Original Article

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A real-world analysis of outcomes and healthcare costs of patients on perindopril/indapamide/amlodipine single-pill vs. multiple-pill combination in Italy

Jacques R. Snyman[a], Luiz Aparecido Bortolotto[b], Luca Degli Esposti[c], Pathiyil Balagopalan Jayagopal[d], Alexandra O. Konradi[e], Valentina Perrone[c], and Claudio Borghi[f]

Objectives: This analysis compared adherence, cardiovascular (CV) events and all-cause mortality incidence, and healthcare costs among hypertensive patients treated with perindopril (PER)/indapamide (IND)/amlodipine (AML) in single-pill combination (SPC) vs. multiple-pill combination, in a real-world setting in Italy.

Methods: In this observational retrospective analysis of Italian administrative databases, adult patients treated with PER/IND/AML between 2010 and 2020 were divided into two cohorts: single-pill vs. multiple-pill. Patient data were available for at least one year before and after index date. Propensity score matching (PSM) was applied to reduce selection bias. Adherence was defined as proportion of days covered: non-adherence, <40%; partial adherence, 40–79%, and adherence ≥80%. Mortality incidence and CV events as single, or composite, endpoints were evaluated after first year of follow-up. Healthcare cost analyses were performed from the perspective of the Italian National Health Service.

Results: Following PSM, the single-pill cohort included 12 150 patients, and the multiple-pill cohort, 6105. The SPC cohort had a significantly higher percentage of adherent patients vs. the multiple-pill cohort (59.9% vs. 26.9%, $P < 0.001$). Following the first year of follow-up, incidence of all-cause mortality, and combined endpoint of all-cause mortality and CV events were lower in the SPC cohort compared with multiple-pill cohort. Average annual direct healthcare costs were lower in the single-pill cohort (€2970) vs. multiple-pill cohort (€3642); cost of all drugs and all-cause hospitalizations were major contributors.

Conclusion: The SPC of PER/IND/AML, compared with multiple-pill combination, is associated with higher adherence to medication, lower incidence of CV events and mortality, and reduced healthcare costs.

Keywords: adherence, cost-outcomes, hypertension, Italy, perindopril/indapamide/amlodipine, real-world evidence, single-pill combination

Abbreviations: ACE, angiotensin converting enzyme; AML, amlodipine; ARB, angiotensin receptor blocker; ATC, anatomical-therapeutic chemical; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; CV, cardiovascular; DRG, diagnosis related group; GDPR, General Data Protection Regulation; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IND, indapamide; INHS, Italian National Health Service; LHU, local health units; PDC, proportion of days covered; PER, perindopril; PSM, propensity score matching; RAAS, renin–angiotensin-aldosterone system; SD, standard deviation; SMD, standardized mean difference; SPC, single-pill combination

INTRODUCTION

High systolic blood pressure (BP), the leading risk factor for death in both men and women in 2019, accounted for 19.2% of deaths [1]; with the prevalence of hypertension in men and women globally at 652 million and 626 million, respectively [2]. The largest ($N = 42\,324$) and most detailed meta-analysis of the stratified effects of achieving lower BP [which included 12.3% of individuals with ≥1 cardiovascular (CV) event] demonstrated that for every 5 mmHg reduction in systolic blood pressure (SBP), the relative risk for CV events was lowered by approximately 10% [3]. The Systolic Blood Pressure Intervention Trial (SPRINT) treatment algorithm for achieving SBP of

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[a]Forte Research (Pty ltd) and Private Practice South Africa, Pretoria, South Africa, [b]Instituto do Coraçao, Hospital das Clinicas-FMUSP, Sao Paulo, Brazil, [c]CliCon S.r.l., Società Benefit-Health, Economics & Outcomes Research, Bologna, Italy, [d]Lakshmi Hospital, Palakkad, Kerala, India, [e]Almazov National Medical Research Centre, Saint Petersburg, Russia and [f]Department of Medical and Surgical Sciences, University of Bologna, IRCCS Ospedale S. Orsola, Bologna, Italy

Correspondence to Prof. Jacques R. Snyman, Forte Research (Pty ltd) and Private Practice South Africa, 8 Buckland Road, Cornwall Hill Estate, Irene X10, Pretoria 0178, South Africa. Tel: +27 828838366; e-mail: jacques@dermav.co.za

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<120 mmHg recommended the use of triple drug therapy if <120 mmHg is not achieved with two-drug therapy [4].

The recommended treatment for hypertension includes lifestyle intervention as well as treatment with renin–angiotensin–aldosterone system (RAAS) blockers [angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs)], beta-blockers, calcium channel blockers (CCBs) and, thiazide/thiazide-like diuretics [5]. Most monotherapy drugs have been shown to reduce SBP and diastolic BP, by 10–15 and 5–10 mm Hg, respectively [6]. The recommended target for treatment in Europe is a BP of <140/90 mmHg, and, if tolerated, <130/80 mmHg [5]. European guidelines recommend initial treatment with a two-drug single-pill combination (SPC) in most patients, however if this does not control BP, a three-drug SPC can be used [5]. Treatment for hypertension consists preferentially of a RAAS blocker combined with a CCB and/or a thiazide/thiazide-like diuretic [5]. Triple combination therapy should control BP in >80% of patients whose BP is not controlled by two-drug therapy [5]. For resistant hypertension, additional drugs may be added to the three-drug SPC, with spironolactone [5], which can further reduce BP [7], being the preferred choice (or other diuretic therapy in the case of intolerance), followed by bisoprolol or doxazosin [5]. Combination therapy can reduce possible adverse effects caused by other therapies, such as hypokalemia caused by a diuretic [5].

The number of medications prescribed is a risk factor for non-adherence, with the odds of non-adherence increasing with each additional medication [8]. Poor adherence to treatment has been identified as a contributing factor to poor BP control [5]. Similarly, a lower number of pills, rather than the type of intervention, has been shown to increase the prevalence of BP control [9]. SPCs could offer an opportunity to improve adherence by simplifying treatment, as demonstrated in elderly patients in Italy, who were more adherent to single-pill therapy than a fixed combination therapy of multiple drugs [10]. SPCs are now recommended as the best clinical practice by the World Health Organization [11], and by European guidelines, to efficiently and rapidly control BP [5].

Perindopril (PER)/indapamide (IND)/amlodipine (AML) SPC consists of a fixed dose of an ACE inhibitor, a thiazide-like diuretic, and a calcium channel blocker [12], and was the first triple single-pill to contain this particular combination [13]. This SPC is a substitution therapy for the treatment of essential hypertension in patients in Italy, who are currently receiving separate treatment with a fixed dose combination of PER/IND and AML at the same dose [12]. The efficacy and tolerability of PER/IND/AML SPC has been demonstrated in clinical trials and real-world studies [14–16], however, data relating to the effect of this triple SPC on adherence, clinical outcomes, such as CV events, and healthcare costs in a real-world setting are limited.

The aim of this study was to evaluate and compare adherence to medication, incidence of CV events and all-cause mortality, and healthcare costs among patients with hypertension treated with PER/IND/AML as a single-pill vs. multiple-pill combinations, in a real-world setting in Italy.

METHODS

Data source

This observational retrospective analysis used the administrative databases of a sample of Local Health Units (LHU) covering approximately seven million health-assisted individuals. These databases store all data concerning the healthcare resources reimbursed by the Italian National Health Service (INHS): beneficiaries' database contains patients' demographic data; pharmaceutical database provides the Anatomical-Therapeutic Chemical (ATC) code and marketing authorization code (AIC code) of drug dispensed, number of packages, number of units per package, and prescription date; hospitalization database includes all hospitalization data with admission and discharge dates, discharge diagnosis codes classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), diagnosis-related group (DRG) and DRG-related charge.

To guarantee privacy of patients, an anonymous univocal numerical code was assigned to each participant included in the study, in full compliance with the European General Data Protection Regulation (GDPR) (2016/679). This code allowed the electronic linkage between all different databases. No identifiers related to patients were provided to the authors. All the results of the 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 – no. 9/2014), and the LHU ethics committees approved the study. All data used for the current study are available from CliCon S.r.l., which is the body entitled to data processing by LHUs.

Study design and study population

The objective of this analysis was to evaluate the change in adherence to prescribed medication in hypertensive patients who were treated with PER+IND+AML in multiple-pill combination (two or three pills) (multiple-pill cohort) or PER/IND/AML single-pill formulation (single-pill cohort), and compare the outcomes and healthcare costs between the two groups. During the study period (2010–2020), all adult patients (≥18 years) treated with PER/IND/AML as SPC were included and allocated to the single-pill cohort, while those prescribed with multiple pills were allocated to the multiple-pill cohort (Fig. 1; Table 1, Supplemental Digital Content, http://links.lww.com/HJH/C297). The index date corresponded to the date (±1 month) of the first prescription of the three active ingredients as a multiple-pill combination in the multiple-pill cohort and to the date of first prescription of PER/IND/AML as a SPC in the single-pill cohort. All patients included had at least one year's data available before (characterization period) and after (follow-up) the index date. Exclusion criteria comprised patients with only one prescription of SPC dispensed during the study period, and those who died or moved to another region during the first year of follow-up.

Baseline variables

Data on baseline clinical characteristics and patient demographics were collected at index date. During the

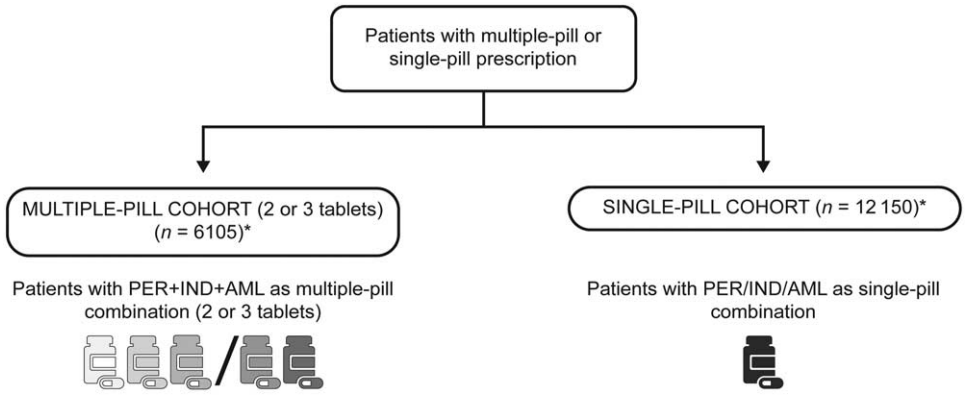


FIGURE 1 Identification of patients with PER/IND/AML multiple-pill vs. single-pill formulation. [a]Post-PSM. AML, amlodipine; IND, indapamide; PER, perindopril.

characterization period, medical history was evaluated by identifying: previous CV events (ischemic heart disease, heart failure, cerebrovascular diseases, peripheral vascular diseases), chronic kidney disease (CKD), and diabetes mellitus hospitalizations. To better assess medical history, the concomitant medicine dispensed during characterization period (as least two prescriptions dispensed), lipid-lowering agents, other antihypertensive treatments (excluding study drugs), and blood glucose lowering agents (Table 2, Supplemental Digital Content, http://links.lww.com/HJH/C297) were integrated in the analyses. Furthermore, presence of anti-inflammatory drugs, antidepressants, antithrombotic agents, antiarrhythmics prior index date was evaluated as well (Table 2, Supplemental Digital Content, http://links.lww.com/HJH/C297).

Adherence to treatment

Adherence was evaluated as proportion of days covered (PDC) by pills, by using the following cut-off: PDC <40% (non-adherence); PDC = 40–79% (partial adherence); PDC ≥80% (adherent). These cut-offs are widely used in the literature to evaluate the levels of adherence [17–19]. Adherence to PER+IND+AML multiple-pill combination was calculated as the PDC by all three molecules (combined in two or three pills), adherence to PER/IND/AML SPC was calculated as the days covered by the single pill. Adherence was evaluated during follow-up after propensity score matching (PSM) (see statistical analysis section).

Clinical outcomes

Incidence of mortality and CV events (ischemic heart disease, heart failure, cerebrovascular diseases, peripheral vascular diseases) (in major diagnosis) as single or composite endpoints were evaluated after the first year of follow-up (and up to the end of data period) and compared between single-pill vs. multiple-pill combination cohorts post-PSM.

Healthcare direct costs analysis

Annualized healthcare direct costs were analyzed during available follow-up period in terms of all drug treatments, all-cause hospitalizations (CV events-related hospitalization) and all outpatient specialist services. Costs were compared among multiple-pill vs. single-pill cohorts post-PSM. The healthcare cost analysis was performed from the perspective of the 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 instrumental and laboratory tests were defined according to tariffs applied by each region.

Statistical analysis

Continuous variables are reported as the mean ± standard deviation (SD), whereas categorical variables are expressed as frequencies and percentages. For comparative analyses, a P value <0.05 was considered for statistical significance. PSM was applied to minimize the selection bias and to reduce potential unbalances both in baseline characteristics and in number of patients among the two cohorts. Patients were matched (matching ratio 2:1, single-pill: multiple-pill) on quintiles of propensity score calculated using a logistic regression model which includes age, sex, comorbidities, concomitant medicines, and medical history (previous CV events, CKD disease, and diabetes mellitus hospitalizations) as previously listed. Standardized mean difference (SMD) values >0.1 is a threshold recommended for declaring imbalance; SMD values above 0.2 are considered small, SMD values >0.5 are considered medium-sized, and SMD values >0.8 are considered large [20]. All analyses were performed using Stata SE version 17.0 (StataCorp, College Station, Texas, USA).

RESULTS

Overall, 37 365 patients (mean age 66.0 years, 54.3% [20 274] male) were identified in the single-pill data pool, and 6105 (mean age 68.2 years, 50.8% [3104] male) in the multiple-pill data pool (of which 97.6%, $n = 5961$ received the two-pill combination plus one). Before PSM, patients in the single-pill data pool were younger, mostly male, and showed a less comorbid profile compared with those with multiple-pill combination, with lower percentages of patients with previous CV events (12.2% single-pill vs. 13.5% multiple-pill, $P < 0.01$), and diabetes mellitus hospitalizations (7.0% single-pill vs. 9.0% multiple-pill, $P < 0.001$) as reported in Table 1. After PSM, the multiple-pill and single-pill cohorts were created and balanced for their

TABLE 1. Baseline characteristics of included patients on multiple-pill vs. single-pill, before and after PSM

	Before PSM			After PSM		
	Data pool multiple-pill ($N = 6105$)	Data pool single-pill ($N = 37\,365$)	*P*-value	Cohort multiple-pill ($N = 6105$)	Cohort single-pill ($N = 12\,150$)	Standardized mean difference
Age, mean (SD)	68.2 (11.9)	66.0 (12.3)	<0.001	68.2 (11.9)	67.8 (11.9)	0.033
Male, n (%)	3104 (50.8)	20 274 (54.3)	<0.002	3104 (50.8)	6 272 (51.6)	0.016
Comorbidity profile						
Without previous CV events, *n* (%)	5280 (86.5)	32 798 (86.1)	<0.01	5280 (86.5)	10 487 (86.3)	0.005
With previous CV events, *n* (%)	825 (13.5)	4567 (12.2)		825 (13.5)	1663 (13.7)	
CKD disease, *n* (%)	50 (0.8)	254 (0.7)	0.226	50 (0.8)	102 (0.8)	0.002
Diabetes mellitus hospitalizations, *n* (%)	548 (9.0)	2629 (7.0)	<0.001	548 (9.0)	1061 (8.7)	0.009

CKD, chronic kidney disease; CV, cardiovascular; PSM, propensity score matching; SD, standard deviation.
Standardized mean difference (SMD) values: >0.1 is a threshold recommended for declaring imbalance.

characteristics and comprised 6105 patients on multiple-pill combination (multiple-pill cohort) vs. 12 150 on SPCs (Table 1) and formed the basis for the study analysis.

Adherence to treatment

There was a significantly higher percentage of adherent patients (PDC $\geq$ 80%) in the single-pill cohort compared with the multiple-pill combination cohort (59.9% single-pill vs. 26.9% multiple-pill, $P < 0.001$; Fig. 2). Accordingly, there were more non-adherent patients in the multiple-pill cohort than in the single-pill cohort (54.0 vs. 20.8%, respectively; $P < 0.001$), while similar values were observed for partial adherence (19% for both cohorts).

Patient outcomes

After the first year of follow-up, mortality rate was lower in the single-pill cohort (29.9 per 1000-person/year, mean follow-up 1.6 ± 0.9 years) vs. multiple-pill cohort (33.7 per 1000-person/year, mean follow-up 3.3 ± 2.3 years) ($P < 0.05$; Fig. 3a). Similarly, a lower incidence of death and CV events as a composite endpoint was seen in patients who were prescribed single pills, 105.8 per 1000-person/year (mean follow-up 1.6 ± 0.9 years) compared with 139.0 per 1000-person/year (mean follow-up 3.0 ± 2.2 years) ($P < 0.001$) for patients on multiple pills (Fig. 3b).

Healthcare costs

Average annual direct healthcare costs evaluated during the available follow-up period were lower in the single-pill (€2970) cohort than in the multiple-pill cohort (€3642) ($P < 0.05$; Fig. 4). The major contributors to costs were expenditures related to the cost of all drugs (€1808 in multiple-pill vs. €1525 in single-pill cohort, $P = 0.118$) and all-cause hospitalizations (€1262 in multiple-pill vs. €953 in single-pill cohort, $P < 0.05$; Fig. 4).

DISCUSSION

In this Italian real-world study involving patients with hypertension, the beneficial effects of single-pill combination therapy were demonstrated by improved patient adherence and better clinical outcomes, compared with patients who were prescribed multiple pills. Administration of SPC was associated with fewer CV events, and lower mortality rates and treatment costs. Dual single-pill combinations as initial treatment for hypertension is now recommended by the most recent international guidelines, and, for patients who remain uncontrolled, triple single-pill combinations (triple SPC), including RAAS inhibitor, CCB and diuretic as the second step is recommended [5]. SPC-based strategy is associated with more efficient and rapid BP control, but also with improved adherence [21], clinical

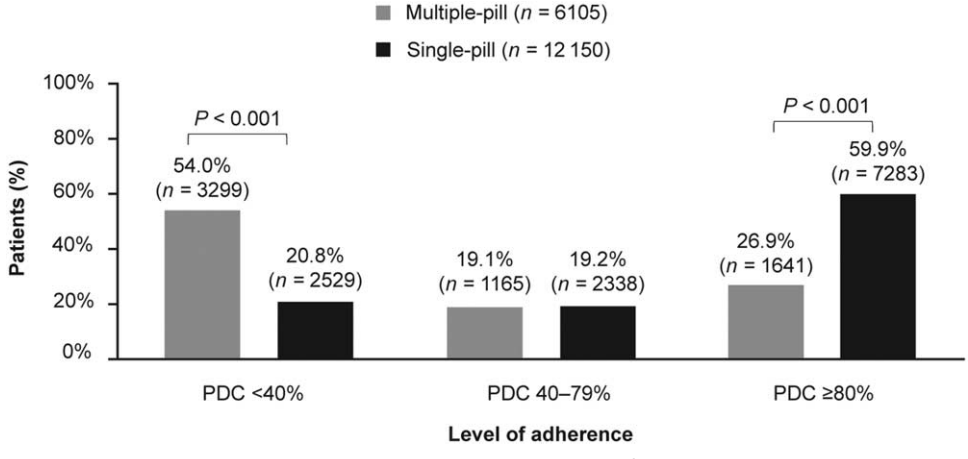
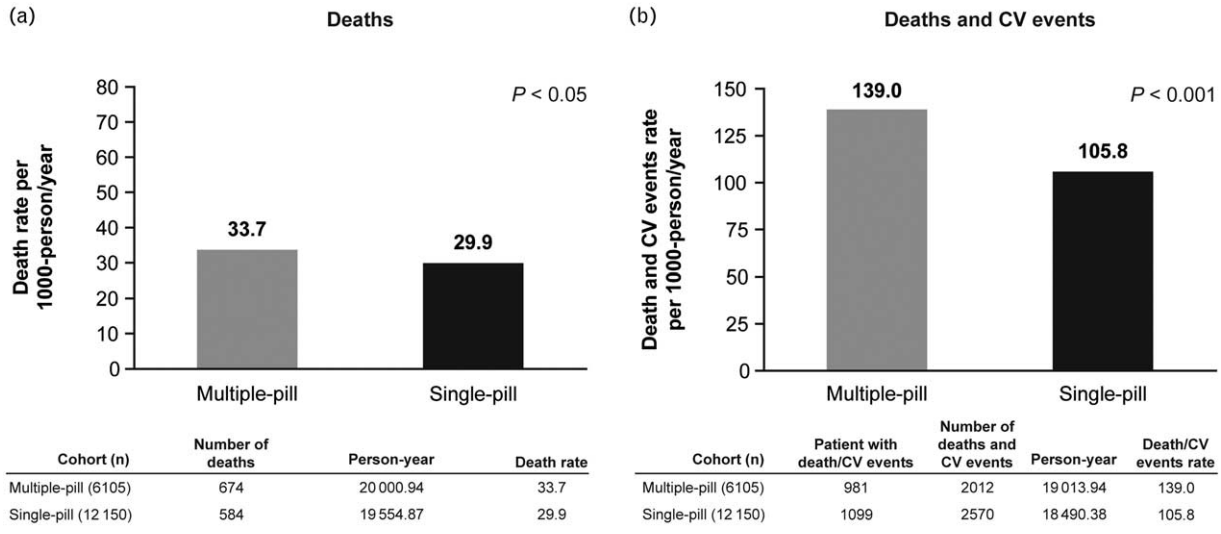


FIGURE 2 Adherence to treatment in patients under multiple-pill vs. SPC, post-PDM, PDC, proportion of days covered; PSM, propensity score matching.



Cohort (n)	Number of deaths	Person-year	Death rate
Multiple-pill (6105)	674	20 000.94	33.7
Single-pill (12 150)	584	19 554.87	29.9

Cohort (n)	Patient with death/CV events	Number of deaths and CV events	Person-year	Death/CV events rate
Multiple-pill (6105)	981	2012	19 013.94	139.0
Single-pill (12 150)	1099	2570	18 490.38	105.8

FIGURE 3 Incidence rate of death (a) and death/CV events (composite endpoint) (b) in patients under multiple-pill vs. SPC, post-PSM, during 1-year follow-up. CV events: ischemic heart, heart failure, cerebrovascular disease, peripheral vascular disease. CV, cardiovascular; PSM, propensity score matching.

outcomes and reduced deaths, providing long-term benefit for patients [22]. The benefits of triple single-pill combination over dual single-pill combination treatments in relation to efficacy, and achievement of BP control have been demonstrated in clinical practice [23]. Effective control of BP in patients with uncontrolled hypertension treated with triple PER/IND/AML SPC has also been reported in several observational studies, conducted using real-world data gathered from routine clinical practice [14,15,24–26].

One recent study [27] demonstrated that major CV events over a 12-year follow-up period were lower in a triple combination PER/IND/AML cohort than in patients treated with ACE-inhibitors + CCBs + thiazides or ARBs + CCBs + thiazides, with 4.6 vs. 8.8 and 8.6%, respectively ($P < 0.05$). The same was true for incidences of left ventricular hypertrophy throughout the study period (2012–2020), at 4.2 vs. 8.4 and 6.9%, respectively ($P < 0.05$) [27].

The results presented here show that patients are more adherent to antihypertensive treatment when prescribed a SPC compared with having to take multiple (two or three) pills per day ($P < 0.001$). These results are supported by similar real-world evidence studies in Italy, for SPC of PER/AML (the AMPERES study) [28], Greece, for SPC of PER/IND/AML [25], and Korea, for SPCs of ARB/CCB therapy [29], which found an improvement in adherence when patients were treated with a SPC [25,28,29]. A real-world study in Italy showed that blood pressure control was better when fewer pills were used for triple combination therapy [9]. Only two randomized controlled trials have demonstrated that treatment with a triple SPC, when compared to a multiple-pill treatment option, resulted in better adherence with reduced pill burden [30,31].

Adherence to antihypertensive treatment is associated with long-term benefits by reducing risk of major adverse CV events [32]. The current study reports that the rate for both mortality and the composite endpoint of death and CV events, was significantly lower for those receiving a single-pill formulation compared to a multiple-pill combination ($P < 0.05$ and $P < 0.001$, respectively). A meta-analysis assessing SPC treatment compared to equivalent multiple-pill combination therapy, also concluded that patient outcomes improved in those with hypertension and/or

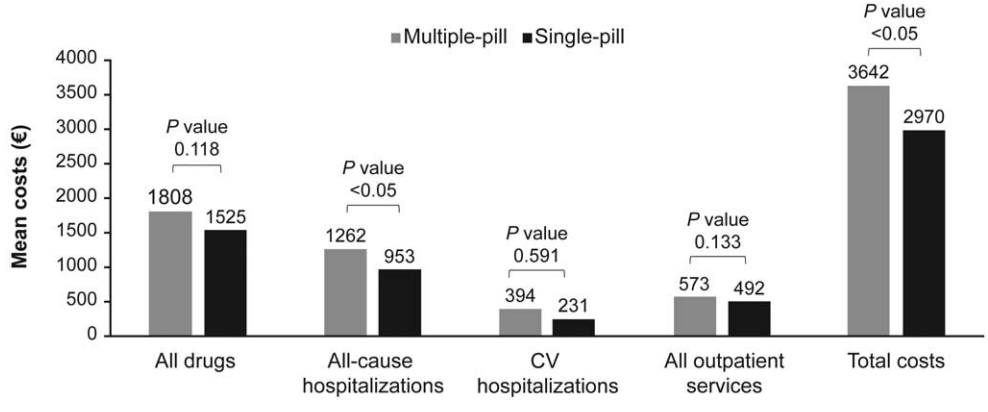


FIGURE 4 Average annual direct healthcare costs in patients under multiple-pill vs. single-pill formulation, post-PSM. Total costs (average annual direct healthcare costs) included the sum of all drugs, all-cause hospitalizations and all outpatient services. CV, cardiovascular; PSM, propensity score matching.

dyslipidemia receiving SPC [33]. The impact on disease outcomes was also observed in a real-world Australian study which found that the risk of mortality of patients was reduced when patients were treated with a SPC of AML + PER compared to treatment with multiple pills [34]. Findings from the real-world Italian AMPERES study demonstrated that those patients at baseline receiving SPC therapy suffered significantly fewer CV events, compared to those treated with multiple pills ($P < 0.001$).[28] Furthermore, interventional studies comparing a triple SPC to multiple pill combinations have demonstrated a reduction in the likelihood of disease progression in patients with hypertension, and in those with hypertension associated with obesity and diabetes [35,36].

Another important issue is cost of life-long therapy in hypertension, however real-world healthcare cost data comparing multiple-pill and single-pill combinations are also limited. In our study, as observed in other studies, the cost related to outcomes was addressed by the event rate. The direct healthcare costs for the multiple-pill cohort were higher than in single-pill cohort, and a major contributor was hospital costs due to a higher event rate. Similar results were found in another real-world study in Italy, where free combination treatment had higher median costs per patient than single-pill combination treatment [37].

Although the focus of this study was to evaluate the outcomes and healthcare costs of SPC compared to multiple-pill combination in the treatment of hypertension, the importance of detecting the cause of hypertension, secondary or not, and taking this, and any comorbidities, into consideration when choosing a treatment strategy [5] should be noted.

The value of real-world data in hypertension, in particular the use of databases, complementary to evidence from randomized clinical trials (RCTs), has been highlighted recently [38]. Databases allow for information to be collected over longer time periods, and provide a large amount of data, which can be quickly available [38,39]. In addition, real-world data may offer an optimal setting in which to evaluate real-world phenomena – such as therapeutic inertia and poor treatment adherence, which cannot be assessed in the RCT setting [38].

It is important to note that this study has some limitations. As an administrative database was used, data on potential confounders such BP values, BMI and other clinical parameters are not available. The time of the introduction of the PER/IND/AML SPC to the market may have resulted in a shorter follow-up duration and in younger patients with a less comorbid profile being initiated on the SPC treatment, although age and comorbidities were taken into account in the PSM. In addition, diabetes is known to influence cardiovascular risk in patients with hypertension [5] and was present in patients from both cohorts. Following PSM, diabetes was evenly distributed in the cohorts included in the analysis. Further limitations of the study design include the fact that data on concomitant treatment prescribed to the patients were gathered only at baseline and not during follow-up, and these data were obtained only in one country (Italy), and therefore the generalization of these results to the entirety of the European or global population may be restricted.

In conclusion, this Italian real-world study of patients with hypertension demonstrates the multiple benefits of triple SPC for patients and funders by reducing pill burden, mortality, and costs. These findings resonate with that of others in the same setting demonstrating the pharmacological advantages of PER/IND/AML combination [27] as a single pill.

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Previous presentations: Abstracts reporting these data were presented at the International Society of Hypertension (ISH) and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Europe congresses. The abstract presented at ISH 2022, 12–16 October 2022, Japan, was entitled: A real-world analysis of pharmaco-utilization and outcomes of patients on perindopril/amlodipine/indapamide free vs. single-pill combination in Italy. The abstract presented at ISPOR Europe 2022, 6–9 November 2022, Vienna, was entitled: Do triple single-pill combinations make a difference in treatment adherence, outcomes and healthcare resource utilization in hypertension? A real-world analysis of patients on perindopril/amlodipine/indapamide in Italy.

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Conflicts of interest

J.R.S. declares support for the present manuscript from Servier; grants or contracts from Servier; consulting fees from Servier; payment or honoraria from Servier; and support for attending meetings and/or travel from Servier. L.A.B. declares consulting fees from Servier; consulting fees from Medtronics to their institution; and payment or honoraria from Servier and Merck. P.B.J. declares support for the present manuscript from Servier; and consulting fees from Servier. A.K. declares support for the present manuscript from Servier; consulting fees from Servier; and payment or honoraria from Servier, Novartis, KRKA, and Shtada. L.D.E. and V.P. have no conflicts of interest. C.B. declares support for the present manuscript from Servier; consulting fees from Sanofi, Novo Nordisk, Alfasigma, Gilead, Recordati, Novartis, and Amarin; payment or honoraria from Servier, Menarini Asia-Pacific, Berlin Chemie, Novo Nordisk, and Gilead; and participation on a data safety monitoring board or advisory board for Alfasigma, Amarin, Boehringer Ingelheim, AstraZeneca, and Novartis.

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