

Impact of Single-Pill Combinations and Level of Adherence on Healthcare Costs in Italian Hypertensive Patients Treated with Perindopril-based Regimens

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INTRODUCTION

Suboptimal adherence to antihypertensive therapy is an important cause of poor blood pressure (BP) control, increased cardiovascular (CV) risk [1,2] and higher healthcare costs [3].

Since pill burden is a key factor influencing medication adherence, the latest guidelines for hypertension endorse the use of **single-pill combinations (SPC)** over **free-pill combinations** for successful antihypertensive therapy [4].



OBJECTIVE

This real-world analysis was performed to evaluate and compare **healthcare resources utilization (HCRU)**, the resulting direct costs, and level of adherence associated with the use of perindopril (**PER**)-based antihypertensive therapy delivered as SPC or free-pill combinations in Italy.



PATIENTS AND METHODS

Study design and data source: This **retrospective** analysis used data extracted from the administrative databases of a sample of Italian Local Health Units (LHUs) corresponding to about 7 million health-assisted.

Study population: The study included adult subjects with a hospitalization discharge diagnosis or an exemption code for **hypertension** between 2011 and 2021 (inclusion period) and with at least one PER-based prescription. Therapeutic schemes were combinations of **PER with amlodipine (AML) and/or indapamide (IND)**, either as SPC or as free-pill combination.

Adherence was measured as the **proportion of days covered (PDC)** over the first 12 months of follow-up. Patients were categorized with good adherence (PDC≥80%), moderate adherence (40%≤ PDC<80%), and poor adherence (PDC <40%).

HCRU and costs: Average HCRU with relative **costs expressed per patient/year** were calculated considering all-cause hospitalizations, CV hospitalizations, all-drugs prescriptions, and delivery of outpatient services. To identify **potential predictors** of costs, a generalized linear model (GLM) was developed, adjusting for confounding variables like age, gender, prior treatments, comorbidities, and pill burden.

RESULTS

SPC users had higher adherence levels

A total of **22,663** patients on SPC and **1,458** patients on free-pill combination regimens were identified. Proportion of adherent patients was **significantly higher among SPC** than with free-pill combination users (75.5% vs 32.0% respectively, p<0.001) (**Fig. 1**).

Higher adherence was associated with decreased HCRU and direct costs

As shown in **Fig. 2**, higher adherence was associated with **decreasing healthcare costs**, overall, and by single cost item (p<0.001).

SPC users had lower HCRU and direct costs

During an average follow-up of 4.5 years, **SPC users had lower rate** (mean ± SD) of **all-cause hospitalizations** (0.2 ± 0.5 vs. 0.4 ± 0.7, p<0.001), **CV hospitalizations** (0.04 ± 0.10 vs. 0.09 ± 0.20, p<0.001), **drug prescriptions** (15.7 ± 9.4 vs.19.7 ± 11.1, p<0.001), and had reduced use of **outpatient specialist services** (4.1 ± 4.7 vs. 4.6 ± 5.2; p<0.001) than free-pill combination users.

SPC users showed significantly **lower relative overall healthcare costs** per patient/year than free-pill combination users. Similar differences were observed when considering each cost item separately (**Fig. 3**).

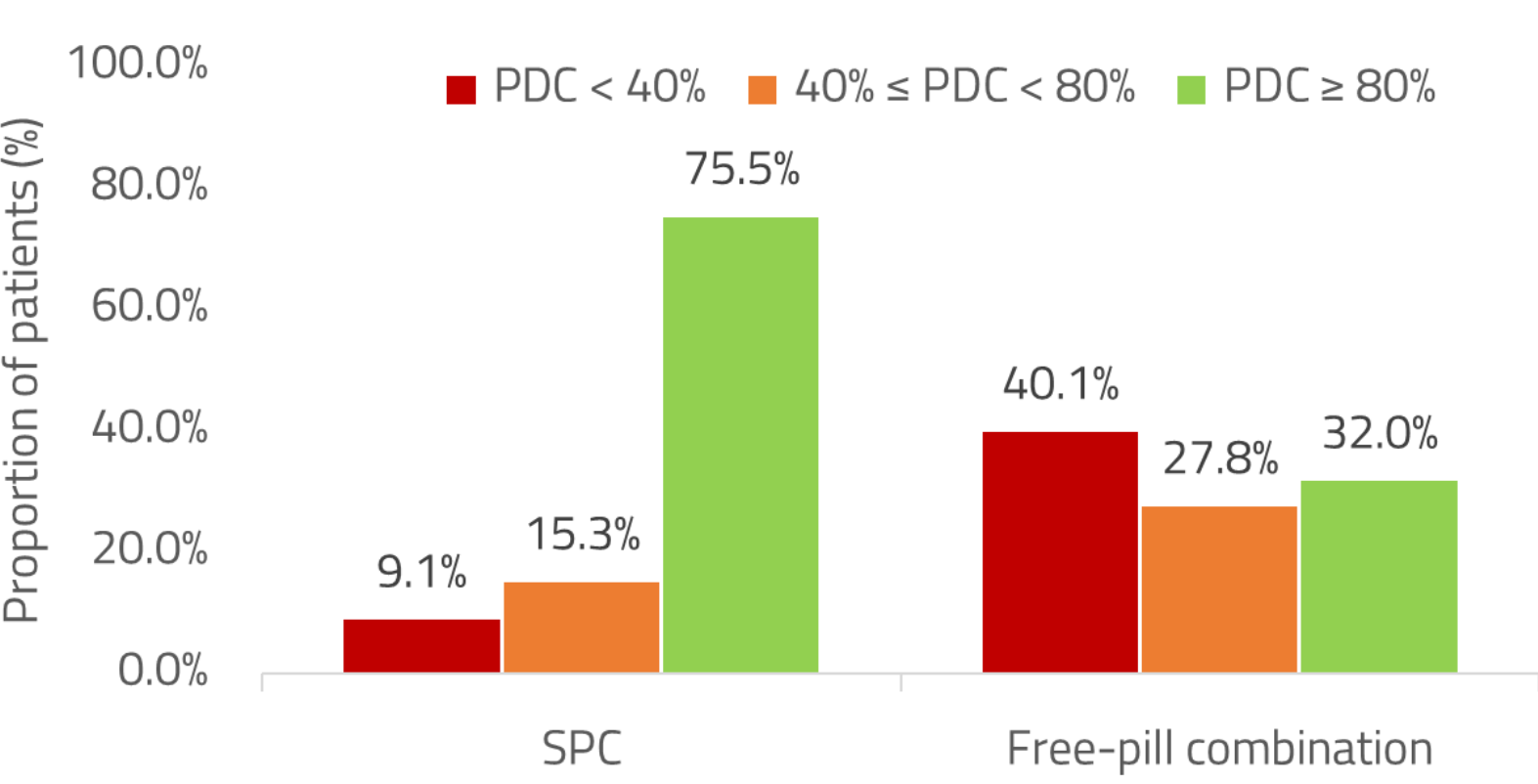


Fig. 1. Proportion of good adherence (PDC≥80%), moderate adherence (PDC 40%-80%) and poor adherence (PDC<40%) in patients on SPC and free-pill combination regimens.

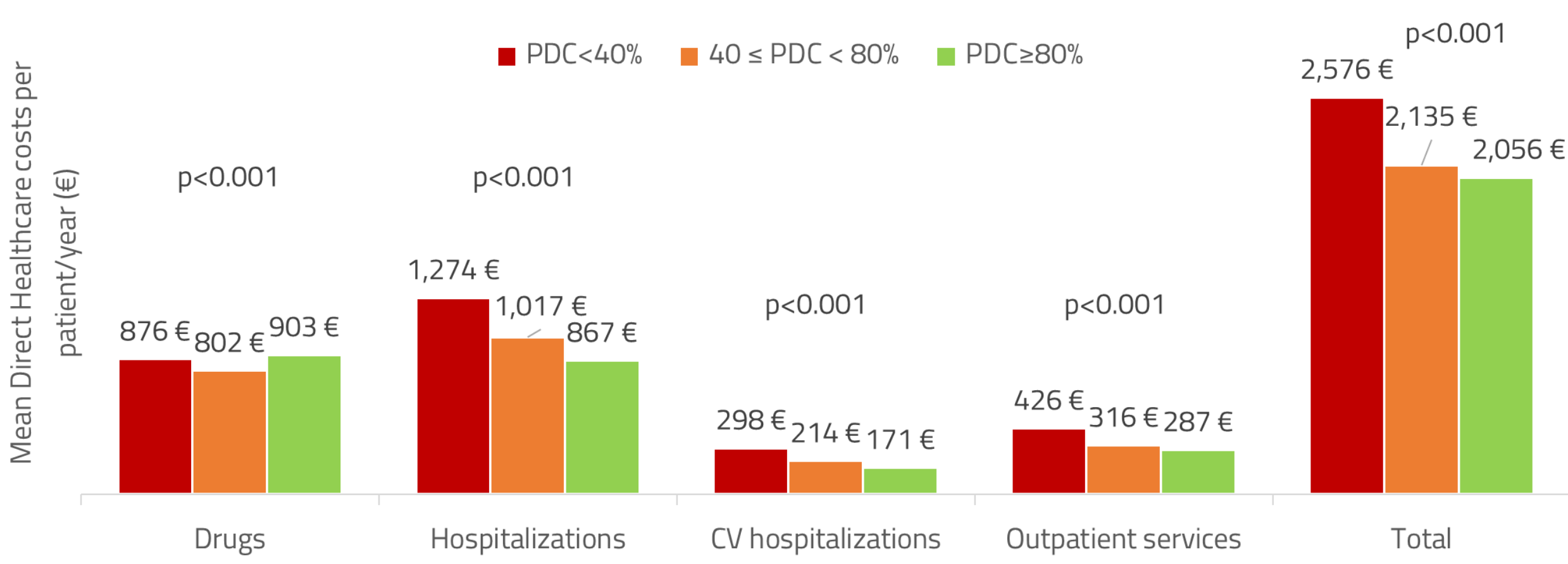


Fig. 2. Healthcare costs per patient/year by adherence levels, total and by cost item (the means of the three groups were compared by ANOVA).

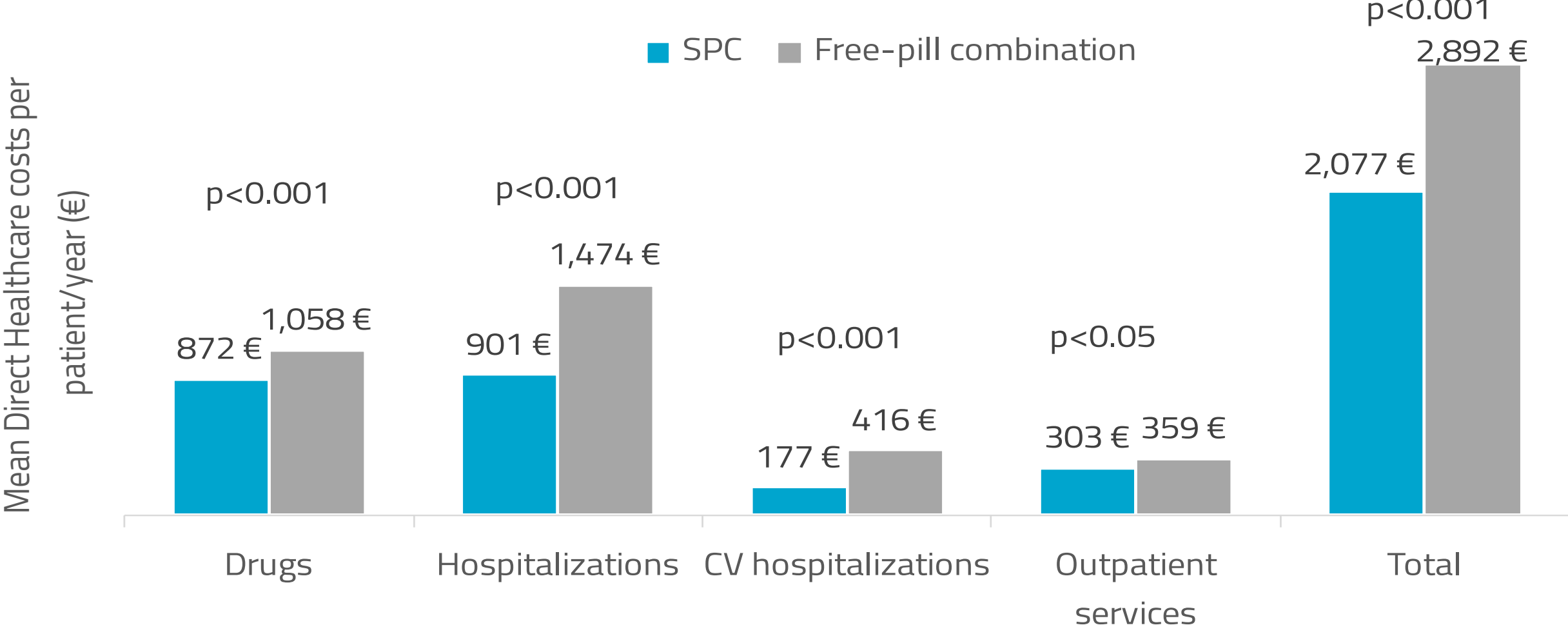


Fig. 3. Healthcare costs per patient/year in SPC vs. free-pill combination users, total and by cost item.

Predictors of healthcare costs

GLM showed that the use of **free-pill combinations resulted in a cost increase +242.96€** per patient/year compared to SPC (95% CI: 55.03-430.89€, p<0.05).

Other predictors of higher healthcare costs were **male gender, older age, and comorbidities** (i.e., renal failure, other cerebrovascular events, diabetes, chronic obstructive pulmonary disease).

Conversely, **good adherence was associated with significant cost reduction -145.82€** per patient/year (95% CI: -263.54€ to -28.10€, p<0.05) (**Table 1**).

	€	95% CI	p-value
Index formulation			
SPC (ref.)	-		
Free-pill combinations	242.96	55.03 430.89	<0.05
Adherence levels			
PDC <40 (ref.)	-		
PDC 40%-80%	-110.07	-242.77 22.63	0.104
PDC ≥80%	-145.82	-263.54 -28.10	<0.05
Gender (ref. female)			
Male	96.27	34.21 158.34	<0.01
Age at index-date			
Age ≥65	32.62	30.88 34.37	<0.001
Comorbidities (Ref. absence)			
Ischemic heart disease	10.81	-242.43 264.05	0.933
Heart failure	235.57	-255.37 726.51	0.347
Renal failure	2,720.90	1,810.92 3,630.88	<0.001
Cerebrovascular events	-8.97	-231.61 213.67	0.937
Other cerebrovascular events	723.32	358.82 1,087.82	<0.001
Diabetes	891.04	761.60 1,020.48	<0.001
Chronic obstructive pulmonary disease	1,178.21	436.93 1,919.49	<0.01
Treatments (Ref. absence)			
Lipid-lowering agents	35.13	-57.85 128.12	0.459
MRAs	411.11	-29.34 851.56	0.067
Beta blocking agents	31.63	-43.84 107.10	0.411
Calcium channel blockers	-31.95	-102.34 38.43	0.374
ACE inhibitors	-176.74	-240.62 -112.87	<0.001
ARBs	-132.80	-212.91 -52.69	0.001
Other antihypertensive	37.26	-98.34 172.86	0.590
Antithrombotic agents	530.27	421.01 639.53	<0.001
Antiarrhythmics	303.91	-24.81 632.62	0.070
Pill burden*	28.25	-6.13 62.62	0.107

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; CI, Confidence Interval; MRAs, mineralocorticoid receptor antagonists; PDC, proportion of days covered; SPC, single-pill combination. *Pill burden stands for the number of different ATC codes (at least 3 prescriptions) among the drugs listed in the table.

CONCLUSIONS

This real-world study conducted in a large Italian real-world clinical practice database showed that:

- The use of **PER-based therapy in the form of SPC** was associated with **lower healthcare resource consumption and costs** compared to free-pill combinations.
- **Good adherence (PDC≥80%)** to antihypertensive therapy resulted in **significantly reduced HCRU and costs**.

These findings support the importance of simplifying treatment regimens by reducing pill burden with the use of SPC. SPC is a valuable strategy to improve adherence to antihypertensive treatment, ultimately resulting in cost savings for the national health system.

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