ORIGINAL RESEARCH

A Retrospective Observational Real-Word Analysis of the Adherence, Healthcare Resource Consumption and Costs in Patients Treated with Bisoprolol/Perindopril as Single-Pill or Free Combination

Stefano Masi · Zhanna Kobalava · Chiara Veronesi · Elisa Giacomini ·

Luca Degli Esposti · Konstantinos Tsioufis

ABSTRACT

Introduction: The present real-world analysis aims to compare the drug utilization, hospitalizations and direct healthcare costs related to the use of single-pill combination (SPC) or free-equivalent combination (FEC) of perindopril and bisoprolol (PER/BIS) in a large Italian population.
Methods: This observational retrospective analysis was based on administrative databases covering approximately 7 million subjects across Italy. All adult subjects receiving PER/BIS as SPC or FEC between January 2017–June 2020 were included. Subjects were followed for 1 year after the first prescription of PER/BIS as FEC (± 1

S. Masi (✉)
Department of Clinical and Experimental Medicine, University of Pisa, Via Roma, 67, 56126 Pisa, Italy
e-mail: stefano.masi@unipi.it

Z. Kobalava
Department of Internal Medicine and Cardiology, RUDN University, Moscow, Russia

C. Veronesi · E. Giacomini · L. Degli Esposti
CliCon S.R.L. Società Benefit, Health, Economics & Outcomes Research, Bologna, Italy

K. Tsioufis
1st Department of Cardiology, National and Kapodistrian University of Athens, Hippocratio Hospital, Athens, Greece

month) or SPC. Before comparing the SPC and FEC cohorts, propensity score matching (PSM) was applied to balance the baseline characteristics. Drug utilization was investigated as adherence (defined by the proportion of days covered, PDC) and persistence (evaluated by Kaplan-Meier curves). Hospitalizations and mean annual direct healthcare costs (due to drug prescriptions, hospitalizations and use of outpatient services) were analyzed during follow-up.
Results: The original cohort included 11,440 and 6521 patients taking the SPC and FEC PER/BIS combination, respectively. After PSM, two balanced SPC and FEC cohorts of 4688 patients were obtained (mean age 70 years, approximately 50% male, 24% in secondary prevention). The proportion of adherent patients (PDC ≥ 80%) was higher for those on SPC (45.5%) than those on FEC (38.6%), $p < 0.001$. The PER/BIS combination was discontinued by 35.8% of patients in the SPC cohort and 41.7% in the FEC cohort ($p < 0.001$). The SPC cohort had fewer cardiovascular (CV) hospitalizations (5.3%) than the free-combination cohort (7.4%), $p < 0.001$. Mean annual total healthcare costs were lower in the SPC (1999€) than in the FEC (2359€) cohort ($p < 0.001$).
Conclusion: In a real-world setting, patients treated with PER/BIS SPC showed higher adherence, lower risk of drug discontinuation, reduced risk of CV hospitalization, and lower healthcare costs than those on FEC of the same drugs.

PLAIN LANGUAGE SUMMARY

Patients with cardiovascular conditions often need to take many pills. This may result in patients not taking their pills as prescribed (i.e., low adherence) and compromise the potential benefits derived from prescription of cardiovascular protective drugs. Simplifying treatment by combining drugs into a single pill can improve adherence and, consequently, patient outcomes. In this analysis using data from real clinical practice, we explored whether using a single pill of perindopril and bisoprolol is associated with higher levels of adherence, lower proportion of patients with hospitalizations and lower economic costs than using the same drugs prescribed as free-equivalent combination in a large sample of the Italian population of approximately 7 million people. We identified two groups of patients taking single pill or free-equivalent combination of perindopril and bisoprolol (4688 patients in each cohort). Over 1-year follow-up, patients taking single pill were more likely to be adherent and were less likely to stop taking their treatment. They also had fewer cardiovascular hospitalizations with shorter hospital admission and had lower healthcare direct costs. In conclusion, simplifying treatment by combining perindopril and bisoprolol in a single pill instead of two may have a positive effect on adherence, outcomes and healthcare costs already after 1 year.

Keywords: Single-pill combination; Perindopril; Bisoprolol; Economic costs; Adherence; Real-world data

Key Summary Points

Suboptimal adherence may impair the benefit of anthypertensive treatments

Reducing pill burden by combining two antihypertensive drugs in a single pill could improve adherence to medication

This real-world analysis compared two matched groups of patients prescribed bisoprolol/perindopril as single-pill combination (SPC) or free-equivalent combination (FEC) in Italy in terms of adherence and persistence, cardiovascular hospitalizations and healthcare resource consumption

The findings showed how patients with SPC displayed a better drug utilization profile in terms of higher level of adherent and persistent patients as well as lower proportion of hospitalizations and overall healthcare resource costs over a 1-year period

The study adds to the growing body of knowledge on the positive impact of the SPC approach on adherence, outcomes and healthcare costs for National Health Systems

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, therefore representing a public health priority [1]. Initiation and evolution of CVD depend on continuous exposure to cardiovascular risk factors, leading to the activation of damaging pathways that promote the accumulation of organ damage, ultimately leading to its clinical manifestations [2, 3]. The sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) have been regarded as central pathways involved in the progression of CVD and its complications [4]. Their upregulation is involved in all steps of the CVD continuum, influencing the control of cardiovascular risk factors, evolution of the subclinical organ damage and early and long-term adaptations which follow acute cardiovascular (CV) events (i.e., myocardial infarction) [2, 3]. Beyond their intrinsic feedback regulation, these two systems also interact with each other as sympathetic activation results in increased renin secretion

and upregulation of the RAAS activity, whereas RAAS activation leads to sympathetic overactivity acting at the level of the central nervous system [5]. This creates the pharmacologic rationale for prescribing drugs that target both neurohormonal pathways, slowing down the CVD continuum's evolution.

Angiotensin-converting enzyme inhibitors (ACE-Is) and β-blockers (BB) have been shown to reduce the overactivity of the RAAS and SNS, leading to improved blood pressure control and lower risk of cardiovascular events in patients with and without established CVD [6, 7]. Furthermore, while BBs were previously recommended in hypertensive patients in the presence of a few specific indications/comorbidities, in the most updated European Society of Hypertension (ESH) guidelines [8], use of BBs was extended in the presence of many additional conditions including various cardiac diseases less or not related to hypertension, other vascular conditions and other non-CV diseases [8]. In many of these conditions, BB has been shown to modify the patient's outcome, reducing the risk of cardiovascular complications. However, the benefits for the general population obtained from CV protective drugs are commonly less evident than what could be expected based on the results of randomized controlled trials [1]. Treatment adherence represents one of the most important factors influencing these differences, given that in the highly controlled environment of a clinical trial, high adherence to the treatment is expected [9], at striking variance from real life in which adherence is lower and is an important determinant of subsequent mortality [10]. Limited adherence to treatment represents a substantial issue in patients receiving BB, as previous meta-analyses and real-life studies suggested that adherence to this class of drugs is limited compared to other cardioprotective medications[11, 12]. Given that an elevated pill burden is the most relevant factor influencing medication adherence, recent hypertension guidelines recommend using a single-pill combination (SPC) as the ideal strategy to start and titrate the antihypertensive treatment [13, 14]. SPC has been shown to improve adherence and persistence to the treatment, resulting in

enhanced CVD risk factor control and better patient outcomes [14–17]. Nevertheless, public health systems often consider the use of SPC as an unnecessary increase in healthcare costs, intensely monitoring their prescription. To date, little evidence is available on the drug utilization of patients prescribed ACE-Is and BB in different formulations. In this regard, the only SPC containing both drug classes and currently available in Italy is the one including perindopril and bisoprolol.

In this study, we used a large Italian dataset of administrative data to assess the drug utilization and economic burden of treatment with ACE-Is and BB as SPC or free equivalent combination (FEC). To do so, we adopted a propensity score matching (PSM) approach to evaluate the differences in the level of adherence and economic costs associated with the prescription of the bisoprolol/perindopril combination as SPC or FEC.

METHODS

Source of Data

Administrative databases including health data from around 7 million Italian subjects (of which 5.9 million are adult subjects), i.e., approximately 11% of the entire Italian population (12% of the adult Italian population) were used for the analyses. Such databases include all the healthcare resources dispensed and reimbursed by the Italian National Health System, which provide universal coverage to all residents. Primarily intended for administrative purposes, the use of administrative data for healthcare research has increased over the years. Furthermore, administrative databases have been previously used and validated for analyses assessing the clinical characteristics and changes in adherence patterns of patients using SPC or FEC [18, 19]. A flow chart of the construction of the dataset is provided in Supplementary Fig. 1. Briefly, the pharmaceutical databases were queried to collect data on the Anatomical-Therapeutic-Chemical (ATC) code of the drug delivered, number of packs, number of units per pack, dosage, unit cost per pack and

prescription date. Using an anonymous univocal numeric code to guarantee patient privacy as a unique identifier, this database was linked with the: (1) Beneficiaries' Database, listing some patients' demographic characteristics such as year of birth, sex, start and end of registration dates; (2) Hospital Discharge Database, which includes all hospitalization data with the admission and discharge dates, patient status at discharge (death, discharged home, transferred to other departments), primary and secondary discharge diagnosis codes classified according to the Ninth Revision of the International Classification of Diseases (ICD-9-CM), Diagnosis Related Group (DRG) and DRG-related charge (provided by Health System); (3) Test and Visit Database, including information on the prescription of laboratory tests or specialist visits and their codes to identify the type of requests and their costs.

All results of analyses were produced as aggregated summaries, which are not possible to assign, either directly or indirectly, to individual patients. Informed consent was not required (pronouncement of the Data Privacy Guarantor Authority, General Authorization for personal data treatment for scientific research purposes—n.9/2014). This observational study was performed in accordance with the principles of the Declaration of Helsinki. The project from which the analyses were drawn has been notified and approved by the local Ethics Committee of the LHUs involved in the study (the list of Ethics Committees is reported in supplementary material).

Study Design and Cohort Definition

The inclusion period was from January 2017 to June 2020. Based on the prescription data, this study included all adults (age > 18 years old) treated with perindopril and bisoprolol as SPC (group 1) or FEC (group 2). The index date was considered the date of both drugs' prescription as SPC or FEC (with a maximum delay of ± 1 month from the first to the second component of the combination in the case of the FEC) during the inclusion period. All patients were followed up for 12 months after the index date.

Subjects who had only one prescription during the study period or who moved to another region during follow-up were excluded from the analysis. Characteristics of patients were evaluated prior to the index date in terms of previous hospitalization (searched in all available period prior to the index date and listed with corresponding ICD-9-CM codes in Supplementary Table 1) or previous treatments (searched in the year before the index date and listed with corresponding ATC codes in Supplementary Table 2). Patients were also identified as in primary or secondary prevention based on the presence/absence of previous hospitalization for ischemic heart diseases, heart failure, cerebrovascular and peripheral vascular diseases.

Definition of Drug Adherence and Persistence

Adherence to the combination of perindopril and bisoprolol was evaluated during follow-up as the proportion of days covered (PDC) by these medications, considering the number of pills dispensed during 1 year of follow-up. Adherence to FEC was calculated as the number of days covered by both medications (perindopril and bisoprolol) during the 12-month follow-up from the index date. Similarly, adherence to the SPC containing perindopril and bisoprolol was calculated as the days covered by SPC during the 12-month follow-up, starting from the initial prescription of the SPC. Given that the bisoprolol/perindopril SPC can be taken as half a tablet a day, the PDC was calculated assuming the prescription of both one tablet/day or half tablet/day. Following the approach used in previous studies [18], the cutoffs of PDC used to stratify the population based on the level of adherence were: PDC < 40% = low adherence; PDC ≥ 40 but < 80% = moderate adherence; PDC ≥ 80% = high adherence to the treatment. Persistence to treatment was measured by evaluating the time to discontinuation (TTD) during the 1 year of follow-up.

Definition of the Economic Costs

Direct healthcare costs in euros (€) were estimated as mean annual cost for all drug treatments, hospitalizations (for both all-cause and more specifically CV-related hospitalization) and all outpatient specialist service usage during the 1 year of follow-up. The healthcare cost analysis was performed from the perspective of the Italian National Health Service (INHS), with costs reported in euros (€). Drug costs were evaluated using the INHS purchase price. Hospitalization costs were determined using DRG tariffs, which represent the reimbursement levels by the INHS to healthcare providers. The costs of outpatient specialist services were defined according to tariffs applied by each region.

Statistical Analyses

Continuous variables are reported as the mean ± standard deviation (SD) and median with quartile Q1–Q3, categorical variables as frequencies and percentages. As parametric test, t-test was used to compare the means of two groups; chi-square test was used to compare the percentages of patients between the different groups. In case of non-normal distribution, Mann-Whitney test was used as non-parametric test to compare means. A p value < 0.05 was considered for statistical significance. A PSM analysis was used to minimize the selection bias and to reduce potential unbalances in both baseline characteristics and number of patients between the two cohorts of FEC and SPC and to compare level of adherence, health outcomes and economic costs between the two groups. Patients were matched 1:1 on quintiles of propensity score calculated using a logistic regression model which includes age, sex, comorbidities listed in Supplementary Table 1 and previous treatments listed in Supplementary Table 2. Standardized mean difference (SMD) values < 0.1 indicated the two cohorts were balanced for their characteristics [20]. TTD was evaluated by Kaplan-Meier curves during 1-year follow-up from therapy start to permanent discontinuation (plus last prescription duration); TTD was censored at the end of follow-up. Mean and median length of hospital stay was calculated per single stay (considering both overall patients and hospitalized only) and as sum of total stays over 1 year (in hospitalized patients). Duration of hospital stays was calculated considering day hospital and ordinary hospitalization together as well as ordinary hospitalization only. Incidence of CV specialist visits was evaluated after the 1 year of follow-up and considered all available periods up to end of data availability, p-value derived from the coefficient of Poisson regression. All analyses were performed using Stata SE version 17.0 (StataCorp, College Station, TX, USA).

RESULTS

According to the inclusion and exclusion criteria, in the entire administrative database we identified 6521 patients taking the FEC and 11,440 subjects taking the SPC bisoprolol/perindopril (Fig. 1). The clinical characteristics and drug prescriptions of the two groups before PSM are reported in Supplementary Tables 3 and 4, respectively. Patients in the SPC group were younger and showed a lower disease burden than those in the FEC group (Supplementary Fig. 2). While the distribution of pill burden was similar between the two groups, the number of tablets was higher in the FEC group (Supplementary Fig. 3). As reported in Table 1, the propensity score matching resulted in a balanced distribution of the clinical characteristics between the two groups (4688 patients in each group), including the pill and disease burden (mean number ± SD of pills: FEC 1.5 ± 1.4 vs SPC 1.6 ± 1.4; mean number ± SD of disease: FEC 0.9 ± 1.1 vs SPC 0.9 ± 1.1). All the following analyses were performed on the two post-PSM cohorts.

Analysis of Treatment Adherence and Persistence

When adherence was evaluated assuming one SPC per day, < 50% of patients in both groups had a PDC ≥ 80% (Fig. 2). However, the prescription of SPC was associated with better

medication adherence, as reflected by a significantly higher percentage of highly adherent patients (PDC ≥ 80%) in the SPC group than in the FEC group (45.5% SPC vs 38.6% FEC, p-value < 0.001) (Fig. 2A). When the PDC was computed considering the consumption of ½ pill a day, most patients in the SPC group were highly adherent to the medication (PDC > 80%) (76.3% in the SPC group vs 61.2% in the FEC group, p-value < 0.001), further increasing the difference in medication adherence when comparing the ½ SPC/day to the adherence to the FEC taken as one pill/day (76.3% in the SPC group vs 38.6% in the FEC group, p-value <

0.001) or as ½ pill of both drugs/day (76.3% in the SPC group vs 61.2% in the FEC group, p-value < 0.001) (Fig. 2B).

Persistence of the treatment was also different between SPC and FEC. Indeed, the bisoprolol/perindopril combination was discontinued by 35.8% of patients in the SPC cohort and 41.7% of patients in the FEC cohort by the end of the follow-up (p < 0.001). In both cohorts, median time to discontinuation was not reached (Fig. 3).
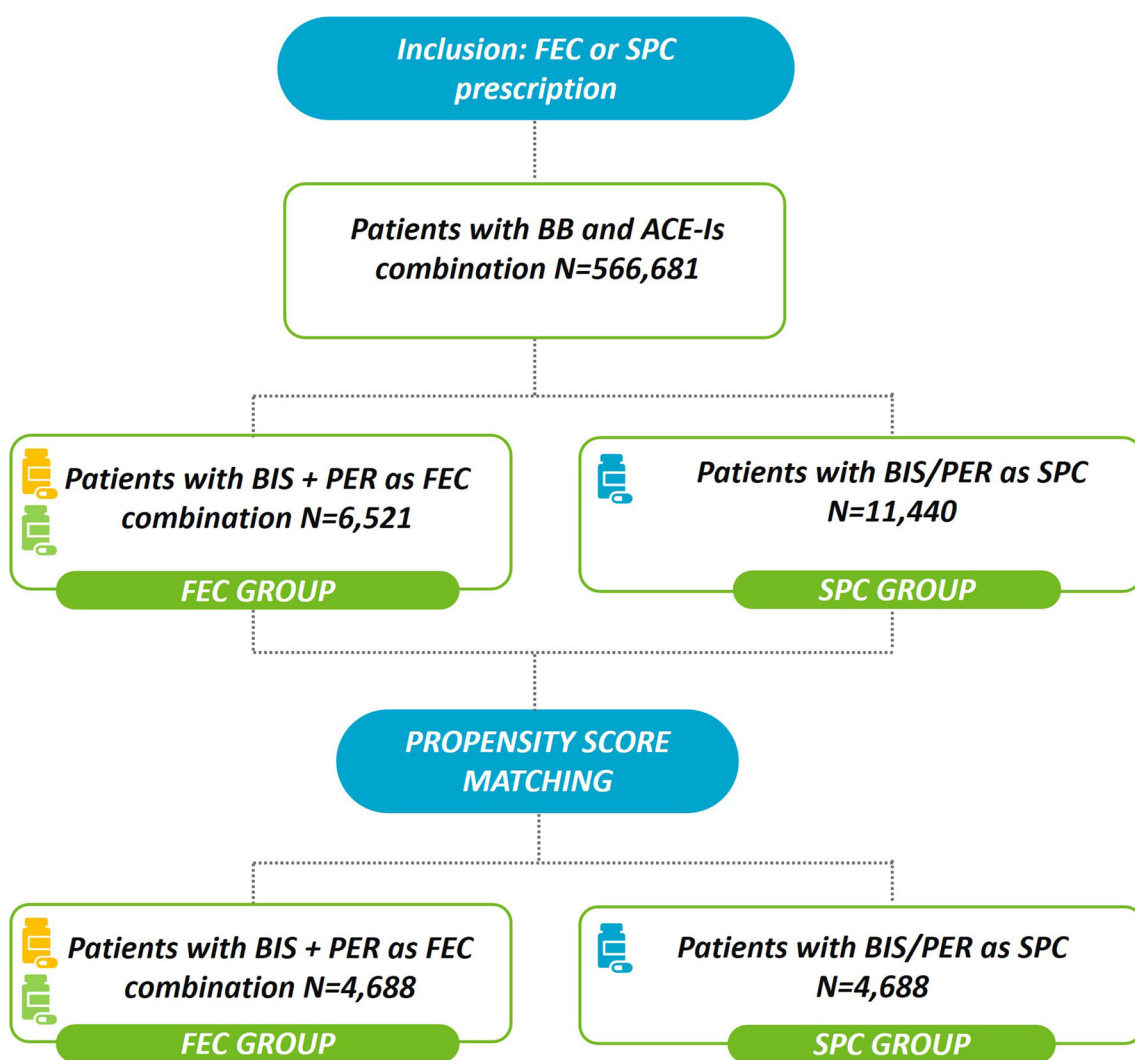
Fig. 1 Flow chart of the study. *ACE-Is* angiotensin-converting enzyme inhibitors, *BB* β-blockers. *BIS/PER* bisoprolol/perindopril, *SPC* single-pill combination, *FEC* free-equivalent combination

Table 1 Clinical characteristics of the population included in the study 1, after propensity score matching

	FEC group (N = 4688)	SPC group (N = 4688)	Standardized mean difference
Age, mean (SD) [median, Q1–Q3]	70.1 (11.9) [71, 63–79]	69.7 (11.7) [71, 62–79]	0.035
Male, n (%)	2329 (49.7)	2327 (49.6)	0.001
COPD, N (%)	1459 (31.1)	1485 (31.7)	0.012
Diabetes, N (%)	1097 (23.4)	1087 (23.2)	0.005
Primary prevention, N (%)	3541 (75.5)	3577 (76.3)	0.018
Secondary prevention, N (%)	1147 (24.5)	1111 (23.7)	
CKD disease, N (%)	64 (1.4)	64 (1.4)	0.000
Psychiatric disease, N (%)	154 (3.3)	147 (3.1)	0.008
Lipid-lowering treatment, N (%)	2483 (53.0)	2437 (52.0)	0.020
*Previous treatments**			
ACE inhibitors, N (%)	2009 (42.9)	2127 (45.4)	0.051
Angiotensin II receptor blockers, N (%)	1149 (24.5)	1214 (25.9)	0.032
Beta blocking agents, N (%)	1145 (24.4)	1214 (25.9)	0.034
Calcium channel blockers, N (%)	1340 (28.6)	1354 (28.9)	0.007
Antithrombotic agents, N (%)	420 (9.0)	393 (8.4)	0.020
Antiarrhythmics, N (%)	392 (8.4)	379 (8.1)	0.010
Diuretics**, N (%)	1285 (27.4)	1233 (26.3)	0.025
Digoxin, N (%)	168 (3.6)	154 (3.3)	0.016
Ivrabadina, N (%)	101 (2.2)	106 (2.3)	0.007
Antiinflammatory treatment, N (%)	2744 (58.5)	2814 (60.0)	0.030
Antidepressants, N (%)	843 (18.0)	855 (18.2)	0.007

*Prescribed in the year prior to the inclusion of patients (characterization period)
**Diuretics analyzed comprised: thiazides, high-ceiling diuretics, spironolactone. A standardized mean difference value < 0.1 indicated the two cohorts were balanced for their characteristics

Healthcare Usage and Economic Costs Associated with Use of SPC or FEC

After PSM, compared to patients in the FEC group, patients using the SPC had a significantly lower incidence of hospitalization (22% FEC vs 16.1% SPC), mean ± SD total number of days spent in the hospital (23.8 ± 49.7 FEC vs 20.7 ± 45.2 SPC) (among hospitalized patients),

and this difference remained highly significant also when considering only cardiovascular hospitalizations (Table 2 and Fig. 4), while no significant differences were observed in the mean length of hospitalization stay among hospitalized patients. Furthermore, the use of SPC was associated with a significantly lower incidence of cardiovascular specialist visits compared to the use of FEC (68.6 vs 111.5 visits
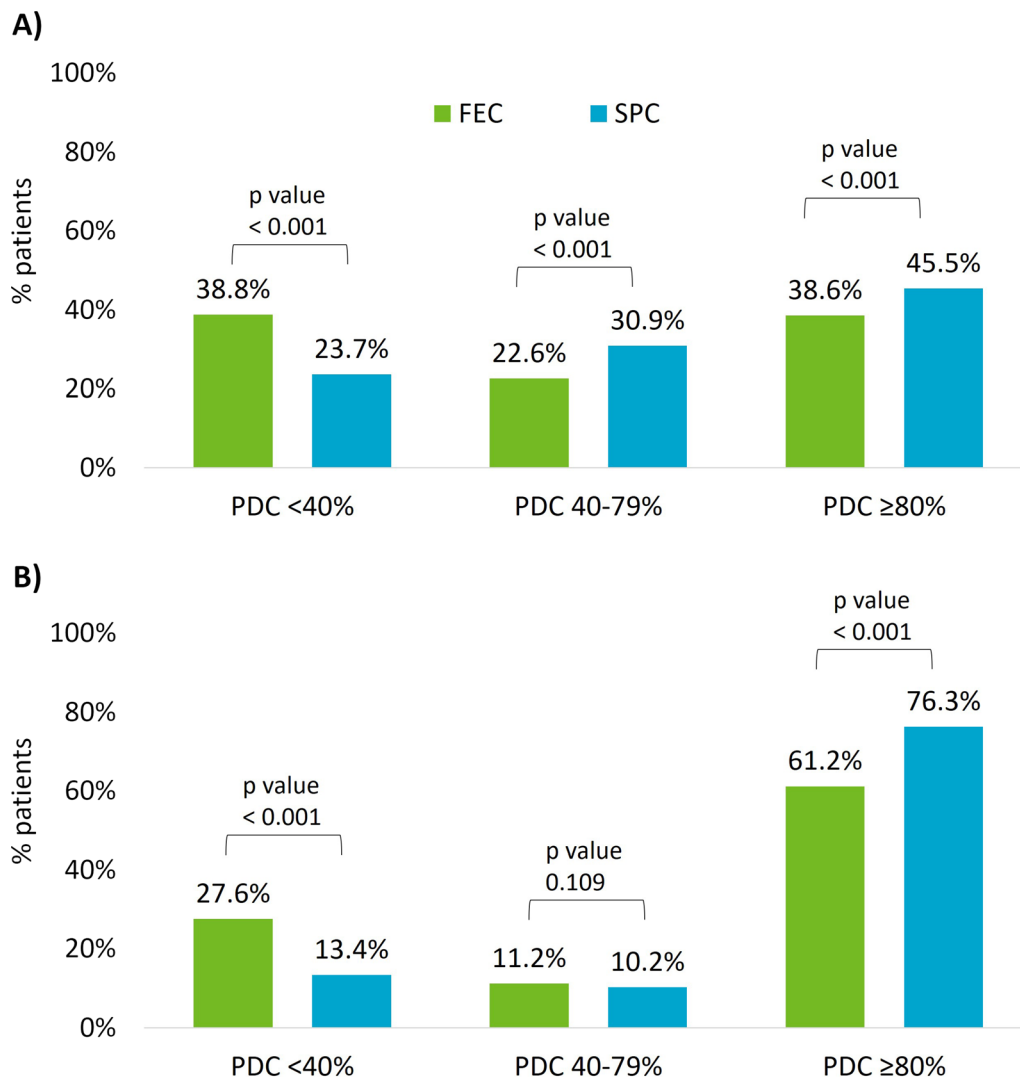
Fig. 2 Treatment adherence in the SPC and FEC groups after propensity score matching and assuming the consumption of 1 SPC/day (**A**) or ½ pill/day for SPC and FEC (**B**). *PDC* proportion of days covered, *SPC* single-pill combination, *FEC* free-equivalent combination. Chi-square test was used to address significance

per 1000-person/year, respectively; *p* values < 0.001) (Fig. 5).

Consequently, the total healthcare costs related to the use of SPC (1999 € per subject/year) were significantly lower compared to those of the FEC group (2359€ per subject/year) (*p*-value < 0.001) (Fig. 6). The cost difference between the two cohorts is evident for the expenditure related to all-cause hospitalization. Among the latter, the mean annual cost related to cardiovascular hospitalizations was also

higher in the FEC group (323€) compared to the SPC group (225€) (*p*-value < 0.001).

DISCUSSION

This study uses a large administrative dataset, including around 11% of the Italian population, to explore the treatment adherence of patients taking a combination of two commonly prescribed drugs in primary and secondary CVD prevention (perindopril and bisoprolol) in the
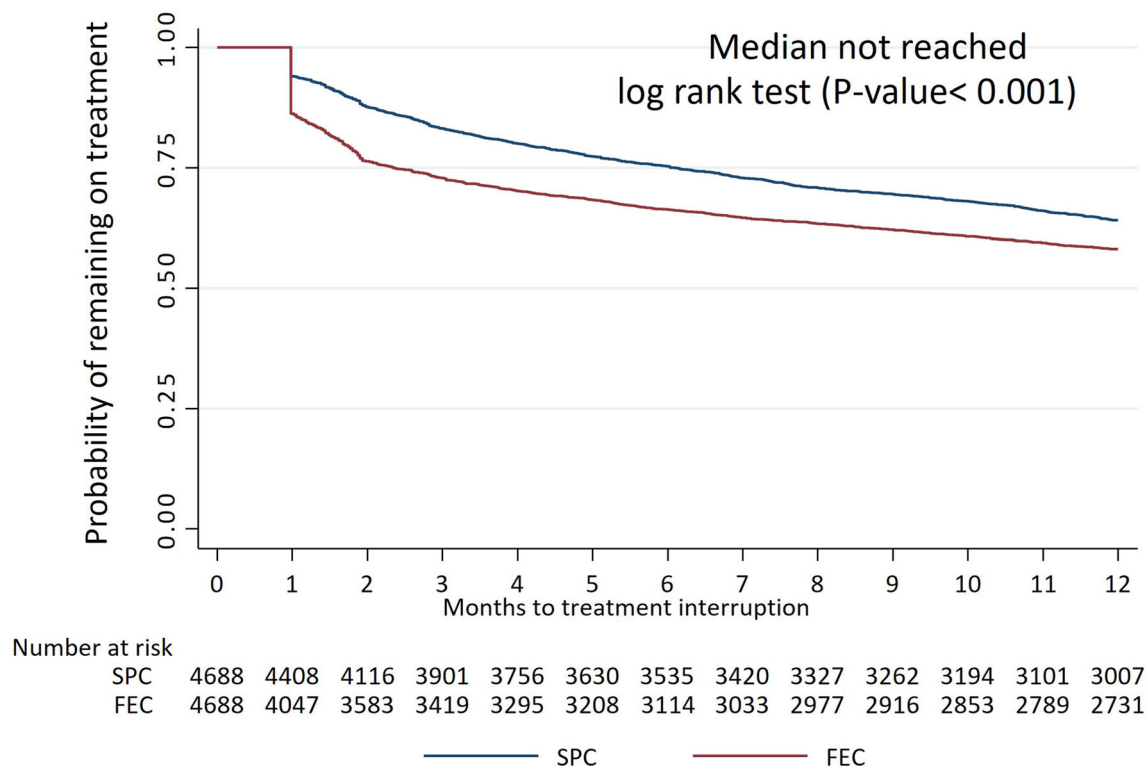
Fig. 3 Kaplan-Meier curve evaluating the probability of remaining on treatment in patients during the first year of follow-up. The 1-month plateau is due to the overlapping prescription at index date (first prescription of PER/BIS) in the FEC group. *SPC* single-pill combination, *FEC* free-equivalent combination

format of FEC or SPC. It also reports the economic burden in terms of hospitalizations, CV visits and overall direct costs related to these two different treatment strategies. The first important finding emerging from the current analysis is that adherence and persistence to cardiovascular drugs remain suboptimal, with a PDC > 80% detectable in < 50% of patients taking the two-drug combination and > 40% of patients in the FEC group discontinuing the drugs during the first year of treatment. The SPC is associated with a significant improvement in medication adherence and persistence compared to the use of FEC. This is likely the main reason explaining the lower risk of hospitalization and lower number of cardiovascular specialist visits observed in patients treated with the SPC than FEC during follow-up. The lower utilization of healthcare resources might explain the lower healthcare costs related to the use of SPC compared to those associated with

the prescription of the FEC. In summary, our data suggest that the use of bisoprolol/perindopril SPC might lead to substantial health benefits and considerable reduction of healthcare costs compared to the prescription of both drugs as FEC.

Cardiovascular disease evolves through several subclinical stages, leading to the progressive accumulation of cardiovascular damage, ultimately resulting in the emergence of its clinical manifestations. The RAAS and SNS are the two major systems involved in all stages of CVD evolution, stimulating the heart and vessels remodeling, inducing a faster progression of the subclinical cardiovascular damage and promoting the processes that lead to CVD complications [2, 3]. For these reasons, several guidelines now consider the combination of ACE-Is and BB among the pillars of the treatments for patients at different stages of the CVD continuum, including subjects with hypertension, ischemic

Table 2 Mean number of hospitalization, patients with hospitalizations and mean length of stay

	Hospitalization parameters	FEC group	SPC group	*p*-value
All-cause hospitalizations	Entire population	N = 4688	N = 4688	
	Hospital days per hospitalization (day hospital + ordinary hospitalization), mean (SD) [median, Q1-Q3]	3.5 (19.7) [0, 0–0]	2.3 (16.5) [0, 0–0]	< 0.001
	Total number of hospital days (day hospital + ordinary hospitalization) during follow-up, mean (SD) [median, Q1-Q3]	23.8 (49.7) [9, 4–21]	20.7 (45.2) [8, 3–19]	< 0.001
	Total number of hospital days limited to ordinary hospitalization (excluding day hospitalizations), mean (SD) [median, Q1-Q3]	13.4 (17.9) [8, 4–15]	13.0 (16.5) [8, 4–16]	0.724
	Hospitalized patients only (n, % of the entire population)	1030 (22.0)	757 (16.1)	< 0.001
	Hospital days per hospitalization (day hospital + ordinary hospitalization), mean (SD) [median, Q1-Q3]	16.0 (39.5) [7, 3–13]	14.5 (38.8) [7, 3–11]	0.405
	Hospital days per hospitalization limited to ordinary admissions (excluding day hospitalizations), mean (SD) [median, Q1-Q3]	8.5 (9.5) [6, 3–11]	8.1 (7.5) [6, 3–11]	0.312
Cardiovascular hospitalizations	Entire population	N = 4688	N = 4688	
	Hospital days per hospitalization (day hospital + ordinary hospitalization), mean (SD) [median, Q1-Q3]	*0.6 (2.9) [0, 0–0]*	*0.4 (2.3) [0, 0–0]*	*< 0.010*
	Total number of hospital days (day hospital + ordinary hospitalization) during follow-up, mean (SD) [median, Q1-Q3]	*10.8 (14.5) [7, 4–12]*	*10.4 (10.9) [7, 4–12]*	*< 0.001*
	Total number of hospital days limited to ordinary hospitalization (excluding day hospitalizations), mean (SD) [median, Q1-Q3]	*10.4 (13.9) [7, 4–11]*	*10.0 (10.4) [7, 4–12]*	*0.747*
	Hospitalized patients only (n, % of the entire population)	*348 (7.4)*	*248 (5.3)*	*< 0.001*
	Hospital days per hospitalization (day hospital + ordinary hospitalization), mean (SD) [median, Q1-Q3]	8.0 (7.6) [6, 3–10]	7.7 (6.9) [6, 3–9]	0.595
	Hospital days per hospitalization limited to ordinary admissions (excluding day hospitalizations), mean (SD) [median, Q1-Q3]	*7.8 (7.7)* [6, 3–10]	*7.5 (6.7)* [6, 3–9]	*0.552*

Mann-Whitney test was used for the comparison of mean length of stay between groups. Chi-square test was used to compare the percentages of patients between the different groups

heart disease and heart failure [14, 21, 22]. Particularly, the recently published guidelines on the management of arterial hypertension (the most important mortality risk factor worldwide) emphasized that ACE-Is and BB should be considered among first-line agents for the treatment of the disease, based on results from RCTs and their meta-analyses [8] showing they effectively reduce SBP and DBP and, consequently, result in a similar or only slightly different reduction in the risk of major CV outcomes and mortality when given as the initial treatment step (while recognizing a lesser stroke prevention for these drugs). In the same guidelines, the indications for the use of BB as preferred treatment strategy in patients with hypertension were largely expanded compared to previous guidelines, including 26 clinical

		Median (€)	Q1-Q3 (€)
Drugs	SPC	537.11	249.83-1185.16
	FEC	705.08	379.59-1314.11
Hospitalizations	SPC	0.00	0.00-0.00
	FEC	0.00	0.00-0.00
CV Hospitalizations	SPC	0.00	0.00-0.00
	FEC	0.00	0.00-0.00
OSS	SPC	157.01	32.54-434.58
	FEC	152.62	34.21-411.52
Total	SPC	949.78	408.44-2193.19
	SPC	1,181.68	579.77-2620.02

Fig. 6 Mean annual healthcare costs in the SPC and FEC groups after propensity score matching. *SPC* single-pill combination, *FEC* free-equivalent combination. Mann- Whitney test was used for the comparison of mean costs between groups

could substantially reduce the risk of hospitalization and time necessary to restore a physiologic cardiovascular homeostasis during hospital admissions. Previous studies have documented that SPC might reduce hospital admissions, although the comparison was done with monotherapy rather than the FEC of the same drugs [32]. Therefore our results extend previous findings, and this is important as one of the most common reasons taken forward by the NHSs to monitor the prescription of SPC scrupulously is related to their higher costs than the use of the FEC of the same drugs. Such immediate increase in the economic costs is often regarded as an unnecessary expansion of the NHS budget, while the potential advantages derived by a better adherence and persistence in the treatment could be seen only in the very long term. We now show that the use of SPC is associated with a significant reduction of the NHS costs for managing CVD and that such economic impact emerges already within 1 year

from the original prescription. This is combined with evident benefits for the patients, with a lower risk of hospitalizations. Another important result emerging from our analysis is the evidence that the use of SPC is associated with an improved treatment persistence than the use of FEC. Beyond the simplification of the treatment achieved with the SPC that might explain this result, it also suggests that the prescription of bisoprolol/perindopril as SPC is well tolerated, leading to a low discontinuation rate.

This study has several important strengths. First, rigorous pharmacoepidemiologic methods that have been previously validated were used to minimize confounding. We also performed extensive adjustments for covariates using propensity score matching. Second, this study provides high generalizability based on the nationally representative database used for the analyses, which includes approximately 10% of the Italian population. Finally, we utilized previously validated claims-based algorithms to

define CV outcomes to minimize misclassification bias. Some limitations should also be recognized. Although the new European Society of Hypertension guidelines extended the use of BB to several conditions, the combination of ACE-IS and BB did not represent the standard of care for hypertension during the study period, therefore the patients analyzed may not be representative of all the hypertensive patients [8]. When looking at characteristics pre-PSM, SPCs tend to be prescribed to younger patients and with fewer comorbidities. PSM minimized the risk of selection bias, obtaining an appropriate balance for age, gender, drug history and comorbidities. However, its inability to balance unmeasured confounding variables or to adjust for disease severity when working with coded variables might have influenced the results of our analyses. Despite these limitations, information about unmeasured confounders may have been captured indirectly through proxies, such as using older age as a proxy for frailty or examining pharmacologic treatment as a proxy for the presence of specific diseases. Previous studies have also documented that propensity score sometimes achieves better balance than in groups randomly assigned to treatment [33]. For these reasons, PSM is increasingly used in real-world analyses [34], and large initiatives of trial emulation have placed this approach at the center of their conceptual framework [35]. While associated with better adherence and persistence, the short follow-up and limited number of hard outcomes did not provide us with the opportunity to test the benefits in terms of cardiovascular risk reduction potentially obtained with the use of bisoprolol/perindopril as FEC or SPC. For the same reasons, we could not test the efficacy of the SPC vs FEC in reducing the cardiovascular risk in different clinical settings where perindopril and bisoprolol are commonly used, including patients with hypertension, ischemic heart disease and heart failure. However, the positive impact of the SPC on the risk of hospitalization provides clear evidence of the potential advantages for the patients of using this treatment approach. Furthermore, when the analysis on the average days per hospitalization was limited to hospitalized patients only, the significant difference in this parameter between SPC and FEC groups was substantially attenuated, likely because the sample decreased significantly. Another limitation related to the use of an administrative database for our analyses is the lack of information on the absolute value of cardiovascular risk factors, making it impossible to test whether the impact of the SPC or FEC on hospitalizations and healthcare costs is effectively mediated by improved control of the patient's cardiovascular risk. In addition, information on the reasons for non-adherence were not retrievable from the databases, nor were those related to the type of therapeutic strategies at index date and reasons behind the discontinuation of therapies. Moreover, pharmacologic databases do not provide information on drugs prescribed during hospitalizations. A further limitation is the lack of information on clinical or other potential confounders that could have influenced our results, especially not-measurable variables, including patient attitude towards medication or social status, which could have affected the level of adherence in both cohorts. Finally, the study was conducted only on an Italian population; therefore, its results should be confirmed in other populations.

CONCLUSIONS

The current results support the use of SPC as opposed to FEC in patients requiring treatment with ACE-I combined with a BB as this is associated with better adherence and persistence, lower risk of hospitalization and reduced healthcare costs. The benefits related to the prescription of SPC are already evident 1 year after the original prescription, making its utilization highly cost-effective for patients and National Health Systems.

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Declarations

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