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ECG analysis in patients with acute coronary syndrome undergoing invasive management: rationale and design of the electrocardiography sub-study of the MATRIX trial

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Abstract

Background. The twelve-lead electrocardiogram (ECG) has become an essential tool for the diagnosis, risk stratification, and management of patients with acute coronary syndromes (ACS). However, several areas of residual controversies or gaps in evidence exist. Among them, P-wave abnormalities identifying atrial ischemia/infarction are largely neglected in clinical practice, and their diagnostic and prognostic implications remain elusive; the value of ECG to identify the culprit lesion has been investigated, but validated criteria indicating the presence of coronary occlusion in patients without ST-elevation are lacking; finally, which criteria among the multiple proposed, better define pathological Q-waves or success of revascularisation deserve further investigations

Methods. The Minimizing Adverse hemorrhagic events via TRansradial access site and systemic Implementation of AngioX (MATRIX) trial was designed to test the impact of bleeding avoidance strategies on ischemic and bleeding outcomes across the whole spectrum of patients with ACS receiving invasive management. The ECG-MATRIX is a pre-specified sub-study of the MATRIX programme which aims at analyzing the clinical value of ECG metrics in 4,516 ACS patients (with and without ST-segment elevation in 2,212 and 2,304 cases, respectively) with matched pre and post-treatment ECGs.

Conclusions. This study represents a unique opportunity to further investigate the role of ECGs in the diagnosis and risk stratification of ACS patients with or without ST-segment deviation, as well as to assess whether the radial approach and bivalirudin may affect post-treatment ECG metrics and patterns in a large contemporary ACS population.

Keywords: ECG, acute coronary syndromes, myocardial infarction, atrial infarction, radial access, percutaneous coronary intervention

Introduction

The twelve-lead standard trans-thoracic electrocardiogram (ECG) remains a fundamental instrument for the diagnosis, risk stratification, and treatment of patients with suspected or confirmed acute coronary syndrome (ACS)[1–3]. Matched pre and post-treatment ECGs analysis provides additional information on the success (or failure) of epicardial flow restoration, as well as microvascular reperfusion, and risk stratification for short- and long-term outcomes[4–6]. Numerous studies have investigated the diagnostic and prognostic role of ECG in patients with ACS undergoing invasive management **(supplementary appendix, Table S1)**[4–12]. However, several issues remain unclear. Among them, P-wave abnormalities identifying atrial ischemia/infarction are largely neglected in clinical practice, as their diagnostic and prognostic implications remain elusive[13–17]. Numerous studies have assessed the value of specific ECG patterns/algorithms to identify culprit lesion, but they suffer from multiple limitations, and their usefulness needs to be reassessed[18–25]. Validated criteria indicating the presence of coronary occlusion in patients without ST-elevation are lacking and would carry major implications for practice[26–30]. Further questions regarding the impact of access site and/or antithrombotic regimens on atrial and ventricular ischemia assessed by ECG analysis remain poorly investigated and would deserve further attention.

The Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox (MATRIX) was a programme of three nested, randomised, multicentre trials[31–34] assessing the comparative safety and effectiveness of radial versus femoral access and bivalirudin versus unfractionated heparin (with optional glycoprotein IIb/IIIa inhibitors) in 8,404 patients with ACS (with or without ST-segment deviation) undergoing invasive management. Within the programme, an electrocardiography sub-study (ECG-MATRIX) was pre-specified in the trial protocol (available online at https://nejm.org/doi/full/10.1056/NEJMoa1507854#article_supplementary_material)[32] and designed in accordance with previously proposed criteria for conducting an ECG sub-study nested within prospective trials in patients with coronary artery disease[35].

In this paper, we intend to highlight the remaining areas of controversies surrounding the role of the ECG in the management of ACS patients coupled with the rationale for and design of the ECG-MATRIX.

Role of P-wave morphology for the diagnosis of atrial infarction and prediction of supraventricular arrhythmias and outcomes

Since its first description in 1925[36], atrial infarction remains an elusive entity and a potentially unrecognized cause of atrial dysfunction and supraventricular arrhythmias[37,38]. Major concepts about the clinical presentation of the disease have been previously reviewed[12,14](search strategy detailed in **supplementary appendix).** Atrial infarction can occur in up to 30% of patients with concomitant ventricular infarction[16,17], while it has been rarely reported as isolated findings[12,39,40]. The majority of atrial infarctions occur as a consequence of atherosclerotic coronary disease, as the result of occlusion of atrial coronary branches, and are either thrombotic or percutaneous coronary intervention (PCI) related. As atrial branches typically arise from proximal right and/or left circumflex coronary arteries, their involvement is generally associated with coronary lesions jeopardizing a large ventricular mass[12,37]. Accidental atrial branch occlusion during elective PCI is a neglected but relatively frequent cause of ischemic atrial damage[37], associated with peri-procedural myocardial infarction (MI), atrial arrhythmias, and intra-atrial conduction delay[37]. Although challenging, the diagnosis of atrial ischemia/infarction can be made via the assessment of suspected ECG alterations, including abnormal P-wave morphology (i.e., notched shape, ‘M’ or ‘W’ pattern), prolonged P-wave duration (i.e., inter-atrial block), PR-segment deviation, or new-onset atrial arrhythmias (i.e., atrial premature beats, atrial fibrillation)[12,13,15,41,42]. Moreover, the ECG confers the possibility of defining atrial injury localization, showing a relatively high incidence of right (81-98%) as compared to left (2-19%) or bi-atrial (19-24%) involvement[14,15]. To date, the definition remains the main issue in diagnosing atrial infarction at ECG because of the lack of universally accepted criteria. Burch suggested that any PR-deviation (even a fraction of a millimeter) should be considered as potentially suspicious for atrial infarction, although this approach may lack adequate accuracy[14,42]. The criteria currently used, were proposed by Liu et al. in 1961 and based

on a small case series **(Figure 1)**[13], and have never been prospectively validated in large cohorts. Moreover, their usefulness in clinical practice has been recently largely questioned[16,17]. Among 224 ST-segment elevation myocardial infarction (STEMI) patients who underwent retrospective assessment, none met the major criteria proposed by Liu. However, the presence of PR-displacement in any leads was common (31% of cases) and independently predicted a 30-day, as well as 1-year mortality (adjusted odds ratio 6.22; 95% confidence interval [CI] 2.33-18.64)[17]. In the setting of a case-control sub-analysis of the APEX-AMI, which included 630 patients with or without new-onset atrial fibrillation, the presence of abnormal P-wave morphology was significantly associated with new atrial fibrillation (adjusted odds ratio, 1.68; 95% CI 1.03-2.73), and was independently associated with mortality at 90-day follow-up in the overall (adjusted hazard rate, 1.90; 95% CI 1.04 to 3.46) and new-onset atrial fibrillation (adjusted hazard rate, 2.43; 95% CI 1.22 to 4.84) cohorts. The current evidence is mainly derived from retrospective and modestly sized STEMI studies. The evidence on patients with NSTE-ACS remains very limited, and few studies have assessed P-wave morphology in association with angiographic data in order to corroborate the occurrence of atrial infarction[12,43]. In addition, none of the previous studies investigated the possible differential impact of measuring PR-displacement at atrial J-point versus maximum point of deviation, the clinical meaning of PR-segment slope (horizontal, slight, marked down- and up-slope), and concordance/discordance between P-wave and PR-deviation polarity, or the prognostic implications of P-wave/PR-segment abnormalities resolution (or persistence) after PCI. Moreover, prior studies focused on P-wave morphology either mainly or exclusively in isolation from other ECG changes. Therefore, it remains unclear whether P-wave/PR-segment morphology truly predicts outcomes, including mortality, independently from other concomitant ECG changes and/or extent of ventricular ischemia. Finally, no study has assessed the association between ECG pattern of atrial infarction and subsequent stroke risk. The **supplementary appendix** provides detailed descriptions of how ECG metrics are centrally assessed.

The prognostic role of Q-wave regression and the issue of a standardized definition

The presence of Q-waves in patients with ACS has more than a mere descriptive or electrocardiographic meaning, as it entails relevant information regarding the pathophysiology,

anatomy, and prognosis[44–46]. Although over the last decades, the diagnostic importance of Q-wave infarction has been overshadowed by a more recent definition centered on ST-segment deviation[47], this entity still to date has a remarkable value[7,48,49]. Approximately 30% of ACS patients have new pathological Q-waves as marker for advanced stages in infarct evolution, more extended and less reversible injury, as well as a worse prognosis[7,45,46,49–52]. A variety of definitions for pathological Q-waves have been previously published **(Table 1)**[53–58]. Earlier studies defined a Q-wave as *pathological* if lasting more than 40 ms with an amplitude of more than 25% of the corresponding R-wave[53,54]. Over the years, the criteria for pathological Q-waves have been redefined from classic[53,54] to the most recent definition reported in the 2018 Universal Definition of MI[47]. The criteria for defining pathological Q-wave (or Q-wave equivalent) have been mainly derived from patients without acute myocardial ischemia[59,60], thus raising potential issues regarding the appropriateness of their use in ACS. Moreover, considering the relevant differences among various criteria, it is not uncommon that Q-waves can be defined as pathological by some definitions, but not by others. As a consequence, patients can be diagnosed as having (or not) pathological Q-waves based on which definition is used. Several studies compared previously published criteria to assess their diagnostic and prognostic implications[61–64]. In a large population study, Q-waves classification based on the Third Universal Definition of MI did not provide advantages compared to simple ≥40 ms Q-wave criteria with respect to predicting the risk of cardiovascular death[63]. In 184 STEMI patients treated with primary PCI, Delewi et al. showed that, among previously proposed Q-wave definitions, classic criteria for Q-wave had the best correlation with infarct size as determined by cardiac magnetic resonance[62]. In agreement with other studies[61,65], these findings suggested high specificity (due to a more strict definition) of classic criteria as opposed to high false positivity of the more recently proposed criteria for detecting myocardial injury. A drawback in using overly stringent (and less sensitive) criteria means risking missing out on clinically relevant information; this is especially so in high-risk patients such as those with ACS. To date, it is largely unclear, although potentially relevant for clinical practice, whether the classic or more recent Q-wave criteria better predict clinical outcomes in ACS patients, pointing to the importance of a contemporary reappraisal of this topic.

Another matter of controversy is whether dynamic Q-wave changes between pre and post-treatment ECGs (either new development, worsening, or regression) can predict clinical outcomes[48,62,66,67]. Q-wave appearance can be transient and due to ischemic conduction delay in *vital* (electrically inactive) myocardium rather than irreversible *necrosis*; thus, their resolution might be a marker of effective myocardial salvage in patients who are readily reperfused[67–69]. On the other hand, their appearance after PCI and/or persistence at discharge might imply more severe ischemic injury and failed reperfusion. As compared with Q-wave persistence, Q-wave regression has been associated with better myocardial recovery and larger improvement in left ventricular function at cardiac magnetic resonance and perfusion SPECT, suggesting potential clinical relevance[62,70]. However, results from imaging and clinical studies actually diverge. The HORIZONS-AMI, evaluating 1,084 STEMI patients with Q-waves on their presenting ECG, failed to show any significant differences in terms of cardiac death (5.1 vs. 9.2%; P=0.10) and all-cause death (2.9% vs. 5.6%; P=0.052), between patients with resolved versus persistent Q-waves at discharge, even though the percentage of events was numerically halved in the former[7]. To note in this study, the definition of pathological Q-waves was based on Selvester QRS criteria[7]. Thus, the contemporary prognostic value of Q-wave development, worsening, or regression after treatment, as well as their definition, remains a topic worth investigating further.

ST-deviation and resolution in STEMI and NSTE-ACS settings

Due to its high specificity, low cost, and near-universal availability, ST-segment deviation plays a central role in the management of patients with suspected ACS[71–74]. The mechanism of regional ST-deviation after occlusion of a coronary artery has been widely studied and is related to regional loss of function of ion channels generating electrical gradients[75]. The characteristic changes of ST-segments on the standard twelve-lead ECG during ischemia and after reperfusion (either by thrombolysis or PCI) have made the analysis of ST an indispensable tool, not only to diagnose ACS but also to localize the occluded coronary artery, detect the site of occlusion (proximal versus distal), predict outcomes, and evaluate treatment success/failure[4,23,25,76,77]. Moreover, the use of additional right precordial leads (especially V4R) is of valid help in diagnosing right ventricular

involvement and carries relevant implications in clinical decision-making[78,79]. Since right precordial leads were not recorded for the purpose of the MATRIX trial, we will investigate the usefulness of standard 12-lead ECGs in identifying the site of culprit lesion in a large and contemporary cohort of patients who underwent routine coronary angiography.

The clinical relevance of ischemic ST-segment changes has been extensively investigated in the STEMI population[6,76,80–85]. The early resolution of ST-deviation (ST-segment recovery) as well as post-treatment residual ST-deviation have been repeatedly shown to carry independent prognostic implications after infarction, well beyond post-treatment angiographic data[6,76,80–84,86,87]. Whether access site and pharmacologic regimen can impact on ST-segment recovery remains unclear. Radial access has been shown to reduce ischemic and bleeding events and mortality as compared to femoral access[33,34,88–91]. In addition, some authors advocated increasing time to reperfusion by radial access due to technical challenges and higher crossover rates, especially in the case of STEMI and non-experienced operators[92,93]. Actually, no large study compared the impact of radial versus femoral access on myocardial reperfusion based on ECGs analysis. Previous studies reported a comparable effect of bivalirudin and unfractionated heparin plus GPI on ST-resolution and residual ST-deviation after PCI[81,94,95]. However, an adequately powered comparison of bivalirudin versus heparin (with or without GPI) on ECG measures of myocardial perfusion had not been previously published. Moreover, no large study prospectively evaluated the possible differential impact of different bivalirudin regimens (either full versus low dose or prolonged versus short-term infusion) on ST-resolution. Among different studies, numerous measurement methods have been proposed, mainly differing for the number of ECGs (index and post-treatment[96], or post-treatment only), number of leads (all leads, selected leads according to MI location, or single worst lead), ST-deviation direction (ST-elevation only, or combined ST-elevation and depression), quantification of ST-recovery (% of resolution, absolute resolution, or residual ST-deviation), speed of ST-recovery, and cut-off/s used[6,76,80–84,97]. In this context, comparative studies aiming at establishing the *gold standard* method for calculating ST-segment resolution/persistence provided controversial results. Buller[6] and Verouden[97] and colleagues came up with conflicting conclusions, reporting that residual ST-elevation measured in the most affected lead on post-treatment ECG only[6] and the sum of ST-

deviation resolution (at a 50% cut-off) on pre and post-treatment ECG[97] were the best independent predictor of mortality, respectively. Although several hypotheses have been put forth to explain differences in results (i.e., timing for ECGs recording, randomized versus real-world study, statistical approach), the puzzle remains unsolved. Further investigation of which ST-recovery measurement methods can better predict outcomes in a contemporary setting of STEMI treated by default primary PCI and potent P2Y12 inhibitors, and with limited use of GPI, is actually of critical importance. Finally, whether combining additional signs of ischemia resolution (i.e., Q-wave disappearance, QRS and T-peak to T-end interval narrowing) might implement the ability to predict successful reperfusion and outcomes remains yet to be determined.

The presence of ST-depression on admission ECG among NSTE-ACS patients is currently used to identify patients at higher risk for events, and who may benefit from an early invasive strategy[72,98–100]. Data from large trials showed the relevant predictive role of ST-depression on admission for death and recurrent MI[101–103], which suggested a positive correlation between the severity of ST-depression and outcomes[101–103]. However, discordant data have also been reported. In the Global Registry of Acute Coronary Events (GRACE) and Canadian ACS Registry registries[104,105], the quantitative assessment of ST-depression failed to show an incremental predictive value for clinical outcomes as compared to the simple qualitative evaluation (presence or absence) of ST-depression[104,105]. Also, the value of post-treatment ST-depression resolution in patients with NSTE-ACS remains under-investigated and less well defined by specific criteria compared with STEMI[106,107], and clear cut-off value, as well as the point for the correct assessment (J-point vs. 60 ms after J point), remain unclear. Thus, considering current limitations, the prognostic role of ST-segment deviation and resolution in the NSTE-ACS patients should be better clarified.

Role of ECG in identifying culprit lesion location and patency among ACS patients

Numerous ECG criteria/algorithms aimed at predicting culprit lesion location (and their potential prognostic implications) have been previously published[18–22,108–111] and reviewed[4,5,112,113]. However, in a recent validation cohort study, their performance was poor, suggesting a lack of generalizability in current practice[114]. Prior studies attempting to correlate ECG patterns with the

culprit lesions location entail several limitations. First, they often implemented a retrospective design and the inclusion of a modest number of patients (often less than a hundred) that were additionally grouped per vessel (i.e., RCA versus LCX) or site (proximal versus distal) of occlusion[4,5,18,23,25]. Moreover, their execution largely predated the modern primary PCI era where immediate angiography provides greater reliability for culprit lesion identification[23,25]. Finally, previous analyses mainly focused on selected ACS populations, such as those with single-vessel disease and inferior or anterior locations, excluding those with multi-vessel disease [18–20, 23,25,108,109].

While most analyses focused so far on the degree of ST-deviation for the identification of culprit lesion location, no large study clarified whether measuring it at the J-point or more downstream (i.e., 20, 60 or 80 ms after the J-point), may impact ECG prediction compatibility[115,116]. Moreover, dynamic changes in the QRS complexes, ST-segments, and T-waves often occur during culprit occlusion. Whether the combination of multiple ECG parameters (i.e., QRS duration and morphology, axis orientation, T-wave characteristics) in a more comprehensive ECG algorithm/score can improve the reliability of currently used criteria for localizing culprit remains to be determined. Finally, no prior study has assessed the capability of ECG in identifying culprit lesion patency and conversely its role on ECG alterations and outcomes in STEMI patients.

Total occlusion of the culprit artery in NSTE-ACS

The presence of a total occlusion of culprit coronary artery is usually associated with ST-elevation on ECG in ACS patients, and requires immediate coronary angiography and revascularization. However, a considerable proportion of acute coronary occlusion may be missed if the ECG is assessed only for ST-elevation in contiguous leads, fulfilling diagnostic criteria for STEMI[26,28,117–119]. Indeed, a subset of NSTE-ACS patients (approximating at ¼ of cases) presents a total culprit vessel occlusion (Thrombolysis in Myocardial Infarction [TIMI] flow grade 0/1) at coronary angiography, without any evidence of classic STEMI pattern[26–28,120–122]. In more than 70% of these cases, either the right coronary or left circumflex artery are involved, with a predominant infero-lateral and posterior infarct distribution[26–28,121]. As proof of concept, occlusion of the left circumflex is underreported in studies recruiting STEMI (only 15% of cases)[26], a possible consequence of the silent nature of

perfused territory on standard twelve-lead ECG[26,27]. These patients with 'missed STEMI' and total occlusion of the culprit artery almost systematically received delayed invasive treatment, being referred to the catheterization laboratory 24-48 hours after initial presentation[26–28,123]. This point poses relevant concerns due to the established detrimental impact of culprit occlusion on outcomes and potential benefit from earlier reperfusion. The TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38) enrolled 13,608 ACS patients, of whom 1,198 or 8.8% presented with anterior ST-depression[27]. Of those, 314 or 26.2% had an occluded culprit at coronary angiography (performed at a median time from ECG of 29.4 h), with a left circumflex involvement in half of the cases. At 30-day follow-up, the rate of death and MI was significantly higher among patients with an occluded artery as compared with those with a patent culprit artery, suggesting the relevant prognostic value of this factor and the inadequate management of these patients[27]. Confirming these data, a recent meta-analysis of 40,777 subjects estimated that NSTE-ACS patients with total occlusion of culprit artery are at a higher risk of both major adverse cardiac events and all-cause mortality at short (risk ratio [RR] 1.41; CI 1.17-1.70; P = 0.0003 and RR 1.67; CI 1.31-2.13; P < 0.0001, respectively) and long-term (RR 1.32; CI 1.11-1.56; P = 0.001 and RR 1.42; CI 1.08-1.86; P = 0.01, respectively) follow-up[28].

Therefore, patients presenting with NSTE-ACS with an occluded culprit vessel on coronary angiography represent a high-risk subset whose identification remains challenging, and for whom current guidelines do not provide specific recommendations[72,98]. Although several ECG criteria, based on the magnitude and location of ST-depression, pathological Q-waves, and R/S ratio in leads V1-V2 have been proposed, results from previous studies conflict and are not validated in the large NSTE-ACS population, making their practical values unclear[26,28,117,121,124–126]. The recognition of subtle ECG findings suggesting the presence and location of ongoing ischemia and possible coronary occlusion (including a distinct ST-elevation in aVR or minor [non-diagnostic] ST-elevation in other leads, T-wave width/morphology following ST-depression [i.e., de Winter's sign], U-wave polarity [positive vs. negative]) may be of value in patients presenting with NSTE-ACS.

To date, implementing the correct and timely identification of acute coronary occlusion in the NSTE-ACS setting by specific ECG patterns/algorithms could be crucial to facilitate earlier revascularization (following a "STEMI-like pathway") and improve patients' prognosis in contemporary practice.

The prognostic role of T-wave morphologies and indices in ACS

Although numerous studies have so far investigated and reviewed the role of T-wave abnormalities in ACS[3,11], their prognostic significance remains a matter of contention[127–129]. In large ACS studies, patients with isolated T-wave inversion (TWI) had similar cardiovascular outcomes and extent of coronary lesions compared with those presenting normal ECG[128,130]. In line with these reports, a recent sub-analysis of GRACE and Canadian ACS registries evaluating 7,201 NSTE-ACS patients[131], TWI was a marker of high-risk profile (i.e., elderly, multiple cardiovascular risk factors) but not an independent predictor of adverse outcomes[131]. On the other hand, other studies identified specific T-wave abnormalities, as defined by Wellens[132] and de Winter[133], which are associated with critical stenosis/occlusion of the proximal LAD and carry adverse prognostic implications if not promptly invasively managed[127,132]. Moreover, Jacobsen et al. demonstrated that patients with diffuse T-wave abnormalities had significantly worse outcomes[134] and benefited from an early invasive as compared with a conservative strategy[135]. Methodological issues, low number of patients undergoing coronary angiography, and considerable heterogeneity among populations might have partially obscured the potential adverse prognostic impact of T-wave abnormalities in previous studies. Further investigations regarding different aspects of T-wave abnormalities, including type, location (anterior vs. non-anterior), extent (number of leads), and dynamics (pre and post-revascularization changes) are necessary to shed light on this persistently ambiguous sign.

An additional T-wave-derived parameter, the T-peak to T-end interval (Tp-e), has been recently proposed as a potential outcomes predictor in patients with ACS. Tp-e prolongation marks an increased ventricular repolarization dispersion, the final substrate for ventricular arrhythmias and sudden cardiac death in ischemic heart disease[136]. Erikssen et al.[136], evaluating 1,384 ACS patients referred to coronary angiography, showing that prolonged Tp-e (relative risk 1.5, 95% CI 1.3 to 1.7) and heart rate-corrected Tp-e (relative risk 1.6; 95% CI 1.4 to 1.9) were strongly associated

with an increased risk of death, particularly for fatal arrhythmias. Initial evidence warrants further investigations to elucidate the relationship between prolonged Tp-e with clinical, angiographic, and outcome data in the whole ACS population, also to clarify which measurement method (tangent versus tail method) should be used, and which is the prognostic impact of Tp-e interval changes from admission to serial follow-up ECGs.

Materials and methods

Study design and population

Between October 11, 2011, and November 7, 2014, the MATRIX trial (NCT01433627) enrolled 8,404 patients with an ACS (both STEMI and NSTE-ACS) for whom invasive management was planned[32–34]. Detailed rationale, design, and results have been previously reported[32–34,137]. Per study protocol, standard twelve-lead ECGs (paper speed of 25 mm/s, calibrated at 1 mm = 0.1 mV) were recorded in all patients, and classified as: (a) index ECG, before coronary angiography (at the time of qualification for the inclusion in the trial); (b) post-procedural ECG, after the index coronary angiography and/or PCI; (c) predischarge ECG, during the hospital stay or at the time of discharge. The ECG-MATRIX is a predefined sub-study of the MATRIX aimed at investigating the role of pre and post-procedural ECG features to predict outcomes as well as angiographic findings in ACS patients receiving invasive management. Moreover, the study sought to evaluate the impact of the access site and/or pharmacological regimens on ECG patterns after PCI to gain further insight into the comparative effectiveness on ECG parameters of procedural success of the two randomly allocated intervention. This sub-study is being executed in accordance to previously proposed criteria for conducting ECG sub-study which is nested within prospective trials in patients with coronary artery disease[35]. Eligible patients for the sub-study were all participants in the trial. Since there was no predefined fee for participating in the ECG-MATRIX sub-study, each site was originally invited to participate on a voluntary basis. A total of 39 centers recruiting 6,764 patients declared their interest in participating. After excluding patients in whom ECGs were not available for central analysis, 4,516 patients (2,212 or 49% STEMI, and 2,304 or 51% NSTE-ACS), which accounts for 53.7% of the

study population, of whom 4,022 patients have matched pre and post-treatment ECGs (1,999 or 49.7% STEMI, and 2,023 or 50.3% NSTE-ACS), are eligible for the study.

From January to August 2018, all collected ECGs were anonymously catalogued, assessed for quality, and digitized for central analysis with a final sampling rate of 500 samples/sec, in accordance with current standards for adult ECGs[138]. The final version of the study design and methods were defined in September 2018. ECG analysis started in October 2018 and is projected to reach completion by Q2 2020. As per June 2, 2019, matched pre and post-treatment ECGs from 644 patients have been analyzed.

Methods for ECG analysis

Central ECG analysis is performed at the Department of Cardiology, Inselspital, University of Bern, Switzerland, by 13 fully trained cardiologists who are blinded to the original randomization scheme and clinical outcomes (**Table 2)**. To avoid inter-reader variability, all matched (index and post-treatment) ECGs for each individual patient are measured by a single assessor. The average time for central reading of a single ECG approximates to 45 minutes. All measurements are performed in a computer environment using professional computer software (EP Calipers®, www.epstudiossoftware.com/about-ep-calipers/). The software allows manual (operator-interactive) measurements of digital ECG images (in high-resolution) using electronic calipers set manually by the operators. This method has been selected for the present ECG sub-study, as it previously showed high accuracy and reproducibility, limiting operator variability, and allowing to work on a large number of ECG recordings easily[139,140].

Inter-reader agreement assessment

Previous studies underscored the importance of minimizing inter-reader differences in ECG analysis and interpretation within and across ECG core laboratories, considering the relevant clinical implications that this entails [141–143]. Moreover, inter-reader agreement analysis for ECG metrics such as P-wave or PR-deviation measurements is rarely reported in the literature. Pearson correlation and Bland-Altman plot analysis between the reference reader and reader 1 for PR-segment depression

(at J-point and maximum point of deviation) are shown in **figure 2,** and detailed methods and results for all readers and metrics are shown in the **supplementary appendix**. Our findings demonstrate a high inter-reader agreement among readers in all the investigated ECG metrics (in line with previous results reported in the literature)[141–143] and support the accuracy of ECG analysis.

ECG-MATRIX pre-specified sub-analyses

For the purpose of this study, the following sub-analyses are pre-specified:

- atrial infarction sub-analysis, to assess the prognostic significance of ECG signs suggestive for atrial infarction on admission and their resolution after PCI;
- Q-wave sub-analysis, to compare the prognostic impact of pathological Q-waves defined according to the 2018 Universal MI definition with the previously reported definitions, and to assess the prognostic value of Q-wave resolution after PCI;
- ECG value for predicting coronary flow and anatomical characteristics in STEMI patients;
- ECG value for predicting culprit vessel occlusion on coronary angiography in NSTE-ACS;
- T-wave pattern sub-analysis, to evaluate the prognostic relevance of T-wave metrics, and their dynamic changes on serial ECGs.

The complete list of pre-specified sub-analyses is reported in the **supplementary appendix**.

Conclusions

The MATRIX trial was designed to test the impact of bleeding avoidance strategies, radial access and bivalirudin in comparison with femoral access and unfractionated heparin with optional GPI respectively, on ischemic and bleeding outcomes in patients with ACS undergoing invasive management.

This will represent the largest contemporary study analyzing the role of ECG for the diagnosis and risk stratification of ACS patients with or without ST-segment deviation, concurrently exploring atrial and ventricular ischemia on matched pre and post-treatment ECGs. The ECG-MATRIX will attempt to answer some outstanding questions regarding specific ECG parameters in the diagnosis and

management of ACS patients as well as reassessing the role of known ECG metrics in contemporary practice consisting of early invasive management.

Declaration of Conflicting Interests

Dr. Valgimigli reports grants from The Medicines Company, grants from Terumo, during the conduct of the study; grants and personal fees from AstraZeneca, personal fees and nonfinancial support from The Medicines Company, personal fees from Terumo, St Jude Vascular, Alvimedica, Abbott Vascular, and Correvio, outside the submitted work.

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Dr. Andò reports non-financial support from Terumo, during the conduct of the study; personal fees from Daiichi Sankyo, personal fees and non-financial support from Bayer, non-financial support from Boeringer-Ingelheim, personal fees from AstraZeneca, personal fees from Menarini, personal fees from Chiesi, personal fees from Pfizer, personal fees from Biosensors, outside the submitted work.

Other Authors declare that there is no conflict of interest.

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Figure legends

Figure 1. Diagnostic criteria for atrial infarction proposed by Liu et al. [13], Hellerstein [15], and Sivertssen et al. [41].

Figure 2. Pearson correlation and Bland-Altman plot analysis for PR-segment depression from the reference (ref.) reader and reader 1.

Table 1. Multiple definitions of pathological Q-waves classification

Classic criteria [53,54,144]	Q-wave with a duration ≥40 ms and/or a depth ≥25% of the R-wave in the same lead or the presence of a Q-wave equivalent
TIMI criteria [55]	Q-wave ≥30 ms in 2 contiguous leads, any Q- or R-wave ≤10 ms and ≤1 mm in lead V2, and R-wave ≥40 ms in V1
Selvester QRS Scoring System [56]	Q-wave duration ≥30 ms in leads I, II, aVL, aVF, V5, V6, or ≥20 ms in V4, or any Q-wave in V1, V2, V3 R-wave duration ≥40 ms in V1, or ≥50 ms in V2, or ≤30 ms in V3 R/Q ratio ≤1 in leads I, aVL, aVF R/S ratio ≥ 1 in lead V1 R/S ratio ≥ 1.5 in lead V2 R/Q or R/S ratio ≤ 0.5 in lead V4 R/Q or R/S ratio ≤ 1 in leads V5, V6
Selvester QRS Screening Criteria [59,60]	Q-wave ≥ 30 ms in aVF R-wave ≤ 1 mm and/or ≤ 10 ms in V2 R-wave ≥ 40 ms in V1 Additional criteria: Q-wave ≥ 40 ms in leads I and aVL Q-wave ≥ 40 ms in ≥ 2 leads of V4, V5, or V6 Any Q-wave in V2
Minnesota Code Manual [57]	Major Q-waves: Q-wave ≥ 50 ms in any leads; Q-wave ≥ 40 ms in any leads other than aVF and III; Q-wave ≥ 30 ms with R/Q < 3 in leads V2-V6, I, or II; QS-wave in lead V4 or V5; or an initial R wave in leads V1–V5 and flag QS in the next leads V2–V6 Moderate Q-waves: Q-wave ≥ 40 ms in lead aVF or III; Q wave ≥ 30 ms V2-V6, I, or II; Q-wave ≥ 20 msec and R/Q < 3 in leads V2-V6, I, or II; or QS-wave in leads V3, I, or II Minor Q-waves: Q-wave ≥ 30 ms in leads aVL, aVF, or III; Q-wave ≥ 20 ms and R/Q < 5 in leads V2-V6, I, or II; or QS in leads aVF, III, or V2
2000 ESC/ACC Consensus [58]	Any Q-wave in leads V1 through V3, Q-wave ≥30 ms in leads I, II aVL, aVF, V4, V5, V6 The Q-wave changes must be present in any two contiguous leads, and be ≥1 mm in depth
2018 Fourth Universal Definition of MI [47]	Any Q-wave in leads V2–V3 ≥20 ms or QS complex in leads V2-V3 Q-wave ≥30 ms and ≥1 mm deep or QS complex in leads I, II, aVL, aVF or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4–V6; II, III, and aVF; V7-V9) R-wave ≥40 ms in V1-V2 and R/S ≥1 with a concordant positive T-wave in the absence of a conduction defect

Table 2. ECG metrics and patterns analyzed in the ECG-MATRIX

Heart rhythm	- Heart rate - Rhythm definition - Rhythm disturbance (supra-ventricular and ventricular arrhythmias) - Premature ectopic beats (atrial and ventricular)
Frontal plane QRS axis	- Normal axis orientation - Left or right axis deviation
Atrial depolarization	- P-wave voltage - P-wave duration - P-wave dispersion - P-wave time-to-peak (atrial intrinsicoid deflection) - P-peak to P-end interval - P-wave peak-to-end interval - P-wave morphology (i.e., irregular, M- / W-shaped) - P-wave terminal force in V1 - Left atrial enlargement - Right atrial enlargement - Interatrial block
Atrial repolarization	- PR-deviation at atrial J-point (elevation and/or depression) - Maximum PR-deviation (elevation and/or depression) - ∑ PR-deviation at atrial J-point (elevation and/or depression) - ∑ Maximum PR-deviation (elevation and/or depression) - PR-deviation resolution at atrial J-point (elevation and/or depression) - Maximum PR-deviation resolution (elevation and/or depression) - PR-segment deviation slope (flat, slightly/markedly down-sloping or up-sloping) - P-wave / PR-segment junction shape distinguishing a smooth-angled versus a sharp-angled - P-wave polarity / PR-deviation concordance (or discordance)
Atrioventricular conduction	- PR-interval duration - Time relation between P-wave / QRS complex - Atrioventricular block - Wolf-Parkinson-White pattern
Ventricular depolarization	- Q-, R-, S-, R'-, S'- (individual) waves voltage - Q-, R-, S-, R'-, S'- (individual) waves duration - R-wave time-to-peak (ventricular intrinsicoid deflection); - Peak-to-peak QRS complex amplitude - Net QRS complex deflection - QRS complex duration - QRS complex dispersion - Complete/incomplete right/left bundle branch block - Left anterior/posterior fascicular block - Bifascicular block
Ventricular repolarization	- ST-segment deviation at J-point (elevation and/or depression) - ST-segment deviation 60 ms after the J-point (elevation and/or depression) - ∑ ST-segment deviation at J-point (elevation and/or depression) - ∑ ST-segment deviation 60 ms after the J-point (elevation and/or depression) - ST-segment resolution at J-point (elevation and/or depression) - ST-segment resolution 60 ms after the J-point (elevation and/or depression) - Non-persistent ST-segment elevation - Dynamic ST-segment shifts

	- T-wave amplitude - Peak-to-peak T-wave amplitude - Net T-wave deflection - T-wave duration - T-wave morphology (i.e., biphasic, hyper-acute) - T-wave time-to-peak (T-wave intrinsicoid deflection) - Tp-e interval with tail method (with and without Bazett's correction) - Tp-e interval with tangent method (with and without Bazett's correction) - Tp-e interval dispersion - JT-interval with tail method (with and without Bazett's correction) - JT-interval with tangent method (with and without Bazett's correction) - JT-interval dispersion - JT-interval prolongation index - QT-interval with tail method (with and without Bazett's correction) - QT-interval with tangent method (with and without Bazett's correction) - QT-interval dispersion - QT-interval prolongation index
Additional metrics (including scores or patterns)	- Wellens' pattern - De Winter's pattern - Sgarbossa's criteria for left bundle branch block - Smiths' criteria for left bundle branch block - Anderson-Wilkins acuteness score - Left ventricular hypertrophy - Right ventricular hypertrophy - Index of Cardiac Electrophysiological Balance (iCEB) - ECG-based Regional Restitution Instability Index (R2I2) - Mechanical systole duration by Waller's formula

1