Hypertension management in the COVID-19 era. Getaway from pandemic snares

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Abstract

On the verge of the second decade of our millennium, controlled hypertension was estimated at the range of approximately 30% to 50% among those European middle-age and older patients who were already treated. Experts agree that non-adherence to pharmacotherapy and physician-related clinical inertia are the utmost challenge in hypertension management. Although treatment with blood pressure lowering drugs with single pill combination (SPC) offers effective solution to that challenge, share of patients using SPC formulation is way under expectations. Few months of COVID-19 pandemic and repetitive lock-downs negatively impacted health condition of the whole societies. Experts report that overall cardiovascular risk profile of majority of patients worsened essentially over the course of several months of pandemic. Aggravated cardiovascular risk factors which clustered with uncontrolled hypertension calls for immediate action. Robust advocacy for wide use of SPC formulation composed of long-acting blood pressure lowering agents appears to be effective and timely getaway from this snare.

Key words: single pill combination; SPC; COVID-19 pandemic; hypertension; blood pressure lowering therapy; long-acting drugs

Arterial Hypertens. 2021, vol. 25, no. 3, pages: 93–99
DOI: 10.5603/AH.a2021.0024

Hypertension prevalence and control prior to COVID-19 pandemic

NCD Risk Factor Collaboration (NCD-RisC), a World Health Organization-endorsed initiative in collaboration with Imperial College London, has just recently issued an update on worldwide trends in hypertension prevalence, progress in treatment and control from 1990 to 2019 [1]. Data based on pooled analysis of 1201 population-representative studies with 104 million participants (representing 99% of global population) demonstrated that hypertension care varied substantially not only worldwide but also within neighboring regions. Although the main message of this report is rather gloomy, i.e., the number of people with hypertension has doubled to 1.28 billion since 1990, with 700 million people receiving no treatment, the authors also pointed at bright sides related to high blood pressure lowering strategies. In general, standardization of hypertension management seen over the last 30 years in upper-middle to newly-high-income countries demonstrated that introduction of modern universal healthcare, which includes novel pharmacotherapeutic formulas, effectively enhanced hypertension control with consequent reduction of hypertension-ascribed health burden [1].

On the verge of the second decade of our millennium, controlled hypertension was estimated at the range of approximately 30% to 50% among

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those European middle-age and older patients who were already treated [2]. Obviously, the problem of the awareness and control of hypertension is a very complex issue and varies essentially even across European countries. However, it has to be clearly stated that growing market share of novel blood pressure-lowering drugs — namely a single-pill combination formulation (SPC; i.e., 2 or more different blood pressure-lowering agents with complementary mechanisms of action placed in one tablet) visibly promotes higher percentage of patients with controlled hypertension [3, 4].

Tackling hypertension according to pre-pandemic guidelines

Given modern blood-lowering pharmacotherapy with single-pill combinations as a standard for vast majority of patients is capable of controlling high blood pressure in more than 80% [5], the pre-pandemic data clearly identifies tasks for healthcare providers and healthcare policies. To name the few, wide access to SPC formulations supported by common reimbursement rules along with educational and non-pharmacological measures should be highest priorities to effectively tackle the enormity of hypertension-related burden.

To further support the importance of large-scale use of SPCs treatment, the possible causes of successful trend breakdown that has only recently been observed in the United States should be scrutinized. Both awareness and control of hypertension in the United States have declined, as reported by the latest National Health and Nutrition Examination Survey (NHANES) that was issued shortly prior COVID-19 pandemic outbreak [6]. Among different causes of less effective BP control, turning back into wider use of monotherapy (which translates in decreasing therapy adherence) was postulated [7].

As for the rule, treatment with SPC formulations should be administered as standard for vast majority of hypertensive patients, which also holds true for treatment initiation (with only few exceptions) [8]. This highly effective strategy is endorsed by main expert documents on hypertension management [5, 9–11]. There are several EBM-based and practical reasons why guidelines consistently encourage SPC pharmacotherapy both for chronic treatment and for the first-line therapy [8]. Clearly, (1) combination of two BP-lowering agents is more efficacious as compared with monotherapy, which enables (2) prompt blood pressure control. One of the key contemporary priorities in hypertension management is three-month timeframe to achieve BP targets which is actually not doable without wide use of SPCs [5]. Treatment with a drug combination is associated with (3) less variability in response, that is almost everybody responds, only if the drug is taken. Complementary drugs in SPC formulation offer (4) less treatment-induced side effects which translates to (5) better adherence and persistence in long-term treatment. Experts agree that non-adherence to pharmacotherapy is the utmost challenge in hypertension management. What is more, a practical aspect of SPC formulation is that (6) patients require substantially less pills (two–three times less over time interval). With all the aforementioned information one should apprehend the fact that (7) at least 80% of all patients treated with SPCs will meet the goals of blood pressure lowering treatment after initiation and (but it is not necessary) following one time dose adjustment [5]. By definition, up-titration of BP-lowering treatment may be achieved either by maximizing doses of ongoing treatment, or — more preferably — by introducing a three-component therapy. Strategy of early introduction of three component drug combination (preferably SPC formulation) rather than maximizing doses of two antihypertensive drugs has been highlighted by 2021 guidelines on cardiovascular disease prevention in clinical practice by European Society of Cardiology (class I level A recommendation) [12]. As shown in the PIANIST study, regardless of ongoing treatment with 2 antihypertensive drugs from different classes (variable combinations) switching to a 3-component BP-lowering SPC (perindopril + indapamide + amlodipine)* was associated with substantial improvement in BP control in 90% of patients. Moreover, recent analysis from the SIMPLIFY study which identified the excess of both physician-related inertia and patients' non-adherence, clearly showed that the longer is a delay in effective antihypertensive treatment with a simpler drug regimen, the less likely is successful cooperation with patients [13]. Altogether, it is a clear-cut evidence that we should not procrastinate the introduction of SPCs, with special emphasis put on the initiation of a triple-pill combination when potentiation of drug therapy is required in the second step. Such strategy increases odds for success in terms of effective BP lowering as well as promoting a more cooperative patient.

All in all, the described features of two- or three-component SPC formulations make these drugs a cornerstone of contemporary hypertension drug therapy.

Metabolic syndrome — a hallmark of hypertensive patients

From epidemiological perspective, hypertension rarely constitutes a sole cardiovascular risk factor. In most of hypertensive patients there are concomitant other classical or newly-recognized risk factors to further aggravate cardiovascular risk profile, i.e., risk-modifiers [5]. One of the most recognized clustering of CV risk factors is the so-called metabolic syndrome, where hypertension is accompanied by abnormal carbohydrate metabolism including type 2 diabetes, obesity and lipid abnormalities.

Lessons from clinical trials repeatedly show that blood pressure control in hypertensive patients with concomitant metabolic syndrome especially with diabetes is exceedingly ineffective [14, 15]. Interestingly, this phenomenon is difficult to address even nowadays, with implementation of modern e-health technologies [16, 17]. The underlying causes accountable for difficulties in blood pressure control in metabolic syndrome patients with or without diabetes include among others: obesity itself, sleep problems with predominant obstructive sleep apnea, autonomic neuropathies, autonomic overdrive, declining kidneys function with albuminuria, hyperinsulinemia, and water retention [18, 19]. Such complex clinical entity inclines both a need for in-depth diagnostic procedures and necessity for tailored pharmacotherapy, preferably with EBM-tested drugs (*see below*).

Cardiovascular risk profile in the COVID-19 era

COVID-19 pandemic unprecedentedly impacted general health condition of the whole societies around the globe. Quite surprisingly, not only countries with less developed healthcare solutions, including telemedicine, paid high costs with regard to both COVID-19 itself and collateral damage [20–22]. For instance, according to the official governmental reports, the excess of all-cause deaths in 2020 in Poland accounted for 62 thousand (+15%) when compared to pre-pandemic year of 2019, and only part of these numbers might be ascribed directly to COVID-19 [23]. Additionally, in the structure of COVID-19-related unpredicted deaths in 2020, the highest percentages were recorded in patients with preexisting cardiovascular disease (16.69% excess) followed by diabetes-related (15.88%) and the lowest in cancer patients (4.7%), according to governmental reports [23]. Although these statistics result from complex medical and non-medical aspects, they clearly identified subgroups of patients at excessive risk of death during pandemic [24].

Repetitive lockdowns along with limited access to medical services conferred cardiovascular risk, which was, recently summarized by ESH-affiliated experts (European Society of Hypertension COVID-19 Task Force) [25]. Although the document does not provide definite information on BP control during and after lockdowns, it clearly shows that most of identifiable and modifiable risk factors have been aggravated after pandemic outbreak with only minor exceptions (e.g., aircraft noise, air pollution). This may be even more important for nearest months to come, which makes us think of disadvantageous prognosis for patients with cardiovascular risk factors and CV disease. Clustering of growing number of CV risk factors in a short period of time inevitably multiplies the risk of fatal and non-fatal events, much earlier that one could expect [26].

Are there strategies available to swiftly improve patients' CV-risk profiles in the peri-pandemic times?

During the worldwide pandemic in which hypertension accounts for the commonest comorbidity to negatively affect COVID-19 patients prognosis, it appears particularly important to strengthen our efforts to improve CV risk factors profile with special emphasis put on BP control [24]. Several misleading reports on differential effects of antihypertensive drugs on the risk of acquiring SARS-CoV-2 infection, which occurred early in 2020, unintentionally complicated matters. In fact, anecdotal reports suggested that patients receiving RAA blockers were supposedly more vulnerable to acquiring COVID-19 [27]. Moreover, outcome analyses of the ICU institutionalized patients rose concerns whether or not RAA blockers should be continuously administered in critically sick SARS-CoV-2 positive patients [28]. On the other hand, basic science studies highlighted contraindicatory effects of RAA blockers suggesting that these drugs may protect against organ injury (e.g., lungs) [29]. In line with this information, recently published clinical data analyses underlined that treatment with RAA blockers in SARS-CoV-2-positive patients implies better outcomes [30]. Unfortunately, all the above-mentioned contraindicatory information left without expert sane comment was disseminated via mass media, which in turn promoted confusion and patients' anxiety, which in some cases resulted in uncontrolled discontinuation of antihypertensive therapy. As for today, it has to be

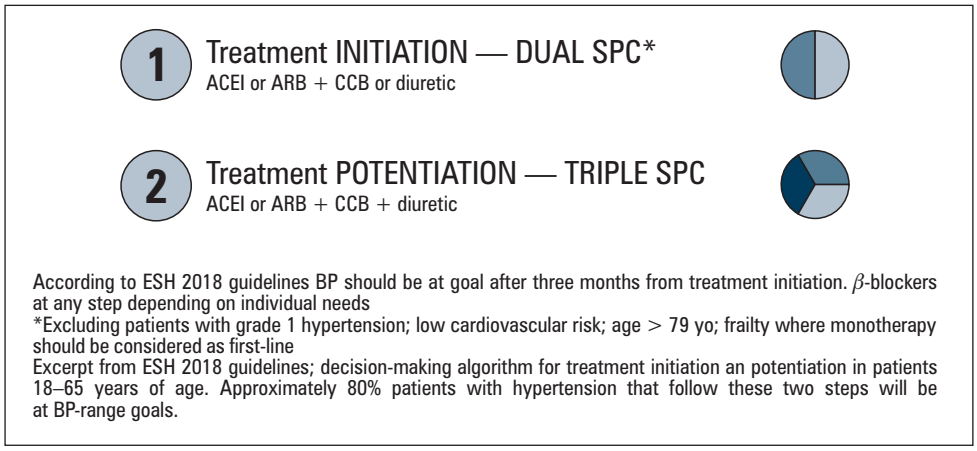

Figure 1. Two rules sufficient to effectively control hypertension with blood pressure (BP) lowering pharmacotherapy in vast majority of patients. SPC — single pill combination; ACEI — angiotensin-converting enzyme; ARB — angiotensin receptor blocker; CCB — dihydropyridine calcium channel blocker; ESH — European Society of Hypertension

clearly stated that effectively controlled hypertension, regardless of drug class, is associated with less severe COVID-19 course and more advantageous outcome. It is particularly evident in patients with ongoing treatment with RAA blockers [30].

Another aspect that needs to be clarified is whether remote healthcare solutions hastily implemented to overloaded healthcare systems conferred the risk of uncontrolled hypertension on a larger scale. Our local experiences suggest that physicians were less likely to fully implement guideline-based treatment strategies, especially with regard to SPC prescriptions (both switching from treatment with separate antihypertensive agents and pharmacotherapy initiation). One of the reasons which withheld doctors from SPC prescriptions were concerns about potential orthostatic hypotension. Lessons from ASCOT-BPLA trial do not support these apprehensions, as hypotension was noted only in 2% of all chronically treated patients with polytherapy [31]. Moreover, even blood pressure-lowering treatment with an SPC as the first-line therapy does not visibly potentiate risk of hypotension which was documented in studies with monotherapy as comparators [32, 33].

Quite surprisingly, it appears that optimal strategies to improve BP control are already available across various countries, namely: common use of SPC formulation, a strategy strongly endorsed by hypertension guidelines. Interestingly, it was only a decade ago that fixed-dose combination therapy was promoted for specific subgroups of patients (e.g., diabetic patients); today we recommend SPCs in vast majority of patients with hypertension. It is rather monotherapy that is reserved for clearly defined minority of hypertensives [5, 9]. Genuinely, only large-scale use of SPCs is capable of ensuring prognostic benefits at the level of whole societies. Treatment with SPCs addresses several obstacles that make BP control highly ineffective, including patients' non-adherence. In fact, there are several forms of inertia recognized, such as patient- and physician-related inertia or diagnostic *vs.* therapeutic inertia. Thus, we need proactive doctors and aware patients to swiftly converse pharmacotherapy of hypertension to SPC-based regimens. From the psychological perspective, the faster BP is fully controlled, the stronger is motivating booster for chronically treated patient. This relationship implies promotion of a triple-pill combination as soon as possible wherever free drugs combination, or dual SPC is ineffective, especially in middle-age patients (Fig. 1).

With this in mind, one comment needs to be made with regard to the International Society of Hypertension (ISH) guidelines [10]. Timing for diuretic therapy in the decision-making algorithm for certain subgroups of patients as recommended by ISH experts may in fact slightly prolong the perspective to tackle BP, as triple therapy may be delayed. European guidelines by ESH underscore that timely reduction of BP is one of the most important pillars of hypertension management [5]. Reaching BP therapy targets within reasonable period of three months may be challenging as middle-age patients with hypertension should have their BP in the range of 120 mm Hg to 129 mm Hg for systolic and 70 mm Hg to 79 mm Hg for diastolic BP, which is more stringent goal as compared to previous guidelines [5].

Clustering or aggravation of multiple risk factors along with uncontrolled hypertension, which is an aftermath of pandemic, resulted in increasing number

of hypertensives at higher CV risk. It is then justified to seek best-tailored and effective BP-lowering treatment in terms of components of the SPC formulations. The rule of A + C or D, and A + C + D defined in guidelines is perfectly applicable now as it was before pandemic outbreak [A — RAA blocker; C — dihydropiridine calcium channel blocker; D — diuretic]. Of note, meta-analyses which included high-risk or very high-risk patients treated with either angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor$_1$ blockers (ARB) highlighted efficacy of ACEIs in terms of better long-term prognosis [34–36]. In line with EBM, some experts therefore suggest that (very-) high risk hypertensive patients (esp. with diabetes or chronic coronary syndromes) should be preferably prescribed with SPCs containing ACEI [11]. The efficacy of treatment with a fixed-dose combination of an ACEI with a thiazide-like diuretic (perindopril + indapamide) was clearly shown in the ADVANCE Study in type 2 diabetic (T2DM) patients with hypertension. These high-to-very high CV risk patients with T2DM routinely receiving the fixed-dose combination (FDC) of perindopril and indapamide for the treatment of high blood pressure (FDC was a precursor of SPC formulation) were characterized by reduced risk of major vascular events and death, as well as good tolerability of the treatment [37]. Interestingly, the same fixed combination that is ACEI + thiazide-like diuretic (perindopril + indapamide) was shown to unanimously reduce BP regardless body mass index (BMI) status [38]. Bearing in mind complex difficulties in BP lowering in obesity, such combination offers reasonable basis for SPCs in the treatment of overweight-to-obese high risk patients. It is also worth mentioning that vivid development of the SPC market today offers availability of the same molecules in whichever combinations (A + D + C or any dual combination). Adjustment of doses and content within just one pill facilitates and makes more predictable hypertension management. Indisputably, one pill for the patient maximizes treatment adherence [5].

Although European and American guidelines do not particularly differentiate thiazides vs. thiazide-like diuretics in the decision-making algorithm, the latest recommendations by ISH suggest, that thiazide-like diuretics, esp. indapamide, may offer additional benefits in specific subgroups of patients [10]. In fact, thiazide-like diuretics perfectly meets the criteria of "ideal characteristics of drug" for the treatment of hypertension, as defined by ISH document [10]. Experts underscore that prescribed drugs (1) should be tested in rigorous protocols providing evidence in relation to morbidity/mortality prevention (reduction of cardiac, renal and cerebrovascular events and deaths); (2) should provide 24-h blood pressure control, so that it can be used in once-daily regimen; (3) should be affordable and/or cost-effective; (4) should be well-tolerated; and (5) should have proven benefits in the population in which it is meant to be used. With these arguments in mind, it is worth emphasizing that indapamide especially in combination with perindopril and/or amlodipine perfectly fulfils these criteria. Indapamide, perindopril, and amlodipine are long acting, potent, and widely tested drugs in monotherapy as well as in drug combination. On top of it, all these drugs were not only studied in terms of intermediate phenotype, which is blood lowering potency, but also with regard to cardiac, renal and cerebrovascular hard end-points [31, 37, 39–41].

Last but not least, as many patients with hypertension gained weight during pandemic due to repetitive lockdowns, those who are uncontrolled in terms of BP may benefit from switching therapy to a fixed-dose perindopril+indapamide-based regimen. As documented in the FORSAGE study uncontrolled hypertensive patients who started such treatment had substantially increased odds to improve BP control. This phenomenon was consistently evident in all BMI subgroups, including obese patients [38].

Time to act

To conclude, we have already learnt sufficient lessons from pandemic to call for immediate implementation of the current guidelines on hypertension management. Any further procrastination of SPCs integration to basic blood pressure lowering regimens, including a triple-pill SPC when potentiation of antihypertensive treatment is required, will further aggravate cardiovascular risk which has already increased over the last few months of pandemic. EBM-tested long-acting blood pressure lowering agents are available in multiple fixed combinations that can be safely and successfully prescribed, including remote-health solutions routes. In light of just recently published data on BP control in elderly it becomes evident that the number of hypertensive patients who may benefit from more stringent BP control is constantly growing [42]. This information is of particular importance when cardiovascular system-related collateral damage resulting from ongoing pandemic is hardly countable. Notably, the cutting-edge evidence from a large-scale clinical trial which underlines strict BP control even in elderly comes from China. The country that was on the front line, and probably took the hardest hit from COVID-19 pandemic.

Acknowledgements

Writing of this article was supported by Servier Polska.

*see your local legal regulations defining the earliest clinical circumstances adequate for prescription of an SPC formulation.

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