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Projecting the long-term benefits of single pill combination therapy for patients with hypertension in five countries

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ABSTRACT

Objective: To project the 10-year clinical outcomes associated with single pill combination (SPC) therapies compared with multi-pill regimens for the management of hypertension in five countries (Italy, Russia, China, South Korea and Mexico).

Methods: A microsimulation model was designed to project health outcomes between 2020 and 2030 for populations with hypertension managed according to four different treatment pathways: current treatment practices (CTP), single drug with dosage titration then sequential addition of other agents (start low and go slow, SLGS), free choice combination with multiple pills (FCC) and combination therapy in the form of a single pill (SPC). Model inputs were derived from the Global Burden of Disease 2017 dataset. Simulated outcomes of mortality, chronic kidney disease (CKD), stroke, ischemic heart disease (IHD), and disability-adjusted life years (DALYs) were estimated for 1,000,000 patients on each treatment pathway.

Results: SPC therapy was projected to improve clinical outcomes over SLGS, FCC and CTP in all countries. SPC reduced mortality by 5.4% in Italy, 4.9% in Russia, 4.5% in China, 2.3% in South Korea and 3.6% in Mexico versus CTP and showed greater reductions in mortality than SLGS and FCC. The projected incidence of clinical events was reduced by 11.5% in Italy, 9.2% in Russia, 8.4% in China, 4.9% in South Korea and 6.7% in Mexico for SPC versus CTP.

Conclusions: Ten-year projections indicated that combination therapies (FCC and SPC) are likely to reduce the burden of hypertension compared with conventional management approaches, with SPC showing the greatest overall benefits due to improved adherence.

Abbreviations: IHME, The Institute for Health Metrics and Evaluation; GBD, Global Burden of Disease, Risk Factors, and Injuries; ACE-inhibitors, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; CTP, current treatment practices; SLGS, single drug with dosage titration first then sequential addition of other agents (start low and go slow); FCC, free choice combination with multiple pills; SPC, single pill combination; CVD, cardiovascular disease; SBP, systolic blood pressure; IHD, ischemic heart disease; CKD, chronic kidney disease; DALYs, disability-adjusted life years.

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1. Introduction

The World Health Organization (WHO) recently estimated that there are approximately 1.13 billion people worldwide living with hypertension (elevated blood pressure), making it the leading preventable risk factor for cardiovascular disease (CVD) [1,2]. The enormous healthcare burden of hypertension is compounded by the challenges associated with managing the condition. Effective management of hypertension patients is often complex, with a multimodal therapeutic concept required to adjust blood pressure, systematic identification of secondary causes of hypertension or pseudo-resistance, lifestyle modification, and assessment of accompanying risk factors and comorbidities [3]. A significant majority (approximately 70%) of hypertensive patients require the combination of at least two antihypertensive agents to reduce blood pressure levels below the recommended goals [4]. For many patients, this can contribute to a substantial pill burden due to the concurrent use of multiple medications. A joint report from the American College of Cardiology and the American Heart Association has stated that, in current cardiology practice, the main obstacles in the management of patients affected by hypertension are comorbidities and poor adherence to pharmacological treatments [5]. One approach to addressing poor adherence could be the use of single pill combination (SPC) therapies to reduce the pill burden faced by patients with hypertension. A number of studies have shown that SPC regimens are associated with improved adherence [6–8]. Moreover, adherence is a key factor in successful hypertension management and high adherence could reduce complications and hospitalizations [9–11]. SPC has also been shown to reduce clinical inertia, one of the main challenges contributing to the low global efficiency of antihypertensive treatment [12].

Currently, there are three strategies commonly used in daily clinical practice for the pharmacological management of hypertension. These include: 1) single drug with dosage titration first, then sequential addition of other agents (start low and go slow), which has been the most widely used strategy (and continues to be so by a large number of doctors and national health systems in countries with low and medium incomes) since it was recommended in its "stepped care" variant by JNC-1 in 1977 and the first ESC/ESH guidelines in 2003; [13,14] 2) free choice combination with multiple pills, which was implicit as a possibility for the second step in the traditional guidelines and was recently indicated by the 2020 ISH guidelines as an essential option when single pill combination therapy is not available; and 3) combination therapy in the form of a single pill, which is indicated preferentially from the first step of the current treatment by most of the guidelines currently accepted in the Americas, Europe and Asia, and it has been included since July 2019 by the WHO in the list of essential medicines [15].

The aim of the present analysis was to evaluate the long-term clinical outcomes associated with different treatment pathways, including SPC therapies in line with ESC guideline recommendations, for the management of hypertension. In the absence of long-term randomized controlled trials directly comparing these strategies, a simulation modeling approach was used based on the best available data to evaluate the long-term outcomes in patients with hypertension in five countries (Italy, Russia, China, South Korea and Mexico).

2. Material and methods

2.1. Modeling overview

Evaluating the long-term effects of different treatment regimens in hypertension can be challenging. In addition to the financial and practical implications of a 10-year clinical study in several thousand patients, there are ethical considerations around the persistent use of any regimens shown to have poorer adherence rates and, as a likely consequence, poorer outcomes. In such situations, computer simulation modeling can be a valuable tool to project outcomes for populations receiving different interventions and evaluate the clinical and economic burden of disease, particularly when it is based on the best available clinical data. The Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease, Risk Factors, and Injuries (GBD) study was the basis of the present analysis and was used to generate data representative of each country's population in terms of age structure, disease patterns, risk factor levels, and treatments, in five countries. These data were then used to feed a long-term microsimulation model to project clinical outcomes (see *Supplementary Material* for details) [16,17]. In the present analysis, simulated populations included non-hypertensive individuals, hypertensive but controlled individuals, and hypertensive not-controlled individuals. Hypertension was defined as systolic blood pressure (SBP) >140 mmHg in untreated individuals. Simulations were designed to evaluate patient-level clinical outcomes for individuals aged ≥40 years from the years 2020–2030 (run in 28-day time steps) according to different treatment pathways. A 10-year time horizon was selected as it was considered long enough to show differences in mortality, cardiovascular and renal outcomes between treatment pathways. This approach is in line with previously published health economic evaluations in hypertension and published guidance [18,19]. The five countries (Italy, Russia, China, South Korea and Mexico) in the present analysis were included in the microsimulation model as they had sufficient data available from the Global Burden of Disease, Risk Factors, and Injuries (GBD) study. They were also selected to ensure representation from a broad geographical area as there is inconsistency between treatment guidelines around the world with respect to the use of SPC therapy first-line.

2.2. Simulated interventions

Simulated patients with hypertension were assumed to be treated with a range of interventions, consisting of single and multiple drug combinations from the following classes: angiotensin converting enzyme inhibitors (ACE-inhibitors), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), beta-blockers and diuretics. Hypertension was managed in the simulations according to four different treatment pathways: current treatment practices (CTP) based on treatment pattern data from the GBD 2017, single drug with dosage titration first then sequential addition of other agents (start low and go slow, SLGS), free choice combination with multiple pills (FCC) and combination therapy in the form of a single pill (SPC) (see Table 1 for details). FCC and SPC regimens were aligned with ESC guidelines [14]. Different adherence rates were used for single and multi-pill regimens in each country based on published data (see *Supplementary Material*).

2.3. Model outputs

The model reported clinical outcomes based on GBD 2017 infrastructure, including mean SBP of the treated population, percentage of patients with controlled blood pressure, percentage of patients who were adherent over the treatment period, stroke events (ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage) and associated mortality, ischemic heart disease (IHD) events (acute myocardial infarction, angina and heart failure) and associated mortality, chronic kidney disease (CKD) and associated mortality, and all-cause mortality. These clinical outcomes were used to estimate disability-adjusted life years (DALYs), a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death (see *Supplementary Material*) [20].

3. Results

Over 10 years, SPC therapy was projected to improve health outcomes compared with SLGS, FCC and CTP in all five countries. Applying ESC recommendations as regards first-step treatment (e.g. FCC and SPC) was projected to improve blood pressure control compared with other treatment regimens. In addition, improved adherence with the single-

Table 1
Summary of antihypertensive treatment scenarios used in the modeling analysis.

Regimen	Description
Current treatment practices (CTP)	• Medications currently in use and the likelihood of use for each, based on data from country-specific literature
Single drug with dosage titration first then sequential addition of other agents (start low and go slow, SLGS)	• Patients are initiated on a single antihypertensive drug, first with dosage titration and then with sequential addition of other agents (up to four drugs in total) to achieve target SBP • For initiation and sequential addition of new agents, drug classes were selected at random from ACE-inhibitors, ARBs, CCBs, beta-blockers and diuretics, and weighted to reflect country-specific usage patterns
Free choice combination with multiple pills (FCC)	Combination therapy is prescribed as follows: • Initiation is at a half-standard dose of both medications in the combination, ramping-up to a standard and then double dose until SBP is controlled • If SBP is still not controlled at a double dose combination, then a third medication is added at the same half, full, then double dose ramp-up schedule
Combination therapy in the form of a single pill (SPC)	• SPC is identical to the FCC scenario except that dual and triple combination therapies are prescribed in the form of a single pill instead of free choice combination of multiple drugs (with the corresponding improvement in adherence associated with a single pill regimen)

Control, or the target SBP, in the scenario is <140 mmHg for all patients in the simulation; ACE-inhibitors, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; SBP, systolic blood pressure.

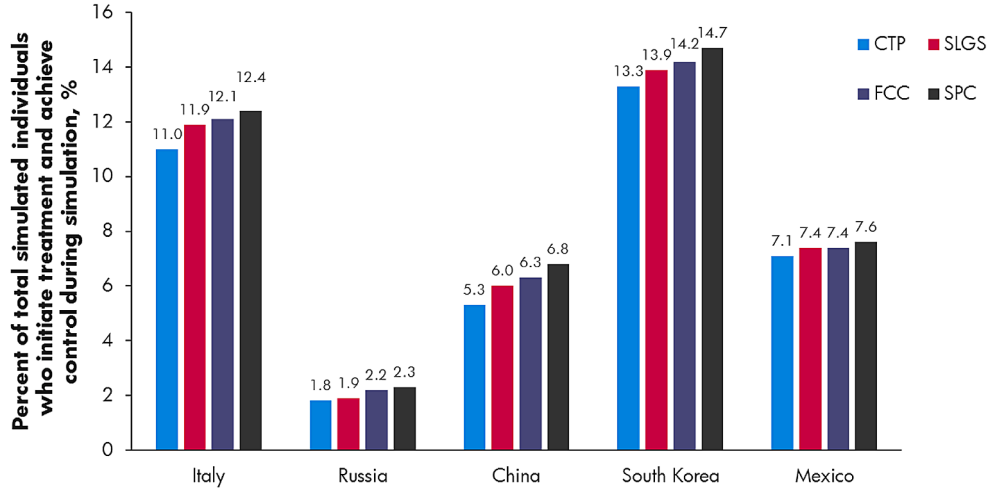
pill regimen was projected to further increase the proportion of patients reaching target SBP levels in all five countries, although absolute rates of patients reaching target varied notably between settings (Fig. 1 and *Supplementary Material*). The lowest absolute values were projected for Russia and China, and these settings were also where the biggest relative increases in patients reaching target SBP were noted, with SPC increasing the number of patients reaching target SBP by 28% relative to CTP in both of these countries (Fig. 2). In the countries with the highest absolute proportions of patients reaching target, Italy and South Korea, SPC was associated with increases of 13% and 11%, respectively, in the number of patients reaching SBP target relative to CTP.

Projected improvements in blood pressure control with SLGS, FCC and SPC versus CTP led to reductions in clinical outcomes of IHD, stroke and CKD over the 10-year time horizon in all five settings, although absolute numbers of clinical events varied widely reflecting geographical variation in treatment practices (Fig. 2). The greatest reductions were projected for the Italian setting, with SPC reducing the incidence of clinical outcomes by 11.5% versus CTP. FCC (9.6%) and SLGS (7.2%) were also associated with substantial reductions in the incidence of clinical outcomes versus CTP in Italy. The most modest benefits in terms of clinical outcomes avoided were projected for South Korea, as CTP was associated with a relatively high rate of patients achieving SBP targets in this setting. The reductions in the 10-year incidence of clinical outcomes versus CTP in this setting were 4.9% for SPC, 3.7% for FCC and 1.6% for SLGS. Reductions in clinical outcomes led to corresponding reductions in DALYs with SPC, FCC and SLGS regimens versus CTP (see *Supplementary Material*).

In all five countries, SPC was projected to reduce mortality relative to all other treatment strategies, although the magnitude of this benefit varied between settings (Fig. 3). In line with other clinical outcomes, the greatest benefits were observed in the Italian setting. SPC therapies were forecast to reduce mortality by 5.4% (Italy), 4.9% (Russia), 4.5% (China), 2.3% (South Korea) and 3.6% (Mexico) versus CTP and showed greater projected reductions in mortality than FCC and SLGS. However, FCC (between 1.7% and 4.5%) and SLGS (between 0.6% and 3.3%) were also projected to reduce mortality relative to CTP in all five settings.

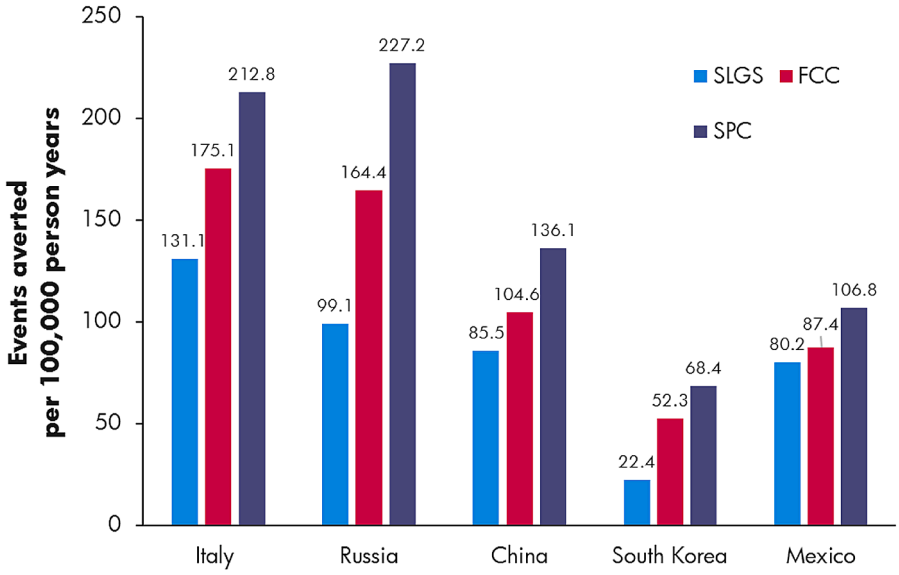
4. Discussion

Based on data from the GBD 2017 study, the present modeling analysis provides evidence that SPC therapies are likely to improve clinical outcomes for patients with hypertension versus CTP in five different countries. The analysis showed that SPC therapies, as well as



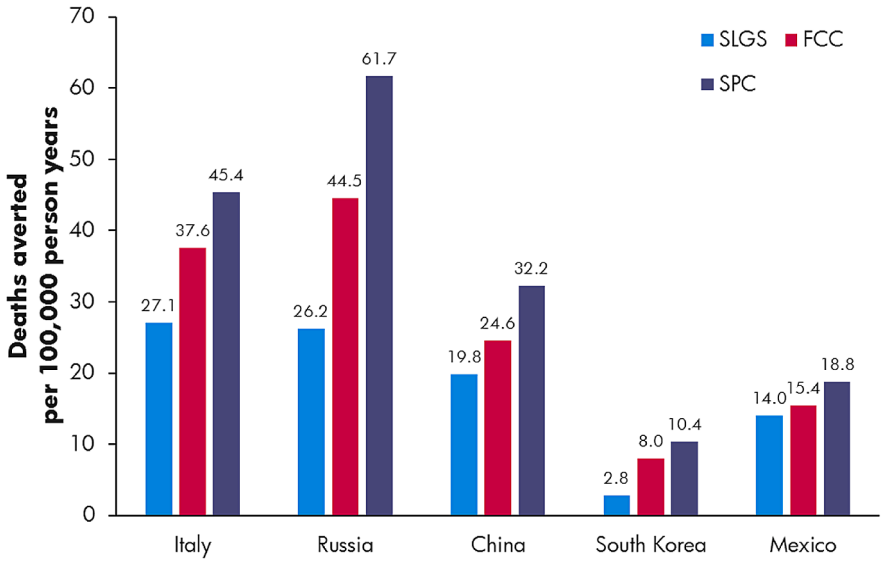
CTP, current treatment practices; SLGS, single drug with dosage titration first then sequential addition of other agents (start low and go slow); FCC, free choice combination with multiple pills; SPC, combination therapy in the form of a single pill

Fig. 1. Percentage of individuals at population level (including both hypertensive and non-hypertensive people) who initiate treatment and achieve target SBP (<140 mmHg) during the simulation by treatment scenario and country.



Clinical events were IHD, stroke and CKD. SLGS, single drug with dosage titration first then sequential addition of other agents (start low and go slow); FCC, free choice combination with multiple pills; SPC, combination therapy in the form of a single pill

Fig. 2. Clinical events averted with different treatments relative to current treatment practices.



SLGS, single drug with dosage titration first then sequential addition of other agents (start low and go slow); FCC, free choice combination with multiple pills; SPC, combination therapy in the form of a single pill

Fig. 3. Deaths averted with different treatment scenarios relative to current treatment practices.

FCC and SLGS regimens, are likely to improve blood pressure control and consequently reduce the risk of clinical events and associated DALYs and mortality relative to the current standard of care. Improved adherence with SPC therapies was a key driver in the analysis, leading to SPC being associated with the greatest benefits relative to CTP. The projections showed that the greatest improvements are likely to be observed in settings where CTP leads to the lowest rates of patients reaching SBP targets. In terms of overall benefits, SPC was projected to result in greater improvements in clinical outcomes than FCC, and both SPC and FCC resulted in greater benefits than SLGS. These observations were true across all five country settings. It is noteworthy that two treatment approaches, SPC and FCC, were associated with the greatest improvements in SBP in the modeling analysis, with improved adherence on SPC therapy providing an additional benefit over FCC.

Hypertension is one of the main risk factors for cardiovascular disease due to its high incidence and direct link to cardiovascular events, and its importance to patients and healthcare providers is well established [21–23]. Despite this, the prevalence of hypertension has remained largely unchanged over the last two decades, primarily due to the sub-optimal use of antihypertensive drugs. As a result, a substantial

proportion of patients fail to achieve blood pressure levels recommended by current guidelines [24]. Adherence represents a key challenge in the optimization of therapy. Non-adherence is common in patients with hypertension and tends to be more common in those with resistant hypertension than in the general hypertensive population [25]. Several studies have shown that single pill therapies are associated with improvements in adherence over multi-pill regimens [8,26,27]. Current guidelines recommend initiating therapy with a combination of two drugs as evidence has shown that combination therapy has the potential to reduce blood pressure more than increasing the dose of a single drug, regardless of the classes of drugs used in combination [14,28]. Moreover, combination therapies are associated with a significantly reduced risk of cardiovascular, coronary and cerebrovascular events compared with monotherapy [26]. In 2017, Iellamo et al. outlined the potential advantages of using an SPC therapy as first-line treatment for hypertension, citing a faster reduction of blood pressure, a greater possibility of reaching target, opposition to the counterregulatory pathways activated by monotherapies, improved tolerability and fewer associated adverse events compared with the uptitration of a single agent [19]. It is clear that SPC regimens could be of great value in efforts to improve the management of patients with hypertension.

Adherence played a similar role in the present modeling analysis. Different adherence rates were used for single and multi-pill regimens in each country based on published data (see *Supplementary Material*). These values are presented as annual probabilities, where zero would be complete non-adherence and 1 would be perfect adherence in the population in each year. For example, a value of 0.409 would be the equivalent of 40.9% of the population being adherent in any given year, with adherence defined as ingestion of ≥80% of prescribed blood pressure medication. Improved adherence was associated with reductions in blood pressure in the population which, along with modeled changes in treatment practices, contributed to differential clinical outcomes for each of the countries and regimens modeled (Figs. 1–3).

In a simulation framework, just as in the real world, differences in the impact of SPC therapy across countries are due to a variety of factors. Without performing sensitivity analyses for each simulation parameter, which would be extremely computationally demanding given the complexity of this simulation, it is not possible to quantify the individual impact of each parameter. However, reviewing the simulation parameters and their role in the simulation may offer a likely explanation of differences in key outcomes. It is logical to assume differences in demographic characteristics and health systems led to the differences observed in SPC therapy outcomes. The greatest reductions in DALYs due to SPC therapy were seen in Italy, and the smallest reductions in South Korea. There are demographic differences between these two settings. For example, 22% of females and 18% of males are aged 60+ years in Italy, while only 16% and 13%, respectively, are aged 60+ years in South Korea. However, the performance of the healthcare system in South Korea would appear to provide the clearest rationale for differences in outcomes due to the intervention. Average SBP among hypertensives in Italy was between 140 and 145 mmHg compared with between 125 and 130 mmHg in South Korea. Based on an internal meta-analysis in the early stages of the present study, this was due in large part to the fact that South Korean patients treated for hypertension had around a 70% probability of achieving blood pressure control compared to a probability of approximately 30% in Italy. While the simulation reported here cannot explain why this was the case (possible reasons could include, for example, more effective conversations between providers and patients and/or easier access and/or more frequent healthcare visits, to name just two) the effect is that there is less room for improvement with SPC in a setting where a high percentage of hypertensive individuals already achieve SBP goals. Despite these differences between settings, the direction of outcomes was consistent across all settings, with SPC therapy projected to improve clinical outcomes over SLGS, FCC and CTP in all five countries.

As with all modeling studies, the present analysis was not without limitations. Data were limited for certain inputs required for the modeling analysis. In particular, data relating to dosing in the CTP scenario were not readily identified in the literature and were not available from the GBD 2017 dataset or drug sales data. Similarly, precise data on the level of adherence with different regimens was lacking. For instance, it was not possible to identify whether patients took none, 30% or 60% of their recommended medication, with patients simply described as adherent or non-adherent in the literature. The present analysis was focused on country-level populations. It could be expected that the findings might vary in certain sub-populations defined clinically, geographically or socio-economically. Such an analysis of sub-populations could be an avenue of future research. For example, to fully capture uncertainty in model input parameters, simulations were performed in a large-scale, general population in the present analysis (1,000,000 simulated patients), which included non-hypertensive, hypertensive but controlled and hypertensive not-controlled simulated patients (with "hypertensive" being an untreated individual with SBP >140 mmHg). Whilst the large number of simulated patients could be considered a strength of the present study, the modeling analysis made no distinction between patients with mild hypertension (SBP <150 mmHg) for which monotherapies might have been enough and patients with moderate or more severe hypertension for whom combination therapy was clearly indicated. That acknowledged, it is important to note that modeling studies are not a clinical decision tool to address each and every clinical situation faced by a physician but instead inform population-level decisions by providing information on how disseminated practice could impact population health. They are, by their very nature, associated with certain limitations and uncertainty in comparison with real-world studies of clinical outcomes. Limitations accepted, it is important to note that computer simulation modeling can play an important role in informing healthcare decision making as they can offer long-term insights across a range of settings and populations that would simply be impracticable to generate from real-world studies. Whilst published guidelines remain the best source of information on the most appropriate therapeutic options for the treatment of hypertension, the present modeling analysis goes further and evaluates health outcomes associated with different treatment pathways in five country settings. It is hoped that this additional information, along with the published guidelines, may be useful when making therapeutic decisions in the management of hypertension in clinical practice.

5. Conclusions

The present analysis provides evidence that, based on 10-year projections of clinical outcomes associated with different antihypertensive treatment pathways, combination therapies (FCC and SPC) are likely to reduce the disease burden of hypertension compared with conventional management approaches. Due to improved adherence, SPC therapies, in line with ESC guidelines, were associated with the greatest overall benefits in terms of improving SBP, reducing clinical events, DALYs and mortality compared with other treatment pathways in five different countries.

CrediT author statement for Int J Cardiol Hypertens

Claudio BORGHI: conceptualization, writing - review and editing **Jiguang WANG:** conceptualization, writing - review and editing **Anton V RODIONOV:** conceptualization, writing - review and editing **Martin ROSAS:** conceptualization, writing - review and editing **Il Suk SOHN:** conceptualization, writing - review and editing **Luis ALCOCER:** conceptualization, writing - review and editing **William J VALENTINE:** writing – original draft **Daniela DEROCHE-CHIBEDI:** conceptualization, methodology, project administration, writing - review and editing, funding acquisition **Denis GRANADOS:** conceptualization, methodology, project administration, writing - review and editing, funding acquisition **Davide CROCE:** conceptualization, writing - review and

editing.

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Declaration of competing interest

C Borghi has given sponsored lecture for Sanofi, Menarini, Servier, Novartis, MSD, Alfasigma and Gilead, and contributed to Advisory Boards for Novartis, Menarini Corporate, Servier, MSD, Berlin-Chemie, Alfasigma, Novo Nordisk, and Daichi-Sankyo. JG Wang reports having received lecture and consulting fees from Merck, Novartis, Omron, Servier, and Takeda. AV Rodionov reports having received lecture and consulting fees from Pfizer, Astra Zeneca, Sanofi, KRKA, Abbott, Novo-Nordisk. L Alcocer receives occasional payments from Sanofi as speaker, or member of advisory boards. WJ Valentine is an employee of Ossian Health Economics and Communications, which has received consulting fees to support the preparation of this manuscript. D Deroche-Chibedi and D Granados are employees of Sanofi. M Rosas, IS Sohn and D Croce have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2021.200102.

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