Consensus Document

The use of single-pill combinations as first-line treatment for hypertension: translating guidelines into clinical practice

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The 2018 European Society of Cardiology/European Society of Hypertension guidelines recommend the first-line prescription of two antihypertensive drugs in single-pill combinations (SPCs), also known as fixed-dose combinations, for the treatment of most patients with hypertension. This recommendation is based on a large amount of data, which shows that first-line treatment with SPCs supports reaching blood pressure targets rapidly and reducing cardiovascular outcome risk while keeping the therapeutic strategies as simple as possible and fostering adherence and persistence. As this approach constitutes a big shift from the stepped-care approaches that have been dominant for many years, practicing physicians have expressed concerns about using SPCs as first-line agents. In this review, we will discuss the barriers to the uptake of this recommendation. We will also offer suggestions to reduce the impact of these barriers and address specific concerns that have been raised.

Keywords: barriers, combination treatment, guidelines, hypertension, single-pill combinations

Abbreviations: ACE, angiotensin-converting enzyme; ARB, AT1 blocker; CCB, calcium channel blockers; CME, continuing medical education; ESH, European Society of Hypertension; MyHEART, My Hypertension Education and Reaching Target; RAAS, renin–angiotensin–aldosterone system; SPC, single-pill combination

INTRODUCTION

Hypertension remains the leading risk factor for mortality worldwide. Its prevalence, which was estimated at 31% of the global adult population in 2010 (1.39 billion persons), continues to rise as life expectancy increases [1]. Given the high burden of disease associated with hypertension, achieving good blood pressure (BP) control might represent the cardiovascular prevention strategy with the greatest impact on public health. However, despite the availability of a wide range of effective antihypertensive drugs, the control of arterial hypertension remains unsatisfactory. Studies have shown that BP control is only reached by ~30–50% of treated patients [1–4].

Much work and thought have been invested in understanding the barriers to BP control and in developing new strategies to support the rapid and effective attaining of goals. First and foremost, extensive data from many randomized controlled trials (RCT) show that to reach BP goals, most patients need to take at least two antihypertensive drugs that target complementary pathways [4–9]. Data, however, have also shown that the timely prescription of a second antihypertensive therapy when targets are not reached, is hampered by physician inertia [9,10] and that these delays have a significant impact on long-term cardiovascular outcomes [11,12]. A recent real-world study of 100 982 hypertensive patients initiated on monotherapy showed that treatment intensification occurred in only 22% of patients after 6 months and 36% of patients after 3 years [10].

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To address these ongoing issues, the previous recommendation that a first-line low-dose combination therapy be considered for high-risk patients as an alternative to a stepped care approach (initial monotherapy followed by the addition of a second therapy) has been expanded to include most hypertensive patients [9,13,14]. The latest European Society of Cardiology/European Society of Hypertension (ESH) guidelines also endorse the use of single-pill combinations (SPCs), which are also known as fixed-dose combinations [9]. This approach supports the need to target multiple pathways, fosters reaching BP goals faster, reduces the risk of poor compliance associated with larger numbers of pills, and reduces the impact of physician inertia [15].

The current narrative review summarizes the discussions that took place during a workshop held on 20–21 June 2019. The goal of the workshop was to train young ESH hypertension specialists from 16 different countries under the supervision of two senior physicians (S.L. and K.N.). Country-specific data were discussed with the goal of improving the implementation of ESH guidelines on SPCs and of writing a consensus document that summarizes key actions that could be implemented in individual countries. We will present data that support the use of SPCs and discuss the potential barriers to the uptake of this recommendation. We will also offer suggestions to reduce the impact of these barriers and address specific concerns that have been raised.

ARGUMENTS SUPPORTING SINGLE-PILL COMBINATIONS AS FIRST-LINE TREATMENT

Observational evidence suggests that first-line combination therapy reduces the time taken to achieve BP control, as well as cardiovascular outcomes, and increases drug adherence, safety, and tolerability, compared with monotherapy and free associations, although no RCT has yet been performed.

Efficacy

The recommendation that first-line combination therapy be considered for most hypertensive patients was based on extensive data [9,13,14]. Data collected from real-world settings, for instance, have shown that treatment initiation with a combination increases the number of patients who reach BP control within 3–6 months and lowers the risk of having cardiovascular events [16,17]. In the United States, analysis of electronic medical records data ($N = 3524$) showed that first-line treatment with combination therapy was associated with a significant decrease in the risk of reaching the combined outcome of acute myocardial infarction (MI), stroke/transient ischemic attack, hospitalization for heart failure, and mortality [incidence rate ratio 0.66 (95% confidence interval (CI), 0.52–0.84); $P = 0.0008$] when compared with first-line treatment with a monotherapy followed by the add-on of a second treatment [17]. Achieving BP goals faster was one of the main contributors to the reduction in risk [17]. Similarly, an analysis of an Italian healthcare utilization database of 44 534 individuals showed that 1 year after the start of treatment, patients who initiated treatment with a two-drug SPC had a reduced risk of hospitalization for a cardiovascular event [hazard ratio 0.79 (95% CI 0.71–0.88); $P < 0.01$] when compared with patients who initiated treatment with a monotherapy [18].

The use of an SPC also has an incremental cardiovascular benefit over the use of the equivalent free association [19–22]. An analysis of data from primary care patients ($N = 1507$) showed that initiating therapy with an SPC rather than a free association resulted in significantly larger reductions in BP (risk adjusted changes; -17.3 ± 11.6 vs. -12.0 ± 11.5 mmHg for SBP; -10.1 ± 6.8 vs. -6.0 ± 7.5 mmHg for DBP, respectively; $P < 0.001$) and more patients reaching BP control (<140/90 mmHg) within a median of 6 months (57.2 vs. 42.5%, respectively; $P < 0.001$) [19]. Another real-world analysis of hypertensive patients treated in the primary care setting ($N = 28\,594$) showed that SPCs, when compared with free associations, improved the 5-year cardiovascular event rate [hazard ratio 0.74 (95% CI 0.70–0.77); $P < 0.0001$] [22].

Adherence

Poor patient adherence and persistence is one of the major barriers to reaching BP control [23]. Analysis of an Italian cohort of 242 594 patients newly treated for hypertension showed that over a 6-year period, 79% of patients had at least one episode of treatment discontinuation and 48% of patients were classified as having low or very low adherence [23]. These results may be, at least in part, attributable to the number of pills prescribed as compliance has been shown to decrease with number of pills [24,25].

Improvements in adherence and persistence with SPC use have been quantified. A meta-analysis of 12 real-world studies showed that in patients initiating treatment, adherence was 8% higher with an SPC than with a free association ($N = 39\,040$) and that persistence was twice as likely ($N = 21\,556$) [26]. Similar results have been found in meta-analyses of clinical and cohort trials [27,28]. A recent Canadian meta-analysis of nine hypertension studies ($N = 62\,481$) showed that treatment with an SPC was associated with a 15% improvement in adherence when compared with the equivalent treatment with a free association and that persistence was higher with the SPC [risk ratio 1.84 (95% CI 1.00–3.39)] [27].

Tolerability and safety

As SPCs combine antihypertensive agents with complementary mechanisms of actions, in many cases, the starting dose of each component is significantly lower than if each component were prescribed sequentially. Lower doses of antihypertensive therapies have been known for many years to be associated with a reduced risk of side effects; and meta-analyses of placebo-controlled randomized trials have shown that the rate of adverse events with combination therapies is significantly lower than the rate with two monotherapies (7.5 vs. 10.4%, respectively; $P = 0.03$) [29]. Recently, a large systematic review and meta-analysis showed that combinations containing a quarter of the standard dose of two antihypertensive agents were

associated with significantly fewer adverse events than a standard dose of monotherapy [30].

In addition, with certain combinations, the side effects of one component can be counterbalanced by the effects of the other component. For instance, ankle edema, which is a common side effect of calcium channel blockers (CCBs) and is caused by precapillary vasodilation and increased hydrostatic pressure, is significantly reduced by the simultaneous administration of a renin–angiotensin aldosterone system (RAAS) inhibitor, which increases postcapillary dilation and attenuates prepost capillary pressure gradient and fluid exudation [31]. A meta-analysis of 17 206 patients showed that the pooled incidence of peripheral edema was 3.2% with a CCB/RAAS inhibitor combination and 6.0% with a CCB in monotherapy [relative risk (RR) 0.62 (95% CI 0.53–0.74); $P < 0.00001$] [32].

An incremental safety and tolerability benefit of SPCs over free associations has also been reported. A meta-analysis of cohort studies and clinical trials ($N = 1775$) [33] found that four out of five trials reported a decreased incidence of adverse events (all severities) with SPCs compared with the corresponding free associations at equivalent doses. This translated into a 20% decrease in the risk of adverse events [odds ratio (OR) 0.80 (95% CI 0.58–1.11); $P > 0.05$] [33].

One last point to consider is that with SPCs, inappropriate combinations [34,35] cannot be prescribed inadvertently. The combination of two RAAS inhibitors, for instance, has been shown to increase the rate of hypotension, hyperkalemia, and renal failure [36]. This safety and tolerability benefit of SPCs over free associations may, however, diminish when a third antihypertensive medication is needed. A recent study of 459 465 prescriptions showed that when SPCs were combined with other antihypertensive medications, they were associated with a significantly higher risk of duplicated prescriptions than free associations [0.9 vs. 0.6%; adjusted RR 2.10 (95% CI 1.67–2.65)] [37]. Thus, though SPCs reduce the risk of inappropriate combinations, a regular review of the therapeutic regimen remains needed when SPCs are combined with additional antihypertensive medications.

Flexibility

More than twenty types of two-drug antihypertensive SPCs with a range of doses have been developed. All of them contain associations of drugs with complementary mechanisms of action [angiotensin converting enzyme (ACE) inhibitor + diuretic, ACE inhibitor + CCB, AT1 blocker (ARB) + diuretic, ARB + CCB, diuretic + CCB, beta-blocker + diuretic, beta-blocker + CCB]. Given the differences between the countries in terms of types of associations and dosage availability, it is not within the scope of this review to provide an exhaustive list of these medications. However, drugs used in such associations include ACE inhibitors (such as enalapril, lisinopril, perindopril, ramipril, trandolapril, quinapril), diuretics (such as chlorthalidone, indapamide, hydrochlorothiazide), ARBs (such as candesartan, irbesartan, losartan, olmesartan telmisartan, valsartan), CCBs (such as amlodipine, lercanidipine, verapamil), and beta-blockers (such as atenolol, bisoprolol, metoprolol). Some molecules are more frequently marketed, within one pharmacological class, for instance amlodipine among CCBs, and hydrochlorothiazide among diuretics.

Drug selection

The current availability of a wide range of SPCs means that therapeutic plans can be individualized according to patient profiles (clinical presentation, hemodynamic characteristics, and comorbidities) [9,15]. Patients who exhibit predominantly fluid and salt retention are well suited for combinations that include a RAAS blocker and a diuretic; patients who present with arterial stiffness and/or vasoconstriction should be treated with a combination of a RAAS blocker and a CCB or a thiazide-like diuretic such as indapamide; and patients with an overactive sympathetic nervous system might benefit from the prescription of combinations that include beta-blockers or RAAS blockers.

In everyday practice, the best approach to choosing an SPC remains combining a thorough physical examination with a detailed medical history that includes an evaluation of comorbidities and a discussion of side effects to previous antihypertensive therapies.

Dose adjustments

The availability of a range of doses now makes it feasible to uptitrate the different components of an SPC in the same way as if the patient were taking a free association. It is, however, important to note that the availability of dosages (either for one or both components) varies from country to country. It should also be reminded that the dose-response curve of ACEIs and ARBs is flat compared with that of CCBs, which has an impact for dose adjustment.

TARGET POPULATION

As underlined above, the target population for first-line low-dose combination therapy includes most hypertensive patients, particularly those at medium to very high cardiovascular risk [9,13,14]. Patients who may not be concerned are patients with grade 1 hypertension [9] and low cardiovascular risk (i.e. with no other cardiovascular risk factors), for whom the monotherapy approach may be reasonable and constitute a prudent measure to avoid excessive BP reduction. However, although this prudent approach may concern patients in the lower range of grade 1 hypertension, it may not concern patients in the higher range (i.e. with an initial SBP > 150 mmHg) who would require a BP reduction of more than 20 mmHg.

It should also be noted that some data, detailed above and reporting an incremental BP control with the use of an SPC over the use of the equivalent free association in patients taking monotherapy, cannot be systematically extended to the patients with mild or very mild hypertension (i.e. the lower range of grade 1 hypertension) of proven recent diagnosis, that represent a growing fraction in current clinical practice in developed countries.

GUIDELINE IMPLEMENTATION: BARRIERS AND SOLUTIONS

Though these new guidelines, which endorse the use of SPCs, are expected to improve patient outcomes

significantly, integration of their use into routine clinical practice might be challenging. A multimodal effort that relies on opinion leaders and national societies of individual countries is likely to be needed.

Physician-related factors

Results from surveys and informal discussions indicate that some of the physician barriers to prescribing SPCs are lack of physician experience with SPCs and difficulty in selecting the right combination and dose, the belief that SPCs do not offer enough flexibility and therefore cannot be tailored to patient profiles, the belief that SPCs are not useful when compared with free associations, and the belief that recommendations are largely dictated by pharmaceutical companies and therefore do not reflect best practices (Fig. 1). Although the ultimate goal is to promote the concept of initiating antihypertensive treatment with a tailored, effective, and well tolerated SPC, as indicated by the guidelines, the first step is to review the data that led to the development of SPCs and address misconceptions.

Among the strategies that might be used for knowledge dissemination, continuing medical education (CME) programs have been proven to be most effective when they are interactive, when they provide multiple exposures to the participant, and when they are focused on outcomes that are important to physicians [38,39]. A 2011 initiative, for instance, showed that physicians who attended a half-day, highly interactive hypertension management CME program, which was based on guidelines and evidence-based medicine, resulted in participants being 52% more likely to adopt guidelines than nonparticipants [38]. Thus, development of CME programs that might better explain the advantages of SPCs in the treatment of hypertension might represent an effective strategy to improve knowledge of the principles behind the guideline recommendations. Such programs would also support their implementation in clinical practice.

A 'top-down' strategy could be adopted to reach a large number of physicians. Opinion leaders and cardiologists could attend CME modules and interactive case-based discussions at international congresses and then return to their countries to develop country-specific CMEs and to run local events, such as small symposia and round table discussions. Opportunities for physicians to meet with the authors of the guidelines could also offer a forum in which concerns about the intellectual independence of recommendations could be addressed.

Accessibility of guidelines could also be increased by initiatives to translate them into the native languages of each country and to develop country-specific materials such as pocket guidelines, short commentaries, and position papers. Digital channels, such as web pages with hotlines, e-mail messages with short communications on selected topics, and social media could also be used to

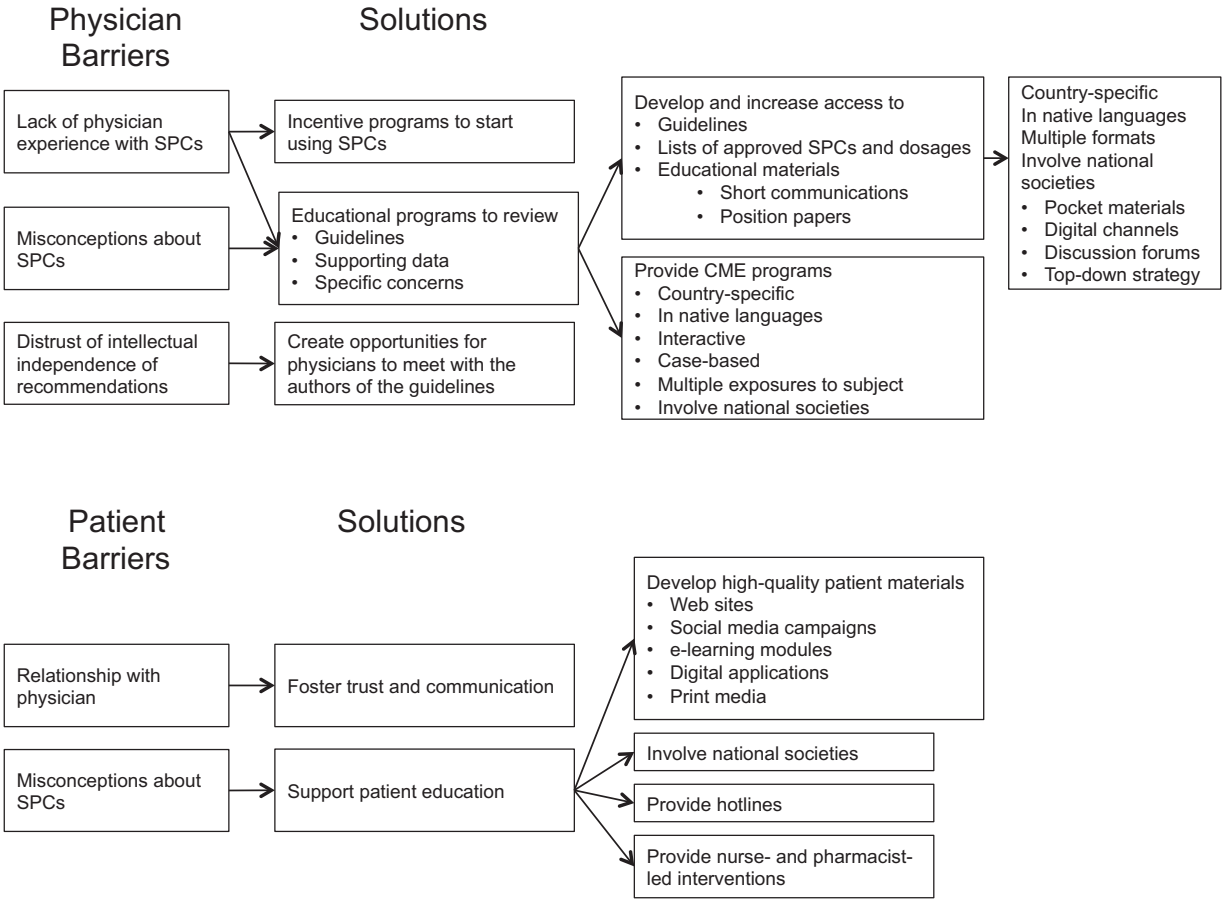

FIGURE 1 Physician and patient barriers to the use of single-pill combinations and solutions. CME, continuing medical education; SPC, single-pill combination.

increase awareness of the newest guideline recommendations. In addition, developing country-specific, up-to-date lists of SPCs and their dosages could help physicians, who are less familiar with SPCs, to select the right combination and the right dose for each patient.

Incentive programs from public health institutions could also be explored as a way to encourage physicians to adhere to guidelines. Although the effects of financial incentives on the delivery of healthcare tend to be small and short lived [40], the hope would be that incentives would encourage physicians to try SPCs and that this would be sufficient to overcome the barrier associated with integrating a new approach into prescription practices.

Some countries have already committed to a more active role in helping their hypertensive population reach BP control. Slovakia, for instance, during the 34th National meeting on Hypertension in April 2019 signed a charter that states that by the year 2023 BP should be controlled in 70% of hypertensive patients [41].

Patient-related factors

The success of hypertension management is often predicated on the relationship between the doctor and the patient (Fig. 1); it can have a significant impact on treatment choices, on buy-in of the patient, and ultimately, on adherence and persistence. The complexity of this relationship was illustrated in a recent study of 15 elderly adults in the Netherlands. Some interviewed patients expressed the desire that their treatment be tailored to their needs and that their discussions with their physicians be more transparent. Other patients reported a fear that a discussion about treatment would lead to a reduction in medication and consequently, an increase in their fear of having a vascular event [42]. Thus, SPCs, which reduce the number of pills and often the dosage of each component, can be perceived as a reduction in medication rather than a more adapted treatment.

Internet media, including social media and web sites, has become a significant factor in the doctor–patient relationship [43]. More and more patients rely on the Internet for information [44], which they then bring to the attention of their physician. In most cases, however, there is little oversight over the accuracy of the information being circulated [45]; and this information is often a poor springboard for a productive discussion.

Digital media does, however, present an opportunity to disseminate patient education materials that highlight the benefits of SPCs and the ramifications of noncompliance [46]. Hypertension experts, patient organizations, and national societies could develop high quality materials, such as web sites and e-learning modules, to educate and counsel patients. Studies have shown that physicians can capitalize on the patient's impulse to consult the Internet by providing preselected URL links. A recent initiative, for instance, showed that in a surgical setting, a majority of patients accessed the URLs provided to them by their physician [47]. Another study showed that evidence-based hypertension education could be disseminated successfully via a web site. The My Hypertension Education and Reaching Target (MyHEART) website was developed by physicians to target young adults with hypertension [48]. Analysis of website access data showed that over a 6-month period, the site received 1090 visits and 2130 page views. The majority of visits (56%) resulted from organic searches (via an unpaid search engine); but, 35% of visits came from patients accessing the MyHEART website directly [48]. Such initiatives could mitigate the impact of low-quality, media-based, sources of information.

Social media can be used to reach patients. A study of Chinese Americans showed that a 48-h Facebook advertisement campaign that linked to an informational video on hypertension management reached 508 people and generated 52 link clicks [49]. Social media platforms, could, thus, be a cost-effective complement to print media [46]. The use of smartphone applications is also becoming an integral part of patient approaches to the management of hypertension and could be used as platforms to disseminate accurate information [50].

Lastly, more traditional methods of educating patients and gaining the patient's trust should not be ignored. These include open discussion, print media, hotlines, and nurse-led interventions.

Addressing concerns and special issues

Increased risk of side effects

With the classic stepped care approach, any tolerability issues or adverse events can easily be attributed to the newly introduced agent. In real-world clinical practice, where poor adherence, poor persistence, and physician inertia are prevalent, the safety benefits of such an approach are quickly outweighed by the cardiovascular consequences of delaying or not reaching BP goals. Initiating treatment with a combination improves the risk : benefit ratio as data suggest that benefits increase, but risks remain roughly the same [9,15].

The issue of polypharmacy and high pill burdens and their impact on adherence and persistence also needs to be considered before choosing a strategy [51]. For many patients, the compliance benefits of simplifying treatment by initiating a carefully chosen, low-dose antihypertensive SPC will outweigh the risk of adverse events.

Hypotension in general and in the elderly

Specific concerns about severe hypotension when initiating treatment with a combination exist. An analysis of the French National Health Insurance System ($N = 1698$) reported a higher risk of hospitalization due to hypotension, syncope, or collapse [OR 1.88 (95% CI 1.15–3.05)] with the prescription of an SPC than with a free association [52]. These data were not, however, collected in treatment naïve patients; ~50% of patients were taking a high-dose RAAS inhibitor; and ~10% of patients were taking a high-dose thiazide diuretic or CCB. These data do, however, underscore the fact that it is important to exclude the presence of orthostatic hypotension and to consider the potential for other adverse events. The risk of hypotension can also be diminished by selecting a combination that includes antihypertensive medications with different drug absorption rates.

Nevertheless, in specific populations, such as patients with high-normal BP or elderly and frail patients, the risk of severe hypotension should be considered before prescribing an SPC. Guidelines clearly recommend a more cautious initial treatment strategy for frail, elderly adults, in whom the systems regulating the homeostatic control of BP may be less competent [9]. Though frailty may represent a more reliable predictor of complications than age, no studies have been performed in this patient population. In the elderly, however, data suggest that the risk of hypotension and other adverse events needs to be weighed against the benefits of treatment. A recent retrospective population-based study of older adults (>65 years of age, $N = 13\,350$) showed that, when first-line antihypertensive SPC therapy with a RAAS inhibitor and a thiazide diuretic was compared with a free association, there was a significantly lower risk of reaching the composite outcome (mortality or hospitalization for acute MI, heart failure, or stroke) with the SPC, but an equivalent risk of reaching the safety outcome (hospitalization for hypokalemia or hyponatremia: 0.5% of cases) [21].

Missed doses

Physicians have expressed concerns that one missed dose of an SPC means that multiple antihypertensive drugs have been missed. Though this concern is legitimate, real-world studies have shown that SPCs improve overall adherence, BP control, and clinical outcomes [19–21,26,53]. These data suggest that the overall benefit of the SPC outweighs the risk associated with a missed SPC dose. Additional studies will be needed to specifically investigate the impact of missed SPC doses on patient health. In the meantime, every patient interaction can be used to perform a compliance check and to encourage patients to use reminders to take their medication.

Drug holidays

Physicians have also expressed unease about the management of SPC therapies when one of the medications needs to be temporarily interrupted either due to intercurrent diseases or surgical intervention. A diuretic, but not the medication that it is combined with, for instance, may need to be interrupted in response to dehydration. Temporary shifts to monotherapy may be needed in such situations and dose titration should always be informed by BP values and fluid status. In some cases, it may be necessary to consult a team of specialists to discuss how to manage the clinical situation.

Chronotherapy

Various studies in healthy volunteers and in hypertensive patients show that the pharmacokinetics of the individual components in SPCs are comparable with the pharmacokinetics of each component in monotherapy and in free associations [54,55]. SPCs can, therefore, be chosen to address concerns such as the dipping pattern of BP, therapeutic troughs at the end of dosing intervals, and increased risk of hypotension.

Patients who have been shown to a have dipper profile, measured by ambulatory BP monitoring, could benefit from a morning administration of an SPC in which each component of the combination has a duration of action of at least 24 h, such as amlodipine, indapamide, perindopril, and lisinopril. For nondippers, an evening administration of an SPC that includes one antihypertensive medication with a 24-h effect and one antihypertensive with a shorter duration of action (such as ramipril and enalapril) could be effective. More studies are needed to investigate the chronotherapeutic effects of different SPCs [56].

Costs/reimbursement

Though the cost of an SPC varies with the combination, the country, and the availability of generics, it is typically higher than that of a monotherapy and sometimes, but not always, higher than the cost of the free association [22,26,57–61]. However, as the cost of medication is relatively low when compared with other healthcare costs, analyses of cost-effectiveness are more informative when the overall cost of hypertension management is considered. Even in the United States where drug costs are high, a 50-year cost simulation based on the population of the SPRINT study [62] showed that the combined cost of antihypertensive drugs, office visits, and monitoring accounted for only 3.0–4.4% of the total of direct medical costs.

In fact, several cost analysis models have included the cost of treating long-term hypertension-related cardiovascular events and healthcare resource utilization and have shown that prescribing an SPC resulted in lower overall healthcare costs than prescribing a free association [26,63–65]. In the Tung *et al.* [63] study ($N = 16\,505$), for instance, total healthcare costs, including medical costs and pharmacy costs, over a 15-month period, were significantly lower in the SPC group than in the free association group (US $1844 vs. 2158; $P < 0.001$). These data were accompanied by lower rates of clinical outcomes such as hospitalization and major cardiac events with SPCs than with free associations [63]. The need for country-specific analyses was underscored by at least one study, which showed that in the United Kingdom, cost of SPCs and free associations was equivalent [22].

Out-of-pocket costs have the potential to impact persistence. In one US study, the average out-of-pocket cost for a brand name SPC was 0.6–3.0 times higher than that of the same free association (brand names) and 0.5–2.8 times higher than that of the same free association as generics [59]. In another US study that evaluated 27 SPCs, the average monthly increase in out-of-pocket cost was $13 compared with that of the equivalent free association [60]. Additional studies are needed to determine the threshold for out-of-pocket cost over which patients might reject a first-line SPC strategy. A study of German patients suggests that 70% of patients would agree to an extra 10€ per month out-of-pocket to halve the number of pills they have to take [66].

To promote reimbursement of the SPCs, transparent communication between the pharmaceutical industry, medical professionals, and regulatory authorities is critical. Lobbying for state reimbursement should be based on strong medical evidence and long-term cost analyses. Patient groups may also help advocate for the broad reimbursement of the first-line use of SPCs. Recently several nonprofit organizations filed an application to include

antihypertensive SPCs on the WHO essential medicines list [67].

Regulation

Concerns about the scientific validity and potential conflicts of interest regarding SPCs should be alleviated by reviewing the regulatory processes that govern the approval of SPCs. Combinations that are authorized as first-line SPCs were developed according to specific guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. In addition, the WHO, US Food and Drug Administration, and European Medicines Agency have developed standards and guidelines for companies developing SPCs [68]. These guidelines also outline the issues that local authorities of each country should consider when deciding on registration and reimbursement of SPCs. Overall, SPCs are only approved if the combination of their components is therapeutically warranted, if clinical trial data support dosage, efficacy, safety, and tolerability, and if an analysis of potential advantages and disadvantages has been performed.

CONCLUSION

An SPC combining two antihypertensive drugs from complementary therapeutic classes is currently the gold standard for the first-line treatment of the majority of patients with hypertension and is endorsed by hypertension guidelines in Europe. Though the first-line use of SPCs is expected to improve patient outcomes significantly, the integration of this new approach into routine clinical practice needs to be supported by programs that target physician and patient barriers. To promote the concept of initiating antihypertensive treatment with a tailored, effective, and well tolerated SPC, such initiatives should include country-specific CME programs and lists of available SPCs, print media, and digital materials.

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Conflicts of interest

E.C.: honoraria from Servier as speaker. V.C.: no disclosures. S.G.: no disclosures. I.G.: speaker and member of advisory boards for: Actavis, Amgen, Astra-Zeneca, Bayer, Berlin Chemie, Egis, Mylan, Novartis, Recordati and Servier. L.M.K.: no disclosures. G.L.: lecture honoraria from Bayer, BMS, Gilead, MSD, Novartis, Servier in the last 5 years.

S.L.: during the last five years, S.L.: received honorarium as speaker or chairman, or for participating to advisory board, or received research grants from the following drug companies: Daichii-Sankyo, Menarini, Novartis, Recordati, Sanofi and Servier. E.L.: lecturer and consultant for Servier. S.M.: recipient of the Servier European Grant in Hypertension in 2013. He has also received honoraria for speaking or writing activities from Amgen, Grünenthal, Malesci, Menarini, Merk and Servier. L.M.: lecture honorarium from KRKA, Novo Nordisk, Sandoz and Servier; personal fees from Amgen, Astra Zeneca, Tricida for clinical trial conduction. K.N.: honoraria or consultation fees from Krka, Berlin-Chemie/Menarini, Egis, Sandoz, Idorsia, Polpharma, Gedeon Richter and Servier. D.I.D.O.: speaker – MSD, Pfizer Sanofi, Servier; Local Ad Board – Sanofi; Research and Travel Grants – Pfizer. M.Z.O.: no disclosures. O.G.F.T.: no disclosures. A.V.: consultancy fees and speakers honoraria from Amomed, Boehringer Ingelheim, MSD, Mylan, Novartis, Servier, Zentiva, Worwag. A.V.: speaker honoraria from Astra Zeneca, Bayer, Berlin Chemie Menarini, Boehringer Ingelheim, Egis, Krka, Merck, Mylan, Novartis, Pfizer, Sanofi, Servier, Terapia, Vifor Pharma. J.W.: fees for lectures from KRKA, Sandoz, Berlin Chemie-Menarini, Resmed, Servier. N.Z.: Speaker Honoraria from Berlin Chemie, Menarini, Egis, Krka, Novartis, Pfizer, Sanofi, Servier.

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