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SYSTEMATIC REVIEW

Do we AGREE on the targets of antihypertensive drug treatment in older adults: a systematic review of guidelines on primary prevention of cardiovascular diseases

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Abstract

Background: translation of the available evidence concerning primary cardiovascular prevention into clinical guidance for the heterogeneous population of older adults is challenging. With this review, we aimed to give an overview of the thresholds and targets of antihypertensive drug therapy for older adults in currently used guidelines on primary cardiovascular prevention. Secondly, we evaluated the relationship between the advised targets and guideline characteristics, including guideline quality.
Methods: we systematically searched PubMed, Embase, Emcare and five guideline databases. We selected guidelines with (i) numerical thresholds for the initiation or target values of antihypertensive drug therapy in context of primary prevention (January 2008–July 2020) and (ii) specific advice concerning antihypertensive drug therapy in older adults. We extracted the recommendations and appraised the quality of included guidelines with the AGREE II instrument.
Results: thirty-four guidelines provided recommendations concerning antihypertensive drug therapy in older adults. Twenty advised a higher target of systolic blood pressure (SBP) for octogenarians in comparison with the general population and three advised a lower target. Over half of the guidelines ($n = 18$) recommended to target a SBP <150 mmHg in the oldest old, while four endorsed targets of SBP lower than 130 or 120 mmHg. Although many guidelines acknowledged frailty, only three gave specific thresholds and targets. Guideline characteristics, including methodological quality, were not related with the recommended targets.
Conclusion: the ongoing debate concerning targets of antihypertensive treatment in older adults, is reflected in an inconsistency of recommendations across guidelines. Recommended targets are largely set on chronological rather than biological age.

Keywords: older people, primary cardiovascular prevention, guidelines, antihypertensive drug therapy, systematic review

Key Points

- The debate concerning blood pressure targets in older adults is reflected in an inconsistency of guideline recommendations.
- Notably for the oldest old and especially across the most rigorously developed guidelines.
- Recommended targets are set on chronological rather than biological age.

Background

Hypertension is the worldwide leading predisposing condition for disease burden, and as the most important modifiable risk factor, its management forms an essential pillar of primary prevention of cardiovascular diseases [1, 2]. Globally, hypertension is prevalent in roughly one in four adults and steadily rises with age [3, 4]. For example, data from the Framingham Heart Study showed that more than 90% of the normotensive participants between 55 and 65 years developed hypertension [5], emphasizing the need for a thoughtful treatment strategy. Nevertheless, an international analysis of health surveys estimated that the proportion of hypertensive adults between 35 and 85 years receiving antihypertensive drug therapy ranges from 29.0% to 80.5% [6].

Only during the last three decades randomized clinical trials (RCTs) have demonstrated that pharmacological treatment of hypertension in older adults is beneficial [7–9]. Although those studies included octogenarians, frail older adults are largely underrepresented as many of them are excluded from trials due to their comorbidities [10–12]. To date, no interventional studies specific to antihypertensive treatment in older frail individuals have been conducted. Several population-based cohort studies [13, 14], in contrast, have shown that low blood pressure (BP) under antihypertensive drug treatment, especially in older adults with frailty or other complex health problems [15], is associated with higher all-cause mortality rates. Despite the high quality of the available evidence, translation into clinical guidance for the heterogeneous population of older adults is challenging.

In the current discussion on hypertension management in older adults, the clinical problem is not only when to start, but predominantly how low the target BP needs to be [12, 16, 17]. This intensity and thereby numerical target of antihypertensive drug therapy is set on the balance between cardiovascular risk reduction and chance of side effects. Recent trial evidence favours intensive treatment for most patients [18, 19]; however, frail older adults seem to be at higher risk for both cardiovascular events and severe side effects of antihypertensive drug therapy, resulting in an unclear net benefit [20, 21].

Because translation of the available evidence concerning primary cardiovascular prevention into clinical guidance for older adults is challenging, insight into the actual guidelines about hypertension management will contribute to the present debate. Therefore, the primary aim of this review was to provide a systematic, cross-continental and present-day overview of the thresholds and targets of antihypertensive drug treatment in older adults recommended in the currently used guidelines. A secondary aim was to explore the potential relationships between the advised targets and guideline characteristics, including methodological quality, continent of origin, intended users and the guideline committee's selection of evidence supporting the recommended targets.

Methods

This systematic review is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [22]. The protocol was registered in PROSPERO (CRD42020131021).

Data sources and searches

In consultation with a medical information specialist, we designed a systematic search in PubMed, Emcare and Embase for references published from 1 January 2008 (search date 15 July 2020). We combined search terms to define 'hypertension', 'high blood pressure', 'cardiovascular diseases' and the concept 'guideline'. (Appendix 1, available in *Age and Ageing* online, provides the complete strategies). The search was limited to English language. In addition, we searched the following websites and guideline-specific databases: Clinical Practice Guidelines Infobase (**CPG Infobase**; https://joulecma.ca/cpg/homepage); Guidelines International Network (**G-I-N**; http://www.g-i-n.net); National Guideline Clearinghouse (**NGC**; http://www.guideline.gov); Scottish Intercollegiate Guidelines Network (**SIGN**; http://www.sign.ac.uk); and UpToDate (https://www.uptodate.com/contents/search). For the database extraction, we used corresponding search terms on 15 July 2020, except for NGC (access date 20 June 2018) due to closure (16 July 2018) of the database.

Guideline selection

After removal of duplicate records, one investigator (JMKB) screened the unique publications by title and abstract. Only clinical practice guidelines were included, as defined by (i) having been extracted from one of the guideline-specific databases (see section **Data Sources and Searches**); (ii) being recorded in Pubmed, Embase or Emcare AND describing itself as 'guideline' in the document title. Publications that explicitly mentioned a disease-specific target population and/or when full version was unavailable in English or inaccessible online, were not included in the full-text screening. Summary reports or superseded documents were also not included.

Two investigators (JMKB and LMvB) screened the full text for the in- and exclusion criteria. For inclusion, guidelines had to (i) concern hypertension management in the general adult population (no age limit) and (ii) include a numerical threshold for initiation and/or target of antihypertensive drug treatment. Exclusion criteria were: (i) exclusively concerning secondary prevention; (ii) only disease-specific hypertension management (e.g. diabetes mellitus or kidney failure); (iii) full version unavailable in English or inaccessible online; (iv) document explicitly describing itself as a non-guideline; or (v) withdrawn. When a guideline was published more than 5 years before another included guideline from the same Society, it was considered superseded. Differences in evaluations were discussed in consensus

meetings, led by a third author (RKEP) until consensus was reached.

Data extraction

As defined by the inclusion criteria, all selected guidelines contained a numerical threshold for initiation and/or target of antihypertensive drug treatment in the general adult population. Specific advices concerning antihypertensive drug therapy in context of age, ageing or frailty were extracted from the included guidelines.

Two investigators (JMKB and LMvB) extracted in context of primary cardiovascular prevention: (i) all age- and frailty-related numerical advices (in mmHg) concerning when to start antihypertensive drug therapy (=threshold) and (ii) all age- and frailty-related numerical targets (in mmHg) of antihypertensive drug treatment. To contextualize these numbers, the corresponding thresholds for initiation and targets in the general adult population (as defined by the guideline) without elevated cardiovascular risk were additionally extracted.

Guideline characteristics

Quality assessment

Two investigators (JMKB and LMvB) individually assessed the methodological quality of each guideline included in the analysis using the Appraisal of Guidelines for Research & Evaluation (AGREE) II online instrument [23]. The AGREE II tool involves 23 items to be rated on a scale of 1 (strongly disagree) to 7 (strongly agree) corresponding to the extent to which the criteria articulated in the User's Manual are met. These 23 items are grouped into six domains: (i) scope and purpose, (ii) stakeholder involvement, (iii) rigor of development, (iv) clarity of presentation, (v) applicability and (vi) editorial independence. After independent appraisal of all included guidelines, JMKB and LMvB discussed each item with a difference of $\geq$3 points, adjusting the initial rating if deemed appropriate. The final score for each domain was calculated by summing the scores of both appraisers and converting them to a percentage of the maximum domain score for two appraisers. Additionally, an overall score was acquired by calculating a weighted mean of the individual domain scores (see Appendix 2, available in *Age and Ageing* online, for details). We rated the quality of a guideline as moderate-to-high when the weighted mean domain score was fifty percent or more.

Continent of origin and intended users

For all guidelines, the origins were categorized in four continents: (i) Asia, (ii) Europe, (iii) North America and (iv) other (including Africa, South America and Australia/Oceania). Intended users were, as stated in the guideline, categorized into three categories: (i) primary care, (ii) all health care professionals and (iii) not explicitly mentioned.

Supporting evidence

Two investigators (JMKB and LMvB) individually assessed the evidence supporting the advised targets. The complete guideline, appendices and references to inform the recommended values were checked. The supporting evidence was then categorized into four categories: (i) only RCT evidence, (ii) evidence from RCT's and observational studies, (iii) predominantly based on other guidelines and (iv) no statement concerning evidence used to underpin the recommended targets and no direct link between references and targets.

Results

A total of 10,080 records were identified by a combined search in PubMed, Embase and Emcare. After exclusion of 3,523 duplicates, 6,557 records were screened by title and abstract, of which 177 were potentially relevant. An additional 43 records were identified through the screening of five different databases (SIGN, NGC, GIN, CPG Infobase and UpToDate). Full-text screening of these 220 records yielded 42 unique guidelines that contained a numerical threshold for initiation and/or target of non-disease-specific antihypertensive drug treatment in context of primary prevention. The reasons of exclusion of the other 178 records are described in Figure 1 (PRISMA flow chart) [22].

Thirty-four (81%), of the total of 42 primary prevention guidelines with a numerical value concerning antihypertensive drug therapy provided recommendations regarding hypertension management in context of age, ageing or frailty and were included in the current analysis.

The 34 included guidelines originated from six different continents (Africa, Asia, Australia, Europe, North America, and South America). Table 1 summarizes the main characteristics of the included guidelines.

Initiation of antihypertensive drug treatments

Thirty-two of 34 included guidelines (excluding [35, 42]) recommended both at least one explicit BP threshold for the start of antihypertensive drug treatment and a corresponding target. A detailed overview of all values is displayed in Table 1. Twenty-three (68%) guidelines-based threshold values on age and/or frailty status, or explicitly mentioned to start drug treatment in older adults according to the same principles as in the general population. The subgroups of chronological age used to describe treatment recommendations were: $\geq$60–65 years (n = 7), both $\geq$60–65 and $\geq$80 years (n = 7), $\geq$80 years (n = 4) and $\geq$ 75 years (n = 2). The three remaining guidelines used the terms 'elderly' and 'older patients' [28, 34, 40].

While 4 out of 23 (17%) guidelines advised lower thresholds for older adults, four guidelines recommended higher thresholds for initiation of antihypertensive drug treatment. Eleven advised comparable values for middle-aged and older adults, of which a majority described separate thresholds for initiation of lifestyle management (LSM) and drug therapy in the general population. The remaining four only focused

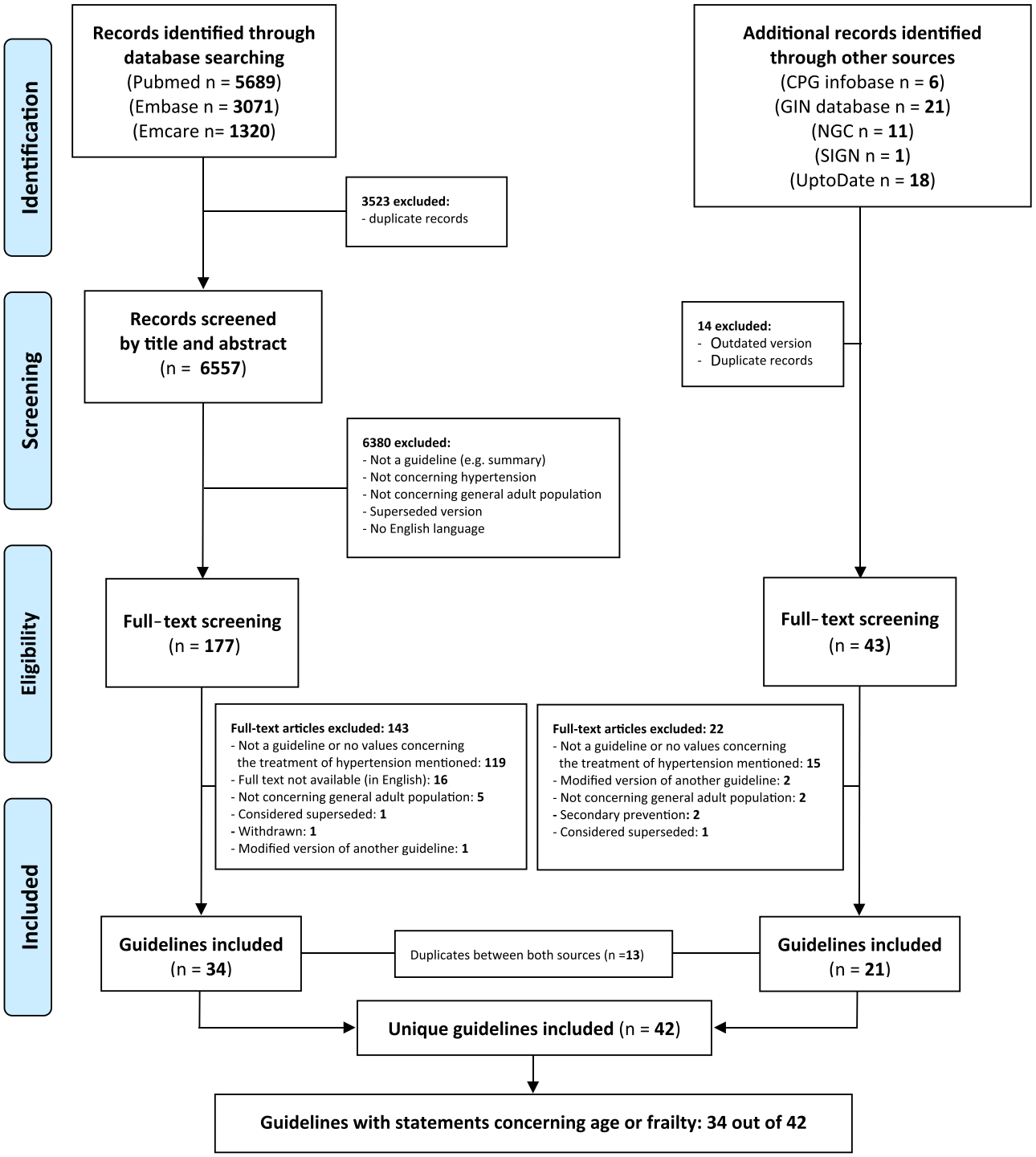

Figure 1. PRISMA flow chart of guideline selection process.

on hypertension management in older adults. The distribution of the recommended threshold values in older adults in comparison with the general population is displayed in Table 2.

Although frequently mentioned, only three of all 34 (9%) guidelines recommended a threshold specifically for the initiation of antihypertensive drug therapy in older adults with frailty. All three guidelines advised the start of pharmacological treatment when systolic blood pressure (SBP) is equal to or higher than 160 mmHg. Whereas one guideline did not define the term frailty [49], the other two guidelines included multiple frailty assessment tools [28, 47].

Targets of antihypertensive drug treatment

All thirty-four included guidelines recommended at least one numerical target (in mmHg) of antihypertensive drug

Table 1. Summary of the 34 guidelines that include thresholds for and targets of antihypertensive drug treatment in older adults

Guideline	Year	Region	Threshold of blood pressure for initiation of antihypertensive drug treatment	Target of antihypertensive drug treatment
R. del Campo [24]	2013	Spain	• General advice: based on risk estimation; when ≥10% (REGICOR) or whenever BP ≥180/110 mmHg • ≥80 years: when SBP ≥160 mmHg	• <60 years: BP <140/90 mmHg • 60–80 years: follow general guidelines • ≥80 years: continue treatment if well tolerated and follow specific guideline in special situation.
Blacher [25]	2013	France	• Whenever BP ≥180/110 mmHg • When BP ≥140/90 mmHg after LSM and a dedicated educational session with the patient	• <80 years: 130 ≤ SBP <140/DBP <90 mmHg • ≥80 years: SBP <150 mmHg, without orthostatic hypotension
James [26]	2014	USA	• <60 years: when SBP ≥140/90 mmHg • ≥60 years: when SBP ≥150/90 mmHg	• <60 years: BP <140/90 mmHg • ≥60 years: BP <150/90 mmHg
JBS [27]	2014	UK	• Whenever BP >160/100 mmHg	• <80 years: BP <140/90 mmHg • ≥80 years: BP <150/90 mmHg
Mallery [28]	2014	Canada	• Frail elderly: consider treatment when SBP ≥160 mmHg	• Frail elderly: 140 ≤ SBP ≤ 160 mmHg (seated and if tolerated) • Very frail elderly/short life expectancy: 160 ≤ SBP ≤ 190 mmHg
Seedat [29]	2014	South Africa	• General advice: when BP ≥160/100 mmHg or when BP ≥140/90 mmHg after 3–6 m LSM • ≥80 years: when SBP >160 mmHg	• <80 years: BP <140/90 mmHg • ≥80 years: 140 ≤ SBP ≤150 mmHg
Gabb [30]	2016	Australia	• Whenever BP ≥160/100 mmHg	• ≤75 years: BP <140/90 mmHg • >75 years: SBP <120 mmHg if well tolerated
Ibrahim [31]	2016	Egypt	• General advice: immediately whenever BP >210/120 mmHg when BP ≥180/110 mmHg after 1–3 w when BP ≥160/100 mmHg after 1–6 m of LSM • >65 years: when BP ≥150/95 mmHg after 3–6 w of LSM	• ≤65 years: BP <150/95 mmHg • >65 years: BP <150/95 mmHg
Malachias [32]	2016	Brazil	• General advice: whenever BP ≥160/100 mmHg when BP ≥140/90 mmHg after 6 m of LSM • ≥60/65 years: when SBP ≥140 mmHg and treatment is tolerated • ≥80 years: when SBP ≥160 mmHg	• <60/65 years: BP <140 mmHg • ≥60/65 years: BP <140 mmHg if in good condition and tolerated • ≥80 years: BP <150 mmHg • Elderly with multiple non-CV morbidities, frailty or dementia: The treatment target should be less strict and individualized.
Piepoli [33]	2016	Europe	• General advice: immediately whenever BP ≥180/110 mmHg when BP ≥140/90 mmHg and LSM fails. • >60 years: when SBP ≥160 mmHg	• <60 years: BP <140/90 mmHg • 60–80 years: 140 ≤ SBP ≤150 mmHg or lower if tolerated and fit • ≥80 years: 140 ≤ SBP ≤150 mmHg if mentally and physically good • Frail elderly: consider careful treatment intensity/BP targets

(Continued)

Table 1. Continued

Guideline	Year	Region	Threshold of blood pressure for initiation of antihypertensive drug treatment	Target of antihypertensive drug treatment
Barbosa [34]	2017	Latin America	• General advice: when BP ≥140/90 mmHg • Elderly: ≥140/90 mmHg when in good physical condition and without important adverse reactions	• General advice: 130 ≤ SBP < 140/DBP <90 mmHg
Chiang [35]	2017	Taiwan	• Not mentioned	• <75 years: BP <140/90 mmHg • ≥75 years: BP <140/90 mmHg (unattended AOBP: SBP <120 mmHg)
Czarnecka [36]	2017	Poland	• General advice: when BP ≥160/100 mmHg when BP ≥140/90 mmHg after LSM • >60 years: when SBP ≥160 mmHg	• ≤60 years: BP <140/90 mmHg • >60 years: SBP ≤150 mmHg or <140 mmHg and lower if tolerated • >80 years: 140 ≤ SBP ≤ 150 mmHg if mentally and physically good
De Oliveira [37]	2017	Intercontinental	• Whenever BP ≥160/100 mmHg • When BP ≥140/90 mmHg after LSM for 3–6 months	• <80 years: BP <140/90 mmHg • ≥80 years: BP <145/85 mmHg
Qaseem [38]	2017	USA	• ≥60 years: when SBP ≥150 mmHg and use shared decision-making	• ≥60 years: SBP <150 mmHg
SIGN [39]	2017	Scotland	• General advice: when BP ≥160/100 mmHg	• General advice: BP <140/90 mmHg, but adapt in the frail or elderly in light of medicine tolerance.
Tay [40]	2017	Singapore	• General advice: when BP ≥140/90 mmHg • Older patients (age not specified): when SBP ≥160 mmHg	• <80 years: BP <140/90 mmHg • Older patients <80 years: SBP <140 mmHg if tolerated • ≥80 years: BP <150/90 mmHg • Fragile elderly: adapt SBP goals to individual tolerability
Whelton [41]	2017	USA	• General advice: when BP ≥140/90 mmHg • ≥65 years and Noninstitutionalized: when SBP ≥130 mmHg • ≥65 years with limited life expectancy: use shared decision making	• <65 years: BP <130/80 mmHg • ≥65 years and Noninstitutionalized: SBP <130 mmHg • ≥65 years and high burden of comorbidities or limited life expectancy: assess risk/benefit
Kinoshita [42]	2018	Japan	• Not mentioned	• <75 years: BP <140/90 mmHg • ≥75 years: BP <150/90 mmHg and <140/90 mmHg if tolerated
MsH, MOH & AMM [43]	2018	Malaysia	• General advice: whenever BP ≥160/100 mmHg when BP ≥140/90 mmHg after 3–6 m LSM • ≥65 years: when SBP ≥160 mmHg	• <65 years: BP <140/90 mmHg • 65–80 years: SBP <140 mmHg and consider SBP <130 mmHg • >80 years: SBP <150 mmHg • Frail, institutionalized, functional and cognitive impairment: consider less strict treatment and consider de-prescribing

(Continued)

Table 1. Continued

Guideline	Year	Region	Threshold of blood pressure for initiation of antihypertensive drug treatment	Target of antihypertensive drug treatment
Williams [44]	2018	Europe	• General advice: whenever BP ≥160/100 mmHg when BP ≥140/90 mmHg after 3–6 m LSM • Fit and 65–80 years: when BP ≥140/90 mmHg and if tolerated • Fit elderly ≥ 80 years: when BP ≥160/90 mmHg	• <65 years: 120 ≤ SBP < 130/70 ≤ DBP <80 mmHg if tolerated • ≥65 years: 130 ≤ SBP < 140/70 ≤ DBP < 80 mmHg if tolerated • Frail older patients: BP targets may need to be modified
Liu [45]	2019	China	• General advice: when BP ≥160/100 mmHg when BP ≥140/90 mmHg after 1–3 m LSM • 65–79 years: start treatment when BP ≥150/90 mmHg and consider treatment when BP ≥140/90 mmHg • ≥80 years: when SBP >160 mmHg	• General advice: BP <140/90 mmHg, BP <130/80 mmHg if tolerated • 65–79 years: BP <150/90 mmHg If tolerated BP <140/90 mmHg • ≥80 years: BP <150/90 mmHg
Feitosa- Filho [46]	2019	Brazil	• ≥80 years: when SBP >160 mmHg	• ≥65 years without frailty: SBP ≤ 130 mmHg • ≤80 years without frailty: SBP <140 mmHg • >80 years and with SBP ≥ 160 mmHg: 140 ≤ SBP ≤ 150 mmHg • Fragile elderly or patients with multiple comorbidities: individualize the therapeutic goal considering risk–benefit ratio
Hua [47]	2019	China	• 65–79 years: when BP ≥140/90 mmHg • ≥80 years: when BP ≥150/90 mmHg • In the very old Frail: when BP ≥160/90 mmHg	• ≥65 years: BP <140/90 mmHg • ≥80 years: BP <150/90 mmHg if tolerated BP <140/90 mmHg • Very old and Frail: 130 ≤ SBP ≤ 150 mmHg
Jimbo [48]	2019	USA	• Whenever BP ≥160/100 mmHg • When BP ≥140/90 mmHg after LSM (up to 12 m)	• General advice: BP <140/90 mmHg • Male sex ≥ 60 years or Female ≥ 70 years: BP <130/80 mmHg • If high risk for hypotension: BP <140/90 mmHg
Lee [49]	2019	South Korea	• General advice: whenever BP ≥160/100 mmHg when BP ≥140/90 mmHg after LSM • Fit and >65–80 years: when SBP >140 mmHg • Frail and old or >80 years: when SBP >160 mmHg	• General advice: BP <140/90 mmHg • >65 years: BP <140/90 mmHg (if DBP <70 mmHg: be careful)
MOPHQa [50]	2019	Qatar	• 18–80 years: consider treatment when BP ≥140/90 mmHg consider treatment when BP levels close to 140/90 mmHg and lifestyle interventions are ineffective. • Any age: whenever BP ≥160/100 mmHg	• General advice: BP <140/90 mmHg and strive to <130/80 mmHg but SBP ≥120 mmHg and DBP ≥70 mmHg • <65 years: 120 ≤ SBP < 130 mmHg • >65 years: 130 ≤ SBP < 140 mmHg • >80 years: 130 ≤ SBP < 140 mmHg and DBP <80 mmHg
NICE [51]	2019	UK	• General advice: whenever BP ≥160/100 mmHg • <60 years: consider treatment when BP ≥140/90 mmHg • >80 years: consider treatment when BP ≥150/90 mmHg • People with frailty or multimorbidity: use clinical judgement	• <80 years: BP <140/90 mmHg • ≥80 years: BP <150/90 mmHg • People with frailty or multimorbidity: use clinical judgement

(Continued)

Table 1. Continued

Guideline	Year	Region	Threshold of blood pressure for initiation of antihypertensive drug treatment	Target of antihypertensive drug treatment
Tykarski [52]	2019	Poland	• General advice: when BP ≥160/100 mmHg when BP ≥140/90 mmHg after 3–6 m LSM • 65–80 years: according to general principles • ≥80 years: when BP ≥160/90 mmHg • Patients with frailty syndrome: individualize decision to treat	• <65 years: BP <140/80 mmHg and strive to BP <130/80 mmHg but SBP ≥120 mmHg and DBP ≥70 mmHg • 65–80 years: 130 ≤ SBP <140/70 ≤ DBP <80 mmHg • >80 years: 130 ≤ SBP <150/70 ≤ DBP < 80 mmHg
Umemura [53]	2019	Japan	• General advice: whenever BP ≥180/110 mmHg (female) whenever BP ≥160/100 mmHg (male) when BP ≥140/90 mmHg after 1 m LSM • Older patients: whenever BP ≥140/90 mmHg • Frail, dementia, nursed, end of life or >75 years: when 140 ≤ SBP < 150 mmHg: add individual assessment	• <75 years: BP <130/80 mmHg if tolerated • ≥75 years: BP <140/90 mmHg • Frailty or requiring nursing: individualize BP target
Rabi [54]	2020	Canada	• General advice: when BP ≥160/100 mmHg • ≥75 years: when SBP ≥130 mmHg	• <75 years: BP <140/90 mmHg • ≥75 years: SBP <120 mmHg (with unattended AOBP)
Shah [55]	2020	India	• When BP ≥140/90 mmHg after 1 m LSM • When BP ≥160/100 mmHg after a shorter period than one month	• General advice: Individualize according to age, activity level and other concomitant diseases therapies. Never <120/70 mmHg. • <60 years: BP ≤130/80 mmHg • >60 years: 130 ≤ SBP ≤ 140/80 ≤ DBP ≤90 mmHg • Frail elderly, postural hypotension and at risk of falls: A higher target BP may be acceptable.
Unger [56]	2020	Intercontinental	• Whenever BP ≥160/100 mmHg • When BP ≥140/90 mmHg after LSM for 3–6 months (If drug availability is limited: only in those aged 50–80 years)	Essential standards (low resource): • General advice: BP <140/90 mmHg Optimal standards: • <65 years: 120 ≤ SBP < 130/70 ≤ DBP ≤80 mmHg if tolerated • ≥65 years: BP <140/90 mmHg if tolerated • In context of frailty (and independence/tolerability): Consider individualized BP Target.
VA/DoD [57]	2020	USA	• Whenever BP ≥130/90 mmHg (after confirmation, if appropriate and if patient is willing to engage in pharmacotherapy)	• General advice: SBP <130/90 mmHg • ≥60 years: SBP <150/90 mmHg with added benefit lowering SBP to between 130 and 150 mmHg

AOBP: Automated office blood pressure. BP: Blood pressure. CV: Cardiovascular. DBP: Diastolic blood pressure. LSM: Lifestyle management. REGICOR: Registre Gironí del cor. SBP: Systolic blood pressure.

Table 2. Distribution of the thresholds for initiation and targets of antihypertensive drug treatment in older adults recommended in the 34 included guidelines for primary prevention of cardiovascular diseases. The numbers in the table correspond with the individual reference (ref.) of the guideline

Value in comparison to the general population		Lower	Higher	Comparable	Only older adults	No value or not specific for older adults
Threshold (ref.)		24, 31, 41, 54	26, 40, 50, 51	29, 32, 33, 34, 36, 43, 44, 45, 49, 52, 53	28, 38, 46, 47	25, 27, 30, 35, 37, 39, 42, 48, 55, 56, 57
Target (ref.)	65–70 years	48	26, 33, 36, 44, 45, 50, 52, 55, 56, 57	24, 25, 27, 29, 30, 31, 32, 35, 37, 40, 41, 42, 43, 49, 51, 53, 54	28, 38, 46, 47	34, 39
	≥80 years	30, 48, 54	25, 26, 27, 29, 32, 33, 36, 37, 40, 42, 43, 44, 45, 50, 51, 52, 53, 55, 56, 57	24, 31, 35, 41, 49	28, 38, 46, 47	34, 39

treatment. A detailed overview of all target values is displayed in Table 1. Thirty-two guidelines (excluding [34, 39]) described specific BP targets for older adults in context of age and/or frailty. Thirty-one (excluding [28, 34, 39]) used chronological age as one of the factors in advising targets. The subgroups of chronological age for description of targets were: both ≥60–65 and ≥80 years ($n = 10$), ≥60–65 years ($n = 9$), ≥80 years ($n = 6$), ≥75 years ($n = 5$) and both ≥60 and ≥70 years ($n = 1$).

Twenty-eight guidelines (excluding [28, 34, 38, 39, 46, 47]) gave both explicit targets for the general adult population and older adults. For adults 65–70 years, 17 guidelines recommended the same target in comparison with the general population, while 10 advised a higher target. Only one recently updated guideline endorsed a lower SBP value for this group of older adults in comparison to the target in the general population [48]. Twenty guidelines advised a higher target for the oldest old compared to the general population. In contrast, three guidelines recommended a lower target. Five guidelines endorsed the same target of antihypertensive drug therapy for the oldest old as for the general population. The distribution of the recommended targets in older adults in comparison with the general population is displayed in Table 2.

Over half of the guidelines ($n = 18$) recommended explicitly or implicitly to treat hypertension in adults aged 80 years and older to a target lower than 150 mmHg. The other 15 guidelines advised more intensive treatment targets for the oldest old. Targets of SBP lower than 130 or even 120 mmHg were endorsed by four different guidelines [30, 41, 48, 54].

Many guidelines gave non-numerical recommendations concerning intensity of treatment in frail older adults, such as '*. . . if tolerated but consider an individualised BP target in context of frailty, independence and likely tolerability of treatment*.' [56]. However, only two of all 34 (6%) guidelines included in the analysis advised an unambiguous target. One guideline recommended to lower SBP in frail older adults <150 mmHg [47], while the other advised to target a SBP <160 mmHg in the frail and <190 mmHg in the very frail [28].

Recommended targets and guideline characteristics

Quality assessment

The quality appraisal by AGREE domain scores for each individual guideline is provided in Appendix 3, available in *Age and Ageing* online. The domains '*Scope and Purpose*' and '*Clarity of Presentation*' were assigned the highest overall median scores of 68% (range 28–100%) and 86% (range 42–97%) respectively. The domain '*Editorial Independence*' was assigned the lowest median score of 33% (range 0–100%). The domains '*Rigor of Development*' and '*Applicability*', both scoring 34%, were as well generally underreported.

Five guidelines scored ≥50% on all six domains and were overall of very good quality. The weighted mean domain score of an additional nine guidelines was ≥50%. Those 14 guidelines together were labelled as of moderate-to-high quality. An overview of the advised target values of antihypertensive drug therapy in context of chronological age in these 14 guidelines is summarized in Figure 2a**.** The advised targets of the other 20 guidelines are displayed in Figure 2b. While approximately more than 60% of the guidelines in Figure 2b suggest to target <140 and <150 mmHg in older adults respectively below and above the age of 80 years, the guidelines of moderate-to-high quality are less consistent. In this subset of rigorously developed guidelines, targets of <150 mmHg (43%), <140 mmHg (36%), <130 mmHg (7%), and, <120 mmHg (14%) were advised in the oldest old.

Continent of origin and intended users

An overview of the advised target values of SBP according to the continent of origin of the corresponding guideline is summarized in Figure 3(1). When grouped per continent of origin, all guidelines showed variation in the advised targets

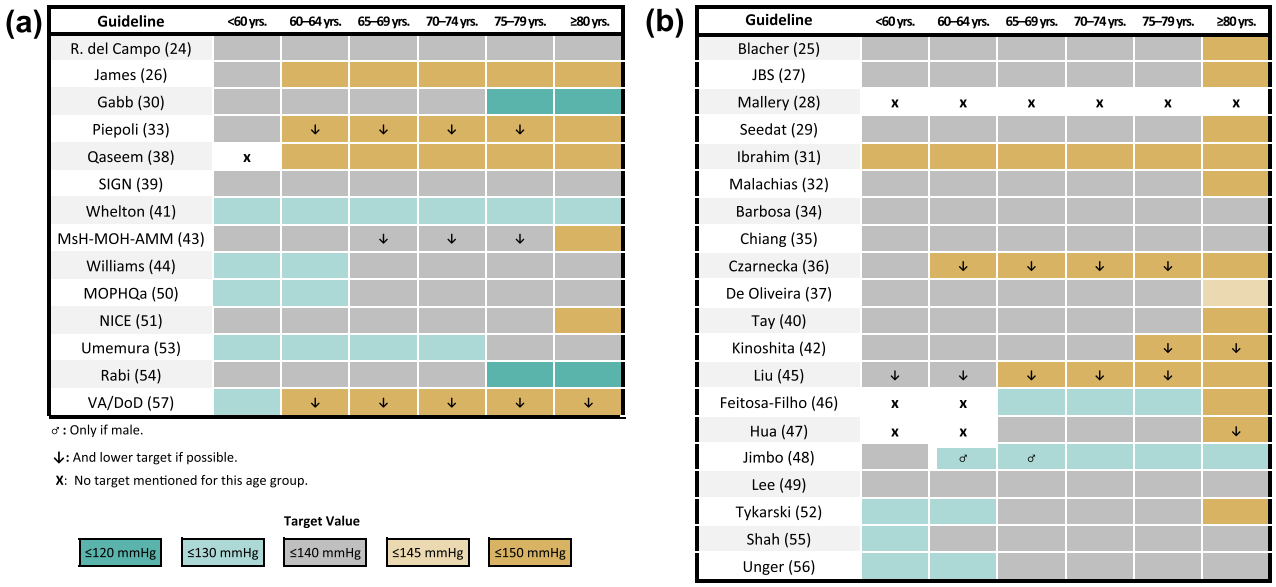

Figure 2. (a). Targets of systolic blood pressure according to age group (in years) recommended in the 14 guidelines of moderate-to-high quality. (b). Targets of systolic blood pressure according to age group (in years) recommended in the 20 other included guidelines.

for adults above the age of 80 years, most predominant in North American guidelines. The same variation was seen when categorized by intended users (Figure 3(2)).

Supporting evidence

Almost all guidelines described or referred to the evidence that was used to support the advised targets (Figure 3(3)). Guidelines that limited supporting evidence to RCT's recommended a target <140 mmHg in adults below the age of 75 years. But otherwise, a variation was seen among all categories, especially for the oldest old.

Discussion

In this systematic review of currently used guidelines on primary cardiovascular prevention, we searched for initiation thresholds and targets of antihypertensive drug treatment in older adults. Thirty-four of the 42 (81%) eligible guidelines did include explicit recommendations regarding antihypertensive drug therapy in old age. Most guidelines gave either no specific threshold for drug therapy in the older patient or one comparable to the general population. Corresponding targets of treatment, notably for the oldest old, were especially across the most rigorously developed guidelines less consistent. This variation between guidelines with the highest quality was also seen when categorized into continent of origin, intended users and supporting evidence. For octogenarians, targets of SBP varied largely from <120 to <150 mmHg. Guidelines do consider biological aspects of ageing, but only a very small minority recommends specific threshold and target values for antihypertensive drug therapy in the frail older patient.

In an earlier systematic review of guidelines on hypertension in older adults (search date December 2014), Alhawassi *et al*. [58] describe a consistency across all guidelines concerning titration of drug therapy to a SBP target of 140–150 mmHg. But despite this consistency, the authors note a continuous scientific debate among experts regarding the optimal target in older adults and the at that time lacking robust trial evidence. A half-decade later, we observe targets ranging from <150 to <120 mmHg (see Figure 2a and b) for the oldest old, reflecting that this debate among experts has been introduced into clinical guidelines. The Systolic Blood Pressure Intervention Trial (SPRINT) [19, 59] is a landmark RCT that plays a pivotal role in this ongoing discussion regarding the optimal target of antihypertensive drug therapy in older adults. SPRINT supports that a target of SBP <120 mmHg in non-diabetic adults above the age of 65 years safely reduces cardiovascular risk. However, the results of SPRINT are not yet unanimously endorsed in the currently used guidelines. This is in contrast to the Hypertension in the Very Elderly Trial (HYVET) [60], an other RCT that showed the benefits of treating hypertensive (SBP >160 mmHg) octogenarians to the nowadays in guidelines more widely implemented target of <150 mmHg (see Figure 2a and b). Although the results of SPRINT [19] became available 7 years after those of HYVET [60], 82% of the included guidelines in this review were published after SPRINT. The European experts of the 2018 ESC/ESH guideline embrace SPRINT, but translate the closely monitored RCT setting to a real-life target of 130–139 mmHg in adults 65 years and older [44]. Both SPRINT and HYVET provide evidence at a high level,

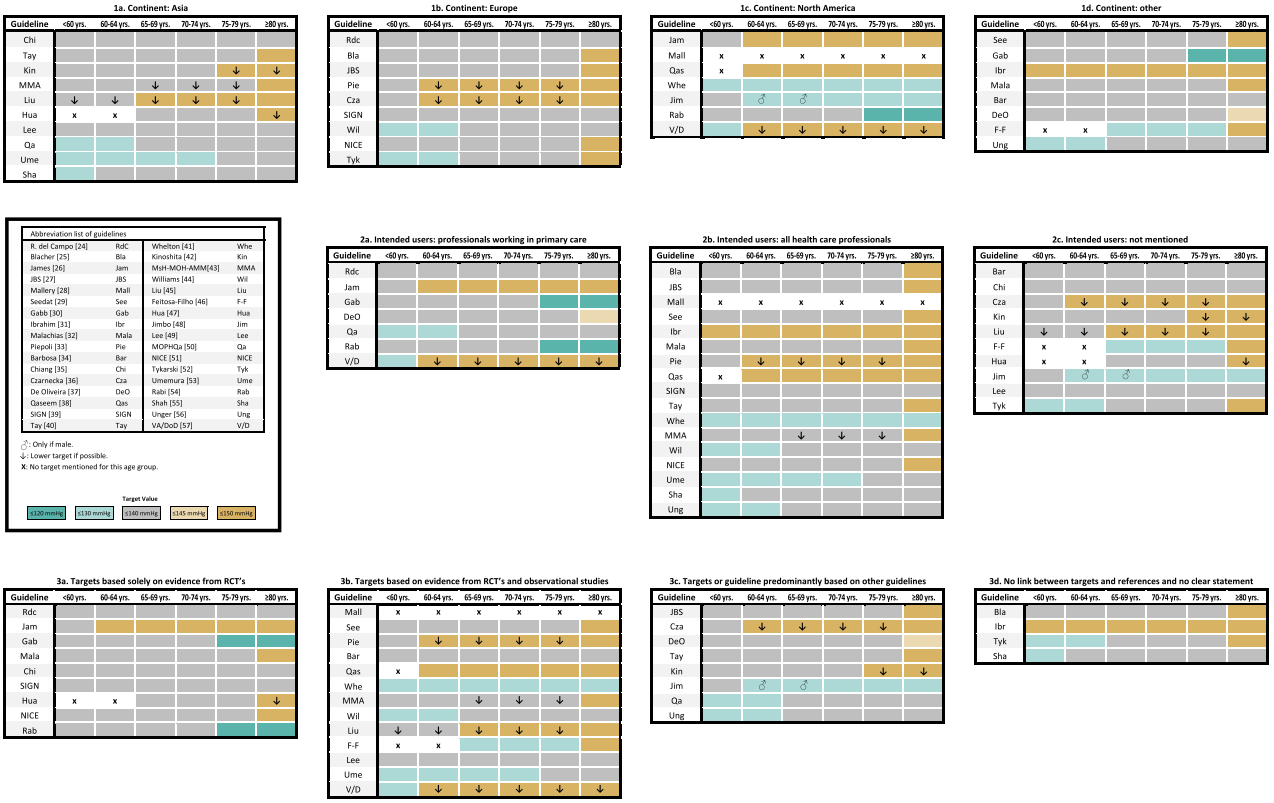

Figure 3. Targets of systolic blood pressure according to age group (in years) recommended in all 34 guidelines according to continent of origin (1), intended users (2) and supporting evidence of the recommended targets (3).

however, due to their exclusion criteria, the generalisability of both trials to the heterogeneous population of older adults remains a matter of debate [10, 12]. In adults aged under 75, this target value is the scarce consistent recommendation when we limit the included guidelines to those with targets based on RCT's. (see Figure 3a). Robust older adults certainly benefit from a SBP <140 mmHg [7–9, 18], however, we found that only two guidelines in line with observational studies suggest different SBP target values for frail compared to vital older adults [28, 47]. Nonetheless, in comparison with a systematic review published in 2015 by Jansen *et al*. [61], guidelines increasingly denote frailty as a factor to consider when setting thresholds for the start and targets of antihypertensive drug therapy (see Table 1).

The current evidence gaps concerning targets of antihypertensive therapy for older adults, especially for the frail, necessitates scientific committees to combine trial evidence with observational data and consensus among experts for guideline development. The significant share of expert opinion in those guidance documents appears to result in a variety of recommended targets. We support the growing consensus that a large RCT is needed to provide sufficient evidence for the (de) prescribing and optimal intensity of antihypertensive drug therapy in the frail older population [12, 20, 62, 63]. Although this study design carries with it well-known difficulties such as feasibility and strict inclusion and exclusion criteria, it could come up with additional insights into the net benefit of antihypertensive drug treatment in frail older adults.

Strengths and limitations

To our knowledge, this is the first study that systematically screened the currently used guidelines for thresholds and targets of antihypertensive drug therapy specifically for older adults with frailty. The other strengths of this study include a systematic search that resulted in a comprehensive overview of the threshold and target values of antihypertensive drug therapy recommended in the currently used international hypertension guidelines. Moreover, the extensiveness of our search resulted in an overview of guidelines not only originating from high income countries. Furthermore, the use of a validated tool [23] that appraises the methodology of a guideline allowed us to present the endorsed targets of treatment in light of the overall quality of the corresponding document.

A limitation of this study is that we only included guidelines in English language. At least two non–English-language guidelines (in Norwegian [64] and Dutch [65]) advise targets for antihypertensive treatment in older adults, but were not included in this study. Nonetheless, our review provides an overview of thresholds and targets from guidelines originating from all over the world. A second limitation may be that our search strategy overestimated the timeframe of

the currently used guidelines; however, 16 (47%) of the total of 34 included guidelines were published in the last three years. Furthermore, 7 (50%) of the moderate-to-high quality guidelines were issued in 2018 or later. A third limitation is that only one author performed the first screening by title and abstract. However, since this straightforward step was conducted in eight distinct databases, it is unlikely that many important guidelines were missed. Finally, we restricted the extraction of targets and thresholds to the context of age, ageing and frailty. Thresholds and targets in context of frailty related terms such as 'limited life expectancy', 'multimorbidity' and 'nursing home' were not systemically extracted, since this would change the scope of the review.

Conclusion

The subject of antihypertensive drug treatment in older adults is well addressed in current international guidelines for primary prevention of cardiovascular diseases. The ongoing scientific and clinical debate concerning how low the target of treatment needs to be, however, is reflected in an inconsistency of recommendations across guidelines especially for adults aged 80 years and older. This inconsistency is independent of methodological quality, originating continent, intended users and supporting evidence of the guideline.

Clinical practice guidelines are developed to standardize treatment, but currently challenge physicians to exercise very active reading and clinical judgement in a complex medical context, especially when treating a frail older adult. In order to accommodate clinical judgement in geriatric cardiovascular prevention, it would be helpful if guidelines defined targets more on base of biological aspects of ageing such as frailty rather than merely on base of chronological age alone. Research that incorporates this heterogeneity in older persons will possibly lead to more uniform guidelines on hypertension management in old age.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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