Practical use of single pill combinations in the treatment of hypertension — an analysis focused on perindopril-based combinations

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Abstract

Hypertension (HTN) is a major modifiable cardiovascular risk factor. Despite availability of effective blood pressure-lowering medications, HTN remains poorly controlled. Causes of suboptimal HTN control include the asymptomatic nature of HTN, low patient compliance, inadequate knowledge regarding the sequelae of HTN, and often complex therapeutic regimen. In the current guidelines, combination therapy using single pill combinations (SPC) has been widely recommended for the treatment of HTN. In the present paper, we evaluated the usefulness of perindopril-based SPC in various clinical scenarios in everyday practice. Perindopril-based SPC, including both two- and three-drug combinations, have been marketed since 2008. Our considerations regarding the use of perindopril-based combinations both within the basic HTN management strategy and for treatment individualization are informed by not only the everyday clinical experience but also the results of numerous clinical studies, including large randomized trials. Perindopril-based SPC are characterized by a long duration of action providing stable 24-hour blood pressure control, and the wide range of perindopril-based SPC allows their use in various clinical scenarios, thus facilitating treatment individualization.

Key words: hypertension; single pill combinations; treatment initiation; treatment intensification; therapeutic regimen

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Introduction

Hypertension (HTN) is a major modifiable cardiovascular risk factor. Despite availability of effective blood pressure-lowering medications, HTN remains poorly controlled. Causes of suboptimal HTN control include the asymptomatic nature of HTN, low patient compliance, inadequate knowl-

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edge regarding the sequelae of HTN, and often complex therapeutic regimen. In the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines, and the 2019 Polish Society of Hypertension (Polskie Towarzystwo Nadciśnienia Tętniczego, PTNT) guidelines, combination therapy using single pill combinations (SPC) was widely recommended for the treatment of HTN [1, 2]. Unfortunately, several years after publication of these guidelines, SPC are still underused in the management of HTN in Poland as they are taken by less than one third of hypertensive patients [3]. Of note, the most recent 2023 ESH guidelines have upheld the recommendation to use SPC at each step of HTN treatment [4].

The purpose of the present paper is to evaluate the usefulness of perindopril-based SPC in various clinical scenarios in the everyday practice. Perindopril-based SPC, including both two- and three-drug combinations, have been marketed since 2008 (Fig. 1). Our considerations regarding the use of perindopril-based combinations both within the basic HTN management strategy and for treatment individualization are informed by not only the everyday clinical experience but also the results of numerous clinical studies, including large randomized trials. Perindopril-based SPC are characterized by long duration of action providing stable 24-hour blood pressure control, and the wide array of perindopril-based SPC allows their use in various clinical scenarios, thus facilitating treatment individualization.

Poland as a high cardiovascular risk country

Cardiovascular diseases remain the major cause of mortality in Poland. The COVID-19 pandemic has negatively affected the lifestyle of the population, with a reduction of physical activity, increase in body weight, and increase in stress level, which in the long-term may increase the cardiovascular risk level in Poland [5]. In the most recent SCORE2 cardiovascular risk assessment tool, Poland was included among high cardiovascular risk countries based on the cardiovascular mortality rate (224 per 100,000/year, 2015 data) [6].

Of note, cardiovascular risk assessment using the recommended risk score charts depends mostly on major cardiovascular risk factors which are either

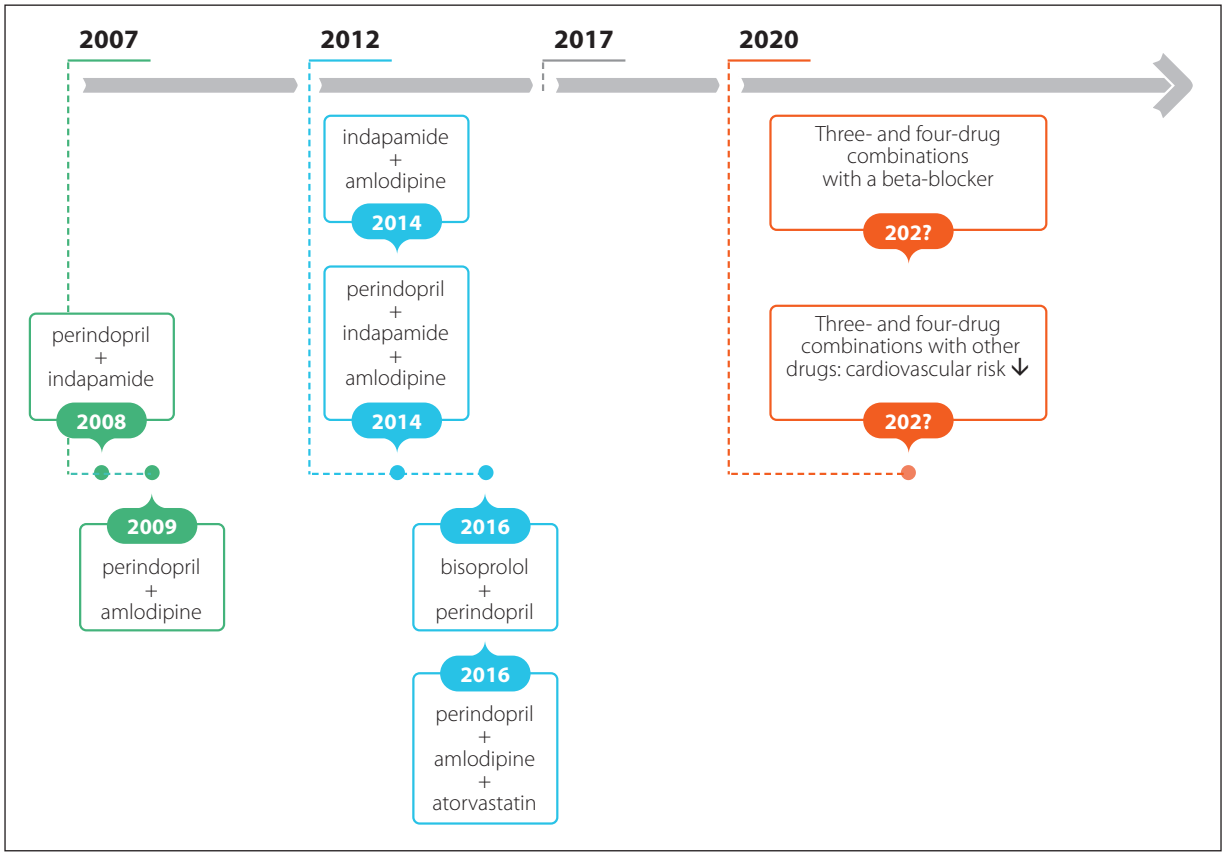

Figure 1. The timeline of introduction of perindopril-based single pill combinations in the clinical practice

non-modifiable (age and sex) or modifiable (high blood pressure, hypercholesterolemia, and smoking). Reducing major modifiable risk factors — HTN and hypercholesterolemia — both at the population level by introducing healthy lifestyle principles, and individually by effective drug treatment to reduce blood pressure and cholesterol level, may reduce cardiovascular risk and reverse the currently observed adverse trends [1,6].

The basic strategy of antihypertensive therapy

Due to the fact that combination therapy is necessary in most patients, a HTN treatment strategy based on three simple steps was endorsed in the 2018 ESC/ESH guidelines, the 2019 PTNT guidelines, and the 2023 ESH guidelines [1, 2, 4]. This strategy applies to most hypertensive patients, except for those with cardiac complications and chronic kidney disease. It is based on single-pill combination therapy used since treatment initiation, introduced in a way that is optimal for the patient (Fig. 2).

The first treatment step is to initiate combination therapy with two antihypertensive drugs using a SPC:

- an angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) + a calcium channel blocker (CCB), most commonly a dihydropyridine (dhp);
- or an ACEI/ARB + a thiazide-like or thiazide diuretic.

If blood pressure has not been reduced to the target values, step 2 therapy is introduced. The treatment is intensified by adding another blood pressure-lowering drug by using a triple-drug SPC:

An ACEI/ARB + a thiazide-like/thiazide diuretic + a dhp CCB.

If blood pressure is still not at target, step 3 involves adding spironolactone, or other drugs if spironolactone is not tolerated (Fig. 2) [1].

As stated in the 2023 ESH guidelines, the treatment of HTN should not be initiated with combination therapy only in exceptional situations: in patients with low cardiovascular risk and blood pressure < 150/95 mm Hg, in patients with high normal blood pressure and very high cardiovascu-

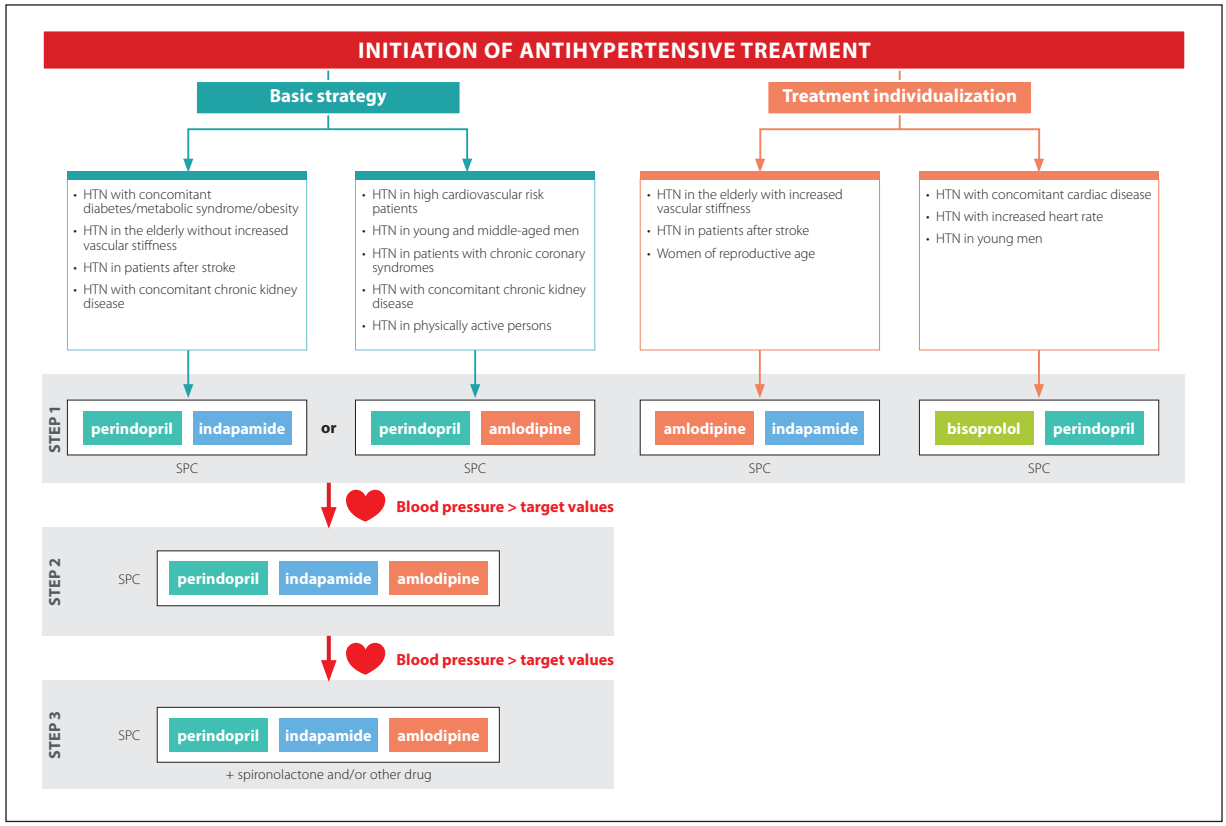

Figure 2. Opportunities for using perindopril-based treatment within the basic hypertension treatment strategy and for treatment individualization. Based on [1, 2, 4]. HTN — hypertension; SPC — single pill combination

lar risk, and in patients who are frail and/or very elderly [4].

The PTNT guidelines have also indicated that when choosing between various antihypertensive drug combinations, the treatment should be individualized based on SPC availability, evidence of the effect on cardiovascular risk, and the possibility of using them in various clinical scenarios. In this regard, ACEI have been considered preferred in patients at high cardiovascular risk, and thiazide-like diuretics have been preferred due to their potency and long duration of action, along with their neutral metabolic profile [1].

The importance of the choice of initial antihypertensive drug combination

In view of the need for combination therapy since treatment initiation in most hypertensive patients, as discussed above, a question arises how to choose specific drug combinations in a way that is most optimal for the patient. Appropriately selected two- and three antihypertensive drug combinations, particularly when using SPC, allow blood pressure to be controlled in most (about 90%) patients with HTN, translating to a cardiovascular risk reduction over the long term [4].

Already when using the initial therapeutic regimen in a given patient, the choice of appropriate drug combinations may determine the patient outcomes. The results of large clinical trials show benefits related to initiating the therapy with combinations based on perindopril and amlodipine or indapamide:

- perindopril-based therapy is associated with a beneficial effect on the cardiovascular risk and mortality (Fig. 3). The choice of perindopril-based therapy is of particular importance in view of the 2019 PTNT guidelines which stated that "in patients with HTN and high cardiovascular risk, particularly due to concomitant cardiac complications, ACEI should be preferred over sartans" [1]. The above statement becomes even more important due to the fact that, as discussed above, Poland is a high cardiovascular risk

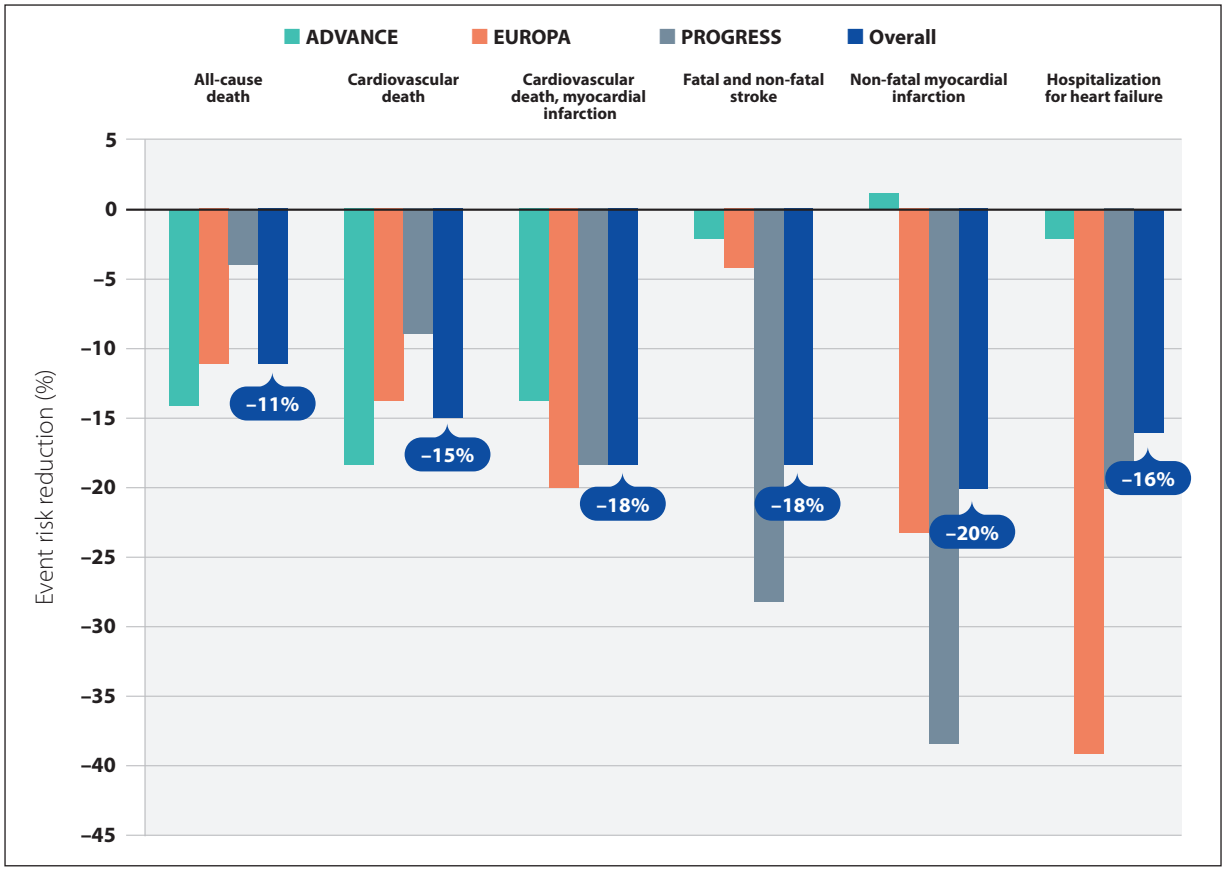

Figure 3. The effect of perindopril-based therapy on the reduction of cardiovascular morbidity and the risk of death in ADVANCE, EUROPA, and PROGRESS trials [10–12]

country. According to the SCORE2 risk chart, each patient with HTN — more specifically, men above 40 years of age and women above 55 years of age — is a priori characterized by at least high cardiovascular risk;

- an analysis of the ASCOT study showed that randomized assignment to the amlodipine ± perindopril regimen was associated with a 43% lower risk of fulfilling the criteria of resistant HTN (not achieving blood pressure control despite use of three drugs) during the follow-up compared to the assignment to the atenolol ± thiazide regimen [7];
- in the ASCOT-Legacy study, long-term follow-up of the ASCOT trial participants, it was shown that high cardiovascular risk patients initially assigned to amlodipine ± perindopril had a lower risk of mortality due to stroke (by 29%) and showed a trend towards lower cardiovascular mortality (by 10%) during the extended follow-up, when the active phase medications were no longer obligatory, compared to the patients initially assigned to atenolol ± thiazide [8];
- the importance of the choice of antihypertensive drug combination when initiating therapy was also evaluated in the long-term follow-up of the ADVANCE trial participants, the ADVANCE-ON study. Over the extended follow-up, it was shown that patients who received perindopril and indapamide during the active phase of the trial, were characterized by a 12% lower cardiovascular mortality compared to patients receiving placebo in the active phase of the trial [9].

In summary, the above observations indicate the importance of choosing an appropriate antihypertensive drug combination already when initiating the therapy. The right choice allows achieving adequate blood pressure control and prevents development of resistant HTN, which translates to better long-term patient outcomes in terms of cardiovascular risk reduction and lower mortality.

Dose selection and "quantitative" blood pressure control

The current guidelines highlight the need for initiating HTN treatment with combination therapy but do not include any suggestions regarding the dose selection when initiating therapy. An analysis of clinical studies of perindopril-based combinations provides some clues regarding the dose selection when initiating and intensifying therapy (Fig. 4). Everyday practice may also be informed by selected study conclusions:

- initiating therapy with a perindopril 5 mg and amlodipine 5 mg combination, compared

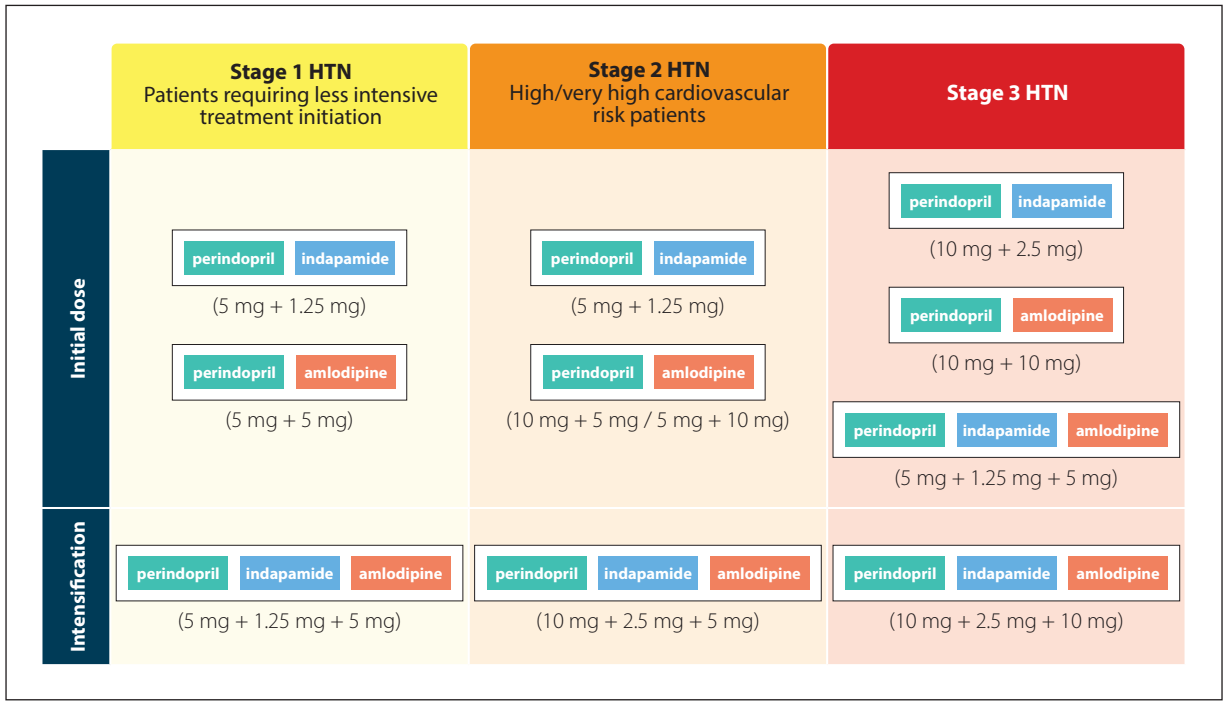

Figure 4. Dosing of perindopril-based combinations during treatment initiation and intensification in relation to baseline blood pressure values and cardiovascular risk. Authors' original compilation based on [13–22]. HTN — hypertension

to a perindopril 5 mg and indapamide 1.25 mg combination, is associated with a similar, significant blood pressure-lowering effect and achievement of target blood pressure values in patients with stage 1 HTN [13];

- studies that evaluated perindopril and indapamide or amlodipine showed that the blood pressure-lowering effect is proportional to baseline blood pressure values — the higher baseline values, the more pronounced blood pressure-lowering effect [14, 15]. This guarantees the safety and effectiveness of antihypertensive therapy, without the risk of hypotension in patients with lower baseline blood pressure values;
- studies that evaluated perindopril and indapamide or amlodipine showed the efficacy of these combinations in various patient groups (the elderly, patients with diabetes or morbid obesity, and patients with coronary artery disease) [16, 17];
- in patients with uncontrolled blood pressure (> 160–200/< 110 mm Hg), the efficacy and safety of a perindopril 10 mg and indapamide 2.5 mg combination was shown [18];
- in patients with blood pressure uncontrolled despite two-drug treatment, the use of a perindopril, indapamide, and amlodipine combination resulted in better antihypertensive efficacy, with significant blood pressure lowering and achievement of target blood pressure values in most patients, as shown in the PETRA, PIANIST, and PAINT studies [19–21];
- although initiating the therapy with a three-drug combination has not been recommended in the guidelines, the study by Tsioufis et al. indicates that initiating treatment with a perindopril, indapamide, and amlodipine combination in hypertensive patients, particularly those with stage 3 HTN, may be associated with a significant blood pressure-lowering effect and more rapid achievement of target blood pressure values in a large proportion of patients. In addition, such therapy was well tolerated and safe [22].

In summary, using perindopril-based combinations allows "quantitative" blood pressure control, i.e., achieving target blood pressure values (Fig. 5) in a large proportion of patients.

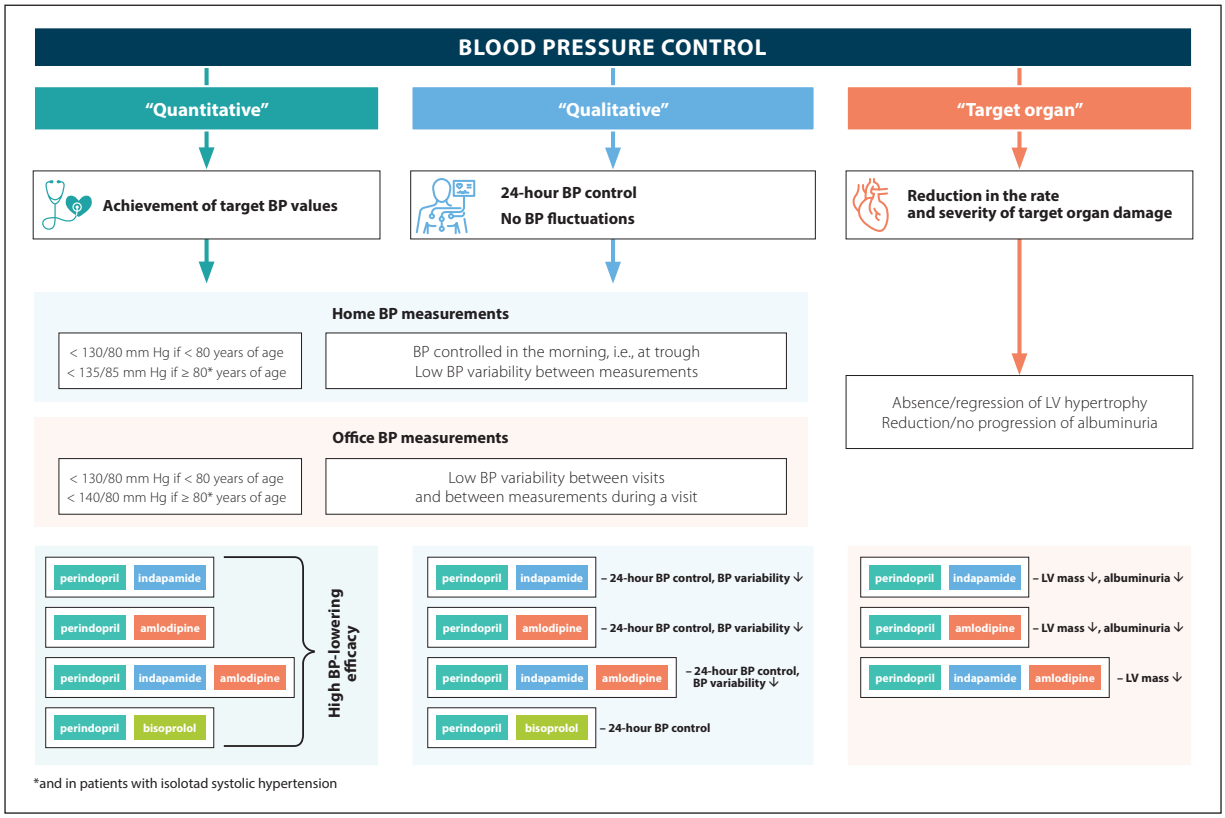

Figure 5. "Quantitative", "qualitative", and "target organ' blood pressure control – benefits from perindopril-based combinations. Based on [4, 11, 13–36]. BP — blood pressure; LV — left ventricle

The importance of „qualitative" and „target organ" control of blood pressure

Use of SPC based on long-acting medications not only reduces the number of tablets taken by the patient but also allows single-pill once-daily treatment. SPC based on drugs that do not provide 24-hour coverage may not allow adequate blood pressure lowering at trough and may not reduce blood pressure variability similarly to long-acting medications. Clinical studies showed that perindopril-based combinations are characterized by a long, 24-hour duration of action which is an element of "qualitative" blood pressure control (Fig. 5), for example:

- perindopril and indapamide — 24-hour blood pressure control, high through/peak ratio of 0.8 [28];
- perindopril and amlodipine — 24-hour blood pressure control [16, 34, 35];
- perindopril, indapamide and amlodipine — significant and uniform reduction of daytime and night-time blood pressure values as evidenced by 24-hour blood pressure monitoring, and morning and evening home blood pressure measurements [23], with uniform 24-hour blood pressure-lowering effect (analysis from the PIANIST study) [21].

Growing data indicate that in addition to the achievement of target blood pressure values ("quantitative" control), an effect on blood pressure variability is also important ("qualitative" control). Increased blood pressure variability exerts a blood pressure level-independent effect on the increase in cardiovascular risk [36]. Clinical studies showed that perindopril-based combinations have a beneficial effect on reducing blood pressure variability:

- perindopril and indapamide — smaller between-doses blood pressure level fluctuations over the 24 hours during perindopril and indapamide therapy compared to atenolol therapy [28];
- perindopril and amlodipine — reduction of blood pressure variability, reduction of morning blood pressure surge [16, 34]; reduction of a number of blood pressure variability indices evaluated in the ASCOT trial [16, 25–27];
- perindopril, indapamide and amlodipine — reduction of blood pressure variability as evaluated by 24-hour blood pressure monitoring [24].

The effect on hypertensive target organ damage is also of importance, in particular on moderately increased albuminuria (formerly called microalbuminuria) and left ventricular hypertrophy, including both prevention of their development and regression of the existing target organ damage [36]. Regarding perindopril-based combinations, beneficial effects were shown for:

- perindopril and indapamide — among others, in the PIXCEL and REASON studies (reduction of the left ventricular mass index) [29, 30], and the PREMIER and ADVANCE studies (prevention of development or regression of moderate albuminuria) [11, 31–33];
- perindopril and amlodipine — reduction of the left ventricular mass index [16];
- perindopril, indapamide and amlodipine — reduction of the left ventricular mass index [24].

The final but the most important aspect of cardiovascular protection is the sum of the above discussed ones. For perindopril, indapamide and amlodipine, which provide all the components of blood pressure control as outlined above (quantitative, qualitative, and target organ control), cardiovascular event rate reduction was shown in large clinical trials including the PROGRESS, ADVANCE, EUROPA, ASCOT, and HYVET studies [10–12, 37, 38].

Treatment intensification by adding another medication instead of increasing the doses of drugs already used

Arguments for treatment intensification by adding another medication instead of increasing the doses of the drugs already used have been highlighted in the available literature [39]:

- utilization of various mechanisms of action of different antihypertensive drug classes;
- an additive/synergistic effect;
- achievement of a greater blood pressure-lowering effect compared to the effect of each drug used separately — the metaanalysis by Wald et al. that included nearly 11,000 patients from 42 studies showed that combining drugs from various classes is approximately 5 times more effective at reducing blood pressure than increasing the dose of a single drug [40];
- among others, a more potent nephroprotective and cardioprotective effect;
- a lower rate of adverse effects.

The rationale of this approach when intensifying treatment in patients already receiving two antihypertensive medications, i.e., initiating optimal three-drug combination treatment, was evaluated in the PIANIST study. It was shown that in patients

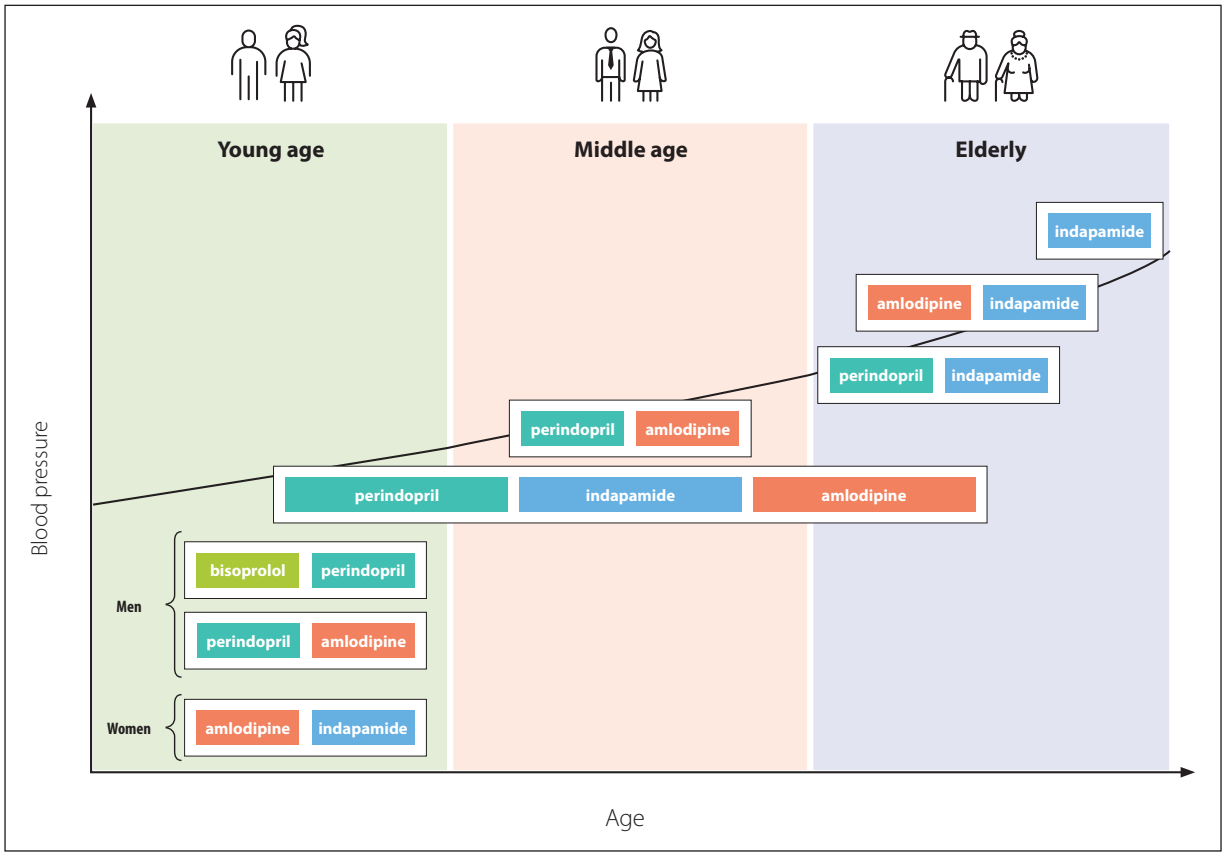

Figure 6. Use of perindopril-based two- and three drug combinations in relation to the patient age

uncontrolled on previous two-drug treatment, use of a three-drug SPC (perindopril + indapamide + amlodipine) was associated with a significant additional blood pressure lowering, by 28/14 mm Hg in office measurements [20].

Treatment of HTN in relation to the patient age

Blood pressure increases with age, and this phenomenon depends on different mechanisms at various stages of life [41, 42], thus making it necessary to adjust blood pressure-lowering therapy to the patient age (Fig. 6).

Young age (by 40 years)

In younger persons, major mechanisms include activation of the sympathetic system, often manifesting as so called hyperkinetic circulatory state (discussed in more detail below), and activation of the renin-angiotensin-aldosterone (RAA) system [41]. In this age group, the optimal choice in men is often the combination of an ACEI with a beta-blocker (BB) or a dhp CCB, e.g., bisoprolol and perindopril or perindopril and amlodipine. As RAA system inhibitors cannot be used in women in this age group, the recommended combinations in young women include a BB plus a dhp CCB and a dhp CCB plus a thiazide-like/thiazide diuretic (Fig. 6) [1, 41].

Middle age (40–65 years)

In middle-aged persons, attention should be paid to RAA system activation, and also to the fact that this is a high cardiovascular risk population. Treatment of HTN must be effective, consistent with the general rule that an effective treatment should not be delayed. In addition, as discussed above, the choice of optimal treatment at this age will result in a reduction of the cardiovascular risk over the long term. Thus, the optimal choice in this age group may be a combination of an ACEI and a dhp CCB (e.g., perindopril and amlodipine), with further treatment intensification to a combination of an ACEI, a thiazide-like diuretic, and a CCB (e.g., perindopril, indapamide and amlodipine) (Fig. 6). Attention should be also paid to special situations, such as HTN in the postmenopausal period (as discussed below) [1, 2].

Older age (65 years and above)

Treatment of HTN in the elderly is of utmost clinical importance due to high prevalence of HTN in this age group. Of note, management of HTN in the elderly patients is often fraught with problems which hinder the achievement of target blood pressure values. These difficulties are related to different pathogenesis of HTN in this age group compared to young and middle-aged patients, mostly related to increasing vascular stiffness [42]. It should be stressed, however, that vascular stiffness is not significantly increased in a large and growing proportion of the elderly population and patients benefit from intensive treatment of HTN build upon the basic treatment strategy. Thus, when choosing the treatment regimen, not only the chronological age but also the biological age should be taken into account (Fig. 6).

Older patients without increased vascular stiffness

In this group of hypertensive patients, a combination of perindopril and indapamide may be a reasonable choice due to:

- a beneficial effect on target organ damage, including reduction of the left ventricular mass and the left ventricular mass index [30, 43, 44]. This may be of particular importance as the elderly patients with HTN and left ventricular hypertrophy are prone to develop heart failure;
- a beneficial effect of arterial structure, pulse pressure, and selected parameters used for the assessment of vascular stiffness [45, 46]. This may be of importance for the prevention of an increase in arterial stiffness and the development of isolated systolic hypertension;
- in the most recent analysis of studies that utilized indapamide or the perindopril and indapamide combination (PATS, PROGRESS, ADVANCE and HYVET, overall nearly 25,000 patients, mean age 60–84 years, mostly patients with systolic-diastolic HTN), it was shown that treatment with indapamide with or without perindopril was associated with a reduction of all-cause mortality and, what may be of particular importance in this age group, a reduction of the risk of fatal stroke and fatal/nonfatal stroke by 36% and 27%, respectively [47];
- in another large analysis that included more than 28,000 patients, including participants of indapamide and/or perindopril trials (HYVET, PROGRESS, ADVANCE), at the mean age of 69 years, it was shown that active treatment was associated with a 13% reduction in the risk of incident dementia [48].

For treatment intensification in this group of patients, when perindopril and indapamide-based therapy is not effective, a SPC of perindopril, indapamide, and amlodipine is a reasonable choice [49].

Older patients with increased vascular stiffness

In HTN with increased vascular stiffness, as evidenced by increased pulse pressure (difference between systolic and diastolic blood pressure), particularly to 60 mm Hg or more, thiazide-like diuretics/thiazide diuretics and dhp CCB are preferred [12]. Clearly, one reason for the preference of thiazide-like diuretics/thiazide diuretics and dhp CCB in patients with isolated systolic hypertension is their high antihypertensive efficacy in this patient group [13]. It was shown that in patients with isolated systolic hypertension (average blood pressure 160/80 mm Hg), the indapamide and amlodipine combination reduced blood pressure by 32/6 mm Hg and pulse pressure by 25.5 mm Hg [50]. In addition, the EFFICIENT study showed that the use of an indapamide and amlodipine SPC in patients not controlled on CCB monotherapy or with untreated stage 2 or 3 HTN was associated with a significant blood pressure reduction, in particular of systolic blood pressure, during a 45-day follow-up [51].

The role of this combination has also been highlighted by the results of the metaanalysis by Rimoldi et al. which showed that compared to other combinations, a combination of a thiazide-like diuretic/thiazide diuretic and a dhp CCB significantly reduced the risk of myocardial infarction and stroke [52].

Treatment of hypertension depending on concomitant conditions

Obesity and metabolic syndrome

A sine qua non condition for the diagnosis of metabolic syndrome is the presence of obesity, usually accompanied by HTN and metabolic disturbances — prediabetes/diabetes and/or atherogenic dyslipidemia. Concomitant presence of these abnormalities determines the management of HTN in this patient group in the following ways [53]:

1. **Lifestyle modifications** should be introduced.
2. Emphasis should be given to **body weight reduction**, including by pharmacological and surgical treatment of obesity.
3. The efficacy of specific medications in obese patients and the effect of antihypertensive drugs on glucose and lipid metabolism should be taken

into account when making the decisions regarding drug treatment of HTN.

2019 PTNT guidelines
First choice drugs: **ACEI**/ARB
Second choice drugs: **dhp CCB**/non-dhp CCB
2022 Polish scientific societies statement
Treatment initiation: **ACEI**/ARB + **dhp CCB** or **thiazide-like diuretic**/thiazide diuretic
Hypertension and cardiac complications: **ACEI** + **BB**

PTNT — Polish Society of Hypertension (Polskie Towarzystwo Nadciśnienia Tętniczego; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker; CCB — calcium channel blocker; dhp — dihydropyridine; BB — beta-blocker

In the statement on the management of metabolic syndrome, it was recommended to initiate the treatment of HTN with a combination of an ACEI/ARB and a dhp CCB or a thiazide-like diuretic/thiazide diuretic (with a preference for SPC) [53]. In addition to the obvious option of using the **perindopril and amlodipine** combination as the first step, it is also possible to choose the combination of **perindopril and indapamide.** The latter is well suited to the pathogenetic mechanisms of HTN in persons with obesity and metabolic syndrome, as the increased renin-angiotensin system activity is inhibited by the ACEI (perindopril), while the thiazide-like diuretic (indapamid) targets increased blood volume and salt-sensitivity of hypertension in obesity [53–55]. In addition, the choice of indapamide in patients with metabolic syndrome is justified by its proven neutral effect on metabolic disturbances, and a high antihypertensive efficacy of the perindopril and indapamide combination in obese patients [1].

Selected study results that justify using perindopril + amlodipine/indapamide in patients with metabolic syndrome are as follows:

- studies of the perindopril and indapamide combination showed a significant blood-pressure lowering effect that was proportional to the baseline blood pressure values, with similar efficacy in obese and non-obese patients [14 ,17];
- in an analysis of perindopril and indapamide studies, it was shown that the use of this combination was associated with no effect of blood potassium, uric acid and glucose levels, as well as on the lipid profile [56];
- it was shown that compared to other drug classes, the higher is the body mass index, the higher benefit of ACEI in terms of cardiovascular risk reduction [57];

In an analysis of the PROGRESS study, it was shown that the benefits of perindopril and indapamide in terms of cardiovascular risk reduction were similar in persons with normal body weight and obese persons [58].

Diabetes

The diagnosis of diabetes places a patient with HTN in at least a high cardiovascular risk group. This translates to the need for effective antihypertensive therapy to reduce this risk, based on RAA system inhibitors (particularly ACEI), which are also characterized by a nephroprotective effect [59].

Specific features of HTN in diabetes should be noted, including the presence of masked HTN, elevated nocturnal blood pressure values and lack of nocturnal blood pressure dip, and the occurrence of orthostatic and postprandial hypotension. This warrants using long-acting antihypertensive medications that provide stable blood pressure control over 24 hours. Use of SPC is also important to simplify the treatment regimen, as in addition to antihypertensive therapy, many other drug classes are often used in this patient group [60].

PTNT 2019
First choice drugs: **ACEI** (**perindopril**/ramipril preferred)/ARB
Second choice drugs: **dhp CCB**/non-dhp CCB/**thiazide-like diuretic**/thiazide diuretic (**indapamide** preferred)
PTD 2023
Treatment initiation: **ACEI**/ARB + **dhp CCB** or **thiazide-like diuretic**/thiazide diuretic
Treatment intensification: **ACEI**/ARB + **thiazide-like diuretic**/thiazide diuretic + **dhp CCB**
Other drugs to be considered: aldosterone antagonists, **BB**

PTNT — Polish Society of Hypertension (Polskie Towarzystwo Nadciśnienia Tętniczego; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker; CCB — calcium channel blocker; dhp — dihydropyridine; PTD — Polish Society of Diabetology (Polskie Towarzystwo Diabetologiczne); BB — beta-blocker

The 2019 PTNT guidelines and the 2023 Polish Diabetes Society (Polskie Towarzystwo Diabetologiczne, PTD) guidelines are consistent in regard to the role of the renin-angiotensin system inhibitors, and in particular ACEI, in patients with HTN and concomitant diabetes [1,61]:

- ACEI are the mainstay of combinations recommended for treatment initiation, i.e., ACEI and dhp CCB or thiazide-like diuretic/thiazide diuretic (use of SPC is preferred, with possible use of perindopril + amlodipine/indapamide combinations based on the studies discussed below);
- in patients with cardiac complications (chronic coronary syndromes, previous myocardial infarction, heart failure), a combination of ACEI and BB is recommended (with possible use of the perindopril + bisoprolol combination);
- in patients with albuminuria/proteinuria, the renin-angiotensin system inhibitors should be pre-

ferred (with possible use of perindopril based on the studies discussed below);
- in addition, it has been indicated in the PTD guidelines that "in persons > 55 years of age in whom other cardiovascular disease risk factors are present, use of ACEI should be considered to reduce the risk of cardiovascular event regardless of blood pressure values".

When discussing the treatment of HTN in patients with diabetes, differences between thiazide and thiazide-like diuretics should be noted. These include differences regarding not only the duration of action and the duration of blood pressure-lowering effect but also the effect on glucose metabolism. As highlighted in the 2019 PTNT guidelines, thiazide-like drugs (indapamide, chlorthalidone) are preferred among diuretics. This results from more evidence for cardiovascular event prevention and a neutral metabolic effect [1]. Such evidence was provided by the ADVANCE study which showed that in patients with diabetes, use of the perindopril and indapamide combination was associated with no adverse effect on glucose metabolism parameters and, more importantly, with a significant reduction in the rates of cardiovascular events that result not only from elevated blood pressure values but also from diabetes. These effects included, among others, a 14% reduction of the coronary event rate, a 21% reduction of the renal event rate, and a 14% reduction of all-cause mortality [11].

Although the PTNT and PTD guidelines did not define the optimal combination of three antihypertensive drugs in patients with diabetes, study results indicate benefits from the use of the combination of perindopril, indapamide, and a dhp CCB, e.g., amlodipine. Such evidence was provided by an analysis of the ADVANCE study results which showed that the use of perindopril, indapamide, and CCB, compared to the use of CCB only, was associated with a reduction in the rate of:
- major cardiovascular events (by 12%);
- cardiovascular deaths (by 24%);
- all-cause deaths (by 28%) [62].

Chronic coronary syndromes

In patients with HTN and a concomitant chronic coronary syndrome, a target blood pressure below 130/80 mm Hg has been recommended in the ESH guidelines. The main drug classes should be BB and renin-angiotensin system inhibitors. It was shown that these drug classes may improve long-term outcomes in post-myocardial infarction patients. Due to their significant antianginal effects, BB are also the drugs of choice in patients with symptomatic coronary artery disease [4, 63].

In the 2019 PTNT guidelines, two major antihypertensive drug classes, ACEI and BB, were recommended in patients with HTN and concomitant ischemic heart disease. Again, it was shown that these drug classes may improve long-term outcomes in post-myocardial infarction patients. The recommended renin-angiotensin system inhibitors are ACEI. As highlighted in the guidelines, ACEI with the evidence of efficacy from large clinical trials in patients with ischemic heart disease should be preferred, and thus the preferred drugs are perindopril, ramipril, and zofenopril. Sartans are considered second choice drugs if ACEI are not tolerated, with preference of telmisartan and valsartan in the management of HTN with concomitant ischemic heart disease [1].

Among BB, bisoprolol and nebivolol are preferred in the PTNT guidelines. Cardiac selectivity of bisoprolol and its efficacy in reducing heart rate have been highlighted in the PTNT guidelines. Taking into account the general recommendation to use SPC, the availability of a perindopril and bisoprolol SPC should be noted [1]. A combination of bisoprolol and perindopril in the management of patients with chronic coronary syndromes is characterized by antihypertensive efficacy and a significant heart rate reduction. In addition, it exerts a beneficial effect on the severity of anginal symptoms [64].

PTNT 2019
First choice drugs: **ACE-I** (**perindopril**/ramipril/zofenopril preferred)/BB
Second choice drugs: **dhp CCB** (with angina)/non-dhp CCB (in case of BB intolerance)/ARB (in case of ACEI intolerance, valsartan/telmisartan preferred)/aldosterone antagonist (post-myocardial infarction)
ESH 2023
Treatment initiation: **ACEI** (ARB if ACEI not tolerated) + **BB**
Treatment intensification: **dhp CCB** in patients with angina, **dhp CCB** or **thiazide-like diuretic**/thiazide diuretic in patients without angina
ESC 2019
ACEI in patients at a very high risk of adverse cardiovascular events
Post-myocardial infarction: **BB** and **ACEI**/ARB (ARB — second choice if ACEI contraindicated or not tolerated)
In patients with angina: **BB** and/or CCB
In patients with diabetes: **ACEI** to prevent cardiac events
Microvascular angina: **BB** + **ACEI**

PTNT — Polish Society of Hypertension (Polskie Towarzystwo Nadciśnienia Tętniczego); ESH — European Society of Hypertension; ESC — European Society of Cardiology; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker; CCB — calcium channel blocker; dhp — dihydropyridine; BB — beta-blocker

To conclude the remarks on the management of HTN in patients with chronic coronary syndromes, the usefulness of an ACEI and dhp CCB combination in this group of patients, e.g., perindopril

and amlodipine, should be highlighted. Clearly, the arguments for using such a combination in this group of patients include its antihypertensive efficacy and stable blood pressure control covering morning hours, the period when most coronary events occur [16]. This combination exerts a significant effect on cardiovascular risk in patients with chronic coronary syndromes. In an analysis from the EUROPA study, it was shown that the use of a CCB and perindopril was associated with a significant reduction of the risk of the primary endpoint (cardiovascular death, non-fatal myocardial infarction, and resuscitated cardiac arrest) by 35%, all-cause mortality by 46%, cardiovascular mortality by 41%, hospitalizations for heart failure by 54%, and myocardial infarction by 28% [65].

Previous stroke

Secondary stroke prevention is defined as preventing recurrent stroke or transient ischemic attack. It is believed that following an ischemic stroke, the risk of recurrent stroke is up to 10–12% during the first year (with the highest risk in the period immediately after stroke, estimated at 3% during the first 30 days) and 5–8% in each subsequent year. It has been estimated that the cumulative 5-year risk or recurrent stroke is 30–40%. In cerebral hemorrhage (excluding those due to an aneurysm), the risk of recurrent bleeding is 3–7% during the first year, and the cumulative 5-year risk is about 19% [1,16]. Effective treatment of HTN reduces the risk of both incident and recurrent stroke [2].

PTNT 2019
First choice drugs: ARB/**thiazide-like diuretic**/thiazide diuretic (indapamide preferred)
Second choice drugs: **ACEI**

PTNT — Polish Society of Hypertension (Polskie Towarzystwo Nadciśnienia Tętniczego); ARB — angiotensin receptor blocker; ACEI — angiotensin-converting enzyme inhibitor

A large analysis of clinical trials published in *Hypertension* showed a higher efficacy of amlodipine in stroke prevention compared to both other antihypertensive drugs and placebo [17]. It was also shown that thiazide-like diuretics significantly reduce the risk of stroke compared to thiazide diuretics (–18%) [19]. Due to high efficacy of thiazide-like diuretics and CCB in the management of the elderly patients, particularly those with isolated systolic hypertension, the guidelines recommend that patients above 65 years of age be treated with CCB or thiazide-like diuretics in monotherapy or combination, optimally using SPC in the latter situation [2]. It should also be noted that both amlodipine and indapamide, either in monotherapy or combination, optimally using SPC, have been shown to reduce the risk of stroke which is particularly high in the elderly patients.

The PROGRESS study results clearly indicate the benefits of using perindopril and indapamide in patients with a history of stroke. In the active treatment group that received perindopril, combined with indapamide if needed, the rate of stroke was reduced by 28%, the rate of dementia was reduced by 34%, and an improvement of cognitive function was noted [10].

Chronic kidney disease

In patients with chronic kidney disease (CKD), preventing further disease progression requires strict HTN control. It was shown that RAA system inhibitors, including ACEI, reduce albuminuria, proteinuria and CKD progression more effectively than other antihypertensive drug classes. In the ACCOMPLISH study, an ACEI and dhp CCB (amlodipine) combination was shown to reduce the rate of CKD progression [1, 2]. Although a loop diuretic is required to reduce hypervolemia in patients with the estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, previous guideline recommendations to withdraw thiazide-like diuretics at this eGFR level have been questioned by the results of the study by Agarwal et al. In that study, it was shown that chlorthalidone, a thiazide-like diuretic, effectively reduced blood pressure in patients with lower eGFR values (mean 23 mL/min/1.73 m^2) [66]. This finding may be explained by the fact that in addition to a diuretic effect, thiazide-like diuretics — chlorthalidone and indapamide — are characterized by a vasodilatatory effect.

Benefits of the perindopril and indapamide combination in the treatment of patients with CKD, particularly due to diabetic nephropathy, should be highlighted. In the ADVANCE study in diabetic patients, the active treatment group showed a reduction in the renal event rate (by 21%), the development or progression of nephropathy (by 18%, p = 0.055), and the development of microalbuminuria (by 21%) compared to the placebo group [11]. In the PREMIER study, which also included patients with diabetes type 2 and HTN, urinary albumin excretion rate was reduced more in the perindopril/indapamide group compared to the enalapril group [31].

In summary, a combination of perindopril and either amlodipine or indapamide may be used in patients with CKD, with further treatment intensifica-

tion to a combination of perindopril, indapamide, and amlodipine if needed.

PTNT 2019
Chronic kidney disease (diabetic/non-diabetic)
First choice drugs: **ACEI**/ARB
Renal failure
First choice drugs: **ACEI**/ARB
Second choice drug: loop diuretic
Albuminuria/proteinuria
First choice drugs: **ACEI**/ARB
Second choice drug: **dhp CCB** (lercanidipine preferred)/non-dhp CCB
ESH 2023
Treatment initiation: **ACEI**/ARB + **CCB** or **ACEI**/ARB + **thiazide-like diuretic**/thiazide diuretic (or loop diuretic if eGFR < 30 mL/min/1.73 m^2)
Treatment intensification: **ACEI**/ARB + **CCB** + **thiazide-like diuretic**/thiazide diuretic (or loop diuretic if eGFR < 30 mL/min/1.73 m^2)

PTNT — Polish Society of Hypertension (Polskie Towarzystwo Nadciśnienia Tętniczego); ESH — European Society of Hypertension; ESC — European Society of Cardiology; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker; CCB — calcium channel blocker; dhp — dihydropyridine; eGFR — estimated glomerular filtration rate

Conditions associated with an increased heart rate

Both the 2023 ESH guidelines and the 2019 PTNT guidelines consider an increased heart rate (> 80 bpm) an independent risk factor for adverse cardiovascular events including mortality, in addition to the conventional cardiovascular risk factors. Thus, all patients with increased heart rate require consideration of its causes and initiation of treatment to reduce heart rate, preferably with BB [1, 4]. As highlighted by the authors of the PTNT guidelines, although two BB subclasses are preferred: vasodilatatory (e.g., nebivolol), and conventional highly cardioselective (e.g., bisoprolol), the latter group should be preferentially used in patients with HTN and an increased heart rate (> 80 bpm). The authors also noted that the preference of conventional highly cardioselective BB also includes the option of using a SPC based on a highly cardioselective BB [1]. Conditions associated with an increased heart rate are also characterized by an increased cardiovascular risk, and thus ACEI should also be considered in these patients, as may be inferred from the PTNT guidelines. If combination treatment is needed, the optimal choice is a SPC of BB + ACEI (e.g., bisoprolol + perindopril). Below, we discuss selected conditions associated with an increased heart rate and often higher cardiovascular risk.

Long-COVID — cardiac symptoms persist in some patients after COVID-19, including an increased heart rate and perceived palpitations. This may warrant BB use in the treatment of HTN [67,68]. Studies also indicate the importance of providing the patient with appropriate protection prior to, during, and after COVID-19 [69, 70]. Benefits from the use of antihypertensive drugs have been shown, in particular for RAA system inhibitors including ACEI. All this reinforces the importance of the already mentioned recommendation from the 2019 PTNT guidelines that ACEI should be the mainstay in the treatment of HTN in patients at high cardiovascular risk (based on, among others, the results of the EUROPA trial with perindopril). Taking into account these arguments, a combination of a BB and an ACEI (e.g., bisoprolol and perindopril), may be warranted in patients with long COVID-19 with an increased heart rate.

Chronic mental stress — the pathogenesis of HTN in patients with chronic mental stress includes activation of two systems: the sympathetic system and the RAA system. An increased sympathetic system activity also leads to an increased heart rate. Thus, it has been highlighted that BB are warranted in the treatment of HTN in persons with episodic blood pressure increases or chronically elevated blood pressure to mental stress [71, 72]. In addition, chronic stress and associated unhealthy lifestyle often lead to the development of metabolic disturbances and obesity which in turn are associated with an increased RAA system activity [73]. Thus, the use of RAA system inhibitors including ACEI is also warranted.

Postmenopausal period — an interesting study by Hsia et al. shows that in women in the postmenopausal period (50–64 years of age), an increase in blood pressure and heart rate correlates with the severity of mood disturbances. This is possibly mediated by an effect of mood disturbances on the sympathetic system activation. In addition, coexistence of HTN, an increased heart rate, and severe mood disturbances leads to a higher risk of coronary events among women in this age group [74]. RAA system activation also occurs in postmenopausal women, leading to sodium retention, fluid overload, and increased blood pressure values [75]. Taking into account the above mechanisms, the use of a combination of a BB and a RAA system inhibitor, particularly ACEI due to an increased coronary event risk, seems warranted in this patient group.

Hypertension in young persons with a hyperkinetic circulatory state — early stages of the development of HTN, particularly in young persons, are characterized by an increased cardiac output

and tachycardia at rest, which is called the hyperkinetic circulatory state [76–78]. The importance of an increased RAA system activity and its inhibition at early stages of the development of HTN was shown [79]. Thus, the use of a BB and ACEI combination (e.g., bisoprolol and perindopril) seems warranted in persons with a hyperkinetic circulatory state.

Atrial fibrillation — HTN is both a risk factor for the occurrence of atrial fibrillation and a common concomitant condition in patients with atrial fibrillation. The authors of the ESH guidelines included the combination of a BB and a RAA system inhibitor among combinations recommended for treatment initiation in patients with HTN and concomitant atrial fibrillation [4].

The need to control heart rate in patients with atrial fibrillation was highlighted in the 2019 PTNT guidelines. According to the PTNT experts, the choice of BB should be based on the drug ability to slow conduction in the atrioventricular junction, and thus "bisoprolol would be more beneficial than vasodilatory BB". As also noted by the authors of the guidelines, SPC of a BB and another drug (among others, bisoprolol + perindopril) allow simultaneous control of heart rate and blood pressure [1].

PTNT 2019
First choice drugs: **BB**/non-dhp CCB
ESH 2023
Treatment initiation: **ACEI**/ARB + **BB** (heart rate ≥ 80 bpm), **ACEI**/ARB + **dhp CCB** or **thiazide-like diuretic**/thiazide diuretic (heart rate < 80 bpm)
Treatment intensification: **ACEI**/ARB **+ BB + dhp CCB and/or thiazide-like diuretic**/thiazide diuretic (heart rate ≥ 80 bpm), or **ACEI**/ARB **+ dhp CCB + thiazide-like diuretic**/thiazide diuretic (heart rate < 80 bpm)

PTNT — Polish Society of Hypertension (Polskie Towarzystwo Nadciśnienia Tętniczego); ESH — European Society of Hypertension; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker; BB — beta-blocker; CCB — calcium channel blocker; dhp — dihydropyridine

Physically active persons

According to the most recent PTNT position statement on physical activity [80], the above discussed basic strategy for the treatment of HTN, appropriate for most hypertensive patients, may be implemented in patients with HTN who engage in recreational physical activity. In patients participating in specific sports, both at the professional and the amateur level, several issues should be taken into account that call for a modification of the basic treatment strategy:

- BB are prohibited in some sports of skill and considered doping, and additionally they may induce bradycardia and reduce exercise tolerance at very high exercise intensity;
- diuretics are prohibited in all competitive sports, and they reduce effective circulating blood volume and thus may impair exercise tolerance, particularly during the first several weeks of treatment, and the increase the risk of hypovolemia with exposure to high ambient temperatures or long-standing exercise. In physically active patients with HTN who continue to be treated with these drugs, it is necessary to provide appropriate hydration and electrolyte balance;
- ACEI, ARB and dhp CCB — drugs preferred in patients engaging in exercise, if not contraindicated. ACEI are associated with the lowest risk of post-exercise hypotension, and thus the combination of an ACEI and a dhp CCB (e.g., perindopril + amlodipine) is the optimal combination in physically active patients with HTN.

Chronic obstructive pulmonary disease

Although the 2019 PTNT guidelines list ARB and CCB as safe drugs in patients with chronic obstructive pulmonary disease (COPD), it should be noted that this is a group characterized by a high or even very high cardiovascular risk. If due caution is exercised during the treatment with ACEI (bradykinine mechanism and cough), patients with COPD may benefit from these drugs, as these are high cardiovascular risk patients. Similarly, it was shown that in patients with COPD and cardiac complications, BB reduce mortality without significantly increasing bronchoconstriction [as measured by a reduction of forced expiratory volume in one second (FEV_1) in spirometry]. It was also shown that chronic BB treatment in patients with COPD may reduce the disease exacerbation rate. In these settings, highly cardioselective drugs should be preferred, with careful dose titration.

Pseudoresistant hypertension

As indicated in the guidelines, using SPC whenever possible is one of the more important methods to improve patient compliance (Fig. 7) [1, 81, 82]. The analysis by Gupta et al. showed that the use of SPC in the treatment of HTN, as compared to free-drug combinations, is associated with [83]:

- an increase in compliance by 21% (a statistically significant effect);
- an increase in compliance and persistence by 29% (a statistically significant effect);
- an increase in the proportion of patients with blood pressure normalization by 30% (p = 0.07);

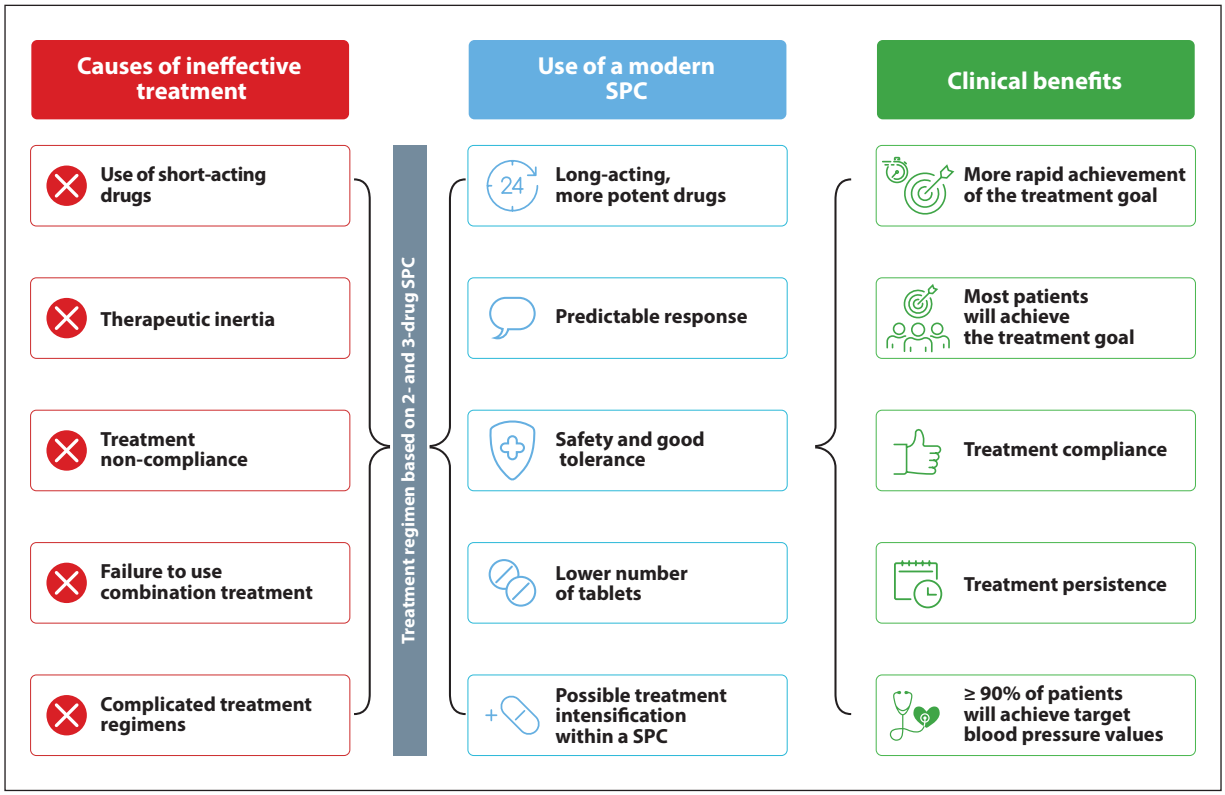

Figure 7. Causes of ineffective hypertension treatment and potential effect of using single-pill combinations (SPC) on the improvement of blood control

- a reduction in adverse events by 20% (non-significant).

The use of an ACEI, thiazide-like diuretic, and dhp CCB combination (e.g., perindopril, indapamide and amlodipine, administered as a SPC) is of major importance in patients with difficult-to-control HTN:

- as indicated in the current guidelines, an optimal combination of three antihypertensive drugs (ACEI/ARB, thiazide-like diuretic/thiazide diuretic, and dhp CCB) must be used before the diagnosis of resistant HTN can be made. Already in 2015, the PTNT experts stressed that in some patients with difficult-to-control HTN, substituting previous therapy with the recommended three-drug combination, including with the use of SPC, may be associated with an improvement in blood pressure control [84];
- it has also been highlighted that in case of difficulties with HTN control, "the treating physician may be ultimately forced to consider withdrawing all previous therapy and starting it anew, using simpler regimens and with strict medical follow-up" [85]. One possible solution is to use a triple-drug SPC;
- use of a perindopril, indapamide, and amlodipine SPC is associated with a reduction in the number of tablets used for the treatment of HTN and an improvement in compliance [22, 86];
- the antihypertensive efficacy of a perindopril, indapamide, and amlodipine SPC was shown in a number of clinical scenarios associated with difficulties in achieving blood pressure control, such as HTN uncontrolled with 2 drugs, stage 3 HTN, obese patients, and high cardiovascular risk patients [86].

Cancer patients

The management of HTN in cancer patients has been discussed in detail in the most recent ESC guidelines on cardiooncology. These issues have also been the subject of dedicated monographs in our country [87, 88]. According to the current guidelines, a major role should be played by SPC which should be used since treatment initiation (a combination of an ACEI/ARB and a dhp CCB) in stage 2 or more severe HTN. In stage 1 HTN, the treatment may be initiated with a renin-angiotensin system inhibitor, with a CCB as add-on therapy if needed. If blood pressure remains uncon-

trolled, additional drugs are added but in contrast to the general recommendations regarding antihypertensive therapy, diuretic treatment and combinations including a diuretic are rather to be avoided (patients are often during chemotherapy, with vomiting, nausea, and the risk of dehydration). Taking into account favorable safety data, and even evidence of anticancer activity of perindopril in experimental models [89], a combination of perindopril and amlodipine may be widely suggested in this patient group. Other studies suggesting a special role of perindopril and also bisoprolol may warrant the use of the perindopril and bisoprolol combination to prevent cardiotoxicity, particularly related to exposure to anthracyclines, anti-HER2 therapies, tyrosine kinase inhibitors, and anti-VEGF drugs [90–92]. A SPC of perindopril and amlodipine may be thus considered as antihypertensive therapy in cancer patients, and perindopril/bisoprolol SPC as treatment to prevent cardiotoxicity in addition to the antihypertensive effect.

Treatment intensity (in general, blood pressure should be lowered to < 140/< 90 mm Hg, and in some cancer patients to < 130/< 80 mm Hg if the treatment is well tolerated) must be dictated by the clinical status of the patient, and thus blood pressure values of 140–160/90–100 mm Hg may be tolerated in some asymptomatic patients with generalized disease and solid organ metastases. The timing of treatment initiation, for example with the two SPC mentioned above (perindopril/amlodipine or perindopril/bisoprolol), depends not only on baseline blood pressure values but also on five broad patient categories defined in the new guidelines, for which different thresholds for initiating antihypertensive therapy and different classes of recommendations regarding antihypertensive therapy were given (these patient categories are: cancer survivors who completed oncological treatment, in whom usual treatment thresholds apply as per the general recommendations; patients during treatment with favorable prognosis, i.e., curable cancer; patients with metastatic cancer and prognosis > 3 years; patients with metastatic cancer and prognosis 1-3 years; and patients with metastatic cancer and prognosis < 1 year) [87, 88].

Summary

SPC have become an indispensable element in the treatment of HTN. For this reason, the role of various drug classes and specific drugs largely depends on the availability of SPC that include a drug from a given class. A good example are perindopril-based SPC which comprise one of the most comprehensive SPC sets compared to SPC sets based on other RAA system inhibitors. As shown above, perindopril-based SPC do not only fit well to the recommended HTN management strategy but also allow complete coverage of antihypertensive treatment algorithms in all age groups, provide qualitative, quantitative, and target organ control of HTN, and allow adjusting the composition and doses of SPC to blood pressure values and concomitant conditions without changing the basic drug in the combination. In addition, some SPC from this set that do not cover the main treatment algorithm allow addressing individual therapeutic needs, e.g. bisoprolol + perindopril and indapamide + amlodipine combinations. Therapeutic regimen simplification using a uniform set of perindopril-based SPC translates to higher treatment persistence, higher antihypertensive efficacy, and as a result, greater cardiovascular risk reduction.

We can expect an introduction of further SPC, also including a BB (Fig. 1). In addition, so called hybrid SPC, based on an antihypertensive drug or drugs and other drugs reducing cardiovascular risk (e.g., statins), are an interesting option for drug treatment to prevent cardiovascular events. Before we welcome new SPC, we should more widely employ the available ones, as best evidenced by the present review of opportunities for using perindopril-based SPC in the treatment of HTN.

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