I Brazilian Position Statement on Arterial Hypertension and Diabetes Mellitus

Departament of Arterial Hypertension of the Brazilian Society of Cardiology by the authors

Concept and Epidemiology

Arterial hypertension (AH) is defined when blood pressure (BP) levels are ≥140 mmHg and/or 90 mmHg for systolic and diastolic BP, respectively, in at least two separate measurements, in the presence or absence of diabetes mellitus (DM)[1].

The diagnosis of DM is confirmed by the finding of fasting plasma glucose ≥ 126 mg/dL in two measurements, and/or blood glucose ≥ 200 mg / dL after overloading with 75g of dextrose, and / or random glucose measurement ≥ 200 mg/dL in the presence of unmistakable symptoms of diabetes, and/or, more recently, glycated hemoglobin ≥ 6.5% in two samples, by the HPLC method[2].

AH and DM represent major public health problems and often coexist in clinical practice. At present, there is a trend to increase in the prevalence of AH and DM, possibly related to the growth of the elderly population, as well as overweight and obesity rates[3].

According to the International Diabetes Federation, there were 285 million diabetic individuals in 2010 worldwide and it is estimated that there will be 438 million in 2030, with 90% of cases of type 2 DM. The impact of this situation in developing countries is immense[4].

The association between AH and DM was first described in the 70s, observed in both sexes and at any age range. The prevalence of hypertension is two to three-fold higher in diabetics than in the general population[5], and about 70% of diabetics are hypertensive[3,6]. A meta-analysis of 102 prospective studies and 698,782 individuals showed that the presence of DM increases by two-fold the risk of coronary artery disease (CAD), cerebrovascular accident (CVA) and CV death. According to this meta-analysis, 10% of CV deaths in developed countries can be attributed to the presence of DM[7].

The coexistence of the two conditions substantially increases the risk of acute myocardial infarction (AMI), CVA and mortality from all causes, as well as the risk of heart failure (HF), kidney disease (KD) and microvascular complications[8].

Keywords

Hypertension; Diabetes Mellitus; Obesity; Adults; Overweight; Cardiovascular Risk.

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DOI: 10.5935/abc.20130123

Origin of Hypertension in DM

Chronic hyperglycemia and hence, the associated insulin resistance can lead to AH through several physiopathological mechanisms that are not fully understood. *In vitro* observations show that insulin can directly stimulate the activity of sodium potassium adenosine-triphosphatase and several ionic channels and pumps, increasing the intracellular ion concentration, with the increase in intracellular calcium being an important determinant of vasoconstriction. It is also known that high levels of leptin cause increased activity of the sympathetic nervous system, which leads to increased cardiac output and peripheral vascular resistance. Excess insulin is also is also able to reduce natriuresis by direct renal tubular mechanism, leading to an accumulation of salt and water. Salt-resistant AH is common in these patients[9,10].

The current and most relevant factor described as a cause of AH in diabetics has been oxidative stress, resulting from hyperactivity of metalloproteinases in patients with metabolic syndrome and DM. This leads to a reduction in the production and activity of protective vasodilator substances such as nitric oxide. Hydrogen peroxides, which are substrates and cofactors of the metabolism of these metalloproteins create, in the subendothelial microenvironment, the activation of potent vasoconstrictors through the local activation of the renin-angiotensin-aldosterone system (RAAS), and finally, increase in local concentration of angiotensin II[11].

All these mechanisms acting in an integrated manner, in a hostile environment of higher risk, are adjuvants not only for the genesis of hypertension, but also for the development of CVD, due to the process of initial endothelial dysfunction to the genesis of atheromatous plaques.

Cardiovascular Risk Stratification

Since 1980, evidence has shown that the presence of DM confers increased risk of CV death, both in men and women[10]. These studies have shown that either isolated or associated with other CV diseases such as hypertension and dyslipidemia, DM is closely related to the increased incidence of atherosclerosis[11].

Outcome studies carried out in the last decade also found in the association between AH and DM, a significantly increased incidence of fatal and nonfatal CV events, which led to the implementation of specific conducts over time to minimize the risk in this group of patients[12].

In this context, in diabetic subjects, even with BP considered normal, there is a moderate increase in CV risk, and in the presence of established AH, the risk will be high or very high (Table 1)[1].

Table 1 – Additional risk of diabetic patients according to blood pressure levels. Modified from the VI Brazilian Guidelines on Arterial Hypertension

BP	Normal	Borderline	Stage 1	Stage 2	Stage 3
risk	moderate	high	high	high	very high

BP: Blood Pressure.

Clinical and Laboratory Assessment

The clinical and laboratory assessment follows the same set of investigations performed in hypertensive patients without DM, plus some additional points[1].

The clinical history is important to verify the time of disease evolution, the search for other associated CV risk factors, the investigation of drugs that can further raise BP, presence of lifestyle habits that can aggravate the clinical presentation, detection of target-organ lesions and the possible presence of established CV disease. Similarly, the physical examination must be thorough and careful, also in search of evidence of secondary hypertension, target-organ lesions and possible signs of cardiovascular disease[13].

BP must be systematically measured in the supine and standing positions due to the possibility of higher incidence of postural hypotension. The measurement of waist circumference (WC) for the evaluation of visceral obesity adds further information to the initial investigation (normal values ≤ 88 cm for women and ≤ 102 cm for men). The dilated fundus examination (DFE) has special indication, as it will be useful to detect changes related to DM, as well as those related to hypertension itself[14].

Laboratory evaluation initially recommended for all hypertensive individuals should be maintained, including: urinalysis; measurement of serum potassium, serum creatinine, fasting glucose, lipid profile, uric acid and electrocardiogram.

In addition to these tests, it is important to perform: a) echocardiography for better assessment of ventricular function and mass b) exercise test to evaluate functional capacity and possible presence of subclinical ischemic alterations c) microalbuminuria may be initially performed by measuring in duplicate the albumin/creatinine ratio in an isolated urine sample. If available, carotid ultrasound should be performed, which may indicate the presence of incipient intima-media thickening of the carotid artery (> 0.9 mm) or presence of atheromatous plaque[15,16].

Additional tests aimed to every organ or system may be indicated depending on the finding of specific alterations.

Diabetes monitoring tests should obviously be routinely performed. In addition to fasting glucose, assessment of postprandial glucose and measurement of glycated hemoglobin (HbA1C) are indicated for this purpose[17].

Kidney Alterations

AH and DM account for more than 50% of the causes of Chronic Kidney Disease (CKD). The kidneys are the target organ that undergoes specific systemic processes entailed in DM and AH. Approximately 5% to 20% of the patients with DM may have albuminuria at the time of diagnosis.

In the early stages, the vascular lesions are usually discrete, but with disease evolution, the lesions become more severe. Approximately 30% to 50% of patients with DM have a parallelism between clinical manifestation and pathological kidney alterations[18].

Among the mechanisms involved is glomerular hyperfiltration, which can cause extracellular matrix accumulation through pathways that increase TGF-β expression. Glomerular hyperfiltration is capable of stimulating the RAAS, protein kinase C, in addition of TGF-β. These facts explain why drugs that block the RAAS have additional beneficial effects in addition to the antihypertensive one[19].

Before the age of effective anti-hypertensive drugs, proteinuria occurred in 40% of patients and more than 18% progressed to end-stage CKD. Albuminuria was present in 15% to 30% of cases, few patients developed proteinuria of around 500 mg / day and some developed nephrotic levels. Serum creatinine elevation occurs in 10% to 20% of patients and the risk is higher in African-Americans, the elderly and patients with predominant systolic hypertension (> 160 mmHg). In 2% to 5% of patients, progression to renal failure occurred in the following 10 to 15 years[20].

Brain Alterations

Brain disease is the leading cause of morbidity in diabetic patients, and cerebrovascular accident (CVA) is responsible for 20% of deaths in diabetics[21]. There is a direct association between BP and mortality from CVA in diabetics and non-diabetics. This association increases with advancing age[22]. A large observational study showed a two-fold higher chance of CVA during 19 years of follow-up in those with the combination of diabetes and hypertension compared to hypertensive individuals only[23].

Diabetics have an increased risk of dementia, including Alzheimer's disease. Even diabetics without dementia have worse performance in cognitive tests, when compared with individuals without DM[24]. In turn, hypertensive diabetics have an increased likelihood of cognitive deficits than normotensive ones[25]. The early identification and treatment of these individuals may have an impact on quality of life, but also on better adherence to prescribed treatments.

Peripheral Artery Disease

Peripheral Arterial Disease (PAD) can affect different vascular territories. In DM, PAD is more often distal, femoropopliteal and tibial, whereas in AH, smoking, and hypercholesterolemia, vascular involvement is mainly proximal, aortoiliac and femoral[26]. Approximately 65% of patients with some form of dysglycemia have PAD[27]. In Brazil, 12% to 20% of patients with lower-limb (LL) PAD have DM and the risk of diabetic men developing PAD is 6.6 times higher than non-diabetic ones[28].

The main causes of PAD identified in the U.S. registry REACH (Reduction of Atherothrombosis for Continued Health) were DM and AH in Hispanics and African-Americans, while hypercholesterolemia was the main cause in Caucasians. The BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) study showed that the duration of DM and the presence of micro/macroalbuminuria are important predictors of PAD severity and left ventricular failure in patients with coronary artery disease (CAD)[29]. The PAMISCA study found 42.6% of PAD in hypertensive patients with acute coronary syndrome. The mortality among those with PAD was higher (2.3% versus 0.2%, $p < 0.01$)[30]. Left ventricular hypertrophy affects up to 50% of patients with PAD, giving them a worse prognosis[31].

Lower-limb PAD assessment includes: (a) Ankle Brachial Index (ABI - important in diabetic patients in the asymptomatic phase of PAD, to identify individuals at high risk of amputation), (b) treadmill exercise test (especially useful in diabetics with atypical LL symptoms or normal ABI and claudication symptoms), (c) lower-limb arterial duplex scan (locates and quantifies arterial lesions, in addition to analyzing the patency of grafts or stents), (d) magnetic resonance angiography (e) CT angiography, (f) coronary angiography (evaluation for revascularization)[32,33].

Heart Disease

Hypertensive patients have a higher risk of developing cardiac abnormalities; however, in association with DM, these alterations are more intense and have an early onset[34].

Studies have shown that alterations in myocardial cells, capillaries and interstitium, which lead to systolic and/or diastolic dysfunction, are much more pronounced in diabetic patients with a history of hypertension[35] and both diabetes and insulin resistance lead to alterations in the structural and molecular mechanisms. The incapacity of the myocardium to metabolize pyruvate results in lipid accumulation in the heart muscle and decrease in glucose uptake by myocytes[36].

Hyperinsulinemia is also associated with increased levels of free fatty acids and increased sympathetic activity, which are factors that lead to cardiac hypertrophy and the accumulation of intracellular triglycerides[37]. However, these physiopathological chains are markedly exacerbated when BP levels are high, triggering other parallel mechanisms that induce hypertrophy, fibrosis and apoptosis. Oxidative stress has a strong participation, promoting the abnormal gene expression and signal transduction alterations, leading to myocyte death[38].

Other disorders also participate in myocardial injury; among them, autonomic neuropathy and mitochondrial dysfunction, common in DM, are adjuvant factors in reducing energy formation for adequate heart performance[39]. These aspects of cardiac injury are the initial pathways for the full development of cardiomyopathy, with all the characteristics of heart failure[40].

Blood pressure, blood glucose and lipid goals

Blood pressure goals recommended by the VI Brazilian Guidelines on Hypertension[1] is 130/80 mmHg, regardless of the presence of micro- or macrovascular complications. More stringent BP reductions have shown no benefit in this population and are not recommended[41].

Glycemic goals recommended by several scientific societies[3,6] include control of fasting blood glucose, postprandial blood glucose and HbA1C[2,42]. Different societies differ in relation to these values and suggest an individualized goal according to age, comorbidities, life expectancy and glycemia variability[2,42]. The Guidelines of the Brazilian Diabetes Society[6] recommend the following:

Pre-prandial glycemia (mg/dL): < 110 (acceptable up to 130)
Post-prandial glycemia (mg/dL): < 140 (acceptable up to 160)
HbA1c (%): < 7

More stringent HbA1c goals (6% to 6.5%) may be recommended in special groups: short disease duration, long life expectancy and in the absence of CV disease, as long as it is safe for the patient and there is no risk of hypoglycemia, as the importance of metabolic memory and glycemic variability in disease complications has been recently recognized. On the other hand, less stringent HbA1c goals (7.5% to 8%) are tolerated in elderly patients with frequent hypoglycemic episodes, short life expectancy, and significant cardiovascular complications and in patients with difficulty to achieve the goal even after effective use of multiple agents, including insulin[12,42].

The lipid levels goals in the diabetic population also differ according to the recommendations by different scientific societies (Table 2).

Individual CV risk must be assessed in hypertensive patients and the recommendations should be similar to those given to the general population regarding lipid goals. However, the European Guidelines[43] consider that the most significant classic risk factors, among which is severe hypertension, constitute a high or very high risk for CV death, deserving an appropriate LDL-C goal (<100 mg/dL), even in primary prevention of CVD and without DM.

Nondrug treatment of DM and AH

The non-drug treatment of AH in diabetics basically consists of decrease in body weight, low-sodium diet, regular exercise, a diet rich in fruits and vegetables (DASH diet), smoking and alcohol consumption cessation and treatment of obstructive sleep apnea. Weight reduction is recommended for all age groups[46]. The reduction of abdominal circumference with weight reduction is associated with improved BP control and some metabolic parameters, such as lipids and glycemia[47]. Some appetite suppressants may induce blood pressure increase, and can therefore be used with caution. In patients with severe obesity, bariatric surgery reduces mortality and decreases blood pressure and is associated with better control of diabetes[48].

The effectiveness of decreasing salt intake in the specific diabetic population is not known, and the indications in this population are based on studies including hypertensive diabetics and non-diabetics.

A diet low in sodium promotes rapid and significant decrease in BP in patients with resistant hypertension[49]. In spite of individual differences in sensitivity, even modest

Table 2 – Lipid goals and recommendations for the diabetic and hypertensive population

DM1 and microalbuminuria or CKD*	Decrease in LDL-C of at least 30% (regardless of basal level of LDL-C)
DM2 **WITH** CVD*,†,‡,§ or CKD*	LDL-C < 70 mg/dL (primary goal)*,†,‡,§ Non-HDL cholesterol < 100 mg/dL and Apo B < 80 mg/dL (secondary goals)*
DM2 **WITHOUT** CVD with age > 40 years and at least 1 classic risk factor or target-organ injury marker*	LDL-C < 70 mg/dL (primary goal) Non-HDL cholesterol < 100 mg/dL and Apo B < 80 mg/dL (secondary goals)
DM2 **WITHOUT** CVD with age < 40 years or absence of factors or CVD risk markers*	LDL-C < 100 mg/dL (primary goal) Non-HDL cholesterol < 130 mg/dL and Apo B < 100 mg/dL (secondary goals)
HDL-c (normal values)	≥ 50 mg/dL (women); ≥ 40 mg dL (men)
TG	< 150 mg/dL

*CKD: chronic kidney disease; TG: triglycerides. Modified from *Recommendations of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)[43]; †Recommendations of the American Diabetes Association (ADA)[2]; ‡Recommendations of the American Association of Clinical Endocrinologists (AACE)[44]; §Recommendations of the Brazilian Society of Diabetes (SBD)[6] and Brazilian Society Cardiology[45].*

reductions in the amount of salt are generally effective in reducing BP. The daily requirement for sodium in humans is contained in 5 g of sodium chloride or table salt. The average intake of Brazilians corresponds to twice the recommended amount[49].

Patients who regularly consume high doses of alcohol should be encouraged to attain total withdrawal from alcohol consumption, as it interferes not only with BP control, but especially with glucose level control.

Aerobic exercises (isotonic) together with resistance exercises lower blood pressure and are indicated not only for the treatment, but also for prevention of hypertension[50]. The recommended amount of exercise is at least five times a week, 30 minutes of moderate continuous or accumulated physical activity.

The use of continuous positive airway pressure (CPAP) is the treatment of choice for patients with severe apnea/obstructive sleep apnea hypopnea syndrome (OSAHS). This procedure improves the episodes of apnea / hypopnea and helps in the correction of metabolic disorders (glucose). There is evidence that the use of this device can help to control blood pressure, in blood pressure drop during sleep, to improve quality of life and to reduce clinically relevant cardiovascular outcomes[51]. Alcohol intake worsens apnea/hypopnea episodes.

Drug Treatment of Dyslipidemia

In diabetics, the most commonly found dyslipidemias are hypertriglyceridemia, low HDL-C and increased small, dense LDL particles. The absolute levels of LDL-C, however, are similar in diabetic patients and the general population[45]. There are no peculiarities regarding the type of dyslipidemia found in hypertensive patients. Although frequently there are no elevated levels of LDL-C, the treatment is indicated to achieve goals related to high risk of CV events for hypertensive patients with DM.

Statins should be the drug of choice for treatment of hypercholesterolemia, while fibrates must be chosen in cases of severe hypertriglyceridemia. Other drugs available are niacin and omega-3 fatty acids for the adjuvant treatment of hypertriglyceridemia and bile acid sequestrants and ezetimibe for the treatment of hypercholesterolemia.

Meta-analysis of statin studies showed that for every reduction of 39 mg/dL of LDL-C observed, there was a 12% reduction in total mortality and 19% in CV mortality[52]. The risk of coronary events was also reduced by 23% and the risk of CVA by 17%[2]. A higher reduction of LDL-C reduces major cardiovascular events by 50%[53]. A meta-analysis evaluating the treatment of dyslipidemia with statins in diabetic patients showed a reduction of cardiovascular mortality as well as cardiovascular outcomes, similarly to the non-diabetic population[54].

Thus, statins have been shown to be effective drugs for the treatment of hypertension or dyslipidemia in diabetic patients, despite recent warning from the FDA[55] regarding its prescription, due to the increased risk of diabetes. The low incidence of diabetes was largely confined to patients with previous dysglycemia, as pre-diabetics and glycemic changes were mild, even among diabetic patients. Regarding fibrates, a meta-analysis published in 2010[56] showed reduced risk of overall cardiovascular events by 10% and coronary events by 13%, but there are no specific meta-analysis data on the use of fibrates in an exclusively diabetic or hypertensive population.

The ACCORD Lipid study[41] involved diabetics who received treatment with placebo or simvastatin associated with fenofibrate. In this study, there was no reduction in cardiovascular outcomes with the combination of fenofibrate and simvastatin. However, subgroup analysis of this study showed that individuals with triglyceride levels > 204 mg/dL concomitant with HDL-C levels < 34 mg / dL had benefited from using fenofibrate. Another large study involving diabetics was the FIELD

study[57], which showed a 24% reduction in nonfatal AMI, 21% in coronary revascularization and 11% in overall cardiovascular events. None of these studies, however, demonstrated a reduction in mortality. There have been, to date, no studies that evaluated fibrates in an exclusively hypertensive population, but they are considered safe drugs when indicated for the treatment of dyslipidemia[58].

The therapeutic goals, as recommended in the guidelines[42,59], are different for diabetics. Table 3 shows the indications for statin use in diabetic patients.

Drug Treatment of DM in the Hypertensive Patient

The algorithm for the treatment of diabetes is updated annually by the American Diabetes Association (ADA)[59] and, according to the final positioning, metformin is recommended as the drug of choice as long as it is well tolerated and in the absence of contraindications[60]. If an effective glycemic control has not achieved within three months, the combination of other drugs is necessary. The choice of the second drug should take into account the patient's age, life expectancy, complications of DM, significant comorbidities, time of disease, need for weight control, risk of hypoglycemia and available resources, with cost being a true limiting factor.

A combination of drugs can be prescribed as early as at the diagnosis when higher blood glucose levels are present[61]. As second choice therapy, there are drugs such as thiazolidinedione, represented by pioglitazone, DPP-4 (dipeptidyl peptidase-4) inhibitors, GLP-1 (glucagon-like peptide-1) agonists, sulfonylureas, as well as insulin[62]. Glinides and alpha glucosidase inhibitors, represented by Acarbose, also represent less validated options for treatment of DM. If good glycemic control is not achieved within three months, other drugs and/or basal insulin should be associated to allow better and faster glycemic control and if this does not occur in three months, the option for multiple-dose insulin therapy may be necessary. According the 2012 position statement of the ADA/EASD, the choice of therapy should be individualized[63].

The change in lifestyle is capable of decreasing HbA1c levels similar to the use of metformin and sulfonylurea, of 1% to 2%. Monotherapy is not always sufficient to control the hyperglycemia, and as in the treatment of AH, the association of different drugs is required to achieve adequate control of blood glucose and glycated hemoglobin (Figure 1)[12].

Drug Treatment of AH in the DM Patient

In patients with diabetes and hypertension, the main determinant of cardiovascular benefits of antihypertensive medications is achieving the BP goal with treatment[64]. Although the role of blood pressure control is unquestionable, a growing number of studies suggest that some drug combinations have advantages in protecting the kidneys, blood vessels and heart, as well as the BP control itself [64].

In diabetic patients with BP between 130-139 mmHg and 80-89 mmHg, the ADA recommends changes in lifestyle for a maximum of three months. These are key elements in reducing blood glucose and for proper control of pressure, especially after weight loss in obese patients, and they should be recommended for all diabetic hypertensive patients. If during this period there is no adequate pressure reduction, drug treatment should be started[2].

If the BP levels are ≥ 140/90 mmHg, in addition to changes in lifestyle, drug treatment should be started immediately[1,59]. In these conditions it is suggested that the BP goal is 130/80 mmHg, reinforced by the results of the ACCORD trial[59]. For this goal to be achieved, it is almost always necessary to start antihypertensive treatment with two or more drugs of different classes. The presence of kidney disease should be stratified to define the best approach[1,59].

Several studies have demonstrated the benefits of Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB) in hypertensive diabetic patients with microalbuminuria (30-300 mg/24 h)[65]. These classes are the first choice for the initial treatment of hypertensive diabetic patients with renal disorders.

In diabetic patients with no established nephropathy, studies as the ALLHAT[66] indicated that other classes of antihypertensive drugs in addition to ACE inhibitors, such as diuretics and calcium channel antagonists (CCA) have similar protective effect in patients with hypertension and diabetes and can be used as first choice for treating this group of patients. ARBs may be used in patients who cannot tolerate ACE inhibitors[1].

The VI Brazilian Guidelines on Hypertension[1] recommend that in diabetic patients without nephropathy, all antihypertensive agents can be used; however, the combination of renin-angiotensin system blockers with CCA may be beneficial[64].

Table 4 summarizes the essential considerations for the use of the major classes of antihypertensive drugs in diabetic patients.

Table 5 shows the main guidelines for the treatment of hypertensive patients with diabetes.

Table 3 – Indication for statin use in diabetics

Recommendations
Indication for statins in DM **WITH** CV disease (regardless of baseline levels of LDL-c)*,†
Indication for statin use in DM **WITHOUT** CV disease - Age > 40 years + one risk factor (regardless of baseline levels of LDL-c)* - Age > 40 years nd LDL-c > 130 mg/dL† - Age < 40 years + presence of other risk factors for CV or long-time DM and LDL-c > 100 mg/dL*,†

*Modified from * American Diabetes Association. Standards of Medical Care in Diabetes - 2012[59]. †Recommendations of the Brazilian Society of Diabetes (SBD)[42].*

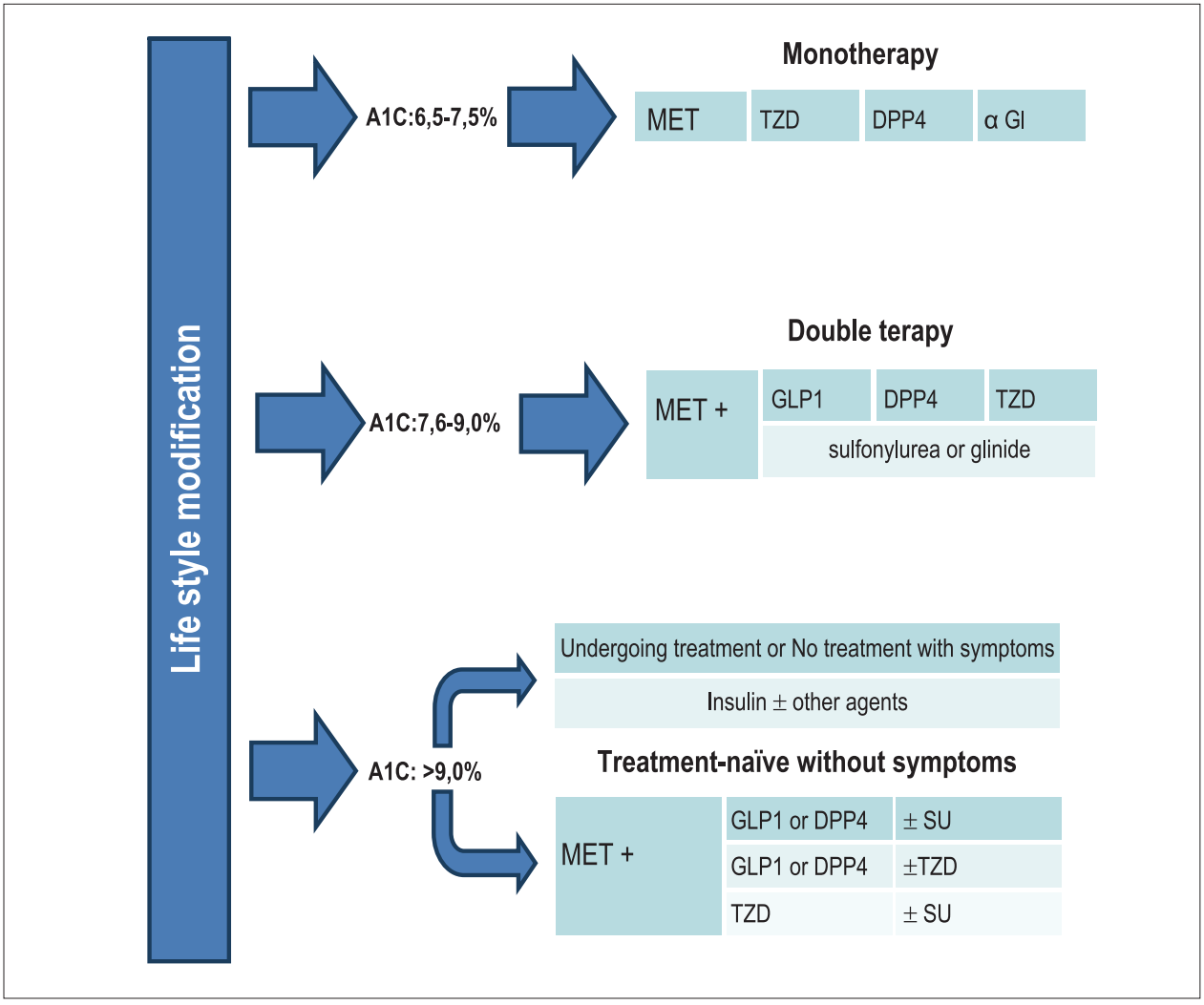

Figure 1 - *Algorithm for glycemic control in DM. MET: metformin; TZD: thiazolidinediones; DPP4: dipeptidyl peptidase-4; αG1: alpha glycosidase; GLP1: glucagon-like peptide-1; SU: sulfonylureas; A1C: glycated hemoglobin.*

Table 4 – Antihypertensive drug use in hypertensive diabetic patients

CLASS OF ANTI-HYPERTENSIVE	CONSIDERATIONS
Diuretics	• Low-dose diuretics - effective in patients with DM • SHEP (Systolic Hypertension in the Elderly Program) study – low-dose chlorthalidone reduces cardiovascular event rates in patients with DM[67]. • Stabilize kidney function
ACEI and ARB	• Reduce albuminuria and progression of kidney disease in diabetics.
Aldosterone Antagonists	• Reduce proteinuria, blood pressure and mortality in hypertensive diabetic patients with CHF[68].
Calcium Channel Antagonists	• Studies (HOT, ALLHAT, Syst-Eur) have demonstrated that CCA reduce rates of cardiovascular events and progression of kidney disease[66,69]
Central and *Peripheral Alpha-Adrenergic Antagonists*	• Peripheral alpha-adrenergic antagonists (doxazosin) should not be used as first choice (hypotensive effect is not very effective[66] and studies have shown an increase in CV events)[70] • Alpha-blockers – the only class of antihypertensive drugs that have a positive effect on insulin sensitivity. • Alpha-adrenergic antagonists with central action can be used as hypotensive agents in patients with DM.
Beta-Blocker	• Can be started early to increase cardioprotection[71]

Recently, it has been demonstrated that some associations have better pharmacological profile than others in DM, such as the combination of diuretics with ACE inhibitors, ARBs, or CCA, the combination of CCA and ACEI or ARB and the combination of beta-blockers and CCA[72].

Table 5 – Guidelines for the treatment of hypertension in diabetes

Treatment should be started quickly and effectively
Nonpharmacological measures should be implemented and encouraged
In most patients, treatment should be started with two antihypertensive agents
The goal is to achieve blood pressure reduction to levels close to 130 x 80 mmHg, with or without proteinuria > 1g / L
Lowering BP is the main objective to minimize cardiovascular risks (using all classes of antihypertensive drugs available for this purpose)
When there is kidney injury, renin-angiotensin system blocking is indicated
Use of beta-blockers has additional cardioprotective effect
Control of metabolic disorders must be strict, and aspirin should be used whenever possible.

Table 6 - Advantages and disadvantages of oral hypoglycemic agents

Drugs	Advantages	Disadvantages
Metformin	Non-hypoglycemiant Does not increase weight Decreases cardiovascular events	
2nd generation Sulfonylureas	Reduce microvascular risk	Hypoglycemiant Increase weight Attenuate myocardial ischemic preconditioning
Thiazolidinedione		Increase weight Cause edema / CHF
Pioglitazone	Non-hypoglycemiant Increase HDL cholesterol Decreases cardiovascular events (?) Decreases triglycerides	
Rosiglitazone		Increases LDL-cholesterol Increases myocardial ischemia?
Inhibitors of dipeptidyl peptidase 4 (DPP4)	Non-hypoglycemiant	
Meglitinides		Hypoglycemiants Increase weight Attenuate myocardial ischemic preconditioning
Acarbose	Decreases cardiovascular events?	
Insulins	Decreases microvascular risk	Hypoglycemiants Increase weight Injectable

**Adapted from Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (Position Statement of the American Diabetes Association [ADA] and European Association for the Study of Diabetes [EASD], 2012)[12]*

Oral Antidiabetic agents and Cardiovascular Risk

The cardiovascular safety of thiazolidinedione (TZD) has been questioned[73] and rosiglitazone, alone or combined, showed an association with myocardial infarction without statistical significance when compared with metformin[74]. The risk profile of pioglitazone seems more favorable, possibly by decreasing the atherosclerotic plaque inflammation, increasing HDL-c and decreasing high-sensitivity C-reactive protein[75]. The ADA/EASD document[76] states that metformin is a useful drug in the presence of CAD, and pioglitazone use results in a modest reduction of major cardiovascular events and alerts for the increased risk of heart failure induced by TZD in the elderly older than 80 years [80]. Table 6 shows the major drugs, their advantages and disadvantages.

Peculiar Aspects of Vascular Intervention

There are certain peculiarities in patients with AH and DM, especially if the BP levels are elevated at the time of the intervention leading to increased vascular and non-vascular complications.

In diabetics, coronary artery disease manifests as the most severe form, with higher frequency of multivessel disease, more severe and diffuse obstructions, smaller caliber arteries, higher prevalence of total occlusions and trunk lesions and greater thrombogenic potential. For these reasons, although the indication for clinical treatment, surgical or percutaneous revascularization is not substantially different between diabetics and non-diabetics, the results are worse for percutaneous revascularization in diabetic patients, especially in insulin-dependent and / or those with poor metabolic control.

While the percutaneous treatment of patients with single-vessel or low anatomical complexity disease is clearly established in practice and substantiated by studies that showed similarity of results in comparison with the surgical outcome, patients with multivessel disease, complex anatomy and basic clinical risk still have CABG as the primary recommendation according to the Syntax[77] and ARTS II[78] studies.

The angiographic success rate of elective percutaneous procedures is similar between diabetic and nondiabetic patients. However, diabetic patients are at increased risk of events than non-diabetic ones, including increased risk of death, a characteristic also observed in surgical procedures.

Hyperglycemia is a condition that enhances the proliferation of smooth muscle cells and fibroblasts, which are histological markers of the restenosis process. It also negatively influences vascular reactivity, inducing endothelial and platelet dysfunction. Therefore, strict metabolic control should be the norm.

The use of drug-eluting stents in diabetic patients significantly reduces the frequency of restenosis, although it did not reduce the frequency of death or myocardial infarction in the general population in large clinical trials. Some registries and sub-studies have shown a reduction of these events in diabetic individuals[79].

Diabetic patients with renal dysfunction deserve special attention. In elective cases, adequate hydration before the procedure, use of the smallest possible volume of contrast, in addition to contrasts with low osmolarity or isosmolar ones should be the norm in order to prevent the development of contrast-induced nephrotoxicity. Metformin should be discontinued 48 hours before the procedure due to the risk of developing lactic acidosis[80].

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