Article Title: Complementary Medicine Mention and Recommendations are Limited across Hypertension Guidelines: A Systematic Review

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Highlights

• Roughly 1/4 of individuals with hypertension have used complementary medicine (CM).

• This study determined the quantity & quality of CM recommendations in clinical practice guidelines (CPGs) for hypertension.

• From 1445 unique search results, 18 eligible CPGs were found, but only 1 contained CM recommendations.

• A lack of CM treatment recommendations exists in CPGs for the treatment and/or management of hypertension.

• Current hypertension CPGs' lack of CM recommendations reflects a large gap in guidance for both clinicians and patients.

Abstract

Objective: The purpose of this study was to determine the quantity of complementary medicine (CM) recommendations and their quality across clinical practice guidelines (CPGs) for the treatment and/or management of hypertension.

Design/Setting: A systematic review was conducted to identify hypertension CPGs. MEDLINE, EMBASE and CINAHL were searched from 2008 to 2018, alongside the Guidelines International Network and the National Centre for Complementary and Integrative Health websites. Eligible articles were assessed with the Appraisal of Guidelines, Research and Evaluation II (AGREE II) instrument.

Outcome/Results: From 1445 unique search results, 18 CPGs for the treatment and/or management of hypertension published in 2008 or later were eligible for review, though only 1 contained CM recommendations. This CPG was published by the European Society of Cardiology and the European Society of Hypertension, and made a recommendation regarding the Mediterranean diet. The scaled domain percentages of this CPG overall scored

significantly better than the CM section across every domain, and were as follows: (overall, CM): scope and purpose (88.9 %, 66.7 %), clarity-of-presentation (88.9 %, 0.0 %), stakeholder involvement (66.7 %, 16.7 %), applicability (60.4 %, 0.0 %), rigor-of-development (35.4 %, 15.6 %), and editorial independence (4.2 %, 0.0 %).

Conclusion: A lack of CM treatment recommendations exists in CPGs for the treatment and/or management of hypertension. Given that it is known that a high proportion of patients with hypertension seek CM, current hypertension guidelines' lack of CM treatment and/or management recommendations reflects a large gap in guidance for both clinicians and patients.

1. Background

Hypertension affects 1.13 billion individuals worldwide1 with less than 20 % of the clinical population able to control their condition and achieve a normal blood pressure. Since 2005, the number of deaths in the US attributable to hypertension has increased by 37.5 %. 2 Successful treatment of hypertension is important in preventing further increasing rates of cardiovascular disease, obesity and metabolic disorders. 3 Hypertension is defined as a systolic blood pressure above 140 mmHg and a diastolic pressure blood pressure above 90 mmHg. 4 While the usage of various medications such as angiotensin converting enzyme inhibitors, beta blockers and angiotensin II receptor blockers have become the standard treatment, 5 many individuals also consider using complementary medicine (CM). 6 Complementary medicine refers to any treatment that is used in addition to a conventional medical practice. 7 Although conventional antihypertensive medications are effective in treating hypertension, the side effects associated with these drugs has often resulted in issues with adherence to prescribed treatments. 8 In comparison, some CM therapies are a more mild form of treatment which can benefit patients without reproducing the severe side effects

that come with conventional hypertensive medications. 8 Self-administered questionnaire data from two studies suggest that patients have turned to CM therapies with a desire to reduce the side effects associated with conventional therapies. 9,10 Additional reasons patients turn to CM therapy include not being satisfied with conventional therapies, having friends who support CM therapy usage, and living in areas that are distant from healthcare institutions. 9,10 As a result, some patients consider using CM therapy to assist with reducing their blood pressure. Globally, 24.7 % of individuals with hypertension have reported using CM as a self-medication practice. 6 One study has found that the most commonly used CM therapies are herbal medicines and dietary supplements. 11 It has also been found that the proportion of patients using CM therapies to treat hypertension varies by jurisdiction; for example, 67 % of patients use CM in Turkey, while only 5% use CM in Singapore. 12,13 Various types of CM therapies have been used in the treatment of hypertension. These include but are not limited to: herbal medicines (e.g. garlic, neem, black seed, olive oil), homeopathic treatments, mind-body interventions and diet modifications. 6 One meta-analysis has found that herbs such as garlic can lower blood pressure through increased nitric oxide production, a potent vasodilator. 14 Another found that Chinese herbal medicine combined with conventional therapy can improve blood pressure variability. 15 A reduction in blood pressure through the use of meditation techniques is believed to be associated with lower psychological stress levels. 4 Additionally, it has been found that yoga may be a potential intervention for reducing blood pressure. 16 Foods such as fibre-rich whole oats have also been shown to reduce both systolic and diastolic blood pressure. 14 Despite these promising findings, CM is rarely recommended during clinician-patient interactions, 17 and it is known that patients who use CM frequently do not disclose this to their healthcare provider. 18,19 Studies analysing CM treatments lack the evidence base to be consistently recommended in clinical settings. Additionally, a recent study has found that only 35 % of

physicians in the US have reported learning about the usage of CM therapies in medical school and only 15 % mentioned they learned about it in residency training. 17

Physicians and other health care professionals rely on evidence-based clinical practice guidelines (CPGs) as a basis for the diagnosis, management and treatment of various medical conditions. These guidelines act as a reference for the associated risks and benefits of using certain treatments for a given clinical population. Conventional antihypertensive medications have been studied extensively for their mechanisms, benefits, and side effects. As a result, most CPGs effectively discuss the benefits and side effects associated with these therapies. In comparison, only some randomized controlled trials and observational studies have evaluated the effectiveness of CM therapy for the treatment and/or management of hypertension. 6,14,15,20 Many studies on CM have also produced both contraindicative and inconclusive evidence. The purpose of this study was to identify the quantity of CM recommendations across CPGs for the treatment and/or management of hypertension and evaluate their quality.

2. Methods

2.1. Approach

A systematic review was conducted to identify hypertension CPGs using Cochrane methods 20 and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. 21 The protocol was registered with PROSPERO, registration number CRD42019132298. Eligible CPGs were assessed with the widely used and validated Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument. 22 Articles with CM recommendations were re-assessed with AGREE II whereby the assessors applied the 23 items to only the CM sections of the CPG. AGREE II consists of 23 items grouped in

six domains: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence.

2.2. Eligibility criteria

Eligibility criteria for hypertension CPGs were based on the Population, Intervention, Comparison and Outcomes framework. Eligible populations were adults aged 19 years and older with hypertension. With respect to interventions, we only included CPGs that included treatment or management of hypertension in order to determine whether any mention or recommendations of CM therapies were included. When considering what therapies constituted CM, we referred to a bibliometric and content analysis of CM trials in the Cochrane Library by Wieland et al. They found that the CM therapies most commonly evaluated in trials included herbal supplements (non-vitamin, non-mineral dietary supplements or Chinese herbal medicine), diet-based therapies, acupuncture, and chiropractic or osteopathic manipulation 23; we used this to restrict our definition of CAM for the purpose of this review. We did not have any criteria for comparisons or outcomes.

Eligible guidelines needed to be developed by non-profit organizations including academic institutions, government agencies, disease-specific foundations, or professional associations or societies. Additionally, they needed to be published in the English language and in 2008 or later (which provides a decade-long window into treatment/management CPGs for hypertension); they also needed to be either publicly available or could be accessed or ordered through our library system. Publications in the form of consensus statements, protocols, abstracts, conference proceedings, letters or editorials; based on primary studies that evaluated hypertension management or treatment; or focused on hypertension curriculum, education, training, research, professional certification or performance were not

eligible. It should be noted that only eligible CPGs that contained CM therapy recommendations were assessed using the AGREE II tool, in order to determine the difference in AGREE II scores between the overall CPG and specifically the CM sections; only demographic information is reported for eligible CPGs that did not contain CM therapy recommendations.

2.3. Search and screening

MEDLINE, EMBASE and CINAHL were searched on January 12, 2019 from 2008 to January 11, 2019 inclusive. The search strategy (Supplementary File 1) included Medical Subject Headings and keywords that reflect terms commonly used in the literature to refer to CM. We also searched the Guidelines International Network, a repository of guidelines [https://www.g-i-n.net/] using keyword searches restricted based on the eligibility criteria including "cardiovascular disease." Next, we searched the NCCIH web site which contained a single list of CM CPGs [https://www.nccih.nih.gov/health/providers/clinicalpractice]. KG and another research assistant screened titles and abstracts from all other sources. KG and the other research assistant screened full-text items to confirm eligibility. JYN reviewed the screened titles and abstracts and full-text items to standardize screening, and helped to discuss and resolve selection differences between the two screeners.

2.4. Data extraction and analysis

The following data were extracted from each CPG and summarized: date of publication, country of first author; type of organization that published the CPG (academic institutions, government agencies, disease-specific foundations, or professional associations or societies); and whether any CMs were mentioned in this CPG. If CMs were mentioned in a CPG, the types of CM mentioned, CM recommendations made, CM funding sources, and whether any

CM providers are part of the guideline panel were also data extracted. Most data were available in the CPG; to assess applicability, the web site of each developer was browsed and searched for any associated knowledge-based resources in support of implementation.

2.5. Guideline quality assessment

The extraction and analysis of data from eligible CPGs followed standardized methods for applying the AGREE II instrument. 13 First a pilot test of the AGREE II instrument was conducted with three separate CPGs during which all three evaluators independently assessed these three CPGs with the AGREE II instrument. Discrepancies were discussed and resolved. KG and the other research assistant then independently assessed all eligible CPGs containing CM therapy recommendations twice (i.e. once for the overall CPG, and once for only the CM sections of the CPG) for 23 items across 6 domains using a seven-point Likert scale from strongly disagree (1) to strongly agree (7) that the item is met; rated the overall quality of each CPG (1–7); and used that information to recommend for or against use of each CPG. The modified AGREE II questions used to guide the scoring of the CM sections of each CPG are found in Supplementary File 2. Understandably, CM recommendations may be found in a specific section of a CPG or integrated within other therapies; here we refer to "CM sections" as the entirety of information pertinent to CM in a given CPG. JYN resolved differences. Average appraisal scores were calculated by taking the average rating for all 23 items of a single appraiser of a single CPG, followed by taking the average of this value for both appraisers. Average overall assessments were calculated as the average of both appraisers' "overall guideline assessment" scores for each CPG. Scaled domain percentages were generated for inter-domain comparison, and were calculated by adding both appraisers' ratings of items within each domain, and scaling by maximum and minimum possible domain

scores, before converting this into a percentage. Average appraisal scores, average overall assessments and scaled domain percentages for each CPG was tabulated for comparison.

3. Results

3.1. Search results (Fig. 1)

Searches retrieved 1676 items, 1445 were unique, and 1400 titles and abstracts were eliminated, leaving 45 full-text CPGs that were considered. Of those, 27 were not eligible, primarily because they were not focused on hypertension (n = 18), were not CPGs (n = 2), could not be retrieved (n = 2) or did not meet other eligibility criteria (n = 5), leaving 18 CPGs eligible for review. Of these CPGs, only 1 of these 18 made mention of CM therapies and provided CM therapy recommendations.

3.2. Guideline characteristics (Table 1)

Eligible CPGs were published from 2008 to 2018 in Canada (n = 5), United States (n = 4), South Africa (n = 2), United Kingdom (n = 2), Italy (n = 1), Australia (n = 1), Brazil (n = 1), Japan (n = 1), and Poland (n = 1). 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41 All CPGs were funded and/or developed by professional associations or societies. Of these 18 CPGs, only 1 CPG made mention of and a specific recommendation of a CM therapy. This CPG was published by the European Society of Cardiology and the European Society of Hypertension, and made a recommendation regarding the Mediterranean diet, and was the only one assessed using the AGREE II tool for the CM section 26 .

3.3. Average appraisal scores, average overall assessments and recommendations regarding use of guidelines: Overall guideline

Average appraisal scores, average overall assessments, and recommendation regarding use for this individual CPG is shown in Table 2. The average appraisal score and overall assessment score for this CPG was 4.3 and 5.5 respectively (where 7 equals strongly agree that the item is met). 26

3.5. Overall recommendations: overall guideline and CM sections (Table 3)

The overall CPG was recommended by both appraisers as a "yes with modifications." However, both appraisers did not recommend the usage of the CM section of the CPG.

3.6. Scaled domain percentage quality assessment (Table 4)

With regards to scaled domain percentages, the overall CPG scored 88.9 % in scope and purpose, 66.7 % in stakeholder involvement, 35.4 % in rigor-of-development, 88.9 % in clarity-of-presentation, 60.4 % in applicability and 4.2 % in editorial independence. The CM section of the CPG scored 66.7 % in scope and purpose, 16.7 % in stakeholder involvement, 15.6 % in rigor-of-development, 0.0 % in clarity-of-presentation, 0.0 % in applicability and 0.0 % in editorial independence.26

3.7. Scope and purpose

The overall objectives and health questions were well defined for the CPG. Information regarding the goal of the CPG and its target population was well-defined. The CM section of the CPG stated the overall objectives but failed to address important health questions and define the target populations. 26

3.8. Stakeholder involvement

The institutional affiliation, credentials and occupation of the members in the overall CPG development group were clearly stated but not in the CM section of the CPG. The geographical location and description of each individual's role in the overall CPG was briefly mentioned but not in the CM section of the CPG. Both the overall CPG and the CM section failed to effectively consider the views and preferences of the target population while creating the recommendations. The target users were clearly identified in the opening paragraphs of both the overall CPG and the CM section. 26

3.9. Rigor of development

The criteria for selecting the evidence along with presentation of the systematic methods used to search for evidence was not clearly stated in the overall CPG or its CM section. The strengths and limitations of the body of evidence were not well described in the overall CPG or the CM section of the CPG. The overall CPG had a vague and unclear presentation regarding the methods for formulating the recommendations. The CM section of the CPG failed to report any methods on how the recommendations were formulated. The health benefits, side effects and risks for the treatment of hypertension was explained in detail for the overall CPG and the CM section. The overall CPG provided an explicit link between their recommendations and the supporting evidence for most of their recommendations but not for all of them. Neither the overall CPG nor the CM section mentioned how updates would be made in the future. 26

3.10. Clarity of presentation

A comprehensible presentation of the easily identifiable treatment recommendations was provided in the overall CPG. Specific and unambiguous recommendations with multiple options for the management of hypertension were also presented in the overall CPG.

However, the CM section of the CPG failed to make specific and unambiguous recommendations in a manner that was easy to understand for the user. 26

3.11. Applicability

Potential facilitators and barriers to the application of the CPG's recommendations were mentioned in a few subsections of the overall CPG but were not brought up in the CM section of the CPG. While the overall CPG effectively considered the tools needed to implement the recommendations into practice, the CM section did not. The potential resource implications were considered for some of the overall CPG's recommendations but not considered in the CM section of the CPG. Monitoring and auditing criteria were provided in a vast amount of detail throughout the entire CPG but not in the CM section. 26

3.12. Editorial independence

Neither the overall CPG nor the CM section mentioned the potential competing interests of CPG development group members. Both the overall CPG and CM section also failed to mention the potential influence the funding body may have had on its content. 26

4. Discussion

The purpose of this study was to identify CM mention across CPGs for the treatment and/or management of hypertension, and determine the quality of CM recommendations. Out of 18 eligible CPGs, only one contained CM recommendations. This single CPG's CM section scored more poorly across all AGREE II domains in comparison to the overall CPG. The highest scoring domains from highest to lowest for the overall guideline were as follows: scope and purpose, stakeholder involvement, rigor-of-development, clarity-of-presentation, applicability and editorial independence. For the CM section, from highest to lowest, scored

domains were as follows: purpose, stakeholder involvement, rigor-of-development, clarity-of-presentation, applicability and editorial independence, with the latter three scoring 0% each.

Despite the high prevalence of CM therapy use among hypertension patients, CM recommendations appear to be largely absent from CPGs for the treatment and/or management of this condition. Unfortunately, based on the fact that only 1 guideline, out of 18, provided a CM recommendation we cannot make an assessment of the overall quality of CM recommendations versus overall recommendations across this subset of CPGs.

Other studies have also noted that many CPGs for chronic conditions fail to significantly mention or recommend CM therapies. For example, the National Institute for Health and Care Excellence (NICE) reported in 2009 that out of the 88 guidelines they had published, the majority of them made no mention of CM. 42 Of the studies that do mention CM, many failed to recommend accurate dosages and often suggested that the patient implement CM through trial and error. A similar trend has been noted in the UK, as another study noted that 44 % of guidelines in the UK provided inconclusive recommendations for CM. 43 There are a number of factors that can explain why a lack of CM mention exists across CPGs. Risks associated with use of CM therapies, a lack of rigorous research on CM therapy usage in patients, as well as negative attitudes from primary care-providers towards CM therapy may all contribute to the fact that a lack of CM recommendations exist across this subset of CPGs. 42,43,44 The evidence supporting CM therapy usage may also be subjected to confirmation bias as one study has noted that CM practitioners support certain therapies despite being presented with conflicting evidence against it. 44 In comparison, a physician's willingness to

recommend CM may depend on their prior experience and the perceived prestige of the journal publishing the evidence supports a specific therapy. 44

The results from this study emphasize the need for future CPG developers to identify CM recommendations for hypertension that are supported by rigorous, evidence-based research. 45 At minimum, CPG developers should address the evidence-based limitations, especially in cases whereby given CM therapies are used prevalently, but that are understudied, across this patient population. As healthcare providers are generally poorly trained in CM, 17 physicians rely on CM-related recommendations to aid effective discussion or make recommendations that avoid CM therapies that are contraindicated with conventional hypertension medications. To aid the CPG development process, numerous principles, frameworks, criteria and checklists are available to help CPG developers generate the highest-quality products. Some tools include the Guideline Development Tool (GDT), the Grading of Recommendations Assessment, Development and Evaluation tool (GRADE), as well as resources from the resources from the World Health Organization (WHO), National Institute for Health and Care Excellence (NICE), and the Scottish Intercollegiate Guidelines Network (SIGN). 45,46

Given that many hypertensive patients have both used and considered CM therapies, it is crucial that guideline developers, at minimum, mention what the current evidence suggests regarding common CM therapies. Examples of common CM therapies include herbal therapies (notably garlic) and yoga, as well as the dosages that have shown promise for patients in the published literature. They can also discuss contraindicated CM therapies and include evidence to support why future patients would benefit from avoiding them. Such measures would assist physicians in advising their patients on CM therapies that are safe and effective. CPGs can further be improved by addressing the patient's needs, preferences, and

desire to implement CM. The guideline can include information on the appropriate referral sources in cases whereby a patient wishes to try a CM unfamiliar to a physician (i.e. appropriate CM or integrative medicine practitioners). It is also important for guideline developers to declare whether CMs were included as a part of their search strategy and PICO when searching for literature, providing the reader with added transparency in how CM-related recommendations were included.

4.1. Strengths and limitations

Our study had a number of strengths, the first being the use of a comprehensive systematic search to identify eligible CPGs. Additionally, our study employed the AGREE II instrument, which is widely-regarded as the gold standard in assessing the quality of CPGs. 22 In regards to limitations, eligible CPGs were only assessed by two AGREE II assessors, as opposed to the recommended four appraisers. To mitigate this, JYN, KG and an additional research assistant participated in a pilot-assessment, whereby all three independently assessed three CPGs (separate to this set, but relating to CM). All discrepancies were discussed, and all three came to a consensus on how to apply the AGREE II instrument. Additionally, following the appraisal of this single CPG, JYN met with KG and the additional research assistant to discuss and resolve any uncertainties without unduly modifying legitimate discrepancies. It should be noted that this review only assessed the English-language academic literature, and therefore may not capture CPGs developed in countries where they may be published in other languages (i.e. traditional Chinese medicine recommendations in Chinese CPGs).

5. Conclusion

This study uncovered a single CPG for the treatment and/or management of hypertension which made mention of a CM therapies (Mediterranean diet) and provided a

recommendation. As we only appraised a single CPG with the AGREE II instrument, we cannot draw any conclusions comparing the quality of CM versus overall recommendations in hypertension CPGs. This study has highlighted a lack of CM recommendations across this subset of CPGs, despite the fact that healthcare providers rely on such resources in order to effectively discuss CM therapy options with hypertension patients. As a high prevalence of CM use exists across hypertension patients, it is of great importance that CPGs developed for the treatment or management of this condition implement CM therapy recommendations. This would bridge the gap between patient demand and physician knowledge, encouraging well-informed and safe usage of CM among patients. Future research should identify CM therapies other than those reviewed here which are supported by enough evidence to serve as the basis for CPG development. Future research should also seek to compare the effectiveness of the most prevalently used CM therapies for hypertension as to increase the efficacy of CM recommendations made.

Author disclosures

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Author contributions

JYN: conceptualized and designed the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.

KG: assisted with the collection and analysis of data, drafted the manuscript, and gave final approval of the version to be published.

Ethics statement

This study involved a systematic review of peer-reviewed literature only; it did not require ethics approval or consent to participate.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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Supplementary data

Supplemental File 1: MEDLINE Search Strategy for Hypertension Guidelines Executed January 12, 2019

Supplementary File 2: Modified AGREE II Questions Used to Guide Scoring of CM Sections of Each Guideline

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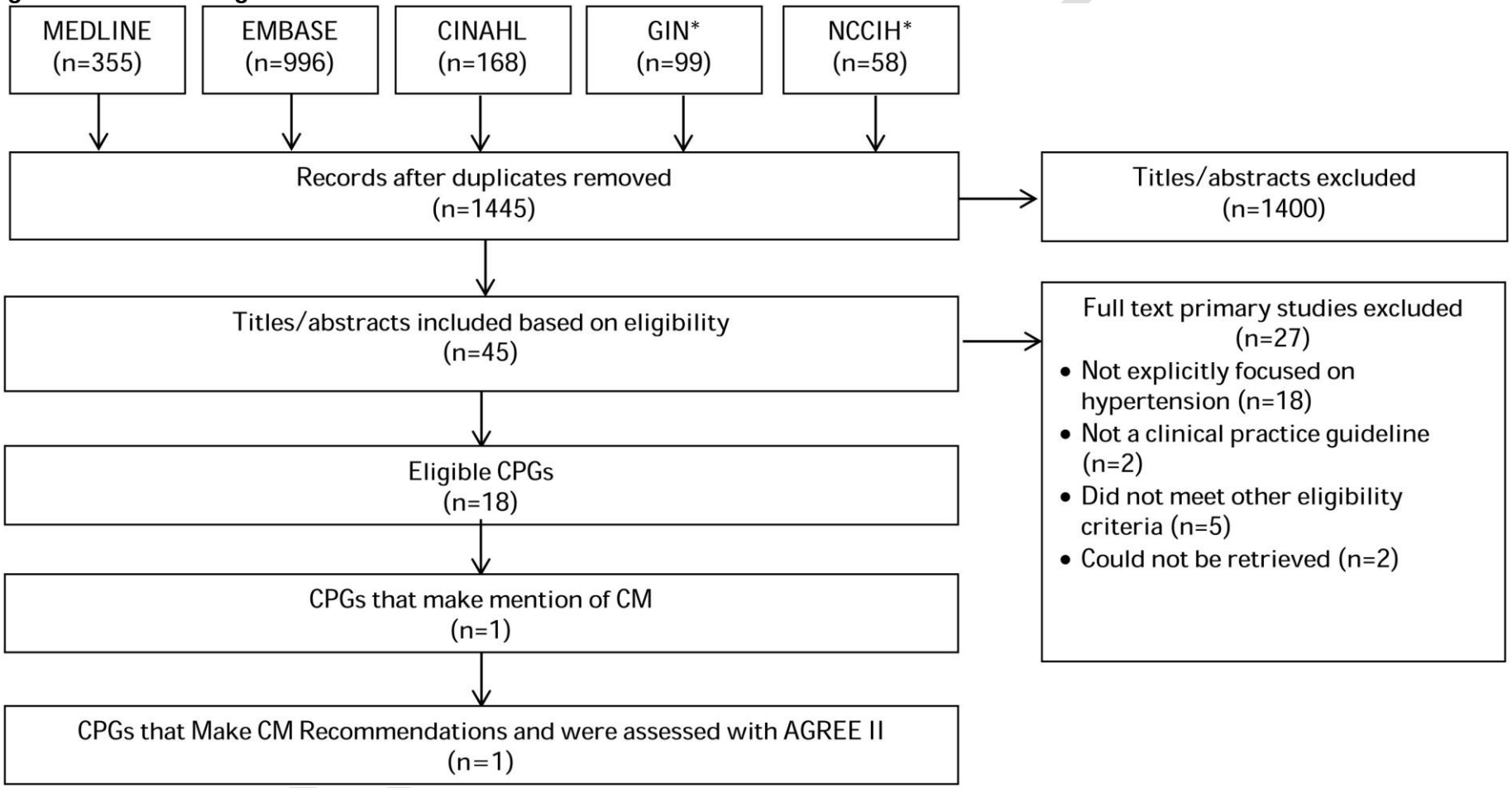
Figures

Figure 1: PRISMA Diagram



Tables

Table 1: Characteristics of Eligible Guidelines

Guideline	Country (First Author)	Developer
Flack 2018 [24]	United States	American College of Cardiology/American Heart Association
Lamb 2018 [25]	Canada	Hypertension Canada
Williams 2018 [26]	United Kingdom	The European Society of Hypertension and European Society of Cardiology
Qaseem 2017 [27]	United States	American College of Physicians and the American Academy of Family Physicians
Gabb 2016 [28]	Australia	The National Blood Pressure and Vascular Disease Advisory Committee
Leung 2016 [29]	Canada	Hypertension Canada
Malachias 2016 [30]	Brazil	Arquivos Brasileiros de Cardiologia
Tykarski 2015 [31]	Poland	Polish Society of Hypertension
James 2014 [32]	United States	Eighth Joint National Committee
Hackam 2013 [33]	Canada	Canadian Hypertension Education Program
Mancia 2013 [34]	Italy	The European Society of Hypertension and European Society of Cardiology
Seedat 2013 [35]	South Africa	Hypertension Guideline Working Group, Southern African Hypertension Society, and Nelson Mandela School of Medicine, Faculty of Health Sciences, University of KwaZulu-Natal, Durban
Daskalopoulou 2012 [36]	Canada	Canadian Hypertension Education Program
NICE 2011 [37]	United Kingdom	National Institute for Health and Care Excellence
Seedat 2011 [38]	South Africa	Hypertension Guideline Working Group, Southern African Hypertension Society, and Nelson Mandela School of Medicine, Faculty of Health Sciences, University of KwaZulu-Natal, Durban
Ogihara 2009 [39]	Japan	The Japanese Society of Hypertension
Sanchez 2009 [40]	United States	Latin America Society of Hypertension
Khan 2008 [41]	Canada	Canadian Hypertension Education Program

Table 2: Average Appraisal Scores and Average Overall Assessments of Each Guideline

Guideline	Metric	Appraiser 1	Appraiser 2	Average	Standard Deviation
Williams 2018 (Overall) [26]	**Appraisal Score**	4.9	3.7	4.3	0.6
	Overall Assessment	6	5	5.5	0.5
Williams 2018 (CM section) [26]	**Appraisal Score**	2.1	1.7	1.9	0.2
	Overall Assessment	3	2	2.5	0.5

Table 3: Overall and CM Recommendations for Use of Appraised Guidelines

	Overall Guideline		**CM Section**	
Guideline	Appraiser 1	Appraiser 2	Appraiser 1	Appraiser 2
Williams 2018 [26]	Yes, with modifications	Yes, with modifications	No	No

Table 4: Scaled Domain Percentages for Appraisers

Guideline		Domain score (%)					
		Scope and purpose	**Stakeholder involvement**	**Rigour of development**	**Clarity of presentation**	**Applicability**	**Editorial Independence**
Williams 2018 [26]	**Overall Guideline**	88.9	66.7	35.4	88.9	60.4	4.2
	CM Section	66.7	16.7	15.6	0.0	0.0	0.0