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Diagnostic and prognostic value of QRS duration and QTc interval in patients with suspected myocardial infarction

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Abstract

Background: *While prolongation of QRS duration and QTc interval during acute myocardial infarction (AMI) has been reported in animals, limited data is available for these readily available electrocardiography (ECG) markers in humans.*

Methods: *Diagnostic and prognostic value of QRS duration and QTc interval in patients with suspected AMI in a prospective diagnostic multicentre study were prospectively assessed. Digital 12-lead ECGs were recorded at presentation. QRS duration and QTc interval were automatically calculated in a blinded fashion. Final diagnosis was adjudicated by two independent cardiologists. The prognostic endpoint was all-cause mortality during 24 months of follow-up.*

Results: *Among 4042 patients, AMI was the final diagnosis in 19% of patients. Median QRS duration and median QTc interval were significantly greater in patients with AMI compared to those with other final diagnoses (98 ms [IQR 88–108] vs. 94 ms [IQR 86–102] and 436 ms [IQR 414–462] vs. 425 ms [IQR 407–445], $p < 0.001$ for both comparisons). The diagnostic value of both ECG signatures however was only modest (AUC 0.56 and 0.60). Cumulative mortality rates after 2 years were 15.9% vs. 5.6% in patients with a QRS > 120 ms compared to a QRS duration ≤ 120 ms ($p < 0.001$), and 11.4% vs. 4.3% in patients with a QTc > 440 ms compared to a QRS duration ≤ 440 ms ($p < 0.001$). After adjustment for age and important ECG and clinical parameters, the QTc interval but not QRS duration remained an independent predictor of mortality.*

Conclusions: *Prolongation of QRS duration > 120 ms and QTc interval > 440 ms predict mortality in patients with suspected AMI, but do not add diagnostic value.* (Cardiol J 2018; 25, 5: 601–610)

Key words: QRS duration, QTc interval, chest pain

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Introduction

Acute myocardial infarction (AMI) is a major cause of death and disability worldwide. As highly effective treatments are available, early and accurate detection of AMI is crucial [1–3]. Clinical assessment, the 12-lead electrocardiogram (ECG) and cardiac troponin (cTn) form the cornerstones for the early diagnosis of AMI [1].

The 12-lead ECG recording devices have been equipped with software more than two decades ago to automatically calculate both QRS duration and corrected QT interval (QTc). Animal studies investigating ECG changes after induction of an ischemic state found an acute prolongation of ventricular depolarization as reflected by QRS duration and of ventricular repolarization as indicated by QTc interval, with some suggesting a dose dependent effect between the amount of ischemia and the prolongation observed [4–6]. In humans, the induction of ischemia during exercise stress testing or balloon angioplasty resulted in prolongation of both QRS duration and QTc interval [7, 8]. QTc prolongation seemed to occur even earlier than conventional ECG markers of ischemia including ST deviation [8]. Despite this promising experimental data, the diagnostic value of QRS duration and QTc interval for the diagnosis of AMI has never been assessed in unselected patients presenting with symptoms suggestive of AMI.

Besides the need to rapidly rule-in or rule-out AMI, risk stratification is important in patients presenting with chest pain. Prolongation of QRS duration and QTc interval have been identified as markers of all-cause and cardiovascular mortality in the setting of AMI in the era of thrombolysis [9–11]. After the emergence of percutaneous coronary interventions as the preferred treatment of AMI, both markers were still found to predict mortality after AMI independently [12–14]. Due to the definitions of AMI applied in these studies, most patients suffered from extensive infarctions [9–14]. With the introduction of more sensitive biomarkers, much smaller AMI's can be diagnosed nowadays [1, 15, 16]. Whether the prognostic value of the QRS duration and the QTc interval found earlier is still valid for contemporary AMI patients diagnosed with high-sensitive cardiac troponin (hs-cTn) assays is unknown.

This study therefore assessed the diagnostic and prognostic value of QRS duration and QTc interval in a large prospective cohort of patients presenting to the emergency department (ED) with symptoms suggestive of AMI and diagnoses adjudicated based on hs-cTn levels.

Methods

Study design and population

Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is an ongoing prospective international multicenter study designed to advance the early diagnosis of AMI (ClinicalTrials.gov registry, number NCT00470587) [17–20].

Unselected patients presenting to the ED with symptoms suggestive of AMI (such as acute chest discomfort and angina pectoris) with an onset or peak within the last 12 h and an age > 18 years were recruited.

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. Written informed consent was obtained from all patients. The authors designed the study, gathered, and analysed the data according to the STARD guidelines for studies of diagnostic accuracy (see **Supplemental Appendix** for details), vouch for the data and analysis, wrote the paper, and decided to publish [21].

Routine clinical assessment and hs-cTnT measurement

All patients underwent a clinical assessment that included medical history, physical examination, 12-lead ECG, pulse oximetry and standard blood test. Levels of high-sensitive cardiac troponin T (hs-cTnT, Roche Diagnostics) were measured at presentation and serially thereafter as long as clinically indicated. For hs-cTnT, limit of blank and limit of detection have been determined to be 3 ng/L and 5 ng/L, an imprecision corresponding to 10% coefficient of variation was reported at 13 ng/L and the 99th-percentile of a healthy reference population at 14 ng/L [22]. Timing and treatment of patients was left to the discretion of the attending physician.

Adjudication of final diagnoses

Two independent cardiologists reviewed all available medical records — patient history, physical examination, results of laboratory testing, radiologic testing, ECG, echocardiography, cardiac exercise stress test, lesion severity and morphology in coronary angiography — pertaining to patients from the time of ED presentation to 90-days follow up. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist. Adjudication of the final diagnosis was performed centrally in a core lab (University Hospital Basel) and included two sets of serial cTn measurements: serial cTn

measurements obtained as part of routine clinical care locally (different (h)s-cTn assays), and serial measurements of hs-cTnT from study blood draws performed centrally in a core laboratory in order to take advantage of the higher sensitivity and higher overall diagnostic accuracy offered by hs-cTnT.

Acute myocardial infarction was defined and hs-cTn levels interpreted as recommended in current guidelines [1]. In brief, AMI was diagnosed when there was evidence of myocardial necrosis with a significant rise and/or fall in a clinical setting consistent with myocardial ischemia. Details on the adjudication of AMI are given in the online **Supplemental Appendix**.

ECG recording, manual analysis and calculation of QRS duration and QTc interval

At presentation to the ED, a standard 10-s 12--lead resting ECG was recorded using a standard ECG device at each of the participating institutions (including Schiller AG, Baar, Switzerland; Philips-Healthcare, Andover, MA, USA; and Customed, Ottobrunn, Germany). The patients were instructed not to talk during the 10 s, but were allowed to breath. The ECG's were recorded using a sampling rate of 500 Hz and a diagnostic signal bandwidth of 0.05 Hz to 150 Hz in all devices. Before measuring the QRS and QT durations, the recorded signals were further filtered with a digital 50 Hz AC filter (fulfilling the requirements by current international ECG device standards). In case of noise on the ECG recording, the attending physician on site decided whether the degree of noise was acceptable for clinical decision making or whether the ECG had to be repeated.

All 12-lead resting ECG's were manually interpreted in the ECG core-lab at the University Hospital Basel by internal-medicine specialists blinded to clinical and biochemical patient's details. ECG changes indicative of AMI being ST-elevations, ST-depressions and T-wave inversions were defined as recommended in current guidelines [1].

QRS duration and QT interval were measured automatically using standard ECG software. The QRS duration was measured from the beginning of the first detected Q-wave from all 12 averaged QRS complexes, to the end of the last S-wave from all 12 averaged QRS complexes. The QT interval was measured from the beginning of the first QRS taken from all 12 averaged leads to the end of the last T-wave taken from all 12 averaged leads. The QT interval was adjusted for mean heart rate to calculate the QTc interval using the Bazett formula [23]. Prolonged QRS interval was prospectively defined as QRS interval > 120 ms [24], and prolonged QTc interval was prospectively defined as QTc interval > 440 ms [25].

The digital ECG archive of the University Hospital Basel was further interrogated with regards to previous ECG's recorded within 90 days before the index admission. If available, those ECG's were used to calculate the difference in QRS duration and QTc interval.

Follow-up

After hospital discharge, patients were contacted after 3, 12 and 24 months by telephone or in written form. Information regarding death was furthermore obtained from the national registry on mortality, the hospital's diagnosis registry and the family physician records.

Statistical analysis

Continuous variables are presented as mean (standard deviation) or median (interquartile range [IQR]); categorical variables as numbers and percentages. Differences in baseline characteristics were assessed using the Mann-Whitney U test for continuous variables and the Pearson χ^2 test for categorical variables. Receiver-operating-characteristic (ROC) curves were constructed to assess the diagnostic accuracy for the diagnosis of AMI for the QRS duration and QTc interval. Survival during 2 years of follow-up according to QRS duration and QTc interval was plotted in Kaplan-Meier curves, and the log-rank test was used to assess differences in mortality between groups. Univariate Cox proportional hazard analysis to compute hazard ratios (HR) and 95% confidence intervals (CI) for the dichotomized QRS duration and QTc interval as well as for other electrocardiographic (conventional ECG changes indicative of AMI, left bundle branch block) and clinical (age, sex, creatinine clearance, hs-cTnT, diagnosis of AMI, history of AMI or coronary artery disease [CAD]) predictors of death were used. A multivariable model was then built including all significant predictors from univariate analysis.

All hypothesis testing was two-tailed and p-values < 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS for Windows 23.0 (IBM SPSS Inc, Chicago, IL).

Results

Enrolment and characteristics of patients

From April 2006 to August 2015, a total of 4323 unselected patients were enrolled. Patients

with unknown diagnosis after adjudication and at least one elevated hs-cTnT level possibly indicating AMI were excluded (n = 99), as were patients with missing ECG at presentation (n = 90) or ECGs with ventricular pacing (n = 92). This left 4042 patients eligible for analysis (Fig. 1). Baseline characteristics of the 4042 patients with acute chest pain are shown in Table 1. The adjudicated final diagnosis was AMI in 764 (19%) patients. Unstable angina was the diagnosis in 377 (9%), cardiac symptoms of origin other than CAD in 552 (14%), non-cardiac symptoms in 2185 (54%) and symptoms of unknown origin in 164 (4%).

Levels of QRS duration and QTc interval

QRS duration of more than 120 ms was recorded in 9% of patients, QTc interval of more than 440 ms in 32% of patients, respectively. Baseline characteristics of those groups are shown in Tables 1 and 2. Patients with prolonged QRS duration or QTc interval were older, had more cardiovascular comorbidities and were more often taking cardiac medication.

Diagnostic value of QRS duration and QTc interval for the diagnosis of AMI

Overall, the median QRS duration was 94 ms (IQR 86–104). Median QRS-duration was significantly longer in patients with AMI compared to those with other causes of chest pain (98 ms [IQR 88–108] vs. 94 ms [IQR 86–102], $p < 0.001$), however with a large overlap. Accordingly, the diagnostic accuracy of QRS duration at presentation for diagnosis of AMI as quantified by the area under the ROC curve (AUC) was only modest with 0.56 (95% CI 0.54–0.59).

The median QTc interval overall was 426 ms (IQR 409–448). Median QTc interval was significantly longer in patients with AMI compared to those with other causes of chest pain (436 ms [IQR 414–462] vs. 425 ms [IQR 407–445], $p < 0.001$). Accordingly, the diagnostic accuracy of QTc interval at presentation for the diagnosis of AMI as quantified by the AUC was again only modest with 0.60 (95% CI 0.58–0.62).

In a subset of 361 patients, a previous ECG within the last 90 days was available for comparison and to assess the value of changes in QRS duration or QTc interval. Between AMI and non-AMI patients, a difference was neither found in the change of QRS duration (median change 0 ms [IQR –5 – 8] vs. 2 ms [IQR –4 – 6], $p = 0.68$), nor in the change of the QTc interval (median change 6.5 ms [IQR –18 – 27] vs –4 ms [IQR –20 – 13], $p = 0.08$).

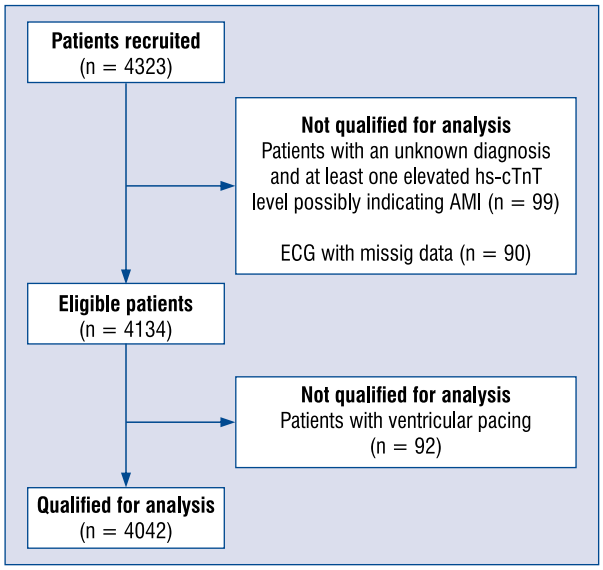

Figure 1. Patient flow diagram; AMI — acute myocardial infarction; ECG — electrocardiogram; hs-cTnT — high-sensitive cardiac troponin T.

Prognostic value of the QRS duration for the prediction of mortality during long-term follow-up

During a median follow-up duration of 25 months in survivors, 285 (7%) patients died. Median QRS duration was significantly higher in patients dying compared to survivors (102 ms [IQR 90–119] vs. 94 ms [IQR 86–102], $p < 0.001$). Cumulative mortality rates after 2 years were 15.9% and 5.6% in patients with a QRS > 120 ms compared to patients with a QRS duration ≤ 120 ms ($p < 0.001$, Fig. 2A). This was observed in both patients with AMI and in patients with other diagnoses ($p < 0.001$ for both comparisons, Fig. 2B, C). These findings were also unchanged if patients with ST-segment elevation myocardial infarction (STEMI) were excluded and only patients with non-ST-segment elevation myocardial infarction (NSTEMI) were analyzed (data not shown).

In univariate Cox proportional hazard analysis, a QRS duration > 120 ms predicted mortality with a HR of 2.95 (95% CI 2.23–3.90, $p < 0.001$). After adjusting for important clinical and electrocardiographic parameters, the QRS duration was no longer significant (Table 3).

Prognostic value of the QTc interval for the prediction of mortality during long-term follow-up

Median QTc interval was significantly higher in patients dying compared to survivors (450 ms [IQR

Table 1. Baseline characteristics of the patients.

	All patients (n = 4042)	AMI (n = 764)	Non–AMI (n = 3278)	P
Age [years]	61 (49–74)	70 (58–80)	59 (47–72)	< 0.001
Female gender	1309 (32%)	202 (26%)	1107 (34%)	< 0.001
History:				
Arterial hypertension	2450 (61%)	576 (75%)	1874 (57%)	< 0.001
Diabetes	677 (17%)	196 (26%)	481 (15%)	< 0.001
Coronary artery disease	1301 (32%)	316 (41%)	985 (30%)	< 0.001
Previous myocardial infarction	918 (23%)	244 (32%)	674 (21%)	< 0.001
COPD	408 (10%)	75 (9.8%)	333 (10%)	0.78
Peripheral occlusive artery disease	217 (5%)	82 (11%)	135 (4%)	< 0.001
Chronic kidney disease	352 (9%)	130 (17%)	222 (7%)	< 0.001
Medication:				
Acetylsalicylic acid	1431 (35%)	344 (45%)	1087 (33%)	< 0.001
Thienopyridines	438 (11%)	95 (12%)	343 (11%)	0.12
Oral anticoagulation	359 (9%)	69 (9.0%)	290 (9%)	0.87
Beta-blocker	1347 (33%)	299 (39%)	1048 (32%)	< 0.001
Ca-antagonists	583 (14%)	129 (17%)	454 (14%)	0.03
Amiodarone	71 (2%)	13 (2%)	58 (2%)	0.90
Diuretics	936 (23%)	266 (35%)	670 (20%)	< 0.001
ACE-inhibitors	848 (21%)	205 (27%)	643 (20%)	< 0.001
AT2-blockers	707 (18%)	159 (21%)	548 (17%)	0.007
Statins	1379 (34%)	303 (40%)	1076 (33%)	< 0.001
Laboratory:				
Hs-cTnT at presentation [ng/L]	8 (4–20)	63 (28–179)	7 (4–12)	< 0.001
Creatinine clearance [mL/min/1.73 m^2]	85 (70–101)	76 (59–97)	87 (72–102)	< 0.001
ECG findings:				
QRS duration [ms]	94 (86–104)	98 (88–108)	94 (86–102)	< 0.001
QTc interval [ms]	426 (409–448)	436 (414–462)	425 (407–445)	< 0.001
ST-segment elevation	193 (5%)	125 (16%)	68 (2%)	< 0.001
ST-segment depression	407 (10%)	237 (31%)	170 (5%)	< 0.001
T-wave inversion	520 (13%)	202 (26%)	318 (10%)	< 0.001
No signs of ischemia	3171 (79%)	370 (49%)	2801 (86%)	< 0.001

Numbers are presented as median (IQR) or numbers (%). ACE — angiotensin converting enzyme; AMI — acute myocardial infarction; AT2 — angiotensin 2; COPD — chronic obstructive pulmonary disease; ECG — electrocardiogram; Hs-cTnT — high-sensitive cardiac troponin T

425–476] vs. 426 ms [IQR 408–446], p < 0.001). Cumulative mortality rates after 2 years were 11.4% and 4.3% in patients with a QTc > 440 ms compared to patients with a QTc interval ≤ 440 ms (p < 0.001, Fig. 3A). This was observed in both patients with AMI and in patients with other diagnoses (p < 0.001 for both comparisons, Fig. 3B, C). These findings were also unchanged if patients with STEMI were excluded and only patients with NSTEMI's were analyzed (data not shown).

In univariate Cox proportional hazard analysis, a QTc interval > 440 ms predicted mortality with a HR of 2.94 (95% CI 2.32–3.71, p < 0.001). After multivariable adjustment as described above, the QTc interval remained an independent predictor of mortality (HR 1.40, 95% CI 1.07–1.83, p = 0.01; Table 3).

Discussion

This study assessed the diagnostic and prognostic value of QRS duration and QTc interval in a large prospective international multicenter cohort of 4141 patients presenting with symptoms

Table 2. Baseline characteristics of the patients according to QRS duration and QTc interval.

	All patients (n = 4042)	QRS > 120 ms (n = 351)	QRS ≤ 120 ms (n = 3691)	P	QTc > 440 ms (n = 1310)	QTc ≤ 440 ms (n = 2732)	P
Age [years]	61 (49–74)	76 (64–82)	60 (48–73)	< 0.001	68 (57–79)	57 (46–70)	< 0.001
Female gender	1309 (32%)	94 (27%)	1215 (33%)	0.02	553 (42%)	756 (28%)	< 0.001
History:							
Arterial hypertension	2450 (61%)	297 (85%)	2153 (58%)	< 0.001	964 (74%)	1486 (55%)	< 0.001
Diabetes	677 (17%)	80 (23%)	597 (16%)	0.002	285 (22%)	392 (14%)	< 0.001
Coronary artery disease	1301 (32%)	189 (54%)	1112 (30%)	< 0.001	485 (37%)	816 (30%)	< 0.001
Previous myocardial infarction	918 (23%)	129 (37%)	789 (21%)	< 0.001	326 (25%)	592 (22%)	0.02
COPD	408 (10%)	57 (16%)	351 (10%)	< 0.001	165 (13%)	243 (9%)	< 0.001
Peripheral occlusive artery disease	217 (5%)	40 (11%)	177 (5%)	< 0.001	106 (8%)	111 (4%)	< 0.001
Chronic kidney disease	352 (9%)	82 (23%)	270 (7%)	< 0.001	185 (14%)	167 (6%)	< 0.001
Medication:							
Acetylsalicylic acid	1431 (35%)	179 (51%)	1252 (34%)	< 0.001	527 (40%)	904 (33%)	< 0.001
Thienopyridines	438 (11%)	58 (17%)	380 (10%)	< 0.001	155 (12%)	283 (10%)	0.21
Oral anticoagulation	359 (9%)	67 (19%)	292 (8%)	< 0.001	190 (15%)	169 (6%)	< 0.001
Beta-blocker	1347 (33%)	181 (52%)	1166 (32%)	< 0.001	524 (40%)	823 (30%)	< 0.001
Ca-antagonists	583 (14%)	79 (23%)	504 (14%)	< 0.001	251 (19%)	332 (12%)	< 0.001
Amiodarone	71 (2%)	16 (5%)	55 (2%)	< 0.001	52 (4%)	19 (1%)	< 0.001
Diuretics	936 (23%)	169 (48%)	767 (21%)	< 0.001	455 (35%)	481 (18%)	< 0.001
ACE-inhibitors	848 (21%)	122 (35%)	726 (20%)	< 0.001	342 (26%)	506 (19%)	< 0.001
AT2-blockers	707 (18%)	99 (28%)	608 (17%)	< 0.001	285 (22%)	422 (15%)	< 0.001
Statins	1379 (34%)	188 (54%)	1191 (32%)	< 0.001	510 (39%)	869 (32%)	< 0.001
Laboratory:							
Hs-TnT at presentation [ng/L]	8 (4–20)	20 (9–47)	8 (4–18)	< 0.001	13 (6–36)	7 (4–14)	< 0.001
Creatinine clearance [mL/min/1.73 m^2]	85 (70–101)	71 (54–90)	86 (71–102)	< 0.001	79 (62–97)	88 (73–103)	0.004
ECG findings:							
QRS duration [ms]	94 (86–104)	140 (130–152)	93 (86–100)	< 0.001	98 (88–114)	94 (86–100)	< 0.001
QTc interval [ms]	426 (409–448)	467 (442–494)	424 (407–444)	< 0.001	459 (448–475)	415 (401–427)	< 0.001
ST-elevation	193 (5%)	1 (0.3%)	192 (5%)	< 0.001	57 (4%)	136 (5%)	0.39
ST-depression	407 (10%)	10 (3%)	397 (11%)	< 0.001	187 (14%)	220 (8%)	< 0.001
T-wave inversion	520 (13%)	55 (16%)	465 (13%)	0.10	243 (19%)	277 (10%)	< 0.001
No signs of ischemia	3171 (79%)	289 (82%)	2882 (78%)	0.07	930 (71%)	2241 (82%)	< 0.001

Numbers are presented as median (IQR) or numbers (%). ACE — angiotensin converting enzyme; AT2 — angiotensin 2; COPD — chronic obstructive pulmonary disease; ECG — electrocardiogram; Hs-cTnT — high-sensitive cardiac troponin T

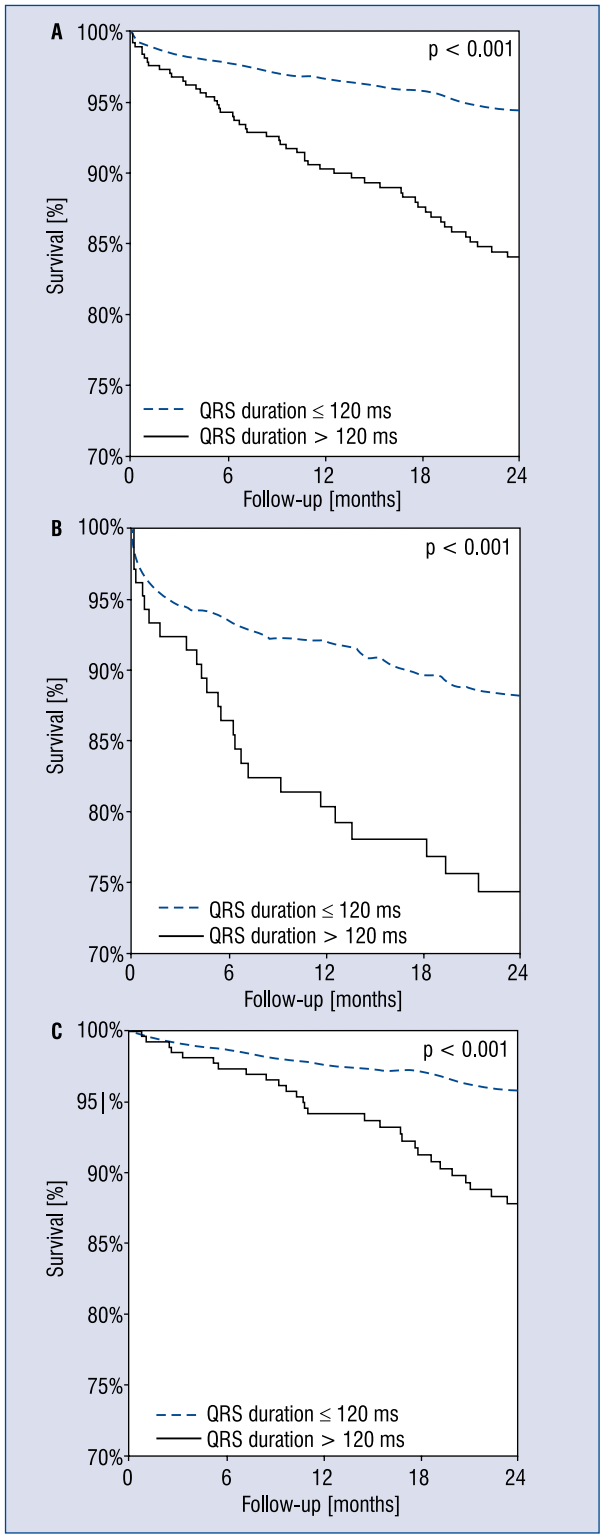

Figure 2. Kaplan-Meier curves for the cumulative survival according to QRS duration. Kaplan-Meier curves displaying survival during 2 years of follow-up according to QRS duration in (**A**) the overall group of patients with chest pain, (**B**) the subgroup of patients with acute myocardial infarction, and (**C**) those with other causes of chest pain. Differences in survival were assessed using the log-rank test.

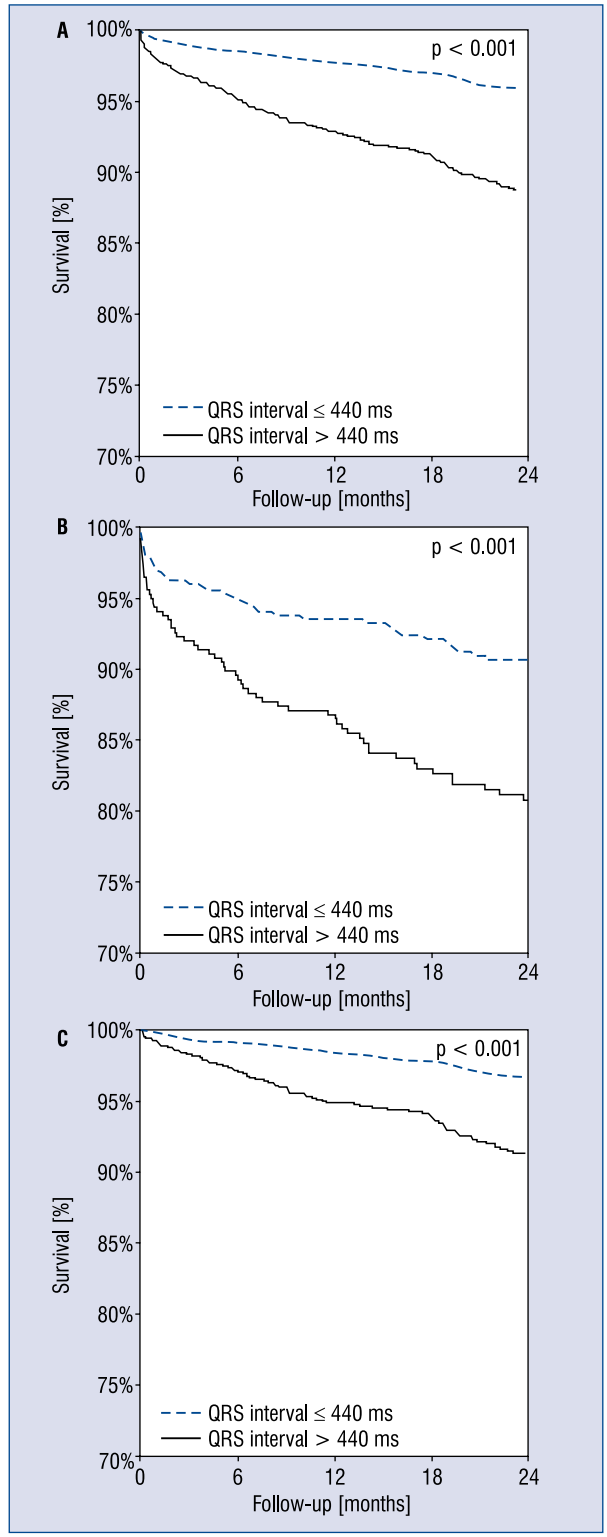

Figure 3. Kaplan-Meier curves for the cumulative survival according to the QTc interval. Kaplan-Meier curves displaying survival during 2 years of follow-up according to the QTc interval in (**A**) the overall group of patients with chest pain, (**B**) the subgroup of patients with acute myocardial infarction, and (**C**) those with other causes of chest pain. Differences in survival were assessed using the log-rank test.

Table 3. Uni- and multivariable Cox regression analysis for prediction of all cause all-cause mortality during long term follow up.

	Univariate analysis		Multivariable analysis	
	Hazard ratio	P	Hazard ratio	P
Age — per year	1.10 (1.09–1.12)	< 0.001	1.07 (1.06–1.09)	< 0.001
Female sex	1.01 (0.79–1.30)	0.94		
History of CAD	3.04 (2.39–3.86)	< 0.001	1.24 (0.86–1.78)	0.25
History of MI	2.68 (2.12–3.38)	< 0.001	1.35 (0.95–1.90)	0.10
Arterial hypertension	4.83 (3.34–6.98)	<0.001	1.13 (0.76–1.67)	0.56
Diabetes	1.94 (1.50–2.52)	< 0.001	1.16 (0.88–1.53)	0.28
COPD	2.57 (1.95–3.39)	< 0.001	1.90 (1.43–2.54)	< 0.001
Use of amiodarone	3.06 (1.75–5.34)	< 0.001	1.48 (0.84–2.62)	0.18
Creatinine clearance*	0.96 (0.96–0.97)	< 0.001	0.99 (0.99–1.00)	0.002
Hs-cTnT > 99 percentile	6.46 (4.92–8.49)	< 0.001	1.54 (1.10–2.15)	0.01
Diagnosis of AMI	3.29 (2.61–4.12)	< 0.001	1.33 (1.01–1.75)	0.04
Conventional ECG changes indicative of AMI	2.53 (2.00–3.21)	< 0.001	1.51 (1.16–1.97)	0.002
Presence of LBBB	3.21 (2.22–4.63)	< 0.001	1.09 (0.65–1.80)	0.75
Heart rate [bpm]	1.01 (1.01–1.01)	< 0.001	1.01 (1.01–1.01)	0.01
QRS duration > 120 ms	2.95 (2.23–3.90)	< 0.001	1.03 (0.70–1.52)	0.87
QTc interval > 440 ms	2.94 (2.32–3.71)	< 0.001	1.40 (1.07–1.83)	0.01

*Per increase in mL/min/1.73 m^2. Conventional electrocardiography (ECG) changes indicative of AMI include ST elevations, ST depressions and T-wave inversions. AMI — acute myocardial infarction; CAD — coronary artery disease; COPD — chronic obstructive pneumopathy; Hs-cTnT — high-sensitive cardiac troponin T; LBBB — left bundle branch block; MI — myocardial infarction

suggestive of AMI. The following major findings are thus reported.

First, QRS duration and QTc interval were significantly longer in patients with AMI compared to patients with other causes of chest pain. However, due to a large overlap, the diagnostic value of both parameters was only modest and insufficient for added value in clinical practice (AUC 0.57 and 0.60). Second, both a prolonged QRS duration and a prolonged QTc interval predicted an increased mortality during follow-up. This was observed both in the overall cohort as well as in important subgroups of patients with AMI and in patients with other causes of chest pain. Third, after multivariable adjustment, prolongation of the QTc interval remained an independent predictor of mortality, while a prolonged QRS duration was not.

These findings have clinical implications: Patients presenting with acute chest pain are frequently seen in the ED and account for up to 10% of all ED consultations [26]. Rapid diagnostic assessment and risk stratification in these patients is crucial medically, given that many have a remarkably increased cardiovascular risk, but also economically given the large amount of patients [26]. Hence, additional easily available markers assisting in the management of these patients are warranted.

Diagnostic value of QRS duration and QTc interval

Current guidelines concerning the interpretation of 12-lead ECGs regarding the diagnosis of myocardial ischemia recommend focusing on ST--segment and T-wave alterations [1]. However, the diagnostic value of the 12-lead ECG particularly in patients without ST-elevations is limited [17].

In animal models, an association between myocardial ischemia and prolongation of QRS duration has been shown [4–6]. Additionally clinical studies investigating QRS duration after induction of ischemia during coronary angiography showed direct proportionality between ischemia and QRS prolongation [6, 7, 27]. With regards to QT prolongation during myocardial ischemia, animal data as well as clinical data obtained during coronary angiography indicate that prolongation of the QT interval occurs much earlier and much more frequent than ST-segment or T-wave changes in the course of myocardial ischemia [8]. Despite the established association between myocardial ischemia and prolongation of both, the QRS duration as well

as the QT interval, the diagnostic value of these two markers for the diagnosis of AMI, according to available research, has not been prospectively studied in unselected patients with chest pain. The present data indicates that despite a statistically significant prolongation of QRS duration and QTc interval in patients with AMI, the diagnostic value is limited and insufficient for use in clinical practice. The major reason for the limited diagnostic value is that there are many other reasons that affect for QRS duration and the QTc interval, particularly the occurrence of bundle branch blocks that dilute the potential effects induced by myocardial ischemia. Of importance, the assessment of intra-individual changes in QRS duration and QT interval compared to a prior ECG did not increase the diagnostic value in this study.

Prognostic value of QRS duration and QTc interval

QRS prolongation and QT interval prolongation have been shown to predict mortality in patients who survived myocardial infarction [9–14]. Early studies have been carried out in the thrombolytic era [9–11]. Others that addressed the question in the era of PCI techniques were still dependent on the elevation of non-specific markers like creatinine kinase and liver enzymes regarding the diagnosis of AMI, and many patients enrolled were STEMI's [12–14]. As a consequence, most of the AMI patients in those cohorts had large myocardial infarctions resulting in a substantial loss of myocardium.

The present data corroborates previous studies in a way that prognostic value of a prolonged QRS duration and QTc interval can be extended to patients with smaller AMIs and NSTEMIs as diagnosed nowadays with high-sensitive cardiac troponin assays. Furthermore, a similar predictive value was found in patients presenting with acute chest pain overall, as well as in the subgroups of AMI patients, NSTEMI patients but also patients with chest pain other than AMI. One previous study has assessed prolongation of the QTc interval in NSTEMI patients and concluded that QTc is also a risk factor for mortality in these patients [28]. However, the findings in that study were based on a very low event rate of 4 deaths.

Limitations of the study

Potential limitations of the present study merit consideration. First, the prognostic endpoint used in this study was all-cause mortality, but not sudden cardiac death. Classification of death in clinical practice can sometimes be difficult and unreliable [29]. In addition, despite the large number of patients, the event rate of sudden cardiac death would have been too limited to allow meaningful analysis. Second, serial ECG's in these patients were not recorded and it cannot therefore provide comment on the impact and significance of fluctuations in QRS duration and QTc interval in short time or during the first 24–48 h. Third, while information on cardiac medication including amiodarone was collected, no information was available on non-cardiac medications potentially prolonging the QTc interval.

Conclusions

QRS duration and QTc interval are significantly prolonged in patients with AMI diagnosed based on hs-cTn levels compared to patients with other causes of chest pain. However, due to a large overlap, the diagnostic value of both parameters was insufficient for added value in clinical practice. With regards to prognosis, a prolongation of the QRS duration > 120 ms and of the QTc interval > 440 ms predicts mortality during follow-up. After adjustment for age and important ECG and clinical parameters, the QTc interval but not QRS duration remains an independent predictor of mortality.

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