Original Article

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Assessing the quality of guidelines for primary aldosteronism: which guidelines are worth applying in diverse settings?

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Objective: To review the validity and applicability of clinical guidelines on the management of primary aldosteronism and to list their discrepancies to allow health-care providers and guideline developers to make informed decisions.

Design and methods: Primary aldosteronism management guidelines, including specialist, subgroup, general guidelines written in English, were obtained from electronic databases. Appraisers independently extracted the data, and used the Appraisal Guidelines Research and Evaluation II (AGREE-II) tool and the Institute of Medicine (IOM) criteria to independently evaluate the methodological quality of the guidelines. Then, the appraisers used the Guideline Implementability Appraisal (GLIA) tool to assess the implementation of the guidelines that complied with AGREE-II and IOM. In addition, we further compared the discrepancies in the primary aldosteronism management recommendations.

Results: We have identified 12 guidelines published between 2006 and 2016. Only the Endocrine Society and the Canadian Hypertension Education Program guidelines of them were of good methodological quality according the AGREE-II and IOM instrument, but with still much room for improvement. Neither of these two was rated as easily implementable according to the GLIA tool. Discrepant recommendations were identified at all management steps (screening, confirmation, classification, treatment and follow-up).

Conclusion: The guidelines quality was mostly poor, and the higher quality guidelines also needed improvement prior to their implementation. Meanwhile, significant differences existed in the recommendation for the same clinical problem. Therefore, future guideline development should be performed in strict accordance with the AGREE-II, IOM and GLIA criteria to improve the diagnosis and treatment of primary aldosteronism.

Keywords: Appraisal Guidelines Research and Evaluation II, critical appraisal, guidelines, implementation, primary aldosteronism, quality

Abbreviations: AACE/AAES, the American Association of Clinical Endocrinologists/American Association of Endocrine Surgeons; AGREE-II, the Appraisal Guidelines Research and Evaluation II; AHA, the American Heart Association; ARR, the plasma aldosterone/renin ratio; AVS, adrenal vein sampling; CHEP, the Canadian Hypertension Education Program; CPG, clinical practice guideline; ESH/ESC, the European Society of Hypertension/European Society of Cardiology; GLIA, the Guideline Implementability Appraisal; IACE, the Italian Association of Clinical Endocrinologists; IOM, the Institute of Medicine; JES, the Japan Endocrine Society; PAC, the plasma aldosterone concentration; POL, Poland; SFE/SFHTA/AFCE, the French Endocrinology Society/French Hypertension Society/Francophone Endocrine Surgery Association; SIIA, the Italian Society of Hypertension (Societa' Italiana dell' Ipertensione Arteriosa)

INTRODUCTION

Primary aldosteronism is a common form of endocrine hypertension characterized by an inappropriate and relatively autonomous production of aldosterone by the adrenal gland. Although the true prevalence of primary aldosteronism is debated, compelling evidence indicates that the prevalence of primary aldosteronism could be up to 3.2–12.7% in primary care and 1–29.8% in referral centers [1]. More importantly, a growing body of research also suggests that primary aldosteronism has greater deleterious cardiovascular and metabolic consequences than does matched essential hypertension [2]. The outcome of primary aldosteronism, however, is excellent if the patient is diagnosed and treated appropriately. Therefore, the diagnostic work-up to timely identify primary aldosteronism and management of primary aldosteronism have become increasingly important in recent years.

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Clinical practice guidelines (CPGs) are systematic statements written to help general practitioners and specialists make appropriate decisions to optimize disease management [3]. Many CPGs for managing primary aldosteronism have been published by several different countries and international organizations over the past 10 years. However, health conditions are researched by different groups and institutions at different dates, and the evidence and statements made in the guidelines are inconsistent [4]. This discrepancy can confuse clinical practitioners regarding the management of clinical events. Therefore, some organizations have developed objective standards to appraise the quality and implementability of the guidelines.

The Appraisal of Guidelines Research and Evaluation (AGREE) instrument is a widely accepted tool to assess the methodological quality of CPGs [5]. The original AGREE Instrument was published in 2003, and the updated 2017 edition (AGREE-II) was released in 2017 and is the most widely used version. In addition, the Institute of Medicine (IOM) tool was also developed and included items that were more detailed than the AGREE-II: guideline updating, external reviews and managing conflicts of interest [6]. To allow high-quality CPG use in the clinical setting, the Guideline Implementability Appraisal (GLIA) can assess the implementability of the CPGs [7]. A suitable guideline needs a high-quality clinical application that will benefit the patients. Therefore, this study used the AGREE-II, IOM and GLIA tools to comprehensively appraise the primary aldosteronism CPGs' quality and compare the CPGs' recommendations for managing primary aldosteronism and provides a roadmap to improve future primary aldosteronism management guidelines.

MATERIALS AND METHODS

Selection of correlative guidelines

We searched for the relevant CPGs for primary aldosteronism management in the following electronic databases: the Guidelines International Network, the National Guidelines Clearinghouse, the National Institute for Health and Care Excellence, the Australia National Health and Medical Research Council, the Scottish Intercollegiate Guidelines Network and PubMed. We used the following twelve search terms first, 'hypertension', second, 'high blood pressure', third, 'arterial blood pressure', fourth, 'arterial hypertension', fifth, 'refractory hypertension', sixth, 'resistant hypertension', seventh, 'adrenal incidentaloma', eighth, 'inapparent adrenal adenomas (mass)', ninth, 'hypokalemia', tenth, 'primary aldosteronism', eleventh, 'primary hyperaldosteronism' and twelfth, 'Conn's syndrome (adenoma)'. In addition, we performed searches in PubMed by combining the above terms with 'guideline' OR 'consensus' OR 'recommendation' OR 'statement'. We restricted the search to documents published between January 2006 and December 2016.

We selected the guidelines by establishing the following four inclusion criteria first, the target group-included adult primary aldosteronism patients; second, the guidelines referred to the diagnosis and/or therapy of primary aldosteronism; third, the full text of the guidelines was available online; and fourth, the guidelines are available in English. The following five exclusion criteria were applied first, the guidelines concentrated on the management of hypertension, hypokalemia or adrenal incidentaloma but did not address primary aldosteronism in detail; second, the guidelines focused entirely on other forms of hypertension or special groups, such as pulmonary hypertension, renovascular hypertension, diabetes, stroke, pregnant women or children; third, the guidelines failed to meet the definition of a guideline; fourth, the guidelines did not present original recommendations; and fifth, the older version of guidelines would be excluded if a later edition was available.

Data collection and extraction from the guidelines

Two reviewers (J.L and J.Z) independently compiled the CPGs' characteristics in detail from the guidelines. The compiled data included the following: the guideline organization, country or region, publication date, guideline panel composition, target users, methods for searching for the evidence, strategy for grading the evidence, guideline review and the funding source. In addition, the two reviewers (W.J.L and W.Q.T) compiled the recommendations pertaining to the primary aldosteronism screening, confirmatory and subtype classification tests and primary aldosteronism management. Because each guideline used different measurement units, we used the following units consistently: the plasma aldosterone/renin ratio (ARR) was expressed as ng/dl/ng/ml/h, the plasma aldosterone concentration (PAC) was expressed as pmol/l, the urinary aldosterone was expressed as nmol/24 h, and the urinary Na was expressed as mmol/24 h.

Quality assessment of the guidelines

The AGREE-II (http://www.agreetrust.org) tool was independently used by two raters to evaluate the guidelines' quality. The instrument comprises 23 items organized into the following six main domains first, the scope and purpose, second, the stakeholder involvement, third, the rigor of development, fourth, the clarity of presentation, fifth, the applicability and sixth the editorial independence [5]. Each item was given a score by the raters ranging from 1 (strongly disagree) to 7 (strongly agree). Any score varying less than three for each item was accepted. If the score varied by more than three, the two raters discussed the topic and reassessed as necessary. Per the AGREE-II instrument, we calculated each item's score and identified the guidelines as 'strongly recommended', 'recommended with modification' or 'not recommended'. If most of the domain scores (four or more domains) were above 60%, the guideline was 'strongly recommended'; 'recommended with modification' was used when most of the domain scores were between 30 and 60% or when three domain scores were above 60%; and if most of the domain scores were at or below 30%, the guideline was 'not recommended' [8].

The IOM was another tool used to appraise the guidelines' methodological quality. The IOM criteria included the following eight standards comprising 20 subcriteria first, establishing transparency, second, managing conflicts of interest, third, the developing group's composition, fourth, the systematic review, fifth, the evidence for the

recommendations and rating the strength of the recommendations, sixth, articulation of the recommendations, seventh, the external review and eighth, updating [6]. Two raters independently evaluated all the guidelines' quality, and if any discrepancies existed, the two raters would discuss the discrepancies.

Implementability of the guidelines

To improve guideline adherence and consequently healthcare, the implementability of the guidelines should be considered. Thus, we added another instrument, GLIA, which identifies the potential implantation obstacles that are primarily intrinsic to the guideline to assess the CPGs' implementability. GLIA (http://gem.med.yale.edu/eglia) includes 31 questions. The questions of the GLIA instrument are all provided in Supplementary Table 1S, http://links.lww.com/HJH/B60. Questions 1–7 (part 1) are global considerations of the guideline, and the remaining questions (part 2) considered each recommendation and were divided into the following nine items first, decidability, second, executability, third, the effect on the process of care, fourth, presentation and formatting, fifth, measurable outcomes, sixth, apparent validity, seventh, novelty/innovation, eighth, flexibility and ninth, computability [7]. The GLIA was originally established as a qualitative tool to make a more intuitive and convenient comparison; however, we optimized the GLIA to a quantitative instrument. Similar to AGREE-II, each question had a score ranging from 1 (no) to 7 (yes). If the recommendation was absolutely fulfilled by the question, the question scored 7. If the recommendation was not absolutely fulfilled by the question, the question scored between 1 and 6; scores increased as more criteria were met, and more considerations were addressed. If the question was not appropriate for the recommendation, it scored a 0. Two raters independently scored the questions, and if the two raters' scores differed by more than three, they discussed and reassessed the question as necessary. GLIA is similar to AGREE-II in that each score was calculated by adding together all the individual questions' scores in part 2 and standardizing them as follows:

$$\frac{\text{Obtained score} - \text{Minimum possible score}}{\text{Maximum possible score} - \text{Minimum possible score}}$$

Then, all the scores were summed and averaged to calculate the score from part 2. The method to calculate the part 1 score was the same as that described above. Part 1 and part 2 scores above 80% demonstrate excellent guideline implementability. If one part's score was at or below 60%, the guideline's implementability was poor. Any other score combination indicated that the implementability was general.

RESULTS

Search for guidelines

In total, 4522 articles were identified in PubMed, and 838 articles were found in the other electronic databases. A total of 12 guidelines fulfilled our inclusion criteria, and the CPGs selection process is presented in Fig. 1.

Characteristics of the guidelines

The CPGs characteristics are provided in Table 1. Because primary aldosteronism involves various disciplines and levels of doctors in diverse settings, we divided the target guidelines into the following three categories first, Specialist Guidelines, second, Subgroup Guidelines and third, General Guidelines. One guideline was developed in Asia [9], five guidelines were developed in the USA [10–14] and the rest were developed in Europe [15–20]. The guidelines were published between 2006 and 2016. The panel composition was multidisciplinary in five guidelines [9,11,14,19], and only the European Society of Hypertension/European Society of Cardiology (ESH/ESC) guideline included family health-care. Four guidelines were produced by clinical endocrinologists and/or endocrine surgeons [10,13,16,17], and the remaining guidelines did not mention who created the guidelines [12,18,19]. To search for evidence, nine guidelines used a systematic review [9–11,13,14,16–18,20], and the rest did not mention the method used [12,15,19]. Only seven guidelines presented the strategy used to grade the evidence [10,11,13,14,17,18,20], and three guidelines used the Grading of Recommendations, Assessment, Development, and Evaluation group system. The American Association of Clinical Endocrinologists/American Association of Endocrine Surgeons (AACE/AAES) guideline and the AACE guideline used the AACE Protocol for Standardized Production of Clinical Practice Guidelines. The Canadian Hypertension Education Program (CHEP) guideline and the ESH/ESC guideline were related to the standard from CHEP and the standard from ESC. Before publication, seven guidelines were reviewed externally and/or internally [9–11,13–15,20]. The Italian Association of Clinical Endocrinologists (IACE) guideline and the American Heart Association (AHA) guideline were reviewed by experts, and the remaining guidelines did not mention any review process [16,18,19]. Four guidelines were funded by varying organizations [9,11,15,18]; the Endocrine Society guideline and the IACE guideline had no funding, and the remaining guidelines did not mention funding [10,12,13,16,19,20].

Comparison of the primary aldosteronism screening recommendations

The guidelines' recommendations are presented in Table 2. Nearly all the guidelines recommended that patients with hypertension and adrenal incidentaloma undergo primary aldosteronism screening except for the Japan Endocrine Society (JES), the AHA and the AACE guidelines. Excluding the Subgroup Guidelines [12,13,16,17], the other guidelines recommended those with hypertension and spontaneous or diuretic-induced hypokalemia as target patients. The Specialist Guidelines [9,14,18–20] recommended hypertensive patients as target patients, but the recommendations were different from those for the degree of blood pressure (BP) as follows. The Italian Society of Hypertension (Societa' Italiana dell' Ipertensione Arteriosa, SIIA) and the Poland (POL) [19] recommended patients with a BP above 160/100 mmHg, and the Endocrine Society guideline recommended patients with a BP above 150/100 mmHg with hypertension (BP > 140/90) resistant to the three conventional antihypertensive drugs (including a diuretic)

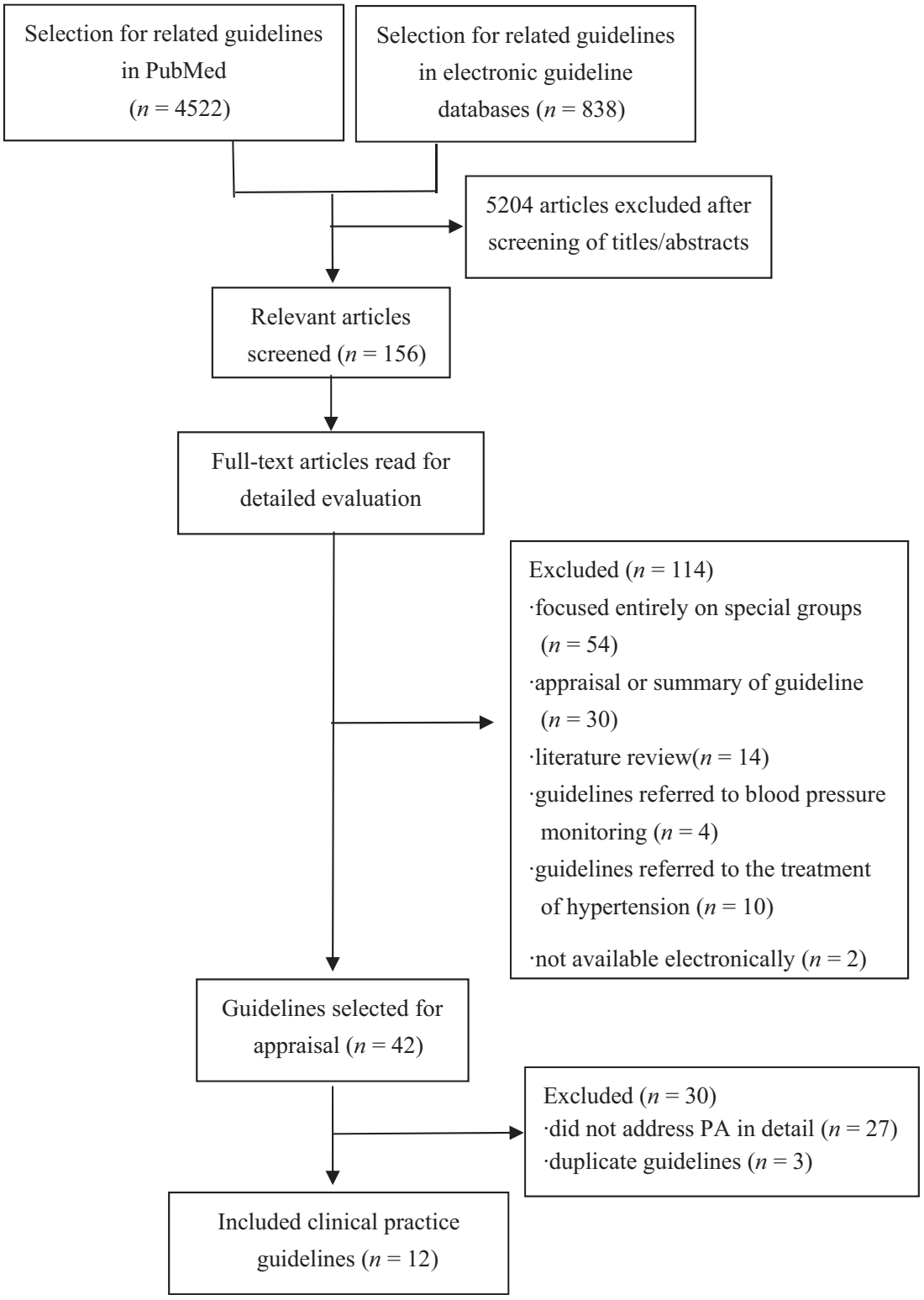

FIGURE 1 Flowchart for selecting the clinical practice guidelines. PA, primary aldosteronism.

or controlled BP (<140/90) on four or more antihypertensive drugs. The French Endocrinology Society/French Hypertension Society/Francophone Endocrine Surgery Association (SFE/SFHTA/AFCE) guideline recommended patients with severe hypertension (SBP $\geq$ 180 mmHg or DBP 110 mmHg). The Specialist Guidelines (the Endocrine Society, JES, SIIA, POL, SFE/SFHTA/AFCE) and the AHA, CHEP and AACE guidelines also recommended patients with resistant hypertension as screening patients. Patients with hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years) were recommended as screening

TABLE 1. Characteristics of the clinical practice guidelines included in this study

Guideline title	Organization	Country / region	Date	Guideline panel composition	Methods of searching for evidence	Strategy for grading the evidence	Guideline review	Funding source
The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline	ES	United States	2016	Multidisciplinary	Systematic review	GRADE	External and internal review	No funding
Guidelines for the Diagnosis and Treatment of Primary Aldosteronism	JES	Japan	2011	Multidisciplinary	Systematic review	NM	External and internal review	The Japanese Ministry of Health, Labour and Welfare
Clinical Management of Primary Aldosteronism 2013 Practical Recommendations of the Italian Society of Hypertension (SIIA)	SIIA	Italy	2014	NM	NM	NM	NM	The Societa' Italiana dell'Ipertensione Arteriosa and the University of Padua to GPR
Primary Aldosteronism: A Common and Important Problem. A Practical Guide to the Diagnosis and Treatment	POL	Poland	2012	NM	NM	NM	NM	NM
SFE/SFHTA/AFCE Primary Aldosteronism Consensus: Introduction and Handbook	SFE/SFHTA/AFCE	France	2016	Multidisciplinary	Systematic review	GRADE	Internal review	NM
American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons Medical Guidelines for the Management of Adrenal Incidentalomas	AACE/AAES	United States	2009	Endocrinologists, surgeons	Systematic review	AACE Protocol	Internal review	NM
AME Position Statement on Adrenal Incidentaloma	IACE	Italy	2011	Endocrinologists	Systematic review	GRADE	Expert review	No funding
Adrenal Incidentaloma in Adults – Management Recommendations by the Polish Society of Endocrinology	PSE	Poland	2016	Endocrinologists	Systematic review	NM	NM	NM
Adrenal Incidentaloma in Adults – Management Recommendations by the Polish Society of Endocrinology	PSE	Poland	2016	Endocrinologists	Systematic review	NM	NM	NM
Resistant Hypertension: Diagnosis, Evaluation, and Treatment. A Scientific Statement from the American Heart Association Professional Education Committee of the Council or High Blood Pressure Research	AHA	United States	2008	NM	NM	NM	Expert peer review	NM
Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension	CHEP	Canada	2016	Multidisciplinary	Systematic review	The standard from CHEP	External review	Hypertension Canada
2013 ESH/ESC Guidelines for the Management of Arterial Hypertension	ESH/ESC	European	2013	Multidisciplinary	Systematic review	The standard from ESC	External review	European Society of Hypertension/European Society of Cardiology
American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Hypertension	AACE	United States	2006	Endocrinologists and hemodynamic experts	Systematic review	AACE Protocol	External review	NM

AACE, the American Association of Clinical Endocrinologists; AACE/AAES, the American Association of Clinical Endocrinologists/American Association of Endocrine Surgeons; AHA, the American Heart Association; CHEP, the Canadian Hypertension Education Program; ES, the Endocrine Society; ESH/ESC, the European Society of Hypertension/European Society of Cardiology; GRADE, the Grading of Recommendations, Assessment, Development, and Evaluation group; IACE, the Italian Association of Clinical Endocrinologists; JES, the Japan Endocrine Society; NM, not mentioned; POL, Poland; PSE, the Polish Society of Endocrinology; SFE/SFHTA/AFCE, the French Endocrinology Society/French Hypertension Society/Francophone Endocrine Surgery Association; SIIA, the Italian Society of Hypertension (Societa' Italiana dell' Ipertensione Arteriosa).

TABLE 2. Clinical practice guideline recommendations for primary aldosteronism screening

	Specialist guideline					Subgroup guideline				General guideline		
Recommendations	**ES**	**JES**	**SIIA**	**POL**	**SFE/SFHA/AFCE**	**AACE/AAES**	**IACE**	**PSE**	**AHA**	**CHEP**	**ESH/ESC**	**AACE**
Screening PA												
Hypertension	R	R	R	R	R	NM	NM	NM	NM	NM	NM	NM
Cutoff (mmHg)	150/100	140/90	160/90	160/100	180/110	NM	NM	NM	NM	NM	NM	NM
Resistant hypertension	R	R	R	R	R	R	NM	NM	R	R	NM	R
Hypertension accompanied by Adrenal incidentaloma	R	NM	R	R	R	R	R	R	NM	R	R	NM
Hypokalemia	R	R	R	R	R	R	NM	NM	NM	R	R	R
A family history of early-onset hypertension or cerebrovascular accident at a young age	R (<40 years)	NM	R (<50 years)	R (<40 years)	NM	NM	NM	NM	NM	NM	R (<40 years)	NM
First-degree relatives of patients with PA	R	NM	R	R	NM	NM	NM	NM	NM	NM	NM	NM
Sleep apnea	R	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Hypokalemia and adrenal incidentaloma	NM	NM	NM	NM	R	NM	R	R	NM	NM	NM	NM
Screening test												
ARR (cutoff value ng/dl/ng/ml/h)	R (30)	R (20)	R (30)	R (7.2–100)	R (30)	R (20)	R (30–50)	R (30)	R (20–30)	R (30)	R	R (25–50)
Times (>2)	R[a]	R	R[b]	NM	R	NM	NM	NM	NM	NM	NM	NM
ARR + PAC (cutoff value; PAC, pmol/l)	NM	R (336–420)	R (336–420)	R (420)	R (240–550)	NM	NM	R (280–420)	NM	NM	NM	R (420)
Screening test preparation												
Liberalize sodium intake	R	NM	R	R	R	NM	R	R	NM	R	NM	NM
Correct hypokalemia	R	NM	NM	R	R	NM	R	R	NM	R	R	NM
Withdraw agents (weeks)	R	R	R	R	R	R	R	R	R	R	R	R
MR antagonists	R (4)	R (6)	R (6)	R	R (6)	R (4–6)	R (6)	R (4)	R	R (4–6)	NM	R
Potassium-wasting diuretics	R (4)	R (6)	R (3)	R	R (2)	R	R (4)	R (4)	R	R (4–6)	NM	R
β-Adrenergic blockers	R (2)	R (2)	R (3)	R	R (2)	R	R (4)	R	NM	R (2)	NM	R
Central α-2 agonists	R (2)	NM	NM	R	NR	NM	R (4)	R	NM	R (2)	NM	NM
NSAIDs	R (2)	NM	NM	R	NM	NM	R (4)	NM	NM	NM	NM	NM
ACEI or ARB	R (2)	NM	R	R	R (2)	R	R (4)	R (2)	NM	R (2)	NM	R
Renin inhibitors	R (2)	NM	R	NM	R (6)	NM	NM	NM	NM	R (2)	NM	NM
Ca2+ blockers	R (2)	NM	NM	R	R (2)	R	R (4)	R	NM	R (2)	NM	R
Contraceptive	R	NM	NM	R	R (6)	NM	NM	R (4)	NM	NM	NM	NM
Conditions for collection of blood samples												
Time (in the morning)	R	R	NM	R	R	R	NM	R	R	R	NM	R
Upright (h)	2	0.5	NM	2	2	2	NM	2	NM	2	NM	NM
Position (sitting, min)	R (5–15)	R (15)	NM	R (5–15)	R (5–15)	R (5–15)	NM	R, NM	NM	R (5–15)	NM	R, NM

AACE, the American Association of Clinical Endocrinologists; AACE/AAES, the American Association of Clinical Endocrinologists/American Association of Endocrine Surgeons; ACEI, Angiotensin converting enzyme inhibitors; AHA, the American Heart Association; ARB, angiotensin II type 1 receptor blockers; ARR, the plasma aldosterone/renin ratio; CHEP, the Canadian Hypertension Education Program; ES, the Endocrine Society; ESH/ESC, the European Society of Hypertension/European Society of Cardiology; IACE, the Italian Association of Clinical Endocrinologists; JES, the Japan Endocrine Society; MR, mineralocorticoid receptor; NM, not mentioned; NR, not recommended; PA, primary aldosteronism; PAC, the plasma aldosterone concentration; POL, Poland; PSE, the Polish Society of Endocrinology; R, recommended; SFE/SFHTA/AFCE, the French Endocrinology Society/French Hypertension Society/Francophone Endocrine Surgery Association; SIIA, the Italian Society of Hypertension (Societa' Italiana dell' Ipertensione Arteriosa).

[a]The ARR should be repeated if the initial results are inconclusive or difficult to interpret due to suboptimal sampling conditions or if PA is strongly suspected clinically but the initial screening results are negative.

[b]If the ARR is borderline or high (between 26 and 100 ng/dl/ng/ml/h), the guideline suggests that the test be repeated.

patients by the Endocrine Society, POL and ESH/ESC guidelines. The SIIA guideline was similar, but the family history of early-onset was defined as less than 50 years. Only the Endocrine Society, SIIA and POL guidelines recommended screening for all hypertensive first-degree relatives of patients with primary aldosteronism, and only the Endocrine Society guideline recommended that hypertensive patients with sleep apnea be screened for primary aldosteronism. The SFE/SFHTA/AFCE guideline and the Subgroup Guidelines, except for the AACE/AAES and AHA guidelines, recommended primary aldosteronism screening for patients with hypokalemia and adrenal incidentaloma.

Before screening, some preparation should occur. Most of the guidelines, except for those of the JES, AACE/AAES, AHA and AACE, strongly recommended correcting hypokalemia and liberalizing sodium intake before primary aldosteronism testing. All the guidelines recommended withdrawing agents that may affect the test results, but only the ESH/ESC guideline did not define specific agents. All the other guidelines specifically listed mineralocorticoid receptor antagonists, β-adrenergic blockers and potassium-wasting diuretics, with the withdrawal time varying from 2 to 6 weeks. Angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers and Ca^{2+} blockers were recommended to be withdrawn for at least 2 weeks by most of the guidelines. Only a minority of the guidelines recommended that NSAIDs, renin inhibitors and contraceptives should be withdrawn. For central α-2 agonists, half of the guidelines recommended withdrawal, and only the SFE/SFHTA/AFCE guideline recommended the patient continue the medication. Most of the guidelines, except for the SIIA and IACE, recommended collecting blood samples in the morning, and a majority of the guidelines recommended that the patient be upright for 2 h and sit for 5–15 min prior to the blood draw. The ARR was recommended as the first screening test by all the guidelines, but the value cut off varied among the guidelines. The Endocrine Society guideline recommended that the ARR should be repeated if the initial ARR results were inconclusive or difficult to interpret due to suboptimal sampling conditions or if primary aldosteronism was strongly suspected clinically even if the initial screening results were negative. The SIIA guideline recommended that a borderline or high ARR (between 26 and 100 ng/dl/ng/ml/h) should be remeasured. Half of the guidelines recommended considering both the ARR and the PAC. The PAC cut-off values varied from 240 to 550 pmol/l. The Endocrine Society and SFE/SFHTA/AFCE guidelines suggested that if the ARR satisfied the cut off and the PAC was more than 550 ng/dl, primary aldosteronism was confirmed, and the CHEP guideline recommended that an ARR more than 50 ng/dl/ng/ml/h with a plasma aldosterone more than 440 pmol/l confirmed primary aldosteronism with no further testing needed.

Comparison of the primary aldosteronism confirmation and subtype classification

Excluding the aforementioned situation, if the ARR satisfied the cutoff, all the guidelines recommended a confirmation test. The recommendations for confirming primary aldosteronism and identifying the subtype classification are presented in Table 3. The saline infusion test (0.9% saline) and the oral sodium loading test were recommended by most of the guidelines. The PAC was used as the criterion for the saline infusion test (SIT; 0.9% saline). The Endocrine Society and CHEP guidelines recommended that a PAC more than 280 pmol/l likely indicates primary aldosteronism, a PAC less than 140 pmol/l excludes primary aldosteronism and a PAC between 140 and 280 pmol/l neither confirms nor denies primary aldosteronism. A PAC more than 238 pmol/l and more than 140 pmol/l was the criterion of the JES and POL guidelines, respectively, for confirming primary aldosteronism. For the oral sodium loading test, the Endocrine Society and CHEP guidelines recommended that the urinary aldosterone more than 33 nmol/24 h confirms primary aldosteronism, and a the urinary aldosterone less than 28 nmol/24 h results in no primary aldosteronism diagnosis. Urinary Na was also used as a qualification measure. The JES guideline recommended primary aldosteronism diagnosis if the urinary aldosterone was more than 22 nmol/24 h or if the urinary Na was more than 170 mmol/24 h, and the AACE/AAES guideline recommended primary aldosteronism diagnosis if the urinary aldosterone was more than 22 nmol/24 h or if the urinary Na was more than 200 mmol/24 h. However, the AACE guideline recommended that a PAC at least 280 pmol/l likely indicates primary aldosteronism. Only half of the guidelines recommended a captopril challenge test as the confirming test, and the Endocrine Society and CHEP guidelines recommended that primary aldosteronism should be confirmed if the PAC suppressed 30% or less. The JES guideline recommended that an ARR more than 20 ng/dl/ng/ml/h or a PAC more than 336 pmol/l confirms primary aldosteronism. Only the Endocrine Society, POL and ESH/ESC guidelines recommended the fludrocortisone suppression test, with a PAC more than 140 or 168 pmol/l resulting in primary aldosteronism consideration. Only the JES guideline recommended the upright furosemide loading test, with a plasma resin activity less than 2 ng/ml/h resulting in a likely consideration of primary aldosteronism.

If primary aldosteronism is confirmed, the subtype classification should be determined next. Except for the SIIA guideline, the guidelines all recommended a computed tomography (CT) scan as the initial step for subtype testing. Half of the guidelines also recommended an MRI scan to help localize the presence of an adrenal lesion. If surgical treatment was feasible and desired, most of the guidelines recommended considering an adrenal vein sampling (AVS) by an experienced radiologist to differentiate unilateral from bilateral adrenal disease. However, only six guidelines referred to the operation procedures and the judgment standards of the AVS [9,10,13,14,19,20]. Five guidelines recommended the sequential technique with cosyntropin stimulation [9,10,13,14,19] with the selectivity index (the ratio of the plasma cortisol concentration in an adrenal vein and in the infra-adrenal inferior vena cava) as the criterion for successful catheterization [21], but the cutoff of the selectivity index varied. The Endocrine Society and JES guidelines recommended a cut off of more than 5, and the AACE recommended a cutoff of more than 10. However, only the SFE/SFHTA/AFCE guideline recommended the bilateral simultaneous technique with no stimulation, with a selectivity index cut off of more than 2. Four

TABLE 3. Clinical practice guideline recommendations for confirming primary aldosteronism and the subtype classification

	Specialist guideline					Subgroup guideline				General guideline		
Recommendations	ES	JES	SIIA	POL	SFE/SFHTA/AFCE	AACE/AAES	IACE	PSE	AHA	CHEP	ESH/ESC	AACE
Confirmatory test												
Saline infusion test	R	R	NM	R	R	R	NM	NM	NM	R	R	R
Judgement criterion (PAC, pmol/l)	R	R	NM	R	NM	R	NM	NM	NM	R	NM	R
Confirm	>10	>8.5	NM	>5	NM	>10	NM	NM	NM	>10	NM	≥10
Exclude	<5	NM	NM	NM	NM	NM	NM	NM	NM	<5	NM	NM
Indeterminate	5–10	NM	NM	NM	NM	NM	NM	NM	NM	5–10	NM	NM
Oral sodium loading Judgement criterion	R	R	NM	R	R	R	NM	NM	NM	R	R	R
Urinary aldosterone (nmol/24 h)	R	R	NM	NM	NM	R	NM	NM	NM	R	NM	NM
Urinary Na (mmol/24 h)	NM	R	NM	NM	NM	R	NM	NM	NM	NM	NM	NM
PAC (pmol/l)	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	R
Confirm	UA > 33	UA > 22 Na > 170	NM	NM	NM	UA > 33 Na > 200	NM	NM	NM	UA > 33	NM	PAC ≥ 280
Exclude	UA < 28	NM	NM	NM	NM	NM	NM	NM	NM	UA < 28	NM	NM
Captopril challenge test	R	R	NM	NM	R	NM	NM	NM	NM	R	R	NM
Confirm ARR (ng/dl/ng/ml/h)	PAC	ARR > 20	NM	NM	NM	NM	NM	NM	NM	PAC	NM	NM
PAC [suppressed (pmol/l or ratio)]	≤30%	PAC > 336								≤30%		
Fludrocortisone suppression	R	NM	NM	R	NR	NM	NM	NM	NM	NM	R	NM
Confirm (PAC, pmol/l)	PAC > 168	NM	NM	PAC > 140	NM	NM	NM	NM	NM	NM	NM	NM
Subtype classification test												
CT	R	R	NR	R	R	R	R	R	R	R	R	R
MRI	NR	NM	R	NM	R	NM	R	R	NM	R	NM	R
AVS	R	R	R	R	R	R	NM	R	NM	R	R	R
Posture stimulation test	R	NM	NM	NM	NR	NM	NM	NM	NM	NM	NM	NM
Iodocholesterol scintigraphy	NR	R	NM	NM	NR	NM	R	R	NM	NM	NM	R
18-Hydroxycorticosterone levels	NR	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	R
C-metomidate PET-computed tomography	R	NM	NM	NM	NR	NM	R	NR	NM	NM	NM	NM
Genetic testing	R	NM	NM	NM	R	NM	NM	NM	NM	R	NM	R

AACE, the American Association of Clinical Endocrinologists; AACE/AAES, the American Association of Clinical Endocrinologists/American Association of Endocrine Surgeons; AHA, the American Heart Association; ARR, the plasma aldosterone/renin ratio; AVS, adrenal vein sampling; CHEP, the Canadian Hypertension Education Program; ES, the Endocrine Society; ESH/ESC, the European Society of Hypertension/European Society of Cardiology; IACE, the Italian Association of Clinical Endocrinologists; JES, the Japan Endocrine Society; NM, not mentioned; NR, not recommended; PA, primary aldosteronism; PAC, the plasma aldosterone concentration; POL, Poland; PSE, the Polish Society of Endocrinology; R, recommended; SFE/SFHTA/AFCE, the French Endocrinology Society/French Hypertension Society/Francophone Endocrine Surgery Association; SIIA, the Italian Society of Hypertension (Societa' Italiana dell' Ipertensione Arteriosa).

guidelines recommended that the unilateral aldosterone excess should be considered when the aldosterone/cortisol ratio on the dominant side was at least four-fold higher than that on the contralateral side [13,14,19,20], but the JES and AACE guidelines stated the judgment standard of the aldosterone/cortisol ratio as 2.6 and 3.0, respectively. The JES guideline also recommended using the PAC as the judgment standard, and unilateral aldosterone excess should be considered when the PAC is more than 39 200 pmol/l.

For young primary aldosteronism patients (those with a confirmed primary aldosteronism diagnosis prior to 20 years old and those with a family history of primary aldosteronism or strokes prior to 40 years old), the Endocrine Society, SFE/SFHTA/AFCE, CHEP and AACE guidelines suggest genetic testing for familial hyperaldosteronism.

Comparison of primary aldosteronism treatment recommendations

Apart from the AHA guideline, the other guidelines recommended unilateral laparoscopic adrenalectomy for unilateral primary aldosteronism patients. Before surgery, the Polish Society of Endocrinology, Endocrine Society, POL, SFE/SFHTA/AFCE and AACE/AAES guidelines recommended that hypertension and hypokalemia should be well controlled. Only the IACE guideline did not mention controlling hypertension and hypokalemia, and medical treatment was recommended by the other guidelines. Mineralocorticoid receptor antagonists were recommended by 11 guidelines as a first-line drug [9–16,18–20], and spironolactone was the first choice recommended by most of the guidelines [10–16,18–20]; however, there was no consensus on the spironolactone dose. Due to spironolactone's side effects, half of the guidelines recommended eplerenone, which is a selective mineralocorticoid receptor antagonist [10,13–16,19,20]. After mineralocorticoid receptor antagonist treatment, if the BP remained above normal, nearly half of the guidelines recommended adding other antihypertensive agents to lower the BP [9,11,12,14,18–20], but the recommended antihypertensive agents were not consistent. For the treatment of glucocorticoid remediable aldosteronism (GRA), only the Endocrine Society, POL, ESH/ESC and AACE guidelines mentioned and recommended glucocorticoids to treat GRA, just as the Endocrine Society guideline recommended adding mineralocorticoid receptor antagonists if the BP was not normal with glucocorticoid treatment alone. Regarding patient follow-up, the Endocrine Society, POL, SFE/SFHTA/AFCE, AACE/AAES and CHEP guidelines recommended a biochemical follow-up, but neither the frequency nor the time interval were mentioned in most of the guidelines.

Quality assessment

The guidelines' domain scores based on the AGREE-II instrument are presented in Table 4. None of the guidelines

TABLE 4. Domain scores of the selected clinical practice guidelines based on the Appraisal Guidelines Research and Evaluation II instrument

Domain scores (%)	ES	JES	SIIA	POL	SFE/ SFHTA/ AFCE	AACE/ AAES	IACE	PSE	AHA	CHEP	ESH/ ESC	AACE	Median
Scope and Purpose	94.4	80.6	72.2	86.1	76.2	83.3	94.4	86.1	55.6	91.7	83.3	83.3	82.6
Stakeholder Involvement	44.4	55.6	5.6	8.3	61.1	33.3	30.6	5.6	30.6	61.1	38.9	58.3	40.0
Rigour of Development	63.5	20.8	5.2	7.3	34.4	40.6	27.1	5.2	12.5	74.0	45.8	53.1	33.6
Clarity of Presentation	97.2	83.3	25	38.9	86.1	91.7	22.2	58.3	36.1	86.1	44.4	61.1	62.8
Applicability	43.8	25	10.4	12.5	33.3	33.3	4.2	8.3	12.5	31.3	16.7	22.9	22.1
Editorial Independence	95.8	29.2	75	0	45.8	41.7	95.8	0	54.2	87.5	64.3	45.8	50.8
Overall Assessment	R	NR	NR	NR	RM	NR	NR	NR	NR	R	NR	NR	

AACE, the American Association of Clinical Endocrinologists; AACE/AAES, the American Association of Clinical Endocrinologists/American Association of Endocrine Surgeons; AHA, the American Heart Association; CHEP, the Canadian Hypertension Education Program; CPGs, clinical practice guidelines; ES, the Endocrine Society; ESH/ESC, the European Society of Hypertension/European Society of Cardiology; IACE, the Italian Association of Clinical Endocrinologists; JES, the Japan Endocrine Society; NR, not recommended; POL, Poland; PSE, the Polish Society of Endocrinology; R, recommended; RM, recommended with modification; SFE/SFHTA/AFCE, the French Endocrinology Society/French Hypertension Society/Francophone Endocrine Surgery Association; SIIA, the Italian Society of Hypertension (Societa' Italiana dell' Ipertensione Arteriosa).

had a satisfactory score in every domain. The scope and purpose received relatively high scores (median, 82.6%), and the applicability domain received the lowest scores (median, 22.1%). When considering the entire assessment, the Endocrine Society and CHEP guidelines were strongly recommended in most domains, and the SFE/SFHTA/AFCE guideline was recommended with modification in one or more domains. The remaining guidelines received poor scores in more than half of the domains and were not recommended based on the AGREE-II criteria.

The results of the IOM are provided in Table 5. None of the guidelines had suitable compliance with each IOM standard. The scores for the Endocrine Society and CHEP guidelines were slightly higher than those for the other guidelines, and they met more than half of the 20 subcriteria. However, certain subcriteria, including the composition of the guideline, the development group, the external review and the updating, had the poorest adherence and were not met by any of the guidelines.

Implementability assessment

Through a systematic literature review, the Endocrine Society and CHEP guidelines received the highest scores using the AGREE-II and IOM assessments; therefore, the implementability of these two guidelines was assessed. The final results were divided into part 1 (global considerations) and part 2 (screening, confirmation, subtype classification and treatment) and are presented in Fig. 2. The details of the Endocrine Society and CHEP guidelines assessment according to the GLIA tool are presented in Supplementary Table 2S, 3S and 4S, http://links.lww.com/HJH/B60. For the Endocrine Society and CHEP guidelines, the scores for part 1 (global considerations) were relatively higher, but the scores for part 2 (screening, confirmation, subtype and treatment) were poor based on the GLIA criteria. In part 2, the scores for confirmation and treatment were slightly higher than those for the other two domains (screening and subtype). The score differences between the two guidelines were not discernible, but the Endocrine Society guideline scored slightly higher than did the CHEP guideline on the overall assessment. On the overall assessment, the two guidelines did not receive satisfactory scores for either part based on the GLIA criteria. The scores for each part were not above 80% and were almost below 60%; therefore, the implementability of the Endocrine Society and CHEP guidelines was poor.

DISCUSSION

Primary aldosteronism is a frequent but underrecognized health disorder; valid and usable guidelines are needed to support practice improvements. Therefore, we want to comprehensively appraise the primary aldosteronism CPGs' quality and compare the CPGs' recommendations for managing primary aldosteronism and points to methodological areas that need to be improved and discrepancies that may need to be resolved. To our knowledge, this is the first study to systematically evaluate and compare the content and quality of the CPGs for the diagnosis and treatment of primary aldosteronism and to investigate the implementability of the suitable guidelines using the GLIA tool to identify potential implementation barriers and to refine the guidelines. Although almost all the guidelines were classified as evidence-based, our findings indicated that the CPGs' recommendation for primary aldosteronism showed marked discrepancies, and a thorough review of their quality using the AGREE or IOM instrument also concluded that a majority of the guidelines failed to reach the expected standards, except for the Endocrine Society and CHEP guidelines. However, for implementability, the Endocrine Society and CHEP guidelines exhibited substantial room for improvement.

Over the past decade, 12 primary aldosteronism guidelines prepared by a variety of competing organizations have been published. Although the multiplicity of the guidelines and the disagreement among the recommendations is not necessarily a sign of poor quality, the best possible care for the patients may need to be based on their health priorities and their social environment [22,23]. For example, recommendations for primary aldosteronism screening tend to be less aggressive or comprehensive in subgroups and general guidelines than they are in the Specialist Guidelines. A weak evidence base may also lead to various conclusions. The evidence-based model is the most rigorous method for guideline development, but it is limited by the quality of the existing evidence [24,25]. For example, although some studies have suggested differences among the confirmatory primary aldosteronism tests in terms of sensitivity, specificity and reliability, there is no definitive high-quality

TABLE 5. Selected clinical practice guidelines' compliance with the Institute of Medicine subcriteria

IOM standard	ES	JES	SIIA	POL	SFE/ SFHTA/ AFCE	AACE/ AAES	IACE	PSE	AHA	CHEP	ESH/ ESC	AACE	Number of standards met
Establishing transparency													
Funding and development should be explicitly stated and publicly accessible	Y	Y	P	N	N	N	Y	N	N	Y	Y	N	6/13
Conflicts of interest management													
Conflicts of interest should be declared before the guideline development group formation	Y	N	Y	N	Y	Y	Y	N	Y	Y	Y	Y	9/13
All conflicts of interest should be reported and discussed	P	N	Y	N	Y	N	Y	N	P	P	N	N	6/13
Guideline development group members should divest conflicts of interest	N	N	Y	N	Y	N	Y	N	N	N	N	N	3/13
Members who have conflicts of interest should be a minority of the panel (except for the chair and cochairs)	Y	N	Y	N	Y	N	Y	N	N	N	N	Y	5/13
Guideline development group composition													
Guideline development group should be multidisciplinary and balanced	P	P	N	N	Y	N	N	N	N	Y	Y	N	5/13
Patients and the public should be represented in the guideline development group	N	N	N	N	N	N	N	N	N	N	N	N	0/13
The representatives should be trained	N	N	N	N	N	N	N	N	N	N	N	N	0/13
Systematic review													
Systematic reviews should be used	Y	Y	N	N	Y	Y	Y	Y	N	Y	Y	Y	9/13
The guideline development group and systematic review team (if used) should communicate	Y	Y	N	N	N	N	Y	N	N	Y	N	Y	5/13
Evidence foundations for and rating of the strength of the evidence													
The strength of recommendations and grading of evidence should be explicitly stated	Y	N	N	N	Y	Y	Y	N	N	Y	Y	Y	7/13
Articulation of recommendations													
Articulate recommendations in a standard form	Y	P	N	N	P	Y	Y	N	N	Y	Y	N	7/13
Strong recommendations should be worded as such	Y	N	N	P	P	Y	Y	N	N	Y	N	N	6/13
External review													
The external review should include the full spectrum of stakeholders	N	N	N	N	N	N	N	N	N	N	N	N	0/13
Authorship of the external review is confidential	N	N	N	N	N	N	N	N	N	N	N	N	0/13
Guideline development group should consider all the external review comments	Y	Y	N	N	N	N	N	N	N	N	Y	N	3/13
The final draft of the CPGs should be available for public comment	N	N	N	N	N	N	N	N	N	N	N	N	0/18
Updating													
The proposed date of future CPG reviews should be documented	N	N	N	N	N	N	N	N	N	Y	N	N	1/13
The literature pertaining to the CPG should be monitored regularly	N	N	N	N	N	N	N	N	N	Y	N	N	1/13
The CPG should be updated if new literature suggests modification	N	N	N	N	N	N	N	N	N	Y	N	N	1/13
Number of standards met	11/20	6/20	5/20	1/20	9/20	5/20	10/20	1/20	2/20	12/20	7/20	5/20	

AACE, the American Association of Clinical Endocrinologists; AACE/AAES, the American Association of Clinical Endocrinologists/American Association of Endocrine Surgeons; AHA, the American Heart Association; CHEP, the Canadian Hypertension Education Program; CPGs, clinical practice guidelines; ES, the Endocrine Society; ESH/ESC, the European Society of Hypertension/European Society of Cardiology; IACE, the Italian Association of Clinical Endocrinologists; JES, the Japan Endocrine Society; N, no; P, partially; POL, Poland; PSE, the Polish Society of Endocrinology; SFE/SFHTA/AFCE, the French Endocrinology Society/French Hypertension Society/Francophone Endocrine Surgery Association; SIIA, the Italian Society of Hypertension (Societa' Italiana dell' Ipertensione Arteriosa); Y, yes.

evidence to recommend one over the other [26,27]. Therefore, almost all the guidelines acknowledge that no available test is recognized as the gold standard and that the recommendation should be based on patient compliance, cost, laboratory routines and local expertise. Moreover, the guidelines may disagree because of the differing values of the panel that developed the guidelines. The differences in experience, availability of resources and cultural and medical systems may deeply influence the guideline development process [28]. The SIT is the most commonly used test worldwide, with alternatives including the oral salt loading test, captopril challenge test, fludrocortisone suppression test and the less frequently used frusemide upright test. Therefore, the recumbent saline suppression testing (RSST) was recommended by the vast majority of the guidelines as a definitive confirmation of autonomous aldosterone production, although recent studies have indicated that RSST is prone to false negatives, even with generous cutoff values [29].

However, guidelines can also differ for nonvalid reasons. Although all the guidelines recommended optimizing the diagnostic process by considering the influence of drugs, posture, time and hormones on the ARR, the cutoff values for the ARR varied by three-fold in the guidelines. The reason for this discrepancy is not fully clear but is partially attributed to the misuse of systematic methods to search for evidence and to the recommendations being based on limited evidence, a panel consensus or expert opinion.

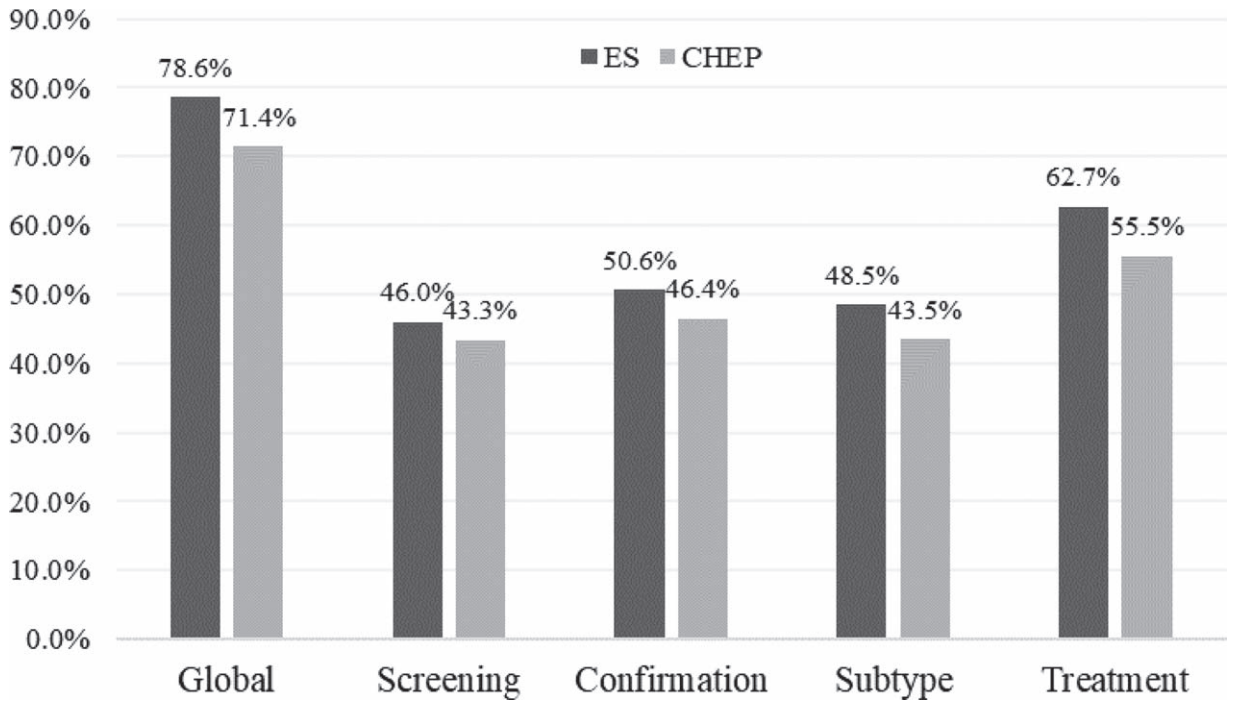

FIGURE 2 Guideline assessment according to the guideline implementability appraisal instrument. CHEP, the Canadian Hypertension Education Program; ES, the Endocrine Society.

For example, the JES and SIIA guidelines predominately cite research from their own country, and the differences in the cited references likely explain several of the discrepancies between the guidelines. Another important reason is the absence of multidisciplinary or balanced stakeholders in the guideline development or the sponsoring societies, especially when the developing team does not include a laboratory specialist with expertise in interpreting the published research, which is supported by our findings that the evidence for the ARR screening threshold was derived from a different setting, cohort selection, design protocol, assay approach and disease definition. Compelling evidence suggests that the most under-appreciated problem in clinical studies is analytical. A lack of standardization between analytical methods and clinical laboratories is a major issue contributing to such variability; unfortunately, the cutoff values in the CPGs are often derived without considering the effect of the analytical methodologies and standardization. In light of the wide variability in the cutoff value for the ARR, establishing a method-specific reference decision-making value is reasonable. In addition, the gold standard for successful primary aldosteronism management is the reversal of symptoms and biochemical testing after therapeutic intervention; however, the specialist guidelines, such as the JES and SIIA guidelines, fail to recommend clinical follow-up. The last updated JES and SIIA guidelines were published in 2011 and 2014, respectively, which is earlier than the most recently published the Endocrine Society guidelines, and the detailed descriptions of the updating procedures were poor. Generally, guidelines should be updated at least every 3 years, as new knowledge is likely to change the recommendations from previous guidelines. For example, a recent international consensus was reached on the criteria for the six outcomes (complete, partial and absent success of clinical and biochemical outcomes) based on BP, the use of antihypertensive drugs, plasma potassium and aldosterone concentration, and plasma renin concentration or activity [30]. These observations highlight the importance of promptly updating a set of guidelines when new clinically relevant evidence becomes available.

Clinical guidelines are intended to improve health-care. However, our findings show that even if guidelines are excellent, their implementation is not assured. Three barriers to implementation were identified. First, the reviewers found that executability was a barrier for screening recommendations. The ARR is the best front-line test to screen for primary aldosteronism, but there are many preanalytical and analytical challenges for a primary practitioner. Thus, fewer patients may benefit from the guidelines despite their soundness. A recent web questionnaire in Germany and Italy indicated that primary aldosteronism is not widely recognized in primary care [31]. However, the implementation failure is not only the fault of the CPGs; effective CPG implementation requires complex changes that involve more than just content, as writing the guidelines in a user-friendly format indeed facilitates adherence. Solutions may include improved tools to aid patient communication regarding the risk and collaboration with a specialist team, accredited training courses for writing CPGs and more staff and resources. Second, the effect on the process of care was identified as another barrier. Subtype classification recommendations included actions that needed extra equipment, staff or provider time to implement the recommendations. For example, not all hospitals have expert and dedicated radiologists, adrenal CT scanning or available AVS facilities. AVS remains a costly and challenging procedure and is only routinely available in some tertiary referral centers.

Although primary aldosteronism care involves multidisciplinary professionals and different levels of health-care providers, most of the guidelines, except for the JES guidelines [9], do not refer to a hierarchical system for the diagnosis and treatment of primary aldosteronism. Third, flexibility was found to be another barrier. Some recommendations lacked specific cutoff values or practice characteristics to allow individualized care. For example, if a patient with a positive ARR test is followed up with a SIT with undetermined results, the guidelines fail to give any subsequent suggestions. A similar situation also occurs if an AVS is unsuccessful or if the result is indeterminate. The evidence for a 'second-line or third-line' modality for an indeterminate patient is collectively very poor, but the guideline panel should feel that providing clear guidance based on expert clinical experience is necessary, and emphasizing discussions that need to be individualized within a multidisciplinary expert team setting is reasonable.

Study limitations

Although we have searched the important guidelines on the topic in English and strictly adhered to searching for CPGs based on a reasonable strategy, we cannot exclude language bias. We have excluded guidelines focusing on other forms of hypertension and guidelines addressing specific issues to ensure readability and conciseness. Our study was also limited by the low number of reviewers; however, the evaluation process was transparent and independent by each reviewer. Finally, the GLIA tool was originally established as a qualitative tool in website edition that was simple and easy to operate. In this study, we optimized the GLIA tool into a quantitative instrument. The result of this improvement was a more intuitive and convenient comparison. In addition, we just list but do not resolve discrepancies across guidelines.

In conclusion, the current study demonstrated numerous differing recommendations for diagnosing and treating primary aldosteronism among the guidelines. Some discrepancies are valid and reasonable, but others are not. Most of the CPGs' quality was not in compliance with the AGREE-II and IOM standards. Although the overall quality of the Endocrine Society and CHEP guidelines is high, the applicability is unsatisfactory. The value of high-quality guidelines that are difficult for clinicians to implement is questionable. In the future, the development process of guidelines should consider the clinical context and complexity of referrals in a hierarchical system with a multidisciplinary team as well as the barriers to implementation to improve the diagnosis and treatment of primary aldosteronism.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Kayser SC, Dekkers T, Groenewoud HJ, van der Wilt GJ, Carel Bakx J, van der Wel MC, *et al.* Study heterogeneity and estimation of prevalence of primary aldosteronism: a systematic review and meta regression analysis. *J Clin Endocrinol Metab* 2016; 101:2826–2835.
2. Ohno Y, Sone M, Inagaki N, Ogawa O, Takeda Y, Kurihara I, *et al.* Prevalence of cardiovascular disease and its risk factors in primary aldosteronism: a multicenter study in Japan. *Hypertension* 2018; 71:530–537.
3. Chen Y, Hu S, Wu L, Fang X, Xu W, Shen G. Clinical practice guidelines for hypertension in China: a systematic review of the methodological quality. *BMJ Open* 2015; 5:e008099.
4. Galopin A, Bouaud J, Pereira S, Seroussi B. Using an ontological modeling to evaluate the consistency of clinical practice guidelines: application to the comparison of three guidelines on the management of adult hypertension. *Stud Health Technol Inform* 2014; 205:38–42.
5. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, *et al.*, for the AGREE Next Steps Consortium. AGREE II: Advancing guideline development, reporting and evaluation in healthcare. *CMAJ* 2010; 182:839–842.
6. IOM (Institute of Medicine). *Clinical practice guidelines we can trust.* Washington, DC: The National Academies Press; 2011.
7. Shiffman RN, Dixon J, Brandt C, Essaihi A, Hsiao A, Michel G, O'Connell R. The GuideLine Implementability Appraisal (GLIA): development of an instrument to identify obstacles to guideline implementation. *BMC Med Inform Decis Mak* 2005; 5:23.
8. Shen J, Sun M, Zhou B, Yan J. Nonconformity in the clinical practice guidelines for subclinical Cushing's syndrome: which guidelines are trustworthy? *Eur J Endocrinol* 2014; 171:421–431.
9. Nishikawa T, Omura M, Satoh F, Shibata H, Takahashi K, Tamura N, *et al.* Guidelines for the diagnosis and treatment of primary aldosteronism – the Japan Endocrine Society 2009. *Endocr J* 2011; 58:711–721.
10. Torre JJ, Bloomgarden ZT, Dickey RA, Hogan MJ, Janick JJ, Jyothinagaram SG, Siragy HM, *et al.* American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of hypertension. *Endocr Pract* 2006; 12:193–222.
11. Leung AA, Nerenberg K, Daskalopoulou SS, McBrien K, Zarnke KB, Dasgupta K, *et al.* Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. *Can J Cardiol* 2016; 32:569–588.
12. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, *et al.* Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Hypertension* 2008; 51:1403–1419.
13. Zeiger MA, Thompson GB, Duh QY, Hamrahian AH, Angelos P, Elaraj D, *et al.* The American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons medical guidelines for the management of adrenal incidentalomas. *Endocr Pract* 2009; 15 (Suppl 1):1–20.
14. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, *et al.* The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2016; 101:1889–1916.
15. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, *et al.* 2013 ESH/ESC practice guidelines for the management of arterial hypertension. *Blood Press* 2014; 23:3–16.
16. Bednarczuk T, Bolanowski M, Sworczak K, Górnicka B, Cieszanowski A, Otto M, *et al.* Adrenal incidentaloma in adults – management recommendations by the Polish Society of Endocrinology. *Endokrynol Pol* 2016; 67:234–258.
17. Terzolo M, Stigliano A, Chiodini I, Loli P, Furlani L, Arnaldi G, *et al.* AME position statement on adrenal incidentaloma. *Eur J Endocrinol* 2011; 164:851–870.
18. Rossi GP, Dalla CA. Clinical management of primary aldosteronism: 2013 Practical Recommendations of the Italian Society of Hypertension (SIIA). *High Blood Press Cardiovasc Prev* 2014; 21:71–75.
19. Mysliwiec J, Gorska M. Primary aldosteronism: a common and important problem. A practical guide to the diagnosis and treatment. *Endokrynol Pol* 2012; 63:324–336.
20. Amar L, Baguet JP, Bardet S, Chaffanjon P, Chamontin B, Douillard C, *et al.* SFE/SFHTA/AFCE primary aldosteronism consensus: introduction and handbook. *Ann Endocrinol (Paris)* 2016; 77:179–186.

21. Rossi GP, Auchus RJ, Brown M, Lenders JW, Naruse M, Plouin PF, *et al*. An expert consensus statement on use of adrenal vein sampling for the subtyping of primary aldosteronism. *Hypertension* 2014; 63:151–160.
22. McClarey M, Duff L. Making sense of clinical guidelines. *Nurs Stand* 1997; 12:34–36.
23. Katterhagen G. Physician compliance with outcome-based guidelines and clinical pathways in oncology. *Oncology (Williston Park)* 1996; 10 (11 Suppl):113–121.
24. Mead P. Clinical guidelines: promoting clinical effectiveness or a professional minefield? *J Adv Nurs* 2000; 31:110–116.
25. Forbes A, Griffiths P. Methodological strategies for the identification and synthesis of 'evidence' to support decision-making in relation to complex healthcare systems and practices. *Nurs Inq* 2002; 9:141–155.
26. Fontes RG, Kater CE, Biglieri EG, Irony I. Reassessment of the predictive value of the postural stimulation test in primary aldosteronism. *Am J Hypertens* 1991; 4:786–791.
27. Streeten DH, Tomycz N, Anderson GH. Reliability of screening methods for the diagnosis of primary aldosteronism. *Am J Med* 1979; 67:403–413.
28. Miller M, Kearney N. Guidelines for clinical practice: development, dissemination and implementation. *Int J Nurs Stud* 2004; 41:813–821.
29. Stowasser M, Ahmed A, Guo Z, Wolley M, Ungerer J, McWhinney B, *et al*. Can screening and confirmatory testing in the management of patients with primary aldosteronism be improved? *Horm Metab Res* 2017; 49:915–921.
30. Miller BS, Turcu AF, Nanba AT, Hughes DT, Cohen MS, Gauger PG, Auchus RJ. Refining the definitions of biochemical and clinical cure for primary aldosteronism using the primary aldosteronism surgical outcome (PASO) classification system. *World J Surg* 2018; 42:453–463.
31. Mulatero P, Monticone S, Burrello J, Veglio F, Williams TA, Funder J. Guidelines for primary aldosteronism: uptake by primary care physicians in Europe. *J Hypertens* 2016; 34:2253–2257.