A retrospective, observational study of adherence, persistence and clinical outcomes with perindopril-based single-pill or free-pill antihypertensive treatments

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SUPPLEMENTARY MATERIALS

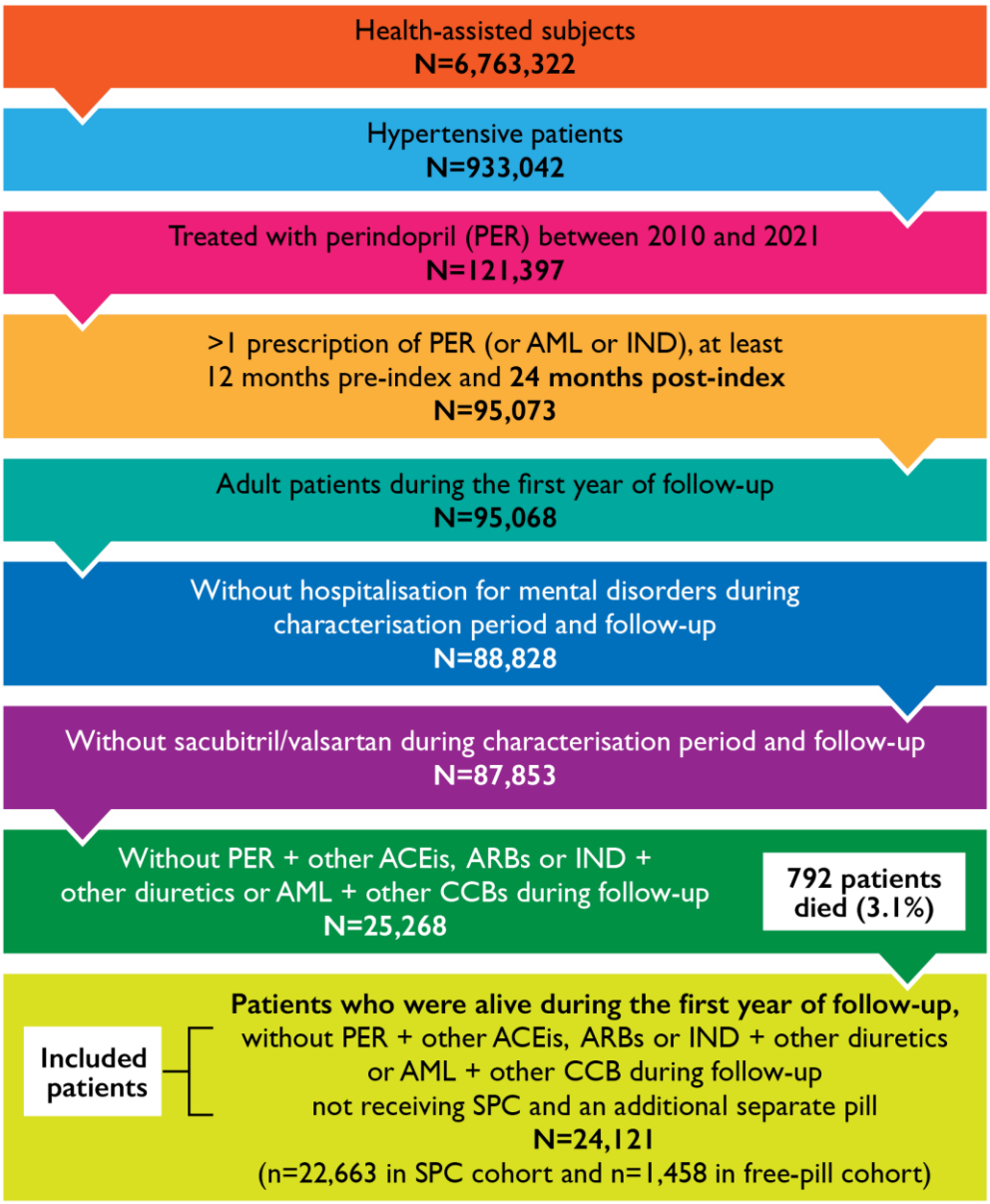

Figure S1 Flow chart showing application of inclusion and exclusion criteria to select data for analyses.

ACEis, angiotensin-converting enzyme inhibitor; AML, amlodipine; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; IND, indapamide; SPC, single-pill combination.

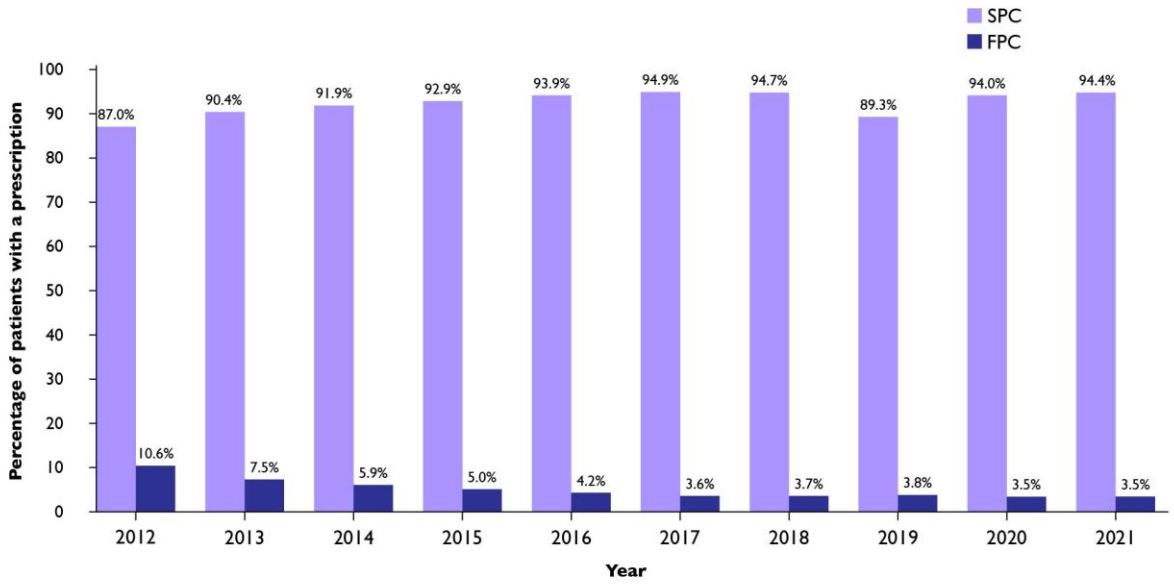

Figure S2 Annual prescription rates of PER-based therapies in the form of SPCs or FPCs between 2012 and 2021.

FPC, free-pill combination; PER, perindopril; SPC, single-pill combination.

Table S1 Ethics review committees and approval numbers

Ethics committee	**Protocol number**	**Approval date**
BAT (Barletta-Andria-Trani) Comitato etico interprovinciale Area I	68/CE/20	3/12/2020
Foggia Comitato etico interprovinciale Area I	63/CE/20	3/12/2020
Frosinone Comitato Etico Lazio 2	0179046/2020	28/10/2020
Genova Comitato Etico Regionale Liguria	0179046/2020	14/06/2021
Napoli 3 Comitato Etico Interaziendale Campania Sud	51	02/09/2020
Roma 5 Comitato Etico Lazio 1	1166/CE Lazio 1	12/10/2020
Roma 6 Comitato Etico Lazio 2	0216084/2020	16/12/2020
Taranto Comitato Indipendente di Etica Medica	48144	28/05/2021
Umbria 2 Comitato Etico Regionale Umbria	19414/20/ON	16/09/2020
Vercelli Comitato Etico Interaziendale A.O. SS. Antonio e Biagio e Cesare Arrigo – Alessandria	0008668	20/04/2021
Viterbo Comitato Etico Lazio 1	1080/CE Lazio 1	23/09/2020

Table S2 Exclusion criteria

Only one prescription of PER (or AML or IND) during the study period (occasional users)
Follow-up <1 year, including due to death within 1 year of the index date
Diagnosis of mental disorders during the characterisation and/or follow-up period, defined by the presence of a hospitalisation discharge diagnosis at any level for mental, behavioural or neurodevelopmental disorders (ICD-9-CM 290–319, Supplementary Table 2)
At least one prescription of sacubitril/valsartan during the characterisation and/or follow-up period
At least one prescription of ACEis other than PER during follow-up, regardless of whether the drug exposure represented a switch or concomitant use during follow-up, including (ATC Classification System): • Plain ACEis (C09AA) • ACEis and diuretics (C09BA) • ACEis and CCBs (C09BB) • Other ACEi combinations (C09BX)
At least one prescription of any ARB during follow-up, regardless of whether the drug exposure represented a switch or concomitant use during follow-up, including (ATC Classification System): • Plain ARBs (C09CA) • ARBs and diuretics (C09DA) • ARBs and CCBs (C09DB) • Other ARB combinations (C09DX01, C09DX03)
At least one prescription of IND and any other diuretic during follow-up, including (ATC Classification System): • Thiazides (C03A) • Low-ceiling diuretics, excluding thiazides (C03B) • High-ceiling diuretics (C03C) • Diuretics and potassium-sparing agents (C03E) • Other diuretics (C03X)
At least one prescription of AML and any other CCB, regardless of whether the drug exposure represented a switch or concomitant use during follow-up, including (ATC Classification System): • Selective CCBs with mainly vascular effects (C08C) • Selective CCBs with direct cardiac effects (C08D) • Non-selective CCBs (C08E) • CCBs and diuretics (C08G)

Table S3 ICD-9-CM codes used to identify and exclude patients with previous mental disorders.

Diagnosis	ICD-9-CM codes
Dementias	290
Alcohol-induced mental disorders	291
Drug-induced mental disorders	292
Transient organic psychotic conditions	293
Persistent mental disorders due to conditions classified elsewhere	294
Schizophrenic disorders	295
Episodic mood disorders	296
Delusional disorders	297
Other nonorganic psychoses	298
Pervasive developmental disorders	299
Anxiety, dissociative and somatoform disorders	300
Personality disorders	301
Sexual and gender identity disorders	302
Alcohol dependence syndrome	303
Drug dependence	304
Nondependent abuse of drugs	305
Physiological malfunction arising from mental factors	306
Special symptoms or syndromes not elsewhere classified	307
Acute reaction to stress	308
Adjustment reaction	309
Specific nonpsychotic mental disorders due to brain damage	310
Depressive disorder, not elsewhere classified	311
Disturbance of conduct, not elsewhere classified	312
Disturbance of emotions specific to childhood and adolescence	313
Hyperkinetic syndrome of childhood	314
Specific delays in development	315
Psychic factors associated with diseases classified elsewhere	316
Intellectual disabilities	317–319

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

Table S4 Codes used for categorisation of baseline diagnoses.

Variable	Codes
Hospitalisation for hypertension	ICD-9-CM codes: 401–405
Exemption for hypertension	Exemption codes: A31, 031
Ischaemic heart diseases[a]	ICD-9-CM codes: 410–414
Heart failure[a]	Exemption code: 021 OR ICD-9-CM codes: 428, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93
Renal failure	Exemption code: 023 OR ICD-9-CM codes: 404, 584–588
Cerebrovascular conditions[a]	ICD-9-CM codes: 430–438
Other cardiovascular conditions	ICD-9-CM codes: 427, 429, 440–443
Diabetes	Exemption code: 013 Antidiabetic drugs ATC code: A10 ICD-9-CM codes: 250, 357.2, 362.0, 366.41, 648.0
Chronic obstructive pulmonary disease (COPD)	Exemption code: 057 ICD-9-CM codes: 491, 493.2, 496

ATC, Anatomical Therapeutic Chemical; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

[a]Codes taken into account for definition of the composite of all cardiovascular events

Table S5 ATC codes for drugs associated with specific diagnoses during the characterisation period.

Drugs	ATC codes
Lipid-modifying agents	C10
Statins	C10AA, C10BX
Fibrates	C10AB
Bile acid sequestrants	C10AC
Nicotinic acid and derivatives	C10AD
Other lipid modifying agents	C10AX
Combinations of various lipid-modifying agents	C10BA
Antihypertensive treatments	
Diuretics	C03
Low ceiling diuretics, thiazides	C03A
Low-ceiling diuretics, excl. thiazides	C03B
High-ceiling diuretics	C03C
Diuretics and potassium-sparing agents in combination	C03E
Other diuretics	C03X
Mineralocorticoid receptor antagonists	C03DA
Beta blocking agents	C07
Beta blocking agents	C07A
Beta blocking agents and thiazides	C07B
Beta blocking agents and other diuretics	C07C
Beta blocking agents, thiazides and other diuretics	C07D
Beta blocking agents and vasodilators	C07E
Beta blocking agents, other combinations	C07F
Calcium channel blockers	C08
Selective calcium channel blockers with mainly vascular effects	C08C
Selective calcium channel blockers with direct cardiac effects	C08D
Non-selective calcium channel blockers	C08E
Calcium channel blockers and diuretics	C08G
ACE inhibitors	C09AA, C09BA, C09BB, C09BX
Angiotensin II receptor blockers (ARBs)	C09CA, C09DA, C09DB
ARBs and other combinations	C09DX01, C09DX03
Other antihypertensives	C02A, C02AB, C02AC, C02C, C02KX, C02L
Antithrombotic agents	B01
Vitamin K antagonists	B01AA
Heparin group	B01AB
Platelet aggregation inhibitors excl. heparin	B01AC
Enzymes	B01AD
Direct thrombin inhibitors	B01AE
Direct factor Xa inhibitors	B01AF
Other antithrombotic agents: Fondaparinux	B01AX05
Antiarrhythmics, Class I and III	C01B
Antiarrhythmics, class Ia	C01BA
Antiarrhythmics, class Ib	C01BB
Antiarrhythmics, class Ic	C01BC
Antiarrhythmics, class III	C01BD
Other antiarrhythmics, class I and III	C01BG
Antidiabetics	A10A, A10BJ, A10B
SGLT2 inhibitors	A10BK01, A10BK02, A10BK03

ACE, angiotensin-converting enzyme; ATC, Anatomical Therapeutic Chemical; SGLT2, sodium–glucose cotransporter-2.

Table S6 Analysis of potential confounding factors in patients treated with SPC or FPC after inverse probability weighting.

Potential confounding factors	Single-pill combination (n=22,663)	Free-pill combination (n=1,458)	Standardised mean difference (SMD)*
Age at index date (years), mean (SD)	64.6 (12.3)	63.8 (13.4)	0.069
Male sex, n (%)	13,485 (59.7)	930 (60.6)	0.017
Ischemic heart disease, n (%)	901 (4.0)	99 (6.5)	0.115
Heart failure, n (%)	340 (1.5)	34 (2.2)	0.059
Kidney failure, n (%)	338 (1.5)	19 (1.3)	0.017
Cerebrovascular events, n (%)	813 (3.6)	86 (5.6)	0.085
Other cardiovascular events, n (%)	712 (3.2)	65 (4.3)	0.055
Diabetes, n (%)	4,916 (21.8)	323 (21.1)	0.017
Chronic obstructive pulmonary disease, n (%)	260 (1.2)	21 (1.4)	0.016
Lipid-lowering agents, n (%)	7,243 (32.1)	485 (31.6)	0.010
Mineralocorticoid receptor antagonists, n (%)	341 (1.5)	36 (2.4)	0.062
Beta-blocking agents, n (%)	7.243 (32.1)	545 (35.5)	0.074
Calcium channel blockers, n (%)	6,068 (26.9)	308 (20.1)	0.144
Angiotensin converting enzyme inhibitors, n (%)	11,744 (52.0)	772 (50.3)	0.036
Angiotensin receptor blockers, n (%)	5,387 (23.9)	369 (24.0)	0.005
Other antihypertensives, n (%)	1,883 (8.3)	150 (9.8)	0.055
Antithrombotic agents, n (%)	7,819 (34.6)	542 (35.3)	0.014
Antiarrhythmics, n (%)	652 (2.9)	46 (3.0)	0.007
Pill burden, mean (SD)	0.8 (0.3)	0.7 (1.2)	0.010
Charlson Comorbidity Index, mean (SD)	0.4 (0.7)	0.4 (0.7)	0.075
Year of inclusion, n (%)			0.191
2011	1,139 (5.0)	67 (4.4)	
2012	1,213 (5.4)	64 (4.2)	
2013	3,379 (15.0)	143 (9.3)	
2014	2,942 (13.0)	154 (10.1)	
2015	2,007 (8.9)	137 (8.9)	
2016	2,208 (9.8)	176 (11.5)	
2017	2,410 (10.7)	182 (11.9)	
2018	2,400 (10.6)	208 (13.6)	
2019	2,543 (11.3)	202 (13.2)	
2020	2,344 (10.4)	201 (13.1)	

*SMD<0.2 means that groups are balanced. For this study groups were balanced for all covariates.

FPC, free-pill combination; SPC, single-pill combination.

Table S7 Multivariable regression model for predictors of high adherence (PDC≥80%) from 2012 to 2021, assessed following application of IPW.

	2012	**2013**	**2014**	**2015**	**2016**
	OR [95% CI]	**OR [95% CI]**	**OR [95% CI]**	**OR [95% CI]**	**OR [95% CI]**
Free-pill combination (ref.)	1.00	1.00	1.00	1.00	1.00
SPC	5.26 [4.48–6.170][§]	5.68 [5.00–6.41][§]	5.26 [4.67–5.92][§]	5.21 [4.61–5.88][§]	5.35 [4.74–6.06][§]
Sex (ref. F)	1.17 [1.05–1.30][^]	1.36 [1.27–1.47][§]	1.33 [1.25–1.42][§]	1.26 [1.19–1.34][§]	1.30 [1.22–1.38][§]
Age at inclusion	1.01 [1.00–1.01][^]	1.01 [1.00–1.01][§]	1.01 [1.00–1.01][§]	1.01 [1.00–1.01][§]	1.01 [1.00–1.01][§]
CCI	1.04 [0.97–1.11]	1.0 [0.95–1.04]	1.03 [0.99–1.07]	0.99 [0.95–1.02]	1.03 [0.99–1.07]
Pill burden[a]	1.14 [1.10–1.19][§]	1.11 [1.08–1.14][§]	1.13 [1.10–1.16][§]	1.08 [1.05–1.12][§]	1.06 [1.03–1.09][§]
	2017	**2018**	**2019**	**2020**	**2021**
	OR [95% CI]	**OR [95% CI]**	**OR [95% CI]**	**OR [95% CI]**	**OR [95% CI]**
Free-pill combination (ref.)	1.00	1.00	1.00	1.00	1.00
SPC	5.52 [4.85–6.29][§]	4.97 [4.38–5.62][§]	4.88 [4.33–5.49][§]	4.74 [4.20–5.35][§]	5.21 [4.61–5.88][§]
Sex (ref. F)	1.29 [1.22–1.37][§]	1.25 [1.18–1.31][§]	1.23 [1.17–1.30][§]	1.21 [1.14–1.27][§]	1.22 [1.16–1.29][§]
Age at inclusion	1.01 [1.00–1.01][§]	1.01 [1.00–1.01][§]	1.01 [1.00–1.01][§]	1.08 [1.00–1.01][§]	1.01 [1.00–1.01][§]
CCI	0.98 [0.95–1.01]	0.98 [0.95–1.01]	0.98 [0.95–1.01]	0.97 [0.94–1.00][#]	1.02 [0.99–1.06]
Pill burden*	1.10 [1.07–1.13][§]	1.01 [0.99–1.04]	1.01 [0.98–1.04]	1.05 [1.02–1.08][^]	1.01 [0.97–1.04]

[#]*P*<0.05; [^]*P*<0.01; [§]*P*<0.001.

[a]Pill burden was calculated as the number of different cardiovascular medications chronically administered (at least three prescriptions among the treatments listed in Table 1).

CCI, Charlson Comorbidity Index; CI, confidence interval; IPW, inverse probability weighting; OR, odds ratio; PDC, proportion of days covered by treatment; SPC, single-pill combination.

Table S8 Cox proportional hazard model for predictors of all-cause mortality, cardiovascular/cerebrovascular outcomes, and the composite outcome of cardiovascular events / all-cause mortality. Outcome rates assessed following application of IPW.

	All-cause mortality	**Composite cardiovascular events**	**Ischaemic heart disease**	**Heart failure**
	HR [95% CI]	**HR [95% CI]**	**HR [95% CI]**	**HR [95% CI]**
Free-pill combination (ref.)	1.00	1.00	1.00	1.00
SPC	0.73 [0.66–0.81]§	0.69 [0.61–0.78]§	0.78 [0.60–1.00]#	0.81 [0.61–1.08]
Sex (ref. F)	1.24 [1.16–1.33]§	1.54 [1.42–1.67]§	2.16 [1.83–2.54]§	1.16 [0.96–1.40]
Age at inclusion	1.11 [1.10–1.11]§	1.05 [1.04–1.05]§	1.01 [1.01–1.02]§	1.10 [1.09–1.12]§
CCI	1.35 [1.32–1.39]§	1.18 [1.13–1.22]§	1.17 [1.09–1.25]§	1.35 [1.26–1.44]§
Pill burden[a]	1.01 [0.99–1.04]	1.07 [1.05–1.10]§	1.11 [1.07–1.16]§	1.10 [1.04–1.16]§
	Cerebrovascular events	**Other cardiovascular events**	**Composite (all-cause mortality and all cardiovascular events)**	
	HR [95% CI]	**HR [95% CI]**	**HR [95% CI]**	
Free-pill combination (ref.)	1.00	1.00	1.00	
SPC	0.54 [0.45–0.66]§	0.78 [0.61–1.01]	0.71 [0.65–0.78]§	
Sex (ref. F)	1.24 [1.09–1.42]^	1.81 [1.55–2.12]§	1.40 [1.32–1.48]§	
Age at inclusion	1.06 [1.05–1.07]§	1.03 [1.03–1.04]§	1.07 [1.07–1.08]§	
CCI	1.14 [1.07–1.21]§	1.19 [1.11–1.27]§	1.27 [1.24–1.30]§	
Pill burden[a]	1.02 [0.98–1.07]	1.09 [1.04–1.14]§	1.04 [1.02–1.06]§	

#$P<0.05$; ^$P<0.01$; §$P<0.001$.

[a]Pill burden was calculated as the number of different cardiovascular medications chronically administered (at least three prescriptions among the treatments listed in Table 1).

CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; IPW, inverse probability weighting; SPC, single-pill combination.

Table S9 Cox proportional hazard model for associations of adherence level with all-cause mortality, cardiovascular/cerebrovascular outcomes, and the composite outcome of cardiovascular events / all-cause mortality. Outcome rates assessed following application of IPW.

	All-cause mortality	**Composite cardiovascular events**	**Ischaemic heart disease**	**Heart failure**
	HR [95% CI]	**HR [95% CI]**	**HR [95% CI]**	**HR [95% CI]**
Moderate/low adherence, PDC <80% (ref.)	1.00	1.00	1.00	1.00
High adherence, PDC ≥80%	0.78 [0.72–0.83]§	0.79 [0.73–0.86]§	0.83 [0.71–0.97]#	0.87 [0.71–1.06]
Sex (ref. F)	1.26 [1.17–1.34]§	1.44 [1.44–1.70]§	2.18 [1.85–2.57]§	1.17 [0.97–1.41]
Age at inclusion	1.11 [1.11–1.11]§	1.05 [1.04–1.05]§	1.01 [1.01–1.02]§	1.11 [1.09–1.12]§
CCI	1.35 [1.32–1.38]§	1.17 [1.13–1.22]§	1.16 [1.09–1.25]§	1.35 [1.26–1.44]§
Pill burden[a]	1.02 [1.00–1.05] #	1.09 [1.06–1.11]§	1.12 [1.07–1.17]§	1.10 [1.05–1.16]§
	Cerebrovascular events	**Other cardiovascular events**	**Composite (all-cause mortality and all cardiovascular events)**	
	HR [95% CI]	**HR [95% CI]**	**HR [95% CI]**	
Free-pill combination (ref.)	1.00	1.00	1.00	
SPC	0.67 [0.59–0.77]§	0.97 [0.82–1.14]	0.78 [0.74–0.83]§	
Sex (ref. F)	1.28 [1.12–1.46] §	1.82 [1.55–2.13]§	1.42 [1.34–1.50]§	
Age at inclusion	1.06 [1.05–1.07]§	1.03 [1.03–1.04]§	1.07 [1.07–1.08]§	
CCI	1.14 [1.07–1.21]§	1.19 [1.11–1.27]§	1.27 [1.24–1.30]§	
Pill burden[a]	1.04 [1.00–1.08]	1.09 [1.04–1.14]§	1.05 [1.03–1.07]§	

#$P<0.05$; §$P<0.001$.

[a]Pill burden was calculated as the number of different cardiovascular medications chronically administered (at least three prescriptions among the treatments listed in Table 1).

CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; IPW, inverse probability weighting; PDC, proportion of days covered; SPC, single-pill combination.