

Type 2 diabetes mellitus and hypertension

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Received: March 2, 2016, Accepted: March 18, 2016

Abstract

Arterial hypertension (HTN) is a major risk factor both for atherosclerotic cardiovascular disease (ASCVD) and for microvascular complications of diabetes mellitus (DM). While the evolution of type 2 DM doubles the cardiovascular risk in men and triples it in women, HTN increases the cardiovascular risk by four times in DM patients. ASCVD represent the main cause of morbidity and mortality for DM patients and it is the highest contributor of direct and indirect costs for DM. Obesity, age, onset of chronic kidney disease (CKD) favor increasing of HTN prevalence. DM and HTN represent additional risk factors for ASCVD. Type 2 DM is characterized by a long duration of insulin resistance, with compensatory hyperinsulinemia and various degrees of hyperglycemia, associated to a high cardiovascular risk and development of macrovascular complications before diagnosis. Decrease of arterial pressure with various treatment plans proved to be efficient in reducing the cardiovascular events. Although proof regarding the distinct advantages of renin-angiotensin system (RAS) inhibitors on the ASCVD results in DM still remain unclear, the high risk for ASCVD associated to DM and high prevalence of undiagnosed ASCVD may continue to favor recommendations for using RAS inhibitors as a first line antihypertensive treatment in persons with DM. The main objective in treating HTN in DM patients is to decrease blood pressure (BP) < 140/90 (ADA and JNC8), or BP < 140/85 (ESC/EASD) mm Hg. In order to reach these values, a combination of several antihypertensive drugs is required in various patients with HTN and DM.

Keywords: hypertension, diabetes mellitus, atherosclerotic cardiovascular disease, insulin resistance

Background

Arterial hypertension (HTN) is a comorbidity frequently associated to diabetes mellitus (DM), affecting most of the patients, with a prevalence related to age, obesity, DM type,

ethnic group, etc. HTN is a major factor risk both for atherosclerotic cardiovascular disease (ASCVD) and for microvascular complications of DM. In type 1 DM, HTN is most often the result of diabetic nephropathy, while in type 2 DM, this coexists with other cardiometabolic risk factors [1].

HTN prevalence in DM patients is higher than in general population: approximately 49% of type 1 DM patients and over 60% of type 2 DM have HTN [2, 4-7].

Obesity, age, onset of chronic kidney disease (CKD) favour HTN prevalence increase. DM and HTN represent

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additional risk factors for ASCVD. While the evolution of type 2 DM doubles the cardiovascular risk in men and triples it in women, HTN increases the cardiovascular risk by four times in DM patients [2, 8-9].

ASCVD defined as: acute coronary syndrome, myocardial infarction, stable or unstable angina pectoris, revascularization in coronary arteries or in other arteries, stroke, transitory ischemic stroke or peripheral arterial disease, supposed to have an atherosclerotic origin, represent the main cause of morbidity and mortality for DM persons and it is the highest contributor of direct and indirect costs for DM [1].

The most frequent diseases associated to type 2 DM (for example, HTN and dyslipidemia) are most certainly risk factors for ASCVD, while the DM presence provides an independent, additional risk.

There is proof that the risk for heart disease after 10 years, in American DM adults, has significantly improved in the last ten years [1, 10] and that mortality and morbidity caused by ASCVD have decreased [1, 11-13].

Risk factors for ASCVD in the hypertensive patient: sex, age (men ≥ 55 years old; women ≥ 65 years old), smoking, dyslipidemia [total cholesterol > 4.9 mmol/L (190 mg/dL), and/or LDL cholesterol > 3.0 mmol/L (115 mg/dL), and/or HDL cholesterol: men < 1.0 mmol/L (40 mg/dL), women < 1.2 mmol/L (46 mg/dL), and/or triglycerides (TG) > 1.7 mmol/L (150 mg/dL)], a jeune glycemia 5.6–6.9 mmol/L (102–125 mg/dL), abnormal glucose tolerance test, obesity [BMI ≥ 30 kg/m²], abdominal obesity (waist circumference: men ≥ 102 cm; women ≥ 88 cm, in Caucasian population), family history including premature cardiovascular disease (CVD) (men < 55 years old; women < 65 years old) [3].

Except for the risk factors, the prognosis of the hypertensive patient is also influenced by: asymptomatic damaging of target organs, presence of DM, stage of CKD and presence of symptomatic ASCVD (Table 1) [3].

There were developed several computerized models in order to estimate the total cardiovascular risk. One of these, the SCORE diagram (Systematic COronary Risk Evaluation) was developed based on extended European cohort studies. This model estimates the risk for cardiovascular cause death risk after 10 years, taking into consideration age, sex, smoking habit, total cholesterol and systolic blood pressure [3, 14].

The risk may be higher than the one in the diagram in the following situations: sedentary subjects and with abdominal obesity; a relatively high risk associated with overweight is higher in the young than in the old; socially underprivileged persons and ethnic minorities; subjects with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT), who do not meet the diagnostic criteria for DM; subjects with high values of TG, fibrinogen, B apolipoprotein, reactive C-protein; persons with a family history of premature ASCVD (before 55 years old in men and 65 years old in women) [3].

Hypertension – Diabetes – Atherosclerotic cardiovascular disease relationship

The cardiovascular continuum in type 2 DM. Type 2 DM is characterized by a long duration of insulin resistance, with compensatory hyperinsulinemia and various degrees of hyperglycemia, associated to a high cardiovascular risk and de-

Table 1. Stratification of total cardiovascular risk in low, moderate, high and very high, according to the systolic blood pressure (SBP), diastolic blood pressure (DBP), risk factors prevalence, asymptomatic organ damaging, CKD stage or symptomatic ASCVD.

| Other risk factors, asymptomatic organ damaging or disease presence | Arterial blood pressure (mmHg) | | | |
|---|--|---|--|---|
| | High normal SBP 130-139 or DBP 85-89 | First degree HTN SBP 140-159 or DBP 90-99 | Second degree HTN SBP 160-179 or DBP 100-109 | Third degree HTN SBP ≥ 180 or DBP ≥ 110 |
| No risk factor | | Low risk | Moderate risk | High risk |
| 1-2 risk factors | Low risk | Moderate risk | Moderate/ high risk | High risk |
| ≥ 3 risk factors | Low/ moderate risk | Moderate/ high risk | High risk | High risk |
| Organ damaging, stage 3 CKD or DM | Moderate/ high risk | High risk | High risk | High / very high risk |
| Symptomatic ASCVD, CKD stage ≥ 4 , or DM with organ damaging/ risk factors | Very high risk | Very high risk | Very high risk | Very high risk |

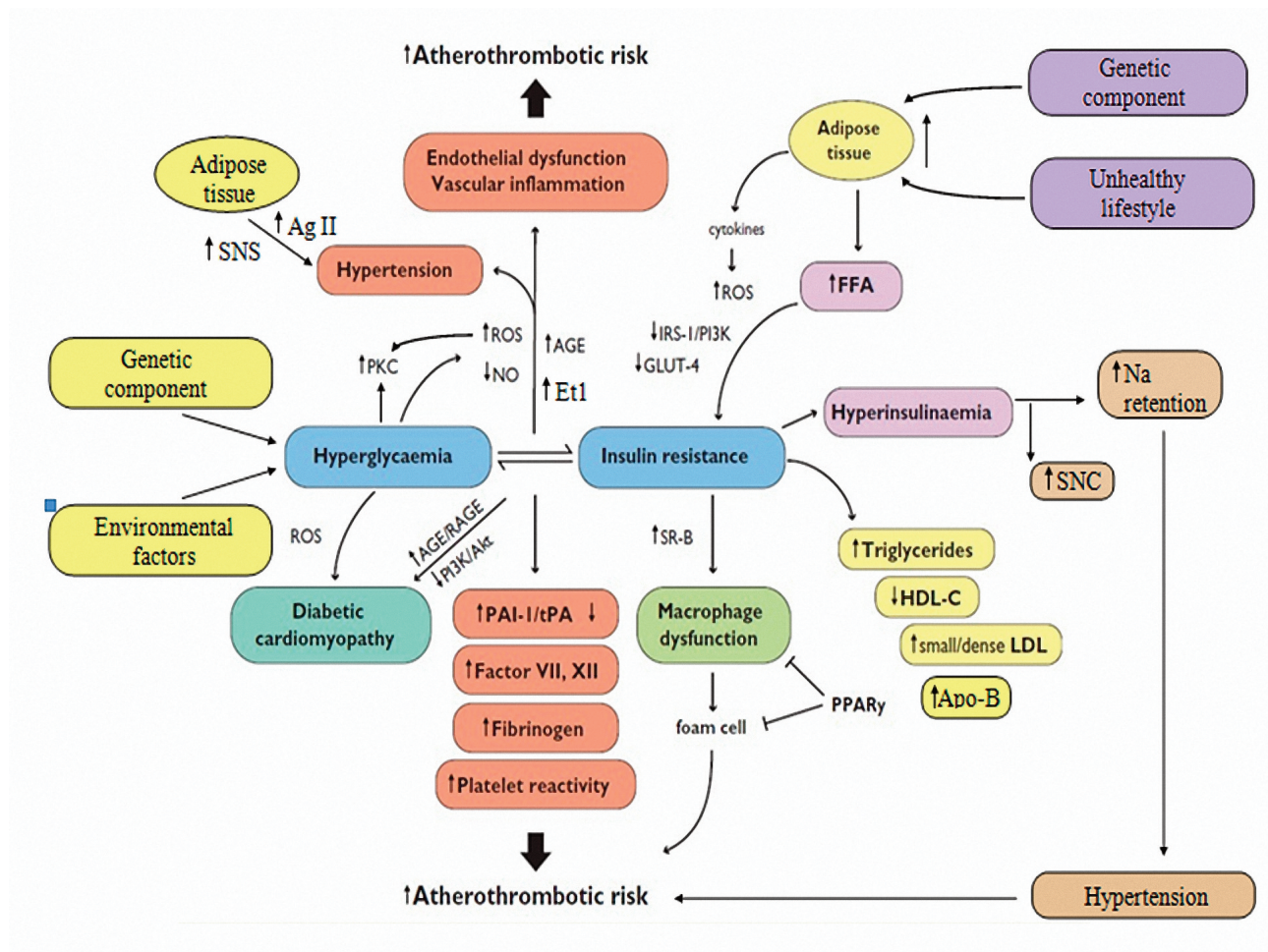


Figure 1. Hyperglycaemia, IR, HTN and ASCVD (adapted from [2]). AGE= advanced glycated end-products; FFA =free fatty acids; GLUT-4 = glucose transporter 4; HDL-C = high-density lipoprotein cholesterol; LDL = low-density lipoprotein particles; NO = nitric oxide; PAI-1 = plasminogen activator inhibitor-1; PKC = protein kinase C; PPAR γ = peroxisome proliferator-activated receptor γ ; PI3K = phosphatidylinositol 3-kinase; RAGE = AGE receptor; ROS = reactive oxygen species; SR-B = scavenger receptor B; tPA = tissue plasminogen activator.

development of macrovascular complications before diagnosis. Prior to DM diagnosing there may be observed the IFG and IGT, followed by DM and ASCVD, thus supporting the continuum glycemic concept [2]. The development of ASCVD in persons with insulin resistance (IR) is a progressive process, characterized by an early onset of endothelial dysfunction and inflammation of vessels, leading to monocyte recruitment, foam cell emergence and subsequent development of lipidic striae, followed by atheroma plaques, which, in the presence of inflammation, become unstable, break and lead to the formation of occlusive thrombi (Figure 1). Atheroma plaques in patients with DM contain various lipids, inflammatory changes and thrombi [2].

Pathophysiology of IR in type 2 DM. IR plays an important part in type 2 DM and ASCVD physiopathology and both genetic and environment factors contribute to its de-

velopment. Over 90% of DM persons are obese [2, 15], the release of free fatty acids (FFA) and cytokines from the adipose tissue directly affecting insulin sensitivity. In the muscles and adipose tissue, the formation of reactive oxygen species (ROS) induced by FFA attenuates the activation of the insulin receptor 1st layer and the PI3K-Akt signal, leading to the phenomenon called downregulation of GLUT-4 carriers (Figure 1) [2, 16-17].

Endothelial dysfunction, oxidative stress and vascular inflammation. FFA induced alteration in the PI3K way attenuates the Akt activity and the endothelial nitric oxide synthase (eNOS), thus resulting in the decrease of nitric oxide (NO) formation, endothelial dysfunction [2, 18] and vascular remodeling (increase of intima-media thickness), all these factors being important predictors for ASCVD (Figure 1) [2, 19-20].

In its turn, the ROS accumulation activates the transcription factor NF- κ B, leading to a high expression of inflammatory adhesion molecules and cytokines [2, 21].

Chronic IR stimulates pancreatic secretion of insulin, thus generating a complex phenotype that includes the beta-cell progressive dysfunction [2, 22], a low insulin level and increase of plasma glycemia.

Recent proof suggests that ROS production induced by hyperglycemia is involved in the persistence of vascular dysfunction, despite the normalizing of plasma glycemia. This phenomenon was called "metabolic memory" and it may explain the progression of macro and microvascular complications, despite the intensive glycemia control, in DM patients (Figure 1) [2, 23-25].

Macrophage dysfunction. Macrophage increase in the adipose tissue in obese persons represents a key process in metabolic inflammation and IR [2, 26]. In the IR presence, the macrophages increase the B scavenger receptor expression and of oxidized low density lipoproteins (LDL), thus promoting the formation of foam cells and atherosclerosis. It seems that macrophage abnormalities provide a cellular connection between DM and ASCVD, both by the IR increase and by contributing to the development of lipidic striae and vascular lesions (Figure 1).

Atherogenic dyslipidaemia. Therefore, the high production of very low-density lipoprotein (VLDL) in the liver appears due to the increase of the lipidic sublayer, decrease of apolipoprotein B-100 degradation (ApoB) and increase of lipogenesis. In type 2 DM and the metabolic syndrome, these changes lead to a lipidic profile characterized by the increase of triglycerides (TGs), decrease of high-density lipoprotein cholesterol (HDL-C), increase of lipoprotein remnants, apolipoprotein B (ApoB) synthesis and of small and dense LDL particles (Figure 1) [2, 27-28].

Coagulation and platelet function. In type 2 DM patients, IR and hyperglycemia participate in the pathogenesis of a prothrombotic state characterized by the increase of plasminogen activator inhibitor-1 (PAI-1), of factors VII and XII and fibrinogen, and the reduction of the tissular plasminogen activator level (tPA). Among the factors that contribute to the high risk of coronary events in DM, hyper-reactivity of thrombocytes has a major relevance. A series of mechanisms contribute to the platelet dysfunction, affecting the adhesion and activation, as well as aggregation, stages of platelet mediated thrombosis (Figure 1) [2, 29-30].

Diabetic cardiomyopathy. Diabetic cardiomyopathy represents the clinical condition diagnosed when faced with ventricular dysfunction in the absence of coronary

atherosclerosis and HTN. The patients with dilating cardiomyopathy were 75% more susceptible to have DM than the patients in the control group with the same age [2, 31]. IR, hyperinsulinemia, hyperglycemia, ROS accumulation, AGE / RAGE signals (advanced glycated end-products), hexosamine flow lead to structural heart abnormalities (myocardial hypertrophy, ventricular rigidity fibrosis, coronary circulation damaging) and functional ones (myocardial contractility damaging, heart dysfunction) (Figure 1) [2, 32-33].

The metabolic syndrome (Mets). Mets is defined as a group of risk factors for ASCVD and type 2 DM, including HTN, dyslipidemia (high TG and low HDL cholesterol), high plasma glycemia and abdominal obesity [34]. Although there is consent that Mets requires importance, there has been an active debate regarding the terminology and diagnosis criteria connected to its definition. Despite all this, the medical community agrees that the term "Mets" is appropriate for representing a combination of multiple risk factors. Even though Mets does not include the well-established risk factors (age, sex, smoking), patients with Mets present a two times higher risk for ASCVD and 5 times higher for developing type 2 DM.

Endothelial progenitor cells (PEC) and vascular repair. It seems that bone marrow derived cells circulating in the blood play a critical part in the endothelial repairing process. PEC, a sub-population of adult stem cells, are involved in maintaining the endothelial haemostasis and contribute to the formation of new blood vessels. Although the mechanisms by which PEC protect the cardiovascular system are unclear, proof shows that function damaging and PEC reduction are characteristic for DM. Therefore, these cells may become a potential therapeutical target for managing the vascular complications of DM [2, 35].

There may be concluded that oxidative stress plays an important role in the development of micro and macrovascular complications of DM. Taking into consideration that the cardiovascular risk is not stopped through an intensive glycemia control associated to the optimal multifactorial treatment, there are required treatment strategies based on the physiopathological mechanisms involved in the onset of chronic complications [2].

HTN management in DM patients

Lifestyle optimization. Even though there are no controlled studies regarding the role of diet and physical exercise in the treatment of DM and HTN patients, the study Dietary Ap-

proaches to Stop Hypertension (DASH) assessed the impact of healthy eating in the patients without DM and proved antihypertensive effects similar to those in the pharmacological monotherapy.

Change of lifestyle consists in reducing body weight excess, limiting sodium intake (<2300 mg/ day), increasing fruit and vegetable intake (8-10 portions a day) and low-fat dairy products (2-3 portions a day), avoiding the excessive intake of alcohol (no more than 2 portions a day in men and no more than one portion a day in women), as well as the increase of physical activity [1,36].

These (non pharmacological) strategies may also positively affect the glycemic and lipidic control and they must also be encouraged in those with moderately high arterial pressure, although the impact of lifestyle change upon the cardiovascular events has not been established yet.

If arterial pressure is confirmed to be ≥ 140 mmHg the systolic one and/ or the diastolic ≥ 90 mmHg, the pharmacological treatment must be initiated together with the non pharmacological one.

Pharmacological therapy. Decrease of arterial pressure with various treatment plans, including a variety of antihypertensive drugs, like angiotensin conversion enzyme inhibitors (ACE Inhibitors), angiotensin receptor blockers (ARBs), beta-blockers, diuretics and calcium channel blockers, proved to be efficient in reducing the cardiovascular events [1,37-39]. Nevertheless, several studies showed that there is no specific advantage for the ACE Inhibitors when initiating the anti HTN treatment in the hypertensive population in general, while treatment initiation with low doses of thiazide diuretics shows some advantage in the cardiovascular results [1,40-41].

Angiotensin Receptor Blockers (ARBs): in persons with DM, the renin-angiotensin system (RAS) inhibitors may show unique advantages for the initial or as early as possible treatment for HTN. In patients with congestive heart failure, also including the subgroup with DM, ARBs showed the reduction of major ASCVD events [1,42]. In the patients with type 2 DM and significant CKD, ARBs were superior to the calcium channel blockers in reducing heart failure [1,43].

Although proof regarding the distinct advantages of RAS inhibitors on the ASCVD results in DM still remain unclear [11,22], the high risk for ASCVD associated to DM and high prevalence of undiagnosed ASCVD may continue to favour recommendations for using RAS inhibitors as a first line antihypertensive treatment in persons with DM [1,44].

The use of combined ACE inhibitors and ARBs is not recommended, taking into consideration the lack of additional ASCVD benefits, but also a high rate of adverse events: hyperkalemia, syncope and kidney failure [1,45].

Other Pharmacological Interventions. In the HTN group from the ADVANCE Study, there was proven that the usual administration of a fixed ACE inhibitor- diuretic combination, namely perindopril-indapamide, significantly reduced the micro and macrovascular complications, and also cardiovascular death and total mortality. These results may also be due to reaching a lower arterial pressure in the perindopril-indapamide arm. Another study proved a morbidity and mortality decrease in the patients receiving benazepril and amlodipine in contrast to those who received benazepril and hydrochlorothiazides (HCTZ) [1,46]. The proven benefits of RAS inhibitors in the patients with DM and albuminuria or kidney failure give additional arguments for using these agents.

When needed, in order to reach the objectives of arterial pressure, there may be added amlodipine, HCTZs or chlorthalidone. When the estimated glomerular filtration rate (eGFR) value is < 30 ml/ min/ 1.73 m², there should be prescribed a diuretic in the ansa instead of HCTZs or chlorthalidone.

Bedtime Dosing. More and more proof suggest that there is an association between the arterial pressure increase during sleep and the increase of ASCVD event incidence. We should take into consideration the administration of one or more antihypertensives in the evenings, before bedtime, as DM patients present a higher percentage of the non dipping phenomenon (lack of pressure decrease values during sleep) [1, 47-48].

Other Considerations. Most patients with DM and HTN require treatment including various drugs in order to reach the therapeutical targets [1, 36]. The barriers staying in the way of treatment adherence (such as adverse effects and costs) should be identified and removed. When arterial pressure remains uncontrolled, despite treatment adherence, in optimal doses of at least three antihypertensives from different classes, from which at least one should be a diuretic, the doctors should take into consideration an assessment for the adverse effects of HTN.

Pregnancy and Antihypertensive Medications. In pregnant women with DM and HTN, the target HTN values are: SBP= 110-129 mmHg and DBP=65-79 mmHg, these contributing to the improvement of the long-term maternal health.

A lower value of BP may be associated to interference in fetal growth. During pregnancy, the treatment with ACE Inhibitors and ARBs is not recommended, as it may lead to fetal malformations. The antihypertensives considered effi-

cient and safe during pregnancy include Metildopa, Labetalol, Diltiazem, Clonidine and Prazosin. The chronic use of a diuretic drug during pregnancy is not recommended, as it was associated to a low volume of maternal plasma, which may reduce the uteroplacental perfusion [1,49].

ESC/ESH 2013 Recommendations. The ESC/ESH 2013 Guide (Table 2) recommends the drugs that should be used in a certain clinical context, based on the fact that these drugs have proved their efficiency in clinical randomized studies. Anyway, the curing doctor should take into consideration the adverse events, even if these may sometimes be subjective ones, as their onset may influence the patients' treatment adherence. If it is considered necessary, the doses or drugs may be changed in order to combine efficiency with tolerance [3].

HTN in the hypertensive old patients with DM. Although it is not unanimously established a definition for the old, it is generally accepted that this concept reflects a continuum that starts around the age of 65 years old, it is characterized by a slow progressive damage of the functions, continuing up to the end of life.

The old have a higher risk of developing type 2 DM due to the combined effect of insulin resistance increase, as well as to the pancreatic function damage with age. Age-related IR seems to be mainly associated to adiposity, sarcopenia and lack of physical activity [50].

Due to the fact that dyslipidemia and HTN are frequent pathologies in the old, it is recommended the decrease of lipids in these patients [51].

The old with DM have a higher rate of inferior extremity amputation, of myocardial infarction, vision damage and final stage CKD, in comparison to the people of the same age, but with no DM. Patients with DM aged over 75 years old come to the emergency 2 times more often for hypoglycemia than the general population, and the ones aged over 75 years old have higher rates of complications than those aged between 64 and 74 years old, as well [50]. There is solid proof showing that BP decrease from high values (for example SBP of 170 mmHg) to moderate values (for example SBP of 150 mmHg) reduces the cardiovascular risk in the old patients with diabetes [50]. In the hypertensive old patients with DM there is a consent regarding the target values of glycemia, arterial pressure and lipidic values (Table 3) [1]

BP target values in patients with DM. SBP target values: persons with DM and HTN should be treated to reach a SBP target value <140 mmHg; a SBP target value < 130 mmHg may be adequate for some persons with DM, such as: the young, patients with albuminuria and/ or HTN and

Table 2. Antihypertensive treatment, according to the clinical context.

| Clinical Context | Antihypertensive Drugs |
|--|---|
| Asymptomatic organ damage | |
| Left ventricle hypertrophy | ACEI, calcium antagonist, ARB |
| Asymptomatic atherosclerosis | calcium antagonist, ACEI |
| Microalbuminuria | ACEI, ARB |
| Kidney damage | ACEI, ARB |
| Clinical cardiovascular event | |
| Stroke in medical history | Any drug may be efficient in decreasing BP |
| Myocardium infarction in medical history | Beta-blockers, ACEI, ARB |
| Angina pectoris | Beta-blockers, calcium antagonist |
| Heart failure | Diuretics, Beta-blockers, ACEI, ARB, mineralcorticoid receptor antagonist |
| Aorta aneurism | Beta-blockers |
| Atrial fibrillation prevention | ARB, ACEI, Beta-blockers or mineralcorticoid receptor antagonist |
| Atrial fibrillation and ventricular allure control | Beta-blockers, non-dihydropyridine calcium antagonists |
| Final stage CKD/ proteinuria | ACEI, ARB |
| Peripheral arteriopathy | ACEI, calcium antagonist |
| Others | |
| Isolated systolic HTN (in the old) | Diuretics, calcium antagonist |
| Metabolic syndrome | ACEI, ARB, calcium antagonist |
| Diabetes Mellitus | ACEI, ARB |
| Pregnancy | Metildopa, beta-blockers, calcium antagonist |
| African-American population | Diuretics, calcium antagonist |

ACEI=angiotensin-converting enzyme inhibitor, ARB=angiotensin receptor blocker

one or more risk factors for ASCVD, when his BP value may be reached without prescribing any excessive treatment [1].

DBP target values: persons with DM should be treated to reach a DBP target value <90 mmHg; a DBP target value < 80 mmHg may be adequate for some persons with DM, such as: the young, patients with albuminuria and/ or HTN

Table 3. Individualization of treatment targets in old patients with DM [1].

| Characteristics of the patients/ health state | (A1C) * | Glycemia (mg/dL) | | BP (mmHg) | Lipids |
|---|---------|------------------------|------------|-----------|--|
| | | a jeun/ preprandial | at bedtime | | |
| Healthy (a few associated chronic diseases, intact functional and cognitive status). Long lifetime expectation | <7.5% | 90–130 | 90–150 | <140/90 | Statines, if tolerated and have no counter indications |
| Complex/ intermediary (multiple chronic disease or more than two daily activities affected or mild or moderate cognitive deterioration). Average lifetime expectation, risk for hypoglycemia | <8.0% | 90–150 | 100–180 | <140/90 | Statines, if tolerated and have no counter indications |
| Very complex/ damaged health state (long term healthcare/ final stage chronic diseases, or moderate to severe deterioration of the cognitive function or more than two daily activities affected). Limited lifetime expectation makes benefits to be uncertain. | <8.5% | 100–180 | 110–200 | <150/90 | It is taken into consideration the probability of the statine benefits (more as a secondary prevention than a primary intervention). |

*a lower target value may be established for certain patients if it may be reached without any risk of repeated or severe hypoglycemia.

and one or more risk factors for ASCVD, when this BP value may be reached without prescribing any excessive treatment [1].

Epidemiological tests proved that blood pressure >115/75 mmHg is associated to a high rate of cardiovascular events and mortality in patients with DM, and that DBP >120 mmHg predicts the onset of CKD in final stage. Still, randomized clinical studies have shown benefits for the DM patients (reduction of coronary events, strokes, CKD) with values of SBP < 140 mmHg and DBP < 90 mmHg. [1,52]

A meta analysis of randomized clinical studies in adults with type 2 DM, comparing the intensive reduction of BP (down to values under 130 mmHg systolic and 80 mmHg diastolic) to the standard values (limits between 140–160 mmHg systolic and 85–100 mmHg diastolic), did not show any significant reduction of mortality or non fatal myocardial infarction. In this meta analysis, the relative risk for stroke was statistically significantly lower, by 35% in the intensive treatment group, while the absolute risk was lower only by 1%, and, moreover, in the intensive treatment group the risk for adverse events increased, such as arterial hypotension and syncope [1,53].

When the studies were stratified according to the basic SBP value: ≥ 140 mmHg or <140 mmHg, the antihypertensive treatment was associated to a lower risk of stroke and al-

buminuria, independent of the initial SBP [1,54]. Thus, in persons where the risk for stroke is a reason of concern, as part of the ordinary decisional process, there may be established lower BP target values, such as SBP < 130 mm Hg.

Clear evidence from randomized clinical studies supports the DBP target value <90 mmHg. Previous recommendations for SBP <80 mmHg were mainly based on the post hoc study of the HOT group [1, 55]. A DBP target value <80 mmHg may be adequate for the patients with a long lifetime expectation, for those with CKD, high albuminuria and for those with additional risk factors for ASCVD, such as dyslipidemia, smoking and obesity [1].

The American Diabetes Association (ADA) Guide in 2016 was revised in order to reflect the high quality existent evidence supporting a DBP target value <90 mmHg. These target values are in accordance with the Eighth Joint National Committee recommendations: the BP target values for the individuals aged over 18 years old with DM are SBP <140 mmHg and DBP <90 mmHg [1,56]

The patients' characteristics in the table above represent a general concept, as not all the patients definitely enter any category. The presence of multiple chronic diseases involves both polymedication and also a thorough management of lifestyle in patients with arthritis, cancer, congestive heart failure, depression, emphysema, HTN, at least stage III CKD,

Table 4. Antidiabetic medication, cardiovascular risk, HTN.

| Class | Action | Advantages | Disadvantages | Cost |
|--------------------------|---|--|--|---------------------|
| Biguanides | ↓ glucose liver production | Longtime experience No hypoglycemia ↓ CVD events (UKPDS) | Gastrointestinal adverse effects vit B12 malabsorption, lactic acidosis (rarely) | Low |
| Sulphonylureas | ↑ insulin secretion | Longtime experience ↓ microvascular risk (UKPDS) | Hypoglycemia ↑ in weight | Low |
| Glinides | ↑ insulin secretion | ↓ postprandial glycemia excursions Flexible dosage | Hypoglycemia ↑ in weight | Moderate |
| TZDs | ↑ insulin sensitivity | No hypoglycemia ↑ HDLc, ↓ TG | ↑ in weight Edemas/heart failure ↑ LDLc (rosiglitazone), ?↑ myocardial infarction (rosiglitazone) | Low |
| α glucosidase inhibitors | ↓ carbohydrate absorption from the digestive tract | No hypoglycemia ↓ postprandial glycemia excursions ↓ CVD events (STOP-NIDDM) | Modest effect in A1C decrease Gastrointestinal adverse effects | Low up to moderate |
| DPP 4 inhibitors | ↑ insulin secretion ↓ glucagon secretion | No hypoglycemia Well-tolerated | Angioedema/rash ? acute pancreatitis ↑ hospitalization for heart failure | High |
| Bile acid sequestrants | ? ↓ glucose liver production ? ↑ incretin level | No hypoglycemia ↓ LDLc | Modest effect in A1C Decrease, ↑ TG, may ↓ the absorption of other drugs | High |
| Dopamine 2 agonists | Modulates the metabolism hypothalamic regulation ↑ insulin sensitivity | No hypoglycemia ? ↓ CVD events (Cycloset Safety Trial) | Modest effect in A1C decrease Dizziness/syncope/nausea/rhinitis | High |
| SGLT2 inhibitors | Block glucose reabsorption by the kidneys and increase glucosuria | No hypoglycemia ↓ in weight ↓ BP Associated to the decrease of CVD events and mortality in CVD patients (EMPA-REG OUTCOME) | Urinary infections Polyuria Hypotension/dizziness ↑ LDLc ↑ creatinine (transitory) Diabetic ketoacidosis Urosepsis, pyelonephritis | High |
| GLP 1 receptor agonists | ↑ insulin secretion ↓ glucagon secretion delay of gastric evacuation ↑ satiability | No hypoglycemia ↓ weight ↓ postprandial glycemia excursions ↓ certain CV risk factors | Gastrointestinal adverse effects ↑ ventricular rate ? increase risk of acute pancreatitis, Injectable, requires training | High |
| Amylina analogues | ↓ glucagon secretion Delay of gastric evacuation ↑ satiability | ↓ postprandial glycemia excursions ↓ weight | Modest effect in A1C decrease Gastrointestinal adverse effects Injectable, requires training | High |
| Insulin | ↓ glucose liver production Cetogenesis suppression | Almost universal response Theoretically unlimited efficiency ↓ microvascular risk (UKPDS) | Hypoglycemia ↑ in weight Injectable, requires training (except for inhalatory insulins) Lung toxicity (insulin inhalatory) | Moderate up to high |

myocardial infarction and stroke. By multiple chronic diseases we refer to at least three associated pathologies, but most patients have five pathologies of this kind, or even more.

The presence of a single chronic disease in final stage, such as stages III–IV congestive heart failure, oxygen-dependent lung conditions, CKD requiring dialysis or metastatic cancer, may cause severe symptoms or organ function damage, in this way the lifetime expectation significantly decreases.

Type 2 DM management and the cardiovascular risk.

In table 4 there are presented the antidiabetic drugs, also observing in certain classes, besides the anti hyperglycemia effect, the effects upon the decrease of blood pressure values, weight and cardiovascular events [1].

In conclusion, the association between type 2 DM and HTN is not a reliable one, with serious consequences on the cardiovascular risk and the ASCVD onset. Choosing the medication for the two conditions should be individualized, permanently monitoring the treatment targets. If there are administered conversion enzyme inhibitors, angiotensin receptor blockers or diuretics, the serum creatinine/ eGFR and the potassium level should be monitored [1].

The main objective in treating HTN in DM patients is to decrease BP < 140/90 (ADA and JNC8), or BP < 140/85 (ESC/EASD) mm Hg [1,2,56]. In order to reach these values, a combination of several antihypertensive drugs is required in various patients with HTN and DM.

A patient centered approach should be used for choosing the DM treatment. There will be taken into consideration the following: efficiency, costs, possible adverse effects, weight, comorbidities, risk for hypoglycemia and patient's preferences.

Conflict of interests

There are no potential, relevant conflicts of interest to this article.

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