# Does corrected QT interval correlate with serum ionised calcium in the ED setting?

The main ECG changes caused by calcium (Ca) abnormalities have been classified as HR corrected QT interval (QTc) prolongation (hypocalcaemia) and shortening (hypercalcaemia).[1] Hypocalcaemia and hypercalcaemia are considered potentially life-threatening conditions, partly because of the theoretical risk of arrhythmia. An experimental study with healthy individuals suggested a relationship between serum ionised calcium ($Ca^{2+}$) and QTc.[2] Only smaller and older clinical studies have, however, tested the correlation of QTc and Ca in patients[3–6] and more often using serum total Ca rather than ionised Ca.[2 3 5] Although the evidence basis for $Ca^{2+}$ and its effects on the ECG are weak and their value clinically questionable, the evidence has been adopted into medical literature and clinical practice.[1] Furthermore, no evidence is available pertaining to the relationship between $Ca^{2+}$ and QTc in the diverse ED population. The aim of our study was to investigate whether this relationship exists in the ED and more importantly if it could be useful clinically.

This was an observational study including two Swedish EDs, one in Skåne University Hospital and another in Helsingborg Hospital. We included all adult (≥18 years of age) patients at their first presentation to the EDs from 1 January 2010 to 31 December 2014, if they had an ECG with a QTc recorded between 1 hour prior to 12 hours after arrival time and had a $Ca^{2+}$ measurement within 2 hours of the ECG. Patients with either hyperkalaemia (>5 mmol/L) or moderate to severe hypokalaemia (<3 mmol/L) were excluded, as well as patients with pacemakers or poor ECG quality.

A personal identification number assigned to every Swedish citizen was used as a cross-reference to link data from multiple registers for each individual patient. Prior pharmaceutical treatment was obtained from the Swedish Prescribed Drug database; relevant blood tests, prior illnesses and contacts with the healthcare system were obtained from the Region Skåne Patient Register and the Swedish National Inpatient Register.

All ECGs were digitally recorded on either Glasgow or GE Healthcare ECG machines and QT was automatically measured. The two algorithms have been found to be only marginally different, with overlapping confidence intervalCIs.[7]

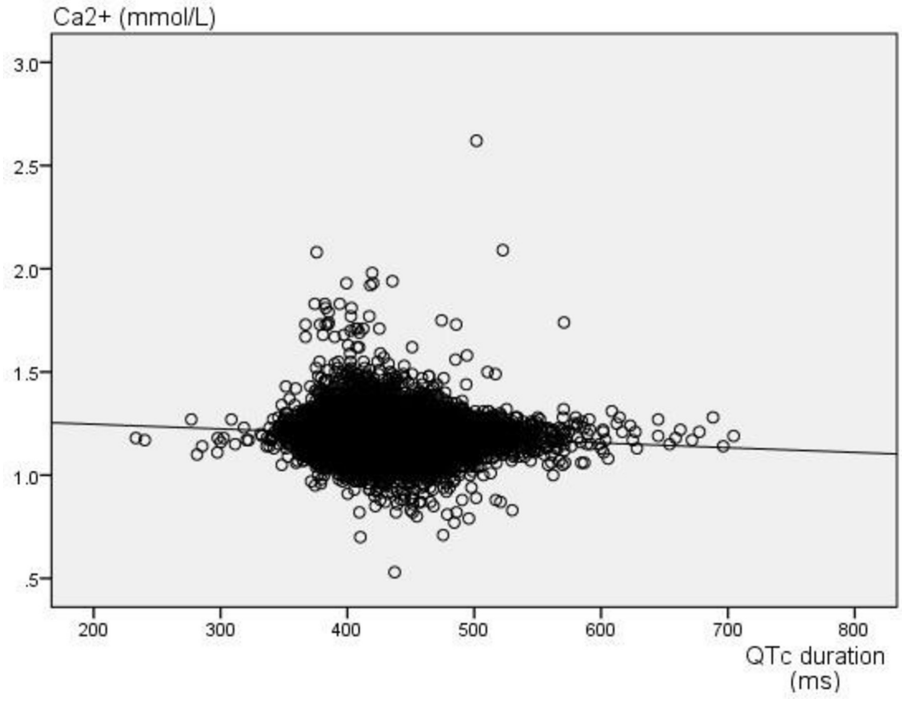


**Figure 1** Ionised calcium concentration (mmol/L) versus HR corrected QT duration (ms).

For QT correction, we chose the Hodges Formula (QTc=QT+1.75 (HR(beats/min)-60). The association between $Ca^{2+}$ and QTc was modelled using univariate linear regression, and the results were illustrated by a scatter plot(figure 1). The strength of the correlation was measured using Pearson's correlation coefficient (r). An analysis of residuals was conducted to determine the viability of using linear regression. Receiver operating characteristic (ROC) curves were established to evaluate the discriminatory value of QTc as a predictor of hypocalcaemia and hypercalcaemia.

A total of 83 888 patients were initially identified. Of these, 61 015 patients remained after applying the exclusion criteria described previously (flowchart can be found in online supplemental material). Of these patients, 0.7% had hypercalcaemia and 2.6% had hypocalcaemia. The median age was 63 years, and 50.1% were female (table 1).

There was a statistically significant correlation between $Ca^{2+}$ and QTc with an r of −0.119 (p<0.001) (figure 1). The proportion of variance in QTc explained by $Ca^{2+}$ was small, with an $R^2$ of 0.014. The areas under the ROC curve for prolonged QTc (>460 ms) as a predictor for hypocalcaemia and short QTc (<370 ms) as a predictor for hypercalcaemia were 0.60 (95% CI 0.59 to 0.62) and 0.54 (95% CI 0.513 to 0.575), respectively, showing that QTc is a poor predictor of calcium abnormalities.

These results indicate that $Ca^{2+}$ fluctuations only have a minimal influence on the QTc. The strong correlation between calcium and QTc seen in prior studies[3 5] could not be reproduced. We instead found that, in ED patients, the QTc is not sensitive to $Ca^{2+}$ changes and is unlikely to be reliable in predicting $Ca^{2+}$ disturbances. A possible reason for the weak correlation between QTc and $Ca^{2+}$ might be that the ED study population is very diverse; the patients have an array of medications, comorbidities and acute medical conditions that influence the QTc more than $Ca^{2+}$ does.

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**Contributors** MC conceived and designed the study, analysed and interpreted the data, and wrote the report. ATL, MB, HK and JLF conceived and designed

**Table 1** Patient characteristics

| | All patients | Hypercalcaemia | Hypocalcaemia |
|---|---|---|---|
| | n = 61 015 (100%) | n = 434 (0.7%) | n= 1599 (2.6%) |
| Female (%) | 30 594(50.1) | 291(67.1) | 642(40.2) |
| Age (median) | 63 | 73 | 65 |
| IQR 25–75 | 45–75 | 63–82 | 51–76 |
| | Patients, n (% of all patients) | Patients, n (% of hypercalcaemia group) | Patients, n (% of hypocalcaemia group) |
| Charlson comorbidity index, n (%) | | | |
| 0 | 34 175 (56) | 151 (34.8) | 698 (43.7) |
| 1 | 12 168 (19.9) | 96 (22.1) | 285 (17.8) |
| 2+ | 14 672 (24) | 187 (43.1) | 616 (38.5) |
| Diagnosis (within 1 year prior to ED visit), n (%) | | | |
| Malignant neoplastic disease | 4799 (7.9) | 79 (18.2) | 175 (10.9) |
| Heart failure | 3811 (6.2) | 39 (9) | 219 (13.7) |
| Hypertension | 15 735 (25.8) | 172 (39.6) | 444 (27.8) |
| Kidney failure | 1337 (2.2) | 26 (6.0) | 129 (8.1) |
| Hypoparathyroidism | 14 (0.0) | <5 (<1.2) | <5 (<0.3) |
| Hyperparathyroidism | 140 (0.2) | 45 (10.4) | 9 (0.6) |
| Vitamin D disorders | 13 (0.0) | <5 (<1.2) | 0 (0.0) |
| Multiple myeloma | 87 (0.1) | 5 (1.2) | <5 (<0.3) |
| Sarcoidosis | 27 (0.0) | <5 (<1.2) | <5 (<0.3) |
| Cardiomyopathy | 291 (0.5) | 4 (0.9) | 12 (0.8) |
| Medication (within 1 year), n (%) | | | |
| Antidepressant | 7901 (12.9) | 56 (15.2) | 273 (17.2) |
| SSRI | 5139 (8.4) | 37 (8.5) | 176 (11.0) |
| Tetracyclic antidepressants | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Tricyclic antidepressants | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Other antidepressants | 2762 (4.5) | 29 (6.7) | 115 (7.2) |
| Opiates | 7831 (12.8) | 83 (19.1) | 234 (14.6) |
| Vitamin D supplements | 336 (0.6) | 12 (2.8) | 36 (2.3) |
| Ca supplements | 3606 (5.9) | 54 (12.4) | 104 (6.5) |
| Mineral supplements | 4118 (6.7) | 63 (14.5) | 134 (8.4) |
| Ca antagonists | 5979 (9.8) | 71 (16.4) | 179 (11.2) |
| Thiazide diuretic | 3654 (6.0) | 43 (10.0) | 95 (5.9) |
| Loop diuretic | 4536 (7.4) | 59 (13.6) | 222 (13.9) |
| Potassium sparing diuretic | 1477 (2.4) | 25 (5.8) | 66 (4.1) |
| GERD medication | 9391 (15.4) | 88 (20.3) | 271 (16.9) |
| Antacids | 212 (0.3) | <5 (<1.2) | 19 (1.2) |
| Centres, n (%) | | | |
| Helsingborg | 34 063 (55.8) | 230 (53.0) | 1054 (65.9) |
| Lund | 26 953 (44.2) | 203 (47.0) | 545 (34.1) |

International Classification of Diseases, 10th Revision, codes representing each condition can be found in online supplemental materials.
Ca, calcium; GERD, gastro-oesophageal reflux disease; SSRI, Selective Serotonin Reuptake Inhibitor.

the study and assisted with analysis, interpretation of the data and writing of the report. All authors have had access to the data and approved the final version of the manuscript. AS, medical statistician, assisted with the design and interpretation of the statistical analysis. AP, professor of clinical pharmacology, helped review the finished article.

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**Competing interests** MC, JLF, AL and MB have nothing to declare. HK owns stocks in HL A/S.

**Patient consent for publication** Not applicable.

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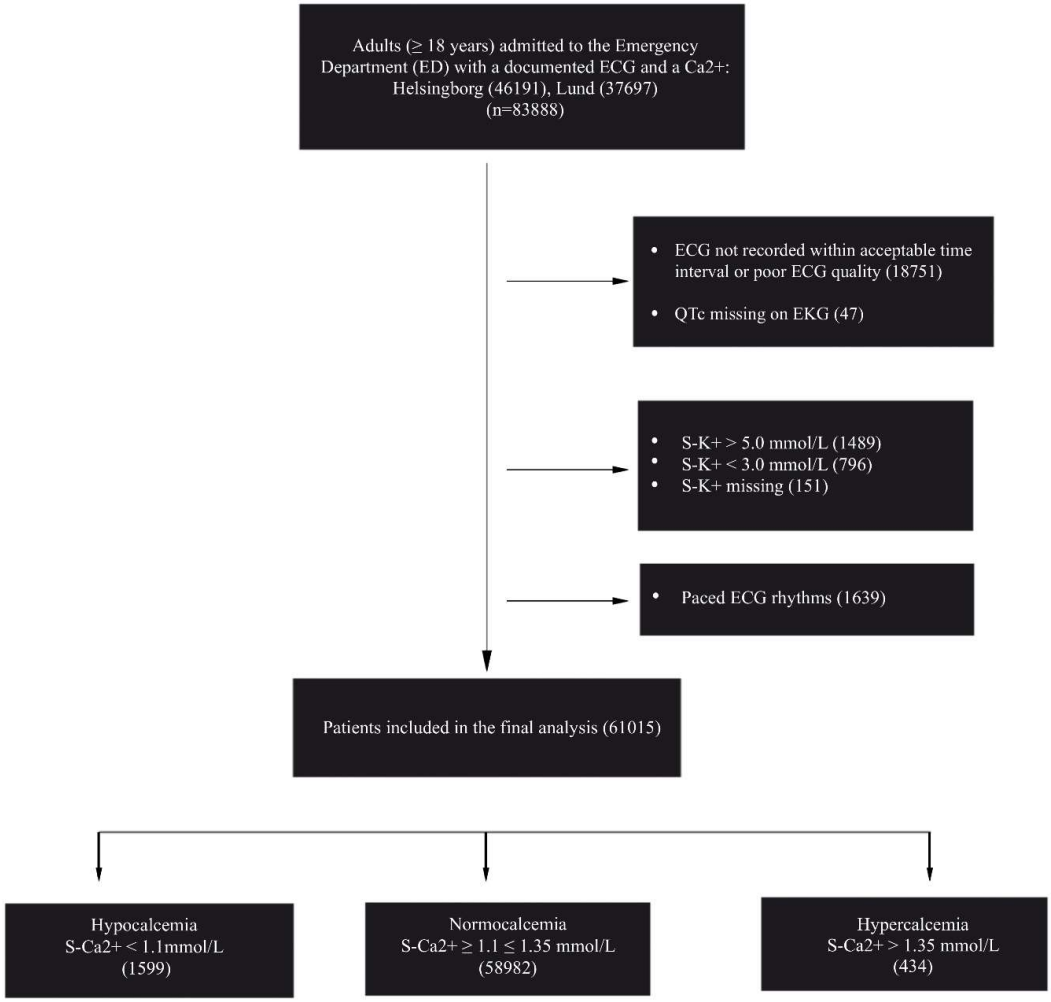
# APPENDIX

## Study flowchart:



CD Definition of Table 1 diagnoses

**Malignant neoplastic disease:** C00 C01 C02 C03 C04 C05 C06 C07 C08 C09 C10 C11 C12 C13 C14 C15 C16 C17 C18 C19 C20 C21 C22 C23 C24 C25 C26 C27 C28 C29 C30 C31 C32 C33 C34 C35 C36 C37 C38 C39 C40 C41 C42 C43 C44 C45 C46 C47 C48 C49 C50 C51 C52 C53 C54 C55 C56 C57 C58 C59 C60 C61 C62 C63 C64 C65 C66 C67 C68 C69 C70 C71 C72 C73 C74 C75 C76 C77 C78 C79 C80 C81 C82 C83 C84 C85 C85 C86 C87 C88 C89 C90 C91 C92 C93 C94 C95 C96 C97

**Heart failure:** I50

**Hypertension:** I10 I11 I12 I13 I14 I15

**Kidney failure:** N17 N18 N19

**Hypoparathyroidism:** E20

**Hyperparathyroidism:** E21

**Vitamin D disorders:** E55, E673

**Multiple myeloma:** C900

**Sarcoidosis:** D869

**Cardiomyopathy:** I42

**ATC-Codes for definition of table 1 medication groups**

**Antidepressant:** N06AB N06AC N06CA N06AX

SSR**I:** N06AB

**Tetracyclic antidepressants:** N06AC

**Tricyclic antidepressants:** N06CA

**Other antidepressants:** N06AX

**Opiates:** N02A

**Vitamin D supplements:** A11CB A11CC

**Calcium supplements:** A12A

**Mineral supplements:** A12

**Calcium blockers:** C02DE C08

**Thiazide diuretic:** C03A C03B C03EA

**Loop diuretic:** C03C C03EB

**Potassium sparing diuretic:** C03D

**GERD medication:** A02B

**Antacids:** A02A