Single-pill combinations (SPCs) and treatment of arterial hypertension in Poland

Expert consensus statement of the Polish Society of Hypertension and Polish Cardiac Society Working Group on Cardiovascular Pharmacotherapy

Andrzej Tykarski[1], Krystyna Widecka[2], Krzysztof Narkiewicz[3], Beata Wożakowska-Kapłon[4], Zbigniew Gaciong[5], Stefan Grajek[6], Tomasz Grodzicki[7], Andrzej Januszewicz[8], Jacek Wolf[3], Aleksander Prejbisz[8], Katarzyna Kostka-Jeziorny[1], Krzysztof J. Filipiak[9]

[1]Chair and Department of Hypertensiology, Angiology and Internal Medicine, Poznan University of Medical Sciences, Poznan
[2]Department of Hypertensiology and Internal Medicine, Pomeranian Medical University, Szczecin
[3]Department of Hypertension, Chair and Department of Hypertension and Diabetology, Medical University of Gdansk, Gdansk
[4]1st Department of Cardiology and Electrotherapy, Faculty of Health Sciences, Jan Kochanowski University, Kielce
[5]Chair and Department of Internal Medicine, Hypertension and Angiology, Medical University of Warsaw, Warsaw
[6]1st Departament of Cardiology, Poznan University of Medical Science, Poznan
[7]Chair and Department of Internal Medicine and Gerontology, Jagiellonian University Medical College, Krakow
[8]Department of Hypertension, Institute of Cardiology, Warsaw
[9]1st Department of Cardiology, Medical University of Warsaw, Warsaw

Arterial Hypertens. 2017, vol. 21, no. 3, pages: 116–126

Praca jest tłumaczeniem artykułu: Tykarski A, Widecka K, Narkiewicz K et al. Leki złożone w terapii nadciśnienia tętniczego w Polsce. Stanowisko Ekspertów Polskiego Towarzystwa Nadciśnienia Tętniczego oraz Sekcji Farmakoterapii Sercowo-Naczyniowej Polskiego Towarzystwa Kardiologicznego. Arterial Hypertens. 2017; 3: 105–115 (DOI: 10.5603.AH.2017.0014). Należy cytować wersję oryginalną.

Hypertension is a major modifiable risk factor for cardiovascular diseases (ischaemic heart disease, stroke, heart failure and ischaemic artery disease of the lower limbs) and the most epidemiologically significant cause of death in the world. At the same time, the prevalence of hypertension in Poland is constantly increasing — according to the 2002 NATPOL study, it was 29% of adult Polish population [1]. In the second NATPOL study, the proportion of hypertensive patients increased to 32% [2] and in the WOBASZ II study in 2014 it reached 43% [3].

Large clinical trials indicate that effective blood pressure control is the most important condition for attaining the primary goal of treating hypertension, i.e., reduction of the mortality and incidence of cardiovascular events. Although the efficacy of blood pressure control in Poland has increased — according to the NATPOL programme, from 12% to 26% between 2002 and 2011 [2], and according to the WOBASZ program, from 10% to 23% between 2005 and 2014 [3], it is still low, which is mainly attributed to poor awareness of the presence and need for treatment of hypertension. However, as indicated by the data from above-mentioned programmes, even among treated patients less than 50% attain target blood pressure. The basic causes of low efficacy of hypertension control are patients' poor adherence to lifestyle changes and low compliance with pharmacotherapy, the therapeutic inertia of doctors and lack of significant progress in the development of new antihypertensive agents in recent years. The progress in the efficacy of treatment of hypertension in Poland, which is observed despite these circumstances, is likely to be associated with the emergence of the single-pill combinations (SPCs) that improve compliance, reduce therapeutic inertia,

Address for correspondence: prof. dr hab. n. med. Andrzej Tykarski, Department of Hypertensiology and Internal Medicine, Pomeranian Medical University, Szczecin, ul. Długa 1/2, 61–848 Poznań, tel.: (061) 854–91–82, faks: (061) 854–90–86, e-mail: tykarski@o2.pl

and are equivalent to progress in the pharmacotherapy of hypertension.

The use of combination drugs in Poland has risen steadily, reaching a total of 12% of all antihypertensives in 2016, which is still unsatisfactory because the European average is twice as high. Hence the efforts of the Polish Society of Hypertension (PSH) to improve the situation, expressed as highlighting the role of the SPCs in the 2011 and 2015 PSH Guidelines [4, 5], as well as cyclical publication of PSH experts' position statement on the role of combination drugs (issued in 2009 and 2013) [6, 7].

The reasons for the publication of current expert consensus statement after 4 years are: the growing number of evidence on the benefits of SPC use in hypertension (also with concomitant dyslipidaemia), the extension of indications for their use in the hypertension management algorithm and the emergence in recent years, after the publication of PSH experts' position statement in 2013, of new types of single-pill combinations available to doctors in Poland, including triple-drug combinations of antihypertensives and the so-called "hybrids" SPC containing not only antihypertensive drugs but also statins or acetylsalicylic acid (ASA). The current position statement of experts summarizes the progress of knowledge and practical application of single-pill combinations of antihypertensives in our country.

Single-pill combination of antihypertensive agents as an expression of progress in the pharmacotherapy of hypertension

The history of progress in the pharmacotherapy of hypertension can be divided into several stages (Table I). After the invention in 1940s and 1950s of a number of sympatholytic drugs that were characterized by frequent adverse effects and were only an alternative to sympathectomy for severe malignant hypertension, the first modern antihypertensive agent was chlorothiazide — a diuretic introduced in 1957. Then, after 10 years, there was the "golden decade" of antihypertensive pharmacotherapy, when almost all major drug classes were invented, and the greatest achievement of that time was the first inhibitor of angiotensin-converting enzyme (ACE), captopril, developed in 1977. Another important group of drugs were sartans which were introduced several years later. The last group of clinically relevant antihypertensive drugs, used since 2000, are the renin inhibitors, but they were not more advanced than the most popular groups of renin-angiotensin-aldosterone (RAA) system inhibitors and are practically not used in Poland.

Table I. History of **progress of antihypertensive pharmacotherapy**

1937	Reserpine	
1947	Hydralazine	Surgical treatment (sympathectomy)
1947	Ganglion-blocking drugs	
1955	Guanethidine	
1957	Thiazide diuretics (chlorothiazide)	
1967	Spironolactone	
1968	Methyldopa	
1973	Beta-blockers (propranolol)	
1970s	Alpha 2 receptor agonists (clonidine)	
1970s	Nod-dihydropyridine calcium antagonists (verapamil)	
1975	Alpha-blockers (prazosin)	
1975	Dihydropyridine calcium antagonists (nifedipine)	
1977	ACE inhibitors (captopril)	
1990	Sartans (losartan)	
2000	Renin inhibitors (aliskiren)	
po 2000	Modern combination drugs	

A review of scientific literature indicates that in the 21st century, despite many attempts, no new class of antihypertensive drugs that could improve the efficacy of blood pressure control (e.g., endothelin receptor antagonists, neutral endopeptidase inhibitors) has been introduced. Current research into new drug classes (including AT2 receptor agonists, aminopeptidase A and N inhibitors, prorenin inhibitors, natriuretic peptide receptor agonists, dopamine inhibitors, intestinal ion exchanger inhibitors Na+/H+, group -SH donors opening potassium channels in vascular smooth muscles, direct cGMP stimulators), although some are promising, do not provide a real basis for expecting significant clinical progress in the field of antihypertensive pharmacotherapy.

In conclusion, it seems that there will be a long pause in the introduction of new classes of antihypertensive drugs, as the development of multiple drugs is in the I/II phase trials, without the guarantee of performing a large clinical trial meeting the evidence-based medicine (EBM) criteria (multicentre, prospective, comparative, randomized, double-blind, including a suitably large population, with an assessment of the drug effect on both blood pressure values and morbidity/mortality due to the assessed disease entity); however, some of them have identified other stronger indications (heart failure, pulmonary hypertension, diabetes mellitus). For example, a new hybrid drug that affects both RAA

and enzymes responsible for the degradation of natriuretic peptide (valsartan/sacubitril) has been approved for the treatment of heart failure, despite clear hypotensive effect.

The only noticeable progress in the pharmacotherapy of hypertension in the last fifteen years, which may explain some increase in the effectiveness of blood pressure control in patients, is more common use of single-pill combinations of antihypertensive drugs. It is worth recalling that the SPCs have a long history in hypertensiology, but in the 1960s the preparations were based on drugs that are no longer used (e.g. reserpine + binazine, reserpine + dihydralazine). Hence, after a period of relatively low interest in SPCs, the introduction of modern SPCs at the beginning of the 21st century, the consolidation and extension of indications for combination therapy in the guidelines of scientific societies, the growing number of combination types, and the studies that have shown the benefits of SPCs have made these preparations increasingly popular among doctors. In Poland, in two years, the use of single-pill combination drugs increased by 50%, reaching in 2016 a total of 12% of all antihypertensive drugs. In this respect, further progress can be anticipated, as this is half that of the European average.

Advantages of combination antihypertensive drugs

The balance of benefits and disadvantages of SPCs in antihypertensive therapy, which we presented in the 2009 expert position statement, is still valid in terms of benefits, which are after 8 years supported by more robust evidence; however, the disadvantages have been largely eliminated (Table II).

The postulated at that time low dose flexibility was due to the fact that many SPC formulations had only one form. The SPCs were previously called FDCs — Fixed-Dose Combinations; the later name could suggest definite and unchangeable doses of components of the combination drug, which, with the current variety of potency of specific SPCs, is no longer true. Currently, most SPCs have from three (two-drug SPCs) to six (three-drug SPCs) forms, thereby allowing for a modification of therapy, which is especially important, considering current recommendation that in the event of insufficient blood pressure control the dose be increased after 2–4 weeks. Potential difficulties in determining the source of adverse effects are limited to possible allergic reactions, as the typical adverse effects of main groups of antihypertensive drugs are different and easily identifiable.

Table II. Pros and cons for using antihypertensive single-pill combinations

Pros	Cons
Fewer tablets to be taken Lower doses of component drugs Better tolerance Comfort Improved adherence Lower costs Rapidly achieved blood pressure control	Lower dosing flexibilit Problems with establishing the source of adverse effects

Some of the benefits of SPC (lower doses of individual components and, therefore, better tolerance; more rapid pressure control) result from the advantages of combination therapy. It should be reminded that the meta-analysis of the results of 42 controlled studies in 11,000 hypertensive patients showed that the additional antihypertensive effect of the combination of drugs from two different groups is almost five times greater than that of doubling the dose of a single drug [8]. This observation performed 8 years ago is of particular importance in the context of the analysis of results of the **VALUE** trial, indicating a significantly greater reduction in cardiovascular risk in those patients who have achieved blood pressure control within the first 6 months of treatment [9]. The advantages of combination therapy and SPC in terms of efficacy can now be significantly better utilized due to the considerable extension of therapeutic indications in 2011 PSH guidelines and 2013 ESH guidelines [4, 5, 10].

Additional benefits, directly associated with the SPC, i.e. the smaller number of tablets and the convenience of dosage, translate into the most important advantage of the SPC which is improving the patient's adherence in terms of both compliance and persistence. In this respect, the most referential study is meta-analysis of Gupta et al. [11], which included 15 studies and more than 32,000 patients, demonstrating that compared to control group, patients taking SPCs were characterized by better compliance (odds ratio [OR] 1.21, 95% confidence interval [CI] 1.03–1.43) and a strong trend towards improved persistence (OR 1.54; CI 0.95–2.49), which translated into a greater reduction in blood pressure (4.1/3.1 mmHg) and a trend toward more frequent normalization of blood pressure (OR 1.30; CI 0.98–1.71). Many overviews and subsequent systematic reviews, meta-analyses and retrospective cohort studies, although not all, confirm the benefits of SPC in treating hypertension with respect to improving patients' compliance [12–14]. The Italian cohort study by Corraro et al. [15], which included 209,650 patients,

found that initiation of SPC therapy resulted in significantly greater reductions in cardiovascular (11%), coronary (8%) and cerebrovascular (12%) risks compared with monotherapy and stepped therapy. In the **ACCOMPLISH** study, switching from the current treatment with separate antihypertensive agents to SPC containing an ACE inhibitor resulted in a two-fold increase in the efficacy of blood pressure control from about 40 to about 80%, regardless of the type of SPC used [16].

It should be assumed that the use of SPC may also contribute to the reduction of the second serious cause of low effectiveness of antihypertensive therapy, i.e. the therapeutic inertia of doctors, by reducing the concerns associated with concurrent use of several antihypertensive drugs.

Indications for the use of combinations of antihypertensive drugs and their role in ESH and PSH guidelines

The increased importance of combination antihypertensive drugs is largely a consequence of the fact that scientific societies have extended the indications for the use of polytherapy in their guidelines. The basic premises of the use of combination antihypertensive therapy have been stated in the 2007 ESH/ESC 2007 guidelines and included too low proportion of patients achieving blood pressure goal with monotherapy. It was suggested that in case of failure of monotherapy, the treatment should be changed to combination therapy and that preferred combinations of two drugs should be used as first-line therapy in stage 2 and 3 hypertension and/or in patients with high cardiovascular risk [17]. In both cases, the 2007 ESH Guidelines assumed the possibility of using the SPC. The next ESH Guidelines, issued in 2013 [10], strengthened this trend, by allowing in the treatment algorithm the possibility of early switching to combination therapy in patients with stage 1 hypertension and including a recommendation to consider initiating of antihypertensive treatment with two-drug combination in stage 2 hypertension and the possibility of preferring combination therapy with SPC. However, both of these recommendations were of a relatively low class IIb, due to the level of evidence B, resulting from only one, according to opinion of the ESH experts, available relevant study — the Canadian **STITCH** trial. It is worth recalling that in this study, the treatment based on the single-pill combination therapy provided better control of blood pressure and faster achievement of target values than the treatment algorithm starting with monotherapy (65% vs. 53% with mean blood pressure reduction of 23/10 versus 18/8 mmHg) [18].

In the opinion of the authors, recommendations for the use of SPC in the ESH Guidelines are too conservative. This document does not include data from the STRATHE study [19], in which initiation of antihypertensive treatment with a SPC was superior to stepped therapy (from monotherapy to combination therapy) or sequential therapy (switching from ineffective drug to another one). Moreover, it is important to realize that the greatest advantage of SPCs over conventional combination therapy with separate agents, that is improved compliance that may translate into increased efficacy, is impossible to assess in accurately performed classic EBM studies which are based on the assumption of good compliance and thus overstate it. Paradoxically, less appreciated retrospective studies are free of this limitation.

It seems that a strong recommendation of SPC preference in combination therapy should be taken on a common sense basis. Since combination drugs provide better patient compliance, this has to translate into better antihypertensive efficacy, as currently the low effectiveness of blood pressure control observed in studies such as the NATPOL study is explained by poor patient cooperation with the physician, although this statement is not confirmed by any direct evidence.

This direction for the positioning of SPCs has been adopted by the authors of PSH Guidelines and its latest version issued in 2015 includes following recommendation: "In combination therapy, it is worthwhile to use single-pill combination of two drugs, which allows for increasing treatment efficacy (STITCH and ACCOMPLISH), simplifying treatment regimen and increasing patients adherence (meta-analysis)" [5]. Already in the document published in 2011 [4], consideration was given in treatment algorithm to the possibility of early switching to combination therapy in patients with stage 1 hypertension, and in 2015 PSH Guidelines this method of intensifying therapy is preferred. In addition, the antihypertensive treatment algorithm indicates that in each case of combination therapy a SPC should be preferred. A novelty resulting from ongoing but not yet completed clinical trials was the prediction in 2015 PSH Guidelines that "in the future, combination therapy with antihypertensive agents in doses smaller than the standard ones, available in two- and three-drug combinations may be an alternative for initiating the therapy in patients with stage 1 and 2/3 hypertension respectively". At present, such a new indication for starting the treatment in stage 1 hy-

pertension with a single-pill combination of drugs in sub-standard doses has become a fact, besides the SPC containing perindopril and indapamide, also for the combination of perindopril and amlodipine (3.5 mg/2.5 mg) after the publication of two clinical trials documenting the superiority of such SPC therapy over monotherapy with perindopril or amlodipine in typical doses [20] and over stepped therapy (sartan –> sartan/amlodipine) in terms of the time to achieving target blood pressure and the percentage of well-controlled patients [21]. This new indication will probably be included in 2018 PSH Guidelines, but it can be recommended already.

Analysis of ESH experts' lectures (Volpe, Williams) during this year's ESH 2017 Annual Meeting in Milan suggests [22] that the next edition of the 2018 ESH Guidelines may include major changes in the antihypertensive therapy algorithm, suggesting the need for initiation of pharmacologic treatment with combination therapy, i.e. SPC, in most patients with hypertension.

Basic SPCs and individualization of their use

Currently there are eight types of two-drug SPCs and two types of three-drug SPCs, excluding the combinations of diuretics with different sites of action within the nephron and hybrids which will be discussed separately. These numbers have doubled over the past 6 years, which is another proof of the intense development of this concept of treating hypertension. Types of combination drugs introduced by the pharmaceutical companies are not accidental and almost perfectly reflect the principles of combining antihypertensive drugs. All available types of SPC, except thiazide diuretics + beta-blockers, are combinations of drugs considered in 2015 PSH Guidelines as optimal due to complementary mechanisms of action, proven cardiovascular risk reduction (as combination therapy or SPC), or unambiguous preference for both components in specific groups of patients.

Of these, ACE inhibitor + calcium antagonist, ACE inhibitor + thiazide/thiazide-like diuretic, sartan + thiazide diuretic and sartan + calcium antagonist should be considered as the key combinations used in the treatment of hypertension, which is supported by some arguments. The experience of Polish doctors in the use of these four combinations is the greatest because all of these drugs have been available for more than 10 years, meet the condition of presence of RAA inhibitor in combination, and three of them (Figure 1) have the largest body of evidence that they reduce cardiovascular risk in combination and provide a natural direction for initiation and/or intensification of therapy in uncomplicated arterial hypertension. It is worth noting that all of these are three-drug combinations including a RAA inhibitor + calcium antagonist + thiazide/thiazide-like diuretic, which are considered to be obligatory in intensive treatment of uncomplicated arterial hypertension.

Among these four combinations, some preferences for their use can be outlined depending on patient's global cardiovascular risk and metabolic status. These preferences are based on the observations described in 2015 PSH Guidelines suggesting that ACE inhibitors, due to additional bradykinin mechanism, are the most effective among all RAA inhibitors in reducing cardiovascular risk, which has been shown in recent meta-analyses [23–25], while thiazide-like diuretics due to additional vasodilatative mechanism are less likely to cause metabolic abnormalities, are more effective in reducing blood pressure and delaying organ damage, and have greater body of EBM

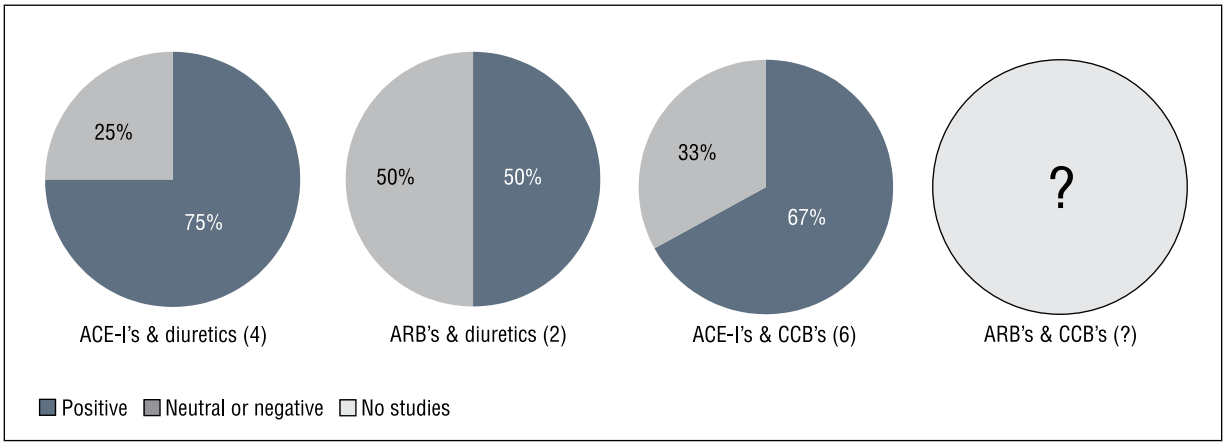

Figure 1. Percentage of positive outcome studies with basic combinations of antihypertensive drugs

evidence for cardiovascular risk reduction in combination with ACE inhibitors. The proportion of successful large clinical trials is different for these four combinations [10].

Combination of an ACE inhibitor + calcium antagonist should be considered optimal in patients with high and very high cardiovascular risk. Undoubtedly, the position of this combination is due to the **ACCOMPLISH** trial in which such SPC was found to be more effective in reducing cardiovascular risk than SPC composed of an ACE-inhibitor + thiazide diuretic [16]. Additionally, many clinical studies have shown the organ-protective effect of such combination. Currently, four combinations of this type are available in Poland: perindopril + amlodipine, ramipril + amlodipine, lisinopril + amlodipine and relatively recent enalapril + lerkanidipine. The strongest clinical evidence for the reduction of "hard" endpoints is available for the combination of perindopril + amlodipine due to the **ASCOT** study, the first large head-to-head trial in patients with uncomplicated arterial hypertension in which significant reduction in cardiovascular mortality was observed in patients receiving amlodipine + perindopril compared to those treated with a beta-blocker + a thiazide diuretic combination [26]. In addition, **CAFÉ** study, accompanying ASCOT study, showed a more effective reduction in central pressure. Moreover, the combination of perindopril + amlodipine in substandard doses, as one of very few along with the combination of perindopril and indapamide in the lowest doses, has the previously described indication for initiation of therapy in stage 1 hypertension [27].

For all these combinations, with good EBM data for its components, available are studies that document their blood pressure-lowering and organ-protective efficacy: perindopril + amlodipine (**STRONG**) [28], ramipril + amlodipine (**ATAR**) [29], lisinopril + amlodipine (**ALFESS, HAMLET**) [30, 31], enalapril + lerkanidipine (**FELT**) [32].

Interestingly for practical reasons, the four listed combinations of ACE inhibitors + calcium antagonists can be differentiated due to the principles of chronotherapy of hypertension. Two ACE inhibitors, perindopril and lisinopril, are characterized by a 24-hour antihypertensive effect similar to amlodipine, so when used in combination, they provide 24-h blood pressure control after morning administration in dippers. Ramipril and enalapril, on the other hand, have shorter time of action, and even in combination with a long-acting calcium antagonist evening dosing may be useful in non-dippers.

Particularly important and frequently prescribed are SPCs containing an ACE inhibitor + thiazide/thiazide-like diuretics which are used to enhance the antihypertensive effect of an ACE inhibitor by inducing hypovolaemia and increasing plasma renin activity by thiazide/thiazide-like diuretic, rather in patients with higher cardiovascular risk. Virtually all ACE inhibitors are available in combination with thiazide diuretic — hydrochlorothiazide. The only one currently available combination of an ACE inhibitor with preferred thiazide-like diuretic is SPC containing perindopril + indapamide, which is distinguished in the 2015 PSH guidelines because of three major clinical trials (**ADVANCE**, **HYVET**, **PROGRESS**) documenting the benefits of this combination in patients with concomitant diabetes mellitus, very elderly and with a history of stroke [33–35]. These are special indications reserved for this combination.

A combination that is most commonly used in Poland — sartan + thiazide diuretic — has similar synergistic antihypertensive effect but should be used in patients with moderate and low cardiovascular risk. This combination is characterized by very good tolerance and it was evaluated in large clinical EBM trials demonstrating a reduction in cardiovascular risk in patients with left ventricular hypertrophy (**LIFE**) [36] and in patients with moderate cardiovascular risk (**VALUE**) [37]. As with ACE inhibitors, practically for all available sartans there are SPCs with hydrochlorothiazide, but two of them (valsartan + hydrochlorothiazide and telmisartan + hydrochlorothiazide) are particularly useful because of the popularity of these sartans. Unfortunately, no combination of a sartan with preferred thiazide-like diuretic is available in Poland, although in some countries such preparations are already available (combinations of sartans with chlortalidone).

The last primary SPC, a sartan + calcium antagonist, is less commonly used due to the lack of large EBM studies. However, combinations of valsartan with amlodipine (**EX-FAST**) [38] and telmisartan with amlodipine (**TEAMSTA**) [39] are worth remembering, especially in patients with metabolic disorders, due to a very good tolerance, favourable metabolic profile and documented antihypertensive effect. These combinations include components with proven efficacy in large clinical trials of patients with hypertension and high cardiovascular risk or coronary artery disease. In controlled clinical trials with single-pill combination of telmisartan and amlodipine, target blood pressure was achieved in 80% of patients with stage 1 or 2 hypertension and 50% of patients with stage 3 hypertension, with low incidence of adverse events.

Another manifestation of advances in the treatment with combined antihypertensive drugs is the

appearance of three-drug SPCs in Poland, which offers the possibility of intensifying the therapy using one tablet also in patients with higher baseline blood pressure values, including stage 3 hypertension. Both types of these combinations: ACE inhibitor + dihydropyridine calcium antagonist + thiazide-like diuretic (the only available SPC is perindopril + indapamide + amlodipine) and older one, sartan + dihydropyridine calcium antagonist + thiazide diuretic (the only available SPC is valsartan + hydrochlothiazide + amlodipine) meet the criterion for optimum combination in uncomplicated hypertension. It is important to note that only for three-drug combination of perindopril + indapamide + amlodipine there are available analyses of randomized trials demonstrating the benefits in terms of cardiovascular risk reduction (**ADVANCE**) [40] and increase in the antihypertensive effect (**PIANIST**) [41]. This combination has a unique pharmacokinetic profile resulting from different peak concentrations of its components, which provides a stable daily antihypertensive effect without sudden blood pressure drop in first hours after administration, despite the activity of three drugs.

New SPCs for specific use

As a result of gradually increasing popularity of combined drugs, further SPCs that meet the criteria for optimal combination of antihypertensive drugs emerged in Poland in 2012–2017. Two of them provided the possibility of using SPC in patients who do not need or should not use RAA inhibitors.

The combination of a beta-blocker + calcium antagonist (the only available SPC is bisoprolol + amlodipine) is particularly applicable in uncomplicated hypertension in younger patients requiring combination therapy, especially in women of childbearing potential. The advantage of this SPC, in addition to the antihypertensive effectiveness (**BETAMLO**) [42], is good tolerance resulting from the opposite chronotropic effect of both components, with a tendency to decrease heart rate [43]. The latter feature makes SPC containing bisoprolol + amlodipine also suitable for use in patients who have cardiac complications and are prone to tachycardia, basically in combination with an ACE inhibitor, since the three-drug SPC of an ACE inhibitor + dihydropyridine calcium antagonist + beta-blocker is not yet available.

Another optimal combination of thiazide-like diuretics + calcium antagonists (the only one available SPC is indapamide + amlodipine) fills the gap in the possibility of using SPC in uncomplicated hypertension in elderly patients requiring combination therapy, since both components are recognized in the ESH and PSH Guidelines as preferred drugs. The antihypertensive efficacy of this combination has been demonstrated in the **EFFICIENT** study [44] and, if intensification of treatment is necessary, it may be convenient to switch the patient to the available three-drug SPC of perindopril + indapamide + amlodipine.

Single-pill combination of a beta-blocker + thiazide diuretic (the only available SPC is nebivolol + hydrochlorothiazide) is recommended as a component of the therapy in patients with hypertension and heart failure rather than for starting antihypertensive therapy. It is worth noting, however, that the presence in this combination of a beta-blocker with vasodilative properties, nebivolol, which has more favourable metabolic effect, mitigates traditional objections to the potential disadvantageous effects of long-term use of the combination of a beta-blocker + thiazide diuretic on carbohydrate or lipid metabolism.

The most recent combination of a beta-blocker + ACE inhibitor (the only one available SPC is bisoprolol + perindopril) is dedicated to patients with hypertension complicated with coronary heart disease, because, according to 2015 PSH Guidelines, in these patients, regardless of myocardial infarction history, antihypertensive therapy should be based on such a combination. Sub-analysis of the **EUROPA** study [45] showed that patients with stable coronary heart disease using perindopril with a beta-blocker had a lower risk of myocardial infarction and cardiovascular death compared to those using a beta-blocker alone. It is worth noting that the SPC containing bisoprolol with perindopril is the only SPC registered simultaneously in the three largest population therapeutic indications: hypertension, coronary heart disease, and heart failure.

The **Pol-Focus** study [46] showed that the combination of a beta-blocker with ACE inhibitor is most commonly used in two-drug therapy by Polish doctors. Therefore, from practical point of view, this combination may be useful in younger patients with uncomplicated hyperkinetic hypertension (bisoprolol component) and already present symptoms of organ damage, e.g. left ventricular hypertrophy (perindopril component).

"Hybrid" SPCs of antihypertensive drugs with other drugs important for cardiovascular prevention

An interesting alternative is the SPC which contains antihypertensive agents along with other drugs used in

cardiovascular prevention: statins and acetylsalicylic acid. This direction in the evolution of pharmacotherapy of hypertension is approaching the concept of "polypill", but the difference consist in that it assumes drug dosage control based on blood pressure and plasma cholesterol measurements in individual patients, while the "polypill" concept is targeted at societies of poor organization of healthcare system and assumes the improvement of cardiovascular risk at population level through the widespread use of the "polypill" containing low-doses of preventive drugs by all individuals above a certain global cardiovascular risk (e.g., based on age) without further detailed control and dosage modification.

Combinations of antihypertensive drugs with statins aim to simultaneously improve the two most important pharmacologically modifiable cardiovascular risk factors: hypertension and hypercholesterolaemia. These factors additively increase global cardiovascular risk, and the number of people who are at the same time at risk of hypertension and hypercholesterolaemia is estimated in Poland at several million people. The first SPC of this type, available in Poland for many years, is the combination of atorvastatin + amlodipine. However, this SPC was characterized by too low doses of atorvastatin available in this combination (10 or 20 mg). The relatively low popularity of this combination was also caused by the fact that statin in primary prevention was indicated only in patients with hypertension and high cardiovascular risk, whereas it is patients with lower risk who are treated with monotherapy alone. The recently introduced combination of rosuvastatin + amlodipine is more likely to succeed because, after announcing the results of the **JUPITER** study [47], we know that statin therapy can be recommended in patients with hypertension and lower cardiovascular risk. In addition, doctors' habits regarding the evening use of statins are progressively changing with respect to modern statins, atorvastatin and rosuvastatin, whose efficacy in lowering LDL-cholesterol is the same irrespective of the time of administration. The decisive factor should be patients' compliance, which can be improved by SPCs. Moreover, new recommendations for lipid lowering therapy and further lowering of the target values of LDL-cholesterol will in practice favour more potent statins, such as rosuvastatin (20 mg or higher dose) or atorvastatin at higher doses (40 mg or 80 mg).

Very interesting "hybrid" SPC, which became available in Poland at the beginning of 2017, is a three-drug combination of a statin + ACE inhibitor + calcium antagonist (the only available SPC is atorvastatin + perindopril + amlodipine). Strong evidence for clinical benefits of this combination was provided by the lipid shoulder of the **ASCOT** study [48] in which atorvastatin caused 3-fold higher reduction of the risk of myocardial infarction in patients taking amlodipine and perindopril than in those receiving atenolol and bendroflumethiazide, with comparable blood pressure and LDL-cholesterol control, suggesting the synergistic effects of atorvastatin, perindopril and amlodipine. Similarly, significant relative reduction (33% vs. 2%) in cardiovascular mortality was observed in the atorvastatin group only in patients taking amlodipine + perindopril. Compared with the previous ones, this SPC meets the criteria for a combination of antihypertensive drugs and therefore may be used as one tablet formulation in patients with stage 2 hypertension with moderate to high cardiovascular risk and concomitant metabolic and/or diabetic complications. Similar three-drug formulations containing a calcium antagonist, an ACE inhibitor or sartan, and atorvastatin or rosuvastatin will be introduced into the Polish pharmaceutical market soon.

The most recent interesting "hybrid" SPC is the combination of a statin + sartan (the only available SPC is rosuvastatin + valsartan) that can be successfully used in stage 1 hypertension with concomitant hypercholesterolaemia, especially in patients with metabolic syndrome, because it contains valsartan (**NAVIGATOR**) [49]. The combined use of sartans and statins also has a beneficial effect on reducing the risk of cardiovascular events (by approximately 40%) in patients with multiple comorbidities [50]. The NAVIGATOR study evaluating the effect of SPC of rosuvastatin + valsartan versus monotherapy on blood pressure and LDL-cholesterol levels has shown that the use of this SPC is associated with better control of both risk factors which can be explained by better adherence to medical recommendations (by 34%) and greater therapeutic persistence.

Another option for "hybrid" SPC therapy is the combination of a beta-blocker + acetylsalicylic acid (the only available SPC is bisoprolol + ASA) for patients with ischaemic heart disease or heart failure regardless of the presence of hypertension. It has been argued to justify the use of this SPC that patients after myocardial infarction are likely to arbitrary discontinue ASA, while they are most persistent with beta-blocker therapy. So far, this SPC has not become popular because of doctors' habits related to the evening administration of ASA. It is dictated by the belief that ASA inhibits more effectively platelet activation when administered in the evening.

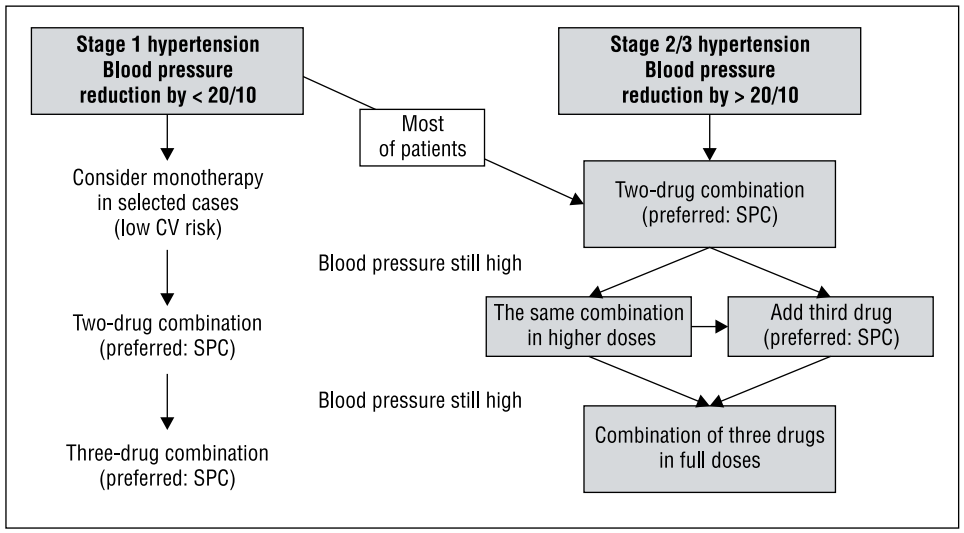

Figure 2. Proposed new algorithm of new antihypertensive therapy

Future development of antihypertensive therapy with SPCs

In the opinion of the authors, the use of SPCs in antihypertensive therapy will increase in Poland, which may contribute to further improve of pressure control in our country. At present, almost all useful anti-hypertensive agents are available in the form of two-drug SPCs. The combination of a sartan with beta-blocker for hypertensive patients with cardiac hypertrophy who do not tolerate ACE inhibitors and a "hybrid" SPC of an ACE inhibitor + statin are still expected. Three-drug combinations: ACE inhibitor + beta-blocker + calcium antagonist, for patients with hypertension and coronary artery disease requiring intensive therapy, and ACE inhibitor + beta-blocker + statin, which will enable single-pill combination therapy for most patients, would also be useful.

However, in order for these favourable trends to gain momentum, two conditions must be met both by the group of experts who develop the guidelines for treatment of hypertension and representatives of authorities responsible for registration process and approving indications for the use of specific drugs, e.g. SPCs.

The first of these conditions is a change in the philosophy of the antihypertensive treatment algorithm consisting in the assumption that pharmacotherapy of hypertension be initiated with combination therapy, with preference for SPC for most patients, and that identified should be those patients who are likely to benefit from monotherapy (stage 1 hypertension with low global cardiovascular risk). As mentioned above, analysis of ESH experts' lectures (Volpe, Williams) at this year's ESH 2017 Congress in Milan suggests that such changes are considered [22] and that new PSH recommendations will also follow this direction (Figure 2).

It is more difficult to fulfil the second condition because it requires a change of approach to the indications for the use of SPC by officials, taking into account expert opinions. Currently, only two combination drugs, perindopril + amlodipine in substandard doses, as described above, and some formulations of perindopril + indapamide at lower doses are indicated for initiation of antihypertensive therapy. Most SPCs have so-called "add-on indication", which means the requirement of lack of control with one component alone, or so-called "substitute indication", that means the requirement of previous adequate control of blood pressure on both components of SPC. It would be logical to give all SPC indications for the initiation of antihypertensive therapy in patients with stage 2 hypertension (i.e., according to the recommendations of the scientific societies), since there is nothing to prevent a doctor from prescribing any two antihypertensive drugs in combination as starting therapy. Such a solution is supported by not only by medical but also economic reasons.

References

1. Zdrojewski T, Bandosz P, Szpakowski P. Ocena wybranych problemów dotyczących rozpowszechnienia i terapii nadciśnienia tętniczego w Polsce na podstawie badania NATPOL-PLUS. W Postępy w nefrologii i nadciśnieniu tętniczym. Vol II. Medycyna Praktyczna, Kraków 2002: 11–15.
2. www.natpol.pl.
3. Niklas A, Tykarski A. Drygas W. Dane z badania WOBASZ 2017.
4. Widecka K, Grodzicki T, Narkiewicz K, et al. Zasady postępowania w nadciśnieniu tętniczym-2011 rok. Wytyczne Polskiego Towarzy-

stwa Nadciśnienia Tętniczego. Nadciśnienie Tętnicze. 2011; 15(2): 55–82.
5. Tykarski A, Narkiewicz K, Gaciong Z, et al. Zasady postępowania w nadciśnieniu tętniczym - 2015 rok. Wytyczne Polskiego Towarzystwa Nadciśnienia Tętniczego. Nadciśnienie Tętnicze w Praktyce. 2015; 1(1): 1–70.
6. Gaciong Z, Narkiewicz K, Tykarski A, et al. Miejsce gotowych połączeń lekowych w terapii nadciśnienia tętniczego – stanowisko ekspertów. Nadciśnienie Tętnicze. 2009; 13: 363–370.
7. Wożakowska-Kapłon B, Filipiak K, Czarnecka D, et al. Miejsce leków złożonych w terapii nadciśnienia tętniczego — aktualne problemy w Polsce Stanowisko Ekspertów Polskiego Towarzystwa Nadciśnienia Tętniczego i Sekcji Farmakoterapii Sercowo-Naczyniowej Polskiego Towarzystwa Kardiologicznego. Kardiologia Polska. 2013; 71(4): 433–438, doi: 10.5603/kp.2013.0081.
8. Wald DS, Law M, Morris JK, et al. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med. 2009; 122(3): 290–300, doi: 10.1016/j.amjmed.2008.09.038, indexed in Pubmed: 19272490.
9. Weber M, Julius S, Kjeldsen S, et al. Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE Trial. Lancet. 2004; 363(9426): 2049–2051, doi: 10.1016/s0140-6736(04)16456-8.
10. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013; 34(28): 2159–2219, doi: 10.1093/eurheartj/eht151, indexed in Pubmed: 23771844.
11. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. Hypertension. 2010; 55(2): 399–407, doi: 10.1161/HYPERTENSIONAHA.109.139816, indexed in Pubmed: 20026768.
12. Waeber B, Burnier M, Brunner HR. Compliance with antihypertensive therapy. Clin Exp Hypertens. 1999; 21(5-6): 973–985, indexed in Pubmed: 10423118.
13. Wan X, Ma P, Zhang X. A promising choice in hypertension treatment: Fixed-dose combinations. Asian J Pharmac Sciences. 2014; 9(1): 1–7, doi: 10.1016/j.ajps.2013.12.005.
14. Mallat SG, Tanios BY, Itani HS, et al. Free versus Fixed Combination Antihypertensive Therapy for Essential Arterial Hypertension: A Systematic Review and Meta-Analysis. PLoS One. 2016; 11(8): e0161285, doi: 10.1371/journal.pone.0161285, indexed in Pubmed: 27548060.
15. Corrao G, Nicotra F, Parodi A, et al. Cardiovascular protection by initial and subsequent combination of antihypertensive drugs in daily life practice. Hypertension. 2011; 58(4): 566–572, doi: 10.1161/HYPERTENSIONAHA.111.177592, indexed in Pubmed: 21825231.
16. Jamerson K, Weber M, Bakris G, et al. Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients. N Engl J Med. 2008; 359(23): 2417–2428, doi: 10.1056/nejmoa0806182.
17. Mancia G, Backer GDe, Dominiczak A, et al. 2007 Guidelines for the Management of Arterial Hypertension. J Hypertens. 2007; 25(6): 1105–1187, doi: 10.1097/hjh.0b013e3281fc975a.
18. Feldman RD, Zou GY, Vandervoort MK, et al. A simplified approach to the treatment of uncomplicated hypertension: a cluster randomized, controlled trial. Hypertension. 2009; 53(4): 646–653, doi: 10.1161/HYPERTENSIONAHA.108.123455, indexed in Pubmed: 19237683.
19. Mourad JJ, Waeber B, Zannad F, et al. Comparison of different therapeutic strategies in hypertension: a low-dose combination of perindopril/indapamide versus a sequential monotherapy or a stepped-care approach. J Hypertens. 2004; 12(22): 2379–2386, indexed in Pubmed: 15614033.
20. Laurent S, Parati G, Chazova I, et al. Randomized evaluation of a novel, fixed-dose combination of perindopril 3.5mg/amlodipine 2.5mg as a first-step treatment in hypertension. J Hypertens. 2015; 33(3): 653–61; discussion 662, doi: 10.1097/HJH.0000000000000440, indexed in Pubmed: 25479022.
21. Mancia G, Asmar R, Amodeo C, et al. Comparison of single-pill strategies first line in hypertension: perindopril/amlodipine versus valsartan/amlodipine. J Hypertens. 2015; 33(2): 401–411, doi: 10.1097/HJH.0000000000000409, indexed in Pubmed: 25380149.
22. Tykarski A. Doniesienie własne.
23. van Vark LC, Bertrand M, Akkerhuis KM, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158,998 patients. Eur Heart J. 2012; 33(16): 2088–2097, doi: 10.1093/eurheartj/ehs075, indexed in Pubmed: 22511654.
24. Cheng J, Zhang W, Zhang X, et al. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on all-cause mortality, cardiovascular deaths, and cardiovascular events in patients with diabetes mellitus: a meta-analysis. JAMA Intern Med. 2014; 174(5): 773–785, doi: 10.1001/jamainternmed.2014.348, indexed in Pubmed: 24687000.
25. Savarese G, Costanzo P, Cleland JG, et al. A meta-analysis reporting effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients without heart failure. J Am Coll Cardiol. 2013; 61(2): 131–142, doi: 10.1016/j.jacc.2012.10.011, indexed in Pubmed: 23219304.
26. Dahlöf B, Sever PS, Poulter NR, et al. ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet. 2005; 366(9489): 895–906, doi: 10.1016/S0140-6736(05)67185-1, indexed in Pubmed: 16154016.
27. Williams B, O'Rourke M. Anglo-Scandinavian Cardiac Outcomes Trial. The Conduit Artery Functional Endpoint (CAFE) study in ASCOT. J Hum Hypertens. 2001; 15 Suppl 1: S69–S73, indexed in Pubmed: 11685915.
28. Bahl VK, Jadhav UM, Thacker HP. Management of hypertension with the fixed combination of perindopril and amlodipine in daily clinical practice: results from the STRONG prospective, observational, multicenter study. Am J Cardiovasc Drugs. 2009; 9(3): 135–142, indexed in Pubmed: 19463019.
29. Miranda RD, Mion D, Rocha JC, et al. An 18-week, prospective, randomized, double-blind, multicenter study of amlodipine/ramipril combination versus amlodipine monotherapy in the treatment of hypertension: the assessment of combination therapy of amlodipine/ramipril (ATAR) study. Clin Ther. 2008; 30(9): 1618–1628, doi: 10.1016/j.clinthera.2008.09.008, indexed in Pubmed: 18840367.
30. Farsang C, Abraham G, Kovacs P, et al. The effictivity and safety of Amlodipin-Lisinopril Fix-combination in patients with ESSential hypertension (ALFESS Study). Hypertonia es Nefrologia. 2009; 13: 81–87.
31. Farsang C. HAMLET Trial Investigation: Advantages of lisinopril amlodypine fixed combination therapy in hypertension. A comparative study of the efficacy and tolerability of amlodipine 5 mg and lisinopril 10 mg administered separately and in combination in hypertension. Hypertonia es Nephrologia. 2004; 8: 72–78.
32. Mancia G, Omboni S, Chazova I, et al. FELT Study Group. Effects of the lercanidipine-enalapril combination vs. the corresponding monotherapies on home blood pressure in hypertension: evidence from a large database. J Hypertens. 2016; 34(1): 139–148, doi: 10.1097/HJH.0000000000000767, indexed in Pubmed: 26630216.
33. Patel A. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007; 370(9590): 829–840, doi: 10.1016/s0140-6736(07)61303-8.
34. Beckett NS, Peters R, Fletcher AE, et al. HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008; 358(18): 1887–1898, doi: 10.1056/NEJMoa0801369, indexed in Pubmed: 18378519.
35. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001; 358(9287): 1033–1041, doi: 10.1016/s0140-6736(01)06178-5.

36. Dahlöf B, Devereux R, Kjeldsen S, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002; 359(9311): 995–1003, doi: 10.1016/s0140-6736(02)08089-3.
37. Julius S, Weber MA, Kjeldsen SE, et al. VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004; 363(9426): 2022–2031, doi: 10.1016/S0140-6736(04)16451-9, indexed in Pubmed: 15207952.
38. Allemann Y, Fraile B, Lambert M, et al. Efficacy of the combination of amlodipine and valsartan in patients with hypertension uncontrolled with previous monotherapy: the Exforge in Failure after Single Therapy (EX-FAST) study. J Clin Hypertens (Greenwich). 2008; 10(3): 185–194, indexed in Pubmed: 18326958.
39. Littlejohn TW, Majul CR, Olvera R, et al. study investigators. Telmisartan plus amlodipine in patients with moderate or severe hypertension: results from a subgroup analysis of a randomized, placebo-controlled, parallel-group, 4 x 4 factorial study. Postgrad Med. 2009; 121(2): 5–14, doi: 10.3810/pgm.2009.03.1972, indexed in Pubmed: 19332958.
40. Chalmers J, et al. ADVANCE Collaborative Group. J Hypertens. 2013; 31(Suppl A): e110.
41. Tóth K. PIANIST Investigators. Antihypertensive efficacy of triple combination perindopril/indapamide plus amlodipine in high-risk hypertensives: results of the PIANIST study (Perindopril-Indapamide plus AmlodipiNe in high rISk hyperTensive patients). Am J Cardiovasc Drugs. 2014; 14(2): 137–145, doi: 10.1007/s40256-014-0067-2, indexed in Pubmed: 24590580.
42. Niewada M, Filipiak KJ, Barszcz E, et al. Dobór optymalnego połączenia beta-adrenolityk–antagonista wapnia w praktyce leczenia osób ze współistniejącą chorobą wieńcową i nadciśnieniem tętniczym — analiza wyników badania ankietowego BETAMLO. Nadciśnienie Tętnicze. 2012; 16(6): 364–373.
43. Rana R, Patil A. Efficacy and Safety of Bisoprolol plus Amlodipine Fixed Dose Combination in Essential Hypertension. Indian Pract. 2008; 61: 225–234.
44. Jadhav U, Hiremath J, Namjoshi DJ, et al. Blood pressure control with a single-pill combination of indapamide sustained-release and amlodipine in patients with hypertension: the EFFICIENT study. PLoS One. 2014; 9(4): e92955, doi: 10.1371/journal.pone.0092955, indexed in Pubmed: 24714044.
45. Bertrand ME, Ferrari R, Remme WJ, et al. Perindopril and β-blocker for the prevention of cardiac events and mortality in stable coronary artery disease patients: A EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) subanalysis. Am Heart J. 2015; 170(6): 1092–1098, doi: 10.1016/j.ahj.2015.08.018, indexed in Pubmed: 26678630.
46. Prejbisz A, Klocek M, Gąsowski J, et al. Factors associated with resistant hypertension in a large cohort of hypertensive patients: the Pol-Fokus study. Pol Arch Med Wewn. 2015; 125(4): 249–259, indexed in Pubmed: 25764004.
47. Ridker PM, Danielson E, Fonseca FA, et al. for the UPITER Study Group. Rosuvastatin to prevent vascular eventsin men and women with elevated C-reactive protein. N Engl J Med. 2008; 359: 2195–2207, doi: 10.1056/NEJMoa0807646.
48. Sever PS, Dahlöf B, Poulter NR, et al. ASCOT Investigators, ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003; 361(9364): 1149–1158, doi: 10.1016/S0140-6736(03)12948-0, indexed in Pubmed: 12686036.
49. McMurray JJ, Holman RR, Haffner SM, et al. NAVIGATOR Study Group. Effect of valsartan on the incidence of diabetes and cardiovascular events. N Engl J Med. 2010; 362(16): 1477–1490, doi: 10.1056/NEJMoa1001121, indexed in Pubmed: 20228403.
50. Galindo-Ocaña J, Bernabeu-Wittel M, Formiga F, et al. PROFUND Project researchers. Effects of renin-angiotensin blockers/inhibitors and statins on mortality and functional impairment in polypathological patients. Eur J Intern Med. 2012; 23(2): 179–184, doi: 10.1016/j.ejim.2011.06.004, indexed in Pubmed: 22284251.