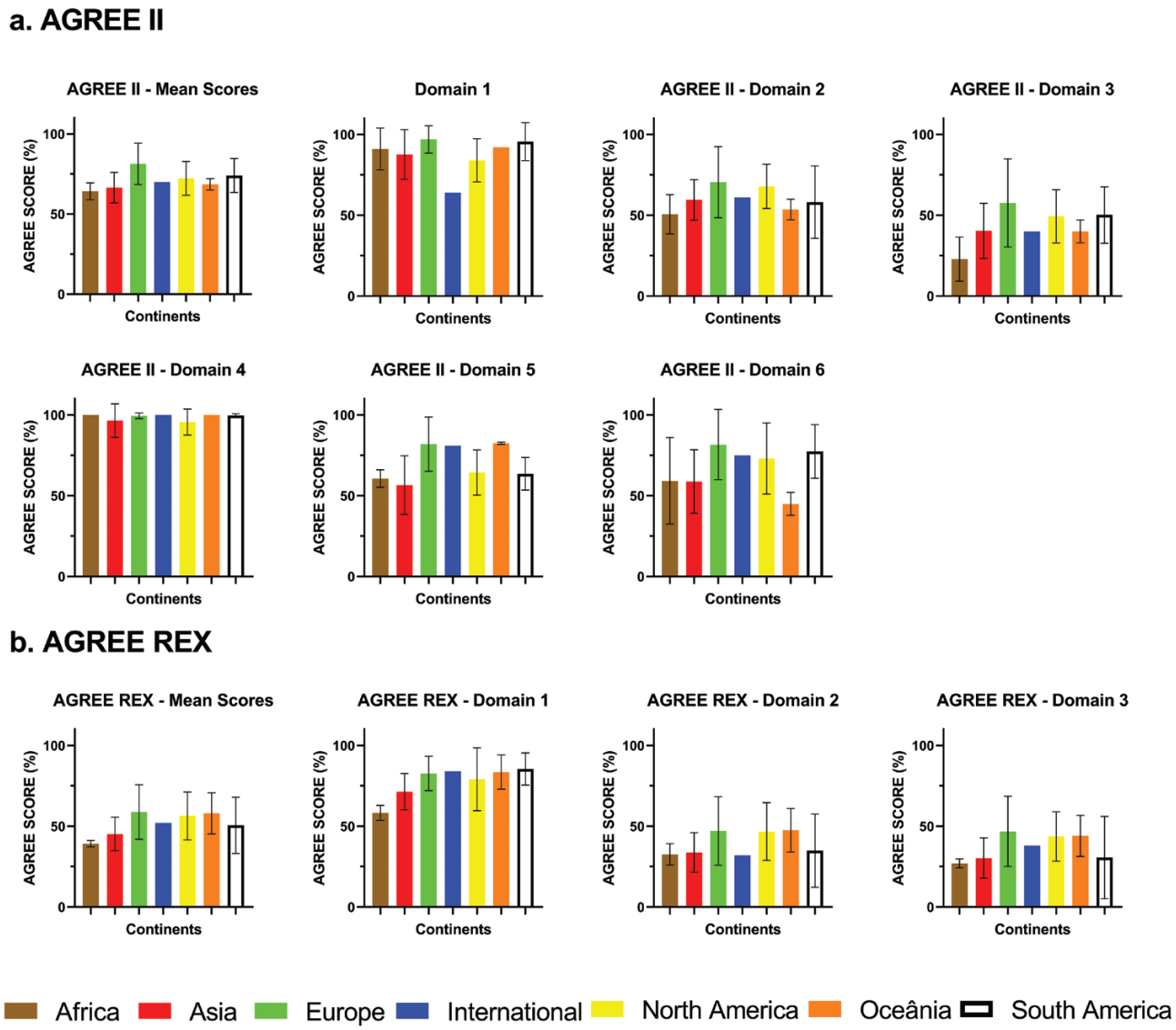

Figure 2. Comparison of AGREE II and AGREE REX domains' scores of the sixty-six CPGs (1988–2023) published in different continents. Results expressed as mean (%) and standard deviation. Note: AII—AGREE II overall assessment (mean of the six domains); AGREE II Domains: AII D1—Scope and Purpose, AII D2—Stakeholder Involvement, AII D3—Rigour of Development, AII D4—Clarity of Presentation, AII D5—Applicability, AII D6—Editorial Independence; AR—AGREE Rex overall assessment (mean of the three domains); AGREE REX domains: AR D1—Clinical Applicability, AR D2—Values and Preferences, AR D3—Implementability

terminology to quantify qualitative opinions can help in identifying urgent issues and address cultural disparities between community needs and healthcare services [89, 92].

Implementability is usually related to extrinsic factors (e.g. resource availability for drug administration, accessibility of recommendations for clinicians) rather than the guideline content itself [93–95]. It has been suggested that physicians' adherence to guidelines correlates with factors such as patient load, frequency of patient visits, and patients' diversity. Yet, we found no CPG mentioning strategies to address the communication between clinicians and patients, including perception of racism, cultural biases, or linguistic barriers in population subgroups (e.g. indigenous). These missing elements can reinforce stigma, increase mistrust, and reduce access to medical treatment [95].

We found clinical recommendations for dyslipidaemias' management and CVD prevention mostly consistent across guidelines. Healthier lifestyle adoption is the primary advice for all patients, followed by pharmacological treatment with statins, with upscaling often involving ezetimibe or PCSK9 inhibitors [48]. Recent real-world studies further indicate that PCSK9 inhibitors (whether alone or in combination) significantly reduce LDL-c levels compared with high-intensity statins or statins with ezetimibe [96]—which might be considered in practice. The strategy for prescribing statins varies among guidelines. While some advocate adjusting statin intensity based on a specific LDL-c target (treat-to-target approach), others recommend initiating moderate- or high-intensity statins for all individuals with high LDL-c or TG levels or those at risk of CVD [96]. While ongoing efforts are aimed at developing a more comprehensive guideline on dyslipidaemia management, some gaps, including differences in LDL-c thresholds, may persist due to genetic and cultural variations among populations. The ESC/EAS guideline

advocates for achieving the lowest possible LDL-c level (<50 mg/dl) for patients [97, 98], despite some studies suggesting that levels between 50 and 70 mg/dl may offer optimal results [99]. The differences also extend to the ideal environments in drugs' clinical trials compared with real-life treatment scenarios, where achieving the intended lipid levels may be hindered by comorbidities or equivocal interpretation of evidence [85, 97, 100, 101].

Our study has some limitations. While AGREE instruments provide a framework for evaluating guidelines, they may not fully account for the level of evidence attributed to recommendations. We did not assess the original studies included in the guidelines. We acknowledge that despite conducting a comprehensive review, certain guidelines may have been excluded due to our strict eligibility criteria—aimed at ensuring more homogeneous data. Although we were able to include CPGs encompassing five Anglo-Saxon and Latin languages, documents written in non-Roman characters were excluded, which may contribute to language bias. The assessment of CPGs with AGREE II and AGREE-REX tools was performed by two reviewers independently following the methodology outlined in the instruments' manuals. This process may have resulted in some arbitrary conclusions, as agreement decisions were restricted to information provided in published materials. We did not evaluate specific cut-off points for recommending guidelines ('I recommend this guideline'). Thus, a low-graded item does not necessarily mean that standardized procedures were not followed during the development of the guideline; poor reporting practices may result in low-quality grades. We evaluated only the methodological quality of guidelines addressing pharmacological treatments for dyslipidaemia and CVD risk reduction; results and conclusions should not be generalized to other conditions. While AGREE instruments facilitate the assessment of evidence and the strength of recommendations, it is important to avoid making specific comparisons between the content of guidelines. Further procedures for prioritizing evidence and establishing appropriate recommendations in each clinical setting should be developed [64, 102].

Conclusion

Significant weaknesses in the implementability, scientific rigour, and data transparency of CPGs on dyslipidaemia persist, potentially undermining decision-making processes in different settings. While European guidelines and those created by governmental bodies are associated with higher quality, modern guidelines have not improved over older ones. To ensure successful implementation, CPG developers should consider stakeholders' values and preferences (including primary care physicians) and strategically adapt existing CPGs to suit individual populations—especially considering that recommendations regarding pharmacological treatments are somewhat dissimilar across regions. Controversies regarding lipid treatment targets and drug availability exist, being probably influenced by external factors as genetics, culture, and health system management.

Supplementary data

Supplementary data is available at *Family Practice* online.

Ethical approval

This research was undertaken by the best scientific research standards and no ethical approval is necessary for systematic reviews evaluation.

Author contributions

Flávia Deffert (Data Curation, Investigation, Methodology, Writing – Original Draft, Writing- Review & Editing), Ana Paula Vilela (Data Curation, Investigation), Alexandre de Fátima Cobre (Data Curation), Luiz Henrique Picolo Furlan (Formal analysis, Writing), Fernanda Stumpf Tonin (Conceptualization, Methodology, Supervision, Formal analysis, Writing - Original Draft, Writing - Review & Editing) Fernando Fernandez-Llimos (Conceptualization, Methodology, Supervision, Formal analysis, Writing-Original Draft, Writing - Review & Editing), and Roberto Pontarolo (Supervision, Funding acquisition, Writing - Review & Editing). All named authors have read and approved the manuscript, and no other persons satisfied the authorship criteria.

Conflict of interest statement

The authors disclose that they do not have any financial or non-financial interests directly or indirectly situations that might raise the question of bias in the work submitted for publication.

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Data availability

All data supporting the findings of this study are available within the paper and its Supplementary material. Further information may be requested from the authors.

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