Diabetes and Hypertension: A Comparative Review of Current Guidelines

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Cardiovascular disease plays a major role in the morbidity and mortality of patients with diabetes mellitus. In turn, hypertension is a major risk factor for cardiovascular disease, and its prevalence is increased in diabetes mellitus. Therefore, the detection and management of elevated blood pressure (BP) is a critical component of the comprehensive clinical management of diabetics. Despite significant advances in our understanding of the pathogenesis and treatment of hypertension, there continues to be debate regarding the pharmacologic treatment of hypertension, especially in high-risk groups such as in patients with diabetes mellitus with and without chronic kidney disease (CKD). This debate largely involves at what BP (ie, treatment threshold BP) to initiate pharmacologic antihypertensive therapy and subsequently what treatment target BP should be achieved (ie, goal BP). Presently, there are several guidelines that address hypertension in diabetes mellitus, including the recently released guideline from the Eighth Report of the Joint National Committee (JNC 8). Therefore, this review will compare and contrast these current guidelines, as they relate to the management and treatment of hypertension in diabetes mellitus. Since diabetes mellitus and CKD are significantly inter-related, the presence of CKD as it relates to patients with diabetes mellitus will also be addressed. *J Clin Hypertens (Greenwich).* 2016;18:95–100.

Cardiovascular disease continues to be the most common cause of morbidity and mortality in adults in the United States, and has rapidly emerged as a similar major risk factor in patients with diabetes mellitus. Hypertension is a major risk factor for cardiovascular disease and, particularly, in diabetes mellitus. As a result of its role as a major risk factor, there has been substantial research, both basic and clinical, in the pathogenesis of hypertension specifically including diabetes mellitus as well as the clinical management and treatment of hypertension in diabetes mellitus.

Several pathogenic mechanisms have been proposed to explain the association between diabetes mellitus and hypertension. These are thought to be mediated through the role of the adrenergic system in both diabetes mellitus and hypertension. Such mechanisms include the incretin-mediated control of the renin-angiotensin-aldosterone system.[1] In addition, the calcium-calmodulin pathway has been extensively investigated in both disorders. Alterations in the calcium-calmodulin system result in elevated levels of intracellular calcium, which have been demonstrated to inhibit transcription of the insulin gene in pancreatic β cells.[2] These changes lead to the development of diabetic nephropathy, extracellular fluid expansion, and increased arteriole stiffness. Interestingly, it has been demonstrated that patients with uncontrolled BP despite antihypertensive therapy are at increased risk for developing diabetes mellitus.[3]

While BP control is universally protective, these proposed mechanisms may explain why some antihypertensive agents are more effective than others at achieving the goal BP. These findings have helped facilitate the development of clinical guidelines for the management of hypertension in patients with diabetes mellitus. While hypertension and diabetes mellitus have been addressed in recent decades, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) in 2004 specifically addressed and detailed guidelines regarding the treatment of hypertension in patients with diabetes mellitus.[4]

Commensurate with the JNC 7 report, numerous organizations, including those specifically representing the field of diabetes mellitus, also developed guidelines addressing the management of hypertension in diabetes mellitus. Most recently, the Eighth Report of the Joint National Committee (JNC 8) guideline was released, which led to a re-evaluation of the management of hypertension in general but importantly included diabetes mellitus and chronic kidney disease (CKD).[5] Thus, there are several present published guidelines, some of which have differing recommendations. While these guidelines have helped improve the care of hypertensive diabetic patients, they have also highlighted areas of incomplete data and gaps in our knowledge base including the need for more evidence-based medicine in hypertension and diabetes mellitus. This review summarizes, compares, and contrasts these major guidelines that specifically address hypertension in diabetes mellitus. Where appropriate, the presence of CKD will also be addressed.

CURRENT GUIDELINES: WHAT DO THEY RECOMMEND?

Given the number of guidelines regarding the management of hypertension in patients with diabetes mellitus with and without coexisting renal dysfunction, it is not

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surprising that there remain differences between them as to what the BP threshold to initiate pharmacologic antihypertensive therapy should be, and, once started, the goal BP to achieve. In addition, while most of these guidelines are comprehensive reviews, others focus on specific questions regarding hypertension in patients with diabetes and attempt to rely to a greater extent on evidenced-based medicine, as opposed to expert opinion. These major guidelines are summarized in Table I and Table II.

While the JNC 7 hypertension guideline was released in 2004, the release of the eighth edition would take an additional 10 years.[4] By the time JNC 8 was published, several other groups had published their own guidelines, including the European Society of Hypertension (ESH), the American Diabetes Association (ADA), the American Society of Hypertension/International Society of Hypertension (ASH/ISH), the World Health Organization/International Society of Hypertension (WHO/ISH), and the Canadian Hypertension Education Program (CHEP).[6–10]

The format of JNC 8 differed from most of the other guidelines in that it focused on addressing three specific questions regarding the pharmacologic treatment of hypertension, as opposed to a comprehensive review of the field. Since the JNC 8 guidelines are recent and are a departure from the format and recommendations of other previous guidelines, a more broad discussion of this guideline is warranted in addition to specifically addressing diabetes mellitus. Briefly, the three questions addressed by the committee were as follows: (1) Does initiating pharmacologic therapy at specific systolic BP (SBP) and diastolic BP (DBP) thresholds improve health outcomes? (2) Does pharmacologic therapy to specific SBP and DBP goals improve health outcomes? (3) Are there clinical differences between the various currently prescribed classes of antihypertensive drugs in health outcomes?[5] In order to best answer these questions, the

TABLE I. Hypertension Thresholds, Goals, and Agents in Diabetics

Guideline	Year Published	Threshold for Treatment	Goal Blood Pressure	First-Line Agents
JNC 7[4]	2004	≥130/80	≤130/80	ACE inhibitor, ARB, BB, CCB
JNC 8[5]	2014	≥140/90	≤140/90	Nonblacks: thiazide-type diuretic, ACE inhibitor, ARB, or CCB Blacks: thiazide-type diuretic or CCB
ASH/ISH[8]	2014	≥140/90	≤140/90	Diabetics: ACE inhibitor or ARB Blacks: thiazide-type diuretic or CCB
ESH/ESC[6]	2013	≥140/85	≤140/85	ACE inhibitor or ARB
CHEP[10]	2014	≥130/80	≤130/80	ACE inhibitor, ARB, CCB, thiazide-type diuretic
ADA[7]	2013	≥140/80	≤140/80	ACE inhibitor or ARB
WHO/ISH[9]	2003	≥130/80	≤130/80	ACE inhibitor or ARB

Abbreviations: ACE, angiotensin-converting inhibitor; ADA, American Diabetes Association; ARB, angiotensin receptor blocker; ASH, American Society of Hypertension; BB, β-blocker; CCB, calcium channel blocker; CHEP, Canadian Hypertension Education Program; ESH/ESC, European Society of Hypertension/European Society of Cardiology; ISH, International Society of Hypertension; JNC 7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; JNC 8, Eighth Report of the Joint National Committee; WHO, World Health Organization.

TABLE II. Summary of Guidelines on the Management of Hypertension in Patients With CKD

Guideline	Year Published	Threshold for Treatment	Goal Blood Pressure	First-Line Agents
JNC 7[4]	2004	≥130/80 mm Hg	≤130/80 mm Hg	ACE inhibitor or ARB
JNC 8[5]	2014	SBP ≥140 mm Hg or DBP ≥90 mm Hg	SBP ≤140 mm Hg and DBP ≤90 mm Hg	ACE inhibitor or ARB
ASH/ISH[8]	2014	Without Proteinuria: ≥140/90 mm Hg Proteinuria: ≥130/80 mm Hg	Without proteinuria: ≤140/90 mm Hg Proteinuria: ≤130/80 mm Hg	ACE inhibitor or ARB
ESH/ESC[6]	2013	SBP ≥140 mm Hg	Without proteinuria: ≤140 mm Hg	ACE inhibitor or ARB
CHEP[10]	2014	≥140/90 mm Hg	≤140/90 mm Hg	ACE inhibitor or ARB
ADA[7]	2013	SBP ≥140 mm Hg or DBP ≥80 mm Hg	Without proteinuria: SBP ≤140 mm Hg and DBP ≤80 mm Hg Proteinuria: SBP ≤130 mm Hg and DBP ≤80 mm Hg	ACE inhibitor or ARB
WHO/ISH[9]	2003	≥130/80 mm Hg	≤130/80 mm Hg	ACE inhibitor or ARB

Abbreviations: ACE, angiotensin-converting inhibitor; ADA, American Diabetes Association; ARB, angiotensin receptor blocker; ASH, American Society of Hypertension; CHEP, Canadian Hypertension Education Program; CKD, chronic kidney disease; DBP, diastolic blood pressure; ESH/ESC, European Society of Hypertension/European Society of Cardiology; ISH, International Society of Hypertension; JNC 7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; JNC 8, Eighth Report of the Joint National Committee; SBP, systolic blood pressure; WHO, World Health Organization.

committee performed an exhaustive review of the literature and focused on high-quality randomized control trials (RCTs) as much as possible. The process of addressing the three critical questions described above formed the basis of nine recommendations that addressed various categories of patients. Each recommendation was discussed in depth and was assigned a score for both strength of recommendation and strength of supporting evidence. In addition to hypertension in the general population, which included patients 60 years and older, JNC 8 specifically addressed high-risk groups including those with diabetes mellitus and CKD.

Based on the JNC 8 recommendations, patients 60 years and older should have pharmacologic treatment initiated with SBP >150 mm Hg or DBP >90 mm Hg and titrated to achieve a goal BP under those thresholds. This recommendation differed from the previous recommendation of JNC 7, which recommended a threshold and treatment goal around 140 mm Hg systolic and 90 mm Hg diastolic regardless of age. In keeping with the previous JNC 7 recommendation, JNC 8 recommended that in patients younger than 60 years, treatment initiation and goals should be 140 mm Hg systolic and 90 mm Hg diastolic. In another departure from the recommendations in JNC 7, JNC 8 recommended that treatment threshold and goals also be 140 mm Hg or 90 mm Hg in all patients older than 18 who have either coexisting diabetes mellitus or CKD.

JNC 8 also recommended that treatment options in non-black patients with hypertension include thiazide-type diuretics, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers (ARBs). In the black population, JNC 8 recommended that initial therapy should be a thiazide-type diuretic or CCB. Furthermore, in patients with CKD, JNC 8 recommended that treatment be centered around ACE inhibitors and ARBs, irrespective of race and diabetic status.

SBP Goals

Following the JNC 8 approach, differences in SBP targets, DBP targets, and pharmacologic antihypertensive classes in hypertensive diabetics between the major guidelines will be addressed. When comparing SBP recommendations, JNC 8 differs from the previous recommendations of JNC 7 and WHO. Both the WHO and JNC 7 recommended that pharmacologic therapy be initiated in diabetic patients when SBP is ≥130 mm Hg and that the SBP treatment goal be ≤130 mm Hg.[4,9] JNC 8 loosened these recommendations and recommended to initiate treatment when SBP is ≥140 mm Hg, with a target SBP goal of ≤140 mm Hg.[5] JNC 8 relied to a large extent on results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD-BP) trial, which specially addressed SBP in hypertensive diabetics.[11]

Published in 2010, the ACCORD-BP study group evaluated the effect of intensive BP control in hypertensive diabetics.[11] Patients must have had diabetes mellitus for at least 10 years, and have had either pre-existing cardiovascular disease or at least two additional cardiovascular risk factors. A total of 4733 patients were randomized to one of two treatment SBP goals: SBP ≤140 mm Hg or SBP ≤120 mm Hg. The mean baseline SBP for both groups was 139.2 mm Hg. For the most part, the average SBPs achieved were 119.3 mm Hg in the intensive treatment group and 133.5 mm Hg in the standard treatment group. The results demonstrated that the intensive therapy group required more antihypertensive drugs and experienced greater adverse events. Importantly, there was no statistically significant difference in primary outcomes between the two treatment groups. Thus, JNC 8 recommended initiating treatment at an SBP of ≥140 mm Hg and a therapeutic target of ≤140 mm Hg, mirroring the general recommendation for hypertensive nondiabetics 60 years and younger.[4] These recommendations of JNC 8 were similar to those of the 2013 ESH guidelines, the 2014 ASH guidelines, and the 2013 ADA guidelines in adopting these new targets.[6–8] While the ADA applied this target for all patients older than 18 years, the ESH limited its recommendation to patients aged between 50 and 80 years.[6,7] In addition to the ACCORD-BP study, additional studies such as the United Kingdom Prospective Diabetes Study Group (UKPDS) and the Action in Diabetes and Vascular Disease (ADVANCE) trials were also reviewed and contributed to the above recommendations.[12,13]

Published in 1998, UKPDS 38 evaluated the potential difference in cardiovascular complication rates in diabetes mellitus with respect to BP control.[12] This study randomized 1148 diabetic patients into two groups: 758 to tight control (goal BP ≤150/85 mm Hg) and 390 to less tight control (goal BP ≤180/105 mm Hg). Since UKPDS 38 targeted both SBP and DBP, both will be addressed in this section. The initial mean BP was 160/94 mm Hg. In follow-up, the intensive BP control group achieved a BP of 144/82 mm Hg, while the less tight BP control group achieved a BP of 154/87 mm Hg. After a median follow-up period of 8.4 years, the tightly controlled BP group exhibited a statistically significant reduction in diabetic endpoints, death related to diabetes mellitus, strokes, microvascular endpoints, and heart failure. In addition, this study demonstrated that BP control was as important as glycemic control in preventing cardiovascular risk in diabetic patients.

The ADVANCE trial was a large, multifaceted trial published in 2008.[13] The primary goal of the study was to evaluate the clinical effect of intensive glycemic control in patients with type 2 diabetes mellitus. In order to accomplish this goal, a total of 11,140 patients were randomized into two glucose arms (intensive glucose control and less intensive glucose control), with a median follow-up of 5 years. The results of this goal demonstrated that intensive glucose control resulted in a significant reduction in cardiovascular events. In addition, a second goal was to determine the effect of lowering BP irrespective of initial BP level. This goal

was addressed by also randomizing the entire cohort to antihypertensive therapy compared with placebo. The initial SBP of the cohort was 145 mm Hg, with antihypertensive therapy lowering SBP by 5.6 mm Hg compared with placebo. The results demonstrated that the antihypertensive therapy group had a significant reduction in multiple cardiovascular events compared with the placebo group. While this study was reviewed in the ESH guidelines and cited by JNC 8, JNC 8 excluded it from formal evaluation on the basis that it lacked specific predetermined BP treatment thresholds or goals.[5,6] It is important to note that, similar to JNC 7, CHEP 2014 still recommends initiating treatment at an SBP of ≥130 mm Hg, with a treatment SBP goal of ≤130 mm Hg.[4,10]

Given the clinical importance and implications of diabetes mellitus and concomitant kidney disease, it is crucial to review recommendations in regards to BP goals in the hypertensive diabetic population with renal disease. Both the WHO and JNC 7 recommended initiating pharmacologic antihypertensive treatment at an SBP ≥130 mm Hg and titrating treatment to achieve an SBP goal of ≤130 mm Hg in CKD.[4,9] However, JNC 8 recommends in patients with CKD 70 years and older that treatment be initiated at an SBP of ≥140 mm Hg and titrated to achieve an SBP goal of ≤140 mm Hg.[5] This position is in line with other guidelines such as ASH and CHEP 2014.[8,10] The ESH guidelines agree with this goal; however, in patients with renal disease and proteinuria, a lower threshold and titration SBP goal of 130 mm Hg is recommended.[6]

DBP Goals

JNC 7 recommended that in diabetic patients, pharmacologic treatment be initiated at a DBP of ≥80 mm Hg, with a target treatment goal of ≤80 mm Hg.[4] In contrast, JNC 8 recommends an initial treatment of ≥90 mm Hg and a treatment goal of ≤90 mm Hg, primarily based on the results of the Hypertension Optimal Treatment (HOT) and UKPDS trials.[12,14] The HOT trial studied 18,790 patients with hypertension who were randomized to three different DBP treatment goals.[14] These three DBP targets were ≤90 mm Hg, ≤85 mm Hg, and ≤80 mm Hg. Entry criteria required a DBP of 100 mm Hg to 115 mm Hg and an age range of 50 to 80 years. The baseline mean DBP across all participants was 105 mm Hg. The mean DBP achieved in each group at the end of the trial was 85.2 mm Hg, 83.2 mm Hg, and 81.1 mm Hg, respectively. The results showed a 28% reduction in myocardial infarctions and a 43% reduction in strokes, as well as a significant reduction in major cardiovascular events and deaths in the lowest DBP group compared with the highest. The optimal DBP to reduce major cardiovascular events was 82.2 mm Hg and to reduce cardiovascular mortality was 86.5 mm Hg. The study also independently examined the outcomes in 1499 patients with diabetes mellitus. Similar to the overall group, the same endpoints were examined and a significant reduction in cardiovascular mortality and major cardiovascular events were observed in the lowest BP target group compared with the highest. While the optimal DBP to achieve was not specifically noted in the diabetic cohort in the study, interestingly, in the diabetic patients there appeared to be a further reduction in events in the lowest DBP group compared with the middle group. This difference was not seen in the overall cohort in that there was no difference in outcomes between the lowest and middle DBP groups. This study reinforced the benefit of lowering DBP to ≤90 mm Hg; however, it did not shed light on DBPs <80 mm Hg.

In addition to HOT, UKPDS further highlighted the importance of DBP control in diabetic patients in relation to cardiovascular risk.[12] In this study, the DBP in hypertensive diabetic patients was treated to either ≤105 mm Hg or ≤85 mm Hg. In the ≤85 mm Hg arm, there was a reduction in cardiovascular events, as well as mortality, with an achieved DBP of 82 mm Hg vs 87 mm Hg in the ≤105 mm Hg arm. Similar to the HOT trial, no inference to the outcome of lowering the DBP to <80 mm Hg can be made.[12] Therefore, the ADA recommends initiating treatment at a DBP of ≥90 mm Hg and achieving a target DBP of ≤90 mm Hg.[7] In contrast, the ASH and CHEP guidelines continue to recommend a lower goal of ≤80 mm Hg.[8,10] The most recent ESH guidelines do, however, recommend a lower DBP target of ≤85 mm Hg.[6] Finally, last updated in 2003 and similar to JNC 7, the WHO guidelines still recommend initiating treatment at a DBP of ≤80 mm Hg with a treatment goal of <80 mm Hg.[9]

DBP goals in patients with CKD are similar to patients with diabetes mellitus in the various guidelines. According to JNC 8, the threshold DBP for patients with CKD is ≥90 mm Hg, with a target treatment goal BP of ≤90 mm Hg.[5] This differs from JNC 7 guidelines, which recommended a DBP centered around 80 mm Hg.[4] Similar to SBP, lower DBP goals may be indicated for patients with significant proteinuria.

Diabetes Mellitus and Hypertension Treatment Regimens

It is clear that classes of pharmacologic antihypertensive agents differ in their BP efficacy and in certain instances in their clinical outcomes such as cardiac and renal protection and reduction in proteinuria. JNC 7 addressed the selection of appropriate pharmacologic drug classes for the treatment of hypertension in those with diabetes mellitus; however, did so regardless of race.[4] The classes recommended were diuretics, ACE inhibitors, β-blockers, ARBs, and CCBs. JNC 8 also addressed the selection of drug classes but now also considered potential differences in BP efficacy based on race, especially in the black population.[5] JNC 8 recommended as initial therapy for non-black patients with diabetes mellitus either thiazide-type diuretics, ACE inhibitors, ARBs, or CCBs. This recommendation took into consideration RCTs that compared different classes of antihypertensive classes with one another, as opposed

to placebo-controlled RCTs. JNC 8 noted that there is insufficient evidence that demonstrates differences in outcomes between these classes of agents. However, in black patients with diabetes mellitus, JNC 8 recommends thiazide diuretics or CCBs as preferred initial treatment classes. These recommendations were based largely on the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which evaluated cardiovascular outcomes of hypertensive individuals treated primarily with a thiazide diuretic, ACE inhibitor, CCB, or α-blocker, which was published in 2002.[15] ALLHAT included 42,428 patients 55 years and older with stage I or II hypertension and at least one other cardiovascular disease risk factor. Pertinent to this review, up to 46% of these patients also had diabetes mellitus. The findings are now well-known in that the α-blocker group was stopped prematurely because of an increase in adverse cardiovascular outcomes when compared with the diuretic-treated group, while the other three groups went on to study completion. There was no significant difference in the primary outcomes in the total cohort between the three remaining treatment groups. However, in black individuals there was a significant reduction in both BP and events in the group treated with thiazides when compared with the group treated with ACE inhibitors. Thus, JNC 8 recommends CCBs and thiazide-type diuretics as initial therapy in black individuals.[5]

The ESH guidelines recommend starting ACE inhibitors or ARBs in patients with diabetes mellitus.[6] Furthermore, the ASH guidelines also recommend ACE inhibitors and ARBs in patients with diabetes mellitus; however, they recommend CCBs and thiazide diuretics in black patients.[8] The utility of using ACE inhibitors or ARBs in patients with diabetes mellitus was also echoed by the most recent ADA guidelines as well as the WHO guidelines.

In CKD and hypertension, irrespective of race, degree of proteinuria, or diabetic status, JNC 8 recommends ACE inhibitors or ARBs as initial therapeutic classes.[5] However, it was also noted that while these agents have been demonstrated to improve kidney outcomes, they did not provide cardiovascular protection. Of note, JNC 8 only supports the use of ACE inhibitors and ARBs in patients aged 18 to 75 years.[5] This is because of the lack of evidence in patients 75 years and older. The utility of ACE inhibitors and ARBs in patients with CKD has been echoed in nearly every other guideline to date.

GAPS IN KNOWLEDGE

Despite a significant amount of work in recent years to improve and guide the management of hypertension in patients with diabetes mellitus, significant gaps in our knowledge remain. One major gap is the relatively limited data on non-Caucasian populations. In addition, there remains ambiguity as to whether specific populations of patients with diabetes mellitus with and without CKD would benefit from more aggressive SBP and DBP reduction, for instance to ≤130/80 mm Hg or lower. Another gap in our knowledge is whether there is a beneficial role of nocturnal dosing of antihypertensive agents and if so, which ones and at what doses.

Of the numerous RCTs used to formulate the various guidelines, few specifically looked at the role of race or ethnicity in hypertension. This is of utmost importance given the known racial and ethnic healthcare disparities in both hypertension and diabetes mellitus. As discussed above in the ALLHAT trial, a subset analysis in black patients who received ACE inhibitors demonstrated clear adverse implications when compared with diuretics.[15] Importantly, the landmark African American Study of Kidney Disease (AASK) trial specifically studied black hypertensive patients with hypertensive nephrosclerosis and randomized them to two groups: intensive SBP control and less intensive SBP control.[16] The AASK trial found that there was no difference in the decline in glomerular filtration rate between the two groups. However, in patients with significant proteinuria and similar to findings observed in the Modification of Diet in Renal Disease (MDRD) study, the AASK trial did demonstrate that intensive BP control slowed the decline of the glomerular filtration rate in individuals with significant proteinuria.[16–18] In the AASK study, this beneficial effect was seen to a greater extent with ACE inhibitors. While the results of this trial have greatly increased our knowledge in the management and selection of drug classes in black hypertensive patients with renal disease, it specifically excluded patients with diabetes mellitus.

Given the propensity of diabetic patients to also have progressive CKD, it is vital to develop therapeutic strategies to address this adverse outcome. Presently, all guidelines recommend BP control of at least ≤140/90 mm Hg for patients with CKD or diabetes mellitus. Others still recommend a more aggressive goal of ≤130/80 mm Hg. In addition, given that proteinuria independently predicts a poorer renal outcome, several of the guidelines recommend more aggressive BP lowering in the presence of proteinuria. However, gaps in our knowledge based on larger cohorts and more definitive evidence-based medicine in this setting remain. Furthermore, as JNC 8 notes, there is a distinct lack of data on patients with CKD older than 70 years.[4] In addition, the diagnostic criteria for CKD do not consider the age-related decline in kidney function, as reflected in estimated glomerular filtration rate. Areas for future consideration as guidelines are developed may include the following considerations: type 1 diabetes mellitus, medical frailty, advanced age (70 years and older), and patients with longer durations of type 2 diabetes mellitus.

The efficacy of nocturnal dosing of antihypertensive agents has been noted in the ADA and ESH guidelines.[6,7] This recommendation is consistent with the observation that diabetic patients are more likely to have nocturnal hypertension or "nondipping" BP status. It has been proposed that this may be the result of increased sympathetic tone at night, in part caused by diabetic autonomic neuropathy. In a recent RCT, there

was significant reduction in CVD risk as well as improved nocturnal BP reduction when at least one antihypertensive agent was given at bedtime.[19] Thus, the approach to nocturnal hypertension is another area for consideration in future guideline development.

CONCLUSIONS: WHERE DO WE GO FROM HERE?

An important question that now arises is whether patients who have been successfully treated based on previously recommended BP targets should have their regimens liberalized given the new recommendations put forth in JNC 8 in the elderly and those with diabetes mellitus and CKD. The JNC 8 committee was clear that more strict BP recommendations in these patient groups in other guidelines, but particularly in JNC 7, are not presently supported by evidence. While there is no definitive answer to this question, it seems reasonable that if a patient is being treated successfully to previous BP targets, that the treatment regimen be continued and the clinical course of the patient be followed closely. Obviously, there is still an art to medical decision-making and this decision should include a full discussion with the patient. Another benefit of JNC 8 is that it has led to a new and fruitful discussion in the medical community as to the extent that we use evidence-based medicine when available and the role of expert opinion. Already the American College of Cardiology and the American Heart Association have formed another guideline committee to address the treatment of hypertension, which is proposed to be completed in 2016. Clearly, this discussion will be continued.

When considering recommendations from any guideline, it is important to remember that the management of hypertension in diabetic patients should be tailored to the individual patient. Given that many of the recommendations are still based to a significant degree on expert opinion rather than high-quality RCTs, it is clear that the clinician must select the appropriate management plan for the individual patient. While the present guidelines that are available are a tremendous help in clinical decision-making and have positively contributed to diabetic patient care and outcomes, the overarching message is that a systematic approach to hypertension management and developing evidence-based medicine to address the present gaps in our knowledge in this setting are crucial to minimizing the consequences of diabetic macrovascular and microvascular disease.

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