Effects of Adherence to Pharmacological Secondary Prevention after Acute Myocardial Infarction on Health Care Costs – An Analysis of Real-World Data

Florian Kirsch (Florian.Kirsch@helmholtz-muenchen.de)
Helmholtz Zentrum Munchen Deutsches Forschungszentrum fur Umwelt und Gesundheit https://orcid.org/0000-0003-0543-592X

Christian Becker
Helmholtz Zentrum Munchen Deutsches Forschungszentrum fur Umwelt und Gesundheit

Christoph Kurz
Helmholtz Zentrum Munchen Deutsches Forschungszentrum fur Umwelt und Gesundheit

Lars Schwettmann
Helmholtz Zentrum Munchen Deutsches Forschungszentrum fur Umwelt und Gesundheit

Anja Schramm
AOK Bayern

Research article

Keywords: AMI, health care expenditures, PDC, secondary prevention, guideline-based medication, DMP

Posted Date: July 1st, 2020

DOI: https://doi.org/10.21203/rs.3.rs-39222/v1

Version of Record: A version of this preprint was published on December 20th, 2020. See the published version at https://doi.org/10.1186/s12913-020-05946-4.

Abstract

Background: Acute myocardial infarction (AMI), a major source of morbidity and mortality, is also associated with excess costs. Findings from previous studies were divergent regarding the effect of adherence to guideline-recommended medication on health care expenditure. However, gender-specific medication effectiveness, correlating effectiveness of concomitant medication and variation in adherence over time were not yet considered.

Methods: We aim to measure this from a third-party payer's perspective in a sample of statutory insured Disease Management Program participants over a follow-up period of 3-years. In 3,627 AMI patients, the proportion of days covered (PDC) for four guideline-recommended medications were calculated. A generalized additive mixed model was used, taking into account inter-individual effects (mean PDC-rate) and intra-individual effects (deviation from the mean PDC-rate).

Results: For the inter-individual effect, only anti-platelet agents had a significant negative influence, higher mean PDC rates lead to higher costs in both sexes. For the intra-individual effect, a higher deviation from the mean PDC-rate for ACE-inhibitors, anti-platelet agents, and statins was associated with higher costs in females. Further, in males, for β-blockers an increasing positive deviation from the PDC-mean increases costs and a negative deviation decreases costs. For anti-platelet agents an increasing deviation from the PDC-mean slightly increases costs.

Conclusion: Positive and negative deviation from the mean PDC-rate, independent of how high the mean was, usually negatively affect health care expenditures. Therefore, continuity in intake of guideline recommended medication is important to save costs.

1. Introduction

Although the recent decades have seen improvements in mortality and survival rates (1), cardiovascular disease (CVD) remains one of the leading causes of mortality and morbidity in industrialized countries (2). Acute myocardial infarction (AMI), a common manifestation of CVD in the elderly, carries increased risk of mortality, morbidity, and excess costs (3, 4). In Germany in 2016, 20,539 deaths in women and 28,130 deaths in men were caused by AMI, which reflected 49.2 and 69.3 deaths per 100,000 inhabitants in women and men, respectively. (5). In the first year after AMI, cumulative total costs for AMI are about €13,061 per patient in Germany (6). In the United States, the first-year costs are $17,532 for fatal and $15,540 for non-fatal AMI (7). In the United Kingdom, between 0.4% and 1.0% of total health care expenditure was spent for AMI (8).

Worldwide, heart societies have released evidence-based guidelines for secondary prevention and management of AMI. Aside from lifestyle modifications, these guidelines encourage pharmacological therapy with anti-platelet agents, statins, β-blockers, and angiotensin-converting enzyme (ACE) inhibitors as long-term treatment (9, 10). There is strong supportive evidence that re-infarction risk and patient mortality after AMI can be considerably reduced by using guideline-recommended medication (11–15). However, studies have revealed discrepancies between recommended therapies and health care actually provided (16–23). Notably, for all four drugs recommended in the guidelines after AMI, discontinuation of medical therapy is common, begins early after discharge, and increases substantially over time (18, 24, 25).

Non-adherence to medication is considered a major health policy issue, accounting for a considerable worsening of the disease, poor prognosis, death, and increased health care costs (26, 27). However, investigations on long-term medication adherence more than 1-year post AMI are scarce (25). So far, three cross-sectional studies have been published measuring the influence of medication adherence on health care expenditures after AMI (focusing on renin–angiotensin system agents (28), statins (29), and statins and ACE inhibitors (30)). To date, no study exists with a longitudinal design that would allow capturing a variation of adherence rate over time, or one evaluating the influence of all guideline-recommended medications on health care expenditures simultaneously.

2. Objective

The aim of the study is to measure the influence of adherence to guideline-recommended medication on health care expenditures in a real-world setting over a follow-up period of 3-years after AMI from the perspective of a third-party payer.

3. Methods

Data

The analysis is based on pseudonymized claims data routinely documented for participants of a Disease Management Program (DMP) for coronary artery disease (CAD), offered by the AOK Bayern, a large regional health insurance fund in the South of Germany with a market share of more than 40%. The cost analysis was based on routine data on individual expenditures for filed claims, including the categories of hospital, outpatient care, medication, rehabilitation (if covered by AOK Bayern), and costs for remedy and aid products. According to the ethics committee of the State Chamber of Physicians of Bavaria, no ethical approval was required.

Study population

Individuals were included in the study if they had at least one hospitalization with a main discharge diagnosis of AMI (ICD-10 I21) between January 1, 2009 and December 31, 2011. AMIs before 2009 were excluded because hierarchical morbidity group (HMG) compensation, which was used as a control variable for morbidity, was not available before 2009. AMIs after 2011 were excluded as the 3-year follow-up period would not be covered by the data available. Further inclusion criteria were, that patients had to be enrolled in the DMP CAD before the inception hospitalization and continuously insured at least 1 year before and 3 years after hospitalization, unless they died. Patients were excluded if documentation for the DMP CAD was missing in the 180 days prior to the AMI, if they died within 30 days after the first hospitalization or had missing values in covariates.

Medication

Adherence to guideline-based secondary prevention for AMI (31) was assessed through the anatomical therapeutic chemical (ATC) classification system for: anti-platelet agents (B01A), statins (C10), β-blockers (C07), and ACE inhibitors (C09A and C09B).

Adherence

Proportion of days covered (PDC) were calculated for the year before AMI and for each year of the 3-year follow-up period. Therefore, we calculated the total number of days supplied in each period based on then number of prescriptions multiplied by the defined daily dose (DDD) per prescription. If the DDDs of a prescription reached into a new period, they were considered as medication stock in this period. DDDs were supplied by the scientific institute of the AOK (WIdO) based on a German adaption of the WHO database.

Outcome measures

Primary outcome measures were the average overall health care expenditures per year. Further analysis were conducted for every single cost category. All costs were inflated to 2014 euros, using the inflation rate as reported for Germany by the OECD (32).

Statistical analysis

We stratified the AMI patients for sex in our analysis as there are gender specific similarities in effectiveness of anti-platelet agents (33, 34), statins (35, 36), but differences in β-blockers (37–39), and ACE inhibitors (40–42), which should also be reflected in costs. Characteristics of patients stratified by sex in the 3 years after AMI were compared (Table 1) using analysis of variance (ANOVA) for continuous variables and Chi²-tests for categorical variables. We examined the association between health care expenditures and PDC-rates (PDC-mean and PDC standard deviation) for anti-platelet agents, statins, β-blockers, and ACE inhibitors. The PDC-mean estimates the inter-personal effect, while the PDC standard deviation measures the intra-

personal effect of adherence (43). We estimated these effects with a generalized additive mixed model (GAMM) with a smoothing function of PDC-rates (PDC-mean and standard deviation). A GAMM is a generalized linear mixed model in which the linear predictor depends linearly on unknown smooth functions of the covariates of interest. For the smooth function, penalized regression spline type smoothers of moderate rank are used. For estimation purposes, the generalized component of each smooth is treated as a random effect term, while the unpenalized component is treated as fixed (44, 45).

Table 1
Descriptive statistics by sex and year

		Year 1			Year 2			Year 3		
		Male	Female		Male	Female		Male	Female	
						Mean (95% CI)		Mean (95% CI)	Mean (95% CI)	
N		2,440	1,180		2,066	940		1,845	816	
Age[a]		71.67 (10.23)	77.60 (9.05)	***	72.03 (10.13)	77.60 (9.02)	***	72.35 (10.10)	77.92 (9.05)	***
Age groups[b]	< 55	184 (7.54%)	28 (2.37%)	***	150 (7.26%)	24 (2.55%)	***	125 (6.78%)	22 (2.70%)	***
	≥ 55 < 65	397 (16.27%)	79 (6.69%)		333 (16.12%)	62 (6.60%)		295 (15.99%)	52 (6.37%)	
	≥ 65 < 75	851 (34.88%)	291 (24.66%)		700 (33.88%)	238 (25.32%)		609 (33.01%)	193 (23.65%)	
	≥ 75	1,008 (41.31%)	782 (66.27%)		883 (42.74%)	616 (65.53%)		816 (44.23%)	549 (67.28%)	
BMI groups[b]	< 18.5	5 (0.20%)	20 (1.69%)	***	5 (0.24%)	12 (1.28%)	***	3 (0.16%)	8 (0.98%)	***
	≥ 18.5 < 25	452 (18.52%)	309 (26.19%)		382 (18.49%)	235 (25.00%)		333 (18.05%)	204 (25.00%)	
	≥ 25 < 30	1,203 (49.30%)	471 (39.92%)		1,002 (48.50%)	362 (38.51%)		869 (47.10%)	300 (36.76%)	
	≥ 30	780 (31.97%)	380 (32.20%)		677 (32.77%)	331 (35.21%)		640 (34.69%)	304 (37.25%)	
BIMD10[b]	Quartile 1	471 (19.30%)	211 (17.88%)		398 (19.26%)	164 (17.45%)		356 (19.30%)	144 (17.65%)	
	Quartile 2	552 (22.62%)	261 (22.12%)		483 (23.38%)	215 (22.87%)		445 (24.12%)	191 (23.41%)	
	Quartile 3	429 (17.58%)	214 (18.14%)		346 (16.75%)	168 (17.87%)		301 (17.29%)	141 (17.28%)	
	Quartile 4	433 (17.75%)	229 (19.41%)		363 (17.57%)	187 (19.89%)		319 (17.29%)	159 (19.49%)	
	Quartile 5	555 (22.75%)	265 (22.46%)		476 (23.04%)	206 (21.91%)		424 (22.98%)	181 (22.18%)	
Smoking status[b]	Smoker	344 (14.10%)	88 (7.46%)	***	292 (14.13%)	66 (7.02%)	***	254 (13.77%)	60 (7.35%)	***
NYHA[b]	0	1,216 (49.84%)	509 (43.14%)	***	991 (47.97%)	401 (42.66%)	*	852 (46.18%)	331 (40.56%)	*
	1	71 (2.91%)	35 (2.97%)		69 (3.34%)	31 (3.30%)		68 (3.69%)	30 (3.68%)	
	2	281 (11.52%)	131 (11.10%)		267 (12.92%)	132 (14.04%)		262 (14.20%)	123 (15.07%)	
	3	446 (18.28%)	226 (19.15%)		397 (19.22%)	183 (19.47%)		381 (20.65%)	172 (21.08%)	

	Year 1			Year 2			Year 3		
4	426 (17.46%)	279 (23.64%)		342 (16.55%)	193 (20.53%)		282 (15.28%)	160 (19.61%)	
DMP COPD[b]	214 (8.77%)	68 (5.76%)	**	186 (9.00%)	53 (5.64%)	**	157 (8.51%)	43 (5.27%)	**
DMP asthma[b]	54 (2.21%)	36 (3.05%)		47 (2.27%)	32 (3.40%)		38 (2.06%)	31 (3.80%)	**
DMP type 1 diabetes[b]	7 (0.29%)	5 (0.42%)		5 (0.24%)	5 (0.53%)		4 (0.22%)	4 (0.49%)	
DMP type 2 diabetes[b]	1,048 (42.95%)	564 (47.80%)	**	907 (43.90%)	450 (47.87%)	*	818 (44.34%)	392 (48.04%)	
Death in observation period[b]	252 (10.33%)	151 (12.80%)	*	145 (7.02%)	79 (8.40%)		113 (6.12%)	62 (7.60%)	
HMG assignment per month[a]	€479.24 (€652.99)	€505.28 (€552.82]		€757.68 (€768,39)	€786.08 (€656.48)		€580.85 (€717.10)	€555.54 (€539.76)	
Days survived in observation period[a]	347.10 (60.87)	342.19 (69.79)	*	354.07 (48.19)	351.78 (52.95)		355.31 (45.53)	353.57 (48.04)	
Angina pectoris[b]	1,122 (45.98%)	510 (43.22%)		441 (21.35%)	191 (20.32%)		881 (47.75%)	385 (47.18%)	
Peripheral vascular disease[b]	2,332 (95.57%)	1,057 (89.58%)	***	1,407 (68.10%)	588 (62.55%)	**	1,784 (96.69%)	754 (92.40%)	***
Dyslipidemia[b]	2,071 (84.88%)	937 (79.41%)	***	1,560 (75.51%)	650 (69.15%)	***	1,620 (87.80%)	680 (83.33%)	**
Congestive heart failure[b]	1,385 (56.76%)	758 (64.24%)	***	868 (42.01%)	453 (48.19%)	**	938 (50.84%)	471 (57.72%)	**
Hypertension[b]	2,341 (95.94%)	1,137 (96.36%)		1,819 (88.04%)	840 (89.36%)		1,780 (96.48%)	790 (96.81%)	
Dialysis[b]	81 (3.32%)	27 (2.29%)		63 (3.05%)	17 (1.81%)		55 (2.98%)	12 (1.47%)	*
PDC-rate ACE inhibitors[a]	72.41% (40.13)	66.96 (42.97)	***	69.16 (42.40)	61.94 (45.57)	***	67.42 (43.88)	60.23 (46.37)	***
PDC-rate β-blockers[a]	47.76% (32.30)	48.03 (33.86)		43.40 (33.14)	43.55 (34.22)		42.75 (33.58)	43.64 (35.37)	
PDC-rate statins[a]	83.69 (32.19)	75.10 (39.70)	***	82.68 (33.53)	73.54 (40.79)	***	80.75 (35.56)	72.40 (41.81)	***
PDC-rate anti-platelet agents[a]	46.42 (41.60)	44.65 (41.16)		32.83 (39.99)	31.78 (38.99)		27.02 (37.97)	25.41 (35.51)	

	Year 1	Year 2	Year 3
[a] p-value based on ANOVA			
[b] p-value based on Chi²-test			
Significant differences between the group 0 drugs and the other groups:* p < 0.05 ** p < 0.01 *** p < 0.001			

The GAMM was adjusted for age (< 55, 55 < 65, 65 < 75, and ≥ 75), Body-Mass-Index (BMI) (underweight, normal weight, overweight, and obesity), smoking status, New York Heart Association classification (NYHA) (no NYHA, NYHA 1 to NYHA 4), enrollment in the DMPs for chronic obstructive pulmonary disease (COPD), asthma, type 1 diabetes, type 2 diabetes, death in observation period, HMG assignment per month, observation year after AMI, days survived in the observation period, angina pectoris, peripheral vascular disease, dyslipidemia, congestive heart failure, hypertension, and dialysis. Additionally, in the absence of data on individual-level socio-economic status the Bavarian Index of Multiple Deprivation of 2010 (BIMD 2010), which indicates area-level deprivation expressed by quintiles reaching from least to most deprived areas, was used as a proxy (46, 47).

Sensitivity analysis

To analyze the robustness of the results two further analysis were conducted. First, patients were excluded spending more than 50% of the follow-up time in hospital and, second, only patients surviving the 3-year follow-up period were considered.

The GAMM was estimated using the statistical software R (version 3.5.1) and applying the gamm4 package (44).

4. Results

Health care expenditures

The data set consisted of 4,609 DMP CAD patients discharged from hospital with a diagnosis of AMI of which 4,245 had a complete DMP documentation sheet in the last 180 days before AMI. Out of this group, 3,952 patients had an AMI in the period between January 1, 2009 and December 31, 2011. Of them, 122 people died within 30 days, while another 203 people were excluded due to insurance gaps or missing data. Hence, the study population comprised 3,627 patients (Fig. 1).

Baseline characteristics are presented in Table 1. In total, observations of 3,620 (1,180 female and 2,440 male), 3,006 (940 female and 2,066 male), and 2,661 (816 female and 1,845 male) subjects were considered in years 1, 2, and 3, respectively. On average, males were more than 5 years younger ($p < 0.001$), had a higher BMI ($p < 0.001$), and the percentage of active smokers was approximately twice as high ($p < 0.001$). Regarding heart related comorbidities, males were less often in a higher NYHA state ($p < 0.05$) and suffered more seldomly from congestive heart failure ($p < 0.01$), but they had higher rates of dyslipidemia ($p < 0.01$), and peripheral vascular disease ($p < 0.01$). Besides that, the percentage of males enrolled in the DMP type 2 diabetes was lower in the first ($p < 0.01$) and second year ($p < 0.05$), and the percentage of males who died in the first year after AMI was lower ($p < 0.05$), leading to a higher number of days survived in the first year ($p < 0.05$). PDC-rates in males were higher in ACE-inhibitors ($p < 0.001$) and statins ($p < 0.001$) but similar in β-blockers and anti-platelet agents.

The results of the GAMM on health care expenditures are presented in Table 2 and Fig. 2. In the model, the highest age group and patients living in least deprived areas are associated with lowest costs ($p < 0.05$). Furthermore, an enrollment in the DMP COPD ($p < 0.05$), a more severe NYHA state ($p < 0.01$), the occurrences of comorbidities angina pectoris ($p < 0.001$), peripheral vascular disease ($p < 0.001$), congestive heart failure ($p < 0.001$), hypertension ($p < 0.01$), and being a dialysis patient ($p < 0.001$) were associated with higher costs. Similarly, death ($p < 0.001$), the number of days insured ($p < 0.001$) in the observation period and higher HMG assignments per month ($p < 0.01$) were associated with higher costs. Contrarily, costs decreased in the consecutive years after AMI ($p < 0.001$).

Table 2
Base Case - Influence on health care expenditures

N = 9,287		Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)		-1089.26	1916.40	-0.57	0.5698
Age	55 < 65	611.05	687.99	0.89	0.3745
	65 < 75	323.90	642.00	0.50	0.6139
	≥ 75	-1481.82	647.83	-2.29	0.0222*
Gender	Female	-147.47	309.84	-0.48	0.6341
BMI	underweight	1076.18	1814.31	0.59	0.5531
	overweight	-287.73	365.01	-0.79	0.4306
	obese	-407.75	395.78	-1.03	0.3029
BIMD10	Q2	-600.25	427.80	-1.40	0.1606
	Q3	-935.95	459.42	-2.04	0.0417*
	Q4	-535.59	454.13	-1.18	0.2383
	Q5	-812.27	430.76	-1.89	0.0594
Smoker	yes	157.39	447.42	0.35	0.7250
NYHA	1	2552.83	810.15	3.15	0.0016**
	2	1548.90	482.24	3.21	0.0013**
	3	2887.35	434.52	6.64	0.0000***
	4	4533.88	457.35	9.91	0.0000***
DMP COPD	yes	1206.22	517.34	2.33	0.0197*
DMP asthma	yes	-829.61	872.64	-0.95	0.3418
DMP diabetes type 1	yes	1946.15	2436.29	0.80	0.4244
DMP diabetes type 2	yes	519.76	288.19	1.80	0.0713
deceased	yes	11012.39	925.20	11.90	0.0000***
HMG assignments per month		1.09	0.24	4.45	0.0000***
year		-5914.40	168.43	-35.11	0.0000***
days insured		34.48	4.72	7.31	0.0000***
Angina pectoris		2115.66	280.69	7.54	0.0000***
Peripheral vascular disease		4415.08	396.30	11.14	0.0000***
Dyslipidemia		480.99	365.24	1.32	0.1879
Congestive heart failure		2074.91	352.90	5.88	0.0000***
Hypertension		1939.37	574.43	3.38	0.0007***
Dialysis		23554.62	991.15	23.77	0.0000***
		edf	Ref.df	F	p-value

N = 9,287	Estimate	Std. Error	t value	Pr(>|t|)
s(PDC mean ACE inhibitors) male	1.26	1.26	0.09	0.7234
s(PDC mean ACE inhibitors) female	1.00	1.00	1.45	0.2292
s(PDC mean β-blockers) male	1.00	1.00	3.01	0.0827
s(PDC mean β-blockers) female	1.29	1.29	0.12	0.8398
s(PDC mean statins) male	1.78	1.78	1.98	0.0851
s(PDC mean statins) female	1.00	1.00	1.43	0.2310
s(PDC mean anti-platelet agents) male	2.99	2.99	21.63	0.0000***
s(PDC mean anti-platelet agents) female	3.08	3.08	4.34	0.0055**
s(PDC standard deviation ACE inhibitors) male	1.90	1.90	0.97	0.4112
s(PDC standard deviation ACE inhibitors) female	2.51	2.51	5.11	0.0038**
s(PDC standard deviation β-blockers) male	3.25	3.25	12.01	0.0000***
s(PDC standard deviation β-blockers) female	1.00	1.00	2.77	0.0960
s(PDC standard deviation statins) male	1.00	1.00	0.26	0.6070
s(PDC standard deviation statins) female	3.35	3.35	2.97	0.0368*
s(PDC standard deviation anti-platelet agents) male	3.99	3.99	4.23	0.0023**
s(PDC standard deviation anti-platelet agents) female	2.69	2.69	4.04	0.0116*
R-sq. (adj.) = 0.324				

The height of the mean PDC-rates (inter-personal effect) in the complete observation period after AMI for ACE inhibitors, β-blockers and statins seemed not to influence health care expenditures in females or males. Only for anti-platelet agents a negative effect of a higher PDC-rate on health care expenditures was found for females ($p < 0.05$) and males ($p < 0.001$). A deviation of these PDC-means (the intra-personal effect), seemed to have a greater ACE inhibitors for females ($p < 0.01$), β-blockers in males ($p < 0.001$), statins in females ($p < 0.05$), and anti-platelet agents in females ($p < 0.01$), and males ($p < 0.001$) affected health care expenditures. For ACE inhibitors and β-blockers in females, an increasing negative or a positive deviation from the mean PDC-rate was associated with higher costs. For statins ($p < 0.05$), first an increase and then a decrease of health care expenditures for an increasing negative deviation and an increase in health care expenditures for an increasing positive deviation from the mean in females were observed. In males, an increasing negative deviation from the PDC-mean in β-blockers reduced the costs and an increasing positive deviation increased costs. For anti-platelet agents in males an increasing negative deviation from the mean was associated with higher costs, while an increasing positive deviation first increased and then decreased costs.

Sensitivity analysis

In the first sensitivity analysis (Table 3 and Fig. 3), all patients who spent more than 50 percent of the observed days in hospital were excluded. This led to 9,147 observations in the 3 years after AMI. Despite very few minor changes with respect to some covariates, the results were quite similar to the base case analysis. Although the significance levels changed slightly, no differences to the base case were found for the association between PDC-mean and deviation from the PDC mean and health care expenditures. Accordingly, the shapes of the curves remained almost exactly the same as in the base case analysis.

Table 3
Sensitivity analysis 1 - Influence on health care expenditures

N = 9,147		Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)		-4388.13	1956.20	-2.24	0.0249*
Age	55 < 65	366.80	667.03	0.55	0.5824
	65 < 75	23.96	622.49	0.04	0.9693
	≥ 75	-1479.16	628.26	-2.35	0.0186*
Gender	female	-182.06	298.09	-0.61	0.5414
BMI	underweight	760.97	1784.07	0.43	0.6697
	overweight	-105.89	352.11	-0.30	0.7636
	obese	-177.73	380.95	-0.47	0.6408
GIMD10	Q2	-342.96	410.99	-0.83	0.4040
	Q3	-745.28	441.27	-1.69	0.0913
	Q4	-299.33	436.92	-0.69	0.4933
	Q5	-781.20	414.84	-1.88	0.0597
Smoker	yes	-49.90	431.94	-0.12	0.9080
NYHA	1	2580.50	776.13	3.32	0.0009***
	2	1378.37	463.25	2.98	0.0029**
	3	2809.18	417.38	6.73	0.0000***
	4	4422.92	440.04	10.05	0.0000***
DMP COPD	yes	1042.85	498.59	2.09	0.0365*
DMP asthma	yes	-759.08	841.90	-0.90	0.3673
DMP diabetes type 1	yes	2033.06	2326.11	0.87	0.3821
DMP diabetes type 2	yes	505.34	276.79	1.83	0.0679
deceased	yes	10472.27	911.95	11.48	0.0000***
HMG assignments per month		1.23	0.24	5.18	0.0000***
year		-5722.92	162.81	-35.15	0.0000***
days insured		42.73	4.86	8.79	0.0000***
Angina pectoris		2027.02	270.66	7.49	0.0000***
Peripheral vascular disease		4179.64	382.42	10.93	0.0000***
Dyslipidemia		498.35	352.61	1.41	0.1576
Congestive heart failure		2090.90	339.30	6.16	0.0000***
Hypertension		1867.35	556.62	3.35	0.0008***
Dialysis		23977.62	964.93	24.85	0.0000***
		edf	Ref.df	F	p-value

N = 9,147	Estimate	Std. Error	t value	Pr(>|t|)
s(PDC mean ACE inhibitors) male	1.04	1.04	0.01	0.9423
s(PDC mean ACE inhibitors) female	1.00	1.00	0.89	0.3465
s(PDC mean β-blockers) male	1.00	1.00	2.70	0.1003
s(PDC mean β-blockers) female	1.00	1.00	0.32	0.5704
s(PDC mean statins) male	1.65	1.65	1.87	0.0949
s(PDC mean statins) female	1.00	1.00	1.61	0.2044
s(PDC mean anti-platelet agents) male	2.49	2.49	18.84	0.0000***
s(PDC mean anti-platelet agents) female	3.38	3.38	6.26	0.0003***
s(PDC standard deviation ACE inhibitors) male	2.35	2.35	1.73	0.1356
s(PDC standard deviation ACE inhibitors) female	2.72	2.72	6.54	0.0005***
s(PDC standard deviation β-blockers) male	3.63	3.63	12.74	0.0000***
s(PDC standard deviation β-blockers) female	1.00	1.00	2.89	0.0893
s(PDC standard deviation statins) male	1.00	1.00	0.43	0.5129
s(PDC standard deviation statins) female	3.58	3.58	3.73	0.0107*
s(PDC standard deviation anti-platelet agents) male	4.05	4.05	4.77	0.0007***
s(PDC standard deviation anti-platelet agents) female	2.79	2.79	4.54	0.0059**
R-sq. (adj.) = 0.333				

In the second sensitivity analysis (Table 4 and Fig. 4), all patients who deceased in the observation period were excluded leading to 7,532 observations in the 3 years after AMI. Therefore, the variables deceased and number of days in the observation period were removed from the model. In contrast to the first sensitivity analysis, some more differences to the base case analysis could be detected. Regarding the covariates, health care costs in the fifth, but not in the third quintile of the BIMD 2010 ($p < 0.05$) are significantly lower than in the first quintile while dyslipidemia ($p < 0.05$) increased health care expenditures. Contrarily, the effect of enrollment in the DMP type 2 diabetes was not significant anymore. However, the shape of the curves for mean PDC-rate and deviation from mean PDC-rate were quite similar to the base case. PDC-means for statins in male ($p < 0.001$) and female ($p < 0.05$) and a deviation from mean PDC-rates in ACE inhibitors ($p < 0.01$), statins ($p < 0.05$), and anti-platelet agents ($p < 0.001$) in females, and β-blockers ($p < 0.001$), and anti-platelet agents ($p < 0.001$) in males remain significant. Additionally to the base case, the intra-individual effect for ACE-inhibitors ($p < 0.01$) in males becomes significant and indicates that a positively or negatively increasing deviation from the PDC-mean also increases costs health care expenditures.

Table 4
Sensitivity analysis 2 - Influence on health care expenditures

N = 7,532		Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)		10032.21	840.93	11.93	0.0000***
Age	55 < 65	-105.27	573.67	-0.18	0.8544
	65 < 75	-44.58	537.60	-0.08	0.9339
	≥ 75	-1067.64	546.18	-1.95	0.0507
Gender	female	-58.70	274.20	-0.21	0.8305
BMI	underweight	1949.13	1756.07	1.11	0.2671
	overweight	-228.12	331.73	-0.69	0.4917
	obese	-140.00	352.75	-0.40	0.6915
GIMD10	Q2	-505.20	371.50	-1.36	0.1739
	Q3	-738.01	404.06	-1.83	0.0678
	Q4	-545.68	398.88	-1.37	0.1713
	Q5	-768.79	376.58	-2.04	0.0412*
Smoker	yes	183.30	387.00	0.47	0.6358
NYHA	1	1852.93	707.26	2.62	0.0088**
	2	1539.45	414.21	3.72	0.0002***
	3	2743.89	381.06	7.20	0.0000***
	4	4034.88	422.76	9.54	0.0000***
DMP COPD	yes	310.39	477.84	0.65	0.5160
DMP asthma	yes	-681.41	731.89	-0.93	0.3519
DMP diabetes type 1	yes	2067.03	1966.07	1.05	0.2931
DMP diabetes type 2	yes	424.88	253.61	1.68	0.0939
HMG assignments per month		1.41	0.24	5.77	0.0000***
year		-5133.93	155.94	-32.92	0.0000***
Angina pectoris		1766.07	249.36	7.08	0.0000***
Peripheral vascular disease		3727.85	358.26	10.41	0.0000***
Dyslipidemia		737.41	334.28	2.21	0.0274*
Congestive heart failure		1761.57	308.12	5.72	0.0000***
Hypertension		1925.66	520.03	3.70	0.0002***
Dialysis		25186.07	1035.41	24.32	0.0000****
		edf	Ref.df	F	p-value
s(PDC mean ACE inhibitors) male		1.00	1.00	0.26	0.6135
s(PDC mean ACE inhibitors) female		1.00	1.00	2.44	0.1179

N = 7,532	Estimate	Std. Error	t value	Pr(>|t|)
s(PDC mean β-blockers) male	1.00	1.00	0.01	0.9286
s(PDC mean β-blockers) female	1.00	1.00	0.01	0.9118
s(PDC mean statins) male	1.00	1.00	3.84	0.0500
s(PDC mean statins) female	1.00	1.00	0.03	0.8529
s(PDC mean anti-platelet agents) male	2.43	2.43	10.20	0.0000***
s(PDC mean anti-platelet agents) female	1.00	1.00	9.76	0.0018**
s(PDC standard deviation ACE inhibitors) male	2.93	2.93	4.86	0.0023**
s(PDC standard deviation ACE inhibitors) female	2.87	2.87	6.88	0.0002***
s(PDC standard deviation β-blockers) male	4.70	4.70	17.23	0.0000***
s(PDC standard deviation β-blockers) female	1.00	1.00	3.78	0.0520
s(PDC standard deviation statins) male	1.18	1.18	1.06	0.3681
s(PDC standard deviation statins) female	3.59	3.59	3.45	0.0136*
s(PDC standard deviation anti-platelet agents) male	3.42	3.42	8.22	0.0000***
s(PDC standard deviation anti-platelet agents) female	2.93	2.93	9.49	0.0000***
R-sq. (adj.) = 0.338				

Individual categories of health care expenditures

The same analyses were done individually for all cost categories (ambulatory, medication, hospitalization, rehabilitation, and remedy and aid costs) for the base case. Similarly, to the analysis in total health care expenditures in all individual cost categories, the inter-individual effect is more influential on costs as the inter-individual effect. In ambulatory costs, the intra-individual effect was significant for ACE inhibitors and antiplatelet agents in female, and the intra-individual effect for ACE inhibitors in female and for β-blockers in both sexes. In medication costs the inter-individual effect for ACE inhibitors, statins, and anti-platelet agents in female and in male for β-blockers and anti-platelet agents. The intra-individual effect was significant for all for medications in female and in male for β-blockers and anti-platelet agents. In hospitalization costs, the inter-individual effect was only significant for anti-platelet agents in male and the inter-individual effect for ACE inhibitors and anti-platelet agents in female and in male for β-blockers and anti-platelet agents. For rehabilitation costs, the inter-individual effect was only significant in male for statins and the intra-individual effect for ACE inhibitors in female and anti-platelet agents in both sexes. For remedy and aid costs the inter-individual effect was only significant for male in statins and anti-platelet agents. The intra-individual effect for female in ACE inhibitors, β-blockers, and antiplatelet agents and for male in β-blockers. The results could also be found in Online Table 1 to 5 and Online Fig. 1 to 5.

5. Discussion

Main results

This is the first study analyzing the influence of PDC-rates in guideline recommended medication after AMI on health care expenditures with longitudinal real-world data. It seems that the absolute mean PDC-rate (inter-individual effect) only has minimal influence, while a deviation from this mean (intra-individual effect) has a large impact on health care expenditures. These results were quite robust in sensitivity analyses. Two different effects may partly explain this phenomenon. First, health care expenditures in the first year after AMI were much higher than in the consecutive years, and the deviation from the mean PDC-rate in the first year is most of the time positive, as the PDC-rates were highest in the first year after AMI. Second, a positive

deviation of PDC-rates might be the reason for reverse causation, as it could be an indicator for worsening of the health status of a patient, leading to higher adherence of guideline-recommended medication. We adjusted for both effects by including the year after AMI and a time varying comorbidity index into the regression analysis.

Previously published literature from clinical trials led to the assumption that differences between sexes might exist regarding effectiveness of β-blockers (37–39), and ACE inhibitors (40–42). Interestingly, mean PDC-rate as well as deviations from mean PDC-rate for both men and women were significant in anti-platelet agents. For statins the intra-individual effect (deviation from the mean PDC-rate) became significant only in female. Significant differences between deviations from the mean were seen in ACE inhibitors in females, and β-blockers in males, which is in line with the findings of the clinical trials. For ACE inhibitors a deviation from the mean PDC-rate seems to be connected to a higher increase in costs in females compared to males. With respect to β-blockers an increasing negative deviation is associated with increasing costs while an increasing positive deviation is associated with increasing costs, which could be found in both sexes, but is more pronounced in male.

Overall, observed mean PDC-rates were lower than expected, given a threshold for adherence of 80% in most publications (48–52). Only the mean for statins was above 80% in men. Especially for anti-platelet agents PDC-rates were low in both sexes, ranging from 46.42% in males in the first year after AMI to 25.41% in females in the third year. The quite moderate declines from year 1 to 3 in β-blockers are interesting, as the guidelines (9, 10) recommend β-blockers after AMI only for up to two years.

Comparison with literature

Only three studies (28–30) were published so far measuring the influence of adherence of one (28, 29) or two (30) guideline-recommended medications after AMI on health care expenditures.

In a retrospective claims data analysis of a large US health insurer Bansilal et al. (30) measured the influence of statins and ACE-inhibitors adherence on hospitalization costs in a follow-up period up to three years, which was measured with PDC-rates (> 80% fully adherent; 40–79% partially adherent; and < 40% non-adherent). Full adherence to statins and ACE inhibitors was associated with reduced per-patient annual hospitalization costs for AMI and for revascularization procedures compared with partial and non-adherence.

Sun et al. (28) analyzed in a large US national pharmacy-benefit database the influence of adherence, which was measured with medication possession ratio (MPR) (> 80% fully adherent; 40–79% partially adherent; and < 40% non-adherent), in a 1-year follow-up period, to renin-angiotensin system agents (ACE inhibitors or angiotensin receptor blockers) on costs. They found that partially adherent and the fully adherent groups had significantly lower cardiovascular-related and total health care costs than the non-adherent group.

Summaria et al. (29) measured in an Italian retrospective observational study of administrative database (not further specified), the influence of statin adherence on health care expenditures in a follow-up period up to 3-years, using MPR (> 80%; 50–79%, 25–50%, < 25%). They found mean health care expenditures to increase from the non-adherent to the fully adherent group.

By focusing on PDCs (30) and MPRs (28, 29) previous studies used measures of adherence that were quite similar, yet with varying adherence thresholds, except for the fully adherent group (which was > 80% in all studies). The results of the two US studies (28, 30) indicate cost savings, while the only European (Italian) study (29) reported the highest health care expenditures in the fully adherent group.

Our results are not directly comparable, as we used a longitudinal approach considering all four guideline-recommended medications simultaneously. In addition, we chose an inter- (mean PDC-rate over the complete period) and intra-individual (deviation of the mean PDC-rate of a person in the observed year) approach to measure the influence of adherence on health care expenditures. Nevertheless, the findings of our analysis are to some degree in line with earlier findings, as we found no influence of statins but a significant negative influence of higher PDC-rates in ACE-inhibitors on health care expenditures in women.

So far, there are no previous observational studies based on German data that would allow comparing our results regarding health care expenditures. Comparison is possible only with respect to adherence to guideline-recommended medication and its development over time (18, 25, 53). In this regard, our findings are quite similar to their observations.

In the Cologne Infarction Model (KIM) Reuter and colleagues (25) measured self-reported adherence of 610 consecutive patients with ST-elevation myocardial infarction (STEMI) treated by primary percutaneous coronary intervention (PCI) at hospital discharge and after a median follow-up period of 36 months. Respective proportions of adherence for ASS, statins, β-blockers, ACE-inhibitors or angiotensin-receptor blockers were at hospital discharge between 90.8 and 97.6% and at follow-up between 79.2% and 90.8%.

Amann et al. (53) measured self-reported adherence in 1,667 AMI patients from the MONICA/KORA cohort in a survey at hospital discharge and at a mean follow-up time of 6.1 years. The proportion of patients taking antiplatelet agents, β-blockers, statins, and renin-angiotensin-aldosterone system blockers were at hospital discharge between 83.6% and 97.5% and at follow-up between 79.3% and 90.9%.

Mangiapane et al. (18) analyzed prescriptions in a sample of 30,028 AMI patients insured at Techniker Krankenkasse. They found that prescription rates declined from 82% in β-blockers, 73% in statins, 69% in ACE inhibitors, and 66% in platelet aggregation inhibitors at hospital discharge to 36% in β-blockers, 17% in statins, 31% in ACE inhibitors, and 10% in platelet aggregation inhibitors after a follow-up of 5-years. Although different methods for determining adherence were used (self-reported adherence (25, 53), treatment persistence (18), and yearly PDC-rates in our study), the findings indicate a general decline in guideline recommended medication intake over time after AMI. The decline appears to be even more pronounced when the data basis are claims data rather than self-reported data.

Limitations

Some potential limitations of this study should be considered while interpreting the results.

For β-blockers, national guidelines (54) recommend intake only for 1 up to 2 years after the AMI; we measured the mean PDC-rate over the complete 3-year follow-up period, which might underestimate the positive impact of adherence to β-blockers.

Pharmacy dispensing data were used as a measure of PDC-rates, which does not allow definite judgment as to whether patients had actually taken the paid for and collected medication. However, pharmacy refill records have been found to be highly correlated with electronic adherence monitoring, and the act of refilling a medication has been argued to reflect the patient's active decision to continue with therapy (55). Furthermore, the number of days that needed to be covered with prescribed medication was reduced by the number of hospital days in the follow-up period because medication was presumably provided by the hospital during hospitalization. This means that a higher percentage of time spent in hospital, which increases costs, also increases the mean PDC-rate and positive deviation from mean PDC-rate.

Adherence to anti-platelet agents may be underestimated, as Aspirin 100 mg has a co-payment of 100% and is available over the counter. Although physicians can still prescribe aspirin after AMI, its removal from reimbursement had a clear effect on prescription incidence, which dropped from 72% in 2003 to 57% in 2004 (18). An ongoing prescription of anti-platelet agents might identify high-risk patients, as the physician makes sure, with the inclusion of Aspirin 100 mg on the prescription, the patient has not to additionally order it in the pharmacy. Therefore, our finding that a higher PDC-rate in anti-platelet agents causes higher health care expenditures should be interpreted with caution.

We did not exclude persons who were never prescribed any of the four medications as other studies measuring adherence or persistence did (29, 30). We wanted to measure adherence to guideline recommended medication, which are the same for every patient after AMI, except for contraindications, which we could not capture in a retrospective claims data analysis. Therefore, the findings might not be directly comparable.

Our study population was enrolled in the DMP CAD at index AMI, which is voluntary, and therefore we could not exclude a self-selection effect of patients leading to an overestimation of PDC rates. However, the DMP CAD might include the more severe

cases, as a diagnosed CAD, which is an inclusion criterion for the DMP, existed before AMI.

Finally, as individual socioeconomic status is usually not sufficiently reflected in routine data, we incorporated an area deprivation index for Bavaria (BIMD 2010) as a proxy. Nevertheless, this procedure is a standard approach in corresponding studies utilizing claims or register data and the index used is a well-established and recognized tool to address such limitations (46).

Aside from these aspects, to the best of our knowledge this is the first study considering the influence of all four guideline recommended medications on health care expenditures, which likely gives a more realistic picture of the effectiveness of adherence to guideline-recommended medications after AMI because positive correlation of adherence to other guideline-recommended medications is accounted for (53). If this effect is not considered, the positive impact of one type of medication might be overestimated, as the positive impact of adherence to another type of medication is attributed to the medication under scrutiny.

Additionally, our sample size was large enough to stratify the analysis for sex, as there is evidence that there are differences in effectiveness of ACE-inhibitors and β-blockers between females and males. To what extend these differences influence health care expenditures were not investigated to date.

Furthermore, the generalized additive mixed model incorporates a longitudinal design which seems to be more appropriate than a cross sectional design, as it also controls for individual changes over time.

In addition, a relatively long period of 4 years was available for every patient, which means that information from the year before AMI could be considered in the analyses, such as medication stocks that patients had before the AMI, leading to a more realistic estimate of the PDC-rate.

6. Conclusion

This is the first study to consider the influence of medications after AMI on health care expenditures for a population of DMP patients reflected by routine care in Germany. Unlike previous studies, we considered adherence regarding all four guideline-recommended medications simultaneously. A longitudinal stratified design allowed capturing variation in adherence over time and sex-specific differences. Using a GAMM, we were able to take into account inter-individual and intra-individual effects and, thereby, allowing for a more complete analysis. The overall low and over time declining PDC-rates for all guideline-recommended medications found in this study may be attributable to using real-world data from a large statutory health insurance rather than self-reported data. While we cannot confirm the results of clinical studies, which found mainly cost-savings of adherence after AMI, we found that deviation of the PDC-means (the intra-personal effect) in either direction seemed to have a greater impact on health care expenditures than the mean PDC-rate (inter-personal effect). It is possible that for the patients who would have been presumably excluded from clinical trials effectiveness is not given in the same way as shown in clinical trials, leading to higher costs despite being adherent. In the same direction, the findings of other observational studies [28–30], are not consistently reporting reductions in health care expenditures. Therefore, it seems to be necessary that further analyses of real-world data, such as registries and claims data be conducted to unveil cost saving potentials related to guideline-recommended adherence after AMI.

7. List Of Abbreviations

ACE - Angiotensin-converting enzyme

AMI - Acute myocardial infarction

ANOVA - Analysis of variance

ATC - Anatomical therapeutic chemical

BIMD 2010 - Bavarian Index of Multiple Deprivation of 2010

BMI - Body-Mass-Index

CAD - Coronary artery disease

COPD - Chronic obstructive pulmonary disease

CVD - Cardiovascular disease

DDD -Defined daily dose

DMP - Disease Management Program

GAMM - Generalized additive mixed model

HMG - Hierarchical morbidity group

KIM - Cologne Infarction Model

MPR - Medication possession ratio

NYHA - New York Heart Association classification

PCI - Percutaneous coronary intervention

PDC - Proportion of days covered

STEMI - ST-elevation myocardial infarction

WIdO - The scientific institute of the AOK

8. Declarations

Ethics approval and consent to participate

According to the ethics committee of the State Chamber of Physicians of Bavaria, no ethical approval was required.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due §75 SGB X to but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

The author(s) received no specific funding for this work

Authors' contributions

FK analysed and interpreted the patient data, performed the statistical analysis and wrote the manuscript. FK, CK, CK, LS and AS created the statistical analysis plan. AS provided the dataset and have been involved in drafting or revising the manuscript. All authors read and approved the final manuscript

Acknowledgements

We would like to thank the AOK Bayern for providing the data and the helpful comments on data.

References

1. Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Flaxman A, et al. The global burden of ischemic heart disease in 1990 and 2010: the Global Burden of Disease 2010 study. Circulation. 2014;129(14):1493-501.
2. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation. 2011;123(8):933-44.
3. Likosky DS, Zhou W, Malenka DJ, Borden WB, Nallamothu BK, Skinner JS. Growth in medicare expenditures for patients with acute myocardial infarction: a comparison of 1998 through 1999 and 2008. JAMA internal medicine. 2013;173(22):2055-61.
4. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Executive summary: heart disease and stroke statistics–2014 update: a report from the American Heart Association. Circulation. 2014;129(3):399-410.
5. Gesundheitsbericherstattung dB. Sterbefälle, Sterbeziffern (je 100.000 Einwohner, alterstandardisiert). https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Todesursachen. 2019.
6. Reinhold T, Lindig C, Willich SN, Brüggenjürgen B. The costs of myocardial infarction—a longitudinal analysis using data from a large German health insurance company. Journal of Public Health. 2011;19(6):579-86.
7. Russell MW, Huse DM, Drowns S, Hamel EC, Hartz SC. Direct medical costs of coronary artery disease in the United States. The American journal of cardiology. 1998;81(9):1110-5.
8. Lacey L, Tabberer M. Economic burden of post-acute myocardial infarction heart failure in the United Kingdom. European journal of heart failure. 2005;7(4):677-83.
9. Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, et al. ESC guidelines on management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. Revista espanola de cardiologia. 2009;62(3):293, e1-47.
10. Gandjour A, Stock S. A national hypertension treatment program in Germany and its estimated impact on costs, life expectancy, and cost-effectiveness. Health policy (Amsterdam, Netherlands). 2007;83(2-3):257-67.
11. Stark R, Kirchberger I, Hunger M, Heier M, Leidl R, von Scheidt W, et al. Improving care of post-infarct patients: effects of disease management programmes and care according to international guidelines. Clinical research in cardiology : official journal of the German Cardiac Society. 2014;103(3):237-45.
12. Zeymer U. [Secondary prevention in outpatients with coronary artery disease. Adherence with recommendations within 4 weeks after hospital discharge]. Deutsche medizinische Wochenschrift (1946). 2007;132(45):2367-70.
13. Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet (London, England). 2012;380(9841):581-90.
14. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ (Clinical research ed). 2009;338:b1665.
15. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet (London, England). 2009;373(9678):1849-60.

16. Boger GI, Hoopmann M, Busse R, Budinger M, Welte T, Boger RH. [Drug therapy of coronary heart disease--are therapeutic guidelines being paid attention to?]. Zeitschrift fur Kardiologie. 2003;92(6):466-75.
17. Frilling B, Schiele R, Gitt AK, Zahn R, Schneider S, Glunz HG, et al. Too little aspirin for secondary prevention after acute myocardial infarction in patients at high risk for cardiovascular events: Results from the MITRA study. American heart journal. 2004;148(2):306-11.
18. Mangiapane S, Busse R. Prescription prevalence and continuing medication use for secondary prevention after myocardial infarction: the reality of care revealed by claims data analysis. Deutsches Arzteblatt international. 2011;108(50):856-62.
19. van der Elst ME, Bouvy ML, de Blaey CJ, de Boer A. Preventive drug use in patients with a history of nonfatal myocardial infarction during 12-year follow-up in The Netherlands: a retrospective analysis. Clinical therapeutics. 2005;27(11):1806-14.
20. Bischoff B, Silber S, Richartz BM, Pieper L, Klotsche J, Wittchen HU. Inadequate medical treatment of patients with coronary artery disease by primary care physicians in Germany. Clinical research in cardiology : official journal of the German Cardiac Society. 2006;95(8):405-12.
21. Gasse C, Jacobsen J, Larsen AC, Schmidt EB, Johannesen NL, Videbaek J, et al. Secondary medical prevention among Danish patients hospitalised with either peripheral arterial disease or myocardial infarction. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2008;35(1):51-8.
22. Senst BL, Achusim LE, Genest RP, Cosentino LA, Ford CC, Little JA, et al. Practical approach to determining costs and frequency of adverse drug events in a health care network. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists. 2001;58(12):1126-32.
23. Rodgers PT, Ruffin DM. Medication nonadherence: Part II--A pilot study in patients with congestive heart failure. Managed care interface. 1998;11(9):67-9, 75.
24. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. Jama. 2002;288(4):455-61.
25. Reuter H, Markhof A, Scholz S, Wegmann C, Seck C, Adler C, et al. Long-term medication adherence in patients with ST-elevation myocardial infarction and primary percutaneous coronary intervention. European journal of preventive cardiology. 2015;22(7):890-8.
26. Osterberg L, Blaschke T. Adherence to medication. The New England journal of medicine. 2005;353(5):487-97.
27. Cutler DM, Everett W. Thinking outside the pillbox--medication adherence as a priority for health care reform. The New England journal of medicine. 2010;362(17):1553-5.
28. Sun SX, Ye X, Lee KY, Dupclay L, Jr., Plauschinat C. Retrospective claims database analysis to determine relationship between renin-angiotensin system agents, rehospitalization, and health care costs in patients with heart failure or myocardial infarction. Clinical therapeutics. 2008;30 Pt 2:2217-27.
29. Summaria F, Ciaralli F, Mustilli M, Sette A, Lanzillo C, Vasselli L. Pharmacoeconomic impact evaluation of statin adherence in high-risk unselected post myocardial infarction population: an administrative database-guided analysis. Medical archives (Sarajevo, Bosnia and Herzegovina). 2013;67(5):314-7.
30. Bansilal S, Castellano JM, Garrido E, Wei HG, Freeman A, Spettell C, et al. Assessing the Impact of Medication Adherence on Long-Term Cardiovascular Outcomes. Journal of the American College of Cardiology. 2016;68(8):789-801.
31. Schafer I, Kuver C, Gedrose B, Hoffmann F, Russ-Thiel B, Brose HP, et al. The disease management program for type 2 diabetes in Germany enhances process quality of diabetes care - a follow-up survey of patient's experiences. BMC health services research. 2010;10:55.
32. Consumer prices [Internet]. 2018. Available from: https://www.oecd-ilibrary.org/content/data/0f2e8000-en.
33. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. Jama. 2006;295(3):306-13.

34. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ (Clinical research ed). 2002;324(7329):71-86.
35. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. Jama. 1999;282(24):2340-6.
36. Cheung BM, Lauder IJ, Lau CP, Kumana CR. Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes. British journal of clinical pharmacology. 2004;57(5):640-51.
37. Labbe L, Sirois C, Pilote S, Arseneault M, Robitaille NM, Turgeon J, et al. Effect of gender, sex hormones, time variables and physiological urinary pH on apparent CYP2D6 activity as assessed by metabolic ratios of marker substrates. Pharmacogenetics. 2000;10(5):425-38.
38. Luzier AB, Killian A, Wilton JH, Wilson MF, Forrest A, Kazierad DJ. Gender-related effects on metoprolol pharmacokinetics and pharmacodynamics in healthy volunteers. Clinical pharmacology and therapeutics. 1999;66(6):594-601.
39. Jochmann N, Stangl K, Garbe E, Baumann G, Stangl V. Female-specific aspects in the pharmacotherapy of chronic cardiovascular diseases. European heart journal. 2005;26(16):1585-95.
40. Shekelle PG, Rich MW, Morton SC, Atkinson CSW, Tu W, Maglione M, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials. Journal of the American College of Cardiology. 2003;41(9):1529-38.
41. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet (London, England). 2003;362(9386):782-8.
42. Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, et al. A comparison of outcomes with angiotensin-converting--enzyme inhibitors and diuretics for hypertension in the elderly. The New England journal of medicine. 2003;348(7):583-92.
43. Hedeker D. An introduction to growth modeling. The Sage handbook of quantitative methodology for the social sciences. 2004:215-34.
44. Wood S, Scheipl F, Wood MS. Package 'gamm4'. Am Stat. 2017;45:339.
45. Wood S, Scheipl F. gamm4: Generalized additive mixed models using mgcv and lme4. URL http://CRAN R-project org/package= gamm4. 2014.
46. Maier W, Fairburn J, Mielck A. [Regional deprivation and mortality in Bavaria. Development of a community-based index of multiple deprivation]. Gesundheitswesen. 2012;74(7):416-25.
47. Bauer H, Maier W. GIMD 2010 – Ein Update des ‚German Index of Multiple Deprivation&lsquo. Berichte des Helmholtz Zentrums München. 2018.
48. Hamood H, Hamood R, Green MS, Almog R. Determinants of adherence to evidence-based therapy after acute myocardial infarction. European journal of preventive cardiology. 2016;23(9):975-85.
49. Ho PM, Magid DJ, Masoudi FA, McClure DL, Rumsfeld JS. Adherence to cardioprotective medications and mortality among patients with diabetes and ischemic heart disease. BMC cardiovascular disorders. 2006;6:48.
50. Chapman RH, Benner JS, Petrilla AA, Tierce JC, Collins SR, Battleman DS, et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. Archives of internal medicine. 2005;165(10):1147-52.
51. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. Journal of clinical epidemiology. 1997;50(1):105-16.
52. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. An empirical basis for standardizing adherence measures derived from administrative claims data among diabetic patients. Medical care. 2008;46(11):1125-33.
53. Amann U, Kirchberger I, Heier M, Thilo C, Kuch B, Meisinger C. Medication use in long-term survivors from the MONICA/KORA Myocardial Infarction Registry. European journal of internal medicine. 2018;47:62-8.

54. Serxner S, Baker K, Gold D. Guidelines for analysis of economic return from health management programs. American journal of health promotion: AJHP. 2006;20(6):suppl 1-17.
55. Krousel-Wood M, Thomas S, Muntner P, Morisky D. Medication adherence: a key factor in achieving blood pressure control and good clinical outcomes in hypertensive patients. Current opinion in cardiology. 2004;19(4):357-62.

Figures

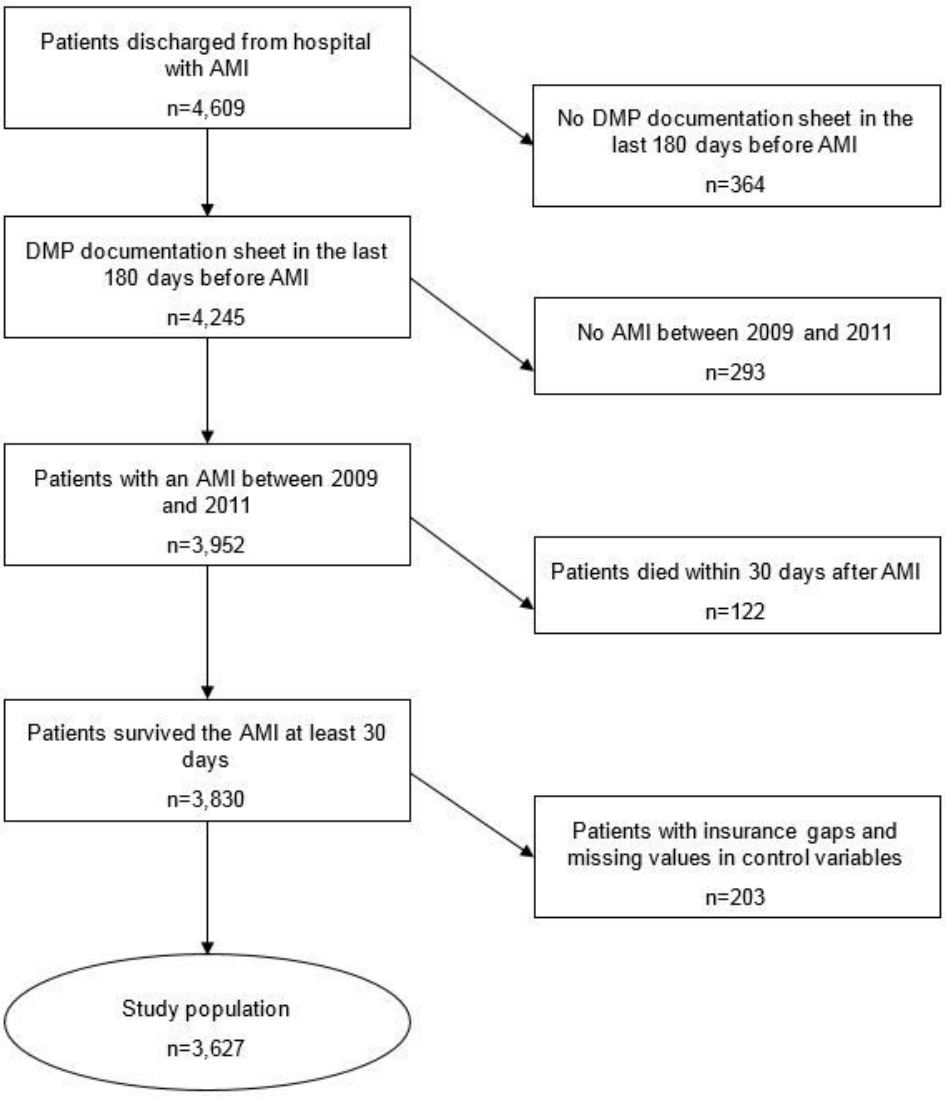

Figure 1

Patient selection

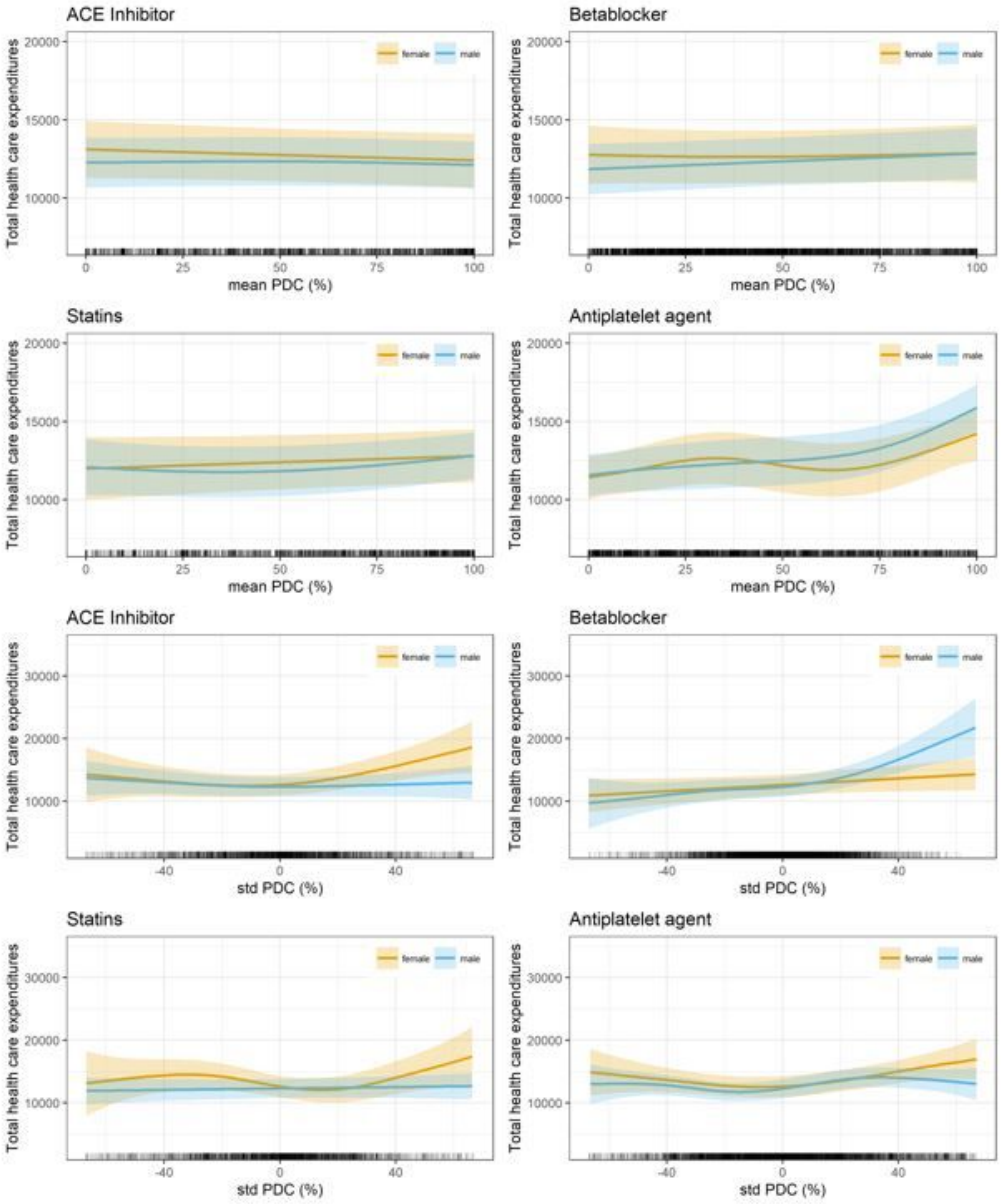

Figure 2

Base case – Influence on total health care expenditures

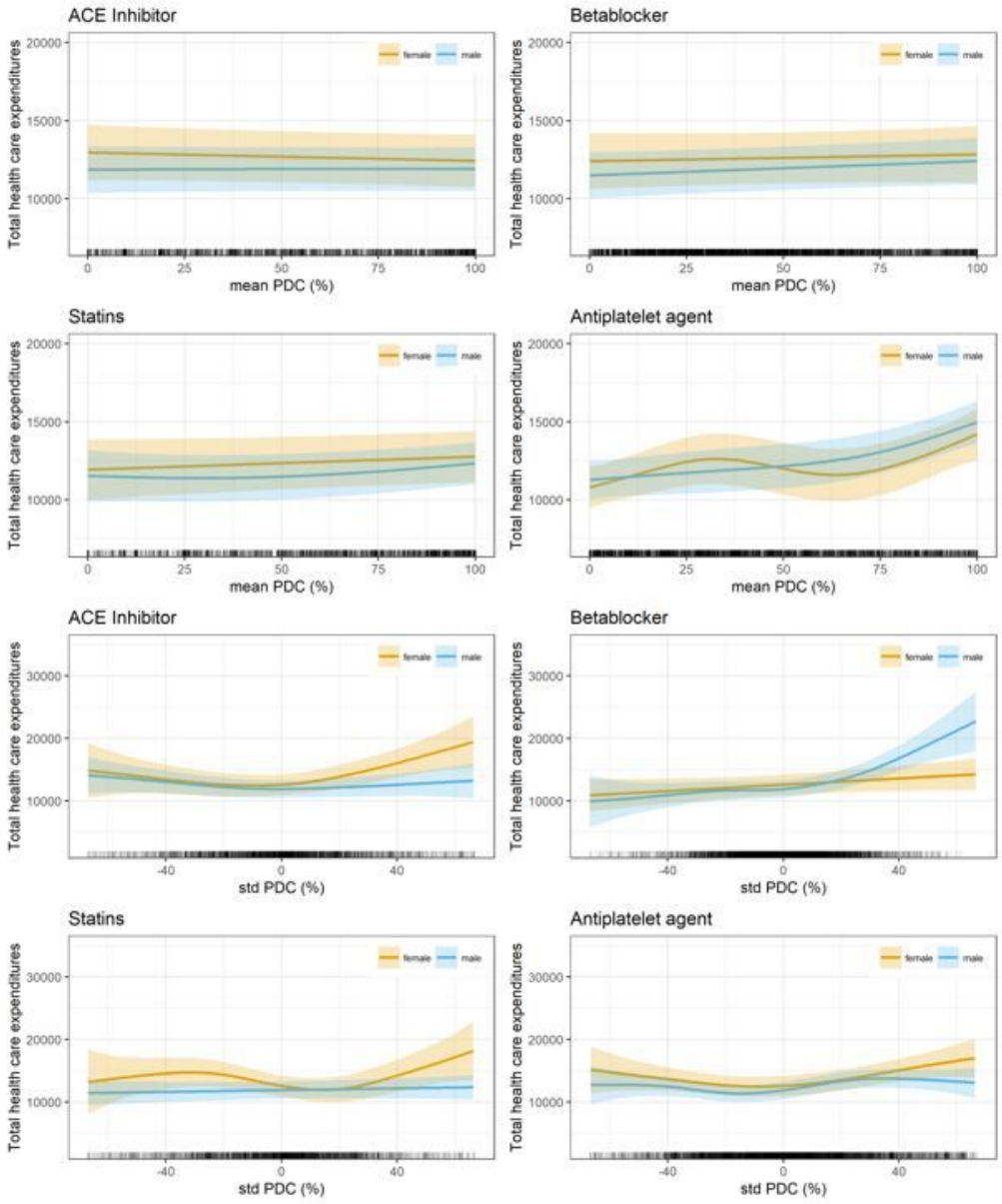

Figure 3

Sensitivity analysis 1 – Influence on total health care expenditures

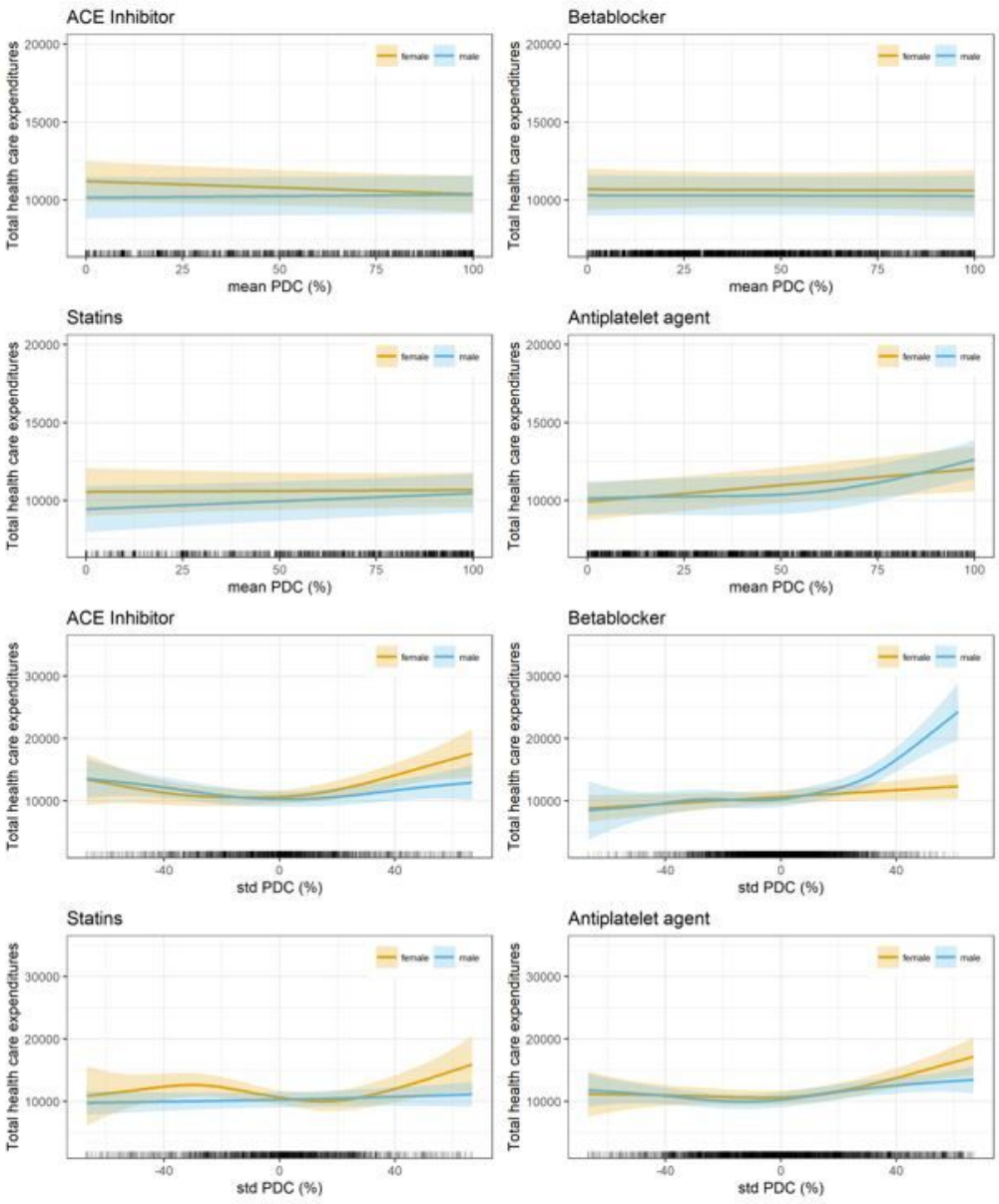

Figure 4

Sensitivity analysis 2 – Influence on total health care expenditures

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- BMCTitlePage.docx
- BMConlinefigures.docx
- BMConlinetables.docx