Clinical Kidney Journal, 2023, vol. 16, no. 11, 1947–1956

https://doi.org/10.1093/ckj/sfad219
Advance Access Publication Date: 4 September 2023
Original Article

ORIGINAL ARTICLE

Contemporary secondary prevention in survivors of ST-elevation myocardial infarction with and without chronic kidney disease: a retrospective analysis

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ABSTRACT

Background. Survivors of myocardial infarction have an elevated risk of long-term mortality. We sought to evaluate guideline-directed medical treatment and its impact on long-term mortality in survivors of ST-elevation myocardial infarction (STEMI) according to their chronic kidney disease (CKD) stage.

Methods. Using German health insurance claims data, 157 663 hospitalized survivors of STEMI were identified. Regarding different CKD stages, we retrospectively analysed the filled prescriptions of platelet inhibitors (PAI)/oral anticoagulation, statins, beta-blocker and angiotensin-converting enzyme inhibitors/angiotensin II type 1 receptor antagonists (ACE-I/AT1-A) and their association with long-term mortality.

Results. Prescription rates for all four guideline-directed drugs were highest in patients without or with mild CKD and lowest in patients on dialysis. They dropped from 73.4% to 39.2% in patients without CKD and from 47.1% to 29% in patients on dialysis within the 5-year follow-up period. Mortality rates were dramatically increased in patients with CKD compared with patients without CKD (5-year mortality: no CKD, 16.7%; CKD stage 3, 47.1%; CKD stage 5d, 69.7%). Filled prescriptions of at least one drug class [one drug: hazard ratio (HR) 0.70, 95% confidence interval (95% CI) 0.66–0.74; four drugs: HR 0.28, 95% CI 0.27–0.30; $P < .001$ for both] as well as the distinct drug classes (statins: HR 0.55, 95% CI 0.54–0.56; ACE-I/AT1-A: HR 0.68, 95% CI 0.67–0.70; beta-blocker: HR 0.87, 95% CI 0.85–0.90; PAI/oral anticoagulation: HR 0.97, 95% CI 0.95–1.00; all $P < .05$) improved long-term mortality.

Conclusions. An improved long-term guideline-recommended drug therapy after STEMI regardless of renal impairment might lead to beneficial effects on long-term mortality.

Received: 1.3.2023; Editorial decision: 2.8.2023

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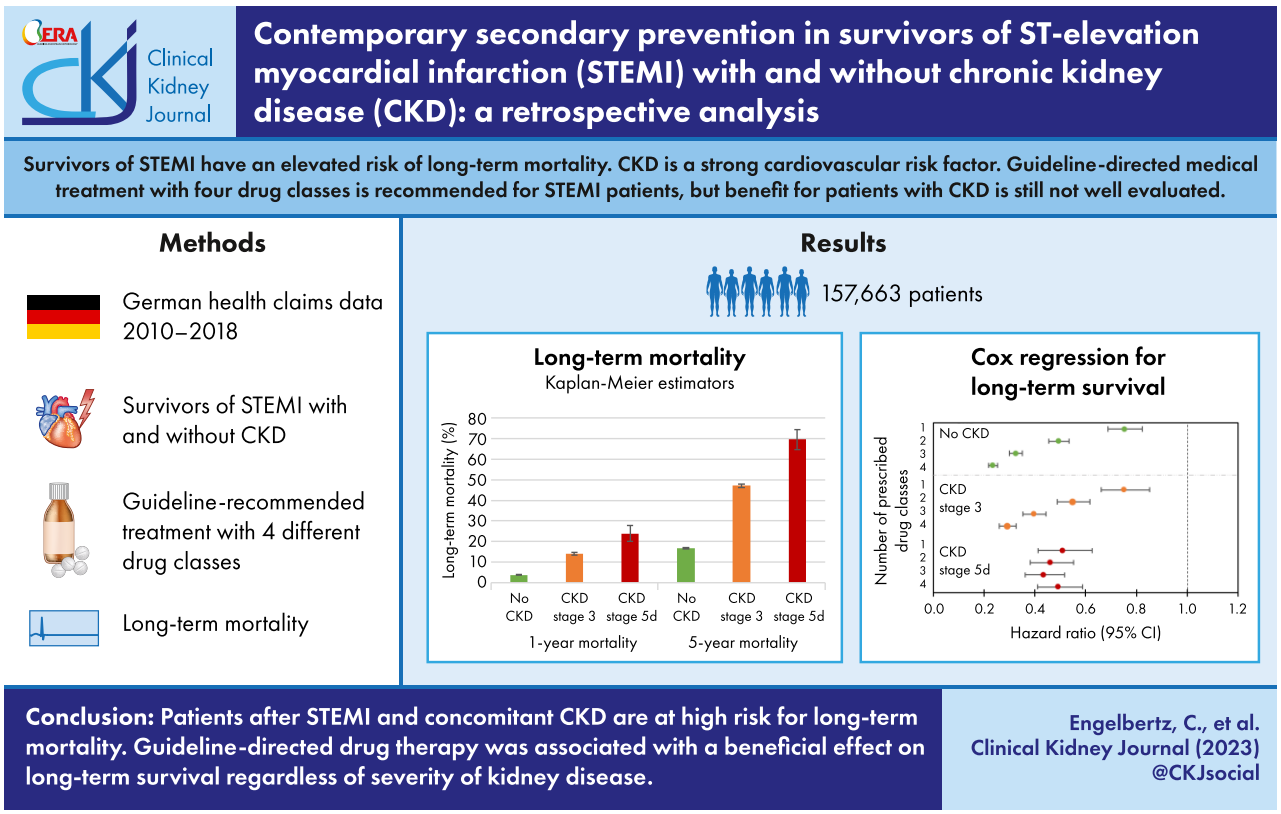
GRAPHICAL ABSTRACT



Keywords: acute myocardial infarction, chronic kidney disease, guideline-directed medication, long-term survival, real world data

INTRODUCTION

Myocardial infarction is still one of the cardiovascular events with high mortality. Survivors of a myocardial infarction need consequent treatment and lifestyle changes to lower their risk for further cardiovascular morbidity and mortality [1, 2]. European and American guidelines recommend four classes of drugs for secondary prevention in ST-segment elevation myocardial infarction (STEMI) patients: lifelong platelet inhibitors (PAI) and statins for all patients, and beta-blockers and angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II type 1 receptor antagonists (AT1-A) for patients with special conditions, like diabetes or reduced left ventricular ejection fraction [3, 4]. Prescription of these drugs is a cornerstone in the care of these patients. Time trends over recent decades have shown increasing prescription rates resulting in decreased mortality and recurrent ischaemic events [5, 6], but optimal medical treatment is still insufficient, even in high-income countries [7]. Analysis of long-term outcome is often limited to 1- or 2-year follow-up periods [8, 9] and data on medical treatment and outcome of patients with severe comorbidities like chronic kidney disease (CKD), which has been shown to be a strong cardiovascular risk factor, are scarce [10, 11]. It is still unclear whether patients with CKD or patients on dialysis benefit from guideline-directed therapies to a similar extent as patients without CKD. Patients with advanced CKD are often excluded from randomized controlled trials [12]. Data on treatment are mainly collected via registries [10, 11, 13] or real-world studies [14]. In order to add knowledge regarding medical treatment and long-term outcome of STEMI patients with and without CKD, we analysed health claim data from a large German health insurance with a follow-up period up to 9 years.

MATERIALS AND METHODS

Our analysis used anonymized data of the Federal Association of the Local Health Insurance Funds (Allgemeine Ortskrankenkasse—AOK). The AOK is a group of 11 German health insurances and provides statutory health insurance for roughly 32% of the German population. Information on German reimbursement is given in the supplements.

Patient selection, baseline characteristics, in-hospital treatment

All patients ≥18 years of age hospitalized with an encoded main diagnosis of STEMI [International Statistical Classification of Diseases, German Modification (ICD-10 GM) codes, see Supplementary data, Table S1] in the years 2010 to 2018 were identified and followed-up until 31 December 2019. The first hospitalization in this period was defined as the

index-hospitalization. For analysis, we selected all patients discharged from hospital and alive 90 days after STEMI (inclusion time point). Excluded patients are depicted in Supplementary data, Fig. S1. For baseline characteristics and in-hospital treatment, ICD-10 GM codes of concomitant diseases and 'Operationen- und Prozeduren-Schlüssel' (OPS) codes of events and interventions were recorded. For baseline characteristics, we analysed the codes at index-hospitalization and up to 2 years before index-hospitalization. For characterization of the in-hospital treatment and complications, codes of the index-hospitalization were used. All applied ICD-10 GM and OPS codes are listed in the Supplementary data, Table S1.

Patients were grouped according to their renal function as determined by the corresponding ICD-10 GM code at index-hospitalization or, if no code was found at index-hospitalization, the timely closest code within the 2 years prior index-hospitalization. For details, see Supplementary data, Table S1.

Medication and follow-up

Medication, i.e. PAI and anticoagulants, beta-blockers, ACE-I/AT1-A and statins, was assessed on the basis of the Anatomical Therapeutic Chemical (ATC) classification system (Supplementary data, Table S1). For baseline characteristics, a filled prescription with an ATC code within 90 days prior to index-hospitalization was regarded as a prescribed drug. The follow-up period started 90 days after STEMI (i.e. inclusion time point). A prescription during follow-up was defined as an ATC code of the distinct drug class. If no further prescription was found within 180 days, the patient was regarded as under no treatment. New prescriptions or restart of a distinct drug class were also recorded.

Information regarding death is precisely recorded in the health claims data. These data were used for the analysis of the long-term outcome.

Ethics approval and consent to participate

The presented data were assessed within the framework of the GenderVasc research project (innovation funds 2019 of the joint federal committee; g-BA Innovationsfonds, number 01VSF18051). This project was approved by the Ethics Committee of Westfalen-Lippe (No 2019-21-f-S). Informed consent was waived because this analysis is based on anonymized data.

Statistical analysis

As the primary questions of the study at hand, the association between guideline-directed pharmaceutical therapy after STEMI and long-term survival depending on renal insufficiency stage was analysed. Therefore, a multivariable Cox regression model with time-dependent co-variables was performed to estimate hazard ratios (HR) for all CKD stages, also accounting for worsening of the patient's risk profile during follow-up. The following variables, depicting the patient's risk profile, were included in the model: age, sex (male as reference), diabetes mellitus, hypertension, dyslipidaemia, atrial fibrillation/flutter, obesity, nicotine abuse, chronic heart failure, peripheral artery disease, cancer, CKD stages 1 to 5d, pharmaceutical therapy, previous myocardial infarction, previous stroke, previous percutaneous coronary intervention, previous coronary artery bypass grafting, previous valve replacement, previous cerebrovascular disease, in-hospital ventilation, in-hospital impella/intra-aortic balloon pump/extracorporeal membrane oxygenation/shock, in-hospital acute renal failure/renal replacement therapy, in-hospital percutaneous coronary intervention, length of hospital stay and year of hospital stay, with diabetes mellitus, atrial fibrillation/flutter, chronic heart failure, peripheral artery disease, cancer, CKD stages and pharmaceutical therapy as time-dependent variables. To address differences between the associations of guideline-directed medication on long-term survival between different CKD stages, an interaction term of CKD stage and pharmaceutical therapy was added to the models. Model fit was performed in two ways: first, all five drugs were considered individually and, second, only the number of prescribed drugs (drug classes defined in the Supplementary data, Table S1) were considered. The observed survival rates were determined by a Kaplan–Meier estimate. The rate of prescribed medication during follow-up was evaluated by determining the actual state probabilities of the respective multi-state models using Aalen–Johansen estimates.

Moreover, differences between categorical and continuous variable (e.g. comorbidities at baseline or in-hospital outcome) between renal insufficiency stages were tested via Chi-square test and Kruskal–Wallis test, respectively.

All analyses were fully exploratory (hypotheses generating), not confirmatory, and an adjustment for multiple testing was not performed. Statistical analyses were performed using SAS software V9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.1.0 (R Foundation, Vienna, Austria).

RESULTS

Baseline characteristics

From 1 January 2010 to 31 December 2018, a total of 157 663 patients who survived the first 90 days after hospitalization for STEMI were identified (Table 1). More than 80% of the cohort had no renal impairment. Of the patients with renal impairment, 10.3% suffered from CKD stage 3, being the most prominent CKD stage. Patients with CKD were 5–17 years older than patients without CKD. All analysed concomitant diseases and previous events occurred more frequently in patients with CKD than in patients without CKD (Table 1).

Treatment and complications during index-hospitalization are displayed in the Supplementary data, Table S2.

Medication before STEMI and at long-term follow-up

Before STEMI, filled prescriptions with guideline-directed drugs was lowest in patients without CKD and increased with increasing renal insufficiency (Table 1). Between 4.7% (no CKD) and 16.3% (CKD staged 5d) had filled prescriptions for all four guideline-directed drug groups. The percentage of patients receiving none of the guideline-directed drugs was highest in patients without CKD (46.4%) and lowest in patients with CKD stage 5d (8.3%).

Regarding the four different drug classes PAI/oral anticoagulants, beta-blockers, statins and ACE-I/AT1-A, the rate of filled prescriptions rose steadily with increasing renal insufficiency (Table 1).

At 180 days after the inclusion time point, the percentage of patients with filled prescription had increased, but was still insufficient according to guidelines: between 47% (CKD stage 5d) and 74% (CKD stage 2) of the patients had filled prescriptions for all four classes of drugs (Fig. 1, Supplementary data, Table S3).

Table 1: Baselines characteristics of 90 day survivors of STEMI with an index-hospitalization due to STEMI in 2010 to 2018.

	No CKD	CKD stage 1	CKD stage 2	CKD stage 3	CKD stage 4	CKD stage 5	CKD stage 5d
Patients, *n* (%)	128319 (81.4)	1323 (0.8)	7437 (4.7)	16269 (10.3)	2981 (1.9)	863 (0.5)	471 (0.3)
Female sex, *n* (%)	38830 (30.3)	467 (35.3)	2771 (37.3)	7646 (47.0)	1644 (55.1)	303 (35.1)	144 (30.6)
Median age, years (IQR)	63 (20)	72 (18)	74 (16)	78 (12)	80 (12)	74 (17)	68 (20)
Concomitant diseases up to 2 years before STEMI, *n* (%)							
Coronary artery disease	59898 (46.7)	909 (68.7)	4690 (63.1)	10758 (66.1)	2007 (67.3)	587 (68.0)	369 (78.3)
Hypertension	106349 (82.9)	1261 (95.3)	6972 (93.7)	15790 (97.1)	2928 (98.2)	852 (98.7)	471 (100.0)
Diabetes mellitus	39895 (31.1)	832 (62.9)	3842 (51.7)	9349 (57.5)	1917 (64.3)	565 (65.5)	251 (53.3)
Dyslipidaemia	96064 (74.9)	1130 (85.4)	6002 (80.7)	13088 (80.4)	2341 (78.5)	686 (79.5)	364 (77.3)
Obesity	31116 (24.2)	494 (37.3)	2562 (34.4)	5659 (34.8)	1087 (36.5)	336 (38.9)	137 (29.1)
Nicotine abuse	38283 (29.8)	323 (24.4)	1645 (22.1)	2391 (14.7)	379 (12.7)	168 (19.5)	100 (21.2)
Atrial fibrillation/flutter	17547 (13.7)	300 (22.7)	1885 (25.3)	5570 (34.2)	1162 (39.0)	338 (39.2)	187 (39.7)
Chronic heart failure	49819 (38.8)	783 (59.2)	4680 (62.9)	11328 (69.6)	2315 (77.7)	673 (78.0)	341 (72.4)
Right heart failure	6138 (4.8)	149 (11.3)	878 (11.8)	3041 (18.7)	795 (26.7)	240 (27.8)	102 (21.7)
Left heart failure							
None	85842 (66.9)	662 (50.0)	3313 (44.5)	6497 (39.9)	983 (33.0)	[a]	173 (36.7)
NYHA 1	4634 (3.6)	60 (4.5)	285 (3.8)	437 (2.7)	47 (1.6)	[a]	10 (2.1)
NYHA 2	11974 (9.3)	156 (11.8)	1085 (14.6)	1690 (10.4)	231 (7.7)	[a]	43 (9.1)
NYHA 3	13314 (10.4)	228 (17.2)	1381 (18.6)	3224 (19.8)	561 (18.8)	[a]	94 (20.0)
NYHA 4	12555 (9.8)	217 (16.4)	1373 (18.5)	4421 (27.2)	1159 (38.9)	[a]	151 (32.1)
LEAD							
No LEAD	120543 (93.9)	1156 (87.4)	6428 (86.4)	13632 (83.8)	2400 (80.5)	620 (71.8)	290 (61.6)
LEAD 1–3	6044 (4.7)	128 (9.7)	661 (8.9)	1739 (10.7)	346 (11.6)	129 (14.9)	87 (18.5)
LEAD 4–6	1732 (1.3)	39 (2.9)	348 (4.7)	898 (5.5)	235 (7.9)	114 (13.2)	94 (20.0)
Cancer	16551 (12.9)	270 (20.4)	1550 (20.8)	3987 (24.5)	763 (25.6)	218 (25.3)	126 (26.8)
Previous events and interventions up to 2 years before STEMI, *n* (%)							
Previous cerebrovascular disease	9252 (7.2)	183 (13.8)	1021 (13.7)	2686 (16.5)	510 (17.1)	162 (18.8)	112 (23.8)
Previous stroke	8041 (6.3)	166 (12.5)	952 (12.8)	2776 (17.1)	553 (18.6)	170 (19.7)	103 (21.9)
Previous myocardial infarction	10587 (8.3)	175 (13.2)	923 (12.4)	2216 (13.6)	423 (14.2)	167 (19.4)	91 (19.3)
Previous percutaneous coronary intervention	3358 (2.6)	75 (5.7)	496 (6.7)	1104 (6.8)	181 (6.1)	97 (11.2)	73 (15.5)
Previous coronary artery bypass grafting	3533 (2.8)	90 (6.8)	469 (6.3)	1257 (7.7)	230 (7.7)	100 (11.6)	57 (12.1)
Previous valve replacement	332 (0.3)	[a]	73 (1.0)	192 (1.2)	27 (0.9)	[a]	20 (4.2)
Previous medical treatment, *n* (%)							
Oral anticoagulation	3996 (3.1)	86 (6.5)	599 (8.1)	1756 (10.8)	360 (12.1)	86 (10.0)	43 (9.1)
Oral anticoagulants, no platelet inhibitors	3437 (2.7)	79 (6.0)	495 (6.7)	1456 (8.9)	289 (9.7)	59 (6.8)	25 (5.3)
PAI	14612 (11.4)	253 (19.1)	1565 (21.0)	4037 (24.8)	845 (28.3)	313 (36.3)	247 (52.4)
PAI, no oral anticoagulants	14053 (11.0)	246 (18.6)	1461 (19.6)	3737 (23.0)	774 (26.0)	286 (33.1)	229 (48.6)
Oral anticoagulants and/or platelet inhibitors	18049 (14.1)	332 (25.1)	2060 (27.7)	5493 (33.8)	1134 (38.0)	372 (43.1)	272 (57.7)
Beta-blocker	36738 (28.6)	581 (43.9)	3394 (45.6)	8874 (54.5)	1802 (60.4)	549 (63.6)	318 (67.5)
Statins	23283 (18.1)	420 (31.7)	2315 (31.1)	5379 (33.1)	1026 (34.4)	347 (40.2)	194 (41.2)
ACE-I/AT1-A	51235 (39.9)	827 (62.5)	4508 (60.6)	11259 (69.2)	2202 (73.9)	534 (61.9)	275 (58.4)
Number of drug groups							
None	59497 (46.4)	288 (21.8)	1783 (24.0)	2441 (15.0)	336 (11.3)	92 (10.7)	39 (8.3)
One	31401 (24.5)	366 (27.7)	1879 (25.3)	3966 (24.4)	658 (22.1)	195 (22.6)	92 (19.5)
Two	20386 (15.9)	330 (24.9)	1728 (23.2)	4513 (27.7)	875 (29.4)	246 (28.5)	130 (27.6)
Three	11008 (8.6)	222 (16.8)	1246 (16.8)	3383 (20.8)	692 (23.2)	205 (23.8)	133 (28.2)
Four	6027 (4.7)	117 (8.8)	801 (10.8)	1966 (12.1)	420 (14.1)	125 (14.5)	77 (16.3)

[a]No results due to data safety reasons.
Differences between CKD stages for categorical and continuous variables were tested via Chi-square test and Kruskal–Wallis test, respectively.
IQR, interquartile range; LEAD, lower extremity artery disease; NYHA, New York Heart Association.

During the follow-up period, the percentage of patients treated with four classes of drugs decreased considerably, especially in patients with renal insufficiency: after 5 years between 27.7% (CKD stage 5) and 40.5% (CKD stage 2) filled prescriptions. Regarding filled prescriptions for three different drug classes, the percentage ranged between 19.4% for CKD stage 2 and 36.4% for CKD stage 5d at 180 days after STEMI and rose to values ranging between 35.3% (CKD stage 2) and 42.7% (CKD stage 5d) at 5 years after the event. In general, patients with severe renal impairment (CKD stage 4, 5 and 5d) least often received all four drug classes, but filled prescriptions for three or two recommended drug classes were highest in those patients. The most remarkable change in prescription rates was observed 1 year and 2 years after the event (Fig. 1, Supplementary data, Table S3).

Furthermore, we analysed the medical treatment according to the filled prescriptions of PAI/oral anticoagulation, beta-blockers, statins and ACE-I/AT1-A (Supplementary data, Fig. S2 and Table S4). At 180 days, prescription rates were stable for PAI/oral anticoagulant (no CKD, 95.6%; CKD stage 3, 94.7%; CKD stage 5d, 94.5%) and a beta-blockers (no CKD, 88.9%; CKD stage 3, 90.8%; CKD stage 5d, 87.5%) regardless of renal insufficiency, for ACE-I/AT1-A, they were stable for patients without CKD (88.3%) up to patients with CKD stage 4 (88.8%) and decreased in patients with severe CKD (CKD stage 5, 79.9%; CKD stage 5d, 74.1%), whereas for statins, prescription rates decreased with increasing CKD stage (no CKD, 89.9%; CKD stage 3, 84.2%; CKD stage 5d, 69.6%). A clear drop of filled prescriptions of about 5% points or more was observed 1 year after the event for all drug classes. Furthermore, regarding treatment with PAI/oral anticoagulation, filled prescription rates further declined markedly after 2 years, especially for patients with no or mild CKD. Of note, 2 years after the events, filled prescriptions for PAI/oral anticoagulation were

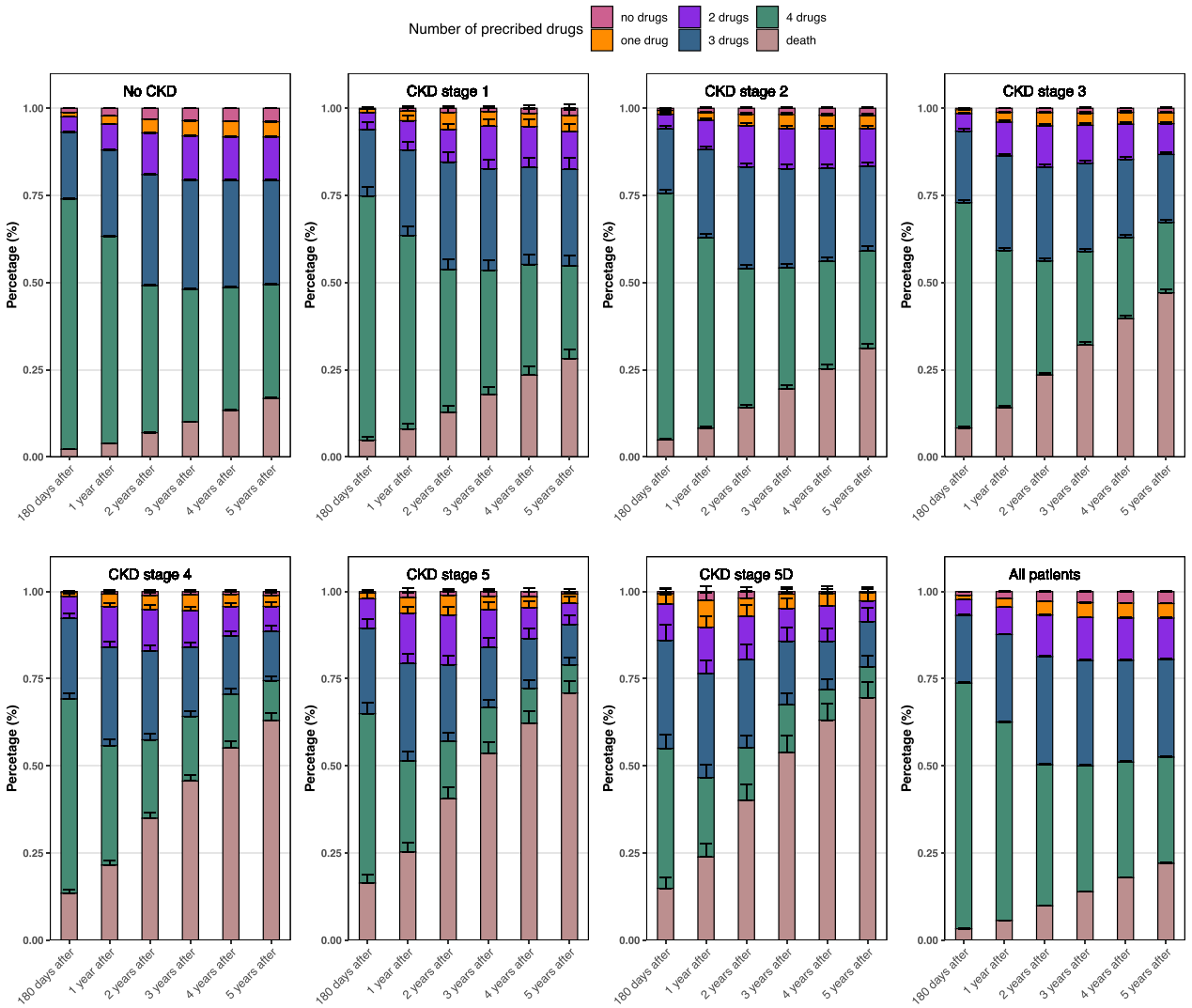


Figure 1: Percentage of filled prescriptions by number of recommended drugs and deceased patients during follow-up. Error bars are added to all columns to depict the variability of the shown data. Bars always represent all patients of the group. Colours of bars from 0.0 to 1.0 as follows: brown, deceased patients; green, patients with four filled prescriptions of drugs; blue, patients with three filled prescriptions of drugs; purple, patients with two filled prescriptions of drugs; orange, patients with one filled prescription of drugs; pink, patients with no filled prescriptions of drugs.

lower in patients with no or mild CKD than in patients with advanced or severe renal insufficiency. In contrast, all other drugs showed decreasing filled prescription over the analysed time period and with decreasing renal function.

Short- and long-term mortality

Kaplan–Meier survival analysis showed dramatically decreased survival with increasing severity of renal impairment (Table 2, amount of deceased patients is also depicted in Fig. 1). The analysed time points (30-day mortality, 1-year mortality, etc.) refer to the inclusion time point, which was 90 days after STEMI. While 30-day mortality was low in patients without CKD (0.5%, 95% CI 0.5%–0.5%), it was 10-fold higher in patients with CKD stage 5 (5.3%; 95% CI 4.0%–7.0%). After 2 years, 6.9% (95% CI 6.8%–7.1%) of the patients without CKD had died, rising to 40.5% (95% CI 37.2%–43.9%) in patients with CKD stage 5. Of note, patients even with mild CKD showed dramatically higher mortality rates than patients without CKD (9-year mortality: no CKD 32.1%, 95% CI 31.6%–32.5%; CKD stage 1 50.0%, 95% CI 44.8%–55.0%).

Association of medical treatment and long-term survival

The filled prescription of at least one guideline-directed drug improved long-term survival compared with patients without medical therapy (one drug: HR 0.70, 95% CI 0.66–0.74; four drugs: HR 0.28, 95% CI 0.27–0.30; Fig. 2, Supplementary data, Table S5). Regarding patients without renal insufficiency and with CKD stages 2–4, the higher the number of prescribed drug classes, the lower was the risk for poor long-term survival. In patients with CKD stages 5 or 5d, one drug showed the same benefit as two or more drugs. In patients with CKD stage 1, we observed

Table 2: Kaplan–Meier estimators for long-term survival of 90 day survivors of STEMI.

	No CKD	CKD stage 1	CKD stage 2	CKD stage 3	CKD stage 4	CKD stage 5	CKD stage 5d
30-day mortality, % (95% CI)	0.5 (0.5–0.5)	0.8 (0.4–1.5)	1.1 (0.9–1.4)	2.2 (2.0–2.4)	3.3 (2.7–4.0)	5.3 (4.0–7.0)	1.5 (0.7–2.9)
1-year mortality, % (95% CI)	3.8 (3.7–3.9)	8.1 (6.7–9.7)	8.2 (7.6–8.8)	14.1 (13.6–14.6)	21.6 (20.1–23.0)	25.3 (22.4–28.2)	23.9 (20.1–27.8)
2-year mortality, % (95% CI)	6.9 (6.8–7.1)	12.7 (10.9–14.6)	14.1 (13.3–14.9)	23.5 (22.8–24.2)	35.0 (33.2–36.7)	40.5 (37.2–43.9)	40.4 (35.9–44.9)
3-year mortality, % (95% CI)	10.0 (9.8–10.2)	17.8 (15.7–20.1)	19.4 (18.5–20.4)	32.1 (31.3–32.8)	45.7 (43.8–47.6)	53.6 (50.0–57.0)	53.9 (49.0–58.5)
4-year mortality, % (95% CI)	13.3 (13.1–13.5)	23.4 (20.9–26.0)	25.2 (24.1–26.3)	39.6 (38.8–40.4)	55.2 (53.2–57.1)	62.2 (58.5–65.6)	63.3 (58.3–68.0)
5-year mortality, % (95% CI)	16.7 (16.5–16.9)	28.1 (25.2–31.0)	31.1 (29.9–32.4)	47.1 (46.2–48.0)	63.1 (61.1–65.1)	70.9 (67.3–74.2)	69.7 (64.6–74.3)
6-year mortality, % (95% CI)	20.3 (20.0–20.6)	32.7 (29.5–35.9)	37.0 (35.6–38.3)	53.4 (52.5–54.3)	70.3 (68.3–72.3)	77.8 (74.2–81.0)	77.0 (71.6–81.4)
7-year mortality, % (95% CI)	24.2 (23.9–24.5)	38.8 (35.1–42.5)	42.4 (40.9–43.9)	59.7 (58.6–60.7)	76.1 (74.0–78.1)	81.4 (77.9–84.5)	81.7 (76.0–86.2)
8-year mortality, % (95% CI)	28.0 (27.7–28.4)	44.1 (40.0–48.2)	47.4 (45.7–49.1)	65.3 (64.1–66.4)	81.0 (78.8–83.1)	85.1 (81.6–88.1)	83.6 (77.6–88.1)
9-year mortality, % (95% CI)	32.1 (31.6–32.5)	50.0 (44.8–55.0)	53.0 (51.0–54.9)	70.2 (68.9–71.4)	83.1 (80.6–85.3)	88.1 (84.2–91.1)	

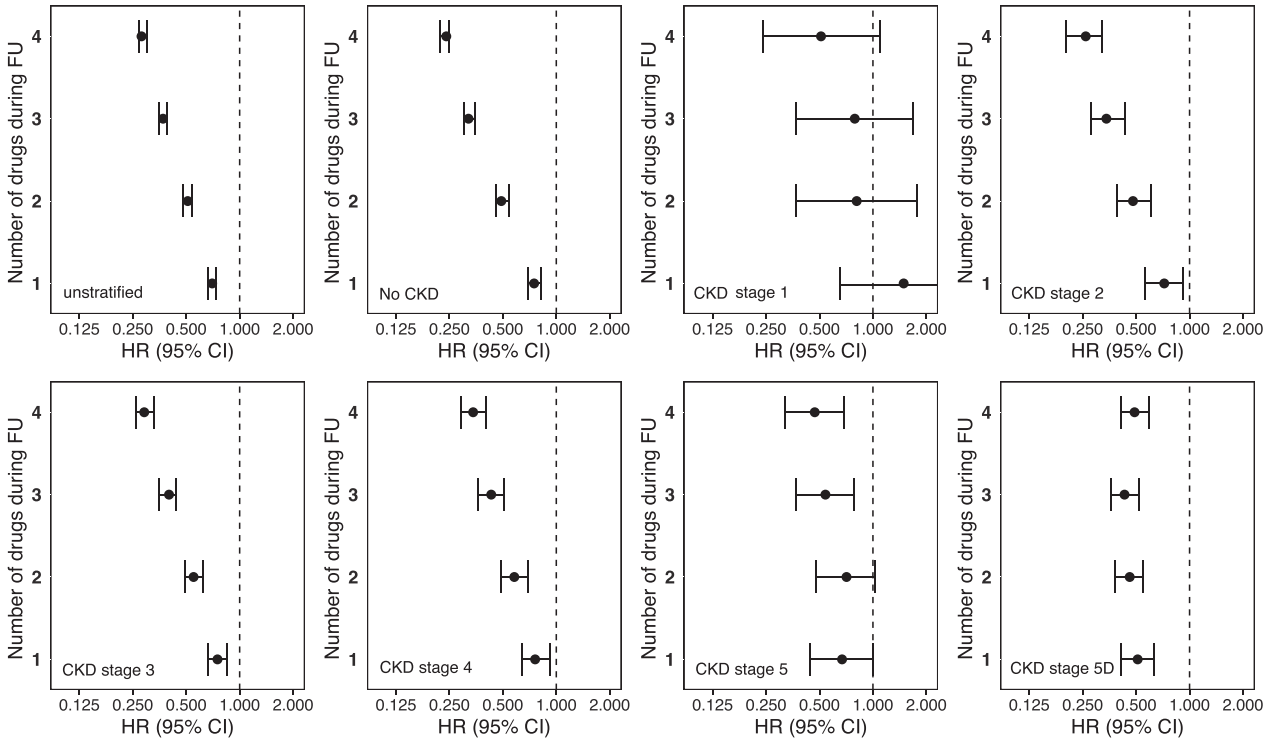


Figure 2: Cox regression for long-term survival depending on number of prescribed drugs and renal function. Included variables in the Cox-regression model: age, sex (male as reference), hypertension, dyslipidaemia, obesity, nicotine abuse, pharmaceutical therapy, previous myocardial infarction, previous stroke, previous percutaneous coronary intervention, previous coronary artery bypass grafting, previous valve replacement, previous cerebrovascular disease, in-hospital ventilation, in-hospital impella/intra-aortic balloon pump/extracorporeal membrane oxygenation/shock, in-hospital acute renal failure/renal replacement therapy, in-hospital percutaneous coronary intervention, length of hospital stay and year of hospital stay. Time-dependent variables included in the model: diabetes mellitus, atrial fibrillation/flutter, chronic heart failure, lower extremity artery disease, chronic limb-threatening ischaemia, cancer, CKD stage 1–5d and pharmaceutical therapy. The HR for these variables are presented in Supplementary data, Table S5 and S6.

only a trend towards improved survival with increasing number of guideline-directed medication. The strongest predictors for poor long-term survival were severe CKD (CKD stages 4, 5 and 5d), chronic limb-threatening ischaemia and cancer (Supplementary data, Table S6).

All prescribed drug classes improved long-term survival (statins: HR 0.55, 95% CI 0.54–0.56; ACE-I/AT1-A: HR 0.68, 95% CI 0.67–0.70; beta-blocker: HR 0.87, 95% CI 0.85–0.90; PAI/oral anticoagulation: HR 0.97, 95% CI 0.95–1.00; Supplementary data, Table S7). Regarding patients with different CKD stages, the positive effect was most prominent for statins and ACE-I/AT1-A (Fig. 3). Beta-blockers reduced the risk for long-term mortality only in patients without CKD, with CKD stage 3 and with CKD stage 4, while in all other stages no effect on mortality was observed. However, we have no information on the percentage of patients with reduced ejection fraction, which is a major limitation in assessing the benefit of beta-blockers. With increasing renal insufficiency, patients showed a tendency to benefit from treatment with PAI/oral anticoagulation. Among others, female sex and in-hospital percutaneous coronary intervention at the index STEMI lowered the risk for long-term mortality (Supplementary data, Table S8). A Cox regression analysing the effect of PAI and oral anticoagulation separately showed that PAI was associated with at least a tendency towards poor survival for all patients except for patients on dialysis, who benefited from PAI, whereas the effect of oral

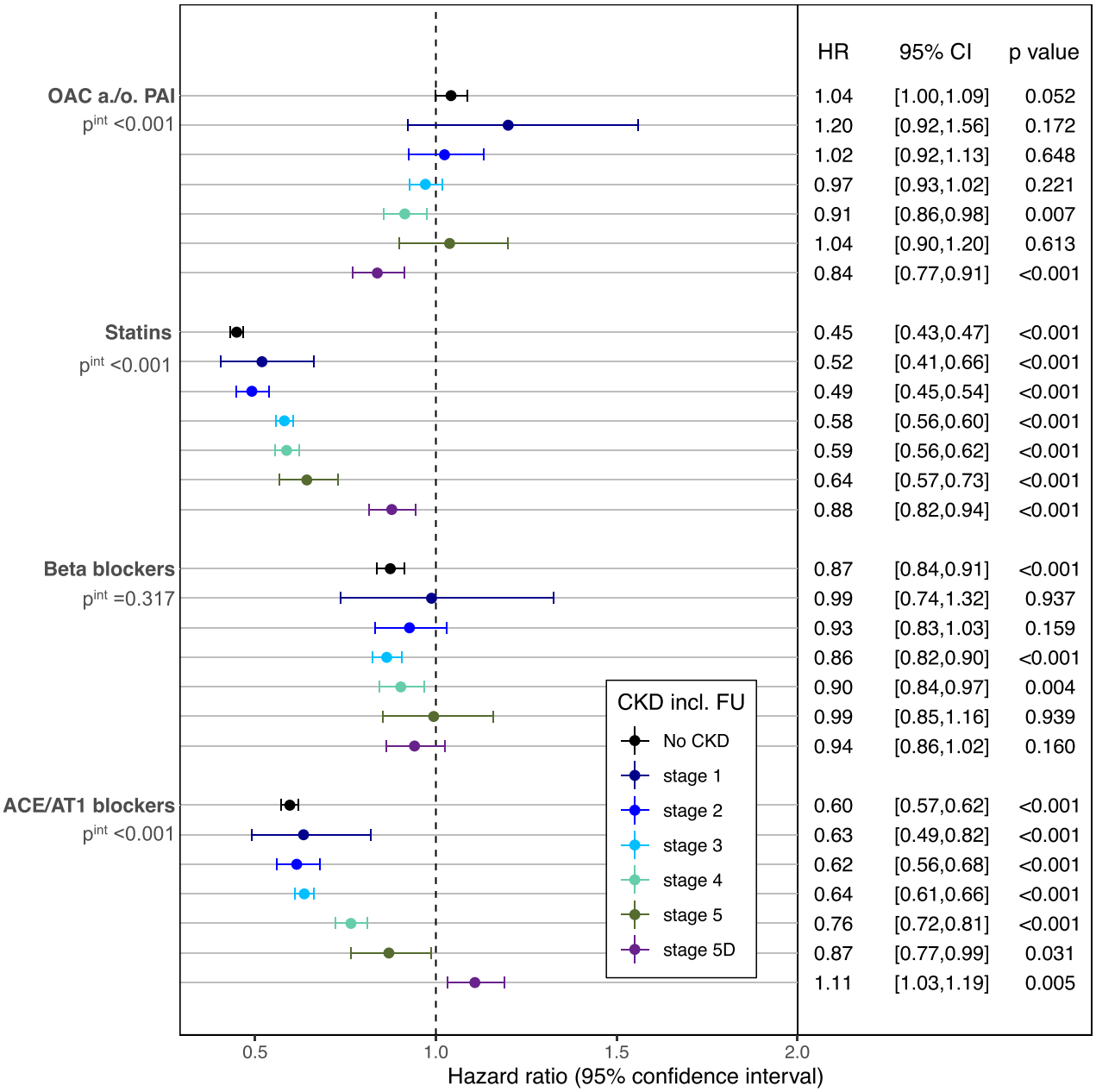


Figure 3: Cox regression for long-term survival for different drug classes depending on renal function. Black, no CKD; dark blue, CKD stage 1; blue, CKD stage 2; light blue, CKD stage 3; light green, CKD stage 4; olive, CKD stage 5; purple, CKD stage 5d. p^{int} refers to the *P*-value for the interaction term CKD stage as time-dependent variable × drug class. Included variables in the Cox-regression model: age, sex (male as reference), hypertension, dyslipidaemia, obesity, nicotine abuse, pharmaceutical therapy, previous myocardial infarction, previous stroke, previous percutaneous coronary intervention, previous coronary artery bypass grafting, previous valve replacement, previous cerebrovascular disease, in-hospital ventilation, in-hospital impella/intra-aortic balloon pump/extracorporeal membrane oxygenation/shock, in-hospital acute renal failure/renal replacement therapy, in-hospital percutaneous coronary intervention, length of hospital stay and year of hospital stay. Time-dependent variables included in the model: diabetes mellitus, atrial fibrillation/flutter, chronic heart failure, lower extremity artery disease, chronic limb-threatening ischaemia, cancer, CKD stage 1–5d and pharmaceutical therapy. The HR for these variables are presented in Supplementary data, Table S8.

anticoagulation was mostly indifferent (Supplementary data, Tables S9 and S10).

DISCUSSION

The results of our analysis of health claims data help to provide insight into medical treatment of survivors of STEMI with and without kidney disease with regard to the long-term supply of guideline-directed medication and the association of guideline-directed drug treatment and long-term survival. Shortly after STEMI (i.e. 180 days after inclusion), more than 70% of patients without CKD and of patients with CKD stages 1–3 filled prescriptions of all four guideline-directed drug classes, but with severe renal insufficiency this percentage decreased to 47% in patients on dialysis. During the follow-up period, declining rates for filled prescriptions of all four drug classes were observed

for all groups, while filled prescriptions for three different drug classes increased. Long-term survival decreased dramatically with declining renal function and not even 15% of patients with severe CKD were still alive after 9 years of follow-up, whereas >65% of patients without CKD had survived the same period. The survival benefit of the guideline-directed medical treatment was greater the more prescriptions for the different drug classes were filled. An analysis of the impact of the distinct drugs on long-term survival revealed that statins and ACE-I/AT1-A had a positive effect on survival regardless of renal impairment, except for patients on dialysis where ACE-I/AT1-A increased the risk of long-term mortality. PAI/oral anticoagulation were mostly beneficial in patients with CKD stage 3 and higher. Beta-blockers showed a heterogeneous, but rather positive treatment effect regarding different CKD stages.

Prescription of guideline-directed drugs shortly after an event has increased during the last decades [11, 15]. At discharge, the reported rates by others [5, 8, 10, 16] are in good accordance with our findings. Therefore, the gap between guideline recommendations and implementation of secondary preventions at discharge has diminished greatly in daily clinical practice during recent years, even for patients with renal insufficiency. Nevertheless, 25% up to 53% of the patients in our study did not fill prescriptions for all four guideline-directed drugs 180 days after the STEMI. Furthermore, during follow-up, the adherence to guideline-directed therapy decreased markedly, both in patients without CKD and in patients with CKD. Reasons for non-adherence might be side effects, as reported by Bruggmann *et al.* [8]. In addition, a lack of understanding of the need for the lifelong intake of the drugs might contribute to non-adherence [17]. Furthermore, undertreatment or even non-prescription of guideline-directed drugs depends to a significant extent on the discretion of the treating physician [18], whose decisions might be affected by the insufficient evidence base on treatment of patients with CKD due to exclusion of these patients from trials [12]. Issued prescriptions and filled prescriptions differ by up to 20% points [19]. Since we have analysed filled prescriptions, it is possible that the number of issued prescriptions was higher. Higher rates of filled prescriptions might be achieved by more and clear communication between health professionals and patients. The application of fixed-dose combination pills might also be a possibility to improve the adherence to guideline-directed therapies, although randomized trials have reported inconsistent results [20, 21].

Guideline-directed therapy lowers the rate of events [5, 13, 22]. In our real-world data, even one guideline-directed drug had a beneficial effect on long-term survival regardless of renal insufficiency, and the association was mostly stronger the more drug classes were filled. This is an encouraging aspect for more consequent prescription of guideline-directed drugs especially for patients with mild to moderate CKD. As we could show, these patients still suffer from greatly elevated mortality rates compared with patients without CKD. A consequent, life-long treatment with aspirin and statins is recommended by the current European and American guidelines [3, 4] for all patients after myocardial infarction, but especially prescriptions for aspirin dropped markedly after 1 and 2 years in our study.

The most prominent risk factors for poor long-term outcome are the CKD stages 4, 5 and 5d, which is also reflected by the dramatically high mortality rates. A recent Japanese observational study found similarly high mortality rates for patients with CKD 3 years after myocardial infarction [23] and—comparable to our study—a worsening renal function was strongly associated with a correspondingly higher rate of adverse outcome. According to our analysis, statins in particular are beneficial for patients with severe CKD, but about one-third of these patients did not fill prescriptions for statins. The outcome of patients with severe CKD can be improved, the more risk factors are controlled by medical treatment and lifestyle changes [24]. Again, a consequent, guideline-directed treatment is warranted also for patients with severe CKD.

Although all drug classes lower the risk for mortality, we could not show a clear association of beta-blockers and PAI/oral anticoagulation on improved long-term mortality for all CKD stages. The recommendation for beta-blockers origins from the pre-reperfusion era and in recent years, there has been a debate on the optimal duration of beta-blocker therapy. Results from large longitudinal registries question the benefit of long-term treatment with beta-blockers after uncomplicated myocardial infarction, but do not provide sufficient evidence for or against the treatment with beta-blocker beyond 1 year after infarction [25]. These findings are also reflected in the latest European Society of Cardiology (ESC) guidelines classifying beta-blocker as a class IIa B recommendation [3]. Regarding the association of PAI/oral anticoagulation and long-term mortality, conflicting data are discussed: the Antithrombotic Trialists Collaboration showed that aspirin taken for secondary prevention seemed to reduce vascular mortality, but had no significant effect on other mortality, yielding in a 10% reduction of all-cause mortality [26]. A recent Cochrane Review evaluated antiplatelet agents in patients with CKD finding no or little effect on all-cause death [27]. Another review questions the life-long therapy with aspirin in patients after myocardial infarction [28]. Most analysed studies, however, were conducted several decades ago and, similar to the studies on beta-blockers, clinical practice was different then, e.g. dosing frequency has changed during recent years, which might explain the inconsistent results of the historical studies compared with our findings.

Limitations

There are several limitations to this study. Administrative claims data lack clinical detail, e.g. laboratory values like blood lipid levels, creatinine levels or HbA1c values as well as blood pressure values or ejection fraction. Knowledge of these data might have led to a different or more detailed interpretation of the results presented. In absence of these data, we could only adjust for co-diagnoses and comorbidities encoded by the ICD codes. The adherence to lifestyle changes (weight control, smoking cessation, diet, exercise-based cardiac rehabilitation as recommended by the ESC guidelines [3]) cannot be captured by ICD codes. Furthermore, the follow-up period of up to 9 years is very long and during that time patients might had to cope with new diagnoses or declining quality of life, which could have an impact on medical adherence and prescription habits. Therefore, the association of the analysed drugs and long-term mortality might only indicate a possible divergent efficacy of these drugs. Furthermore, the cohort of real-world data differs from the cohort of randomized controlled studies regarding age and the extent of comorbidities, resulting in a more diverse patient population. Despite adjusting the analyses for several covariates, we cannot rule out the possibility of confounding due to unmeasured or undetermined patient characteristics. As a further major limitation it should be noted that the group of patients without any medications is small, which may have some statistical implications, e.g. variability, generalizability or width of confidence intervals. Finally,

as a characteristic of retrospective studies, we can only describe associations, but we cannot explore causations.

CONCLUSION

Our data reveal an extremely high risk for long-term mortality for patients with CKD after STEMI. The rate of guideline-directed medical treatment decreased over the years and with decreasing renal function. Guideline-directed drug therapy had a beneficial effect on long-term mortality regardless of renal function. Therefore, a more consequent medical treatment might be beneficial for the long-term outcome of patients after STEMI.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

FUNDING

The project upon which this publication is based was funded by The Federal Joint Committee, Innovation Committee (G-BA, Innovationsfonds, number 01VSF18051). The study was conducted within the framework of the GenderVasc project (Gender-specific real care situation of patients with arteriosclerotic cardiovascular diseases). GenderVasc is a cooperation project with the AOK health insurance federal association and the Scientific Institute of the AOK (WIdO).

AUTHORS' CONTRIBUTIONS

H.R., J.G., J.K.: study design; C.G., P.D., T.R.: data retrieval, routine data structure, advisory support in project planning; J.K., J.F., J.G.: statistical analysis; C.E., J.K.: drafting of the initial manuscript; C.E., J.F., L.M., S.A.L., J.G., H.R., J.K.: interpretation of the data, critical revision; all authors: approval of the final manuscript.

DATA AVAILABILITY STATEMENT

The authors confirm that the data utilized in this study cannot be made available in the manuscript, the supplementary files or in a public repository due to German data protection laws ('Bundesdatenschutzgesetz', BDSG). Therefore, they are stored on a secure drive in the AOK Research Institute (WIdO), to facilitate replication of the results. Generally, access to data of statutory health insurance funds for research purposes is possible only under the conditions defined in German Social Law (SGB V § 287). Requests for data access can be sent as a formal proposal specifying the recipient and purpose of the data transfer to the appropriate data protection agency. Access to the data used in this study can only be provided to external parties under the conditions of the cooperation contract of this research project and after written approval by the sickness fund. For assistance in obtaining access to the data, please contact: wido@wido.bv.aok.de.

CONFLICT OF INTEREST STATEMENT

C.E. has received travel support from Abbott outside the submitted work. L.M. has received travel support from Bayer Vital and Abbott outside the submitted work. S.A.L. reports travel support from Daiichi Sankyo and Bayer Vital, outside the submitted work. J.G. has received honoraria from TESARO, QUIRIS Healthcare, Ecker + Ecker, Dr August Wolff, Roche, University Hospital Schleswig-Holstein and RWTH Aachen University, all outside the submitted work. H.R. has received speaker honoraria from NeoVasc, Corvia, BMS, MedUpdate, StremedUp, NephroUpdate and Pfizer. He has acted as a consultant for BMS, Pfizer and Pluristem, receiving in part also financial compensations for this work. He has received research grants from the German Federal Ministry for Education and Research (BMBF). His division within the University Hospital of Muenster has taken or is still taking in multicentre trials of BARD, Bayer, BIOTRONIK, Novartis and Pluristem, receiving patient fees and financial compensation for these efforts. All other authors declare no conflict of interest.

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Received: 1.3.2023; Editorial decision: 2.8.2023

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