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

Timo Schmitz1, Bastian Wein2, Jakob Linseisen1,3, Margit Heier4,5, Annette Peters5,6, Christa Meisinger1

1Chair of Epidemiology, University of Augsburg, University Hospital Augsburg

2University Hospital of Augsburg, Department of Cardiology

3 IRG Clinical Epidemiology, Helmholtz Zentrum München

4University Hospital of Augsburg, KORA Study Centre

5Institute of Epidemiology, Helmholtz Zentrum München

6German Center for Diabetes Research (DZD) Neuherberg Germany

Correspondence to: Timo Schmitz, timo.schmitz@med.uni-augsburg.de

***Abstract***

***Background:*** Several prior studies examined differences in long-term mortality between ST-elevation myocardial infarctions (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and myocardial infarction associated with bundle branch blocks (BBB). Yet, observational periods are mostly short and there is no clear evidence on different ECG changes within the NSTEMI group and whether they have different predictive values regarding long-term outcome.

***Methods:*** From January 2000 until December 2017 all acute myocardial infarction (AMI) cases (n=9,689) in the study area of Augsburg, Germany, were prospectively recorded by the KORA myocardial infarction registry team. Median observational time was 6.7 years (IQR: 3.6-10.9). Each case was assigned to one of the following groups according to the presented admission ECG: `ST-elevation´, `ST-depression´, ` T-negativity´, `unspecific changes´, `normal ECG´ and `predominantly bundle branch block´. Multivariable adjusted COX regression models were calculated to compare long-term all-cause mortality between the ECG groups.

***Results:*** The final regression model revealed a significantly higher mortality among patients with `bundle branch block´ (HR: 1.49 [1.31-1.69]) and `ST-depression´ (HR: 1.15 [1.03-1.29]) compared to the STEMI group (reference group). The `normal ECG´ group (HR: 0.74 [0.65-0.86) on the other hand was associated with significantly lower long-term mortality. The `T-negativity´ group (HR: 1.07 [0.96-1.21]) and the `unspecific changes´ group (HR: 1.05[0.94-1.17]) did not differ significantly from the STEMI group.

***Conclusion:*** AMIs without classical ST-elevations are not per se less severe events in regards to long-term all-cause mortality and in some cases even go along with a higher mortality risk. This should be taken into account by physicians when treating patients with NSTEMIs. Only the complete absence of AMI-related ECG changes predicts a more favorable outcome.

***Keywords:*** *Myocardial infarction, admission ECG, long-term mortality*

***Introduction***

Acute myocardial infarctions (AMI) can be grouped into two main categories according to admission ECG: ST-Elevation myocardial infarction (STEMI) and non-ST-myocardial infarction (NSTEMI). STEMIs represent the primary type of AMIs. They are characterized by higher peak-CK-MB level [1,2], which is correlated with greater infarct size [3–8]. In spite of the greater infarct size, several prior studies found similar mid-to long-term mortality for STEMI and NSTEMI patients[1,9–12]. Beyond, there are actually some publications showing a better mid- to long-time survival for the STEMI group [13–17]. Nevertheless, observational periods of the most studies were limited to only a few years. This raises the question whether reported results remain stable even for longer follow-up periods.

Apart from the comparison of STEMI vs. NSTEMI, the NSTEMI group can be further split up in several subgroups according to ECG. Some researchers did so und examined differences in outcomes for certain ECG changes within the NSTEMI group [18–22]. 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 pretty weak. Hence, this study aimed to contribute to the knowledge on these scientific questions.

***Material and Methods***

***Patients***

The underlying data for this research was collected by the Augsburg Myocardial Infarction Registry. It was established in 1984 as a part of the MONIKA-project (Monitoring Trends and Determinants in Cardiovascular disease). 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 hours after hospital admission and had its primary residence within the study area. Trained study nurses carried out interviews using standardized questionnaire during the hospital stay. Further data collection was done by elaborating the patient´s 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. Mortality Follow-ups were performed regularly in order to keep data on long-term survival of patients up to date. Therefore, necessary information was obtained from the regional registration offices and health offices. For this study, the last extensive mortality follow-up update was performed in 2019. More detailed information on data collection is available in previous publications [23,24]. 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 incident 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. Figure 1 provides a flow chart 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 [25].

**Figure 1:** *Flow Charts displaying all inclusions and exclusions.*



Admission ECG was evaluated by clinical physicians. Each case with available admission ECG was allocated to one of six groups according to the following principle: If there were significant ST-elevations identified, then this case was assigned to the STEMI group regardless of any other changes. Significant ST-elevations were defined as new ST-segment elevations at the J point in 2 or more contiguous leads greater than 0.1 mV. For the remaining cases, they were classified as `ST-Depression´ group if significant ST-Depression was found in the admission ECG regardless of further changes. The now remaining cases with T-negativity in 2 or more contiguous leads were assigned to the `T-negativity´ group. The leftover cases then 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-negativity, poor R wave progression or comparable changes. The ‘bundle branch block’ (BBB) group consisted of all cases with right or left bundle branch with missing changes as mentioned above or bundle branch blocks with such great extent, that it impossible to properly asses ST-segment and T wave changes.

Estimated GFR was calculated by admission creatinine levels according to the CKD-EPI formula. Four categories were defined: normal renal function (eGFR > 60 ml/min/1.73m²), slightly impaired renal function (eGFR between 30 and 60 ml/min/1.73m²), heavily impaired renal (eGFR < 30 ml/min/1.73m²) and no information on renal function (values for creatinine levels were only available since 2005).

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).

***Statistical Analysis***

Baseline characteristics are presented as total number and percentages for categorical variables, and as median and interquartile range for continuous variables. To determine differences in baseline characteristics, Chi2 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, cook´s distance was calculated for each variable. Extreme outliers were identified by visually evaluating the plots of the cook´s 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 ≤ 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. The final model was then 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 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.

***Results***

Of 9,689 patients included, 7027 (72.5%) were men. Mean age was 63.4 (SD: 11.2) years. 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.

***Table 1:*** *Case distribution and number of events by ECG group*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | *Total sample* | *STEMI* | *ST-De-pression* | *T-nega-tivity* | *unspecific changes* | *normal ECG* | *Bundle branch block* |
| *Number of incident cases (%)* | 9,689 (100%) | 3,697 (38.2%) | 1,110 (11.5%) | 1,282 (13.2%) | 1,676 (17.3%) | 1,242 (12.8%) | 682 (7.0%) |
| *Number of deaths within each group (%)* | 3,180(32.8%). | 1,018 (27.5%) | 528 (47.6%) | 462 (36.0%) | 560 (33.4%) | 252 (20.9%) | 360 (52.8%) |

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.

***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 median (IQR).*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | ***STEMI*** | ***ST-Depression*** | ***T-negativity*** | ***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 (mean (SD))* | 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) | - |  |
| ***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* | 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 (mean (SD))* | 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 |
| *any in-hospital complication* | 788 (21.3) | 144 (13) | 135 (10.5) | 199 (11.9) | 109 (8.8) | 129 (18.9) | < 0.001 | 9689 |
| ***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) | - |  |
| ***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) | - |  |
| ***Laboratory value*** |
| *peak CK-MB (U/L)* | 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)* | 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)* | 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)* | 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 therapy* | 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 |
| *all four evidence based medications* | 2889 (78.1) | 724 (65.2) | 874 (68.2) | 1137 (67.8) | 864 (69.6) | 433 (63.5) | < 0.001 | 9689 |

Figure 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-Depression´, `T-negativity´ 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 parsimonious COX 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. After full adjustment, `T-negativity´ and `unspecific changes´ were no longer significantly associated with long-term mortality. However, `ST-Depression´ and `Bundle branch block´ remained being independent predictors of a higher long-term mortality. Contrary, `normal ECG´ predicted a more favorable long-term outcome also in the final COX model (see Table 3).

***Figure 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-depression*** | *1.99* *[1.79-2.21]* | *< 0.001* | *1.58* *[1.42-1.76]*  | *< 0.001* | *1.15* *[1.03-1.29]* | *0.014617* |
| ***T-negativity*** | *1.35* *[1.21-1.51]* | *< 0.001* | *1.20* *[1.07-1.34]*  | *0.001275* | *1.07* *[0.96-1.21]* | *0.217410* |
| ***unspecific changes*** | *1.47* *[1.33-1.64]* | *< 0.001* | *1.27* *[1.15-1.41]* | *< 0.001* | *1.05**[0.94-1.17]* | *0.425965* |
| ***normal ECG*** | *0.75* *[0.65-0.86]* | *< 0.001* | *0.74* *[0.64-0.85]* | *< 0.001* | *0.74* *[0.65-0.86]* | *< 0.001* |
| ***Bundle branch block*** | *2.78 [2.46-3.13]* | *< 0.001* | *1.95**[1.73-2.21]*  | *< 0.001* | *1.49* *[1.31-1.69]* | *< 0.001* |

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

***Discussion***

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

For this analysis only patient with an incident myocardial infarction were included. Former myocardial infarction can cause persisting ECG changes [26], which leads to the situation that it can´t be distinguished between old changes due to prior events and changes caused by the current infarction.

With about 38% of all cases included in the long-term analysis the STEMI group was the largest of the 5 ECG groups. While STEMI´s went along with the highest peak-CK-MB levels, the other groups had comparable peak-CK-MB values. Prior studies found higher CK-MB levels for STEMI cases as well [1,2]. It is suspected, that this is associated with higher myocardial damage caused by hypoxia [3–8]. Nevertheless, peak CK-MB did not reach significance in a COX model together with ECG and so did not make it into the final model. Interestingly, the higher peak-CK-MB values in STEMI patients didn´t go along with higher percentages of impaired left ventricular function (EF ≤ 30%) in our data. In contrast, other studies found reduced EF in STEMI patients compared to patients with NSTEMI [9]. AMI patients presenting predominantly with bundle branch block had the highest percentage of impaired left-ventricular EF and was present about twice as often as in any other group.

***Long-term mortality***

Conventionally, groups of `ST-depression´, `T-negativity´, `unspecific changes´ and `normal ECG´ are subsumed as NSTEMI events. In this study, one of these groups was associated with higher (`ST-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 [1,9–11]. Nevertheless, there are also studies that found better mid- to long-term survival for the STEMI group [12–16]. 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 [27]. They have found a worse short- and long-term prognosis for STEMI´s compared to NSTEMI´s and so contradicting results than several other studies. When they had a look on survival rates from 6 months to 4 years, they found NSTEMI´s 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.

Since ST-elevations are very common changes in AMI, it simplifies the diagnostic process and leads to faster and more reliable diagnosis of AMI [9]. Because of this and since ST-segment elevations are a class I indication for a primary PCI strategy [28], it is not surprising, that in this study PCI treatment was most 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 [12,29]. In-hospital cardiac catheterization is known to be associated with lower mortality, especially in high risk patient [13,30,31]. 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. These factors (faster diagnosis, more frequent PCI, younger age) 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 years) after AMI or acute coronary syndrome (ACS). Two studies from Atar et al.[18]. and Yan et al. [32] found that specific ST-Depressions went along with higher 1-year mortality among NSTMI patients. Similar results are reported by two further studies [22,33]. 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-Depressions in 367 patients with ACS [21]. 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-Depression or T-Negativity [21]. 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 [25], 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 [14,34–38]. BBB’s are often the result of an ongoing process of degeneration like left ventricular hypertrophy, CAD or valvular heart disease [39,40]. 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 [40]. 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 [41]. 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.

***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 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, why 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.

***Conclusion:*** Although STEMI cases have higher peak CK-MB values and so presumably go along with higher myocardial damage, long-term mortality is not higher than for the majority of NSTEMI events. So regarding long-term mortality, NSTEMI cases in general are not less severe cases in comparison to STEMIs and generally must be taken as seriously as STEMI events. Nevertheless, there are distinct differences within the NSTEMI group. BBB is associated with the highest long-mortality compared to all other NSTEMI subgroups and also in comparison to STEMI events. `Normal ECG´ on the other hand is associated with lowest long-term mortality among all groups, which implies that the absence of AMI-related ECG changes predict a more favorable long-term outcome. These differentiations in risk assessment should be taken into account by physicians when treating AMI patients with different admission ECG presentations.

***Acknowledgments:*** We would like to thank all members of the Helmholtz Zentrum München, Institute of Epidemiology and the field staff in Augsburg who were involved in the planning and conduct of the study. Many thanks for their support go to the local health departments, the office-based physicians and the clinicians of the hospitals within the study area. Finally, we express our appreciation to all study participants.

***Authors´ contribution:*** TS and CM conceived the study. TS performed the statistical analysis and drafted the manuscript. CM supervised data analysis and manuscript drafting. CM was responsible for the acquisition of the data and contributed to the interpretation of data. JL, BW, MH and AP contributed to data acquisition and revised the manuscript. All authors approved the final manuscript.

***Competing interest:*** The authors declare that they have no competing interests.

***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.

***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.

***Funding***: This work was supported by the Helmholtz Zentrum München, German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education, Science, Research and Technology and by the State of Bavaria and the German Federal Ministry of Health.

### ***List of abbreviations:***

ANOVA: analysis of variance

AMI: Acute myocardial infarction

BBB: Bundle branch block

CAD: coronary artery disease

CK-MB levels: peak creatine kinase-MB levels

CRP: C-reactive protein

EBM: all four evidence based medications at discharge

ECG: electrocardiogram

EF: left-ventricular ejection fraction

eGFR: estimated glomerular filtration rate

IQR: Inter quartile range

NSTEMI: non-ST-elevation myocardial infarction

PCI: percutaneous coronary intervention

SD: Standard deviation

STEMI: ST-elevation myocardial infarction

References

[1] H. Yaku, H. Shiomi, T. Morimoto, Y. Yamashita, Y. Furukawa, Y. Nakagawa, K. Ando, K. Kadota, M. Abe, M. Shinji, S. Shizuta, K. Ono, T. Kimura, Comparison of short- and long term mortality between ST-segment elevation and non-ST-segment elevation myocardial infarction, Journal of the American College of Cardiology 67 (2016) 50.

[2] C.T. Chin, T.Y. Wang, S. Li, S.D. Wiviott, J.A. deLemos, M.C. Kontos, E.D. Peterson, M.T. Roe, Comparison of the prognostic value of peak creatine kinase-MB and troponin levels among patients with acute myocardial infarction: a report from the Acute Coronary Treatment and Intervention Outcomes Network Registry-get with the guidelines, Clinical cardiology 35 (2012) 424–429.

[3] T. Dohi, A. Maehara, S.J. Brener, P. Généreux, A.H. Gershlick, R. Mehran, C.M. Gibson, G.S. Mintz, G.W. Stone, Utility of peak creatine kinase-MB measurements in predicting myocardial infarct size, left ventricular dysfunction, and outcome after first anterior wall acute myocardial infarction (from the INFUSE-AMI trial), The American journal of cardiology 115 (2015) 563–570.

[4] E. Hedström, K. Aström-Olsson, H. Ohlin, F. Frogner, M. Carlsson, T. Billgren, S. Jovinge, P. Cain, G.S. Wagner, H. Arheden, Peak CKMB and cTnT accurately estimates myocardial infarct size after reperfusion, Scandinavian cardiovascular journal SCJ 41 (2007) 44–50.

[5] T. Hashimoto, H. Kambara, T. Fudo, S. Tamaki, R. Nohara, Y. Takatsu, R. Hattori, S. Tokunaga, C. Kawai, Early estimation of acute myocardial infarct size soon after coronary reperfusion using emission computed tomography with technetium-99m pyrophosphate, The American journal of cardiology 60 (1987) 952–957.

[6] A.T. Turer, K.W. Mahaffey, D. Gallup, W.D. Weaver, R.H. Christenson, N.R. Every, E.M. Ohman, Enzyme estimates of infarct size correlate with functional and clinical outcomes in the setting of ST-segment elevation myocardial infarction, Current controlled trials in cardiovascular medicine 6 (2005) 12.

[7] S. Chia, F. Senatore, O.C. Raffel, H. Lee, F.J.T. Wackers, I.-K. Jang, Utility of cardiac biomarkers in predicting infarct size, left ventricular function, and clinical outcome after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction, JACC. Cardiovascular interventions 1 (2008) 415–423.

[8] P. Pöyhönen, M. Kylmälä, P. Vesterinen, S. Kivistö, M. Holmström, K. Lauerma, H. Väänänen, L. Toivonen, H. Hänninen, Peak CK-MB has a strong association with chronic scar size and wall motion abnormalities after revascularized non-transmural myocardial infarction - a prospective CMR study, BMC cardiovascular disorders 18 (2018) 27.

[9] D.A. Cox, G.W. Stone, C.L. Grines, T. Stuckey, P.J. Zimetbaum, J.E. Tcheng, M. Turco, E. Garcia, G. Guagliumi, R.S. Iwaoka, R. Mehran, W.W. O'Neill, A.J. Lansky, J.J. Griffin, Comparative early and late outcomes after primary percutaneous coronary intervention in ST-segment elevation and non-ST-segment elevation acute myocardial infarction (from the CADILLAC trial), The American journal of cardiology 98 (2006) 331–337.

[10] V. Bongard, J. Ferrieres, J. Dallongeville, M. Moitry, M. Montaye, B. Haas, J.B. Ruidavets, P3635Comparison of short-term and long-term mortality between patients with ST- and non ST-segment elevation myocardial infarction in three French population registries of myocardial infarction, European heart journal 38 (2017).

[11] A. Marceau, J.-M. Samson, N. Laflamme, S. Rinfret, SHORT AND LONG-TERM MORTALITY AFTER STEMI VERSUS NON-STEMI: A SYSTEMATIC REVIEW AND META-ANALYSIS, Journal of the American College of Cardiology 61 (2013) E96.

[12] G. Montalescot, J. Dallongeville, E. van Belle, S. Rouanet, C. Baulac, A. Degrandsart, E. Vicaut, STEMI and NSTEMI: are they so different? 1 year outcomes in acute myocardial infarction as defined by the ESC/ACC definition (the OPERA registry), European heart journal 28 (2007) 1409–1417.

[13] M.Y. Chan, J.L. Sun, L.K. Newby, L.K. Shaw, M. Lin, E.D. Peterson, R.M. Califf, D.F. Kong, M.T. Roe, Long-term mortality of patients undergoing cardiac catheterization for ST-elevation and non-ST-elevation myocardial infarction, Circulation 119 (2009) 3110–3117.

[14] C.J. Terkelsen, J.F. Lassen, B.L. Nørgaard, J.C. Gerdes, T. Jensen, L.B.-H. Gøtzsche, T.T. Nielsen, H.R. Andersen, Mortality rates in patients with ST-elevation vs. non-ST-elevation acute myocardial infarction: observations from an unselected cohort, European heart journal 26 (2005) 18–26.

[15] C.E. Darling, K.A. Fisher, D.D. McManus, A.H. Coles, F.A. Spencer, J.M. Gore, R.J. Goldberg, Survival after hospital discharge for ST-segment elevation and non-ST-segment elevation acute myocardial infarction: a population-based study, Clinical epidemiology 5 (2013) 229–236.

[16] K.C. Nikus, M.J. Eskola, V.K. Virtanen, J. Harju, H. Huhtala, J. Mikkelsson, P.J. Karhunen, K.O. Niemelä, Mortality of patients with acute coronary syndromes still remains high: a follow-up study of 1188 consecutive patients admitted to a university hospital, Annals of medicine 39 (2007) 63–71.

[17] D.D. McManus, J. Gore, J. Yarzebski, F. Spencer, D. Lessard, R.J. Goldberg, Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI, The American journal of medicine 124 (2011) 40–47.

[18] S. Atar, Y. Fu, G.S. Wagner, S. Rosanio, A. Barbagelata, Y. Birnbaum, Usefulness of ST depression with T-wave inversion in leads V(4) to V(6) for predicting one-year mortality in non-ST-elevation acute coronary syndrome (from the Electrocardiographic Analysis of the Global Use of Strategies to Open Occluded Coronary Arteries IIB Trial), The American journal of cardiology 99 (2007) 934–938.

[19] S. Savonitto, D. Ardissino, C.B. Granger, G. Morando, M.D. Prando, A. Mafrici, C. Cavallini, G. Melandri, T.D. Thompson, A. Vahanian, E.M. Ohman, R.M. Califf, F. van de Werf, E.J. Topol, Prognostic value of the admission electrocardiogram in acute coronary syndromes, JAMA 281 (1999) 707–713.

[20] S. Savonitto, M.G. Cohen, A. Politi, M.P. Hudson, D.F. Kong, Y. Huang, K.S. Pieper, F. Mauri, G.S. Wagner, R.M. Califf, E.J. Topol, C.B. Granger, Extent of ST-segment depression and cardiac events in non-ST-segment elevation acute coronary syndromes, European heart journal 26 (2005) 2106–2113.

[21] T.A. Hyde, J.K. French, C.-K. Wong, I.T. Straznicky, R.M. Whitlock, H.D. White, Four-year survival of patients with acute coronary syndromes without ST-segment elevation and prognostic significance of 0.5-mm ST-segment depression, The American journal of cardiology 84 (1999) 379–385.

[22] C.Y. Shim, J.B. Kim, S.H. Choi, W.H. Kim, S.H. Park, Y.G. Ko, D.H. Choi, Y.S. Jang, N.S. Chung, W.H. Shim, S.Y. Cho, The Prognostic Significance of ST Segment Depression Score in Acute Non ST Elevation Myocardial Infarction, Korean Circ J 34 (2004) 1182.

[23] B. Kuch, M. Heier, W. von Scheidt, B. Kling, A. Hoermann, C. Meisinger, 20-year trends in clinical characteristics, therapy and short-term prognosis in acute myocardial infarction according to presenting electrocardiogram: the MONICA/KORA AMI Registry (1985-2004), Journal of internal medicine 264 (2008) 254–264.

[24] C. Meisinger, A. Hörmann, M. Heier, B. Kuch, H. Löwel, Admission blood glucose and adverse outcomes in non-diabetic patients with myocardial infarction in the reperfusion era, International journal of cardiology 113 (2006) 229–235.

[25] T. Schmitz, C. Thilo, J. Linseisen, M. Heier, A. Peters, B. Kuch, C. Meisinger, Admission ECG changes predict short term-mortality after acute myocardial infarction less reliable in patients with diabetes, Scientific reports 11 (2021) 6307.

[26] N.D. Wong, D. Levy, W.B. Kannel, Prognostic significance of the electrocardiogram after Q wave myocardial infarction. The Framingham Study, Circulation 81 (1990) 780–789.

[27] L. Ren, H. Ye, P. Wang, Y. Cui, S. Cao, S. Lv, Comparison of long-term mortality of acute ST-segment elevation myocardial infarction and non-ST-segment elevation acute coronary syndrome patients after percutaneous coronary intervention, International Journal of Clinical and Experimental Medicine 7 (2014) 5588–5592.

[28] B. Ibanez, S. James, S. Agewall, M.J. Antunes, C. Bucciarelli-Ducci, H. Bueno, A.L.P. Caforio, F. Crea, J.A. Goudevenos, S. Halvorsen, G. Hindricks, A. Kastrati, M.J. Lenzen, E. Prescott, M. Roffi, M. Valgimigli, C. Varenhorst, P. Vranckx, P. Widimský, 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC), European heart journal 39 (2018) 119–177.

[29] J. Knot, P. Kala, R. Rokyta, J. Stasek, B. Kuzmanov, O. Hlinomaz, J. Bĕlohlavek, F.P. Rohac, R. Petr, D. Bilkova, S. Djambazov, M. Grigorov, P. Widimsky, Comparison of outcomes in ST-segment depression and ST-segment elevation myocardial infarction patients treated with emergency PCI: data from a multicentre registry, Cardiovascular journal of Africa 23 (2012) 495–500.

[30] W.J. Cantor, S.G. Goodman, C.P. Cannon, S.A. Murphy, A. Charlesworth, E. Braunwauld, A. Langer, Early cardiac catheterization is associated with lower mortality only among high-risk patients with ST- and non-ST-elevation acute coronary syndromes: observations from the OPUS-TIMI 16 trial, American heart journal 149 (2005) 275–283.

[31] D. Acharya, Predictors of Outcomes in Myocardial Infarction and Cardiogenic Shock, Cardiology in review 26 (2018) 255–266.

[32] A.T. Yan, R.T. Yan, M. Tan, C.-M. Chow, D.H. Fitchett, A.A. Georgescu, Q. Hassan, J. Luchansky, A. Langer, S.G. Goodman, ST-segment depression in non-ST elevation acute coronary syndromes: quantitative analysis may not provide incremental prognostic value beyond comprehensive risk stratification, American heart journal 152 (2006) 270–276.

[33] C.P. Cannon, C.H. McCabe, P.H. Stone, W.J. Rogers, M. Schactman, B.W. Thompson, D.J. Pearce, D.J. Diver, C. Kells, T. Feldman, M. Williams, R.S. Gibson, M.W. Kronenberg, L.I. Ganz, H. Anderson, E. Braunwald, The Electrocardiogram Predicts One-Year Outcome of Patients With Unstable Angina and Non–Q Wave Myocardial Infarction: Results of the TIMI III Registry ECG Ancillary Study fn1fn1The TIMI III Clinical Centers are supported by Grant R01-HL42311 and the Data Coordinating Center by Grant R01-HL42428 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Additional support was supplied by Genentech, Inc., South San Francisco, California, Journal of the American College of Cardiology 30 (1997) 133–140.

[34] E.S. Brilakis, R. Wright, S.L. Kopecky, G.S. Reeder, B.A. Williams, W.L. Miller, Bundle branch block as a predictor of long-term survival after acute myocardial infarction, The American journal of cardiology 88 (2001) 205–209.

[35] A.T. Timóteo, T. Mendonça, S. Aguiar Rosa, A. Gonçalves, R. Carvalho, M.L. Ferreira, R.C. Ferreira, Prognostic impact of bundle branch block after acute coronary syndrome. Does it matter if it is left of right?, International journal of cardiology. Heart & vasculature 22 (2019) 31–34.

[36] J. Wang, H. Luo, C. Kong, S. Dong, J. Li, H. Yu, Y. Chu, Prognostic value of new-onset right bundle-branch block in acute myocardial infarction patients: a systematic review and meta-analysis, PeerJ 6 (2018) e4497.

[37] A. Melgarejo-Moreno, J. Galcerá-Tomás, L. Consuegra-Sánchez, N. Alonso-Fernández, Á. Díaz-Pastor, G. Escudero-García, L. Jaulent-Huertas, M. Vicente-Gilabert, E. Galcerá-Jornet, A. Padilla-Serrano, J. de Gea-García, E. Pinar-Bermudez, Relation of New Permanent Right or Left Bundle Branch Block on Short- and Long-Term Mortality in Acute Myocardial Infarction Bundle Branch Block and Myocardial Infarction, The American journal of cardiology 116 (2015) 1003–1009.

[38] B. al Rajoub, S. Noureddine, S. El Chami, M.H. Haidar, B. Itani, A. Zaiter, E.A. Akl, The prognostic value of a new left bundle branch block in patients with acute myocardial infarction: A systematic review and meta-analysis, Heart & lung the journal of critical care 46 (2017) 85–91.

[39] N.Y. Tan, C.M. Witt, J.K. Oh, Y.-M. Cha, Left Bundle Branch Block: Current and Future Perspectives, Circulation. Arrhythmia and electrophysiology 13 (2020) e008239.

[40] E. Surkova, L.P. Badano, R. Bellu, P. Aruta, F. Sambugaro, G. Romeo, F. Migliore, D. Muraru, Left bundle branch block: from cardiac mechanics to clinical and diagnostic challenges, Europace European pacing, arrhythmias, and cardiac electrophysiology journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 19 (2017) 1251–1271.

[41] O.A. Smiseth, J.M. Aalen, Mechanism of harm from left bundle branch block, Trends in cardiovascular medicine 29 (2019) 335–342.