Кардиоваскулярная терапия и профилактика. 2024;23(3):3328.
doi: 10.15829/1728-8800-2024-3328
ISSN 1728-8800 (Print)
ISSN 2619-0125 (Online)

Differing treatment pathways for the management of hypertension: long-term clinical projections in Russia

Rodionov A. V.[1], Granados D.[2], Kontsevaya A. V.[3]

[1]I. M. Sechenov First Moscow State Medical University. Moscow, Russia; [2]Sanofi R&D, Epidemiology and Benefit-Risk, Chilly-Mazarin, France; [3]National Medical Research Center for Therapy and Preventive Medicine. Moscow, Russia

Aim. Management of hypertension, a major cause of mortality worldwide, is difficult, with adherence a common problem. The present study aimed to estimate the long-term clinical outcomes associated with different treatment pathways in people with hypertension in Russia.
Material and methods. Outcomes were projected over 10 years using a microsimulation model. Four 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 a single pill (SPC)) were evaluated based on the Global Burden of Disease 2017 dataset. Clinical outcomes were simulated for 1,000,000 individuals for each pathway.
Results. Long-term projections associated SPC therapy with reductions in mortality (4.9%), disability-adjusted life years (DALYs, 5.2%), and incidence of complications (including chronic kidney disease, stroke and ischemic heart disease, 9.2%) versus CTP, with greater reductions in all outcomes versus SLGS and FCC. SPC was projected to save 1,193 DALYs compared with CTP over 10 years. Adherence was identified as a key driver in the analysis.
Conclusion. Based on 10-year projections, combination therapies (including SPC and FCC) appear likely to reduce the burden of hypertension compared with conventional treatment options in Russia.
Keywords: adherence, hypertension, blood pressure, antihypertensive agents, Russia, combination therapy.

Relationships and Activities: none.

Acknowledgements. Data extraction and the modeling analysis was performed by the institute for health metrics and evaluation at the University of Washington and supported by funding from Sanofi. Medical writing support was provided by William Valentine and Samuel Malkin at Ossian health economics and communications GMBH (Basel, Switzerland), supported by funding from Sanofi. The authors would like to thank Daniela Deroche-Chidebi at Sanofi for her support throughout the project.

Rodionov A. V. ORCID: 0000-0003-1565-5440, Granados D.* ORCID: 0000-0002-9889-3358, Kontsevaya A. V. ORCID: 0000-0003-2062-1536.

Received: 21/06-2023
Revision Received: 29/11-2023
Accepted: 23/02-2024

CC BY 4.0

For citation: Rodionov A. V., Granados D., Kontsevaya A. V. Differing treatment pathways for the management of hypertension: long-term clinical projections in Russia. *Cardiovascular Therapy and Prevention.* 2024;23(3):3328. doi: 10.15829/1728-8800-2024-3328. EDN WZDHOL

Различные подходы к терапии артериальной гипертензии: отдаленные клинические прогнозы в России

Родионов А. В.[1], Granados D.[2], Концевая А. В.[3]

[1]ФГАОУ ВО "Первый Московский государственный медицинский университет им. И. М. Сеченова" Минздрава России (Сеченовский Университет). Москва, Россия; [2]Sanofi R&D, Epidemiology and Benefit-Risk, Chilly-Mazarin, France; [3]ФГБУ "Национальный медицинский исследовательский центр терапии и профилактической медицины" Минздрава России. Москва, Россия

Цель. Лечение артериальной гипертензии (АГ), ведущей причины смертности в мире, является трудной задачей, которая осложняется высокой распространенностью низкой приверженности терапии. Целью настоящего исследования было оценить долгосрочные клинические прогнозы, связанные с различными подходами к терапии АГ в России.
Материал и методы. Прогностическая модель с использованием метода микростимуляции включала 10 лет. Мы оценивали четыре подхода к лечению (текущий подход к терапии (CTP), использование одного препарата с титрованием дозы с последующим последовательным добавлением других препаратов (SLGS), нефиксированная комбинация препаратов (FCC) и фиксированная комбинация препаратов (SPC)) на основе данных проекта "Глобальное бремя болезней (2017 год)". Прогностическая модель была составлена на 1000000 человек для каждого подхода.
Результаты. В долгосрочной перспективе, применение SPC связано со снижением смертности (4,9%), лет жизни с поправкой на инвалидность (5,2%) и частоты осложнений (включая хроническую болезнь почек, инсульт и ишемическую болезнь сердца, 9,2%) относительно CTP, с более значимым снижением всех исходов по сравнению с SLGS и FCC. Предполагается, что SPC сократит количество лет жизни с поправкой на инвалидность на 1193 по срав-

*Автор, ответственный за переписку (Corresponding author):
e-mail: denis.granados@sanofi.com

[Rodionov A. V. — доцент кафедры факультетской терапии № 1, ORCID: 0000-0003-1565-5440, Granados Denis* — сотрудник, ORCID: 0000-0002-9889-3358, Kontsevaya A. V. — д.м.н., доцент, зам. директора по научной и аналитической работе, ORCID: 0000-0003-2062-1536].

нению с СТР за 10 лет. Приверженность терапии была ключевым показателем в анализе.

Заключение. Исходя из десятилетней прогностической модели, фиксированный и нефиксированный подходы к комбинированной терапии, вероятно, снизят бремя АГ по сравнению с традиционными вариантами лечения в России.

Ключевые слова: приверженность, артериальная гипертензия, артериальное давление, гипотензивные средства, Россия, комбинированная терапия.

Благодарности. Извлечение данных и моделирование были выполнены в Вашингтонском университете при финансовой поддержке компании Sanofi. Поддержка в написании медицинских статей была оказана William Valentine и Samuel Malkin из Ossian Health Economics and Communications GMBH (Базель, Швейцария) при финансовой поддержке компании Sanofi. Авторы выражают благодарность Daniela Deroche-Chidebi из компании Sanofi за ее поддержку на протяжении всего проекта.

Отношения и деятельность: нет.

Поступила 21/06-2023
Рецензия получена 29/11-2023
Принята к публикации 23/02-2024

Для цитирования: Родионов А. В., Granados D., Концевая А. В. Различные подходы к терапии артериальной гипертензии: отдаленные клинические прогнозы в России. *Кардиоваскулярная терапия и профилактика.* 2024;23(3):3328. doi: 10.15829/1728-8800-2024-3328. EDN WZDHOL

ACE — Angiotensin converting enzyme, ARB — Angiotensin receptor blocker, CCB — Calcium channel blocker, CKD — Chronic kidney disease, CTP — Current treatment practices, CVD — Cardiovascular disease, DALY — Disability-adjusted life year, ESC — European Society of Cardiology, ESH — European Society of Hypertension, FCC — Free choice combination with multiple pills, GBD — Global Burden of Disease, Risk Factors, and Injuries, GDP — Gross domestic product, IHD — Ischemic heart disease, ISH — International Society of Hypertension, MMAS-4 — Morisky Medication Adherence Scale, SBP — Systolic blood pressure, SLGS — Start low and go slow, SPC — Single pill combination

Ключевые моменты

Что известно о предмете исследования?

- Клиническое и экономическое бремя артериальной гипертензии, ведущего предотвратимого фактора риска сердечно-сосудистых заболеваний и связанной с ними смертности, в России остается высоким, а контроль над ней остается недостаточным, несмотря на многочисленные попытки повысить осведомленность и приверженность к лечению.

Что добавляют результаты исследования?

- Десятилетняя прогностическая модель показала, что использование фиксированных комбинаций связана со снижением смертности и частоты осложнений (включая хроническую болезнь почек, инсульт и ишемическую болезнь сердца) по сравнению с текущим подходом к терапии, с более значимым снижением всех исходов по сравнению с терапией одним препаратом с титрованием дозы и последовательным добавлением других препаратов и нефиксированной комбинированной терапией.
- Комбинированная терапия, вероятно, снизит бремя АГ по сравнению с традиционными вариантами лечения в России, при этом повышение приверженности терапии является ключевым фактором благоприятного прогноза.

Key messages

What is already known about the subject?

- The clinical and economic burden of hypertension, the leading preventable risk factor for cardiovascular disease and associated mortality, is high in Russia, and its control remains insufficient despite numerous attempts to raise awareness of the condition and efforts to improve treatment adherence.

What might this study add?

- Ten-year projections indicated that single-pill combination therapy would be associated with reductions in mortality and incidence of complications (including chronic kidney disease, stroke and ischemic heart disease) versus current treatment practices, with greater reductions in all outcomes versus single drug with dosage titration first, then sequential addition of other agents and free choice combination with multiple pills.
- Combination therapies (including single-pill and free choice) appear likely to reduce the burden of hypertension compared with conventional treatment options in Russia, with improved adherence a key driver of outcomes.

Introduction

Hypertension (elevated blood pressure) is the leading preventable risk factor for cardiovascular disease (CVD) and associated mortality, with more than 1 billion people living with the condition worldwide[1] [1]. Recent studies have indicated that Russia and other Eastern European countries are responsible for a large proportion of the global burden of hypertension, and that its control remains insufficient despite numerous attempts to raise awareness of the condition [2, 3]. Indeed, a 2017 evaluation of four regions in Russia (Krasnodar, Omsk and Ryazan, and the Republic of Karelia) estimated that the age-standardized prevalence of hypertension to be 44%, with 33% of patients living with blood pressure

[1] World Health Organization. Hypertension Fact Sheet, September 13, 2019. Available at: https://www.who.int/news-room/fact-sheets/detail/hypertension. Accessed on March 20, 2020.

values ⩾140/90 mm Hg [2]. Moreover, only 50% of patients who were prescribed antihypertensive therapy were estimated to be achieving effective treatment [2]. Further published data has indicated that the probabilities of being hypertensive, being hypertensive and receiving treatment, and being hypertensive and having controlled blood pressure are low in in Russia [4-6]. The economic burden associated with hypertension is also substantial, accounting for 1% of Russian gross domestic product (GDP) in 2016, higher than any other major chronic non-communicable disease [7, 8].

Overcoming the burden of hypertension is limited by inefficiencies in management of the condition. Inefficiencies can manifest in the identification of underlying causes and risk factors, lifestyle modification, and prescription of appropriate multimodal therapy, with a majority (70%) of hypertensive individuals requiring at least two antihypertensive agents to achieve target blood levels [9, 10]. Indeed, a 2017 regional study in Russia indicated that improved diagnosis and control of hypertension can lead to marked improvements in blood pressure control rate, reductions in the percentage of patients with a systolic blood pressure (SBP) ⩾180 mm Hg, and reductions in stroke incidence rate [3]. However, combination therapy increases the burden of self-administration on antihypertensive individuals, which has been associated with reduced adherence and, consequently, reduced blood pressure control [9]. Indeed, data from four Russian regions have indicated that only 25% of patients achieve blood pressure control [2]. Moreover, a review of studies evaluating antihypertensive treatment in Russia found that adherence varied from 11-44% (when measured using the Morisky Medication Adherence Scale (MMAS-4)) [11]. Improving adherence to antihypertensive agents and, consequently, blood pressure control, could therefore elucidate substantial clinical benefits for individuals with hypertension in Russia [1].

Recommendations for the treatment of hypertension in Russia follow the recent guidance published by the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) [12]. These guidelines recommended initiation of an antihypertensive treatment with a two-drug combination, preferably in a single pill combination (SPC), with exceptions in frail, older patients and those with grade 1 hypertension (e.g., SBP <150 mm Hg) [11]. This is in contrast to traditional treatment strategies recommended in previous guidelines, such as single drug with dosage titration first, then sequential addition of other agents (start low and go slow (SLGS)), which was recommended in its "stepped care" variant by JNC-1 in 1977 and the first ESC/ESH guidelines in 2003; and free choice combination with multiple pills (FCC), which was previously specified as an intensification treatment option but has now been indicated as an essential option when SPC therapy is not available by the International Society of Hypertension (ISH) [13-15]. Moreover, the updated guidance placed strong emphasis on the importance of evaluating treatment adherence as a major cause of poor blood pressure control.

In the absence of data from long-term clinical trials, which can be difficult to perform due to financial, practical and ethical concerns, modeling studies can help to inform decision making around hypertensive treatment strategies by projecting the impacts of different therapies on blood pressure and the incidence of associated clinical events. Previous modeling studies have evaluated the long-term clinical outcomes associated with the management of hypertension, including an analysis projecting outcomes for different therapies in five countries (Italy, China, South Korea, Mexico and Russia) and a study investigating the effects of different treatment programs on cardiovascular outcomes in Russia [16, 17]. However, the present paper aimed to focus on bespoke, 10-year projections for the Russian setting, alongside additional and complementary data, to better emphasize the findings of the analysis and provide pertinent information for physicians and healthcare payers in the country. The aim of this specific analysis was therefore to model and estimate the long-term clinical outcomes associated with different treatment pathways for hypertension in the Russian setting, with a particular focus on the effects of adherence with SPC versus multiple pill combinations.

Material and methods

Modeling approach

The long-term effects of antihypertensive agents can be difficult to evaluate in real-world practice or clinical trials. A 10-year study enrolling thousands of people with hypertension is associated with substantial practical and financial challenges, as well as ethical implications of continuing use of regimens associated with poor adherence and, consequently, poor outcomes. In absence of long-term clinical trial data or real-world evidence assessing different antihypertensive agents, a microsimulation modeling approach was deemed the best way of evaluating the long-term effects of antihypertensive agents over 10 years. Computer simulation modeling can be a valuable tool for projecting health and economic outcomes for populations receiving different interventions, particularly when informed by the best available data.

The microsimulation approach has been previously utilized to estimate the long-term clinical outcomes of antihypertensive pathways in five different countries [15]. A microsimulation model was specifically developed by the Institute for Health Metrics and Evaluation (IHME) to leverage population health data generated from the Global Burden of Disease, Risk Factors, and Injuries (GBD) study, to project outcomes related to health intervention scenarios and provide decision-makers with guidance on how to optimize healthcare in the Russian setting[2]. For each simulation,

[2] Institute for Health Metrics and Evaluation Global Burden of Disease (GBD) 2017. Available at: http://www.healthdata.org/gbd/gbd-2017-resources. Accessed on March 20, 2020.

Table 1

Summary of antihypertensive treatment scenarios used in the modeling analysis

Regimen	Description	Applied adherence rate		
		Age <45 years	Age 45-60 years	Age >60 years
CTP	• Medications currently in use and the likelihood of use for each, based on data from country-specific literature	0.136	0.326	0.516
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	0.136	0.326	0.516
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	0.136	0.326	0.516
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 FCC of multiple drugs (with the corresponding improvement in adherence associated with a single pill regimen)	0.359	0.500	0.641

Note: Control, or the target SBP, in the scenario is <140 mm Hg for all patients in the simulation, ACE-inhibitors — angiotensin converting enzyme inhibitors, ARBs — angiotensin receptor blockers, CCBs — calcium channel blockers, CTP — current treatment practices, FCC — free choice combination with multiple pills, SBP — systolic blood pressure, SLGS — start low and go slow, SPC — single pill combination therapy.

the model was used to generate a population of simulated individuals based on age, gender and health characteristics (SBP, history of ischemic heart disease (IHD), intracerebral or subarachnoid hemorrhage (stroke), chronic kidney disease (CKD) and disability) from Russia-specific data from the GBD 2017. In the model, simulants were exposed to a risk of background mortality, and could transition between health states in the model based on probabilities of developing complications associated with each simulated patient's risk factor profile. Transition probabilities for the model (based on rates of IHD incidence and excess mortality, CKD incidence and excess mortality, stroke incidence and excess mortality, and background mortality) were also derived from the GBD 2017. Simulants included non-hypertensive individuals, hypertensive but controlled individuals, and hypertensive not-controlled individuals, with hypertension defined as SBP >140 mm Hg in untreated individuals. Simulations were designed to evaluate patient-level clinical outcomes for individuals aged ⩾40 years over 10 years (run in 28-day time steps) according to four different treatment pathways (see *Modeled interventions*). A 10-year time horizon was used to demonstrate sufficient differences in mortality, cardiovascular and renal outcomes between treatment pathways.

Input data

Clinical input data were primarily based on data from the GBD 2017, for which the analytic process has been previously described [18-20]. Utilized data included age and gender distributions, mortality rates, health status, SBP, rates of stroke, IHD, CKD and associated mortality, treatment attributes and healthcare services utilization rates. Transition probabilities between states in the model were also derived from the GBD 2017. Adherence was defined in terms of the percentage of patients who took medication for hypertension on ⩾80% of the days they were prescribed, with different adherence rates for each treatment pathway based on published data (Table 1) [4, 10, 21]. Adherence values were included as annual probabilities, where zero would be complete non-adherence and 1 would be perfect adherence in the population each year.

Modeled interventions

Modeled treatments for simulated individuals were designed to capture a range of interventions, comprising both single and multiple drug combinations. Captured medication classes included angiotensin converting enzyme inhibitors (ACE-inhibitors), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), beta-blockers and diuretics.

Four different treatment pathways were modeled: 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). The four pathways are described in detail in Table 1.

Model outputs

Included clinical outcomes captured mean SBP of the treated population, percentage of patients with controlled blood pressure, percentage of patients who were adherent over the treatment period, all-cause mortality, and clinical events, which encompassed stroke events (ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage), IHD events (acute myocardial infarction, angina and heart failure), and CKD. Clinical events also comprised stroke-, IHD- and CKD-related mortality. 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[3].

Compliance with ethics guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

[3] World Health Organization: Health statistics and information systems. Available at: https://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/. Accessed on April 9, 2020.

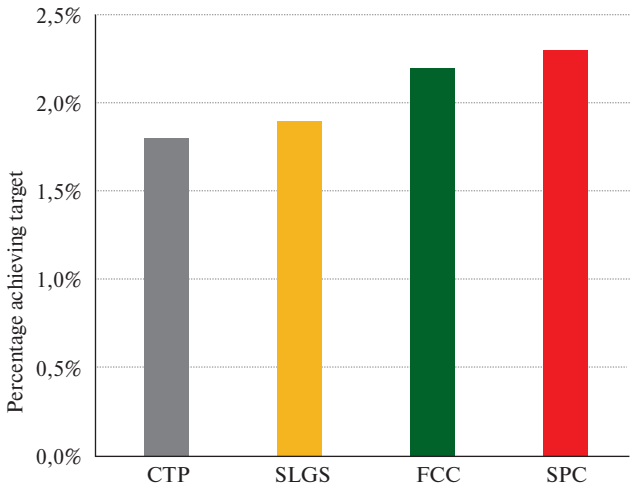

Figure 1 Percentage of simulated individuals at population level (including both hypertensive and non-hypertensive individuals) initiating treatment and achieving blood pressure control (SBP <140 mm Hg) over 10 years.

Note: CTP — current treatment practices, FCC — free choice combination with multiple pills, SBP — systolic blood pressure, SLGS — start low and go slow, SPC — single pill combination therapy.

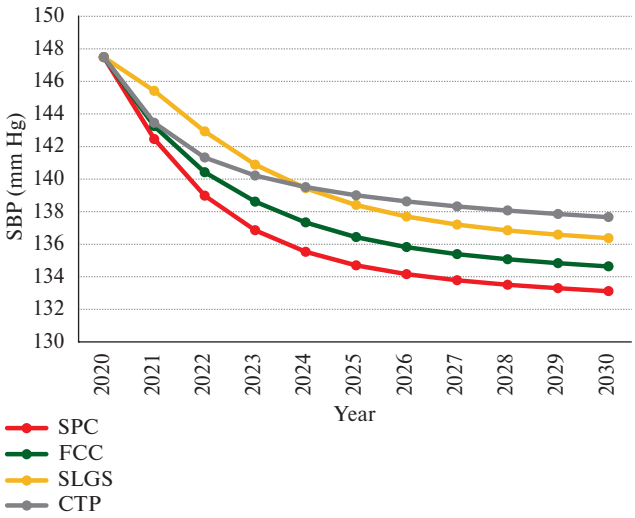

Figure 2 Average SBP in treated individuals over the course of the 10-year analysis.

Note: CTP — current treatment practices, FCC — free choice combination with multiple pills, SBP — systolic blood pressure, SLGS — start low and go slow, SPC — single pill combination therapy. It is important to note that, as the simulation begins, new simulants who had high blood pressure but were not yet on treatment are added to the pool of people on treatment. The addition of simulants with uncontrolled blood pressure slows the reduction in average SBP plotted here, especially initially.

Results

SPC, FCC and SLGS were all projected to improve health outcomes compared with CTP over 10 years, with SPC therapy demonstrating the largest clinical benefits due to the greatest number of simulated individuals achieving blood pressure control (Figure 1). At population level, the average number of days taken to achieve blood pressure control after initiating treatment was also lowest with SPC, with patients achieving control after 827 days. Patients receiving CTP took an average of 833 days to achieve control, while patients receiving FCC and SLGS took an average of 856 and 1,031 days, respectively. Average SBP was lowest with SPC over the duration of the analysis, followed by FCC (Figure 2). CTP was associated with the highest average SBP after 10 years, but lower than SLGS for the first 4 years of the analysis (Figure 2). Reductions in SBP and time to achieve control with all treatment pathways, particularly initially, were mitigated by the addition of newly diagnosed but not yet treated simulated hypertensive individuals throughout the analysis.

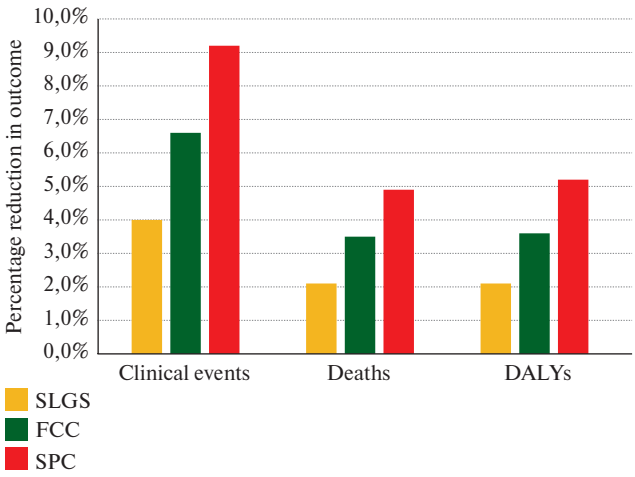

Figure 3 Percentage reductions in clinical events, deaths and DALYs with different treatments relative to current treatment practices.

Note: DALYs — disability-adjusted life years, FCC — free choice combination with multiple pills, SLGS — start low and go slow, SPC — single pill combination therapy. Clinical events captured stroke events (ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage) and associated mortality, ischemic heart disease events (acute myocardial infarction, angina and heart failure) and associated mortality, and chronic kidney disease and associated mortality.

Reductions in SBP led to reductions in clinical events in all pathways. The percentage of individuals experiencing a clinical event (stroke, IHD or CKD) was lowest with SPC (10.4%), followed by FCC (10.7%), SLGS (11.0%) and CTP (11.4%). SPC, FCC and SLGS were associated with reductions in the incidence of clinical events of 227, 164 and 99 events per 100,000 person-years, respectively, versus CTP. SPC, FCC and SLGS were therefore associated with reductions in the incidence of clinical events of 9.2%, 6.6% and 4.0%, respectively, versus CTP (Figure 3).

Mortality was also influenced by reductions in SBP and the incidence of clinical events. Mortality associated with clinical events was substantially reduced with SPC therapy, with 62 deaths averted per 100,000 person-years versus CTP. FCC and SLGS were also associated with reduced mortality, with 45 and 26 deaths averted per 100,000 person-years, respectively, versus CTP. Mortality was therefore projected to be 4.9%, 3.5% and 2.1% lower with SPC, FCC and SLGS, respectively, versus CTP (Figure 3).

Combining the incidence of clinical events and early mortality showed that SPC was associated with 1,193 DALYs averted per 100,000 person-years versus CTP. FCC and SLGS were associated with 834 and 476 DALYs averted per 100,000 person-years, respectively, versus CTP. Projected DALYs were therefore estimated to be 5.2%, 3.6% and 2.1% lower with SPC, FCC and SLGS, respectively, versus CTP (Figure 3). Consistently improved outcomes with SPC were due to the improved adherence, and consequent improved blood pressure, versus FCC, SLGS and CTP.

Discussion

Based on long-term projections, SPC therapies are likely to improve clinical outcomes for people with hypertension versus CTP in Russia. SPC, FCC, and even SLGS regimens that are no longer recommended by current guidelines, are likely to improve blood pressure control versus CTP and thereby reduce the risk of adverse clinical events and associated DALYs and mortality. The high number of days to achieve blood pressure control following treatment initiation was due to new untreated patients continually entering the model over the course of the analysis — but this outcome was still lowest with SPC therapy.

Hypertension in Russia is responsible for a substantial proportion of the global clinical burden, with an estimated age-standardized prevalence of 44% and 33% of individuals living with blood pressure values ⩾140/90 mm Hg [2]. However, with only 50% of patients who are prescribed antihypertensive therapy estimated to be achieving effective treatment, and only 25% of patients achieving blood pressure control, there is significant scope for improving health outcomes for hypertensive individuals in Russia [2]. The present analysis has shown that SPC and FCC were associated with the greatest improvements in SBP, with improved adherence a key driver of the projected clinical benefits, and a differentiating factor versus FCC. Adherence was highlighted as having a large scope for improvement in a recent Russian study that found adherence varied between 11-44% on the MMAS-4 scale, a widely used, generic, medication-taking behavior scale originally developed for individuals with hypertension [10, 22]. With combination therapy often required in hypertensive individuals, and the benefits associated with blood pressure control, the present analysis has shown that therapies that can reduce the burden on patients by combining efficacious compounds in the form of a single pill (thereby improving adherence) can have a marked impact on blood pressure control, incidence of complications and associated DALYs [3, 8, 9]. Use of SPC therapies could therefore decrease non-adherence and elucidate substantial clinical benefits for individuals with hypertension in Russia [1].

That acknowledged, improvements in adherence are possible beyond use of SPC that would further benefit populations with hypertension in Russia, and this unmet need should be the focus of future research in the country. Indeed, a 2020 systematic review of Russian studies indicated that the most effective ways to improve adherence are patient education and the use of medications in fixed combinations [22]. A recent population-based study in Russia also found that a high prevalence of untreated hypertension, particularly in men [23]. Moreover, a large proportion of untreated, hypertensive individuals were unaware of their condition. Recommended initiatives from this study included an annual general health check for individuals aged ⩾40 years and extending healthcare professional hours to allow increased contact time with patients, as well as indicating that more effective strategies could be employed to better detect hypertensive individuals and improve adherence to antihypertensive therapies [24]. While developments in healthcare accessibility could help to improve diagnosis, SPC treatments could offer solutions to individuals with uncontrolled blood pressure due to adherence-related issues, and future studies should evaluate the impact of increased prescription of these medications to hypertensive populations in Russia.

Current treatment guidelines with Russia follow recommendations published by the ESC/ESH in 2018, which indicate SPC therapy as an essential therapy in non-frail and non-elderly individuals [11]. The present analysis has indicated that wider provision of SPC therapy would greatly improve health outcomes for people with hypertension in Russia. Even wider use of more traditional treatment strategies, such as SLGS or FCC, was shown to substantially improve health outcomes. These findings demonstrate the importance of appropriate prescription of medications and implementing methods to regularly evaluate and maintain adherence levels, as indicated in the ESC/ESH guidelines and shown by both the results of the present analysis and numerous published studies [3, 8, 9, 11].

DALYs are a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death, and are a way of combining morbidity and mortality into a single outcome measure. For example, a person with a BMI <25 kg/m^2 has 1.04 fewer DALYs than a person with a BMI >30 kg/m^2, or a person receiving a kidney transplant is associated with 1.4 fewer DALYs compared with chronic dialysis [25, 26]. Use of DALYs puts the findings of the present study into context and allows comparison across disease areas, demonstrating the magnitude of the clinical benefits associated with SPC therapy.

A previous publication has evaluated the long-term outcomes associated with different treatment strategies for hypertension in five countries, including Russia [15]. The present study aims to build on that analysis by illustrating and discussing outcomes specifically for the Russian setting, and to provide pertinent information for physicians, patients, and healthcare payers in the

country, with novel data in the present analysis capturing the time to achieving blood pressure control and average SBP levels over time with the four evaluated treatment strategies. Discussing these results specifically for Russia, particularly given the large prevalence of hypertension and the unmet treatment need in the country, provides a better background for contextualizing outcomes in terms of the improvements available to the hypertensive population in the Russian setting.

A limitation of the study was that the GBD 2017, as well as additional searches in the published literature, did not elucidate data relating to dosing for the CTP scenario, or precise adherence data for the different treatment regimens. Adherence in the analysis was also modeled as a binary outcome, which may not reflect clinical practice where patients can have varying levels of adherence. However, data limitations are often inherent in all modeling analyses, and in absence of long-term clinical trial data (which are often highly costly and associated with substantial ethical dilemmas such as non-intensification of poorly controlled individuals), modeling studies arguably represent the best basis for decision making by healthcare payers and professionals.

Conclusion

Based on long-term projections, the present analysis indicates that combination therapies (including SPC and FCC) are likely to reduce the burden of hypertension compared with conventional treatment options in Russia. Improved adherence was the key driver of benefits, with SPC therapies associated with the greatest overall benefits in terms of improving SBP and reducing clinical events, DALYs and mortality compared with other treatment pathways.

Acknowledgements. Data extraction and the modeling analysis was performed by the institute for health metrics and evaluation at the University of Washington and supported by funding from Sanofi. Medical writing support was provided by William Valentine and Samuel Malkin at Ossian health economics and communications GMBH (Basel, Switzerland), supported by funding from Sanofi.

The authors would like to thank Daniela Deroche-Chidebi at Sanofi for her support throughout the project.

Relationships and Activities: none.

Литература/References

1. Stanaway JD, Afshin A, Gakidou E, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392:1923-94. doi:10.1016/S0140-6736(18)32225-6. Erratum in: Lancet. 2019;393(10167):132. Erratum in: Lancet. 2019;393(10190):e44.
2. Ionov MV, Zvartau NE, Konradi AO. Status of hypertension in Russia and Eastern Europe. eJ Cardiol Pract. 2019;17(24).
3. Balanova YA, Shalnova SA, Imaeva AE, et al. Prevalence, Awareness, Treatment and Control of Hypertension in Russian Federation (Data of Observational ESSERF-2 Study). Ration Pharmacother Cardiol. 2019;15(4):450-66. (In Russ.) Баланова Ю. А., Шальнова С. А., Имаева А. Э. и др. Распространенность артериальной гипертонии, охват лечением и его эффективность в Российской Федерации (данные наблюдательного исследования ЭССЕ-РФ-2). Рациональная Фармакотерапия в Кардиологии. 2019;15(4):450-66. doi:10.20996/1819-6446-2019-15-4-450-466.
4. Mozheyko M, Eregin S, Danilenko N, et al. Hypertension in Russia: Changes Observed After 4 Years of a Comprehensive Health System Improvement Program in the Yaroslavl Region. Clin Hypertens (Greenwich). 2017;19(2):198-204. doi:10.1111/jch.12885.
5. Cybulsky M, Cook S, Kontsevaya AV, et al. Pharmacological treatment of hypertension and hyperlipidemia in Izhevsk, Russia. BMC Cardiovasc Disord. 2016;16:122. doi:10.1186/s12872-016-0300-9.
6. Oshchepkova EV, Lazareva NV, Kantorova AU, Chazova IE. Treatment of patients with arterial hypertension in primary health care (according to the Russian Arterial Hypertension Register). J Hypertens. 2017;35:e214.
7. Gheorghe A, Griffiths U, Murphy A, Legido-Quigley H, Lamptey P, Perel P. The economic burden of cardiovascular disease and hypertension in low- and middle-income countries: a systematic review. BMC Public Health. 2018;18(1):975. doi:10.1186/s12889-018-5806-x.
8. Kontsevaya AV, Mukaneeva DK, Myrzamatova AO, et al. Economic damage of risk factors associated with morbidity and mortality from major chronic non-communicable diseases in Russia in 2016. Cardiovascular Therapy and Prevention. 2020;19(1):48-55. (In Russ.) Концевая А. В., Муканеева Д. К., Мырзаматова А. О. и др. Экономический ущерб факторов риска, обусловленный их вкладом в заболеваемость и смертность от основных хронических неинфекционных заболеваний в Российской Федерации в 2016 году. Кардиоваскулярная терапия и профилактика. 2020;19(1):48-55. doi:10.15829/1728-8800-2020-1-2396.
9. Kulenthiran S, Ewen S, Böhm M, Mahfoud F. Hypertension up to date: SPRINT to SPYRAL. Clin Res Cardiol. 2017;106(7):475-84. doi:10.1007/s00392-017-1095-0.
10. Guerrero-García C, Rubio-Guerra AF. Combination therapy in the treatment of hypertension. Drugs Context. 2018;7:212531. doi:10.7573/dic.212531.
11. Bochkareva EV, Butina EK, Kim IV, et al. Adherence to antihypertensive medication in Russia: a scoping review of studies on levels, determinants and intervention strategies published between 2000 and 2017. Arch Public Health. 2019;77(1):43. doi:10.1186/s13690-019-0366-9.
12. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021-104. doi:10.1093/eurheartj/ehy339. Erratum in: Eur Heart J. 2019;40(5):475.
13. Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: a cooperative study. JAMA. 1977;237(3):255-61.
14. European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of

Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens. 2003; 21(6):1011-53. doi:10.1097/00004872-200306000-00001. Erratum in: J Hypertens. 2003;21(11):2203-4. Erratum in: J Hypertens. 2004;22(2):435.

15. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. J Hypertens. 2020;38(6):982-1004. doi:10.1097/HJH.0000000000002453.
16. Borghi C, Wang J, Rodionov AV, et al. Projecting the long-term benefits of single pill combination therapy for patients with hypertension in five countries. Int J Cardiol Cardiovasc Risk Prevent. 2021;10:200102. doi:10.1016/j.ijcrp.2021.200102.
17. Shum K, Alperin P, Shalnova S, et al. Simulating the impact of improved cardiovascular risk interventions on clinical and economic outcomes in Russia. PLoS One. 2014;9(8):e103280. doi:10.1371/journal.pone.0103280.
18. Dicker D, Nguyen G, Abate D, et al. Global, regional, and national age-sex-specific mortality and life expectancy, 1950–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018;392:1684-735. doi:10.1016/S0140-6736(18)31891-9. Erratum in: Lancet. 2019;393(10190):e44.
19. Roth GA, Abate D, Abate KH, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018;392:1736-88. doi:10.1016/S0140-6736(18)32203-7. Erratum in: Lancet. 2019;393(10190):e44. Erratum in: Lancet. 2018;392(10160):2170.
20. James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018;392:1789-858. doi:10.1016/S0140-6736(18)32279-7. Erratum in: Lancet. 2019;393(10190):e44.
21. Kontsevaya A, Romanenko T, Vygodin V, Fitilev SB. Evaluation of the regularity of antihypertensive drugs usage as a component of treatment adherence in outpatients of a specialized cardiology center. Ration Pharmacother Cardiol. 2015;11(3):238-46. (In Russ.) Концевая А. В., Романенко Т. С., Выгодин В. А., Фитилев С. Б. Анализ регулярности приема антигипертензивной терапии как компонента приверженности лечению у амбулаторных пациентов специализированного кардиологического учреждения. Рациональная Фармакотерапия в Кардиологии. 2015;11(3):238-46. doi:10.20996/1819-6446-2015-11-3-238-246.
22. Bochkareva EV, Butina EK, Kim IV, et al. Adherence to Antihypertensive Therapy: A Systematic Review of Russian Prospective Studies from 2000 to 2019. Ration Pharmacother Cardiol. 2020;16(5):770-9. (In Russ.) Бочкарева Е. В., Бутина Е. К., Ким И. В. и др. Приверженность к антигипертензивной терапии: систематический обзор российских проспективных исследований с 2000 по 2019 гг. Рациональная Фармакотерапия в Кардиологии. 2020;16(5):770-9. doi:10.20996/1819-6446-2020-10-20.
23. Petersen J, Kontsevaya A, McKee M, et al. Untreated hypertension in Russian 35-69 year olds — a cross-sectional study. PLoS One. 2020;15(5):e0233801. doi:10.1371/journal.pone.0233801.
24. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986;24(1):67-74. doi:10.1097/00005650-198601000-00007.
25. May AM, Struijk EA, Fransen HP, et al. The impact of a healthy lifestyle on Disability-Adjusted Life Years: a prospective cohort study. BMC Med. 2015;13:39. doi:10.1186/s12916-015-0287-6.
26. Yaghoubi Fard S, Goudarzi R, Etminan A, et al. Cost-effectiveness analysis of dialysis and kidney transplant in patients with renal impairment using disability adjusted life years in Iran. Med J Islam Repub Iran. 2016;30:390.