Purchases of medical therapy recommended for coronary artery disease before and after elective revascularisation

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Received: 22 February 2019 / Accepted: 5 August 2019 / Published online: 11 October 2019
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Abstract

Aims We studied the purchases of medical therapy recommended for coronary artery disease patients before and after elective revascularisation (percutaneous coronary intervention (PCI) or coronary bypass grafting (CABG)).

Methods All patients who underwent an elective PCI ($N = 1557$) or CABG ($N = 1768$) at the Heart Center, Kuopio University hospital between 2007 and 2014 were included. Data were collected from the hospital's coronary register and national registers, and obtained for 3 years before and 1 year after the revascularisation.

Results Altogether 85.2% of PCI patients and 88.1% of CABG patients had purchased lipid-modifying agents before the procedure, and 94.9% and 96.8% during the post-procedure follow-up year, respectively. Beta-blocking agents were purchased by 84.9% of PCI patients before and by 87.9% after the procedure and by 86.3% of CABG patients before and 97.1% after the operation. Of PCI patients, 64.3% had purchased organic long-acting nitrates before the procedure and 54.4% also after the procedure. Among CABG patients, the purchase of organic long-acting nitrates fell from 59.7% before to 10.1% after the operation. The use of ADP receptor blocking agents increased in PCI patients (26.3 to 83.9%) and the use of warfarin in CABG patients (9.4 to 21.3%). Medication purchases were more common among those who had greater use of hospital services before and after the procedures.

Conclusions In both PCI and CABG patients, the use of medical therapy before and after revascularisation procedure complied with current guidelines. Purchases of long-acting nitrates were common in the PCI group even after the procedure.

Keywords Evidence-based medicine · Public health · Medical research · Healthcare · Coronary disease · Revascularisation · Optimal medical therapy

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00228-019-02735-9>) contains supplementary material, which is available to authorized users.

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Introduction

Optimal medical therapy (OMT) is essential for symptom control, as well as for primary and secondary prevention of coronary artery disease (CAD). Event prevention in CAD consists of acetylsalicylic acid (ASA), lipid-lowering agents and beta-blockers. In addition, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blocking (ARB) agents are often indicated for patients with co-existing hypertension, left ventricular ejection fraction (LVEF) $\leq 40\%$, diabetes or chronic kidney disease. A combination of ASA and adenosine diphosphate (ADP) receptor inhibitors is used in those with acute coronary syndrome and in those undergoing elective percutaneous coronary intervention (PCI). In addition, nitrates are the cornerstone of symptom relief in angina pectoris [1–8].

The recommendations on postoperative OMT in patients with stable CAD are similar after percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), with one exception. ADP inhibitor (clopidogrel, prasugrel and ticagrelor) and ASA combination is used for the first year after percutaneous coronary intervention (PCI) but not after CABG [1, 4–8]. Otherwise, if there are no contraindications, the OMT should continue as a lifelong secondary prevention therapy after the revascularisation procedure [6–8].

Secondary prevention and drug adherence are essential for the development of effective critical pathways and prevention of future cardiovascular events in patients undergoing revascularisation. According to earlier research [9–13], the overall adherence to secondary prevention measures tended to improve regardless of revascularisation type, although there was still room for improvement. According to a recent Danish study [14], there was an increasing trend in drug use for primary prevention in the first decade of the twenty-first century.

The aims of this study were to compare the use of medical therapy recommended for coronary artery disease patients before and after an elective revascularisation procedure and to assess temporal trends and factors associated with the use of OMT.

Methods

Patients

The Coronary Artery TreatmentS (CATS) study includes all CAD patients who underwent an elective revascularisation procedure at the Heart Center, Kuopio University hospital (KUH) between 2007 and 2014 ($N=1768$ CABG, $N=1557$ PCI). The functional clinical status of the patients was assessed by the New York Heart Association (NYHA) [15, 16] and the Canadian Cardiovascular Society (CCS) grading system [17–20].

Data linkage and registers

The clinical data from the hospital revascularisation registers were linked to national registers with personal identification numbers. Data on mortality were obtained from the Statistic Finland [21]. The Care Register for Health Care covers, as mandated by law, all inpatient hospital admissions.

The National Prescription Register contains information on all reimbursed prescription medication purchased by the patients. Information about medications

dispensed in the non-community settings (hospital, public nursing homes) was not available from the register. Drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system.

Use of cardiovascular medication was identified as any ATC code C. These drugs were further classified into cardiac therapy drugs (C01) and combinations. OMT drugs were categorised more precisely as follows: Nitrates (C01DA) were divided by medicine form into short-acting nitrates (C01DA02: sublingual nitroglycerin and C01DA08: oral spray) and long-acting nitrates (C01DA02: transdermal patch, ointments; C01DA08: tablets; C01DA14: tablets). Antihypertensives (C02, C07F) included diuretics (C03, C02L, C07B, C07C, C07D, C08G, C09DA, C09DX01, C09DX03, C09BX01); beta-blockers (C07, C09BX02); calcium channel blockers (C08, C07F, C09BB, C09DB, C09BX01, C09DX01, C10BX03); agents acting on the renin-angiotensin system (C09), such as ACE inhibitors (C09A, C09B); and angiotensin II antagonists (C09C, C09D, C09DX03). Lipid-lowering drugs were identified by code (C10). ADP inhibitors were identified as platelet aggregation inhibitors excluding heparin (B01AC) and more specific ATC codes for clopidogrel (B01AC04), prasugrel (B01AC22) and ticagrelor (B01AC24) were used. In addition, a minor proportion of ADP inhibitor purchases consisted of ticlopidine (B01AC05). Other antiaggregatory agents listed were acetylsalicylic acid B01AC06, dipyridamole B01AC07 and combinations B01AC30.

Statistical analyses

The proportion of users in each medication group was calculated from the eligible population (community dweller and alive) 3 years before and 1 year after the procedure. All statistical analyses were conducted by STATA14.0 (Stata Corp LP, Station, TX, USA).

Exact McNemar's test to assess the statistical significance of differences on dichotomous dependent variables between two related groups was used for analysing differences in purchase proportions before and after the procedure for both the PCI and CABG groups. Logistic regression models were used to analyse overall cardiovascular medication purchases. Independent variables in regression models were age, sex, operation year, hospitalisation during follow-up time and disease severity (NYHA/CCS class).

Persons with missing CCS/NYHA data (PCI group $n=40$) were excluded from logistic regression analyses. There were no other missing data. Those who died during the follow-up (PCI group $n=39$) and (CABG group $n=28$) were excluded.

Standard protocol approvals, registrations and patient consents

The study was approved by the ethics committee of Kuopio University hospital (KUH) and by the ethics committee of the Finnish National Institute for Health and Welfare which gives the permissions to use the data from the Hospital Discharge Register (HILMO). The permission to use the Special Reimbursement and Prescription registers was given by the Social Insurance Institution of Finland (SII). The permission to use national mortality data was given by Statistics Finland. Informed consent was not deemed necessary by the Ethics committees or register maintainers because participants were not contacted. The study complies with the Declaration of Helsinki.

Results

Patient characteristics

During the study period (2007–2014) elective PCI was performed in 1557 patients and elective CABG in 1768 patients. The mean age of PCI patients was 67.1 years and that of CABG patients 66.3 years. Majority of patients (70.8% of PCI and 80.1% of CABG patients) were men. CABG patients had more severe symptoms as indicated by CCS/NYHA class (Table 1).

All-cause mortality rates during the one-year follow-up were 2.7% and 1.7% for PCI and CABG, respectively. Three (0.2%) PCI and two (0.1%) CABG patients died during the revascularisation procedure.

The median numbers of hospital inpatient days before the revascularisation were 7 (range 0–655) and 7 (range 0–355) in the PCI and CABG groups, respectively. A total of 131 (8.4%) PCI and 13 (0.7%) CABG patients

did not have any inpatient admissions during the 3 years before the operation. Majority of both CABG (53.4%) and PCI (65.4%) patients had 1–10 inpatient days before the procedure (Table 1).

The median numbers of inpatient admissions within 1 year after the revascularisation were 3 (range 0–193) and 3 (range 0–164) in the PCI and CABG groups, respectively. A total of 279 (17.9%) PCI and 163 (9.2%) CABG patients did not have any inpatient admissions during the one-year follow-up after the procedure. Majority of PCI patients (71.4%) and CABG patients (65.4%) had 1–10 inpatient days after the intervention (Table 1).

Purchases of recommended medical therapy

A total of 1519 (97.6%) PCI and 1690 (95.6%) CABG patients had purchased any cardiovascular drugs within the three-year timeframe before the intervention (Table 2). Correspondingly, nearly all patients (99.3% of PCI patients ($n = 1546$) and 98.4% of CABG patients ($n = 1740$)) had purchased cardiovascular drugs within 1 year after the intervention.

The most commonly purchased drug classes before the operation were lipid-modifying agents, beta-blocking agents and nitrates (Table 2). Purchases of lipid-modifying agents and beta-blockers increased after the operation among both PCI ($p < 0.001$) and CABG ($p < 0.001$) patients (Table 2). Long-acting nitrates were purchased before the operation by 64.3% of PCI patients and 59.7% of CABG patients ($p = \text{NS}$). However, after the operation, the purchase of long-acting nitrates changed differently in PCI and CABG patients: It decreased in PCI patients (to 54.4%, $p < 0.001$) and much more in CABG patients (to 10.1%, $p < 0.001$) (Table 2). Agents acting on the renin-angiotensin system (ACE inhibitors and angiotensin II receptor antagonists) were purchased more often in the PCI group ($p < 0.001$) after the intervention (Table 2).

Table 1 Study population

	PCI ($N = 1557$)	CABG ($N = 1768$)
Age mean, 95% CI	67.1 (66.6–67.6)	66.3 (65.9–66.7)
Men, n (%)	1102 (70.8)	1416 (80.1)
CCS/NYHA class		
0	44 (2.8)	4 (0.2)
1	103 (6.6)	47 (2.7)
2	694 (44.6)	553 (31.3)
3	510 (32.8)	900 (50.9)
4	166 (10.7)	263 (14.9)
Missing CCS/NYHA	40 (2.6)	0
Died during procedure	3 (0.2)	2 (0.1)
Died within 12 months after the procedure	39 (2.6)	28 (1.6)

Table 2 Purchase of cardiovascular and antithrombotic drugs or their combinations before and after PCI or CABG

Medication group	PCI (N = 1557)		CABG (N = 1768)		<i>p</i> [†]
	3 years before the operation, <i>n</i> (%)	1 year after the operation, <i>n</i> (%)	3 years before the operation, <i>n</i> (%)	1 year after the operation, <i>n</i> (%)	
Cardiac therapy overall (C01)	1322 (84.9)	1106 (71.0)	< 0.001 1498 (84.7)	563 (31.8)	< 0.001
Nitrates (C01DA)	1304 (83.8)	1087 (69.8)	< 0.001 1489 (84.2)	500 (28.3)	< 0.001
Short-acting Nitrates (C01DA02, C01DA08)	1194 (76.7)	693 (44.5)	< 0.001 1378 (77.9)	402 (22.7)	< 0.001
Long-acting Nitrates (C01DA02, C01DA08, C01DA14)	1001 (64.3)	847 (54.4)	< 0.001 1055 (59.7)	179 (10.1)	< 0.001
Antihypertensives and combinations (C02, C07F)	69 (4.4)	45 (2.9)	< 0.001 48 (2.7)	23 (1.3)	< 0.001
Diuretics and combinations (C03, C02L, C07B, C07C, C07D, C08G, C09BA, C09DA, C09DX01, C09DX03, C09BX01)	642 (41.2)	592 (38.0)	< 0.001 647 (36.6)	719 (40.7)	< 0.001
Lipid-modifying agents ((3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor (C10))	1327 (85.2)	1477 (94.9)	< 0.001 1557 (88.1)	1712 (96.8)	< 0.001
First-line anti-anginal drugs (beta blockers (C07) or/and calcium channel blockers (C08) or/and nitrates (C01DA))	1394 (89.5)	1424 (91.5)	0.020 1580 (89.4)	1723 (97.5)	< 0.001
Beta blockers (C07)	1322 (84.9)	1369 (87.9)	< 0.001 1525 (86.3)	1717 (97.1)	< 0.001
Calcium channel blockers and combinations (C08, C07F, C09BB, C09DB, C09DX01)	607 (39.0)	538 (34.6)	< 0.001 581 (32.9)	432 (24.4)	< 0.001
ACE inhibitors, plain (C09AA)	539 (34.6)	538 (34.6)	1.000 590 (33.4)	636 (36.0)	0.024
Angiotensin II antagonists, plain (C09CA)	414 (26.6)	399 (25.6)	0.333 401 (22.7)	386 (21.8)	0.412
Antithrombotic agents (B01)	642 (41.2)	1442 (92.6)	< 0.001 467 (26.4)	607 (34.3)	< 0.001
Vitamin K antagonists (B01AA)	271 (17.4)	281 (18.1)	0.391 166 (9.4)	377 (21.3)	< 0.001
Heparin group (B01AB)	83 (5.3)	46 (3.0)	< 0.001 53 (3.0)	29 (1.6)	0.009
Platelet aggregation inhibitors excl. heparin (B01AC; incl. ADP inhibitors)	409 (26.3)	1355 (87.0)	< 0.001 297 (16.8)	255 (14.4)	0.022
Clopidogrel (B01AC04)	398 (25.6)	1307 (83.9)	< 0.001 212 (12.0)	208 (11.8)	0.858
Prasugrel (B01AC22)	5 (0.3)	16 (1.0)	0.003 4 (0.2)	3 (0.2)	1.000
Ticagrelor (B01AC24)	6 (0.4)	36 (2.3)	< 0.001 2 (0.1)	3 (0.2)	1.000
Other ADP inhibitors (ticlopidine (B01AC05), acetylsalicylic acid (B01AC06), dipyridamole (B01AC07), combinations (B01AC30))	105 (6.7)	30 (1.9)	< 0.001 100 (5.7)	47 (2.7)	< 0.001
Direct thrombin inhibitors (B01AE)	1 (0.1)		1.000 4 (0.2)	1 (0.1)	0.375
Direct factor Xa inhibitors (B01AF)	5 (0.3)		0.063 2 (0.1)		0.500
Other antithrombotic agents (B01AX)	12 (0.8)	2 (0.1)	0.013 13 (0.7)	1 (0.1)	0.002

[†] Exact McNemar's test

Purchases of calcium channel blockers decreased after both types of intervention ($p < 0.001$). Diuretics purchases decreased moderately in the PCI group ($p < 0.001$) but increased moderately in the CABG group ($p < 0.001$). Other antihypertensive drug purchases were rare in both groups (Table 2 and Supplementary Table 1).

The purchase of ADP inhibitors increased among PCI patients ($p < 0.001$) but decreased among CABG patients ($p = 0.022$). On the other hand, the purchase of vitamin K antagonists (VKA) increases after CABG ($p < 0.001$).

Predictors of purchases

Older persons and those with more severe disease, indicated by previous hospital stays or higher CCS/NYHA class, had more often purchased cardiovascular drugs before PCI (Table 3). The association between drug purchases and previous hospital stays was also observed when assessing the predictors of purchase after PCI. However, CCS/NYHA class was not associated with cardiovascular drug purchases after PCI, and the association of age was reversed, i.e. older patients were less likely to buy drugs. Intervention year was not associated with cardiovascular drug purchases before or after PCI (Table 3).

Older persons had more often purchased cardiovascular drugs before CABG (Table 4). Those with the most severe disease, indicated by CCS/NYHA class 4, had very low drug purchase activity. Also the intervention year was associated with lower cardiovascular drug purchases before CABG during the years 2009 and 2010 (Table 4). The association between drug purchases and

age was reversed, i.e. older patients were less likely to buy drugs after CABG (Table 4). However, CCS/NYHA class was not associated with cardiovascular drug purchases after PCI or CABG.

Discussion

The main finding of our study was that the use of medical therapy recommended for coronary artery disease evaluated on the basis of purchased drugs before and after revascularisation was in line with the European and Finnish guidelines and recommendations [1–7]. Almost all patients used recommended coronary artery disease drugs during the follow-up time (3 years before and 1 year after the elective PCI or CABG). The decrease in nitrate purchases, especially long-acting nitrates, suggests that the revascularisation procedure was in most cases considered successful in alleviating the CAD symptoms. The reasons for the higher percentage of patients having bought long-acting nitrates after PCI (54%) cannot be evaluated with our data. However, in earlier randomised studies comparing PCI and CABG, the need for repeat revascularisation has been higher among PCI-treated patients [22]. Thus, it is possible that PCI-treated patients have more angina symptoms after revascularisation than CABG-treated patients.

Another difference between PCI and CABG patients was seen in the purchase of ADP receptor blocking agents. They were more commonly used after PCI: Their purchase increased from 26.3 (pre-intervention) to 87.0% (post-intervention). The most commonly used antithrombotic agent was clopidogrel which was used by 25.6% of PCI patients before

Table 3 Associations of overall cardiovascular therapy drug (C) purchase three years before and one year after PCI procedure with clinical parameters

Dependent variable overall cardiovascular therapy drug (C) purchase [†]		Before procedure				<i>p</i>	After procedure				<i>p</i>								
		Drug (C) purchase		OR	95% CI		Drug (C) purchase		OR	95% CI									
		Yes, <i>n</i> (%)	No, <i>n</i> (%)				Yes, <i>n</i> (%)	No, <i>n</i> (%)											
Mean age		67.3	61.3	1.05	1.02–1.09	0.004	67.1	75.0	0.89	0.82–0.97	0.008								
Sex	Men	1519 (97.6)	38 (2.4)				1546 (99.3)	11 (0.7)											
	Women	1074 (70.7)	28 (73.7)	1.00	Reference		1094 (70.8)	8 (72.7)											
Hospitalisation	No	445 (29.3)	10 (26.3)	0.70	0.32–1.56	0.388	452 (29.2)	3 (27.3)	1.72	0.41–7.29	0.461								
	Yes	25 (65.8)	13 (34.2)	1.00	Reference		127 (8.2)	4 (36.4)											
CCS/NYHA class	1	1401 (92.2)	118 (7.8)	6.70	3.12–14.37	< 0.001	1419 (91.8)	7 (63.6)	11.1	2.89–42.84	< 0.001								
	2	138 (9.3)	9 (24.3)	1.00	Reference		147 (9.8)	n/a	1.00										
	3	680 (46.0)	14 (37.8)	3.42	1.40–8.39	0.007	690 (45.8)	4 (36.4)	1.00	Reference									
	4	506 (34.2)	4 (10.8)	6.97	2.00–24.26	0.002	505 (33.5)	5 (45.5)	0.64	0.15–2.74	0.550								
		156 (10.5)	10 (27.0)	0.82	0.31–2.18	0.690	164 (10.9)	2 (18.2)	0.45	0.07–2.72	0.383								

[†] Independent variables: mean age, sex, hospitalisation, operation year, CCS class

Table 4 Associations of overall cardiovascular therapy drug (C) purchase three years before and one year after CABG operation with clinical parameters

Dependent variable overall cardiovascular therapy drug (C) purchase [†]	Before operation			After operation			<i>p</i>			
	Drug (C) purchase			Drug (C) purchase						
	OR	95% CI		OR	95% CI					
	Yes, <i>n</i> = 1690 (95.6%)			Yes, <i>n</i> = 1740 (98.4)			No, <i>n</i> = 28 (1.6)			
	No, <i>n</i> = 78 (4.4%)									
Mean age	66.4	63.9	1.03	1.01–1.06	0.017	66.2	72.5	0.87	0.81–0.94	<0.001
Sex										
Men	1355 (80.2)	61 (78.2)	1.00	Reference		1399 (80.4)	17 (60.7)			
Women	335 (19.8)	17 (21.8)	1.00	Reference	0.918	1419 (91.8)	11 (39.3)	0.40	0.16–1.03	0.057
Operation year										
2007	234 (13.9)	6 (7.7)	1.00	Reference		234 (13.5)	6 (21.4)	1.00	Reference	
2008	204 (12.1)	10 (12.8)	0.47	0.15–1.42	0.178	209 (12.0)	5 (17.9)	1.28	0.33–0.93	0.724
2009	208 (12.3)	16 (20.5)	0.28	0.10–0.78	0.015	220 (12.6)	14.3 (4)	2.42	0.54–10.89	0.251
2010	209 (12.4)	15 (19.2)	0.31	0.11–0.89	0.029	219 (12.6)	5 (17.9)	2.55	0.55–11.82	0.231
2011	290 (17.2)	13 (16.7)	0.49	0.17–1.43	0.192	300 (17.2)	3 (10.7)	3.26	0.73–14.62	0.123
2012	215 (12.7)	6 (7.7)	0.78	0.23–2.63	0.691	221 (12.7)	0	1	n/a	
2013	191 (11.3)	7 (9.0)	0.76	0.23–2.59	0.666	197 (11.3)	1 (3.6)	19.93	1.18–337.45	0.038
2014	139 (8.2)	5 (6.4)	0.91	0.21–3.98	0.896	140 (8.1)	4 (14.3)	2.73	0.43–17.20	0.285
Hospitalisation										
No	3 (0.2)	10 (12.8)	1.00	Reference		3 (0.7)	18 (64.3)			
Yes	1687 (99.8)	68 (87.2)	241.2	44.73–1300.9	<0.001	1737 (99.3)	10 (35.7)	2097.07	250.36–17,565.87	<0.001
CCS/NYHA class										
1	49 (2.9)	2 (2.6)	1.00	Reference		51 (2.9)	0	1	n/a	
2	545 (32.3)	8 (10.3)	5.52	0.96–31.6	0.055	543 (31.2)	10 (35.7)	1.00	Reference	
3	885 (52.4)	15 (19.2)	2.34	0.51–10.79	0.274	887 (51.0)	13 (46.4)	0.81	0.27–2.48	0.717
4	210 (12.4)	53 (68.0)	0.15	0.04–0.67	0.013	258 (14.8)	5 (17.9)	1.88	0.37–9.59	0.445

[†] Independent variables: mean age, sex, hospitalisation, operation year, NYHA class

and by 83.9% after the PCI procedure. In CABG patients, the use of ADP receptor blockers was less prevalent: Only 16.8% of CABG patients had purchased them before and 14.4% after the operation. The difference between PCI and CABG patients was to be expected as guidelines recommend the use of ADP receptor antagonists and ASA combination after PCI whereas after CABG only in patients with acute coronary syndrome. In patients undergoing elective CABG, only ASA is usually recommended. On the other hand, the use of VKA more than doubled after CABG. Most likely, the indication for VKA was postoperative atrial fibrillation. Postoperative atrial fibrillation develops in 20–30% of patients after CABG, which is in line with the purchase of VKA in our CABG patients (21.3%).

One important reason for the low use of antithrombotic agents after CABG can be that those patients are prescribed ASA drugs, which in Finland are non-reimbursable over the counter drugs for both cardiovascular and analgesic indications. Consequently, they are not recorded in the prescription register, except for a few special cases in which they had been purchased based on a prescription.

A major strength of our study is the representative study population. We identified all eligible patients from the electronic medical records, and the proportion of missing data on patient characteristics was small. The number of persons that were lost to follow-up was small and likely had no effect on the results or conclusions. Possible risk for bias was the validity of register data. The validity of the data from the national registers has been established earlier [23]. Kuopio University hospital is the only university hospital in its catchment area and performs all surgical revascularisations in the area. Thus, the patients were not selected on any basis.

A potential weakness of the study is that we only studied one of the five catchment areas performing coronary revascularisation procedures in Finland and the drug prescribing habits may be different in other regions. This limits the generalisation of purchase habits regarding single medications. We had no information on the setting where the medications were prescribed and lacked data on dosage, dose titration and adherence or compliance on a patient level. However, we had data on purchased medications instead of mere prescriptions.

In conclusion, our study demonstrates that physicians treating revascularisation patients prescribe the recommended medical therapy according to current guidelines and that the patient compliance, at least during the first year after the revascularisation procedure, is high.

Author contributions AMT, RPR, JHA, HMI, MHI and JMA contributed to the conception or design of the work. JHE and AMT contributed to the acquisition and analysis. All contributed to the interpretation of data for the work. JHE drafted the manuscript. AMT, RPR, JHA, HMI, MHI and JMA critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Funding Open access funding provided by University of Eastern Finland (UEF) including Kuopio University Hospital. RPR acknowledges financial support by European Structural Funds, European Social Fund by the Regional Council of North Savo and State Research Funding (VTR). AMT acknowledges support from the Academy of Finland (grants 307232 and 295334) and University of Eastern Finland. JHA acknowledges financial support from European Union FP7 and EU Horizon 2020 frameworks, Finnish Cardiovascular Research Foundation and State Research Funding (VTR). The funders had no role in study design, data collection or analysis, decision to publish or preparation of the manuscript. The views expressed in this paper are those of the authors and not necessarily those of any funding body or others whose support is acknowledged.

Compliance with ethical standards The study was approved by the ethics committee of Kuopio University hospital (KUH) and by the ethics committee of the Finnish National Institute for Health and Welfare which gives the permissions to use the data from the Hospital Discharge Register (HILMO). The permission to use the Special Reimbursement and Prescription registers was given by the Social Insurance Institution of Finland (SII). The permission to use national mortality data was given by Statistics Finland. Informed consent was not deemed necessary by the Ethics committees or register maintainers because participants were not contacted. The study complies with the Declaration of Helsinki.

Conflict of interest JHE, AMT, RPR, JHA, MHI and HMI have nothing to disclose and declare that there is no conflict of interest. JM is a partner of ESIOR Oy, which carries out health economic and outcome research studies for pharmaceutical, medical device and food companies.

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