

How to implement the new 2018 ESH/ESC guidelines for the management of arterial hypertension in patients with metabolic syndrome and diabetes?

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Abstract

Blood pressure (BP) control in hypertensive patients remains poor worldwide, particularly in high-risk patients with hypertension and diabetes.

New ESH/ESC guidelines recommend more stringent BP targets (on-treatment values of $\leq 130/80$ mm Hg in the general population and $\leq 140/90$ mm Hg in older hypertensive people), which will make the achievement of BP control even more challenging.

The most effective evidence-based treatment strategy to improve BP control is one that: encourages the use of combination treatment, enables the use of single-pill combination (SPC) therapy for most patients to improve adherence to treatment, with the use of SPC therapy as initial therapy.

The combination of perindopril with thiazide-like diuretic indapamide is one of the widely tested SPC in multicentre clinical trials for diabetic patients. Studies suggested that two-drug combination therapy will control BP in approximately two-thirds of patients. For patients whose BP is not controlled by two-drug combination therapy, the logical option is to increase treatment to three-drug combination therapy: usually a RAS blocker, a CCB and a diuretic.

The combination of perindopril with indapamide and amlodipine is particularly recommended in population of hypertensive patients with metabolic complications because of favourable, neutral effect on blood glucose and cholesterol level. This combination has proven hypotensive effect in group of patients with difficult-to-control hypertension.

Key words: guidelines ESH/ESC 2018; hypertension; diabetes, single-pill combination

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A new strategy for the treatment of hypertension

Hypertension is currently the most important mortality risk factor in the world and a major public health problem, especially in developed countries. It is esti-

mated that currently there are over one billion people living with hypertension worldwide, and by 2025 this number is predicted to increase by 60% [1, 2].

Thanks to the advances in antihypertensive drug therapy we can effectively lower blood pressure in

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individual patients and, thereby, reduce the main risk factor of cardiovascular (CV) events. Despite this, epidemiological studies clearly indicate poor blood pressure control in the whole population. The lowest rate of adequate control of hypertension is observed among patients with diabetes, chronic kidney disease, stable angina, acute coronary syndrome and left ventricular dysfunction [3–5].

The authors of the 2018 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines emphasize that their main goal was to develop a strategy that ensures improved blood pressure (BP) control in treated patients. The most important elements of this strategy are:

1. Lowering of blood pressure treatment targets

According to current guidelines, BP should be lowered to less than 140/90 mm Hg in all patients and if the treatment is well tolerated, further lowering of BP to 130/80 mm Hg or less, but not below 120/70 mm Hg, is recommended. Target BP values in patients with grade 2 and 3 hypertension should be achieved within 3 months of treatment.

2. Recommendation of a single-pill combination for the initiation of treatment in the majority of patients

The first step should be two-drug combination therapy, preferably in a single-pill combination. The preferred two-drug combinations include a renin-angiotensin system (RAS) inhibitor with a calcium channel blocker or a diuretic. Monotherapy is recommended only in low-cardiovascular-risk patients with grade 1 hypertension, in very-high-risk patients with high normal BP, in people over 80 years of age and those with frailty syndrome.

3. Recommendation of three-drug combination in the second step

If the treatment goal is not achieved with two-drug combination therapy, a three-drug combination based on a RAS inhibitor, a calcium channel blocker (CCB) and a diuretic should be used [6].

Single-pill combinations — an effective way to improve the effectiveness of treatment

Factors determining insufficient control of blood pressure include factors related to the patient (adherence/compliance, knowledge) and factors related to the doctor (therapeutic inertia).

A common problem that contributes to insufficient BP control worldwide is poor patient adherence to dosing schedules and treatment advice. The degree to which patients' behaviour is consistent with the prescribed treatment is referred to as adherence (or compliance) [7]. Studies assessing patient-doctor relations by means of electronic monitoring have found that 50–60% of all patients strictly follow medical recommendations (referred as 'adherent' patients), 30–40% take at least 80% of the prescribed doses ('partially adherent' patients), while 5–10% of patients take less than 80% of the prescribed doses or do not take drugs at all ('non-adherent' patients) [8, 9]. Adherence to treatment decreases as the number of pills taken daily increases [10].

The introduction of single-pill combinations was helpful in improving antihypertensive effectiveness. It has been shown that adherence to treatment can be significantly improved by reducing the number of pills [11].

It is widely believed that inappropriate doctor's behaviour, including insufficient determination in treatment and not using all therapeutic options, is also an important source of treatment failure. Therapeutic inertia (TI) is defined as failure to intensify treatment despite the fact that therapeutic goals are not achieved. This problem concerns not only BP control, but also other chronic diseases, including diabetes and hyperlipidaemia [12–14].

The above phenomenon is observed especially in patients with relatively slightly elevated blood pressure. The problem of therapeutic inertia was evaluated in an American, retrospective cohort study involving 7253 hypertensive patients treated in 62 medical practices. The TI index was calculated for each patient, with higher values corresponding to higher therapeutic inertia. The main manifestation of TI in his study was the failure to increase the dose of the antihypertensive drug or to add a new drug even though BP values measured during the clinical visit were above the target range. The study confirmed that the proportion of patients with sufficient blood pressure control is lower in 'real-life' clinical practice than in large clinical trials, and that the incidence of TI is high. Another important observation in this study was the lack of appropriate action, especially in a group of patients at high risk of cardiovascular diseases, defined as coexistence of diabetes, heart failure or other overt cardiovascular diseases, who would benefit the most from appropriate treatment. It was estimated that reducing the TI by 50% would reduce the average systolic blood pressure by more than 5 mm Hg and allow for achieving a BP control rate of 65–70%, which is similar to values reported

in many clinical trials [15]. Sustained reduction of systolic blood pressure by 5 mm Hg for several years reduces the risk of major cardiovascular events by 15–20% [16].

Problems related to hypertension in metabolic syndrome and diabetes

Hypertension is 1.5–2 times more prevalent in diabetic patients compared with healthy subjects. The coexistence of these two conditions leads to endothelial dysfunction, vascular damage and acceleration of the atherosclerotic process, and consequently increases the risk of cardiovascular events [17, 18]. It is estimated that CV risk in this group of patients is 5 times higher than in those without diabetes and without hypertension. Moreover, the presence of hypertension is responsible for a 7.2-fold increase in the risk of death in people with diabetes [19, 20].

Metabolic syndrome, often referred to as pre-diabetes, is an independent risk factor of cardiovascular and cerebral events [21].

In the published studies, the risk of cardiovascular events was significantly higher among patients with metabolic syndrome and remained high even after adjusting for age, gender, total cholesterol, creatinine, smoking, left ventricular hypertrophy and 24-hour systolic blood pressure [21, 22].

The pathophysiology of hypertension in diabetes and metabolic syndrome is complex. Currently, it is believed that the basic pathophysiological mechanism is endothelial dysfunction manifested by vasoconstriction, increased oxidative stress, vasculitis, prothrombotic state, smooth muscle cell proliferation and impaired repair mechanisms. Along with endothelial damage, the renin-angiotensin-aldosterone system is activated as a key modulator of vascular function [23, 24].

Another important pathophysiological mechanism of hypertension in this group of patients is insulin resistance which induces the activation of the sympathetic and the renin-angiotensin-aldosterone systems and the retention of sodium and water [25, 26].

Selection of optimal treatment in the light of the 2018 ESH/ESC guidelines

Step one: initiation of antihypertensive therapy

The choice of antihypertensive therapy in patients with metabolic syndrome and/or diabetes should be

made according to current medical standards, selecting drugs with antihypertensive efficacy and cardiovascular protective effect confirmed in EBM trials.

The current 2018 ESH/ESC guidelines indicate the need to lower blood pressure to 130/80 mm Hg or less (but not lower than 120/70) within 3 months using the first-choice combination of a RAS inhibitor with a calcium channel blocker (CCB) or a diuretic, preferably in the form of a single-pill combination (SPC) [6].

Considering new recommendations and EBM approach, the optimal therapy for the initiation of antihypertensive treatment in patients with diabetes is the combination of perindopril with indapamide. As indicated by evidence from clinical trials, this treatment ensures a significant reduction in CV risk and a reduction in all-cause and cardiovascular mortality (ADVANCE and ADVANCE-ON) as well as a complete normalization of blood pressure (PICASSO) and metabolic parameters (FORTISSIMO) [27–30].

The use of individualized combination antihypertensive treatment is supported by the fact that the majority of patients with diabetes and hypertension do not achieve blood pressure target values. Analysis of data from the I-SEARCH (International Survey Evaluating Microalbuminuria Routinely by Cardiologists in patients with Hypertension) study showed that among diabetic patients only 19% of men and in 16% of women had good blood pressure control, although 93.5% of patients received antihypertensive drugs [31].

In the ADVANCE (Action in Diabetes and Vascular Disease study: PreterAx and DiamicroN Controlled Evaluation) trial including 11,140 patients with type 2 diabetes, after 4.3 years of treatment with fixed combination of perindopril and indapamide statistically significant reduction compared to placebo was observed in:

- all-cause mortality [relative risk reduction (RRR) 14%; $p = 0.025$];
- cardiovascular mortality (RRR 18%; $p = 0.027$);
- total renal events (RRR 21%; $p < 0.0001$);
- total coronary events (RRR 14%; $p = 0.02$);
- primary endpoint (total micro- and macroangiopathic events) (RRR 9%; $p = 0.041$).

Treatment with perindopril and indapamide was well tolerated; the percentage of adherent patients was 73% in the experimental group and 74% in the placebo group [27].

All surviving participants of ADVANCE trial were invited to participate in ADVANCE-ON (Action in Diabetes and Vascular Disease: Preterax and DiamicroN Modified Release Controlled Evalu-

ation Observational Study), both those who were treated with perindopril/indapamide and those receiving placebo. In total, 8494 patients participated in the ADVANCE-ON. The median follow-up after the end of the randomized trial was 5.9 years, and the total duration of the ADVANCE trial and post-trial follow-up was 9.9 years. The analysis of data obtained during nearly 10 years of observation of patients with type 2 diabetes, including the period of the randomized trial and post-trial follow-up, showed a statistically significant reduction in the number of deaths from cardiovascular causes and deaths for any cause, resulting from previous 4.5-year antihypertensive treatment with perindopril and indapamide. The results obtained in the ADVANCE-ON were mainly due to sustained benefits of intensive antihypertensive treatment with a fixed combination of perindopril and indapamide in the ADVANCE study [28]. This proves that an early and effective reduction in blood pressure by fixed combination of perindopril and indapamide translates into long-term clinical benefits.

It is also worth paying attention to the results of the trials assessing the effectiveness of the highest doses of the perindopril/indapamide combination (PICASSO and FORTISSIMO). In an open observational PICASSO (Prevention of Cardiovascular Events in Ischaemic Stroke Patients with High Risk of Cerebral Haemorrhage) trial, the effectiveness of fixed-dose combination of perindopril 10 mg/indapamide 2.5 mg was evaluated in hypertensive patients who failed to achieve BP target values < 140/90 mm Hg using standard treatment. Blood pressure significantly decreased from $158.9 \pm 14.3/93.0 \pm 9.4$ mm Hg to $131.5 \pm 9.5/79.9 \pm 6.2$ mm Hg. Target BP values were achieved by 72.7% of the 9257 patients included in the final analysis. The BP reduction was significant regardless of the initial values. Interestingly, significant improvement in the metabolic parameters such as total cholesterol, LDL and HDL cholesterol, triglycerides and blood glucose levels was also observed. The authors conclude that treatment with the perindopril 10 mg/indapamide 2.5 mg combination is effective and safe in patients with poorly controlled blood pressure [29]. Similar conclusions were reached by the authors of the FORTISSIMO (Full-dose Perindopril/Indapamide in the Treatment of Difficult-to-Control Hypertension) trial [30].

This combination is also indicated in patients with metabolic syndrome, which was confirmed by the OPTIMAX study: Real-life Rates of Blood Pressure Normalization With First-Line Therapy (OPTIMAX 2) [32].

The coexistence of abdominal obesity, dyslipidaemia and impaired glucose tolerance is related to a very high risk of developing type 2 diabetes and cardiovascular diseases.

Patients with metabolic syndrome should be treated with medications that have additional beneficial metabolic effects, beyond lowering blood pressure, and delay the development of diabetes [33, 34]. It has been known for a long time that the majority of antihypertensive drugs affects carbohydrate metabolism. Thiazide diuretics, especially when given in high doses, enhance metabolic disorders and increase the risk of diabetes. In a prospective multicentre TROPHY (Treatment in Obese Patients With Hypertension) trial, obese hypertensive patients were randomized to treatment with an ACE inhibitor or hydrochlorothiazide (HCTZ). The therapeutic goal of lowering the diastolic blood pressure below 90 mm Hg was obtained by 60% of patients in the ACE inhibitor group and only 43% of patients in the HCTZ group. In addition, patients receiving HCTZ showed significant deterioration of the metabolic profile with significantly higher plasma glucose levels and a significant reduction in serum potassium compared to the ACE inhibitor group. This study emphasized that ACE inhibitors are more advantageous and safer in patients with obesity [35]. At the same time, it has been found that HCTZ — not only in monotherapy, but also in combination with other drugs — unfavourably affects the metabolic profile. A subanalysis of the International Verapamil SR Trandolapril STUDy (INVEST) published in 2013, based on pharmacogenetics, demonstrated that the use of HCTZ, even at low doses (12.5 mg and 25 mg), in combination with an ACE inhibitor may be in some patients an environmental factor in the development of diabetes. In practice, every 6 months of treatment resulted in a 16% increase in the risk of developing diabetes [36].

In connection with the above, the guidelines of the Polish Society of Hypertension emphasize that the preferred diuretics should be thiazide-like diuretics (chlorthalidone, indapamide). This recommendation is justified by the evidence for their beneficial effect on CV risk reduction and a more favourable metabolic profile [5].

Differences in the chemical structure of diuretics are the basis for dividing this group of drugs into thiazides and thiazide-like diuretics (chlorthalidone, indapamide). Different chemical structure translates into different pharmacokinetic properties and potential additional effects. Unique features of indapamide, which are associated with its chemical structure, include its considerable lipophilicity, vaso-

dilating and antioxidant effects and neutral effect on the lipid profile.

Due to these beneficial pharmacokinetic properties, indapamide is now widely used both in monotherapy and in single-pill combinations with an ACE inhibitor and a CCB. Indapamide is characterized by one of the highest trough-to-peak (T/P) ratios indicating duration of action of more than 24 hours. In a published meta-analysis of 10 randomized trials comparing directly indapamide with HCTZ, indapamide was shown to have significantly higher antihypertensive efficacy than HCTZ [37].

Another published meta-analysis showed that thiazide-like diuretics, including indapamide, statistically significantly reduce the risk of cardiovascular events such as stroke, coronary events and heart failure. For thiazide diuretics, including HCTZ, the reduction of cardiovascular events did not reach statistical significance [38]. The current guidelines of the Polish Society of Hypertension indicate indapamide as the preferred thiazide-like diuretic, and in some groups of patients (those aged over 80) it is the only one recommended [5].

Step two: intensification of treatment

Based on the research, it is estimated that two-drug therapy can effectively control BP in nearly two thirds of patients [39]. For patients who fail to achieve target BP values, the logical option would be to use a combination of three antihypertensive drugs. A three-drug combination enables achieving the target BP values in more than 80% of patients [40].

Considering the above, the new 2018 ESH/ESC guidelines recommend that the combination of a RAS inhibitor, a CCB and a diuretic, preferably as a three-drug SPC, should be used for treatment intensification [6].

The Polish Society of Hypertension guidelines highlight the importance of a new group of three-drug combinations and indicate the superiority of single-pill combination of perindopril/indapamide/amlodipine [5]. This recommendation is supported by EBM studies confirming its effectiveness in reducing CV risk [27, 41, 42]. In addition, this new three-drug combination is characterized by 24-hour antihypertensive effects of all three drugs which have complementary pharmacokinetic properties in terms of time required to achieve maximum concentration of individual components [43].

Subanalysis of the ADVANCE trial showed significantly more favourable effects in patients with type 2 diabetes receiving single-pill combination of perindopril and indapamide with amlodipine. There was a 2-fold reduction in the risk of death compared

to perindopril/indapamide therapy in the entire population of the ADVANCE trial [44].

In the PIANIST (Perindopril-Indapamide plus Amlodipin in high-risk hypertensive patients) trial, the efficacy of triple combination of perindopril, indapamide and amlodipine was evaluated in patients with difficult-to-control blood pressure. One third of respondents had ischaemic heart disease or diabetes, and half of the subjects had grade 2 hypertension. The mean office BP value was $160.5 \pm 13.3/93.8 \pm 8.7$ mm Hg. The target BP values were achieved in 72% of all subjects, in 81% of patients previously treated with an ACE inhibitor and HCTZ, and in 91% of patients receiving a sartan and HCTZ prior to the study entry. This analysis of treatment effects in nearly five thousand patients with high or very high cardiovascular risk confirmed the effectiveness of the above triple antihypertensive therapy, regardless of the type of previously used two-drug combination [45]. Another study assessing the combination of perindopril, indapamide, and amlodipine, PETRA (Perindopril based TRiple combination therapy to Achieve 24-hours controlled hypertension), included over 11,000 patients with grade 1, 2 and 3 hypertension with associated cardiovascular risk factors and concomitant diseases (dyslipidaemia, diabetes, obesity and coronary heart disease). After 3 months of treatment with perindopril, indapamide and amlodipine, systolic blood pressure decreased by 25 mm Hg, and diastolic blood pressure by 11 mm Hg. In the context of new recommendations, it should be emphasized that the above combination made it possible to achieve more stringent therapeutic goals of $<130/80$ mm Hg in only 3 months. What's more, 45% of patients received the lowest dose of the drug (5/1.25/5 mg) on the last visit [46].

Summary

Hypertensive patients with diabetes or metabolic syndrome are characterized by high or very high cardiovascular risk. According to the new 2018 ESH/ESC guidelines, effective prevention of incidents in this group of patients requires achieving target BP values of systolic blood pressure between 130 and 120 mm Hg and diastolic blood pressure between 80 and 70 mm Hg within 3 months. The first step of antihypertensive pharmacotherapy should be a two-drug combination of a RAS inhibitor with a diuretic or a CCB, preferably in a SCP. In the second step, a combination of three drugs: a RAS inhibitor, a diuretic and a CCB, preferably in a SPC, should be used in order to intensify the treatment. In accor-

dance with the current guidelines, respective steps for patients with diabetes and metabolic syndrome should be as follows: the combination of perindopril/indapamide as the first step of treatment and three-drug combination of perindopril/indapamide/amlodipine for treatment intensification. This treatment strategy is supported by many EBM trials confirming its effectiveness in achieving target BP values and organ-protective effects.

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