Original article

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Estimating the impact of single pill combination therapy for hypertension: projections of patient outcomes in Italy

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Introduction Hypertension affects almost a third of the Italian population and is a major risk factor for cardiovascular disease. Management of hypertension is often hindered by poor adherence to complex treatment regimens. This analysis aimed to estimate the 10-year clinical outcomes associated with single pill combination (SPC) therapies compared with other treatment pathways for the management of hypertension in Italy.

Methods A microsimulation modeling approach was used to project health outcomes over a 10-year period for people with hypertension. Input data for 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 SPC] were sourced from the Global Burden of Disease 2017 data set. The model simulated clinical outcomes for 1 000 000 individuals in each treatment pathway, including mortality, chronic kidney disease (CKD), stroke, ischemic heart disease (IHD) and disability-adjusted life years (DALYs).

Results Through improved adherence, SPC was projected to improve clinical outcomes versus CTP, SLGS, and FCC. SPC was associated with reductions in mortality, incidence of clinical events, and DALYs versus CTP of 5.4%, 11.5%, and 5.7%, respectively. SLGS and FCC were associated with improvements in clinical outcomes versus CTP, but smaller improvements than those associated with SPC.

Conclusions Over 10 years, combination therapies (including SPC and FCC) were projected to reduce the burden of hypertension compared with conventional management approaches in Italy. Due to higher adherence, SPC was associated with the greatest overall benefits versus other regimens.

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Keywords: antihypertensive agents, blood pressure, combination therapy, hypertension, Italy, single pill

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Introduction

Hypertension, defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, is the leading preventable risk factor for cardiovascular disease, and affects approximately 1.13 billion people around the world.[1,2] Globally, in 2017 high SBP accounted for 10.4 million deaths and 218 million disabilityadjusted life years (DALYs): more than smoking, high fasting plasma glucose, and high body mass index (BMI).[2] Hypertension is associated with an increased risk of cardiovascular disease, including heart failure, peripheral arterial disease, stable angina, stroke, and myocardial infarction.[3,4] Additionally, people with hypertension develop cardiovascular disease at an earlier age than people with normal blood pressure (BP).[3] Effective management of hypertension can be challenging and approximately 70% of patients require a combination of at least two antihypertensive agents to reduce BP levels below the recommended goals.[5] Approximately 25% require three antihypertensive agents.[5] Globally, between 1990 and 2019, less than half of patients treated for hypertension achieved BP control, and one reason for this was poor adherence to treatment.[6,7] Poor adherence to treatment can result in uncontrolled hypertension, which increases the risk of cardiovascular disease.[8]

In 2017, an estimated 31% of Italian adults had hypertension.[9] Only 61% of Italians with hypertension were receiving treatment and BP was controlled in only 34% of those patients.[10] Such low control rates in patients receiving therapy may be a result of poor adherence to treatment. In the management of hypertension in Italy, monotherapy was the first-line treatment for 72.5% of patients, which may be a result of excessive confidence in the efficacy of monotherapy, and approximately 55% discontinued treatment at 12 months. Combination therapy was first-line treatment in the remaining 27.5% of cases and was discontinued by 37% of patients within 12 months, with discontinuation higher amongst those receiving free combinations versus fixed combinations.[11] The resulting elevated risk of cardiovascular disease is compounded by the high prevalence (83%) of additional cardiovascular risk factors (e.g. diabetes, renal disease, obesity) amongst the Italian population often requiring additional drug treatments.[12,13]

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Complex treatment regimens and the high pill burdens of hypertension therapies have been often cited as causes of low treatment adherence.[7,11] Single pill combination (SPC) therapies can reduce pill burden for patients with hypertension and are associated with improved adherence.[14–16] By comparison multimodal therapies have been linked to reduced adherence and poor BP control due to the increased pill burden.[6] A systematic review of randomized controlled trials showed a 27% improvement in BP control with two-drug SPC therapies compared with monotherapy, together with no increase in patient withdrawals due to adverse events.[17]

Currently, antihypertensive treatment recommendations in Italy follow the 2018 guidance published by the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH).[18] The ESC-ESH 2018 guidelines stressed the need for improved BP control through multiple methods such as lowering SBP target ranges, using combination drug therapy, and improving poor adherence through the use of SPC therapies.[18] In the ESC-ESH 2018 guidelines patients were recommended to begin a two-drug combination with exceptions for frail, elderly patients and those with grade 1 hypertension (e.g. SBP $<$ 150 mmHg).[18] For treatment with a two-drug combination, SPC was recommended as the preferred treatment. Similar recommendations were included in the more recent guidelines released by the International Society of Hypertension suggesting a progressive increase from low-dose to high-dose combinations.[19] The guidelines emphasized that poor adherence was directly associated with the number of pills prescribed, and stressed the importance of the detection of patients with poor adherence to treatment, as poor adherence can lead to an increased risk of cardiovascular complications.[18] Additionally, the guidelines also recommended less conservative treatment of BP in patients $\geq$65 years, with new SBP target ranges of 130–139 mmHg for these patients, due to the reduced relative risk of all major cardiovascular outcomes.[18]

The benefits of SPC therapy on BP control are well recognized in published guidelines, but how this benefit translates into wider clinical and economic benefits is not fully known. Understanding the effects of SPC therapy on outcomes such as mortality and quality of life may aid therapeutic decision-making in the management of hypertension in clinical practice. The aim of the present study was to model and estimate the long-term clinical outcomes associated with different antihypertensive treatment pathways in the Italian setting including new data on the reaching of SBP targets amongst the population, building on the previously published analysis conducted in five countries.[20]

Methods

Modeling approach

In a previous analysis of the long-term clinical outcomes of antihypertensive pathways a microsimulation approach was deemed the best method of projecting long-term effects over a 10-year time horizon.[20] The earlier analysis provided high level results for five countries (China, Italy, South Korea, Mexico, and Russia), and the present analysis focused on Italy-specific data aimed to provide additional information on the long-term effects and the drivers of outcomes. The Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease, Risk Factors, and Injuries (GBD) study[21,22] was the basis for the analysis. The GBD was developed by the IHME as a source of epidemiological data of diseases and health outcomes. In the present analysis, the IHME GBD data was used to generate a population of distinct simulated individuals based on age, sex, and health status attributes (SBP, history of ischemic heart disease [IHD], intracerebral or subarachnoid hemorrhage, chronic kidney disease [CKD] and disability). A microsimulation model was developed, which projected outcomes related to health intervention scenarios using data generated from the GBD 2017. Additionally, transition probabilities for the model were derived from the GBD 2017.

The present analysis used simulated individuals that included nonhypertensive individuals, hypertensive but controlled individuals, and hypertensive not-controlled individuals, where hypertension was defined as $>$140 mmHg in untreated individuals. The simulation projected patient-level clinical outcomes for individuals aged $\geq$40 years, according to four different treatment pathways, from 2020 to 2030 (run in 28-day time steps). The full simulation was run for 1 000 000 individuals that were representative of the real-world Italian population with respect to age structure, disease patterns, risk factor levels, and treatment.

Input data

The GBD 2017 study was used as the primary data source for the analysis, for which the analytic process has been previously described.[21,23–25] The input data included age and sex distributions, mortality rates, health status, SBP, rates of stroke, IHD, CKD and associated mortality, treatment attributes and healthcare services utilization rates. To identify Italy-specific data, including current treatment practices, likelihood of treatment for patients with hypertension, and SBP measurement errors, a supplementary literature review was conducted.

Patients in the simulation were assumed to be treated according to four different treatment pathways (Table 1): current treatment practices (CTP) based on treatment pattern data from the GBD 2017, single drug with dosage

Table 1 Summary of antihypertensive treatment pathways

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 was <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.

titration first then sequential addition of other agents (start low and go slow, SLGS), free choice combination with multiple pills (FCC) or combination therapy in the form of a single pill (SPC). Assumed adherence to the treatment was treatment pathway specific and adherence rates were based on published data (Table 2).[26,27] Patients who took medication for hypertension on ≥80% of the days they were prescribed were defined as being adherent to treatment. Adherence rates were presented as annual probabilities, ranging from zero, complete nonadherence, to one, perfect adherence. The adherence rate was the only model input that differed between treatment pathways, with the same data from the GBD 2017 used for all treatment pathways for all other model inputs.

Model outputs

The model generated clinical outcomes based on the GBD 2017 infrastructure. The modeled clinical outcomes included those directly related to BP (mean SBP of treated population, percentage of patients who were adherent over the treatment period), as well as the effect of treatments on hypertension-related complications. Modeled complications included stroke events, IHD events, and CKD, and associated mortality of each complication. All-cause mortality was also included as a model output. In addition, clinical outcomes were used to estimate DALYs, a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death.[28]

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.

Results

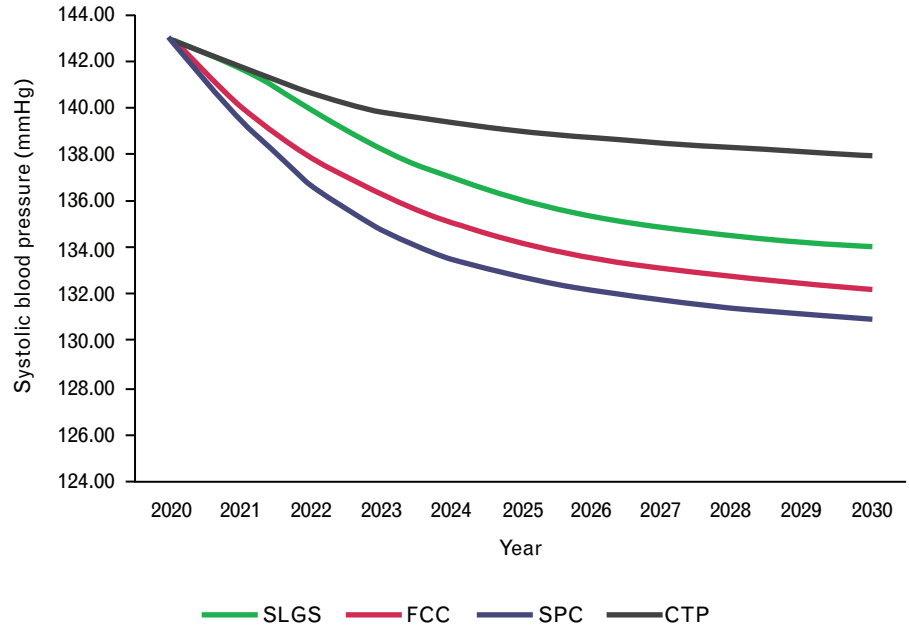
Over a 10-year time horizon, SPC therapy was projected to improve health outcomes compared with SLGS, FCC and CTP. The average SBP among patients with hypertension was lower in those receiving SPC than in patients receiving SLGS, FCC, and CTP throughout the 10-year time horizon (Fig. 1). Of the patients who initiated treatment, 12.4% of patients treated with SPC achieved SBP control during the simulation, compared with 11.9%, 12.1%, and 11.0% of patients receiving SLGS, FCC,

Table 2 Annual probabilities of adherence in the modeling analysis by regimen type and age group

Regimen	Adherence rate			Source
	Age <45 years	Age 45–60 years	Age >60 years	
CTP	0.409	0.599	0.789	28
SLGS	0.409	0.599	0.789	28
FCC	0.409	0.599	0.789	28
SPC	0.561	0.702	0.843	27

CTP, current treatment practices; FCC, free choice combination with multiple pills; SLGS, start low and go slow; SPC, single pill combination therapy.

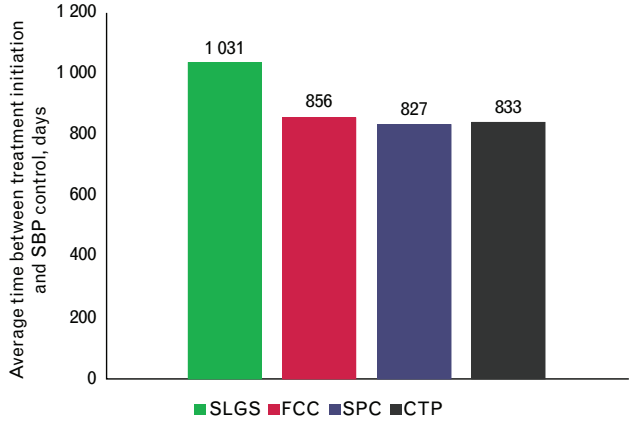
Fig. 1



Predicted average SBP among the population receiving antihypertensive treatment. Note that for each scenario 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. 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.

and CTP, respectively. The average time to SBP control in patients receiving SPC was shorter than those treated with SLGS (827 days versus 1031 days), but patients treated with CTP and FCC achieved SBP control in 833 and 856 days, respectively (Fig. 2). At the start of the simulation, new individuals who are not yet receiving treatment were added to the pool of individuals already receiving treatment, which slowed the reduction in average SBP and increased the time to SBP control.

Fig. 2

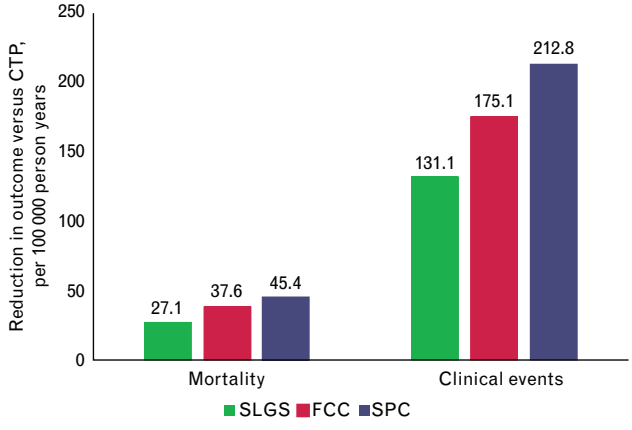


Projected time between treatment initiation and SBP control by treatment. Continuous addition of simulants with uncontrolled blood pressure increases time to SBP control. CTP, current treatment practices; FCC, free choice combination with multiple pills; SBP, systolic blood pressure; SLGS, start low and go slow; SPC, single pill combination therapy.

The model projected improvements in mortality and incidence of clinical events for patients treated with SPC, compared with the three other treatment pathways. SLGS, FCC, and SPC were associated with 3.3%, 4.5%, and 5.4% reductions in mortality versus CTP, respectively. Patients receiving SPC were projected to have a reduction in mortality of 45.4 deaths per 100 000 person years compared with CTP, whilst SLGS and FCC were associated with a reduction of 27.1 and 37.6 deaths per 100 000 person years, respectively, versus CTP (Fig. 3). Patients treated with SPC, SLGS, and FCC were projected to have 7.2%, 9.6%, and 11.5% reductions in the incidence of clinical events, respectively, compared with CTP. In the model clinical events were defined as IHD, stroke, and CKD. SPC was associated with a reduction in the incidence of clinical events of 212.8 events per 100 000 person years versus CTP. Patients treated with SLGS and FCC were projected to have a reduction in the incidence of clinical events of 131.1 and 175.1 events per 100 000 person years, respectively, compared with CTP (Fig. 3).

As a result of the improvements in clinical outcomes, patients treated with SPC were projected to have improvements in DALYs compared with patients treated with

Fig. 3



Predicted rate reductions in mortality and incidence of clinical events associated with different antihypertensive treatment pathways relative to current treatment practices. CTP, current treatment practices; FCC, free choice combination with multiple pills; SLGS, start low and go slow; SPC, single pill combination therapy.

SLGS, FCC, and CTP. Patients treated with SPC were projected to have a 5.7% reduction in DALYs compared with CTP, whereas those treated with SLGS and FCC were projected to have reductions in DALYs of 3.4% and 4.7%, respectively (Table 3). In the model, treatment with SPC was projected to result in 622.2 DALYs saved per 100 000 person years compared with CTP. Approximately, 367.0 and 506.6 DALYs per 100 000 person years were projected to be saved in people treated with SLGS and FCC, respectively, versus CTP (Table 3).

Discussion

Based on this microsimulation analysis using GBD 2017 data, SPC therapies are likely in a time horizon of 10 years to improve clinical outcomes for people with hypertension versus CTP in Italy. SPC, FCC, and SLGS regimens are likely to improve BP control compared with CTP, and thereby reduce the risk of adverse clinical events and associated DALYs and mortality. Improved adherence with SPC therapies was a key driver in the analysis, leading to SPC being associated with greatest benefits relative to CTP. Currently, only 34% of Italians treated for hypertension achieve BP control.[10] The present analysis showed that SPC and FCC were associated with the greatest improvements in SBP. The increased adherence to treatment is especially important in a population with substantial treatment discontinuation and with the majority of the population having additional risk factors for cardiovascular disease.[11,12]

Table 3 **Predicted reduction in disability-adjusted life years associated with different antihypertensive treatments relative to current treatment practices**

Regimen	DALYs saved, per 100 000 person years	Reduction in DALYs (%)
SLGS	367.0	3.4
FCC	506.6	4.7
SPC	622.2	5.7

DALYs, disability-adjusted life years; FCC, free choice combination with multiple pills; SLGS, start low and go slow; SPC, single pill combination therapy.

SPC was associated with decreased DALYs compared with CTP, FCC, and SLGS. DALYs are a measure of morbidity and mortality that are used in other settings. Cardiovascular risk factors impact quality of life; for example when comparing with current smokers, former and never smokers have lower DALYs of 0.91 and 1.15, respectively, whilst a person with a BMI of <25 has 1.04 fewer DALYs than a person with a BMI of >30.[29] Therapies improving quality of life such as receiving a cadaveric kidney transplant following chronic dialysis or a cochlear implant in children with severe-to-profound sensorineural hearing loss are associated with 1.4 and 6.92 fewer DALYs, respectively.[30,31] The present analysis found that SPC was associated with 622.2 fewer DALYs per 100 000 person years compared with CTP, and this benefit to quality of life was largely driven by the increased adherence to treatment in patients receiving SPC.

In Italy treatment recommendations follow the ESC/ESH 2018 guidelines that recommend SPC therapy for patients with hypertension (excluding frail, older patients and those with grade 1 hypertension). The guideline also introduced recommendations for lower SBP target ranges for patients $\geq$65 years old.[18] The improved adherence associated with SPC was a key driver of the present analysis, and a key driver of the clinical benefits of SPC over FCC. Detection and resolution of nonadherence to treatment were emphasized in the guideline due to the correlation with a higher risk of cardiovascular events, and SPC has been shown to be associated with increased adherence compared with CTP, FCC, and SLGS.[14–18] The present analysis complements recommendations of the guideline by showing that that SPC therapy would greatly improve health outcomes for people with hypertension in Italy.[18]

The previously published analysis of SPC in five countries provided a high level overview of long-term clinical outcomes, therefore the aim of the present analysis was to give a more detailed analysis in the Italian setting to aid healthcare professionals and payers in making more informed decisions when selecting hypertension therapies. The previous analysis, evaluated long-term clinical outcomes of SPC versus CTP, FCC, and SLGS. The analysis included an overview of the data generated, and did not include detailed Italy-specific results of the projected benefits of SPC.[20] The present analysis further detailed the

effects of increased adherence associated with SPC on clinical outcomes, including the lower SBP of patients receiving SPC versus the three other treatment pathways, and shorter time to SBP control in patients treated with SPC compared with SLGS. This additional data showed the positive effect of increased adherence on SBP, which resulted in the improved clinical outcomes associated with SPC (i.e. reduced mortality and incidence of clinical events) and improvements in DALYs. Therefore, the inclusion of the SBP data presented the entire benefits of increased adherence and how these benefits can be seen in many aspects of patient-related outcomes.

As with any modeling study, the present analysis had some potential limitations. Adherence rates used in the model were sourced from published literature, but in the model it was assumed that the adherence rates for CTP, SLGS, and FCC were the same.[26,27] In the analysis adherence was treated as binary and individual patient-level adherence was not known (e.g. some patients may be adherent 50% of the time, but in the model adherence was defined as taking medication on $\geq$80% of the days prescribed). Incorporating the precise level of adherence of each patient in the model would have created significant complexity without necessarily improving the analysis, so the assumption of adherence at $\geq$80% was used as a stand-in for the range of treatment adherence expected in a real-world population. Whilst every effort has been made to use relevant and accurate data in the model inputs, data surrounding dosing in the CTP scenario were not readily available, in the literature or from the GBD 2017 data set or drug sales data. Whilst modeling studies are associated with more uncertainty than real-world evidence, the long-term projections that can be generated remain a useful tool for healthcare decision makers. Additionally, in a meta-analysis, antihypertensive agents were shown to be associated with increased risk of adverse events (e.g. hyperkalemia, hypotension, acute kidney injury, syncope).[32] These adverse events were not specifically taken into account in the present analysis, as differences in event rates in patients treated with SPC, CTP, SLGS, and FCC have not been shown. The lack of relevant adverse event data specific to each comparator creates difficulty in accurately projecting outcomes, so these events were not taken into account, and comparisons between treatments were made based on existing evidence.

Conclusion

Over a 10-year time horizon, this analysis projected that combination therapies (including SPC and FCC) are likely to reduce the burden of hypertension compared with conventional treatment options in Italy. SPC treatment was associated with the greatest overall benefits in terms of improving SBP and reducing clinical events, DALYs and mortality compared with CTP, FCC, and SLGS. Improved adherence was a key driver of projected benefits.

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Conflicts of interest

C.B. 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.

D.G. is an employee of Sanofi and may hold shares and/or stock options in the company.

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