What Should Be the Target Blood Pressure in Elderly Patients With Diabetes?

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Diabetes Care 2016;39(Suppl. 2):S234–S243 | DOI: 10.2337/dcS15-3027

Hypertension is very common in elderly subjects with type 2 diabetes. The coexistence of hypertension and diabetes can be devastating to the cardiovascular system, and in these patients, tight blood pressure (BP) control is particularly beneficial. Little information is available regarding the target BP levels in elderly hypertensive patients with type 2 diabetes, and therefore extrapolation from data in the general population should be done. However, it is difficult to extrapolate from the general population to these frail individuals, who usually have isolated systolic hypertension, comorbidities, organ damage, cardiovascular disease, and renal failure and have a high rate of orthostatic and postprandial hypotension. On the basis of the available evidence, we provide arguments supporting the individualized approach in these patients. Target BP should be based on concomitant diseases, orthostatic BP changes, and the general condition of the patients. It is recommended to lower BP in the elderly patient with diabetes to <140–150/90 mmHg, providing the patient is in good condition. In patients with isolated systolic hypertension, the same target is reasonable providing the diastolic BP is >60 mmHg. In patients with coronary artery disease and in patients with orthostatic hypotension, excessive BP lowering should be avoided. In elderly hypertensive patients with diabetes, BP levels should be monitored closely in the sitting and the standing position, and the treatment should be tailored to prevent excessive fall in BP.

High blood pressure (BP) is a major risk factor for cardiovascular (CV) events. Linear relationships between CV morbidity and mortality risk and both systolic BP (SBP) and diastolic BP (DBP) levels starting from 115 and 75 mmHg, respectively, have been reported in the general population, independently of age, sex, ethnicity, and presence of comorbidities (1,2). A similar association either for micro- or for macrovascular complications has also been noted for patients with type 2 diabetes (3). The incidence of hypertension in patients with type 2 diabetes is approximately twofold higher than in age-matched subjects without the disease (4), and data from the Framingham study show that the excess CV risk in type 2 diabetes is attributable to coexistent hypertension (5). Therefore, the definition of hypertension is more stringent in diabetes, and BP levels >130/80 mmHg are already defined as hypertension (6).

Life expectancy has increased over the years, and the world population is getting older. Hypertension is very common in elderly people (>60 years of age), reaching a prevalence of 60–80% in individuals in the U.S. (7). The rate of events in the elderly is high, and despite the fact that the association between BP levels and CV events is less steep in the elderly than in the young, the impact of elevated BP, in particular SBP, on CV morbidity and mortality in the elderly is significant (1,8). Therefore, BP control is also expected to provide benefits in aging individuals. A recent cost-effective analysis

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This publication is based on the presentations at the 5th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this supplement were made possible in part by unrestricted educational grants from AstraZeneca.

showed that implementation of the 2014 hypertension guidelines for U.S. adults between the ages of 35 and 74 years could potentially prevent ~56,000 CV events and 13,000 deaths annually while saving costs (9). However, how much BP should be lowered in aging individuals with type 2 diabetes is a controversial matter. The perfusion to vital organs, such as the brain and the heart, is dependent on BP levels, and elderly are more sensitive than young subjects to low BP values, making it extremely difficult to extrapolate targets and treatment criteria applied in the general population to these frail individuals, who are more likely to have associated diseases, organ damage, or clinical CV disease (10); orthostatic and postprandial hypotension; and chronic renal failure (10,11). They are also frequently characterized by isolated systolic hypertension with normal or low DBP, and their BP decreases less during nighttime (12). The frequent use of polypharmacy, with a high rate of side effects from antihypertensive drugs (8,13), makes the picture even more complicated. For all these reasons, treatment of elderly hypertensive patients with type 2 diabetes represents management dilemmas because most hypertension trials used upper age limits or did not present age-specific results.

In this article, we consider the theoretical advantages and disadvantages of aggressive BP lowering in these patients on the basis of the limited available evidence, also discussing the opportunity to define specific BP targets for them.

Target BP in Elderly Patients With Diabetes According to Recently Published Guidelines

There are no clear guidelines as to what should be the target BP in elderly patients with diabetes. Most guidelines do not refer to target BP specifically in these patients; therefore, we reviewed the target BP recommended by the various guidelines for the general population, patients with diabetes, and elderly patients (Table 1). It is noteworthy that the recommendations, even mostly recommending less ambitious BP targets in individuals ≥80 years old, do not take into consideration specific problems such as previous stroke, coronary artery disease (CAD), chronic kidney disease (CKD), orthostatic or postprandial hypotension, recurrent falls, and/or cognitive decline, which are common in the elderly and may change the target BP.

The British National Institute for Health and Care Excellence (NICE) recommended commencing antihypertension treatment for patients with diabetes with stage 1 hypertension (clinic BP >140/90 mmHg) (14). In addition, the recently published 2015 American Diabetes Association (ADA) guidelines recommend that hypertensive patients with diabetes be treated if they have a DBP of >90 mmHg or an SBP >140 mmHg, with a target BP value of <140/90 mmHg (15). The American Heart Association (AHA) and American College of Cardiology (ACC) recommend a target BP of <140/90 mmHg but point out that lower targets may be considered (16). The American Society of Hypertension (ASH) and International Society of Hypertension (ISH) suggest a BP goal of <140/90 mmHg in patients with diabetes (17). The panel members appointed to the Eighth Joint National Committee suggest a cutoff value of 140/90 mmHg for initiating antihypertension treatment in adult patients older than 18 years. These (i.e., BP values <140/90 mmHg) are also the recommended treatment target values (18). The Canadian Hypertension Education Program (CHEP) guidelines recommend lowering BP to <130/80 in patients with diabetes (19). The 2013 European Society of Hypertension and European Society of Cardiology recommend lowering SBP to <140 mmHg and DBP to <85 mmHg (20). The International Diabetes Federation suggests different BP targets according to age and recommends BP target values <130/80 mmHg for patients with diabetes younger than 70 years, target values <140/90 mmHg for patients 70–80 years old, and target values of <150/90 mmHg for patients over 80 years old (21).

Most guidelines recommend a target BP <150/90 mmHg in patients >80 years old (Table 1). The ACC/AHA 2011 expert consensus document on hypertension in the elderly recommended for persons <80 years of age a target BP of <140/90 mmHg and for persons ≥80 years of age a target SBP of 140–145 mmHg, if tolerated (10). The American Geriatrics Society and the ADA recommend a target BP <140/90 mmHg (15,22).

For patients with CAD, the recent AHA/ACC/ASH scientific statement recommended lowering BP to <140/90 mmHg in those aged 65–79 years and to <150/80 mmHg in those ≥80 years old (23). The different recommendations of the various societies indicate the lack of clarity regarding target BP in elderly patients with diabetes. To better clarify this issue, we summarized the literature dealing with target BP in patients with diabetes and elderly hypertensive patients.

How Strong Is the Evidence for the Concept of "the Lower, the Better" in Patients With Diabetes?

Over the past decade, the dominating doctrine has stressed the need for target BP <130/80 mmHg for patients with diabetes. This paradigm was based on several cornerstone studies. The UK Prospective Diabetes Study 36 (UKPDS 36) has documented an association between lower BP and improved outcome, showing that any reduction in SBP was associated with significant risk reductions for diabetes-related complications (12%), diabetes-related death (15%), myocardial infarction (11%), and microvascular complications (13%), with no threshold of risk for any end point and with SBP of <120 mmHg having the lowest risk (3). The Hypertension Optimal Treatment (HOT) study displayed evidence that lowering BP to the lowest target level (DBP ≤80 mmHg) in hypertensive subjects with type 2 diabetes resulted in a 51% reduction of major CV events compared with the usual target group (DBP ≤90 mmHg) (24). Additionally, the UPKDS 38 study (25) showed that tight (<150/80 mmHg) compared with modest (<180/105 mmHg) BP control was associated with a reduction in diabetes-related death (32%), stroke (44%), and microvascular end points (37%). In Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation (ADVANCE) (26), active treatment (BP 136/73 mmHg) reduced the relative risk of a major macrovascular or microvascular event by 9% compared with placebo (BP 140/73 mmHg).

Nevertheless, meticulous review of the literature and recently published data have cast doubt on the dominant doctrine supporting a more stringent BP treatment approach. In most of these studies, the initial baseline SBP levels were >160 mmHg and probably even higher, since most patients were already medically treated when recruited to participate in the studies. In these ranges, one would expect a significant risk reduction even for a relatively modest BP reduction. Furthermore, in almost all studies that showed the benefit of aggressive BP lowering in patients with type 2 diabetes, the achieved BP was >130/80 mmHg (27). Additionally, recent publications did not support the concept that lower BP is indeed better. In the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) (28), despite the fact that combination therapy of telmisartan and ramipril reduced BP more than the ramipril-only regimen, the rate of primary end points was the same in both treatment arms. In a subgroup analysis of the International Verapamil SR/Trandolapril Study (INVEST-DM), performed in patients with type 2 diabetes and with CAD, there was no difference in short-term outcome between lowering SBP <130 mmHg or <140 mmHg, and in the long-term a more tight BP control was even associated with an increase in all-cause mortality (29). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) BP trial has shown that intensive lowering of SBP (<120 mmHg) in hypertensive patients with diabetes did not improve the overall outcome of CV events or deaths, except for a modest reduction in the risk for stroke (30). Yet, it increased serious adverse events from 1.3 to 3.3%, including syncope and hyperkalemia that can be attributed to antihypertension treatment (30). More recently, Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS), which included 5,743 patients with diabetes, demonstrated no difference in stroke recurrence, despite a BP lowering difference of 3.8/2.0 mmHg with telmisartan (31). In Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) (32), a placebo-controlled study that included 2,118 (35.8%) patients with diabetes, mean BP was lower in the telmisartan arm by 4.0/2.2 mmHg, but the rate of the primary end point (composite CV death, myocardial infarction, stroke, or hospitalization due to heart failure) was similar in both groups.

In the last 5 years, several meta-analyses have been published regarding BP-lowering target values among hypertensive patients with type 2 diabetes (Table 2). A meta-analysis of 13 randomized control studies including >37,000 hypertensive patients with diabetes has showed that intensive SBP control (<130 mmHg) was associated with a 10% reduction in all-cause mortality, yet no effects on microvascular or macrovascular events were noted. Regarding stroke, such intensive BP reduction led to a 17% risk reduction, accompanied by an additional risk reduction with further lowering of SBP to <120 mmHg, without an increased risk for adverse effects (33). Another meta-analysis, comprised of 31 randomized control studies including >73,000 hypertensive patients with diabetes, showed that more intensive BP reduction led to a 31% reduction in relative risk of stroke, with a 13% reduction for every 5-mmHg SBP or 2-mmHg DBP reduction; however, the risk of myocardial infarction was not significantly reduced with the more intensive BP control (34). McBrien et al. (35) analyzed five large randomized control studies including 7,800 hypertensive patients with diabetes and demonstrated that intensive BP control (<130/80 mmHg) did not improve the risk of mortality or myocardial infarction compared with the standard BP treatment goal (<140–160/85–100 mmHg). It did, however, significantly decrease the risk of stroke with a relative risk of 0.65, but with only a small, albeit significant, absolute risk difference of 0.01. The accumulating literature suggests that intensive BP lowering in subjects with diabetes reduces the risk of stroke but does not improve the overall outcome of CV events or deaths.

Does the Notion "the Lower, the Better" Hold in the Elderly?

The Framingham data suggested an age-dependent and sex-dependent threshold for hypertension (36). The suggested SBP threshold is ~140 mmHg in men aged 45–54 years and 160 mmHg in those between 65 and 74 years; on this basis, even with the lack of epidemiological observations precisely addressing this issue, we may hypothesize that the threshold for men over 75 years old is even higher. This concept seems to be supported by some observational studies: Jacobs et al. (37) showed that elevated SBP was not associated with increased 5-year mortality in a cohort of community-dwelling 85-year-old individuals. Two other observational studies conducted in elderly

Table 1—Recommended BP target (mmHg) in elderly patients and patients with diabetes according to different guidelines

Guidelines	General	Diabetes	Elderly
NICE, 2011 (14)	140/90	140/90	Age ≥80 years, <150/90
ASH/ISH, 2014 (17)	140/90	<140/90	AGE ≥80 years, <150/90
ACC/AHA, 2014 (16)	<140/90	<140/90	Age ≥80 years, <150/90
ESH/ESC, 2013 (20)	<140/90	<140/85	Age ≥80 years, <150/90 SBP <140 if healthy
AGS, 2013 (22)	<140/90; SBP <120 has potential harm		
JNC 8, 2014 (18)	140/90	<140/90	Age ≥60 years, <150/90
CHEP, 2013 (19)	140/90	<130/80	Age ≥80 years, <150/NA
VA/DoD, 2015 (23)	<150/90	<150/85 SBP <140 if tolerated	Age ≥60 years, <150/90
ADA, 2015 (15)		<140/90; <130/80 may be appropriate if achieved without undue treatment burden	
IDF, 2014 (21)		<130/80	Age 70–80 years, <140/90; ≥80 years, <150/90
ACC/AHA, 2011, in the elderly (10)		Age <80 years, <140/90; ≥80 years, SBP 140–145	

AGS, American Geriatrics Society; ESH/ESC, European Society of Hypertension/European Society of Cardiology; IDF, International Diabetes Federation; JNC 8, Eighth Joint National Committee; NA, not available; VA/DoD, Veterans Administration/Department of Defense.

Table 2—List of some major meta-analyses that analyzed different target BP levels and outcomes

First author/study (ref. no.)	Number of patients	Conclusions
Bangalore (33)	>37,000 with diabetes	Intensive SBP control (<130 mmHg) is associated with a 10% reduction in all-cause mortality and 17% reduction in stroke, without effects on micro- or macrovascular events. An additional risk reduction in stroke with further lowering SBP to <120 mmHg, without an increased risk for adverse effects
Reboldi (34)	73,000 hypertensive with diabetes	Intensive BP reduction is associated with a 31% reduction in relative risk of stroke, with a 13% reduction for every 5-mmHg SBP or 2-mmHg DBP reduction. The risk of myocardial infarction is not significantly reduced with more intensive BP control
McBrien (35)	7,800 hypertensive with diabetes	Intensive BP control (<130/80 mmHg) does not improve the risk of mortality or myocardial infarction compared with the standard BP treatment goal (<140–160/85–100 mmHg). It decreased significantly the risk of stroke, with a relative risk of 0.65
INDANA (44)	1,670 elderly (>80 years) hypertensive	Antihypertension therapy led to a reduction in stroke (33%), CV morbidity (22%), and heart failure (39%), with no effect on coronary events
Blood Pressure Lowering Treatment Trialists' Collaboration meta-analysis (45)	190,066	A similar benefit of lowering BP in young and elderly subjects
Emdin (46)	>100,000	No association between BP-lowering treatment and lower CV risk in subjects with baseline SBP ≤140 mmHg
Xie (47)	44,989	Intensive BP lowering (133/76 mmHg) provides greater vascular protection than standard regimens (BP of 140/81 mmHg). The main benefit of intensive BP lowering is observed in patients with diabetes and in those older than 62 years
Arguedas (63)	7,314	The only benefit of "lower" SBP (119.3/64.4 vs. 133.5/70.5 mmHg) is an absolute risk reduction of 1.1% in the incidence of stroke, with no effect on mortality and with the price of increased serious adverse events

individuals with diabetes demonstrated an inverse relationship between mortality and BP levels (38,39). van Hateren et al. (39) showed that a decrease of 10 mmHg in SBP and DBP led to a mortality increase of 22 and 30%, respectively. These observational studies, however, may be misleading, since low BP in high-risk patients may be a marker of poor health rather than a cause of mortality. Data from prospective randomized trials are not consistent. Some suggest that lowering BP in the elderly is beneficial, but others fail to show any benefit from intensive BP control (Table 3).

The Hypertension in the Very Elderly Trial (HYVET) documented the benefits of lowering BP in persons ≥80 years of age: after 2 years of follow-up, mean BP was 15/6 mmHg lower in subjects receiving active treatment than in those receiving the placebo, and this difference led to a significant reduction in total mortality (21%), fatal stroke (39%), fatal and nonfatal stroke (30%), CV disease (23%), and heart failure (64%) (40). A more recent reanalysis of HYVET showed no evidence of interaction between the beneficial effect of lowering BP and frailty (41). This reanalysis suggests that frail and healthy individuals gain the same benefit from lowering BP. However, it should be pointed out that in HYVET, only <7% of the study population had type 2 diabetes and that enrolled individuals were in good physical and mental condition, had low rate of previous CV disease, and did not have orthostatic hypotension and are therefore hardly representative of the typical very elderly. In subanalysis of ADVANCE by age, it was shown that lowering BP is safe and reduces the risk of major clinical outcomes in patients with diabetes of at least 75 years of age (8). The absolute benefits of BP-lowering therapy on major macrovascular events and death were even greater in older than in younger patients with diabetes (8) and were not offset by an increased risk of side effects. Indeed, there were too few patients over the age of 80 years for meaningful analysis to be done. The Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS) included 4,418 elderly (65–85 years old) hypertensive Japanese patients, of whom only 11.8% had type 2 diabetes (42). This prospective, randomized, open-label study with blinded assessment of end points compared the 2-year effect of strict treatment to maintain SBP <140 mmHg with that of mild treatment to maintain SBP <160 but ≥140 mmHg. The study showed that reducing SBP <140 mmHg did not provide any further benefit over a SBP target <160 mmHg in terms of mortality and CV or renal events. A further subanalysis of the same cohort according to the average achieved BP levels documented a similar incidence of primary end points (43).

Given the scarce availability of specifically designed studies, some meta-analyses

Table 3—List of the main prospective studies that evaluated different target BP levels in elderly hypertensive patients with diabetes

Trial acronym	Patients (N)	Age (years)	Follow-up (years)	Initial SBP (mmHg)	Achieved SBP (mmHg)		Design	Primary end point	Secondary end points
					Active	Comparator			
SHEP-DM	583	70	4.5	170	145	155	Double-blind, randomized, placebo-controlled trial comparing chlorthalidone vs. placebo	Decrease in CV disease 34%, $P < 0.05$	
Syst-Eur-DM	492	70	2	175	153	162	Double-blind, randomized, placebo-controlled trial comparing nitrendipine vs. placebo	Decrease in stroke 73%, $P = 0.02$	Decrease in all CV end points 55%, $P = 0.09$ Decease in CV mortality 76%, $P = 0.01$
Syst-China-DM	98	66.5	3	172	150	156	Double-blind, randomized, placebo-controlled trial comparing nitrendipine vs. placebo	Decrease in stroke 45%, $P = 0.42$	Decrease in all CV end points 74%, $P = 0.03$
ADVANCE	11,140	66	4.3	145	134	140	Randomized controlled study comparing perindopril plus indapamide vs. placebo	Decrease in combined major macro- and microvascular events 9%, $P = 0.04$	Decrease in all-cause mortality 14%, $P = 0.03$; decrease in CV mortality 18%, $P = 0.03$. Decrease in total coronary events 14%, $P = 0.02$; decrease in all renal events 21%, $P < 0.0001$. No difference in total stroke, HF, visual deterioration, neuropathy, cognitive function
HOT-DM	1,505	61.5	3.8	169	144	148	PROBE design to determine target DBP. Felodipine as the first drug	Decrease in CV end points 51%, $P = 0.005$	
INVEST-DM	6,400	66	2.7 (5 for all-cause mortality in the U.S. cohort)	Tight 144, usual 149, uncontrolled 159	Tight 121.5, usual 131.2	Uncontrolled 146.1	Observational, secondary analysis of INVEST: a prospective, randomized double-blind trial that compared a CA-based with a β-blocker–based treatment in hypertensive patients with CAD. Outcome was analyzed according to the level of BP control. Tight (SBP <130 mmHg) vs. usual control (SBP 130 to <140 mmHg) vs. uncontrolled (SBP ≥140 mmHg)	Decrease in the first occurrence of composite of all-cause death, nonfatal MI, or nonfatal stroke in the usual control vs. uncontrolled blood pressure 32%, $P < 0.001$	Decrease in all-cause mortality, nonfatal MI, nonfatal stroke, total MI, and total stroke in the usual and tight control vs. uncontrolled blood pressure ($P < 0.05$). During extended follow-up, adjusted increase in all-cause mortality in the tight vs. usual control 15% ($P = 0.04$)
ACCORD	4,733	62.2	4.7	139	119	133	Prospective, randomized nonblinded trial assessing the benefit of intensive therapy (SBP <120 mmHg) vs. standard therapy (SBP <140 mmHg)	No difference in composite of nonfatal MI, nonfatal stroke, or death from CV causes, $P = 0.20$	Decrease in rate of stroke 47% ($P = 0.01$). No difference in other secondary end points

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Table 3—Continued

Trial acronym	Patients (*N*)	Age (years)	Follow-up (years)	Initial SBP (mmHg)	Achieved SBP (mmHg) Active	Achieved SBP (mmHg) Comparator	Design	Primary end point	Secondary end points
JATOS	4,418 (521 had DM)	73.6	2	171.6	135.9	145.6	Randomized, open-label study with blinded assessment of end points evaluating the effect of strict antihypertensive treatment and mild treatment in elderly hypertensive patients	No difference in the rate of combined incidence of CV disease and renal failure	No difference between groups in the rate of total death (P = 0.22)
HYVET	3,845 (263 had DM)	83.6	1.8	173	143.5	158.5	Randomized, double-blind, placebo-controlled study assessing the effect of indapamide vs. matching placebo in very elderly (>80 years of age) subjects	A 30% decrease in the rate of fatal or nonfatal stroke, P = 0.06	A 39% decrease in fatal stroke (P = 0.05), 23% decrease in CV mortality (P = 0.06), 21% decrease in all-cause mortality (P = 0.02), 64% decrease in the rate of HF ($P < 0.001$)
FEVER	9,711 (1,241 had DM)	61.5	3.3	154.2	137.3	142.5	Randomized, double-blind, placebo-controlled study assessing the effect of low-dose felodipine vs. placebo	A 28% decrease in the rate of fatal or nonfatal stroke, P = 0.002	A 27% decrease in all CV events ($P < 0.001$), 35% decrease in all cardiac events (P = 0.012), 31% decrease in all-cause mortality (P = 0.006), 32% decrease in coronary events (P = 0.024), 30% decrease in HF

CA, calcium antagonists; DM, diabetes mellitus; HF, heart failure; MI, myocardial infarction; PROBE, Prospective, Randomized, Open-Label, Blinded Endpoint Evaluation; Syst-China, Systolic Hypertension in China.

may offer further contribution to the knowledge (Table 2). The INdividual Data ANalysis of Antihypertensive intervention trials (INDANA), published in the late 1990s, showed in a small subset of individuals aged ≥80 years that antihypertension therapy led to a reduction in stroke (33%), CV morbidity (22%), and heart failure (39%), with no effect on coronary events (44). The Blood Pressure Lowering Treatment Trialists' Collaboration meta-analysis documented a similar benefit of lowering BP in young and elderly subjects (45).

A large meta-analysis evaluating >100,000 participants, mostly aging between 65 and 75 years, failed to identify an association between BP-lowering treatment and lower CV risk in subjects with baseline SBP ≤140 mmHg (46). When trials were stratified by the SBP achieved in the treatment group (≥130 or <130 mmHg), significant interactions were observed for mortality, CAD, CV disease, heart failure, and albuminuria, with lower relative risk for patients with SBP ≥130 mmHg than for those with SBP ≤130 mmHg. A recent meta-analysis that included 44,989 participants showed that intensive BP lowering (133/76 mmHg) provided greater vascular protection than standard regimens (BP of 140/81 mmHg). The main benefit of intensive BP lowering was observed in patients with diabetes and in those older than 62 years (47).

The Systolic Blood Pressure Intervention Trial (SPRINT), which was recently published, randomized 9,361 persons with SBP >130 mmHg and increased CV risk, but without type 2 diabetes, to an SBP target <120 mmHg (intensive treatment) or <140 mmHg (standard treatment) (48). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from CV causes. At 1 year, the mean SBP was 121.4 mmHg in the intensive treatment group and 136.2 mmHg in the standard treatment group. The study was stopped early after a median follow-up of 3.26 years owing to 25% lower rate of the primary composite outcome in the intensive treatment group than in the standard treatment group ($P < 0.001$). All-cause mortality was also lower by 27% in the intensive treatment group (P = 0.003). The main benefit was observed in elderly subjects (> 75 years), who constituted 28% of the study population. Rates of serious adverse events of

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hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls, were higher in the intensive treatment group than in the standard treatment group (48). This recent study supports intensive BP lowering in elderly patients without diabetes and with increased CV risk. The results of this study cannot be applied to elderly hypertensive patients with diabetes, but it is speculated that elderly with diabetes may also benefit from intensive BP lowering. Indeed, ACCORD failed to show any benefit from intensive BP lowering in patients with diabetes, but this study included fewer elderly subjects, since the mean age of the study group was 62.2 years, whereas in SPRINT the mean age was 67.9 years (30,48).

It is also noteworthy that in ACCORD, despite the failure to show a decrease in primary end points in the intensive treatment arm the rate of stroke was significantly lower in the intensive than in the usual treatment arm (30). In SPRINT, the rate of stroke was the same in the intensive and the standard treatment arms (48). It is possible that ACCORD was underpowered, with a much lower event rate than anticipated, and therefore the benefit of intensive BP lowering was not observed. Recently, new results from a long-term follow-up of the ACCORD patients (ACCORD Follow-on Study [ACCORDION], were presented at the 2015 AHA meeting (49). In this extended study, 3,957 patients were followed for an additional 54–60 months. During this time, patients who had been in the intensive BP arm in the main trial were no longer aiming for the lower BP goals, so the difference in BP between the two groups narrowed from 14.5 mmHg at the end of the main trial to 4.2 mmHg at the end of the follow-up period. Results from the follow-up period showed a 9% nonsignificant reduction in the primary end point of major CV events over a median follow-up of 8.8 years from randomization. During the long-term follow-up, an interaction between BP and glycemia interventions became significant (*P* for interaction 0.037), with evidence of benefit for intensive BP lowering in participants randomized to standard glycemia therapy (hazard ratio 0.79 [95% CI 0.65–0.96]). These long-term results of ACCORD do take on enhanced importance when viewed alongside the SPRINT results. Indeed, the evidence to treat patients with diabetes to a target of $<$120 mmHg is weak, but we should keep in mind that in most previous trials the benefits of BP reduction in patients with diabetes were at least as good if not better than in individuals without diabetes. Taking into account results from the standard glycemic control arm of ACCORD, including those from long-term follow-up, and the stroke benefit seen in the main trial, together with the SPRINT results, it seems that elderly hypertensive patients with diabetes may benefit from intensive BP lowering if they can tolerate low BP levels.

The Approach to Elderly Patients With Diabetes With Isolated Systolic Hypertension

Special attention should be paid to isolated systolic hypertension, defined as SBP $>$140 mmHg and DBP $<$90 mmHg. This entity is a reflection of increased arterial stiffness and is characterized by a tendency to pronounced salt retention, likely due to a combination of reduced renin-angiotensin activity and reduced β-1 sensitivity (50).

Isolated systolic hypertension is frequently observed in aging (approximately 25–30% in individuals $>$80 years old), even though its prevalence, in untreated elderly individuals, seems to follow an encouraging, descending trend in the U.S. (12).

There is no clear indication of the ideal target SBP in these patients. The recently published REasons for Geographic And Racial Differences in Stroke (REGARDS) study, a large observational survey with ~30% patients with type 2 diabetes, showed a linear association between higher SBP categories and all-cause mortality risk among participants aged 55–64 and 65–74 years, while in individuals ≥75 years old no association was present between SBP and all-cause mortality (51). In Systolic Hypertension in the Elderly Program (SHEP) (52) in elderly patients (age $>$60 years) with isolated systolic hypertension, chlorthalidone reduced the rate of total stroke by 36%, the rate of major CV events by 32%, and the rate of all-cause mortality by 13%. The beneficial effects of chlorthalidone were the same in participants with and participants without diabetes, and no additional benefits were reported in terms of stroke reduction in patients with achieved SBP $<$140 vs. $<$150 mmHg.

In the Systolic Hypertension in Europe (Syst-Eur) trial (53), which included 4,600 elderly participants, significant improvements in the incidence of stroke and fatal and nonfatal cardiac end points were obtained, apparently in the absence of a J-curve effect. However, mortality benefits decreased with increasing age (54). Subanalysis in 492 patients with diabetes showed that lowering BP is particularly beneficial in these patients. Active treatment lowered overall mortality by 55%, mortality from CV disease by 76%, all CV events combined by 69%, and fatal and nonfatal strokes by 73% (55). The Felodipine EVEnt Reduction (FEVER) study showed a reduced risk of stroke (44%) in elderly patients in the intensively treated group, whose mean SBP was 138 mmHg (56). Patients with isolated systolic hypertension usually have low DBP, and consequently, lowering SBP will also lower DBP. Several studies have shown a J-curve association between DBP and CV events with a nadir between 60 and 70 mmHg (57,58). This may explain why some of the potential benefits of lowering SBP may be offset by the decrease in DBP. Therefore, it seems reasonable, in elderly patients with diabetes with isolated systolic hypertension, to recommend lowering SBP to levels ranging from 140 to 150 mmHg providing the DBP is $>$60 mmHg. In patients with DBP of ≤60 mmHg, a target SBP of 160 mmHg may be adequate.

Target BP in Elderly Patients With CKD

A certain decline in glomerular filtration rate with aging is considered physiologic, and the prevalence of CKD is high in elderly individuals with diabetes (59). SBP and DBP are among the strongest independent predictors of decline in renal function as well as albuminuria in the elderly (60). A general perception is that, in patients with type 2 diabetes and/or CKD, a lower target BP should be achieved, even though it has not been established whether lower targets will result in reduced morbidity or mortality or delay decline in renal function; in this view, there is no specific BP target for elderly hypertensive patients with diabetes and with CKD.

Kidney Disease Improving Global Outcomes (KDIGO) recommends a target BP ≤140/90 mmHg, with a lower target

(130/80 mmHg) in patients with type 2 diabetes and CKD and with a further lower target only in albuminuric (>30 mg/g creatinine) individuals (61). These recommendations are based solely on observational studies and reflect opinions rather than compelling evidence (61). The rationale behind the recommendation to lower BP more intensively in patients with diabetes and with CKD is the increase risk of stroke in patients with CKD (62). Since intensive BP lowering in patients with diabetes is mainly beneficial in reducing the rate of stroke (33), it is speculated that these patients may benefit from intensive BP lowering. However, this speculation has not been supported by clinical studies. A recent Cochrane review (63), focusing on trials comparing people with diabetes randomized to lower (<130/85 mmHg) or to standard (140–160/100 mmHg) BP targets, identified five studies that evaluated patients with CKD stage 3b or higher (estimated glomerular filtration rate <45 mL/min/1.73 m^2). The conclusion was that despite achievement of a significantly lower BP (119.3/64.4 vs. 133.5/70.5 mmHg), the only benefit of "lower" SBP was an absolute risk reduction of 1.1% in the incidence of stroke, but with no effect on mortality, and with the price of increased serious adverse events. For analysis of the effect of "lower" DBP, the authors found four trials that specifically compared clinical outcomes associated with "lower" (128/76 mmHg) versus "standard" targets (135/83 mmHg). Low target DBP did not reduce the rate of stroke, myocardial infarction, or congestive heart failure, and the effects on end-stage renal failure and total serious adverse events were not reported in any of the trials. The authors of this meta-analysis concluded that there is no evidence to support BP targets that are lower than the standard targets in hypertensive patients with diabetes and with CKD. On this basis, a group of experts has recently discouraged applying low BP targets in patients with diabetes and CKD stage 3b or higher (64).

In summary, there is no specific BP target for elderly hypertensive patients with diabetes and with CKD. It seems that treatment of these patients should be tailored by careful consideration of age, comorbidities, and concomitant therapies with specific attention to adverse events related to BP treatment.

Target BP in Elderly Patients With Diabetes and CAD

Older hypertensive patients with already established vascular disease, especially with CAD, may be more vulnerable to low BP levels. The recent Second Manifestations of ARTerial disease (SMART) trial included 5,788 patients, of whom 966 had diabetes, with symptomatic vascular disease. Patients were followed up for a median of 5 years for the occurrence of new vascular events. The nadir BP, where the event rate was lowest, was 143/82 mmHg. BP ≥143/82 mmHg was an independent risk factor for recurrent vascular events in aging patients (65). Messerli et al. (66) showed that in hypertensive patients with CAD, the risk for the primary outcome, all-cause death, and myocardial infarction progressively increased with low DBP. These data suggest that excessive reduction in DBP should be avoided in patients with CAD who are being treated for hypertension. Subanalysis of INVEST by age showed that in hypertensive patients with CAD the nadir SBP, where the event rate was lowest, increased with increasing age and was 140 mmHg (67). Since many elderly patients with diabetes have CAD (even silent), aggressive lowering of BP in this population should be avoided.

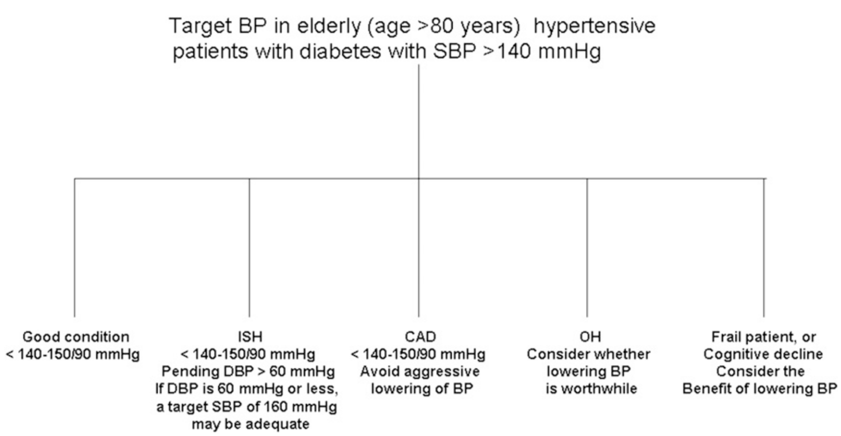

Figure 1—Individualized target BP in elderly hypertensive patients with diabetes. ISH, isolated systolic hypertension; OH, orthostatic hypotension.

Target BP in Elderly Patients With Diabetes With Orthostatic Hypotension

The presence of orthostatic hypotension, defined as a decrease >20 mmHg in SBP or >10 mmHg in DBP moving from a supine to a standing position, is a challenge in the treatment of elderly hypertensive individuals with diabetes. The presence of orthostatic hypotension, occurring in up to 30% of aging hypertensive individuals, and even more frequently in individuals with diabetes due to the neuropathic involvement (11), predisposes to CV events and may determine further complications, such as falls (68). Lowering BP in these patients may excessively decrease standing BP, leading to recurrent falls and hypoperfusion to vital organs. It is noteworthy that patients with orthostatic hypotension were excluded from HYVET; therefore, there are no outcome data on the benefit of lowering BP in these individuals. It seems that the potential long-term benefit of lowering BP is offset by the short-term side effects of falls; since there are no guidelines on how to treat these patients, we consider it reasonable not to lower BP in elderly patients with diabetes with orthostatic hypotension or recurrent falls.

Conclusion

Further clinical research is definitely needed in elderly individuals with diabetes to properly clarify what target BP should be. The available data suggest that lowering BP more aggressively may reduce the risk of stroke but with a price of increased cardiac events and side effects. Based on the limited available data and the main international guidelines, we suggest in elderly, but otherwise healthy, patients with diabetes a BP target of <140–150/90 mmHg. Lower BP levels may be adequate if tolerated by the patients. Since most of these patients, however, have concomitant diseases and many are very frail, a personalized BP target would be more appropriate, with adjustment of care plans periodically, trying to adequately manage the patient and minimize orthostatic hypotension and any drug-related complications and to maintain a reasonably good quality of life (Fig. 1). The presence of geriatric syndromes, including cognitive impairment, reduced vision and hearing, depression, and chronic pain, should also be considered, and in the light of the dangerous consequences of excessively low BP values, the patient's conditions regarding mobility, risk of falls, social support, and home safety need to be properly balanced.

Duality of Interest. E.G. is a consultant for Bayer, Pfizer, and Dexel. No other potential conflicts of interest relevant to this article were reported.

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