Hypertension in diabetes and the risk of cardiovascular disease

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Hypertension (HTN) is an important risk factor for cardiovascular disease and its many manifestations. It shares pathogenic pathways with diabetes and is part of a common metabolic entity, the metabolic syndrome. When combined with diabetes, HTN has been shown to predict and promote increased risk for cardiovascular disease events over and above each risk factor alone. Of the components of this metabolic syndrome, HTN is relatively easy to diagnose and thereby more accessible for implementing preventive and treatment strategies. The recent release of Joint National Committee-8 guidelines for the treatment of HTN has fueled a debate on treatment target goals. *Cardiovasc Endocrinol* **6:33–38**

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Introduction

Blood pressure (BP) is the driving force of the circulatory system. William Harvey, physician to Charles I, was the first to accurately describe how the blood circulates through the human body in his 1628 work 'De Motu Cordis' (also known as 'On the Motion of the Heart and Blood') [1]. The first published measurement of BP was by clergyman Stephen Hales in 1733 [2]. The pioneering works of Thomas Young, Richard Bright, Moahomed, and Sir Clifford Allbutt established hypertension (HTN) and its association with kidney, heart, and neurological manifestations [2]. The definition of essential HTN as a clinical entity was more firmly established, however, only after the development of noninvasive methods for measuring BP. At the beginning of this century, RivaRocci's sphygmomanometer facilitated systolic blood pressure (SBP) measurement noninvasively and Nicolai Korotkoff's description of Korotkoff sounds facilitated measurement of diastolic blood pressure (DBP) and SBP [2,3].

Systemic arterial HTN is the condition of persistent, nonphysiologic elevation of systemic BP. It is currently defined as a resting SBP of at least 140 mmHg or DBP (DBP) of at least 90 mmHg or receiving therapy for the indication of lowering BP [4]. Historically, HTN (BP $\geq$ 140/90 mmHg) was believed to be the major driver of risk for cardiovascular disease (CVD) [5], but BP levels between 120 and 139/80 and 89 mmHg (pre-HTN) are not only more prevalent but also increase cardiovascular (CV) risk [6]. Compared with many other risk factors for stroke, acute myocardial infarction, and heart failure, HTN is among the simplest to diagnose, has the widest variety of treatment options, and (particularly in high-risk individuals) is the most cost-effective preventive strategy [4,7,8]. Because of its high prevalence in the USA [9], HTN ranks first among the chronic conditions for which Americans visit a healthcare provider. One of the major reasons for the impressive reduction in age-adjusted stroke mortality (~62%) and coronary heart disease mortality (~45%) in the USA since 1972 is the widespread acceptance of the need to treat HTN and our increased ability to reduce BP effectively [10].

Diabetes mellitus (DM) is a known risk factor for CVD [11]. HTN and DM are frequently coexisting entities, causing more damage than each alone. This coexistence may be linked to a combination of genetics, common metabolic pathophysiologic pathways, and environmental factors. Epidemiologic studies have shown that DM patients are twice as likely to develop HTN relative to those without DM and, conversely, patients with HTN are at a 2–3 times higher risk of developing DM compared with normotensive patients [12,13]. The presence of both increases CVD risk relative to either HTN or DM alone.

Epidemiology

HTN is a common problem in patients with both type 1 and type 2 diabetes; however, the time course of association is different [14,15]. In type 1 diabetics, the incidence of HTN increases progressively with age from 5% at 10 years to 70% at 40 years and is closely associated with albuminuria. In a study of 981 patients who had type 1 diabetes for 5 or more years, HTN was present in 19% of patients with normoalbuminuria, 30% with moderately increased albuminuria, and 65% with severely increased albuminuria [15]. The incidence of HTN eventually reaches 75–85% in patients with progressive diabetic

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nephropathy [16]. The risk of HTN is highest in Blacks, who are also at a much higher risk for renal failure because of diabetic nephropathy.

Among type 2 diabetics, 39% already have HTN when newly diagnosed with diabetes. In approximately one-half of these patients, the elevation in BP occurred before the onset of moderately increased albuminuria. HTN was strongly associated with obesity and the HTN patients were at an increased risk for CV morbidity and mortality [17]

There is considerable overlap between diabetes and HTN, reflecting marked overlap in their etiology and disease mechanisms. In the Hong Kong Cardiovascular Risk Factor Prevalence Study, only 42% of patients with diabetes had normal BP and only 56% of patients with HTN had normal glucose tolerance [18,19]. In the USA population, HTN occurs in ~30% of patients with type 1 diabetes and in 50–80% of patients with type 2 diabetes [20]. 2013–2014 CDC data indicate the prevalence of HTN in adults ages 20 and older in the USA at 33.5%, increased from 30.9% reported previously [9]. 76 million USA adults are estimated to have HTN; this number is expected to increase over the next few decades because of the current pandemic of obesity and aging of the population [13].

African Americans, and especially African American women, have a prevalence of HTN that is among the highest in the world. Currently, it is estimated that 38.6% of African American adults have HTN compared with 32.3% of non-Hispanic Whites and 17.3% of Mexican Americans [21,22]. Asian Americans and most other ethnic groups tend to have similar BP levels and HTN prevalence as Whites. The prevalence of HTN increased to a similar extent in all ethnicities during the decade of the 1990s. Prevalence rates are similar between men and women, but they increase considerably with age, from 7.4 to 35.6 to 69.7%, among those aged 18 to 39, 40 to 64, and of at least 65 years, respectively [23].

The prevalence of HTN and DM is increasing worldwide. 972 (26%) million individuals are estimated to have HTN globally and 29.1 million in the USA [24]. WHO estimates the number to increase by 60% to 1.56 billion by 2025 [25]. DM affects estimated 360 million individuals, with predicted 552 million adults affected by 2030 [26]. A number of factors, in addition to HTN, contribute toward the high prevalence of CVD in type 2 diabetic persons. 5000 patients were followed for 12 years in the MRFIT trial and we learned that the occurrence of CVD was up to three times more in diabetic men than non-diabetic controls, irrespective of systolic pressure, age, cholesterol, ethnic group, or use of tobacco. This study also confirmed that systolic HTN, elevated cholesterol, and cigarette smoking were independent predictors of mortality and that the presence of at least one of these risk factors had a greater impact on increasing CVD mortality in patients with diabetes than in those without diabetes [27].

Pathophysiology

Environmental, behavioral, and genetic factors interplay in causing the various components of metabolic syndrome, of which diabetes and HTN are important components. Multiple genes with small associations have been reported to be associated with diabetes and HTN, including, but not limited to, genes encoding angiotensinogen, adrenomedullin, apolipoprotein, and α-adductin, to name a few. Interestingly, in studies in Chinese women, single nucleotide polymorphisms that predict the development of diabetes were also found to predict the development of HTN [28].

Environmental factors predisposing a fetus to cardiometabolic syndrome in adulthood include the period in utero, high birth weight, gestational diabetes, and fetal malnutrition [29,30]. Later in life, high intake of sodium, alcohol, unsaturated fat, smoking, lack of physical activity, and mental stress are examples of an unhealthy lifestyle predisposing to the cardiometabolic syndrome. HTN and diabetes considerably share common pathways such as obesity, inflammation, oxidative stress, insulin resistance, and mental stress [19]. Obesity is one of the most important risk factors for HTN and diabetes [31]. Obesity is determined by genetic and environmental factors and represents an imbalance between energy intake and expenditure and genetic variations [28]. Currently, more than one-third (36.5%) of USA adults have obesity and the estimated annual medical cost of obesity was 147 billion dollars in 2008 [32]. Obesity, especially central, has been shown to be associated with a low-grade inflammatory process [33,34]. This inflammatory process is shown to predispose to insulin resistance [35–37]. A low-grade inflammatory process occurs in both diabetes and HTN [38]. Even chronic periodontitis is a latent factor in the development of diabetes, HTN, CVDs, and the metabolic syndrome [39,40]. In this meta-analysis of a total of 19 000 patients, there was a significant dose–response association of interleukin-6 levels and C-reactive protein with the risk of type 2 diabetes [41]. These markers, in addition to adhesion molecules such as vascular cell adhesion molecule – 1, cellular adhesion molecule – 1, and chemokines, are shown to be associated with an increased risk of HTN [42].

Insulin resistance occurs when normal levels of insulin do not trigger the signal for glucose absorption, indicating an impaired response to insulin in skeletal muscle, liver, adipose, and CV tissue [43,44]. Insulin resistance arises because of various genetic, acquired, and environmental factors, including obesity [45]. Increased renin angiotensin sympathetic system axis activities may also cause insulin resistance by the stimulation of angiotensin II type 1 receptors, which trigger increased production of reactive oxygen species in adipocytes, skeletal muscle,

and CV tissue of obese individuals [46]. Insulin resistance is a prothrombotic state characterized by an elevation of PAI-1 and fibrinogen levels, leading to an increased risk of CV events [47]. Insulin resistance may be the result of an overproduction of proinflammatory cytokines (e.g. interleukin-6, tumor necrosis factor, and C-reactive protein) and a relative deficiency of anti-inflammatory cytokines (e.g. adiponectin) [48]. Most patients with type 2 diabetes are insulin resistant and about half of those with essential HTN are insulin resistant [49,50]. Therefore, insulin resistance is an important common link between diabetes and HTN.

Diabetes has also been shown to cause volume expansion, induced by both insulin and increased glucose load in the proximal tubule, leading to sodium retention and thereby increasing BP levels [51]. Protein glycation in diabetes also predisposes to vascular stiffness, leading to a reduction in arterial distensibility and an increase in systolic pressure [52].

Treatment

This includes nonpharmacologic interventions to prevent HTN and pharmacologic interventions treating HTN. The American Diabetes Association 2015 guidelines recommend that for patients with a SBP of 120–139 mmHg, or a diastolic pressure of 80–89 mmHg, nonpharmacologic methods should be used to reduce BP, such as weight reduction, increased consumption of fresh fruits, vegetables, and low-fat dairy products, exercise, salt restriction, and avoidance of smoking and excess alcohol ingestion. Pharmacological agents should be initiated in patients who develop HTN (BP $\geq$ 140/90 mmHg) [53].

Although there are no well-controlled studies of diet and exercise in the treatment of elevated BP or HTN in individuals with diabetes, The Dietary Approaches to Stop Hypertension study evaluated the impact of healthy dietary patterns in individuals without diabetes and has shown antihypertensive effects similar to those of pharmacological monotherapy with reduced BP by 5.5 mmHg and DBP by 3.0 mmHg ($P < 0.001$) [54]. The lifestyle changes advocated include reducing excess body weight, restricting sodium intake (2300 mg/day), increasing consumption of fruits and vegetables (8–10 servings/day) and low-fat dairy products (2–3 servings/day), avoiding excessive alcohol consumption (no >2 servings/day in men and no >1 serving/day in women), and increasing activity levels. These lifestyle (nonpharmacological) strategies may also positively affect glycemia and lipid control and should be encouraged.

As HTN places diabetic patients at high risk for CV complications, in all diabetic patients with persistent BP above 140/90 mmHg, early treatment of HTN is important both to prevent CVD and to minimize progression of renal disease and diabetic retinopathy [55]. Successful implementation of nonpharmacologic therapy in these patients may enable later reduction in the dose or the number of antihypertensive agents.

Drug therapy in hypertensive diabetic patients has been shown to be protective on the basis of results from multiple trials, including United Kingdom Prospective Diabetes Study (UKPDS), ADVANCE, and Hypertension Optimal Treatment, as well as meta-analyses of these and other trials [56–63]. In this meta-analysis of 40 trials, compared with placebo in 100 354 patients, antihypertensive therapy reduced mortality related to CVD, myocardial infarction, and stroke. A 10 mmHg reduction in systolic pressure with antihypertensive therapy was associated with a hazard ratio (HR) for death of 0.87 [95% confidence interval (CI): 0.78–0.96] and a HR for total CVD of 0.89 (95% CI: 0.83–0.95). However, analyses that divided patients according to their baseline systolic pressures showed that, with the exception of stroke, the benefit of antihypertensive therapy was limited to those whose initial systolic pressures greater than 140 mmHg. The benefit of reduction in stroke was observed even in BP less than 140 mmHg systolic. For most outcomes, no class of drugs was superior to the others [56]. However, calcium channel blockers reduced the risk of stroke compared with others [relative risk (RR) 0.86, 95% CI: 0.97–0.77] and β-blockers were shown to increase the risk of stroke compared with other agents (RR 1.25, 95% CI: 1.05–1.50).

The UKPDS, using captopril or atenolol as the primary therapy, evaluated a goal BP of less than 150/85 versus less than 180/105 [57]. At a median 8.4-year follow-up, patients with lower BP showed a 24% reduction in diabetes-related endpoints, including microvascular disease (37 vs. 49%), a 32% reduction in deaths related to diabetes, 44% fewer strokes, and a 34 and 47% reduction in significant deterioration in retinopathy and visual acuity, respectively. After 9 years of follow-up, 29% of patients in the group assigned to tighter control required three or more drugs to continue to achieve target BP [64]. These significant improvements were lost within 2 years of termination of tight BP control. In a subsequent observational report utilizing data from the UKPDS trial, there was an inverse correlation between the updated mean SBP and the aggregate endpoint at the 10-year follow-up for any complication related to diabetes [65]. Each 10 mmHg reduction in systolic pressure was associated with a 12% risk reduction; the lowest risk occurred at a systolic pressure below 120 mmHg [65]. However, UKPDS was not designed to assess the efficacy of systolic pressures below 140 mmHg.

In the Hypertension Optimal Treatment trial, which evaluated target diastolic pressures of $\leq$90, $\leq$85, or $\leq$80 mmHg, in the diabetic subgroup of 3000 patients, but not in other patients, the RR of a CV event was significantly reduced in less than or equal to 80 mmHg group compared with less than or equal to 90 mmHg group (RR 0.49, 95% CI: 0.29–0.81) [61].

In the ADVANCE trial, in 11 000 patients with type 2 diabetes, a fixed combination of perindopril-indapamide was compared with placebo. A target BP was not used to guide protocol therapy, and all other agents, except angiotensin-converting enzyme inhibitors and thiazides, were initiated at the discretion of the treating clinicians. After a mean of 4.3 years, in addition to a decrease in the mean BP by 5.6/2.2 mmHg, major microvascular and macrovascular events were lower as well as CV mortality and all-cause mortality (15.5 vs. 16.8, 3.8 vs. 4.6 and 7.3 vs. 8.5, respectively) [62]. During the 6-year post-trial open-label follow-up in 8494 of the trial patients, those who had been assigned perindopril-indapamide had a lower death rate during the cohort phase (15.3 vs. 16.7%) as well as a lower incidence of major CV events (13.3 vs. 14.2%) [66]. On combining both the trial and the cohort phases (~10 years of follow-up), all-cause mortality was significantly lower among those in the treatment group (HR 0.91, 95% CI: 0.84–0.99) [66].

The normotensive Appropriate Blood Pressure Control in Diabetes Trial evaluated enalapril or nisoldipine treated to a target DBP of 10 mmHg below baseline. The mean BP in the intensive group was $128 \pm 0.8/75 \pm 0.3$ versus $137 \pm 0.7/81 \pm 0.3$ mmHg in the moderate group. At 5 years, there was no difference between the two groups in creatinine clearance, which was the primary endpoint, but reductions in some secondary endpoints, such as progression of retinopathy (34 vs. 46%), microalbuminuria, and macroalbuminuria. There was no reduction in the rate of all CV events, although there was a significant reduction in stroke ($P = 0.03$) [67].

The Action to Control Cardiovascular Risk in Diabetes Blood Pressure Trial (ACCORD BP) also evaluated a lower treatment goal. This study randomized 4733 patients with type 2 diabetes who had CVD or at least two additional risk factors for CVD to either intensive therapy (goal SBP < 120 mmHg) or standard therapy (goal SBP < 140 mmHg). At a mean follow-up of 4.7 years, no significant difference in the annual rate of the primary composite outcome of nonfatal myocardial infarction, nonfatal stroke, or death from CV causes (1.87 vs. 2.09%, HR 0.88, 95% CI: 0.73–1.06), annual all-cause mortality rate (1.28 vs. 1.19%), or in the rate of death from CV causes (0.52 vs. 0.49%) was observed. The annual rates of total stroke and nonfatal stroke (0.32 vs. 0.53%, HR 0.59, 95% CI: 0.39–0.89, for total stroke and 0.3 vs. 0.47%, HR 0.63, 95% CI: 0.41–0.96, for nonfatal stroke) were lower in the intensive treatment group. Moreover, the intensive group also had a higher rate of an increase in serum creatinine of more than 1.5 mg/dl in men or more than 1.3 mg/dl in women and severe adverse effects related to treatment [68].

The SANDS trial of 499 American Indian men and women with type 2 diabetes and no history of previous CVD events showed no difference in clinical CV mortality with aggressive therapy (≤ 115 mmHg) and higher adverse events related to antihypertensive agents [69].

Conducted in nondiabetic patients at increased CV risk, The Systolic Blood Pressure Intervention Trial (SPRINT) showed that targeting a systolic pressure less than 120 mmHg compared with less than 140 mmHg reduced CV events and mortality when using automated oscillometric blood pressure (AOBP). AOBP readings were typically 5–10 mm lower than with manual measurement. The mean systolic pressure was 121 mmHg in the intensive lowering group [70].

Data from NHANES 2001–2010 indicate that ~78% of hypertensive individuals were aware of their elevated BP, 73.7% of them were receiving antihypertensive therapy, but only 48.4% had a BP of less than 140/90 mmHg – the level considered to be 'controlled' or at goal. The prevalence of antihypertensive medication use increased from 63.5% in 2001 to 2002 to 77.3% in 2009 to 2010 ($P_{trend} < 0.01$). Most notably, there was a large increase in the use of multiple antihypertensive agents (from 36.8 to 47.7%, $P_{trend} < 0.01$) [71]. In comparison with monotherapy, single-pill combinations and multiple-pill combinations were associated with 55 and 26% increased likelihoods of BP control, respectively. By the 2009–2010 time period, 47% of all hypertensive patients and 60% of treated hypertensive patients had achieved BP control. However, higher treated but uncontrolled HTN rates continued to persist among older Americans, non-Hispanic Blacks, diabetic patients, and those with chronic kidney disease. Also, Mexican Americans with HTN were still less likely to take antihypertensive medication than non-Hispanic Whites with HTN [71].

Joint National Committee-8 came up with the following recommendations for the treatment of HTN in diabetic patients after analyzing available data for treatment goals.

(1) In patients with HTN and diabetes, pharmacologic treatment should be initiated when BP is 140/90 mmHg or higher, irrespective of age.
(2) Initial antihypertensive treatment should include a thiazide diuretic, a calcium channel blocker, an angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker in the general non-Black population or a thiazide diuretic or a calcium channel blocker in the general Black population.
(3) If the target BP is not reached within 1 month after initiating therapy, the dosage of the initial medication should be increased or a second medication should be added.

The American Diabetes association has similar recommendations, but recognizes the need for additional data in special subgroups and supports lower targets in special

situations, individualized to each patient. In individuals in whom stroke risk is a concern, as part of shared decision-making, ADA recommends that having a lower systolic target of 130 mmHg may be appropriate. This is especially true if lower BP can be achieved with few drugs and without the side effects of therapy. A DBP of 80 mmHg may still be appropriate for patients with long life expectancy, those with chronic kidney disease, elevated urinary albumin excretion, and additional ASCVD risk factors such as dyslipidemia, smoking, or obesity [53].

The degree of BP reduction is a major determinant of reduction in CV risk than the choice of an antihypertensive drug [72,73]. In this meta-analysis of 31 trials and 190 606 participants, no difference was noted between the effects of drug classes on major CV events ($P > 0.24$) [74]. Similar findings were obtained in this meta-analysis of 147 randomized trials and 464 000 patients [75].

Conclusion

Diabetes and HTN share common patient behavior factors and pathophysiologic pathways. These pathways interact and influence each other and may even lead to a vicious cycle. HTN and diabetes are components of a metabolic process – the metabolic syndrome. They may, therefore, develop one after the other in the same individual. Lifestyle factors play an important role in the pathogenesis. Therefore, optimization of lifestyle remains the cornerstone in the prevention and treatment of diabetes and HTN.

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Conflicts of interest

There are no conflicts of interest.

References

1 Annotations. *Br Med J* 1957; **1**:1292–1295.
2 Ruskin A. *Classics in arterial hypertension*. Springfield, IL: Charles C Thomas; 1956.
3 Riva Rocci Sphygmomanometer | Wood Library-Museum. Available at: *https://www.woodlibrarymuseum.org/museum/item/14/riva-rocci-sphygmomanometer*. [Accessed 21 October 2016].
4 James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, *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.
5 Grossman E, Messerli FH. Diabetic and hypertensive heart disease. *Ann Intern Med* 1996; **125**:304–310.
6 Huang Y. Prehypertension and incidence of cardiovascular disease: a meta-analysis. *BMC Med* 2013; **11**:177.
7 National Clinical Guideline Centre (UK). *Hypertension: the clinical management of primary hypertension in adults: update of clinical guidelines 18 and 34*. London, UK: National Institute for Health and Clinical Excellence; 1984.
8 Arterial Hypertension (Management of). Available at: *https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Arterial-Hypertension-Management-of*. [Accessed 21 October 2016].
9 High Blood Pressure Facts | cdc.gov. Available at: *http://www.cdc.gov/bloodpressure/facts.htm*. [Accessed 21 October 2016].
10 Go AS, Roger VL, Benjamin EJ, Berry JD, Borden WB, *et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee*. Heart disease and stroke statistics – 2013 update: a report from the American Heart Association. *Circulation* 2013; **127**:e6–e245.
11 Matheus AS, Tannus LR, Cobas RA, Palma CC, Negrato CA, Gomes MB. Impact of diabetes on cardiovascular disease: an update. *Int J Hypertens* 2013; **2013**:653789.
12 Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease. *Hypertension* 2001; **37**:1053–1059.
13 Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *N Engl J Med* 2000; **342**:905–912.
14 Epstein M, Sowers JR. Diabetes mellitus and hypertension. *Hypertens Dallas Tex* 1992; **19**:403–418.
15 Parving HH, Hommel E, Mathiesen E, Skøtt P, Edsberg B, Bahnsen M, *et al.* Prevalence of microalbuminuria, arterial hypertension, retinopathy and neuropathy in patients with insulin dependent diabetes. *Br Med J (Clin Res Ed)* 1988; **296**:156–160.
16 Mogensen CE, Hansen KW, Pedersen MM, Christensen CK. Renal factors influencing blood pressure threshold and choice of treatment for hypertension in IDDM. *Diabetes Care* 1991; **14** (Suppl 4):13–26.
17 [No authors listed]. Hypertension in Diabetes Study (HDS): I. Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardiovascular and diabetic complications. *J Hypertens* 1993; **11**:309–317.
18 Cheung BM. The hypertension-diabetes continuum. *J Cardiovasc Pharmacol* 2010; **55**:333–339.
19 Cheung BM, Li C. Diabetes and hypertension: is there a common metabolic pathway? *Curr Atheroscler Rep* 2012; **14**:160–166.
20 Landsberg L, Molitch M. Diabetes and hypertension: pathogenesis, prevention and treatment. *Clin Exp Hypertens* 2004; **26**:621–628.
21 Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, *et al. American Heart Association Advocacy Coordinating Committee; Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Arteriosclerosis; Thrombosis and Vascular*. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation* 2011; **123**:933–944.
22 Ritchey M, Chang A, Power C, Loustalot F, Schieb L, Ketcham M, *et al.* Vital signs: disparities in antihypertensive medication nonadherence among medicare part D beneficiaries – United States, 2014. *MMWR Morb Mortal Wkly Rep* 2016; **65**:967–976.
23 Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. *JAMA* 2003; **290**:199–206.
24 Alex ADA. 1701 N. B. S., ria & 1-800-Diabetes, V. 22311. Statistics About Diabetes. *American Diabetes Association*. Available at: *http://www.diabetes.org/diabetes-basics/statistics/*. [Accessed 21 October 2016].
25 Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; **27**:1047–1053.
26 WHO Diabetes. *WHO*. Available at: *http://www.who.int/mediacentre/factsheets/fs312/en/*. [Accessed 21 October 2016].
27 [No authors listed]. Multiple risk factor intervention trial. Risk factor changes and mortality results. Multiple Risk Factor Intervention Trial Research Group. *JAMA* 1982; **248**:1465–1477.
28 Wang MH, Li J, Yeung VS, Zee BC, Yu RH, Ho S, Waye MM. Four pairs of gene–gene interactions associated with increased risk for type 2 diabetes (CDKN2BAS–KCNJ11), obesity (SLC2A9–IGF2BP2, FTO–APOA5), and hypertension (MC4R–IGF2BP2) in Chinese women. *Meta Gene* 2014; **2**:384–391.
29 Smith CJ, Ryckman KK. Epigenetic and developmental influences on the risk of obesity, diabetes, and metabolic syndrome. *Diabetes Metab Syndr Obes* 2015; **8**:295–302.
30 Perrone S, Santacroce A, Picardi A, Buonocore G. Fetal programming and early identification of newborns at high risk of free radical-mediated diseases. *World J Clin Pediatr* 2016; **5**:172–181.
31 Davy KP, Hall JE. Obesity and hypertension: two epidemics or one? *Am J Physiol Regul Integr Comp Physiol* 2004; **286**:R803–R813.
32 Adult Obesity Facts | Overweight & Obesity | CDC. Available at: *https://www.cdc.gov/obesity/data/adult.html*. [Accessed 21 October 2016].
33 Van Greevenbroek MM, Schalkwijk CG, Stehouwer CD. Obesity-associated low-grade inflammation in type 2 diabetes mellitus: causes and consequences. *Neth J Med* 2013; **71**:174–187.
34 Smith SR, Lovejoy JC, Greenway F, Ryan D, de Jonge L, de la Bretonne J, *et al.* Contributions of total body fat, abdominal subcutaneous adipose tissue

compartments, and visceral adipose tissue to the metabolic complications of obesity. *Metabolism* 2001; **50**:425–435.
35 Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest* 2006; **116**:1793–1801.
36 Shoelson SE, Lee J, Yuan M. Inflammation and the IKK beta/I kappa B/NF-kappa B axis in obesity- and diet-induced insulin resistance. *Int J Obes Relat Metab Disord* 2003; **27** (Suppl 3):S49–S52.
37 Yuan M, Konstantopoulos N, Lee J, Hansen L, Li ZW, Karin M, Shoelson SE. Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikkbeta. *Science* 2001; **293**:1673–1677.
38 Ouwens DM, Sell H, Greulich S, Eckel J. The role of epicardial and perivascular adipose tissue in the pathophysiology of cardiovascular disease. *J Cell Mol Med* 2010; **14**:2223–2234.
39 Preshaw PM, Alba AL, Herrera D, Jespan S, Konstantinidis A, Makrilakis K, Taylor R. Periodontitis and diabetes: a two-way relationship. *Diabetologia* 2012; **55**:21–31.
40 Iacopino AM. Periodontitis and diabetes interrelationships: role of inflammation. *Ann Periodontol* 2001; **6**:125–137.
41 Wang X, Bao W, Liu J, Ouyang YY, Wang D, Rong S, *et al*. Inflammatory markers and risk of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care* 2013; **36**:166–175.
42 Stefanadi E, Tousoulis D, Androulakis ES, Papageorgiou N, Charakida M, Siasos G, *et al*. Inflammatory markers in essential hypertension: potential clinical implications. *Curr Vasc Pharmacol* 2010; **8**:509–516.
43 Jellinger PS. Metabolic consequences of hyperglycemia and insulin resistance. *Clin Cornerstone* 2007; **8** (Suppl 7):S30–S42.
44 Deedwania P. Hypertension, dyslipidemia, and insulin resistance in patients with diabetes mellitus or the cardiometabolic syndrome: benefits of vasodilating β-blockers. *J Clin Hypertens Greenwich Conn* 2011; **13**:52–59.
45 Stump CS, Clark SE, Sowers JR. Oxidative stress in insulin-resistant conditions: cardiovascular implications. *Treat Endocrinol* 2005; **4**:343–351.
46 Leiter LA, Lewanczuk RZ. Of the renin-angiotensin system and reactive oxygen species Type 2 diabetes and angiotensin II inhibition. *Am J Hypertens* 2005; **18**:121–128.
47 Fonseca V, Desouza C, Asnani S, Jialal I. Nontraditional risk factors for cardiovascular disease in diabetes. *Endocr Rev* 2004; **25**:153–175.
48 Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *The Lancet* 2005; **365**:1415–1428.
49 Yeni-Komshian H, Carantoni M, Abbasi F, Reaven GM. Relationship between several surrogate estimates of insulin resistance and quantification of insulin-mediated glucose disposal in 490 healthy nondiabetic volunteers. *Diabetes Care* 2000; **23**:171–175.
50 Reaven GM. Relationships among insulin resistance, type 2 diabetes, essential hypertension, and cardiovascular disease: similarities and differences. *J Clin Hypertens Greenwich Conn* 2011; **13**:238–243.
51 Nosadini R, Sambataro M, Thomaseth K, Pacini G, Cipollina MR, Brocco E, *et al*. Role of hyperglycemia and insulin resistance in determining sodium retention in non-insulin-dependent diabetes. *Kidney Int* 1993; **44**:139–146.
52 Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation* 2002; **106**:2085–2090.
53 Cefalu W. Diabetes Care 2016 standars of care. Available at: *http://care.diabetesjournals.org/content/suppl/2015/12/21/39.Supplement_1.DC2/2016-Standards-of-Care.pdf*. [Accessed 21 October 2016].
54 Harsha DW, Lin PH, Obarzanek E, Karanja NM, Moore TJ, Caballero B. Dietary approaches to stop hypertension: a summary of study results. DASH Collaborative Research Group. *J Am Diet Assoc* 1999; **99**:S35–S39.
55 Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. *Lancet Lond Engl* 1999; **353**:617–622.
56 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.
57 [No authors listed]. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998; **317**:703–713.
58 Vijan S, Hayward RA. Treatment of hypertension in type 2 diabetes mellitus: blood pressure goals, choice of agents, and setting priorities in diabetes care. *Ann Intern Med* 2003; **138**:593–602.
59 Jackson GL, Edelman D, Weinberger M. Simultaneous control of intermediate diabetes outcomes among veterans affairs primary care patients. *J Gen Intern Med* 2006; **21**:1050–1056.
60 Reboldi G, Gentile G, Manfreda VM, Angeli F, Verdecchia P. Tight blood pressure control in diabetes: evidence-based review of treatment targets in patients with diabetes. *Curr Cardiol Rep* 2012; **14**:89–96.
61 Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, *et al*. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet Lond Engl* 1998; **351**:1755–1762.
62 Patel A, MacMahon S, Chalmers J, Neal B, Woodward M. ADVANCE Collaborative Group, *et al*. 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 Lond Engl* 2007; **370**:829–840.
63 Turnbull F, Neal B, Algert C, Chalmers J, Chapman N, Cutler J, *et al*. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med* 2005; **165**:1410–1419.
64 Holman RR, Paul SK, Bethel MA, Neil HAW, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med* 2008; **359**:1565–1576.
65 Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, *et al*. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ* 2000; **321**:412–419.
66 Zoungas S, Chalmers J, Neal B, Billot L, Li Q, Hirakawa Y, *et al*. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* 2014; **371**:1392–1406.
67 Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int* 2002; **61**:1086–1097.
68 ACCORD Study Group, Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, *et al*. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; **362**:1575–1585.
69 Howard BV, Roman MJ, Devereux RB, Fleg JL, Galloway JM, Henderson JA, *et al*. Effect of lower targets for blood pressure and LDL cholesterol on atherosclerosis in diabetes: the SANDS randomized trial. *JAMA* 2008; **299**:1678–1689.
70 SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, *et al*. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015; **373**:2103–2116.
71 Gu Q, Burt VL, Dillon CF, Yoon S. Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension: the National Health And Nutrition Examination Survey, 2001 to 2010. *Circulation* 2012; **126**:2105–2114.
72 Rosendorff C, Black HR, Cannon CP, Gersh BJ, Gore J, Izzo JL Jr, *et al*. *American Heart Association Council for High Blood Pressure Research; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Epidemiology and Prevention*. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement From the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. *Circulation* 2007; **115**:2761–2788.
73 Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, *et al*. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; **31**:1281–1357.
74 Blood Pressure Lowering Treatment Trialists' Collaboration, Turnbull F, Neal B, Ninomiya T, Algert C, Arima H, Barzi F, *et al*. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ* 2008; **336**:1121–1123.
75 Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009; **338**:b1665.