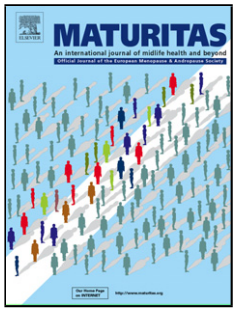

Title: Hypertension in patients with type 2 diabetes mellitus: targets and management

Authors: Dimitra I. Pavlou, Stavroula null. Paschou, Panagiotis Anagnostis, Michael Spartalis, Eleftherios Spartalis, Andromachi Vryonidou, Nicholas Tentolouris, Gerasimos Siasos

PII: S0378-5122(18)30141-5
DOI: https://doi.org/10.1016/j.maturitas.2018.03.013
Reference: MAT 6982

To appear in: *Maturitas*

Received date: 26-2-2018
Revised date: 24-3-2018
Accepted date: 29-3-2018

Please cite this article as: Pavlou Dimitra I, Paschou Stavroula x391;, Anagnostis Panagiotis, Spartalis Michael, Spartalis Eleftherios, Vryonidou Andromachi, Tentolouris Nicholas, Siasos Gerasimos.Hypertension in patients with type 2 diabetes mellitus: targets and management.*Maturitas* https://doi.org/10.1016/j.maturitas.2018.03.013

Hypertension in patients with type 2 diabetes mellitus: targets and management

Short Title: Hypertension and type 2 diabetes

Dimitra I. Pavlou (1), Stavroula A. Paschou (2), Panagiotis Anagnostis (3), Michael Spartalis (4), Eleftherios Spartalis (5), Andromachi Vryonidou (6), Nicholas Tentolouris (7), Gerasimos Siasos (8)

1) Forth Department of Internal Medicine, Hippokration Hospital, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece
2) Division of Endocrinology and Diabetes, "Aghia Sophia" Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece
3) Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece
4) Division of Cardiology, Onassis Cardiac Surgery Center, Athens, Greece
5) Laboratory of Experimental Surgery and Surgical Research, Medical School, National and Kapodistrian University of Athens, Athens, Greece
6) Department of Endocrinology and Diabetes, Hellenic Red Cross Hospital, Athens, Greece
7) Diabetes Center, First Department of Propaedeutic Internal Medicine, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Greece
8) First Department of Cardiology, Hippokration Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Corresponding author: Dr. Gerasimos Siasos, MD, PhD, Associate Professor, First Department of Cardiology, Hippokration Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece, e-mail: gsiasos@med.uoa.gr

Highlights

- Two-thirds of patients with type 2 diabetes mellitus have arterial hypertension.
- Hypertension increases the incidence of both micro- and macrovascular complications in these patients, while the co-existence of these two major risk factors leads to a four-fold increased risk for cardiovascular disease.
- A blood pressure target of <140/90mmHg applies to most patients.
- All classes of antihypertensive drugs can be used in the management of hypertension in patients with type 2 diabetes mellitus.
- Gender-specific characteristics regarding blood pressure, type 2 diabetes mellitus and cardiovascular disease should be taken into consideration, even if different recommendations do not exist yet.

Abstract

Two-thirds of patients with type 2 diabetes mellitus (T2DM) have arterial hypertension. Hypertension increases the incidence of both micro- and macrovascular complications in these patients, while the co-existence of these two major risk factors leads to a four-fold increased risk for cardiovascular disease (CVD) compared with normotensive non-diabetic controls. The aim of this article is to comprehensively review the literature and present updated information on targets for blood pressure (BP) and on the management of hypertension in patients with T2DM. A BP target of <140/90mmHg applies to most patients, but individualization is always important. All classes of antihypertensive drugs can be used in the management of hypertension in patients with T2DM, as long as they are effective and

safe and after taking co-morbidities into account. Angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are the ideal choice for initial or early treatment of hypertension in patients with T2DM and albuminuria. Combination of two or more drugs seems to be inevitable as most of these patients demonstrate resistant hypertension. The combination of ACE inhibitors with ARBs should be avoided. Thiazide and thiazide-like diuretics might be beneficial, alone or in a fixed-dose combination with ACE inhibitors or ARBs. Calcium channel blockers (CCBs) constitute an ideal option as a second- or third-line agent. Beta-blockers are not considered as first-line antihypertensive agents, except for those patients with heart failure or previous myocardial infarction. The addition of mineralocorticoid receptor antagonists to a triple-drug therapy seems the next ideal step. Gender-specific characteristics regarding BP, T2DM and CVD should be taken into consideration, even if different recommendations do not exist yet.

Keywords: type 2 diabetes, hypertension, targets, management

1. Introduction

Hypertension and type 2 diabetes mellitus (T2DM) seem to be two aspects of common pathophysiological pathways, especially in people who suffer from metabolic syndrome. It is estimated that almost two thirds of the population with T2DM is also affected by hypertension (1). Elevated arterial blood pressure (BP) contributes to increased incidence of both micro- and macrovascular complications in patients with T2DM (2-4). Besides that, co-existence of these two major risk factors, leads to a four-fold increased risk for cardiovascular disease (CVD) as compared to normotensive non-diabetic controls (5). The magnitude of simultaneous prevalence of T2DM and hypertension depends on age, BMI and ethnicity. While in patients with type 1 diabetes mellitus, hypertension occurs when kidney function is

affected, in patients with T2DM, hypertension usually presents early and in combination with other cardiovascular risk factors (6,7). Furthermore, uncontrolled BP has been associated with increased risk for diabetes development, independently of age, body mass index (BMI), baseline BP or fasting glucose (8).

Many mechanisms have been proposed to explain why hypertension and T2DM co-exist in the same individuals. Obesity and increased visceral adiposity present as the most important pathogenetic factors (1), as they lead to chronic low-grade inflammation which along with oxidative stress in adipose tissue finally cause increased production of angiotensinogen and angiotensin II (9,10). The sequential inappropriate activation of renin-angiotensin system (RAAS) is considered to be the leading factor for co-existence of hypertension and T2DM. Moreover, insulin resistance is also a very important component for the development of both entities, as approximately 50% of hypertensive patients manifest systemic insulin resistance (11, 12). Insulin resistance is associated with increased vascular adhesion molecules expression, oxidative stress, inflammation, and decreased vascular nitric oxide levels, which in turn promote vascular stiffness resulting in persistent hypertension (13-16). It is obvious, that the need of a multifaceted approach of T2DM is imperative. The management of diabetes should go always along with the appropriate treatment of elevated BP, as well as the rest cardiovascular risk factors, in order to minimize micro- and macrovascular complications.

2. Methods

In order to identify publications on T2DM and hypertension, literature search in English language was conducted in PubMed until the end of the year 2017. We collected, analyzed and qualitatively resynthesized data regarding the effect of BP control in patients with T2DM in order to identify the optimal ones, while we reviewed the various current guidelines for such targets. We present then updated information regarding proper assessment, as well as

appropriate management of hypertension in patients with T2DM. Gender-specific characteristics are also discussed.

3. Targets

3.1 The effect of BP control in patients with T2DM

The importance of BP control in preventing diabetes-related morbidity has been proved in a large amount of evidence. It appears that tight BP control in hypertensive diabetics achieves a clinically important reduction in diabetes-related mortality and complications as well as a delay in progression of diabetic retinopathy. The United Kingdom Prospective Diabetes Study (UKPDS 38) evaluated the possible difference in the incidence of cardiovascular events, in diabetic patients who were enrolled in two groups of different BP control. It showed a significant reduction (44%, 32% and 34%, respectively) in the risk of stroke, diabetes related deaths and retinopathy at the more tight BP control group (target BP < 150/85 mmHg) compared with the less strict BP control group (17). The Hypertension Optimal Treatment (HOT) trial emphasized in the need for more aggressive diastolic BP control in diabetic patients by showing a lower incidence of strokes, myocardial infarctions, major cardiovascular disease (CVD) events and deaths, in patients who achieved diastolic BP of 82.6 mm Hg (18).

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial pioneered by being the first trial to evaluate BP control specifically in patients with diabetes. It demonstrated a remarkable reduction in cardiovascular events for the antihypertensive therapy group compared with placebo (mean achieved BP of 134/74 mmHg versus 140/76 mmHg) (19). In The Systolic Hypertension in Europe (Syst-Eur) Trial, the inception of antihypertensive treatment with a dihydropyridine calcium-channel blockers in elderly patients with isolated systolic hypertension proved to be

particularly beneficial in diabetic patients compared to non-diabetics (20). Therefore, as there are many randomized control trials (RCTs) to support the benefit from reducing BP in patients with T2DM, especially regarding the risk for cardiovascular events and stroke, the control of BP must be a major priority for the physicians treating these patients.

3.2 Optimal targets of BP in patients with T2DM and hypertension

During the past years, the optimal targets for BP in diabetic patients were more strict compared to patients without diabetes. For a long time, major medical societies, such as the American Diabetes Association (ADA) and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP (JNC 7) in 2004, recommended a target BP level below 130/80 mm Hg. Following the JNC 7 report, many other organizations with special interest in diabetes, developed guidelines for the management of BP in diabetic patients. The goal of BP less than 130/80 mmHg was also supported by the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines (ESC/ESH 2007) (21-25). However, the evidence for this BP target was weak and based on small observational studies.

Since these initial recommendations were addressed, many clinical trials were carried in order to investigate the reliability and safety of the aforementioned thresholds. In the Normotensive Appropriate BP Control in Diabetes (ABCD) trial, the mean achieved BP of 128/75 mm Hg in the tight control group was under the goal of 130 mm Hg. After a follow up of five years, there were no significant differences in any cardiovascular events, or progression of renal disease (as the primary outcome), neither in retinopathy, when compared with the placebo group (mean BP achieved 137/81 mmHg). Interestingly, in the intensive treatment group, significant reductions occurred in the progression of retinopathy, albuminuria and absolute risk of stroke (26).

In 2010, the Action to Control Cardiovascular Risk in Diabetes – BP Arm (ACCORD – BP) study, really challenged the cut-offs for BP in diabetics and became the springboard for the change in BP targets by major medical societies. This large RCT compared a systolic target of <120 mmHg (intensive group) with a systolic target of <140 mmHg (standard therapy), in terms of its effect on the incidence of CVD events in 4,733 high risk diabetic patients. After a mean follow up of 4.7 years, there was no significant difference between the two groups, as far as, combined CVD outcomes, were concerned (non-fatal myocardial infarction, stroke or CVD death). On the other hand, there was a significant reduction in the incidence of stroke in subjects allocated to the intensive group, with the cost of an elevation in undesirable and serious side effects such as, severe hypotension, hyperkalemia, syncope, bradycardia, arrhythmia or renal function impairment. Moreover, the ACCORD trial proved that reducing systolic BP (SBP) to below 115 mmHg could be harmful (27).

In a recent post-hoc analysis of the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET), there was also an observation of no benefit in reducing SBP <130 mmHg in patients with diabetes, but an increase in CVD mortality in the intensive therapy group (SBP <125 mmHg) (28). In the Irbesartan Diabetic Nephropathy Trial (IDN-T), an achieved level of BP <120/85 mmHg was related to increased incidence of CVD events (29). Furthermore, in a retrospective analysis of the United Kingdom General Practice Research Database (UKGPRD), excessive lowering of BP <110/75 mmHg in diabetic patients with a positive CVD history, was related to increased mortality (30).

A very recent meta-analysis, which included 40 trials and 100,354 patients, showed that each 10 mmHg reduction in SBP, was associated with a significantly lower risk of mortality, CVD events, coronary heart disease, stroke, albuminuria and retinopathy. When the trials were stratified in subgroups according to a BP threshold of greater or less than 140 mmHg, the risk for outcomes other than stroke, retinopathy and renal failure appeared to be greater for the

target group of BP <140 mmHg. Additionally, it showed that in high risk subgroups, such as those with a history of stroke and retinopathy, intensive antihypertensive therapy with a target of BP <130 mmHg, should be commenced, even in those with an initial SBP level < 140 mmHg (31).On the occasion of the ACCORD-BP trial findings and other studies that followed, the ADA revised its recommendations in 2013, determining a new BP target of 140/80 mmHg for patients with diabetes (32). The need for individualization was emphasized in the new recommendations.

3.3 Current guidelines for targets of BP control in patients with T2DM

In recent years, most of the major medical societies have revised and published renewed guidelines for the management and treatment of hypertension in patients with diabetes, with and without renal dysfunction (33-36). Slight differences can be found among them, with respect to the level of BP above which, pharmacologic antihypertensive therapy should be initiated and, subsequently, which BP target to attain. The most important guidelines and the recommended targets are presented in *Table 1.*

Since 2013 and after the change of BP threshold at <140/80 mmHg in ADA recommendations and <140/90 mmHg in their recommendations since 2015, this new target was supported by other guidelines as well, with a differentiation in diastolic BP (DBP) target levels. In the current revision of ESH/ESC 2013 guidelines, the recommended BP goal was changed to 140/85 mmHg, however, a target of systolic BP (SBP) <130 mmHg remained for diabetics with overt proteinuria and diabetic nephropathy. Similarly, in the UK's National Institute for Health and Clinical Excellence (NICE) guidelines, the target of BP is set at <140/80 mmHg, with the exception of patients with retinopathy, history of stroke, and microalbuminuria where a BP level <130/80 mmHg was recommended (36).

The Eighth Report of the Joint National Committee (JNC 8) hypertension guidelines were released in 2014, ten years after JNC 7 (35). The reviewers in JNC8 focused in three specific questions: 1) Does initiating antihypertensive pharmacologic therapy at specific BP thresholds improve health outcomes? 2) Does treatment with antihypertensive drugs to a specific BP goal lead to improvement in health outcomes? and 3) are there differences between various drugs which are used for the treatment of hypertension in health outcomes? In order to give trustworthy answers to the above questions, the reviewers based new recommendations on high-quality randomized control trials (RCTs) possible. The thorough and evidence-based answers to these questions lead to the recommendations of JNC 8 for patients with diabetes and hypertension according to which antihypertensive treatment should be started in patients aged 18 years or older, when BP is ≥140 mmHg and DBP ≥90 mmHg. Very recently the American Diabetes Association (ADA) released the Standards of Medical Care in Diabetes for the year 2018 (34). The levels of BP above which hypertensive treatment should begin, remain >140 mmHg for SBP and >90 mHg for DBP. However, they propose more intensive control (SBP <130 mmHg) for individuals at high risk of CVD, including stroke, as long as they can be achieved without harmful side effects. In the same way, a DBP goal of < 80 mmHg may be beneficial for patients with long life expectancy, chronic kidney disease, albuminuria, evidence of CVD, or additional risk factors such as dyslipidemia, smoking or obesity. Nevertheless, a SBP goal <130 mmHg and DBP < 70 mmHg for older adults, probably does not improve CVD outcome or may even worsen them, as it has been associated with an increased mortality (myocardial ischemia due to decreased blood flow in coronary arteries).

It seems that a BP target of <140/90 mmHg applies to a large number of patients with diabetes, but it is important to remember that the management of hypertension in diabetics

should be adapted depending on each patient's age, medical history, additional cardiovascular risk factors and co-morbidities. "Individualization" is the key word when BP goals are set.

4. Assessment

During evaluation of a patient with T2DM, an overall approach and management of all CVD risk factors that are usually involved in these patients, such as hypertension, dyslipidemia and obesity, should be considered. Among these factors, elevated BP is the one that mostly contributes to increased CVD morbidity and mortality in these patients. BP should be measured by the clinician in a medical office at every routine visit of a patient with T2DM (37). BP assessment should be done under conditions that adhere to the rules which apply to general population, which means measurement at the seated position, with feet on the floor and arm supported at the heart level, after 5 minutes of rest. It is important that the cuff size is appropriate for the upper arm circumference. If BP is elevated, a second measurement should be repeated in another visit. Assessing BP both at seated and postural position helps in identifying those patients who might suffer from autonomic diabetic neuropathy. Once hypertension is confirmed in office measurements, home BP self-monitoring is mandatory for risk stratification and decisions on antihypertensive treatment initiation or adjustment. Moreover, a 24-h ambulatory BP monitoring will help to confirm the existence of white-coat hypertension, masked and nocturnal hypertension or elucidate other unclear fields between office and real BP (38-39). There are studies in people without diabetes showing a better correlation between home measurements and the risk for a cardiovascular event. The Home BP measurement with Olmesartan Naïve patients to Establish Standard Target BP (HONEST) study (40) demonstrated the importance of treating hypertension regarding home BP self-monitoring as far as cardiovascular prognosis is concerned. HONEST included 21,000 patients with hypertension who had home BP measurements. It showed that morning

home systolic BP levels < 125 mmHg, were not associated with an increase in cardiovascular events, even among patients with office SBP ≥ 150 mmHg, compared to patients with morning home SBP < 125 mmHg and office SBP < 130 mmHg. Furthermore, elevated morning home BP might be better correlated to the risk for future CVD events and strokes when compared to office measurements (40).

5. Treatment

Treatment of hypertension in patients with T2DM is a really difficult task, as resistant hypertension is encountered more often in this population (58). It seems that about 50% of such patients have uncontrolled hypertension. Factors that are associated with poor BP control are implicated in the cross-sectional Reasons for Geographic And Racial Differences in Stroke (REGARDS) cohort study and comprise African-American ethnicity, male sex, low income and medication non-adherence (41). Therefore, most of the times, two or more antihypertensive drugs might be necessary to properly control BP levels in the diabetics in addition to lifestyle changes.

5.1 Lifestyle intervention

Healthy lifestyle and its impact in the treatment of hypertension has been well-demonstrated in the Dietary Approaches to Stop Hypertension (DASH) study (42). This study showed that lifestyle modification in hypertensive patients without diabetes has the same effect on BP control as pharmacological monotherapy. Lifestyle advice includes a number of interventions such as: body weight loss through reducing daily caloric intake, restriction of sodium to < 2.3 g/d, increased consumption of fruits, vegetables and whole grains (8-10 servings/d) and low-fat dairy products (2-3 servings/d), avoidance of excessive alcohol consumption (no more than two drinks/d for men and no more than one drink/d for women) (43), smoking cessation

(44) and regular exercise that consists of aerobic physical activity of about 30 minutes brisk walking 3-5 times per week (45). Changes in lifestyle can be very beneficial for glycemic control and the management of dyslipidemia as well and should be recommended for all patients with even mildly elevated BP (46-47), even though there is not enough evidence for its effect in reducing CVD events. Diabetic patients with hypertension who are going to benefit mostly from lifestyle changes are those with SBP > 120 mmHg or DBP >80 mmHg. For all the other patients with diabetes and SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, a healthy lifestyle should be combined with pharmacological antihypertensive treatment (48-49).

5.2 Pharmacological treatment

According to recent systematic reviews and meta-analyses of RCTs, all classes of antihypertensive drugs can be used in the management of hypertension in diabetes, including angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), diuretics and calcium channel blockers (CCBs), as long as they are effective and safe (50, 51). This conclusion is supported in JNC 8 and ESC/ESH guidelines for the management of hypertension in diabetes for patients without kidney disease. When making a decision on which one to choose, co-morbidities should be taken into account. Combination of two or more drugs seems to be inevitable as many diabetic patients demonstrate resistant hypertension. These combinations have synergistic action in lowering BP and can lead to fewer side effects. Furthermore, receiving two or more different drugs in one pill, contributes to better adherence (53), consequently better BP control and it is cost-effective. While deciding on starting antihypertensive drugs in a diabetic patient, the choice between monotherapy or combination drug therapy depends on the severity of hypertension. Thus, in patients with a BP between 140/90 mmHg and 159/99 mmHg, monotherapy seems to be a

rationale treatment. But, for patients with BP ≥ 160/100 mmHg, a combination of two antihypertensive drugs an initial approach, is recommended (52). It has been found that more diabetic patients with average BP above 160/100 mmHg, who are treated initially with a two antihypertensive drug combination, may achieve BP target compared with patients who receive monotherapy [SHIELD (Coronary InterventionS in HIgh-Risk PatiEnts Using a Novel Percutaneous Left Ventricular Support Device) and STITCH (Surgical Treatment for Ischemic Heart Failure) trials] (54, 55).

ACE inhibitors or ARBs probably constitute the ideal choice for initial or early treatment of hypertension in patients with diabetes and albuminuria (56). It has been demonstrated that these drugs exert kidney protective properties either by preventing microalbuminuria or by reducing the risk of diabetic nephropathy progression to end-stage renal failure. Regarding the prevention of cardiovascular events, a superiority of ACE inhibitors or ARBs over other drugs, has not been established (57-59). Additionally, the combination of ACE inhibitors with ARBs is not recommended and should be avoided in patients with diabetes. [Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE)] (50, 57). Thiazide and thiazide-like diuretics might be beneficial for the management of hypertension in diabetic patients (60), alone or in a fixed-dose combination with ACE inhibitors or ARBs (61). Nevertheless, attention should be paid regarding hypokalemia, hyperglycemia and hyperuricemia, when diuretics are prescribed in patients with diabetes. For individuals with an estimated glomerular filtration rate < 30mL/min/1.73m^2, a loop diuretic instead of thiazide diuretics should be preferred (60, 61).

Calcium Channel Blockers constitute an ideal option as a second or third-line agent for treatment of hypertension in diabetics. CCBs have been shown to be notably effective when they are combined with RAS blockers. In the Avoiding Cardiovascular Events through

Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, patients at high risk for CVD events (60% with diabetes) that received a combination of ACE inhibitor benazepril plus CCB amlodipine, demonstrated lower rates of morbidity and mortality, compared with those who received benazepril plus the thiazide-like diuretic hydrochlorothiazide (62). CCBs are well tolerated by most patients. Headache, peripheral edema and flushing are some of the most common side effects of CCBs that may worry the practitioner.

With respect to beta-blockers are concerned, they have not been considered as first-line antihypertensive agents, excluding those patients with heart failure or who have suffered a myocardial infarct. It is well-known that beta-blockers might reduce insulin sensitivity and bring on deregulation of T2DM. Nebivolol, as a highly selective beta-1-blocker, could be an option for diabetic patients, but further trials are needed to confirm such a suggestion (64). Furthermore, reduced perception of hypoglycemia that is observed in patients who receive beta-blockers, confines the use of this drug category only when it is strictly indicated. Appropriate algorithm steps for treating hypertension in patients with diabetes are shown in *Table 2.*

5.3 Resistant hypertension

Resistant hypertension is defined as a BP above 140/90 mmHg, despite appropriate modification of diet and exercise and medical treatment which consists of a diuretic and two other antihypertensive drugs of different classes at doses optimized to provide maximum benefit in the absence of intolerable side effects. Before coming to the conclusion that resistant hypertension is the issue, many other conditions should be thoroughly looked for and excluded, such as lack of medication adherence, poor BP measurement technique, secondary hypertension, masked and white-coat hypertension. In patients with resistant

hypertension and T2DM, adding mineralocorticoid receptor antagonists (MARs) to a triple drug therapy (RAS blocker + CCB + diuretic), seems to be the next step in the treatment algorithm (65-70). Nevertheless, attention should be paid to the risk of hyperkalemia, especially when MARs are combined with ARBs or ACE inhibitors. Also, the patient should be checked out frequently for renal function deterioration.

5.4 Impact of new glucose-lowering agents on BP

Reductions in BP of about 3-5 mmHg have been observed consistently in sodium glucose cotransporter 2 (SGLT-2) inhibitor trials (71, 72). Treatment with SGLT-2i empagliflozin has consistently been shown to reduce BP in patients with T2DM, with statistically significant reductions in both office and ambulatory BP (73). Similar reductions in BP have been observed with dapagliflozin and canagliflozin (74). The mechanisms by which these reductions are achieved are not fully clear, but factors like volume contraction due to osmotic dieresis, weight loss, better glucose control and improved arterial stiffness seem to be involved. Glucagon-like peptide 1 receptor agonists (GLP-1RA) may lead to a mild reduction of 2-3 mmHg in SBP. However, BP lowering attributed o GLP-1RA has not been consistently observed in all trials or confirmed in meta-analyses (75, 76).

6. Gender-specific characteristics

Considering the prevalence of diabetes in men and women separately, there is only little difference between the two sexes (77). When taking CVD risk into account, many cross-sectional studies and meta analyses have demonstrated a higher relative risk for CVD events and death from CVD in diabetic women than in men (in comparison with their non-diabetic counterparts), after adjustment of multiple CVD factors (78-83). This difference could be interpreted by factors, such worse lipid status, higher systemic inflammation, decreased

adherence to lipid and BP treatment and a different effect of diabetes in the endothelium, that characterize women mostly. However, it is not clear if women incur a greater absolute CVD risk than men at a specific glycemic status or even in prediabetes (83-84). As far as hypertension is concerned, middle aged men seem to have a greater prevalence than women, but this correlation is reversed in favor of women after the age of 65, across all racial and ethnic groups (85-87). The INTERHEART study showed a higher risk of CVD events in hypertensive women compared with men and possibly this can be attributed to greater prevalence of hypertension in older women (88). Guidelines from major medical associations for the treatment of hypertension suggest the same approach between men and women. However, it is not known if there are differences between the two sexes regarding specific antihypertensive medications and their impact in BP control. Data from NHANES 1999-2004 show that hypertensive women seem to be more likely to take medication for hypertension than men but they often don't achieve BP targets (89). Therefore, gender-specific characteristics regarding BP, T2DM and CVD should be taken into consideration, even if clearly different recommendations do not exist yet.

7. Conclusions

As the majority of patients with T2DM present also hypertension and the co-existence of the two entities essentially increase the incidence of both micro- and macrovascular complications, the optimal control of BP must be a major priority for physicians treating such patients. Evidence shows that a BP target of <140/90 mmHg applies to most patients with T2DM, but individualization is always important. Proper assessment of BP is essential for diagnosis, while healthy lifestyle should be the cornerstone for the treatment. All classes of antihypertensive drugs can be used in the management of hypertension in patients with T2DM, as long as they are effective and safe and after taking into consideration co-

morbidities. ACE inhibitors or ARBs constitute the ideal choice for initial or early treatment of hypertension in patients with diabetes and albuminuria. Combination of two or more drugs seems to be inevitable as most of these patients demonstrate resistant hypertension. The combination of ACE inhibitors with ARBs is not recommended and should be avoided. Thiazide and thiazide-like diuretics might be beneficial, alone or in a fixed-dose combination with ACE inhibitors or ARBs. CCBs constitute an ideal option as a second or third-line agent. Beta-blockers are not considered as first-line antihypertensive agents, excluding those patients with heart failure or those who have suffered a myocardial infarction. The addition of mineralocorticoid receptor antagonists to a triple drug therapy seems the next ideal step in the treatment algorithm. Gender-specific characteristics regarding BP, T2DM and CVD should be taken into consideration, even if different recommendations do not exist yet.

Contributors

Dimitra I. Pavlou performed the literature search and wrote the manuscript.

Stavroula A. Paschou conceived and designed the review, performed the literature search and wrote the manuscript.

Panagiotis Anagnostis critically revised the article for important intellectual content and contributed to the discussion.

Michael Spartalis critically revised the article for important intellectual content and contributed to the discussion.

Eleftherios Spartalis critically revised the article for important intellectual content and contributed to the discussion.

Andromachi Vryonidou critically revised the article for important intellectual content and contributed to the discussion.

Nicholas Tentolouris critically revised the article for important intellectual content and contributed to the discussion.

Gerasimos Siasos conceived and designed the review, critically revised the article for important intellectual content and contributed to the discussion.

All authors read and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

No funding was received for the preparation of this review.

Provenance and peer review

This article has undergone peer review.

References

1. Sowers JR. Diabetes mellitus and vascular disease. Hypertension. 2013; 61(5):943–7.

2. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: an update. Hypertension. 2001; 37:1053–1059.

3. Kannel WB, Wilson PW, Zhang TJQ. The epidemiology of impaired glucose tolerance and hypertension. Am Heart J 1991, 121: 1268-1273.

4. Adler AI, Stratton IM, Neil HA, et al Association of systolic BP with macrovascular and microvascular complications of type 2 diabetes(UKPDS 36). BMJ. 2000;321(7258):412–419

5. Hu G, Jousilahti P, Tuomilehto J. Joint effects of history of hypertension at baseline and Type 2 diabetes at baseline and during follow-up on the risk of coronary heart disease. Eur Heart J. 2007; 28:3059–3066.

6. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovasculardisease: a scientific statement from the American Heart Association and American Diabetes Association. Circulation 2014;130:1110–1130.

7. 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 CardiovascularSurgery 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.

8. Raffaele Izzo, Giovanni de Simone, Marcello Chinali, Guido Iaccarino, Valentina Trimarco, Francesco Rozza, Renata Giudice, Bruno Trimarco, and Nicola De Luca, Insufficient Control of BP and Incident Diabetes. Diabetes Care 2009; 32: 845–850.

9. Massiera F, Bloch-Faure M, Ceiler D, et al. Adipose angiotensinogen is involved in adipose tissue growth and BP regulation. FASEB J. 2001; 15:2727–2729.

10. Boustany CM, Bharadwaj K, Daugherty A, et al. Activation of the systemic and adipose renin angiotensin system in rats with diet-induced obesity and hypertension. Am J Physiol Regul Integr Comp Physiol. 2004; 287:R943–R949.

11. Ferrannini E, Buzzigoli G, Bonadonna R, et al. Insulin resistance in essential hypertension. N Engl J Med. 1987; 317:350–357.

12. Bonora E, Capaldo B, Perin PC, et al. Hyperinsulinemia and insulin resistance are independently associated with plasma lipids, uric acid and BP in non-diabetic subjects. The GISIR database. Nutr Metab Cardiovasc Dis. 2008; 18:624–631.

13. Muniyappa R, Quon MJ. Insulin action and insulin resistance in vascular endothelium. Curr Opin Clin Nutr Metab Care. 2007; 10:523–530.

14. Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: insights into insulin action. Nat Rev Mol Cell Biol. 2006; 7:85–96

15. Vincent MA, Montagnani M, Quon MJ. Molecular and physiologic actions of insulin related to production of nitric oxide in vascular endothelium. CurrDiab Rep. 2003; 3:279–288.

16. Smulyan H, Lieber A, Safar ME. Hypertension, Diabetes Type II, and Their Association: Role of Arterial Stiffness Am J Hypertens. 2016;29:5-13.

17. UK Prospective Diabetes Study Group. Tight BP control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ. 1998; 317:703–713.

18. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive BP lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension OptimalTreatment (HOT) randomised trial. HOT Study Group. Lancet. 1998; 351:1755–62.

19. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes The ADVANCE Collaborative Group N Engl J Med 58:2560-72.

20. Fagard RH, Staessen JA. Treatment of isolated systolic hypertension in the elderly: the Syst-Eur trial. Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Clin Exp Hypertens. 1999;21(5-6):491-7

21. American Diabetes Association: Treatment of hypertension in adults with diabetes. Diabetes Care 2002, 25:199–201.

22. Sixth Join National Committee: The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP. Arch Intern Med 1997;157:2413–2446.

23. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, National Heart, Lung, and:Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP; National High BP Education Program Coordinating Committee: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP: the JNC 7 report. JAMA 2003; 289:2560–2572.

24. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, StruijkerBoudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, et al: 2007 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). Eur Heart J 2007; 2007:1462–1536.

25. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, Cifkova R, Clément D, Coca A, Dominiczak A, Erdine S, Fagard R, Farsang C, Grassi G, Haller H, Heagerty A, Kjeldsen SE, Kiowski W, Mallion JM, Manolis A, Narkiewicz K, Nilsson P,

Olsen MH, Rahn KH, Redon J, Rodicio J, Ruilope L, Schmieder RE, Struijker-Boudier HA, Van Zwieten PA, et al: Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens 2009; 27:2121–2158.

26. Schrier RW, Estacio RO, Jeffers B: Appropriate BP Control in NIDT2DM (ABCD) Trial. Diabetologia 1996, 39:1646–1654.

27. ACCORD Study Group. Cushman WC, Evans GW, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010; 362:1575–1585.

28. Redon J, Mancia G, Sleight P, et al. ONTARGET Investigators. Safety and efficacy of low blood pressures among patients with diabetes: subgroup analyses from the ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial). J Am Coll Cardiol 2012; 59:74–83.

29. Cooper-DeHoff RM, Gong Y, Handberg EM, Bavry AA, Denardo SJ, Bakris GL, Pepine CJ: Tight BP control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. JAMA 2010, 304:61–68.

30. Haller H, Ito S, Izzo J, Januszewicz A, Katayama S, Menne J, Mimran A, Rabelink TJ, Ritz E, Ruilope L, Rump LC and Viberti G, for the ROADMAP Trial Investigators: Olmesartan for delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med 2011, 364:907–917.

31.Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. BP lowering in type 2 diabetes: a systematic review and meta-analysis JAMA 2015;313:603-615.

32. Standards of Medical Care in Diabetes-2013 American Diabetes Association Diabetes Care 2013; 36(Suppl. 1): S11-S66

33. 2013 ESH/ESC Guidelines for themanagement of arterial hypertension TheTask Force for the management ofarterial hypertension of the European Society of Hypertension (ESH)

and of the European Society of Cardiology (ESC) Journal of Hypertension 2013;31:1281–1357.

34. Standards of Medical Care in Diabetes-2018. Diabetes Care 2018 Jan; 41 (Supplement 1): S4-S6.

35. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high BP in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507–520.

36. Hypertension: The Clinical Management of Primary Hypertension in Adults. Update of Clinical Guidelines 18 and 34. National Clinical Guideline Centre, Ed. Commissioned by the National Institute for Health and Clinical Excellence (NICE), Royal College of Physicians (UK), London, 2011. Available from: http://www.nice.org.uk/guidance/cg127/documents/hypertension-update-full-guideline2.

37. Pickering TG, Hall JE, Appel LJ, et al. Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood care.diabetesjournals.org de Boer and Associates 1281 Pressure Research. Recommendations for BP measurement in humans and experimental animals: part 1: BP measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High BP Research. Hypertension 2005;45: 142–161.

38. Home BP monitoring is better than office BP and ambulatory BP: update. J Hypertens. 2016 Sep; 34 Suppl 1 - ISH 2016 Abstract Book:e24.

39. Staessen JA, Li Y, Hara A, Asayama K, Dolan E, O'Brien E. BP Measurement Anno 2016 Am J Hypertens. 2017 May 1;30(5):453-463.

40. Kario K, Saito I, Kushiro T, Teramukai S, Tomono Y, Okuda Y, Shimada K Morning Home BP Is a Strong Predictor of Coronary Artery Disease The HONEST Study. J Am Coll Cardiol. 2016;67:1519-1527.

41. Racial Differences in the Prevalence of Chronic Kidney Disease among Participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Cohort Study J Am Soc Nephrol 17: 1710 –1715, 2006.

42. 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.

43. Sacks FM, Svetkey LP, Vollmer WM, et al.; DASH-Sodium Collaborative Research Group. Effects on BP of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med 2001;344:3-10.

44. 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.

45. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high BP in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507-520.

46. 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.

47. 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 2014. Rockville, MD, Agency for Healthcare Research and Quality (US), 2014. Available from http://www.ncbi.nlm.nih.gov/books/ NBK241537/.

48. Whelton PK, Appel L, Charleston RN, et al. The effects of nonpharmacologic interventions on BP of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. 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 BP control: main results of the PREMIER clinical trial. JAMA 2003;289: 2083–2093.

50. 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.

51. BP Lowering Treatment Trialists' Collaboration. Effects of different BP-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.

52. Diabetes and Hypertension: A Position Statement by the American Diabetes Association Diabetes Care 2017;40:1273-1284.

53. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med 2007;120:713-719.

54. Bakris GL, Weir MR; Study of Hypertension and the Efficacy of Lotrel in Diabetes (SHIELD) Investigators. Achieving goal BP in patientswith type 2 diabetes: conventional versus fixed-dose combination approaches. J Clin Hypertens (Greenwich) 2003;5:202–209.

55. 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.

56. Bangalore S, Fakheri R, Toklu B, Messerli FH. Diabetes mellitus as a compelling indication for use of rennin angiotensin system blockers: systematic review and meta-analysis of randomized trials. BMJ. 2016;352:i438.

57. Hans-Henrik Parving et al., for the ALTITUDE Investigators Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes The ALTITUDE Trial N Engl J Med 2012;367:2204-13.

58. Mancia G, Schumacher H, Redon J, Verdecchia P, Schmieder R, Jennings G, et al. BP targets recommended by guidelines and incidence of cardiovascular and renal events in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET). Circulation 2011; 124:1727–1736.

59. Catala-Lopez F, Macıas Saint-Gerons D, Gonzalez-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.

60. Hansson L. Results of the STOP-Hypertension-2 trial. Blood Press Suppl. 2000;2:17-20.

61. 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.

62. 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.

63. Lewis EJ, Hunsicker LG, ClarkeWR, 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.

64. Hillebrand U, Lang D, Telgmann RG, Hagedorn C, Reuter S, Kliche K, Stock CM, Oberleithner H, Pavenstädt H, Büssemaker E, Hausberg M. Nebivolol decreases endothelial cell stiffness via the estrogen receptor beta: a nano-imaging study J Hypertens. 2009;27:517-26.

65. 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.

66. 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.

67. Williams B,MacDonaldTM,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 randomized, double-blind, crossover trial. Lancet 2015;386:2059–2068.

68. Filippatos G, Anker SD, Bohm 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.

69. Bomback AS, Klemmer PJ. Mineralocorticoid receptor blockade in chronic kidney disease. Blood Purif 2012;33:119-124.

70. Low dose spironolactone reduces BP in patients with resistant hypertension and type 2 diabetes mellitus: a double blind randomized clinical trial. J Hypertens 2013;31:2094-102.

71. 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.

72. Oliva RV, BakrisGL. BP effects of sodium-glucose co-transport 2 (SGLT2) inhibitors. J Am Soc Hypertens 2014;8:330-339.

73. Tikkanen I, Narko K, Zeller C, Green A, Salsali A, Broedl UC, Woerle HJ; EMPA-REG BP Investigators Diabetes Care. Empagliflozin reduces BP in patients with type 2 diabetes and hypertension. Diabetes Care. 2015;38:420-8.

74. Townsend RR, Machin I, Ren J, Trujillo A, Kawaguchi M, Vijapurkar U, Damaraju CV6, Pfeifer M. Reductions in Mean 24-Hour Ambulatory Blood Pressure After 6-Week Treatment With Canagliflozin in Patients With Type 2 Diabetes Mellitus and Hypertension. J Clin Hypertens (Greenwich). 2016;18:43-52.

75. Wang B, Zhong J, Lin H, Zhao Z, Yan Z, He H, Ni Y, Liu D, Zhu Z. BP-lowering effects of GLP-1 receptor agonists exenatide and liraglutide: a meta-analysis of clinical trials. Diabetes Obes Metab. 2013;15:737-749.

76. Katout M, Zhu H, Rutsky J, Shah P, Brook RD, Zhong J, Rajagopalan S. Effect of GLP-1 mimetics on BP and relationship to weight loss and glycemia lowering: results of a systematic meta-analysis and meta-regression. Am J Hypertens 2014;27:130-9.

77. International Diabetes Federation. IDF Diabetes Atlas, 6th edn. Brussels Belgium: International Diabetes Federation, 2013. http://www.idf.org/diabetesatlas

78. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ. 2006; 332:73–78.

79. Heyden S, Heiss G, Bartel AG, Hames CG. Sex differences in coronary mortality among diabetics in Evans County, Georgia. J Chronic Dis. 1980;33:265–273.

80. Lee WL, Cheung AM, Cape D, Zinman B. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. Diabetes Care. 2000;23:962–968.

81. Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. Diabetologia. 2014;57: 1542–1551.

82. Liang H, Vallarino C, Joseph G, Manne S, Perez A, Zhang S. Increased risk of subsequent myocardial infarction in patients with type 2 diabetes mellitus: a retrospective cohort study using the U.K. General Practice Research Database. Diabetes Care. 2014;3: 1329–1337.

83. Anagnostis P, Majeed A, Johnston DG, Godsland IF. Cardiovascular risk in women with type 2 diabetes mellitus and prediabetes: is it indeed higher than men? Eur J Endocrinol. 2014;171:R245–R255.

84. Paschou SA, Leslie RD. Personalizing guidelines for diabetes management: twilight or dawn of the expert? BMC Med. 2013;11:161.

85. Stamler J, Stamler R, Riedlinger WF, Algera G, Roberts RH. Hypertension screening of 1 million Americans. Community Hypertension Evaluation Clinic (CHEC) program, 1973 through 1975. JAMA. 1976;235:2299-306.

86. Flegal KM, Ogden CL, Carroll MD. Prevalence and trends in overweight in Mexican-american adults and children. Nutr Rev. 2004;62:S144-8.

87. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-52.

88. Qiuping Gu, Vicki L. Burt, Ryne Paulose-Ram and Charles F. Dillon Gender Differences in Hypertension Treatment, Drug Utilization Patterns, and Blood Pressure Control Among

US Adults With Hypertension: Data From the National Health and Nutrition Examination Survey 1999–2004 Am J Hypertens. 2008;21:789-98.

Table 1. Blood pressure targets for patients with type 2 diabetes mellitus according to guidelines

Medical Society	BP Target
ADA 2018	< 140/90 mmHg
ESC/ESH Diabetes guideline 2013	< 140/85 mmHg
JNC 8 2014	< 140/90 mmHg
NICE (UK 2013)	< 140/80 mmHg, but if retinopathy, cerebrovascular disease, or microalbuminuria is present: <130/80 mm Hg

ADA: American Diabetes Association; ESC: European Society of Cardiology; ESH: European Society of Hypertension; JNC: Joint National Committed; NICE: National Institute for Health and Care Excellence

Table 2. Algorithm steps for the treatment of hypertension in patients with type 2 diabetes mellitus

Steps	Diet and Exercise	ACE inhibitors	ARBs	CCBs (dihydropyridine)	Diuretics	Beta-blockers	MARs
BP < 140/90 mmHg	+	-	-	-	-	-	-
BP ≥ 140/90 mmHg and < 160/100 mmHg							
Monotherapy	+	+	+	+	+	-	-
Albuminuria	+	+	+	-	-	-	-
BP ≥ 160/100mmHg Dual Therapy*	+	+	+	+	+	-	-
Triple Therapy	+	+	+	+	+	-	-
Myocardial infarction	+	+	+	+	+	+	-
Resistant hypertension	+	+	+	+	+	+	+

*the simultaneous administration of ACE inhibitors and ARBs should be avoided

ACE: angiotensin-converting-enzyme; ARBs: angiotensin receptor blockers, CCBs: calcium channel blockers, MARS: mineralocorticoid receptor antagonists