Sudėtiniai vaistai

UAB „Servier Pharma“

2020.05.06

Vieno gamintojo sudėtiniai vaistai

- Les Laboratoires Servier gaminami vieno gamintojo sudėtiniai vaistai
  - COSIMPREL (Bisoprololis/Perindoprilis)
  - TRIVERAM (Atorvastatinas/Perindoprilis/Amlodipinas)
  - NATRIXAM (Indapamidas/Amlodipinas)
  - EUVASCOR (Atorvastatinas/Perindoprilis)
  - CARIVALAN (Karvedilolis/Ivabradinas)
  - Implicor (Metoprololis/Ivabradinas)

Sudėtinis vaistas	**COSIMPREL**	**TRIVERAM**	**NATRIXAM**	**EUVASCOR**	**CARIVALAN**	**Implicor**	**VISO**
Pacientų skaičius, vartojusių kompensuojamą vaistą 2019 metais	65891	22541	9054	7485	589	3293	108853
Kompensuojamų pakuočių kiekis 2019 metais	362659	126935	47982	17385	2494	20465	577920

PSDF išlaidos

Pavadinimas	PSDF išlaidos sudėtiniam vaistui 2019 metais, Eur	Galimos PSDF išlaidos, jeigu būtų skiriami monokomponentai atskirai (2020 II ketvirčio kainos), Eur	Skirtumas, Eur
COSIMPREL	1.748.611	2.169.349	420.738
TRIVERAM	552.868	938.606	385.738
NATRIXAM	158.928	233.414	74.486
EUVASCOR	56.303	88.281	31.978
CARIVALAN	22.894	25.643	2749
Implicor	182.876	207.042	24.166
VISO	2.722.480	3.662.335	939.855

- Vien tik 6 Servier kompensuojamus vieno gamintojo sudėtinius vaistus 2019 metais vartojo 108853 pacientai.
- Tai PSDF biudžetui kainavo 2.7 mln Eur ir SUTAUPĖ daugiau nei 900.000 Eur PSDF biudžeto lyginant su išlaidomis, kurios būtų patirtos, jeigu pacientai monokomponentus vartotų atskirai.
- PSDF išlaidos taupomos, nes sudėtiniam vaistui taikomas tik vienas didmeninės ir mažmeninės prekybos antkainis (1.51Eur+PVM). To pasekoje kiekviena sudėtinio vaisto pakuotė ženkliai mažina PSDF išlaidas:
  - Sudėtinio vaisto iš 2 veikliųjų medžiagų taupo 1,59 Eur (1.51 Eur + PVM)
  - Sudėtinio vaisto iš 3 veikliųjų medžiagų taupo 3,17 Eur (2x(1.51 Eur + PVM))

- 2020 balandžio 15 registruotas LR Vyriausybės nutarimo projektas, kuriuo dar kartą keičiama vieno gamintojo sudėtinių vaistų kainodara.
- Atkreipiame dėmesį, kad įsigaliojus šiam teisės aktui, tam, kad vieno gamintojo sudėtiniai vaistai atitiktų teisės aktų reikalavimus ir liktų kompensuojami, jų kainos Lietuvai turėtų mažėti iki 76% (detali informacija sekančioje skaidrėje).
- Tokia kainodara užkerta kelią ir naujų sudėtinių vaistų patekimui į kompensuojamų vaistų sąrašą, nes kaina Lietuvai nepadengia vaisto gamybos, transportavimo, sandėliavimo kaštų, jau nekalbant apie sanaudas, patirtas kuriant ir registruojant naują sudėtinį vaistą.

PAVADINIMAS	Gamintojo kaina Lietuvai 2020 II ketvirtis, Eur	Gamintojo kaina Lietuvai, įsigaliojus naujai 994 redakcijai, Eur	Reikalaujamas gamintojo kainos Lietuvai pokytis.
EUVASCOR 10 mg/10 mg	7.50	2.82	-62%
EUVASCOR 10 mg/5 mg	5.77	1.37	-76%
EUVASCOR 20 mg/10 mg	7.89	3.23	-59%
EUVASCOR 20 mg/5 mg	6.28	1.96	-69%
EUVASCOR 40 mg/10 mg	8.54	4.01	-53%
EUVASCOR 40 mg/5 mg	7.29	3.10	-57%
TRIVERAM 10 mg/5 mg/5 mg	6.57	2.58	-61%
TRIVERAM 20 mg/10 mg/10 mg	8.97	4.83	-46%
TRIVERAM 20 mg/10 mg/5 mg	8.43	4.19	-50%
TRIVERAM 20 mg/5 mg/5 mg	7.08	3.17	-55%
TRIVERAM 40 mg/10 mg/10 mg	9.61	5.61	-42%
COSIMPREL 10 mg/10 mg	9.96	5.70	-43%
COSIMPREL 10 mg/5 mg	8.73	4.80	-45%
COSIMPREL 5 mg/10 mg	8.57	4.05	-53%
COSIMPREL 5 mg/5 mg	7.83	3.17	-60%
NATRIXAM 1,5 mg/10 mg	6.98	2.83	-59%
NATRIXAM 1,5 mg/5 mg	6.23	2.19	-65%
Implicor 25 mg/5 mg	10.92	7.44	-32%
Implicor 25 mg/7,5 mg	13.90	10.45	-25%
Implicor 50 mg/5 mg	11.70	8.38	-28%
Implicor 50 mg/7,5 mg	14.65	11.36	-22%
CARIVALAN 12,5 mg/5 mg	11.52	8.16	-29%
CARIVALAN 12,5 mg/7,5 mg	14.47	11.14	-23%
CARIVALAN 6,25 mg/5 mg	10.85	7.36	-32%
CARIVALAN 6,25 mg/7,5 mg	13.80	10.34	-25%

Įspėjame, kad gamintojas negalės pateikti tokių kainų Lietuvai, todėl tikėtina, kad įsigaliojus šiam teisės aktui, daugiau nei 100.000 pacientų patirs nepatogumų dėl jau paskirto ir jiems tinkamo gydymo:

- Jiems turės būti skiriamas gydymas monokomponentais atskirai, kas padidins PSDF išlaidas daugiau nei 900.000 Eur/metus
- Pacientai pirks vaistus pilna kaina vaistinėje.

- Atreipiame dėmesį, kad Lietuvoje didžiausias mirštamumas yra nuo širdies kraujagyslių ligų ir antroje vietoje esančias onkologines ligas lenkia tris kartus (https://osp.stat.gov.lt)

			Mirusiųjų skaičius, tenkantis 100 tūkst. gyventojų | asmenys				
			2014	2015	2016	2017	2018
Miestas ir kaimas	Vyrai ir moterys	Iš viso pagal mirties priežastis	1 372,7	1 438,1	1 433,1	1 419,2	1 412,6
		Tam tikros infekcinės ir parazitų sukeliamos ligos	23,1	25,3	27,9	22,4	21,9
		Piktybiniai navikai	273,8	287,4	285,8	282,7	286,6
		Kraujotakos sistemos ligos	768,1	812,0	805,5	795,9	782,5
		Kvėpavimo sistemos ligos	40,2	46,7	45,0	47,5	49,6
		Virškinimo sistemos ligos	71,3	72,2	75,5	70,5	67,8
		Išorinės mirties priežastys	113,8	110,4	106,8	99,3	93,4
		Transporto įvykiai	11,1	10,6	8,6	8,8	8,0
		Nukritimai	12,0	13,6	14,0	15,0	16,1
		Atsitiktinis paskendimas	7,8	5,0	6,6	5,0	5,5
		Atsitiktinis apsinuodijimas alkoholiu bei jo pavelkis	8,3	8,7	6,7	6,8	5,6
		Tyčiniai susižalojimai (savižudybė)	31,7	30,8	28,7	26,4	24,4
		Pasikėsinimas (nužudymas)	3,8	4,2	3,5	2,8	2,6
		Kitos mirties priežastys	82,4	84,1	86,7	100,9	110,8

Sudėtinių vaistų pridėtinė vertė yra pripažinta tiek Europoje, tiek visame pasaulyje, jų nauda yra įrodyta moksliniais tyrimais:

- Vaistų vartojamumas – viena didžiausių problemų kardiologijoje (8-10 skaidrės);
- Sudėtiniai vaistai rekomenduojami Europos gydymo gairėse (11-12 skaidrės);
- Sudėtiniai vaistai yra ekonomiškai naudingi (13-17 skaidrės);
- Sudėtiniai vaistai gerina vaistų vartojamumą, ligos kontrolę, mažina komplikacijų riziką ir mirštamumą (18-26 skaidrės)

Kas antras hipertenzija sergantis pacientas nevartoja visų jam paskirtų vaistų jau pirmais metais

Of patients with HT, half do not adhere to, or stop taking their recommended regimen within one year of initiation[1]

Patient adherence in HT

1 2

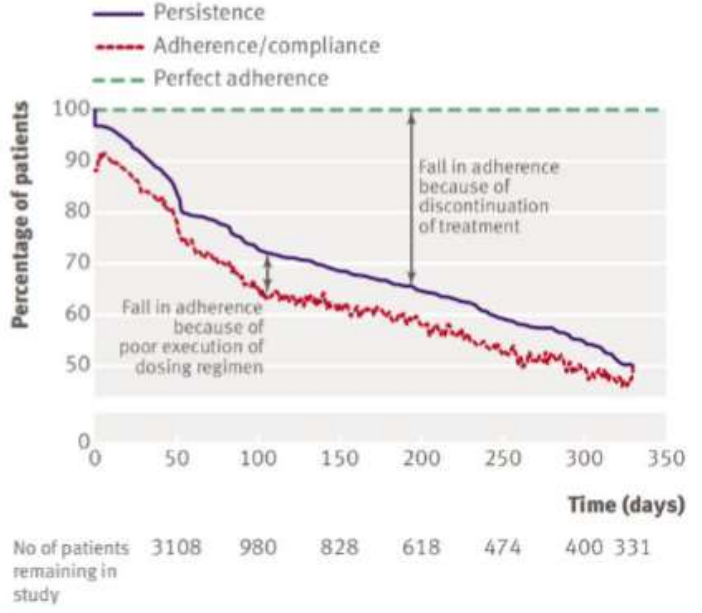
Of patients with HT, **half do not adhere** to their recommended regimen within one year of initiation[1]

Non-adherence is associated with a high risk of CV events and can reduce life expectancy[2-4]

In particular, patients who are co-prescribed statins have reduced adherence, which is associated with a broad range of adverse outcomes, including:[5,6]

- All-cause mortality
- CV mortality
- Higher rate of hospitalisations

Poor adherence includes poor execution of the dosing regimen and treatment discontinuation[1]

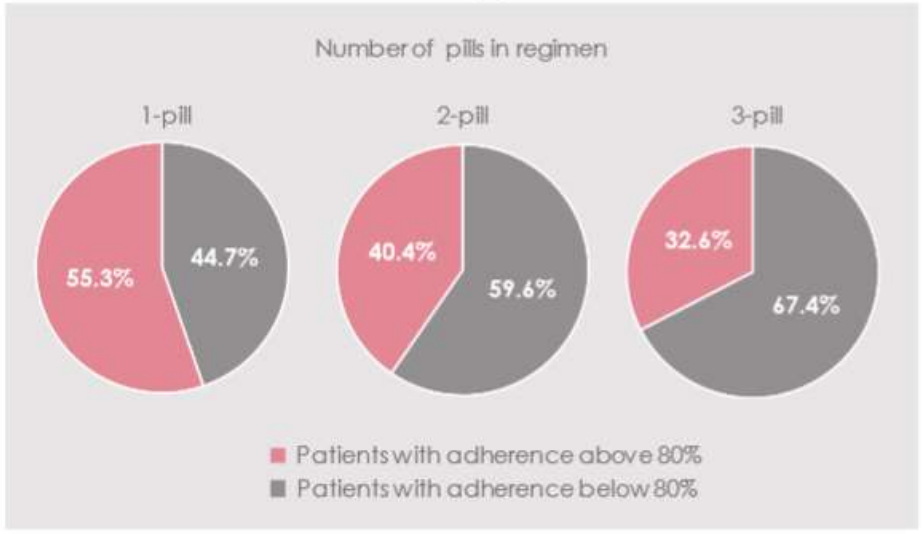


1. Vrijens et al. 2008; 2. Williams et al. 2018; 3. Ho et al. 2009; 4. Bitton et al. 2013

Studijos įrodė, kad kuo didesnis tablečių skaičius, tuo blogesnis vartojamumas

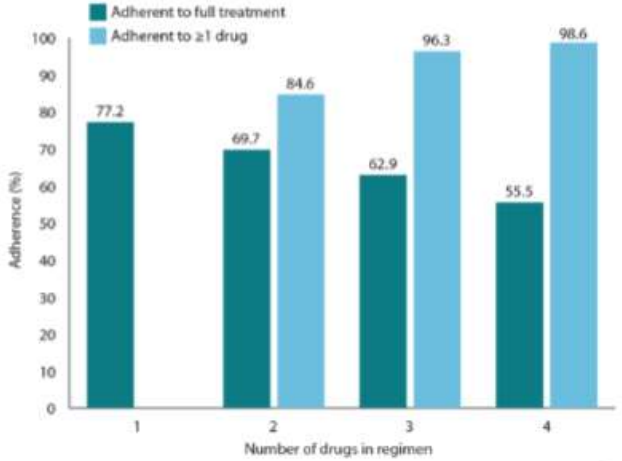
Studies have shown that increasing the number of pills in a regimen has a negative effect on adherence

Adherence to HT therapy reduces as the number of pills in a regimen increases[1-5]



Retrospective US study of 17,465 patients ($p<0.0001$)[4]

Patients may be **selectively non-compliant,** which can be avoided if SPC therapy is used



A historical cohort study of 84,929 US Medicare patients[1]

Adherence is lower with greater pill burden, but **more than half of patients need combination therapy**

1. Fung et al. 2007; 2. Ram et al. 2013; 3. Hilleman 2014; 4. Xie et al. 2014; 5. Bramlage et al. 2018

Vien tik pagerinus vaistų vartojamumą, 5 didžiosios ES šalys sutaupytų 330 mln Eur ir išsaugotų 82000 gyvybių

Estimation of costs avoided over 10 years due to an increase in adherence (Scenario 1 vs Scenario 2 – average and CI 95%)[1]

Scenario 1 = 70% of patients prescribed for an antihypertensive treatment **take at least 80% of their given regimen.**

Scenario 2 = Current situation

Increase EU5 adherence to 70%:[1]

- **82,235** fewer CV events
- Save **€332m**

Over 10 years

Similar **US study:[2]**
Increase adherence from current 40% to 100%

- Approx. **8.5m fewer CV events**
- Save about **$72bn costs**

1. Mennini et al. 2015; 2. Kockaya et al.2011

Blogas vaistų vartojimas – pagrindinė nekoreguoto kraujo spaudimo priežastis

10.4 Improvement in blood pressure control in hypertension: drug adherence

There is growing evidence that poor adherence to treatment—in addition to physician inertia (i.e. lack of therapeutic action when the patient's BP is uncontrolled)—is the most important cause of poor BP control.[293,619–621] Non-adherence to antihypertensive therapy correlates with higher risk of CV events.[312,622]

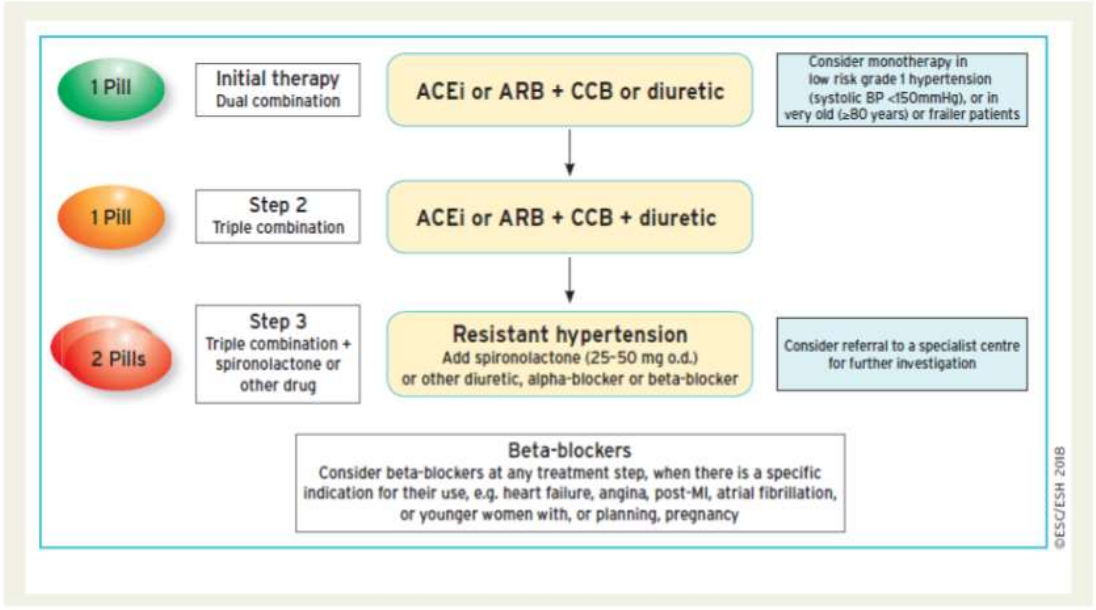
ESC European Society of Cardiology
European Heart Journal (2018) 00, 1–98
doi:10.1093/eurheartj/ehy339
ESC/ESH GUIDELINES

2018 ESC/ESH Guidelines for the management of arterial hypertension

Early discontinuation of treatment and suboptimal daily use of the prescribed regimens are the most common facets of poor adherence. After 6 months, more than one-third, and after 1 year, about one-half of patients may stop their initial treatment.[623] Studies based on the detection of antihypertensive medications in blood or urine have shown that low adherence to the prescribed medications can affect ≤ 50% of patients with apparently resistant hypertension,[352,624] and that poor adherence is strongly and inversely correlated with the number of pills prescribed. Early recognition of a lack of adherence might reduce the number of costly investigations and procedures (including interventional treatment), and avoid the prescription of unnecessary drugs.[625]

Europos kardiologų draugijos gidai rekomenduoja hipertenziją gydyti vienos tabletės sudėtiniu vaistu

Figure 2: ESC/ESH drug treatment algorithm for uncomplicated hypertension



Reference: Williams et al. 2018[3]
The core algorithm is also appropriate for most patients with HMOD, cerebrovascular disease, diabetes, or PAD.
ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CCB: calcium channel blocker; HMOD: Hypertension-mediated organ damage; MI: Myocardial infarction; o.d: Omni die (every day); PAD: Peripheral artery disease

Table 9: Drug treatment recommendations in the 2018 ESC/ESH guidelines

Recommendation
The initiation of treatment in most patients with an SPC comprising two drugs, to improve the speed, efficiency, and predictability of BP control
Preferred two-drug combinations are a RAS blocker with a CCB or a diuretic. A beta-blocker in combination with a diuretic or any drug from the other major classes is an alternative when there is a specific indication for a beta-blocker, e.g. angina, post-MI, heart failure, or heart rate control
Use monotherapy for low-risk patients with stage 1 hypertension whose SBP is <150 mmHg, very high-risk patients with high-normal BP, or frail older patients
The use of a three-drug SPC comprising a RAS blocker, a CCB, and a diuretic if BP is not controlled by a two-drug SPC
The addition of spironolactone for the treatment of resistant hypertension, unless contraindicated
The use of other classes of antihypertensive drugs in the rare circumstances in which BP is not controlled by the above treatments
Information on availability and recommended doses of individual drugs, as well as SPCs and free combinations, can be found in national formularies

Reference: Williams et al. 2018[3]
BP: Blood pressure; CCB: Calcium channel blocker; MI: Myocardial infarction; RAS: Renin-angiotensin system; SBP: Systolic blood pressure; SPC: Single-pill combination

Sudėtiniai vaistai mažina KV įvykius, mirštamumą bei išlaidas gydymui

BMJ

Cost-effectiveness and public health benefit of secondary cardiovascular disease prevention from improved adherence using a polypill in the UK

Virginia Becerra,[1] Alfredo Gracia,[1] Kamal Desai,[2] Seye Abogunrin,[2] Sarah Brand,[3] Ruth Chapman,[2] Fernando García Alonso,[1] Valentín Fuster,[4,5] Ginés Sanz[5]

Results: The model estimates that for each 10% increase in adherence, an additional 6.7% fatal and non-fatal CV events can be prevented. In the base case, over 10 years, the polypill would improve adherence by ~20% and thereby prevent 47 of 323 (15%) fatal and non-fatal CV events per 1000 patients compared with multiple monotherapy, with an incremental cost-effectiveness ratio (ICER) of £8200 per QALY gained. Probabilistic sensitivity analyses for the base-case assumptions showed an 81.5% chance of the polypill being cost-effective at a willingness-to-pay threshold of £20 000 per QALY gained compared with multiple monotherapy. In scenario analyses that varied structural assumptions, ICERs ranged between cost saving and £21 430 per QALY gained.

Conclusions: Assuming that some 450 000 adults are at risk of MI, a 10 percentage point uptake of the polypill could prevent 3260 CV events and 590 CV deaths over a decade.The polypill appears to be a cost-effective strategy to prevent fatal and non-fatal CV events in the UK.

BMJ Open 2015;5: e007111. doi:10.1136/ bmjopen-2014-007111

Usefulness of a Cardiovascular Polypill in the Treatment of Secondary Prevention Patients in Spain: A Cost-effectiveness Study

Vivencio Barrios [a], Lisette Kaskens [b], José María Castellano [c,d,e], Juan Cosin-Sales [f], José Emilio Ruiz [b], Ilonka Zsolt [b], Valentín Fuster [c,d], Alfredo Gracia [b]

Results

Over a 10-year period, use of the cardiovascular polypill instead of its monocomponents simultaneously would avoid 46 nonfatal and 11 fatal cardiovascular events per 1000 patients treated. The polypill would also be a more effective and cheaper strategy. Probabilistic analysis of the base case found a 90.9% probability that the polypill would be a cost-effective strategy compared with multiple monotherapy at a willingness-to-pay of 30 000 euros per quality-adjusted life year.

Conclusions

The polypill would be a cost-effective strategy for the Spanish National Health System with potential clinical benefits.

Rev Esp Cardiol. 2017;70:42-9 - Vol. 70 Num.01 DOI: 10.1016/j.rec.2016.05.009

Inovatyvi gydymo sudėtiniais vaistais strategija gerina vaistų vartojamumą, mažina komplikacijas bei yra ekonomiškai naudinga

The polypill approach – An innovative strategy to improve cardiovascular health in Europe

Valentin Fuster[1,2], Francesc Gambús[3], Aldo Patriciello[4*], Margaretha Hamrin[5] and Diederick E. Grobbee[6]

Abstract

Background: Cardiovascular disease (CVD) is a major cause of disability and premature death. Despite European guidelines advocating the use of medical therapies in CVD, many patients still do not achieve the guideline-recommended treatment, which highlights the need for change and innovations in this field. This requirement has been widely recognised by the national ministries of health, several European cardiology societies, and the European Parliament, who support the initiation of strategies to improve and promote cardiovascular health.

Discussion: One of the key risk factors to recurrent cardiovascular events is the lack of adherence to medication and this has been added to the agenda of the European Commission. With the intention to improve treatment adherence in CVD, polypills have been investigated and numerous studies demonstrate that they significantly improve medication adherence, which contributes to the improvement of health outcomes. In Europe, the first cardiovascular polypill, developed by a public-private partnership (CNIC-Ferrer), recently became available for general prescription as a therapy for CVD prevention. This polypill significantly improves adherence, preventing fatal and non-fatal cardiovascular events, and appears to be a cost-effective strategy to improve sustainability of the health care systems in CVD.

Conclusions: Given the importance of urgent and simple solutions to restraining the pandemic nature of CVD, the polypill approach should therefore be considered by physicians and public health systems as an available and innovative option to improve cardiovascular health.

The authors' call to action is therefore directed to payers, patient associations, industry, research funders, regulators, and healthcare professionals, to ensure that polypills are developed, made available and accessible to patients in diseases than benefit from improving the adherence to their treatments.

Fuster et al. BMC Pharmacology and Toxicology (2017) 18:10

Sudėtiniai vaistai, lyginant su gydymu atskirais monokomponentais, mažina sveikatos sistemos išlaidas

Compared with free combination, SPC use was associated with:

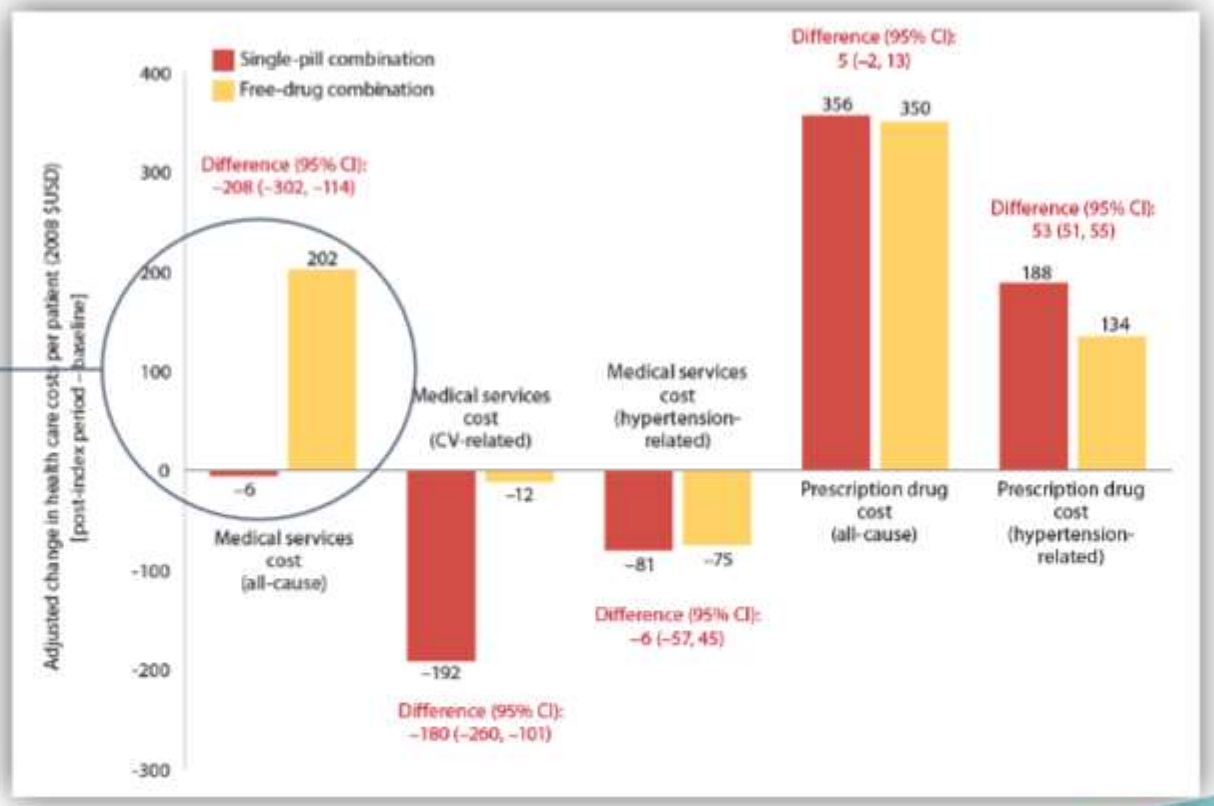
- Better compliance/persistence
- Fewer hospitalisations
- Fewer ER visits

Reduction in healthcare costs over 6 months treatment (vs 6 months pre-treatment baseline) was $208 GREATER per patient on SPC than for free combination[1,2]

Large reductions in medical costs with SPC use more than offset higher drug costs[1]

Analysis of US MarketScan Database (2006–2008)
Changes in healthcare costs were estimated using multivariate regression models while controlling for demographics and baseline comorbidities, prescription drug use, and health care resource utilization during the 6-month baseline period
Details of SPCs analysed are included on the following (hidden) slide

Change from baseline in health care costs (US) in patients with hypertension using either a single-pill combination or a free combination[1,2]



Changes in healthcare costs calculated as the costs incurred during the 6-month post-index period minus those incurred in the 6-month baseline period

1. Ram 2013, 2. Yang et al. 2010

Geras vaistų vartojamumas sumažina hospitalizacijų bei greitosios pagalbos atvejus – mažėja sveikatos priežiūros kaštai

MEDICATION ADHERENCE & SPENDING

By M. Christopher Roebuck, Joshua N. Liberman, Marin Gemmill-Toyama, and Troyen A. Brennan

Medication Adherence Leads To Lower Health Care Use And Costs Despite Increased Drug Spending

DOI: 10.1377/hlthaff.2009.1087
HEALTH AFFAIRS 30,
NO. 1 (2011): 91–99

ABSTRACT Researchers have routinely found that improved medication adherence—getting people to take medicine prescribed for them—is associated with greatly reduced total health care use and costs. But previous studies do not provide strong evidence of a causal link. This article employs a more robust methodology to examine the relationship. Our results indicate that although improved medication adherence by people with four chronic vascular diseases increased pharmacy costs, it also produced substantial medical savings as a result of reductions in hospitalization and emergency department use. Our findings indicate that programs to improve medication adherence are worth consideration by insurers, government payers, and patients, as long as intervention costs do not exceed the estimated health care cost savings.

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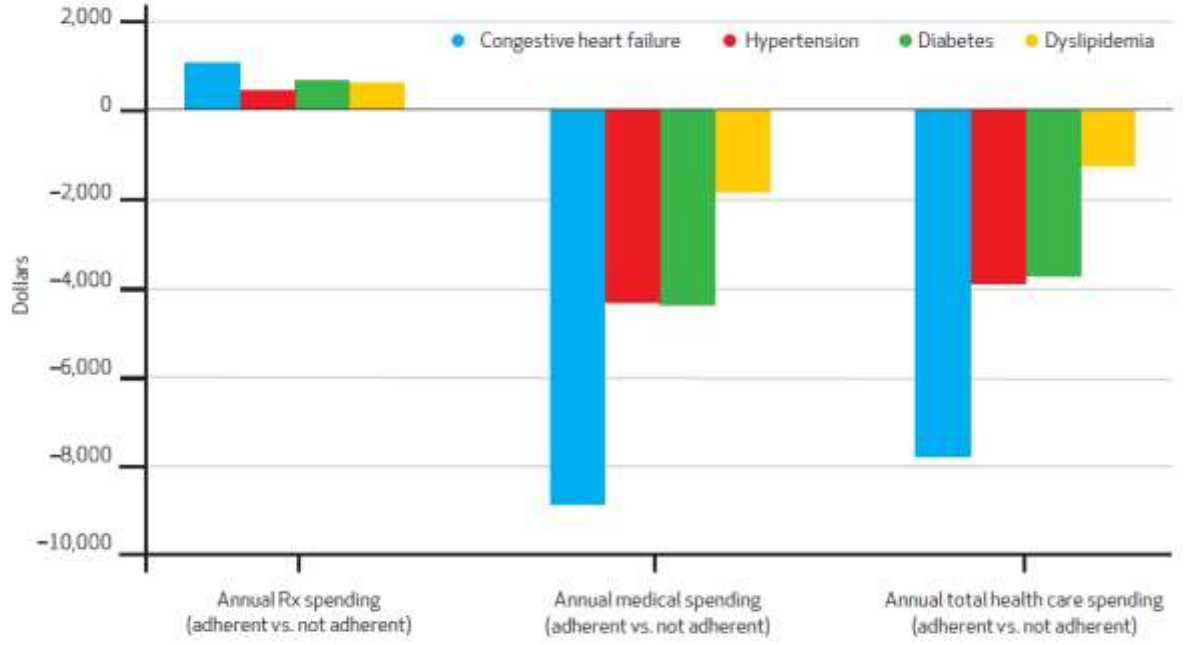
Joshua N. Liberman was vice president of strategic research, analytics, and outcomes at CVS Caremark in Hunt Valley when this research was conducted.

Marin Gemmill-Toyama is a health insurance specialist at the Centers for Medicare and Medicaid Services, in Baltimore, Maryland.

EXHIBIT 3

Impact Of Medication Adherence In Chronic Vascular Disease On Health Services Spending, 2005–08



SOURCE CVS Caremark integrated pharmacy and medical administrative claims data, January 1, 2005–June 30, 2008. NOTES Presented are marginal effect estimates from linear fixed-effects models of health services cost. All models included a weighted Charlson Comorbidity Index (see Notes 18–20 in text); two year-indicator variables; dummy variables for age 65 or older, male, and adherent; and interaction terms for adherent with male and age 65 or older. All estimates were significant at $p < 0.01$.

Sudėtiniai vaistai, lyginant su gydymu atskirais monokomponentais, mažina sveikatos sistemos išlaidas

Multiple studies in the USA have quantified cost savings associated with using SPCs vs free-combination therapy in patients with hypertension

Cost category	Annual cost impact (US) reported per patient per year
Hypertension-related services	-$188 (P = 0.012)[1]
Ambulatory services	-$526 (P = 0.001)[2]
Hospital services	-$76 (P = 0.502)[2]
Medicare crossover costs	-$827 (P = 0.012)[2]
Medical costs	-$474 (P = 0.001)[3]
Hypertension- or CV-related care	-$710 (95% CI: $118-$1,302)[4]
All-cause care	-$2,039 (95% CI: $1,031-$3,048)[4]

Savings associated with using SPCs vs free-combination therapy

1. Hess et al. 2008; 2. Dickson et al. 2008; 3. Brixner et al. 2008; 4. Sherrill et al. 2011

Vartojant sudėtinius vaistus, mažėja papildomų vaistų vartojimas

In addition to healthcare use reductions, patients using SPCs are **less likely to be prescribed additional HT medications** versus patients using free-combinations

	Ramipril/amlodipine combination				Candesartan/amlodipine combination			
	SPC N = 10 938	Free therapy N = 60 525	Adj. OR (95% CI)	P value	SPC N = 1413	Free therapy N = 9082	Adj. OR (95% CI)	P value
Any	53.1	69.5	0.78 (0.72-0.84)	<.001	44.9	64.8	0.55 (0.48-0.61)	<.001
Diuretic	21.0	36.2	0.58 (0.56-0.60)	<.001	18.7	35.3	0.54 (0.46-0.62)	<.001
β-blocker	36.9	48.1	0.73 (0.70-0.76)	<.001	31.1	44.4	0.67 (0.59-0.76)	<.001
CA	3.2	4.0	0.88 (0.78-0.98)	.025	3.6	5.3	0.76 (0.56-1.03)	.072
ACEi	6.2	13.3	0.42 (0.39-0.46)	<.001	3.3	4.1	0.89 (0.64-1.22)	.456
ARB	7.2	7.0	0.99 (0.91-1.07)	.786	6.7	10.3	0.62 (0.50-0.78)	<.001

Patients managed with SPCs were significantly less likely to be prescribed additional anti-HT therapies vs. those managed with free combinations[1]

Analysis of electronic medical records of 81,958 patients provided by 2500 physician practices across Germany[1]

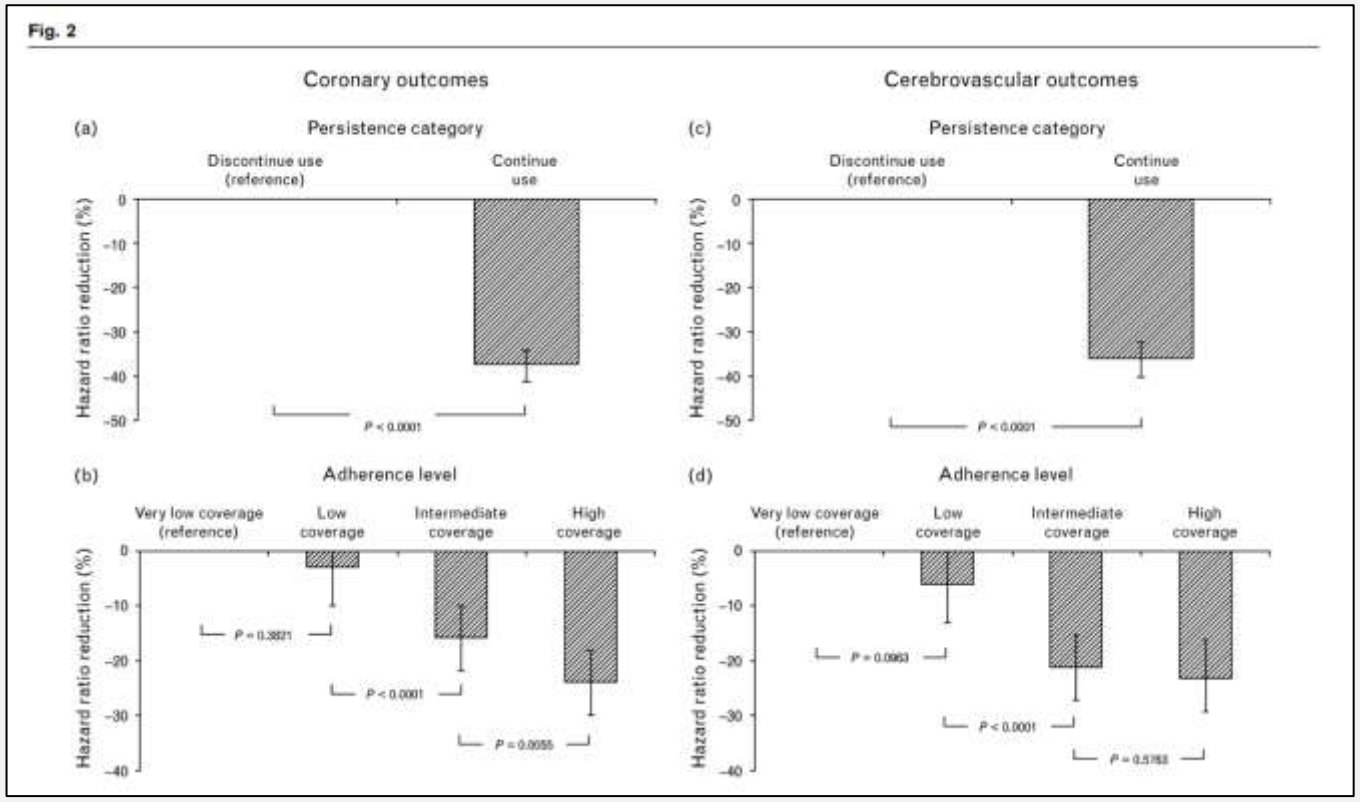
Patients managed with SPCs were also more likely to persist with treatment at 12 months compared with those managed with free combinations[1]

1. Bramlage et al. 2018

Geras vaistų vartojamumas mažina kardiovaskulines ir cerebrovaskulines komplikacijas -37%

Better compliance to antihypertensive medications reduces cardiovascular risk

Giovanni Corrao[a], Andrea Parodi[a], Federica Nicotra[a], Antonella Zambon[a], Luca Merlino[b], Giancarlo Cesana[c] and Giuseppe Mancia[c]



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Objective The effect of compliance with antihypertensive medications on the risk of cardiovascular outcomes in a population without a known history of cardiovascular disease has been addressed by a large population-based prospective, cohort study carried out by linking Italian administrative databases.

Methods The cohort of 242 594 patients aged 18 years or older, residents in the Italian Lombardy Region, who were newly treated for hypertension during 2000–2001, was followed from index prescription until 2007. During this period patients who experienced a hospitalization for coronary or cerebrovascular disease were identified (outcome). Exposure to antihypertensive drugs from index prescription until the date of hospitalization or censoring was assessed. Proportional hazards models were fitted to assess the association between persistence on and adherence with antihypertensive drug therapy and outcome. Data were adjusted for several covariates.

Results During an average follow-up of 6 years, 12 016 members of the cohort experienced the outcome. Compared with patients who experienced at least one episode of treatment discontinuation, those who continued treatment had a 37% reduced risk of cardiovascular outcomes (95% confidence interval 34–40%). Compared with patients who had very low drug coverage (proportion of days covered ≤ 25%), those at intermediate (from 51 to 75%) and high coverage (>75%) had risk reductions of 20% (16–24%) and 25% (20–29%), respectively. Similar effects were observed when coronary and cerebrovascular events were considered separately.

Conclusions In the real life setting, fulfillment compliance with antihypertensive medications is effective in the primary prevention of cardiovascular outcomes. *J Hypertens* 29:610–618 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Geras vaistų vartojamumas mažina mirštamumą -38%

Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences

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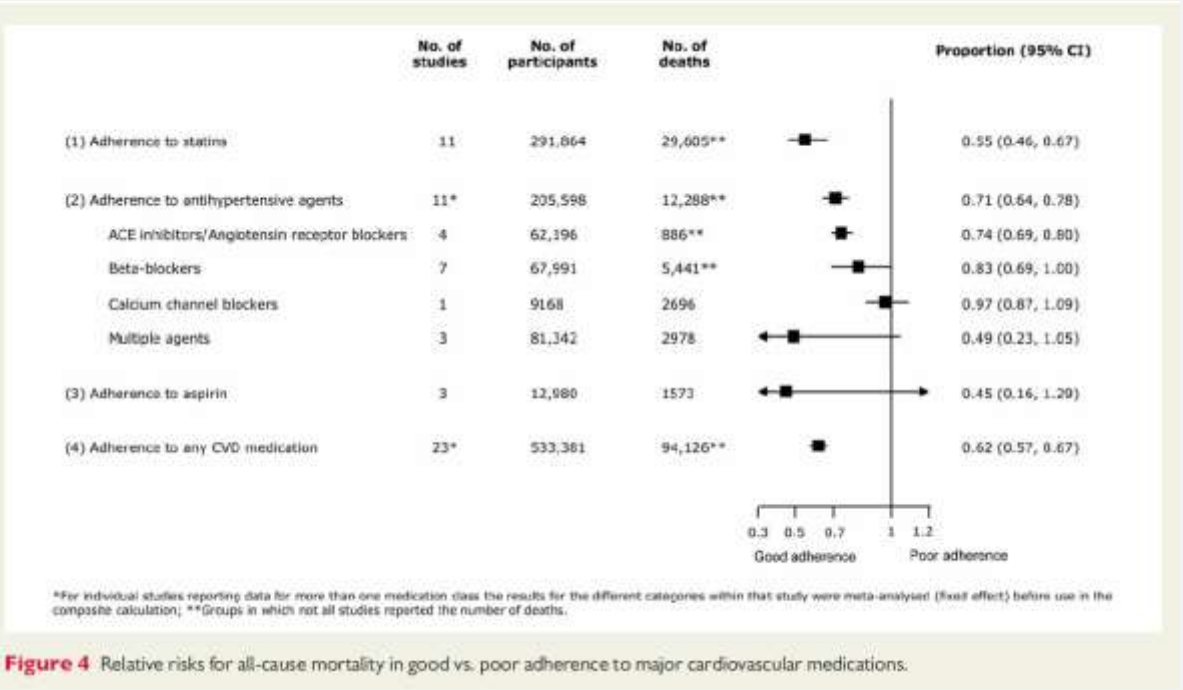

Figure 4 Relative risks for all-cause mortality in good vs. poor adherence to major cardiovascular medications.

Aims The aim of this study was to determine the extent to which adherence to individual vascular medications, assessed by different methods, influences the absolute and relative risks (RRs) of cardiovascular disease (CVD) and all-cause mortality.

Methods and results We performed a systematic review and meta-analysis of prospective epidemiological studies (cohort, nested case–control, or clinical trial) identified through electronic searches using MEDLINE, Web of Science, EMBASE, and Cochrane databases, involving adult populations (≥18 years old) and reporting risk estimates of cardiovascular medication adherence with any CVD (defined as any fatal or non-fatal coronary heart disease, stroke or sudden cardiac death) and/or all-cause mortality (defined as mortality from any cause) outcomes. Relative risks were combined using random-effects models.

Forty-four unique prospective studies comprising 1 978 919 non-overlapping participants, with 135 627 CVD events and 94 126 cases of all-cause mortality. Overall, 60% (95% CI: 52–68%) of included participants had good adherence (adherence ≥80%) to cardiovascular medications. The RRs (95% CI) of development of CVD in those with good vs. poor (<80%) adherence were 0.85 (0.81–0.89) and 0.81 (0.76–0.86) for statins and antihypertensive medications, respectively. Corresponding RRs of all-cause mortality were 0.55 (0.46–0.67) and 0.71 (0.64–0.78) for good adherence to statins and antihypertensive agents. These associations remained consistent across subgroups representing different study characteristics. Estimated absolute risk differences for any CVD associated with poor medication adherence were 13 cases for any vascular medication, 9 cases for statins and 13 cases for antihypertensive agents, per 100 000 individuals per year.

Conclusion A substantial proportion of people do not adhere adequately to cardiovascular medications, and the prevalence of suboptimal adherence is similar across all individual CVD medications. Absolute and relative risk assessments demonstrate that a considerable proportion of all CVD events (~9% in Europe) could be attributed to poor adherence to vascular medications alone, and that the level of optimal adherence confers a significant inverse association with subsequent adverse outcomes. Measures to enhance adherence to help maximize the potentials of effective cardiac therapies in the clinical setting are urgently required.

Keywords Medication adherence • Cardiovascular disease

European Heart Journal (2013) 34, 2940–2948

Geras vaistų vartojamumas mažina mirštamumą -45%

BMJ

A meta-analysis of the association between adherence to drug therapy and mortality

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Objective To evaluate the relation between adherence to drug therapy, including placebo, and mortality.
Design Meta-analysis of observational studies.
Data sources Electronic databases, contact with investigators, and textbooks and reviews on adherence.
Review methods Predefined criteria were used to select studies reporting mortality among participants with good and poor adherence to drug therapy. Data were extracted for disease, drug therapy groups, methods for measurement of adherence rate, definition for good adherence, and mortality.
Results Data were available from 21 studies (46 847 participants), including eight studies with placebo arms (19 633 participants). Compared with poor adherence, good adherence was associated with lower mortality (odds ratio 0.56, 95% confidence interval 0.50 to 0.63). Good adherence to placebo was associated with lower mortality (0.56, 0.43 to 0.74), as was good adherence to beneficial drug therapy (0.55, 0.49 to 0.62). Good adherence to harmful drug therapy was associated with increased mortality (2.90, 1.04 to 8.11).
Conclusion Good adherence to drug therapy is associated with positive health outcomes. Moreover, the observed association between good adherence to placebo and mortality supports the existence of the "healthy adherer" effect, whereby adherence to drug therapy may be a surrogate marker for overall healthy behaviour.

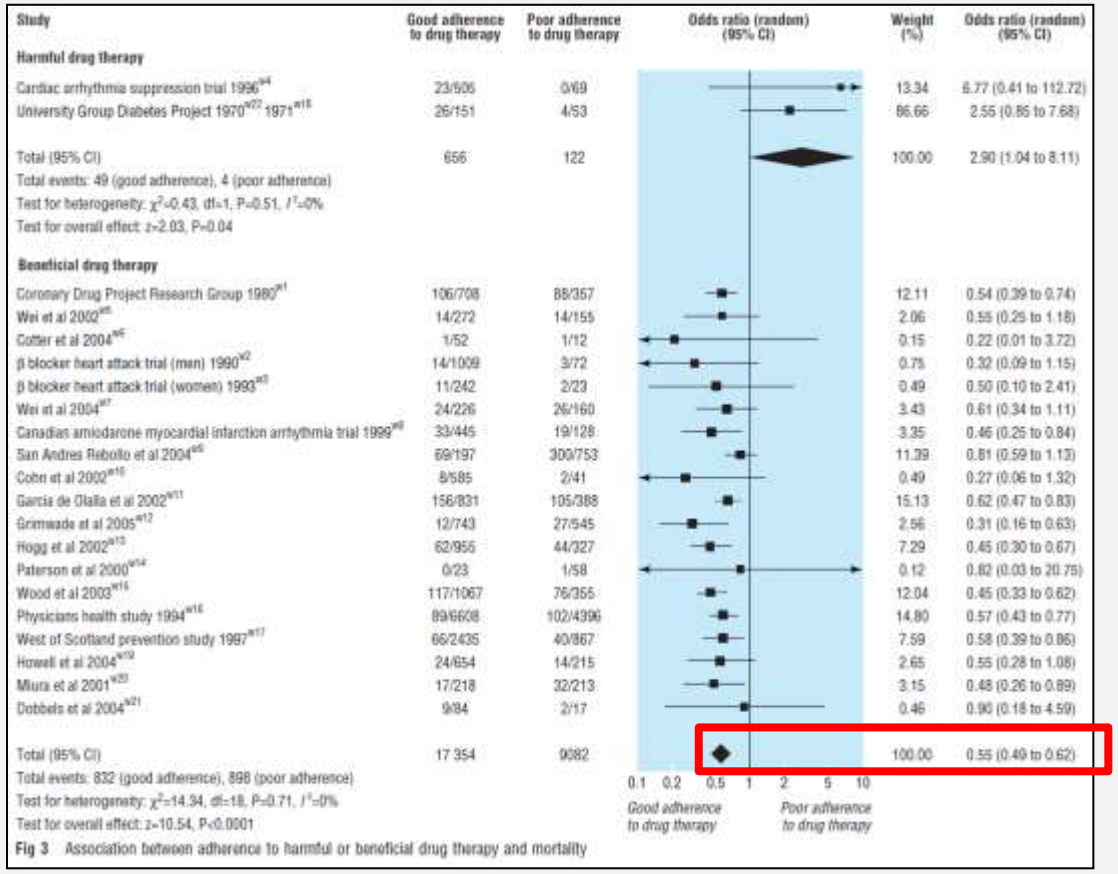


Fig 3 Association between adherence to harmful or beneficial drug therapy and mortality

Sudėtinis vaistas lyginant su atskiromis tabletėmis pagerina vartojamumą, ~2 kartus sumažina mirštamumą

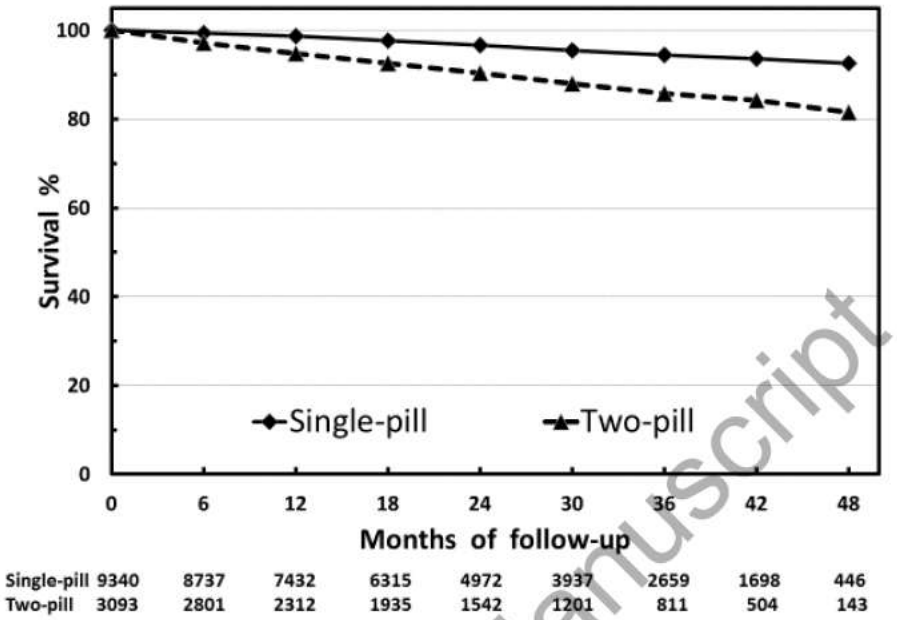
Objective:
To study treatment persistence and mortality using a single-pill, fixed-dose combination tablet compared with a two-pill combination for hypertension.

Research design and methods:
We analyzed Australian Pharmaceutical Benefit Scheme records 2011-2014 in a 10% random sample of concessional patients prescribed concomitant amlodipine and perindopril -- either as a single-pill, fixed-dose combination tablet (n=9340) or as two-pill combination therapy (n=3093). Main outcome measures were: (a) proportions failing to continue amlodipine + perindopril over time, (b) proportions failing to continue any subsequent calcium channel and angiotensin inhibition therapy over time and (c) proportions dying.

Results:
After 12 months, 34% of single-pill and 57% of two-pill users discontinued amlodipine + perindopril, median persistence time 42 months versus 7 months; 28% and 47% respectively discontinued any calcium channel-angiotensin inhibition therapy. After 48 months, 8% of single-pill and 18% of two-pill users had died. In a multivariate model adjusted for age, gender, duration and intensity of prior hypertension therapy, initial dose of amlodipine and perindopril, diabetes, hyperlipidemia, and complexity of care, the hazard ratio for risk of discontinuation over 42 months in the two-pill versus single-pill amlodipine + perindopril group was 1.94 (95%ci 1.83-2.06). Hazard ratio for discontinuation in two-pill versus single-pill users of any calcium channel-angiotensin inhibition therapy was 1.86 (1.74-1.99). The adjusted hazard ratio for risk of death over 48 months was 1.83 (1.55-2.16), but the mortality outcome may be an overestimate due to residual confounding.

Conclusions:
Use of a single-pill, fixed-dose combination in hypertension is associated with superior persistence and reduced mortality compared with use of two pills, suggesting higher priority for use of fixed-dose combinations.

Fig. 3: Mortality survival curves based on the original single-pill and two-pill allocations. Sample numbers at time points are shown.

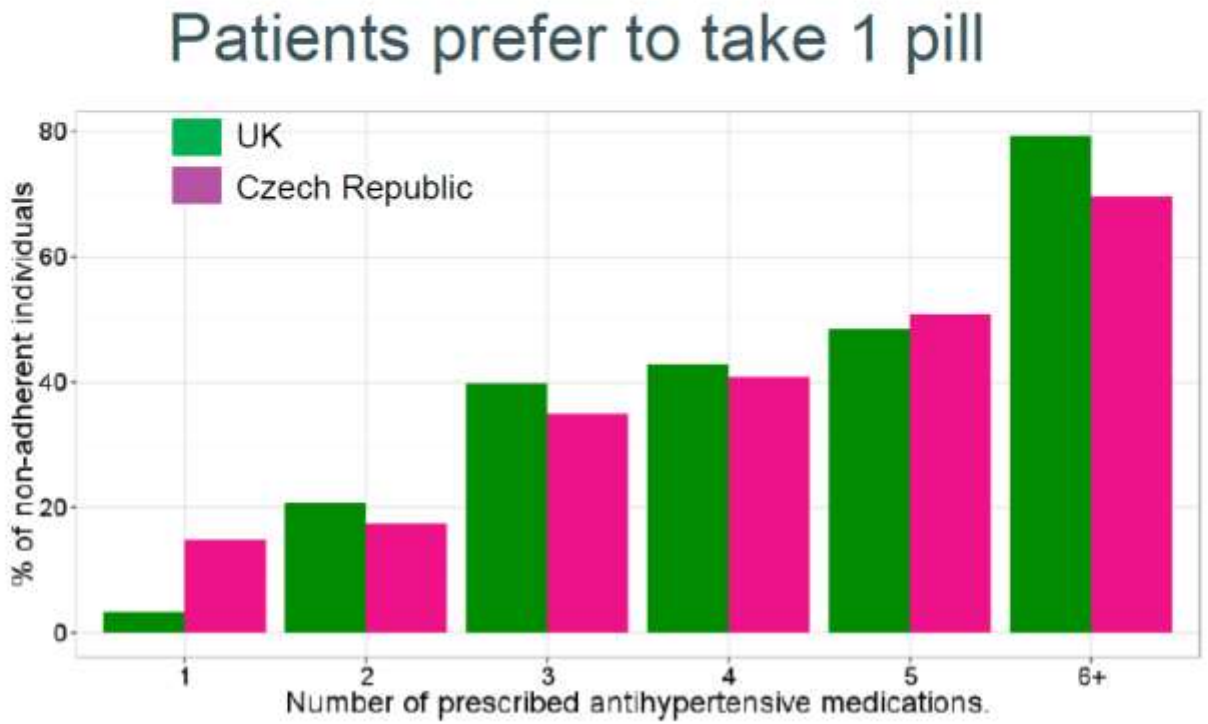


Mortality survival curves based on the original group allocations (but with no exclusions) are shown in Figure 3. After 48 months, 8% of single-pill users and 18% of two-pill users had died. In the unadjusted univariate model. the hazard ratio for risk of death in the two-pill versus single-pill group was 2.81 (95%ci 2.42-3.26). In the multivariate model adjusted for potential confounding variables in Table 1, the hazard ratio for risk of death was markedly reduced, 1.83 (95%ci 1.55-2.16).

Simons LA et al, Curr Med Res and Opin, **2017**

Nėra geresnio sprendimo vartojamumui pagerinti, kaip tablečių skaičiaus mažinimas

Non-adherence to antihypertensive medicines according to number of medicines

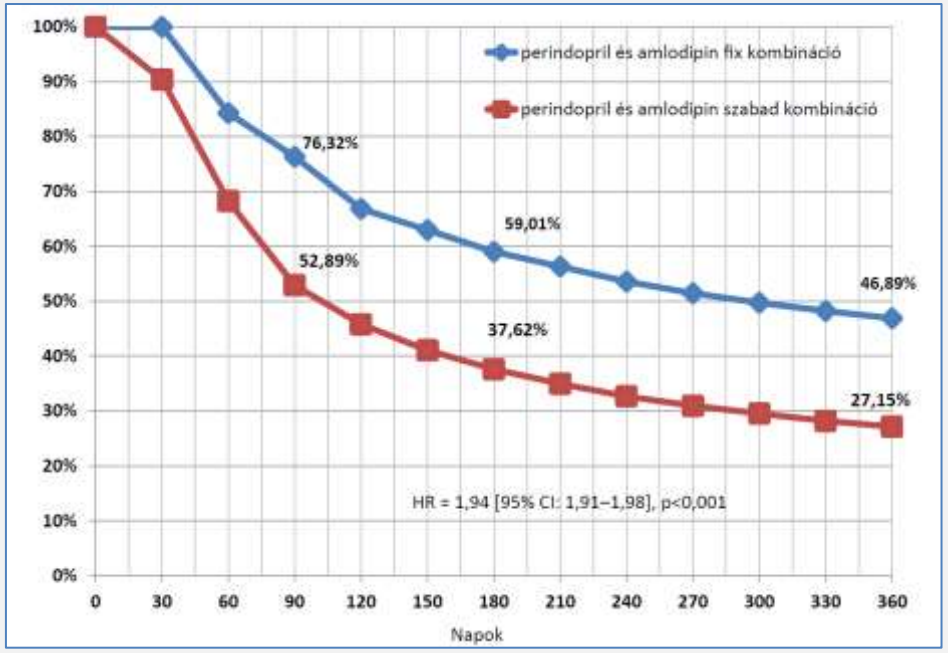


Gupta P, Tomazewski M, Williams B, et a. et al. *Hypertension* 2017

Sudėtinis vaistas lyginant su atskiromis tabletėmis ~2 kartus pagerina vaistų vartojamumą

One year persistence of free and fixed dose combinations of perindopril/amlodipine

Introduction: In management of hypertension patient adherence is one of the most important factors. In hypertension the cardiovascular risk reduction can be reached only by prolonged and effective pharmacotherapy.
Aim: To evaluate the persistence of one-year treatment of free and fixed-dose combination of perindopril/amlodipine in hypertension.
Method: Information from the National Health Insurance of Hungary prescriptions database on pharmacy claims between October 1, 2012 and September 30, 2013 was analysed. Authors identified patients who filled prescriptions for free and fixed-dose combination of perindopril/amlodipine, prescribed for the first time for hypertension. Patients have not received antihypertensive therapy with similar active substances during the one year before. Apparatus of survival analysis was used, where "survival" was the time to abandon the medication. As it was available to month precision, discrete time survival analysis was applied.
Results: 109,248 patients met the inclusion criteria. Combination antihypertensive therapy with perindopril/amlodipine was started with a free or a fixed-dose combination of these agents in 19,365 and 89,883 patients, respectively. One year persistence rate in patients taking perindopril/amlodipine as a free combination was 27.15%, whereas it was 46.89% in those on the fixed-dose combination. Mean duration of persistence was 177.6 days in patients on the perindopril/amlodipine free, whereas 245.7 days on fixed-dose combination. Actual rate of discontinuation was approximately twice higher with the treatment of free, compared with the use of the fixed-dose combination (hazard ratio =1.94 [95% CI: 1.91–1.98], p<0.001).

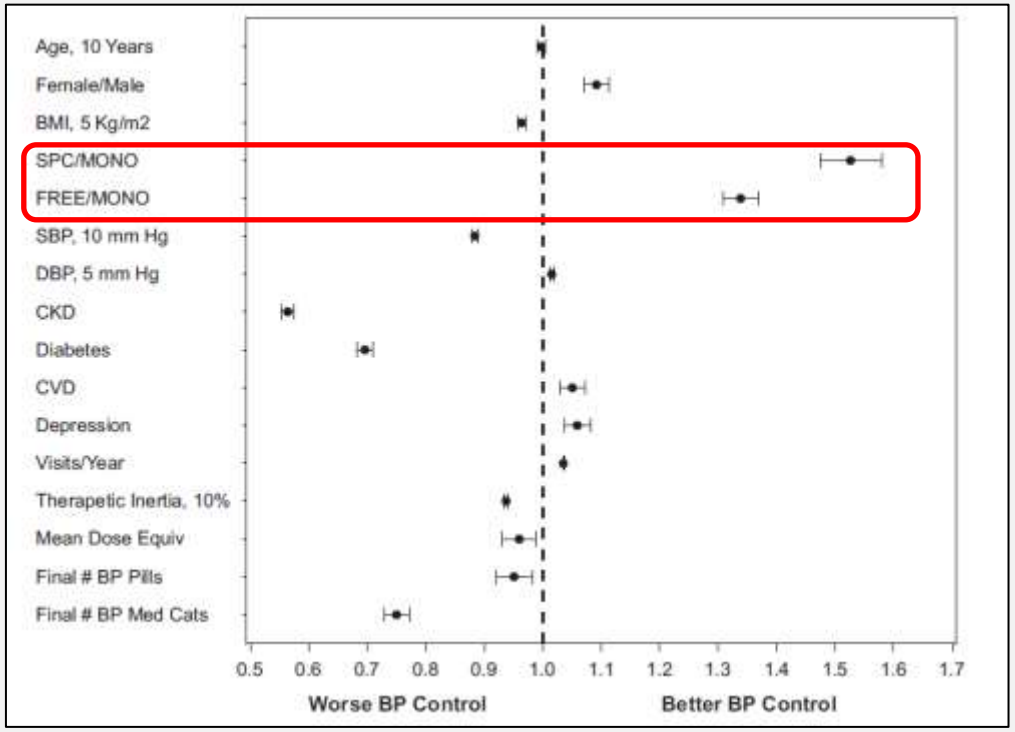


Simonyi G, Ferenci T, Medvegy M, Gasparics R, Finta E. Orv Hetil. **2017**; 158(36): 1421–1425.

Sudėtiniai vaistai lyginant su atskiromis tabletėmis pagerina AKS kontrolę

Initial Monotherapy and Combination Therapy and Hypertension Control the First Year

Abstract—Initial antihypertensive therapy with single-pill combinations produced more rapid blood pressure control than initial monotherapy in clinical trials. Other studies reported better cardiovascular outcomes in patients achieving lower blood pressure during the first treatment year. We assessed the effectiveness of initial antihypertensive monotherapy, free combinations, and single-pill combinations in controlling untreated, uncontrolled hypertensives during their first treatment year. Electronic record data were obtained from 180 practice sites; 106621 hypertensive patients seen from January 2004 to June 2009 had uncontrolled blood pressure, were untreated for ≥6 months before therapy, and had ≥1 one-year follow-up blood pressure data. Control was determined by the first follow-up visit with blood pressure <140/<90 mm Hg for patients without diabetes mellitus or chronic kidney disease and <130/<80 mm Hg for patients with either or both conditions. Multivariable hazards regression ratios (HRs) and 95% CIs for time to control were calculated, adjusting for age, sex, baseline blood pressure, body mass index, diabetes mellitus, chronic kidney disease, cardiovascular disease, initial therapy, final blood pressure medication number, and therapeutic inertia. Patients on initial single-pill combinations (N=9194) were more likely to have stage 2 hypertension than those on free combinations (N=18328) or monotherapy (N=79099; all $P<0.001$). Initial therapy with single-pill combinations (HR, 1.53 [95% CI, 1.47–1.58]) provided better hypertension control in the first year than free combinations (HR, 1.34; [95% CI, 1.31–1.37]) or monotherapy (reference) with benefits in black and white patients. Greater use of single-pill combinations as initial therapy may improve hypertension control and cardiovascular outcomes in the first treatment year. (*Hypertension*. 2012;59:1124-1131.) • Online Data Supplement



Hypertension. 2012;59:1124- 1131.

Portugalijos patirtis patvirtina, kad sudėtinių vaistų platesnis taikymas pagerina arterinės hipertenzijos kontrolę šalyje

Prevalence, awareness, treatment and control of hypertension and salt intake in Portugal: changes over a decade. The PHYSA study

Jorge Polonia[a,e], Luis Martins[b,e], Fernando Pinto[c,e], and Jose Nazare[d,e]

Objective: To determine prevalence, awareness, treatment and control of hypertension and the 24-h sodium excretion (24h-UNa) in the Portuguese adult population and to examine their changes from a similar study done in 2003.

Design and setting: A population-based cross-sectional survey conducted in 2011–2012.

Results: The overall prevalence of hypertension at V1 was 42.2% (44.4% in men, 40.2% in women) (42.1% in 2003). The age-specific prevalence of hypertension was 6.8, 46.9 and 74.9% in people below 35 years, 35–64 years and above 64 years. Comorbidities were 2.2–6.3 times more common in hypertensive patients vs. normotensive individuals. Overall, among the hypertensive patients, 76.6% were aware of the hypertension condition, 74.9% were treated and 42.5% were controlled (BP <140/90 mmHg), that is, respectively, 1.7, 1.9 and 3.8 times higher vs. data in 2003, with lower values in men vs. women and younger vs. older people. Global mean BP was 127.4/74.6±17.7/10.5 vs. 134.7/80.4±21.2/14.1 mmHg in 2003. From V1 to V2, control of hypertension increased on average by 14.8%. Multivariate analysis showed that

Evolution in hypertension status in Portugal (2003 to 2012)

improved considerably in recent years. Concerning treatment, in our study, patients with adequate control of hypertension were more frequently treated with combination of antihypertensive drugs (65% being fixed combinations) than those with uncontrolled BP. Also, this is in accordance with other studies that reported an association of a more frequent use of drug combinations with a progressive increase in an adequate control of hypertension [37]. Again, this is in good agreement with European [12] and American [11] guidelines, particularly in regard to the recommendations of the need of a more frequent use of combinations of antihypertensive drugs as a way to reach the desirable hypertension control. Thus, our data suggest that Portugal has made important progress in the management of hypertension over the past decade, since not only the percentage of treated patients increased, but particularly the quality of the treatment was markedly improved. In

Prašome atkreiptį dėmesį į pateiktus faktus ir argumentus ir nekeisti vieno gamintojo sudėtinių vaistų bazinės kainos ir maksimalios priemokos apskaičiavimo tvarkos.