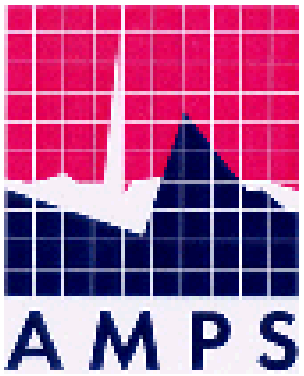
QT Measurements on-screen Methods

Fabio Badilini, PhD

AMPS LLC

New York, NY



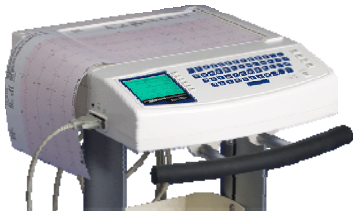
Background
New Regulatory Push for Digital ECGs

- The FDA's Digital ECG Initiative from 2001 mandates that for new drug approvals, digital ECGs must be submitted from definitive ("thorough") QT studies and that the interval measurements be performed with annotations detailing exact offset and onset points on the ECG.

- Most recent guidelines (ICH E14) recommend that manual methods, "whether or not assisted by a computer" should be used by central labs (1).

- In consequence, digital ECG tracings and on-screen calipers systems have replaced paper ECG printouts and digitizing board as the primary tools for ECG acquisition and interval measurement in intensive QT assessment in clinical trials (2,3).

Review Old Paper ECG Lifecycle

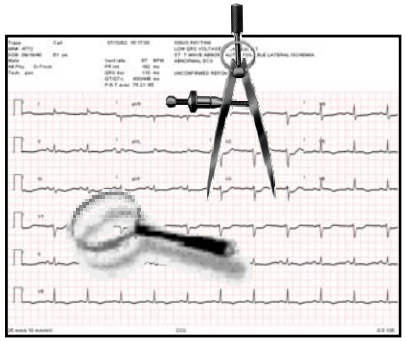


Acquire Paper ECG

Paper ECG

Mail Paper ECG
To Core Lab

Paper ECG



Manual Measurements
On Paper Using
Rhythm Waveforms

Paper ECG

Archive Paper ECGs

407 ms
435 ms
456 ms

Findings

Trial Analysis

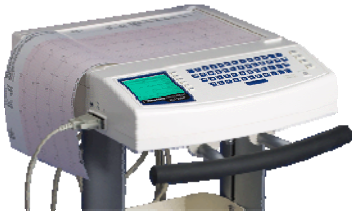
SAS Datasets

Submission

FDA

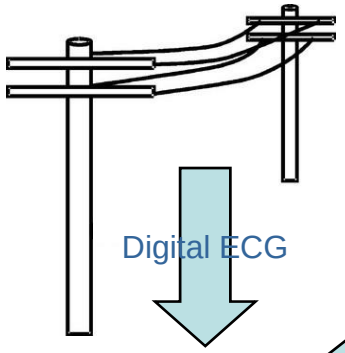
By courtesy of Mortara Instruments

New Digital ECG Lifecycle



Acquire Digital ECG

Digital ECG



Digital ECG

ECG Management Server At Core Lab

Digital ECG

Manual or Semi-automatic Measurements ***Onscreen*** Using Rhythm Waveforms or Representative Beat

407 ms

435 ms

456 ms

Findings

Trial Analysis

SAS Datasets

Submission

Annotated ECG

ECG Warehouse

Review aECGs

By courtesy of Mortara Instruments

Background
ECG Measurements in Drug Development

- The only written recommendations for ECG interval measurement widely accepted before the digital era were published in 1997 by the European Committee for Proprietary Medicinal Products (CPMP) and were based on annotating three consecutive sinus complex, preferably from lead II (4).

- At that time, detection of drug effects on cardiac repolarization was mostly exclusively based on paper ECG, and was associated with considerable degree of variability and measurement errors (5).

Background
ECG Measurements in Drug Development

- The introduction of on-screen methodologies based on digital ECGs has completely changed the measuring environment. For example, the potential advantages of implementing digital algorithms is now being considered.

- Consequently, pharmaceutical sponsors nowadays commonly use semi-automated methods for centralized ECG interval measurement, where a trained human analyst decides if the ECG interval annotations by the automated algorithm should be adjusted based on visual inspection of annotated waveforms on a computer screen.

From Paper to Digital:
Summary of Implications

- Forget rulers and magnifying lens ….
- More data to deal with
  - Typically 10 seconds available in all Leads,
  - Representative beats (medians or other).
- A new measurement environment, with new challenges (manual, automated, ….).
- A whole new perspective on how to assess Quality which should be strongly based on the digital ECG characteristics.

On-Screen Methods:

Which Waveforms to Measure?

- Rhythm strips (raw data)
  - Measurements from the actual recorded signal
  - X seconds of signal per lead is available
    - Typically 10 seconds
- Representative beats
  - Measurements on mathematically derived waveforms that represent the typical shape of one lead (e.g. medians)
  - A single complex (P-QRS-T) per lead from each heart beat is available
    - Typically 1.2 seconds

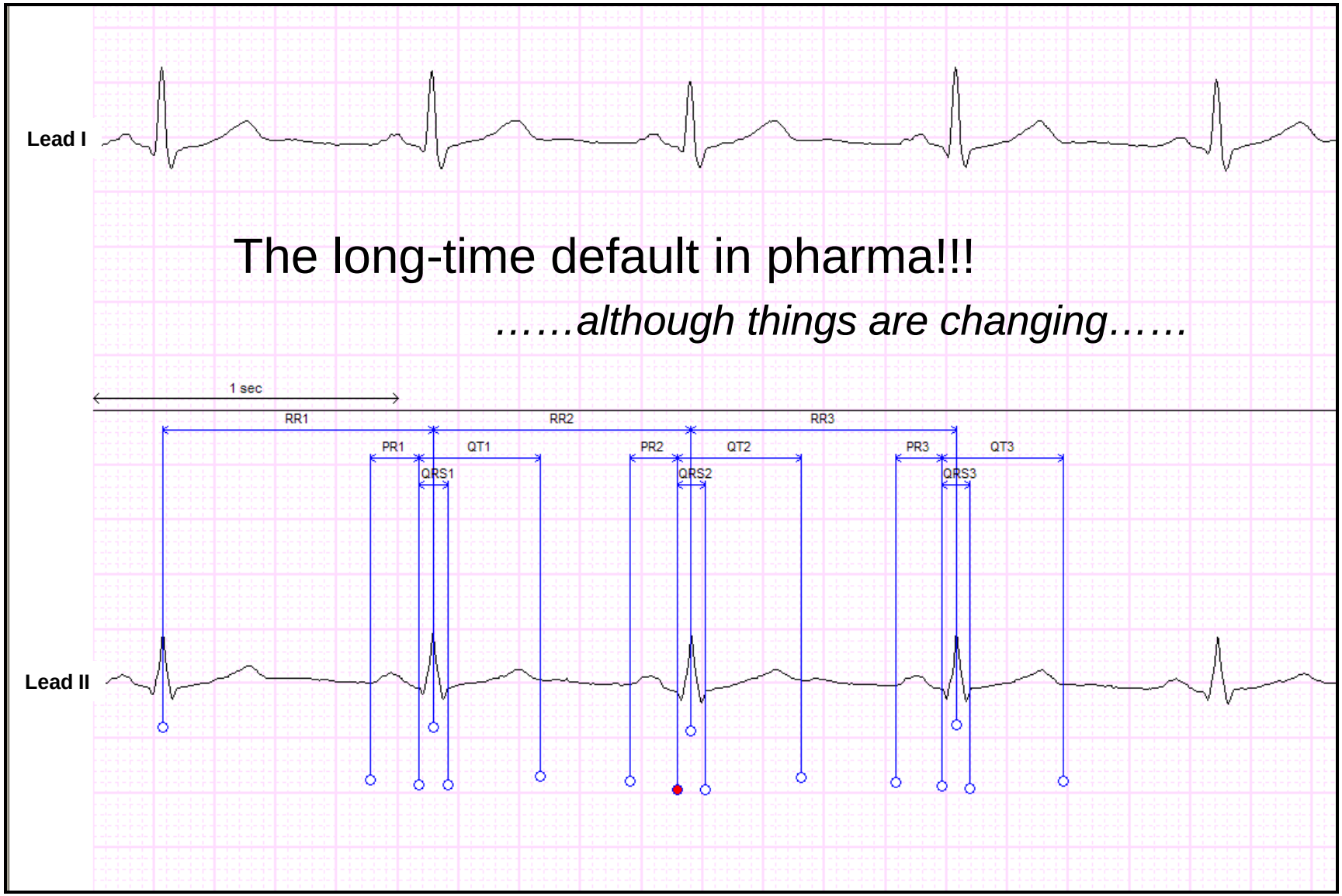
On-Screen Methods:
Which Lead to Measure?

- Single lead approach
  - One specific lead is used to generate the measurements (e.g. lead II)
    - Need to pre-specify backup lead in the protocol
- Global lead approach
  - Measurements produced taking into account all leads
  - Typically this is done/represented using the butterfly (superimposed) plots

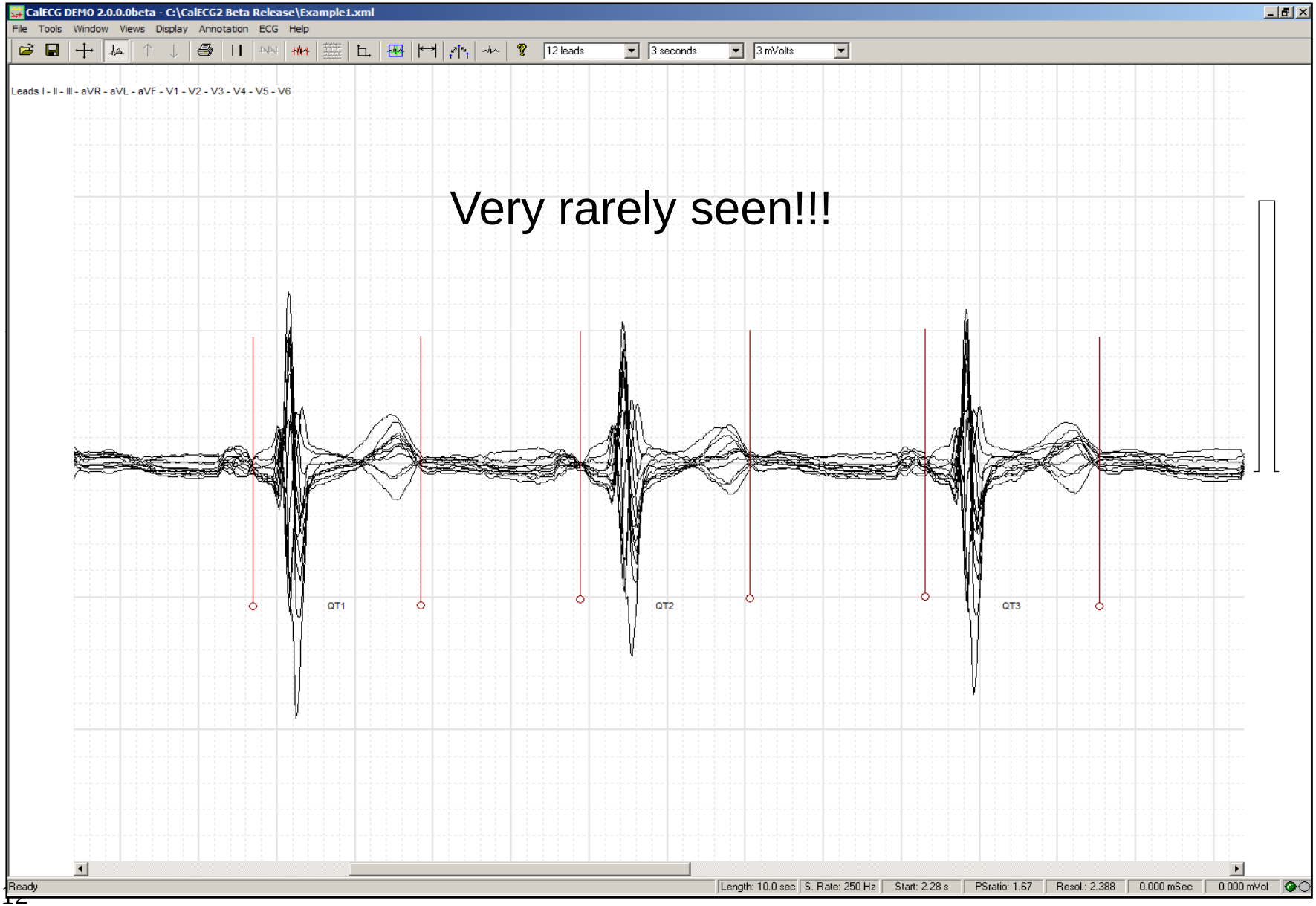
To Summarize:

Lead → / Waveform ↓	Lead-based	Global (typically superimposed)
Raw data	Ex: 3 QT from lead II	Ex: 3 global QT from the 10-second ECG
Rep beats (e.g medians)	Ex: one QT from lead II Rep. beat	Ex: one global QT from all rep. beats

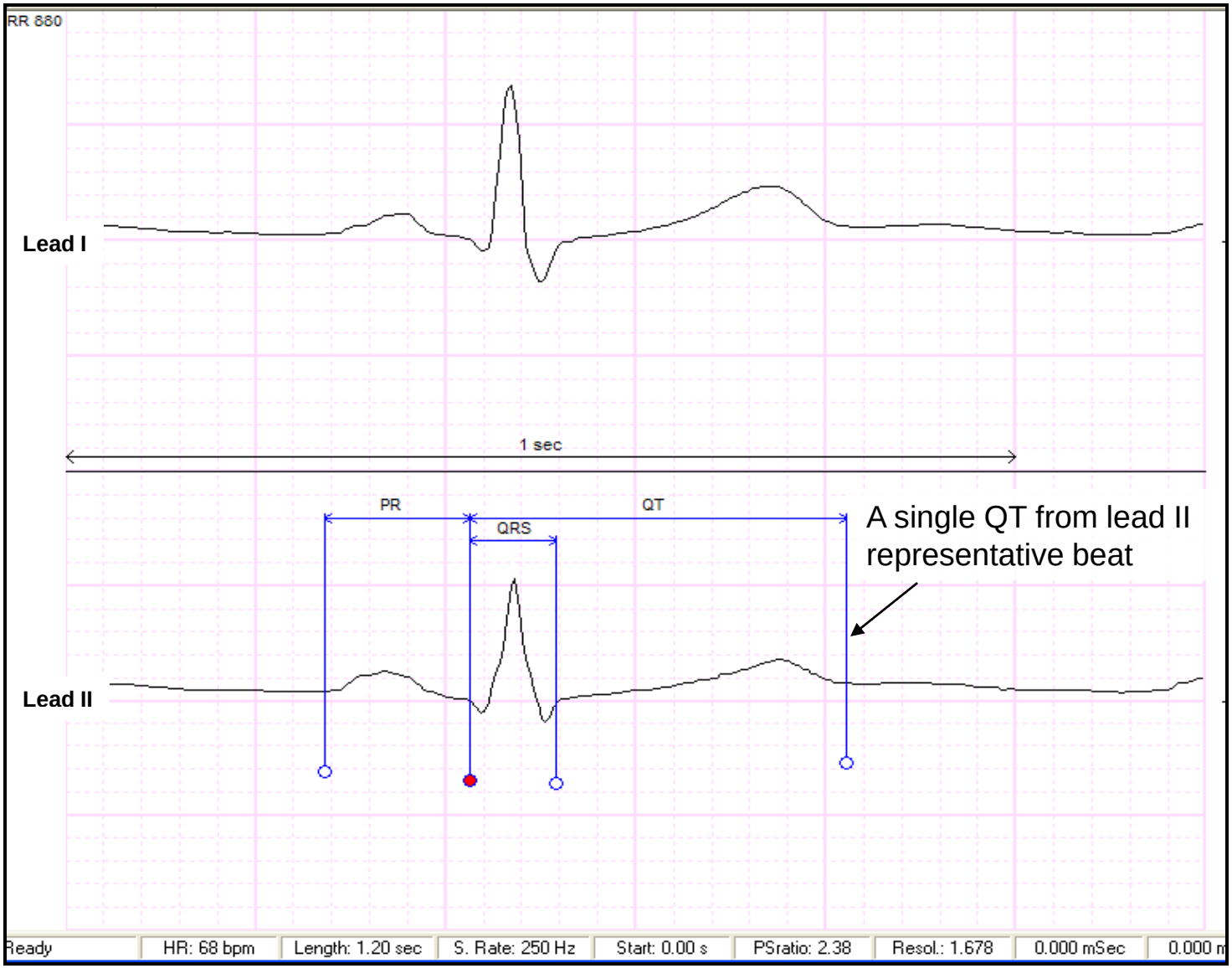
Single-Lead on Rhythm Data



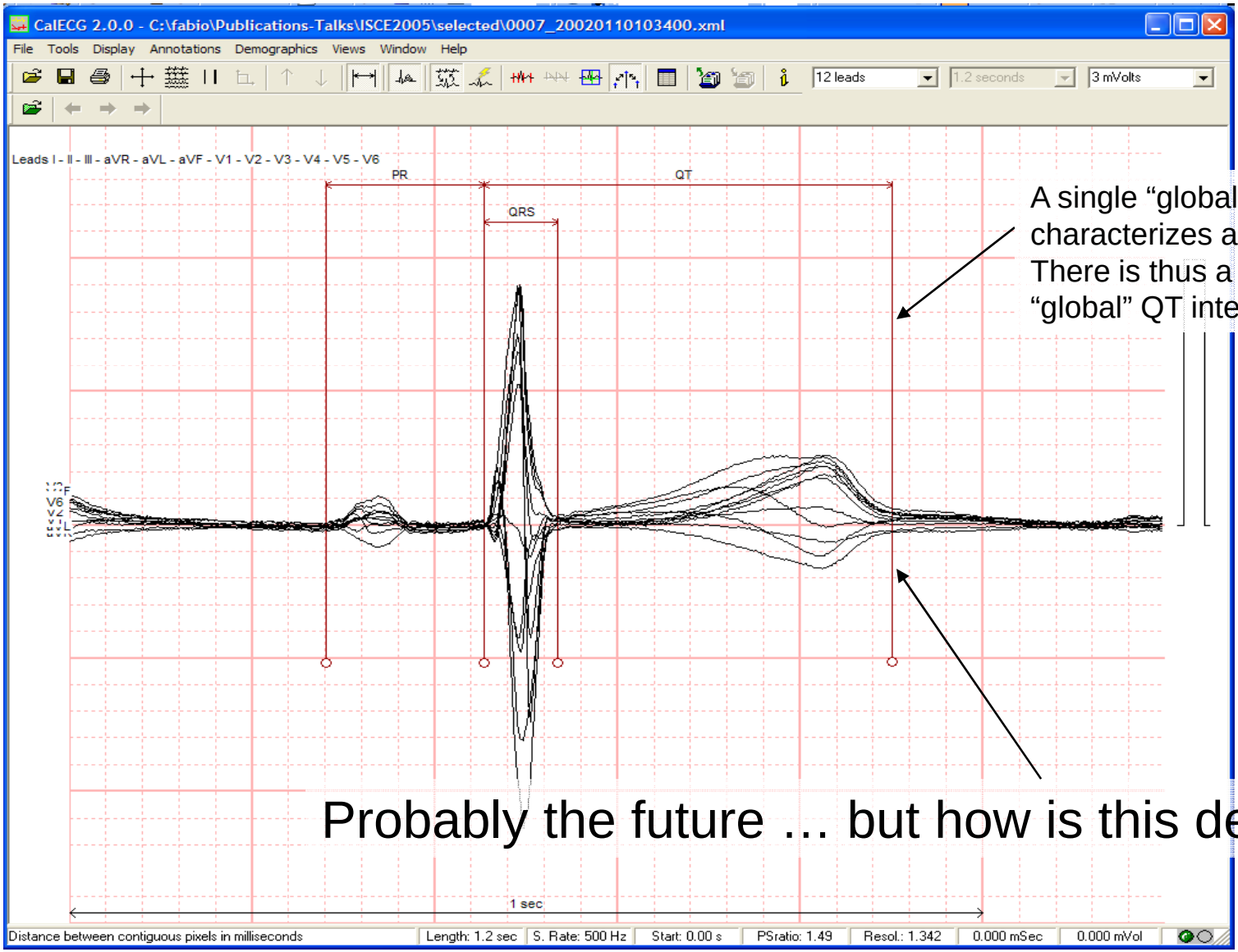
Global on Rhythm Data



Single Lead on Representative Beats



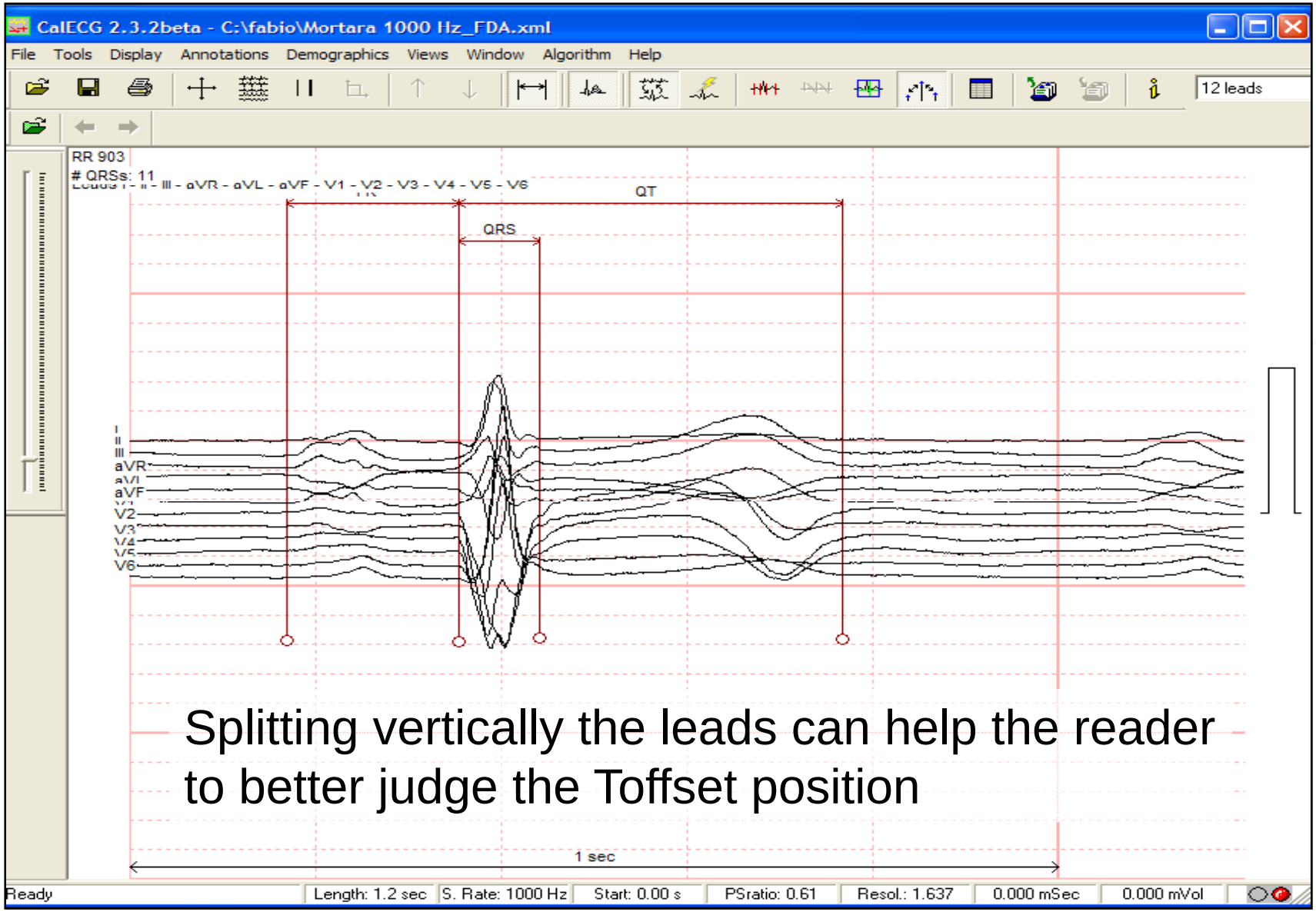
Global on Representative Beats



A single “global” Toffset characterizes all the leads… There is thus a single “global” QT interval

Probably the future … but how is this defined?

Global on Representative Beats



Global on Representative Beats

- One key question remains:

  How should the global Toffset be defined?

  – Should it be the longest of the 12 (latest offset)?
  – Should it be the shortest of the 12 (earliest offset)?
  – Should it be the mean or median of the 12?
  – Should it be a single Toffset measured on a synthetized waveform from the 12 individual representative beats (e.g. the vector magnitude)?

As of today this question doesn't have an answer…
There is maybe a tendency toward the last option
but that is far from being a guideline

Comparing Different Methods
Test Case 1 (6)

- Semi-automated analysis by CalECG2 (AMPS-LLC).
- QT using four measurement approaches by a single reader on 4 separate occasions separated by at least 3 weeks.
- Blinded measurements in randomized order
- 26 normal subjects, 4 ECGs per subject
  - Predose, 1h, 2h and 3h after dosing with sotalol 160 mg PO

Badilini et al. J Electrocardiol 2006; 39:S152-156.

Comparing Different Methods

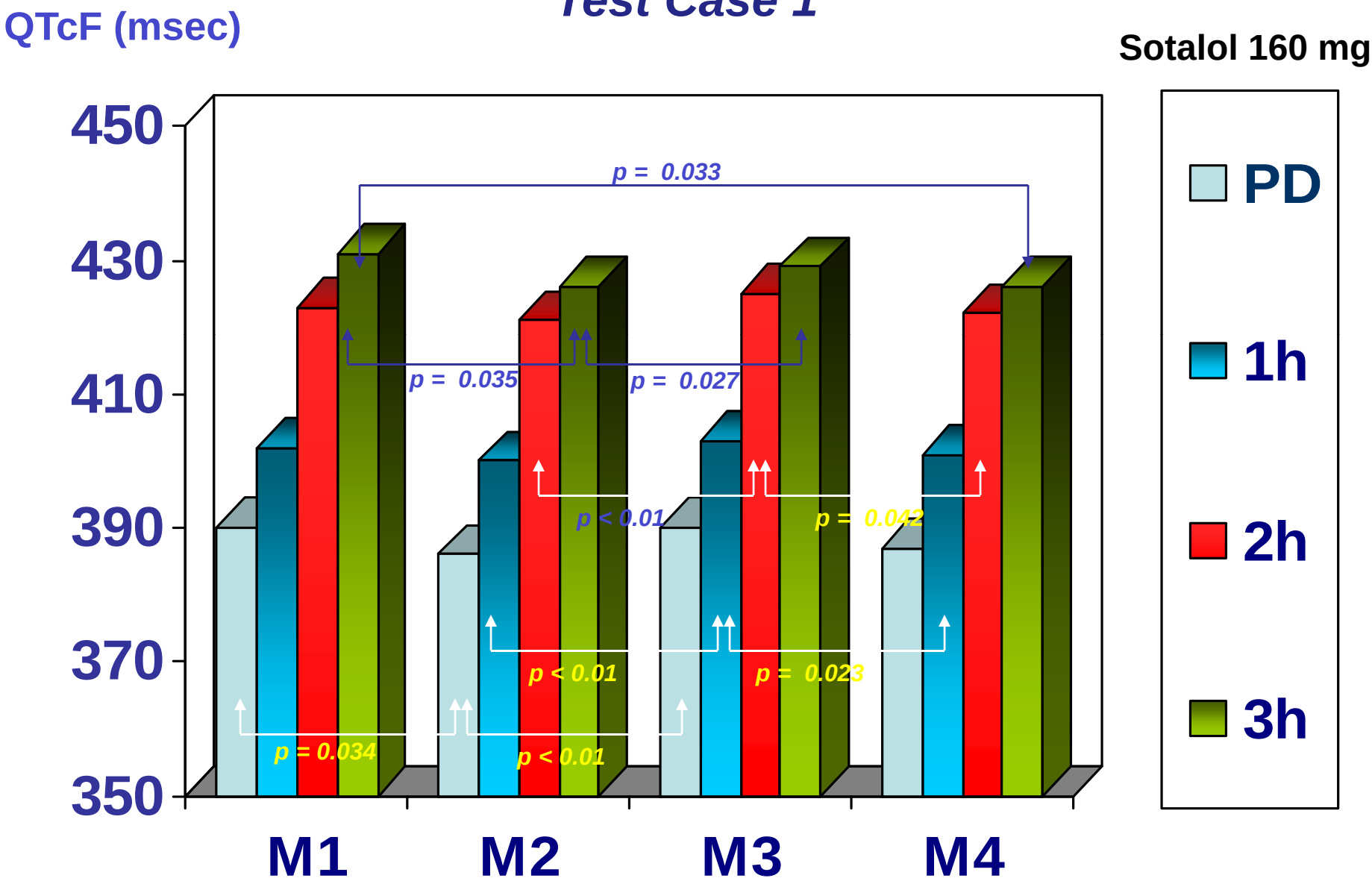
Test Case 1

- 3 QT/RR from rhythm lead II (M1)
- Global QT/RR from representative beats (M2)
- 1 QT/RR from lead II representative beat (M3)
- Global QT/RR from rhythm lead (M4)
  - Global QT was the median of 12 individual QT intervals

Badilini et al. (6)

Comparing Different Methods

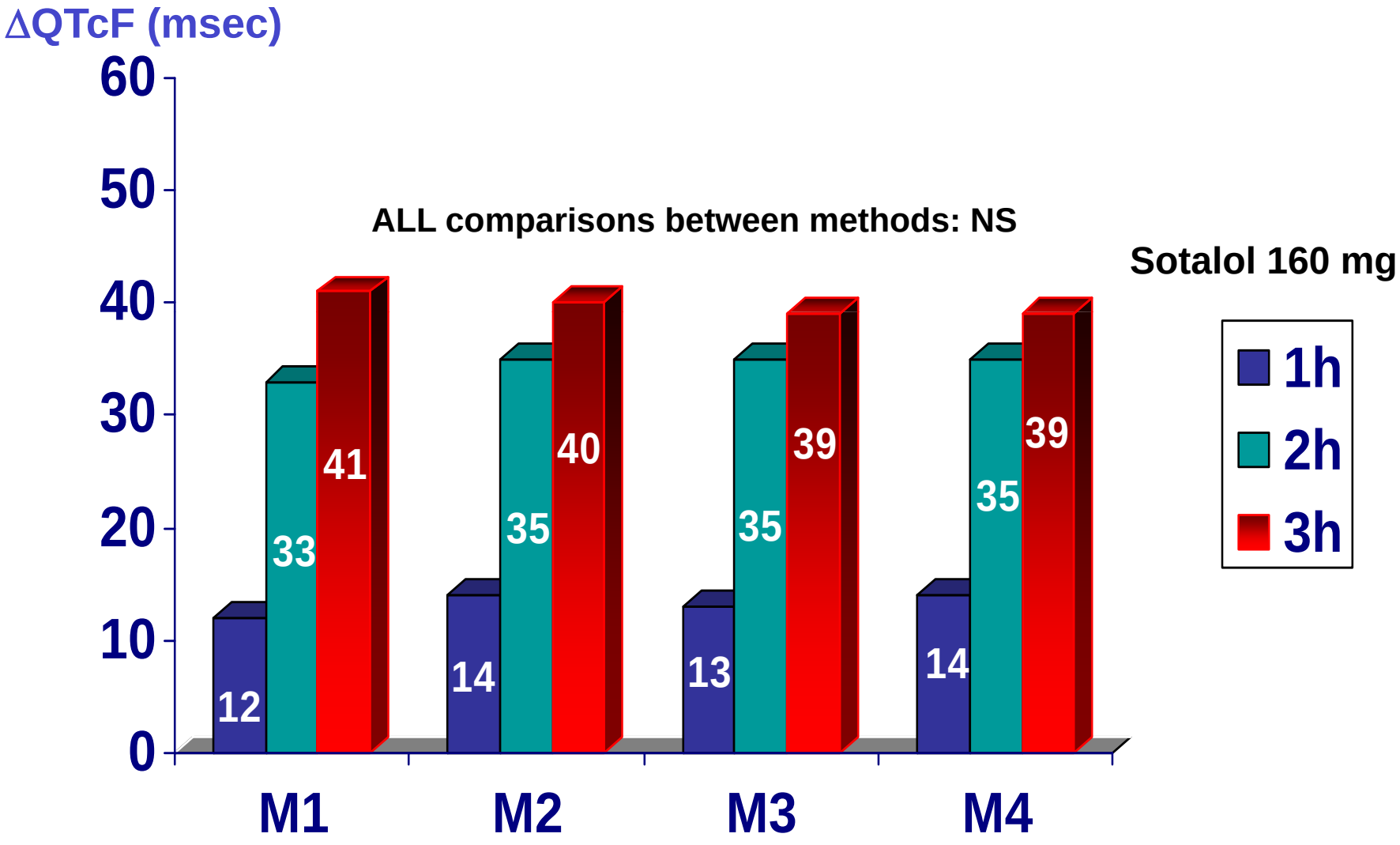
Test Case 1



Badilini et al. (6)

Comparing Different Methods

Test Case 1



Badilini et al. (6)

Comparing Different Methods
Test Case 1 Conclusions

- Different methods can bring different results.
- However, all methods equally detect the prolongation effect of sotalol.

Comparing Different Methods

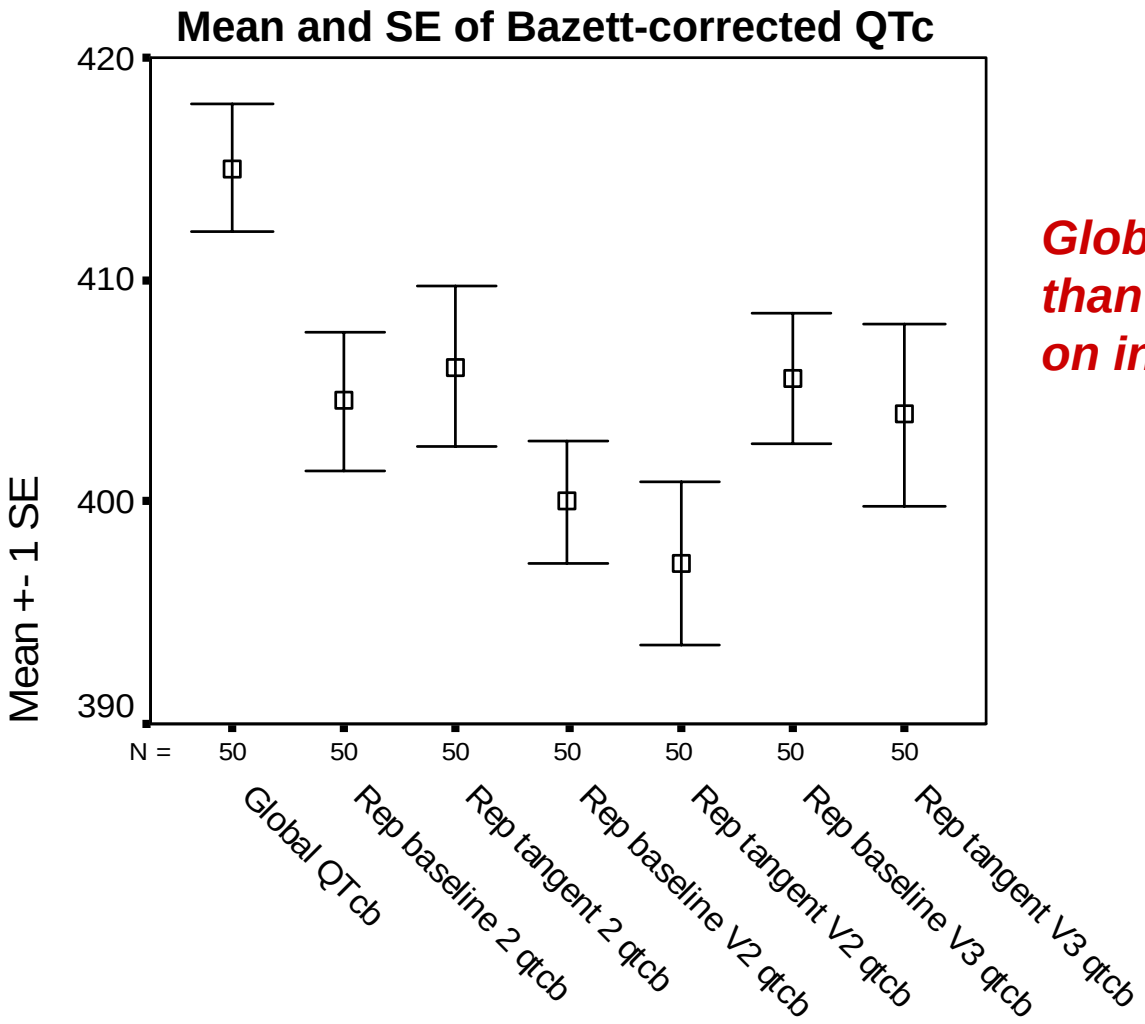
Test Case 2 (7)

- Semi-automated analysis by Cardionics, Belgium.
- All measurements based on representative beats.
- Global QTc compared with Lead II, V2 and V3 QTc (using tangent and baseline methods)
- 50 subjects, with and without disease
- Global QT is from earliest onset to latest offset.

Kligfield et al. A.N.E. 2007; 12(2):145-152 .

Comparing Different Methods

Test Case 2



Global QTc systematically larger than any other QTc computed on individual beats

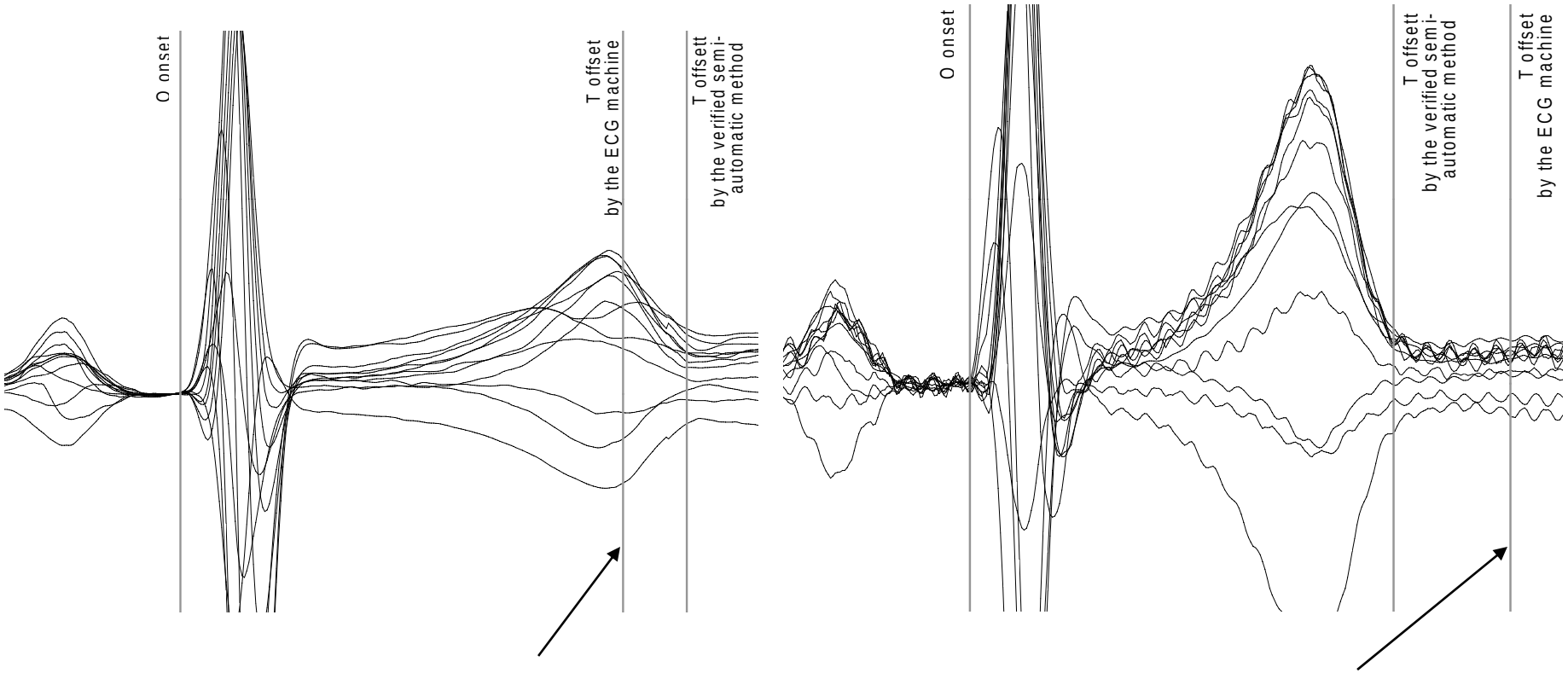
Kligfield et al. (7)

On-Screen Methods:

How to Measure?

- Manual
- Fully automated
- Semi-automated

Semi-automated IDM
The best of both worlds?



By courtesy of Dr. M. Malik (8)

On-screen Methods: How to measure?

Points to consider with manual and semi-automated methods where the reader is likely to edit (move around) electronic calipers

- Screen size
  - Is it the same to use a 14” or a 21” screen?
- Screen resolution
  - Is it the same to use 800x600, 1024x768 or 1400x1050 resolution?
- Display organization
  - Which aspect-ratio (voltage vs. time) should be used?
- Pixels and samples
  - Should the “amount” of ECG displayed depend on the available screen pixels (which only depend on the screen resolution) in relation to the digital samples to be displayed (which only depend on the sampling rate of the ECG)?
- In-between samples option
  - Should the reader be allowed to place electronic calipers between digital samples?

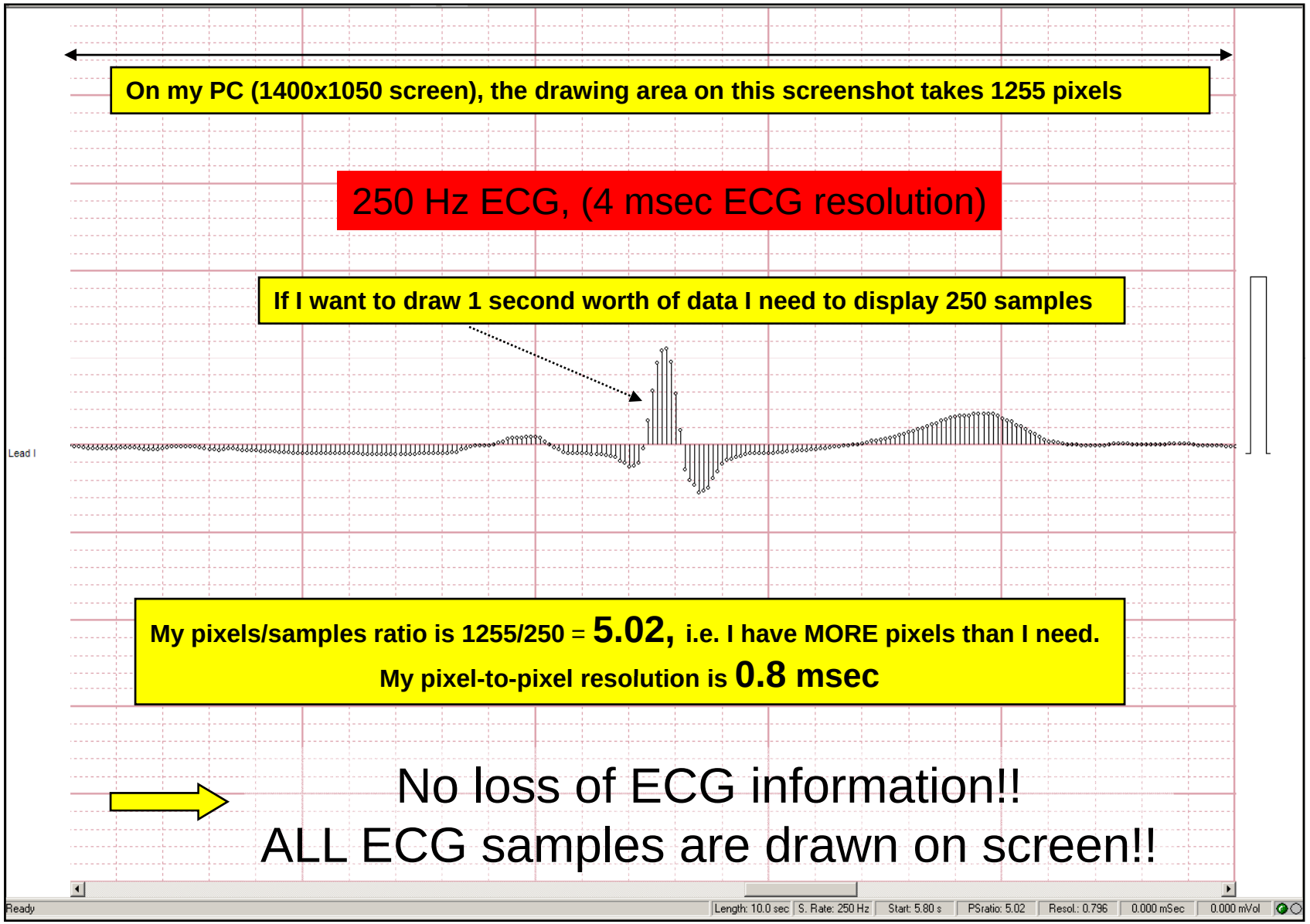
No guidelines on any of the above……..

Controlling Pixels and Samples

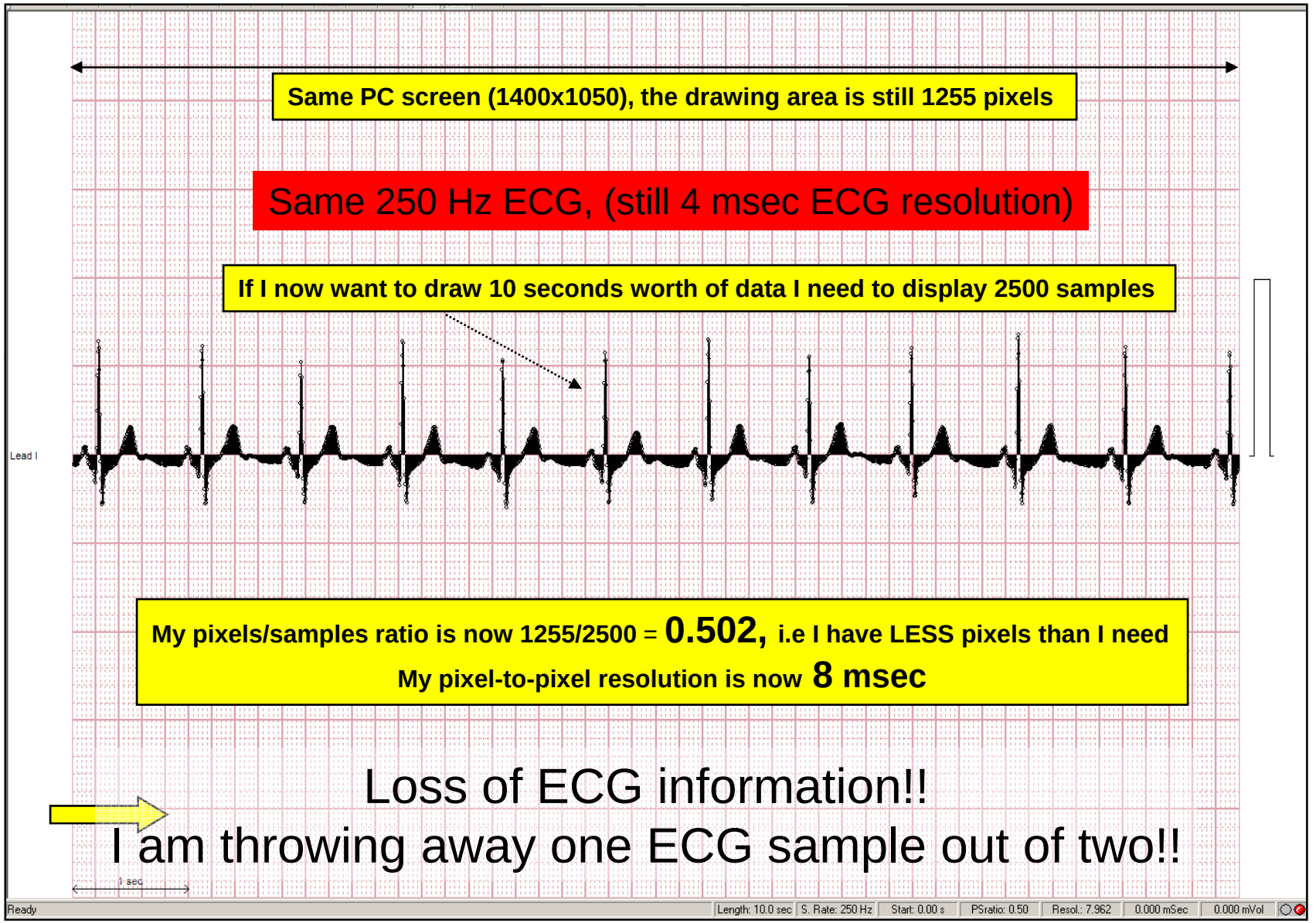
- The concept of ***resolution*** is often unclear with on-screen systems. This is because two different type or resolutions are involved:
  - The **ECG resolution** is an intrinsic feature of a digital ECG (*nothing to do with a computer screen*) and is solely determined by the sampling rate of the ECG (e.g. 500 Hz means that digital **samples** are 2 msec apart).
  - The **Screen resolution** is a feature intrinsic of a computer screen (*nothing to do with an ECG*) and tell us how many screen **pixels** are available (e.g. with a 1024x768 resolution I have 1024 horizontal and 768 vertical pixels).
- When a digital ECG is displayed on a computer screen the two concepts are merged together and we need to clarify how pixels and samples are related to each other.

- *A couple of examples to clarify…..* 

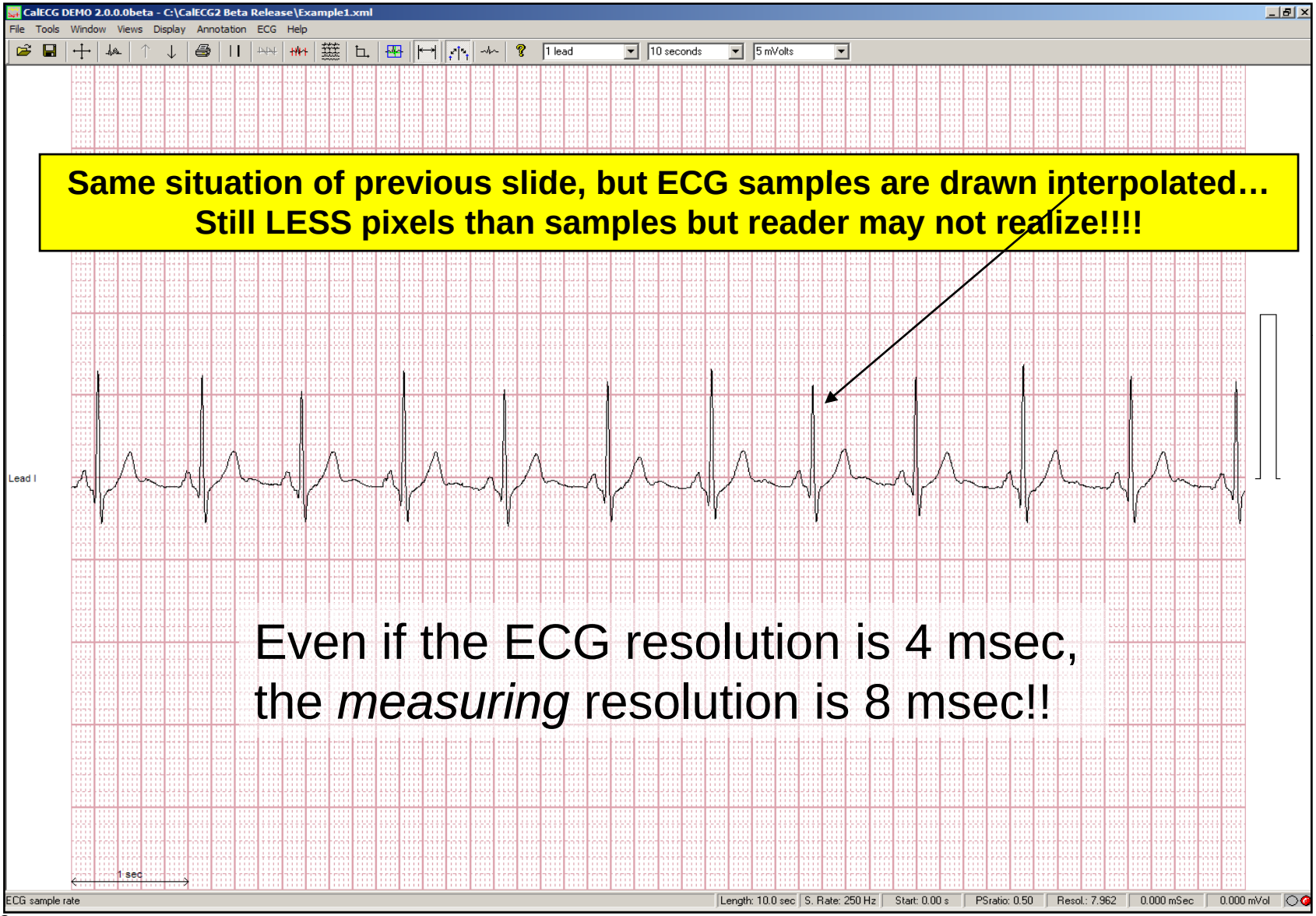
Controlling Pixels and Samples



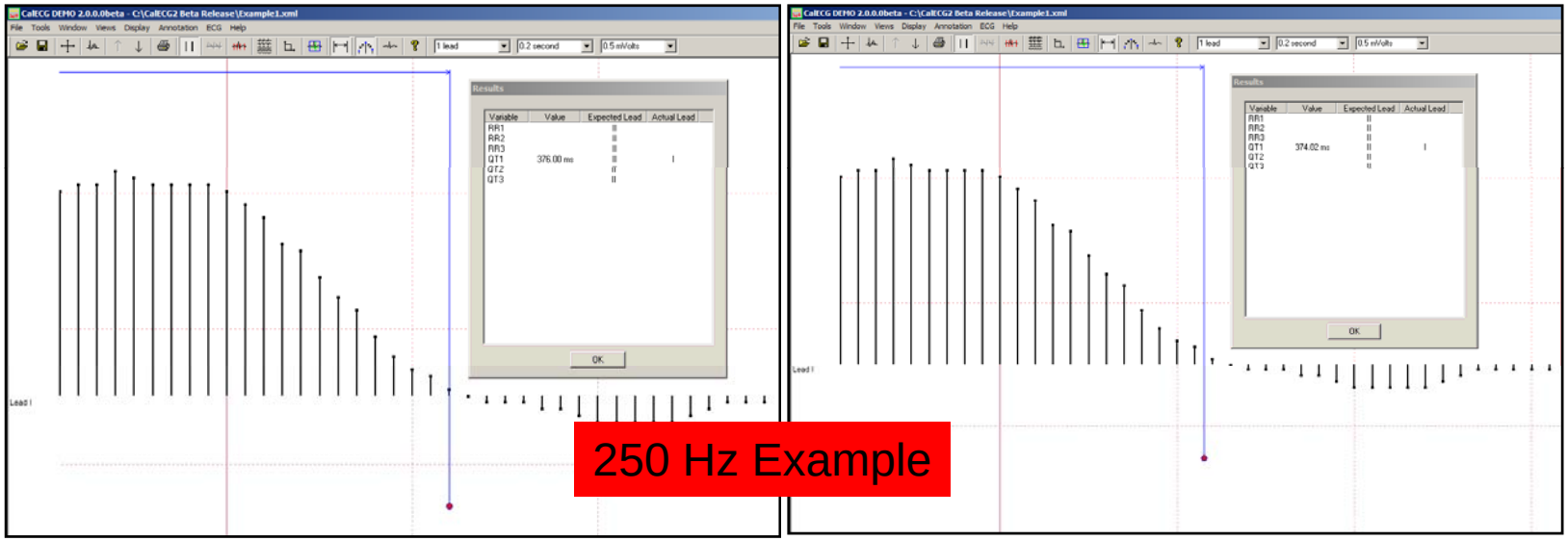
Controlling Pixels and Samples



Controlling Pixels and Samples



Should Measurements Between Samples be Allowed?



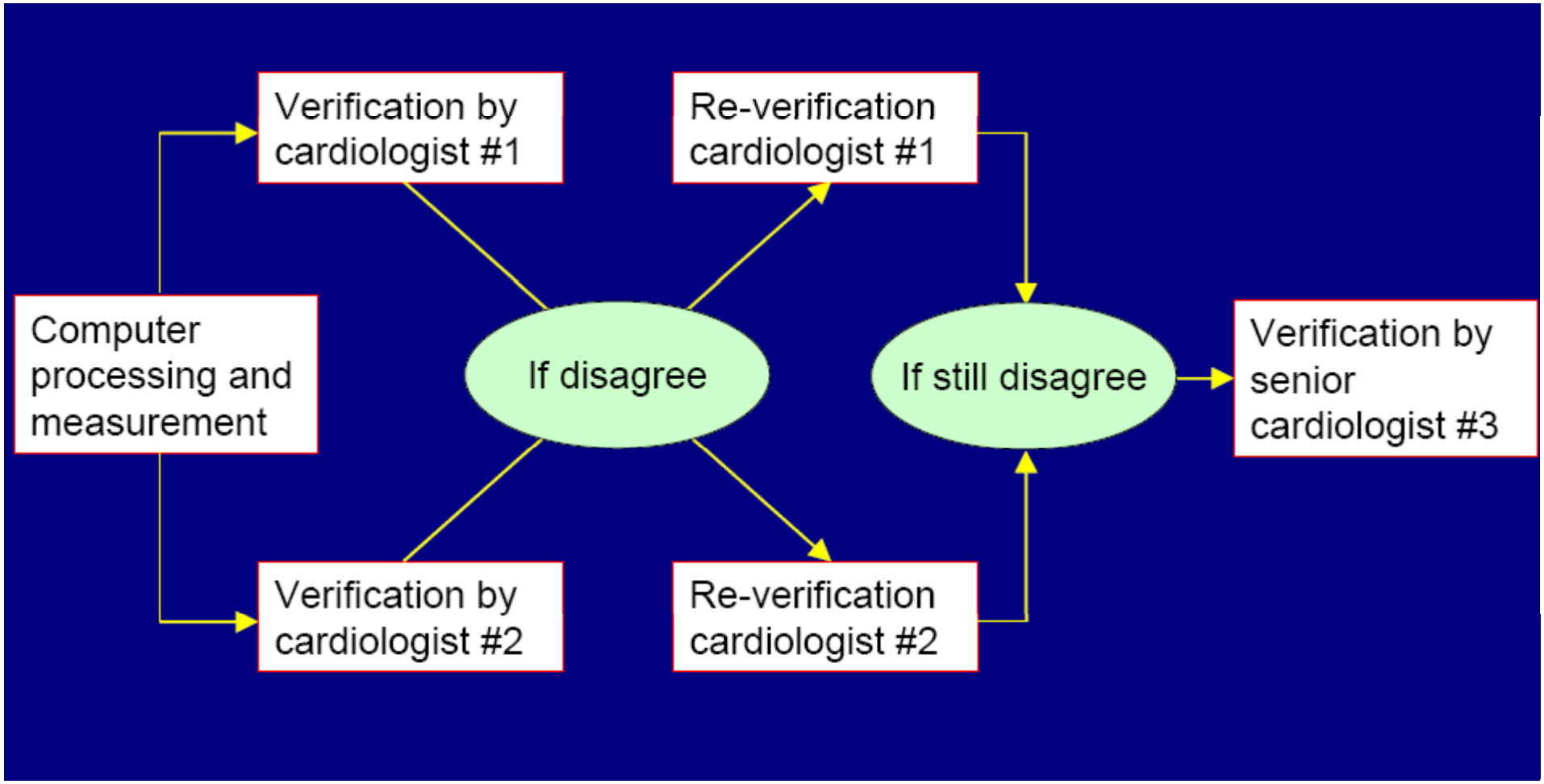
QT = 376 (multiple of 4 msec)

QT = 374 (NON multiple of 4 msec)

Is it a crime to claim 2 msec resolution?

On-Screen Methods:

How Many Readers?



Workflow from the most sophisticated system known by the author…

Conclusions

- New Regulatory guidelines have recently induced the spread of on-screen measurement methods on digital ECGs.
- However, detailed guidance on how these on-screen systems should be implemented are not yet available.
- On-screen Systems should be designed to be consistent with respect to many factors that could otherwise bias the outcome of a study:
  - Where to Measure QT (on which waveforms and lead).
  - How to Measure QT (automated, manual, or semi-automatic).
  - Number of readers involved in the process.
- If a human reader is involved, the on-screen system must also be used consistently with respect to computer screen related factors, and in particular the relation between screen pixels and digital samples used whenever electronic calipers are moved around.

References

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). E14 Guidance on clinical evaluation of QT/QTc interval prolongation and proarrhythic potential for non-antiarrythmic drugs. 2005
   Available from URL: http://www.fda.gov/cder/guidance/6922fnl.pdf

2. Stockbridge N, Throckmorton DC. Regulatory advice on evaluation of the proarrhythmic potential of drugs. J Electrocardiol 2004; 37 (Suppl.):40-41.

3. Stockbridge N, Brown, BD. Annotated ECG waveform data at FDA. J Electrocardiol 2004; 37 (Suppl.):83-84.

4. Points to Consider: the assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. Committee for Proprietary Medicinal Products (CPMP), London, 17 December 1997.

5. Murray A, McLaughlin NB, Bourke JP, Doig JC, Furniss SS,Campbell RWP. Errors in manual measurement of QT intervals. Br Heart J 1994;71:386-390

6. Badilini F, Sarapa N. Implications of Methodological Differences in Digital Electrocardiogram Interval Measurement. J Electrocardiol 2006; 39:S152-156.

7. Kligfield P, Tyl B, Maarek M, Maison-Blanche P. Magnitude, Mechanism, and Reproducibility of QT Interval Differences Between Superimposed Global and Individual Lead ECG Complexes. A.N.E. 2007; 12(2):145-152.

8. Malik M. Errors and Misconceptions in ECG Measurements Used for the Detection of Drug Induced QT Interval Prolongation. J Electrocardiol 2004; 37:S25-33.