

Appraisal of Guidelines for the Management of Blood Pressure in Patients with Diabetes Mellitus: The Consensuses, Controversies and Gaps

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Background: Currently available guidelines contain conflicting recommendations on the management of blood pressure (BP) in patients with diabetes mellitus (DM). Therefore, it is necessary to appraise the guidelines and summarize the agreements and differences among recommendations.

Methods: Four databases and the websites of guideline organizations were searched for guidelines regarding BP targets and thresholds for pharmacologic therapy in DM patients, and the included guidelines were appraised with the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument.

Results: In 6,498 records identified, 20 guidelines met our inclusion criteria with 64.0% AGREE II scores (interquartile range, 48.5% to 72.0%). The scores of the European and American guidelines were superior to those of the Asian guidelines (both adjusted $P < 0.001$). Most of the guidelines advocated systolic BP targets < 130 mm Hg (12 guidelines, 60%) and diastolic BP targets < 80 mm Hg (14 guidelines, 70%) in DM patients. Approximately half of the guidelines supported systolic BP thresholds > 140 mm Hg (10 guidelines, 50%) and diastolic BP thresholds > 90 mm Hg (nine guidelines, 45%). The tiny minority of the guidelines provided the relevant recommendations regarding the lower limit of official BP targets and the ambulatory BP monitoring (ABPM)/home BP monitoring (HBPM) targets and thresholds in DM patients.


Conclusion: The lower official BP targets ($< 130/80$ mm Hg) in patients with DM are advocated by most of the guidelines, but they contain conflicting recommendations on the official BP thresholds. Moreover, the gaps regarding the lower limit of official BP targets and the ABPM/HBPM targets and thresholds need to be considered by future study.


Keywords: Blood pressure; Diabetes mellitus; Guideline; Systematic review

INTRODUCTION

In 1984, a report from the Joint National Committee [1] acknowledged that patients with diabetes mellitus (DM) represented special populations in the management of blood pres-

sure (BP). BP-lowering treatment in patients with DM was associated with a significantly lower risk of all-cause mortality and cardiovascular disease (CVD) events [2]. Thus, the guideline-recommended BP management strategy is key for DM patients. However, conflicting recommendations about the BP

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targets and thresholds for pharmacologic therapy in patients with DM were observed across guidelines. In August 2019, the guidelines published by the European Society of Cardiology (ESC)/European Association for the Study of Diabetes (EASD) advocated that the BP goal for DM patients was to target BP to 130/80 and <130/80 mm Hg if tolerated [3]. Similar recommendations were also supported by the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines [4]. However, in August 2019, the National Institute for Health and Clinical Excellence (NICE) guidelines recommended BP targets below 140/90 mm Hg [5]. Given these differences, clinicians might be confused when using guidelines to manage BP for DM patients. Therefore, assessing the quality of guidelines and summarizing the recommendations regarding BP management strategies in DM patients might help physicians better use guidelines in clinical work.

The aim of the present study is to systematically appraise the guidelines and summarize the agreements and the differences among recommendations regarding BP targets and thresholds for pharmacologic therapy to serve as a guide for BP management in patients with DM.

METHODS

Guideline search

A systematic search was performed in the PubMed, EMBASE, Web of Science, and Cochrane Library databases using the keywords “hypertension,” “diabetes mellitus,” and “guideline” from January 2009 to December 2019. In addition, the websites of guideline organizations and professional societies were searched for additional guidelines. The detailed search strategy of each database and the websites of guideline organizations and professional societies are listed in Supplementary Tables 1 and 2.

Guideline selection

Guidelines were strictly selected in the present study according to inclusion and exclusion criteria. The inclusion criteria included the following. (1) The publication fulfilled the Institute of Medicine definition for clinical practice guidelines [6]. (2) The guidelines focused on the management of hypertension or DM. (3) The recommendations for the treatment targets and thresholds of BP in patients with DM were contained in the guidelines. (4) The guidelines were published in English. (5) The latest version of the guidelines were selected. Guidelines were excluded if they referred exclusively to hypertension pa-

tients or special or inpatient care for DM patients. Expert consensus or statements, review articles, and original research were also excluded.

Based on the above criteria, two reviewers independently performed the review of titles and abstracts and then performed full-text screening. Discrepancies were discussed and resolved by consensus. The final selection of articles was performed by both reviewers and was checked by a third reviewer.

Quality assessment of guidelines

The rigor of development for final extracted guidelines was appraised using the latest 23-item Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument [7] that included six domains: Domain 1 (D1): scope and purpose; (D2) stakeholder involvement; (D3) rigor of development; (D4) clarity of presentation; (D5) applicability; (D6) editorial independence (the details of six domains are presented in Supplementary Table 3). Each item was independently rated on a 7-point Likert scale by two reviewers. The rigor scores for each domain were calculated by the scores of two reviewers according to the formula from AGREE II: (obtained score–minimum possible score)/(maximum possible score–minimum possible score) [7]. The average AGREE II scores for each of the guidelines were calculated by averaging the six domain scores. Finally, the guidelines were defined as “strongly recommended” if most domains (>3 domains) scored above 60%; the guidelines were “recommended” if most domains scored between 30% and 60%; and the guidelines were “not recommended” if most domain scores were <30% [8].

Data extraction and synthesis

All relevant recommendations from each of the included guidelines were extracted by three independent reviewers in accordance with the steps outlined in a predesigned schematic. Any disagreement on recommendation abstraction was resolved by a group discussion to reach consensus. The extracted information contained the target populations of each recommendation, the pharmacologic therapy targets and thresholds for BP in patients with DM, and the level of evidence of each recommendation. The BP target was defined as the control goal of official BP monitoring, home blood pressure monitoring (HBPM) or ambulatory blood pressure monitoring (ABPM) after the patient with DM takes the anti-hypertensive medications. The BP threshold was defined as the boundary of the official BP, HBPM, or ABPM that was needed to begin

treatment for the patient with DM with anti-hypertensive medications. A table was created for comparison of the recommendations among different guidelines.

Statistical analysis

Continuous variables that were normally distributed are presented as the mean \pm standard deviation. Otherwise, these data are presented as the median and interquartile range (IQR). Agreement between reviewers on the 23-item AGREE II scores was assessed utilizing the intraclass correlation coefficient by the two-way random model with the type absolute agreement. The differences in overall AGREE II scores and each domain score among different regional guidelines (i.e., European, American, Asian, and Other regions) were examined using the independent-samples *t*-test or Mann-Whitney *U* test. A $P < 0.05$ was accepted as statistically significant. All analyses were performed using IBM SPSS version 20.0 (IBM Co., Armonk, NY, USA) and GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA, USA) software.

Ethics approval

This article does not contain examinations performed on human participants or animals. Then, ethical approval was not necessary.

RESULTS

Guideline selection and characteristics

Our systematic search identified 6,498 published citations in the PubMed, EMBASE, Web of Science, and Cochrane Library databases and the websites of guideline organizations in January 2009 to December 2019. A total of 6,478 records did not meet the inclusion criteria after titles, abstracts and full-text review. Data from the remaining 20 guidelines reported BP management in DM patients and were included in the analysis (Fig. 1).

The guideline characteristics are shown in Table 1, and the guideline references are listed in Supplementary Table 4. The 20 included guidelines were published from different regions around the world (five guidelines from the USA, four guidelines from Europe, six guidelines from Asia, five guidelines from other regions). The target population of 10 guidelines was hypertension patients, and the remaining 10 guidelines focused on DM patients. The AGREE II scores and the guideline status of each of the guidelines are described in Table 1.

Guideline appraisal

The 20 included guidelines (including 12 “strongly recommended” guidelines and eight “recommended” guidelines) were appraised utilizing the AGREE II [7], and the average score was 64.0% (IQR, 48.5% to 72.0%) (Table 1). The reproducibility of the average AGREE II scores of the two reviewers was great, with an intraclass correlation coefficient of 0.86.

Through appraisal of the guidelines, we found different AGREE II scores across regions. Thus, we divided these guidelines by region of origination to compare these differences and analyse the potential reasons for these differences. Such information might provide a reference for the development of future guidelines in different regions. The results showed that all guidelines from Europe and the USA were “strongly recommended” and that all Asian guidelines were “recommended.” The AGREE II scores of Asian guidelines were significantly lower than those of guidelines from Europe and the USA, as intuitively presented in Fig. 2. The pairwise comparisons among different regional guidelines (European, American, Asian, and Other regions) showed that the average AGREE II scores of the Asian guidelines were significantly lower than those of the guidelines from Europe (adjusted $P < 0.001$) and the USA (adjusted $P < 0.001$) (Supplementary Fig. 1A). Similar results were also found in the D3 (rigor of development), D5 (applicability), and D6 (editorial independence) scores (all adjusted $P < 0.05$) (Supplementary Table 5, Supplementary Fig. 1).

In addition, we found generally low D5 scores (29% [IQR, 21% to 53%]) and extensive heterogeneity in D6 scores (90% [IQR, 31% to 92%]) in all included guidelines (Supplementary Fig. 2).

Official BP targets and thresholds for pharmacologic therapy

The 20 included guidelines (12 of which were “strongly recommended” guidelines) contained 22 recommendations on the official BP targets and thresholds for pharmacologic therapy in patients with DM (Table 2). Regarding the targets of official systolic blood pressure (SBP), the recommendations from 12 (60%) guidelines (eight “strongly recommended” guidelines) supported treatment to get SBP below 130 mm Hg, while a target SBP of less than 140 mm Hg was supported by only five guidelines (Table 2). The 14 (70%) guidelines (nine “strongly recommended” guidelines) that advocated an official diastolic blood pressure (DBP) less than 80 mm Hg were markedly more than the three guidelines (15%) that supported an official

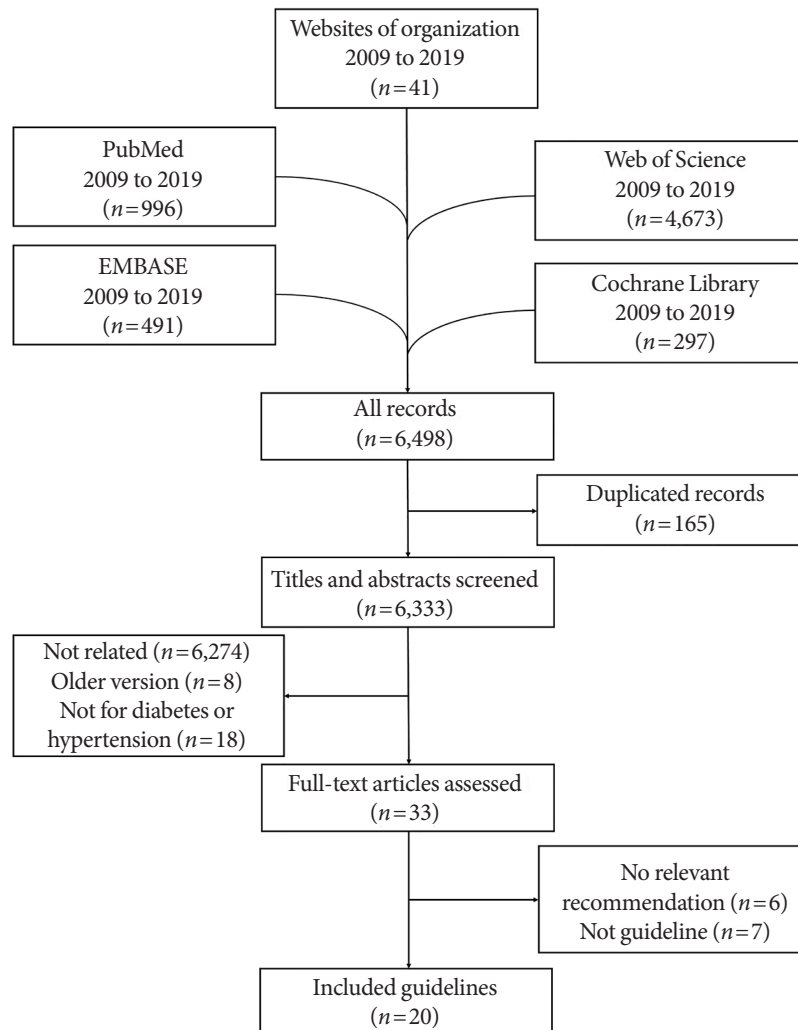


Fig. 1. Flow chart of the search for and selection of guidelines.

DBP below 90 mm Hg (Table 2). In addition, three guidelines with similar recommendations [9-11] advocated that different official BP targets were appropriate for DM patients with/without CVD or with different CVD risks (official BP targets <130/80 mm Hg in DM patients with high CVD risk or CVD; official BP targets <140/85–90 mm Hg in DM patients with lower CVD risk) (Table 2). Furthermore, we compared AGREE II scores of the 20 included guidelines according to official BP targets and found that most guidelines (12 guidelines, 60%) advocated official BP targets less than 130/80 mm Hg, although the quality of these guidelines was spotty with 64.0% AGREE II scores (IQR, 52.3% to 74.8%), and the other official BP targets were advocated only by a few guidelines (Supplementary Fig. 3).

In addition, recommendations regarding the lower limits (120/70 mm Hg) of official BP targets were formulated only by two guidelines [3,12] that were developed by the same organization (ESC). The remaining 18 included guidelines did not provide relevant recommendations (Table 2).

Regarding the BP thresholds for pharmacologic therapy in patients with DM, SBP/DBP thresholds greater than 140/90 mm Hg were advocated by the recommendations from 10 (50%)/9 (45%) guidelines (Fig. 3). However, four guidelines (20%) supported BP thresholds greater than 130/80 mm Hg, and six guidelines (30%) did not contain recommendations on BP thresholds for pharmacologic therapy in patients with DM (Table 2).

Table 1. General characteristics of the included 20 guidelines

Guidelines identifier, year ^a	Organization(s) responsible for guidelines development	Region	Target population	AGREE II score, %	Guideline status
ADA, 2019	American Diabetes Association	USA	Diabetes	72	Strongly recommended
VA/DoD, 2017	U.S. Department of Veterans Affairs and Department of Defense	USA	Diabetes	67	Strongly recommended
ACC/AHA, 2017	American College of Cardiology and American Heart Association	USA	Hypertension	74	Strongly recommended
AACE/ACE, 2015	American Association of Clinical Endocrinologists	USA	Diabetes	63	Strongly recommended
JNC 8, 2014	Eighth Joint National Committee	USA	Hypertension	72	Strongly recommended
ESC/EASD, 2019	European Society of Cardiology and European Association for the Study of Diabetes	Europe	DM and pre-diabetes	76	Strongly recommended
ESC/ESH, 2018	European Society of Cardiology and European Society of Hypertension	Europe	Hypertension	77	Strongly recommended
NICE, 2019	National Institute for Health and Clinical Excellence	UK	Hypertension	71	Strongly recommended
SIGN, 2010	Scottish Intercollegiate Guidelines Network	UK	Diabetes	66	Strongly recommended
KDA, 2019	Korean Diabetes Association	Korea	Diabetes	39	Recommended
JSH, 2019	Japanese Society of Hypertension	Japan	Hypertension	50	Recommended
KSH, 2018	Korean Society of Hypertension	Korea	Hypertension	39	Recommended
MOH, 2017	Ministry of Health, Singapore	Singapore	Hypertension	48	Recommended
TSOC/THS, 2017	Taiwan Society of Cardiology and Taiwan Hypertension Society	China (Taiwan)	Hypertension	44	Recommended
JDS, 2016	Japan Diabetes Society	Japan	Diabetes	41	Recommended
CDA, 2018	Canadian Diabetes Association	Canada	Diabetes	75	Strongly recommended
CHEP, 2018	Canadian Hypertensive Education Program	Canada	Hypertension	64	Strongly recommended
NHFA, 2016	National Heart Foundation of Australia	Australia	Hypertension	57	Recommended
Baker IDI, 2015	Baker Heart and Diabetes Institute	Australia	Diabetes	64	Strongly recommended
IDF, 2012	International Diabetes Federation	International	Diabetes	59	Recommended

^aThe guideline references were listed in Supplementary Table 4.

Targets and thresholds for ABPM and HBPM

Only three guidelines provided recommendations regarding ABPM/HBPM targets and thresholds in patients with DM (Table 2). Two guidelines [13,14] from the same region (Japan) considered the boundary (125/75 mm Hg) as the HBPM targets and thresholds in patients with DM, but a boundary of 135/85 mm Hg in ABPM/HBPM was considered by the 2019 NICE guidelines (Table 2) [5].

DISCUSSION

In the present study, 20 guidelines on BP management in patients with DM were included and appraised utilizing the AGREE II instrument [7]. Through appraisal of the guidelines, the quality of the European and American guidelines on BP management in DM patients was superior to that of the Asian guidelines, and the European and American guidelines were

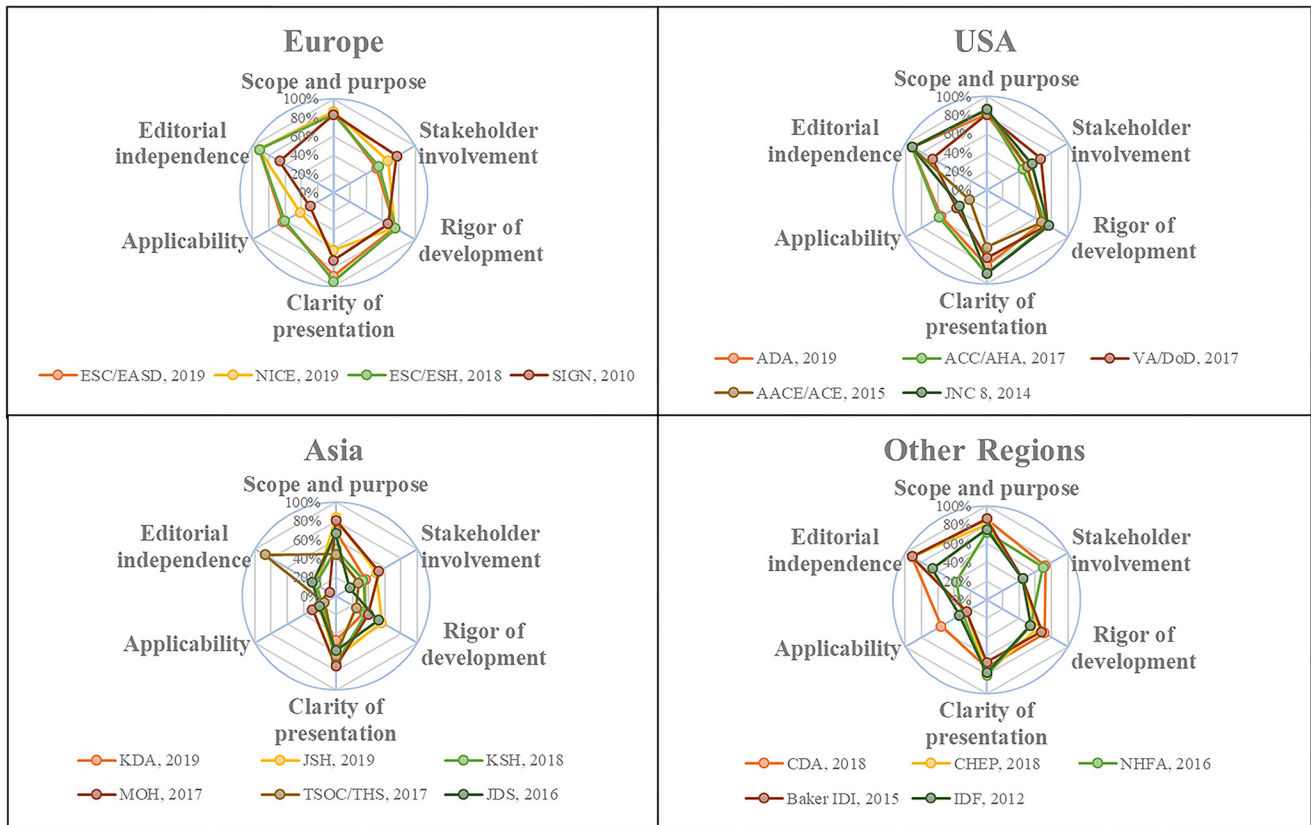


Fig. 2. Appraisal of Guidelines for Research and Evaluation (AGREE) II scores of the guidelines in the six domains across different regions. ESC, European Society of Cardiology; EASD, European Association for the Study of Diabetes; NICE, National Institute for Health and Clinical Excellence; ESH, European Society of Hypertension; SIGN, Scottish Intercollegiate Guidelines Network; ADA, American Diabetes Association; ACC, American College of Cardiology; AHA, American Heart Association; VA/DoD, U.S. Department of Veterans Affairs and Department of Defense; AACE/ACE, American Association of Clinical Endocrinologists; JNC 8, Eighth Joint National Committee; KDA, Korean Diabetes Association; JSH, Japanese Society of Hypertension; KSH, Korean Society of Hypertension; MOH, Ministry of Health, Singapore; TSOC, Taiwan Society of Cardiology; THS, Taiwan Hypertension Society; JDS, Japan Diabetes Society; CDA, Canadian Diabetes Association; CHEP, Canadian Hypertensive Education Program; NHFA, National Heart Foundation of Australia; Baker IDI, Baker Heart and Diabetes Institute; IDF, International Diabetes Federation.

considered “strongly recommended” guidelines but the Asian guidelines were not. Further summarizing the recommendations on the BP targets and thresholds for pharmacologic therapy from these guidelines (Fig. 3), we found that most of the guidelines and “strongly recommended” guidelines advocated official BP targets less than 130/80 mm Hg, but the consistency of guideline recommendations on the official BP thresholds was inadequate. Moreover, hardly any of the guidelines provided relevant recommendations on the lower limit of official BP targets and the targets and thresholds with ABPM and HBPM in patients with DM.

The AGREE II scores for the European and American guide-

lines on BP management in DM patients were significantly higher than those for the Asian guidelines, and a similar tendency was also observed with the D1, D5, and D6 scores. In addition, the D5 scores (applicability) were generally lower in all included guidelines, mainly due to the neglect of guideline application by most of the committee for practice guidelines. For example, most guideline organizations failed to provide relevant tools to help put the recommendations into practice with the exception of the ESC and ACC, which provided mobile apps. Improvements with this item would help make the clinical guidelines more accessible to a wider audience [15]. These results indicated that better methodologies and more

Table 2. Recommendations on the target and threshold of BP in patients with DM

Guidelines identifier, year ^a	Target populations	BP targets, mm Hg	Level of evidence ^b	BP thresholds, mm Hg	Level of evidence ^b
ADA, 2019	DM with higher risk ^c	Official BP <130/80	C	Official BP >140/90	A
ADA, 2019	DM with lower risk ^c	Official BP <140/90	A	Official BP >140/90	A
VA/DoD, 2017	DM	Official BP <140/80	A	Official BP ≥140/90	A
ACC/AHA, 2017	DM	Official BP <130/80	I	Official BP ≥130/80	I
AACE/ACE, 2015	DM	Official BP <130/80	B	-	-
JNC 8, 2014	DM	Official BP <140/90	E	Official BP ≥140/90	E
ESC/EASD, 2019	DM	120/70 ≤ Official BP ≤ 130/80	IA	Official BP >140/90	IA
ESC/ESH, 2018	DM	120/70 ≤ Official BP ≤ 130/80	IA	Official BP >140/90	IA
NICE, 2019	DM	Official BP <140/90; ABPM/HBPM <135/85	-	Official BP ≥140/90; ABPM/HBPM ≥135/85	-
SIGN, 2010	DM	Official BP <130/≤80	D/A ^d	-	-
KDA, 2019	DM	Official BP <140/85	B	-	-
KDA, 2019	DM with CVD	Official BP <130/80	B	-	-
JSH, 2019	DM	Official BP <130/80; HBPM <125/75	2B	Official BP ≥140/90 ^e	-
KSH, 2018	DM	Official BP <140/85	IA/IB ^d	Official BP >140/90 ^e	IB
KSH, 2018	DM with CVD	Official BP <130/80	Ia C	Official BP >140/90 ^e	IA
MOH, 2017	DM	Official BP <140/80	B 2 ⁺	-	-
TSOC/THS, 2017	DM	Official BP <130/80	IB	-	-
JDS, 2016	DM	Official BP <130/80	B	Official BP ≥140/90 ^e ; HBPM ≥125/75	Consensus
CDA, 2018	DM	Official BP <130/80	C/A ^d	Official BP ≥130/80	C/A ^d
CHEP, 2018	DM	Official BP <130/80	C/A ^d	Official BP ≥130/80	C/A ^d
NHFA, 2016	DM	Official BP <140/90	I	Official BP: SBP ≥140	I
Baker IDI, 2015	DM	Official BP ≤130/80	Consensus	-	-
IDF, 2012	DM	Official BP ≤130/80	-	Official BP >130/80	-

BP, blood pressure; DM, diabetes mellitus; ADA, American Diabetes Association; VA/DoD, U.S. Department of Veterans Affairs and Department of Defense; ACC, American College of Cardiology; AHA, American Heart Association; AACE/ACE, American Association of Clinical Endocrinologists; JNC 8, Eighth Joint National Committee; ESC, European Society of Cardiology; EASD, European Association for the Study of Diabetes; ESH, European Society of Hypertension; NICE, National Institute for Health and Clinical Excellence; ABMP, ambulatory blood pressure monitoring; HBPM, home blood pressure monitoring; SIGN, Scottish Intercollegiate Guidelines Network; KDA, Korean Diabetes Association; CVD, cardiovascular disease; JSH, Japanese Society of Hypertension; KSH, Korean Society of Hypertension; MOH, Ministry of Health, Singapore; TSOC, Taiwan Society of Cardiology; THS, Taiwan Hypertension Society; JDS, Japan Diabetes Society; CDA, Canadian Diabetes Association; CHEP, Canadian Hypertensive Education Program; NHFA, National Heart Foundation of Australia; SBP, systolic blood pressure; Baker IDI, Baker Heart and Diabetes Institute; IDF, International Diabetes Federation.

^aThe guideline references were listed in Supplementary Table 4, ^bThe level of evidence on each recommendation was adopted from respective guideline, ^cHigher risk was defined as existing arteriosclerotic cardiovascular disease or 10-year atherosclerotic cardiovascular disease risk >15%, otherwise lower risk, ^dThe level of evidence on SBP and diastolic blood pressure are in front of and behind the slash, respectively, ^eLifestyle interventions are recommended in DM patients with the BP of 130–139/80–89 mm Hg, and antihypertensive agents are to be initiated immediately when lifestyle modification is considered to be unlikely to achieve the BP target.

Recommendations		Proportion of “Strongly recommended” guidelines ^a	Proportion of guidelines ^b	(Consensus)
Official SBP targets <130 mm Hg in patients with DM		67%	60%	100%
Official DBP targets <80 mm Hg in patients with DM		75%	70%	80%
Official SBP thresholds in patients with DM	>140 mm Hg	50%	50%	60%
	>130 mm Hg	25%	20%	40%
Official DBP thresholds in patients with DM	>90 mm Hg	50%	45%	40%
	>80 mm Hg	25%	20%	20%
The points were neglected by most of guidelines in patients with DM	Lower limit of official BP targets	17%	10%	20%
	Optimal ABPM targets and thresholds	8%	5%	10%
	Optimal HBPM targets and thresholds	8%	15%	10%

Fig. 3. Summary of recommendations regarding blood pressure management in patients with diabetes mellitus (DM). SBP, systolic blood pressure; DBP, diastolic blood pressure; ABPM, ambulatory blood pressure monitoring; HBPM, home blood pressure monitoring. ^aThe proportion of “strongly recommended” guidelines that provided relevant recommendations among the 12 “strongly recommended” guidelines, ^bThe proportion of guidelines that provided relevant recommendations among the 20 included guidelines.

rigorous strategies were used in the European and American guideline development process. The rigorous methodology and strategy in guideline development played a crucial role in overall credibility and quality, which would contribute to improving the reliability of recommendations from guidelines and successfully implementing the resulting recommendations [16-18]. Therefore, in future guideline development processes, methodological rigor and transparency and guideline applicability should be considered, particularly in Asian regions or other developing countries. Given the available guidelines, the European and American guidelines might be more reliable in helping clinicians make decisions for BP management in DM patients.

Additionally, another possible reason for the low AGREE II scores in Asian countries and regions might be associated with limited evidence. Most of the evidence regarding BP management in DM patients came from studies in the United States/Europe, such as the Appropriate Blood Pressure Control in Diabetes (ABCD) trial [19], Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [20], and Systolic Blood Pressure

Intervention Trial (SPRINT) [21]. The guidelines from Asian countries and regions might have difficulty creating solid recommendations due to the limited evidence. Therefore, more evidence from Asian populations is also necessary for the development of guidelines in the future.

The current analysis revealed that BP targets below 130/80 mm Hg in DM patients were generally recommended by most of the guidelines. The evidence for these recommendations was principally derived from high-quality meta-analyses [22] and large randomized controlled trials (RCTs) [19-21]. A lower DBP target (<80 mm Hg) for adults with DM was supported by the ABCD trial [19]. The SPRINT [21] formed the basis for the current recommendations of lower BP targets contained in most of the guidelines, although this trial included only patients at high risk for cardiovascular events but without DM. A *post hoc* analysis of the SPRINT demonstrated that the beneficial effects were similar among those with prediabetes and normoglycaemia [23], and similar quantitative benefits from BP-lowering regimens in patients with and without DM were confirmed by a previous study [24]. Furthermore, al-

though negative results were reported by the ACCORD trial [20], the careful comparison of effects on individual outcomes in the SPRINT and ACCORD trial were generally consistent [25], and a *post hoc*, multivariate, subgroup analysis of ACCORD-BP in SPRINT-eligible participants showed that intensive BP control might reduce cardiovascular risk in high-risk patients with DM [26]. Through appraisal of the guidelines, official BP targets below 130/80 mm Hg in DM patients were also advocated by most of the “strongly recommended” guidelines. Therefore, the consensus on official BP targets below 130/80 mm Hg in DM patients should be referenced in clinical decisions. It is worth noting that the guidelines from diabetes societies in many countries were consistent with the guidelines of hypertension societies, such as the ESC/EASD and ESC/European Society of Hypertension (ESH), the Canadian Diabetes Association (CDA) and Canadian Hypertensive Education Program (CHEP), and the Korean Diabetes Association (KDA) and Korean Society of Hypertension (KSH), but similar results (most guidelines [9/16, 56.3%] supported the official BP targets below 130/80 mm Hg) with the primary outcomes were also found when removing one of guidelines from the diabetes or hypertension societies in the same country.

Among the included guidelines, few guidelines provided relevant recommendations on the lower limits of official BP targets with the exception of the ESC guidelines [3,12]. However, the relationship between BP and major adverse cardiovascular event (MACE) risk might be more complex than a simple linear function, especially regarding DBP [27]. Lower DBP might impair coronary perfusion to the myocardium, which is uniquely dependent on diastolic blood flow [28]. More recently, the Atherosclerosis in Communities (ARIC) cohort study showed that low DBP (<70 mm Hg) was associated with subclinical myocardial damage with troponin leakage, and at the 21-year follow-up, it was associated with MACEs but not incident stroke (as expected because cerebral blood flow is not diastolic dependent) [29]. Focusing on the J-curve relationship between DBP and MACEs [27,29-31] appeared to be particularly important in the context of the lower BP targets (<130/80 mm Hg) in DM patients that were supported by most of the guidelines. Therefore, providing recommendations on the lower limit of BP targets in the guidelines would contribute to better BP management in DM patients, and the lower limit of BP targets should be considered by clinicians.

Although lower official BP targets (<130/80 mm Hg) were a general consensus, inconsistencies were observed among the

guidelines regarding official BP thresholds in adults with DM, including two “strongly recommended” guidelines (2019 ESC/EASD guideline: >140/90 mm Hg [3]; 2017 ACC/AHA guideline: >130/80 mm Hg [4]). The distinction between the recommendations might lie in the following. First, nearly all of the evidence documented a substantial benefit below 140/90 mm Hg in patients with DM [2,32,33], but the benefit below 130/80 mm Hg was controversial, based on the results from the SPRINT and ACCORD trial [20,21]. A conservative view always sets the threshold of drug intervention at a boundary that has been confirmed by sufficient evidence. Second, lifestyle interventions were an effective strategy in lowering BP and reducing the long-term risk of CVD [34,35]. Choosing lifestyle interventions seemed reasonable in the context of the ambiguous benefits of more tightly controlled BP in DM patients with a BP of 130–139/80–89 mm Hg. Indeed, the guidelines from Japan advocated that lifestyle interventions were recommended in DM patients with a BP of 130–139/80–89 mm Hg, and antihypertensive agents were to be initiated immediately when lifestyle modification was considered to be unlikely to achieve the BP target [13,14]. Nevertheless, the threshold for initiating antihypertensive treatment in DM patients remains inconclusive. Further examination focusing on this point is needed in the future.

A major advantage of both ABPM and HBPM was the diagnosis of white-coat and masked hypertension, which were accounted for in the current guideline consensus [4,12]. In people with DM, masked hypertension and a blunted nocturnal fall in BP were not infrequent [36] and were associated with an increased risk of CVD and target organ damage [37,38]. However, hardly any of the guidelines provided relevant recommendations on the targets and thresholds with ABPM and HBPM in patients with DM. The interpretation in the 2018 ESC guidelines [12] was that formal ABPM or HBPM BP targets for treated patients were not provided due to the lack of an outcome-based RCT. Therefore, future studies should also place particular stress on the value of using ABPM or HBPM to guide BP management in patients with DM.

Our study has certain limitations. First, the included Asian guidelines from a small number of regions or countries could not represent other Asian country guidelines, although these guidelines were published by more developed regions or countries in Asia. Second, the AGREE II tool only considered the reported information related to the development of the guideline. However, we could not rule out the possibility that de-

tailed information was not reported in some guidelines, causing lower AGREE II scores. Third, the AGREE II tool provides the overall scores for the guideline development process. Although the quality of development across the whole guideline had a high potential to influence the quality of individual recommendations [16-18], a solid recommendation might also be created within a poorly developed guideline and *vice versa*. Fourth, although the applicability of guidelines was evaluated using the AGREE II tool, a comprehensive evaluation was difficult due to language and accessibility limitations, especially among the Asian guidelines. Last, it was difficult to comprehensively evaluate the true degree of the influence of industry relationships, although several means and tools were used in the appraisal for conflicts of interest.

In conclusion, the lower official BP targets (<130/80 mm Hg) in patients with DM are advocated by most of the guidelines, but inconsistency was observed among the recommendations on the official BP thresholds for pharmacologic therapy. Moreover, the gaps regarding the lower limit of official BP targets and the ABPM/HBPM targets and thresholds in patients with DM need to be considered in future studies, as such information contributes to the decisions of clinicians regarding BP management in patients with DM.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at <https://doi.org/10.4093/dmj.2020.0134>.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: M.L., S.Z., X.Z., X.L.

Acquisition, analysis, or interpretation of data: M.L., S.Z., Z.X., Y.L., H.Z., Y.H., Z.Z., L.W.

Drafting the work or revising: M.L., S.Z., X.C., Y.G., X.Z.

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