QT Variability: Risk Stratification and Drug Studies

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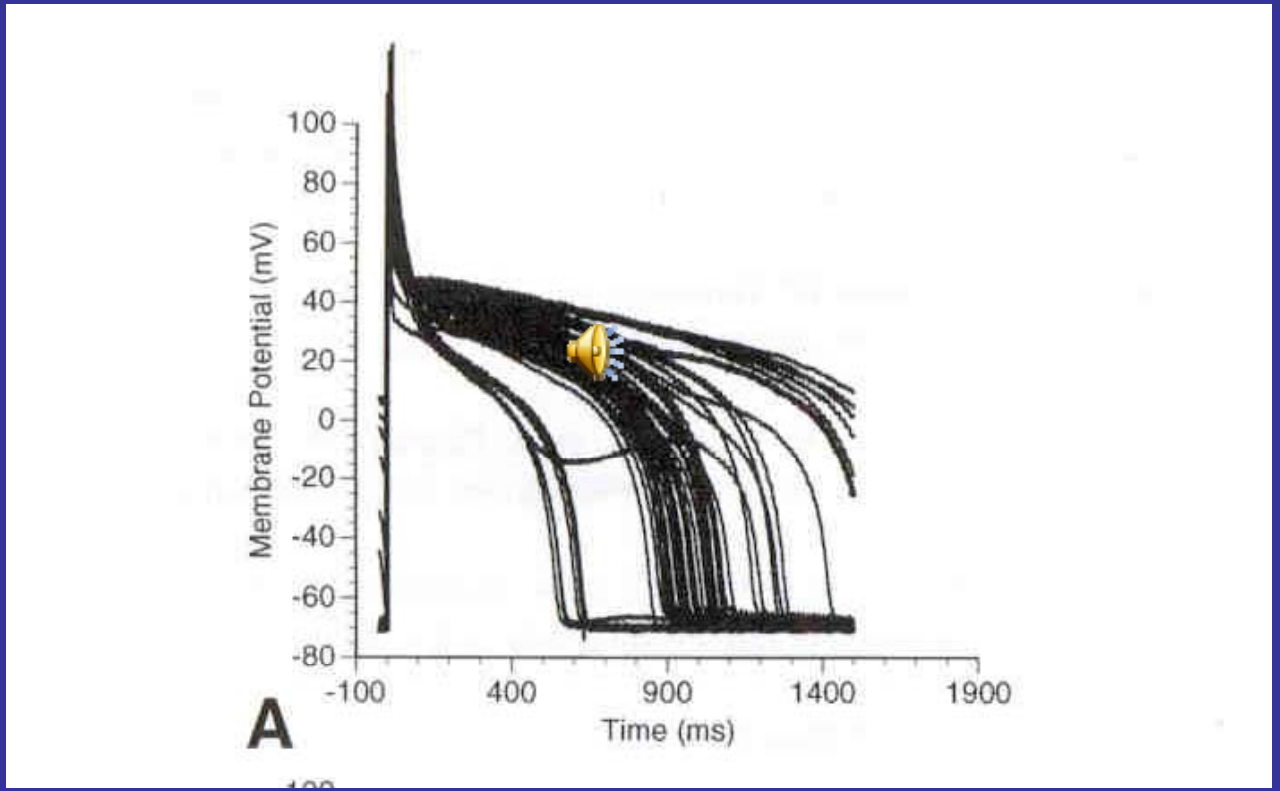
No relationships to disclose

Analogies Between HF- and Drug-induced Proarrhythmia

- Drug-induced and congenital LQTS associated with excessive prolongation of action potential in midmyocardial M cells
  - Sicouri S, Antzelevitch C. Circ Res 1991
- Heart failure results in action potential prolongation in M cells and QT prolongation in ECG
  - Akar F, Rosenbaum D. Circ Res 2003

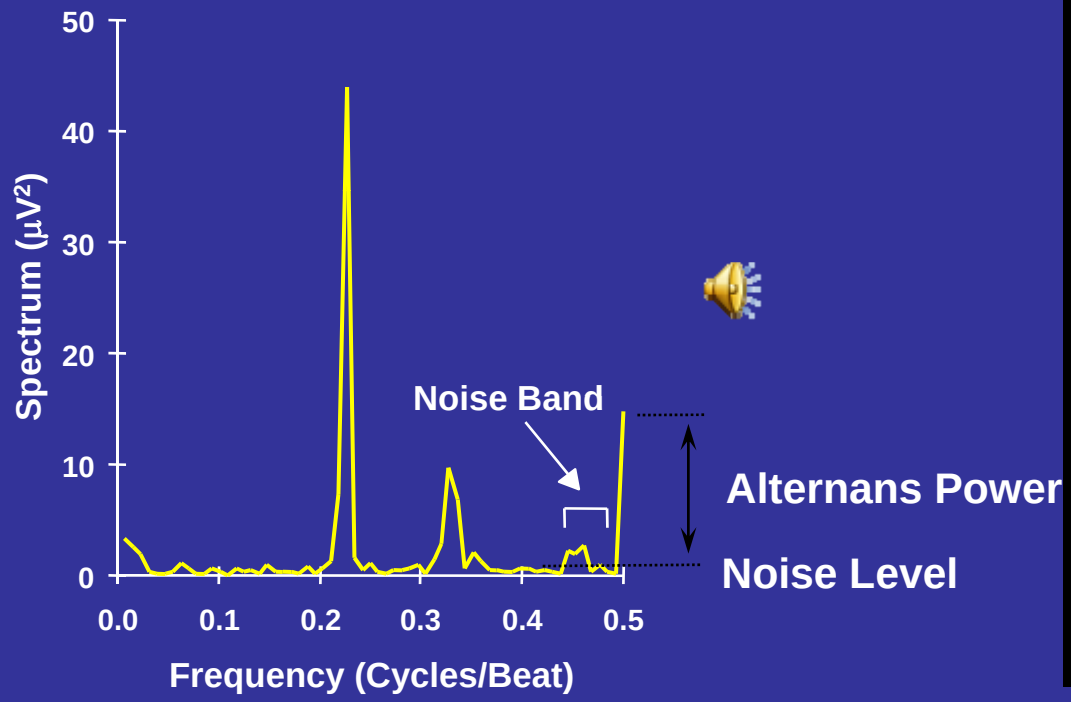
Repolarization is prolonged and unstable in Heart Failure



Haigney, et al. JACC,1998

Does repolarization instability contribute to the development of ventricular tachyarrhythmias?

T Wave Alternans:
A special case of repolarization variability?



Alternans Voltage (V_{alt})

$V_{alt} = (\text{Alternans Power})^{1/2}$

Alternans Ratio (k)

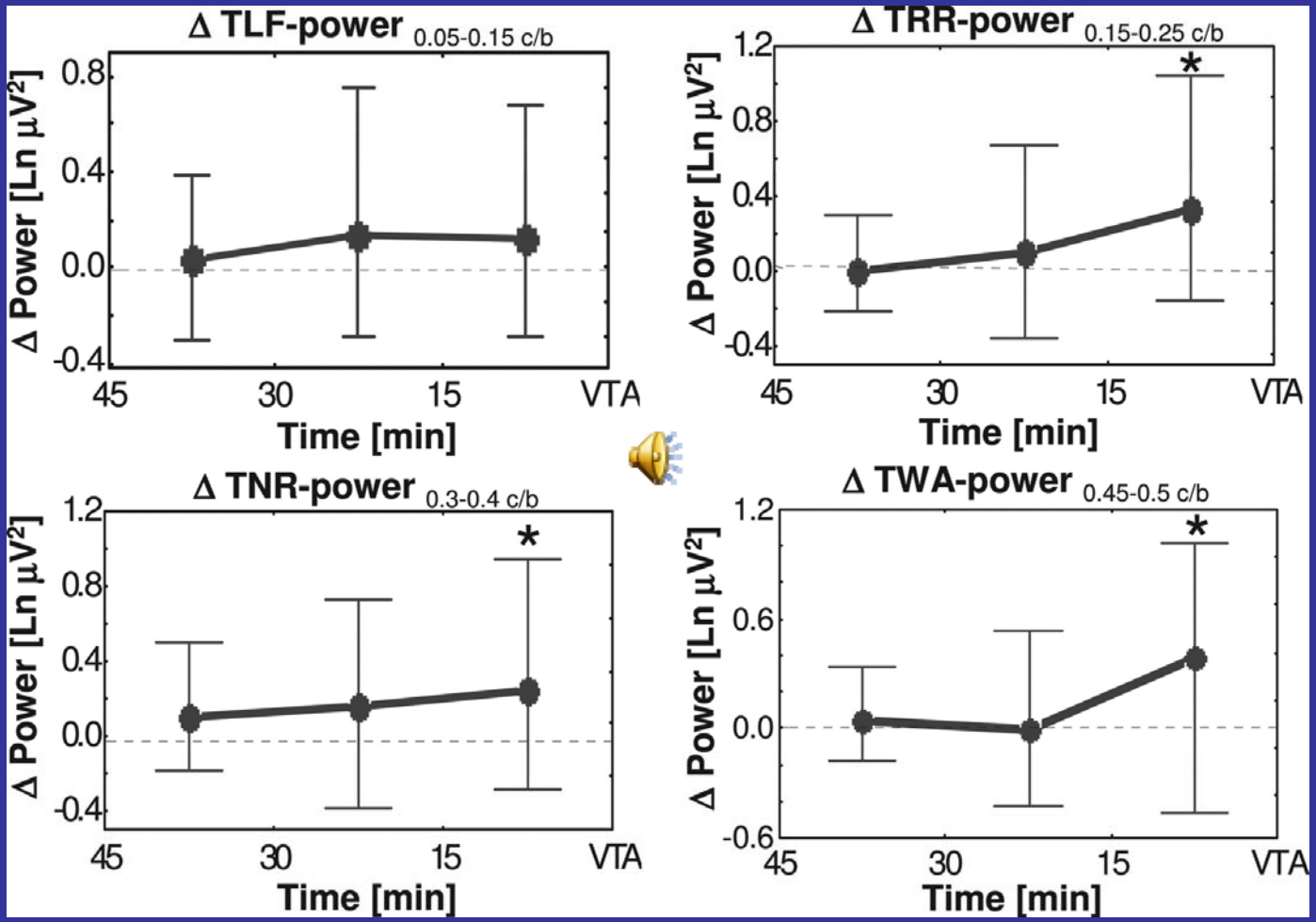
$$k = \frac{\text{Alternans Power}}{\text{Noise Std. Dev.}}$$

What about variability at non-alternans frequencies?

Repolarization Variability Precedes Ventricular Arrhythmias

- Holters from Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM)
  - 42 subjects with sustained VT
- Increased variability at alternans and non-alternans frequency prior to VT

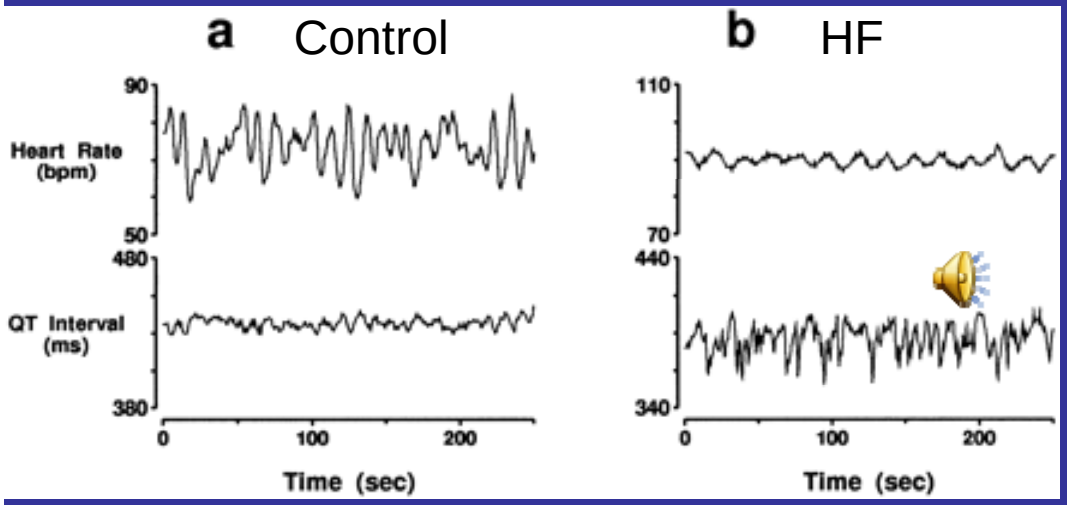
Changes in the spectral power of beat-to-beat oscillations in the mean amplitudes of successive T waves before the onset of VTA



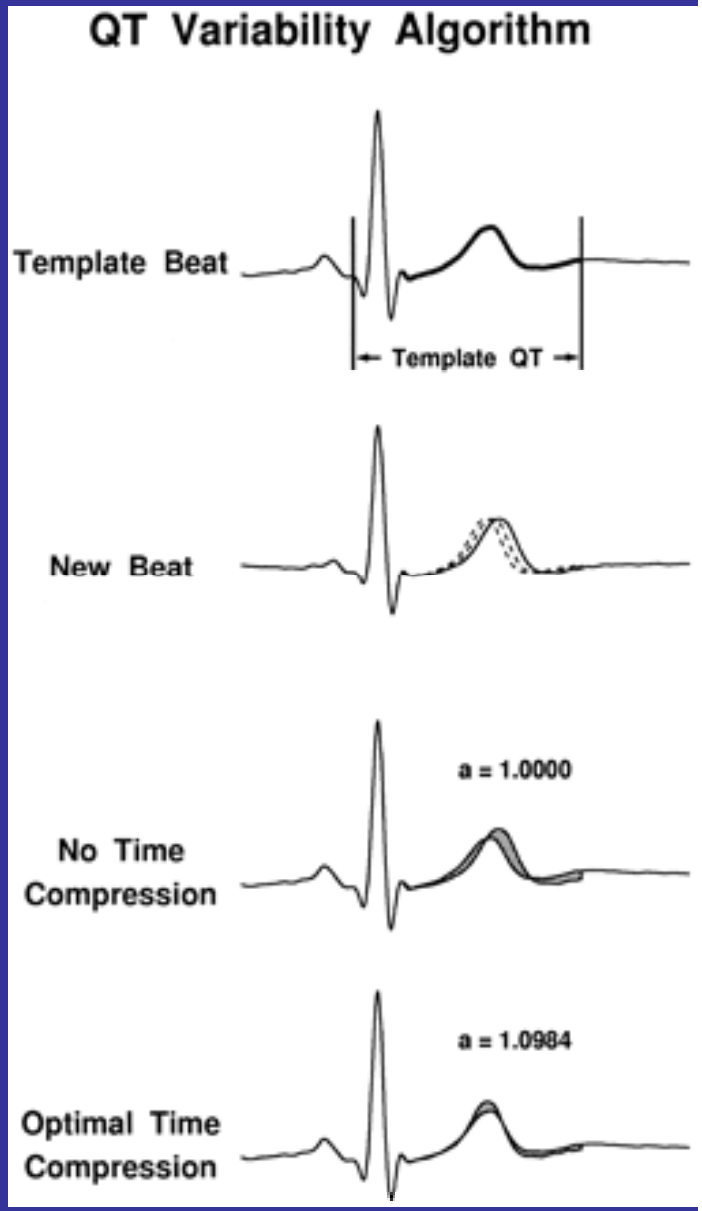
Shusterman, V. et al. Circulation 2006;113:2880-2887

QTVI

QT Variability Index



Time series of QT and HR generated



Berger, et al.

Circulation. 1997;96:1557-1565

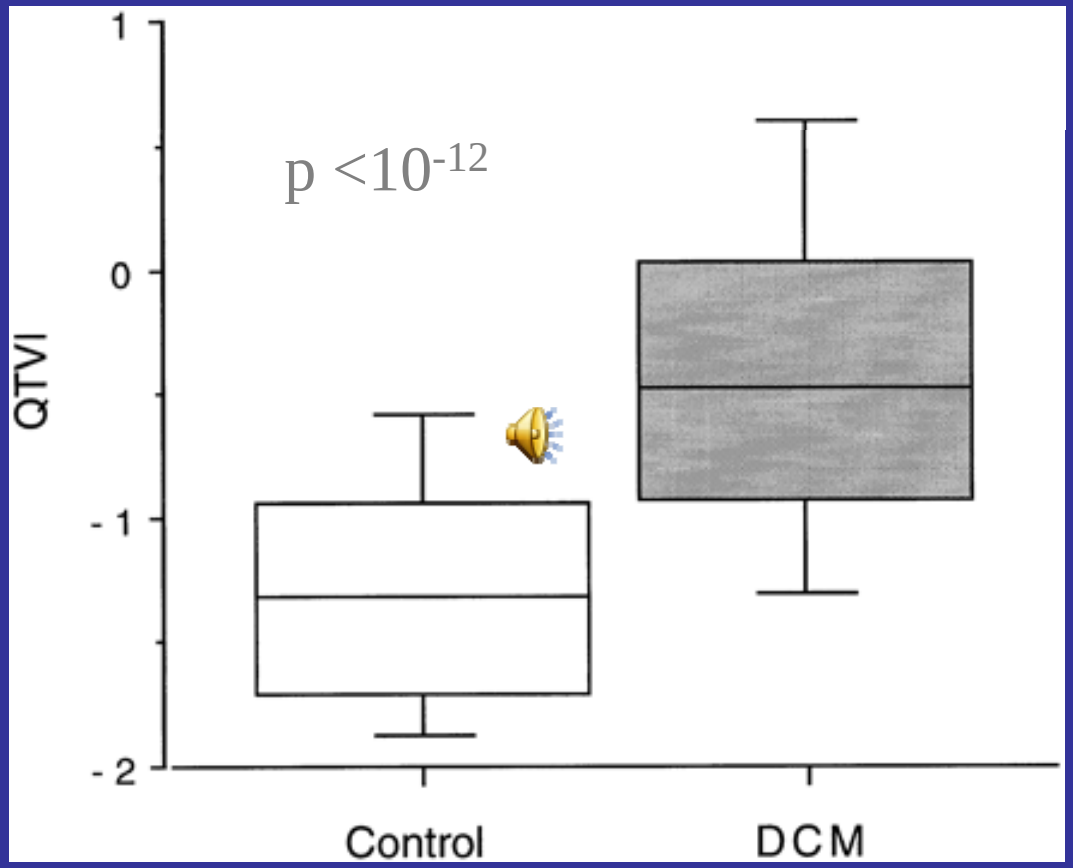
QT Variability Index

$$QTVI = \log\left(\frac{QTV/\text{mean } QT^2}{HRV/\text{mean } HR^2}\right)$$

QT Variability Normalized

$$QTVN = (QTV/\text{mean } QT^2)$$

QTVI is increased in Ischemic and Non-ischemic DCM



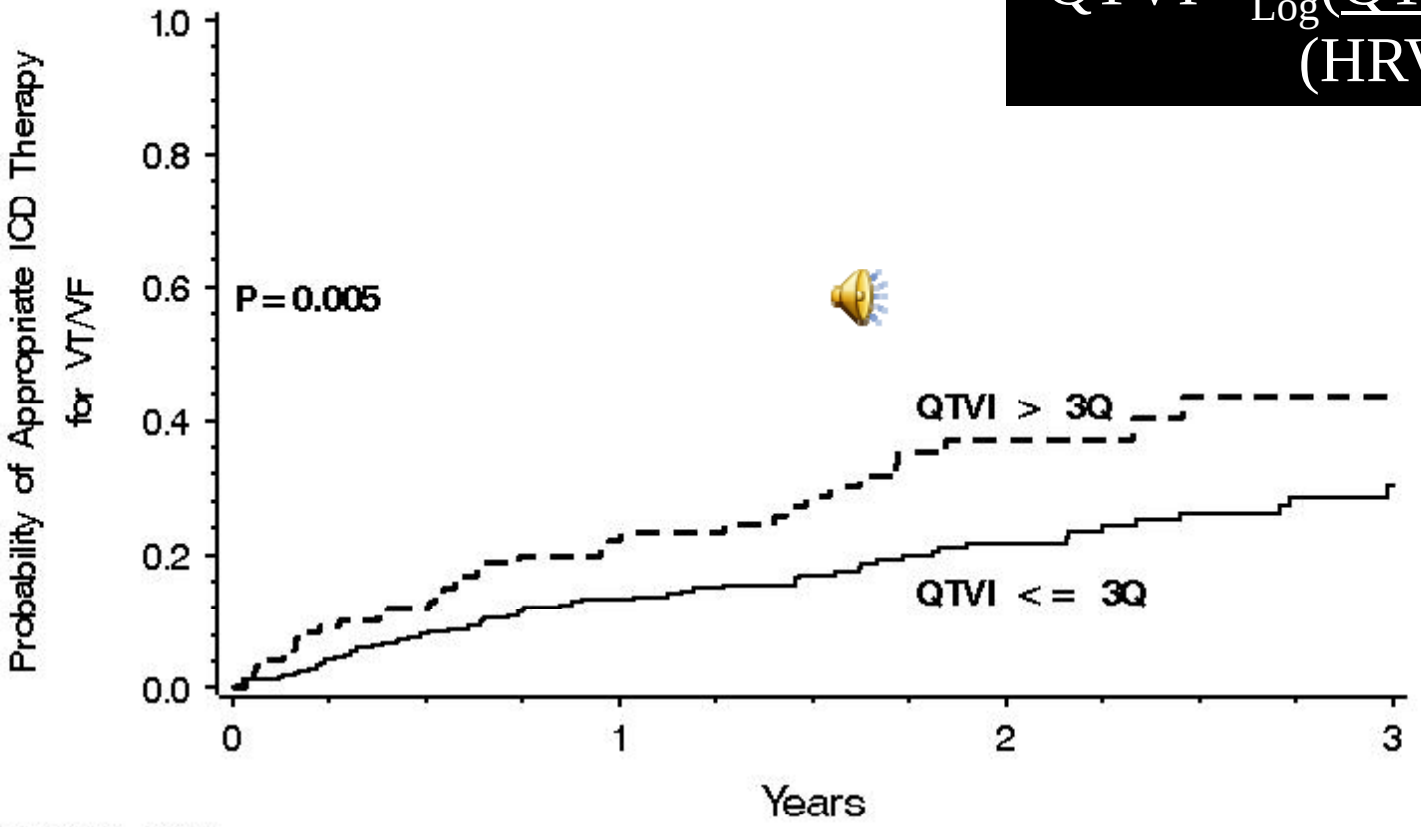
Berger, et al. *Circulation*. 1997;96:1557-1565

QTVI and VT/VF in MADIT II

- Of 1,232 subjects, 1,197 with Holter
  - 310 initially excluded
    - 111 paced, 98 Afib, 76 noise
- Analysis attempted in 912 subjects
  - 95 rejected (Atrial fibrillation in 64)
  - 817 successfully analyzed
  - 476 ICDs (742 ICDs in the trial)
  - 22.5% had appropriate ICD therapy for VT/VF
  - Compared the top quartile for QTVI and QTVN

QTVI and Appropriate ICD Therapy

$$QTVI = \text{Log}\frac{(QTV/\text{mean } QT^2)}{(HRV/\text{mean } HR^2)}$$



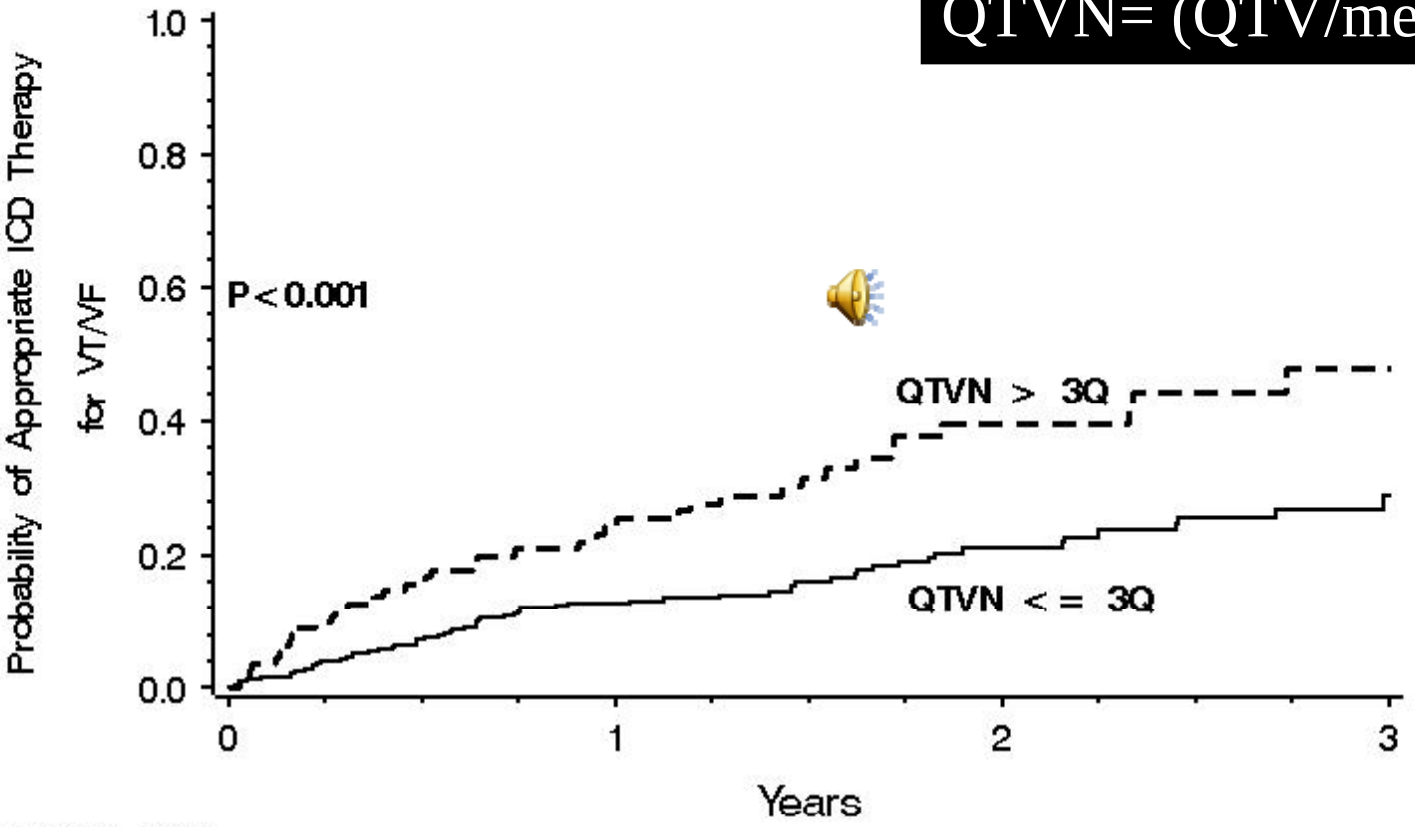
PATIENTS AT RISK

QTVI > 3Q	120	68 (0.22)	27 (0.37)	8 (0.44)
QTVI <= 3Q	343	215 (0.13)	109 (0.22)	36 (0.30)

Haigney, Zareba, Gentlesk et al. *JACC* 2004; 44(7): 1481-1487.

QTVN and Appropriate ICD Therapy

QTVN= (QTV/mean QT^2)

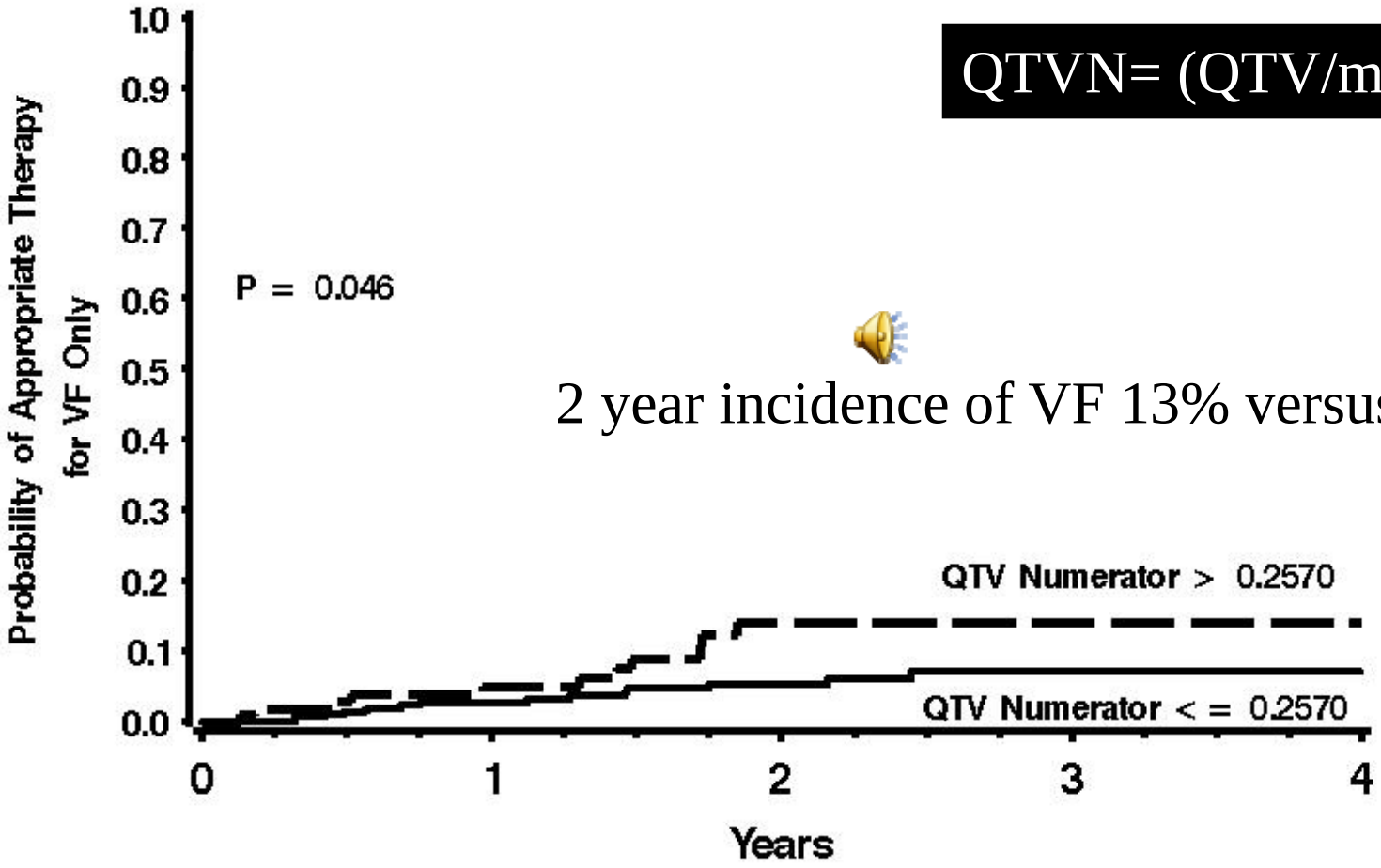


PATIENTS AT RISK				
QTVN > 3Q	112	68 (0.24)	30 (0.40)	11 (0.48)
QTVN < = 3Q	351	215 (0.13)	106 (0.21)	33 (0.29)

Haigney, Zareba, Gentlesk et al. *JACC* 2004; 44(7): 1481-1487.

HRQ for QTVN Associated with VF

QTVN= (QTV/mean QT^2)



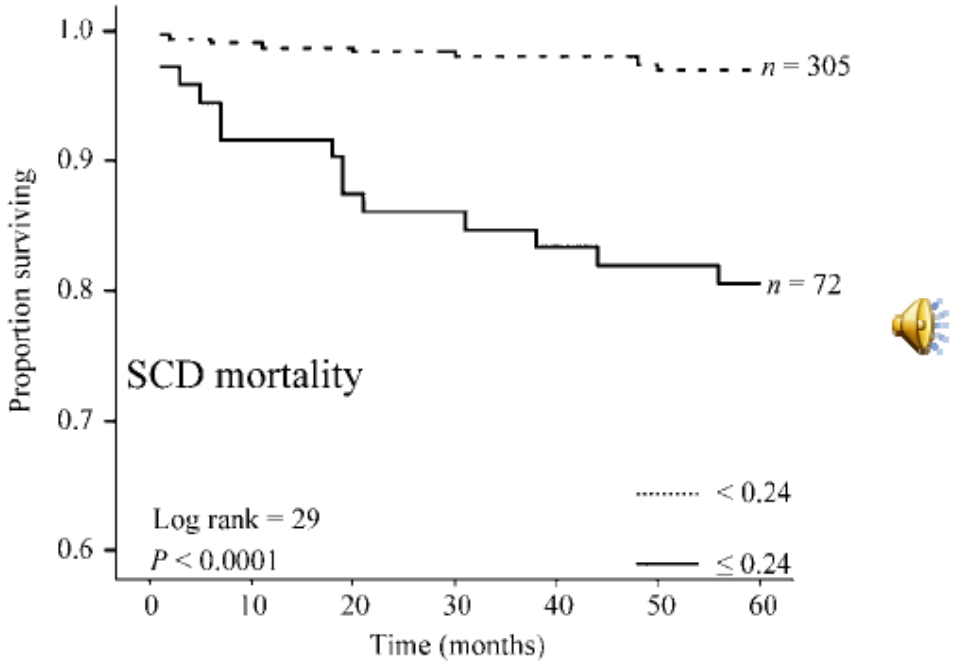
2 year incidence of VF 13% versus 5%

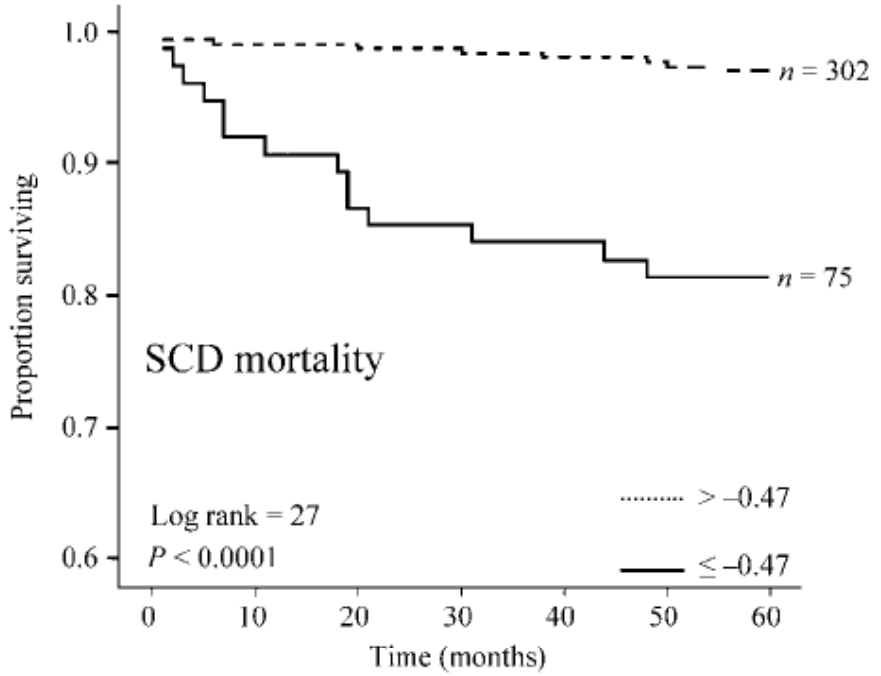
Haigney, Zareba, Gentlesk et al. *JACC* 2004; 44(7): 1481-1487.

Multivariate Cox Analysis

- **significant independent increase in risk of appropriate therapy for VT/VF after adjustment for relevant clinical covariates (race, NYHA class, time after myocardial infarction)**
  - **HR for QTVN 2.18, CI: 1.34 to 3.55, p=0.002;**
  - **HR for QTVI 1.80, CI: 1.09-2.95, p=0.021**
  - **HR for EF<25** 1.21 CI 0.77-1.87, (p=0.41)
  - **HR for EPS** (n= 593) 1.26 CI 1.26 CI 0.86-1.86 (p=0.24)

QTVN and QTVI in Non-ischemic DCM



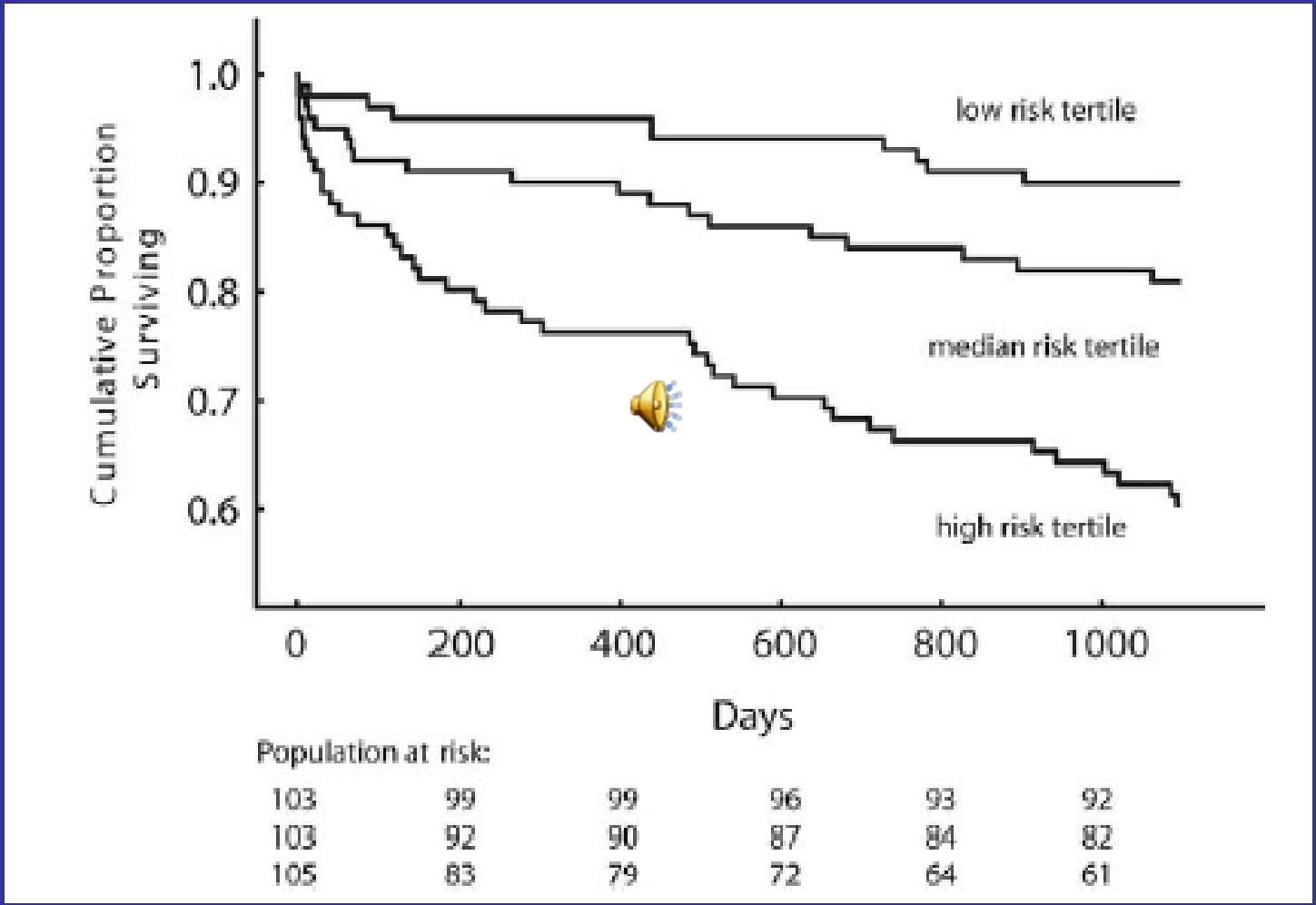


QTVN

QTVI

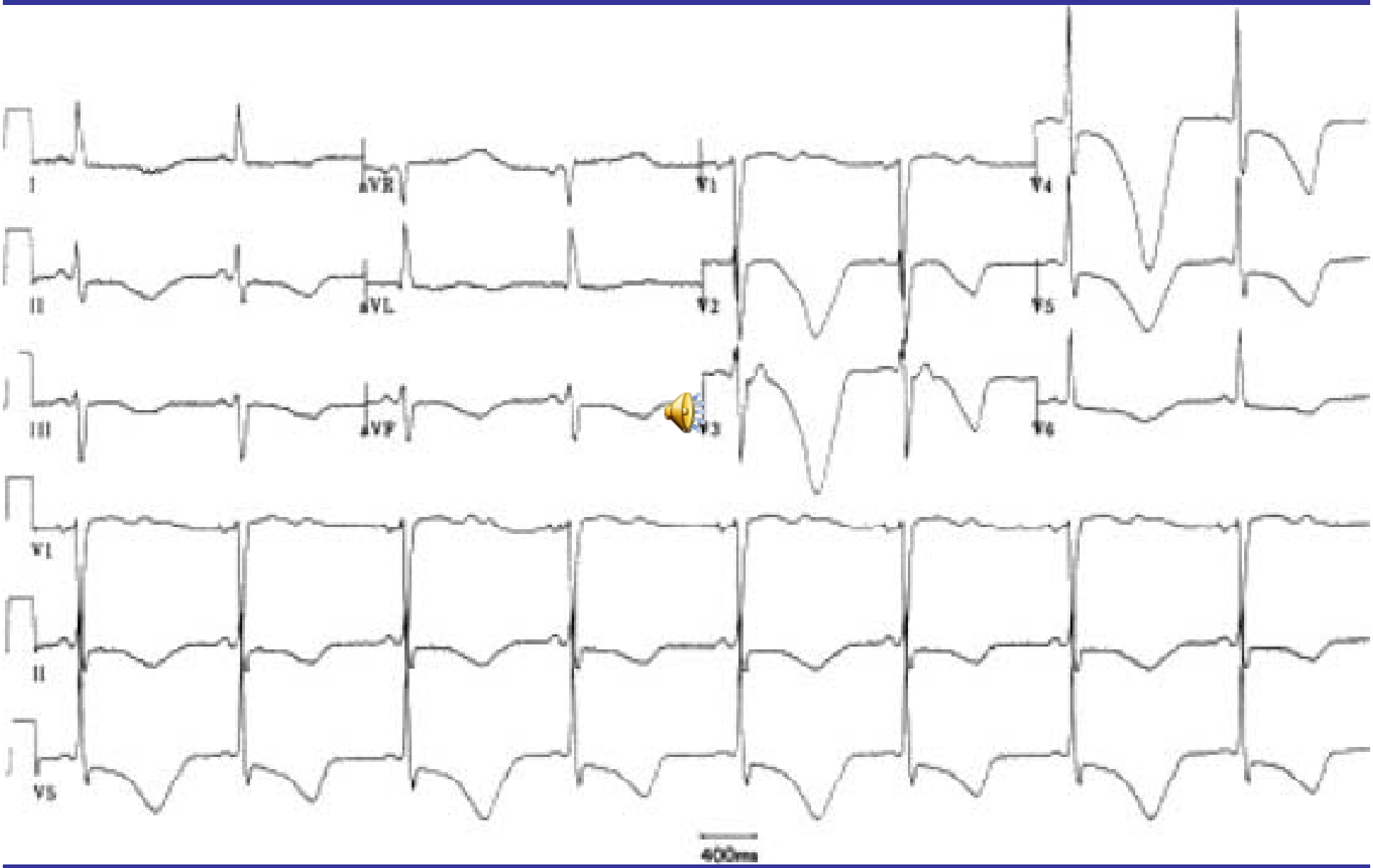
Piccirillo et al. EHJ 2007

24-hour VR (SDQT/SDNN) independent predictor of total, cardiac, and sudden death mortality post MI



Jensen et al. Heart Rhythm 2005

QT Variability is significantly increased in LQTS



Perkiomaki et al. JCE 2002

Repolarization Variability as a Predictor of Torsades de Pointes

- Evidence of pro-arrhythmic tendencies the leading cause of new drug withdrawal
- QT prolongation only modest predictor of TdP
- Presence or induction of repolarization instability may enhance predictive power

T wave Variability Prior to TdP

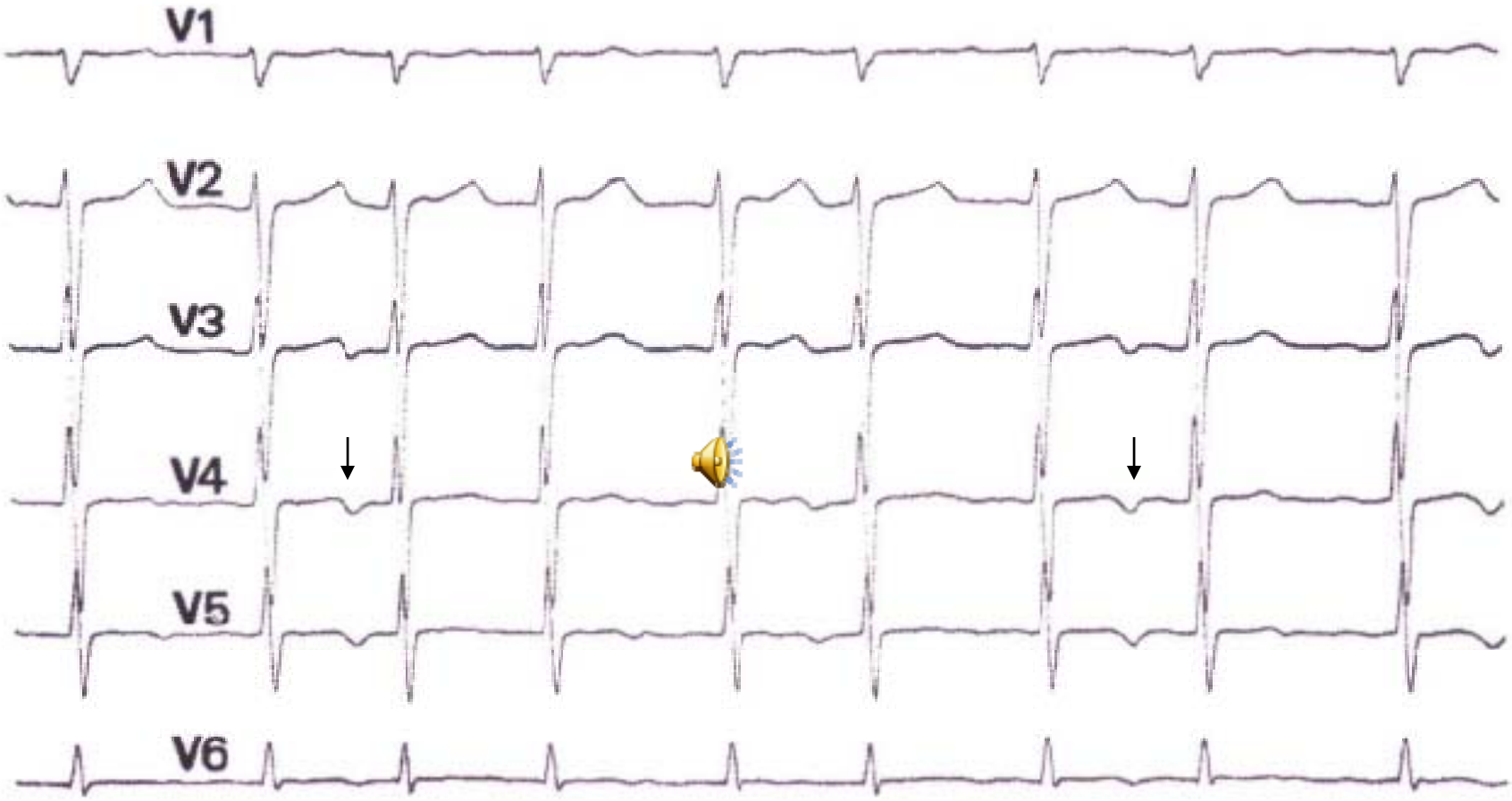
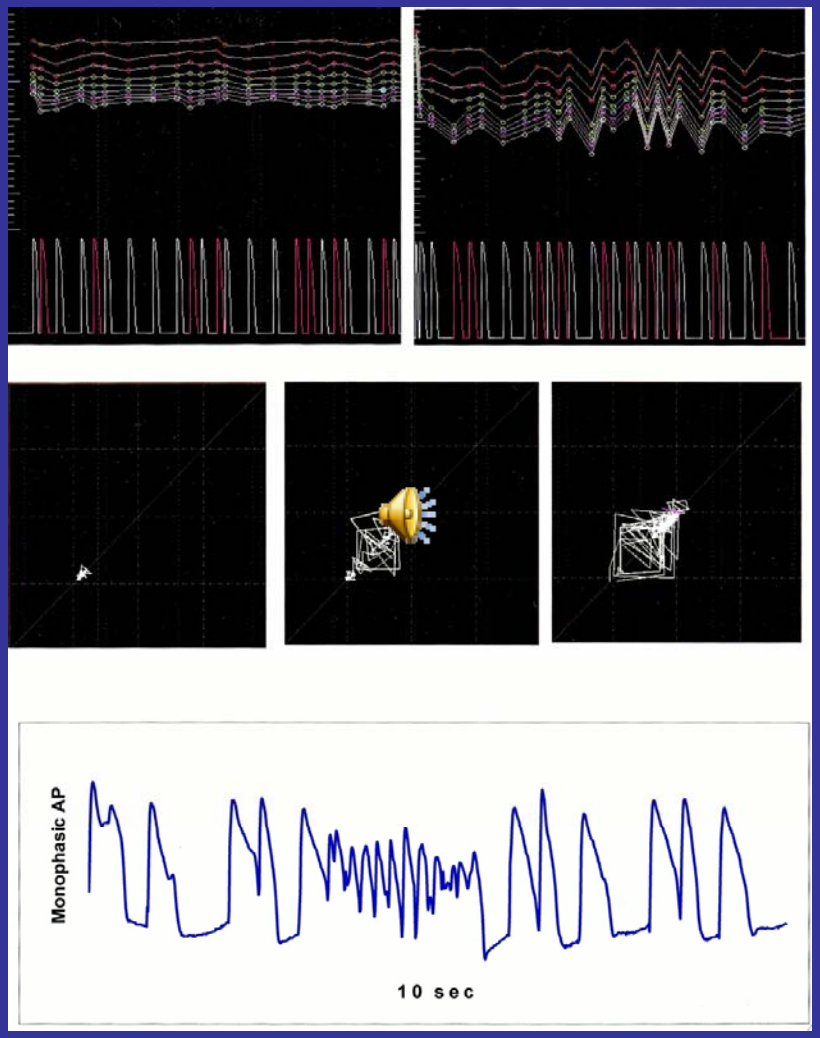


Figure 2. *ECG registration of T wave alternans at baseline before the almokalant infusion in TdP patient 3 (see Table II). The registration shows shifting polarity of the T waves, most visible in leads V_3-V_5.*

Houltz et al. PACE 1998

Instability, Poincare plot, and TdP



Hondeghem, L. M. et al. Circulation 2001;103:2004-2013

Circulation

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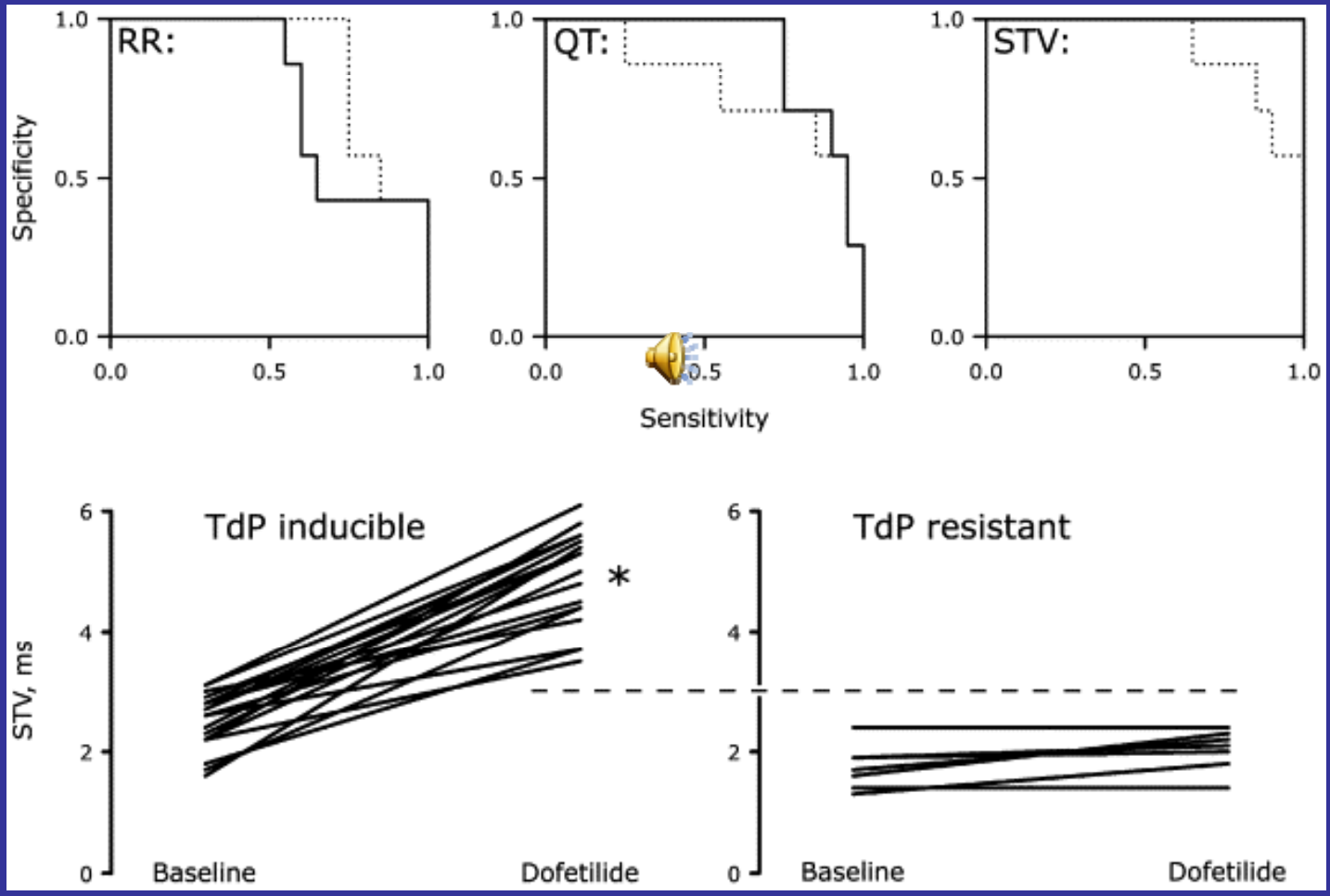
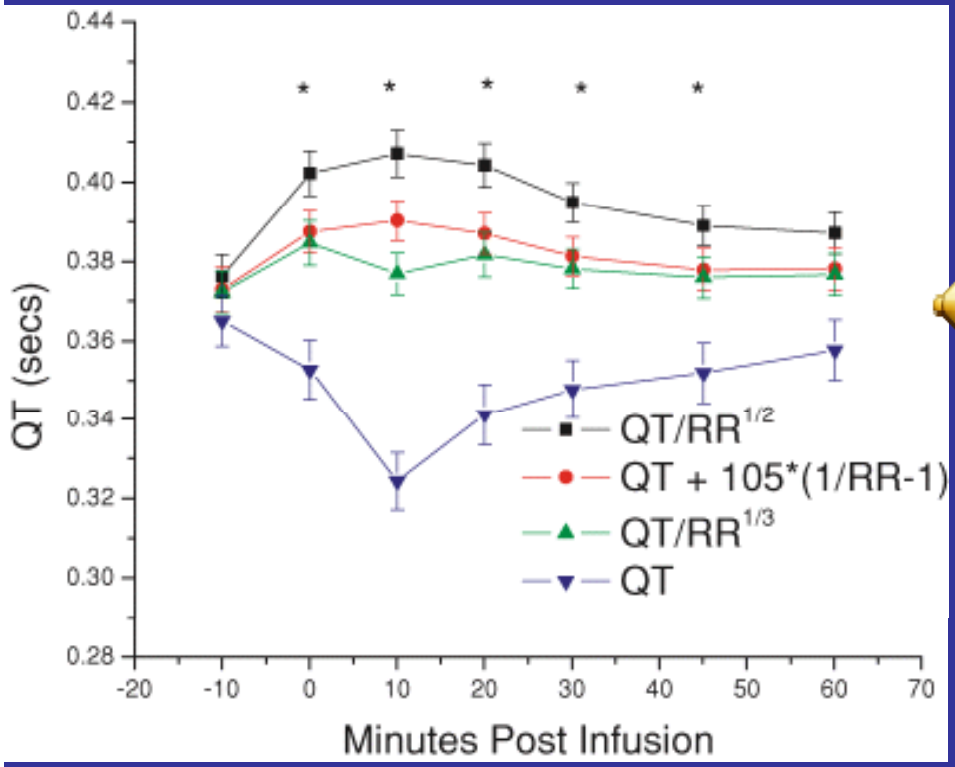
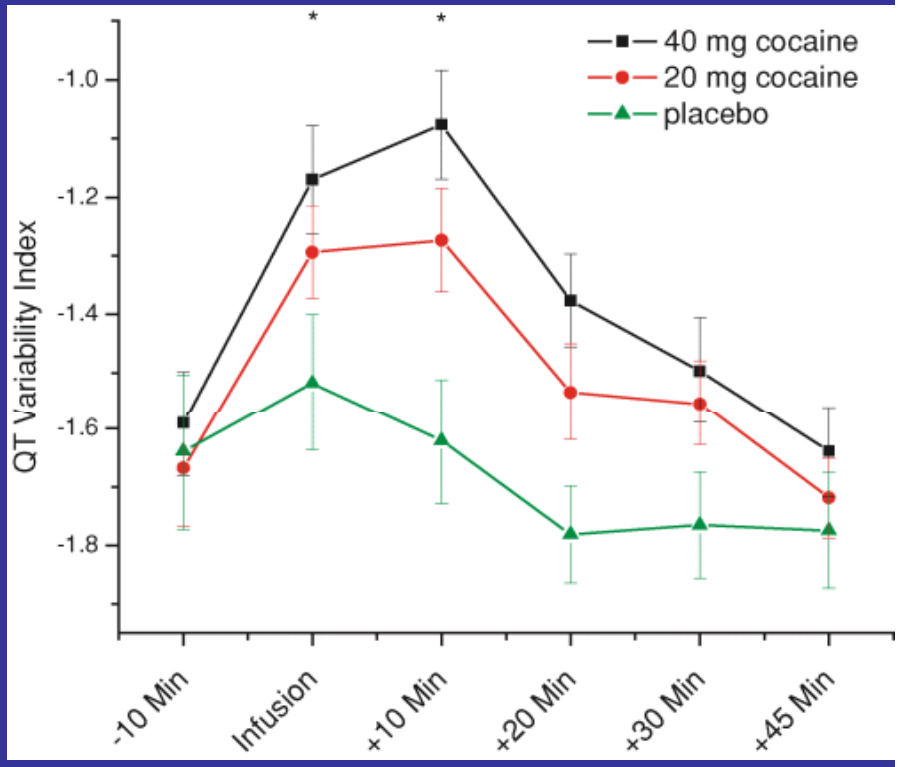
Induction of Short-term Variability in MAP Predicts TdP



Thomsen et al Cardiovascular Res 2007

QTVI and Cocaine





Haigney et al., JCE 2006

Table 2

Electrophysiological and hemodynamic responses to HMR1556 and HMR1556 plus isoproterenol in TdP-inducible dogs

	Baseline	HMR1556	HMR1556 + isoproterenol
Heart rate, bpm	78±4	74±6	140±7*†
QT, ms	249±6	316±11*	329±13*
QT_cVdW, ms	265±6	331±10*	373±13*†
LV $MAPD_{90}$, ms	2[illegible]±8	289±9*	292±13*
RV $MAPD_{90}$, ms	211±7	251±11*	244±11*
LV-RV$MAPD_{90}$, ms	14±2	26±4*	38±7*
LV $MAPD_{endo-epi}$, ms	29±5	62±11*	74±18*
T_{peak}–T_{end} interval, ms	33±4	56±6*	74±10*
LV BVR, ms	1.7±0.2	2.2±0.7	4.9±0.8*†
QT BVR, ms	1.4±0.3	1.9±0.4	4.9±0.9*†
QT STI, ms	1.4±0.5	1.9±0.4	4.6±1.3*†

Gallacher, et al. Cardiovasc Res, ePub June 2007

Conclusions

- Variability in repolarization (alternans and non-alternans) is associated with increased incidence of VT/VF, SCD, and TdP
- The utility of QT (or T wave variability) in assessing the risk of drug-induced proarrhythmia has not been adequately tested in humans
- The ideal method for measuring *in vivo* repolarization instability unclear
  - Combine TWA and non-alternans methods?
  - T wave amplitude versus QT duration?