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Relationship between QT Interval Dispersion in acute stroke and stroke prognosis: A Systematic Review

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Abstract

Background—QT dispersion (QTd) has been proposed as an indirect ECG measure of heterogeneity of ventricular repolarization. The predictive value of QTd in acute stroke remains controversial. We aimed to clarify the relationship between QTd and acute stroke and stroke prognosis.

Methods—A systematic review of the literature was performed using pre-specified medical subjects heading (MeSH) terms, Boolean logic and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Eligible studies (a) included ischemic or hemorrhagic stroke and (b) provided QTd measurements.

Results—Two independent reviewers identified 553 publications. Sixteen articles were included in the final analysis. There were a total of 888 stroke patients: 59% ischemic and 41% hemorrhagic. There was considerable heterogeneity in study design, stroke subtypes, ECG assessment-time, control groups and comparison groups. Nine studies reported a significant association between acute stroke and baseline QTd. Two studies reported that QTd increases are specifically related to hemorrhagic strokes, involvement of the insular cortex, right-side lesions, larger strokes, and increases in 3, 4-dihydroxyphenylethylene glycol in hemorrhagic stroke. Three studies reported QTd to be an independent predictor of stroke mortality. One study each reported increases in QTd in stroke patients who developed ventricular arrhythmias and cardiorespiratory compromise.

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Conclusions—There are few well-designed studies and considerable variability in study design in addressing the significance of QTd in acute stroke. Available data suggest that stroke is likely to be associated with increased QTd. While some evidence suggests a possible prognostic role of QTd in stroke, larger and well-designed studies need to confirm these findings.

Keywords

ECG; QT dispersion; acute stroke; prognosis

Introduction

The cardiovascular manifestations of acute neurological events have been well documented (1–4). Several ECG abnormalities have been reported in patients following acute cerebrovascular events including QT interval prolongation, ST segment deviation and T wave changes (5). These abnormalities have been attributed to transient increases in sympathetic activity (6–10).

QT dispersion (QTd) has been proposed as an indirect (ECG) measure of heterogeneity of ventricular repolarization more than two decades ago (11). QTd is defined as the maximal inter-lead difference in QT interval on a 12-lead ECG. (figure 1). Conflicting results have been reported on the prognostic value of QTd in patients following acute myocardial infarction (12–16), and in other clinical settings (17–21) including acute stroke (22, 23). Therefore its association and predictive value in acute stroke remains controversial.

The objective of this study was to systematically review the available published literature to determine the effect of acute stroke on QTd, and to clarify the prognostic value of QTd in the setting of acute stroke.

Materials and Methods

Search Strategy

A systematic literature search following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (24) was performed and completed on January 2014. A search in MEDLINE and EMBASE was performed by 2 independent reviewers (YL, LS). We did not apply any language restrictions to our search. The search terms in MEDLINE included a) QT Interval b) QT Dispersion c) QT Interval Dispersion matched together with the following (MeSH) terms: “Stroke”, “Brain Ischemia” “Hemorrhage”, “Intracranial Hemorrhage”, “Subarachnoid Hemorrhage”, “Ischemic Attack, Transient”, “Stroke, Lacunar”, “Brain Infarction”, “Brain Stem Infarctions”, “Cerebral Infarction”, “Infarction, Middle Cerebral Artery”, “Infarction, Middle Cerebral Artery”, “Infarction, Anterior Cerebral Artery”, “Infarction, Posterior Cerebral Artery”, “Cerebrovascular Disorders”. For our literature search in EMBASE, we used the Emtree vocabulary, the equivalent of (MeSH) terms in MEDLINE.

Inclusion criteria

We used a broad selection criterion for determining study eligibility. We included all articles that evaluated and reported data about the relationship between QTd in stroke, both retrospective and prospective in design. All the articles retrieved in the primary search were filtered by title and/or abstract, and were screened by two independent reviewers (YL, LS). Any abstract that included references to QT dispersion together with any reference of stroke was included. In the case of uncertainty or disagreement of article inclusion, the articles were reviewed by all authors and inclusion was adjudicated by consensus. See figure 2.

Results

Study Characteristics

Sixteen articles (22, 23, 25–38) were included in the final analysis. They were published between 1999 and 2011. There was substantial heterogeneity in study design, types of stroke, sample size, ECG assessment time, control/comparison groups, and QTd evaluation. See table 1 for an overview of study heterogeneity.

Study Design and Sample Size

Ten out of 16 studies were prospective (22, 25–33), of which 6 (25, 26, 30–33) evaluated fewer than 50 stroke patients. Six studies were retrospective (23, 34–38) of which 4 (34, 36–38) evaluated fewer than 50 stroke patients.

Type of Stroke

When considering stroke type, 4 studies (25,29,34,35) included subjects with both ischemic and hemorrhagic stroke, while 7 studies (22, 23,26,30,31,37,38) included only hemorrhagic stroke [4 of these studies (30,31,37,38) included only subarachnoid hemorrhage (SAH)]. Five studies (27, 28, 32, 33, 36) included only ischemic stroke patients.

Demographics

There were a total of 1,244 subjects of which 888 (71%) had a stroke (526 ischemic, 362 hemorrhagic), 60 (5%) had a transient ischemic attack (TIA) and 296 (24%) were non-stroke controls. In one study, demographics of stroke patients and TIA were reported together, and therefore we were unable provide frequency of age and gender by group. Of the combined 948 stroke and TIA patients, the range of the mean age was 45 ± 10 – 68 ± 12 . There were 397 (42%) men, 384 (40%) women, and gender was unspecified in 167 (18%) patients. Of the 296 non-stroke control subjects, the range of the mean age was 44 ± 13 – 62 ± 12 . There were 130 (44%) men, 116 (39%) woman, and gender was unspecified in 50 (17%) controls.

Control/Comparative Groups

QTd of stroke patients was compared to QTd of a non-stroke control group in 9 studies (25–27,29–32,37,38). Five included hemorrhagic stroke patients exclusively, and 2 included only ischemic stroke patients. QTd of stroke survivors and non-survivors were compared in 6 studies (22, 23, 26, 28, 35, 36). Three included only hemorrhagic stroke patients and 2 included only ischemic stroke patients.

Timing of QTd Measurements

Nine studies (22, 23, 27,28,30,33, 35, 37,38) reviewed or performed only a single QTd measurement at baseline. Serial QTd measurements were recorded in 6 studies (25,26 29,31,32,36). Four out of 6 studies measured QTd twice (25,29,32,36) and 2 out of 6 studies performed QTd measurements daily (26,31): Golbasi et al evaluated QTd continuously for 5 days, and Randell et al evaluated QTd for 9 days. One additional study (34) compared pre-stroke and post-stroke QTd.

Correction for Heart Rate

QTd was corrected for heart rate (QTcd) in 14 studies (22, 23, 25, 27–34, 36–38). The Bazzet's formula (39) was used in 13 out of 14 studies and Fridericia's formula (40) was used in one study (31). Two studies did not correct for heart rate (26,35).

Confounding Variables

Age was controlled for in all studies, while 14 out of 16 studies controlled for gender (22,26–29,31–38). Some of the stroke risk factors considered included diabetes mellitus and hypertension. Patients with diabetes mellitus were excluded in one study (29) and controlled for in 7 studies (22,28,32,34–36,38) while hypertension was controlled for in 8 studies (22,27,28,32,34–36,38). There was considerable heterogeneity in the methods used to account for different variables including heart disease, electrolyte disturbances and medications known to affect the QT Interval (41,42). See table 2.

The Effect of Stroke on QTd

Nine studies, with a combined total of 384 stroke patients (200 ischemic, 184 hemorrhagic) compared baseline QTd values of stroke patients to a non-stroke control group (25–27 29, 30–32, 37, 38). On baseline ECG, significant increases in absolute QTd values between stroke patients as compared to non-stroke patient controls were reported in all 9 studies. See table 3(A–D) for baseline QTd and QTcd values as reported in the studies and arranged according to stroke type.

Variability of QTd over Time

Serial QTd measurements were reported in 6 studies (25,26,29,31,32,36). Three out of 6 (25,29,32) evaluated an admission ECG and found that stroke patients had significantly greater QTd values as compared to non-stroke controls. On a 3-day ECG follow-up, QTd values of stroke patients decreased to non-stroke control values. In another study (26), QTd was significantly greater in ICH patients as compared to controls during the first 5 days from admission. Additionally, QTd values of stroke patients appeared to gradually decrease over time (26).

A decrease in QTd values after baseline measurements was not consistent throughout all studies. One study (31) compared QTd measurements, performed over a 9-day period in SAH patients, to the baseline QTd measurement of the control group. QTd remained increased in SAH patients when compared to controls. An additional study (36) reported that ischemic stroke patient's QTd values increased on a follow up ECG (median 3 days) as

compared to admission QTd. See table 4 for a comparison of QTd and QTcd values for stroke patients at baseline and follow-up ECGs.

QTd and Stroke Type

The association between QTd and different stroke types was determined in 4 studies (25, 29, 34, 35). Two studies (29, 35) found that hemorrhages, specifically ICH in one study (35) were associated with higher QTd values as compared to ischemic strokes and TIA. However, there were no significant differences in QTd values between 6 patients with parenchymal hemorrhages and ischemic strokes at both admission and follow-up ECG in one study (25). An additional study (34), comparing pre and post stroke ECG's found no significant differences in QTd changes between stroke subtypes.

QTd and Stroke Severity

Four studies (30, 36–38) evaluated the correlation between QTd and stroke severity. One study (36) which included only patients treated with intravenous thrombolysis, found a significant association between changes in QTd and stroke severity quantified by the National Institute of Health Stroke Scale (NIHSS) (43). The HUNT and HESS grading system (44) was used to evaluate stroke severity in SAH patients in two studies (37, 38). Baseline QTd positively correlated with HUNT and HESS in only one of these studies (37). Two studies (30, 38) found no correlation between the Glasgow Coma Score (GCS) (45) for SAH patients and QTd.

QTd and Stroke Location

Six studies (23, 25, 29, 32, 33, 37) explored the potential relationship between QTd and stroke location. The mean QTd was higher in a group of patients with right-sided lesions as compared to left-sided lesions in 2 (25, 29) out of 3 studies (25, 29, 32). One of these studies (29) reported differences in both the 24 and 72 hour ECG. Conversely, the other study (25) only found differences in QTd values at the 72 hour ECG. Two (32, 33) out of 3 studies (25, 32, 33) that evaluated patients with ischemic stroke (unilateral strokes in one study), found that strokes involving the Insular Cortex had significantly greater QTd values than strokes without insular involvement. In addition, Alabd et al found no significant differences in QTd values between ischemic strokes in the cortical, subcortical, brainstem, and cerebellar regions, measured on day one and day 3 from hospital admission. In hemorrhagic strokes, higher QTd values in brainstem ICH compared to ICH in all other territories were found in one study (23). However, brainstem ICH had a lower GCS scores when compared to ICH in other locations. Sato et al found that QTd was longest in patients with ruptured aneurysms of the basilar artery as compared to ruptured aneurysms in other locations.

QTd and Stroke Lesion Size

Two studies (25, 29) determined the relationship between QTd and stroke lesion size. At 24 hours from stroke onset, both studies found that larger lesions [defined for ischemic strokes as total anterior circulation infarct (TACI) (46) and for hemorrhagic strokes as a lesion greater than 33 mm in diameter (47)] had higher QTd as compared to smaller lesions. These differences were diminished when QTd was assessed at the 72 –120 hour ECG (25, 29).

QTd Prognostic Value

Five studies (22, 23, 26, 28, 35) compared the baseline QTd of stroke survivors and non-survivors. Four included hemorrhagic strokes and only one included solely ischemic strokes. Admission QTd was an independent predictor of mortality in 3 studies (23,28, 35), while 2 studies (22,26) did not find QTd to have any significant predictive value. An additional study (35) found that changes in QTd values, using a follow-up ECG (median 3 days), were significantly greater in non-survivors (death during hospitalization) as compared to changes in survivors. For comparisons of baseline QTd and QTcd stroke survivors versus non-survivors, see table 5. One study (37) reported significantly higher QTd values in SAH patients who developed ventricular arrhythmias than in patients who did not develop ventricular arrhythmias. In addition, another study (30) found that patients suffering from severe SAH with elevated admission QTd levels were more likely to develop cardiorespiratory compromise as compared to patients with lower QTd values. One study (35) showed a positive trend between baseline QTd and discharge NIHSS and mRS (Modified Rankin Scale) (48).

Plasma Catecholamine Concentrations

Three studies (31, 33, 38) evaluated the association between plasma catecholamine concentration and QTd in both ischemic and hemorrhagic stroke. Hanci et al and Randell et al reported that the concentration of 3, 4-dihydroxyphenylethylene glycol, a metabolite of norepinephrine, positively correlated with QTd in hemorrhagic stroke. Eckardt et al did not find any relationship between 3, 4-dihydroxyphenylethylene glycol and QTd in ischemic stroke.

Supplemental Tables summarize individual studies on admission QTd with ventricular arrhythmias and cardiorespiratory compromise.

Discussion

Our systematic literature review analyzed studies assessing the relationship between QTd and acute stroke. We found studies exploring the effect of various stroke characteristics, including stroke type, severity, location, size, on QTd magnitude, and the role of QTd in stroke prognosis.

The Effect of Stroke on QTd

In all the studies (25–27,29,30–32,37,38) evaluating the magnitude of QTd in acute stroke, QTd values were greater in stroke subjects compared to non-stroke subjects at baseline ECG, suggesting an association between stroke and QTd. This was true for both ischemic and hemorrhagic strokes.

Variability of QTd over Time

Some studies (25,26,29,32) showed that QTd of stroke patients was highest at stroke onset and decreased over time, supporting the hypothesis that acute stroke increases QTd. A minority of studies (31,36), however, showed that QTd values in stroke patients remained consistently greater as compared to in controls or even increased over time.

The explanation, however, for differences in QTd values between those in stroke patients and in non-stroke controls and between those in stroke patients in the acute phase and in the subacute phase remains unclear. Multiple studies have explored differences in several stroke characteristics to more precisely understand the effects of acute stroke on QTd value increases.

QTd and Stroke Type

The weight of the evidence suggests that hemorrhagic strokes have higher QTd values compared to ischemic strokes (29,35). The only study (25) in which QTd values were not significantly greater in hemorrhagic patients as compared to ischemic patients included only 6 hemorrhagic patients.

QTd and Stroke Severity

Some studies have attempted to clarify if QTd increases are related to the severity of the stroke. However, there is limited evidence that suggests a positive correlation between QTd and NIHSS in ischemic stroke patients treated with thrombolytic therapy (36). The only study that reported this association, measured ECGs at both baseline and at a median of 3 days, while the NIHSS was performed at baseline and a mean of 13 ± 11 days. Given variability of intervening time interval between the two measures (ECG and NIHSS) this relationship remains unclear.

In SAH, while baseline QTd was found to be related to the HUNT and HESS grading system (37), it was not associated with the GCS (30, 38). A more consistent approach including serial ECGs coupled with clinical assessments over time may help determine the relationship between stroke severity and QTd.

QTd and Stroke Size

Larger stroke lesions were associated with greater QTd in the early stages of stroke in the 2 studies (25, 29) that directly explored this relationship. However, QTd at day 3 post-stroke did not correlate with stroke size. While this may suggest that stroke lesion size exerts an effect on QTd in the acute stroke setting, the contributory role of other factors in the subacute phase may have either confounded this relationship, or this relationship is only true in the acute phase.

QTd and Stroke location

There are studies that suggest higher QTd in right-sided cerebral lesions versus left-sided cerebral lesions (25, 29), and in insular cortex versus other areas of the brain (32,33). However, these findings have not been confirmed in other studies. Among hemorrhagic strokes, those in the brainstem had greater QTd than hemorrhagic strokes in other areas of the brain. As shown in one study (23), this may due to greater clinical severity of brainstem ICH as measured by the GCS, as opposed to ICH in other areas of the brain.

Prognostic Value of QTd

QTd was found to be significantly greater in non-surviving stroke patients as compared to surviving stroke patients, and was shown to be an independent predictor of mortality in most

studies (23,28,25). While this evidence supports a possible predictive role of QTd in stroke outcome, it must be noted the range of QTd was broad and overlapping across studies. Therefore, QTd's prognostic value should be addressed in future studies to confirm these findings.

Potential mechanisms for the effect of Stroke on QTd

QTd was found to be associated with stroke patients who developed ventricular arrhythmias (37) and cardiorespiratory compromise (30) as well as to an increase in serum catecholamine concentration (31,38). These findings support the idea that an increased QTd to be secondary to sympathetic hyperactivity which may mediate the occurrence of cardiac abnormalities. The mechanisms mediating the effect of stroke on QTd need to be further explored.

QTd's Clinical Utility

Given that QTd can be easily measured, its potential clinical value has been assessed in a variety of cardiac and other clinical settings including acute stroke. However, the use of QTd as an indirect measure to assess myocardial repolarization heterogeneity and ventricular recovery times remains controversial. Still, QTd is considered a crude measure of repolarization abnormalities (49).

Measurement of QTd

Standard ECG machines report a single QT interval but do not routinely provide measurement of QTd. Depending on the manufacturer, the QT interval that is reported is a computerized measurement of either: 1-the QT interval in lead 2 only or 2-the longest QT interval from any of the 12 leads. In part, QTd became popular because it can be easily calculated from ECG tracings retrospectively. However, computer software programs have been developed in which 12 leads can be measured simultaneously and can supplement ECG recordings (50,51). However, the reliability of both manual and automated methods in determining T-wave termination remains in question (52–54). The main contributing flaws in these measurements are low T wave amplitude, merges of T waves with U and/or P waves, as well as T wave morphology (49). In the studies included in this review, QTd has been measured manually (22, 23, 25–38) and automatically in one study (25).

Factors influencing QTd measurement

We found that most studies corrected for heart rate. However, although the Bazett's formula and other heart rate corrections have been reliable in QT interval measurements, its value in QTd remains controversial. Since QTd does not correlate with heart rate the same way the QT interval does, some have claimed that it is incorrect to apply any heart rate correction in QTd (49). In addition, although significant differences in QTd values between stroke and control/comparative groups were recorded across the studies, there are no generally accepted QTd reference values (49).

Limitations

Our literature review has several limitations. We included retrospective studies with small sample sizes, which were potentially inadequate to detect meaningful differences. We

limited our search to published data and we did not require a neuroimaging based definition of stroke or TIA as inclusion criteria for studies reviewed.

Conclusion

In summary, we found high heterogeneity in study design, study population, including composition of control/comparison groups, QTd assessment, and follow-up data. This variability limited our ability to perform a quantitative analysis and eventually to provide clear conclusions. The current data suggest that stroke is likely to be associated with increased QTd. However, the effect of various stroke characteristics on QTd and the predictive value of QTd on stroke outcome need to be further clarified. Future studies with an adequate sample size can help clarify how stroke type, stroke lesion size and stroke location may affect QTd and the possible pathophysiological mechanisms behind this effect.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. EXAMPLE OF QT DISPERSION MEASUREMENT

Measurement of QT dispersion. **A**, QT intervals (*horizontal bars*) measured from one cardiac cycle recorded in each lead of a 12-lead ECG obtained from a de-identified patient. *Vertical bars* mark the beginning of Q waves and the end of T waves. *Numbers* under the *horizontal bars* indicate the QT intervals in ms. **B**, The shortest (**a**; QT_{min}) and longest (**b**; QT_{max}) QT intervals in the ECG shown in **A** were from leads aVL and V3, respectively. **Bc**, Calculation of the QT dispersion as the difference between the shortest and longest QT intervals from the ECG in **A**.

Figure 2.
PRISMA FLOW DIAGRAM FOR SYSTEMATIC REVIEW

Table 1

Summary of Study Key Variables

Author and Year and Country	Study Design	Stroke Type and patient number (n)	Control/Comparison groups	Time of Baseline ECG	QTcd and/or QTcd	Investigators Blinded to Clinical Data
1. Chao et al ²² 2009 (Taiwan)	Prospective	Hemorrhagic 93	Stroke non-survivors.	< 6 hours from stroke onset	QTcd and QTcd	Not Reported
2. Afsar et al ²⁵ 2003 (Turkey)	Prospective	Ischemic/Hemorrhagic 36	Hospitalized patients admitted for something other than cardiac or neurological impairment	<24 hours of stroke onset	QTcd and QTcd*	Yes
3. Golbasi et al ²⁶ 1999 (Turkey)	Prospective	Hemorrhagic 28	Stroke non-survivors and healthy controls	Admission (specific time unspecified)	QTcd	Yes
4. Familoni et al ²⁷ 2006 (Nigeria)	Prospective	Ischemic** 64	age and sex matched controls (without specifying the presence of other conditions or the health status)	<24 hours of Admission	QTcd and QTcd	Not Reported
5. Bicakci et al ²⁸ 2008 (Turkey)	Prospective	Ischemic 148	Stroke non-survivors	< 6 hours of admission	QTcd	Not Reported
6. Chugh et al ²⁹ 2011 (India)	Prospective	Ischemic/Hemorrhagic 100	Healthy controls	<24 hours of stroke onset	QTcd	Not Reported
7. Macmillan et al ³⁰ 2003 (United Kingdom)	Prospective	Hemorrhagic* 27	Healthy controls	<24 hours of stroke onset	QTcd	Yes
8. Randell et al ³¹ 1999 (Finland)	Prospective	Hemorrhagic 26	Patients with unruptured aneurysms	<72 hours of Admission	QTcd	Yes
9. Alabd et al ³² 2009 (Egypt)	Prospective	Ischemic 30	Healthy controls	< 24 hours of admission	QTcd and QTcd	Yes
10. Eckardt et al ³³ 1999 (Germany)	Prospective	Ischemic 40	Stroke patients with no insular cortex involvement	<72 hours of Admission	QTcd	Not Reported
11. Mulcahy et al ³⁴ 2009 (United Kingdom)	Retrospective	Ischemic/Hemorrhagic 45	Post-stroke ECG	Admission (specific time unspecified)	QTcd and QTcd	Not Reported
12. Huang et al ²³ 2004 (Taiwan)	Retrospective	Hemorrhagic 68	Stroke non-survivors	<24 hours of stroke onset	QTcd	Not Reported
13. Lazar et al ³⁵ 2003 (United States)	Retrospective	Ischemic/Hemorrhagic/Transient Ischemic Attack 140	Stroke non-survivors	Admission (specific time unspecified)	QTcd	Yes
14. Lazar et al ³⁶ 2008 (United States)	Retrospective	Ischemic 30	Stroke non-survivors	Admission (specific time unspecified)	QTcd and QTcd	Yes
15. Sato et al ³⁷ 2001 (Japan)	Retrospective	Hemorrhagic 38	Patients with unruptured aneurysms	Admission (specific time unspecified)	QTcd and QTcd	Not Reported

Author and Year and Country	Study Design	Stroke Type and patient number (n)	Control/Comparison groups	Time of Baseline ECG	QTd and/or QTcd	Investigators Blinded to Clinical Data
16. Hanci et al ³⁸ 2010 (Turkey)	Retrospective	Hemorrhagic 35	Hospitalized patients without neurological impairment	<48 hours of stroke onset	QTcd and QTd	Yes

* aQTd (automated QTd as well)
** All African American patients
• intensive care unit patients
○ critical care unit patients

Table 2

Exclusion Criteria/Confounding Variables

Authors	Heart disease ¹	Electrolyte disturbances ¹	Medications with ECG effects ¹
1. Chao et al ²²	Excluded: AF ² on ECG.	Controlled: Presence of Ca ³ concentration abnormalities	Excluded: Current use of beta blockers, ACE inhibitors, Calcium Channel blockers
2. Afsar et al ²⁵	Excluded: Ischemic or Valvular heart disease; heart failure; cardiac arrhythmias; cardiomyopathies; LVH ⁴ ; BBB ⁵ .	Excluded: Abnormal serum K ⁶ or Ca concentrations	Excluded: phenothiazines, tricyclic antidepressant drugs, digoxin, theophylline, levodopa, phenothiazines, lithium carbonate
3. Golbasi et al ²⁶	Excluded: Heart disease, signs of MI ⁷ on ECG, AF,	No electrolyte abnormalities (K, Ca, Mg ⁸) were found in patients or controls	Excluded: Did not specify which medications were excluded
4. Familoni et al ²⁷	Controlled: Arrhythmias Included patients with: Pre-existing heart disease; history of angina pectoris, MI, heart surgery, use of cardiotonic drugs, LVH on ECG, chamber enlargement, BBB	N/A	Excluded: anti-malarials such as <i>halofantrine</i> , <i>antiarrhythmic</i> and psychotropic drugs
5. Bicakci et al ²⁸	Excluded: CAD ⁹ (history of MI; coronary artery bypass grafting or angioplasty; angina; abnormal stress test; positive coronary angiograms) Valvular heart disease; Heart failure; Cardiac arrhythmia; ECG evidence of BBB; Cardiomyopathies	Excluded: patients with a correctable cause offer an electrolyte imbalance (K, Ca Mg)	Excluded: <i>digoxine</i> , <i>lithium carbonate</i> , <i>tricyclic antidepressant drugs</i> , <i>phenothiazines</i> , <i>erythromycin stearate</i> , <i>levodopa</i> , <i>theophylline</i>
6. Chugh et al ²⁹	Excluded: Ischemic, Valvular or hypertensive heart disease; Heart failure due to any cause.	N/A	Excluded: <i>Erythromycin</i> , <i>theophylline</i> , <i>levodopa</i> , <i>lithium carbonate</i> , <i>antiarrhythmics</i> , <i>phenothiazine</i>
7. Macmillan et al ³⁰	Controlled: Cardio respiratory compromise; Myocardial dysfunction	N/A	Excluded: Intropes or nimodipine
8. Randell et al ³¹	N/A	Electrolyte disorders if any were corrected prior to study entry	N/A
9. Mulcahy et al ³⁴	Excluded: AF/flutter; Ventricular pacemaker rhythm; BBB; Controlled: Ischemic heart disease, Cardiac failure; Arrhythmias	Controlled: Ca	Controlled: Did not specify which medications
10. Huang et al ²³	Excluded: Heart Disease, such as Arrhythmias, Coronary Heart Diseases, Cardiomyopathies; recent MI; AF.	Controlled: Electrolyte concentrations (Na ¹⁰ , K, Ca, Mg)	N/A
11. Hanci et al ³⁸	No patients had CAD, or A-V block or BBB.	Controlled: electrolytes:(Na, K, Ca, Mg, Cl ¹¹)	N/A
12. Lazar et al ³⁵	Controlled: AF, prior MI, CAD; Recent Cardiac Surgery	Excluded: Metabolic disorders (not otherwise defined in the study)	One patient included in the analysis was on anti arrhythmic medication (not otherwise defined in the study)
13. Lazar et al ³⁶	Controlled: AF; Recent Cardiac Surgery, CHF ¹² , CAD.	Excluded: Metabolic disturbance (not otherwise defined in the study)	One patient included in the analysis was on anti arrhythmic medication (not otherwise defined in the study)

Authors	Heart disease ¹	Electrolyte disturbances ¹	Medications with ECG effects ¹
14. Sato et al ³⁷	Controlled: PVCs ¹³	Controlled: Electrolyte concentrations(K, Mg)	N/A
15. Eckardt et al ³³	Excluded: Cardiomyopathies; MI; BBB Controlled: Myocardial failure; Coronary; heart disease; Arrhythmias.	Excluded: Abnormal electrolyte levels (K, Ca, Mg)	Excluded: <i>digitalis, procainamide, disopramide, encainide, fleca inide, amiodarone, sotalol, phenothiazines, butyrophenone, tricyclic or tetracyclic anti depressants, anti histamines, erythromycin</i>
16. Alabd et al ³²	Excluded: Previous MI within the previous four weeks; Previously diagnosed congenital long QT syndrome; AF; Paced rhythm or BBB; Known organic heart disease (valvular, ischemic or cardiomyopathies). Controlled: Family history of ischemic heart disease	N/A	Excluded: <i>quinidine and amiodarone</i>

N/A – Not available

¹ Either as exclusion criteria or a controlled variable

² AF= Atrial Fibrillation

³ Ca= Calcium

⁴ LVH = Left Ventricular Hypertrophy

⁵ BBB = Bundle Branch Block

⁶ K = Potassium

⁷ MI = Myocardial Infarction

⁸ Mg = Magnesium

⁹ CAD = Coronary Artery Disease

¹⁰ Na = Sodium

¹¹ Cl = chlorine

¹² CHF= Congestive Heart Failure

¹³ PVC = Premature ventricular contractions

¹⁴ QTcd = QTd corrected for heart rate

Table 3

(A–D) Baseline QTd of Stroke Patients versus Controls (arranged according to stroke type)

A. Subarachnoid Hemorrhage (SAH) Studies					
Reference	Stroke subjects (n) & QTd, msec (mean, SD)	Control subjects (n) & QTd msec (mean, SD)	P values	Control Group	Baseline ECG Time
1. Sato et al ³⁷	38 QTcd = 109±49	30 QTcd = 64±21	<0.01	Patients with unruptured aneurysms	Admission
2. Randell et al ³¹	26 QTcd = 78 (62 and 108) [○]	16 QTcd = 25 (15 and 33) [○]	<0.001	Patients with unruptured aneurysms	<72 hours of admission
3. Macmillan et al ³⁰	27 [□] QTcd = 74.13±26.1	27 QTcd = 48.3±12.0	<0.0001	Healthy controls	< 24 hours of strokes symptom onset
4. Hanci et al ³⁸	35 QTd = 66.86±23.48 QTcd = 79.77±29.41	35 QTd = 41.14±11.31 QTcd = 44.54±12.90	<0.001	Patients hospitalized without neurological impairment	<48 of symptom onset
B. Intracerebral Hemorrhage (ICH) studies					
5. Golbasi et al ²⁶	28 QTd = 54.7±17.3	29 QTd = 36.9±14.2	<0.001	Healthy controls	Admission
C. Ischemic/Hemorrhagic studies					
6. Chugh et al ²⁹	100 QTd values were not reported	50 QTd values were not reported	No P value recorded. However, reported significant difference	Healthy controls	< 24 hours of strokes symptom onset
7. Afsar et al ²⁵	36 Baseline QTd = 60 (20–80) [○] Baseline QTcd = 56±19 Baseline [■] aQTd=50 (14–94) [○]	19 Baseline QTd = 20 (0–40) [○] Baseline QTcd = 30±14 Baseline [■] aQTd= 28(10–42) [○]	<0.005 <0.001 <0.001	Patients hospitalized for something other than cardiac or neurological impairment	< 24 hours of strokes symptom onset
D. Ischemic studies					
8. Familoni et al ²⁷	64 QTd = 60.6±25.1 QTcd = 72.3±52	60 QTd = 48.8±13.2 QTcd = 51.7±15.4	0.03 0.02	Did not specify health status of controls	< 24 hours of admission
9. Alabd et al ³²	30 QTd = 56±19 QTcd = 62±21	30 QTd = 43±5 QTcd = 48±5	0.001 0.001	Healthy controls	< 24 hours of admission

Table 1: A: Studies that included only SAH Patients; B: Studies that included only ICH Patients; C: Studies that included both Hemorrhagic and Ischemic Patients; D: Studies that included only ischemic patients

[○] median values and (range)

□ SAH patients admitted to intensive care unit

▫ African American patients only

■ aQTd = Automated QTd

Table 4

Baseline and Follow-up QTd and QTcd Values in Stroke Cases

Author	Baseline ECG Time	QTd msec (mean, SD)	Follow up ECG Time	QTd	p value
1. Afsar et al ²⁵	<24 hours of stroke	QTd = 60 (20–80) $\bigcirc$ QTcd = 56±19	Day 3	QTd = 40 (0–80) $\bigcirc$ QTcd = 36±21	<0.001
2. Chugh et al ²⁹ **	<24 hours of stroke	N/A	Day 3	N/A	N/A
3. Alabd et al ³²	< 24 hours of admission	QTd = 56±19 QTcd = 62±21	Day 3	QTd = 43±10 QTcd = 50±13	<0.001 <0.001
4. Lazar et al ³⁶	Admission	QTcd = 78±30	Day 3	QTcd = 88±30	<0.001
5. Golbasi et al ²⁶	<24 hours of admission	QTd = 54.7±17.3	Day 3	QTd = 43.6±17.1	N/A
6. Randell et al ³¹ ***	<3 days of stroke	QTcd = 61 (41, 118) $\bigcirc$	Day 3	QTcd = 70 (60–80) $\bigcirc$	N/A (authors state the difference was not statistically significant)

$\bigcirc$ median and (range)

** Chugh et al reported a significant difference between baseline and follow-up QTd values however data are not provided in the manuscript.

*** Randell et al reported day 3 QTcd values for only one of two groups of SAH patients included in the study.

Table 5
Baseline QTd and QTcd of Surviving Stroke Patients Versus Non-Surviving Stroke Patients

Study	Stroke type	Surviving subjects QTd msec (mean, SD)	Non-surviving subjects QTd msec (mean, SD)	P value	ECG Time
1. Bicakci et al ²⁸	Ischemic	QTcd= 7.4±3.7	QTcd= 10.1±4.6	0.002	< 6 hours of admission
2. Lazar et al ³⁵	Hemorrhagic (ICH)/ischemic/Transient Ischemic Attack	QTd= 50±15	QTd= 83±20	0.004	Admission
3. Huang et al ²³	Hemorrhagic (ICH)	QTcd= 39±11	QTcd= 78±32	<0.001	<24 hours of stroke onset
4. Chao et al ²²	Hemorrhagic (ICH) and (SAH) and brain stem	QTcd= 131.8±59.3 QTd = 102.7±41.2	QTcd = 134±10 QTd = 107.5±46.1	0.85 0.62	< 6 hours of stroke onset
5. Golbasi et al ²⁶	Hemorrhagic (ICH)	QTd= 51.3±17.7	QTd = 58.5±16.8	>0.05	Admission