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Arterial Hypertension in Diabetes Mellitus

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Hypertension is very common among patients with diabetes mellitus (DM), with a prevalence approximately twice that of the non-diabetic population, and may precede the onset of diabetes[1,2]. The prevalence of hypertension is further increased in patients with type 2 diabetes and renal disease, as manifested by elevated urinary albumin excretion rates, compared with patients with type 2 diabetes and no evidence of renal involvement (80% of the patients, ranging from 71% of patients with normal urinary albumin excretion - UAE £30 mg/day- to 93% in patients with macroalbuminuria - UAE^3 300 mg/day)[3].

The insulin resistance is the main mechanism which leads to cardiovascular disease through hyperglycemia, hyperinsulinemia, hypertension, dyslipidemia, decreased fibrinolytic activity (PAI-1), endothelial dysfunction, subclinical vascular inflammation – oxidative stress and microalbuminuria[4,5].

The insulin resistance is also the major pathophysiology mechanism of hypertension in diabetics since it leads to volume expansion and vascular resistance through increased activity of sympathetic nervous system and rennin-angiotensin – aldosterone system[6].

In the UK Prospective Diabetes Study (UKPDS) the relation between systolic blood pressure over time and the risk of macrovascular or microvascular complications in patients with type 2 diabetes was considered. Rates for both myocardial infarction and microvascular endpoints were strongly associated, to a similar degree, with increasing systolic blood pressure. Each 10 mmHg decrease in updated mean systolic blood pressure was associated with reductions of risk of 11% for myocardial infarction (14% to 7%, $P<0.0001$), and 13% for microvascular complications (16% to 10%, $P<0.0001$). Furthermore, was considered the relation between exposure to glycemia over time and the risk of microvascular or macrovascular complications in the same patients. The incidence of clinical complications was associated significantly with glycemia. Each 1% reduction in updated mean HbA1c was associated with reductions in risk of 14% for myocardial infarction (21% to 8%, $P<0.0001$), and 37% for microvascular complications (41% to 33%, $P<0.0001$)[7]. Both in UKPDS study (1998), as in the Steno-2 study (1999), it was established that a multifactorial and intensive treatment of all car-

diovascular risk factors in patients with DM is associated with a huge reduction in micro- & macrovascular complications of DM (63% and 53% respectively). Followed by a 10-year post-interventional benefit, which was called as phenomenon of inherited effect[8,9]! However the ADVANCE trial was the study according to the results of which, blood pressure (BP) should be routinely treated to the level of optimal normal if not and lower (<130/80 mmHg), if tolerated, in all patients with DM[10]. On the other hand, the ACCORD study revealed contradictory results according to which a reduction in systolic BP<120 and diastolic BP<70 mmHg with the intensive versus the standard procedure (140 mmHg vs < 120 mmHg) was not associated with statistically significant benefit in reduction of the primary outcome, a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. There were also no differences in any of the secondary outcomes except for a reduction in stroke. However, the incidence of stroke in the group treated to lower than 140 mmHg was much lower than expected, so the absolute difference in fatal and nonfatal stroke between the 2 groups was only 0.21% per year. Moreover, the glucose-lowering arm of the study (intensive glucose control with a target of HbA1c <6%) was prematurely discontinued due to a rise in hypoglycemia and cardiovascular episodes (~35%)[11,12].

Based on the contradictory results of the various studies in hypertensive diabetics and the fact that just in one study, the antihypertensive treatment reduced the mean systolic BP<130 mmHg (with only partial benefit micro- and macrovascular complications), the European Society of Hypertension / European Society of Cardiology issued the revised guidelines at 2009 as reappraisal of European guidelines on hypertension management[13]. The most recent Guidelines —both European and American— confirm the Reappraisal of European guidelines on hypertension management, recommending higher blood pressure levels target since there are no enough data to support that a lower blood pressure actually reduces the cardiovascular events (Fig. 1, Fig. 2)[14,15].

Over the past 30 years many guidelines about

Blood pressure goals in hypertensive patients			
Recommendations	**Class[a]**	**Level[b]**	**Ref/[c]**
A SBP goal < 140 mmHg:			
a) is recommended in patients at low-moderate CV risk;	I	B	266, 269, 270
b) is recommended in patients with diabetes;	I	A	270, 275, 276
c) should be considered in patients with previous stroke or TIA;	IIa	B	296, 297
d) should be considered in patients with CHD;	IIa	B	141, 265
e) should be considered in patients with diabetic or non-diabetic CKD	IIa	B	312, 313
In elderly hypertensives less than 80 years old with SBP≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg	I	A	265
In fit elderly patients less than 80 years old SBP values <140 mmHg may be considered, whereas in the fragile elderly population SBP goals should be adapted to individual tolerability	IIb	C	–
In individuals older than 80 years and with initial SBP≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg provided they are in good physical and mental conditions	I	B	287
A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated	I	A	269, 290, 293

CHD, coronary heart disease; CKD, chronic kidney disease; CV, cardiovascular; DBP, diastolic blood pressure; SBP, systolic blood pressure; TIA, transient ischaemic attack.
[a]Class of recommendation
[b]Level of evidence
[c]Reference(S) supporting levels of evdence

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Fig. 1. *ESC/ESH Guidelines for Management of Hypertension.*

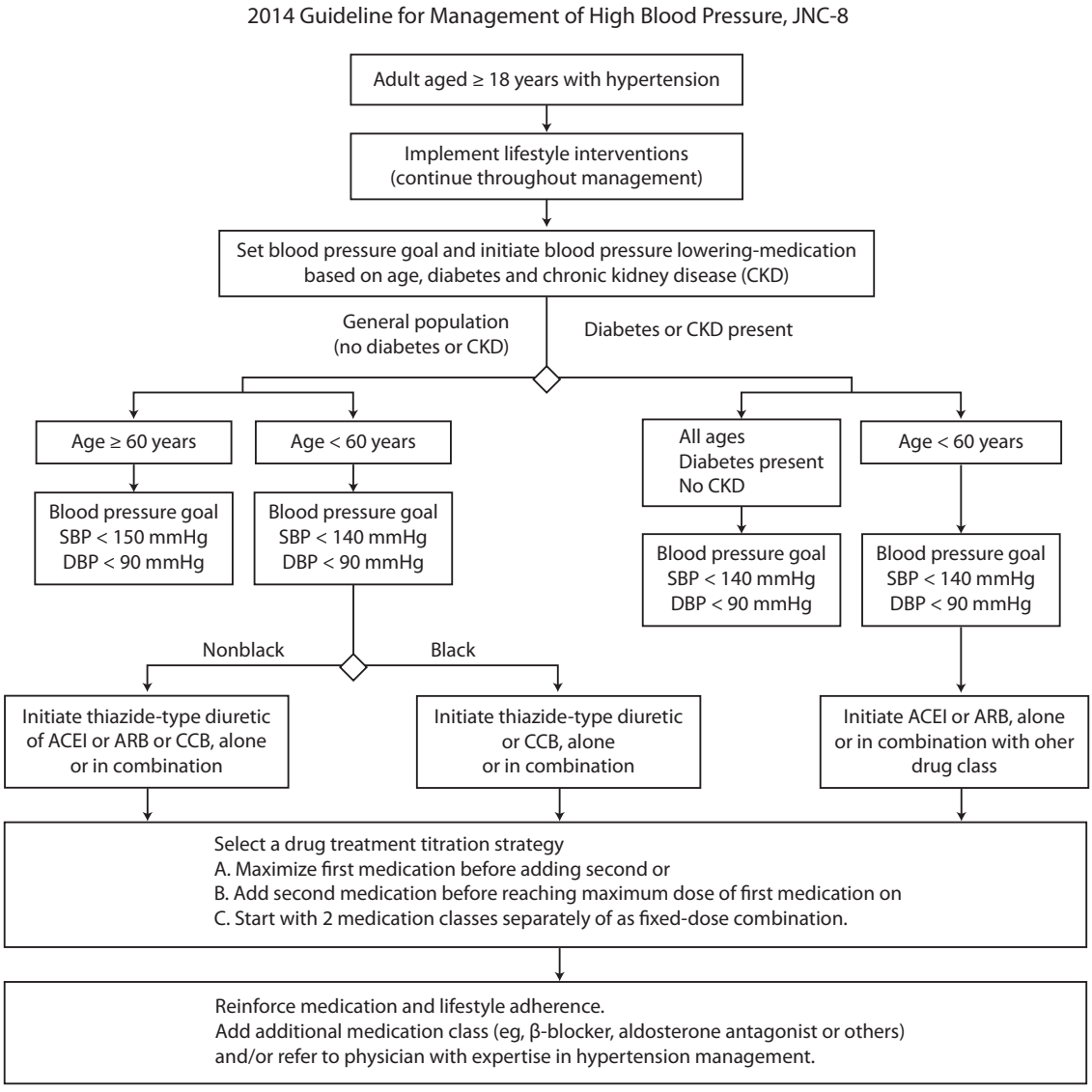

Fig. 2. *Guidelines for Management of High Blood Pressure, Join National Committee-8 (JNV-VIII).*

BP control in hypertensive diabetics have appeared. It is remarkable that for the first time in these recent guidelines, patients are classified according to their age with regards to the BP levels target. Also, the initiation of antihypertensive treatment is not only determined by the absolute levels of BP but also by the total cardiovascular risk as it is calculated by several scores (Framingham, Score, etc).

The most recent consensus report on BP by the American Diabetes Association (ADA) has also evaluated all recent data from the main trials and meta-analyses. The conclusion is the a BP target of 140/90 mmHg that is sustained at these levels and if the patient agrees and can tolerate BP reductions to levels between 125-130 mmHg for systolic BP, every effort should be done to achieve this level since it is associated with fewer cardiovascular events and reduced mortality[16]. Recently completed the SPRINT Study with somewhat similar protocol as in ACCORD Trial, but in non-diabetic patients, showed almost one-quarter reduction in all-cause mortality and one-third reduction of cardiovascular events with systolic BP goal ≤120 mmHg[17]. However in SPRINT Trial, BP was measured using a research technique (SPRINT specified 5 minutes of seated rest in a quiet room followed by 3 oscillometric measurements without an observer in the room). Furthermore, patients with DMor prior strokewere

excluded and frail elderly were underrepresented (28.2%). The fact that the study was open label in a strategy close to usual care with frequent visits may have helped to adjust the antihypertensive treatment if serious side effects occurred and thus minimized the risk of events. So, generalizability of the findings of SPRINT to patients with DM, stroke and to frail elderly is problematic[17].

With regard the initial choice of antihypertensive therapy –beyond the non-pharmaceutical measures with lifestyle changes that offers a similar benefit with monotherapy (~20-38 mmHg)– it is also based on the coexisting conditions (co-morbidities). The initial choice of a certain antihypertensive category will be based on the effectiveness and safety of them (individualized) and taking into account the coexistence of subclinical target organ damage, overt cardiovascular or renal disease, the specific beneficial properties (pliotropic actions) of each class of drug beyond the reduction of BP, the selective organ protection of the heart, kidneys, brain, peripheral vessels, the coexistence of conditions for which some medicines are contraindicated and the likelihood of interactions between other drugs and the favorable metabolic profile, better tolerance / differences in the appearance of side effects of the newer drugs[18]. Renin-angiotensin-aldosterone system (RAAS) blocker is recommended in the treatment of hypertension in DM, particularly in the presence of proteinuria or micro-albuminuria. However, ACE inhibitors and angiotensin receptor blockers are only mandated for those with kidney disease (eGFR < 60 ml/min/ 1.73 m^2) with > 300 mg/day of albuminuria. They are not preferred in normotensives with normal kidney function with or without microalbuminuria or hypertensives without albuminuria. The cornerstone is achieving BP reduction and not the drug class![18]

When the systolic BP is > 20 mmHg or diastolic BP > 10 mmHg from BP target, we can use a combination (usual fixed combination which increase the compliance of the patients) of 2 antihypertensive drugs. Since resistant hypertension in diabetics is more often than hypertensive patients without DM, the average number of antihypertensive drugs are at least three[19,20]. The most appropriate combination seems to be the combination of a RAAS blocker with a calcium channel antagonist –in particular in hypertensive diabetics– since despite the similar reduction of BP in comparison with other combinations (e.g. RAAS blocker with diuretics), there is a higher reduction in cardiovascular events and fewer cases of newly-diagnosed DM[21,22]. On the other hand, as in case of some antihypertensive classes which exert a beneficial effect on the glycemic profile, so some new classes of antidiabetic drugs such the Sodium – Glucose Contransporter-2 (SGLT2) inhibitors and the incretin mimetics and in particular the GLP-1 Agonists have a beneficial effect on BP by lowering these levels[22,23]. In particular, they exert vasodilatation, diuresis, sodium excretion, weight reduction while they also improve the aortic stiffness and the sodium-sensitivity to sodium-resistance (increased in DM)[23,24].

Despite the fact that currently various antihypertensive drugs and their fixed combinations are available, it is striking that the BP control –and especially in diabetics– has remained low (1 out of 3 patients, namely ~33%) worldwide over the last 15-20 years. Chronotherapy could contribute to this issue since chronotherapy investigate the administration of the correct amount of an active substance through the appropriate pathway at an appropriate time. Some data suggest that nocturnal rather than daytime dosing of antihypertensive agents may have beneficial effects on consequent cardiovascular outcomes[25,26]. In this frame, Hellenic-Anglo Research into Morning Or Night antihypertensive drug deliverY Trial (HARMONY Trial) designed to evaluate whether Ambulatory BP Monitoring (ABPM) levels differ by timing of drug dosing, as a possible explanation for these observations and theory of chronotherapy. According to its preliminary results, in patients with stable BP levels and hypertension diagnosed at least one year ago, the timing of antihypertensive drug administration (morning or evening) did not effect the mean 24 hour ABPM levels recorded[27].

In conclusion, the coexistence rate of hypertension in DM is much higher and increases synergistically the risk cardiovascular events and chronic kidney disease. Physicians should strictly regulate all risk factors in any hypertensive diabetic patient in order to reduce the total cardiovascular risk and to avoid both macrovascular complications and microvascular complications and in particular albuminuria and its progress to end stage renal disease. The percentage of BP control is very poor in total of hypertensives and especially in diabetics. It is usually necessary to combine antihypertensive drugs including as one component RAAS blockers since they have nephro- and cardio-protection!

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