Association between admission ECG changes and long-term mortality in patients with an incidental myocardial infarction: Results from the KORA myocardial infarction registry

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1. Introduction

Acute myocardial infarction (AMI) is a major cause of morbidity and mortality in Germany and worldwide [1,2]. It is grouped into two main categories according to admission ECG: ST-Elevation myocardial infarction (STEMI) and non-ST-Elevation myocardial infarction (NSTEMI). STEMI is characterized by persistent ST segment elevation, high peak-CK MB levels [3,4] and greater infarct size [5–10], whereas NSTEMI tend to occur in older people with more extensive coronary disease and more cardiovascular risk factors. ESC guidelines do reflect on this, as the recommendations for STEMI and NSTEMI differ with regards to therapy and disease management [11,12]. Even though, despite the greater infarct size, several prior studies found similar mid-to long-term mortality for STEMI and NSTEMI patients [3,13–16], while others even showed a better mid- to long-time survival for the STEMI group [17–21]. Nevertheless, observational periods of the most studies were limited to only several years. This raises the question whether reported results remain stable even for longer follow-up periods.

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Moreover, the NSTEMI group can be further divided into several subgroups according to the presenting ECG, which can predict differences in outcomes [22–26]. Since most of those studies only examined short-term mortality and partly have very limited number of included cases, scientific evidence on associations between long-term mortality and specific changes in the admission ECG is weak. Hence, this study aimed to detect associations between certain ECG changes and long-term mortality. This might help to identify high risk groups with potential implications on treatment [27].

2. Material and methods

2.1. Patients

The underlying data for this research was collected by the Augsburg Myocardial Infarction Registry as part of the MONICA-project (Monitoring Trends and Determinants in Cardiovascular disease). More detailed information on data collection is available in previous publications [28,29]. In brief, the study area consists of the city of Augsburg, Germany, and the two adjacent counties comprising a total of approximately 680,000 inhabitants. For this analysis, all cases of hospitalized AMI were recorded on following conditions: patients age was between 25 and 74 years (2000 until 2008) or between 25 and 84 years (2009 until 2017), the patient survived the first 24 h after hospital admission and had its primary residence within the study area. Trained study nurses carried out interviews using standardized questionnaires during the hospital stay. Further data collection was done by elaborating the patients' medical files. In this way a large amount of data for each case of AMI was collected including sociodemographic characteristics, risk factors, comorbidities, diagnostics and treatment.

Information on long-term survival was obtained regularly from the regional registration and health offices. For this study, the last mortality follow-up update was performed in 2019. Data collection of this registry has been approved by the ethics committee of the Bavarian Medical Association (Bayerische Landesärztekammer) and the study was performed in accordance with the Declaration of Helsinki. All study participants have given written informed consent.

For this study, all patients with a first-time AMI, who survived the first 28 days, were considered. After excluding all cases with missing data on admission ECG or relevant covariates as well as missing information on long-term survival, 9,689 patients were taken into account for the final analysis. Fig. 1. provides a flowchart displaying all inclusion and exclusions. Prior events may have left behind permanent ECG abnormalities and consequently negatively affecting the reliability of the results. Since this study concentrates on long-term survival exclusively, patients who died within the first 28 days after AMI were excluded. In a recent study from this population-based registry the association between admission ECG changes and short-term mortality has already been examined [30].

All admission ECGs were evaluated by physicians. The classification generally matches the 2020 ESC guidelines [11]. Each case of AMI with available admission ECG was allocated to one of six groups: STEMIs were defined as new ST-segment elevations at the J point in 2 or more contiguous leads greater than 0.1 mV that persisted >20 min [11] (for the lead V2 and V2 the cut off points were set higher with >0.2 mV for men and >0.15 mv for women) [31,32]. The remaining patients were assigned to the 'ST-segment depression' group in case admission ECG exhibited new ST-segment depressions at the J point in 2 or more contiguous leads greater than 0.1 mV regardless of any further ECG changes (e.g. T-wave inversion). Some authors suggest lower thresholds for ST-segment depressions of >0.05 mV [31,32], but we used a threshold of 0.1 mm mV as we only wanted clearly evident ST-segment depressions to be categorized as such. All remaining patients with T-wave inversion of >0.1 mV in 2 or more contiguous leads were assigned to the 'T-wave inversion' group. ST-segment elevation, ST-segment depression and T-wave inversion are considered to be

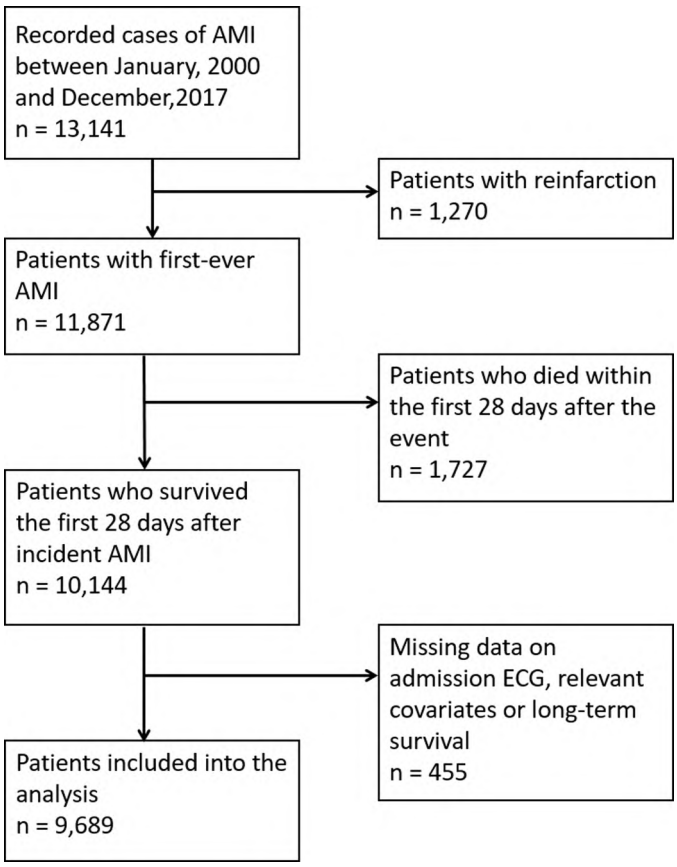

Fig. 1. Flow Chart displaying all inclusions and exclusions.

characteristic abnormalities in AMI patients [11]. Remaining patients were either assigned to the 'normal ECG' group (without any relevant ECG changes) or the 'unspecific changes' group including non-significant ST-segment changes, non-significant T-wave inversion, poor R wave progression or comparable changes. The 'bundle branch block' (BBB) group consisted of all cases with either right or left bundle branch (complete or incomplete) and simultaneously the absence of changes as mentioned above or bundle branch blocks with such great extent, that it was impossible to properly asses ST-segment and T-wave inversion.

For any in-hospital complication including cardiogenic shock, left ventricular decompensation, bradycardia, in-hospital reinfarction, ventricular tachycardia and ventricular fibrillation, one variable was generated (yes/no).

One further variable was generated whether the patient received all four evidence-based medications (EBM) at discharge (antiplatelet drug, ACE blockers/ ATII antagonist, beta-blockers, statins).

2.2. Statistical analysis

Baseline characteristics are presented as total number and percentages for categorical variables. Continuous variables are displayed either as median and interquartile range (IQR) or mean and standard deviation (SD). To determine differences in baseline characteristics, Chi^2 test for categorical variables and one-way ANOVA (analysis of variance) for continuous variable were performed. Some continuous variables (especially laboratory values) contained a very small number of implausible values. In order to prevent such observations from negatively affecting the statistical reliability of the models, very few extreme outliers were removed from the analyses. Therefore, Cooks distance was calculated for each variable. Extreme outliers were identified by visually evaluating the plots of the Cooks distance values.

There were high percentages of missing values for the numeric variable peak CKMB, Troponin I at admission, hemoglobin at admission, peak CRP, prehospital time and days in intensive care. These variables were supposed to be included in the COX regression models. In order not to disregard all cases with missing values, multiple imputation by chained equations was conducted. The imputation method was linear regression, the number of iterations was 5 and the number of created imputed data sets was 5 as well. The imputation process was performed with MICE-package (R statistic software). The subsequent regression models were calculated for each of the 5 imputed data sets and results were pooled in the end.

To investigate the association between ECG changes and long-term mortality, three different COX regressions models were calculated. The first model included only the variable 'ECG group'. The second model was further adjusted for sex and age. The final model was calculated using backwards elimination. Starting point was a COX model with the following initially considered covariates: sex, age, typical chest pain symptoms, prehospital time, diabetes, smoking, hyperlipidemia, hypertension, left-ventricular EF $\leq$ 30%, impaired renal function (according to GFR), peak CKMB, Troponin I at admission, hemoglobin at admission, peak CRP, PCI, Bypass surgery, Lysis therapy, days at intensive care unit, any in-hospital complication and EBM. In a step-by-step process, the covariable with the least significant contribution to the model was eliminated. This algorithm was performed until all covariables contributed significantly to the model (*p*-value was set at 0.05). The final model was then adjusted for the following covariables: sex, age, typical chest pain symptoms, diabetes, smoking, hyperlipidemia, hypertension, left-ventricular EF $\leq$ 30%, impaired renal function (according to eGFR), hemoglobin at admission, peak CRP, PCI, bypass surgery, lysis therapy, days at intensive care unit, EBM.

The proportional hazards assumption was checked by plotting the Schoenfeld residuals against time and searching for any visible correlation. Additionally, a test was performed to check for a significant correlation of the Schoenfeld residuals with time and consequently a violation of the proportional hazard assumption. Furthermore, log(-log (survival)) plots were inspected for crossing curves. Since many covariables violated the proportional hazard assumption most likely as a consequence of the long follow-up period, a time step function was implemented for all covariables (but not for the ECG variable) in the parsimonious model (time split at 2500 days after AMI). Yet, Hazard Ratio's (HR) for the six ECG groups were almost identical in both models (with time-step function and without).

The statistical analysis was performed by R version 3.6.1 and the significance level was set at p-value < 0.05.

3. Results

Mean age of the 9,689 patients included was 63.4 (SD: 11.2) years, a majority of 7,027 (72.5%) patients were men. The median follow-up time was 6.7 years (IQR 3.6–10.9). During the follow-up period, 3,180 patients had died (32.8%). The distribution of cases according to the presented admission ECG and number of events is displayed in Table 1.

Patients' baseline characteristics are summarized in Table 2. STEMI patients were slightly younger than those of any other group and had most frequently typical chest pain symptoms. Median peak-CK-MB levels were more than twice as high as for any other group. There were higher rates of PCI and EBM in STEMI patients compared to patients with NSTEMI (especially compared to the ST-segment depression group and the BB group). Table 1. of the supplementary material displays medication at discharge in greater detail.

Fig. 2 displays the unadjusted Kaplan-Meier curves stratified by admission ECG. The summarized results of the COX regression model can be found in Table 3. The 'STEMI group' was set as the reference group in each of the models. In the unadjusted model, the three NSTEMI groups 'ST-segment depression', 'T-wave inversion ' and 'unspecific changes' had significantly higher HR's than the STEMI group. Of all ECG groups the 'bundle branch block' group was associated with the highest mortality risk. The 'normal ECG' group on the other hand had a significantly lower mortality risk than the STEMI group.

Even after adjustment for sex and age the results remained significant for each ECG group. Yet, differences between the groups and the reference group (STEMI) attenuated compared to the crude model. An exception from this trend was the 'normal ECG' group with almost identical HR values even after age-/sex-adjustment.

The multivariate COX regression model was adjusted for the following covariables: sex, age, typical chest pain symptoms, diabetes, smoking, hyperlipidemia, hypertension, left-ventricular EF $<$ 30%, impaired renal function (according to eGFR), hemoglobin value at admission, peak CRP, PCI, bypass surgery, lysis therapy, days at intensive care unit, EBM. In this model, 'ST-segment depression' and BBB but not 'T-wave inversion' or 'unspecific changes' remained independent predictors of long-term mortality. Contrary, 'normal ECG' predicted a more favorable long-term outcome also in the final COX model (see Table 3).

4. Discussion

In this study we found a significantly higher long-term mortality for AMI patients with 'bundle branch block' or ' ST-segment depression' (without ST-elevation) compared to the reference group of patients with STEMI. Normal ECG on the other hand was associated with a lower long-term mortality.

We included only patient with a first-time myocardial infarction for this analysis. Former myocardial infarction can cause persisting ECG changes [33], which can affect the classification of admission ECG changes.

With about 38% of all cases included the STEMI group was the largest of the 5 ECG groups. While STEMI's went along with the highest peak-CK-MB levels, the peak-CK-MB values were comparable within the NSTEMI groups. Prior studies found higher CK-MB levels for STEMI cases as well [3,4], which is suspected to be associated with higher myocardial damage caused by hypoxia [5–10]. It must be considered though, that there is a higher percentage of delayed revascularization in NSTE-ACS cases. Acute reopening of the infarction-related artery might lead to anticipated and therefore higher CKMB levels which may overestimate myocardial damage [34]. Anyhow, the variable peak CK-MB did not contribute significantly in a COX model together with ECG and wasn't included into the final model. Interestingly, the higher peak-CK-MB values in STEMI patients' didn't go along with higher percentages of severely impaired left ventricular function (EF $\leq$ 30%). In contrast, other studies found reduced EF in STEMI patients compared to patients with NSTEMI [13]. AMI patients of the bundle branch block

Table 1
Case distribution and number of events by ECG group.

	Total sample	STEMI	ST-segment depression	T-wave inversion	unspecific changes	normal ECG	Bundle branch block
Number of incident cases (%)	9689 (100%)	3697 (38.2%)	1110 (11.5%)	1282 (13.2%)	1676 (17.3%)	1242 (12.8%)	682 (7.0%)
Number of deaths within each group (%)	3180 (32.8%).	1018 (27.5%)	528 (47.6%)	462 (36.0%)	560 (33.4%)	252 (20.9%)	360 (52.8%)

Table 2
Baseline characteristics of patients with available data on long-term survival. Categorical data is presented as total numbers (%). Numeric data is presented as mean (SD) or median (IQR).

	STEMI	ST-segment depression	T-wave inversion	Unspecific changes	Normal ECG	BBB	*P*-Value	*n*
male sex	2745 (74.2)	737 (66.4)	849 (66.2)	1253 (74.8)	939 (75.6)	504 (73.9)	< 0.001	9689
age	61.2 (11.4)	66.4 (10.3)	64.1 (10.7)	64.6 (10.9)	61.6 (10.9)	69.1 (9.8)	< 0.001	9689
Comorbidities								
hypertension	2647 (71.6)	935 (84.2)	1025 (80)	1335 (79.7)	944 (76)	577 (84.6)	< 0.001	9689
diabetes	1001 (27.1)	430 (38.7)	395 (30.8)	548 (32.7)	323 (26)	268 (39.3)	< 0.001	9689
hyperlipidemia	2212 (59.8)	694 (62.5)	793 (61.9)	1008 (60.1)	824 (66.3)	410 (60.1)	0.002	9689
Smoking status							< 0.001	9689
current smoker	1483 (40.1)	285 (25.7)	399 (31.1)	494 (29.5)	395 (31.8)	143 (21)		
never smoker	969 (26.2)	350 (31.5)	380 (29.6)	546 (32.6)	402 (32.4)	250 (36.7)	–	
ex-smoker	1081 (29.2)	354 (31.9)	398 (31)	523 (31.2)	402 (32.4)	229 (33.6)	–	
no information on smoking status	164 (4.4)	121 (10.9)	105 (8.2)	113 (6.7)	43 (3.5)	60 (8.8)	–	
Kidney function							< 0.001	9689
eGFR > 60 (ml/min/1.73m²)	2104 (56.9)	481 (43.3)	608 (47.4)	926 (55.3)	775 (62.4)	298 (43.7)		
eGFR 30–60 (ml/min/1.73m²)	528 (14.3)	271 (24.4)	208 (16.2)	372 (22.2)	165 (13.3)	199 (29.2)	–	
eGFR <30 (ml/min/1.73m²)	62 (1.7)	62 (5.6)	56 (4.4)	87 (5.2)	19 (1.5)	55 (8.1)	–	
missing information on eGFR	1003 (27.1)	296 (26.7)	410 (32)	291 (17.4)	283 (22.8)	130 (19.1)	–	
Vital parameters at admission								
Heart rate (bpm)	79.1 (18.7)	84.2 (21.2)	77.9 (16.8)	85 (23.8)	74.3 (14.3)	85.5 (22.8)	< 0.001	9563
Systolic blood pressure (SBP)	142.9 (28.9)	145 (29.6)	145.6 (26.5)	147.6 (27.4)	148.5 (24.3)	144 (28.4)	< 0.001	9539
Diastolic blood pressure	82.7 (17.4)	81.3 (17.2)	82.2 (15.7)	83.8 (16.1)	83.5 (14.7)	80.8 (16)	< 0.001	9267
Shock index (Heart rate/SBP) (median (IQR))	0.54 (0.46 - 0.66)	0.56 (0.47 - 0.69)	0.53 (0.44 - 0.642)	0.550 (0.456 - 0.684)	0.50 (0.43 - 0.58)	0.562 (0.467 - 0.71)	< 0.001	9689
Clinical characteristics								
typical chest-pain symptoms	3269 (88.4)	825 (74.3)	1020 (79.6)	1294 (77.2)	1073 (86.4)	501 (73.5)	< 0.001	9689
prehospital time in minutes (median (IQR))	130.0 (78 - 358)	163.0 (85 - 478.75)	343.5 (107 - 1192.5)	189.0 (95 - 591)	162.0 (83 - 533.5)	184.5 (97 - 569.25)	< 0.001	7715
days at intensive care unit	3.1 (4.9)	4.5 (6.9)	3 (5.1)	3.4 (5.7)	2.2 (3.1)	4.3 (6.6)	< 0.001	9368
left ventricular EF							< 0.001	9689
≤ 30%	182 (4.9)	52 (4.7)	39 (3)	70 (4.2)	9 (0.7)	69 (10.1)		
> 30%	2852 (77.1)	816 (73.5)	955 (74.5)	1208 (72.1)	969 (78)	446 (65.4)	–	
no information on EF	663 (17.9)	242 (21.8)	288 (22.5)	398 (23.7)	264 (21.3)	167 (24.5)	–	
In-hospital complication								
cardiogenic shock	169 (4.6)	36 (3.2)	21 (1.6)	39 (2.3)	5 (0.4)	34 (5)	< 0.001	9689
pulmonary edema	91 (2.5)	39 (3.5)	20 (1.6)	60 (3.6)	5 (0.4)	37 (5.4)	< 0.001	9689
any in-hospital complication	788 (21.3)	144 (13)	135 (10.5)	199 (11.9)	109 (8.8)	129 (18.9)	< 0.001	9689
Laboratory value								
peak CK-MB (U/L) (median (IQR))	113 (47–231)	41 (21–87)	29 (14–58)	37 (19–76.5)	33 (17–61)	38 (19–89)	< 0.001	8595
admission Troponin I (ng/ml) (median (IQR))	0.700 (0.1–5.96)	0.560 (0.14–3.05)	0.805 (0.18–4.54)	0.480 (0.12–2.48)	0.300 (0.08–1.38)	0.655 (0.14–3.72)	0.0071	5960
hemoglobin at admission (g/l) (median (IQR))	144 (134–153)	138 (121–149)	141 (128–152)	142 (130 153)	145 (134–154)	138 (124.25–150)	< 0.001	7286
peak CRP levels (mg/l) (median (IQR))	4.160 (1.48–12.1)	6.60 (1.52–17.02)	3.31 (0.945–12.7)	3.55 (0.9–12.82)	1.60 (0.53–6.23)	6.08 (1.4–15.1)	< 0.001	9379
Treatment								
PCI	3080 (83.3)	609 (54.9)	850 (66.3)	1042 (62.2)	890 (71.7)	407 (59.7)	< 0.001	9689
bypass surgery	346 (9.4)	281 (25.3)	219 (17.1)	282 (16.8)	155 (12.5)	108 (15.8)	< 0.001	9689
lysis therapy	361 (9.8)	17 (1.5)	24 (1.9)	24 (1.4)	23 (1.9)	15 (2.2)	< 0.001	9689
any revascularization therapy	3450 (93.3)	880 (79.3)	1056 (82.4)	1311 (78.2)	1042 (83.9)	508 (74.5)	< 0.001	9689
evidence based medications at discharge							< 0.001	9689
yes	2889 (78.1)	724 (65.2)	874 (68.2)	1137 (67.8)	864 (69.6)	433 (63.5)		
no	740 (20.0)	346 (31.2)	368 (28.7)	482 (28.8)	351(28.3)	222 (32.6)		
insufficient information	68 (1.8)	40 (3.6)	40 (3.1)	57 (3.4)	27 (2.2.)	27 (4.0)		

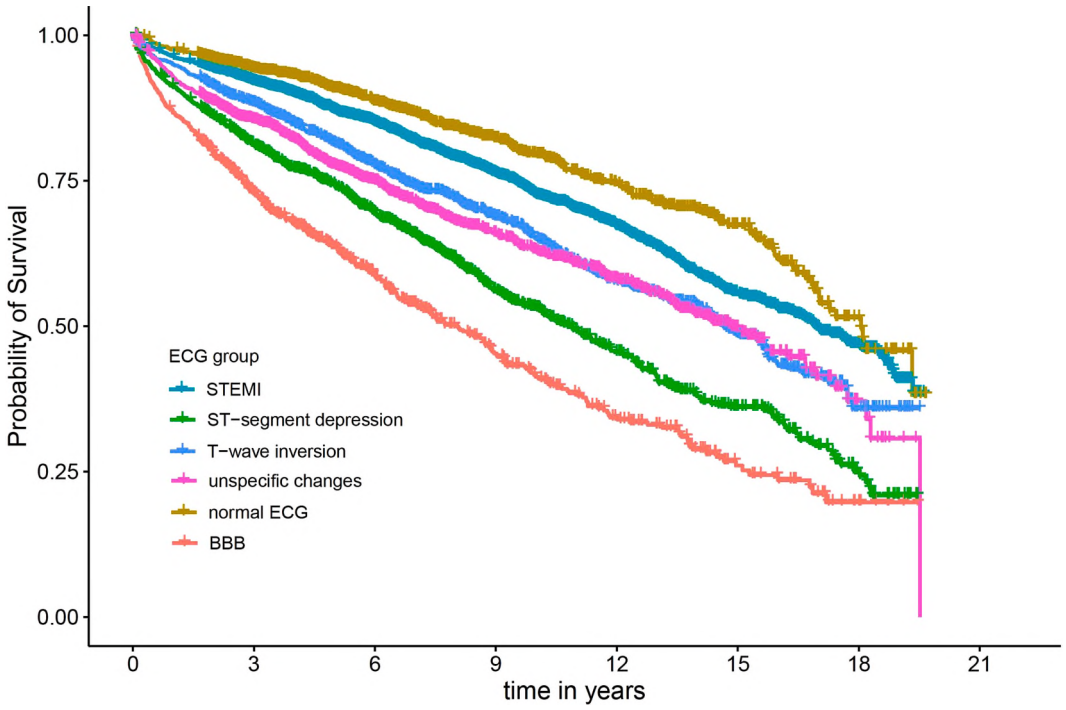

Fig. 2. Kaplan-Meier survival curves by ECG groups.

Table 3
Results of the COX regression models. The STEMI group was set as the reference group.

ECG group	Unadjusted Model		Adjusted for sex and age		Parsimonious model *	
	HR [95% CI]	*p*-value	HR [95% CI]	*p*-value	HR [95% CI]	p-value
STEMI	*1*		*1*		*1*	
ST-segment depression	*1.99 [1.79–2.21]*	*< 0.001*	*1.58 [1.42–1.76]*	*< 0.001*	*1.16 [1.03–1.29]*	*0.01252*
T-wave inversion	*1.35 [1.21–1.51]*	*< 0.001*	*1.20 [1.07–1.34]*	*0.00128*	*1.08 [0.96–1.21]*	*0.18270*
unspecific changes	*1.47 [1.33–1.64]*	*< 0.001*	*1.27 [1.15–1.41]*	*< 0.001*	*1.05 [0.94–1.117]*	*0.37422*
normal ECG	*0.75 [0.65–0.86]*	*< 0.001*	*0.74 [0.64–0.85]*	*< 0.001*	*0.76 [0.66–0.87]*	*< 0.001*
Bundle branch block	*2.78 [2.46–3.13]*	*< 0.001*	*1.95 [1.73–2.21]*	*< 0.001*	*1.52 [1.34–1.73]*	*< 0.001*

* adjusted for sex, age, typical chest pain symptoms, diabetes, smoking, hyperlipidemia, hypertension, left-ventricular EF $\leq$ 30%, impaired renal function (according to eGFR), hemoglobin at admission, peak CRP, PCI, Bypass surgery, Lysis therapy, days at intensive care unit, EBM.

group had the highest percentage of severely impaired left-ventricular EF which was the case about twice as often as in any other group.

4.1. Long-term mortality according to ECG

On average, mortality for the different ECG groups was up to 5% per year, which is markedly higher than the mortality found in most primary prevention studies. This could likely be explained by the population-based character of this registry compared to a selected group of patients included in primary prevention studies.

Conventionally, groups of 'ST-segment depression ', 'T-wave inversion ', 'unspecific changes' and 'normal ECG' are subsumed as NSTEMI events. In this study, one of these groups was associated with higher ('ST-segment depression ') and one group ('normal ECG') with lower long-term mortality compared to the STEMI group. The other two groups did not vary significantly. Generally speaking, the NSTEMI group as a whole did not show major deviation from the STEMI group in terms of long-term mortality after incident AMI. This is mainly in line with results from several prior studies that didn't find significant differences in long-term mortality between STEMI and NSTEMI [3,13–15]. Nevertheless, there are also studies that found better mid- to long-term survival for the STEMI group [16–20]. A study performed in Beijing by Lihui Ren et al. examined the short- and long-term mortality (up to 4 years) of AMI patients treated with PCI [35]. They have found worse short- and long-term prognosis for STEMIs compared to NSTEMIs and so contradicting results than several other studies. When they had a look on survival rates from 6 months to 4 years, they found NSTEMIs to have just slightly higher mortality. So, the overall worse long-term outcome of STEMI in their study is likely be driven by the higher short-term mortality. Since we only took patients into our long-term analysis who survived 28 days after their incident AMI, the results of their study are similar to what we found. The more or less conflicting results reported in scientific literature regarding differences in long-term mortality between STEMI and NSTEMI might be explained by several factors, among these: varying observational periods, deviating inclusion criteria for patients with AMI (e.g. including only patient that were treated with PCI, different age groups etc.) and differences in ECG classification.

ST-segment elevations are very characteristic ECG changes in AMI. They are a class I indication for a primary PCI strategy [12], which leads to a shorter door to balloon time in this patients [13]. In a recent

Editorial, Coiro and Cavallini have discussed and reviewed the importance of fast intervention. They concluded, that a short therapeutic delay remains critical in the care of STEMI cases also with regards to mid- and long-term outcome after the event [36]. When performing an angiography in STEMI cases, it is very likely to find a culprit lesion in an artery for which a revascularization can be performed. For NSTEMI cases on the other hand, there is a higher chance not to find arteries suitable for revascularization (e.g. non-significant lesions or lesions in very small, inaccessible vessels). Furthermore, in comparison to STEMI cases, higher percentage of NSTEMI patients need bypass surgery. For those reasons it is not much of a surprise, that in this study PCI treatment was more frequently conducted in the STEMI group (74.8%) than in any other ECG group (range from 51.7% to 66.9%). Similar results are found in other studies as well [16,37]. In-hospital cardiac catheterization is known to be associated with lower mortality, especially in high risk patients [17,38,39]. In addition, the patients in the STEMI group are slightly younger (mean of 61.2 years) at the event than patients in the other groups. Moreover, STEMI patients had the most favorable cardiovascular risk profile (lowest rates of diabetes, hypertension, hyperlipidemia) of all the ECG groups and especially compared to the ST-segment depression and BBB group, which were associated with the highest mortality among the NSTEMI groups. These factors (faster diagnosis, more frequent PCI, younger age, better cardiovascular risk profile) might contribute to the comparable long-term mortality in STEMI and NSTEMI cases despite higher myocardial damage in STEMI patients.

Several prior studies examined, whether specific ECG changes within the NSTEMI group were associated with short- to mid-term mortality (up to one year) after AMI or acute coronary syndrome (ACS). Two studies from Atar et al [22] and Yan et al [40] found that specific forms of ST-segment depression went along with higher 1-year mortality among NSTEMI patients. Similar results are reported by two further studies [26,41]. Concerning long-term mortality, scientific evidence is very weak. One study from Hyde et al. reports an increasing 4-year mortality risk with increasing ST-segment depression in 367 patients with ACS [25]. These results are in agreement with the results of the present study. Hyde et al. further reported lower 4-year mortality rates for patients with normal ECG compared to patients with ST-segment depression or T-wave inversion [25]. This matches our findings as well, as we found the lowest mortality for patients with normal ECG compared to other NSTEMI groups. Remarkably, the relative risk for long-term mortality for the 'normal ECG' group remained almost unchanged even after multivariable adjustment. This strongly indicates, that the absence of AMI-related ECG changes is indeed a reliable predictor for favorable long-term outcome after incident AMI. Beyond that, a previous study from the Augsburg Myocardial Infarction Registry found that the absence of AMI-typical changes is also a predictor for lower 28-day case fatality in AMI patients [30], so that it can be concluded, that 'normal ECG' at admission goes along with overall lower mortality rates in comparison to events with AMI-related ECG changes.

In the present study, the 'Bundle branch block' group had the highest mortality risk of all six ECG groups. Hence, the clinical presentation of an admission ECG with predominantly bundle branch block (left or right or both) can be viewed as an independent risk factor for unfavorable long-term prognosis in patients with first-time AMI. These results confirm the findings of several prior investigations, that also found an increased mortality for patients with BBB [18,42–46]. BBB's are often the result of an ongoing process of degeneration like left ventricular hypertrophy, CAD or valvular heart disease [47,48]. In a long term, such processes of progressive degeneration may lead to various life threatening complications, sudden cardiac death and an overall increased risk of cardiovascular mortality [48]. Moreover, BBB can lead to unsynchronized mechanical heart contractions and less efficient heart work and in this way accelerates the ongoing degeneration process in the heart [49]. These pathophysiological aspects are likely to be responsible for higher all-cause mortality in patients after AMI. The results of this study suggest, that this effect remains stable years after the incident event. While interpreting these results, it must be considered, that we did not differ between left and right BBB and had no possibility to differentiate between preexisting BBB and newly developed BBB in the context of the acute AMI.

Finally, it is conspicuous, that the STEMI group was by far the most likely to receive EBM at discharge. Interestingly, the two groups with the highest long term mortality, ST-segment depression and BBB, were the ones with lowest rates of EBM at discharge. These medications have been shown to improve the outcome after AMI and therefore lack in EBM might account for the worse long-term outcome in these two NSTEMI groups. Nevertheless, the multivariable COX regression model was adjusted for EBM, which is supposed to take the effects of EBM into consideration. For sure, we can not exclude some residual confounding as we did not consider the exact drug and or dosage nor did we have any information on medication compliance or information on the duration of long-term use. Anyhow, the results of this study would still be consistent with the assumption that an underuse of intensive secondary prevention measures such as EBM may contribute to the higher long-term mortality in the ST-segment depression and BBB group. This would underline the importance of intensive secondary prevention measures especially in these NSTEMI groups. Nevertheless, further studies are necessary to precisely investigate the underlying associations.

5. Strengths and limitations

This study is characterized by some particular strengths. First to mention is the high number of included cases from a population-based registry with consecutive enrollment, which reduces the risk of selection bias. For the long-term analysis the post-event observation period was higher than in most comparable studies (median Follow-up time of 6.7 years). In addition to information on the actual event, a large number of sociodemographic data, risk factors, comorbidities and information on in-hospital complications and treatment was collected for each case. This extensive data set allowed multivariable adjustment for the COX regression model. The fine distinction in the assessment of admission ECG was performed by physicians and allowed a more specific sub-classification than the commonly used distinction of AMI cases (STEMI vs. NSTEMI).

There are some limitations to our study as well. Since only patients up to 74 years (2000 until 2008) and up to 85 years (2009 until 2017) were included, results cannot be applied to older patients especially in regards to long-term mortality. In the almost two decades of case recording (18 years), processes and standards in diagnostics and treatment of AMI patients have changed considerably, which might have affected the validity of the results. Furthermore, our findings may not be generalizable to all ethnic groups since no information on ethnicity was available. Moreover, we might not have considered all relevant confounders (in the sense of residual confounding) and cannot exclude possible reverse causation.

6. Conclusion

Although STEMI cases have higher peak CK-MB values and so presumably go along with higher myocardial damage, having survived the first 28 days, their long-term mortality is not higher than for the majority of NSTEMI events. Patients with ST-segment depression or BBB NSTEMI even face a multifactorial higher long-term mortality risk, which physicians must be aware of. Therefore, especially these patients should be offered intensive secondary prevention measures and close follow-up in clinical practice. Furthermore, respective trials should prespecify this high-risk subgroup to identify specific therapeutic options to improve long-term survival.

Availability of data and materials

The data will not be shared. Due to restrictions from Helmholtz Zentrum München, data are available upon request for any researcher based on a standard agreement on data provision within the KORA Research Platform.

CRediT authorship contribution statement

Timo Schmitz: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Bastian Wein:** Funding acquisition, Writing – review & editing. **Heiko Methe:** Funding acquisition, Writing – review & editing. **Jakob Linseisen:** Funding acquisition, Writing – review & editing. **Margit Heier:** Funding acquisition, Writing – review & editing. **Annette Peters:** Funding acquisition, Writing – review & editing. **Christa Meisinger:** Conceptualization, Supervision, Writing – original draft, Funding acquisition, Methodology, Writing – review & editing.

Declaration of Competing Interest

None declared.

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Ethics approval and consent to participate

Data collection of the MONICA/KORA MI registry has been approved by the ethics committee of the Bavarian Medical Association (Bayerische Landesärztekammer) and the study was performed in accordance with the Declaration of Helsinki. All study participants have given written informed consent.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.03.009.

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