Hypertension and Diabetes

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Colleen Majewski and George L. Bakris

Contents

Abstract

Hypertension is seen in most people with hypertension and accentuates cardiovascular risk and accelerates development of kidney function decline. In most cases there is a genetic predisposition to develop hypertension in people with diabetes compounded by the presence of obesity and high sodium intake. While reduction in weight and sodium intake ameliorates elevations in blood pressure in most cases medications are needed. With proper control of blood pressure to levels below 140/90 mmHg there has been a marked reduction cardiovascular events and a slowing of kidney disease progression from 10–12 ml/min/year before decline in estimated glomerular filtration rate before 1985 to 2–4 ml/min/year decline currently. Moreover, those born after 1980 with type 1 diabetes have a 40% lower risk of developing end stage kidney disease than those born previously. Treatment of hypertension depends on stage of kidney disease. A low sodium i.e., <2300 mg/d diet, at least 6–7 hours of uninterrupted sleep and weight loss are the cornerstones of therapy. Drug treatment will be much less effective if these lifestyle issues are not in place. Those with macroalbuminuria

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i.e., greater than 300 mg/day and a blood pressure $\geq$ 140/90 mmHg must be treated if with an angiotensin converting enzyme inhibitor or an angiotensin converting enzyme inhibitor as part of the regimen. In all others it is important to lower blood pressure to <140/90 mmHg and use of either a renin angiotensin system blocker, thiazide-type diuretic or calcium antagonist may be used alone or in combination.

Keywords
Hypertension · Nephropathy · Blood pressure · Diabetes

Introduction

More than 75% of adults with diabetes have hypertension (defined as a blood pressure >130/80 mmHg) or are using antihypertensive medication (National Kidney Foundation 2007). In the natural history of Type 1 diabetes, development of an elevated blood pressure is a major predictor of nephropathy and future declines in kidney function (National Kidney Foundation 2007; Bakris 2004). In contrast, hypertension is already evident in most patients with Type 2 diabetes at the time of diagnosis. The implications of hypertension on cardiovascular risk, however, are similar in both types of diabetes (National Kidney Foundation 2007; Sarafidis and Bakris 2008). Mortality is increased 7.2-fold when hypertension is present in patients with diabetes (National Kidney Foundation 2007).

Hypertension is the most prevalent risk factor for the development of cardiovascular and kidney disease (National Kidney Foundation 2007; Stamler et al. 1993). The prevalence of hypertension is estimated at about 30% of the adult population in developed countries, and is predicted to increase by almost 60% in the next two decades (Hajjar and Kotchen 2003; Kearney et al. 2005). Diabetes is a major risk factor for cardiovascular disease and the most common cause of kidney failure in the Western world (National Kidney Foundation 2007; Buse et al. 2007). Moreover, cardiovascular mortality and morbidity is increased substantially in the presence of diabetes (Nag et al. 2007).

Pathophysiology of Hypertension and Diabetes Mellitus

Hypertension is a genetic disease expressed phenotypically as elevated blood pressure earlier in lifespan than would occur with normal aging (Giles et al. 2009). Expression is based on environmental factors such as diet and exercise (Giles et al. 2009). It is a key component of the metabolic syndrome, which is a collection of cardiovascular risk factors including abdominal obesity, impaired glucose tolerance, and dyslipidemia (Sharma 2003; Kannel et al. 1993).

Several studies demonstrate a clear relationship between obesity and hypertension (Kannel et al. 1993; Must et al. 1999). Hypertension and obesity rates are increasing in developed countries with hypertension being the most prevalent risk

factor contributing to the development of cardiovascular disease and chronic kidney disease (National Kidney Foundation 2007; Giles et al. 2009; Egan et al. 2010).

Abdominal obesity is a major risk factor in the development of hypertension (Thompson et al. 1999; Gorzelniak et al. 2002). Several mechanisms contribute to the development of hypertension in obese individuals. Excess weight gain is associated with sodium and fluid retention as well as increases in components of the renin-angiotensin aldosterone system (RAAS), and both contribute to the development of hypertension (Robles et al. 1993). A study of obese dogs treated with RAAS blockers resulted in a natriuresis, volume loss, and reduced arterial pressure (Robles et al. 1993). Studies of obese subjects demonstrate increases in plasma renin activity, plasma angiotensinogen (AGT), angiotensin-converting enzyme (ACE) activity, plasma angiotensin (Ang) II, and aldosterone levels (Hall 2003; Goodfriend and Calhoun 2004). Weight loss decreases these RAAS components (Engeli et al. 2005).

Adipose tissue itself produces angiotensinogen (AGT), and AGT concentration is correlated with body mass index and hypertension (Massiera et al. 2001). Furthermore, there is a correlation between 24-h blood pressure and the expression of genes related to the RAAS in adipocytes (Gorzelniak et al. 2002; Sharma 2002). AGT and Ang II also play a local role in adipocyte differentiation and metabolism (Sharma 2002; Sharma et al. 2002).

The contributing factors in the pathogenesis of hypertension in diabetes are multifactorial. For many years, it has been recognized that hypertension is common to both obese subjects and those with Type 2 diabetes (Hypertension in Diabetes Study Group 1993). Blood pressure elevations in both these groups may be, in part, due to the presence of insulin resistance and resultant hyperinsulinemia as well as increased salt sensitivity. Support for this proposal is evident from studies of behaviors that improve insulin action, such as weight loss and increased physical activity and the resultant reduction in blood pressure into the normal range (Sowers et al. 1982; Tuck et al. 1981; Becton et al. 2012). Additionally, studies that are more recent demonstrate blunting of vasodilator responses to known stimuli and reduced nitric oxide release; factors associated with increases in salt sensitivity, i.e., both systolic and diastolic blood pressure increase by >5 mmHg more than someone given the same salt load of 400 mmol/d (Wedler et al. 1992; Yatabe et al. 2010).

To understand the contribution of insulin resistance in the genesis of hypertension fully, one has to evaluate the effects of insulin resistance and hyperinsulinemia on factors that contribute to blood pressure elevation. Insulin resistance is a metabolic disorder that is manifested by a reduction in peripheral skeletal muscle utilization of glucose, fatty acid, and protein metabolism (Kadowaki et al. 1990). Hence, higher concentrations of insulin (hyperinsulinemia) are needed to achieve the same level of glucose utilization in these tissues. Hyperinsulinemia is also associated with a number of physiologic changes in cellular function. Hyperinsulinemia may also contribute to the genesis of hypertension through its effects on sodium homeostasis and the sympathetic nervous system. Lastly, the effect of insulin on various growth factors contributes to the development of vascular injury through its potentiation of the atherosclerotic process (Liu et al. 2011).

Most obese individuals develop insulin resistance and subsequent hyperinsulinemia. Yet, they do not all develop Type 2 diabetes or hypertension. The reasons for this lack of consistency with disease development are likely due to varied genetic and environmental factors.

Work by various investigators to isolate a "hypertensive gene" or group of genes has been ongoing for many years (International Consortium for Blood Pressure Genome-Wide Association Studies et al. 2011). Many candidate genes for hypertension have been found, including genes for ion channels within the kidney that affect transporters (SLC12A3, SLC12A1, KCNJ1, SCNN1A, SCNN1B, SCNN1G, CLCNKB), ion channel regulation (WNK1, WNK4, SGK1, ADD1, ADD2, GRK4), aldosterone signaling (REN, AGT, ACE, AGTR1), catecholamine pathways (TH, COMT, DBH, DRD1, DRD2, ADRB1, ADRB2, ADRB3, ADRA1A), vasoconstriction (NOS3, EDN1, EDNRA, CYP2C8), and inflammation (TGF-beta) (Simino et al. 2012).

There are also studies investigating for genes that increase risk for development of both hypertension and diabetes. Kraja et al. evaluated the 22,161 participants in the seven studies of the STAMPEED consortium to determine if subjects with the metabolic syndrome phenotype had common genetic variants. Using genome-wide association analyses, they identified two single-nucleotide polymorphisms (SNPs) located between $LOC_{100128354}$ (similar to small nuclear ribonucleoprotein polypeptide G, 11q21) and MTNR1B (melatonin-receptor 1B) that were significantly associated with both elevated blood glucose and hypertension (Kraja et al. 2011).

A study by Patel et al. investigated variations in the angiotensin-converting enzyme 2 (ACE2) gene in Caucasian men and women with type 2 diabetes. ACE2 is a homologue of ACE and degrades angiotensin II to the vasodilator angiotensin I-7. The researchers found certain polymorphisms of ACE2 in men and women with type 2 diabetes that were associated with hypertension (Patel et al. 2012). Bengtsson et al. investigated polymorphisms of the ACE gene and angiotensinogen (AGT) gene and their association with hypertension and type 2 diabetes. They found the D-allele of the ACE gene ID polymorphism increases susceptibility to hypertension, particularly when associated with type 2 diabetes (Bengtsson et al. 1999). A smaller study of 69 subjects with insulin-dependent diabetes found the CC-genotype of the A1166C gene polymorphism of the angiotensin type 1 receptor gene polymorphism is associated with hypertension (van Ittersum et al. 2000).

A number of other factors have been associated with hypertension development in diabetes. Haptoglobin polymorphisms were examined in 120-subject study, the results of which predicted the development of hypertension in patients with diabetes. The Hp1–2 genotype was the most common among those with refractory hypertension and type 2 diabetes (Wobeto et al. 2011).

Renalase is an important enzyme in catecholamine metabolism and is linked with changes associated with worsening of cardiac ischemia and kidney disease (Wu et al. 2011; Xu et al. 2005; Buraczynska et al. 2011). Buraczynska et al. found an association between the renalase gene polymorphism (C allele of rs2296545 SNP) with hypertension in 892 patients with type 2 diabetes (Buraczynska et al. 2011).

Lastly, a recent study by Groop et al. investigated the association between polymorphisms of the glycogen synthase gene and the associated risk of developing Type 2 diabetes (Groop et al. 1993). These investigators found two polymorphic alleles (A_1 and A_2) in this gene located on chromosome 19. Moreover, they documented a twofold greater prevalence of hypertension among subjects without diabetes who had the A_2 allele expressed. Unfortunately, no such distinction was noted in the group studied with diabetes. Note, however, that among the group with diabetes, both the A_1 and A_2 allelic groups had hyperinsulinemia and were hypertensive. Taken together, these studies provide evidence that supports the concept that a different "genetic load" is required for the development of either hypertension or diabetes. Specifically, each of these disorders appears to be inherited in a polygenic (i.e., to involve more than one gene) and heterogeneous (involving different constellations of disease genes in different persons) fashion. Since hypertension does not develop in all people with diabetes, the presence of certain environmental factors, i.e., diet, sedentary lifestyle, high salt intake, etc., are mostly required to express the concomitant generation of both diseases.

Goals of Blood Pressure Treatment

For many years, most guidelines in the Western world uniformly recommended two blood pressure (BP) goals, <140/90 mmHg for the general population and <130/80 mmHg for those with diabetes or chronic kidney disease (CKD) (Chobanian et al. 2003; Mancia et al. 2007a). More recent guidelines like those from the Expert Panel Report (also called JNC 8) took a purely evidence-based approach to blood pressure guidelines and recommended a goal blood pressure of <140/90 in patients with diabetes (James et al. 2014). The 2016 ADA Standards of Medical Care in Diabetes supported this recommendation stating that a systolic blood pressure <140 mmHg is appropriate in most patients and the diastolic blood pressure should be treated to <90 mmHg (Standards of Medical Care in Diabetes-2016).

Meta-analyses of all clinical trials, to date, demonstrate that reducing BP reduces risk for stroke and coronary heart disease. However, almost all prospective studies in patients with diabetes have not achieved a mean BP goal of <130/80 mmHg (Staessen et al. 2005). Moreover, no trial was powered to detect a difference between two BP goals for kidney disease progression, hence, there are no trials in diabetes patients with kidney disease that fully support a BP level of <130/80 mmHg. This lack of lower BP goal achievement is even true in CVD outcome trials of diabetes (Table 1).

In trials like the United Kingdom Prospective Diabetes Study (UKPDS) (UKPDS Group 1998) and the Hypertension Optimal Treatment Trial (HOT) (Hansson et al. 1998), the systolic BP was more than 10 mm of mercury higher than this lower goal. Note also that HOT had a diastolic goal set but only a fraction of the patients had diabetes. In the post hoc analysis of HOT, the lower diastolic goal of 80 mmHg did result in few CVD events but at best was hypothesis generating. Nevertheless, a benefit occurred on CVD reduction. One prospective study that achieved this lower

Table 1 Achieved blood pressure values from clinical outcome trials with cardiovascular outcomes involving patients with diabetes

Clinical outcome trial	Achieved level of systolic BP (mmHg)
ACCORD (primary)	119 (intensive); 133 (conventional)
UKPDS (primary)	144 (intensive); 154 (conventional)
ACCOMPLISH (secondary)	Overall mean 133
INVEST (secondary)	144 (tight);149 (conventional)
ONTARGET (secondary)	Averaging around 140
VADT (secondary)	127 (intensive);125 (conventional)
ADVANCE (secondary)	145 (in both intensive and conventional glucose control)

Note: Intensive and conventional refer to glycemic control NOT blood pressure

BP goal in patients with diabetes and no overt nephropathy was the Appropriate Blood Pressure Control in Diabetes (ABCD) trial (Estacio et al. 2000). This trial demonstrated reduced CV risk, but there was no difference between the groups with a mean systolic pressure of 138 mmHg versus the intensive group at 132 mmHg. Note, however, that this trial was underpowered for a BP goal outcome.

The ACCORD trial thus provides a more definitive answer, albeit still weak because not statistically powered to assess BP differences on CV outcomes compared to conventional BP control (Accord Study Group et al. 2010). This prospective randomized trial demonstrated a separation of mean systolic blood pressure of 14 mmHg (133 mmHg vs. 119 mmHg). In spite of this sustained difference in blood pressure for more than 4 years, there was no additional benefit on the primary endpoint, i.e., CV events. There was a reduction, however, on stroke events, albeit, at a cost of a higher side effect profile from medications. Longer-term follow-up of ACCORD demonstrated a significant interaction between the powered portion of the trial, i.e., glycemic control such that an analysis of the blood pressure groups in this context did show a CVD risk reduction at the lower BP goal of 120 mmHg (Margolis et al. 2014).

Post hoc analyses of the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) and International Verapamil SR – Trandolapril Study (INVEST) demonstrate, however, that the benefit of lower levels of blood pressure on CV risk reduction is lost when systolic BP levels fall below 130 mmHg (Cooper-DeHoff et al. 2010; Sleight et al. 2009). INVEST further demonstrated an increase in CV events at systolic blood pressures <115 mmHg, although 100% of these patients had coronary artery disease (Cooper-DeHoff et al. 2010). A review of all trials in patients with diabetes including the ACCORD trial made it clear that blood pressure reduction to levels below 140/90 mmHg are associated with fewer CV events; however, there is less data to support below 130/80 mmHg (Accord Study Group et al. 2010).

The systolic blood pressure intervention (SPRINT) trial which randomized over 9000 subjects to a blood pressure of less than 120 versus less than 140 mmHg challenge the most recent blood pressure guidelines. Although none of the subjects had diabetes, they all had at least one risk factor for cardiovascular disease. The trial was stopped early because of the significant reduction in the primary composite

outcome of myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes in the intensively treated blood pressure group compared to the standard group (SPRINT Research Group et al. 2015).

A number of recent meta-analyses have specifically compared studies in both cohorts with and without diabetes. In general, there is a consensus that BP in the range below a systolic of 130 mmHg is associated with fewer CVD events in diabetes compared to levels below 140 mmHg (Emdin et al. 2015; Perkovic and Rodgers 2015; Xie et al. 2016). Hence, in the first quarter 2016 update of UpToDate, we expanded our evidence-based approach to guideline BP ranges based on confidence intervals from trials that evaluated CVD outcomes and concluded that a systolic range of 125–130 mmHg is appropriate for people who can tolerate it to achieve maximal CVD risk reduction from BP. Please note that people with diastolic BP below 60 were not included in any of these trials. Thus, in those with large pulse pressures the reduction in SBP should also be guided by the magnitude of diastolic pressure reduction such that levels in patients without angina do not fall below 60 mmHg, as this has been associated with higher CV risk as well as a higher incidence of progression to dialysis among nephropathy patients (Peralta et al. 2012; Bangalore et al. 2010; Kjeldsen et al. 2016).

A substantial amount of epidemiological and post hoc analyses clinical trial data supports the notion that the presence of diabetic nephropathy manifested by proteinuria above 300 mg/day is associated with higher cardiovascular event rates (Ibsen et al. 2004; So et al. 2006). Moreover, all studies among patients with diabetes indicate that proteinuria reduction of >30% within the first 6–12 months of BP-lowering therapy reduces cardiovascular events and development of heart failure as well as slows kidney disease progression (Berl et al. 2005; de Zeeuw et al. 2004). Taken together, this data supports the notion that treatment of blood pressure in people with diabetes must focus not only on achievement of BP goal but also reducing proteinuria, if present. This recommendation is also consistent with the Kidney Disease Improving Global Outcomes (KDIGO) guidelines to achieve a BP <130/80 mmHg in such patients. Thus, as suggested by guidelines, all patients with diabetes should be evaluated for albuminuria at least once annually (National Kidney Foundation 2007). Antihypertensive agents found to maximally reduce proteinuria when blood pressure is reduced include blockers of the renin angiotensin Aldosterone System (RAAS) either alone or combined along with nondihydropyridine calcium channel blockers (CCBs) (National Kidney Foundation 2007; Sarafidis et al. 2007a).

Effect of Antihypertensive Agents on Diabetes

The different medications used in the treatment of hypertension can have variable metabolic effects. This should be considered when prescribing and monitoring diabetic patients. Since the publication of JNC 7, several important observations regarding BP management and glycemic control in patients with diabetes are now apparent. First, post hoc analyses of two different cardiovascular outcome trials note that even though diuretics worsen glycemic control, cardiovascular event rates were

not higher (Kostis et al. 2005; Whelton et al. 2005). Specifically, a post hoc analysis of the Systolic Hypertension in the Elderly Program (SHEP) notes that worsening of glycemic control with diuretics did not result in a reduced long-term benefit of thiazide-type diuretic (chlorthalidone) induced lowering of systolic pressures on cardiovascular risk (Kostis et al. 2005). Additionally, an analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) subgroup with diabetes failed to show a higher cardiovascular event rate in the diuretic group even though they had the greatest worsening of glycemic control (Whelton et al. 2005).

While these trials do not answer the question fully as these were post hoc analyses and patients followed only over a limited period of time. A more recent study with over a decade of follow-up from the ALLHAT demonstrates that those randomized to chlorthalidone who developed diabetes and were treated had similar CVD outcomes to those who did not develop diabetes (Barzilay et al. 2012). Further, the impact of drug-induced increases in diabetes incidence on microvascular diseases such as retinopathy and nephropathy, although not systemically studied, are likely substantial.

Many post hoc analyses, however, uniformly demonstrate that diuretics and beta blockers not only worsen glycemic status among those with diabetes but also increase development of new onset diabetes in those with impaired fasting glucose (Elliott and Meyer 2007; Mancia et al. 2006; Sarafidis and Bakris 2006a). Hence, they increase the number of medications taken and need for more frequent physician visits. Both thiazide and thiazide-like diuretics, through hypokalemia and other mechanisms related to increased visceral adiposity (Carter et al. 2008), and vasoconstricting β-blockers worsen insulin sensitivity (Sarafidis et al. 2007b); exceptions to this statement include the newer vasodilating β-blockers, such as carvedilol and nebivolol. These vasodilating agents have neutral effects on glycemic control and increase insulin sensitivity (Bakris et al. 2004; Kaiser et al. 2006; Sarafidis and Bakris 2006b).

Angiotensin-converting enzyme (ACE)-inhibitors, angiotensin II receptor blockers (ARBs), and calcium channel blockers (CCBs) have beneficial or neutral effects on insulin sensitivity and glycemic control (Sarafidis and Bakris 2006a; Sarafidis et al. 2007b; DREAM Trial Investigators et al. 2006). Note also that renin-angiotensin system (RAS) blockers administered concomitantly with thiazide diuretics do not prevent worsening of glycemic control in obese people with impaired fasting glucose (Bakris et al. 2006). These data, taken together with the findings of a meta-analysis by the blood pressure trialists (Blood Pressure Lowering Treatment Trialists Collaboration et al. 2008) indicate that since it is BP lowering and not the class of antihypertensive agent used that reduces cardiovascular events, one should use antihypertensive agents that do not worsen preexisting metabolic conditions.

Approach to Treatment

To achieve a blood pressure goal, the cornerstone of therapy is lifestyle modification with a focus on reduced sodium intake and good sleep hygiene of at least 6 h of uninterrupted sleep a night (Hwang et al. 2015; Liu et al. 2016). Additional lifestyle

changes include weight loss, increase in physical exercise, reduction of alcohol intake, smoking cessation, and, perhaps most importantly, low sodium intake to levels below 2.4 g per day. Low salt intake should be encouraged through appropriate dietary counseling and encouragement by the physician and staff (Table 2). The differential effects of sodium restriction in different patient groups are, in part, related to their RAAS activity, the lower the renin state the less likely a low sodium diet will help lower pressure (He et al. 2001).

A high potassium diet in those who have an estimated glomerular filtration rate above 45 ml/min/1.73m^2 can help counteract the blood pressure raising effects of high salt intake (Sebastian et al. 1999). Failure to achieve a serum potassium level of at least 3.8 mEq/L will also blunt the antihypertensive activity of agents due to sustained vasoconstriction at low levels of potassium (Adrogue and Madias 2007). In addition to diet changes, patients should be educated on the importance of maintaining weight range that is below the obesity level and ideally closer to BMI <26 (Appel et al. 2006). Most clinical trials support the notion that weight loss results in blood pressure reduction (Neter et al. 2003; Stevens et al. 2001; Knowler et al. 2002).

Additionally, the American Diabetes Association guidelines should also be followed to optimize glycemic control (Standards of Medical Care in Diabetes-2016). This is important especially for morbidity reduction, i.e., reduction of neuropathy and blindness. While mortality reduction is associated with good glycemic control the level to which glucose needs reduction appears to be higher than previously thought.

The ACCORD trial tested whether a lower level of glucose, defined as a HbA1c <6.5%, would result in a lower cardiovascular event rate was stopped early by the Data Safety Monitoring Board secondary to a higher cardiovascular event rate in the lower glucose control group (Action to Control Cardiovascular Risk in Diabetes Study Group et al. 2008). Similarly, the advance trial did not show any improvement in cardiovascular outcome with aggressive treatment of glycated hemoglobin to less than 6.5% (Advance Collaborative Group et al. 2008). This study did show a 20% reduction in new onset nephropathy with aggressive glycemic treatment, however.

Table 2 Lifestyle modifications to prevent and manage hypertension[a]

Weight reduction	Maintain normal body weight (body mass index 18.5–24.9 kg/m^2)
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride)
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min per day, most days of the week)
Moderate alcohol use	Limit consumption to no more than 2 drinks (e.g., 24 oz. beer, 10 oz. wine, or 3 oz. 80-proof whiskey) per day in most men and to no more than 1 drink per day in women and lighter weight persons

DASH dietary approaches to stop hypertension

[a]Adopted from the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Chobanian et al. 2003)

Thus, the guideline put forth by the American Diabetes Association of an HbA1c of <7% appears to be the one that would provide the greatest cardiovascular risk reduction along with BP reduction.

In addition to the lifestyle measures, all patients with diabetes with a sustained BP ≥ 140/90 mmHg should be started on antihypertensive medication. It is critically important to reduce BP to levels well below 140/90 mmHg regardless of medication class. Current guidelines recommend initial treatment with an angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), calcium channel blocker (CCB), or thiazide-like diuretic. If, within a month after monotherapy titration, the BP goal is not achieved, then either a CCB, e.g., amlodipine or a low dose thiazide-like diuretic like 1.25 mg of indapamide or 12.5 mg chlorthalidone (found only in combination with the ARB, azilsartan) may be tried. Note that the CCB/ACE inhibitor combination was found to provide significantly greater reduction in CV events in people with diabetes compared to an ACE inhibitor diuretic combination (Weber et al. 2010, 2013). Additionally, chlorthalidone and indapamide are effective for BP lowering down to an eGFR of 30 ml/min/1.73m^2 (Agarwal et al. 2014). In the case of a patient with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m^2, the thiazide-like diuretic should be replaced by a long acting loop diuretic in adequate doses, e.g., once daily torsemide starting at 5 or 10 mg daily.

If the initial blood pressure is more than 20/10 mm Hg above goal, then *two agents* with complementary mechanisms should be started (Gradman et al. 2010). Blood pressure should be monitored every week at home and a return to the office with those readings in 1 month. If blood pressure remains elevated on *two* agents, then consider either titrating or adding a third agent, Fig. 1. The 4th antihypertensive medication recommended is a mineralocorticoid antagonist or if not tolerated or risk of hyperkalemia, a vasodilating beta-blocker such as carvedilol or nebivolol, which has a better tolerability profile and less metabolic consequences and little to no weight gain compared to older agents (Action to Control Cardiovascular Risk in Diabetes Study Group et al. 2008; Advance Collaborative Group et al. 2008).

In patients with asthma, diltiazem or in some cases verapamil are very good alternative (Weber et al. 2010). Other alternative 4th or 5th-line agents include an aldosterone receptor blocker or a CCB from a different subclass than is already being used, e.g., diltiazem added to amlodipine. Two randomized trials clearly showed additive BP lowering effects when low doses of these two subclasses are combined (Gradman et al. 2010; Saseen et al. 1996). Since no difference in cardiovascular outcomes has been noted between antihypertensive agents if BP is appropriately lowered, this approach mitigates against worsening of metabolic control and is in concert with both the Expert Panel Report and the 2013 European Guidelines (James et al. 2014; Mancia et al. 2007b).

Recent data do *not* support older concepts that high albuminuria (formerly microalbuminuria) is synonymous with kidney disease. However, high albuminuria is a CVD risk marker in some cases as good as C-reactive protein (Bakris and Molitch 2014). Thus, routine annual measurement of albuminuria is important as it is a CV risk marker and indicates inflammation but also a rise into the very high

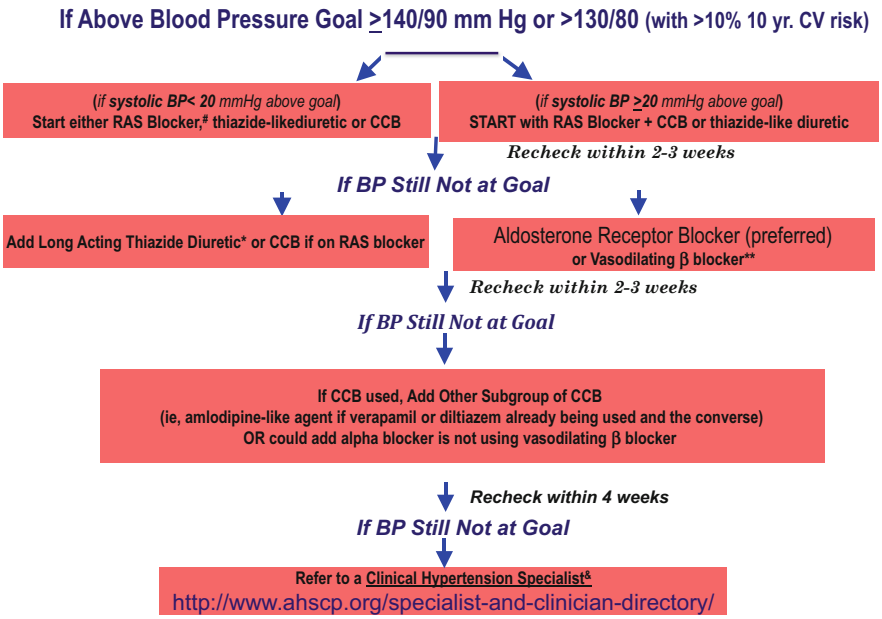

Fig. 1 American Society of Hypertension Algorithm for BP management in diabetes. *Thiazide-type diuretic is chlorthalidone or indapamide; **refers to either carvedilol or nebivolol. (Note: Ratio of beta:alpha is 7:1 for labetolol and 3:1 for carvedilol, hence, carvedilol is more balanced). #Must start with ACE inhibitor or angiotensin receptor blocker (ARB)-collectively known as renin angiotensin system (RAS) blockers if >300 mg/day albuminuria. &Website for hypertension specialists http://www.ahscp.org/specialist-and-clinician-directory/- (Bakris GL, Sowers JR (2008) ASH position paper: treatment of hypertension in patients with diabetes-an update. J Clin Hypertens (Greenwich) 10:707–713 and de Boer IH, Bangalore S, Benetos A, Davis AM, Michos ED, Muntner P, Rossing P, Zoungas S, Bakris G (2017) Diabetes and hypertension: a position statement by the American Diabetes Association. Diabetes Care 40(9):1273–1284)

albuminuria range, i.e., >300 mg/day indicates nephropathy (Bakris and Molitch 2014). Nevertheless, most guidelines prefer a once daily RAS blocker with dose maximized within the first month as an initial antihypertensive as it is relatively low on side effects and efficacies. Whether choosing an ACE inhibitor or an ARB, dosage should be titrated to the highest tolerated dose necessary for BP to reach goal.

The Food and Drug Administration issued a guidance in 2011 that all ARBs should be started at the maximal dose since they have no dose-dependent side effects. If an ACE inhibitor is started and the side effect of cough appears, treatment should be changed to an appropriate dose of an ARB. Note the mean incidence of cough from ACE inhibitors is 20% and more than double that in the Asian population.

RAS blockers have demonstrated positive effects on the development of metabolic conditions. A study of 53 premenopausal females that were treated with RAS blockade or placebo found higher levels of plasma adiponectin in subjects treated with RAS blockade. Adiponectin is an adipokine that has beneficial effects in

obesity-associated conditions (Flynn and Bakris 2011). This study also found that the insulin sensitivity of subcutaneous and omental adipocytes was better in the RAS blockade-treated subjects (Tian et al. 2010).

A common problem among people with diabetes and kidney disease with RAAS blockers is hyperkalemia. People most prone to develop hyperkalemia includes everyone regardless of diabetes status with an eGFR <45 ml/min/1.73m^2 and/or a serum potassium of >4.5 mEq/L already receiving an appropriately dosed diuretic (Lazich and Bakris 2014). There is no substitute or guide for good clinical judgment, however, for any given patient. Therefore, in anyone meeting these criteria it is important before initiating RAS-blocking therapy, to review all high potassium containing foods and substances as well as over the counter agents that cause hyperkalemia such as NSAIDs must be discussed. Observational data support reductions of up to 0.6 mEq/L in serum potassium can be achieved just by following these lifestyle interventions. Under a circumstance when potassium levels are elevated, use of loop diuretics may be appropriate twice daily to enable use of RAS-blocking agents or use of the newly approved potassium binding agents, patiromer or ZS-9. Both of these potassium binders are far better tolerated than sodium polystyrene and are once daily preparations (Bakris et al. 2015; Kosiborod et al. 2014).

While there are no cardiovascular outcome data in patients with relatively high potassium levels, post hoc analyses that primarily evaluated kidney disease progression among those with GFR values of <50 ml/min show a reduction in cardiovascular events and surrogate risk factors for CV risk among those with diabetes (Berl et al. 2005; Lewis et al. 2001).

Minimization of the number of antihypertensive pills improves patient adherence and effectiveness of lowering BP (Gerbino and Shoheiber 2007; Bangalore et al. 2007). Thus, conversion of the full combination treatment to a single pill combination of RAS blocker/diuretic or RAS blocker/CCB should be given strong consideration. Combinations of an ACE inhibitor and ARB while further reducing proteinuria (Knowler et al. 2002) are contraindicated for BP lowering in patients with diabetic nephropathy (Mann et al. 2008; Parving et al. 2012) as they did not reduce mortality and increased risk of acute kidney injury (Stevens et al. 2001). The American Society of Hypertension Consensus report of Combination Therapies is summarized in Table 3.

The role of aldosterone blockade as a fourth line strategy is very important in patients with diabetes and obesity. Individuals with obstructive sleep apnea and central obesity have demonstrated major benefits in BP reduction with the use of aldosterone antagonism (Pratt-Ubunama et al. 2007; Calhoun et al. 2008). In a study of 76 patients with uncontrolled BP on an average of four medications, including an ACE inhibitor or ARB and a thiazide diuretic addition of spironolactone (12.5–25 mg daily) resulted in an average 25 mmHg reduction of SBP and 12 for DBP after 6 months of follow-up (Nishizaka et al. 2003). Reductions in BP were similar in African American and Caucasian individuals. Moreover, the BP lowering response was not predicted by baseline plasma aldosterone, 24-h urinary aldosterone, plasma renin activity, or plasma aldosterone/renin ratio.

Table 3 Evidenced-based fixed-dose antihypertensive combinations

Preferred
• ACE inhibitor/diuretic[a]
• ARB/diuretic[a]
• ACE inhibitor/CCB[a]
• ARB/CCB[a]
Acceptable
• Beta blocker/diuretic[a]
• CCB (dihydropyridine)/β-blocker
• CCB/diuretic
• Renin inhibitor/diuretic[a]
• Renin inhibitor/ARB[a]
• Thiazide diuretics/K+ sparing diuretics[a]
Less effective
• ACE inhibitor/ARB
• ACE inhibitor/β-blocker
• ARB/β-blocker
• CCB (nondihydropyridine)/β-blocker
• Centrally acting agent/β-blocker

Note: Less effective combinations do not further lower BP and can create dangerous situations with very low heart rates or increased risk for acute kidney injury
[a]Indicates single pill combinations

The BP-lowering effects of aldosterone receptor blockade were confirmed in a report of 1411 participants in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)-Blood Pressure Lowering Arm, unselected for plasma aldosterone and plasma renin activity. They received spironolactone mainly as a fourth-line antihypertensive agent for uncontrolled BP on an average of three drugs (Chapman et al. 2007). Use of spironolactone was again associated with a BP drop of 21.9/9.5 mmHg, that was largely unaffected by factors like age, sex, smoking, and diabetic status. Recent data in obese patients demonstrates that the adipocyte releases substances that increase aldosterone and this may be the reason for this observation (Krug and Ehrhart-Bornstein 2008). Given the benefits of aldosterone blockade in these individuals and those with sleep apnea, one is reminded of hyperkalemia as a limiting factor in their use (Pratt-Ubunama et al. 2007; Chapman et al. 2007). The reader is referred to this chapter's discussion on this topic.

The SGLT2 inhibitors are a relatively new class of agents used to control blood sugar in diabetes mellitus and they also have the added benefit of blood pressure lowering. The SGLT2 transporter mediates glucose reabsorption in the proximal tubule and it regulates 90% of all glucose reabsorption by the kidney (Scheen 2015a). The SGLT2 inhibitors act by competitive and selective inhibition of the SGLT2 transporter. Patients with type 2 diabetes mellitus overexpress SGLT2 receptors, a compensatory mechanism to try and remove more glucose through the urine. Use of these medications decreases the renal glucose threshold leading to an increase in urinary glucose excretion. The glycosuric effect also leads to some

weight loss and a reduction in blood pressure, due to the mild natriuretic and osmotic diuretic effects.

The average BP reduction with these agents is 4–5 mmHg systolic pressure and the newer combined SGLT2/SGLT1 inhibitor averages almost double in this BP reduction. The mechanism for BP reduction is unknown but probably multifactorial and is reviewed elsewhere (Oliva and Bakris 2014).

These medications have been used safely in patients with Stage 3 (estimated glomerular filtration rates (eGFR) down to 30 ml/min) chronic kidney disease (CKD). However, the glycemic reduction response to the SGLT2 inhibitors declines with decreasing kidney function because a decrease in eGFR results in a decrease in urinary glucose excretion (Scheen 2015b). The FDA has approved canagliflozin and empagliflozin for use down to eGFR of 45 ml/min/1.73m^2, whereas dapagliflozin is approved down to 60 ml/min/1.73m^2. Studies with canagliflozin show clear benefit on BP and eGFR down to eGFR of 30 ml/min/1.73m^2 (Yamout et al. 2014).

Due to this reduced glycemic control based on level of kidney function, further studies have attempted to determine the renal effects of SGLT2 inhibitors. Ojima et al. treated streptozocin-induced diabetic rats with the SGLT-2 inhibitor empagliflozin for 4 weeks. In addition to improving blood glucose levels, the rats treated with empagliflozin had decreased levels of markers of oxidative stress in the diabetic kidney. Specifically, levels of advanced glycation end products (AGE) and receptor advanced glycation end products (RAGE) were significantly lowered (Ojima et al. 2015).

Hyperfiltration is considered an early marker of risk for diabetic nephropathy and is associated with abnormally high plasma glucose levels (Jerums et al. 2010). Experimental animal models using phlorizin, a nonspecific inhibitor of SGLT1 and SGLT2, demonstrate a restoration of tubuloglomerular feedback that is altered in renal hyperfiltration (Malatiali et al. 2008). Due to the poor tolerability of phlorizin in humans, the effects of this drug on renal hyperfiltration are not known. Now that the more specific SGLT2 inhibitors are available, Cherney et al. investigated the effects of empagliflozin 25 mg daily on renal hyperfiltration in patients with type 1 diabetes mellitus (Cherney et al. 2014). Forty subjects completed the study, 13 with normal filtering kidneys, and 27 with renal hyperfiltration. The subjects were treated with empagliflozin for 8 weeks. In the subjects with renal hyperfiltration, treatment with empagliflozin for 8 weeks resulted in a significant reduction in hyperfiltration during both clamped euglycemic and hyperglycemic conditions (Cherney et al. 2014).

Changes in tubuloglomerular feedback examined by Cherney relate to the natriuretic effects of the SGLT2 agents and wane over time as a new level of glucose homeostasis is achieved. Another factor important in assessing volume status in diabetes that is affected in animal models of diabetes is atrial natriuretic peptide (ANP) (Ortola et al. 1987). Diabetes is a volume-expanded state for many reasons and hence, a compensatory increase in ANP is well documented. ANP results in suppression of the renin angiotensin system and contributes to hyperfiltration. Animal studies demonstrate that phlorizin through its osmotic diuretic and natriuretic effects reduces ANP and reestablishes a new volume status in animals over

two to three days (Thomson et al. 2012). This improvement in volume also contributes to reductions in blood pressure (Oliva and Bakris 2014; Baker et al. 2014).

A dual SGLT1 and SGLT2 inhibitor, sotagliflozin, is another emerging therapy for treating patients with diabetes mellitus. SGLT1 is the major transporter for the absorption of glucose and galactose in the intestine (Wright et al. 2011). SGLT1 knockout mice have demonstrated a dramatic reduction in postprandial glucose. Also, these knockout mice had an increase in glucagon-like peptide 1 (GLP-1) by L-cells which is involved in glucose control (Powell et al. 2013). Inhibiting SGLT1 has also been demonstrated to stimulate the release of polypeptide tyrosine tyrosine (PYY), which is involved in appetite control (Powell et al. 2013). These knockout mice had watery or unformed stools when fed a diet of glucose or galactose. However, mice with a partial knockout of SGLT1 had normal stools when fed glucose but still maintained an increase in glucose load to the distal small intestine with a rise in GLP-1 (Powell et al. 2013). These animal studies suggest the dual SGLT1/SGLT2 inhibitor may provide even more powerful reductions in glucose and weight as well as blood pressure in patients with type 2 diabetes.

In order to investigate the effects of sotagliflozin in patients with renal impairment, 31 patients with type 2 diabetes mellitus and a GFR of 15–59 mL/min/1.73 m^2 were randomly assigned to sotagliflozin or placebo. There was a significant reduction in postprandial glucose on day 7 in the sotagliflozin compared to placebo group. Of those patients with a GFR <45 mL/min/1.73 m^2, the magnitude of the effect on postprandial glucose was maintained. There was also a significant reduction in systolic blood pressure in the treatment group compared to placebo after 7 days (Zambrowicz et al. 2015). These studies show promising results of a new agent to use in the management of patients with diabetes.

In cardiovascular outcome trials among patients with hypertension, the proportion of participants achieving BP goals is roughly double that of clinical practice. An assessment of the subgroup with diabetes in these outcome trials over the past decade indicates that an average of 2.9 appropriately dosed antihypertensive medications are required to achieve BP goals. Among persons with diabetes and preexisting kidney disease, Stage 3 or higher, this average increases to about 3.5 medications (Chua and Bakris 2004). Thus, a key tenet in the approach to achieve BP goal in patients with diabetes is to select agents for maximal efficacy and tolerability that have the fewest side effects and, if possible, cost.

Summary

Patients with diabetes and hypertension have an increased risk of cardiovascular disease and death from cardiovascular disease. It is important to treat both the elevated blood sugars and elevated blood pressure in these patients. The agents used to treat the hypertensive patient with diabetes are important to both lower blood pressure and improve kidney outcomes, and to use agents that do not adversely affect metabolic outcomes.

Use of antihypertensive agents as well as glycemic control and lipid control are critical in these patients to maximally reduce cardiovascular events. Only the SGLT2 inhibitors have thus far shown CVD risk reduction and many other new classes or glucose-lowering agents have proven no harm on CVD events. Moreover, BP lowering and lipid control show the greatest benefit in the shortest time i.e., 3–5 years in regard to reducing CVD risk and slowing of CKD progression. Glycemic control takes an average of 10–12 years to see benefits on CVD risk and CKD progression. Lastly, there is no "legacy effect" of glucose of BP control on CVD events but apparently it does exist for glycemic control.

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