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Prolonged QT interval: accuracy of the " rule of thumb" method for measuring the QT interval in the elderly attending geriatric clinical practices

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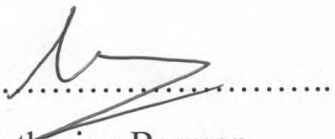
Prolonged QT Interval: Accuracy of the "Rule of Thumb" method for measuring the QT interval in the elderly attending geriatric clinical practices.

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A research report submitted to the University of Witwatersrand, Johannesburg in fulfilment for the requirements of the degree of Master of Medicine 2017

DECLARATION

I, Catherine Berman, declare that this research report is my own work which is being submitted for the degree Master of Medicine (in the submissible format with my protocol and an extended literature review) in the branch of Internal Medicine at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



Catherine Berman

Signed ....9.. day of ...November.....2017

ACKNOWLEDGEMENTS

Undertaking an MMED is a daunting task. From deciding on a topic, to completing the thesis and handing it in for assessment would not be possible without the assistance and support of many individuals and organizations.

I would like to say a very sincere thanks to Prof. Brent Tipping, my supervisor whose wisdom helped me to choose my topic. Furthermore, Dr. Tipping has offered extremely valuable advice and I am grateful to have experienced his guidance and encouragement.

No MMED would be complete without all the statistical calculation and interpretation of the relevant data. I would like to thank Petra Gaylard for all her assistance in calculating and interpreting the results of my research.

Thanks too to Dr June Fabian, Head of Research at Donald Gordon Medical Centre for her guidance and assistance.

To my dear husband, Shaun goes my sincerest, deepest thanks for his IT support, and understanding whilst I have spent hours away from my family to collect and collate this data. Specialising in Internal Medicine is a daunting task, and with my two small children requires a support system in order for you to complete the research. Thank you Shaun for your support and understanding.

Finally, I wish to thank my parents, Walter and Linda Kloeck for all the time and assistance they have given me in completing this research.

ABSTRACT

Background

Long QT syndrome (LQTS) is characterized by a prolonged QT interval on the electrocardiogram (ECG), a risk for sudden cardiac death. A simple 'rule of thumb' method states that if a patient's heart rate is between 60-100 bpm, the QT interval should not be more than half the R-R interval. The clinical accuracy of this method has not been tested in the elderly.

Objectives

To determine if the 'rule of thumb' to calculate QT interval prolongation, is accurate, compared to the corrected QT interval calculated using Bazett's formula. Secondary objectives include the prevalence of long QT and risk factors for QT prolongation.

Methods

The QT interval was calculated using Bazett's formula, and the 'rule of thumb' method, from ECG's collected from patients over 60 years old, on their first visit to a geriatric clinical service. Only data from patients with heart rates in the range 60-100 were analyzed. Medications and electrolyte levels were recorded.

Results

A total of 1000 ECGs were collected. 776 ECGs were included in the study. Prevalence of prolonged QT interval was 37.8% using Bazett's formula. Compared to Bazett's formula, the 'rule of thumb' method had a sensitivity of 65.2% and a specificity of 96.9%. ECG computer analysis calculated QTc was available for 42.5% of the cases and had a sensitivity of 58.1% and specificity of 95.3% compared to Bazett's formula. Of the 23.3% of patients taking medications known to prolong the QT interval only 38.6% had a prolonged QT interval. There was a significant association between QT interval prolongation and hypokalaemia.

Conclusion

The 'rule of thumb' method to determine QT interval prolongation, has high specificity but low sensitivity. This bedside measure is similar in accuracy to QT determination using an ECG computer analysis calculation in this population of older persons.

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ABBREVIATIONS

ECG	Electrocardiogram
LQTS	Long QT Syndrome
WDGMC	Wits Donald Gordon Medical Centre
QTc	Corrected QT Interval
EMI	Elite Medical Instrument
Bpm	Beats per minute
PI	Principal investigator

CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

INTRODUCTION

The electrocardiogram (ECG) is a quick and simple investigation that records the electrical activity of the heart. It is an essential part of the cardiac assessment of any patient and can provide a wealth of useful information to the clinician.

An effort should be made to evaluate the QT interval on every electrocardiogram to determine whether the QT interval is normal or prolonged. The QT interval is the sum of action potentials of the ventricular myocytes. It includes both depolarization (QRS complex) and repolarization (T-wave). [1] It is the time from the start of the QRS complex to the end of the T wave, the end of the T wave being the time at which ventricular repolarization is completed and the T wave voltage amplitude returns to baseline. [2]

Long QT syndrome (LQTS) is characterized by a prolonged QT interval on the ECG and is associated with an increased risk of a characteristic, life–threatening cardiac arrhythmia, torsades de pointes, a risk for sudden cardiac death.[3] The vulnerable period during which the arrhythmia can be provoked is the relative refractory period of the ventricular myocardium during repolarization. This corresponds to the declining limb of the T-wave from peak to isoelectric line (Figure 1). Repolarization of the ventricle is slower than depolarization, and therefore more likely to be affected by disease, drugs and biochemical abnormalities. [1]

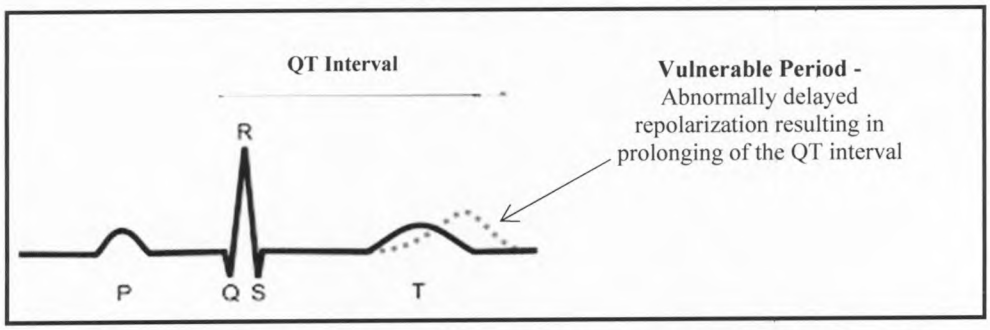


Figure 1: Prolongation of repolarization resulting in lengthening of the QT interval

The LQTS can be genetic or acquired. There are two congenital LQTS; autosomal dominant Romano-Ward syndrome and the less common Jervell and Lange Neilsen syndrome. [4]] In addition to congenital LQTS, there is increasing evidence of genetic variants that healthy people may inherit, which places them at higher risk of prolonged QT interval caused by certain drugs.[5]

Acquired LQTS results from numerous other physiological and pathological factors. Diurnal variation in the QT interval makes it important to consider time of day when assessing the QT interval. [6] Female gender is associated with a longer QT interval of approximately 20ms compared with men. [4]. Increasing age is an independent risk factor for QT prolongation. [7] Electrolyte abnormalities, including hypokalaemia, hypomagnesaemia and hypocalcaemia are associated with a prolonged QT interval. [8][9]

Drug-induced LQTS can occur as a side effect of commonly used cardiac and non-cardiac drugs. [10] Many drugs have been implicated to prolong the QT interval and additional medications continue to be identified [11]. The removal of many drugs from use due to the risk of inducing torsades de pointes has intensified pharmaceutical industry research on the drug effect on the QT interval. This has improved medical balancing of the QT prolongation versus the benefit of the drug. [4]

QT measurements are not always available for the patient, prior to commencement of taking a particular drug. Often the risk assessment is made on the presenting ECG at the time the patient is seen for the first time. Common drugs causing LQTS can be seen in Table 1. [4]

Table 1: List of drugs associated with a high risk of QT prolongation [Adapted from reference 4]

Drug Class	Name of drug
Cardiac drugs	Amiodarone Sotalol Disophyramide Dofetilide Procainamide Quinidine
Antidepressants	Selective serotonin re-uptake inhibitors:citalopram,escitalopram,fluoxetine Moclobemide Tricyclic antidepressants Lithium
Antipsychotics	Amisulpride Chlorpromazine Haloperidol Ziprasidone Thioridazine
Antihistamines	Loratadine Astemirzole Diphenhydramine
Antimicrobials	Ciprofloxacine, moxifloxacin, sparfloxacin Clarithromycine, erythromycin Fluconazole, voriconazole Pentamidine
Other drugs	Chloroqine Cisapride Dolesatron Methadone Arsenic

A more comprehensive list of drugs associated with QT prolongation is available at www.qtdrugs.org. (Appendix A). [12] Drugs are reviewed on an ongoing basis according to the available evidence that supports their continued placement on this list.

Other identified pathological risk factors include heart disease (congestive cardiac failure, myocardial infarction, cardiomyopathies), hypoglycaemia, obesity, hypertension [4], treatment with diuretics, impaired hepatic or renal drug metabolism and bradycardia. The greatest risk for development of acquired LQTS and torsades de pointes is the clustering of multiple recognizable risk factors in a single patient. [13]

Measuring the QT interval is especially relevant in the elderly population since the QT interval is known to increase with age. [13] Furthermore, elderly patients have multiple risk factors for LQTS such as poly pharmacy, myocardial damage, renal or hepatic dysfunction and electrolyte disturbances.[14] In the US 35.6% of elderly patients had poly pharmacy [15]. In a recent Scottish study, the prevalence of polypharmacy in patients over the age of 65 was high, with 16.4% receiving ten or more medications. [16]

By measuring the QT interval of an ECG and correcting for heart rate (QTc), a prolonged QT interval can be determined. Although computerized analysis and interpretation of the QT interval are sometimes printed on the ECG, these might well over- or underestimate the QT interval. This is particularly evident with unusual T-wave morphologies and technically suboptimal ECGs. The algorithms used to measure the QT on standard ECG machines are inferior and often have significant errors. Where this method runs into difficulty, is that the computer can calculate a formula with accuracy, but cannot measure the end point of the QT interval. [17]

Manual measurement is a more practical way to measure the QT interval.[18] Multiple formulas exist to estimate the QT interval. These formulas correct the QT interval for heart rate to enable comparison to reference values. The formulae require that the ECG is in a stable sinus rhythm for accuracy. Exponential, logarithmic and linear formulae have been formulated. Table 2. Generally, at heart rates between 60 and 100bpm there is no difference in the formulae applied. [19]

Table 2: QT-Heart Rate Correction Formulae [adapted from reference 19]

Method	Description	Formula	Comment
Exponential	Bazett	$QT_C = QT/RR^{1/2}$	Advantage: Widely used Disadvantage: Inaccurate <60bpm & >100bpm
	Fridericia	$QT_C = QT/RR^{1/3}$	Advantage: Widely used. More consistent at faster heart rates
Linear	Framingham	$QT_C = QT+0.154(1-RR)$	Advantage: More consistent rate correction over wide range of heart rates
	Hodges	$QT_C = QT+1.75(HR-60)$	Advantage: More uniform correction over a wide range of heart rates
	Rautaharju Females & males <15 And >50 years Males 15-50 years	QTI = (QT[HR+100])/656 QTI = (QT[HR+100]/656 QTI=100(QT)/([656/(1+0,01hr])+0.4-25)	Advantage: More uniform correction over a wide range of heart rates
Logarithmic	Ashman	QT =K1 x log(10 x [RR+K2]) K2=0.07, and K1=0.380 K2=0.07, and K1=0.390	Advantage: More uniform correction over a wide range of heart rates

The disadvantages of the heart rate correction formulae are that they correct the QT for heart rate at a population level. In the formula $QTc = QT/RR^{\alpha}$ There is only one correction factor α which is ½ for Bazett's formula and ⅓ for Fridericia's formula. Research has shown that the relationship between HR and QT interval is different for each patient. [20]

An alternative to calculating the QTc using one of the formulae is the QT Nomogram. The QT interval is plotted against heart rate. This method is reliable in determining whether the QT is abnormal. [19]

The most accurate method of measuring the QT interval is using digitized high-resolution 12 lead Holter ECG recordings with advanced algorithms and on-screen magnification for manual correction. The disadvantage of this method is that it is expensive and rarely available in clinical practice. [17]

Manual measurement of the QT interval has been shown to render similar results to the High-resolution Holter technique. The Bazett's formula is the most commonly used formula when calculating the QT interval on an ECG with a heart rate between 60-100 bpm. [21] Accordingly, most references for normal or abnormal values have been derived from Bazett's formula.[19] A QTc of more than 0.45sec is considered prolonged in men and more than 0.47sec prolonged in women. [22]

Accurate manual assessment of the QT interval appears to be difficult for clinicians worldwide. [23] To make it simpler for clinicians, ECGs have been interpreted using a "rule of thumb" method to determine if a QT interval is normal. This rule states that if a patient's heart rate is between 60-100bpm, the QT interval should not be more than half of the R-R interval. This simple measure is well described in numerous publications [24] but the accuracy of this method has not been proven in the elderly population.

Older persons frequently undergo routine ECG monitoring during both out-patient and in-patient sub-specialist geriatric assessments due to a clinically suspected higher yield of abnormalities in this population group at greater risk of cardiovascular disease.

RESEARCH QUESTION

Is the "rule of thumb" method for measuring the QT interval accurate in determining whether the QT interval is prolonged or not in the elderly population?

OBJECTIVES

1. The primary objective of this study is to determine if the "rule of thumb" method of calculating whether the QT interval is prolonged or not, is accurate, when compared to the corrected QT interval calculated using the Bazett's formula in ECGs from an elderly population attending the geriatric clinical practices at Wits Donald Gordon Medical Centre (WDGMC).

2. Secondary objectives include the following:

    a) Determining the prevalence of a prolonged QT interval in an elderly population at first presentation to the geriatric clinical practices at WDGMC.
    b) To review the patient's drug list on first presentation, to assess if the patient was taking any of the drugs listed in table 1 (appendix A) and determine if there is an association with a prolonged QT interval.
    c) Of the ECGs determined to have a prolonged QT interval, to assess if the patient had hypokalemia (K < 3.5mmol/l), hypomagnesaemia (Mg <0.7mmol.l) or hypocalcaemia (Ca< 2.12mmol/l).
    d) To compare the QTc calculated by the ECG machine, with the QTc calculated by Bazetts formula and with the "rule of thumb" method.

METHODOLOGY

1. Study Design

This study is a retrospective review, analyzing the QT interval of ECGs from an elderly population at their first presentation to the geriatric clinical practices at WDGMC.

2. Site of Study

The ECGs will be collected from the geriatric clinical practices at Wits Donald Gordon Medical Centre, Johannesburg, South Africa.

3. Population Sample

ECGs will be collected from the files of patients attending the geriatric clinical practices at WDGMC. Only the ECG of the patient's first presentation to the geriatric service, including inpatient and outpatient consultations, will be analyzed. The total number of patient's files reviewed will be recorded.

- **Inclusion Criteria**

a) Patient aged 60 years or older
b) Heart rate between 60 and 100 bpm
c) ECG settings at a paper speed of 25mm/sec

- **Exclusion Criteria**

a) Patients who do not have an ECG at their first presentation to the geriatric service

4. Sample Size

All the ECGs that comply with the inclusion criteria, of the patient's first clinical presentation to the geriatric practices at WDGMC will be analyzed. ECGs will be collected from March 2007 to January 2015. It is anticipated that approximately 1,000 cases will be included in the study.

Calculation of sample size requirements is based on the key research questions to be answered, in this case:

a) The agreement between the different methods used to determine the length of the QT interval (as normal vs. prolonged)
b) The prevalence of a long QT interval in the study group.

For (a) above, inter-method agreement is assessed by Cohen's kappa. For all kappa-like agreement coefficients, the required number of subjects (n) depends on the relative error (r), the number of subjects in the entire population (N) and the difference p_a-p_e between the overall agreement probability p_a and the chance agreement probability p_e as follows:

$$n = \frac{n^*}{1 + \frac{n^*}{N}}, \text{where } n^* = \frac{1}{r^2(p_a - p_e)^2}$$

Assuming that N is very large, and that the chance-agreement probability is 0, the overall agreement probability is at least 0.5, and a relative error of 20%, the required n is 100. [25]

For (b) above, the estimation of a proportion is required. The proportion of patients with a long QT interval is expected to be 4%. The estimation of this proportion with a sample size of 1,000 will give a precision of the estimate of ± 1.2%, which is adequate for a study of this nature.

Sample size for prevalence was determined using the formula:

$$n = \frac{Z^2 P(1 - P)}{d^2}$$

where n = sample size,

Z = Z-statistic for the chosen level of confidence,

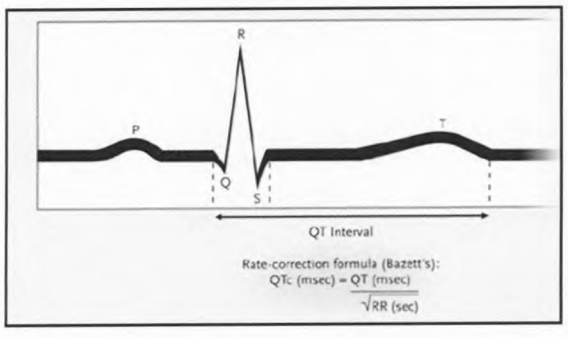
P = expected prevalence or proportion

d = precision [26]

Thus, the anticipated sample size is adequate to meet the key objectives of the study.

5. Method

- To maintain confidentiality, each ECG included in the study will be allocated a number starting at 0001.
- The age and gender of the patient will be documented. The QTc calculated by the ECG machine will be recorded. A list of drugs that the patient was taking, as well as their potassium, magnesium and calcium levels will be recorded on the data sheet (Appendix B)
- The QT interval of each ECG will be evaluated by two methods
  a) The Bazett's formula – $QTc = QT/\sqrt{RR}$



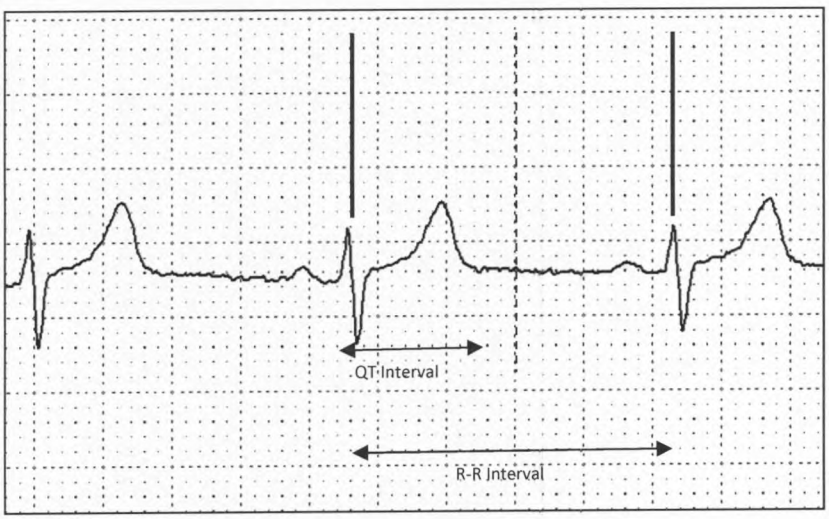
[Adapted from reference 11]

The value of the QTc will be recorded.

In male patients, the QT interval will be classified normal if the QTc ≤0.45s and prolonged if QTc >0.45s.

In female patients, the QT interval will be classified normal if the QTc ≤0.47s and prolonged if QTc >0.47s.

b) The "rule of thumb" method – the QT interval should not be more than half of the R-R interval.



If the QT interval is less than half the RR interval it will be classified as normal. If the QT interval is more than half the RR interval it will be classified as prolonged.

- Elite Medical Instrument (EMI) calipers will be used to measure the QT interval, the R-R interval and the midpoint of the R-R interval. The accuracy of manual determination with a caliper is within 20-40ms. [27]
- The QT interval will be measured in either lead II, V5 or V6. The longest value will be used in order to improve accuracy of the measurement [27]
- The patient's medication list will be compared to the QT drugs list, table 1 (appendix A) to assess if the patient is on any drugs proven to prolong the QT interval.
- Patients with prolonged QT intervals as measured by the Bazett's formula will also be reviewed for electrolyte abnormalities, namely hypokalaemia, hyponatraemia or hypocalacaemia.
- The QTc calculated by the ECG machine will be compared to the QTc calculated by the Bazett's formula and by the "rule of thumb" method.

6. **Statistical Analysis**

- The demographics (age, gender) of the study group will be described.
- Agreement between the different methods used to determine the QT interval will be assessed by the overall agreement, Bowker's test of symmetry and Cohen's kappa.
- The prevalence of a long QT interval in the study group will be determined, together with a 95% confidence interval.
- The use of the listed medications will be tabulated, categorized by normal and long QT interval groups. The association between the use of each medication and the presence/absence of a long QT interval will be determined by Fisher's exact test.
- For those cases with a long QT interval, the presence of electrolyte abnormalities will be tabulated.
- Data analysis will be carried out in SAS. [28] The 5% significance level will be used.

LIMITATIONS OF THE STUDY

One limitation to this study is the specific sample population. The selected sample is an elderly population that feeds the WDGMC area. Most of these patients are on medical aids or have access to private funds. This is not a good representation of the general elderly population of South Africa. The reason for choosing this population is that medication records and electrolyte results are more likely to be available for interpretation.

Another limitation to this study is that some patients may not have had blood tests and hence electrolyte values at their first consultation. This may result in missing data.

Finally, when comparing the computer generated QTc with the QTc calculated by the Bazetts formula and the "rule of thumb" method, there may be missing data as many ECG machines don't record the calculated QTc on the ECG print out. Secondly, of the ECGs that do have a QTc value recorded, the model of ECG machine will not be known, and different models may calculate the QTc differently due to machine – specific calibration.

COSTS OF THE STUDY

The costs will be funded privately by the principal investigator (PI).

a) Data retrieval and capturing

   The costs of this study will be minor. As the PI will be obtaining the information personally, no other staff members, and therefore no other staff costs, will be involved.

b) Elite Medical Instrument (EMI) calipers

c) Stationery

   Ink and paper costs for the photocopier and computer will be required.

ETHICAL CONSIDERATIONS

The following ethical considerations will be adhered to:

a) Written permission will be obtained from the Faculty of Health Sciences Ethics Committee to approve the study.

b) Permission to conduct this study at WDGMC will be obtained from Dr Sue Tager (CEO)

c) Permission to access patient records from the two Geriatric Specialist Physicians at WDGMC will be obtained.

d) The identities of the patients whose information is being assessed will be protected. In order to achieve this, each patient record (participant) will be randomly allocated a number, starting at 0001. A list will be created that links the random number allocated for the purposes of this study to the patient's name. This will be kept separate from the rest of the collected data to ensure anonymity. Only the PI will know which number correlates with which ECG record.

e) The required ECG will be photocopied from each file and attached to the data collection sheet, which will only have the random study number on it. If there are any identifying data on the ECGs, the data will be temporarily covered for the purposes of photocopying. No identifiers will be on the photocopied version. No patient names or hospital numbers will be noted so as to maintain patient anonymity. Data will be correlated according to the allocated number and not to the patients' personal details. All conclusions drawn from the patient data will be reported on collectively, thus not focusing on one specific patient. Results will be published collectively

TIMING

Research proposal and ethics clearance:	February – March 2015
Data collection:	March – April 2015
Data analysis:	May – June 2015
Writing of paper:	July – September 2015
Writing of article for publication:	October – December 2015

REPORTING OF RESULTS

Results will be presented to the academic community through posters, presentations and will also be submitted to a suitable peer review journal.

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CHAPTER 2: SUBMISSIBLE ARTICLE

Prolonged QT Interval: Accuracy of the 'rule of thumb' method for measuring the QT interval in the elderly attending geriatric clinical practice

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ABSTRACT

Background

Long QT syndrome (LQTS) is characterized by a prolonged QT interval on the electrocardiogram (ECG), a risk for sudden cardiac death. A simple 'rule of thumb' method states that if a patient's heart rate is between 60-100 bpm, the QT interval should not be more than half the R-R interval. The clinical accuracy of this method has not been tested in the elderly.

Objectives

To determine if the 'rule of thumb' to calculate QT interval prolongation, is accurate, compared to the corrected QT interval calculated using Bazett's formula. Secondary objectives include the prevalence of long QT and risk factors for QT prolongation.

Methods

The QT interval was calculated using Bazett's formula, and the 'rule of thumb' method, from ECG's collected from patients over 60 years old, on their first visit to a geriatric clinical service. Only data from patients with heart rates in the range 60-100 were analysed. Medications and electrolyte levels were recorded.

Results

A total of 1000 ECGs were collected. 776 ECGs were included in the study. Prevalence of prolonged QT interval was 37.8% using Bazett's formula. Compared to Bazett's formula, the 'rule of thumb' method has a sensitivity of 65.2% and a specificity of 96.9%. Of the 23.3% of patients taking medications known to prolong the QT interval only 38.6% had a prolonged QT interval. There was a significant association between QT interval prolongation and hypokalaemia.

Conclusion

The 'rule of thumb' method to determine QT interval prolongation, has high specificity but low sensitivity. If the QT interval is determined by the 'rule of thumb' method as prolonged, the clinician can be confident that the QT interval is indeed prolonged.

INTRODUCTION

The electrocardiogram (ECG) is a rapid and simple investigation that records the electrical activity of the heart. It is an essential part of the cardiac assessment of any patient and can provide a wealth of useful information to the clinician. An effort should be made to evaluate the QT interval on every ECG to determine whether the QT interval is normal or prolonged. The QT interval is the sum of action potentials of the ventricular myocytes. It includes both depolarization (QRS complex) and repolarization (T-wave). [1]

Long QT syndrome (LQTS) is characterized by a prolonged QT interval on the ECG and is associated with an increased risk of a characteristic, life–threatening cardiac arrhythmia, torsades de pointes, a risk for sudden cardiac death.[2] The vulnerable period during which the arrhythmia can be provoked is the relative refractory period of the ventricular myocardium during repolarization. Repolarization of the ventricle is slower than depolarization, and therefore more likely to be affected by disease, drugs and biochemical abnormalities. [1]

The LQTS can be genetic or acquired. There are two congenital LQTS; autosomal dominant Romano-Ward syndrome and the less common Jervell and Lange Neilsen syndrome. [3] In addition to congenital LQTS, there is increasing evidence of genetic variants that healthy people may inherit, which places them at higher risk of prolonged QT interval caused by certain drugs.[4]

Acquired LQTS usually results from drug therapy or electrolyte abnormalities, including hypokalaemia, hypomagnesaemia and hypocalcaemia. [5][6] Drug-induced LQTS can occur as a side effect of commonly used cardiac and non-cardiac drugs. [2] Many drugs have been implicated to prolong the QT interval and additional medications continue to be identified. [7]

Acquired LQTS results from numerous other factors. Diurnal variation in the QT interval makes it important to consider time of day when assessing the QT interval. [8] Female gender, increasing age, heart disease, hypoglycaemia, obesity, hypertension, treatment with diuretics, impaired hepatic or renal drug metabolism and bradycardia is associated with a longer QT

interval [7]. Measuring the QT interval is especially relevant in the geriatric population as elderly patients have multiple risk factors for LQTS.

Multiple formulae exist to estimate the QT interval. These formulae correct the QT interval (QTc) for heart rate to enable comparison to reference values, and thus a prolonged QT interval can be determined. The formulae require that the ECG is in a stable sinus rhythm for accuracy. Exponential (Bazett and Fridericia), logarithmic (Framingham, Hodges and Rautaharju) and linear (Ashman) formulae have been formulated. Generally, at heart rates between 60 and 100bpm there is no difference in the formulae applied. [9]

The Bazett's formula is the most commonly used formula when calculating the QT interval on an ECG with a heart rate between 60-100 bpm. [10] Although computerized analysis and interpretation of the QT interval are sometimes printed on the ECG, these might well over- or underestimate the QT interval.

To make it easier for clinicians, ECGs have been interpreted using a 'rule of thumb' method to determine if a QT interval is prolonged. The 'rule of thumb' method is a quick and simple tool for clinicians to use when reading ECG's. This rule states that if a patient's heart rate is between 60-100 bpm, then a normal QT interval should not be more than half of the R-R interval. This simple measure is well described in numerous publications but the accuracy of this method has not been proven in the elderly population. [11]

OBJECTIVES

The primary objective of this study is to determine if the 'rule of thumb' method of calculating whether the QT interval is prolonged or not, is accurate, when compared to the corrected QT interval calculated using the Bazett's formula in ECGs from an elderly population attending the sub-specialist geriatric clinical practice at Wits Donald Gordon Medical Centre (WDGMC).

Secondary objectives include the following:

a. Determining the prevalence of a prolonged QT interval in an elderly population at first presentation to the geriatric clinical practice at WDGMC.
b. To review the patient's drug list on first presentation, to assess if the patient was taking any drugs known to prolong the QT interval as listed on the QT drugs list [11] and determine if there is an association with a prolonged QT interval.

c. Of the ECGs determined to have a prolonged QT interval, to assess if the patient had hypokalemia (K < 3.5 mmol/l), hypomagnesaemia (Mg < 0.7 mmol.l) or hypocalcaemia (Ca < 2.12 mmol/l).
d. To compare the QTc calculated by the ECG computer analysis, with the QTc calculated by Bazett's formula, and with the 'rule of thumb' method.

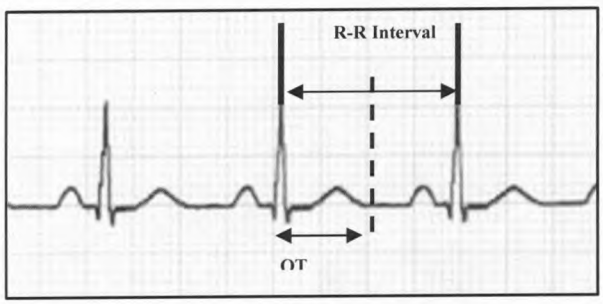
METHODS

Study oversight and design

A retrospective review was conducted, analyzing ECGs collected from March 2007 to January 2015. A total of 1000 ECGs were collected from the files of elderly patients attending the geriatric clinical practice at Wits Donald Gordon Medical Centre (WDGMC), Johannesburg, South Africa. Only the ECG of the patient's first presentation to the geriatric service, including inpatient and outpatient consultations, was collected. Ethical approval was obtained from the University of the Witwatersrand Human Research Ethics Committee.

From the ECG, the age, gender and heart rate of the patient was documented. The QT interval of each ECG was evaluated. The QT interval was measured using Elite Medical Instrument (EMI) calipers and the QTc was calculated using the Bazett's formula ($QTc = QT/\sqrt{RR}$). The QTc was classified as prolonged or not prolonged. A QTc of more than 0.45 sec is considered prolonged in men and more than 0.47 sec prolonged in women.[12] The QT interval was then documented as prolonged or not prolonged according to the 'rule of thumb' method seen in Fig. 1. The QTc calculated by the ECG computer analysis was also recorded and classified as prolonged or not prolonged in ECGs that had this value recorded.

Fig. 1. 'Rule of thumb' method – a normal QT interval should not be more than half of the R-R interval.



To determine the accuracy of the researcher's measurements, 42 ECGs were co-evaluated by the researcher and an expert. The intraclass correlation (ICC) was 0.95, indicating very good inter-rater reliability.

A list of medications the patient was taking at the time of the ECG, was recorded. The patient's medication list was compared to the QT drugs list [13] to assess if the patient was on any drugs known to prolong the QT interval. The patient's potassium, magnesium and calcium levels at the time of the ECG, were recorded.

Population sample

ECGs from patients aged 60 years or older were collected. The heart rate was between 60 and 100 bpm and the ECG settings were at a paper speed of 25 mm/sec.

Statistical Analysis

The demographics of the study group was described. Using the Bazett's formula to calculate the QTc interval as the gold standard, the sensitivity and specificity of the 'rule of thumb' and the computer calculated QTc methods was calculated. The prevalence of a long QT interval in the study group was determined, together with a 95% confidence interval. The use of the listed medications was tabulated, categorized by normal and prolonged QT interval groups. The association between the use of medications known to prolong the QT interval and the presence/absence of a long QT interval was determined by Fisher's exact test. For those cases with a long QT interval, the presence of electrolyte abnormalities was tabulated.

RESULTS

A total of 1000 ECGs were collected, of which 776 (77.6%) met the inclusion and exclusion criteria and were further analysed. The reasons why 224 (22.4%) ECGs were excluded from the study are seen in Table 1.

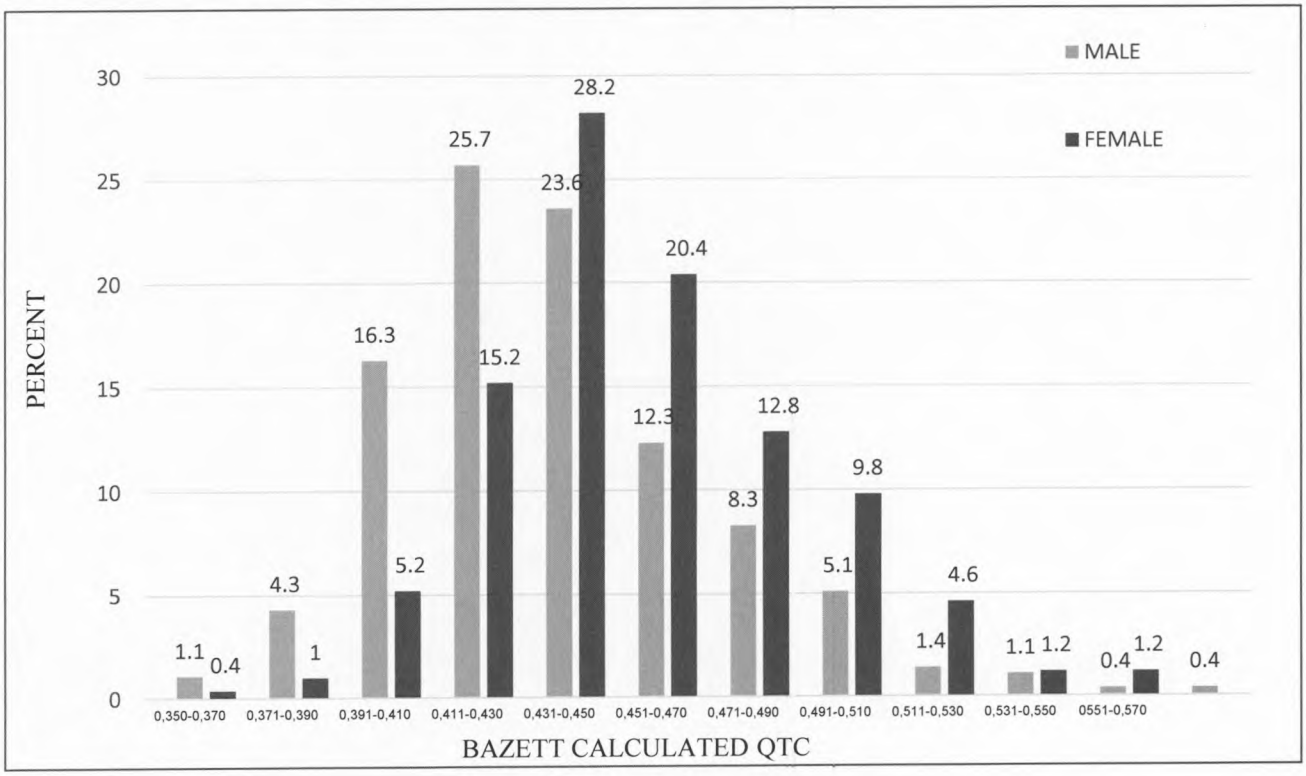
Table 1. Reason ECGs excluded from the study

Excluded ECGs	n (%)
Heart Rate < 60	90 (40.2)
Heart Rate > 100	76 (33.9)
Atrial Fibrillation	49 (21.9)
Pacemaker	7 (3.1)
Bigeminy	1 (0.4)
Poor Quality ECG	1 (0.4)

Of the 776 ECGs analysed, 500 (64.4%) ECGs were from female patients and 276 (35.6%) from male patients. The mean age of the study group was 78.3 years (range 60-101 years). The median heart rate of the ECGs analysed was 74 bpm (range 60-100 bpm).

The mean QTc as calculated using Bazett's formula was 0.458 (range 0.383 – 0.606) for male patients and 0.456 (range 0.361-0.566) for female patients. The QTc distribution as calculated by Bazett's formula is shown in Figure. 2.

Fig. 2. The QTc distribution calculated using Bazett's formula



The prevalence of a prolonged QT interval in this study group as measured by each of the three methods is seen in Table 2. There was no significant difference in the prevalence of prolonged QT in males versus females.

Table 2. Prevalence of a prolonged QT interval by 3 methods

Method	**% of patients with a prolonged QT interval**	**Population size (n)**	**95% confidence interval**
Bazett's	37.8	776	34.3-41.3
Rule of Thumb	26.6	776	23.5-29.8
ECG Computer	25.3	446	21.4 -29.6

Using the Bazett's formula as a gold standard, the 'rule of thumb' method has a sensitivity of 65.2% (confidence interval 59.4 – 70.6), and a specificity of 96.9% (confidence interval 94.9 – 98.3).

Data for the ECG computer analysis QTc calculation was available in only 42.5% of the cases (n=446). The missing data was at random and not biased with regard to any of the study variables. The ECG computer analysis calculation of the QT interval has a sensitivity of 58.1% (confidence interval 50.4 – 65.6) and a specificity of 95.3% (confidence interval 92.0 – 97.5.)

In this population group, 23.3% of 776 patients in whom ECGs were analysed, were taking medications known to prolong the QT interval. From this group of patients, only 38.6% had a prolonged QT interval as measured by the Bazett's formula. There was no significant association between the QT interval and medications known to prolong the QT interval (p=0.79).

The proportion of missing data for hypomagnesaemia is in excess of 50%, and therefore this variable could not be analysed. The prevalence of hypokalaemia and hypocalcaemia in this study is tabulated in Table 3. The proportion of missing data for hypocalcaemia was 26.7%, which means that the results must be interpreted with caution.

Table 3. Prevalence of hypokalaemia and hypocalcaemia

Condition	Category	Overall		Bazett's Classification				p-value
				Not prolonged		Prolonged		
		n	%	n	%	n	%	
Hypokalaemia	No	612	78.9	394	81.6	218	74.4	0.0001
	Yes	91	11.7	39	8.1	52	17.7	
	Unknown	73	9.4	50	10.4	23	7.8	
Hypocalcaemia	No	547	70.5	347	71.8	200	68.3	0.11
	Yes	22	2.8	10	2.1	12	4.1	
	Unknown	207	26.7	126	26.1	81	27.6	

In this study, 11.7% and 2.8% of the patients were documented as having hypokalaemia and hypocalcaemia, respectively. There was no significant association between QT interval and hypocalcaemia (p=0.11). There was a significant, weak, association between QT interval (prolonged / not prolonged) and hypokalaemia (n=703; p=0.0001; phi coefficient=0.15). In

those patients without a prolonged QT interval, 9.0% had hypokalaemia, compared to 19.3% in the prolonged QT interval group.

DISCUSSION

Multiple formulae exist to estimate the QT interval on an ECG, Bazett's formula being the most commonly used.[7] The 'rule of thumb' method for determining if the QT interval is prolonged or not is a simple measure that clinicians have used for many years. The primary purpose of this study was to assess the accuracy of the 'rule of thumb' method when compared to measuring the QT interval using Bazett's formula in an elderly population with a heart rate of 60-100bpm.

The analysis of 776 QTc's by Bazett's formula classified more patients as having a prolonged QT interval than determined by the 'rule of thumb' method. We can conclude that the 'rule of thumb' method has a low sensitivity of 65.2%, but high specificity of 96.9%. A recent study by Isbister and Berling examined the accuracy of the 'rule of thumb' method in a sample of ECG's with known prolonged QT interval. Their results revealed that the 'rule of thumb' method in ECG's with heart rates > 60 bpm was highly sensitive in determining that the QT interval was indeed prolonged, but showed low specificity.[14]

These findings corroborate this study in that the sensitivity of determining whether the QT is prolonged or not prolonged is low, but the specificity is high. As the Isbister and Berling study population already determined that the QT was prolonged, the findings were expected. The Isbister and Berling control ECG's were normal with no prolonged QT. Therefore, one would expect their specificity to be low.[14]

In this study, the 'rule of thumb' method was tested on a population of 776 random ECG's to determine if the QT was prolonged or not. This study concluded that if the QT interval is determined as NOT prolonged, the QT interval should be re-evaluated using another method. If the QT interval IS determined by the 'rule of thumb' method as prolonged, the clinician can be confident that the QT interval is indeed prolonged.

The prevalence of prolonged QTc in the elderly is documented in various studies. A study conducted in Israel showed a prevalence of 32% of a prolonged QTc in hospitalized elderly patients.[15] A study in Netherlands, Europe revealed a prevalence of prolonged QT of 29% in

a population of older adults [16]. This study revealed a prevalence of 37.8%. This finding supports literature indicating that the elderly have a relatively high prevalence of LQTS. The results also showed an equal prevalence of prolonged QTc in both male and female patients.

ECG computer analysis revealed a low sensitivity of 58.1% and a high specificity of 95.3% for determining a prolonged QTc when compared to Bazett's formula. Given this result, clinicians cannot rely solely on the computer generated QTc. This however was not specific for any individual ECG machine as ECGs in this study were printed from a variety of different ECG machines.

It was noted that 23.3% of patients on first presentation to geriatric clinical services were prescribed medications known to prolong the QT interval. Of these patients, 38.6% had a prolonged QT interval as measured by Bazett's formula. Should patients be taking medication known to prolong the QT interval, this study found that there was no significant interaction between medication and the QT interval. From this we can deduce that acquired LQTS is caused by a number of factors and not necessarily drugs along.

It is known that electrolyte disturbances, specifically hypokalaemia, hypomagnesaemia and less commonly hypocalcaemia are associated with a prolonged QTc.[5] During collection of data, it was noted that not all patients had calcium, potassium and magnesium blood results. There were not enough magnesium values to render significant results to this study. The prevalence of hypokalaemia in this study was 11.7%. A significant, weak, association between hypokalaemia and prolonged QT interval was shown in the results. However, there was no significant association seen between hypocalcaemia and the QT interval.

CONCLUSION

The 'rule of thumb' method in determining whether the QT interval is prolonged or not, has high specificity but low sensitivity. This bedside assessment is as marginally more accurate than ECG computer analysis QTc calculation in this sample of older persons. It is a rapid and useful method of diagnosing a LQTS on a patient's ECG without requiring additional tools. It can however only be accurate in heart rates between the values of 60 and 100 bpm. Clinicians should be wary of a possible false negative result when using this tool.

LIMITATIONS OF THE STUDY

One of the limitations of the Bazett's formula is that it is inaccurate at lower and higher heart rates. To eliminate these limitations, the study excludes heart rates lower than 60bpm and higher than 100bpm. It however remains the standard for clinical use.

Another limitation to this retrospective study was that some patients did not have blood tests at their first consultation resulting in absent electrolyte values. This resulted in missing data. The relevance of magnesium affecting the QT interval, could not be analyzed in this study.

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Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Drugs with conditional TdP risk			
Amantadine	Symmetrel®, Symadine®	Anti-viral	Anti-infective/ Parkinson's Disease
Amisulpride	Solian®, Supitac®, Soltus®, Amitrex®, Amazeo®	Anti-psychotic, atypical	Psychosis
Amitriptyline	Elavil® (Discontinued 6/13), Tryptomer®, Tryptizol®, Laroxyl®, Saroten®, Sarotex® Lentizol®,	Anti-depressant, Tricyclic	Depression
Amoxapine	Asendin®, Amokisan®, Asendis®, Defanyl®, Demolox®, Moxadil®	Anti-depressant, Tetracyclic	Depression
Chloral hydrate	Aquachloral®, Novo-Chlorhydrate®, Somnos®, Noctec®, Somnote®	Sedative	Sedation/ insomnia
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®	Antibiotic	Bacterial infection
Clomipramine	Anafranil®	Anti-depressant, Tricyclic	Depression
Desipramine	Pertofrane®, Norpramine®	Anti-depressant, Tricyclic	Depression
Diphenhydramine	Benadryl®, Nytol®, Unisom®, Sominex®, Dimedrol®, Daedalon®	Antihistamine	Allergic rhinitis, insomnia
Doxepin	Sinequan®, Silenor®, Aponal®, Adapine®, Doxal®, Deptran®, Sinquan®	Anti-depressant, Tricyclic	Depression
Fluconazole	Diflucan®, Trican®	Anti-fungal	Fungal infection
Fluoxetine	Prozac®, Sarafem®, Fontex®	Anti-depressant, SSRI	Depression
Furosemide (Frusemide)	Lasix®, Fusid®, Frumex®	Diuretic	Increase urine & salt loss
Galantamine	Reminyl®, Nivalin®, Razadyne-ER®,	Cholinesterase inhibitor	Dementia, Alzheimer's
Hydrochlorothiazide	Apo-Hydro®, Aquazide H®, BP Zide®, Dichlotride®, Hydrodiuril®, HydroSaluric®, Hydrochlorot	Diuretic	Increase urine & salt loss
Hydroxychloroquine	Plaquenil®, Quineprox®	Anti-malarial, Anti-inflammatory	Malaria, Lupus, Arthritis
Hydroxyzine	Atarax®, Vistaril®, Aterax®, Alamon®, Durrax®, Equipose®, Masmoran®, Orgatrax®, Paxis	Antihistamine	Allergies, Anxiety disorders
Imipramine (melipramine)	Tofranil®	Anti-depressant, Tricyclic	Depression
Indapamide	Lozol®, Natrilix®, Insig®	Diuretic	Increase urine & salt loss
Itraconazole	Sporanox®, Onmel®	Anti-fungal	Fungal infection
Ivabradine	Procoralan®, Coralan®, Corlentor®, Coraxan®, Ivabid®, Bradia®	Anti-anginal	Angina Pectoris (heart pain)
Ketoconazole	Nizoral®, Sebizole®, Ketomed®, Keton®	Anti-fungal	Fungal infection
Metoclopramide	Reglan®, Afipran®, Maxolon®, Cerucal®, Clopamon®, Clopra®, Maxeran®, Maxolon®, Me	Anti-emetic	Nausea, vomiting
Metronidazole	Flagyl® and many others	Antibiotic	Trichomoniasis, amebiasis, bacterial infection
Nelfinavir	Viracept®	Anti-viral	HIV/AIDS
Nortriptyline	Pamelor®, Sensoval®, Aventyl®, Norpress®, Allegron®, Noritren®, Nortrilen®	Anti-depressant, Tricyclic	Depression
Pantoprazole	Protonix® and others	Proton Pump Inhibitor	Gastro-esophageal reflux disease
Paroxetine	Paxil®, Aropax®, Pexeva®, Seroxat®, Sereupin®	Anti-depressant, SSRI	Depression
Posaconazole	Noxafil®, Posamol®	Anti-fungal	Fungal infection
Protriptyline	Vivactil®	Anti-depressant, Tricyclic	Depression
Quinine sulfate	Qualaquin®	Anti-malarial	Malaria or leg cramps
Ritonavir	Norvir®	Anti-viral	HIV/AIDS
Sertraline	Zoloft®, Lustral®, Daxid®, Altruline®, Besitran®, Deprax®, Elrval®, Emergen®, Gladem®, Implic	Anti-depressant, SSRI	Depression
Solifenacin	VESIcare®	Muscle relaxant	Treatment of overactive bladder
Telaprevir	Incivek®, Incivo®	Anti-viral	Hepatitis C
Trazodone	Desyrel® (discontinued 6/13), Oleptro®, Beneficat®, Deprax®, Desirel®, Molipaxin®, Thombra	Anti-depressant, SARI	Depression, insomnia
Trimipramine	Surmontil®, Rhotrimine®, Stangyl®	Anti-depressant, Tricyclic	Depression
Voriconazole	VFend®	Anti-fungal	Fungal infection

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Drugs with known TdP risk			
Amiodarone	Cordarone®, Pacerone®, Nexterone®	Anti-arrhythmic	Abnormal heart rhythm
Anagrelide	Agrylin®, Xagrid®	Phosphodiesterase 3 inhibitor	Thrombocythemia
Arsenic trioxide	Trisenox®	Anti-cancer	Leukemia
Astemizole	Hismanal®	Antihistamine	Allergic rhinitis
Azithromycin	Zithromax®, Zmax®	Antibiotic	Bacterial infection
Bepridil	Vascor®	Anti-anginal	Angina Pectoris (heart pain)
Chloroquine	Aralen®	Anti-malarial	Malaria infection
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	Anti-psychotic / Anti-emetic	Schizophrenia/ nausea
Cisapride	Propulsid®	GI stimulant	Heartburn
Citalopram	Celexa®, Cipramil®	Anti-depressant, SSRI	Depression
Clarithromycin	Biaxin®, Prevpac®	Antibiotic	Bacterial infection
Cocaine	Cocaine	Local anesthetic	Topical anesthetic
Disopyramide	Norpace®	Anti-arrhythmic	Abnormal heart rhythm
Dofetilide	Tikosyn®	Anti-arrhythmic	Abnormal heart rhythm
Domperidone	Motilium®, Motillium®, Motinorm Costi®, Nomit®	Anti-nausea	Nausea
Dronedarone	Multaq®	Anti-arrhythmic	Atrial Fibrillation
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	Anti-psychotic / Anti-emetic	Anesthesia adjunct, nausea
Erythromycin	E.E.S.®, Robimycin®, EMycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythro	Antibiotic	Bacterial infection; increase GI motility
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E® (India), Exodus® (Brazil), Esto® (Israel), Seroplex®,	Anti-depressant, SSRI	Major depression/ Anxiety disorders
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	Anti-arrhythmic	Abnormal heart rhythm
Grepafloxacin	Raxar®	Antibiotic	Bacterial infection
Halofantrine	Halfan®	Anti-malarial	Malaria infection
Haloperidol	Haldol® (US & UK), Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol® (Germany),	Anti-psychotic	Schizophrenia, agitation
Ibutilide	Corvert®	Anti-arrhythmic	Abnormal heart rhythm
Levofloxacin	Levaquin®, Tavanic®	Antibiotic	Bacterial infection
Levomethadyl	Orlaam®	Opiate	Pain control, narcotic dependence
Mesoridazine	Serentil®	Anti-psychotic	Schizophrenia
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadon®	Opiate	Pain control, narcotic dependence
Moxifloxacin	Avelox®, Avalox®, Avelon®	Antibiotic	Bacterial infection
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®	Anti-emetic	Nausea, vomiting
Pentamidine	Pentam®	Antibiotic	Pneumocystis pneumonia
Pimozide	Orap®	Anti-psychotic	Tourette's tics
Probucol	Lorelco®	Antilipemic	Hypercholesterolemia
Procainamide	Pronestyl®, Procan®	Anti-arrhythmic	Abnormal heart rhythm
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®	Anti-arrhythmic	Abnormal heart rhythm
Sevoflurane	Ulane®, Sojourn®	Anesthetic, general	Anesthesia
Sotalol	Betapace®, Sotalex®, Sotacor®	Anti-arrhythmic	Abnormal heart rhythm
Sparfloxacin	Zagam®	Antibiotic	Bacterial infection
Sulpiride	Dogmatil®, Dolmatil®, Eglonyl®, Espiride®, Modal®, Sulpor®	Anti-psychotic, atypical	Schizophrenia
Terfenadine	Seldane®	Antihistamine	Allergic rhinitis
Thioridazine	Mellaril®, Novoridazine®, Thioril®	Anti-psychotic	Schizophrenia
Vandetanib	Caprelsa®	Anti-cancer	Thyroid cancer

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Drugs with possible TdP risk			
Alfuzosin	Uroxatral®	Alpha1-blocker	Benign prostatic hyperplasia
Apomorphine	Apokyn®, Ixense®, Spontane®, Uprima®	Dopamine agonist	Parkinson's disease
Aripiprazole	Abilify®, Aripiprex®	Anti-psychotic, atypical	Psychosis, Adjunct for Depression
Atazanavir	Reyataz®	Anti-viral	HIV/AIDS
Bedaquiline	Sirturo®	Antibiotic	Tuberculosis, drug resistant
Bortezomib	Velcade®, Bortecad®	Proteasome inhibitor	Multiple Myeloma,lymphoma
Bosutinib	Bosulif®	Tyrosine kinase inhibitor	Leukemia
Clozapine	Clozaril®, Fazaclo®, Versacloz®	Anti-psychotic, atypical	Schizophrenia
Crizotinib	Xalkori®	Kinase inhibitor	Anti-cancer
Dabrafenib	Tafinlar®	Anti-cancer	Melanoma
Dasatinib	Sprycel®	Tyrosine kinase inhibitor	Leukemia
Dexmedetomidine	Precedex®, Dexdor®, Dexdomitor®	Sedative	Sedation
Dihydroartemisinin+piperaquine	Eurartesim®	Anti-malarial	Malaria
Dolasetron	Anzemet®	Anti-nausea	Nausea, vomiting
Eribulin	Halaven®	Anti-cancer	Metastatic breast neoplasias
Famotidine	Pepcid®, Fluxid®, Quamatel®	H2-receptor antagonist	Peptic ulcer/ GERD
Felbamate	Felbatol®	Anti-convulsant	Seizure
Fingolimod	Gilenya®	Sphingosine phospate receptor modulator	Multiple Sclerosis
Foscarnet	Foscavir®	Anti-viral	HIV/AIDS
Fosphenytoin	Cerebyx®, Prodilantin®	Anti-convulsant	Seizure
Gatifloxacin	Tequin®	Antibiotic	Bacterial infection
Gemifloxacin	Factive®	Antibiotic	Bacterial infection
Granisetron	Kytril®, Sancuso®, Granisol®	Anti-nausea	Nausea, vomiting
Iloperidone	Fanapt®, Fanapta®, Zomaril®	Anti-psychotic, atypical	Schizophrenia
Isradipine	Dynacirc®	Anti-hypertensive	High blood pressure
Lapatinib	Tykerb®, Tyverb®	Anti-cancer	Breast cancer, metastatic
Lithium	Eskalith®, Lithobid®	Anti-mania	Bipolar disorder
Mifepristone	Korlym®, Mifeprex®	Progesterone antagonist	Pregnancy Termination
Mirabegron	Myrbetriq®	Beta3 adrenergic antagonist	Overactive bladder
Mirtazapine	Remeron	Anti-depressant, Tetracyclic	Depression
Moexipril/HCTZ	Uniretic®, Univasc®	Anti-hypertensive	High blood pressure
Nicardipine	Cardene®	Anti-hypertensive	High blood pressure
Nilotinib	Tasigna®	Anti-cancer	Leukemia
Norfloxacin	Noroxin®, Ambigram®	Antibiotic	Bacterial infection
Ofloxacin	Floxin®	Antibiotic	Bacterial infection
Olanzapine	Zyprexa®, Zydis®, Relprevv®	Anti-psychotic, atypical	Schizophrenia, bipolar
Oxytocin	Pitocin®, Syntocinon®	Oxytocic	Labor stimulation
Paliperidone	Invega®, Xepilon®	Anti-psychotic, atypical	Schizophrenia
Pasireotide	Signifor®	Somatostatin analog	Cushings Disease
Pazopanib	Votrient®	Tyrosine kinase inhibitor	Anti-cancer
Perflutren lipid microspheres	Definity®	Imaging contrast agent	Echocardiography
Pipamperone	Dipiperon (E.U), Propitan (Japan)	Antipsychotic	Schizophrenia

Promethazine	Phenergan®	Anti-psychotic / Anti-emetic	Nausea
Quetiapine	Seroquel®	Anti-psychotic, atypical	Schizophrenia
Ranolazine	Ranexa®, Ranozex®	Anti-anginal	Chronic angina
Rilpivirine	Edurant®, Complera®, Eviplera®	Anti-viral	HIV/AIDS
Risperidone	Risperdal®	Anti-psychotic, atypical	Schizophrenia
Roxithromycin	Rulide®, Xthrocin®, Roxl-150®, Roxo®, Surlid®, Rulide®, Biaxsig®, Roxar®, Roximycinv®, Roxo	Antibiotic	Bacterial infection
Saquinavir	Invirase®(combo)	Anti-viral	HIV/AIDS
Sertindole	Serdolect®, Serlect®	Anti-psychotic, atypical	Anxiety, Schizophrenia
Sorafenib	Nexavar®	Tyrosine kinase inhibitor	Anti-cancer
Sunitinib	Sutent®	Anti-cancer	Renal cell cancer, GIST
Tacrolimus	Prograf®, Prograf®, Advagraf®, Protopic®	Immunosuppressant	Immune suppression
Tamoxifen	Nolvadex®(discontinued 6/13), Istubal®, Valodex®	Anti-cancer	Breast cancer
Telavancin	Vibativ®	Antibiotic	Bacterial infection
Telithromycin	Ketek®	Antibiotic	Bacterial infection
Tetrabenazine	Nitoman®, Xenazine®	Monoamine Transporter Inhibitor	Chorea (Huntington's disease)
Tizanidine	Zanaflex®, Sirdalud®	Muscle relaxant	Spasticity
Tolterodine	Detrol®, Detrusitol®	Muscle relaxant	Bladder spasm
Toremifene	Fareston®	Estrogen agonist/antagonist	Anti-cancer
Vardenafil	Levitra®	Phosphodiesterase inhibitor	Vasodilator
Vemurafenib	Zelboraf®	Kinase inhibitor	Anti-cancer
Venlafaxine	Effexor®, Efexor®	Anti-depressant, SNRI	Depression
Vorinostat	Zolinza®	Anti-cancer	Lymphoma
Ziprasidone	Geodon®, Zeldox®	Anti-psychotic, atypical	Schizophrenia

APPENDIX B - DATA COLLECTION SHEET

Participant No. [ ]

Age: [ ]

Gender: [M] [F]

Rule of Thumb Method: [Normal] [Prolonged]

Bazett's Formula: QTc [ ] [Normal] [Prolonged]

ECG machine calculation: QTc [ ] [Normal] [Prolonged]

List of Medications:

[ ]

Electrolyte Values: K [ ] Mg [ ] Ca [ ]

APPENDIX C – ETHICS CLEARANCE

R14/49 Dr Catherine Berman

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150226

NAME: (Principal Investigator)	Dr Catherine Berman
DEPARTMENT:	Internal Medicine Wits Donal Gordon Medical Centre
PROJECT TITLE:	Prolonged QT Interval: Accuracy of the "Rule of Thumb" Method for Measuring the QT Interval in the Elderly Attending Geriatric Clinical Practices
DATE CONSIDERED:	27/02/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr B Tipping

APPROVED BY: Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 02/03/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX D –TURNITIN REPORT

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American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. "Prevention of Torsade de Pointes in Hospital Settings", Journal of the American College of Cardiology, 20100302

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BEITLAND, S, E. S. PLATOU, and K. SUNDE. "Drug-induced long QT syndrome and fatal arrhythmias in the intensive care unit : Drug-induced long QT syndrome", Acta Anaesthesiologica Scandinavica, 2014.

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Rashmi R. Shah. "Interpretation of Clinical ECG Data", Cardiac Safety of Noncardiac Drugs, 2005

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WATARU SHIMIZU. "Differential Response of QTU Interval to Exercise, Isoproterenol, and Atrial Pacing in Patients with Congenital Long QT Syndrome", Pacing and Clinical Electrophysiology, 11/1991

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"Cardiac Causes of Syncope.", EMS World, August 2015 Issue

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Trolle, Christian, Kristian H. Mortensen, Lisbeth N. Pedersen, Agnethe Berglund, Henrik K. Jensen, Niels H. Andersen, and Claus H. Gravholt. "Long QT Interval in Turner Syndrome – A High Prevalence of LQTS Gene Mutations", PLoS ONE, 2013.

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van Langen, I M, N Hofman, H L Tan, and A A M Wilde. "Family and population strategies for screening and counselling of inherited cardiac arrhythmias", Annals of Medicine, 2004.

paper text:

MMED RESEARCH – DR. C. BERMAN ABSTRACT

Background 2**Long QT syndrome (LQTS) is characterized by a prolonged QT interval on the electrocardiogram** (ECG), a **risk** for sudden cardiac death. A simple 'rule of thumb' method states that if a patient's heart rate is between 60-100 bpm, the 4**QT interval should** not **be** more **than half the R-R interval.** The clinical accuracy of this method is not tested in the elderly. Objectives To determine if the 'rule of thumb' to calculate QT interval prolongation, is accurate, compared to the corrected QT interval calculated using Bazett's formula. Secondary objectives include the prevalence of long QT and risk factors for QT

prolongation. Methods The QT 17**interval was calculated using Bazett's formula, and** the 'rule of thumb' method, from ECG's collected from patients over 60 years old, on their first visit to a geriatric clinical service. Only data from patients with heart rates in the range 60-100 were analysed. Medications and electrolyte levels were recorded. Results A total of 1000 ECGs were collected. 776 ECGs were included in the study. Prevalence of prolonged QT interval was 37.8% using Bazett's formula. Compared to Bazett's formula, the 'rule of thumb' method has a sensitivity of 65.2% and a specificity of 96.9%. Of the 23.3% of patients taking medications known to prolong the QT interval only 38.6% had a prolonged QT interval. There was a significant 9**association between QT interval prolongation and** hypokalaemia. Conclusion **The** 'rule **of** thumb' method to determine QT interval prolongation, has high specificity but low sensitivity. QT interval prolongation is caused by a number of factors including hypokalemia and not necessarily drugs alone. INTRODUCTION The electrocardiogram (ECG) is a rapid and simple investigation that records the electrical activity of the heart. It is an essential part of the cardiac assessment of any patient and can provide a wealth of useful information to the clinician. An effort should be made to evaluate the QT interval on every ECG to determine whether the QT interval is normal or prolonged. Long QT syndrome (LQTS) is 6**characterized by a prolonged QT interval on the ECG** and **is associated with** an increased **risk of** a characteristic, **life–threatening** cardiac **arrhythmia,** torsades **de pointes,** a risk for **sudden cardiac death.[** 1] The LQTS can be 12**genetic or acquired. Acquired LQTS usually results from drug therapy or** electrolyte abnormalities, including hypokalaemia, hypomagnesaemia and hypocalcaemia. [2][3] 8**Drug-induced LQTS can occur as a side effect of commonly used cardiac and non-cardiac drugs.** [1] Many drugs have been implicated to prolong the QT interval and additional medications continue to be identified. [4] Measuring the QT interval is especially relevant in the elderly population since the QT interval is known to increase with age. Furthermore, elderly patients have multiple risk factors for LQTS such as poly-pharmacy, myocardial damage, renal or hepatic dysfunction and electrolyte disturbances.

[5] The greatest risk for development of acquired LQTS is 7**the clustering of multiple recognizable risk factors in a single patient.** [6] Multiple formulas exist to estimate the QT interval. These formulas 7**correct the QT interval** (QTc) **for heart rate** to enable comparison to reference values, and thus a prolonged QT interval can be determined. The 1**Bazett's formula is the most commonly used** formula when calculating the QT interval on an ECG with a heart rate between 60-100 bpm. [7] Although computerized analysis and interpretation of the QT interval are sometimes printed on the ECG, these might well over- or underestimate the QT interval. To make it easier for clinicians, ECGs have been interpreted using a 'rule of thumb' method 16**to determine if a QT interval is** prolonged. **The** 'rule of thumb' method is a quick and simple tool for clinicians to use when reading ECG's. This rule states that if a patient's heart rate is between 60-100 bpm, then 4**a normal QT interval should not be** more **than half of the R-R interval.** This simple measure is well described in numerous publications but the accuracy of this method has not been proven in the elderly population. [8][9][10] OBJECTIVES The primary objective of this study is to determine if the 'rule of thumb' method of calculating whether the QT interval is prolonged or not, is accurate, when compared to the corrected QT interval calculated using the Bazett's formula in ECGs from an elderly population attending the sub-specialist geriatric clinical practice at Wits Donald Gordon Medical Centre (WDGMC). Secondary objectives include the following: a. Determining 5**the prevalence of a prolonged QT interval** in an elderly population at first presentation to the geriatric clinical practice at WDGMC. b. To review the patient's drug list on first presentation, to assess if the 3**patient was taking** any drugs **known to prolong the QT interval** as listed on **the** QT drugs list [11] and determine if there is an association with a prolonged QT interval. c. Of the ECGs determined to have a prolonged QT interval, to assess if the patient had hypokalemia (K < 3.5 mmol/l), hypomagnesaemia (Mg < 0.7 mmol.l) or hypocalcaemia (Ca < 2.12 mmol/l). d. To compare the QTc calculated by the ECG computer analysis, with 5**the QTc**

calculated by Bazett's formula, and with the 'rule of thumb' method. METHODS Study oversight and design A retrospective review was conducted, analyzing ECGs collected from March 2007 to January 2015. A total of 1000 ECGs were collected from the files of elderly patients attending the geriatric clinical practice at 14Wits Donald Gordon Medical Centre (WDGMC), Johannesburg, South Africa. Only the ECG of the patient's first presentation to the geriatric service, including inpatient and outpatient consultations, was collected. Ethical approval was obtained from the University of the Witwatersrand Human Research Ethics Committee. From the ECG, the age, gender and heart rate of the patient was documented. The QT interval of each ECG was evaluated. The QT interval was measured using Elite Medical Instrument (EMI) calipers and the 11QTc was calculated using the Bazett's formula (QTc= QT/√RR). The QTc was classified as prolonged or not prolonged. A QTc of more than 0.45 sec is considered prolonged in men and more than 0.47 sec prolonged in women.[12] The QT interval was then documented as prolonged or not prolonged according to the 'rule of thumb' method seen in Fig. 1. The QTc calculated by the ECG computer analysis was also recorded and classified as prolonged or not prolonged in ECGs that had this value recorded. Fig. 1. 'Rule of thumb' method – 10a normal QT interval should not be more than half of the R-R interval. R-R Interval QT Interval To determine the accuracy of the researcher's measurements, 42 ECGs were co-evaluated by the researcher and an expert. The intraclass correlation (ICC) was 0.95, indicating very good inter-rater reliability. A 13list of medications the patient was taking at the time of the ECG, was recorded. The patient's medication list was compared to the QT drugs list [11] to assess if the patient was on any 1drugs known to prolong the QT interval. The patient's potassium, magnesium and calcium levels at the time of the ECG, were recorded. Population sample ECGs from patients aged 60 years or older were collected. The heart rate was between 60 and 100 bpm and the ECG settings were 15at a paper speed of 25 mm/sec. Statistical Analysis The demographics of the study group was described. Using the Bazett's formula to calculate the QTc interval as the

gold standard, the sensitivity and specificity of the 'rule of thumb' and the computer calculated QTc methods was calculated. The prevalence of a long QT interval in the study group was determined, together with a 95% confidence interval. The use of the listed medications was tabulated, categorized by normal and prolonged QT interval groups. The association between the use of medications known to prolong 18the QT interval and the presence/absence of a long QT interval was determined by Fisher's exact test. For those cases with 1a long QT interval, the presence of electrolyte abnormalities was tabulated. RESULTS A total of 1000 ECGs were collected, of which 776 (77.6%) met the inclusion and exclusion criteria and were further analysed. The reasons why 224 (22.4%) ECGs were excluded from the study are seen in Table 1. Table 1. Reason ECGs excluded from the study Excluded ECGs n (%) Heart Rate < 60 90 (40.2) Heart Rate > 100 76 (33.9) Atrial Fibrillation 49 (21.9) Pacemaker 7 (3.1) Bigeminy 1 (0.4) Poor Quality ECG 1 (0.4) Of the 776 ECGs analysed, 500 (64.4%) ECGs were from female patients and 276 (35.6%) from male patients. The mean age of the study group was 78.3 years (range 60-101 years). The median heart rate of the ECGs analysed was 74 bpm (range 60-100 bpm). The mean QTc as calculated using Bazett's formula was 0.458 (range 0.383 – 0.606) for male patients and 0.456 (range 0.361-0.566) for female patients. The QTc distribution as calculated by Bazett's formula is shown in Fig. 2. In both male and female patients, the incidence of prolonged QTc was 29% and 29.6% respectively. Fig. 2. The QTc distribution calculated using Bazett's formula 30 MALE 28.2 25.7 FEMALE 25 23.6 20.4 PERCENT 20 16.3 15.2 15 12.3 12.8 10 9.8 8.3 5 4.3 4.6 5.2 5.1 1.1 1.4 1.1 1.2 1.2 0.4 1 0.4 0.4 0 0,350-0,370 0,371-0,390 0,391-0,410 0,411-0,430 0,431-0,450 0,451-0,470 0,471-0,490 0,491-0,510 0,511-0,530 0,531-0,550 0551-0,570 BAZETT CALCULATED QTC 5The prevalence of a prolonged QT interval in this study group as measured by each of the three methods is seen in Table 2. Table 12. Prevalence of a prolonged QT interval by 3 methods Method % 1of patients with a prolonged QT interval Population size (n) 95% confidence interval Bazett's 37.8 776 34.3-41.3 Rule of Thumb 26.6 776 23.5-29.8 ECG Computer 25.3 446 21.4 -29.6 Using the Bazett's formula as a gold standard, the 'rule of thumb' method has a sensitivity of 65.2% (confidence interval 59.4 – 70.6), and a specificity of 96.9% (confidence interval 94.9 – 98.3). Data for the ECG computer analysis QTc calculation was available in only 42.5% of the cases (n=446). The missing data was at random and not biased with regard to any of the study variables. The ECG computer analysis calculation of the QT interval has a sensitivity of 58.1% (confidence

interval 50.4 – 65.6) and a specificity of 95.3% (confidence interval 92.0 – 97.5.) In this population group, 23.3% of patients were taking medications 1known to prolong the QT interval. From this group of patients, only 38.6% had a 1prolonged QT interval as measured by the Bazett's formula. There was no significant association between the QT interval and medications 1known to prolong the QT interval (p=0.79). The proportion of missing data for hypomagnesaemia is in excess of 50%, and therefore this variable could not be analysed. The prevalence of hypokalaemia and hypocalcaemia in this study is tabulated in Table 3. The proportion of missing data for hypocalcaemia was 26.7%, which means that the results must be interpreted with caution. Table 3. Prevalence of hypokalaemia and hypocalcaemia Condition Category n Overall % Not prolonged n Bazett's Classification % n Prolonged % p-value Hypokalaemia No 612 78.9 394 81.6 218 74.4 0.0001 Yes 91 11.7 39 8.1 52 17.7 Unknown 73 9.4 50 10.4 23 7.8 Hypocalcaemia No 547 70.5 347 71.8 200 68.3 0.11 Yes 22 2.8 10 2.1 12 4.1 Unknown 207 26.7 126 26.1 81 27.6 In this study, 11.7% and 2.8% of the patients were documented as having hypokalaemia and hypocalcaemia, respectively. There was no significant association between QT interval and hypocalcaemia (p=0.11). There was a significant, weak, association between QT interval and hypokalaemia. In those patients without a prolonged QT interval, 9.0% had hypokalaemia, compared to 19.3% in the prolonged QT interval group. DISCUSSION Multiple formulae exist to estimate the QT interval on an ECG, Bazett's formula being the most commonly used.[7] The 'rule of thumb' method for determining if the QT interval is prolonged or not is a simple measure that clinicians have used for many years. However, to date, there is no literature assessing whether this measure is accurate. The primary 2purpose of this study was to assess the accuracy of the 'rule of thumb' method when compared to measuring the QT interval using Bazett's formula in an elderly population with a heart rate of 60-100bpm. The analysis of 776 QTc's by Bazett's formula classified more patients as having a prolonged QT interval than determined by the 'rule of thumb' method. We can conclude that the 'rule of thumb' method has a low sensitivity of 65.2%, but high specificity of 96.9%. When interpreting the QT interval using the 'rule of thumb' method, if the QT interval is determined as not prolonged, the QT interval should be re- evaluated using another method. However, if the QT interval is determined as prolonged, the clinician can be confident that the QT interval is indeed prolonged. 9The prevalence of prolonged QTc in the elderly is documented in various studies between 25%-32%[13][14][15] This study revealed a prevalence of 37.8%. This finding

supports literature indicating that the elderly have a relatively high prevalence of LQTS. The results also showed an equal incidence of prolonged QTc in both male and female patients. ECG computer analysis revealed a low sensitivity of 58.1% and a high specificity of 95.3% for determining a prolonged QTc when compared to Bazett's formula. Given this result, clinicians cannot rely solely on the computer generated QTc. This however was not specific for any individual ECG machine as ECGs in this study were printed from a variety of different ECG machines. It was noted that 23.3% of patients on first presentation to geriatric clinical services were prescribed medications 3known to prolong the QT interval. Of these patients, 38.6% had a 1prolonged QT interval as measured by Bazett's formula. Should patients be taking 3medication known to prolong the QT interval, this study confirms that they don't necessarily affect the QT interval. From this we can deduce that acquired LQTS is caused by a number of factors and not necessarily drugs along. It is known that electrolyte disturbances, specifically hypokalaemia, hypomagnesaemia and less commonly hypocalcaemia are associated with a prolonged QTc.[2] During collection of data, it was noted that not all patients had calcium, potassium and magnesium blood results. There were not enough magnesium values to render significant results to this study. The prevalence of hypokalaemia in this study was 11.7%. A significant, weak, association between hypokalaemia and prolonged QT interval was shown in the results. However, there was no significant association seen between hypocalcaemia and the QT interval. CONCLUSION The 'rule of thumb' method in determining whether the QT interval is prolonged or not, has high specificity but low sensitivity. This bedside assessment is as marginally more accurate than ECG computer analysis QTc calculation in this sample of older persons. It is a rapid and useful method of diagnosing a LQTS on a patient's ECG without requiring additional tools. It can however only be accurate in heart rates between the values of 60 and 100 bpm. Clinicians should be wary of a possible false negative result when using this tool. LIMITATIONS OF THE STUDY One of the limitations of the Bazett's formula is that it is inaccurate at lower and higher heart rates. To eliminate these limitations, the study excludes heart rates lower than 60bpm and higher than 100bpm. It however remains the standard for clinical use. Another limitation to this retrospective study was that some patients did not have blood tests at their first consultation resulting in absent electrolyte values. This resulted in missing data. The relevance of magnesium affecting the QT interval, could not be analyzed in this study.

APPENDIX E – CORRECTION LIST

EXTERNAL EXAMINER

MAJOR CORRECTIONS

THE LITERATURE REVIEW AND DISCUSSION DO NOT ADEQUATELY NOR CRITICALLY DISCUSS THE METHODS USED TO MEASURE THE QT INTERVAL, ADVANTAGES AND DISADVANTAGES OF EACH
Page 12 – 13

By measuring the QT interval of an ECG and correcting for heart rate (QTc), a prolonged QT interval can be determined. Although computerized analysis and interpretation of the QT interval are sometimes printed on the ECG, these might well over- or underestimate the QT interval. This is particularly evident with unusual T-wave morphologies and technically suboptimal ECGs. *The algorithms used to measure the QT on standard ECG machines are inferior and often have significant errors. Where this method runs into difficulty is that the computer can calculate a formula with accuracy, but cannot measure the end point of the QT interval.* [17]

Manual measurement is a more practical way to measure the QT interval[18] Multiple formulas exist to estimate the QT interval. These formulas correct the QT interval for heart rate to enable comparison to reference values. *The formulae require that the ECG is in a stable sinus rhythm for accuracy. Exponential, logarithmic and linear formulae have been formulated. Table 2. Generally, at heart rates between 60 and 100bpm there is no difference in the formulae applied.* [19]

Table 2: QT-Heart Rate Correction Formulae [adapted from reference 19]

Method	*Description*	*Formula*	*Comment*
Exponential	*Bazett*	$QT_C = QT/RR^{1/2}$	*Advantage: Widely used Disadvantage: Inaccurate <60bpm & >100bpm*
	Fridericia	$QT_C = QT/RR^{1/3}$	*Advantage: Widely used. More consistent at faster heart rates*
Linear	*Framingham*	$QT_C = QT+0.154(1-RR)$	*Advantage: More consistent rate correction over wide range of heart rates*
	Hodges	$QT_C = QT+1.75(HR-60)$	*Advantage: More uniform correction over a wide range of heart rates*
	Rautaharju *Females & males <15 And >50 years* *Males 15-50 years*	*QTI = (QT[HR+100])/656* *QTI = (QT[HR+100]/656* *QTI=100(QT)/([656/(1+0,01hr])+0.4-25)*	*Advantage: More uniform correction over a wide range of heart rates*
Logarithmic	*Ashman*	*QT =K1 x log(10 x [RR+K2])* *K2=0.07, and K1=0.380* *K2=0.07, and K1=0.390*	*Advantage: More uniform correction over a wide range of heart rates*

The disadvantages of the heart rate correction formulae are that they correct the QT for heart rate at a population level. In the formula QTc = QT/RR$^{\alpha}$ There is only one correction factor α which is ½ for Bazett's formula and ⅓ for Fridericia's formula. Research has shown that the relationship between HR and QT interval is different for each patient. [20]
An alternative to calculating the QTc using one of the formulae is the QT Nomogram. The QT interval is plotted against heart rate. This method is reliable in determining whether the QT is abnormal. [19]

The most accurate method of measuring the QT interval is using digitized high-resolution 12 lead holter ECG recordings with advanced algorithms and on-screen magnification for manual correction. The disadvantage of this method is that it is expensive and rarely available in clinical practice. [17]

Manual measurement of the QT interval has been shown to render similar results to the high-resolution holter technique. The Bazett's formula is the most commonly used formula when calculating the QT interval on an ECG with a heart rate between 60-100 bpm. [21] *Accordingly, most references for normal or abnormal values have been derived from Bazett's formula.*[19] A QTc of more than 0.45sec is considered prolonged in men and more than 0.47sec prolonged in women. [22]

THE PHYSIOLOGICAL SIGNIFICANCE OF THE QT INTERVAL AND THE IMPLICATIONS OF A PROLONGED INTERVAL.

Page 10

An effort should be made to evaluate the QT interval on every electrocardiogram to determine whether the QT interval is normal or prolonged. *The QT interval is the sum of action potentials of the ventricular myocytes. It includes both depolarization (QRS complex) and repolarization (T-wave).* [1] It is the time from the start of the QRS complex to the end of the T wave, the end of the T wave being the time at which ventricular repolarization is completed and the T wave voltage amplitude returns to baseline. [2]

Long QT syndrome (LQTS) is characterized by a prolonged QT interval on the ECG and is associated with an increased risk of a characteristic, life–threatening cardiac arrhythmia, torsades de pointes, a risk for sudden cardiac death.[3] *The vulnerable period during which the arrhythmia can be provoked is the relative refractory period of the ventricular myocardium during repolarization. This corresponds to the declining limb of the T-wave from peak to isoelectric line (Figure 1). Repolarization of the ventricle is slower than*

depolarization, and therefore more likely to be affected by disease, drugs and biochemical abnormalities. [1]

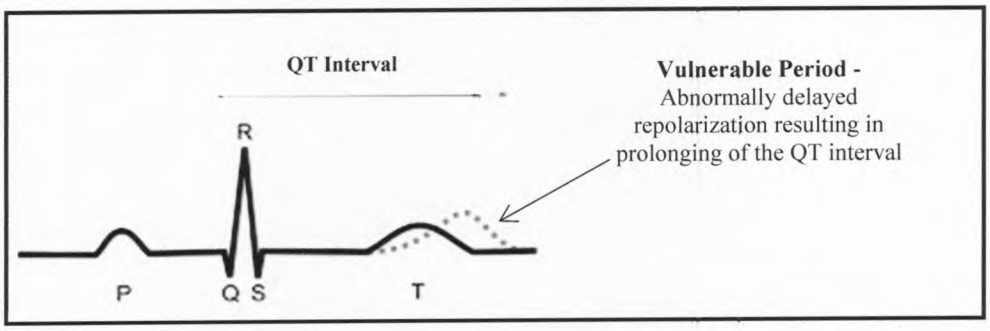


Figure 1: Prolongation of repolarization resulting in lengthening of the QT interval

INADEQUATE REFERENCE TO RESEARCH ARTICLES

Removed the following references:

[13] Mary Boudreau Conover. Understanding Electrocardiography. (8th edition), Mosby. An affiliate of Elsevier Science. Page 381

[14] Thomas B. Garcia, Geoffrey T. Miller. Arrhythmia Recognition: The Art of Interpretation. Jones and Bartlett Publishers, 2004. Page 415

[15] Dubin D. Rapid Interpretation of EKG's. (6th edition), Cover Publishing Company 2006. Page 28

Supplemented with following reference:

Page 22

[24] Phoon,CK. Mathematic validation of a shorthand rule for calculating QTc. Am J Cardiol 1998;82:400-2

MORE DETAILED LITERATURE RESEARCH

Page 21 - 23

References/research articles added

[1] Kenny RA, Sutton R. The prolonged QT interval-a frequently unrecognized abnormality. Postgrad Med J. 1985; 61(715):379-386

[4] Isbister GK, Page CB. Drug induced QT prolongation: the measurement and assessment of the QT interval in clinical practice. Br J Clin Pharmacol 2013; 76:48–57

[5] Newton-Cheh C, Eijgelsheim M, Rice KM, et al. Common variants at ten loci influence QT interval duration in the QTGEN Study. Nat Genet. 2009;41:399–406

[6] Molnar J, Zhang F, Weiss J, et al. Diurnal pattern of QTc interval: how long is prolonged? Possible relation to circadian triggers of cardiovascular events. J Am Coll Cardiol. 1996;27:76–83

[7] Mangoni AA, Kinirons MT, Swift CG, et al. Impact of age on QT interval and QT dispersion in healthy subjects: a regression analysis. Age Ageing. 2003;32:326–331

[15] Golchin N, Frank SH, Vince A, et al. Polypharmacy in the elderly. J Res Pharm Pract. 2015;4(2):85-88

[16] Cantlay A, Glyn T, Barton N. Polypharmacy in the elderly. InnovAiT 2016; 9(2):69-77

[17] Isbister GK. How do we assess whether the QT interval is abnormal: Myths, formulae and fixed opinion. Clin Toxicol (Phila) 2015:1-3

[18] Isbister GK, Calver L, van Gorp F, Stokes B, Page CB. Inter-rater reliability of manual QT measurement and prediction of abnormal QT, HR pairs. ClinToxicol (Phila) 2009; 47:884–888

[19] Goldenberg I, Moss AJ, Zareba W. QT Interval: How to Measure It and What Is "Normal." J Cardiovasc Electrophysl 2006; 17:333-336

[20] Batchvarov V, Malik M. Individual patterns of QT/RR relationship. Card Electrophysiol Rev 2002; 6:282–288

[24] Phoon,CK. Mathematic validation of a shorthand rule for calculating QTc. Am J Cardiol 1998;82:400-2

BERLING AND ISBISTER ARTICLE: THE HALF RR: A POOR RULE OF THUMB AND NOT A RISK ASSESSMENT TOOL FOR QT PROLONGATION (ACADEMIC EMERGENCY MEDICINE, 2015;22: 1139-1144)

Page 31

The analysis of 776 QTc's by Bazett's formula classified more patients as having a prolonged QT interval than determined by the 'rule of thumb' method. We can conclude that the 'rule of thumb' method has a low sensitivity of 65.2%, but high specificity of 96.9%. *A recent study by Isbister and Berling examined the accuracy of the 'rule of thumb' method in a sample of ECG's with known prolonged QT interval. Their results revealed that the 'rule of thumb' method in ECG's with heart rates > 60 bpm was highly sensitive in determining that the QT interval was indeed prolonged, but showed low specificity.*

These findings corroborate this study in that the sensitivity of determining whether the QT is prolonged or not prolonged is low, but the specificity is high. As the Isbister and Berling study population already determined that the QT was prolonged, the findings were expected.

The Isbister and Berling control ECG's were normal with no prolonged QT. Therefore, one would expect their specificity to be low.

In this study, the 'rule of thumb' method was tested on a population of 776 random ECG's to determine if the QT was prolonged or not. This study concluded that if the QT interval is determined as NOT prolonged, the QT interval should be re-evaluated using another method. If the QT interval IS determined by the 'rule of thumb' method as prolonged, the clinician can be confident that the QT interval is indeed prolonged.

MINOR CORRECTIONS

RECONSIDER THE TITLE ESPECIALLY "GERIATRIC" CLINICAL PRACTICES

We have reconsidered changing the title, but would prefer to leave the title, which was supposed to hint at specialised services rather than elderly patients attending general clinical practices.

ABSTRACT PAGE 4: UNDER RESULTS, THIRD LINE, CORRECT TENSE AND OMIT LAST SENTENCE IN CONCLUSION.

Page 4

Changed has to had

Removed - QT interval prolongation is caused by a number of factors including hypokalemia and not necessarily drugs alone.

PAGE 11, 4TH PARAGRAPH, IS THIS REALLY AN "UNDOCUMENTED" RULE? REFERENCES ARE INAPPROPORATE

Page 14

Removed -' undocumented' and following references

[13] Mary Boudreau Conover. Understanding Electrocardiography. (8th edition), Mosby. An affiliate of Elsevier Science. Page 381

[14] Thomas B. Garcia, Geoffrey T. Miller. Arrhythmia Recognition: The Art of Interpretation. Jones and Bartlett Publishers, 2004. Page 415

[15] Dubin D. Rapid Interpretation of EKG's. (6th edition), Cover Publishing Company 2006. Page 28

Changed reference [24] Phoon,CK. Mathematic validation of a shorthand rule for calculating QTc. Am J Cardiol 1998;82:400-2

PAGE 20: REFERENCE 17: CORRECT FORMAT OF JOURNAL

Page 22

[17] Gwet KL. Computing inter-rater reliability and its variance in the presence of high agreement. *Br J Math Stat Psychol 2008;* 61:29-48

PAGE 21: UNDER BACKGROUND: 4TH LINE : CORRECT TENSE

Page 24
'Is not' – changed to has not been

PAGE 22 : RECONSIDER LAST SENTENCE OF CONCLUSION

Page 25

Removed - QT interval prolongation is caused by a number of factors including hypokalemia and not necessarily drugs alone.

Replaced - If the QT interval is determined by the 'rule of thumb' method as prolonged, the clinician can be confident that the QT interval is indeed prolonged.

PAGE 31: CORRECT JOURNAL FORMAT

Page 35
[13]: Moved [PMID 19544703] next to reference.

INTERNAL EXAMINER

PREVALANCE OF QT PROLONGATION AND METHODS OF MEASUREMENT IN ELDERLY POPULATIONS REPORTED IN OTHER PARTS OF THE WORLD

Page 31
The prevalence of prolonged QTc in the elderly is documented in various studies [13][14][15]. *A study conducted in Israel showed a prevalence of 32% of a prolonged QTc in hospitalized elderly patients.[13] A study in Netherlands, Europe revealed a prevalence of prolonged QT of 29% in a population of older adults [14].* This study revealed a prevalence of 37.8%. This finding supports literature indicating that the elderly have a relatively high prevalence of LQTS. The results also showed an equal prevalence of prolonged QTc in both male and female patients.

COMMON DRUGS USED THAT CAUSE LONG QT SYNDROME

Page 11

QT measurements are not always available for the patient, prior to commencement of taking a particular drug. Often the risk assessment is made on the presenting ECG at the time the patient is seen for the first time. Common drugs causing LQTS can be seen in Table 1. [4]

Table 1: List of drugs associated with a high risk of QT prolongation [Adapted from reference 4]

Drug Class	*Name of drug*
Cardiac drugs	*Amiodarone* *Sotalol* *Disophyramide* *Dofetilide* *Procainamide* *Quinidine*
Antidepressants	*Selective serotonin re-uptake inhibitors:citalopram,escitalopram,fluoxetine* *Moclobemide* *Tricyclic antidepressants* *Lithium*
Antipsychotics	*Amisulpride* *Chlorpromazine* *Haloperidol* *Ziprasidone* *Thioridazine*
Antihistamines	*Loratadine* *Astemirzole* *Diphenhydramine*
Antimicrobials	*Ciprofloxacine, moxifloxacin, sparfloxacin* *Clarithromycine, erythromycin* *Fluconazole, voriconazole* *Pentamidine*
Other drugs	*Chloroqine* *Cisapride* *Dolesatron* *Methadone* *Arsenic*

OTHER AETIOLOGIES OF A PROLONGED LONG QT

Pages 10 and 11

The LQTS can be genetic or acquired. *There are two congenital LQTS; autosomal dominant Romano-Ward syndrome and the less common Jervell and Lange Neilsen syndrome.* [4]] *In addition to congenital LQTS, there is increasing evidence of genetic variants that healthy people may inherit, which places them at higher risk of prolonged QT interval caused by certain drugs.*[5]

Acquired LQTS results from *numerous other physiological and pathological factors. Diurnal variation in the QT interval makes it important to consider time of day when assessing the QT interval.* [6] *Female gender is associated with a longer QT interval of approximately 20ms compared with men.* [4]. *Increasing age is an independent risk factor for QT prolongation.* [7] Electrolyte abnormalities, including hypokalaemia, hypomagnesaemia and hypocalcaemia are associated with a prolonged QT interval. [8][9]

ELDERLY AND ISSUES OF POLY-PHARMACY

Page 12

Measuring the QT interval is especially relevant in the elderly population since the QT interval is known to increase with age. [13] Furthermore, elderly patients have multiple risk factors for LQTS such as poly pharmacy, myocardial damage, renal or hepatic dysfunction and electrolyte disturbances.[14] *In the US 35.6% of elderly patients had poly pharmacy* [15]. *In a recent Scottish study, the prevalence of polypharmacy in patients over the age of 65 was high, with 16.4% receiving ten or more medications.* [16]

PAGE 25 LAST PARAGRAPH: CLARIFY INCIDENCE AND PREVALENCE OF PROLONGED QT IN RESULTS

Page 29

Removed sentence - In both male and female patients, the incidence of prolonged QTc was 29% and 29.6% respectively.

Added Sentence - There was no significant difference in the prevalence of prolonged QT in males versus females.

PAGE 27 FIRST PARAGRAPH : CLARIFICATION OF POPULATION GROUP

Page 30

In this population group, 23.3% of *776 patients in whom ECGs were analysed*, were taking medications known to prolong the QT interval

CORRECTION OF TABLE 3: PREVALANCE OF HYPOKALAEMIA AND HYPOCALCAEMIA

Page 31

In this study, 11.7% and 2.8% of the patients were documented as having hypokalaemia and hypocalcaemia, respectively. There was no significant association between QT interval and hypocalcaemia (p=0.11). *There was a significant, weak, association between QT interval (prolonged / not prolonged) and hypokalaemia (n=703; p=0.0001; phi coefficient=0.15).* In

those patients without a prolonged QT interval, 9.0% had hypokalaemia, compared to 19.3% in the prolonged QT interval group.

PAGE 28, PARAGRAPH 4: REPHRASE SENTENCE.

Page 32

Re phrase sentence: Should patients be taking medication known to prolong the QT interval, this study confirms that they don't necessarily affect the QT interval.
Should patients be taking medication known to prolong the QT interval, this study found that there was no significant interaction between medication and the QT interval.

DISCUSSION: DISCUSS THE AUTHOR'S FINDINGS TO OTHER PUBLISHED STUDIES

Page 31

The analysis of 776 QTc's by Bazett's formula classified more patients as having a prolonged QT interval than determined by the 'rule of thumb' method. We can conclude that the 'rule of thumb' method has a low sensitivity of 65.2%, but high specificity of 96.9%. *A recent study by Isbister and Berling examined the accuracy of the 'rule of thumb' method in a sample of ECG's with known prolonged QT interval. Their results revealed that the 'rule of thumb' method in ECG's with heart rates > 60 bpm was highly sensitive in determining that the QT interval was indeed prolonged, but showed low specificity.*
These findings corroborate this study in that the sensitivity of determining whether the QT is prolonged or not prolonged is low, but the specificity is high. As the Isbister and Berling study population already determined that the QT was prolonged, the findings were expected.

The Isbister and Berling control ECG's were normal with no prolonged QT. Therefore, one would expect their specificity to be low.
In this study, the 'rule of thumb' method was tested on a population of 776 random ECG's to determine if the QT was prolonged or not. This study concluded that if the QT interval is determined as NOT prolonged, the QT interval should be re-evaluated using another method. If the QT interval IS determined by the 'rule of thumb' method as prolonged, the clinician can be confident that the QT interval is indeed prolonged.

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6th November 2017

To: Head of Department of Internal Medicine

Re: MMED Thesis – Dr Catherine Berman (0503313T)

I hereby certify that I have checked the corrections recommended by the two examiners of Dr Berman's thesis entitled: "Prolonged QT Interval: Accuracy of the "Rule of Thumb" method for measuring the QT interval in the elderly attending geriatric clinical practices".

I am satisfied with the corrections made by Dr Berman. Specifically, that she has adequately increased her extended literature review by just over 750 additional words to address the suggestions of examiner1 including the 12 additional/more relevant references which clarifies to the reader, her expert understanding of her thesis topic.

As her supervisor, I recommend that Dr Berman be awarded her MMED degree and be allowed to proceed to write her FCP part 2 examinations.

Regards
Brent Tipping



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9 November 2017

MMed Protocol Committee
Department of Medicine
University of the Witwatersrand

re: **MMED DISSERTATION: DR. C. BERMAN**

Title: PROLONGED QT INTERVAL: ACCURACY OF THE "RULE OF THUMB" METHOD FOR MEASURING THE QT INTERVAL IN THE ELDERLY ATTENDING GERIATRIC CLINICAL PRACTICES

This is to certify that the corrections on the MMed Dissertation of Dr. C. Berman, titled: "Prolonged QT Interval: Accuracy of the 'Rule Of Thumb' Method for Measuring the QT Interval in the Elderly Attending Geriatric Clinical Practices", have been done satisfactorily.

Yours sincerely

DR. J.M.L. TSITSI
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