



Modern approach to combined therapy of arterial hypertension in the light of current guidelines

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Abstract

Introduction and Objective. Arterial hypertension affects approximately 12 million people in Poland, with control rates remaining suboptimal due to therapeutic inertia and treatment non-adherence. The study analyzes contemporary management approaches based on the latest guidelines and clinical evidence, specifically focusing on the benefits of early single-pill combination implementation and treatment optimization within the Polish population.

Review Methods. A review of 26 sources published between 2018–2026 was conducted utilizing PubMed, Google Scholar, and official databases of various scientific societies. Key words focused on combination pharmacotherapy, blood pressure variability, and adherence barriers. Inclusion criteria encompassed recent clinical guidelines, individual patient data meta-analyses, and relevant epidemiological studies.

Brief description of the state of knowledge. Poland exhibits significant regional disparities and low treatment efficacy. Modern diagnostics emphasize the stabilization of diurnal blood pressure fluctuations to ensure organ protection and cognitive function preservation. Management is anchored in early combination therapy and novel active substances to mitigate therapeutic inertia. Non-adherence, driven by complex dosing schedules and fear of polypharmacy, remains a primary barrier; therefore, single pill combinations represent the gold standard for enhancing physician-patient cooperation.

Summary. Implementing early combination therapy represents a public health priority in Poland. Novel treatment regimens offer high efficacy while minimizing adverse effects. Long-term therapeutic success depends on bridging the current gap between clinical guidelines and daily practice, supported by intensive patient education.

Key words

arterial hypertension, adherence, SPC, BPV

INTRODUCTION AND OBJECTIVE

Arterial hypertension remains one of the most significant modifiable risk factors for cardiovascular disease, directly associated with increased mortality from myocardial infarction, stroke, and renal failure. Globally, this condition affects more than one billion individuals; in Poland, it is estimated that hypertension affects one-third of the population, corresponding to approximately 12 million people [1, 2]. Despite the wide variety and availability of effective antihypertensive agents, results from nationwide epidemiological studies indicate that hypertension is only well-controlled in less than half of affected patients [3, 4].

An analysis of the causes of this phenomenon highlights a

complex issue involving the failure to initiate therapy or its inadequate intensification, as well as patient non-adherence to medical recommendations. The conventional treatment model, based on gradual dose titration in monotherapy, has frequently proved ineffective, leading to treatment discontinuation by patients due to the necessity of taking multiple medications in separate tablets. The contemporary therapeutic model, outlined in the latest guidelines from the Polish Society of Hypertension (PTNT 2024), the European Society of Cardiology (ESC 2024), and the European Society of Hypertension (ESH 2023), emphasizes the early initiation of combination therapy [2, 5–7].

The cornerstone of this strategy is the utilization of single-pill combinations (SPCs). These formulations exert a synergistic effect on diverse pathophysiological pathways responsible for blood pressure elevation, thereby enhancing therapeutic efficacy while minimizing the risk of adverse events through the use of low doses of active substances.

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Table 1. Characteristics of key studies and publications included in the literature review

Study/Author	Study design	Characteristics of the study population	Key findings
WOBASZ II [3]	Nationwide cross-sectional study	Representative sample of the adult Polish population	Revealed critically low rates of effective BP control (achieved by fewer than 50% of treated women and about 25% of treated men).
NOMED-AF [4]	Cross-sectional observational study	Representative sample of the Polish population aged ≥65 years	Demonstrated a high prevalence of arterial hypertension co-occurring with AF in the elderly population.
PAMELA [9]	Cross-sectional sub-study within a prospective cohort	Subjects from the PAMELA population cohort evaluated at 10-year follow-up	Established that the short-term erratic component of blood pressure variability (individual residual BPV), rather than absolute BPV, correlates significantly with cognitive decline.
GMRx2 [10]	Multi-centre, randomized, double-blind, active-controlled trial	Patients with grade 1 or grade 2 hypertension (untreated or on monotherapy)	Demonstrated that a novel low-dose triple SPC (telmisartan/amlodipine / indapamide) provides superior BP reduction and control compared to dual combinations.
BPLTTC [11]	Large-scale individual participant-level data meta-analysis	Patients across diverse cardiovascular risk profiles from multiple randomized trials	Confirmed that the relative reduction in cardiovascular events is directly proportional to the magnitude of SBP lowering, regardless of baseline risk levels.
SUNG K-C et al. [12]	Phase III randomised controlled trial	Patients with mild-to-moderate (grade 1 or 2) essential hypertension	Demonstrated that single-pill low-dose triple combination therapy achieves BP reductions superior to standard-dose monotherapy with similar short-term tolerability.
AZIZI M et al. [13]	State-of-the-art narrative review (Seminar)	Not applicable (comprehensive analysis of global clinical evidence)	Synthesised recent evidence on emerging drug therapies targeting novel pathways such as selective aldosterone modulation (baxdrostat) to reduce therapeutic inertia.
SALAM A et al. [14]	Open-label extension phase of a randomised trial	Patients with mild-to-moderate hypertension followed for 1 year	Confirmed the long-term (52-week) safety and efficacy of GMRx2-based triple therapy, maintaining a high clinic BP control rate (88%) with excellent tolerability.
QUADRO [15]	Multi-centre, Phase 3, randomised, double-blind, controlled trial	Patients with true resistant hypertension uncontrolled on standard triple therapy	Demonstrated that a full-dose quadruple SPC perindopril/ indapamide/ amlodipine/bisoprolol achieves significantly greater reductions in office SBP (-8 mmHg) and 24-h ambulatory BP values compared to triple therapy.

AF – atrial fibrillation; BP – blood pressure; BPV – blood pressure variability; SBP – systolic blood pressure; SPC – single-pill combination

Notably, this contemporary approach focuses not only on lowering office blood pressure measurements but also aims to minimize blood pressure variability, which is essential for target organ protection, including the preservation of cognitive function [8, 9].

OBJECTIVE

The aim of the study is to analyze the contemporary approach to combination therapy in the management of arterial hypertension, based on current guidelines from scientific societies, and conclusions from recent clinical reports. The article outlines the key aspects highlighting the benefits of early initiation of single-pill combinations (SPCs) and presents promising data from studies on novel agents and low-dose, multi-drug combinations of previously established active substances. Furthermore, the study aims to identify challenges encountered in daily clinical practice and to underscore the value of simplifying therapeutic regimens in improving treatment outcomes among hypertensive patients in Poland.

REVIEW METHODS

A literature review was conducted across online databases, including PubMed/MEDLINE and Google Scholar; a detailed analysis was also performed on the official websites of scientific societies: the Polish Society of Hypertension (PTNT), the European Society of Cardiology (ESC), and the European Society of Hypertension (ESH). The literature selection methodology included publications released between 2018 – 2026. The search was performed using the following key words in both Polish and English, including

their combinations with the Boolean operators AND and OR: arterial hypertension, single-pill combination, SPC, adherence, blood pressure variability, Polish population, GMRx2, QUADRO trial, dual and triple combination therapy.

A total of 26 source papers were selected for the final literature compilation, meeting the following inclusion criteria: the latest guidelines and expert consensus statements; individual patient data meta-analyses and randomized controlled trials evaluating modern multi-drug strategies; nationwide and regional reports, as well as epidemiological studies reflecting the health status of the Polish population; and papers published in Polish and English focusing on treatment challenges and contemporary therapeutic goals, taking into account the critical role of target organ protection.

Exclusion criteria included: case reports with low methodological quality; literature published prior to 2017 (with the exception of landmark prospective studies with long-term follow-up); publications concerning experimental and phase I trials; and papers written in languages other than English or Polish. To ensure data integrity and minimize selection bias, the literature screening, evaluation against eligibility criteria, and data extraction were conducted independently by the authors, with any discrepancies resolved through discussion.

The primary strength of this review lies in the compilation of the most recent clinical data from 2025 and 2026, which incorporate the realities of the Polish healthcare system and the psychosocial dimension within the Polish population. Conversely, a limitation is the inherent nature of a review paper, which carries a potential risk of selection bias. Additionally, the relatively short follow-up period for the patient population treated with the newest medicinal substances requires further validation of their long-term safety profile through real-world evidence studies (Tab. 1).

DESCRIPTION OF THE STATE OF KNOWLEDGE

Epidemiological situation and challenges in blood pressure control in Poland. An analysis of the current epidemiological situation in Poland indicates that arterial hypertension continues to represent one of the greatest public health challenges. Data from the National Health Fund (NFZ) registries and the National Institute of Hygiene demonstrate that the number of adult patients with diagnosed and documented hypertension in Poland stands at approximately 10 million. However, when accounting for undiagnosed individuals, the true burden of this condition affects a larger proportion of the population, estimated at around 12 million Poles [1]. Despite substantial progress and the continuous emergence of novel pharmacotherapeutic modalities, the efficacy of blood pressure control in the general population remains far from optimal. Findings from the nationwide population-based WOBASZ II study revealed significant shortcomings in hypertension management; although awareness of the condition has increased over the years, therapeutic targets are achieved by fewer than 50% of treated women and only approximately 25% of treated men [2, 3].

This issue is characterized by high dynamism and significant geographic variation. A comparison of nationwide cross-sectional studies reveals substantial regional disparities in hypertension awareness and treatment efficacy. This suggests that regional determinants of healthcare access, alongside underlying socio-economic factors, continue to result in disparate patient prognoses depending on the region of Poland they inhabit [16]. The elderly constitute a particularly vulnerable population, among whom arterial hypertension is highly prevalent. Data from the NOMED-AF study underscore that within the geriatric population, hypertension frequently coexists with other cardiovascular comorbidities, such as atrial fibrillation; this poses additional challenges for clinicians, complicates therapeutic regimens, and demands meticulous management to achieve blood pressure normalization [4].

The contemporary epidemiology of hypertension in Poland must also take into account other external risk factors. Mass migrations and the accompanying chronic psychological stress – as observed, for instance, in the population of female Ukrainian refugees – correlate with elevated blood pressure values and an increased prevalence of stress-related disorders. This poses a distinct challenge to primary healthcare in Poland, further compounded by differing clinical guidelines and treatment availability across the eastern border [17]. Poor dietary habits and a lack of proficiency in preparing balanced meals tailored to the patient's specific disease profile remain a consistently significant issue. Global and local analyses demonstrate a direct link between excessive dietary sodium intake and difficulties in achieving therapeutic targets, reaffirming the critical role of nutritional education within the broader strategy of antihypertensive management [18].

Diagnostics and novel targets for Target Organ Protection – significance of Blood Pressure Variability. The cornerstone of effective combination therapy lies in accurate and accessible diagnostics, which in recent years have increasingly shifted toward out-of-office measurements. In accordance with the practice guidelines of the European Society of Hypertension (ESH), the standardization of blood pressure measurement procedures is of paramount importance, encompassing office blood pressure monitoring

(OBPM), home blood pressure monitoring (HBPM), and ambulatory blood pressure monitoring (ABPM). Proper measurement technique and awareness of phenomena such as white-coat hypertension and masked hypertension are essential to prevent diagnostic errors and optimize dose selection within single-pill combinations [19].

Contemporary hypertensiology is based not only on the control of mean blood pressure values but also focuses on its variability and the associated risks (blood pressure variability – BPV). The ESH position statement emphasizes that BPV, encompassing both short-term (diurnal) and long-term (visit-to-visit) fluctuations, constitutes an independent risk factor for cardiovascular complications and target organ damage. High BPV is associated with the accelerated progression of atherosclerosis, left ventricular and atrial hypertrophy, and renal impairment, making the stabilization of the haemodynamic profile one of the priorities in contemporary pharmacotherapy [8].

A particularly significant clinical aspect of BPV is its impact on the central nervous system. Findings from the PAMELA study, which involved the long-term follow-up of patients, demonstrate a significantly strong correlation between high systolic blood pressure variability and cognitive decline. It has been shown that patients with an unstable blood pressure profile are more susceptible to cognitive impairment. This suggests that the choice of antihypertensive agents with a long duration of action and a proven capability to stabilize blood pressure fluctuations (e.g., long-acting calcium channel blockers) is of paramount importance in neuroprotection and the prevention of vascular dementia [9].

Foundations of combination therapy in the light of 2023–2024 guidelines. The contemporary paradigm of arterial hypertension management has undergone significant evolution in recent years, shifting away from gradual dose titration in monotherapy toward the early initiation of combination therapy. This shift is underpinned by robust evidence from meta-analyses, such as the BPLTTC, which unequivocally demonstrate that the reduction in the risk of cardiovascular events is directly proportional to the magnitude of systolic blood pressure reduction achieved through prompt initiation of combination therapy, irrespective of the baseline cardiovascular risk profile or the presence of comorbidities. These findings provide a solid rationale for pursuing increasingly ambitious therapeutic targets in both primary and secondary prevention [11].

The latest guidelines from the European Society of Cardiology and the Polish Society of Hypertension are consistent in this regard: in the majority of hypertensive patients, the therapeutic target is to achieve blood pressure values within the range of 120–129 mmHg SBP and 70–79 mmHg DBP [2, 6, 7]. To attain this objective effectively and safely, initiating therapy with dual single-pill combinations (SPCs) containing at least two active substances with distinct pharmacological profiles has become the standard of care [2]. This approach enables the multidirectional inhibition of diverse hypertensiogenic mechanisms, resulting in a synergistic antihypertensive effect with a superior tolerability profile compared to high-dose monotherapy [2, 6]. Furthermore, first-line SPC therapy significantly shortens the time required to stabilize the patient's condition and prevents therapeutic inertia, defined as the delay in intensifying treatment despite the insufficiency of monotherapy [2, 5].

Despite the previously outlined facts concerning arterial hypertension management, the medical community highlights the challenges associated with implementing these recommendations in daily clinical practice. Ongoing debates regarding the harmonization of guidelines from different scientific societies (ESH and ESC) underscore that, although therapeutic targets are becoming increasingly stringent, the key to success remains their practical implementation and the simplification of treatment regimens, which constitutes the foundation of contemporary hypertensiology [20, 21].

Modern strategies for treatment intensification – triple and quadruple therapy and novel pharmacotherapeutic targets.

To address the challenges associated with conventional therapeutic regimens, contemporary management strategies rely on the early initiation of low-dose triple combination therapy. Studies investigating the novel GMRx2 combination (telmisartan, amlodipine, and indapamide at fractional doses) demonstrate that targeting three distinct pathophysiological mechanisms simultaneously enables rapid blood pressure control in nearly 90% of patients while maintaining a highly favourable safety profile [10, 14]. The clinical superiority of this strategy is further confirmed in mild-to-moderate hypertension by trials, such as those by Sung et al. [12], which show that low-dose triple single-pill combinations (SPCs) provide a more stable 24-hour blood pressure profile and superior organ protection compared to standard monotherapy dose titration. By offering clinicians a highly effective and well-tolerated first-line option, this multi-mechanism approach serves as a valuable tool to overcome therapeutic inertia and optimize long-term treatment adherence.

In cases of resistant or particularly difficult-to-control arterial hypertension, quadruple combination therapy is emerging as a novel strategy. Findings from the QUADRO trial have provided evidence that the utilization of an SPC containing four active substances (perindopril, amlodipine, indapamide, and spironolactone) enables effective blood pressure control in patients who previously required multiple separate formulations, a factor associated with a higher frequency of medication errors or treatment discontinuation. Combining four agents into a single pill significantly improves adherence within the highest cardiovascular risk patient population, for whom the prior complexity of the therapeutic regimen was the primary cause of therapeutic failure [2, 15].

Concurrently with the optimization of synergistic effects and dosing regimens of established therapeutic agents, promising data regarding novel active compounds are emerging. Research on baxdrostat – a selective aldosterone synthase inhibitor – highlights novel strategic avenues for the management of difficult-to-control or resistant arterial hypertension. Direct inhibition of aldosterone production has been demonstrated to induce a significant, dose-dependent reduction in blood pressure among patients with resistant hypertension. This paves the way for novel therapeutic regimens that surpass conventional modalities, which frequently prove inadequate [13].

Barriers to treatment and the patient perspective – the adherence challenge. The efficacy of state-of-the-art pharmacological strategies is constrained in clinical practice by low rates of patient adherence. Survey-based studies

conducted under the auspices of the ESH within the Polish patient population demonstrate that the course of therapy from the patient's perspective frequently diverges from clinical expectations. Patients cite the absence of subjective symptoms and anxiety regarding potential adverse effects as the primary drivers of irregular medication intake. Importantly, the level of awareness regarding treatment goals remains insufficient among Polish patients; this underscores the critical need to strengthen the doctor-patient relationship within the therapeutic management plan, and highlights the pivotal role of primary care physicians in this process [2, 22].

This issue extends beyond patients with overt hypertension to encompass individuals with so-called masked hypertension. Analyses indicate that patients with normotensive office blood pressure measurements but elevated home readings demonstrate a greater propensity to disregard therapeutic recommendations. The absence of continuous monitoring by healthcare professionals renders this patient cohort particularly vulnerable to complications arising from the silent progression of target organ damage, concurrently predisposing them to the discontinuation of pharmacotherapy [23].

A pivotal factor in enhancing adherence is the simplification of the therapeutic regimen, which effectively mitigates both physical and psychological barriers. Clinical evidence demonstrates that utilizing single-pill combinations (SPCs) – including those targeting concurrent hypertension and hypercholesterolemia – significantly increases treatment persistence by reducing the objective pill burden. Furthermore, qualitative research indicates that multi-drug regimens are frequently perceived by patients as a stigma of severe illness, triggering anxiety over polypharmacy and prompting self-directed dose reductions or complete treatment cessation. Consequently, consolidating treatment into a single daily pill not only optimizes key haemodynamic parameters but also enhances patients' quality of life, pharmacological safety, and psychological well-being. [24, 25].

Regrettably, despite the established benefits of modern SPC strategies, clinical practice continues to lag behind current guidelines. The magnitude of the discrepancy between the recommendations of scientific societies and daily therapeutic decisions – the so-called guideline-practice gap – remains substantial within the Polish healthcare system. Clinical inertia regarding the transition from monotherapy to SPCs, coupled with reimbursement barriers, prevents many patients from receiving treatment aligned with current medical knowledge. This generates unwarranted healthcare and societal costs, while adversely affecting the national healthcare budget due to the expenditures incurred from managing the complications of arterial hypertension [26].

CONCLUSIONS

An analysis of the latest data spanning the years 2018–2026 allows for the delineation of clear trajectories for the advancement of arterial hypertension management in Poland. The cornerstone paradigm of contemporary hypertension treatment is the early implementation of single-pill combinations (SPCs), shifting away from the model of gradual dose titration in monotherapy. Epidemiological data regarding the Polish population indicate that monotherapy has failed to achieve satisfactory blood pressure control,

thereby rendering the widespread integration of SPCs into pharmacotherapy a public health priority.

A pivotal achievement in recent years within the field of hypertensiology is the demonstrated efficacy of low-dose, triple- and quadruple-drug combinations. Findings from trials evaluating novel treatment intensification regimens (GMRx2, QUADRO) and innovative molecules (baxdrostat) delineate new strategies to combat resistant and difficult-to-control arterial hypertension. The synergistic action of multiple active agents at low doses enables more rapid attainment of therapeutic targets while concurrently mitigating the risk of adverse events, thereby serving as a cornerstone in combating therapeutic inertia.

Contemporary hypertension diagnostics in 2026 no longer rely solely on office blood pressure measurements, but place particular emphasis on the stabilization of blood pressure variability (BPV). Understanding the role of BPV in target organ protection by both patients and healthcare professionals – particularly in the prevention of cognitive decline – opens new avenues for preserving central nervous system (CNS) function for as long as possible within the aging Polish population.

However, the primary therapeutic objective is not merely prescribing the appropriate medication, but rather ensuring its consistent intake by the patient. Overcoming psychosocial barriers, including apprehensions regarding polypharmacy, alongside simplifying dosing regimens to a single daily pill, remains the most effective strategy for enhancing patient adherence. Bridging the guideline-practice gap represents a critical challenge for the coming years; this endeavour demands not only advanced pharmacotherapies but also effective education and an individualized approach to patient care within the Polish healthcare system.

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