HEART FAILURE AND CARDIOMYOPATHY

QRS and QTc interval prolongation in the prediction of long-term mortality of patients with acute destabilised heart failure

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Heart 2007;**93**:1093–1097. doi: 10.1136/hrt.2006.102319

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Accepted 9 January 2007
Published Online First 29 March 2007

Objectives: To quantify the prognostic utility of QRS and QTc interval prolongation in patients presenting with acute destabilised heart failure (ADHF) to the emergency department (ED).

Design: Prospective cohort study among patients enrolled in the B-Type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) study. QRS and QT intervals were measured in 173 consecutive patients with ADHF. QT interval was corrected using the Bazett formula. The primary end point was all-cause mortality during the 720-day follow-up.

Results: QRS interval was prolonged (⩾120 ms) in 27% of patients, and QTc interval was prolonged (⩾440 ms) in 72% of patients. Baseline demographic and clinical characteristics were comparable in patients with normal and prolonged QRS or QTc intervals. A total of 78 patients died during follow-up. Interestingly, the 720-day mortality was similar in patients with prolonged and normal QTc (44% vs 42%, p = 0.546), but was significantly higher in patients with prolonged QRS interval than in those with normal QRS (59% vs 37%, p = 0.004). In Cox proportional hazards analysis, prolonged QRS interval was associated with a nearly twofold increase in mortality (HR 1.94, 95% CI 1.22 to 3.07; p = 0.005). This association persisted after adjustment for variables routinely available in the ED.

Conclusions: Prolonged QRS interval, but not prolonged QTc interval, is associated with increased long-term mortality in patients with ADHF.

Current American College of Cardiology/American Heart Association and European Society of Cardiology guidelines recommend that electrocardiography be performed in all patients presenting with acute destabilised heart failure (ADHF).[1–3] Electrocardiography is an important tool in the diagnosis of ADHF, particularly in the identification of the cause of acute decompensation including tachyarrhythmia and myocardial infarction.[1–4] It is unknown whether electrocardiography also provides prognostic information in patients with ADHF. This would be attractive, as electrocardiography is routinely performed, easy, safe and inexpensive.

Recently, electrocardiography has received increasing recognition as a prediction tool in patients with chronic heart failure (HF). Prolongation of the QRS and the QTc interval have both been associated with increased mortality in chronic HF.[5–9] QRS duration emerged as an important predictor of mortality in various cohorts of patients with chronic HF, including patients with systolic left ventricular dysfunction and patients with implantable cardioverter defibrillators (ICDs).[5–9] Recently, prolonged QTc interval was suggested to be a powerful predictor of mortality in patients with advanced chronic HF.[10] Kaplan–Meier survival rates were three times higher in patients with normal QTc interval than in those with prolonged QTc in a study excluding patients taking class III drugs for arrhythmia.[10]

It was the aim of this study to evaluate the prognostic utility of QRS and QTc interval prolongation in a contemporary cohort of consecutive patients presenting with ADHF to the emergency department (ED).

METHODS

Setting and study population

This study specifically evaluated the prognostic utility of QRS and QTc interval prolongation in patients with ADHF enrolled in the B-Type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) study.[11] The BASEL study was a prospective study conducted in the ED of the University Hospital in Basel, Switzerland. The study was carried out according to the principles of the Declaration of Helsinki and was approved by our local ethical committee. Written informed consent was obtained from all participants. A total of 452 patients were enrolled in the BASEL study; 217 patients were diagnosed as having ADHF according to current guidelines, and 173 patients (80%) qualified for this study.[1–4] We excluded patients with pacemakers or ICDs and patients taking type III drugs for arrhythmia.[10] The final discharge diagnosis of ADHF was based on clinical presentation and standard investigations, and adjudicated by an internal medicine specialist not involved in the ED care on the basis of all available medical records pertaining to the individual patient, including the response to treatment and autopsy data in those patients dying in hospital. B-type natriuretic peptide (BNP) levels were measured and available for the final discharge diagnosis in 50% of patients.

QRS and QTc interval measurement

At the time of presentation to the ED, resting 12-lead ECGs were recorded at a paper speed of 25 mm/s. A cardiologist blinded to clinical and survival data determined QRS and QT duration. QRS duration was measured using leads V_3–V_6.[7]

Prolonged QRS interval was prospectively defined as QRS interval ⩾120 ms.[12] In accordance with the latest recommendations for clinical QT interval measurement, QT interval duration was recorded for three consecutive beats through leads II and V_4.[10 13] With calipers used on printed ECGs, each QT interval was measured from the beginning of the QRS complex to the visual return of the T wave to the isoelectric line. When the T wave was interrupted by the U wave, the end of the T wave was

Abbreviations: ADHF, acute destabilised heart failure; BNP, B-type natriuretic peptide; BASEL, B-Type Natriuretic Peptide for Acute Shortness of Breath Evaluation; ED, emergency department; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction

Table 1 Baseline patient characteristics

	All patients (n = 173)	QRS <120 ms (n = 127)	QRS ⩾120 ms (n = 46)	p Value	QTc <440 ms (n = 47)*	QTc ⩾440 ms (n = 121)*	p Value
Age (years)	75 (11)	75 (11)	76 (11)	0.256	75 (12)	75 (11)	0.944
Female sex	78 (45)	59 (47)	19 (41)	0.547	19 (40)	56 (46)	0.493
History							
Coronary artery disease	120 (69)	86 (68)	34 (74)	0.435	28 (60)	89 (74)	0.077
Arterial hypertension	111 (64)	85 (67)	26 (57)	0.207	31 (66)	79 (65)	0.953
COPD	37 (21)	27 (21)	10 (22)	0.946	11 (23)	23 (19)	0.524
Diabetes mellitus	60 (35)	40 (32)	20 (44)	0.143	18 (38)	41 (34)	0.591
Chronic kidney disease	65 (38)	47 (37)	18 (39)	0.799	17 (36)	45 (38)	0.824
Symptoms							
Paroxysmal nocturnal dyspnoea	81 (47)	56 (44)	25 (54)	0.232	21 (45)	58 (48)	0.705
Nocturia	73 (42)	50 (39)	23 (50)	0.211	22 (47)	51 (42)	0.584
Weight gain	26 (15)	20 (16)	6 (13)	0.660	9 (19)	15 (12)	0.262
Vital status							
Systolic blood pressure (mm Hg)	149 (32)	150 (33)	146 (29	0.414	148 (26)	151 (33)	0.548
Diastolic blood pressure (mm Hg)	88 (22)	90 (23)	83 (20)	0.041	89 (20)	89 (23)	0.971
Heart rate (per minute)	100 (26)	102 (27)	95 (22)	0.150	105 (30)	99 (24)	0.149
Temperature (℃)	37.3 (0.9)	37.3 (1.0)	37.0 (0.8)	0.047	37.5 (1.0)	37.1 (0.9)	0.029
Signs							
Tachypnoea (>20/min)	79 (46)	57 (45)	22 (48)	0.731	22 (47)	53 (44)	0.725
Elevated JVP	39 (23)	25 (20)	14 (30)	0.135	11 (23)	28 (23)	0.971
Hepatojugular reflux	26 (15)	17 (13)	9 (20)	0.315	10 (21)	14 (12)	0.107
Rales	107 (62)	79 (62)	28 (61)	0.873	29 (62)	74 (61)	0.948
Lower-extremity oedema	78 (45)	56 (44)	22 (48)	0.663	24 (51)	52 (43)	0.344
Laboratory tests							
Ejection fraction (%)†	41 (15)	44 (15)	33 (15)	0.001	47 (16)	39 (15)	0.024
Creatinine clearance (ml/min/1.73 m^2)	55 (29)	56 (31)	51 (22)	0.277	58 (33)	53 (28)	0.376
Haemoglobin (g/dl)	12.9 (2.5)	13.0 (2.5)	12.7 (2.4)	0.404	12.8 (2.5)	13.0 (2.4)	0.655
Serum albumin (g/l)	33 (6)	33 (6)	33 (6)	0.504	33 (6)	33 (6)	0.475
Troponin I (μg/l)	0.6 (0.3–2.4)	0.5 (0.3–2.1)	1.0 (0.3–3.3)	0.214	0.5 (0.3–1.9)	0.6 (0.3–2.3)	0.446
BNP (pg/ml)	805 (456)	777 (452)	877 (465)	0.215	687 (469)	833 (449)	0.075
Outcome							
Hospitalisation	153 (88)	110 (87)	43 (94)	0.212	40 (85)	108 (89)	0.456
Intensive care admission	48 (28)	36 (28)	12 (26)	0.769	13 (28)	35 (29)	0.870
Time to discharge (days)	13.4 (11.3)	14.0 (12.2)	12.0 (8.2)	0.319	14.0 (13.3)	12.6 (10.0)	0.450
30-day mortality	22 (13)	14 (11)	8 (17)	0.267	5 (11)	16 (13)	0.649
720-day mortality		37.5 (4.4)	59.3 (7.3)	0.004	41.8 (7.4)	44.1 (4.5)	0.546

BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; JVP, jugular venous pressure.
Data are presented as mean (SD), median (interquartile range) or n (%) of patients. The p value is given for the comparison of patients with prolonged versus normal QRS and QTc intervals.
*QTc interval could not be determined in 5 (2.9%) patients.
†Determined in 117 patients during hospitalisation.

defined as the nadir between the T and the U waves. When the nadir was not clearly visible or the maximal T-wave amplitude in leads II or V_4 did not exceed 0.25 mV, the patient was excluded from the study. Heart rate correction was performed by the Bazett formula, and QTc interval duration was defined as the mean duration of all QTc intervals measured. Prolonged QTc interval was prospectively defined as QTc interval ⩾440 ms.[10]

End point and statistical analysis

All-cause mortality was the primary end point of this study. Patients were contacted 6, 12 and 24 months after the initial presentation by telephone interview performed by a single trained researcher. In addition, referring doctors were contacted in the case of uncertainties regarding health status or hospitalisations. The administrative databases of the respective home towns were assessed to ascertain the vital status of those patients who could not be contacted by telephone. All information derived from contingent hospital readmission records or provided by the referring doctor or by the outpatient clinic was reviewed and entered into the computer database. The statistical analyses were performed using the SPSS V.13.0 software package. Comparisons were made using the t test, Mann—Whitney U test, Fisher's exact test and χ^2 test as appropriate. All hypothesis testing was two tailed. The Kaplan–Meier method was used to analyse and compare survival in the prolonged and normal QRS and QTc groups. Cox proportional hazards analysis was used to identify predictors of death in univariate and multivariate analysis. Together with QRS and QTc prolongation, all baseline, demographic, clinical and laboratory variables routinely available in the ED were entered in a univariate Cox regression analysis. All variables associated with long-term mortality in univariate analysis ($p<0.05$) were entered into the multivariate models.

RESULTS

QRS interval was prolonged (⩾120 ms) in 27% of patients, and QTc interval was prolonged in 72% of patients. Baseline demographic and clinical characteristics were similar in patients with normal and prolonged QRS or QTc interval (table 1). Among patients with QRS prolongation, 58% had a left bundle branch block.

No patient was lost to follow-up within the first 12 months. The median duration of follow-up until the patient's death or last contact was 680 days. None of the patients had cardiac resynchronisation therapy initiated during the reported follow-up

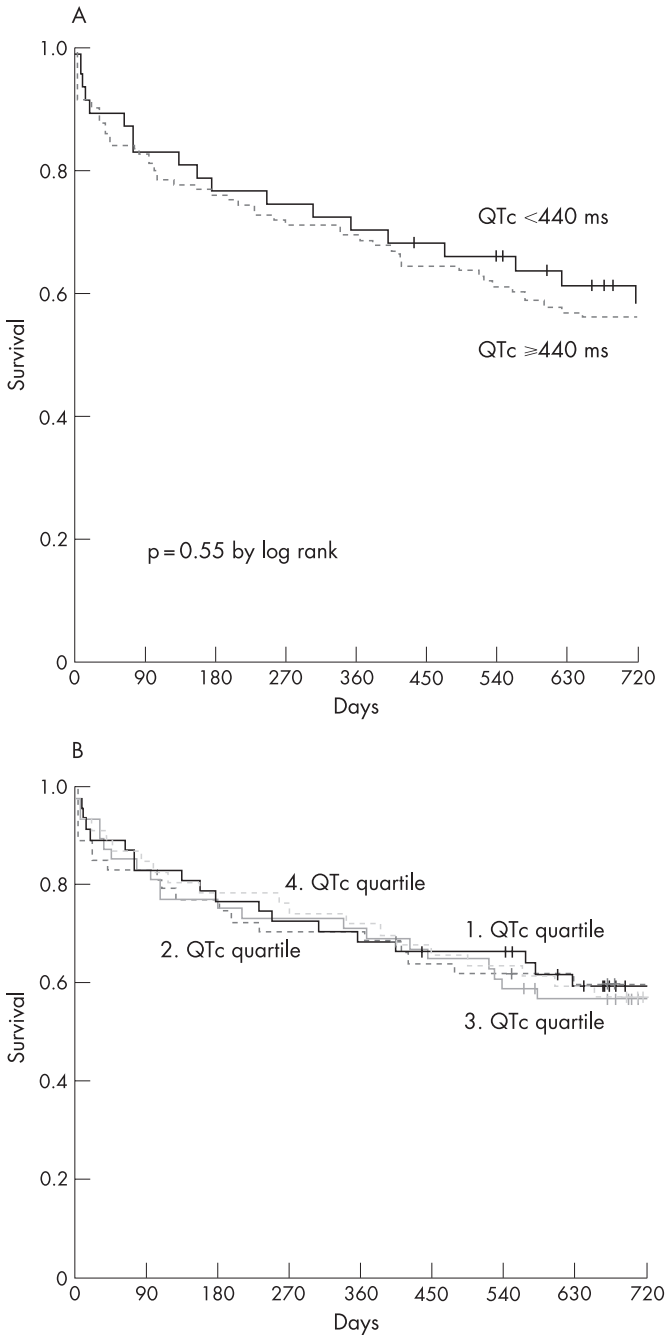

Figure 1 (A) Survival rates in patients with prolonged versus normal QTc interval. (B) Survival rates in relation to QTc quartiles (p = 0.995 by log rank).

period. A total of 78 patients died during follow-up. Kaplan–Meier analysis revealed that the 720-day mortality was comparable in patients with prolonged and normal QTc (44% vs 42%, p = 0.546; fig 1A). Mortality was also similar when patients were stratified according to QTc quartiles ((1) quartile QTc <411 ms; (2) quartile 411–436 ms; (3) quartile 436–462 ms; and (4) quartile >462 ms; fig 1B).

In contrast, the 720-day mortality was significantly higher in patients with prolonged QRS interval than in those with normal QRS (59% vs 37%, p = 0.004; fig 2). In Cox proportional hazards analysis, prolonged QRS interval was associated with a nearly twofold increase in mortality (HR 1.94, 95% CI 1 22to 3.07; p = 0.005). This association persisted after multivariate adjustments in several models (table 2).

Echocardiography was performed in a subgroup of 117 patients (68%) during hospitalisation. QRS prolongation was present significantly more often in patients with significant left ventricular systolic dysfunction defined as a left ventricular ejection fraction (LVEF) of ⩽40% (38% vs 17%, p = 0.007). Also, BNP levels >500 pg/ml were present significantly more often in patients with LVEF of ⩽40% (72% vs 49%, p = 0.007).

LVEF was lower in both patients with prolonged QRS interval (33% vs 44% in patients with normal QRS, p = 0.001) and in patients with prolonged QTc interval (39% vs 47% in patients with normal QTc, p = 0.024).

When LVEF was added to the variables routinely available in the ED (echocardiography subgroup multivariate model 3) in these 117 patients, prolonged QRS interval fell short of being a significant predictor of mortality (p = 0.058). Only age and BNP remained independently associated with death in this subgroup.

DISCUSSION

In patients presenting with ADHF to the ED, the ECG offers important diagnostic and prognostic information. In addition to providing clues regarding the cause of acute decompensation including tachyarrhythmia or myocardial infarction, QRS prolongation, but not QTc prolongation, identifies patients with a significantly increased risk of death during long-term follow-up. This finding has important clinical implications. First, patients with ADHF have a high mortality. Despite this, there are few data regarding long-term outcome of patients with ADHF.[1 2] Therefore, risk stratification in patients with ADHF is by far less well validated than in patients with chronic HF. Second, increased QRS duration can easily be detected on the 12-lead ECG immediately on presentation. Third, rapid initiation of intensive care and several specific therapeutic interventions possibly including levosimendan[14] or selective phosphodiesterase type 5 inhibition[15] may particularly benefit high-risk patients identified by prolongation of QRS duration. Fourth, in addition to a multidrug regimen and disease management programme for HF, biventricular pacing seems to provide symptomatic and prognostic benefit in HF patients with prolonged QRS interval.[16] Given the dismal short- and long-term prognosis of patients with prolonged QRS duration admitted for ADHF, this high-risk subgroup of patients with ADHF should be evaluated for biventricular pacing. Until now, biventricular pacing has been appropriately validated in randomised controlled clinical trials only in patients with chronic HF.[16] The high rates of mortality and hospital re-admission in patients with ADHF provide a strong rationale to evaluate this treatment also in high-risk ADHF.[3]

Prolonged QRS duration is due to delayed ventricular electrical activation. This changed electrical activation sequence may result in mechanical dyssynchrony.[17 18] The resulting alteration in mechanical activation may lead to impaired haemodynamic performance and mitral regurgitation.[18 19] The common consequence of these adverse effects is reduced ventricular pumping function and increased risk of heart failure and death. QRS prolongation could be interpreted as an easy and simple obtainable marker for significant left ventricular dysfunction. The association between QRS prolongation and impaired left ventricular systolic function might, at least in part, explain the association between QRS prolongation and mortality.

This study corroborates and extends previous studies on QRS duration prolongation as a predictor of mortality in patients with chronic HF.[5–9] In a cohort of 100 patients referred for cardiac transplantation, 34% had QRS duration ⩾120 ms. This group did have more than twice the event rate (death or transplantation) as compared with the group with normal QRS

Table 2 Univariate and multivariate analysis of prolonged QRS and QTc interval as predictors of all-cause mortality

	Univariate p	HR (95% CI)	Multivariate p (Model 1*)	HR (95% CI)	Multivariate p (Model 2†)	HR (95% CI)	Multivariate p (Model 3‡)	HR (95% CI)
QRS interval ⩾120 ms	0.005	1.94 (1.22 to 3.07)	0.016	1.77 (1.11 to 2.81)	0.024	1.73 (1.07 to 2.78)	0.058	1.67 (0.98 to 2.85)
QTc interval ⩾440 ms	0.547	1.17 (0.70 to 1.97)						

HR, hazard ratio.
*Model 1: adjusting for age and coronary artery disease (CAD).
†Model 2: adjusting for age, history/comorbidity and vital signs. Variables in the final model included age, CAD, arterial hypertension, chronic obstructive pulmonary disease (COPD), systolic blood pressure and diastolic blood pressure.
‡Model 3 (echocardiography subgroup): adjusting for age, history/ comorbidity, vital signs and laboratory tests including left ventricular ejection fraction. Variables in the final model included age, CAD, arterial hypertension, COPD, systolic blood pressure, diastolic blood pressure, haemoglobin, albumin, creatinine clearance, B-type natriuretic peptide and cardiac troponin I.

interval.[9] Similar results were obtained in 165 patients with ICD with HF. Although there was no difference in survival between patients with LVEF >35% and LVEF ⩽35%, mortality was significantly increased in patients with QRS duration ⩾150 ms.[8] Our study included consecutive "real-life patients admitted with ADHF. These patients were significantly older and have more extensive comorbidity than patients offered cardiac transplantation or ICD implantation. Therefore, it is reassuring to note that QRS duration does provide important prognostic information at both extremes of HF. In addition to HF, prolongation of QRS duration has been associated with increased risk of death in sinus node dysfunction[18] and acute myocardial infarction.[20]

QT interval prolongation has been proposed as a risk factor for ventricular arrhythmia and death in an apparently healthy population,[21] in patients after myocardial infarction[22] and in patients with diabetes.[23] Although a recent study in 241 selected patients with advanced chronic HF suggested that prolonged QTc interval was a powerful predictor of mortality,[5] overall, the data on the predictive value of QTc interval duration in HF are scarce and variably negative and positive with differences in results only partly explained by differences in study details.[24–27] Our study complements and extends these studies with regard to the use of QTc prolongation as a predictor of mortality in patients with chronic HF.[5 24–27] Despite applying methods identical with those in the latest positive study in patients with chronic HF,[10] we were unable to show any predictive value of QTc interval prolongation in patients with ADHF. This exemplifies the need for specific research targeting ADHF as a distinct clinical entity. Differences in age, comorbidity, non-cardiac medication and heart rate may account for our negative result regarding QTc interval.

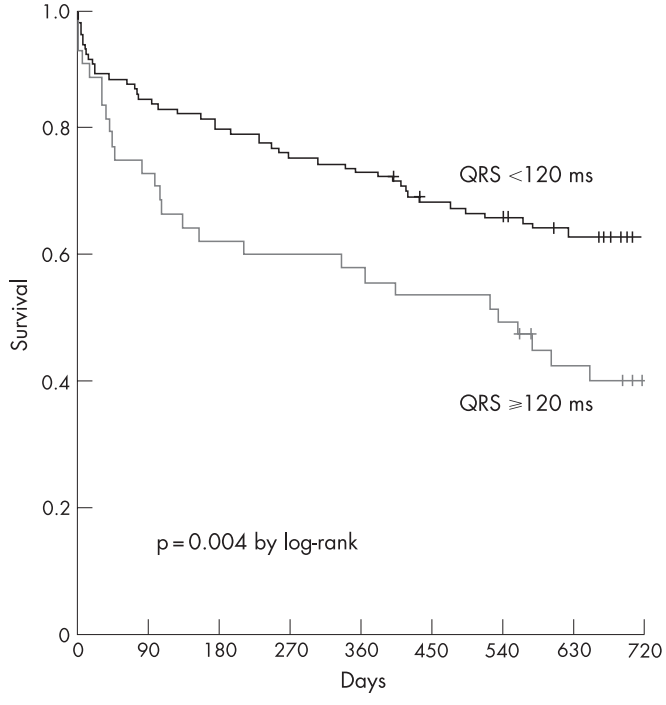

Figure 2 Survival rates in patients with prolonged vs normal QRS intervals.

Potential limitations of this study merit consideration. First, owing to respiratory distress and tachypnoea, the quality of ECG recordings are often suboptimal in patients presenting with ADHF to the ED. This may have contributed to the negative result regarding QTc. Second, QRS and QT intervals were measured by a single cardiologist. Therefore, we cannot assess whether interobserver variability would affect the predictive value of QRS duration. As previous studies have reported interobserver and intraobserver correlations for QRS durations of 0.97 and 0.98, respectively, this issue seems to be minor. By using only lead II and V_4 to determine QT interval length, we minimised the intra-observer variability. Third, the onset of prolongation of QRS duration and potential disappearance during follow-up was unknown in our cohort. Systematic ECG follow-up might reveal whether patients have improved outcome once prolongation of QRS duration disappears. Fourth, LVEF was determined during hospitalisation in two-thirds of patients. As a previous study of patients with chronic HF suggested that the prognostic information provided by QRS duration is additive to and independent of echocardiographic variables,[7] further studies are necessary to evaluate whether QRS duration maintains its incremental prognostic value if echo data are available for all patients, and, particularly, whether echocardiography can be performed within the first hours of presentation to the ED.[28] Unfortunately, this service is currently not available in most hospitals. Fifth, this was a post hoc analysis of a randomised controlled trial. However, as the BASEL study recruited consecutive patients, we are not aware of any bias potentially confounding our results.

Our analysis has three particular strengths. First, it included a large contemporary cohort of consecutive patients. Second, the study population was highly representative of the elderly population of patients with ADHF in clinical practice.[4] Third, it was one of the first studies of patients with ADHF to provide long-term follow-up data.

In conclusion, prolonged QRS interval, but not prolonged QTc interval, is associated with increased long-term mortality in patients with ADHF. Attention to this easily accessible parameter may improve patient management.

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Funding: This study was supported by research grants from the Swiss National Science Foundation and the Swiss Heart Foundation (to CM).

Competing interests: None.

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