KARDIOLOGIA POLSKA
Polish Heart Journal
The Official Peer-reviewed Journal of the Polish Cardiac Society since 1957
Online first
This is a provisional PDF only. Copyedited and fully formatted version will be made available soon
ISSN 0022–9032 e-ISSN 1897–4279

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Article type: Review

Received: December 5, 2023

Accepted: December 19, 2023

Early publication date: December 28, 2023

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ABSTRACT

Hypertension is the leading risk factor for cardiovascular diseases, however, only one-fifth of the treated population is believed to attain sufficient blood pressure control levels. A common barrier to the effectiveness of antihypertensive treatment is suboptimal adherence to medications. Non-adherence often stems from low health literacy and unawareness, complex medication regimens and asymptomatic nature of the disease itself. Increased co-morbidities of the patient and side effects of the drugs also play significant role in drug adherence problems. Another common challenge in achieving blood pressure control is therapeutic inertia, marked by the reluctance to raise drug dosage or introduce additional medications. Employing single pill combination therapy, as recommended by the guidelines, has the potential to overcome this problem and address issues related to drug non-adherence. Novel antihypertensive drugs, which are still under development, show promise for achieving long-term blood pressure control with just a single dose. Non-pharmacological interventions, such as weight loss, low sodium intake and increased physical activity play a crucial role in achieving target blood pressure levels. In this review, key factors for improving the effectiveness of antihypertensive treatment are summarized under the headings of implementing the guideline recommendations, increasing medication compliance, encouraging lifestyle changes and future perspectives for increased treatment efficacy. We aimed to outline the strategies to overcome the global problem of

insufficient blood pressure control levels in the light of latest scientific data and recommendations.

Key words: adherence, antihypertensive treatment, efficacy, lifestyle modifications

INTRODUCTION

Hypertension is the strongest modifiable risk factor for cardiovascular diseases and the most common cardiovascular disorder in the world [1]. Globally, it affects nearly 1.28 billion adults aged 30–79 years and two thirds of them are living in low to middle income countries [2]. In a pooled analysis, the average prevalence of hypertension in adults of 30–79 years was documented as 34% in men and 32% in women in the year 2019 and the total number of adults with hypertension has doubled from 1990 to 2019 [3]. The well-established correlation between elevated blood pressure (BP) and the heightened risk of heart failure, stroke, and the progression of chronic kidney disease is widely recognized. This association begins with systolic BP exceeding 115 mm Hg and diastolic BP exceeding 75 mm Hg in office measurements. The target BP is aimed at <140/90 mm Hg and only around 20% of the hypertensive population has been reported to achieve the target levels worldwide [4].

European Society of Hypertension (ESH) presented the latest clinical practice guideline on hypertension in June 2023 [2]. There was a noticeable shift towards placing greater importance on out-of-office BP measurements and encouraging patient empowerment to enhance adherence. This recognition stems from the acknowledgement that new strategies are necessary to attain improved global outcomes in BP control. Efforts to enhance the proper implementation of guidelines are essential, and considerable progress is required to achieve effective BP control at satisfactory levels. In this review main strategies for improving the efficacy of antihypertensive treatment are summarized, aligning with the latest guidelines and highlighting the most recent pieces of evidence.

IMPLICATIONS TO ENHANCE THE EFFICACY OF ANTIHYPERTENSIVE TREATMENT

During the last decades, high BP prevalence has shifted from high income to low to middle income countries. This is mostly due to the insufficient changes at the rates of control, awareness and treatment of hypertension at those regions [5]. Despite the extensive endeavors in education and screening as well as the availability of various effective antihypertensive drugs, controlled BP rates remain unsatisfactory, even in the developed regions of the world

(6). To effectively combat the insufficient control rates, a comprehensive strategy is essential. This should encompass a multifactorial approach, involving individualized strategies targeting both the patients and healthcare providers, as well as considering socioeconomic factors and improvements to the healthcare system. Proper implementation of the guidelines, drug adherence and lifestyle modifications are the key factors for positive clinical outcomes [6]. Other potential steps for the enhanced treatment efficacy, such as heightened awareness and education, personalized approach and utilization of telemonitoring, will be discussed under the heading of adherence.

Proper implementation of the guidelines:

The universal guidelines clearly establish well-defined target levels for BP. Various strategies for initiating and combining antihypertensive drugs have been developed. Until 2018, the recommended approach was stepped care, where additional drugs were introduced when patient could not achieve target BP levels on the maximum dose of monotherapy. At 2018, European Society of Cardiology (ESC)/ESH guidelines of hypertension recommended a simple and pragmatic treatment strategy, highly applicable for most of the patients [7]. Initial combination therapy, preferably with single pill combination (SPC) was recommended as effective evidence based strategy to improve BP control. This recommendation was strongly emphasized in the latest update ESH guideline at 2023 [2]. Evidence indicates that with guideline directed therapy BP control can be achieved in majority of the patients, with 90-95% of them reaching target levels [8]. According to this evidence, the main problem at the era of insufficiently controlled BP is not the inefficiency of the drug therapies. Improper implementation of the guidelines might be one of the problems, as therapeutic inertia was shown to exert an important role at lack of BP control [9]. This means the hesitation or failure of the doctor to initiate or intensify the treatment and it exerts a major adverse role on the lack of BP control [10]. In randomized controlled trials therapeutic inertia is minimal, for example at ACCOMPLISH, 80% of study participants were at target BP levels [9, 11]. Among randomized controlled trials conducted in the western world, this trial achieved the highest rates of BP control [9]. However in real-world practice, high rates of inertia with low levels of adherence are one of the major problems contributing to ineffective BP control rates [10].

Initial combination therapy, as recommended, can easily bypass the problem of inertia of dose uptitration and it was shown to decrease the incidence of adverse outcomes with better short and long term results [12]. There is an emphasis on achieving a BP target of <130/80 mm Hg in most of the patients and present guidelines imply the requirement of combination therapy,

preferably as SPC. Research indicates that combination therapy at low doses is more effective than monotherapy at maximal doses, likely due to the targeting of multiple mechanisms [13]. Combined treatment leads to faster BP reduction with minimal side effects and more frequent BP control within the first year of treatment. This period is crucial, as it corresponds to the highest rates of discontinuation [12, 14]. It should be considered that the drug tolerability profile becomes more favorable when used in low dose combinations, as opposed to their high dose mono forms [15]. Reducing therapeutic inertia while improving persistence and adherence are essential pillars for an effective antihypertensive treatment. These goals can readily be accomplished by adopting the single combination pill strategy, as outlined in the guidelines [2, 7]. The polypill strategy, which consists of antihypertensive drugs combined with statin, with or without low dose acetyl salicylic acid, is recommended by the guidelines for primary and secondary cardiovascular prevention [2]. The justification for this strategy is that hypertensive patients commonly exhibit dyslipidemia and elevated cardiovascular risk and streamlining treatment through a single pill, instead of multiple pills daily, enhances adherence and treatment persistence [6].

Proper office BP assessment is the fundamental step in diagnosis of hypertension, however recent guidelines recommended the application of out of office BP measurements; home BP monitoring (HBPM) and ambulatory BP monitoring (ABPM) [2, 7]. Those are valid tools for diagnostic work up and follow up. HBPM is more acceptable by the patients and is an easily accessible tool. Latest trials have demonstrated the good correlation between ABPM and HBPM for diagnostic accuracy [16–18]. The evidence supports the clinically significant BP reductions by HBPM in hypertensive patients [19–21]. Self monitoring of the patient enables the self engagement and increases adherence to the therapy [19, 22]. Moreover, obtaining BP values outside the office setting reduces the therapeutic inertia exhibited by doctors. Much of the hesitation in dose escalation often stems from uncertainty related to high office BP values. A Dutch cohort study conducted in primary care settings in 2021 assessed that there was therapeutic inertia in 87% of the cases with uncontrolled hypertension. It was similar in men and women and was more likely to occur when BP was near target, compared with very high levels [23]. Reasons for ongoing therapeutic inertia was documented as skepticism regarding the high office measurements, waiting for out of office readings, near target values of the patient and patient’s choice of not having their medications intensified [23, 24]. Implementation of the out of office BP measurement recommendation can serve to persuade both the patient and the doctor to initiate or adjust the doses of antihypertensive drugs.

Adherence

Patient non-compliance or non-adherence to antihypertensive treatment is one of the best documented, but least understood health behaviors [25]. It's a multifactorial problem including the patient, doctor, patient's family and health myths passing around in many different regions. A statement of Dr. C. Everett Koop is relevant here: "Drugs don't work in those who don't take them".

In the management of hypertension, inadequate adherence to medication poses a specific challenge. The chronic and asymptomatic nature of the disease may lead individuals to perceive occasional or frequent omission of drug doses as inconsequential. As a result, adherence tends to vary significantly throughout the treatment process, typically decreasing with the rise in the number of medications and the complexity of the dosing regimen [26]. One year after initiation, medication adherence for hypertension management is reported to be less than 50% [27]. It has also been demonstrated that 20-30% of the newly prescribed medications are not obtained or filled by the patients [28]. A trial from Italy revealed that around 36% of the newly treated patients did not renew their initial prescriptions a second time [29]. In general, non-adherence rates are higher in low to middle income countries, compared with westernized societies and more common in patients with suboptimal BP control compared with general hypertensive group [13, 30].

Screening for non-adherence should be a routine part of the follow up of hypertensive patients. Adherence should be checked at every appointment; especially before escalation of the BP lowering treatment, before screening for secondary hypertension and on the suspicion of resistant hypertension. Objective methods for detecting non-adherence, either indirect or direct (such as reviewing pharmacy records, using electronic monitoring devices, directly witnessing medication intake, or detecting medicine in urine biochemically), are generally preferable over subjective approaches such as physician's impressions from patient interviews [31]. However, in settings with limited resources, obtaining confirmation of non-adherence from the patient can still provide valuable information. Medical history taking should provide precise details regarding the use of drugs or substances that could potentially interfere with BP control, such as non-steroidal anti-inflammatory drugs, glucocorticoids, decongestants, estrogens and progestins, substances of abuse and stimulants [2].

ESC/ESH hypertension guideline has recommended multiple strategies for improvement of the drug adherence and they are summarized at Table 1 [732]. There is not a single strategy that can help to manage non-adherence in all patients, it should be tailored to the modifiable drivers of the problem in each patient individually. Discussion between the patient and the doctor in

non-judgemental way will help to identify the barriers to adherence. It was shown that there is a positive association between patients' perceived risk of complications and adherence to the antihypertensive therapy [33]. Strong communication between patients and doctors is essential, as poor communication increases the risk of non-adherence by 19% [34]. Doctors should take time to educate the patient on risks of uncontrolled hypertension and benefits of therapy. The implementation of a healthcare model, led by non-physician health workers, but involving primary care physicians, has shown to improve BP control and cardiovascular risks [35]. Healthcare team organized educations and screening programs will further rise the awareness of the disease.

A further step for increased medical adherence should be involving the patient in the medical decision process [36]. Shared decision making increases the patient's engagement to the therapy and self BP monitoring increases patient empowerment. Newly diagnosed hypertensive patients, younger age and accompanying depressive symptoms are other factors interfering with adherence [37]. By implementation of the HBPM with the use of validated and low cost automated BP measuring devices, patient can take role in treatment follow up and tailoring the therapy. While practical cuffless devices for BP monitoring applied on smart electronic devices has been introduced, their applicability and accuracy in clinical practice needs to be proven [38]. E-health and telehealth technologies, which have gained increased importance lately, may play important role in patient integration to the therapy with increased awareness and adherence. The use of technology may range from simple text message reminders to more complex telemonitoring and wearable devices [39, 40]. Additionally, mobile health system relying on smartphone applications, has been found to improve certain clinical outcomes [41]. In a meta-analysis of 13 875 patients, home BP telemonitoring by self measurement at home and transmitting data to their doctors resulted in significant BP reductions, with systolic and diastolic decrease by 3.99 mm Hg and 1.99 mm Hg, respectively, when compared to usual care [42].

Antihypertensive drugs have the potential to induce side effects, ranging from mild to, in certain cases, severe, prompting treatment discontinuation. Side effects play a significant role in treatment non-adherence and discontinuation and can be either associated with BP reduction itself or arise due to class-specific effects [43]. The major recommended antihypertensive drugs generally exhibit good tolerability, although some medications like diuretics showed lower persistence than others [44]. One-size-fits-all strategy does not work in the precision medicine era and patients can significantly benefit from personalized treatment approaches. [45]. Tailoring treatment based on factors such as age, sex, comorbidities, ethnicity, metabolic

profile, past experiences with different drugs, and personality traits allows for more appropriate selection of individual treatment plan [46]. Patients with hypertension and other comorbidities are typically elderly individuals on multiple medications and need to be paid particular attention. The guidelines recommend against considering age alone as a barrier to antihypertensive treatment and recent studies suggest support for an intensive approach to BP lowering, emphasizing the importance of targeting tight control [2, 47, 48]. However, the cardiovascular benefits of intensive therapy may be accompanied by significant drawbacks, especially in older patients who typically face a higher risk of complications related to hypotension [49]. Several observational studies involving older individuals indicate an elevated risk of serious adverse effects under intensive antihypertensive treatment, particularly when they are frail [50, 51].

Despite numerous clinical trials for hypertension, there is often underrepresentation of women, or no sex-specific analysis is conducted to assess the effects of treatment. Polaczyk et al. conducted an analysis of the frequency of adverse drug reactions in women and men with hypertension and comorbidities, and aimed to assess the sex-specific predisposing factors. Women were found to be more prone to reporting adverse reactions such as hypotension, coughing and edema compared to men, risk increasing with age [52]. Drug reactions can have a substantial impact on the quality of life for patients influencing their acceptance of the disease and adherence to therapy, consequently leading to a less favorable prognosis [53].

The debate over whether it is preferable to take antihypertensive drugs in the morning or evening has persisted for years. TIME Study assigned 21 104 patients randomly to evening or morning dosing groups. After a median follow-up of 5.2 years they found no significant difference in the risk of cardiovascular events, with hazard ratio: 0.95 [95% CI, 0.83–1.10]; $P = 0.53$. No safety concerns were identified and non-adherence was noted as 22.5% with morning dosing as opposed to 39% with evening dosing ($P < 0.001$) [54]. Also, in a meta-analysis of randomized clinical trials where patients were randomized to morning versus evening dosing, evening dosing was shown to have no clear impact on cardiovascular outcomes [55]. These data align with the guidelines, which suggest allowing individuals to choose the timing based on their convenience [2, 7].

Reducing the pill burden is probably the most effective approach to increase treatment adherence. Recent data suggests that with each additional antihypertensive medication, there may be an associated increase of non-adherence, around 80% [44]. As discussed before, SPC is the preferred treatment regimen to achieve better results of drug adherence and cardiovascular endpoints [2]. START-study analysed propensity score matching data from 57 998

hypertensive patients using SPC or identical multiple pill forms. Results revealed that employing antihypertensive combination therapy by using up to three antihypertensive drugs in a SPC led to a reduction in both all-cause mortality and cardiovascular events, compared to the use of the same drugs administered separately in a multipill combination. [56]. Patients who rapidly attain their target BP need fewer modifications in their treatment plans. Likewise, individuals who do not encounter adverse effects are less prone to frequent alterations in prescriptions, all increasing the likelihood of adhering to the prescribed treatment.

At the population level, national health agencies should organize nationwide screening calls and increase public health awareness about hypertension. A recent European study revealed that, increasing the antihypertensive therapy adherence to a level of 70% in 5 European countries (France, Germany, Italy, Spain and England) would lead into total savings of €332 million over a 10 year period and lead to 82.235 fewer cardiovascular events [57]. Improving access to healthcare with reduced costs will undoubtedly increase adherence. Other health system strategies to support drug adherence are summarized in Table 1.

Achieving hypertension control extends beyond prescribing medications. It involves forming a medical alliance and taking actions to support adherence, not only to medication but also to lifestyle. It should be kept in mind that hypertension treatment is a multifactorial strategy with several functional pillars. Pharmacological treatment plan can work effectively only with functional non-pharmacological strategies, mainly implementing the proper lifestyle changes.

Lifestyle modifications

The adoption of a heart-healthy lifestyle is a crucial strategy for preventing onset of hypertension and increasing efficacy of antihypertensive treatment. Individuals maintaining a favorable lifestyle experience an approximately 4–5 mm Hg lower BP compared to those with an unfavorable lifestyle. Additionally, embracing a healthy lifestyle can enhance the BP lowering effects of pharmacological interventions, potentially reducing the need for multiple drugs to control BP [58]. The effectiveness of lifestyle interventions tends to be more pronounced when the start is with higher BP levels. Nevertheless, it's crucial to emphasize that lifestyle changes should not impede the initiation of drug therapy in cases where antihypertensive drugs are proven to be protective and benefits necessitate BP reductions beyond what lifestyle changes alone can achieve [2].

While the available evidence primarily stems from observational studies and their meta-analyses, all lifestyle interventions appear to confer heart-healthy benefits that extend beyond their impact on BP. Among the most significant and well-established lifestyle interventions

proven to help BP control and decrease morbidity and mortality are; weight loss, adherence to the DASH diet, reduction of salt intake, increased consumption of potassium, regular physical exercise and moderation of alcohol consumption [59–64]. Furthermore, quitting smoking and implementing additional lifestyle measures are crucial not only for BP management but also for overall well-being.

The vulnerability of treatment strategies based on non-pharmacological interventions lies in the limited sustainability of the prescribed measures. Following the prescription of lifestyle changes to hypertensive patients for achieving BP control, physicians should establish a follow up program and aim to assess adherence, determine the attained therapeutic goals, and crucially motivate and integrate the patient to the therapy [65]. Implementing such a program is notably essential to increase the efficacy of antihypertensive treatment, especially in patients persisting with uncontrolled BP. Below, the proven lifestyle measures for BP control are summarized.

Weight reduction: Being obese or overweight is directly associated with hypertension and weight loss strategies are recommended to lower BP [66]. A meta-analysis concluded that for each loss of one kilogram body weight, systolic and diastolic BP reduced approximately by 1 mm Hg [59]. Encouraging modest weight loss is a crucial recommendation, ideally attained through a combination of a low-caloric diet and regular exercise [67]. Prehypertensive adults were shown to experience reductions of 6.5 mm Hg for systolic BP and 4.6 mm Hg for diastolic BP after adopting a low-caloric diet [67]. For individuals who do not achieve their targets through non-pharmacological interventions, the consideration of pharmacotherapy is an option. Recent advancements in the pharmacological treatment of obesity using glucagon-like peptide-1 receptor agonists revealed the potential to address excess body weight as a means to enhance BP control [68]. Alternatively, bariatric surgery proves to be an effective and enduring strategy for managing BP and cardiovascular risk factors in morbidly obese patients. It may be considered in cases where all measures have failed, particularly in patients with severe obesity [69].

Restriction of sodium intake: There is compelling evidence indicating a link between elevated sodium consumption and higher BP, in both general population and individuals with hypertension [70]. Additionally, randomized trials and meta-analyses have consistently affirmed the relationship between sodium-restricted diets and improved BP control [2, 71]. A meta-analysis investigating the reduction of sodium intake to levels as low as 800 mg/day (1000 mg sodium = 2500 mg salt) demonstrated a linear decrease in BP [61, 71]. Nevertheless, the optimal therapeutic approach regarding unlimited sodium restriction remains a subject of debate. Observational studies have indicated an increased mortality in both hypertensive

patients and general population below the further reduction of sodium intake below 3.5 g/day [72]. However, the most significant limitation in those results is the lack of proper long-term randomized trials assessing the effects of various degrees of sodium restriction on outcomes. In studies revealing a J-shaped curve in the relationship between dietary sodium and cardiovascular outcomes, sodium intake was evaluated based on sodium excretion in spot urine and faced criticism for its inability to accurately reflect the 24-hour amount of urinary sodium excretion [73]. To provide more clarity on this issue, larger sized and more precisely controlled intervention studies with longer follow ups are required.

Any reduction in sodium intake is advantageous, as the correlation between sodium and BP reduction follows almost a linear pattern. A decrease of 1000 mg in sodium intake is associated with a systolic BP reduction of approximately 3 mm Hg [61]. An ideal alternative would be a salt substitute with low-sodium content and evidence is supporting the use of substitutes in adults with prehypertension and hypertension [74]. Recent 2023 ESH guideline recommends daily salt intake to <5 g/day (<2 g sodium) as class I, level of evidence B indication to reduce BP in hypertensive adults [2].

Increasing dietary potassium intake: Dietary potassium is linked to BP and recent data suggested a U-shaped relationship. It indicates that an adequate intake of potassium is desirable for achieving a lower BP level, but excessive potassium intake should be avoided [75]. The Salt Substitution and Stroke Study, a recent large randomized controlled trial, found that increasing potassium intake by substituting 25% of sodium chloride with potassium chloride in salt, reduced the risk of stroke, cardiovascular diseases and mortality in patients with elevated cardiovascular risk and with low potassium and high sodium intake at baseline [74]. Diets rich in potassium are favored over potassium supplementation through pills. Noteworthy sources of dietary potassium are fruits, vegetables, low-fat dairy products, certain fish and meats and nuts. Generally, four to five servings of fruits and vegetables can furnish 1500 to over 3000 mg of potassium. Adhering to a potassium-rich diet, such as the DASH diet, proves to be an effective way to achieve these recommended levels [2].

Physical activity: Physical activity is a key lifestyle modification for managing hypertension. Extensive epidemiological studies, accounting for age and other influencing factors, consistently provide evidence of an inverse relationship between hypertension and habitual physical activity levels. The acute rise in BP during dynamic and isometric exercise should not discourage the adoption of regular, long-term physical activity. Notably, 10 metabolic equivalent of task hours per week in leisure time physical activity, corresponding to the recommended minimum of 150 minutes per week, was associated with a 6% reduction in the

risk of developing hypertension [76]. In adults with normal BP, aerobic exercises such as brisk walking, swimming, dancing or gym exercises typically result in an average reduction of 2–4 mm Hg in systolic BP. For individuals with hypertension, the average systolic BP reductions tend to be higher, ranging from approximately 5–8 mm Hg [77].

Moderation of alcohol intake: Observational studies reveal a positive linear correlation between alcohol consumption and BP [78]. It's noteworthy that, the global attributable impact of alcohol intake on mortality is more than four times higher in men than in women [79]. The risk for hypertension increases in both men and women when daily alcohol intake reaches at least one to two drinks, equivalent to at least 10–20 grams of alcohol per day [80]. Binge drinking should be avoided as its' hypertensiogenic effect is revealed by clinical data [81]. A meta-analysis involving 36 randomized controlled trials demonstrated that reducing alcohol consumption, close to abstinence, was associated with a reduction of 3.3/2.0 mm Hg in systolic/diastolic BP [64].

Other lifestyle interventions: Tobacco smoking stands as the single largest preventable cause of death and is notably linked to a significant increase in the risk of cardiovascular diseases. Smokers often exhibit masked hypertension, characterized by normal office and higher daytime ambulatory BP values. Smoking a cigarette leads to sympathetic nervous system activation and a prolonged increase in BP, approximately 30 minutes, contributing to increased daytime BP variability with fluctuations in BP levels [82]. Smoking cessation and supportive care programs should be recommended.

Stress and anxiety are linked to an elevated risk of hypertension and BP control. Individuals experiencing mental distress may encounter a sudden rise in BP, which could normalize when the distress is alleviated [83]. Meditation and breath control practices, such as yoga, are recognized as effective stress reduction interventions for reducing BP [67]. However, it's important to note that while these practices are beneficial, their effect sizes are relatively smaller compared to the primary lifestyle interventions.

Combined lifestyle modifications exert the maximal benefit among non-pharmacologic approaches. DASH diet combined with weight management strategy was compared with DASH diet alone and usual diet control groups in ENCORE trial. DASH diet combined with weight management revealed 16.1/9.9 mm Hg BP reduction, compared to 11.2/7.5 mm Hg reduction in DASH diet group and 3.4/3.8 mm Hg reduction in usual diet control group [84]. Another trial compared high sodium intake control group with low sodium content DASH diet in hypertensive individuals. Results showed a reduction of 11.5 mm Hg in systolic BP [85]. It's

noteworthy to realize that these values are equal to the BP lowering effect of a single drug regimen.

In TRIUMPH trial, BP lowering effect of multiple lifestyle interventions were examined during a cardiac rehabilitation program. Supervised, center based exercise training with low salt DASH diet and behavioral weight loss strategies during a 4 month cardiac rehabilitation program resulted an ambulatory BP decrease of 7/3.9 mm Hg. Control group was the patients having educational sessions on BP control and applying low salt DASH diet with exercise and weight loss recommendations [86]. Cardiac rehabilitation programs represent a significant opportunity to implement comprehensive programs addressing various health promoting behaviors. These may include smoking cessation, weight reduction, adopting a healthy diet, reducing salt intake, supervised exercise and providing behavioral change support. These are particularly important for individuals with complex clinical conditions such as resistant hypertension [65].

FUTURE PERSPECTIVES ON ENHANCING TREATMENT EFFICACY

Despite the strategies to overcome the problem of insufficient BP control, effectively treated hypertensive population is still at significantly low levels. Main obstacle is poor adherence to medications. Furthermore, novel therapies aiming the target key regulatory mechanisms with minimal counter-regulatory escape and simplified therapeutic regimens which are better tolerated are needed [87].

In recent years, there has been notable interest in a novel therapeutic approach for hypertension involving small interfering RNAs (siRNAs) that target angiotensinogen. Zilebesiran is an innovative first-in-class siRNA therapeutic, which recently revealed successfull results at the end of the phase II clinical evaluation, KARDIA-1 trial (unpublished data). Single dose, long lasting vaccine therapy for hypertension control may be a promising approach for long term adherence and efficacy of antihypertensive treatment.

Other recent advancements in hypertension field include interventional strategies to control BP, such as renal sympathetic denervation, baroreflex activation therapy, carotid body ablation, and central iliac arteriovenous anastomosis [88]. However, with the exception of renal denervation, other interventional strategies are still far from routine clinical use. According to recent evidence from a meta-analysis, renal denervation has shown a significant but modest reduction in both ambulatory and office BP (by approx. 4/2 mm Hg) [89]. ESH guideline for hypertension reported that renal denervation therapy can be an additional treatment option for patients with true resistant hypertension, provided that the estimated glomerular filtration rate is greater than 40 ml/min/1.73m^2. The recommendation level is class II, level of evidence B [2].

The growing recognition of the potential role of artificial intelligence (AI) in cardiovascular medicine and hypertension is evident. The rise of digital technologies, including social media, mobile applications and wearable devices capable of generating continuous and real-time health data, highlights the potential for utilizing AI and big data analytics. Furthermore, AI could assist in crafting accurate risk prediction models for individuals and it has the potential to contribute to the formulation of personalized treatment strategies for hypertensive patients [90]. Results from ongoing and upcoming clinical trials of AI-integrated healthcare will furnish additional insights into the advantages and practicality of incorporating AI into clinical practice and will hopefully help to increase the efficacy of antihypertensive therapy.

CONCLUSION

Hypertension stands as the most prevalent cardiovascular disease globally. While effective BP control is shown to be achievable in 90% of patients through the proper use of the drugs and combination therapies, the reality of insufficient global control rates is alarming. We need to intensify our efforts to combat this global threat. Limited awareness about hypertension, coupled with its often asymptomatic progression results in non-compliance with medication and lifestyle recommendations, all significantly diminishing the effectiveness of antihypertensive treatment. A comprehensive and multi-focused solution is essential, involving not only the physician and patient, but also national health services, pharmaceutical companies, and the media. Adhering to recommendations of guidelines, promoting medication compliance, and encouraging lifestyle changes are fundamental steps to enhance the effectiveness of antihypertensive interventions. Focusing on effective BP control rates should be a global public health strategy. It necessitates attention and additional efforts, encompassing not only increased number of high quality clinical researches, but also greater emphasis on heightened public awareness.

Article information

Conflict of interest: None declared.

Funding: None.

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Table 1. Strategies for improvement of drug adherence

Levels	**Strategies**
Physician	— Patient counseling with providing enough time, improving health literacy and hypertension awareness — Positive feedback on behavioral and clinical improvement — Collaboration with other healthcare personnel (especially nurses and pharmacists) — Identify adherence related issues, avoid high doses of drugs with adverse effects — Reduce pill burden, prefer SPC

	— Simplify drug regimen, match therapy with daily routines — Empowerment and integration of the patient
Patient	— Self monitoring of BP — Telemonitoring, using applications and reminders — Motivation of the patient with health care provider, nurse, family members — Self management with simple patient guiding systems
Health system	— Increasing medication accessibility, reducing co-payments — Increased population awareness about hypertension — Supporting development of monitoring systems such as telemonitoring and e-health — Reimbursement of SPC — Availability of national database of prescription
Pharmacy companies	— Public educational activities — Monetary incentive in drug refills — Reminder packaging

Abbreviations: BP, blood pressure; SPC, single pill combination