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The prognostic significance of the electrical QRS axis on long-term mortality in acute coronary syndrome patients - The TACOS study

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ABSTRACT

Introduction: There are several potential causes of QRS-axis deviation in the ECG, but there is limited data on the prognostic significance of QRS-axis deviation in ACS patients.
Subjects and methods: We evaluated the long-term prognostic significance of acute phase frontal plane QRS-axis deviation and its shift during hospital stay in ACS patients. A total of 1026 patients who met the inclusion criteria were divided into three categories: normal ($n = 823$), left ($n = 166$) and right/extreme axis ($n = 37$).
Results: The median survival time was 9.0 years (95% CI 7.9—10.0) in the normal, 3.6 years (95% CI 2.4—4.7) in the left and 1.3 years (95% CI 0.2—2.4) in the right/extreme axis category. Both short and long-term all-cause mortality was lowest in the normal axis category and highest in the right/extreme axis category. Compared to normal axis, both admission phase QRS-axis deviation groups were independently associated with a higher risk of all-cause mortality. When including left ventricular hypertrophy in the ECG, only the right/extreme axis retained its statistical significance (aHR 1.76; 95% CI 1.16—2.66, $p = 0.007$). Axis shift to another axis category had no effect on mortality.
Conclusion: In ACS patients, acute phase QRS-axis deviation was associated with higher risk of all-cause mortality. Among the axis deviation groups, right/extreme QRS-axis deviation was the strongest predictor of mortality in the multivariable analysis. Further studies are required to investigate to what extent this association is caused by pre-existing or by ACS-induced axis deviations. QRS-axis shift during hospital stay had no effect on all-cause mortality.

Introduction

The electrical QRS axis represents the direction of the mean QRS vector in the frontal plane, and it is determined using the hexaxial reference system derived from the Einthoven equilateral triangle [1]. A deviation from the normal range of the QRS axis in the frontal plane can be due to many causes, such as fascicular or bundle branch blocks, ischemic or infarcted myocardium, ventricular hypertrophy or ventricular strain [2–5]. Some of these conditions are pre-existing, while others can be caused by rapidly emerging etiologies, such as myocardial infarction, pulmonary embolism or acute valvular dysfunction.

Fascicular blocks may mask Q waves of myocardial infarction, but on

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the other hand, Q waves may mask fascicular blocks [6]. There is limited published data regarding the prognostic significance of the QRS axis in the presenting ECG in acute coronary syndrome (ACS), and even less is known about the clinical significance of changes in the QRS axis during hospital stay.

Our aim was to investigate the prognostic significance of the acute phase frontal plane QRS axis and its possible shift during hospitalization on the long-term mortality of ACS patients.

Material and methods

A detailed description of the original research settings has been published earlier [7]. Briefly, the Tampere Acute Coronary Syndrome (TACOS) study included consecutive patients from Tampere University Hospital with a diagnosis of ACS. Overall, 1188 patients with ST-elevation myocardial infarction (STEMI) ($n = 343$), non-ST-elevation myocardial infarction (NSTEMI) ($n = 655$) or unstable angina ($n = 190$) were included during the study period 1.1.2002–31.3.2003. The criteria and methods for the classification of ACS groups were described earlier [7]. For the present study, follow-up was set to begin on the day of a patient's first ECG recording used for analysis, and it ended at death or at the end of follow-up – March 31st 2013. The mortality data was gathered by linking the personal identity code from the TACOS study to the Causes of Death register, maintained by Statistics Finland, which records 100% of deaths of Finnish citizens at home and nearly 100% abroad.

The study complies with the Declaration of Helsinki. The Ethics Committee of the Pirkanmaa Hospital District approved the study protocol (Permission R02100). All subjects gave their written informed consent for participation.

ECG analysis

For this study, all the ECGs were analyzed by one investigator (OP) to determine the electrical QRS axis. The admission ECGs were recorded in the referring health care unit, on-site by the emergency care personnel or in the hospital. The ECGs were recorded by ECG machines used by the respective units. In all cases, standard ECG electrode placement was used. According to clinical routine during the study, the discharge ECG was recorded on the last day of the hospital stay in most patients. In some patients ($n = 103$ cases), it was impossible to define the last ECG (discharge ECG) during hospital stay because of missing recording dates from the photocopies of original ECGs; in these cases, an ECG with the last identifiable recording date was used as discharge ECG for 44 patients. In the remaining ($n = 59$) cases, it was impossible to define the discharge ECG due to the following reasons: 1) all ECGs had the same recording date as the admission ECG ($n = 29$), 2) only one ECG was available ($n = 27$) or 3) the death occurred on the day of hospital arrival ($n = 3$).

ECG's included in the study were required to display electrical impulse conduction from the atrium to ventricles through the AV-node, thus attempting to standardize the frontal plane electrical QRS axis. Patients with their admission and discharge ECG's showing either sinus rhythm (SR, $n = 787$), or atrial fibrillation (AF, $n = 239$) were included. Atrial fibrillation was included since this dysrhythmia does not alter the electrical impulse conduction system and frontal plane electrical QRS axis. A total of 78 patients were excluded because at least one of the analyzed ECG's showed arrhythmias, such as pacemaker rhythm or grade III atrio-ventricular block, which could alter the frontal QRS axis. Eleven patients were excluded due to the fact that the QRS axis could not be measured on one or both of the analyzed ECG's.

We used the Minnesota code 7–1–1 to define left bundle branch block (LBBB) and the code 7–2–1 to define right bundle branch block (RBBB) [8]. For left anterior fascicular blocks (LAFB) we used the following definition: frontal QRS axis between $-30°$ and $-90°$, rS configuration in II, III and aVF, and qR configuration in aVL, with a QRS duration less than 120 ms [9]. Left posterior fascicular block (LPFB) was defined as frontal QRS axis $> 120°$, lead I rS configuration, leads II, III and aVF qR configuration, and no pathological Q waves in leads II, III, and aVF [9]. A total of 162 patients fulfilled the criteria for bundle branch block or fascicular block.

The presence of left ventricular hypertrophy (LVH) in the ECG (ECG-LVH) was analyzed using both the Sokolow-Lyon and Cornell voltage-duration product criteria [10,11]. Patients fulfilling at least one of these ECG-LVH criteria were categorized to the LVH group. In 152 patients, LVH could not be assessed mainly due to a wide QRS complex.

The preferred value for the frontal QRS axis was the value provided by the automatic analysis system of the ECG machines. The validity of the automatic measurement was verified by the investigator. In cases of illegibility, such as loss of the automatic calculations in the processing of photocopied ECGs, manual analysis of the QRS axis was executed. The manual analysis was conducted by identifying the isoelectric frontal QRS axis lead and calculating the mathematically correct QRS axis direction perpendicular to it.

Electrical QRS axis group classification

The ECGs were divided into three categories based on the QRS axis on the admission and discharge ECG's with the following method: 1) Normal QRS axis, range $+90°$ — -29°, 2) Left QRS axis, range $-30°$ — -90°, 3) Right & Extreme QRS axis, range $-91°$ — $+91°$. In the literature, the hexaxial reference system separates the extreme axis deviation group (range $-91°$ — -180°) as its own category. Because of the small number of patients in the right and extreme axis categories, we decided to combine the two categories into one.

Categorization based on the change of the frontal QRS axis between the discharge and admission ECG's was constructed as follows: 1) QRS axis shift 0 — $+30°$, 2) QRS axis shift $> +30°$, 3) QRS axis shift $-1°$ — $-30°$, 4) QRS axis shift $< -30°$.

Of the original 1188 patients, 1026 patients were included in the final analysis. Along with the 59 patients, who were excluded because only one ECG was available for analysis and the 78 patients with arrhythmias precluding analysis, we excluded 25 patients due to missing data, including the absence of both ECG recordings or unmeasurable QRS-axis in one or both ECGs.

Statistical analysis

Continuous variables were presented with median and Q_1-Q_3 range, while categorical variables were presented with numerical values or percentages. Unpaired *t*-test was used for parametric and Mann-Whitney *U* test for non-parametric continuous variables. Chi-Square was applied for the categorical variables. If its assumptions were violated, Fisher's exact test was used instead. A p-value <0.05 was considered statistically significant and 95% confidence intervals (CI) were used. Unadjusted survival data was presented with Kaplan-Meier curves. The adjusted hazard ratios (aHR) were calculated using Cox Regression analysis. In the two-step multivariable analysis, the axis categories were first adjusted for age, hypertension, systolic and diastolic blood pressure, gender, diabetes, ACS category, revascularization during hospital stay, previous revascularization, previous acute myocardial infarction, and creatinine level. As a second step, we added ECG-LVH as an additional variable in the multivariable analysis. Of the 1026 patients, in-hospital data on ejection fraction was available in 492 cases, of which 401 belonged to the sinus rhythm group. Due to missing data in a large proportion of patients, ejection fraction was not included in the multivariable analysis. All computations were carried out with SPSS 26.0.

Results

The baseline characteristics of the different admission phase frontal QRS-axis categories are shown in Table 1. From all of the included

Table 1
Baseline characteristics, medication at hospital admission and discharge, angiography findings, proportion of invasive coronary procedures and in-hospital laboratory results in different axis categories.

	Valid cases	Normal axis (n = 823)		Left axis (n = 166)		Right or extreme axis (*n* = 37)		p-value
		N/median	%/(Q_1-Q_3)	N/median	%/(Q_1-Q_3)	N/median	%/(Q_1-Q_3)	
Age	1026	72	(62–79)	75	(67.75–82.25)	76	(65–80)	0.001
Female Gender	1026	338	41.1	71	42.8	13	35.1	0.692
Active smoking	943	159	20.9	21	14.4	7	19.4	0.195
Ex-smoker	736	270	45.5	54	47.0	15	55.6	0.576
Diabetes mellitus	1024	197	24.0	46	27.7	11	29.7	0.467
Previous PCI or CABG	1011	102	12.6	25	15.2	3	8.1	0.457
Previous MI	1011	187	23.1	47	28.5	14	37.8	0.055
LVH	874	161	23.0	31	22.0	5	15.2	0.565
ACS classification	1026							0.731
STEMI		251	30.5	49	29.5	10	27.0	
NSTEMI		445	54.1	96	57.8	23	62.2	
UAP		127	15.4	21	12.7	4	10.8	
CCS class	918							0.472
0		392	52.8	82	57.3	21	63.6	
1–2		263	35.4	50	35.0	9	27.3	
3–4		87	11.7	11	7.7	3	9.1	
Angiography in hospital	1026	363	44.1	50	30.1	6	16.2	<0.001
Number of diseased vessels[a]	495							0.485
< 50% stenosis		53	12.4	9	15.5	0	0.0	
1-vessel disease		129	30.1	19	32.8	1	12.5	
2-vessel disease		105	24.5	16	27.6	2	25.0	
3-vessel disease		142	33.1	14	24.1	5	62.5	
Left main disease[a,b]	495	34	7.9	4	6.9	1	12.5	0.637
PCI in hospital	1026	135	16.4	16	9.6	3	8.1	0.041
CABG in hospital	1026	89	10.8	12	7.2	1	2.7	0.121
Revascularization in hospital	1026	222	27.0	28	16.9	4	10.8	0.003
Medication at admission:								
ASA	1023	366	44.6	68	41.0	17	45.9	0.668
Beta-blocker	1024	411	50.1	83	50.0	16	43.2	0.718
Nitrate	1024	385	46.9	80	48.2	19	51.4	0.839
Calcium-antagonist	1024	168	20.5	33	19.9	8	21.6	0.969
Digitalis	1025	82	10.0	36	21.7	6	16.2	<0.001
Diuretic	1024	245	29.8	74	44.6	16	43.2	<0.001
ACE-inhibitor	1023	167	20.3	39	23.6	6	16.2	0.501
ARB	1024	57	6.9	13	7.8	4	10.8	0.638
Statin	1025	185	22.5	40	24.1	4	10.8	0.208
Clopidogrel	1024	8	1.0	1	0.6	0	0.0	1.000
Warfarin	1025	84	10.2	28	16.9	5	13.5	0.045
Medication at discharge:								
ASA	918	600	80.4	101	71.6	21	67.7	0.021
Beta-blocker	919	672	90.0	131	92.9	26	83.9	0.269
Nitrate	917	440	59.1	87	61.7	19	61.3	0.825
Calcium-antagonist	916	117	15.7	25	17.9	2	6.5	0.288
Digitalis	918	81	10.9	27	19.1	5	16.1	0.018
Diuretic	918	318	42.6	74	52.5	19	61.3	0.017
ACE-inhibitor	918	285	38.2	65	46.1	12	38.7	0.212
ARB	916	72	9.7	14	9.9	3	9.7	0.996
Statin	914	476	64.1	75	53.6	13	41.9	0.005
Clopidogrel	915	27	3.6	5	3.5	4	12.9	0.033
Warfarin	915	133	17.9	37	26.4	10	32.3	0.013
Delay to ECG (minutes)	525	140	(80–270)	120	(79–333)	188	(90–353)	0.484
Systolic BP (mmHg)	1025	148	(129–170)	142	(124–166)	140	(118–163)	0.130
Diastolic BP (mmHg)	1025	80	(69–91)	80.5	(70–92)	80	(70–92)	0.805
Plasma creatinine (μmol/L)	1024	86	(71–106)	90	(75–120)	92	(77–123)	0.013
C-reactive protein (mg/L)	1008	4.1	(1.4–17.2)	4.9	(1.9–22.3)	10.6	(2.25–36.4)	0.032
First cTnI (μg/L)	1026	0.6	(0.0–3.8)	0.7	(0.0–6.525)	1.1	(0.2–4.2)	0.199
cTnI 6–12 h (μg/L)	1020	4.75	(0.6–25)	3.6	(0.5–24)	10.4	(0.85–43)	0.284
Ejection fraction	492	57	(45–70)	50	(40–65)	45	(40–60)	0.008

Values are described with median and Q_1–Q_3 range.
ACE = angiotensin-converting enzyme; ARB = Angiotensin receptor blocker; ASA = acetylsalicylic acid; BP = blood pressure; CABG = coronary artery bypass surgery; CCS = Canadian Cardiovascular Society; Delay to ECG = delay from symptom onset to baseline ECG recording; EF = ejection fraction; LVH = Left ventricular hypertrophy; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; Q1 = the first quartile; Q3 = the third quartile; UAP = unstable angina pectoris; First cTnl = cardiac troponin l at hospital admission; cTnl 6-12 h = cardiac troponin I 6–12 h after hospital admission. [a] *n* = 495; [b] = Includes patients with left main disease either isolated or in combination with 1-, 2- or 3-vessel disease.

patients, 823 (80.2%) presented with a normal QRS axis, 166 (16.2%) with a leftward axis and 37 (3.6%) with right or extreme axis in the acute phase. Compared to the patients with a normal QRS axis, those with a left or right/extreme QRS axis were older, more often had a history of a previous MI and also a higher rate of diuretic or digitalis medication usage both at admission and at hospital discharge. Patients with a normal QRS axis more often received revascularization in hospital, had a higher ejection fraction and a lower rate of oral anticoagulation use during both hospital admission and discharge compared with the patients with QRS-axis deviation. The patients with right or

extreme QRS axis had a higher level of cardiac troponin I in both the acute stage measurements compared with those from the other QRS-axis categories.

The median survival times for the admission phase normal, left and right or extreme QRS axis groups were 9.0 years (95% CI 7.9–10.0), 3.6 years (2.4–4.7) and 1.3 years (0.2–2.4), respectively. Similar results were found when analyzing the last recorded ECG during the hospital stay: 8.0 years, 4.9 years and 0.4 years, respectively. Short-term (30-day) mortality was 9.6% for the normal QRS axis category, 18.1% for the left axis category and 21.6% for the right or extreme axis category, whereas the 1-year mortality rates were 18.3%, 30.1% and 45.1%, respectively. The 5-year mortality rates for the normal, left and right or extreme QRS axis groups were 35.5%, 56.0% and 73.0%, whilst the 10-year mortality rates were 53.3%, 72.9% and 78.4%, respectively.

The Kaplan-Meier curve estimates for all-cause mortality within different admission phase QRS-axis categories are shown in Fig. 1. The most notable separation is seen within the first three years of the follow-up. The three survival curves stay clearly detached from each other for the whole follow-up time. Towards the end of follow-up, the gap between the normal and left axis group extends, while the gap between the left and right/extreme axis categories diminishes. The corresponding survival curves for the discharge phase QRS-axis categories are shown in Supplementary Fig. 1.

Regarding the survival rates within the three different ACS categories, the left and right or extreme QRS axis categories had higher all-cause mortality during the whole follow-up time compared to the normal QRS-axis category. The right or extreme QRS axis presented with the highest rate of all-cause mortality in both the STEMI and NSTEMI categories. Regarding the UAP category, no firm conclusions could be made due to the small number of cases with QRS axis deviation.

Axis change to another axis category during hospital stay was detected in 152 patients (14.8%). The distribution of axis shift was: 0 — +30° in 416 (40.5%) patients, >30° in 85 (8.3%) patients, −1 — -30° in 405 (39.5%) patients, and > −30° in 120 (11.7%) patients. The QRS-axis shift had no statistically significant effect on all-cause mortality (shown in Fig. 2, $p = 0.202$).

The results of the two-step multivariable analysis are shown in Tables 2A and 2B. Patients with bundle branch block or fascicular block were excluded ($n = 162$). Also, in 23 patients one or more variable was missing. Thus 841 patients were included in the final multivariable analysis. In the first analysis without adjusting for ECG-LVH, both left QRS axis (adjusted hazard ratio [aHR] 1.27; 95% CI 1.01—1.60, $p = 0.041$) and right or extreme QRS axis (aHR 1.81; 95% CI 1.22—2.70, $p = 0.003$) were independently associated with a higher rate of all-cause mortality when compared to patients with normal frontal plane QRS axis (Table 2A).

After including ECG-LVH in the multivariable analysis and excluding patients with no known LVH-categorization, only the right/extreme QRS axis was independently associated with a higher risk of all-cause mortality (aHR 1.76; 95% CI 1.16—2.66, $p = 0.007$) when compared to patients with normal frontal plane QRS axis (Table 2B).

The multivariable analyzes were also conducted for the discharge phase QRS axis categorization. The right/extreme QRS axis group retained its statistical significance on all-cause mortality for both multivariable adjustments while the left QRS axis group lost the statistical significance in both analyzes.

Discussion

In this study with patients from all the three ACS categories (UAP, NSTEMI, STEMI), both left and right/extreme QRS frontal axis deviation was associated with higher mortality compared with patients with a normal QRS axis. Both admission phase QRS axis deviation groups were independently associated with a higher risk of all-cause mortality when compared with a normal axis. However, after including ECG-LVH to the multivariable analysis, only right/extreme QRS axis retained its statistical significance on all-cause mortality. The ECG from the acute stage and the ECG closest to hospital discharge carried similar prognostic information for the right/extreme QRS axis group but not for the left QRS axis group. Axis shift from the ECG at hospital arrival to the discharge ECG did not carry any significant prognostic information.

Etiology of QRS-axis deviation

In most individuals without evident heart disease, the frontal plane QRS axis is located between −29° and + 90°. With advancing age, axis shift to the left is frequent, although the axis does not normally reach −30° [12]. In young, lean individuals, a mild axis shift to the right (vertical heart) is also a rather frequent finding [13]. Left axis deviation (≥ −30°) can be caused by LAFB, inferior MI, ventricular paced rhythm,

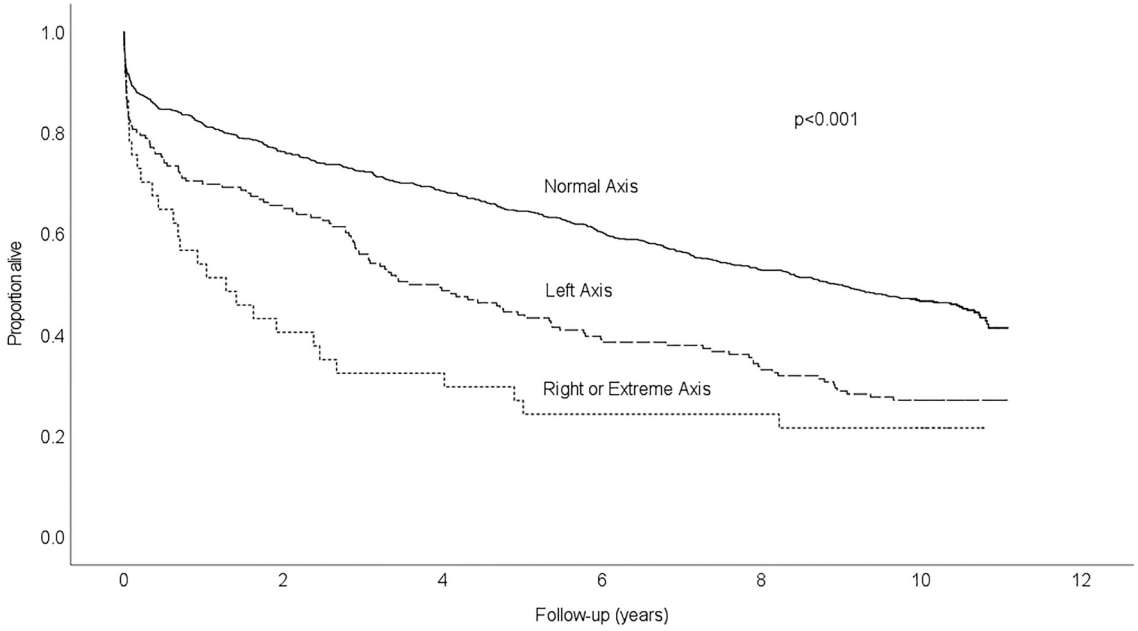

Fig. 1. Kaplan-Meier survival curves in the three admission phase QRS-axis categories.

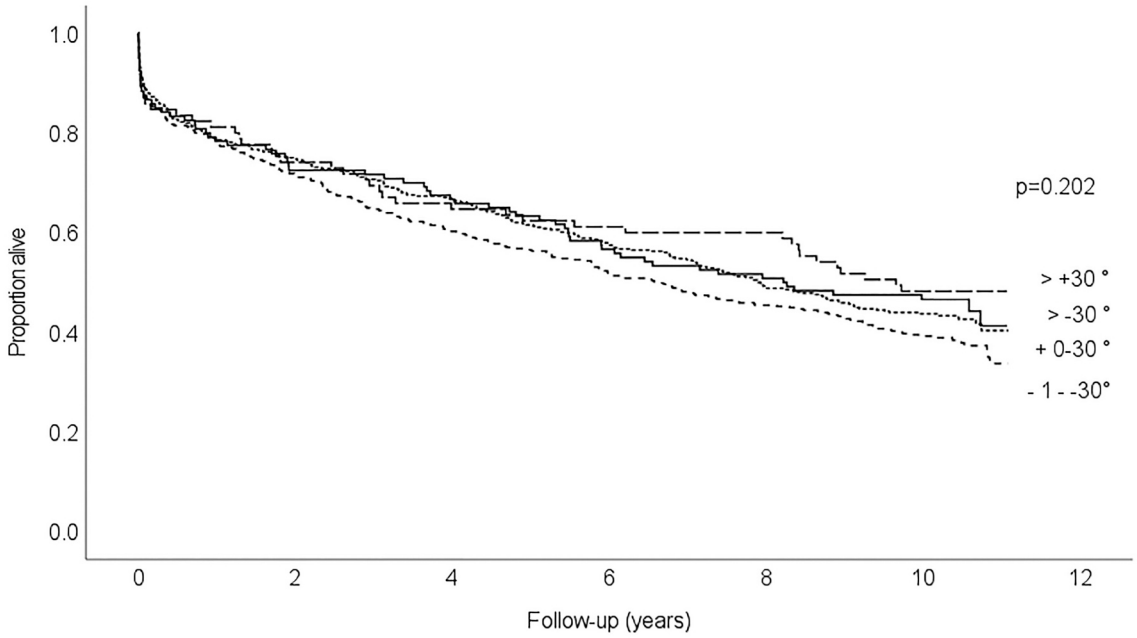

Fig. 2. Kaplan-Meier survival curves in the four QRS-axis shift categories.

Table 2A
Multivariable Cox regression analysis with all-cause mortality as the end point.

Variable	Valid cases	Adjusted Hazard Ratio	95% CI	p-value
Age	841	1.067	1.056–1.079	<0.001
Male gender	841	0.999	0.820–1.217	0.991
Diabetes	841	1.487	1.220–1.813	<0.001
Plasma creatinine (/10 μmol/L)[a]	841	1.033	1.019–1.047	<0.001
Hypertension	841	0.889	0.734–1.077	0.229
Systolic blood pressure	841	0.997	0.993–1.001	0.097
Diastolic blood pressure	841	0.813	0.994–1.008	0.682
History of myocardial infarction	841	1.259	1.024–1.549	0.029
Previous revascularization	841	0.925	0.690–1.240	0.601
PCI or CABG in hospital	841	0.590	0.454–0.768	<0.001
Category of ACS	841			<0.001
UAP	129	1		
STEMI	258	1.325	0.939–1.869	0.109
NSTEMI	454	1.822	1.337–2.483	<0.001
Admission phase QRS axis	841			<0.001
Normal	669	1		
Left	137	1.270	1.010–1.598	0.041
Right or Extreme	35	1.813	1.217–2.702	0.003

For abbreviations, see Table 1.
[a] For plasma creatinine, hazard ratio and confidence interval were calculated using values per 10 μmol/L.

Table 2B
Multivariable Cox regression analysis with all-cause mortality as the end point. LVH-variable included.

Variable	Valid cases	Adjusted Hazard Ratio	95% CI	p-value
Age	790	1.066	1.054–1.079	<0.001
Male gender	790	1.027	0.837–1.260	0.799
Diabetes	790	1.483	1.208–1.820	<0.001
Plasma creatinine (/10 μmol/L)[a]	790	1.031	1.017–1.046	<0.001
Hypertension	790	0.927	0.760–1.131	0.455
Systolic blood pressure	790	0.996	0.992–1.000	0.066
Diastolic blood pressure	790	1.001	0.994–1.009	0.682
History of myocardial infarction	790	1.322	1.067–1.639	0.011
Previous revascularization	790	0.882	0.651–1.196	0.419
PCI or CABG in hospital	790	0.582	0.443–0.765	<0.001
Left ventricular hypertrophy	790	0.865	0.688–1.087	0.214
Category of ACS	790			<0.001
UAP	122	1		
STEMI	242	1.292	0.909–1.838	0.154
NSTEMI	426	1.739	1.268–2.387	<0.001
Admission phase QRS axis	790			<0.001
Normal	629	1		
Left	128	1.259	0.991–1.599	0.059
Right or Extreme	33	1.760	1.163–2.664	0.007

For abbreviations, see Table 1.
[a] For plasma creatinine, hazard ratio and confidence interval were calculated using values per 10 μmol/L.

obesity (horizontal heart) or advanced LBBB with delayed transseptal depolarization in the superoanterior area [2]. Left axis deviation is also associated with disease states with left ventricular remodeling, such as valvular heart disease, cardiomyopathies and systolic heart failure. Long-term arterial hypertension causes left ventricular hypertrophy, which can lead to left axis deviation. In addition to the increase in left ventricular mass, the axis shift may also be caused by myocardial fibrosis affecting the distal parts of the left ventricular conduction pathways (Purkinje fibers), thereby altering the electrical conductivity [14]. Right axis deviation may be caused by right ventricular remodeling, lateral myocardial infarction, altered conduction pathways, or LPFB [15].

Intraventricular conduction disorders and QRS axis

In a hospital-based population, left axis deviation (−30° — -90°, QRS duration <110 ms) was associated with higher risk of all-cause death and major adverse cardiovascular events in multivariable analysis, while right axis deviation was not [16]. In heart failure patients treated with cardiac resynchronization therapy, both left and right axis deviation were independent predictors of poor prognosis [17]. Both left and right axis deviation in association with LBBB have been associated with an increased incidence of myocardial dysfunction, more advanced

conduction disease, and greater mortality compared with LBBB with a normal axis [18–20]. In LBBB patients, who underwent ECG recordings for any reason, an axis shift from normal to left axis deviation was associated with higher mortality during a 17-year follow-up period [21]. Left axis deviation was associated with heart failure. In patients with pulmonary hypertension, a frontal axis shift to the right was observed when comparing ECGs from the time of diagnosis to recordings close to death of the patients [22].

RBBB does not affect the frontal QRS axis, but in ACS, associated LAFB is a rather frequent finding, especially in proximal occlusion of the left anterior descending coronary artery (LAD) [23]. The reason for the frequent coexistence is the fact that both the right bundle branch and the left anterior fascicle receive their blood supply from proximal septal side branches [24]. The left posterior fascicle is a more robust structure than the anterior fascicle, and it receives its blood supply from two coronary systems (the LAD and the right coronary artery). The left posterior fascicle runs through a more protected area, the left ventricular inflow tract, with less mechanical pressure impact [25]. Therefore, both isolated LPFB and its association with RBBB are infrequent findings in ACS and also generally. Left septal fascicular block results in prominent anterior forces (high R waves) in the right precordial leads but does not affect the frontal QRS axis [26].

As in LAFB, inferior Q-wave MI may also result in left axis deviation [2]. Vectorcardiography may be necessary to differentiate between inferior Q-wave MI associated with LAFB and "pure" inferior MI [4]. However, QS morphology with notches in leads III and aVF is typically recorded in LAFB associated with MI, while a Qr morphology is frequently recorded in isolated inferior MI [6].

Bar et al. studied patients, who underwent cardiac catheterization for chest pain [5]. Almost half of the patients had suffered a previous MI at least three weeks before the invasive evaluation. Of the 204 patients with coronary artery disease based on angiographic findings, 177 (87%) had a normal frontal QRS axis, and 20 (10%) had left axis deviation. Right or indeterminate axis was found in only three and four subjects, respectively. Left axis deviation was strongly associated with left ventricular asynergy. The proportion of patients with left axis deviation was slightly lower than in the present study (166 patients, 16.2%).

QRS-axis shift in ACS patients

There are very scarce previous literature reports regarding the clinical significance of QRS-axis deviation or axis shift during hospital stay in ACS patients. In STEMI patients treated with thrombolytic therapy, the researchers found no correlation between infarct size (defined as CK-MB level) and change in the QRS axis between an ECG recorded before and 90 min after therapy [27]. The time interval was clearly shorter compared to our study. One could speculate that more than a few hours would be necessary for possible disease-associated remodeling associated with axis change to develop. However, in our study with a longer time between the two ECGs, the message from the study results was similar: no association was found between frontal QRS-axis shift and outcome.

According to our study definitions, right axis deviation included extreme axis deviation, which in turn includes the infrequent indeterminate axis ("Northwest axis", "No man's land"). Extreme axis deviation is defined as a frontal QRS axis between +180° and + 270° and has been associated with ventricular rhythms and severe right ventricular hypertrophy [28,29]. In a single-center retrospective study, the clinical significance of new-onset extreme axis deviation in ACS patients without bundle branch block was explored [30]. Out of the 30 patients, three quarters presented with acute STEMI, and the most frequent location was anterolateral. In our study population, only 10 out of the 37 patients with acute phase right/extreme QRS axis presented with STEMI. Accordingly, the LAD was the culprit artery in 70% of the patients, while half of the patients had multi-vessel disease. Cardiac arrest due to ventricular fibrillation at presentation, cardiogenic shock during the hospital stay and cardiac death (23.3%) were common. The authors speculated that the new-onset extreme right axis deviation may be related to extensive myocardial ischemia and/or necrosis. Also, they speculated that in some cases, patients with pre-existing left axis deviation could have undergone a further axis shift to the left ending up with an extreme axis between +180° and − 90°. The study was limited by the fact that it was descriptive — there was no reference group.

In patients with acute MI, Lewin et al. found LPFB in 0.41% and right axis deviation not fulfilling the criteria for LPFB in 1.8% of the patients. The patients with LPFB more often had heart failure and higher mortality rates compared with those without the conduction delay. [31]. Those who died had severe three vessel disease on autopsy, and those who survived remained symptomatic. Only the patients with acute right axis deviation lasting for more than 24 h had a higher incidence of symptoms. Right axis deviation without LPFB was most frequent in inferior MI, and mortality did not differ significantly from those without LPFB or right axis deviation.

In the study of acute MI patients by Hirano et al., culprit artery location in the left main coronary artery was associated with a clear frontal QRS axis shift to the left [32]. The average axis was −10°±77°, while in the patients with a LAD, left circumflex or right coronary artery culprit lesion, the average QRS axis was normal. In about one third of the patients with left main culprit, the ECG manifestation was RBBB with left axis deviation or "Northwest axis". In some patients, there was extreme left axis deviation up to −135°. However, more than half of the patients with the left main as the culprit artery manifested as anterior STEMI without axis deviation.

Ozdemir et al. found that 25 out of 172 (14.5%) acute MI patients developed LAFB [33]. LAD culprit and multivessel disease was more frequent and the ejection fraction was lower in the patients with LAFB compared to those without the conduction delay. However, coronary angiography was performed within two weeks, not in the acute stage in all patients, and the effect of LAFB on patient outcome was not studied.

We decided to combine the patients with milder right axis deviation and those with extreme axis deviation into one category because of the small number of patients in the both groups — the combined group consisted of 37 patients (3.6% of the whole study population). After adjusting for confounding factors this combined group of patients had the worst outcome both in the ECG from the acute phase and in the ECG closest to hospital discharge, when comparing with those with a normal QRS axis or left axis.

Limitations

No comparison with ECGs recorded before the acute coronary event was done. Therefore, we were not able to draw any conclusions about possible differences in prognosis between pre-existing QRS axis deviations and new axis deviation caused by the ACS. Due to small number of patients in both the right and extreme QRS-axis categories, these categories were combined. Data on ejection fraction during hospital stay was missing in a considerably large amount of patients, and we decided not to include this parameter in the multivariable analysis.

Conclusion

In ACS patients, both left and right/extreme QRS-axis deviation in the acute phase ECG was associated with higher all-cause mortality compared with a normal axis. Both admission phase QRS axis deviation groups were independently associated with a higher risk of all-cause mortality when compared with a normal axis. After including ECG-LVH in the multivariable analysis, only right/extreme QRS axis retained its statistical significance. Abnormal QRS axis should be considered as a high-risk feature in ACS patients, highlighting the importance of proper handling of background risk factors and of optimal therapy during the hospital stay and long term. Further studies are required to investigate to what extent this association is caused by pre-

existing or by ACS-induced axis deviations. Shift in the QRS axis during hospital stay had no statistically significant effect on all-cause mortality.

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Olli Punkka: Formal analysis, Investigation, Writing – original draft. **Henri-Jussi Kurvinen:** Formal analysis, Investigation, Writing – original draft. **Kimmo Koivula:** Writing – review & editing. **Markku J. Eskola:** Project administration, Resources, Supervision. **Mika Martiskainen:** Writing – review & editing. **Heini Huhtala:** Formal analysis, Validation, Writing – review & editing. **Vesa K. Virtanen:** Resources. **Jussi Mikkelsson:** Project administration, Resources. **Kati Järvelä:** Supervision, Writing – review & editing. **Jari Laurikka:** Supervision. **Kari O. Niemelä:** Project administration, Resources. **Pekka J. Karhunen:** Project administration, Resources, Writing – review & editing. **Andrés Ricardo Pérez-Riera:** Writing – review & editing. **Kjell C. Nikus:** Project administration, Conceptualization, Resources, Supervision, Writing – review & editing.

Declaration of Competing Interest

None.

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