



The Value of Holter Arrhythmia Analysis in TQT Trials

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The Assumptions of E-14

- ❑ Determine drug effect on cardiac repolarization detected by QTc prolongation
- ❑ Negative if upper 1-sided 95% CI of the mean QTc excludes 10 ms at all time points
- ❑ Characterization of concentration ~ QT relationship



The Real Challenge of E-14

- ❑ **Determine cardiac safety**
- ❑ Since Holter recordings are the preferred method of data acquisition then ...
- ❑ Why not review all the data?



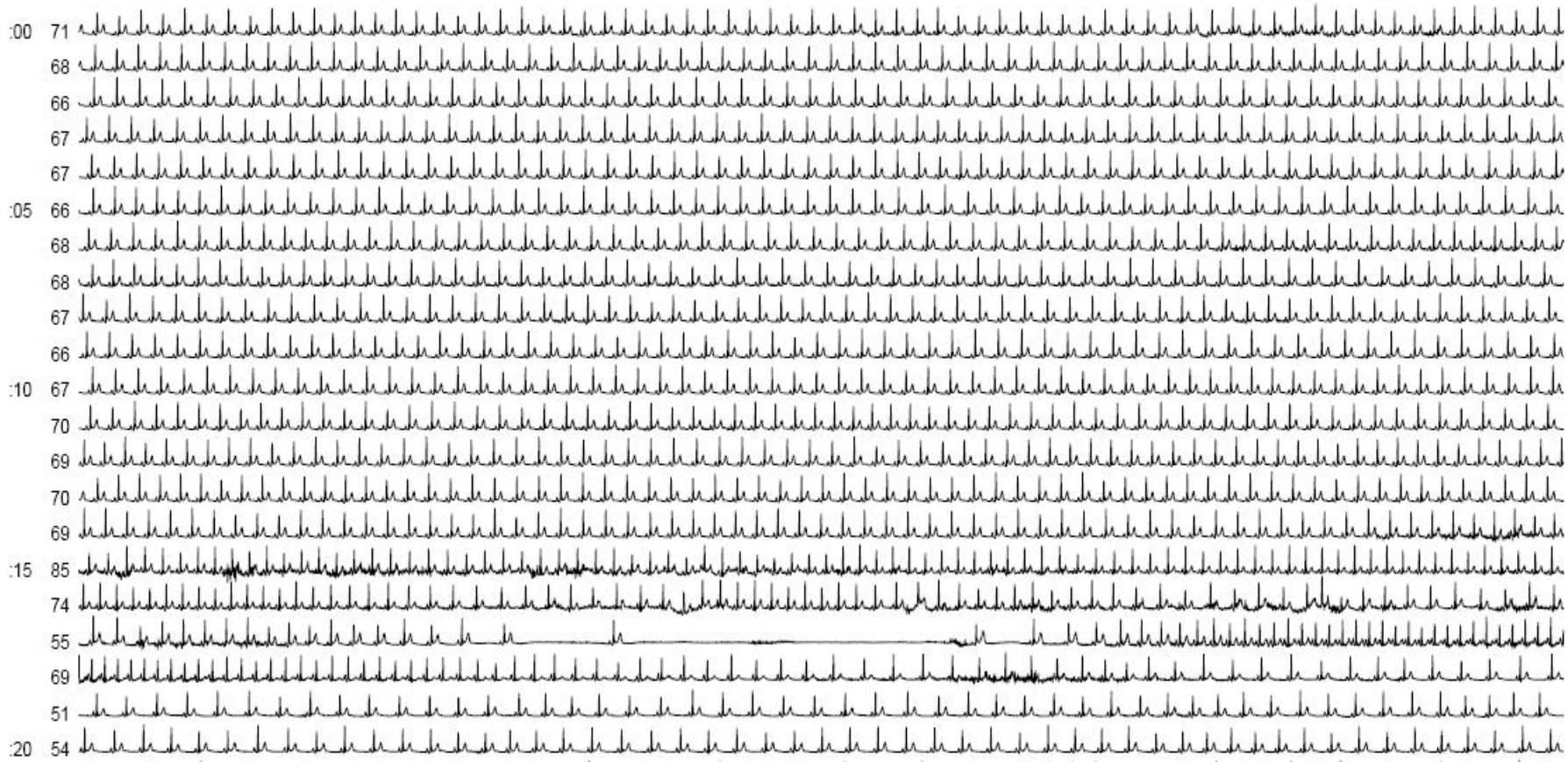
Added value of Holter Analysis

- ❑ There is a lot more potential cardiac safety information than just 10-15 ECG extractions that last just 10 seconds each
- ❑ Why not scan 110,000 heart beats for arrhythmia?



Syncope and Sinus Arrest 15 sec

Rate



What is normal cardiac rhythm

DISEASE	PREVALENCE	STATISTIC SOURCE
ARRHYTHMIAS OVERALL	14.4 million in US	53 per 1,000 NIH study 1995
SINUS NODE DISEASE	N/A	No Information
TACHYCARDIA	4.4 million in US	16 per 1,000 NIH study 1955
ATRIAL FIBRILLATION	2.0 million in US	2 million NHLBI study 1995
WPW SYNDROME	272,000 in US	1-3 per 1,000 worldwide Genetics Home Ref. website
NON-SUSTAINED VEN. TACHY.	2.5% women > 65, many reports in seemingly normals	Katritsis and Camm 2003, many other authors
SINUS ARREST	Elderly former athletes	Jensen-Urstad 1998
SUPRA VENTRICULAR TACHY.	Unknown	No Information
PACs	Unknown	No Information
VPCs	Unknown	No Information
OTHER SERIOUS ARRHYTHMIAS	Unknown	No Information



THEW opportunity

- ❑ Incidence of cardiac arrhythmias in healthy human volunteers
- ❑ Incidence of arrhythmias post-dosing in TQT trials looking beyond QTc
- ❑ Early experience suggests added cardiac safety value

