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# Prospective validation of current quantitative electrocardiographic criteria for ST-elevation myocardial infarction

Petra Hillinger [a,b,1], Ivo Strebel [a,1], Roger Abächerli [a,c], Raphael Twerenbold [a], Karin Wildi [a,d], Denise Bernhard [a], Thomas Nestelberger [a], Jasper Boeddinghaus [a,e], Patrick Badertscher [a,f], Desiree Wussler [a,e], Luca Koechlin [a,g], Tobias Zimmermann [a,e], Christian Puelacher [a,e], Maria Rubini Gimenez [a], Jeanne du Fay de Lavallaz [a], Joan Walter [a], Nicolas Geigy [h], Dagmar I. Keller [i], Tobias Reichlin [a], Christian Mueller [a,*], for the APACE Investigators

[a] Department of Cardiology & Cardiovascular Research Institute Basel (CRIB), University Hospital Basel, University of Basel, Switzerland
[b] Department of Anesthesia and Intensive Care Medicine, University Hospital Innsbruck, University of Innsbruck, Austria
[c] Institute of Medical Engineering, Lucerne University of Applied Sciences and Arts, Horw, Switzerland
[d] Department of Anesthesia, Critical Care Research Group, The Prince Charles Hospital, Brisbane, Australia
[e] Department of Internal Medicine, University Hospital Basel, Switzerland
[f] Division of Cardiology, University of Illinois at Chicago, Chicago, United States
[g] Department of Cardiac Surgery, University Hospital Basel, Switzerland
[h] Emergency Department, Kantonsspital Liestal, Switzerland
[i] Emergency Department, University Hospital Zurich, Zurich, Switzerland

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ABSTRACT

*Background:* Rapid and reliable diagnosis of ST-elevation myocardial infarction (STEMI) as a surrogate for acute coronary occlusion is critical for early reperfusion therapy.
*Objectives:* We aimed to examine the diagnostic performance of current guideline-recommended Electrocardiogram (ECG) STEMI criteria.
*Methods:* In a prospective diagnostic multicenter study, we objectively quantified the extent of ST-segment elevation in all ECG leads using an automated software-based analysis of the digital 12-lead-ECG in adult patients presenting to the emergency department (ED) with suspected myocardial infarction (MI). Classification according to current guideline-recommended ECG criteria for STEMI at ED presentation was compared against a final diagnosis adjudicated by two independent cardiologists after reviewing all available medical records including serial ECGs, cardiac imaging and coronary angiograms.
*Results:* Among 2486 patients, 52 (2%) were found to have significant ST-segment elevation on ECG at ED presentation according to current guideline-recommended ECG criteria for STEMI. Eighty-one (3%) patients received a final adjudicated diagnosis of STEMI. Only 35% (28 of 81) of all patients with a final diagnosis of STEMI were correctly identified (PPV 54% (95% CI 41–66%), sensitivity 35% (95% CI 24–46%), NPV 97.8% (95% CI 97.5–98.1%). Four reasons for missing STEMIs emerged: timing (significant STE at an earlier/later time point) in 25%, incorrect measurement points in 30%, non or borderline-significant STE in 36% and inferoposterior MI localisation in 9%.
*Conclusions:* A computerized analysis of current guideline-recommended ECG criteria for STEMI showed suboptimal diagnostic performance when applied to a single 12 lead ECG performed at ED presentation.
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## 1. Introduction

Rapid and reliable diagnosis of ST-elevation myocardial infarction (STEMI) is critical for the early initiation of life-saving reperfusion therapy [1–3]. Patients with symptoms suggestive of myocardial ischemia and ST-segment elevation in the electrocardiogram (ECG) as a surrogate for acute coronary occlusion need to undergo reperfusion therapy as soon as possible, as timely reperfusion therapy reduces morbidity and

* Corresponding author at: Department of Cardiology and Cardiovascular Research Institute Basel (CRIB), University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland.
*E-mail address:* Christian.Mueller@usb.ch (C. Mueller).
[1] Both authors have contributed equally and should be considered first author.

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mortality of patients with STEMI and as higher mortality rates were observed with increasing time to primary percutaneous intervention [1–3]. False-negative STEMI diagnosis leads to prolonged time to reperfusion and false-positive STEMI diagnosis to unnecessary and possibly harmful invasive procedures.

In contrast to the common assumption among cardiologists, the rapid detection of STEMI in the emergency department (ED) at times is not trivial [1–6]. Uncertainty in the STEMI diagnosis may be related to several factors. First, ST-segment elevation is not unique to STEMI, but also occurs secondary to left ventricular hypertrophy, conduction abnormalities, early repolarization pattern, peri-/myocarditis or electrolyte disturbances. Persistent ST-segment elevation can also be due to an old myocardial infarction (e.g. LV aneurysm morphology) [7–9]. Second, ST-segment elevation in STEMI may be temporal in nature and therefore e.g. present preclinical, but not in the ECG recorded at ED presentation. Third, it may be difficult to exactly locate the J-point. Fourth, the amplitude of ST-segment elevation may be borderline below or above the threshold defined in current guidelines [10]. Fifth, the exact quantitative amplitude requirements for STEMI vary by age and sex [11]. Sixth, the ECG criteria defining STEMI in the universal definition of MI do include qualitative aspects of the ST-segment elevation [11].

In addition, deciding which patients have to undergo emergent reperfusion therapy is complex. A subset of patients with total occlusion of the culprit artery present without ST-elevation [12,13]. Those NSTEMI patients have a higher risk of MACE and all-cause mortality [12].

Unfortunately, the diagnostic performance of the quantitative ECG criteria for STEMI defined in current clinical practice guidelines is largely unknown [1–9]. Continuous optimization of these criteria would however require exact analysis of their diagnostic performance.

Recent technical advances including high-frequency sampling and high-speed data processing have enabled the development and refinement of digital ECG data recording and analysis [14–16]. Applying this novel technology, we aimed to prospectively validate current ECG STEMI criteria against a final adjudicated diagnosis of STEMI (primary analysis) and myocardial infarction (MI) in general (secondary analysis) in a large diagnostic study.

## 2. Methods

### 2.1. Study design and patient population

Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is an ongoing prospective international diagnostic multicenter study conducted in five countries (Switzerland, Spain, Italy, Poland, Czech Republic; Clinical.Trials.gov number NCT00470587) [17–20]. Adult patients presenting to the ED with any sort of acute chest discomfort (pain, pressure, burning, stabbing or angina pectoris) with an onset or peak within the last 12 h were recruited, after written informed consent was obtained. While recruitment was independent from renal function at presentation, patients with terminal kidney failure on chronic dialysis were excluded.

For the present analysis, patients were excluded if A) no digital ECG was available or B) the final diagnosis remained unclear after adjudication and at least one high-sensitivity cardiac troponin T (hs-cTnT) concentration was elevated; thus possibly indicating the presence of an MI. For the accurate application of the STEMI criteria according to the fourth universal definition of myocardial infarction [11], we also excluded all patients with left bundle branch block (LBBB), electrocardiographic signs of left ventricular hypertrophy (LVH) or pacemaker rhythm (stimulation of the ventricular depolarization by the pacemaker) on ECG at presentation. Left ventricular hypertrophy was defined according to the Sokolow-Index criteria (S in V1 or V2 + R in V5 or V6 > 3.5 mV) [21,22].

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. The authors designed the study, gathered, and analysed the data according to the STARD guidelines for studies of diagnostic accuracy (Appendix A), vouch for the data and analysis, wrote the paper, and decided to submit it for publication.

### 2.2. Routine clinical assessment

All patients underwent an initial clinical assessment that included medical history, physical examination, 12-lead ECG at first medical contact (if preceding ED presentation, 12-lead ECG at ED presentation and repeated if clinically indicated e.g. due to a new chest pain episode), continuous ECG rhythm monitoring, pulse oximetry, standard blood tests (including local c-Tn/hs-cTn assays), and chest radiography. Levels of cTn/hs-cTn were measured at presentation and serially thereafter as long as clinically indicated. Timing of the assessments and treatment of patients were left to the discretion of the attending physician. Data were collected on predefined study-specific case report forms.

### 2.3. Digital Electrocardiography Sampling and Analysis

The digital electrocardiography sampling and analysis methodology is available in Appendix B.1.

### 2.4. Manual ECG reading

The ECG recorded at ED presentation was "visually" interpreted by an internist/cardiologist blinded to all other clinical information. "Visual interpretation" by definition is less standardized regarding the application of the quantitative criteria, however, best reflects current clinical practice as it also takes into consideration e.g. qualitative aspects of ST-segment elevation and reciprocal ST-segment depression [1–9].

### 2.5. STEMI ECG Criteria

STEMI ECG criteria according to current ESC/AHA/ACC/WHO guidelines were used [1,2,11]. These include new, or presumed new, ST-segment elevation in two contiguous leads with the following cut-off points: ≥0.1 mV in all leads other than leads V2–V3. In V2-V3, the following cut-off points apply: ≥0.2 mV in men ≥40 years; ≥0.25 mV in men <40 years, or ≥0.15 mV in women. The J point was utilized to determine the magnitude of the ST-segment shift relative to the onset of the QRS (PQ junction) [1,2,11,23]. 'Contiguous leads' refers to lead groups such as anterior leads (V1–V6), inferior leads (II, III, aVF) or lateral/apical leads (I, aVL). Supplemental leads such as V3R and V4R reflect the free wall of the right ventricle and V7–V9 the infero-basal wall [1,2,11].

### 2.6. Adjudicated final diagnosis

STEMI was adjudicated according to the 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation and the fourth universal definition of myocardial infarction. The vast majority of STEMIs are type 1 MI (with evidence of a coronary thrombus) and have total or subtotal occlusion of a major coronary artery with TIMI flow of 0/1 at the time of coronary angiography, However, STEMI is a dynamic event and the time at which ST-segment elevation was observed in the ECG is not always the same as the time of coronary angiography. Some patients who had significant ST-segment elevation in the ECG and were brought to the catheterization laboratory, at the time of angiography (perhaps 40–60 min after the ECG recording) may have already had some degree of reperfusion (either spontaneously or pharmacologically) and coronary angiography is NOT showing occlusion (any more) and again TIMI flow of 2/3. A very small subset of STEMI patients may even present without a culprit lesion and thus in the absence of angiographic obstructive coronary artery disease (MINOCA, myocardial infarction with non-obstructive coronary arteries). Possible causes for MINOCA are atherosclerotic plaque disruption, coronary spasm or spontaneous coronary dissection [1,11].

Final diagnosis was adjudicated by two independent cardiologists not based on measurements of the ECG at presentation, but after reviewing all available medical records including all ECGs performed during the index hospitalisation, as well as all available preceding ECGs, serial levels of cTn/hs-cTn, cardiac imaging and especially coronary angiograms.

Further details of the adjudication process are accessible in Appendix B.2.

### 2.7. Statistical analysis

The primary analysis was to prospectively validate current quantitative ECG STEMI criteria against a final adjudicated diagnosis of STEMI. Secondary analysis included the comparison against a final adjudicated diagnosis of any MI (including STEMI and NSTEMI) to reflect the fact that the medical consequences of a false positive STEMI diagnosis would be by far less harmful if the true diagnosis was NSTEMI versus a diagnosis other than MI.

Additional secondary analysis included the comparison of the "visual" interpretation of the ECG recorded at ED presentation by an internist/cardiologist blinded to all other clinical information against a final adjudicated diagnosis of STEMI and MI. Sensitivity, specificity, negative and positive predictive values (NPV and PPV) with their 95% confidence intervals (CI) of the computerized analysis of the current STEMI ECG criteria for a final adjudicated diagnosis of STEMI and of MI were calculated.

In clinical practice, a previous ECG for comparison helps to minimize the rate of false-positive STEMI diagnoses. In a subgroup analysis, sensitivity, specificity, NPV and PPV were calculated for the delta ST-segment elevation in patients who had a prior digital ECG available for comparison. Delta ST-segment elevation was defined as difference between the J-point of the ECG at presentation and the J-point of the previous ECG (if value ≥ 0). Cut-offs were chosen according to current STEMI ECG criteria.

Continuous variables (all non-normally distributed) are presented as medians with interquartile ranges (IQR), categorical variables are expressed as counts and percentages. Mann-Whitney *U* test was run to compare continuous data between study groups. Categorical variables were compared by Pearson Chi-square test and Fisher's exact test as appropriate. Glomerular filtration rate was calculated using the abbreviated Modification of Diet in Renal Disease formula [24].

All hypothesis testing was two-tailed and a p-value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS for Windows 21.0 (SPSS Inc., Chicago, IL) and MedCalc 9.6.4.0 (MedCalc software, Ostend, Belgium).

## 3. Results

### 3.1. Baseline characteristics

A total of 2486 patients with available digital ECG data were eligible for this analysis (Fig. 1, patient flow). Baseline characteristics of patients with digital ECG data were similar to the overall study cohort (Appendix C, Table C.1). Patients with an adjudicated diagnosis of STEMI (and MI in general) were older, more often male, and had more cardiovascular risk factors as compared to patients with other adjudicated diagnosis (Tables 1A/1B).

### 3.2. Adjudicated diagnosis

The final adjudicated diagnosis was MI in 438/2486 patients (18%) and STEMI in 81/2486 patients (3%).

### 3.3. Sensitivity and specificity of current STEMI ECG criteria for STEMI and MI

Computerized analysis of current guideline-recommended STEMI ECG criteria at ED presentation revealed significant ST-segment elevation in 52/2486 patients (2%). Of these, 28 patients had an adjudicated diagnosis of STEMI (=35% of all STEMI patients), and 33 patients had an adjudicated final diagnosis of MI (STEMI or NSTEMI). This resulted in a PPV and specificity for STEMI of 54% (95%CI 41–66%) and 99% (95%CI 98.5–99.4%), and for AMI of 63% (95%CI 50–75%) and 99.1% (95%CI 98.6–99.4%). Sensitivity for STEMI was 35% (95%CI 24–46%; Appendix C, Tables C.2 und C.3).

### 3.4. Missed diagnosis of STEMI (by quantitative ECG criteria)

In 53 out of 81 patients (65%) with a final adjudicated diagnosis of STEMI, the diagnosis was missed by applying current guideline-recommended quantitative STEMI ECG criteria to the ECG recorded at ED presentation (Table 2, Appendix C, Table C.4). Four reasons emerged for missing an adjudicated final diagnosis of STEMI. One common reason was timing (n = 13 [25%], e.g. ST-segment elevation on paramedic/outpatient ECG, but not on the ECG at ED presentation, Fig. 2a). In 5 patients (9%), ECG at presentation showed nearly significant inferior ST-segment elevation and pronounced anterior ST-segment depression; in view of the clinical context, inferoposterior MI was diagnosed (Fig. 2b). Another reason was ST-segment elevation just below the cut-off, often in conjunction with reciprocal ST-segment depression (n = 19 [36%], e.g. significant ST-elevation in III, and ST-elevation of 0.095 mV in aVF, Fig. 2c). In some patients, the reason for the missed diagnosis was a questionable or incorrect determination of the J-point by the ECG-analysis software (n = 16 [30%], Fig. 2d).

### 3.5. False positive ST-segment elevation

Overall, 24 patients had significant ST-segment elevation, but a final adjudicated diagnosis other than STEMI (46% of patients with significant ST-segment elevation). Final diagnoses in these patients included cardiac but non-coronary disease such as Takotsubo cardiomyopathy and myocarditis in 14 patients (58%), NSTEMI in 5 patients (21%), a non-cardiac cause of chest pain in 4 patients (17%), and an unknown (other than MI) cause in 1 patient (Fig. 2d/e/f). In 3 of the 5 patients with a final adjudicated diagnosis of NSTEMI, no new significant ST-segment elevation was detected when comparing the ECG at ED presentation to a prior ECG. In the remaining 2 patients, software determination of the J-point was incorrect (e.g. due to right bundle branch block).

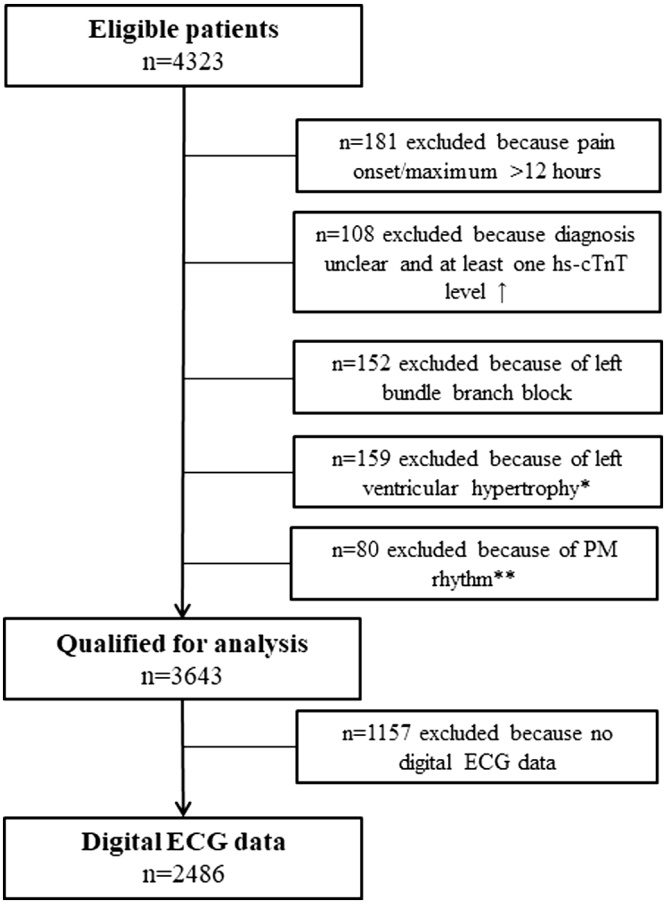



**Fig. 1.** Patient flow. * defined according to the Sokolow-Index criteria (S in V1 or V2 + R in V5 or V6 > 3.5 mV). ** stimulation of the ventricular depolarization by the pacemaker (PM).

### 3.6. Secondary analysis: visual interpretation

Visual interpretation of the ECG at presentation performed blinded to all other medical information resulted in a PPV of 58% (95% CI 51–65%) for STEMI (sensitivity 82% (95% CI 72–89%), specificity 98% (95% CI 97.4–98.5%), NPV 99.4% (95% CI 99–99.6%, Appendix C, Table C.5).

ST-elevation was interpreted as not significant or as subtle ST-elevation in 86% of patients with missed STEMI. In other cases, a missed diagnosis was due to timing (e.g. STE on paramedic ECG, already declining on ECG at presentation).

### 3.7. Findings in coronary angiography

Early coronary angiography (within 24 h) was performed in 71% of patients with an adjudicated final diagnosis of AMI and in 91% of patients with a final diagnosis of STEMI (within 72 h: 79% of AMI, 96% of STEMI patients). 57% of adjudicated STEMI patients had emergency coronary angiography within 90 min of hospital admission.

In the vast majority of cases (78/81 patients, 96%), the adjudicated STEMIs had acute occlusion of one ore more epicardial vessels on emergent angiogram. Of 236 NSTEMI patients who underwent early coronary angiography, total occlusion of a culprit lesion was detected in 58 patients (25%). In total, 136 of 2486 patients (5.5%) with symptoms suggestive of ACS presented with total occlusion of a culprit lesion.

When comparing patients with STEMI who were correctly identified by current guideline-recommended quantitative ECG criteria versus those who were missed, no significant differences were found regarding the culprit lesion or the extent of CAD (single vessel versus multi-vessel disease, Table 2).

**Table 1A**
Baseline characteristics of patients with versus without AMI.

| Characteristic | All patients (n = 2486) | AMI (n = 438) | No AMI (n = 2048) | p-Value |
|---|---|---|---|---|
| Age, median (IQR), yrs | 60 (48–73) | 70 (58–80) | 58 (46–71) | <**0.001** |
| Female, no. (%) | 793 (32) | 101 (23) | 692 (34) | <**0.001** |
| *Risk factors, no. (%)* | | | | |
| Hypertension | 1470 (59) | 328 (75) | 1142 (56) | <**0.001** |
| Hypercholesterolemia | 1155 (47) | 270 (62) | 885 (43) | <**0.001** |
| Diabetes mellitus | 400 (16) | 112 (26) | 288 (14) | <**0.001** |
| History of smoking | 924 (37) | 180 (41) | 744 (36) | 0.061 |
| Current smoking | 668 (27) | 112 (26) | 556 (27) | 0.499 |
| BMI, median (IQR), kg/m$^2$ | 26 (24–29) | 26 (24–29) | 26 (24–29) | 0.976 |
| *History, no. (%)* | | | | |
| Coronary artery disease | 828 (33) | 196 (45) | 632 (31) | <**0.001** |
| Previous MI | 593 (24) | 152 (35) | 441 (22) | <**0.001** |
| Previous revascularization | 714 (29) | 163 (37) | 551 (27) | <**0.001** |
| Peripheral artery disease | 134 (5) | 47 (11) | 87 (4) | <**0.001** |
| Previous stroke | 127 (5) | 29 (7) | 98 (5) | 0.113 |
| *ECG findings, no. (%)* | | | | |
| Heart rate (bpm) | 72 (63–83) | 73 (63–83) | 71 (63–83) | 0.680 |
| QRS duration (ms) | 96 (88–104) | 100 (90–108) | 96 (88–104) | <**0.001** |
| QTc time (ms) | 428 (412–446) | 438 (420–461) | 426 (410–445) | <**0.001** |
| ST-segment depression | 215 (9) | 129 (30) | 86 (4) | <**0.001** |
| T-wave inversion | 292 (12) | 114 (26) | 178 (9) | <**0.001** |
| No ECG abnormalities | 1999 (80) | 214 (49) | 1785 (87) | <**0.001** |
| *Chest pain characteristics, no. (%)* | | | | |
| Prior episode of chest pain | 1653 (67) | 293 (67) | 1360 (66) | 0.539 |
| *Pain quality* | | | | |
| Pressure-like | 1669 (67) | 321 (73) | 1348 (66) | **0.003** |
| Stabbing | 690 (28) | 83 (19) | 607 (30) | <**0.001** |
| Burning or aching | 453 (18) | 84 (19) | 369 (18) | 0.568 |
| *Aggravating factors* | | | | |
| Aggravated by exertion | 935 (38) | 201 (46) | 734 (36) | <**0.001** |
| Aggravated by breathing/coughing | 796 (32) | 81 (19) | 715 (35) | <**0.001** |
| Aggravated by movements | 549 (22) | 72 (16) | 477 (23) | **0.003** |
| Induced by emotional stress | 675 (27) | 88 (20) | 587 (29) | <**0.001** |
| *Pain radiation* | | | | |
| None | 962 (39) | 137 (31) | 825 (40) | <**0.001** |
| Throat | 455 (18) | 81 (19) | 374 (18) | 0.909 |
| Left shoulder/arm | 931 (37) | 207 (47) | 724 (35) | <**0.001** |
| Right shoulder/arm | 287 (12) | 88 (20) | 199 (10) | <**0.001** |
| Back | 340 (14) | 53 (12) | 287 (14) | 0.290 |
| Both shoulders | 811 (33) | 166 (38) | 645 (32) | **0.009** |
| Abdominal region | 185 (7) | 29 (7) | 156 (8) | 0.471 |
| *Pain duration* | | | | |
| Duration <10 min | 478 (19) | 73 (17) | 405 (20) | 0.216 |
| Duration 10–30 min | 335 (14) | 64 (15) | 271 (13) | 0.315 |
| Duration >30 min | 1589 (64) | 277 (63) | 1312 (64) | 0.654 |
| Accompanying dyspnea | 1181 (48) | 202 (46) | 979 (48) | 0.479 |
| *Lab. findings, median (IQR)* | | | | |
| eGFR[a] | 87 (71–102) | 77 (61–97) | 88 (74–103) | <**0.001** |
| hs-cTnT at 0 h (ng/l) | 8 (4–18) | 58 (29–155) | 6 (4–12) | <**0.001** |
| peak hs-cTnT (ng/l) | 9 (5–22) | 93 (42–277) | 7 (4–12) | <**0.001** |
| *Chronic medication, no. (%)* | | | | |
| ASA | 898 (36) | 209 (48) | 689 (34) | <**0.001** |
| Beta blockers | 834 (34) | 172 (39) | 662 (32) | **0.005** |
| Statins | 834 (34) | 179 (41) | 655 (32) | <**0.001** |
| ACEIs/ARBs | 924 (37) | 210 (48) | 714 (35) | <**0.001** |
| Calcium antagonists | 358 (14) | 67 (15) | 291 (14) | 0.556 |
| Nitrates | 215 (9) | 61 (14) | 154 (8) | <**0.001** |

[a] eGFR was estimated using the abbreviated Modification of Diet in Renal Disease formula, (ml/min/1.73 m$^2$). **ACEI** indicates angiotensin converting enzyme inhibitor; **ARB**, angiotensin receptor blocker; **ASA**, acetylsalicylic acid; **BP**, blood pressure; **CV**, cardiovascular; **ECG**, electrocardiogram; **eGFR**, estimated glomerular filtration rate; **hs-cTnT**, high-sensitivity cardiac troponin T; **MI**, myocardial infarction. Values are expressed in numbers and percentages or medians and interquartile ranges (**IQR**).

In particular, no difference regarding the culprit lesion was observed in STEMI patients who were missed because of inferoposterior MI localisation (n = 5). The culprit lesion was the left circumflex coronary artery (LCX) in 2 patients and the right coronary artery (RCA) in 3 patients.

### 3.8. ST-segment elevation on previous ECG

A previous digital ECG for comparison of the ST-segment was available in 1306 patients (53% of the total study cohort) of whom 30 patients had an adjudicated final diagnosis of STEMI (37% of all STEMI

**Table 1B**
Baseline Characteristics of patients with versus without STEMI.

| Characteristic | STEMI (n = 81) | No STEMI (n = 2405) | p-Value |
|---|---|---|---|
| Age, median (IQR), yrs | 65 (53–77) | 60 (48–73) | **0.007** |
| Female, no. (%) | 21 (26) | 772 (32) | 0.241 |
| *Risk factors, no. (%)* | | | |
| Hypertension | 55(68) | 1415 (59) | 0.103 |
| Hypercholesterolemia | 42 (52) | 1113 (46) | 0.323 |
| Diabetes mellitus | 22 (27) | 378 (16) | **0.007** |
| History of smoking | 30 (37) | 894 (37) | 0.980 |
| Current smoking | 23 (28) | 645 (27) | 0.753 |
| BMI, median (IQR), kg/m$^2$ | 26 (24–29) | 26 (24–29) | 0.656 |
| *History, no. (%)* | | | |
| Coronary artery disease | 19 (24) | 809 (34) | 0.056 |
| Previous MI | 16 (20) | 577 (24) | 0.379 |
| Previous revascularization | 14 (17) | 700 (29) | **0.021** |
| Peripheral artery disease | 5 (6) | 129 (5) | 0.751 |
| Previous stroke | 3 (4) | 124 (5) | 0.559 |
| *ECG findings, no. (%)* | | | |
| Heart rate (bpm) | 75 (60–84) | 72 (63–83) | 0.900 |
| QRS duration (ms) | 98 (92–108) | 96 (88–104) | **0.027** |
| QTc time (ms) | 440 (421–462) | 428 (412–446) | <**0.001** |
| ST-segment depression | 31 (38) | 184 (8) | <**0.001** |
| T-wave inversion | 29 (36) | 263 (11) | <**0.001** |
| *Chest pain characteristics, no. (%)* | | | |
| Prior episode of chest pain | 37 (46) | 1616 (67) | **0.001** |
| Pain quality | | | |
| Pressure-like | 56 (69) | 1613 (67) | 0.697 |
| Stabbing | 15 (19) | 675 (28) | 0.059 |
| Burning or aching | 7 (9) | 446 (19) | **0.023** |
| *Aggravating factors* | | | |
| Aggravated by exertion | 32 (39) | 903 (38) | 0.409 |
| Aggravated by breathing/coughing | 12 (15) | 784 (33) | **0.002** |
| Aggravated by movements | 13 (16) | 536 (22) | 0.249 |
| Induced by emotional stress | 10 (12) | 665 (28) | **0.003** |
| *Pain radiation* | | | |
| None | 21 (26) | 941 (39) | **0.016** |
| Throat | 12 (15) | 443 (18) | 0.409 |
| Left shoulder/arm | 40 (49) | 891 (37) | **0.024** |
| Right shoulder/arm | 17 (21) | 270 (11) | **0.007** |
| Back | 10 (12) | 330 (14) | 0.723 |
| Both shoulders | 34 (42) | 777 (32) | 0.068 |
| Abdominal region | 4 (5) | 181 (8) | 0.383 |
| *Pain duration* | | | |
| Duration <10 min | 2 (2) | 476 (20) | <**0.001** |
| Duration 10–30 min | 4 (5) | 331 (14) | **0.027** |
| Duration >30 min | 69 (85) | 1520 (63) | <**0.001** |
| Accompanying dyspnea | 35 (43) | 1146 (48) | 0.470 |
| *Lab. findings, median (IQR)* | | | |
| eGFR[a] | 78 (61–100) | 87 (72–103) | **0.016** |
| hs-cTnT at 0 h (ng/l) | 138 (33–596) | 8 (4–17) | <**0.001** |
| peak hs-cTnT (ng/l) | 455 (93–1935) | 8 (5–19) | <**0.001** |
| *Chronic Medication, no. (%)* | | | |
| ASA | 25 (31) | 873 (36) | 0.317 |
| Beta blockers | 21 (26) | 813 (34) | 0.140 |
| Statins | 24 (30) | 810 (34) | 0.448 |
| ACEIs/ARBs | 32 (40) | 892 (37) | 0.658 |
| Calcium antagonists | 9 (11) | 349 (15) | 0.391 |
| Nitrates | 2 (3) | 213 (9) | **0.044** |

[a] eGFR was estimated using the abbreviated Modification of Diet in Renal Disease formula, (ml/min/1.73 m$^2$). **ACEI** indicates angiotensin converting enzyme inhibitor; **ARB**, angiotensin receptor blocker; **ASA**, acetylsalicylic acid; BP, blood pressure; **CV**, cardiovascular; **ECG**, electrocardiogram; **eGFR**, estimated glomerular filtration rate; **hs-cTnT**, high-sensitivity cardiac troponin T; **MI**, myocardial infarction. Values are expressed in numbers and percentages or medians and interquartile ranges (**IQR**).

patients). When calculating delta ST-elevation by using the previous ECG, specificity for STEMI improved to 99.4% (95%Cl 98.8–99.7%); PPV 53% (95% CI 28–77%, Appendix C, Table C.6).

## 4. Discussion

We prospectively collected digital and visual ECG data within a diagnostic multicenter study of patients presenting to the ED with acute chest discomfort to evaluate the diagnostic performance of current guideline-recommended STEMI criteria. Methodological strengths of this study include its international multicenter design using central adjudication of the final diagnosis according to the universal definition of MI by two independent cardiologists.

We report six major findings. First, the diagnostic performance of current guideline-recommended STEMI ECG criteria at ED presentation was suboptimal.

Particularly, sensitivity (only 35%) was by far lower than expected. Specificity was high (99%) and PPV (54%) was reasonable. Second, detailed review of missed STEMIs revealed four key aspects: timing (ST-segment elevation significant at an earlier/later time point) in 25%, incorrect measurement points mainly due to incorrect J-point measurement of the software (in some due to poor ECG quality), in 30%, non or borderline-significant ST-elevation (e.g. significant ST-elevation in one lead, nearly significant ST-elevation in a contiguous lead) in 36% and inferoposterior MI localisation in 9%. In some patients, ECG at presentation showed nearly significant ST-elevation in the inferior leads and ST-depression in the anterior leads. In most of these patients, additional posterior leads were recorded which showed significant ST-segment elevation (no computerized analysis of the posterior leads available). In view of the clinical context, a final diagnosis of inferoposterior STEMI was adjudicated. Third, culprit lesion or the type of CAD (single- or multiple vessel disease) did not help to predict missed STEMI by current guideline-recommended ECG criteria.

Fourth, prevalence of total occlusion of a culprit lesion in patients who present with symptoms suggestive of ACS was low. In total, 18% of all patients had a final adjudicated diagnosis of AMI and 3% a diagnosis of STEMI. The vast majority of STEMI patients (96%) as well as 25% of NSTEMI patients who underwent early coronary angiography showed total occlusion of a culprit lesion (5.5% of all patients).

Fifth, a subgroup analysis of patients with a prior digital ECG available for comparison showed that a prior ECG modestly improved the specificity for STEMI.

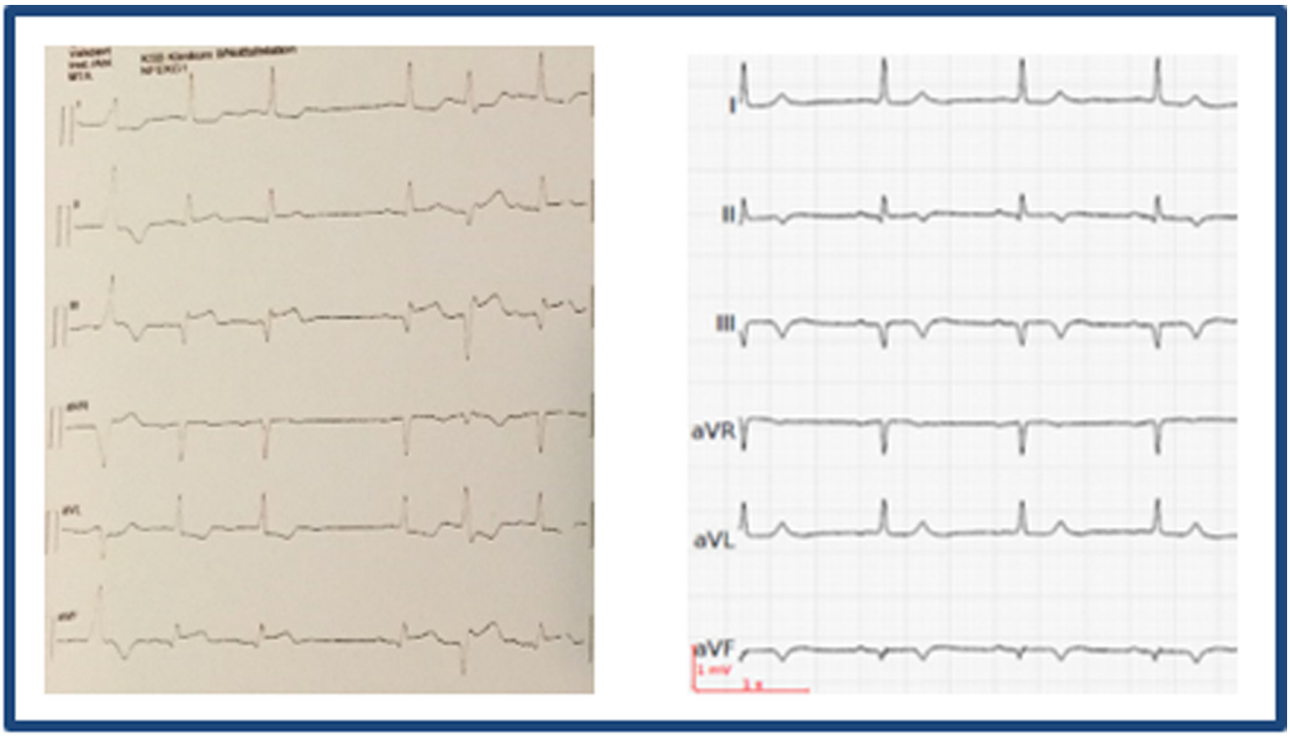
Sixth, visual interpretation of the ECG at ED presentation, blinded to all other clinical information, integrated e.g. reciprocal ST-depression as well as qualitative ECG criteria and achieved higher sensitivity (82%) as compared to the computerized analysis. In the cases missed by visual interpretation, the majority of patients presented with non-significant ST-elevation. Different ECG patterns have been characterized to help detecting patients with total occlusion who would benefit from emergent reperfusion, despite not fulfilling standard STEMI criteria; e.g. the de Winter ST/T waves as a sign for proximal LAD occlusion or diffuse ST depression with ST elevation in aVR as an ECG pattern for left main occlusion [25,26].

They can also help to reduce false-positive diagnoses of STEMI by demonstrating possible ECG patterns to differentiate between STEMI and benign early repolarization or pericarditis [27–31].

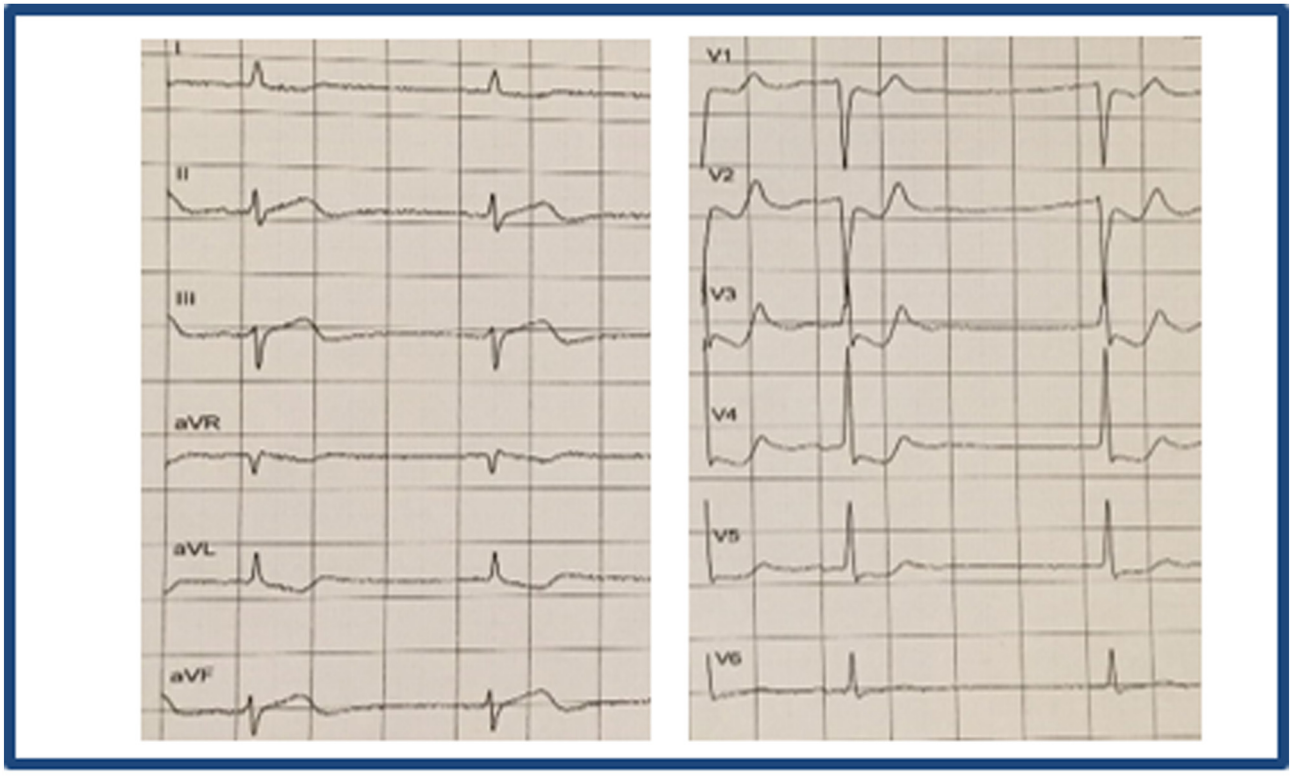
In a retrospective single-center study, terminal QRS distortion (absence of an S-wave and J-wave in V2 or V3) was found to be absent in benign early repolarization but often present in anterior STEMI [31].

Smith and colleagues derived a logistic regression 3-variable formula to differentiate subtle anterior STEMI from early repolarization. In patients with subtle anterior STEMI, R-wave amplitude was lower, ST-segment elevation greater and QTc longer as compared to early repolarization [27]. The addition of the QRS voltage in V2 (4-variable formula) seemed to further improve the accuracy of the formula [29,30].

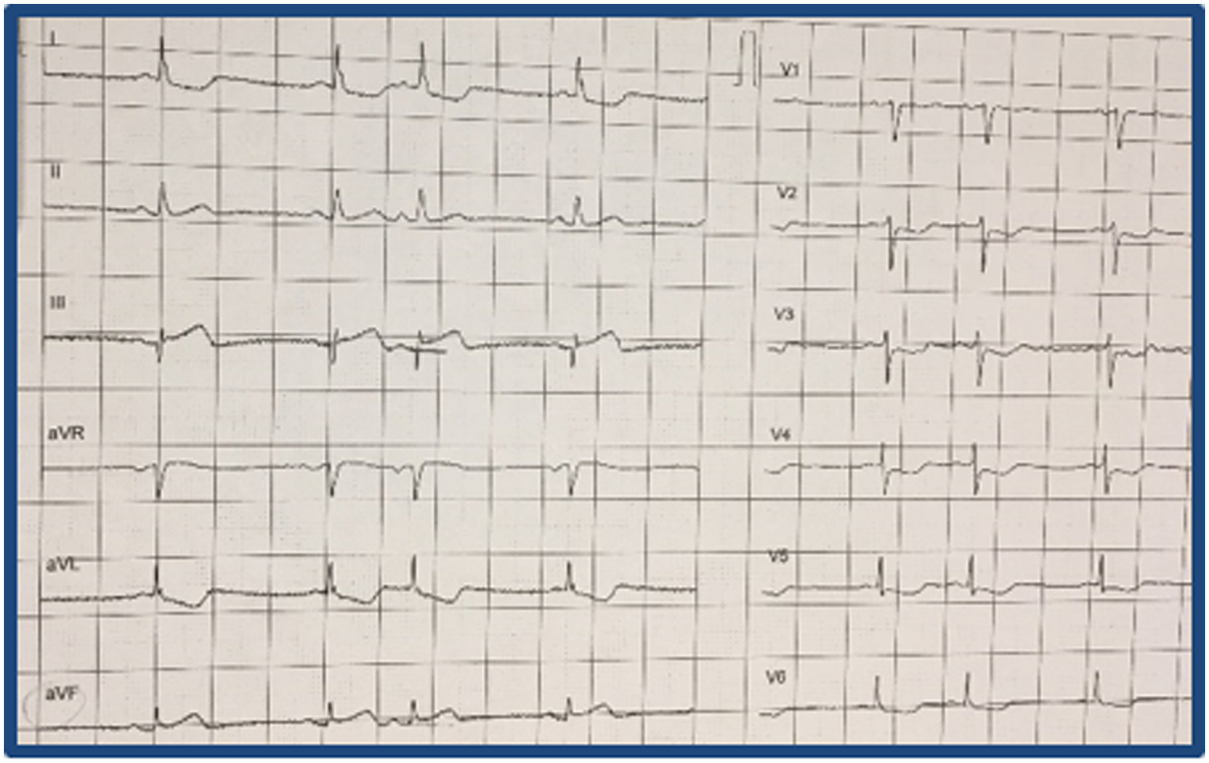
Bischof and colleagues found any amount of ST depression in aVL to be highly sensitive for coronary occlusion in patients presenting with inferior ST elevation and very specific for differentiating inferior MI from pericarditis [28].



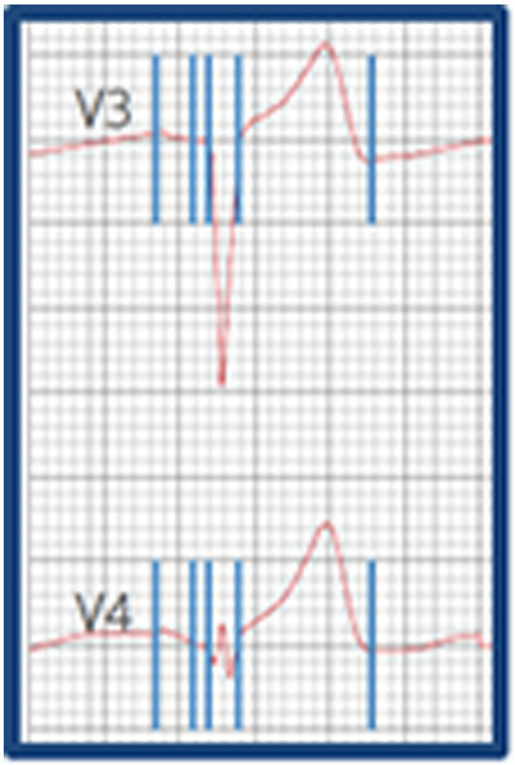

a.




b.

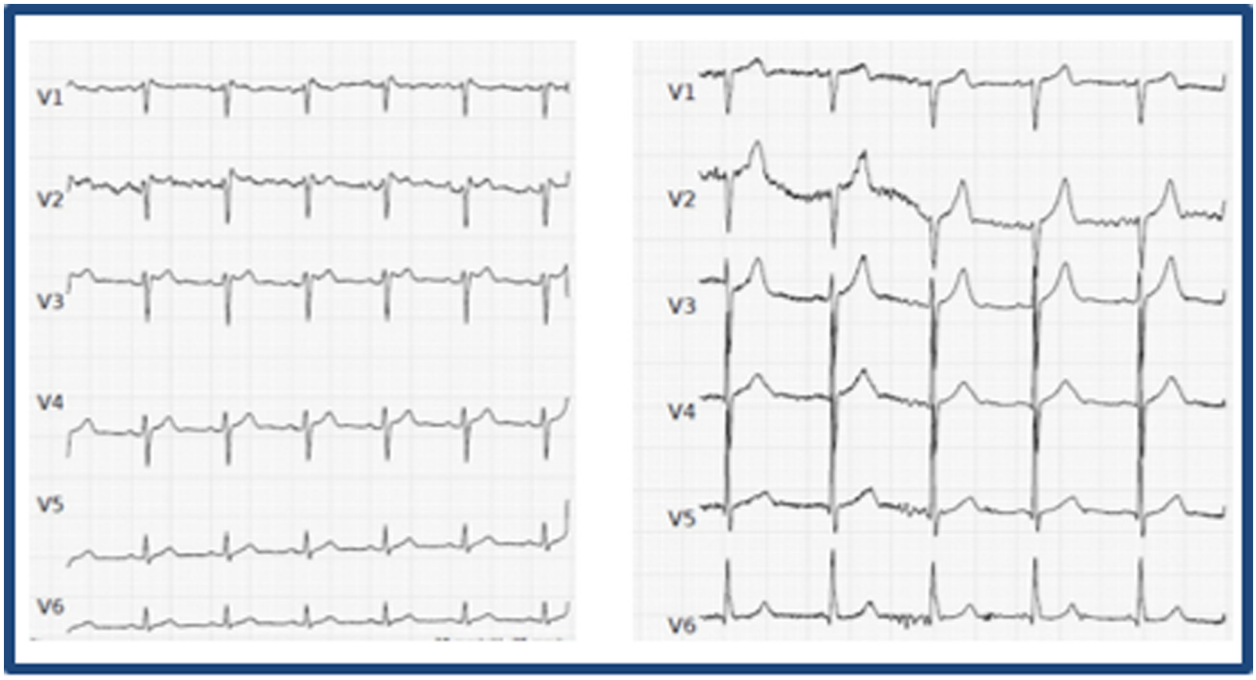



c.

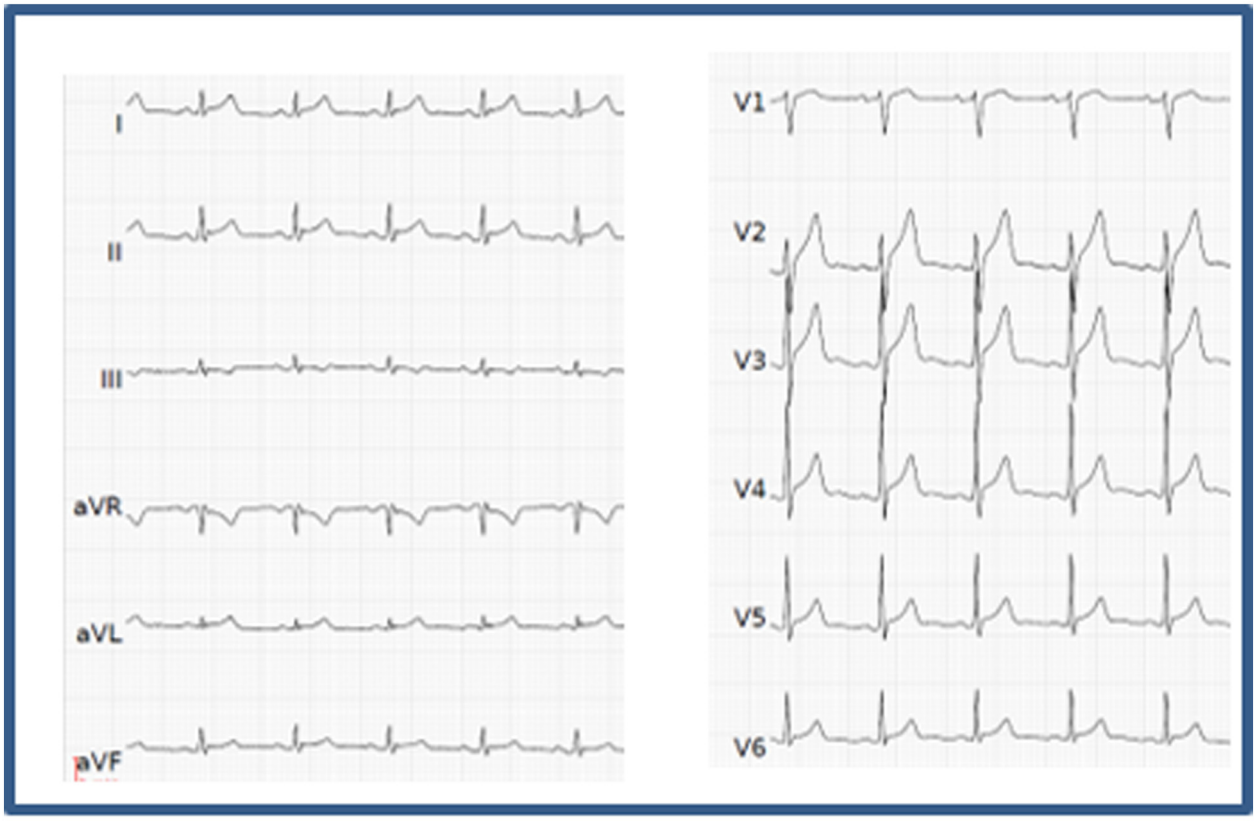



d.

**Fig. 2** (*continued*).

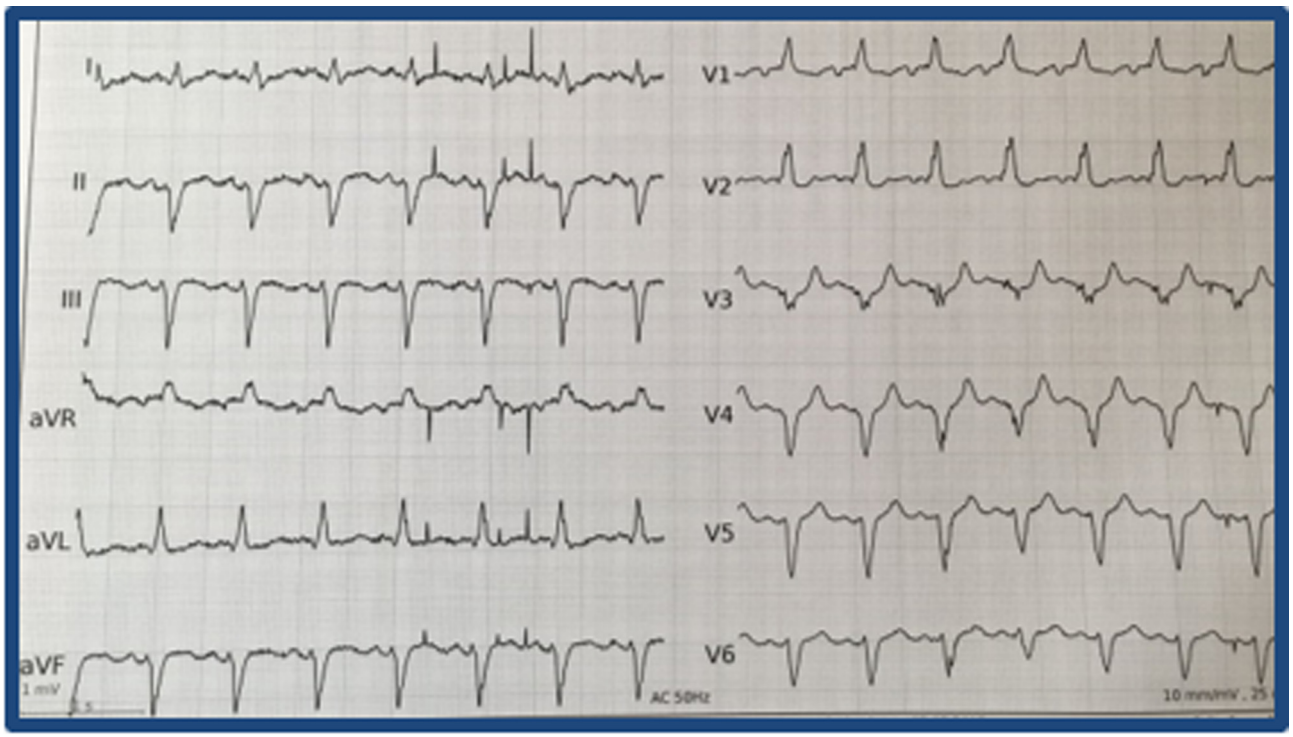



e.

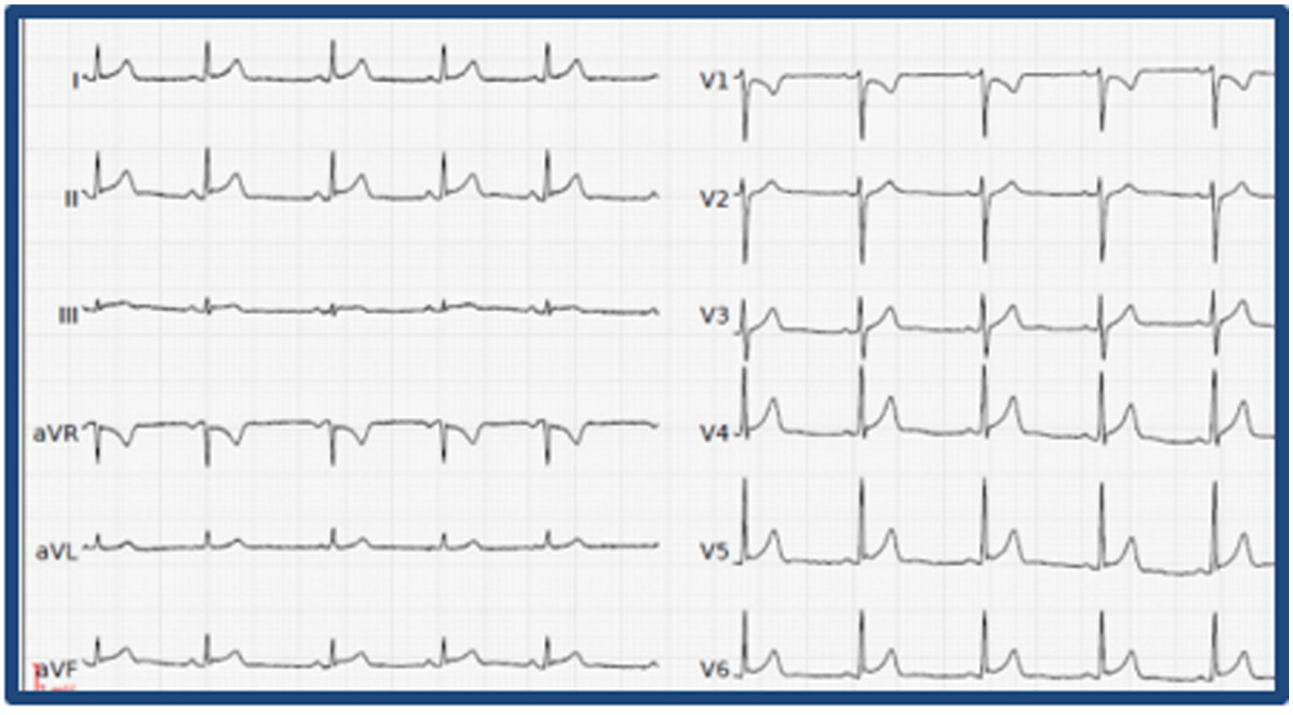



f.

**Fig. 2** (*continued*).

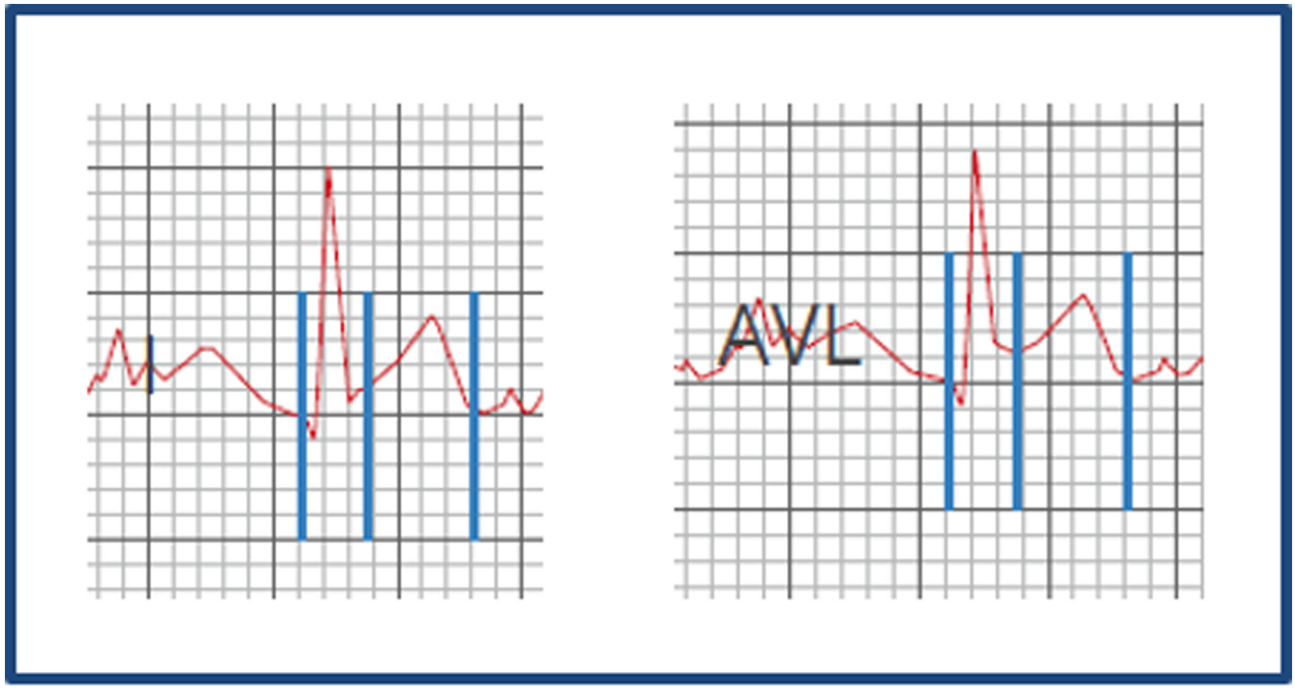



g.




h.

**Fig. 2** (*continued*).




i.

**Fig. 2.** a. Missed STEMI due to timing. Significant inferior ST-segment elevation on ECG at presentation (only manual ECG available, no digital ECG); on first digital ECG 2 h later ST-elevation already declining (83-year-old male patient). b. Inferoposterior STEMI. Pronounced ST-segment depression in V1-V5, nearly significant ST-elevation inferior (90-year old male patient) c. Nearly significant ST-elevation. Inferior ST-elevation (significant in III, not significant in aVF), reciprocal ST-depression (73-year-old female patient). d. Wrong measurement points (false negative). 53-year old male patient with significant anterior ST-elevation. e. ST-elevation on previous ECG. ECG at presentation shows significant anterior ST-elevation. No significant ST-elevation on ECG at presentation (left) when comparing it to a previous ECG (right) and using the J-points from the previous ECG as the new J-points (43-year-old patient with somatization disorder). f. Significant ST-elevation without cTn-elevation. 53-year-old male patient with significant anterior ST-elevation without cTn-elevation at presentation or in serial measurement. In view of the clinical context, the patient was discharged with a diagnosis of musculoskeletal chest pain. g. Concomitant left anterior fascicular block (LAFB) and/or right bundle-branch block (RBBB). ECG at presentation showed LAFB and RBB; leading to a limited interpretation of the ST segment (significant ST-elevation was measured in III and aVF, 81-year-old male patient). h. False positive ST-elevation. Significant ST-elevation inferior (33-year-old male patient with perimyocarditis). i. Wrong measurement points (false positive). 45-year-old male patient with dilated cardiomyopathy of unknown etiology and atrial fibrillation. Wrong measurement point in lead I.

Our findings corroborate and extend previous studies on the use of ECG in the early diagnosis of STEMI and AMI [7–9]. In summary, 5.5% of patients who presented with symptoms suggestive of ACS had total occlusion of a culprit lesion on early coronary angiography. In a retrospective case-control study investigating 297 patients who underwent emergent coronary angiography for suspected STEMI, 31 patients (10.4%) did not have a clear culprit coronary lesion and were classified as false-positive [7]. Concave ST-segment elevation and no reciprocal ST-segment depression occurred more often in false-positive STEMI patients (52% vs 24%, $p = 0.001$; 65% vs 19%, $p < 0.001$), supporting the concept to actively incorporate reciprocal ST-segment depression when evaluating an ECG showing borderline ST-segment elevation [7]. Similarly, in another series of 489 patients who received emergency cardiac catheterization indicated for STEMI, 54 (11.0%) had no culprit

**Table 2**
Correctly identified versus missed STEMI patients.

| Characteristic | All STEMI patients (n = 81) | Missed STEMI (n = 53) | Correctly identified STEMI (n = 28) | p-Value |
|---|---|---|---|---|
| ECG findings visual, n (%) | | | | |
| ST depression | 37 (46) | 19 (36) | 18 (64) | **0.015** |
| T wave inversion | 29 (36) | 21 (40) | 8 (29) | 0.324 |
| Coronary angiography performed, n (%) | 79 (98) | 51 (96) | 28 (100) | |
| Findings, n (%) | | | | |
| Culprit lesion/coronary intervention[a] | | | | ns[†] |
| Left main | 2 (2) | 1 (2) | 1 (4) | |
| LAD | 36 (44) | 23 (43) | 13 (46) | |
| LCX | 10 (12) | 7 (13) | 3 (11) | |
| RCA | 26 (32) | 16 (30) | 10 (36) | |
| Bypass graft | 3 (4) | 2 (4) | 1 (4) | |
| Other | 7 (9) | 5 (9) | 2 (7) | |
| CAD | | | | |
| 1-vessel | 29 (36) | 19 (36) | 10 (36) | |
| 2-vessel | 21 (26) | 13 (25) | 8 (29) | |
| 3-vessel | 29 (36) | 19 (36) | 10 (36) | |

[a] Multi-vessel coronary intervention at presentation was performed in 4 patients (number of intervened vessels: 3,2,2,2).
[†] All p-values non-significant (**ns**).

lesion on coronary angiography [9]. Again, absence of reciprocal ST-segment changes (OR 12) was an independent predictor of false-positive STEMI [9]. Nonetheless, absence of reciprocal ST-segment depression should not automatically be reassuring, especially in patients with anterior ST-segment elevation. Noriega et al. observed that in patients with occlusion of the LAD, reciprocal ST-segment depression was only detected when the occlusion affected the proximal but not the mid-distal LAD segment [32].

In contrast to the enormous advances made in the last decade due to the clinical introduction of hs-cTn assays [18–20,33–36], by less progress has been made using novel ECG signatures in the early diagnosis of AMI. E.g. the V-index, a novel ECG marker quantifying spatial heterogeneity of ventricular repolarization, was investigated in 497 patients presenting to the ED with suspected NSTEMI [14]. Digital 12-lead ECGs of five-minute duration were recorded at presentation and the V-index automatically calculated in a blinded fashion. The use of the V-index in addition to conventional ECG-criteria improved the diagnostic accuracy for the diagnosis of NSTEMI as quantified by area under the ROC curve from 0.66 to 0.73 ($p = 0.001$) and the sensitivity of the ECG for AMI from 41% to 86% ($p < 0.001$). Similarly, the cardiac electrical biomarker (CEB) is a novel ECG marker quantifying the dipolar activity of the heart with higher levels indicating myocardial injury [37]. Among 1097 patients presenting with suspected NSTEMI to the ED, digital 12-lead ECGs were recorded at presentation and the CEB values were calculated in a blinded fashion. The final diagnosis was adjudicated by two independent cardiologists. The use of the CEB in addition to conventional ECG criteria improved the diagnostic accuracy for the diagnosis of NSTEMI as quantified by the area under the receiver operating characteristics curve from 0.66 to 0.71 ($p < 0.001$) and the sensitivity improved from 43% to 79% ($p < 0.001$) [37].

### 4.1. Study limitations

Potential limitations of the present study merit consideration when interpreting our findings. First, we cannot comment on patients who present later than 12 h after symptom onset or patients with terminal kidney failure on chronic dialysis, since these patients were excluded from our study. Second, this was a secondary analysis from a large ongoing multicenter study designed to improve the early diagnosis of AMI. As such, no specific power analysis was performed to justify the sample size for this hypothesis. Third, a majority of STEMI patients goes directly to the catheterization laboratory to prevent treatment delay. As recruitment of patients was in the ED, there was a relatively small number of STEMI patients and this may imply limited generalisability of conclusions.

Fourth, the ECG-analysis software was susceptible to interference (e.g. ECG artefacts due to skeletal muscle activity, electrical interference or poor conduction) resulting in incorrect J-point determination and was therefore partially responsible for the poor diagnostic performance.

Fifth, the adjudicating cardiologists had access to all available ECGs of the index hospitalisation as well as to all preceding ECGs. The final adjudicated diagnosis was not at all soley based on ECG findings, but was adjudicated based on all available medical findings including coronary angiograms, serial levels of cTn/hs-cTn and cardiac imaging. Thus, we deem the possible risk of incorporation bias as low.

Sixth, we did not have ECG data of all consecutive patients included into the study. This was primarily due to the fact that digital ECG was not available in all study centers. Overall, baseline characteristics of patients with digital ECG were comparable to patients without digital ECG. Therefore, it is very unlikely that this selection bias has had a relevant effect on our findings.

## 5. Conclusions

In conclusion, a computerized analysis of current guideline-recommended ECG criteria for STEMI showed suboptimal diagnostic performance, particularly low sensitivity, when applied to the ECG performed at ED presentation. Clinicians need to be aware of this major limitation and address it by more holistic interpretation of the ECG, as well as liberal use of additional (posterior and right precordial) leads and serial ECGs to optimize and accelerate the diagnosis of STEMI.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.04.041.

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