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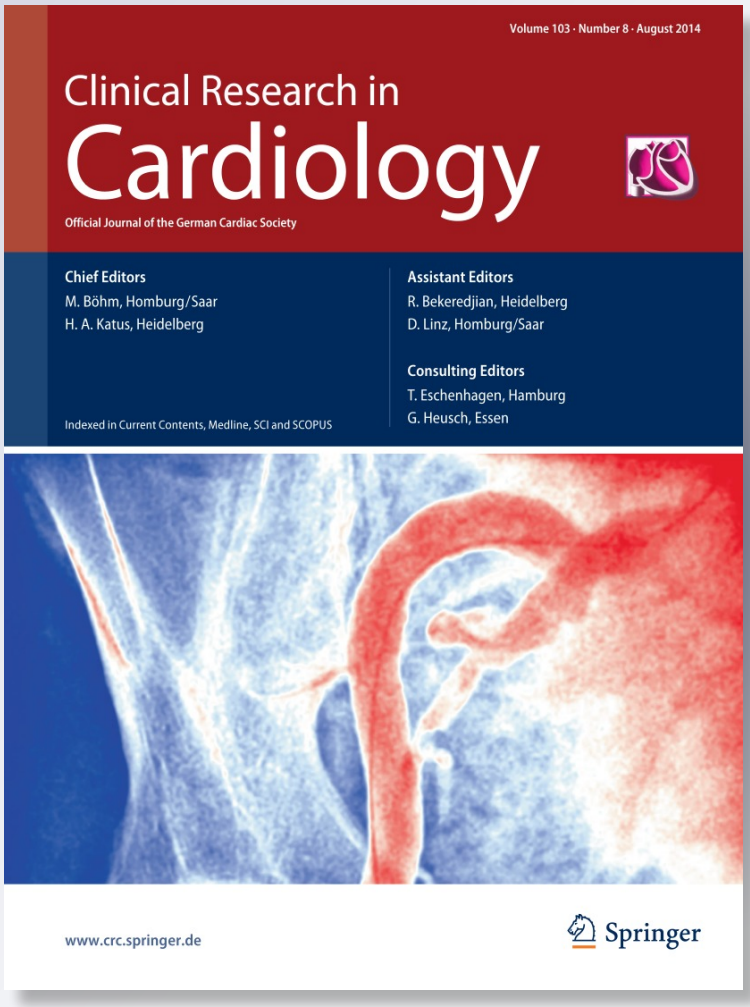

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ORIGINAL PAPER

Long-term survival in patients with different combinations of evidence-based medications after incident acute myocardial infarction: results from the MONICA/KORA Myocardial Infarction Registry

Ute Amann · Inge Kirchberger · Margit Heier · Hildegard Golüke · Wolfgang von Scheidt · Bernhard Kuch · Annette Peters · Christa Meisinger

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Abstract
Background Use of the four evidence-based medications [EBMs: antiplatelet agent, beta-blocker, statin and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ACEI/ARB)] after acute myocardial infarction (AMI) has a clear impact on 1-year survival. Aim of this study was to evaluate the association between different EBM combinations at discharge and long-term survival after AMI.
Methods From a German population-based AMI registry, 2,886 men and 958 women were included, aged 28–74 years, hospitalized with an incident AMI between 2000 and 2008. All data were collected by standardized interviews and chart review. All-cause mortality was assessed for all registered persons in 2010. Median follow-up time was 6.0 years (interquartile range 4.1 years). Survival analyses and multivariate Cox regression analysis were conducted.
Results Of the 3,844 patients, 70.3 % were prescribed all four EBMs; 23.8 % received three, 4.6 % two, and 1.3 % were discharged with one or no EBM. Long-term survival was 71.7 % [95 % confidence interval (CI) 55.4–82.9 %], 64.7 % (95 % CI 59.2–69.6 %) and 60.2 % (95 % CI 51.9–67.5 %) in patients with four, three and <3 EBMs, respectively. Patients prescribed three or less EBMs without ACEI/ARB showed similar long-term survival to those receiving four EBMs. In Cox regression analysis after adjustment for confounding variables, the hazard ratio for long-term mortality in patients with four EBMs versus three or less EBMs was 0.63 (95 % CI 0.53–0.74).
Conclusions Prescribing of a combination of all four EBMs appeared to improve clinical outcomes in AMI patients by significantly reducing long-term mortality. Hospital discharge is a critical time for optimal long-term management.

Keywords Acute myocardial infarction · Mortality · Secondary prevention drug therapy · Drug combination

U. Amann (✉) · I. Kirchberger · M. Heier · C. Meisinger
MONICA/KORA Myocardial Infarction Registry, Central Hospital of Augsburg, Stenglinstr. 2, 86156 Augsburg, Germany
e-mail: ute.amann@helmholtz-muenchen.de

U. Amann · I. Kirchberger · M. Heier · H. Golüke · A. Peters · C. Meisinger
Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany

W. von Scheidt · B. Kuch
Department of Internal Medicine I, Cardiology, Central Hospital of Augsburg, Augsburg, Germany

B. Kuch
Department of Internal Medicine/Cardiology, Hospital of Nördlingen, Nördlingen, Germany

Background

Beside lifestyle changes and control of risk factors, use of comprehensive medication therapy after acute coronary syndrome (ACS) has a major impact on cardiovascular morbidity and mortality and is recommended as long-term management in all ACS patients without known contraindications regardless of age, sex or medical history [1–3].

Over the last decades, a large number of randomized clinical trials (RCTs) have demonstrated the efficacy of secondary prevention drug therapy in survivors of acute myocardial infarction (AMI) for each of the following four medications: antiplatelet agents (aspirin and/or P2Y12

receptor inhibitors as clopidogrel), beta-blockers, statins and agents acting on the renin-angiotensin system [angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)] [4–6]. This comprehensive evidence for each individual medication led to an international consensus at least from 2004 onwards that treatment with a combination of these four evidence-based medications (EBMs) should be the standard of care for patients after an AMI [7].

In addition to RCTs, studies in real-world settings which investigated combined medication therapies in unselected populations, showed a clear benefit for prescribing a combination of all four EBMs at hospital discharge in terms of lower 1-year mortality rate compared with those who have not received it [8–11]. However, less information exists on the association between EBMs and outcome of 2 years or longer after the acute coronary event [12–15]. Three of these long-term studies were based on administrative data and reported major limitations due to unknown information on aspirin use [15], and on clinical data (e.g., type of AMI or body mass index) and lifestyle factors (e.g., smoking) [13, 14]. An adjustment for these potentially confounding variables was therefore not possible.

The aim of this study was to assess the association between different EBM combinations prescribed at hospital discharge and long-term survival in patients with an incident AMI between 2000 and 2008 using data of a population-based myocardial infarction registry including all consecutive AMI cases and taking into account relevant potential confounders.

Methods

The population-based myocardial infarction (MI) registry in Augsburg, Germany, was established in 1984 as part of the World Health Organization MONICA Project (MONItoring Trends and Determinants in CArdiovascular disease) [16]. After the termination of MONICA in 1995, the MI registry became part of the framework of KORA (Cooperative Health Research in the Augsburg Region). Since 1984, all cases of coronary deaths and at least 24 h surviving AMI of the 25- to 74-year old study population in the city of Augsburg and the two adjacent counties (about 600,000 inhabitants) have been continuously registered. About 80 % of all AMI cases of the study region are treated in the region's major hospital, Klinikum Augsburg, a tertiary care center offering interventional cardiovascular procedures, as well as heart surgery facilities. The methods of case identification, diagnostic classification of events, and data quality control have been described in detail elsewhere [16, 17].

Data collection

Patients were interviewed during hospital stay by trained nurses using a standardized questionnaire to collect sociodemographic characteristics, cardiovascular risk factors, comorbidities, history of medical and drug treatment, and information on the acute event. Further information on laboratory data, type of AMI, procedures and complications during hospital stay, vital signs, medical history, and medication use during hospitalization as well as at discharge were collected by review of medical chart and discharge report. Data collection and follow-up questionnaires of the MONICA/KORA MI registry have been approved by the Bavarian State Ethics Committee. The type of AMI was defined as ST-segment elevation MI (STEMI), Non-ST-segment elevation MI (NSTEMI), bundle branch block (BBB), or non-classifiable/missing. The BBB group contains newly developed left BBB, right BBB, and chronic BBB; because we do not know exactly whether all patients with a BBB had a newly developed left BBB, which is considered as STEMI, we displayed the BBB group as separate category.

All medications were recorded and classified in the registry according to the international Anatomical Therapeutic Chemical Classification System (ATC) of the WHO Collaborating Centre for Drug Statistics Methodology (http://www.whocc.no/atc_ddd_index/). The EBMs at hospital discharge considered for this analysis were: antiplatelet agents (ATC code: B01AC), beta-blockers (ATC code: C07), statins (ATC code: C10AA, C10BA), ACEIs or ARBs (ATC code: C09A, C09B, C09C, C09D). To assess the proportion of dual antiplatelet therapy (DAPT), the following definition was used: aspirin (ATC code: B01AC06, B01AC56) and clopidogrel (ATC code: B01AC04) or ticlopidine (ATC code: B01AC05). New antiplatelet agents such as prasugrel and ticagrelor could not be studied because they were not yet available during the study period of this analysis. The following combinations of EBMs were studied: four-drug treatment [any antiplatelet agent, beta-blocker, statin and ACEI or ARB (ACEI/ARB)], three-drug treatment (any combination of three of the four designated drug classes), two-drug treatment (any combination of two), one-drug treatment (only one), and zero-drug treatment (none of the designated EBM).

The end point of this study was all-cause mortality. Mortality was assessed by checking the vital status of all registered persons of the KORA MI registry through the population registries inside and outside the study area in 2010; this procedure guaranteed that the vital status of cohort members who had moved out of the study area could also be assessed. Death certificates were obtained from local health departments.

Study population

In the present study, all patients registered with an incident AMI from January 1, 2000, to December 31, 2008 (study period) and who were discharged alive were included. From the total of 4,708 patients with non-fatal incident AMI we excluded patients with no data on discharge medication ($n = 16$), patients who died during hospital stay ($n = 285$), and patients whose data on any of the relevant covariables included in the final regression model were incomplete ($n = 563$), leaving 3,844 patients for analysis. Excluded patients with missing covariable information were older (median age 64 vs. 62 years, $p = 0.001$), had more frequently a NSTEMI (62.5 vs. 54.2 %, $p < 0.001$), a history of stroke (22.2 vs. 6.1 %, $p < 0.0001$) and diabetes (37.5 vs. 28.5 %, $p < 0.0001$), were less likely to receive any reperfusion therapy (71.4 vs. 84.5 %, $p < 0.0001$) and the four-drug treatment (54.7 vs. 70.3 %, $p < 0.0001$), and showed a higher rate of in-hospital complications (12.8 vs. 8.9 %, $p = 0.003$); also long-term mortality was higher (31.1 vs. 15.4 %, $p < 0.0001$) compared to patients included in the study population.

Data analysis

Continuous data were expressed as median values with interquartile range (IQR). Categorical variables were reported as percentage, and the χ^2 test was used to evaluate differences in frequencies. For continuous variables, comparisons were made using Student's t test. Survival times for different EBM combinations were calculated according to the method of Kaplan–Meier; statistical significance was determined by log-rank χ^2 test.

To investigate the association of four-drug treatment (yes/no) and long-term mortality, relative risks were assessed using Cox proportional hazard regression model. The crude association was sequentially adjusted for age, sex and all other significant variables. The associations of potential covariates with long-term all-cause mortality were assessed in univariate Cox proportional hazard models. To test for crude association with the primary independent variable 'four-drug treatment', all potential confounding factors were cross-tabulated and χ^2 tested. Only variables that were statistically significant at the 0.05 level with either the outcome variable or the primary independent variable were included in the multivariate regression analysis. Variables analyzed as potential confounding factors were sex (male/female), age (continuous), smoking (at time of the acute event) (yes/no), employed (yes/no), married (yes/no), body mass index >30 kg/m^2 (yes/no), medical history of stroke, diabetes, hyperlipidemia, hypertension (yes/no), and angina pectoris (yes/no), type of AMI (STEMI, NSTEMI, BBB, or non-classifiable/missing), any reperfusion therapy [percutaneous transluminal coronary angioplasty (PTCA) with or without stenting, coronary artery bypass grafting (CABG), or thrombolysis] (yes/no), any in-hospital complication (cardiac arrest or cardiogenic shock or ventricular fibrillation or recurrent infarction or pulmonary edema) (yes/no), and pre-hospital delay time (continuous). Regarding the variable 'reduced left ventricular ejection fraction (LVEF < 30 %)' we had a considerable number of patients ($n = 1,189$) with missing data in our study population. Instead of reducing the study population by around 30 %, we decided to perform a sensitivity analysis for patients with information on LVEF ($n = 2,655$), where an additional adjustment for reduced LVEF was possible.

We considered a sparing model with only significant variables kept in the final model except for sex and age (forced-in variables). The proportional hazard assumption of each predictor variable was tested graphically. The assumption was satisfied for all variables used in the Cox model except for the variables 'smoking', 'history of hypertension' and 'any reperfusion therapy', shown by parallel lines of log (−log(survival)) versus log of survival times. The three non-proportional variables were tested by generating time-dependent covariates. The time-dependent covariate of 'history of hypertension' was significant ($p = 0.01$), but further stratification on this non-proportional predictor showed almost the same parameter estimates compared to the model where 'history of hypertension' was included as a proportional predictor. Therefore, stratification was not necessary, and we decided to report the results of the non-stratified model. Interaction effects of age and sex with the four-drug treatment (yes/no) were tested, but failed to reach statistical significance. In all analyses, a significance level of 5 % was applied. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

The median age of the 3,844 patients in the study population was 62 years (range 28–74 years), 2,886 (75.1 %) were men, and 3,250 (84.5 %) were provided with a reperfusion therapy. Altogether, 38.9 % of the patients presented with a STEMI, 54.2 % with an NSTEMI, 5.0 % with a BBB, and 1.9 % with a non-classifiable infarction or missing data on type of AMI. The discharge prescription rates of antiplatelet agents, beta-blockers, statins, and ACEI/ARBs were 96.3, 95.5, 88.5, and 82.7 %, respectively (Table 1).

Over the total study period from 2000 to 2008, 70.3 % of all cases were prescribed the four-drug treatment, 23.8 % received the three-drug treatment and 4.6 % the two-drug treatment. Only 1.3 % of the study population

Table 1 Characteristics of the total study population and stratified by secondary prevention drug treatment group during study period from 2000 to 2008

	All $n = 3,844$ (%)	Patients with four EBMs $n = 2,702$ (70.3 %)	Patients with 0–3 EBMs $n = 1,142$ (29.7 %)	p Value
Age (years)[a]	62/14/28−74	61/15/28−74	63/15/28–74	0.0493
Men	2,886 (75.1)	2,054 (76.0)	832 (72.9)	0.0383
Body mass index >30 kg/m^2	957 (24.9)	719 (26.6)	238 (20.8)	0.0002
Smoking	1,408 (36.6)	1,006 (37.2)	402 (35.2)	0.2325
Employment	1,449 (37.7)	1,046 (38.7)	403 (35.3)	0.0454
Medical history of				
Hypertension	2,917 (75.9)	2,146 (79.4)	771 (67.5)	<0.0001
Diabetes mellitus	1,097 (28.5)	796 (29.5)	301 (26.7)	0.0516
Stroke	235 (6.1)	148 (5.5)	87 (7.6)	0.0114
Hyperlipidemia	2,685 (69.9)	1,970 (72.9)	715 (62.6)	<0.0001
Angina pectoris	552 (14.4)	391 (14.5)	161 (14.1)	0.7669
LVEF <30 %	296 (7.7)	208 (7.7)	88 (7.7)	0.0965
LVEF-missing data	1,189 (30.9)	808 (29.9)	381 (33.4)	
Type of AMI				
STEMI	1,494 (38.9)	1,098 (40.6)	396 (34.7)	0.0024
NSTEMI	2,085 (54.2)	1,434 (53.1)	651 (57.0)	
Bundle branch block	191 (5.0)	122 (4.5)	69 (6.0)	
Non-classifiable/missing data	74 (1.9)	48 (1.8)	26 (2.3)	
Treatment in hospital				
Coronary artery bypass grafting	597 (15.5)	326 (12.1)	271 (23.7)	<0.0001
PTCA with stenting	2,384 (62.0)	1,931 (71.4)	453 (39.7)	
PTCA without stenting	153 (4.0)	100 (3.7)	53 (4.6)	
Thrombolysis	116 (3.0)	56 (2.1)	60 (5.3)	
No reperfusion therapy	594 (15.5)	289 (10.7)	305 (26.7)	
Any in-hospital complication[b]	341 (8.9)	214 (7.9)	127 (11.1)	0.0014
Medication at discharge				
Antiplatelet agents	3,700 (96.3)	2,702 (100)	998 (87.4)	<0.0001
Beta-blockers	3,672 (95.5)	2,702 (100)	970 (84.9)	<0.0001
Statins	3,402 (88.5)	2,702 (100)	700 (61.3)	<0.0001
ACEI/ARBs	3,178 (82.7)	2,702 (100)	476 (41.7)	<0.0001
DAPT	2,512 (65.4)	2,029 (75.1)	483 (42.3)	<0.0001
Follow-up data				
Follow-up time (years) Median/IQR	6.0/4.1	5.9/3.8	6.3/5.1	<0.0001
1-year mortality	124 (3.2)	58 (2.2)	66 (5.8)	<0.0001
Death	593 (15.4)	311 (11.5)	282 (24.7)	<0.0001

EBM evidence-based medication (antiplatelet agent, beta-blocker, statin, ACE inhibitor or angiotensin receptor blocker), *LVEF* left ventricular ejection fraction, *STEMI* ST-segment elevation myocardial infarction, *NSTEMI* non-ST-segment elevation myocardial infarction, *PTCA* percutaneous transluminal coronary angioplasty, *ACEI/ARBs* angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, *DAPT* dual antiplatelet therapy: aspirin and clopidogrel or other oral platelet aggregation inhibitor

[a] Median/interquartile range (IQR)/minimum–maximum

[b] Complications during hospital stay: cardiac arrest or cardiogenic shock or ventricular fibrillation or recurrent infarction or pulmonary edema

was discharged with one (1.0 %) or none (0.3 %) of the four EBMs. Besides the four-drug treatment, the most common EBM combinations were three-drug treatment without ACEI/ARB (12.9 %), without statin (7.1 %), or without beta-blocker (2.2 %), followed by two-drug treatment with beta-blocker and antiplatelet agent (2.1 %), and the three-drug treatment without any antiplatelet agent (1.7 %). All other drug treatment strategies (0–2 EBMs) were observed in <1 % of all patients. Over the study period, the strongest increase of the four-drug treatment was seen between 2000 and 2002, and the peak of 80.1 % was observed in 2008, whereas the three-drug and two-drug treatments declined over time (Fig. 1). By splitting the 9-year study period into three equal time periods, greatest increase was found for statins from 79.4 % of all cases between 2000 and 2002 to 94.2 % between 2006 and 2008, followed by ACEI/ARBs from 75.5 to 85.7 %, respectively. Prescribing of DAPT was done predominantly with a combination of aspirin and clopidogrel (99.4 % of all DAPT), and increased over the study period

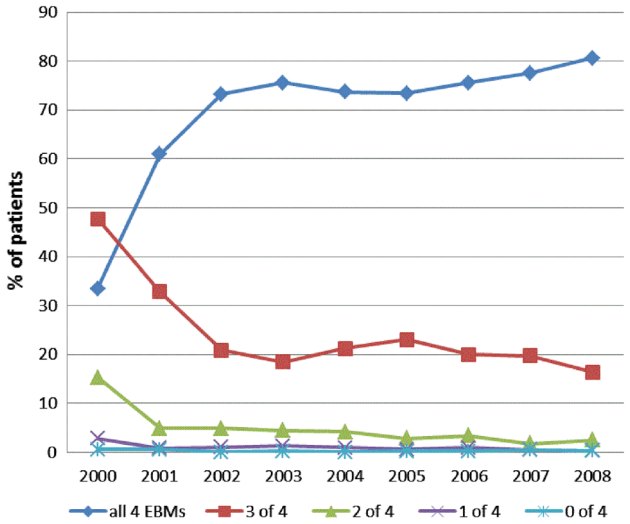

Fig. 1 Discharge evidence-based medication (EBM) use in the MONICA/KORA Myocardial Infarction Registry sample ($n = 3{,}844$) between 2000 and 2008

from 51.2 % between 2000 and 2002 to 77.0 % between 2006 and 2008. Non-use of DAPT was mainly seen in patients with 0–3 EBMs (Table 1) and in all patients who were treated with CABG or conservatively (thrombolysis or no reperfusion therapy).

During the median follow-up period of 6.0 years (IQR 4.1 years; min. 3 days, max. 4,384 days) 593 (15.4 %) patients died, of these 124 (3.2 %) deaths occurred within 1 year after discharge (Table 1). In the unadjusted analysis, the survival rate at the end of the follow-up period was 71.7 % (95 % CI 55.4–82.9 %) in patients receiving the four-drug treatment. Whereas in patients who received three EBMs or <3 EBMs, the long-term survival was 64.7 % (95 % CI 59.2–69.6 %) and 60.2 % (95 % CI 51.9–67.5 %), respectively ($p < 0.001$, four-drug vs. three-drug vs. zero- to two-drug treatment) (Fig. 2). Figure 3 presents Kaplan–Meier curves for each analyzed EBM. Long-term survival was significantly higher in patients who were prescribed the four-drug treatment (red line) compared with those having received the respective EBM combined with up to two other EBMs (green line), and also with those having received at least one other EBM without the respective EBM (blue line) (log-rank test $p < 0.0001$).

By stratifying the study population into two groups, patients with or without the four-drug treatment, major differences in characteristics of the patient population were seen (Table 1). For example, differences were observed for body mass index >30 kg/m^2 (26.6 vs. 20.8 %, $p = 0.0002$), employment (38.7 vs. 35.3 %, $p = 0.045$), type of AMI (e.g., STEMI 40.6 vs. 34.7 %, $p = 0.002$), reperfusion therapy (e.g., PTCA with stenting: 71.4 vs. 39.7 %, $p < 0.0001$), any in-hospital complication (7.9 vs. 11.1 %, $p = 0.014$), and for mortality data (e.g., death at end of follow-up time: 11.5 vs. 24.7 %, $p < 0.0001$). No significant difference was observed related to reduced LVEF (7.7 vs. 7.7 %, $p = 0.10$). By analyzing the rate of PTCA with stenting for each single year in patients with 0–3 EBMs, there was a clear increase of patients receiving PTCA with stenting between 2000 and 2008 from 26 % up to 53 % (data not shown). In addition, patients with 0–3

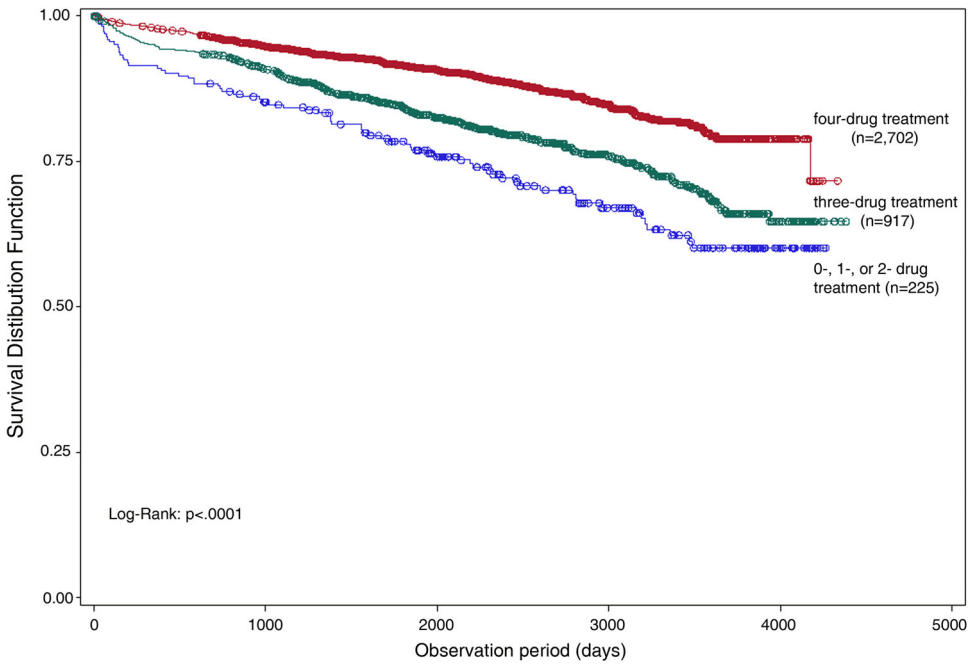

Fig. 2 Long-term survival in hospital survivors with incident myocardial infarction according to the drug combination strategy prescribed at discharge: four-drug treatment (all four evidence-based medications (EBMs), three-drug treatment (three of four EBMs), 0-, 1-, or 2-drug treatment (<3 EBMs)

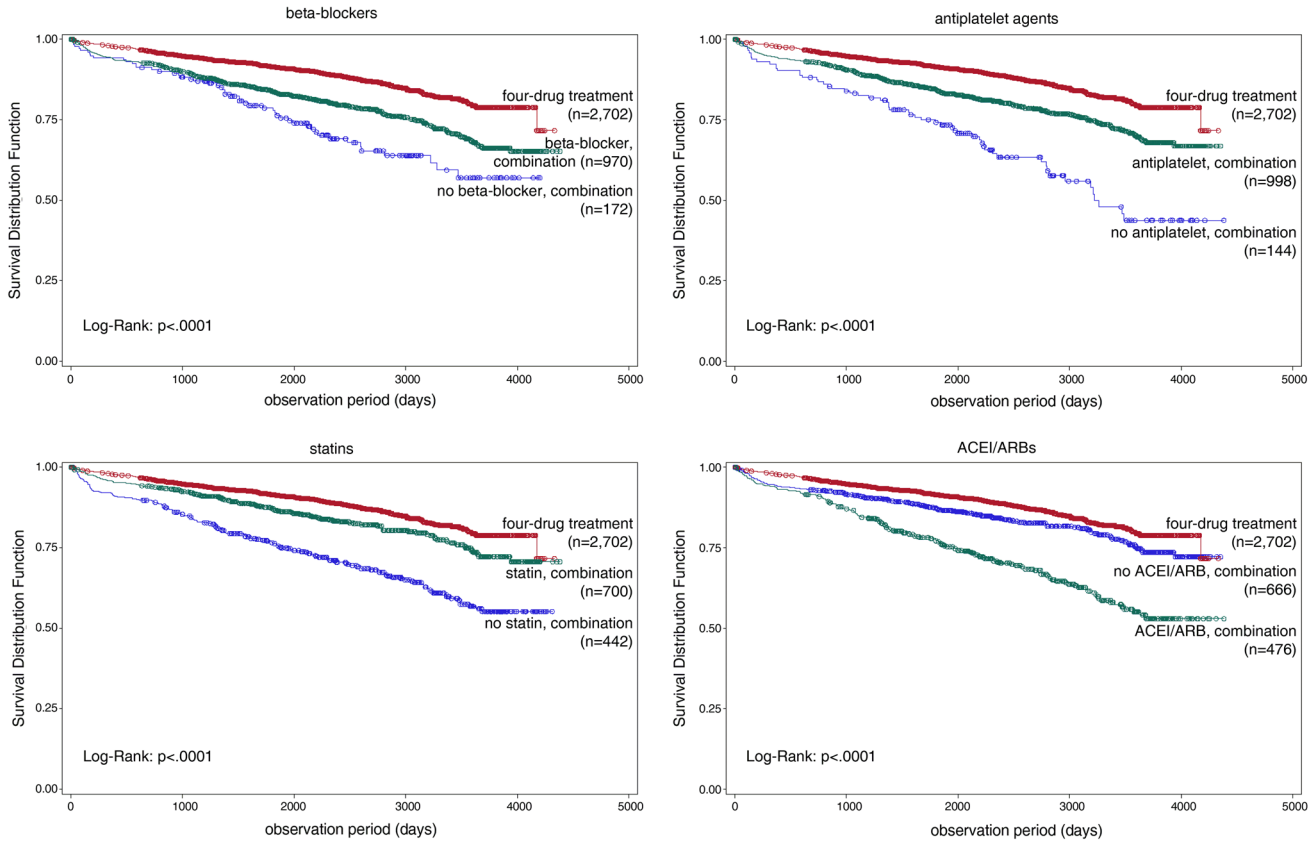

Fig. 3 Kaplan–Meier survival analysis for each of the four evidence-based medications [EBMs: beta-blocker, antiplatelet agent, statin and ACE inhibitor or angiotensin receptor blocker (ACEI/ARB)] comparing patients who received all four EBMs (four-drug treatment; *red line*) with those having received the respective EBM combined with up to two other EBMs (*green line*), and also with those having received at least one other EBM without the respective EBM (*blue line*)

Table 2 Association between four EBMs versus 0–3 EBMs received at hospital discharge and long-term mortality

Total (n = 3,844)	HR (95 % CI)	p Value
Unadjusted	0.52 (0.44–0.61)	<0.0001
Model 1[a]	0.53 (0.45–0.62)	<0.0001
Model 2[b]	0.53 (0.45–0.63)	<0.0001
Model 3[c]	0.63 (0.53–0.74)	<0.0001
Model 4[d]	0.63 (0.53–0.74)	<0.0001

EBM evidence-based medication (antiplatelet agent, beta-blocker, statin, ACE inhibitor or angiotensin receptor blocker) *HR* hazard ratio, *CI* confidence interval

[a] Adjusted for age (cont.) and sex

[b] Additional adjustment for employment, smoking

[c] Additional adjustment for type of AMI, reperfusion therapy, and any in-hospital complication

[d] Additional adjustment for history of stroke, diabetes, hyperlipidemia, and hypertension

EBMs were more likely to receive a CABG, and had a previous history of stroke as seen in Table 1. Furthermore, we had around 6 % of all patients treated with CABG who received a prior PTCA with stenting, but those patients were counted only once in the CABG group.

In the multivariate Cox model, the four-drug treatment combination showed a strongly inverse relation with long-term mortality as compared to patients without a four-drug treatment (Table 2). After adjustment for age and sex, the hazard ratio (HR) was 0.53 (95 % CI 0.45–0.62). Further stepwise adjustment for smoking, employment, type of AMI, any reperfusion therapy, any in-hospital complication, and medical history of stroke, diabetes, hyperlipidemia and hypertension attenuated the association to a HR of 0.63 (95 % CI 0.53–0.74) ($p < 0.0001$). In a sensitivity analysis for patients with information on LVEF (n = 2,655) an additional adjustment for reduced LVEF was performed. However, the HR observed (0.67; 95 % CI 0.54–0.83) was similar compared with the above-mentioned HR of the final model with all patients included.

In a further sensitivity analysis including the patients with missing information on relevant covariables of the final model (n = 563), the Cox model showed only a 4 % difference in the unadjusted HR (0.48; 95 % CI 0.42–0.55) compared to the study population.

Discussion

In the present population-based study including consecutive incident AMI cases occurring between 2000 and 2008 with a median follow-up of 6 years, we found that the guideline-recommended four-drug treatment prescribed at hospital discharge is independently associated with long-term survival. Our observational study showed that most of the 3,844 patients received a combination of all four (70.3 %) or three (23.8 %) of the guideline-recommended medications. The proportion of patients with all four EBMs reported from other studies ranged from 27 to 71 %. In general, lower proportions were found in the studies conducted before 2004 [9, 10, 12, 18–24]. Our study period ranged from 2000 to 2008, and we found an increase of prescription of the four-drug treatment over time with the highest proportion of 80 % in 2008. This temporal increase in use of the combined EBMs is in line with previous studies [9, 24], and reflects the international consensus from 2004 onwards that treatment with a combination of all four EBMs should be the standard of care post-AMI [7]. The reason for the strong increase of the four-drug treatment observed between 2000 and 2002 in our registry was the change of the chief physician of the department of cardiology in the region's major hospital in 2000 where about 80 % of all AMI cases were treated. In accordance with other recently published national and international studies, a high proportion of patients were treated with antiplatelet agents (96 %), beta-blockers (96 %), statins (89 %) and ACEI/ARBs (83 %) [10–12, 23, 25–27]. We observed a marked increase in the use of statins and DAPT during 2000 and 2008. This was also reported by other researchers [9, 21, 28, 29], and is very likely due to the growing evidence of efficacy and safety of statin therapy reported from clinical trials in patients with ACS [5], and also for DAPT in patients with high risk of thromboembolic events (e.g., stent implantation) as reflected by the updated guideline for secondary prevention therapy in 2006 [30]. Almost all DAPT was done with a combination of aspirin and clopidogrel. This was expected, because of the known adverse potential of ticlopidine, and the fact that the new P2Y12 receptor inhibitors prasugrel and ticagrelor were not yet approved at the time of the present study period.

In our study, we found a 37 % reduction of long-term all-cause mortality risk for patients with four-drug treatment compared to patients prescribed three or less EBMs. Several observational studies reported a 46–75 % reduction of 1- or 2-year mortality in patients receiving at least four EBMs [8–12]. To our knowledge, an observation period longer than 2 years was so far only studied based on administrative data [13–15]. The 2- and 4-year mortality risk reduction of 28 %, and 65 %, respectively, determined in two prior German studies are not comparable to our study results due to considerable methodological differences, for example in drug exposure (proportion of days covered calculated from administrative data vs. discharge medication use from medical chart and discharge report), in study type (nested case–control study vs. registry study), and in limited adjustment for potential confounding factors (e.g., lifestyle factor and clinical information). A recently published Australian study reported a 11-year mortality risk reduction of 34 % in patient aged 65–84 years receiving a combination of beta-blocker, statin, and ACEI/ARB. Due to unknown antiplatelet use, no comparable results on four-drug treatment exist [15]. However, this very long-term mortality risk reduction with the combined use of EBMs is in line with the present study.

The somewhat smaller benefit in our study might be explained by the comparison group we used, which included a high proportion of patients with three-drug treatment, whereas in previous studies, the comparison groups were predominantly patients receiving one or none of the evidence-based cardiovascular drugs [9, 11, 12, 15]. As in our sample, only 1.3 % of patients were discharged with one or no medication we decided in accordance with another study [10] to use a more realistic comparison group.

The unadjusted results of non-users of ACEI/ARBs which showed almost the same long-term survival rate as patients with the four-drug treatment were surprising. Gunnell et al. [15] also reported marked differences in long-term mortality between specific combinations of EBMs, and found a similar mortality risk for patients on 'beta-blockers and statins' compared with those on 'beta-blockers, statins, and ACEI/ARBs'. However, our results should be interpreted with caution due to many factors which could have contributed to the higher mortality rate in patients with ACEI/ARBs compared to those not receiving this treatment. For example, patients receiving ACEI/ARBs may have per se a worse prognosis because of having a clear indication for ACEI/ARB prescribing such as hypertension, diabetes, chronic kidney disease, heart failure or reduced LVEF. This might be strengthened by the fact, that there exists still uncertainty around the benefits of ACEIs in all AMI patients without a clear indication [29, 31–33].

Major strength of our study is the setting in a population-based registry with patients consecutively hospitalized with validated incident AMI. Compared to previous studies, the present study is characterized by a long observational period and adjustment for major clinical factors which influence mortality.

Of note, some limitations for interpretation of our study results should be kept in mind. Despite adjustment for several confounding variables, residual confounding cannot be entirely excluded due to further unknown

comorbidities or complications such as multimorbidity, frailty, atrial fibrillation, chronic kidney disease, and further aspects which could have influenced long-term mortality. For example, we did not know whether the procedures in hospital were successful or not. Also, we cannot exclude that patients treated with all four EBMs received better medical and hospital care or had lower risks to start with. Furthermore, since in our study population the discharge prescription rate of antiplatelet agents and beta-blockers was 96 %, the analyses regarding those 4 % of patients without such a treatment may be of limited value. Our results are limited to patients up to 74 years, and we did not address the issue of how well (adherence) and how long (persistence) patients were taking their discharge medication. Non-adherence to efficacious cardiovascular drugs is often underestimated, but recognized as important factor of improved survival rates [34, 35]. However, in our analysis we could constrain along with other researchers in this field that discharge after a survived AMI is a critical time at which use and prescription of the secondary prevention combination therapy is very important for optimal long-term management and is therefore associated with long-term survival benefit, regardless of adherence measurements [12, 22].

Conclusion

Our study supports the hypothesis that optimal secondary prevention with all four EBMs at hospital discharge is associated with long-term survival benefit. Long-term survival was different for patients receiving four, three or even less EBMs. In real-life patient care, we observed almost the same mortality for non-users of ACEI/ARBs as for patients with the four-drug treatment. Therefore, it remains important to analyze drug effects in population-based longitudinal studies where combined medications can be studied. Further research on drug effectiveness of ACEI/ARBs in combination with other cardiovascular drugs might be necessary including information on patient-individual dose, tolerability, persistence, and further information on chronic comorbidities and non-cardiovascular medications.

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Conflict of interest No conflict of interest to declare.

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