

# Use of single pill combinations in the treatment of arterial hypertension in Poland: The current practice and guidelines, the impact on reimbursement spending and patient co-payment

Marcin Czech<sup>1</sup>, Stefan Boguslawski<sup>2</sup>, Anna Smaga<sup>2</sup>, Krzysztof J. Filipiak<sup>3</sup>

<sup>1</sup>Department of Pharmacoeconomics, the Institute of Mother and Child, Warsaw, Poland

<sup>2</sup>Department of Population Health Monitoring and Analysis, the National Institute of Public Health NIH — National Research Institute, Warsaw, Poland

<sup>3</sup>Maria Skłodowska-Curie Medical Academy, Warsaw, Poland

## Abstract

**Background:** *Clinical guidelines recommend using single pill combinations (SPC) when initiating and intensifying the treatment of arterial hypertension (AH), which is not reflected in the Summaries of Product Characteristics (SMPC) for individual preparations. The drug reimbursement system in Poland (with a few exceptions) does not provide for reimbursement outside the indications specified in the SMPC. Therefore, it excludes the use of SPC under reimbursement. In 2020 the share of SPC in the treatment of AH amounted to 12.8% of unit volume and was lower than the 80% based on the guidelines of the Polish Society of Hypertension.*

**Methods:** *Using the data from a sample of pharmacies in Poland over the period November–December 2020, the potential was assessed of switching from existing AH therapy with monocomponent drugs containing selected combinations of active ingredients to the equivalent SPC.*

**Results:** *The potential of switching from AH treatment in the analyzed period using monocomponent drugs with the equivalent SPC amounted to 19% of unit volume (a reduction of 212M units), with the highest switch potential (43.9%) for drugs containing amlodipine. The public payer's savings would be EUR 12.3 million and patient savings would amount to EUR 5.0 million.*

**Conclusions:** *Enabling reimbursement of SPC in Poland in line with the clinical guidelines can significantly increase the share of SPC in the treatment of AH, which will result in better health outcomes and a significant reduction in the payer's drug reimbursement spending and will lower the financial barrier for patients to access this type of treatment. (Cardiol J 2022; 29, 3: 405–412)*

**Key words:** hypertension, treatment, single pill combination

## Introduction

The way single pill combinations (SPC) are reimbursed in Poland affects clinical practice in the treatment of arterial hypertension (AH), thus

hindering the implementation of the guidelines of scientific societies. It restricts their introduction into therapy, which according to numerous studies has a negative impact on health outcomes, while unnecessarily increasing the costs incurred by the

**Address for correspondence:** Dr. Stefan Boguslawski, Department of Population Health Monitoring and Analysis, the National Institute of Public Health NIH — National Research Institute, ul. Chocimska 24, 00–791 Warszawa, Poland, tel/fax: +48 22 5421298, e-mail: sboguslawski@pzh.gov.pl

Received: 26.10.2021

Accepted: 6.05.2022

Early publication date: 13.05.2022

This article is available in open access under Creative Commons Attribution-Non-Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0) license, allowing to download articles and share them with others as long as they credit the authors and the publisher, but without permission to change them in any way or use them commercially.

public payer — the National Health Fund (NFZ) and patients [1–6]. The purpose of the analysis was to estimate the size of the hypertension treatment segment in Poland, which according to the current guidelines of scientific societies [7–9] may experience an increase in the share of SPC. A simulation of switching from the already existing therapy comprising two or three monocomponent drugs to SPC was carried out, keeping the equivalence of the used active ingredients and the doses within the range of hypotensive preparations available in the Polish reimbursement system. Additionally, potential economic benefits for patients and the NFZ resulting from the switch were also calculated.

Arterial hypertension is one of the most prevalent risk factors for cardiovascular complications in the population [10–15]. The epidemiological situation in the world and in Poland is poor in this regard, with the situation in Poland having deteriorated in recent decades [11–20]. The number and the percentage of AH patients are increasing, while the percentage of patients with well-controlled blood pressure is still low [13, 16, 17]. On the other hand, the appropriate pharmacotherapy reduces the risk of AH-related complications by up to 40% [21, 22]. In particular, using SPC in line with the guidelines has been instrumental in achieving better health outcomes from AH treatment in countries with comprehensive AH programs (Portugal, Spain) [1–5, 23–25].

The guidelines of the European Society of Cardiology/the European Society of Hypertension (ESC/ESH) published in 2018 [7] have changed the rules of hypotensive treatment in Europe recommending that the treatment of the majority of AH patients be initiated with two-component SPC (first step of treatment) and a switch to three-component SPC in the second step of treatment. Initiating treatment with monotherapy has been reserved for rare, strictly defined situations, therefore it can be assumed that practically all patients with AH should be treated with SPC [8].

The basic two-component SPC used to initiate the treatment of AH patients include:

- angiotensin-converting enzyme (ACE) inhibitors with dihydropyridine calcium antagonist;
- ACE inhibitors with a diuretic (optimally thiazide-like diuretic);
- sartans with a diuretic;
- sartans with a calcium antagonist.

The basic three-component SPC are:

- ACE inhibitors with a diuretic and a calcium antagonist;
- sartans with a diuretic and a calcium antagonist.

The value of using SPC at the beginning of AH therapy particularly strongly implies the need to increase the availability of SPC preparations for AH patients in every country and the simplification of therapy intensification with a quick shift to three-component therapy, although Summaries of Product Characteristics (SMPC) of many SPC lack indications for their use in line with guidelines. The guidelines of the Polish Society of Hypertension (PTNT) published in 2019 [8] have also adopted the same algorithms, emphasising that in the case of approximately 60% of AH patients well controlled pressure is achieved with increasing doses of two hypotensive drugs and in the case of 20% of AH patients — with three drugs i.e., a three-component SPC. This means that at least 80% of AH patients should be treated with SPC in the given country. The PTNT guidelines [8] have assumed that almost all AH patients under 65 years of age should start treatment with a two-component SPC.

Therapy initiation with a two-component SPC is also recommended to patients aged 65–80 (stage 2/3 hypertension; some patients with stage 1 hypertension). Its introduction is also recommended in second step of treatment (other patients with stage 1 hypertension). PTNT suggests introducing a two-component SPC at the onset of treatment (stage 3 hypertension) or as a second step treatment (other patients) even for patients in their ninth and later decades of life.

The strengths of using SPC include: a lower number of units taken by the patient, better tolerability of treatment, convenience of use, improved patient compliance, quicker blood pressure control, demonstrated better arterial pressure control in the population [1–3, 23–25]. Compared to those who use the same active ingredients, in the same doses, but in separate units, patients taking SPC show: better adherence, a strong trend towards greater persistence in treatment continuation, a greater arterial pressure reduction, and greater pressure normalization [4, 5].

Despite the educational efforts of PTNT, SPC are still too rarely used in the treatment of AH in Poland. In 2020 6.1 billion units of drugs used in AH were sold in retail pharmacies in Poland, including 0.8 billion SPC units (Table 1). The share of SPC has been steadily increasing — in 2020 it amounted to 12.8% of the sales volume, in units (Table 2).

Paradoxically, the legal changes introduced in Poland by the Reimbursement Act in 2011 have restricted the possibility of using SPC in the treatment of AH. Prior to its entry going into force, when using a drug included in the list of

**Table 1.** Sale of monocomponent drugs and single-pill combination (million units).

	2016	2017	2018	2019	2020
Monocomponent drugs	4,952.3	4,925.3	4,987.7	5,278.2	5,301.2
Single-pill combination	580.0	620.4	662.8	733.9	775.8
Total	5,532.2	5,545.7	5,650.5	6,012.1	6,077.0

**Table 2.** Share of monocomponent drugs and single-pill combination in units.

	2016	2017	2018	2019	2020
Monocomponent drugs	89.5%	88.8%	88.3%	87.8%	87.2%
Single-pill combination	10.5%	11.2%	11.7%	12.2%	12.8%

reimbursed drugs a physician could rely on either the indications specified in SMPC, current medical knowledge or scientific evidence. After the Reimbursement Act entered into force the drugs can be reimbursed for the full or limited range of indications registered within the SMPC at the time of the respective reimbursement decision. It can also be reimbursed for a specific indication defined by the clinical condition outside SMPC, as long as this condition is precisely indicated by the reimbursement list. Almost 100% of SPC have substitution indications in their SMPC, which are not in line with Evidence Based Medicine (EBM) or guidelines of scientific societies. Hence, the availability of SPC within the reimbursement system in Poland has gone down, because they can be prescribed with reimbursement in accordance with their SMPC i.e., in the treatment of AH, only in a substitution indication. In practice, following therapy initiation (typically, with one drug), a patient (in the absence of control) gets two monocomponent drugs, which are subsequently, if necessary, replaced by a corresponding SPC.

At the same time, in line with the existing financing rules, the public payer reimburses the drug at the level of monotherapy — just one, the most expensive component of the SPC with two or three active ingredients. Public financing of SPC is limited to the cost of the monotherapy, on which the limit is based, by applying the rule of  $1+1=1$  or  $1+1+1=1$ , which increases the level of patient co-payment for such drugs, hence reducing their availability. Hence, it is worth noting that when applying the substitution principle, the payer often finances two monocomponent drugs (separate units) instead of paying for one SPC containing the same two components in one unit.

Widening the scope of SPC reimbursement with the indications in line with the current guidelines will significantly increase their use, which will have a positive impact on health outcomes, while reducing the amounts allocated by the NFZ to the reimbursement of drugs used in the treatment of AH and the level of patient co-payments.

## Methods

### Source of data

The analyses were carried out using data from the pharmacy panel of PEX PharmaSequence, which in the period November–December 2020 included 6,100 retail pharmacies and pharmacy points. The sample is representative for the all-Poland population of retail pharmacies (13,395 pharmacies and pharmacy points as of December 2020), the 16-county coverage varies from 42% to 53%. Its sample structure is controlled in terms of geographical distribution, sales volume, and pharmacy chain affiliation. The raw data are projected to the national level and the difference versus census reimbursement data from NFZ is measured, indicating insignificant volume deviation (< 1% to < 5% depending on the individual product sales volume). Transaction data are automatically and continuously extracted from IT systems. To prepare this analysis, data from receipts issued by pharmacies was used to determine the different combinations co-occurrence rate of active ingredients and doses at the level of the anonymised unique patient and doctor ID. The analysis was based on the data of more than 2 million transactions (single receipts) concluded in the period November–December 2020, within which patients bought at least one hypotensive drug. The transac-

**Table 3.** Combinations of two active ingredients in single-pill combination used in hypotensive therapy — included in the reimbursement lists and covered by the analysis.

	Amlodipine	Felodipine	Indapamide	Hydrochlorothiazide
Amiloride				(excluded from the analysis)
Indapamide	X			
Ramipril	X	X (excluded felodipine 2.5 mg)		X
Cilazapril				X
Lisinopril	X			X
Perindopril	X		X (excluded indapamide 0.625 mg + perindopril 2.5 mg)	
Candesartan	X			X
Losartan	X			X
Telmisartan	X			X
Valsartan	X			X

tion data also provided information on the number of packs of hypotensive drugs sold split by active ingredient and dose, as well as on the share of sales for packs dispensed within the list of free drugs for persons over 75.

### Choice of active ingredients

The analysis was carried out on all SPC included in the reimbursement list in November–December 2020, which contain active ingredients from the group of basic hypotensive therapies listed in the guidelines of the PTNT [8] (drugs with a proven impact on prognosis, recommended in combination therapy and available in the form of SPC, and used in monotherapy in specific situations), i.e., thiazide diuretics, beta-adrenolitics, calcium antagonists, ACE inhibitors, AT<sub>1</sub> receptor antagonists (sartans).

On the basis of the 18 reimbursed combinations of active substances including the above-named drug groups, further analyses were carried out on products containing 12 active ingredients: amlodipine, candesartan, cilazapril, felodipine, hydrochlorothiazide, indapamide, lisinopril, losartan, perindopril, ramipril, telmisartan, and valsartan (Table 3).

Due to the lack of registration for AH monotherapy and the actual market unavailability, amiloride was excluded from the analyses. A combination of small dose indapamide and perindopril (i.e., 0.625 mg and 2.5 mg) was also excluded from the analyses due to the registration indications according to which the combination that can be used for AH therapy initiation — and is therefore not affected by the restriction, which is the subject of this analysis. A combination of felodipine 2.5 mg

with other active ingredients was also excluded due to the actual market unavailability of drugs with this dose for use in monotherapy. Moreover, the analysis included a three-component SPC including amlodipine, hydrochlorothiazide, and valsartan.

### Method description

The analytical work carried out consisted of the following stages:

1. Determining the rate of using monocomponent drugs, which can be replaced by reimbursed SPC on the basis of items appearing on a single receipt with a single patient code and prescribed by a single physician;
2. Estimating the maximum potential switch from concomitantly purchased monocomponent drugs to SPC by applying an iterative switch algorithm seeking to reflect the SPC sales structure over the observed period in order to avoid arbitrariness in the allocation to a particular SPC. For the purpose of the analysis, it was assumed that all the therapies, which are currently carried out using two or three monocomponent drugs can be switched over to the SPC equivalent in terms of active ingredients and doses. The result of the switch algorithm was the number of units within the molecule-doses of SPC that can replace the current monocomponent therapy;
3. Calculating the cost, for the payer and the patient, of buying monocomponent drugs, which can be replaced or the potential cost of purchasing SPC, which can be used instead;
4. Estimating a reduction in the number of units/packs purchased following the potential switch.

**Table 4.** Potential of switching from monocomponent drugs to single-pill combination (SPC) (per year).

Active ingredient	Number of units per year (+000)	Potential of the switch to SPC — units (+000)	Potential of the switch (%)	Potential of the switch to SPC — packs* (+000)
Amlodipine	381,591.4	167,503.5	43.9%	5,583.5
Candesartan	55,706.0	4,504.3	8.1%	150.1
Cilazapril	5,828.7	43.6	0.7%	1.5
Felodipine	847.7	44.7	5.3%	1.5
Hydrochlorothiazide	22,742.1	4,133.6	18.2%	137.8
Indapamide	404,952.9	63,919.3	15.8%	2,130.6
Lisinopril	46,561.5	4,940.5	10.6%	164.7
Losartan	71,635.5	7,236.5	10.1%	241.2
Perindopril	161,070.7	36,339.8	22.6%	1,211.3
Ramipril	600,772.4	66,335.5	11.0%	2,211.2
Telmisartan	207,786.2	18,445.9	8.9%	614.9
Valsartan	123,238.3	12,990.9	10.5%	433.0
Total	2,082,733.4	386,438.1	18.6%	12,881.3

\*30-tab pack equivalents estimated on the basis of the number of units

The financial impact of the switch for the public payer and the patient was determined using retail prices/co-payment by NFZ and patients per unit, taking into account the weights resulting from the volume of individual reimbursed packs in the period November–December 2020. The reimbursement list in Poland changes every 2 months in terms of the composition and the patient co-payment level, impacting the individual products share within the reference price groups. Therefore, the period of 2 months was chosen for the analysis, as the individual products share stayed stable during this period. An estimate of the approximate impact of the switch on a 12-month basis was obtained by multiplying the data obtained by 6. It was possible as the bimonthly SPC volume share (within AH products group) variation to the 2020 average did not exceed 1.2%.

## Results

### Potential of the switch

The estimated switch potential for the analysed active ingredients amounts to 18.6% of monocomponent units. The highest, in terms of the share and the number of units, potential switch exists for amlodipine — 43.9% of the currently sold units, 167.5 million units, which accounts for 5.6 million 30-unit packs. In terms of the volume of the potential switch, the next active ingredients are ramipril, indapamide, and perindopril (Table 4).

Assuming the switch potential is realized, the unit sales volume for the SPC included in the analysis would increase by 31.3%. The highest increase in the number of units sold would be for amlodipine and ramipril SPC and amlodipine and indapamide SPC (together 55.8% of the potential increase in the number of packs sold) (Table 5).

### The impact of the switch on patients' and the public payer's spending and the number of units bought

Replacing the existing politherapies using monocomponent drugs with equivalent SPC available within the reimbursement system would reduce the total annual cost of hypotensive treatment in Poland by EUR 12.3 million (PLN 55.3 million) from the public payer's perspective and by EUR 5.0 million (PLN 22.6 million) from patients' perspective. The NFZ savings would amount to EUR 8.4 million (PLN 37.9 million) and the savings for the Ministry of Health — EUR 3.9 million (PLN 17.4 million) within the budget dedicated to financing free drugs for people aged 75+ (Table 6). At the same time, due to therapy switch to SPC patients would buy almost 212 million units less per year, which might have a positive impact on compliance, thus generating improved health outcomes and reducing the cost concerning the treatment of AH-related complications. Realising the estimated scope of the switch would increase the share of SPC from 12.8% in 2020, to 17%.

**Table 5.** Potential change in the level of single-pill combination (SPC) purchases (per year).

Active ingredient	Number of units per year (+000)	Potential of the switch to SPC — units (+000)	Potential of the switch (%)	Potential of the switch to SPC — packs* (+000)
Amlodipine, candesartan	6,272.2	4,296.5	68.5%	143.2
Amlodipine, hydrochlorothiazide, valsartan	3,852.1	6.9	0.2%	0.2
Amlodipine, indapamide	21,847.5	42,378.6	194.0%	1,412.6
Amlodipine, lisinopril	15,244.9	4,629.6	30.4%	154.3
Amlodipine, losartan	1,791.4	6,897.3	385.0%	229.9
Amlodipine, perindopril	87,891.7	14,799.1	16.8%	493.3
Amlodipine, ramipril	70,411.3	65,439.6	92.9%	2,181.3
Amlodipine, telmisartan	11,543.8	17,446.9	151.1%	581.6
Amlodipine, valsartan	13,702.8	11,608.9	84.7%	387.0
Candesartan, hydrochlorothiazide	31,576.9	207.8	0.7%	6.9
Cilazapril, hydrochlorothiazide	170.4	43.6	25.6%	1.5
Felodipine, ramipril	1,378.6	44.7	3.2%	1.5
Hydrochlorothiazide, lisinopril	18,824.7	310.9	1.7%	10.4
Hydrochlorothiazide, losartan	43,835.7	339.1	0.8%	11.3
Hydrochlorothiazide, ramipril	8,919.9	851.1	9.5%	28.4
Hydrochlorothiazide, telmisartan	102,025.2	999.0	1.0%	33.3
Hydrochlorothiazide, valsartan	87,710.7	1,375.1	1.6%	45.8
Indapamide, perindopril	91,056.2	21,540.7	23.7%	718.0
Total	618,055.9	193,215.6	31.3%	6,440.5

\*30-tab pack equivalents estimated on the basis of the number of units

**Table 6.** Estimated annual savings connected with a polytherapy change in hypotensive treatment.

Change in spending when switching to SPC million Euro (million PLN)	
Public payer’s spending, included:	-12.3 (-55.3)
reimbursement	-8.4 (-37.9)
subsidy for people aged 75+	-3.9 (-17.4)
Patients’ spending	-5.0 (-22.6)

SPC — single-pill combination

### Discussion

The analysis only takes into account the switches from the existing, currently carried out, therapies using several (two or three) active ingredients and does not take into account potential switches from monocomponent drugs to SPC containing different active ingredients. Therefore, the presented analytical approach can be deemed conservative. It is worth noting that once an incentive for wider use of SPC is offered by broadening reimbursed indications beyond possible switching covered by this analysis, additional uses of SPC

will appear, which will result in a further reduction in the number of units taken by patients and savings for the payer and patients. In particular, this concerns:

- use of SPC instead of monotherapy for hypotensive therapy initiation; or
- use of SPC instead of monotherapy for therapy intensification (increasing a dose or the need to add another active ingredient).

Either of these situations will generate additional financial savings due to the mechanism where the financing limit is based on one molecule only.

The analysis only takes into account the direct cost of drug purchase. Apart from the immediate financial effect presented in this document, broadening indications for SPC reimbursement should also be expected to significantly influence the patient's compliance and persistence, and consequently to influence AH monitoring indicators, the incidence of AH-related complications and pre-mature deaths, as well as the related costs, including indirect costs. As shown by the results of the analysis carried out in 2015 concerning the appropriateness, under Polish conditions, of treating AH patients with an indapamide and amlodipine SPC compared to polytherapy, SPC therapy means additional 7.6 days of life in full health and extra 2.9 days of survival [4]. Despite the relatively low clinical effects per patient, if the total population of AH patients is considered clinical benefits can be significant.

Therefore, in Poland AH therapy using SPC is financed under the drug reimbursement system contrary to the latest medical knowledge, the guidelines, against the welfare of the patient (if there is an indication for polytherapy), and the financial interests of the payer.

## Conclusions

The current SPC reimbursement status causes a significant dissonance between the recognized medical knowledge, which is in line with EBM principles in the field of hypertension and the resulting guidelines from national and international medical societies, and the regulations governing drug reimbursement. As a result, the treatment of AH patients is often inconsistent with the guidelines of scientific societies, thus compromising the health outcomes and leading to a sub-optimal allocation of scarce resources available in the reimbursement budget.

**Conflict of interest:** Marcin Czech — lecture fees, participation in satellite sessions, in Polish and European advisory groups, research grants and clinical trials sponsored by: AstraZeneca, Berlin Chemie Menarini, Sanofi, Servier; Stefan Boguslawski — consultancy projects for: Merck, Sanofi, Servier; Anna Smaga — consultancy projects for: Adamed, Merck, Sanofi, Servier; Krzysztof J. Filipiak — lecture fees, participation in satellite sessions, in Polish and European advisory groups, research grants and clinical trials sponsored by: Adamed, Alfasigma, Amgen, AstraZeneca, Bausch Health, Bayer, Berlin Chemie Menarini, Boehringer Ingelheim, Egis, Krka, Merck, Mylan, Sandoz, Sanofi, Servier, Zentiva.

## References

1. Tsioufis K, Kreutz R, Sykara G, et al. Impact of single-pill combination therapy on adherence, blood pressure control, and clinical outcomes: a rapid evidence assessment of recent literature. *J Hypertens.* 2020; 38(6): 1016–1028, doi: [10.1097/HJH.0000000000002381](https://doi.org/10.1097/HJH.0000000000002381), indexed in Pubmed: [32371789](https://pubmed.ncbi.nlm.nih.gov/32371789/).
2. Weisser B, Predel HG, Gillessen A, et al. Single pill regimen leads to better adherence and clinical outcome in daily practice in patients suffering from hypertension and/or dyslipidemia: results of a meta-analysis. *High Blood Press Cardiovasc Prev.* 2020; 27(2): 157–164, doi: [10.1007/s40292-020-00370-5](https://doi.org/10.1007/s40292-020-00370-5), indexed in Pubmed: [32219670](https://pubmed.ncbi.nlm.nih.gov/32219670/).
3. Sicras Mainar A, Galera Llorca J, Muñoz Ortí G, et al. [Influence of compliance on the incidence of cardiovascular events and health costs when using single-pill fixed-dose combinations for the treatment of hypertension]. *Med Clin (Barc).* 2011; 136(5): 183–191, doi: [10.1016/j.medcli.2010.01.038](https://doi.org/10.1016/j.medcli.2010.01.038), indexed in Pubmed: [21106209](https://pubmed.ncbi.nlm.nih.gov/21106209/).
4. Kawalec P, Holko P, Stawowczyk E, et al. Economic evaluation of single-pill combination of indapamide and amlodipine in the treatment of arterial hypertension in the Polish setting. *Kardiol Pol.* 2015; 73(9): 768–780, doi: [10.5603/KPa2015.0089](https://doi.org/10.5603/KPa2015.0089), indexed in Pubmed: [25987296](https://pubmed.ncbi.nlm.nih.gov/25987296/).
5. Baser O, Andrews LM, Wang Li, et al. Comparison of real-world adherence, healthcare resource utilization and costs for newly initiated valsartan/amlodipine single-pill combination versus angiotensin receptor blocker/calcium channel blocker free-combination therapy. *J Med Econ.* 2011; 14(5): 576–583, doi: [10.3111/13696998.2011.596873](https://doi.org/10.3111/13696998.2011.596873), indexed in Pubmed: [21728914](https://pubmed.ncbi.nlm.nih.gov/21728914/).
6. Wierzejska E, Giernaś B, Lipiak A, et al. A global perspective on the costs of hypertension: a systematic review. *Arch Med Sci.* 2020; 16(5): 1078–1091, doi: [10.5114/aoms.2020.92689](https://doi.org/10.5114/aoms.2020.92689), indexed in Pubmed: [32863997](https://pubmed.ncbi.nlm.nih.gov/32863997/).
7. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J.* 2018; 39(33): 3021–3104, doi: [10.1093/eurheartj/ehy339](https://doi.org/10.1093/eurheartj/ehy339), indexed in Pubmed: [30165516](https://pubmed.ncbi.nlm.nih.gov/30165516/).
8. Tykarski A, Filipiak KJ, Januszewicz A, et al. Zasadę postępowania w nadciśnieniu tętniczym — 2019 rok Wytuczne Polskiego Towarzystwa Nadciśnienia Tętniczego. *Nadciśnienie Tętnicze w Praktyce.* 2019; 5(1): 1–86.
9. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure In Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018; 71(6): e13–e115, doi: [10.1161/HYP.0000000000000065](https://doi.org/10.1161/HYP.0000000000000065), indexed in Pubmed: [29133356](https://pubmed.ncbi.nlm.nih.gov/29133356/).
10. Yusuf S, Joseph P, Rangarajan S, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet.* 2020; 395(10226): 795–808, doi: [10.1016/S0140-6736\(19\)32008-2](https://doi.org/10.1016/S0140-6736(19)32008-2), indexed in Pubmed: [31492503](https://pubmed.ncbi.nlm.nih.gov/31492503/).
11. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension.* 2020; 75(6): 1334–1357, doi: [10.1161/HYPERTENSIONAHA.120.15026](https://doi.org/10.1161/HYPERTENSIONAHA.120.15026), indexed in Pubmed: [32370572](https://pubmed.ncbi.nlm.nih.gov/32370572/).

12. Waśkiewicz A, Zujko ME, Szcześniewska D, et al. Polyphenols and dietary antioxidant potential, and their relationship with arterial hypertension: A cross-sectional study of the adult population in Poland (WOBASZ II). *Adv Clin Exp Med*. 2019; 28(6): 797–806, doi: [10.17219/acem/91487](https://doi.org/10.17219/acem/91487), indexed in Pubmed: [30968608](https://pubmed.ncbi.nlm.nih.gov/30968608/).
13. Hering D, Szymański FM. Comparison of hypertension epidemiology and treatment in Poland and Australia. *Kardiol Pol*. 2018; 76(3): 520–528, doi: [10.5603/KPa2018.0002](https://doi.org/10.5603/KPa2018.0002), indexed in Pubmed: [29313567](https://pubmed.ncbi.nlm.nih.gov/29313567/).
14. Yang Q, Cogswell ME, Flanders WD, et al. Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults. *JAMA*. 2012; 307(12): 1273–1283, doi: [10.1001/jama.2012.339](https://doi.org/10.1001/jama.2012.339), indexed in Pubmed: [22427615](https://pubmed.ncbi.nlm.nih.gov/22427615/).
15. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet*. 2016; 387(10017): 435–443, doi: [10.1016/S0140-6736\(15\)00805-3](https://doi.org/10.1016/S0140-6736(15)00805-3), indexed in Pubmed: [26559744](https://pubmed.ncbi.nlm.nih.gov/26559744/).
16. Niklas A, Flotyńska A, Puch-Walczak A, et al. Prevalence, awareness, treatment and control of hypertension in the adult Polish population - Multi-center National Population Health Examination Surveys - WOBASZ studies. *Arch Med Sci*. 2018; 14(5): 951–961, doi: [10.5114/aoms.2017.72423](https://doi.org/10.5114/aoms.2017.72423), indexed in Pubmed: [30154875](https://pubmed.ncbi.nlm.nih.gov/30154875/).
17. Filipiak KJ, Tomaniak M, Płatek AE, et al. Negative predictors of treatment success in outpatient therapy of arterial hypertension in Poland. Results of the CONTROL NT observational registry. *Kardiol Pol*. 2018; 76(2): 353–361, doi: [10.5603/KPa2017.0211](https://doi.org/10.5603/KPa2017.0211), indexed in Pubmed: [29131289](https://pubmed.ncbi.nlm.nih.gov/29131289/).
18. Rossier BC, Bochud M, Devuyst O. The hypertension pandemic: an evolutionary perspective. *Physiology (Bethesda)*. 2017; 32(2): 112–125, doi: [10.1152/physiol.00026.2016](https://doi.org/10.1152/physiol.00026.2016), indexed in Pubmed: [28202622](https://pubmed.ncbi.nlm.nih.gov/28202622/).
19. Mills KT, Bundy JD, Kelly TN, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation*. 2016; 134(6): 441–450, doi: [10.1161/CIRCULATIONAHA.115.018912](https://doi.org/10.1161/CIRCULATIONAHA.115.018912), indexed in Pubmed: [27502908](https://pubmed.ncbi.nlm.nih.gov/27502908/).
20. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol*. 2020; 16(4): 223–237, doi: [10.1038/s41581-019-0244-2](https://doi.org/10.1038/s41581-019-0244-2), indexed in Pubmed: [32024986](https://pubmed.ncbi.nlm.nih.gov/32024986/).
21. Mancia G. Hypertension: Does antihypertensive treatment have long-term benefits? *Nat Rev Cardiol*. 2012; 9(3): 130–132, doi: [10.1038/nrcardio.2012.11](https://doi.org/10.1038/nrcardio.2012.11), indexed in Pubmed: [22310709](https://pubmed.ncbi.nlm.nih.gov/22310709/).
22. Staessen JA, Thijs L, Fagard R, et al. Effects of immediate versus delayed antihypertensive therapy on outcome in the Systolic Hypertension in Europe Trial. *J Hypertens*. 2004; 22(4): 847–857, doi: [10.1097/00004872-200404000-00029](https://doi.org/10.1097/00004872-200404000-00029), indexed in Pubmed: [15126928](https://pubmed.ncbi.nlm.nih.gov/15126928/).
23. Düsing R, Waeber B, Destro M, et al. Triple-combination therapy in the treatment of hypertension: a review of the evidence. *J Hum Hypertens*. 2017; 31(8): 501–510, doi: [10.1038/jhh.2017.5](https://doi.org/10.1038/jhh.2017.5), indexed in Pubmed: [28230062](https://pubmed.ncbi.nlm.nih.gov/28230062/).
24. Parati G, Kjeldsen S, Coca A, et al. Adherence to single-pill versus free-equivalent combination therapy in hypertension: a systematic review and meta-analysis. *Hypertension*. 2021; 77(2): 692–705, doi: [10.1161/HYPERTENSIONAHA.120.15781](https://doi.org/10.1161/HYPERTENSIONAHA.120.15781), indexed in Pubmed: [33390044](https://pubmed.ncbi.nlm.nih.gov/33390044/).
25. Chrysant SG. Single-pill triple-combination therapy: an alternative to multiple-drug treatment of hypertension. *Postgrad Med*. 2011; 123(6): 21–31, doi: [10.3810/pgm.2011.11.2492](https://doi.org/10.3810/pgm.2011.11.2492), indexed in Pubmed: [22104451](https://pubmed.ncbi.nlm.nih.gov/22104451/).