

ORIGINAL ARTICLES

FROM EVIDENCE TO PRACTICE: UTILIZATION OF FIXED-DOSE (SINGLE-PILL) COMBINATIONS FOR TREATMENT OF HYPERTENSION IN BULGARIA (2021–2024)

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ABSTRACT

International guidelines have favoured initiating and intensifying antihypertensive (AHT) therapy with single-pill combinations (SPCs) since 2018. However, the real-world uptake of SPCs varies and may be shaped by national reimbursement policies. The SPC utilization in Bulgaria under the National Health Insurance Fund (NHIF) reimbursement framework in the 2021–2024 period was evaluated. A retrospective analysis of NHIF-reimbursed AHTs (01/2021–06/2024) was conducted. The analysis encompassed all fixed-dose combination (FDC) AHT products available on the Bulgarian market. For comparison, the reference group included the full range of AHT medicinal products as classified under the Anatomical Therapeutic Chemical (ATC) system: C02, C03, C07, C08, C09, C10BX. Outcomes were: the number and share of insured patients receiving SPCs vs monotherapy, trends by drug class (ACE inhibitors, ARBs, etc.), and policy context. Descriptive, trend, and comparative analyses were applied; a compound quarterly growth rate was additionally calculated. Over the study period, the number of SPC users changed dynamically and peaked in Q2/2024. The SPC share increased and reached ~29% in Q1/2022, thereafter remaining at similar levels; in the hypertension-only subset, the share reached up to 32%. The most frequently dispensed SPCs combined ARBs or ACE inhibitors with other classes. Despite strong guideline support, SPC uptake in Bulgaria remains modest, likely influenced by reimbursement differentials and therapeutic inertia.

Keywords: *hypertension, fixed-dose combinations, single-pill combinations, reimbursement*

INTRODUCTION

Arterial hypertension (AH) is becoming an increasingly significant concern for patients, society, and healthcare systems. It is the most important contributor to the global burden of disease as number of patients living with hypertension (30–79 years) doubled for the period from the 1990s to 2019 (1,2). Wang et al. (2020) pointed out that hypertension is associ-

ated with a higher risk for cardiovascular disease and all-cause mortality, and the associations are stronger with a younger age of onset (3). According to Zheng et al. (2022) longer duration of hypertension is associated with increased risks of cardiovascular diseases and overall death in a linear fashion, and these associations are independent of blood pressure (BP) control levels (4). Naseva et al. (2023) pointed out that the number of persons who died from AH and the number of years of life lost increase accordingly. They concluded that this results in a lot of lost benefits and losses for the society (5). According to Parati et al. (2021) a large number of hypertensive patients are not properly identified, and a significant proportion of those who receive antihypertensive (AHT) treatment fail to achieve satisfactory control of their BP levels (6). Bulgaria is a country with very high risk of cardiovascular diseases and because of this following

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the prevalence and the control of hypertension are crucial. According to Postadzhiyan et al. (2023) the percentage of people with hypertension in Bulgaria is high and there is a need of improving knowledge about diseases, treatment options, and control (7).

Elnaem et al. (2022), in their systematic review, identified several barriers to hypertension control. The most important among them are classified as barriers related to patients. The second place is for barriers linked to medication adherence followed by those linked to lifestyle, to affordability and accessibility, to awareness and to prescribed pharmacotherapy (8).

There is a lot of scientific data in the literature on how single-pill combination (SPC) or fixed-dose combination address the aforementioned barriers. Treatment with SPC is the emerging best practice for safe, effective, rapid, and convenient hypertension control. It improves the affordability, adherence and control of AH (9). Based on a study, including 28 210 patients, Rea et al. (2023) pointed that SPCs with three drugs improve adherence to the prescribed therapy significantly in comparison with same combination but with two tablets. It is important to note the conclusion that this improvement of adherence is not dependant on the sex or age of the patients, their comorbidities, or other treatments (10). Ott and Schmieder (2021) pointed that, in the recent years, several evidence-based, national, and international guidelines on the management of AH have been published, mostly with concordant recommendations, but in some aspects – with discordant opinions. New data of interest present a simplified AHT drug treatment such as SPCs, which enhance the adherence to medication and speeds up the process of getting into the BP target range (11). Even The 2018 European Society of Cardiology/European Society of Hypertension Guidelines advocate SPC medicines for hypertension management. Compared to starting free-dose combination medication, this therapy improves adherence, BP control, and/or cardiovascular outcomes (12). In subsequent editions of the clinical guidelines and studies, the concept of using SPCs has been further refined and expanded. Beyond the already established advantages of fixed combinations containing two AHT agents, the updated recommendations now emphasize the use of triple or higher-order combinations, as well as the potential to in-

tegrate AHT therapy with treatments targeting other comorbid conditions. Wang et al. (2023), in their systematic review and meta-analysis, concluded that low-dose combination with 3 or 4 AHTs provided an effective and well-tolerated BP-lowering treatment option for the initial management of hypertension. Low-dose combination AHTs provide a single-step solution that has been shown to achieve 70% sustained BP control rates (13). According to Prejbisz et al. (2023), as SPCs have become an indispensable element in the treatment of hypertension, the role of various drug classes and specific drugs largely depends on the availability of SPCs that include a medicinal product from a given class (14).

Schmieder et al. (2022) analysed data from 57 998 patients and pointed that AHT combination therapy reduces all-cause mortality and cardiovascular events when provided as single pill compared to identical drugs as multipills (15).

Current evidence indicates that national measures supporting the use of fixed-dose combination (FDC) AHT therapies – such as including them on essential medicines lists, incorporating FDC recommendations into hypertension guidelines, and ensuring broad market availability at an affordable price – substantially increase their adoption in clinical practice. When treatment pathways are designed to start therapy with an FDC and are coupled with continuous monitoring and feedback regarding adherence to the protocol, health systems can achieve hypertension control rates that repeatedly surpass 80% (16). Bruyn et al. (2022), in their assessment of 30 low- and middle-income countries, reported that both market access and global policy support for SPC AHT therapies are generally strong. Although SPCs – including multiple generic options – are widely available across markets, availability by itself is not sufficient to ensure their optimal use; alignment with national policy frameworks remains essential. The authors noted that many national hypertension guidelines do not fully reflect international recommendations, as monotherapy continues to dominate treatment practice. Additionally, SPC AHT agents are often absent from national essential medicines lists, further limiting their integration into routine care (17). Indication for such issues are visible also in high income country. Bryan et al. (2023) raised the alarm that despite guidelines recommendation SPCs are used by only

one-third of treated hypertensive US adults. They estimated the cost-effectiveness of initial treatment with SPC dual AHT medications compared with usual care monotherapy and pointed that initiating treatment with SPC dual therapy is more effective at no greater cost than usual care initial monotherapy and has the potential to improve BP control rates and reduce the burden of cardiovascular disease (18). Mahfoud et al. (2023) analysed usage of FDC AHTs in Germany between 2016 and 2020 and report that only 10.9% of the prescribed packs of AHT drugs in 2020 were FDC products (19). Czech et al. (2022) examined the use of SPCs in the management of AH in Poland and concluded that aligning SPC reimbursement policies with clinical guideline recommendations can markedly increase their utilization. Expanding access through reimbursement not only promotes a higher share of SPC therapy but is also expected to improve patient outcomes, reduce overall drug-reimbursement expenditures for the payer, and lower financial barriers for patients who require this treatment option (20).

In Bulgaria, no specific national guidelines for the management of AH are currently available. The medical and scientific community predominantly adheres to the most recent recommendations issued by the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). At the same time, there is a notable absence of active national-level health policies aimed at facilitating the market introduction, uptake, and broader utilization of FDC therapies. This lack of strategic support may hinder the optimization of hypertension management, particularly given the established benefits of SPCs for improving treatment adherence and achieving better BP control (21).

Mills, Stefanescu, and He (2020) concluded that hypertension remains a global public health challenge, as it is estimated that the global financial burden of hypertension is about 10% of the world's overall healthcare expenditures, varying from about 22.6% of all healthcare expenditures in Eastern Europe and Central Asia to 7.2% in East Asia and Pacific (22). In this context, it is particularly important for countries such as Bulgaria to prioritize the optimization of therapeutic strategies and the reduction of both public and individual patient expenditures.

The aim of the article is to assess the utilization of FDCs (single-pill) for treatment of hypertension in Bulgaria (2021–2024).

METHODOLOGY

The analysis is based on data from the National Health Insurance Fund of Bulgaria (NHIF) for reimbursed products. The observed period is 01.2021–06.2024. The analysis encompassed all FDC AHT products available on the Bulgarian market and number of treated patients. For comparison, the reference group included the full range of AHT medicinal products as classified under the Anatomical Therapeutic Chemical (ATC) system: AHTs (C02), diuretics (C03), beta-adrenergic blockers (C07), calcium channel blockers (C08), angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) (C09), as well as statin-containing combinations with AHT agents (C10BX). The collected information was processed and analysed by the Microsoft Excel software, using:

- ◆ descriptive statistics – to present the main characteristics of selected market;
- ◆ trend analysis – to study the development of medical prescriptions over time;
- ◆ comparative analysis – to compare results from different periods.

In the study were compared trends in FDC and mono products as were analysed absolute number of treated patients and share of fixed dose combination in AHT medicinal products. Compound Quarterly Growth Rate (CQGR) was calculated for all groups of AHT medicines. In order to include valid clinical guidelines and trends of the market, the study was focused on the main INNs from the ACEI and ARB classes. Detailed comparison of monotherapies and FDCs was done within INNs in the indicated classes.

RESULTS AND DISCUSSION

During the study period, the NHIF reimbursed 47 INNs as monotherapy products and 39 FDCs within the market segment selected for analysis.

The number of insured individuals receiving SPCs changed dynamically over the study period, reaching its maximum in Q2 2024 (Fig. 1). At the same time, the proportional share of SPCs increased during the entire observation window and reached 29% in the first quarter of 2022 after which it re-

maintained at comparable levels throughout the study period (Fig. 2).

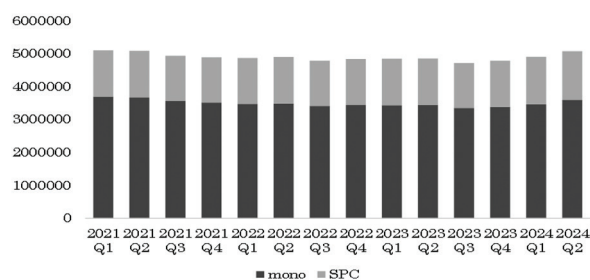


Fig. 1. Number of patients receiving SPCs and monotherapy.

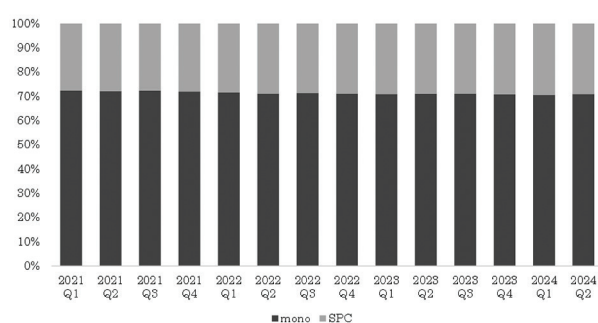


Fig. 2. Share of patients receiving SPCs and monotherapy.

An additional analysis was performed on the selected anatomical–therapeutic classes prescribed to patients with diagnoses related to AH. The proportion of patients receiving SPCs increased gradually over the study period and reached 32%.

Despite the fact that clinical guidelines issued since 2018 consistently prioritize SPCs as the preferred therapeutic strategy, the proportion of patients treated with SPCs remains comparatively low among those receiving AHT medications. This limited uptake may be attributable to several factors, including reimbursement policies and regulatory constraints imposed by the NHIF, as well as persistent therapeutic inertia within clinical practice.

Medicinal products indicated for “essential hypertension” that contain a single active substance (monotherapy products) and are included in the Positive Drug List are reimbursed by the NHIF at a 100% reimbursement rate. In April 2024, an additional policy change introduced the possibility for monotherapy products covering 54 INNs to be reimbursed at

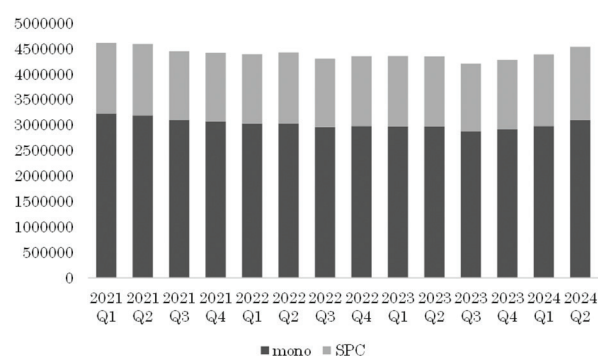


Fig. 3. Number of patients receiving SPCs and monotherapy (only hypertension).

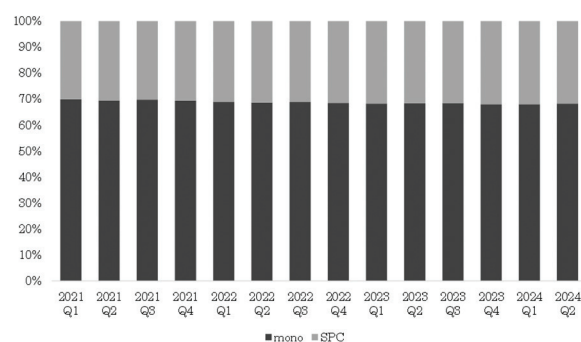


Fig. 4. Share of patients receiving SPCs and monotherapy (only hypertension).

100%, without restrictions related to the specific type of hypertension.

In contrast, FDC products continue to be reimbursed at a 50% reimbursement rate.

The NHIF is one of the principal payers within the healthcare system, and its policies have a direct impact on pharmaceutical consumption. Despite the short period since the introduction of the increased reimbursement level for monotherapy, an upward trend is already observable in the monitored parameters for this group of medicines. The effect of this policy change should be evaluated over longer future periods, yet it has the potential to increase the proportional share of monotherapy products – an outcome that would run counter to contemporary recommendations for the therapeutic management of hypertension.

The most frequently dispensed FDCs were combinations with ARBs and combinations with ACEIs. These findings are not surprising when considered in the context of current clinical guideline recommen-

dations. Of particular interest is the development of the market for monotherapy agents and combinations containing ARBs and ACEIs. Although current guidelines do not clearly favour one of these drug classes over the other, the market trends show different trajectories in their utilization (Fig. 5). Considering the fact that reimbursement levels are identical for both groups, these observations suggest that prescribing preferences play a decisive role in therapy selection, which may represent an additional factor in shaping market dynamics.

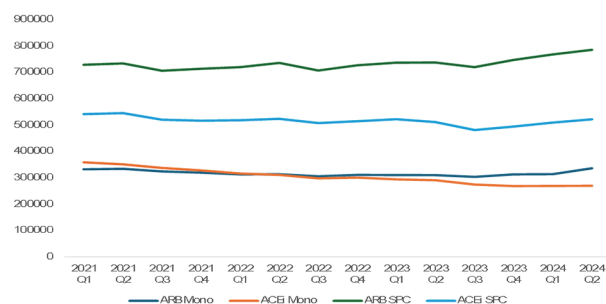


Fig. 5. Number of patients with hypertension receiving SPCs and monotherapy with ARBs and ACEIs.

Additionally, the CQGR was calculated for all groups of AHT medicines. The findings indicate that SPCs that include beta-blockers, as well as SPCs combining statins with AHT medications, stand out within the analysed therapeutic groups. These combinations appear to contribute meaningfully to overall utilization patterns and may reflect evolving prescribing practices aimed at improving cardiovascular risk management.

Current clinical guidelines prioritize the use of FDCs containing ACEIs or ARBs together with diuretics or calcium channel blockers. Using this as a basis, the current study analysed the absolute number of insured individuals receiving the main INNs from the classes of ACEIs and ARBs, both as monotherapies and as FDCs (Fig. 6). The proportional distribution between these therapeutic forms was also examined to better understand prescribing patterns and the extent to which FDCs are utilized in clinical practice (Fig. 7). For the purposes of the study, data from the second quarter of 2024 was used.

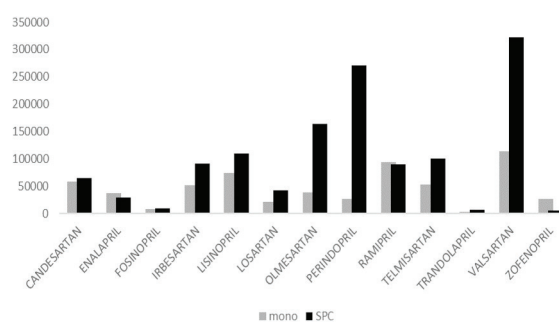


Fig. 6. Number of patients receiving SPCs and monotherapy.

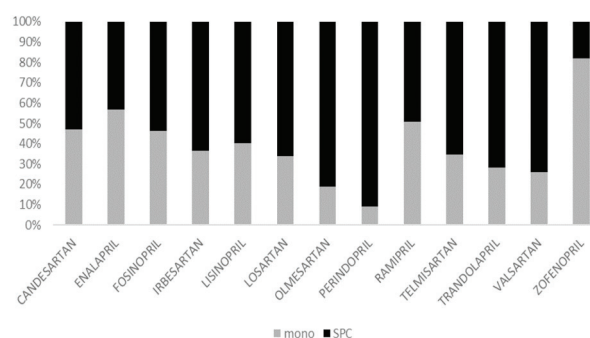


Fig. 7. Share of patients receiving SPCs and monotherapy.

Notable differences in the proportion of monotherapy products versus FDCs were identified within the ACEI and ARB classes. Among patients treated with ARBs, 70.0% received SPCs, whereas among those treated with ACEIs, the corresponding proportion was 65.9%. These findings suggest a slightly higher adoption of SPC therapy within the ARB class, which may reflect prescribing preferences or perceived tolerability profiles.

The current study found that the highest number of patients were treated with SPCs containing valsartan, followed by those containing perindopril and olmesartan. When examining the proportional use of monotherapy versus SPC formulations, the highest SPC-to-monotherapy ratio was observed for perindopril, followed by olmesartan and valsartan.

For example, four different SPC formulations containing perindopril are currently available, including one triple-drug combination and a dual combination with bisoprolol – an option not offered by any other therapeutic agent within the examined classes. An interesting comparison can be made with another ACEI, ramipril. While the SPC-to-monotherapy ratio for perindopril reaches 91.1%, the cor-

responding ratio for ramipril is only 49.1%. Triple SPC for ramipril is available since Q3 2022, relatively latter than perindopril.

A similar correlation between the availability of triple-component FDCs and the higher proportion of SPC use can also be observed for valsartan, olmesartan, and the remaining representatives within the ARB class. This pattern suggests that broader availability of combination formulations may play a key role in shaping prescribing behavior and promoting the transition from monotherapy to SPC-based regimens. In this context, the proactive engagement of the pharmaceutical industry in introducing innovative FDC therapies may help overcome limitations associated with the reimbursement policies of publicly funded payers.

Limitations:

This analysis is limited by the fact that the same patient may have been receiving both monotherapy and an SPC during the observation period. Another important limitation is the short time window following the reimbursement policy change, which does not allow the full impact of the reform to be assessed.

CONCLUSION

In Bulgaria, the use of SPCs increased gradually between 2021 and 2024, yet their share among all patients treated with AHT medicines remains relatively limited despite strong international guideline support.

The NHIF reimbursement policies likely contribute to the modest uptake of SPCs: monotherapy products for essential hypertension are reimbursed at 100% (with the scope expanded in April 2024 to 54 INNs without subtype restrictions), whereas SPC/FDC products remain at a 50% reimbursement level, creating an economic incentive in favour of monotherapy.

Over the study period, the NHIF reimbursed 47 INNs as monotherapies versus 39 SPCs within the analysed market segment; the number of insured individuals receiving SPCs peaked in Q2 2024.

The most frequently dispensed SPCs were ARB-based and ACEI-based combinations. Given identical reimbursement levels between ARB and ACEI monotherapy classes, the observed differences in utilization likely reflect prescribing preferences.

Policy and Practice Implications:

Aligning reimbursement with evidence-based guidelines – e.g., enhanced or full reimbursement for appropriately indicated SPCs – could increase their uptake, improve medication adherence and BP control, and optimize long-term public expenditures.

Further research should quantify clinical outcomes (BP control, hospitalizations, cardiovascular events) and the budget impact of alternative reimbursement scenarios.

Given the growing burden of hypertension and the associated cardiovascular risk, enhancing the cost-effectiveness of treatment – through wider adoption of evidence-based therapeutic options, including FDCs – represents a critical component of improving national health outcomes and ensuring sustainable resource allocation.

By expanding the availability of clinically meaningful combination products, industry-driven innovation can facilitate broader access to optimized AHT regimens, even in health systems where financial constraints may otherwise restrict the adoption of such therapies.

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