ISHNE –
International Society for Holter and Noninvasive Electrocardiology

1st Worldwide Internet Symposium on Drug-Induced QT Prolongation
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Pacing in Drug Testing

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Disclosures: former investigator in the NESI study sponsored by Servier

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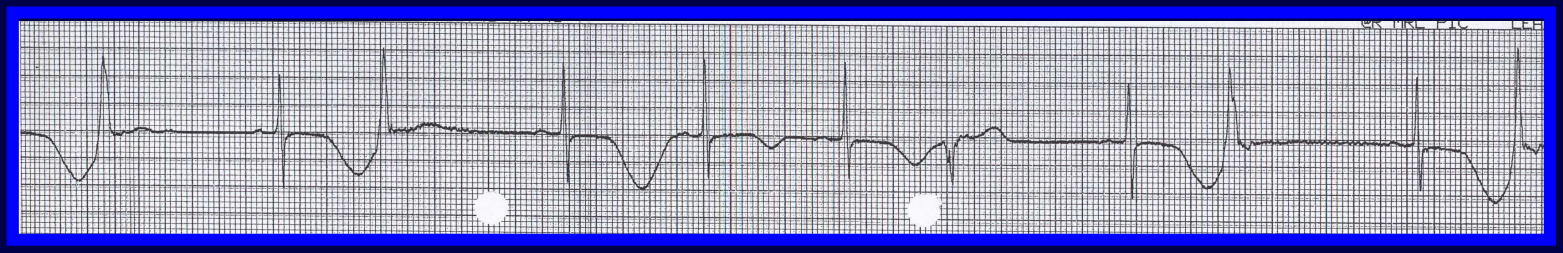
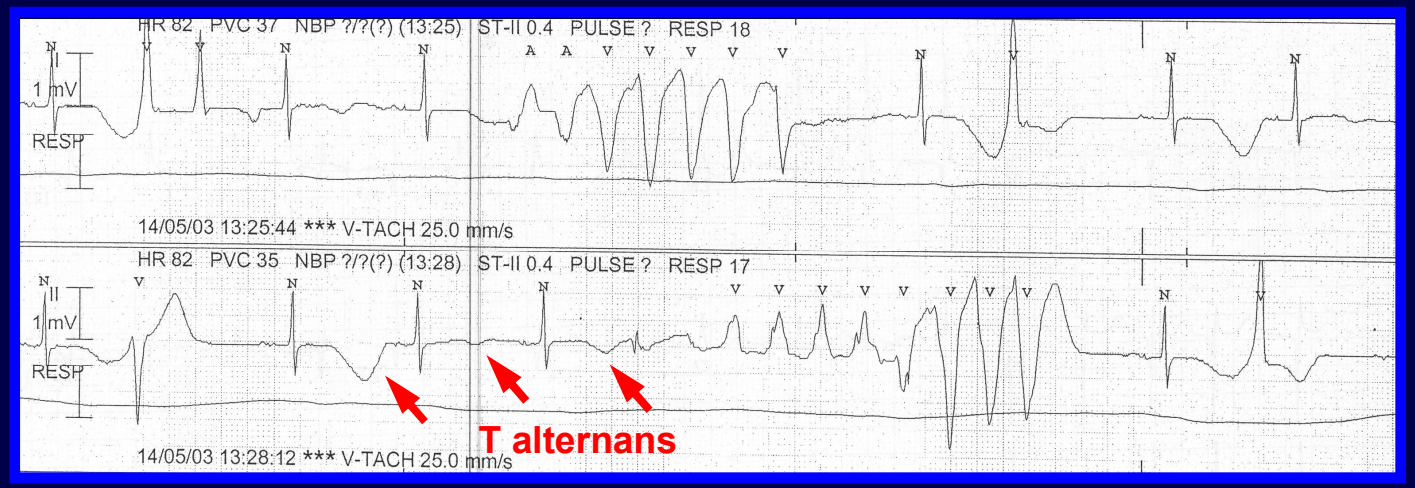
Scope of the Problem – Amiodarone-Induced QT Prolongation Resulting in TdP

- 72-year old man with controlled hypertension, no left ventricular hypertrophy, no evidence of coronary artery disease, no family or personal history of prolonged QT
- Electrically cardioverted for new onset (~ 6 months) persistent atrial fibrillation and started on Amiodarone for prevention of AF recurrence
- Admitted with pronounced bradycardia, prolonged QT, T wave alternans, bigeminy, and ventricular tachycardia





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Scope of the Problem

- The potential of both cardiovascular and non-cardiovascular drugs to prolong the QT interval has important implications for drug development and may lead to a withdrawal or restricted use of approved agents[1]
- The U.S. survey of outpatient prescription claims database has shown that drugs with an official warning on QT prolongation or with published data on QT effects may represent up to 20% of total prescriptions[2]
- Therefore, testing for a potential to influence cardiac repolarization in the so called 'thorough QT/QTc study' in man is a necessary component of the clinical portfolio of every new compound submitted for regulatory approval[3]

1. Haverkamp W, Breithardt G, Camm AJ, et al. The potential for QT prolongation and proarrhythmia by non-antiarrhythmic drugs: clinical and regulatory implications: Report on a Policy Conference of the European Society of Cardiology. Eur Heart J 2000;21:1216-1231

2. Curtis LH, Ostbye T, Sendersky V, et al. Prescription of QT-prolonging drugs in a cohort of about 5 million outpatients. Am J Med. 2003;114:135-141

3. U.S. Food and Drug Administration. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Preliminary concept paper. Available at: http://www.fda.gov/cder/calendar/meeting/qt4jam.pdf

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Limitations of Existing Models - Need for Correction for Heart Rate

- One of the significant problems of the QT studies is the appropriate correction of the QT interval for heart rate. A number of mathematical formulae for rate correction of the QT interval have been proposed to describe the physiological QT/RR interaction but none has been accepted as universally applicable

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Proposed Forms of QT/RR Regressions

Model	Expression
Bazett	$QTc = QT/RR^{1/2}$
Fridericia	$QTc = QT/RR^{1/3}$
Linear	$QTc = QT + \alpha \times (1 - RR)$
Hyperbolic	$QTc = QT + \alpha \times (1/RR - 1)$
Parabolic log/log	$QTc = QT/RR^{\alpha}$
Logarithmic	$QTc = QT - \alpha \times \ln(RR)$
Shifted logarithmic	$QTc = \ln(e^{QT} + \alpha \times (1 - RR))$
Exponential	$QTc = QT + \alpha \times (e^{-RR} - 1/e)$,
Arcus tangent	$QTc = QT + \alpha \times (\text{arctg}(1.0) - \text{arctg}(RR))$,
Hyperbolic tangent	$QTc = QT + \alpha \times ((e^2-1)/(e^2+1) - \text{tgh}(RR))$
Arcus hyperbolic sine	$QTc = QT + \alpha \times (\ln(1+\sqrt{2}) - \text{arcsinh}(RR))$
Arcus hyperbolic cosine	$QTc = QT + \alpha \times (\ln(2+\sqrt{3}) - \text{arccosh}(RR+1))$
Square root linear	$QTc = QT + \alpha \times (1 - RR^{1/2})$
Cube root linear	$QTc = QT + \alpha \times (1 - RR^{1/3})$

Summarised by Malik M. PACE 2004; 27:1659-69

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Limitations of Existing Models
Problems With Traditional Formulae

The most commonly used Bazett and Fridericia formulae for rate correction are tempered by the non-linear, complex relationship between QT and RR intervals and often lead to overcorrecting (QTc shortening) or undercorrecting (QTc lengthening) of the QT interval, respectively, which in some cases may exceed the accepted safety threshold of 5-10 ms

Drug-unrelated variations in QTc corrected using different formulae are 4.7 ± 8.9 ms
Malik M. PACE 2004; 27:1659-69

In animal pacing models, Bazett's formula was associated with a mean overcorrection of 67.9 ms, and Fridericia's formula with a mean error of 28.7 ms
King A, et al. ANE 2006;11:289-8

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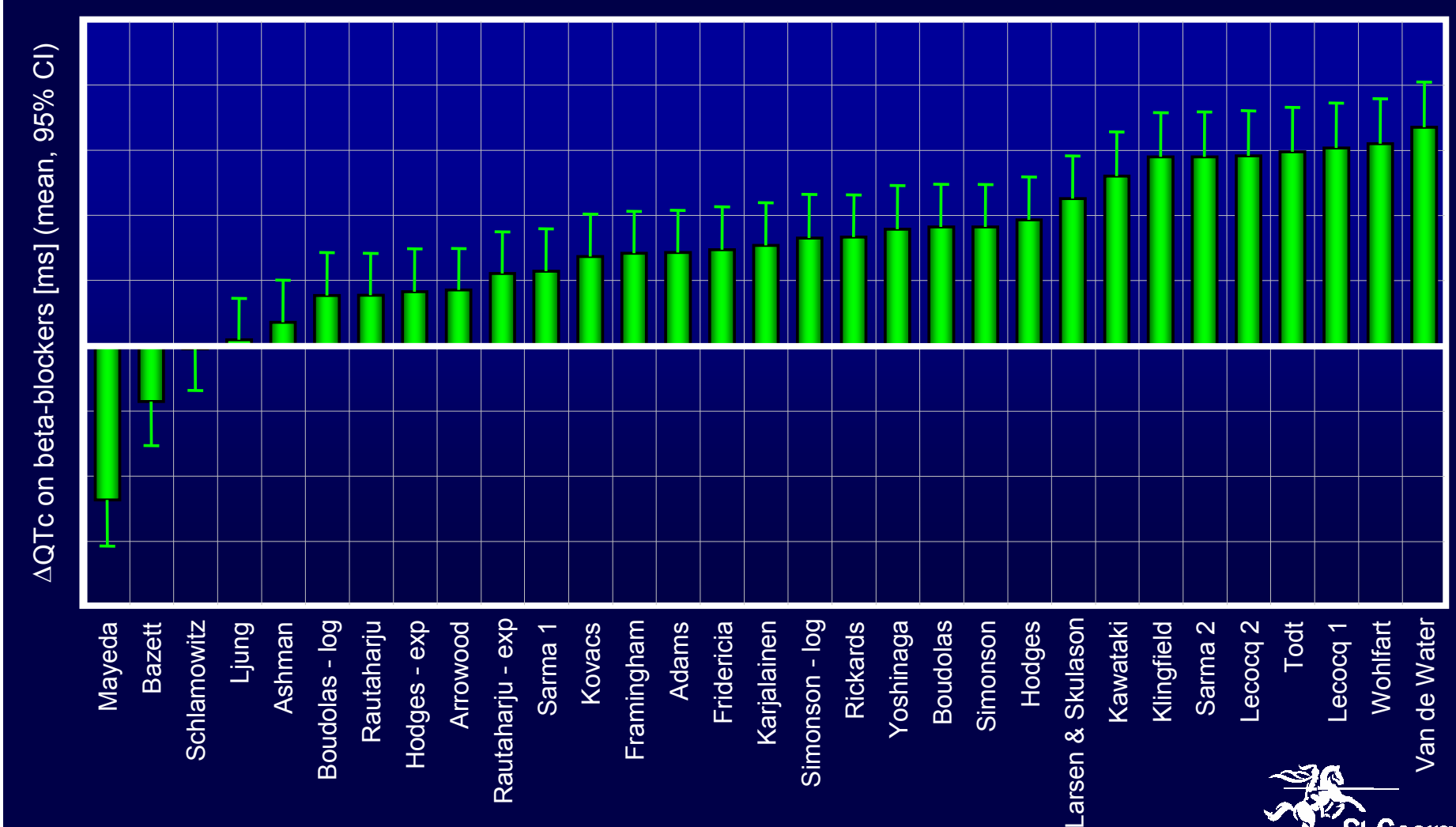
Assessment of the Effects on QT of Beta-Blockers Using Different Rate Correction Formulae: EMIAT Data



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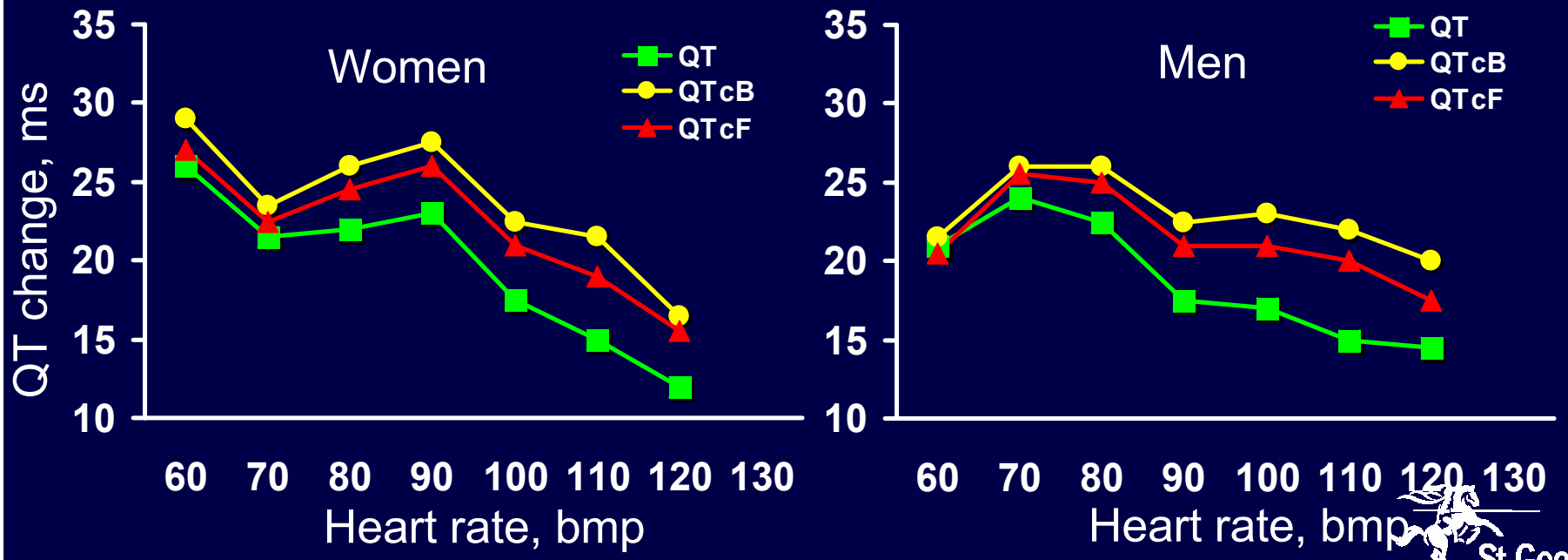
Malik M. Data from St George's University of London

Limitations of Existing Models -
Bazett and Fridericia Formulae Interfere With QT Assessment

Healthy subjects	Women n = 9	Men n = 9
Age, years	27.9	25.6
Height, cm	162.8	175
Weight, kg	63.2	72.2
BMI, kg/m^2	23.9	23.8
Ibutilide PK, pg/mL	557.9	558.7

Rate correction of QT intervals using the standard Bazett and Fridericia formulas can introduce significant errors in the assessment of drug effects on the QT interval. This has implications for the clinical assessment of drug effects and for the safety assessment of new drugs under development

QT change assessed during ibutilide



Indik JH, et al. Heart Rhythm 2006;2006;3:1003-7

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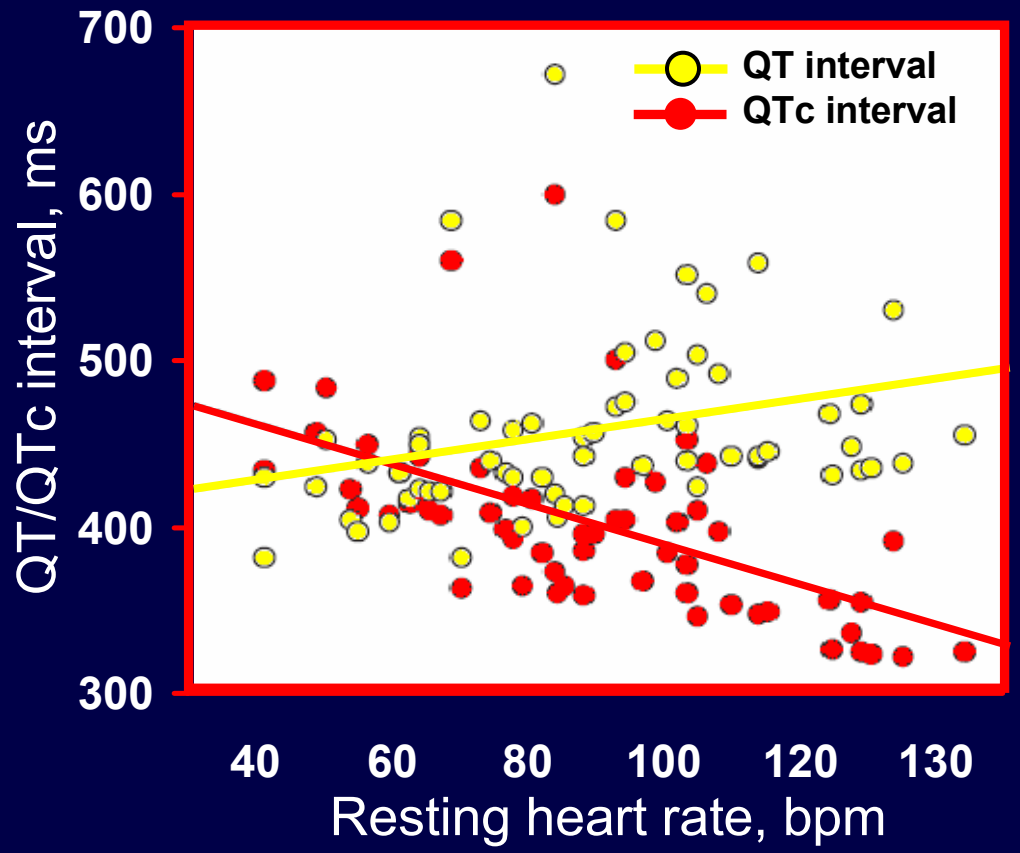
Limitations of Existing Models -
Overcorrection of the QT interval by Bazett Formula

Data obtained at rest from a population of controls and patients with heart failure, left ventricular hypertrophy. There is a significant negative correlation between heart rate and QT interval, and a positive correlation between heart rate and QTc interval



Davey PP, et al. Clin Cardiol 1999;22:793-9

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Limitations of Existing Models - QT Hysteresis

- In addition, the QT interval adapts to changes in heart rate with a delay, a phenomenon termed QT interval hysteresis, which makes it difficult to compare the QT interval recorded at non-constant heart rates

Hysteresis of the ventricular paced QT interval in response to abrupt changes in pacing rate

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From the Department of Cardiological Sciences, St George's Hospital Medical School, London

SUMMARY The rate of QT adaptation to abrupt changes in pacing rate was studied in seven patients v newly diagnosed complete heart block with a ventricular escape rate of less than 40 beats·min^{-1}. T median age was 70 (range 36-84) years, and none was taking any cardioactive medication known to af the QT interval. From a baseline pacing rate of 50 or 110 beats·min^{-1} the ventricular rate was increase decreased to a new level. The time taken for the ventricular paced QT interval to complete 90% of change secondary to the change in rate was found to be 136(16) s (mean(SEM)) when the rate increasing and 189(25) s when the rate was decreasing ($p<0.01$). This time interval was independent of magnitude of the rate change and the baseline heart rate from which the change occurred. Furthermore time course of QT adaptation was found to be exponential and was characterised by a time constar 49.1(2.2) s when the rate was increasing and 60.4(2.0) s when the rate was decreasing ($p<0.01$). concluded that QT measurements in response to a change in pacing rate should take into account the dependent nature of QT changes.

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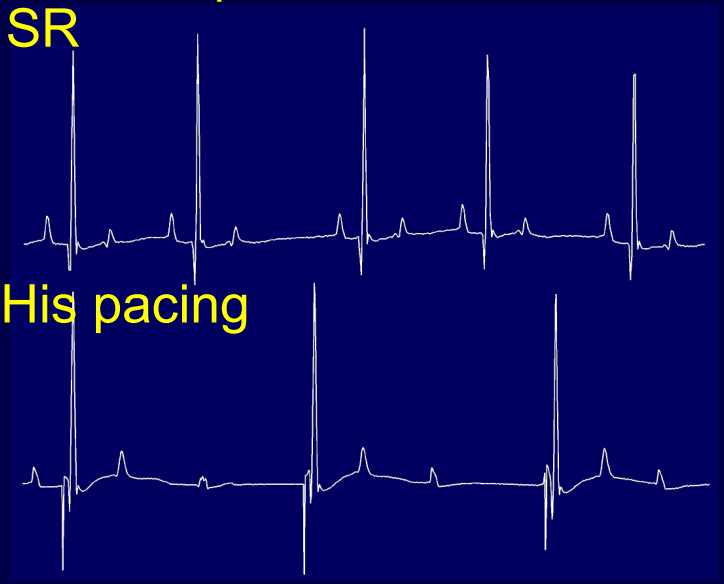
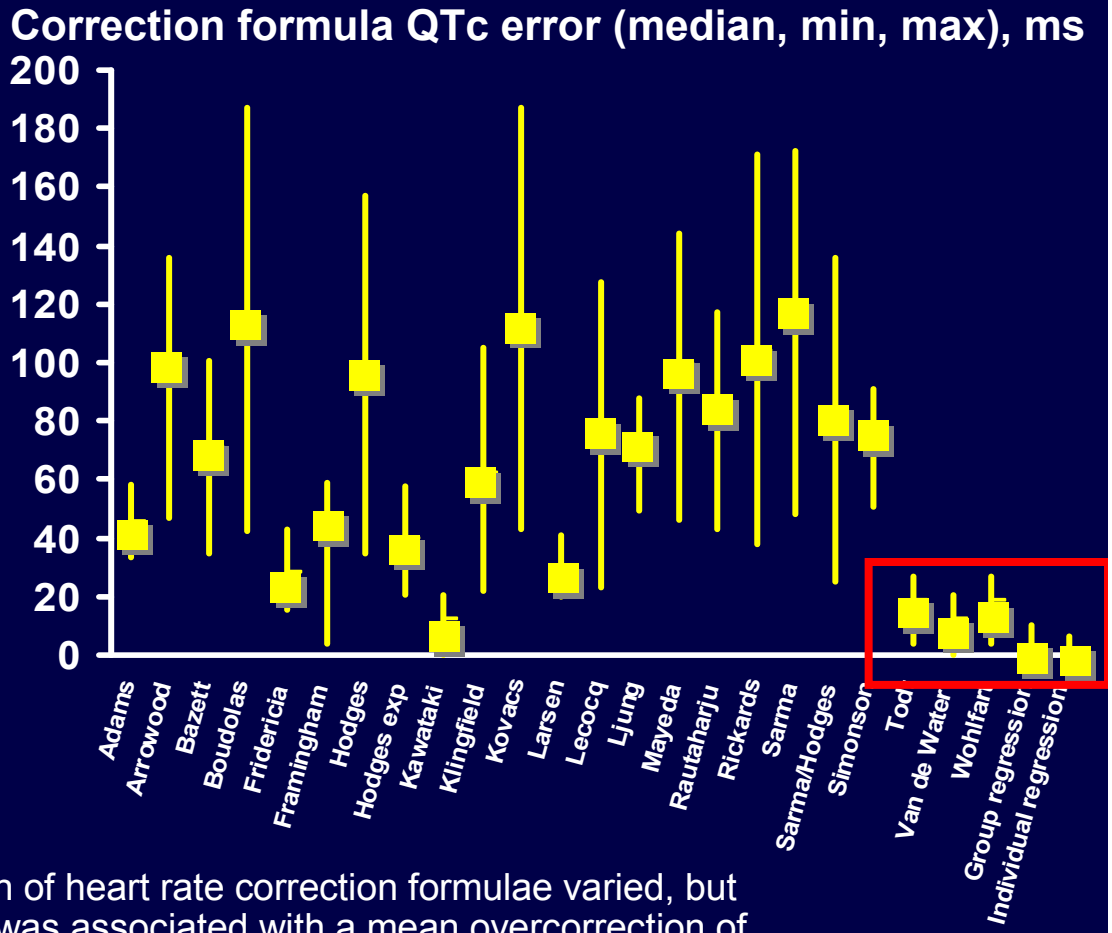
Magnitude of Error Introduced By Rate Correction Formulae: Assessment in a Canine Model

Chronic atrioventricular dissociated His-paced canine model



Lead II electrocardiogram of a representative dog in sinus rhythm and after AV dissociation and His bundle pacing. The morphology of the QRS complex is almost identical



The magnitude of error discovered by application of heart rate correction formulae varied, but in many cases was very large. Bazett's formula was associated with a mean overcorrection of 67.9 ms; Fridericia's 28.7 ms. As expected, group and individual corrections derived from linear regression of the HR-QT data offered improvement over the traditional formulas. Both were able to predict QTc values independent of the heart rate. However, errors of the magnitude of 10 and 6 ms, respectively, were still introduced

King A, et al. A.N.E. 2006;11:289-98

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