Diabetes and Hypertension: A Position Statement by the American Diabetes Association

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POSITION STATEMENT

Hypertension is common among patients with diabetes, with the prevalence depending on type and duration of diabetes, age, sex, race/ethnicity, BMI, history of glycemic control, and the presence of kidney disease, among other factors (1–3). Furthermore, hypertension is a strong risk factor for atherosclerotic cardiovascular disease (ASCVD), heart failure, and microvascular complications. ASCVD—defined as acute coronary syndrome, myocardial infarction (MI), angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin—is the leading cause of morbidity and mortality for individuals with diabetes and is the largest contributor to the direct and indirect costs of diabetes. Numerous studies have shown that antihypertensive therapy reduces ASCVD events, heart failure, and microvascular complications in people with diabetes (4–8). Large benefits are seen when multiple risk factors are addressed simultaneously (9). There is evidence that ASCVD morbidity and mortality have decreased for people with diabetes since 1990 (10,11) likely due in large part to improvements in blood pressure control (12–14). This Position Statement is intended to update the assessment and treatment of hypertension among people with diabetes, including advances in care since the American Diabetes Association (ADA) last published a Position Statement on this topic in 2003 (3).

DEFINITIONS, SCREENING, AND DIAGNOSIS

Recommendations

- Blood pressure should be measured at every routine clinical care visit. Patients found to have an elevated blood pressure (≥140/90 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. **B**
- All hypertensive patients with diabetes should have home blood pressure monitored to identify white-coat hypertension. **B**
- Orthostatic measurement of blood pressure should be performed during initial evaluation of hypertension and periodically at follow-up, or when symptoms of orthostatic hypotension are present, and regularly if orthostatic hypotension has been diagnosed. **E**

Blood pressure should be measured at every routine clinical care visit (15). At the initial visit, blood pressure should be measured in both arms to detect and account for abnormalities that may lead to spurious blood pressures, such as arterial stenosis. Patients with elevated blood pressure (≥140/90 mmHg) who are not known to have hypertension should have elevated blood pressure confirmed on a separate day, within 1 month, to confirm the diagnosis of hypertension.

Office-based semiautomated oscillometric blood pressure (conventional or office blood pressure) is the conventional method used to diagnose hypertension and monitor treatment response. Blood pressure should be measured by a trained individual (15) in the seated position, with feet on the floor and arm supported at heart level. Cuff size should be appropriate for the upper-arm circumference (Table 1). To reduce within-patient variability, blood pressure should be measured after 5 min of rest, 2–3 readings should be taken 1–2 min apart, and blood pressure measurements should be averaged (16). It is particularly important to make and average repeated measurements of blood pressure for the diagnosis of hypertension and titration of antihypertensive treatment.

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For further information on the ADA evidence grading system and the levels of evidence, please see Table 1 in the American Diabetes Association's Introduction section of the Standards of Medical Care in Diabetes—2017. *Diabetes Care 2017;40(Suppl. 1):S2, https://doi.org/10.2337/dc17-S001.*

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Table 1—Recommended blood pressure measurement cuff size for a given arm circumference

Arm circumference (cm)	Usual cuff size
22–26	Small adult
27–34	Adult
35–44	Large adult
45–52	Adult thigh

Automated office blood pressure (AOBP) is an alternate method to measure blood pressure in which a fully automated device is used to make and average multiple readings (usually 3–5) taken over a few minutes, ideally while a patient rests quietly alone (17). AOBP was used in two large, important clinical trials, Action to Control Cardiovascular Risk in Diabetes (ACCORD) (18) and Systolic Blood Pressure Intervention Trial (SPRINT) (19). If the patient is alone when the readings are taken, the approach is also useful for diagnosing white-coat hypertension (20). AOBP generates values 5–10 mmHg lower than conventional office readings, on average. Thus, results of trials using this technique cannot be directly applied to practices that measure conventional office blood pressure (17,21–23). With the exception of ACCORD (18), most of the evidence of benefits of hypertension treatment in people with diabetes is based on conventional office measurements.

Hypertension is defined as a sustained blood pressure ≥140/90 mmHg. This definition is based on unambiguous data that levels above this threshold are strongly associated with ASCVD, death, disability, and microvascular complications (1,2,24–27) and that antihypertensive treatment in populations with baseline blood pressure above this range reduces the risk of ASCVD events (4–6,28,29). The "sustained" aspect of the hypertension definition is important, as blood pressure has considerable normal variation. The criteria for diagnosing hypertension should be differentiated from blood pressure treatment targets.

Hypertension diagnosis and management can be complicated by two common conditions: masked hypertension and white-coat hypertension. Masked hypertension is defined as a normal blood pressure in the clinic or office (<140/90 mmHg) but an elevated home blood pressure of ≥135/85 mmHg (30); the lower home blood pressure threshold is based on outcome studies (31) demonstrating that lower home blood pressures correspond to higher office-based measurements. White-coat hypertension is elevated office blood pressure (≥140/90 mmHg) and normal (untreated) home blood pressure (<135/85 mmHg) (32). Identifying these conditions with home blood pressure monitoring can help prevent overtreatment of people with white-coat hypertension who are not at elevated risk of ASCVD and, in the case of masked hypertension, allow proper use of medications to reduce side effects during periods of normal pressure (33,34).

Home blood pressure measurements include daytime blood pressure measured with ambulatory blood pressure monitoring as well as measurements taken with home blood pressure monitors. The cuff size is very important, as too small a cuff will give higher than actual blood pressure values and too large a cuff will give values that are lower than actual blood pressure. The correct cuff size, such that the bladder encircles 80% of the arm (Table 1), should be used. The cuff should be placed such that the middle is on the patient's upper arm at the level of the right atrium (the midpoint of the sternum), and it should never be placed over clothes.

Orthostatic Hypotension

Diabetic autonomic neuropathy or volume depletion can cause orthostatic hypotension (35), which may be further exacerbated by antihypertensive medications. The definition of orthostatic hypotension is a decrease in systolic blood pressure of 20 mmHg or a decrease in diastolic blood pressure of 10 mmHg within 3 min of standing when compared with blood pressure from the sitting or supine position (36). Orthostatic hypotension is common in people with type 2 diabetes and hypertension and is associated with an increased risk of mortality and heart failure (37).

It is important to assess for symptoms of orthostatic hypotension to individualize blood pressure goals, select the most appropriate antihypertensive agents, and minimize adverse effects of antihypertensive therapy. Additionally, antihypertensive medication type or timing (switch to nocturnal dosing) may require adjustment. In particular, α-blockers and diuretics may need to be stopped. People with orthostatic hypotension may benefit from support stockings or other approaches (38).

BLOOD PRESSURE TARGETS

Recommendations

- Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90 mmHg. **A**
- Lower systolic and diastolic blood pressure targets, such as <130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease if they can be achieved without undue treatment burden. **B**

Epidemiologic analyses show that blood pressure ≥115/75 mmHg is associated with increased rates of ASCVD (27), heart failure, retinopathy, kidney disease, and mortality in a graded fashion, contributing to the evidence that blood pressure control is important in the clinical outcomes of diabetes (1,2,24,26,39). However, observational studies of blood pressure targets are subject to confounding factors and do not directly assess the effects of blood pressure lowering. Clinical trials and meta-analyses of clinical trials provide the strongest evidence addressing blood pressure and offer substantial guidance for treatment targets, particularly for patients with type 2 diabetes.

Treatment of hypertension to blood pressure <140/90 mmHg is supported by unequivocal evidence that pharmacologic treatment of blood pressure ≥140/90 mmHg reduces cardiovascular events as well as some microvascular complications. In type 2 diabetes, the UK Prospective Diabetes Study (UKPDS) showed that targeting blood pressure <150/85 mmHg versus <180/105 mmHg reduced composite microvascular and macrovascular diabetes complications by 24% (28). Moreover, meta-analyses of clinical trials demonstrate that antihypertensive treatment of populations with diabetes and baseline blood pressure ≥140/90 mmHg reduces the risks of ASCVD, heart failure, retinopathy, and albuminuria (4–8,40). Therefore, most patients with type 1 or type 2 diabetes who have hypertension should, at a minimum, be treated to blood pressure targets of <140/90 mmHg.

Intensification of antihypertensive therapy to target blood pressures lower than <140/90 mmHg (e.g., <130/80

or <120/80 mmHg) may be beneficial for selected patients with diabetes. Such intensive blood pressure control has been evaluated in landmark clinical trials and meta-analyses of clinical trials.

Randomized Clinical Trials of Intensive Blood Pressure Control

The ACCORD blood pressure (ACCORD BP) trial examined the effects of intensive blood pressure control (goal systolic blood pressure <120 mmHg) versus standard blood pressure control (target systolic blood pressure <140 mmHg) among people with type 2 diabetes. Additional studies, such as Hypertension Optimal Treatment (HOT) trial and SPRINT, also examined the potential benefits of intensive versus standard blood pressure control, though the relevance of their results to people with diabetes is less clear. The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation–Blood Pressure (ADVANCE BP) trial, which tested the effects of a fixed-dose combination of antihypertensive interventions versus placebo among people with type 2 diabetes, also informs blood pressure targets (41). Study details are given in Table 2.

In ACCORD BP, intensive blood pressure control did not reduce total major atherosclerotic cardiovascular events but did reduce the risk of stroke, at the expense of increased adverse events (18). Specifically, compared with a target systolic blood pressure <140 mmHg, a target systolic blood pressure <120 mmHg resulted in no significant difference in the primary composite outcome of MI, stroke, or cardiovascular death (hazard ratio 0.88, 95% CI 0.73 to 1.06). Stroke was reduced by 41% (hazard ratio 0.59, 95% CI 0.39 to 0.89), but serious adverse events attributed to antihypertensive therapy occurred in 3.3% vs. 1.3% of participants, with significantly increased incidence of hypotension, electrolyte abnormalities, and elevated serum creatinine. Therefore, the ACCORD BP results suggest that blood pressure targets more intensive than <140/90 mmHg may be reasonable in selected patients who have been educated about added treatment burden, side effects, and costs (18,42). The achieved blood pressure in ADVANCE in the intervention group (136/73) was

Table 2—Randomized controlled trials of intensive vs. standard hypertension treatment strategies

Clinical trial	Population	Intensive	Standard	Outcomes
ACCORD BP (18)	4,733 participants with T2D aged 40–79 years with prior evidence of CVD or multiple cardiovascular risk factors	Systolic blood pressure target: <120 mmHg Achieved (mean) systolic/diastolic: 119.3/64.4 mmHg	Systolic blood pressure target: 130–140 mmHg Achieved (mean) systolic/diastolic: 133.5/70.5 mmHg	• No benefit in primary end point: composite of nonfatal MI, nonfatal stroke, and CVD death • Stroke risk reduced 41% with intensive control, not sustained through follow-up beyond the period of active treatment • Adverse events more common in intensive group, particularly elevated serum creatinine and electrolyte abnormalities
ADVANCE BP (43)	11,140 participants with T2D aged 55 years and older with prior evidence of CVD or multiple cardiovascular risk factors	Intervention: a single-pill, fixed-dose combination of perindopril and indapamide Achieved (mean) systolic/diastolic: 136/73 mmHg	Control: placebo Achieved (mean) systolic/diastolic: 141.6/75.2 mmHg	• Intervention reduced risk of primary composite end point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%) • 6-year observational follow-up found reduction in risk of death in intervention group attenuated but still significant (134)
HOT (135)	18,790 participants, including 1,501 with diabetes	Diastolic blood pressure target: ≤80 mmHg	Diastolic blood pressure target: ≤90 mmHg	• In the overall trial, there was no cardiovascular benefit with more intensive targets • In the subpopulation with diabetes, an intensive diastolic target was associated with a significantly reduced risk (51%) of CVD events
SPRINT (19)	9,361 participants without diabetes	Systolic blood pressure target: <120 mmHg Achieved (mean): 121.4 mmHg	Systolic blood pressure target: <140 mmHg Achieved (mean): 136.2 mmHg	• Intensive systolic blood pressure target lowered risk of the primary composite outcome 25% (MI, acute coronary syndrome, stroke, heart failure, and death due to CVD) • Intensive target reduced risk of death 27% • Intensive therapy increased risks of electrolyte abnormalities and acute kidney injury

CVD, cardiovascular disease; T2D, type 2 diabetes.

higher than that achieved in ACCORD intensive arm (119/64 mmHg) and would be consistent with a target blood pressure of <140/90 mmHg, though ADVANCE did not explicitly test blood pressure targets (43). Of note, ACCORD BP and SPRINT measured blood pressure using AOBP, which yields values that are generally lower than typical office blood pressure by approximately 5–10 mmHg (17), suggesting that implementing the ACCORD BP or SPRINT protocols in a typical clinic might require a systolic blood pressure target higher than <120 mmHg.

Meta-analyses of Trials

Meta-analyses of placebo-controlled clinical trials using multiple classes of antihypertensive medications clearly demonstrate that antihypertensive treatment in general reduces the risks of ASCVD, heart failure, retinopathy, albuminuria, and mortality among people with diabetes (4–8,40). Overall, compared with people without diabetes, the relative benefits of antihypertensive treatment are similar, and absolute benefits may be greater (5,8,40). To clarify optimal blood pressure targets in the setting of diabetes, meta-analyses have stratified clinical trials by mean baseline blood pressure or mean blood pressure attained in the intervention or intensive treatment arm. Based on these analyses, antihypertensive treatment appears to be beneficial when mean baseline blood pressure is ≥140/90 mmHg or mean attained intensive blood pressure is ≥130/80 mmHg (4,6–8). Among trials with lower baseline or achieved blood pressure, antihypertensive treatment reduced the risk of stroke, retinopathy, and albuminuria, but effects on other ASCVD and heart failure were not evident. A critical point is that these are all trial-level meta-analyses that are subject to confounding and imprecise in their stratification, as opposed to individual-level meta-analyses, which are needed to best address the issue (8). In addition, meta-analyses have focused largely on treatment benefits, and additional data weighing potential harms are needed. Taken together, these meta-analyses consistently show that treating patients with baseline blood pressure ≥140 mmHg to targets <140 mmHg is beneficial, while more intensive targets may offer additional though probably less robust benefits.

Individualization of Treatment Targets

Patients and clinicians should engage in a shared decision-making process to determine individual blood pressure targets, with the acknowledgment that the benefits and risks of intensive blood pressure targets are uncertain and may vary across patients. Following the ADA approach to the management of hyperglycemia, factors that influence treatment targets may include risks of treatment (e.g., hypotension, drug adverse effects), life expectancy, comorbidities including vascular complications, patient attitude and expected treatment efforts, and resources and support system (44). Specific factors to consider are the absolute risk of cardiovascular events (40,45), risk of progressive kidney disease as reflected by albuminuria, adverse effects, age, and overall treatment burden. Patients who have higher risk of cardiovascular events (particularly stroke) or albuminuria and who can attain intensive blood pressure control relatively easily and without substantial adverse effects may be best suited to intensive blood pressure control. In contrast, patients with conditions more common in older adults, such as functional limitations, polypharmacy, and multimorbidity, may be best suited to less intensive blood pressure control.

Notably, there is an absence of high-quality data available to guide blood pressure targets in type 1 diabetes. Associations of blood pressure with macrovascular and microvascular outcomes in type 1 diabetes are generally similar to those in type 2 diabetes and the general population (1). Given an absence of randomized trials with clinical outcomes in type 1 diabetes, effects of antihypertensive therapy can only be extrapolated from trials in other populations, potentially drawing from both ACCORD BP and SPRINT. Of note, diastolic blood pressure, as opposed to systolic blood pressure, is a key variable predicting cardiovascular outcomes in people under age 50 years without diabetes and may be prioritized in younger adults (46,47). Though convincing data are lacking, younger adults with type 1 diabetes might more easily achieve intensive blood pressure levels and may derive substantial long-term benefit from tight blood pressure control.

TREATMENT

Lifestyle Management

Recommendation

- For patients with systolic blood pressure >120 mmHg or diastolic blood pressure >80 mmHg, lifestyle intervention consists of weight loss if overweight or obese; a Dietary Approaches to Stop Hypertension (DASH)-style dietary pattern including reduced sodium and increased potassium intake; increased fruit and vegetable consumption; moderation of alcohol intake; and increased physical activity. **B**

Lifestyle management is an important component of hypertension treatment because it lowers blood pressure, enhances the effectiveness of some antihypertensive medications, promotes other aspects of metabolic and vascular health, and generally leads to few adverse effects. In addition, patients with diabetes and systolic blood pressure >120 mmHg or diastolic blood pressure >80 mmHg are at risk for developing hypertension and its complications (48,49), and lifestyle management may help prevent or delay a diagnosis of hypertension with need for pharmacologic therapy. To facilitate long-term maintenance of behavioral change, lifestyle therapy should be adapted to suit the needs of the patient and discussed as part of diabetes management.

Although there are no well-controlled studies of diet and exercise in the treatment of elevated blood pressure or hypertension in individuals with diabetes, the Dietary Approaches to Stop Hypertension (DASH) study evaluated the impact of healthy dietary patterns in individuals without diabetes and has shown antihypertensive effects similar to those of pharmacologic monotherapy (50). A recent meta-analysis found that lifestyle intervention can help lower blood pressure in patients with type 2 diabetes (51). Medium- or high-intensity combined lifestyle counseling has shown benefit in patients selected for cardiovascular risk factors, including diabetes, for the intermediate outcomes of blood pressure, lipids, fasting blood glucose, and weight, especially over 12 to 24 months (52).

Lifestyle therapy consists of reducing excess body weight through caloric restriction, restricting sodium intake (<2,300 mg/day), increasing consumption of fruits

and vegetables (8–10 servings per day) and low-fat dairy products (2–3 servings per day), avoiding excessive alcohol consumption (no more than 2 servings per day in men and no more than 1 serving per day in women) (53), smoking cessation, reducing sedentary time (54), and increasing physical activity levels (55). These lifestyle strategies may also positively affect glycemic and lipid control and should be encouraged in those with even mildly elevated blood pressure. In addition, clinicians are encouraged to routinely review patient medication lists for agents that may raise blood pressure, including over-the-counter and herbal ones. As an example, one meta-analysis suggested that nonsteroidal anti-inflammatory drugs increase systolic blood pressure on average by 5 mmHg (56).

Sodium

Sodium reduction has not been tested in controlled clinical trials in people with diabetes. However, results from trials in primary hypertension have shown a reduction in systolic blood pressure of ~5 mmHg and diastolic blood pressure of 2–3 mmHg with moderate sodium reduction (from a daily intake of 200 mmol [4,600 mg] to 100 mmol [2,300 mg] of sodium per day) (57). A dose-response effect has been observed with sodium reduction. Even when pharmacologic agents are used, there may be a better response when there is concomitant salt restriction due to the volume component of hypertension.

Physical Activity

Moderately intense physical activity, such as 30–45 min of brisk walking most days of the week, has been shown to lower blood pressure (58). Regular exercise may lower blood pressure, necessitating dose adjustment of antihypertension medications (59). β-Blockers may reduce maximal exercise capacity, while diuretics may increase risk of dehydration. Physical activities should be promoted in all patients including older adults with physical limitations. The type and intensity of physical activities should be adapted to the preferences and functional status of the patient.

Weight Loss

Weight reduction should be considered in the management of blood pressure. The loss of 1 kg in body weight has been associated with a decrease in blood pressure of ~1 mmHg (60). Some weight-loss medications may induce increases in blood pressure levels, so these must be used with care.

Sleep Apnea

Treatment of obstructive sleep apnea has been shown to reduce blood pressure in randomized studies of people with diabetes (61).

Pharmacologic Antihypertensive Treatment

Recommendations

- Patients with confirmed office-based blood pressure ≥140/90 mmHg should, in addition to lifestyle therapy, have timely titration of pharmacologic therapy to achieve blood pressure goals. **A**
- Patients with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. **A**
- Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes: ACE inhibitors, angiotensin receptor blockers (ARBs), thiazide-like diuretics, or dihydropyridine calcium channel blockers. Multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and ARBs). **A**
- An ACE inhibitor or ARB, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urine albumin-to-creatinine ratio ≥300 mg/g creatinine (**A**) or 30–299 mg/g creatinine (**B**). If one class is not tolerated, the other should be substituted. **B**
- For patients treated with an ACE inhibitor, ARB, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored. **B**

Initial Number of Antihypertensive Medications

Initial treatment for people with diabetes depends on the severity of hypertension (Fig. 1). Those with blood pressure between 140/90 mmHg and 159/99 mmHg may begin with a single drug. For patients with blood pressure ≥160/100 mmHg, initial pharmacologic treatment with two antihypertensive medications is recommended. The Study of Hypertension and the Efficacy of Lotrel in Diabetes (SHIELD) trial was one of the first trials to evaluate whether a higher percentage of people with diabetes would achieve the blood pressure goal when a single-pill combination was given rather than monotherapy at average blood pressures above 160/100 mmHg. The 214 patients received initial therapy with an ACE inhibitor plus dihydropyridine calcium channel blocker (CCB) compared with the ACE inhibitor alone, which resulted in an increased proportion of participants achieving the target blood pressure at 3 months (63% vs. 37%; $P = 0.002$) (62). The Simplified Treatment Intervention to Control Hypertension (STITCH) trial randomized over 2,000 patients with and without diabetes whose mean blood pressure was ~160/95 mmHg to an ACE inhibitor alone or ACE inhibitor plus thiazide-like diuretic and found that the proportion of patients achieving a blood pressure <140/90 mmHg at 6 months was higher in the combination intervention group (65% vs. 53%; $P = 0.026$) (63). Single-pill combinations may improve medication adherence (64).

Classes of Antihypertensive Medications

Initial treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes: ACE inhibitors (65,66), angiotensin receptor blockers (ARBs) (65,66), thiazide-like diuretics (67), or dihydropyridine CCBs (68). For patients with albuminuria (urine albumin-to-creatinine ratio [UACR] ≥30 mg/g creatinine), initial treatment should include an ACE inhibitor or ARB in order to reduce the risk of progressive kidney disease, detailed below. In the absence of albuminuria, risk of progressive kidney disease is low, and ACE inhibitors and ARBs have not been found to afford superior cardioprotection when compared with other antihypertensive agents (69). β-Blockers may be used for the treatment of coronary disease or heart failure but have not been shown to reduce mortality as blood pressure–lowering agents in the absence of these conditions (5,70).

Multiple-Drug Therapy

Multiple-drug therapy is often required to achieve blood pressure targets, particularly in the setting of diabetic kidney disease.

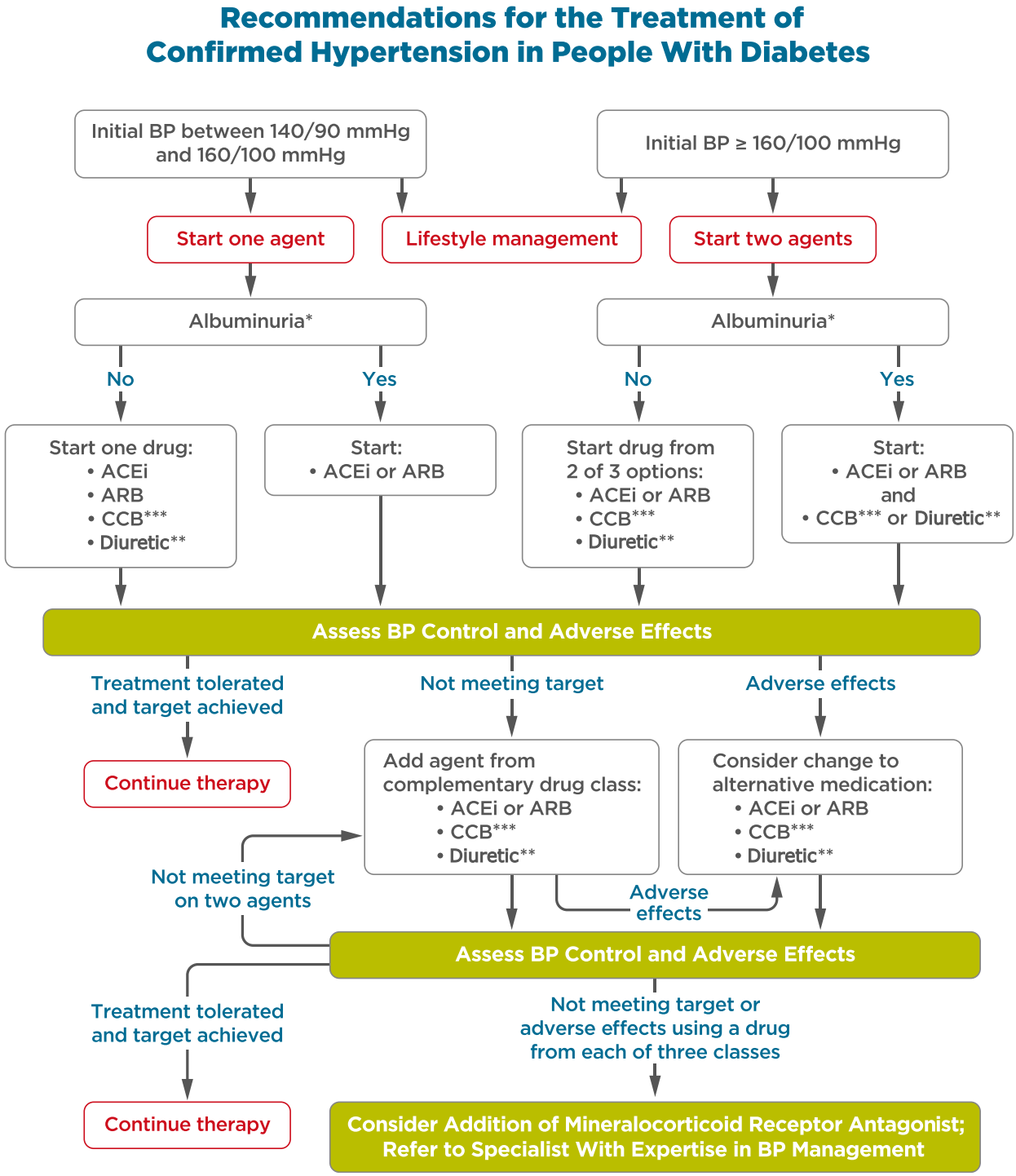

Figure 1—Recommendations for the treatment of confirmed hypertension in people with diabetes. *An ACE inhibitor (ACEi) or ARB is suggested to treat hypertension for patients with UACR 30–299 mg/g creatinine and strongly recommended for patients with UACR ≥300 mg/g creatinine. **Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred. ***Dihydropyridine. BP, blood pressure.

However, the use of both ACE inhibitors and ARBs in combination is not recommended given the lack of added ASCVD benefit and increased rate of adverse events—namely, hyperkalemia, syncope, and acute kidney injury (71–73). Titration of and/or addition of further blood pressure medications should be made in a timely fashion to overcome clinical inertia in achieving blood pressure targets.

There is only one large trial including people with diabetes that randomized two single-pill combinations and assessed cardiovascular and renal outcomes. The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial enrolled participants at high risk of cardiovascular events (60% with diabetes) and demonstrated a decrease in morbidity and mortality with the ACE inhibitor benazepril

plus the dihydropyridine CCB amlodipine versus benazepril and the thiazide-like diuretic hydrochlorothiazide (68,74). Other such trials are needed to confirm these outcomes and assess other antihypertensive medication combinations.

Diabetic Kidney Disease

Patients with diabetes and albuminuria (UACR ≥30 mg/g creatinine and particularly ≥300 mg/g creatinine) are at increased risk of progressive kidney disease (24). In this setting, ACE inhibitors and ARBs have unique renoprotective advantages in the treatment of hypertension. Outcome trials of people with type 1 and type 2 diabetes and established diabetic kidney disease (including urinary albumin excretion ≥300 mg/g creatinine) have demonstrated that an ACE inhibitor or ARB, at a maximal antihypertensive dose, slows the progression of kidney disease compared with placebo (75–77). Therefore, patients with urinary albumin excretion ≥300 mg/g creatinine should have an ACE inhibitor or an ARB included as part of their blood pressure–lowering regimen. Clinicians should also consider an ACE inhibitor or ARB in patients with hypertension at any level of albuminuria (urinary albumin excretion ≥30 mg/g creatinine) (66).

In the absence of albuminuria, the superiority of ACE inhibitors or ARBs over other antihypertensive agents for prevention of cardiovascular outcomes has not been consistently shown (66,69,78,79), although smaller trials suggest reduction in composite cardiovascular events and reduced progression to advanced stages of kidney disease (80–82). In general, ACE inhibitors and ARBs are considered to have similar benefits and risks, and if one is not tolerated, the other can often be used (65,83).

Hyperkalemia and Acute Kidney Injury

In people with diabetic kidney disease, hyperkalemia risk dramatically increases when the estimated glomerular filtration rate (eGFR) is below 45 mL/min/1.73 m^2 or serum potassium is >4.5 mEq/L while the patient is already receiving a diuretic (84). Moreover, the combination of reduced eGFR and elevated potassium in a given patient can raise the risk eightfold for hyperkalemia development if spironolactone and an ACE inhibitor or ARB are added (85).

Thiazide-like diuretics are only effective in maintaining volume and reducing the risk of hyperkalemia down to an eGFR of 30 mL/min/1.73 m^2 (86,87). Below an eGFR of 30 mL/min/1.73 m^2, a long-acting loop diuretic, such as torsemide, should be prescribed instead.

To prevent inadvertent declines in eGFR, patients treated with an ACE inhibitor or ARB should be aware of volume status and avoid volume depletion to reduce the risk for acute kidney injury. Also, in volume depleted states, risk for hyperkalemia increases (71,72,88).

Bedtime Dosing

Evidence suggests an association between absence of nocturnal blood pressure dipping and ASCVD events. A meta-analysis of clinical trials found a small benefit of evening versus morning dosing of antihypertensive medications with regard to blood pressure control but no data on clinical effects (89). In two subgroup analyses of a single subsequent randomized clinical trial, moving at least one antihypertensive medication to bedtime significantly reduced cardiovascular events, but results were based on small numbers of events (90,91).

Monitoring

Recommendation

- In patients receiving pharmacologic antihypertensive treatment, home blood pressure should be measured to promote patient engagement in treatment and adherence. **B**

Self-management is a key component of diabetes care and extends to antihypertensive treatment. Home blood pressures may improve patient medication adherence (92–94) and reduce cardiovascular risk factors (95). Furthermore, evidence suggests home blood pressure monitoring is as accurate as 24-h ambulatory blood pressure monitoring (96,97) and may better correlate with ASCVD risk than office measurements (98,99).

Interactions with Diabetes Medications

Hyperinsulinemia and exogenous insulin may theoretically lead to hypertension through vasoconstriction and sodium and fluid retention (100). However, insulin can also promote vasodilation, and basal insulin compared with standard care was not associated with a change in blood pressure in the Outcome Reduction With an Initial Glargine Intervention (ORIGIN) trial of people with type 2 diabetes or prediabetes (101).

Sodium–glucose cotransport 2 inhibitors are associated with a mild diuretic effect and a reduction in blood pressure of 3–6 mmHg systolic blood pressure and 1–2 mmHg diastolic blood pressure (102,103). Glucagon-like peptide 1 receptor agonists are also associated with a reduction in systolic/diastolic blood pressure of 2–3/0–1 mmHg (104).

RESISTANT HYPERTENSION

Recommendations

- Patients with resistant hypertension who are not meeting blood pressure targets on conventional drug therapy with three agents, including a diuretic, should be referred to a certified hypertension specialist. **E**
- Patients with resistant hypertension who are not meeting blood pressure targets on conventional drug therapy with three agents should be considered for mineralocorticoid receptor antagonist therapy. **B**

Resistant hypertension is defined as blood pressure ≥140/90 mmHg despite a therapeutic strategy that includes appropriate lifestyle management plus a diuretic and two other antihypertensive drugs belonging to different classes at adequate doses. Prior to diagnosing resistant hypertension, several other conditions should be excluded (Table 3).

Since multiple agents are often necessary to achieve blood pressure targets, medication adherence issues may present as resistant hypertension. Potential barriers to medication adherence (such as cost, number of medications, and side effects) should routinely be assessed. If blood pressure remains uncontrolled despite confirmed adherence, clinicians should consider an evaluation for secondary causes of hypertension.

Mineralocorticoid receptor antagonists (MRAs) are effective for management of resistant hypertension in patients with type 2 diabetes when added to existing treatment with a renin-angiotensin system (RAS) inhibitor, diuretic, and CCB (105), in part because they reduce sympathetic nerve activity (106). MRAs also reduce albuminuria and have additional cardiovascular benefits (107–110). However, adding an MRA to an ACE inhibitor or ARB may increase the risk for hyperkalemic episodes. Hyperkalemia can be managed with dietary potassium

restriction, potassium-wasting diuretics, or potassium binders (111), but long-term outcome studies are needed to evaluate the role of MRAs (with or without adjunct potassium management) in blood pressure management.

PREGNANCY

Recommendations

- Pregnant women with diabetes and preexisting hypertension or mild gestational hypertension with systolic blood pressure <160 mmHg, diastolic blood pressure <105 mmHg, and no evidence of end-organ damage do not need to be treated with pharmacologic antihypertensive therapy. **E**
- In pregnant patients with diabetes and preexisting hypertension who are treated with antihypertensive therapy, systolic or diastolic blood pressure targets of 120–160/80–105 mmHg are suggested in the interest of optimizing long-term maternal health and fetal growth. **E**

The American College of Obstetricians and Gynecologists (ACOG) does not recommend that women with mild gestational hypertension (systolic blood pressure <160 mmHg or diastolic blood pressure <110 mmHg) be treated with antihypertensive medications, as there is no benefit identified that clearly outweighs potential risks of therapy (112). A Cochrane systematic review did not find conclusive evidence for or against blood pressure treatment for mild to moderate preexisting hypertension to reduce the risk of preeclampsia, preterm birth, small-for-gestational-age infants, or fetal death (113). For pregnant women at high risk of preeclampsia, low-dose aspirin is recommended starting at 12 weeks of gestation to reduce the risk of preeclampsia (114).

For women requiring antihypertensive therapy, blood pressure should be maintained between 120 and 160 mmHg systolic and 80 and 105 mmHg diastolic, as lower blood pressure levels may be associated with impaired fetal growth. Pregnant women with hypertension and evidence of end-organ damage including cardiovascular and renal diseases may be considered for lower blood pressure targets (i.e., <140/90 mmHg) to avoid the progression of these diseases during pregnancy.

During pregnancy, treatment with ACE inhibitors, ARBs, or spironolactone is contraindicated, as they may cause fetal damage. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, hydralazine, and long-acting nifedipine. Diuretics may be used during late-stage pregnancy if needed for volume control (115). Postpartum patients with gestational hypertension, preeclampsia, and superimposed preeclampsia should have their blood pressures observed for 72 h in the hospital and for 7–10 days' postpartum (112). Long-term follow-up is recommended for these women, as they have increased lifetime cardiovascular risk.

OLDER ADULTS (AGED ≥65 YEARS)

Arterial stiffness may develop during the aging process and contribute to an increase in systolic and decrease in diastolic blood pressure in older adults (116,117). Diabetes is itself associated with an increase in arterial stiffness (118), leading to a greater age-related increase in systolic blood pressure compared with people without diabetes (119–121). Older adults with diabetes and hypertension (mainly systolic) typically present with high risk for cardiovascular events and other age-related diseases (122–124), difficulties achieving blood pressure targets due to arterial stiffness, and high risk of iatrogenic complications, including hypoglycemia, orthostatic hypotension, and volume depletion.

In older adults with diabetes and hypertension, functional status, comorbidities, and polypharmacy are important considerations when establishing therapeutic strategies and blood pressure goals (125). Systolic blood pressure should be the main target of treatment. In fitter patients, a therapeutic strategy similar to that used in younger individuals may be used. In the subgroup with loss of autonomy and major functional limitations (e.g., those needing daily assistance for their basic activities), higher systolic blood pressure goals should be considered (e.g., 145–160 mmHg) and treatment should be reduced in the presence of low supine systolic blood pressure (<130 mmHg) or presence of orthostatic hypotension (125,126).

In older people with impaired vascular compliance, as indicated by a difference of >60 mmHg between systolic and diastolic pressures (i.e., pulse pressure), attempts to reach a target systolic pressure must be balanced against the risk of lowering diastolic pressure below 65–70 mmHg. Lowering diastolic pressures below this range in older adults may increase the risk for coronary heart disease, mortality, and other adverse cardiovascular outcomes (127–130).

When considering pharmacologic antihypertensive treatment in older adults with diabetes, note that β-blockers may mask signs of hypoglycemia, antihypertensive drugs can worsen orthostatic hypotension, and diuretics can exacerbate volume depletion. Cognitive dysfunction may affect medication-taking behaviors, particularly in the context of poor overall health status, multiple comorbidities, acute illness, polypharmacy, and poor nutrition. Tolerance of the antihypertensive treatment should be regularly assessed, especially orthostatic hypotension.

Table 3—Conditions to exclude before making the diagnosis of resistant hypertension

Conditions	Definition
Secondary hypertension (136)*	Hypertension elicited or exacerbated by other drugs or diseases
Pseudoresistance (136,137)	Apparent hypertension due to lack of medication adherence, poor blood pressure measurement technique
Masked hypertension (137)	Clinic blood pressure <140/90 mmHg; daytime blood pressure ≥135 or ≥85 mmHg
White-coat hypertension (137)	Clinic blood pressure ≥140 or ≥90 mmHg; daytime blood pressure <135/85 mmHg

*Secondary causes of hypertension include endocrine issues, renal arterial disease, excessive edema in advanced kidney disease, and hormones, such as testosterone. Drugs that increase blood pressure include NSAIDs, decongestants, and some illicit substances.

ANTIHYPERTENSIVE TREATMENT IN THE ABSENCE OF HYPERTENSION

For people with diabetes and untreated blood pressure <140/90 mmHg, there is little evidence that antihypertensive treatment improves health outcomes. Some have suggested treatment with an ACE inhibitor or ARB to prevent or delay diabetic kidney disease, but the data do not support such an approach. In a trial of people with type 2 diabetes and normal urine albumin excretion with and without hypertension, an ARB reduced or suppressed the development of albuminuria but increased the rate of cardiovascular events (131). In two trials of patients without albuminuria or hypertension, one including people with type 1 diabetes (132) and the other type 2 diabetes (133), RAS inhibitors did not prevent the development of diabetic glomerulopathy assessed by kidney biopsy. *Therefore, RAS inhibitors are not recommended for patients without hypertension to prevent the development of diabetic kidney disease.*

CONCLUSIONS

Hypertension is a strong, modifiable risk factor for the macrovascular and microvascular complications of diabetes. Robust literature demonstrates the clinical efficacy of lowering blood pressure, with cardiovascular and microvascular benefits demonstrated for multiple classes of antihypertensive medications. Strong evidence from clinical trials and meta-analyses supports targeting blood pressure reduction to at least <140/90 mmHg in most adults with diabetes. Lower blood pressure targets may be beneficial for selected patients with high cardiovascular disease risk if they can be achieved without undue burden, and such lower targets may be considered on an individual basis. In addition to lifestyle modifications, multiple medication classes are often needed to attain blood pressure goals. ACE inhibitors, ARBs, dihydropyridine CCBs, and thiazide-like diuretics have been demonstrated to improve clinical outcomes and are preferred for blood pressure control. For patients with albuminuria, an ACE inhibitor or ARB should be part of the antihypertensive regimen. Treatment should be individualized to the specific patient based on their comorbidities; their anticipated benefit for reduction in ASCVD, heart failure, progressive diabetic kidney disease, and retinopathy events; and their risk of adverse events. This conversation should be part of a shared decision-making process between the clinician and the individual patient.

FUTURE UPDATES

As more evidence becomes available to guide the assessment and treatment of hypertension among people with diabetes, updated, refined, and additional recommendations will be published in the annual ADA "Standards of Medical Care in Diabetes," available from https://professional.diabetes.org/content/clinical-practice-recommendations.

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References

1. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Circulation 2014;130:1110–1130
2. Fox CS, Golden SH, Anderson C, et al.; American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Cardiovascular Surgery and Anesthesia, Council on Quality of Care and Outcomes Research; American Diabetes Association. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care 2015;38:1777–1803
3. Arauz-Pacheco C, Parrott MA, Raskin P; American Diabetes Association. Treatment of hypertension in adults with diabetes. Diabetes Care 2003; 26(Suppl. 1):S80–S82
4. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA 2015;313:603–615
5. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957–967
6. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. BMJ 2016;352:i717
7. Bangalore S, Kumar S, Lobach I, Messerli FH. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and Bayesian random-effects meta-analyses of randomized trials. Circulation 2011;123:2799–2810
8. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 - Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. J Hypertens 2017;35:922–944
9. Gæde P, Oellgaard J, Carstensen B, et al. Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial. Diabetologia 2016;59:2298–2307
10. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990-2010. N Engl J Med 2014;370:1514–1523
11. Rawshani A, Rawshani A, Franzén S, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. N Engl J Med 2017;376:1407–1418
12. Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW. Achievement of goals in U.S. diabetes care, 1999-2010. N Engl J Med 2013; 368:1613–1624
13. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. JAMA 2016;316:602–610
14. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. N Engl J Med 2007;356:2388–2398
15. Pickering TG, Hall JE, Appel LJ, et al.; Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood

Pressure Research. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Hypertension 2005;45:142–161
16. Powers BJ, Olsen MK, Smith VA, Woolson RF, Bosworth HB, Oddone EZ. Measuring blood pressure for decision making and quality reporting: where and how many measures? Ann Intern Med 2011;154:781–788
17. Bakris GL. The implications of blood pressure measurement methods on treatment targets for blood pressure. Circulation 2016;134:904–905
18. Cushman WC, Evans GW, Byington RP, et al.; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–1585
19. Wright JT Jr, Williamson JD, Whelton PK, et al.; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103–2116
20. Myers MG, Valdivieso M, Kiss A. Use of automated office blood pressure measurement to reduce the white coat response. J Hypertens 2009;27:280–286
21. Myers MG, Godwin M, Dawes M, Kiss A, Tobe SW, Kaczorowski J. The conventional versus automated measurement of blood pressure in the office (CAMBO) trial: masked hypertension substudy. J Hypertens 2012;30:1937–1941
22. Agarwal R. Implications of blood pressure measurement technique for implementation of Systolic Blood Pressure Intervention Trial (SPRINT). J Am Heart Assoc 2017;6:e004536
23. Myers MG, Campbell NRC. Unfounded concerns about the use of automated office blood pressure measurement in SPRINT. J Am Soc Hypertens 2016;10:903–905
24. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care 2014;37:2864–2883
25. Chobanian AV, Bakris GL, Black HR, et al.; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560–2572
26. Adamsson Eryd S, Gudbjörnsdottir S, Manhem K, et al. Blood pressure and complications in individuals with type 2 diabetes and no previous cardiovascular disease: national population based cohort study. BMJ 2016;354:i4070
27. Forouzanfar MH, Liu P, Roth GA, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. JAMA 2017;317:165–182
28. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703–713
29. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000;355:253–259
30. Pickering TG, Eguchi K, Kario K. Masked hypertension: a review. Hypertens Res 2007;30:479–488
31. Kikuya M, Hansen TW, Thijs L, et al.; IDACO investigators. Diagnostic thresholds for ambulatory blood pressure monitoring based on 10-year cardiovascular risk. Blood Press Monit 2007;12:393–395
32. Franklin SS, Thijs L, Hansen TW, O'Brien E, Staessen JA. White-coat hypertension: new insights from recent studies. Hypertension 2013;62:982–987
33. Stergiou GS, Asayama K, Thijs L, et al. Prognosis of white-coat and masked hypertension: International Database of HOme blood pressure in relation to Cardiovascular Outcome. Hypertension 2014;63:675–682
34. Yano Y, Bakris GL. Recognition and management of masked hypertension: a review and novel approach. J Am Soc Hypertens 2013;7:244–252
35. Pop-Busui R, Boulton AJM, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. Diabetes Care 2017;40:136–154
36. Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Auton Neurosci 2011;161:46–48
37. Fleg JL, Evans GW, Margolis KL, et al. Orthostatic hypotension in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) blood pressure trial: prevalence, incidence, and prognostic significance. Hypertension 2016;68:888–895
38. Briasoulis A, Silver A, Yano Y, Bakris GL. Orthostatic hypotension associated with baroreceptor dysfunction: treatment approaches. J Clin Hypertens (Greenwich) 2014;16:141–148
39. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903–1913
40. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet 2016;387:435–443
41. Zoungas S, de Galan BE, Ninomiya T, et al.; ADVANCE Collaborative Group. Combined effects of routine blood pressure lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes: New results from the ADVANCE trial. Diabetes Care 2009;32:2068–2074
42. Margolis KL, O'Connor PJ, Morgan TM, et al. Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: the ACCORD randomized trial. Diabetes Care 2014;37:1721–1728
43. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370:829–840
44. American Diabetes Association. Glycemic targets. Sec. 6. In *Standards of Medical Care in Diabetes—2017*. Diabetes Care 2017;40(Suppl. 1):S48–S56
45. Sundström J, Arima H, Woodward M, et al.; Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet 2014;384:591–598
46. Franklin SS. Cardiovascular risks related to increased diastolic, systolic and pulse pressure. An epidemiologist's point of view. Pathol Biol (Paris) 1999;47:594–603
47. Franklin SS, Gustin W 4th, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. Circulation 1997;96:308–315
48. Whelton PK, Appel L, Charleston RN, et al. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I [published correction appears in JAMA 1992;267:2330]. JAMA 1992;267:1213–1220
49. Appel LJ, Champagne CM, Harsha DW, et al.; Writing Group of the PREMIER Collaborative Research Group. Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. JAMA 2003;289:2083–2093
50. Azadbakht L, Fard NRP, Karimi M, et al. Effects of the Dietary Approaches to Stop Hypertension (DASH) eating plan on cardiovascular risks among type 2 diabetic patients: a randomized crossover clinical trial. Diabetes Care 2011;34:55–57
51. Chen L, Pei J-H, Kuang J, et al. Effect of lifestyle intervention in patients with type 2 diabetes: a meta-analysis. Metabolism 2015;64:338–347
52. Lin JS, O'Connor EA, Evans CV, Senger CA, Rowland MG, Groom HC. Behavioral Counseling to Promote a Healthy Lifestyle for Cardiovascular Disease Prevention in Persons With Cardiovascular Risk Factors: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force [Internet], 2014. Rockville, MD, Agency for Healthcare Research and Quality (US), 2014. Available from http://www.ncbi.nlm.nih.gov/books/NBK241537/. Accessed 11 November 2016
53. Sacks FM, Svetkey LP, Vollmer WM, et al.; DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med 2001;344:3–10
54. Young DR, Hivert MF, Alhassan S, et al.; Endorsed by The Obesity Society; Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Functional Genomics and Translational Biology; and Stroke Council. Sedentary behavior and cardiovascular morbidity and mortality: a science advisory from the American Heart Association. Circulation 2016;134:e262–e279
55. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507–520
56. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. Ann Intern Med 1994;121:289–300
57. Arauz-Pacheco C, Parrott MA, Raskin P. The treatment of hypertension in adult patients with diabetes. Diabetes Care 2002;25:134–147

58. Brook RD, Appel LJ, Rubenfire M, et al. Beyond medications and diet: alternative approaches to lowering blood pressure: a scientific statement from the American Heart Association. Hypertension 2013;61:1360–1383
59. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. Diabetes Care 2016;39:2065–2079
60. Semlitsch T, Jeitler K, Berghold A, et al. Long-term effects of weight-reducing diets in people with hypertension. Cochrane Database Syst Rev 2016;Mar 3:CD008274
61. Shaw JE, Punjabi NM, Naughton MT, et al. The effect of treatment of obstructive sleep apnea on glycemic control in type 2 diabetes. Am J Respir Crit Care Med 2016;194:486–492
62. Bakris GL, Weir MR; Study of Hypertension and the Efficacy of Lotrel in Diabetes (SHIELD) Investigators. Achieving goal blood pressure in patients with type 2 diabetes: conventional versus fixed-dose combination approaches. J Clin Hypertens (Greenwich) 2003;5:202–209
63. Feldman RD, Zou GY, Vandervoort MK, Wong CJ, Nelson SAE, Feagan BG. A simplified approach to the treatment of uncomplicated hypertension: a cluster randomized, controlled trial. Hypertension 2009;53:646–653
64. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med 2007;120:713–719
65. Catalá-López F, Macías Saint-Gerons D, González-Bermejo D, et al. Cardiovascular and renal outcomes of renin-angiotensin system blockade in adult patients with diabetes mellitus: a systematic review with network meta-analyses. PLoS Med 2016;13:e1001971
66. Palmer SC, Mavridis D, Navarese E, et al. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. Lancet 2015; 385:2047–2056
67. Barzilay JI, Davis BR, Bettencourt J, et al.; ALLHAT Collaborative Research Group. Cardiovascular outcomes using doxazosin vs. chlorthalidone for the treatment of hypertension in older adults with and without glucose disorders: a report from the ALLHAT study. J Clin Hypertens (Greenwich) 2004;6:116–125
68. Weber MA, Bakris GL, Jamerson K, et al.; ACCOMPLISH Investigators. Cardiovascular events during differing hypertension therapies in patients with diabetes. J Am Coll Cardiol 2010;56: 77–85
69. Bangalore S, Fakheri R, Toklu B, Messerli FH. Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials. BMJ 2016;352:i438
70. Carlberg B, Samuelsson O, Lindholm LH. Atenolol in hypertension: is it a wise choice? Lancet 2004;364:1684–1689
71. Yusuf S, Teo KK, Pogue J, et al.; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547–1559
72. Fried LF, Emanuele N, Zhang JH, et al.; VA NEPHRON-D Investigators. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med 2013;369:1892–1903
73. Makani H, Bangalore S, Desouza KA, Shah A, Messerli FH. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. BMJ 2013;346:f360
74. Jamerson K, Weber MA, Bakris GL, et al.; ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 2008;359:2417–2428
75. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; The Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med 1993;329: 1456–1462
76. Brenner BM, Cooper ME, de Zeeuw D, et al.; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–869
77. Lewis EJ, Hunsicker LG, Clarke WR, et al.; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851–860
78. Whelton PK, Barzilay J, Cushman WC, et al.; ALLHAT Collaborative Research Group. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med 2005;165:1401–1409
79. Remonti LR, Dias S, Leitão CB, et al. Classes of antihypertensive agents and mortality in hypertensive patients with type 2 diabetes—network meta-analysis of randomized trials. J Diabetes Complications 2016;30:1192–1200
80. Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. Diabetes Care 1998;21:597–603
81. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med 1998;338: 645–652
82. Schrier RW, Estacio RO, Mehler PS, Hiatt WR. Appropriate blood pressure control in hypertensive and normotensive type 2 diabetes mellitus: a summary of the ABCD trial. Nat Clin Pract Nephrol 2007;3:428–438
83. Barnett AH, Bain SC, Bouter P, et al.; Diabetics Exposed to Telmisartan and Enalapril Study Group. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med 2004;351:1952–1961
84. Lazich I, Bakris GL. Prediction and management of hyperkalemia across the spectrum of chronic kidney disease. Semin Nephrol 2014;34: 333–339
85. Khosla N, Kalaitzidis R, Bakris GL. Predictors of hyperkalemia risk following hypertension control with aldosterone blockade. Am J Nephrol 2009; 30:418–424
86. Agarwal R, Sinha AD, Pappas MK, Ammous F. Chlorthalidone for poorly controlled hypertension in chronic kidney disease: an interventional pilot study. Am J Nephrol 2014;39:171–182
87. Sica DA. Diuretic use in renal disease. Nat Rev Nephrol 2011;8:100–109
88. Parving H-H, Brenner BM, McMurray JJV, et al.; ALTITUDE Investigators. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med 2012;367:2204–2213
89. Zhao P, Xu P, Wan C, Wang Z. Evening versus morning dosing regimen drug therapy for hypertension. Cochrane Database Syst Rev 2011;Oct 5: CD004184
90. Hermida RC, Ayala DE, Mojón A, Fernández JR. Influence of time of day of blood pressure-lowering treatment on cardiovascular risk in hypertensive patients with type 2 diabetes. Diabetes Care 2011;34:1270–1276
91. Hermida RC, Ayala DE, Mojón A, Fernández JR. Bedtime dosing of antihypertensive medications reduces cardiovascular risk in CKD. J Am Soc Nephrol 2011;22:2313–2321
92. Ralston JD, Cook AJ, Anderson ML, et al. Home blood pressure monitoring, secure electronic messaging and medication intensification for improving hypertension control: a mediation analysis. Appl Clin Inform 2014;5:232–248
93. Grant S, Greenfield SM, Nouwen A, McManus RJ. Improving management and effectiveness of home blood pressure monitoring: a qualitative UK primary care study. Br J Gen Pract 2015;65:e776–e783
94. Omboni S, Gazzola T, Carabelli G, Parati G. Clinical usefulness and cost effectiveness of home blood pressure telemonitoring: meta-analysis of randomized controlled studies. J Hypertens 2013; 31:455–467; discussion 467–468
95. DeAlleaume L, Parnes B, Zittleman L, et al. Success in the Achieving CARdiovascular Excellence in Colorado (A CARE) home blood pressure monitoring program: a report from the Shared Networks of Colorado Ambulatory Practices and Partners (SNOCAP). J Am Board Fam Med 2015; 28:548–555
96. Juhanoja EP, Niiranen TJ, Johansson JK, Puukka PJ, Jula AM. Agreement between ambulatory, home, and office blood pressure variability. J Hypertens 2016;34:61–67
97. Ntineri A, Stergiou GS, Thijs L, et al. Relationship between office and home blood pressure with increasing age: The International Database of HOme blood pressure in relation to Cardiovascular Outcome (IDHOCO). Hypertens Res 2016;39: 612–617
98. Bobrie G, Genès N, Vaur L, et al. Is "isolated home" hypertension as opposed to "isolated office" hypertension a sign of greater cardiovascular risk? Arch Intern Med 2001;161:2205–2211
99. Sega R, Facchetti R, Bombelli M, et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. Circulation 2005;111:1777–1783
100. Ferrannini E, Cushman WC. Diabetes and hypertension: the bad companions. Lancet 2012; 380:601–610
101. Gerstein HC, Bosch J, Dagenais GR, et al.; ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367:319–328
102. Monami M, Nardini C, Mannucci E. Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2014;16:457–466

103. Oliva RV, Bakris GL. Blood pressure effects of sodium-glucose co-transport 2 (SGLT2) inhibitors. J Am Soc Hypertens 2014;8:330–339
104. Vilsbøll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ 2012;344:d7771
105. Iliescu R, Lohmeier TE, Tudorancea I, Laffin L, Bakris GL. Renal denervation for the treatment of resistant hypertension: review and clinical perspective. Am J Physiol Renal Physiol 2015;309:F583–F594
106. Raheja P, Price A, Wang Z, et al. Spironolactone prevents chlorthalidone-induced sympathetic activation and insulin resistance in hypertensive patients. Hypertension 2012;60:319–325
107. Bakris GL, Agarwal R, Chan JC, et al.; Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy (ARTS-DN) Study Group. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. JAMA 2015;314:884–894
108. Williams B, MacDonald TM, Morant S, et al.; British Hypertension Society's PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 2015;386:2059–2068
109. Filippatos G, Anker SD, Böhm M, et al. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. Eur Heart J 2016;37:2105–2114
110. Bomback AS, Klemmer PJ. Mineralocorticoid receptor blockade in chronic kidney disease. Blood Purif 2012;33:119–124
111. Bakris GL, Pitt B, Weir MR, et al.; AMETHYST-DN Investigators. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial [published correction appears in JAMA 2015]. JAMA 2015;314:731
112. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122–1131
113. Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev 2014;Feb 6:CD002252
114. LeFevre ML; U.S. Preventive Services Task Force. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2014;161:819–826
115. Al-Balas M, Bozzo P, Einarson A. Use of diuretics during pregnancy. Can Fam Physician 2009;55:44–45
116. Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. Circulation 2003;107:2864–2869
117. Franklin SS, Larson MG, Khan SA, et al. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. Circulation 2001;103:1245–1249
118. Salvi P, Safar ME, Labat C, Borghi C, Lacolley P, Benetos A; PARTAGE Study Investigators. Heart disease and changes in pulse wave velocity and pulse pressure amplification in the elderly over 80 years: the PARTAGE Study. J Hypertens 2010;28:2127–2133
119. Rönnback M, Fagerudd J, Forsblom C, Pettersson-Fernholm K, Reunanen A, Groop PH; Finnish Diabetic Nephropathy (FinnDiane) Study Group. Altered age-related blood pressure pattern in type 1 diabetes. Circulation 2004;110:1076–1082
120. Salomaa V, Riley W, Kark JD, Nardo C, Folsom AR. Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. The ARIC Study. Atherosclerosis Risk in Communities Study. Circulation 1995;91:1432–1443
121. Schram MT, Kostense PJ, Van Dijk RA, et al. Diabetes, pulse pressure and cardiovascular mortality: the Hoorn Study. J Hypertens 2002;20:1743–1751
122. Bruce DG, Casey GP, Grange V, et al.; Fremantle Cognition in Diabetes Study. Cognitive impairment, physical disability and depressive symptoms in older diabetic patients: the Fremantle Cognition in Diabetes Study. Diabetes Res Clin Pract 2003;61:59–67
123. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. Alzheimers Dement 2015;11:718–726
124. Satizabal C, Beiser AS, Seshadri S. Incidence of dementia over three decades in the Framingham Heart Study. N Engl J Med 2016;375:93–94
125. Benetos A, Rossignol P, Cherubini A, et al. Polypharmacy in the aging patient: management of hypertension in octogenarians. JAMA 2015;314:170–180
126. Benetos A, Bulpitt CJ, Petrovic M, et al. An expert opinion from the European Society of Hypertension-European Union Geriatric Medicine Society Working Group on the management of hypertension in very old, frail subjects. Hypertension 2016;67:820–825
127. Yano Y, Rakugi H, Bakris GL, et al. On-treatment blood pressure and cardiovascular outcomes in older adults with isolated systolic hypertension. Hypertension 2017;69:220–227
128. Vamos EP, Harris M, Millett C, et al. Association of systolic and diastolic blood pressure and all cause mortality in people with newly diagnosed type 2 diabetes: retrospective cohort study. BMJ 2012;345:e5567
129. Vidal-Petiot E, Ford I, Greenlaw N, et al.; CLARIFY Investigators. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. Lancet 2016;388:2142–2152
130. McEvoy JW, Chen Y, Rawlings A, et al. Diastolic blood pressure, subclinical myocardial damage, and cardiac events: implications for blood pressure control. J Am Coll Cardiol 2016;68:1713–1722
131. Haller H, Ito S, Izzo JL Jr, et al.; ROADMAP Trial Investigators. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med 2011;364:907–917
132. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. N Engl J Med 2009;361:40–51
133. Weil EJ, Fufaa G, Jones LI, et al. Effect of losartan on prevention and progression of early diabetic nephropathy in American Indians with type 2 diabetes. Diabetes 2013;62:3224–3231
134. Zoungas S, Chalmers J, Neal B, et al.; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med 2014;371:1392–1406
135. Hansson L, Zanchetti A, Carruthers SG, et al.; HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351:1755–1762
136. Calhoun DA, Jones D, Textor S, et al.; American Heart Association Professional Education Committee. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation 2008;117:e510–e526
137. Pierdomenico SD, Lapenna D, Bucci A, et al. Cardiovascular outcome in treated hypertensive patients with responder, masked, false resistant, and true resistant hypertension. Am J Hypertens 2005;18:1422–1428