Holter Technology in Drug Safety
A Technical Point of View

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Holter Technology
How is it used in drug studies?

12 lead Extractions

- Manual extractions
- Automated (optimized) extractions
- The standard in drug studies
- Is this really the way Holter should be used?

Use Continuous data

- Holter bin 1
- BioQT
- New Biomarkers
- Restitution
- …….
- NOT the standard in drug studies…..

(Part of the) problem is lack of guidelines on how "truly" continuous data should be used!

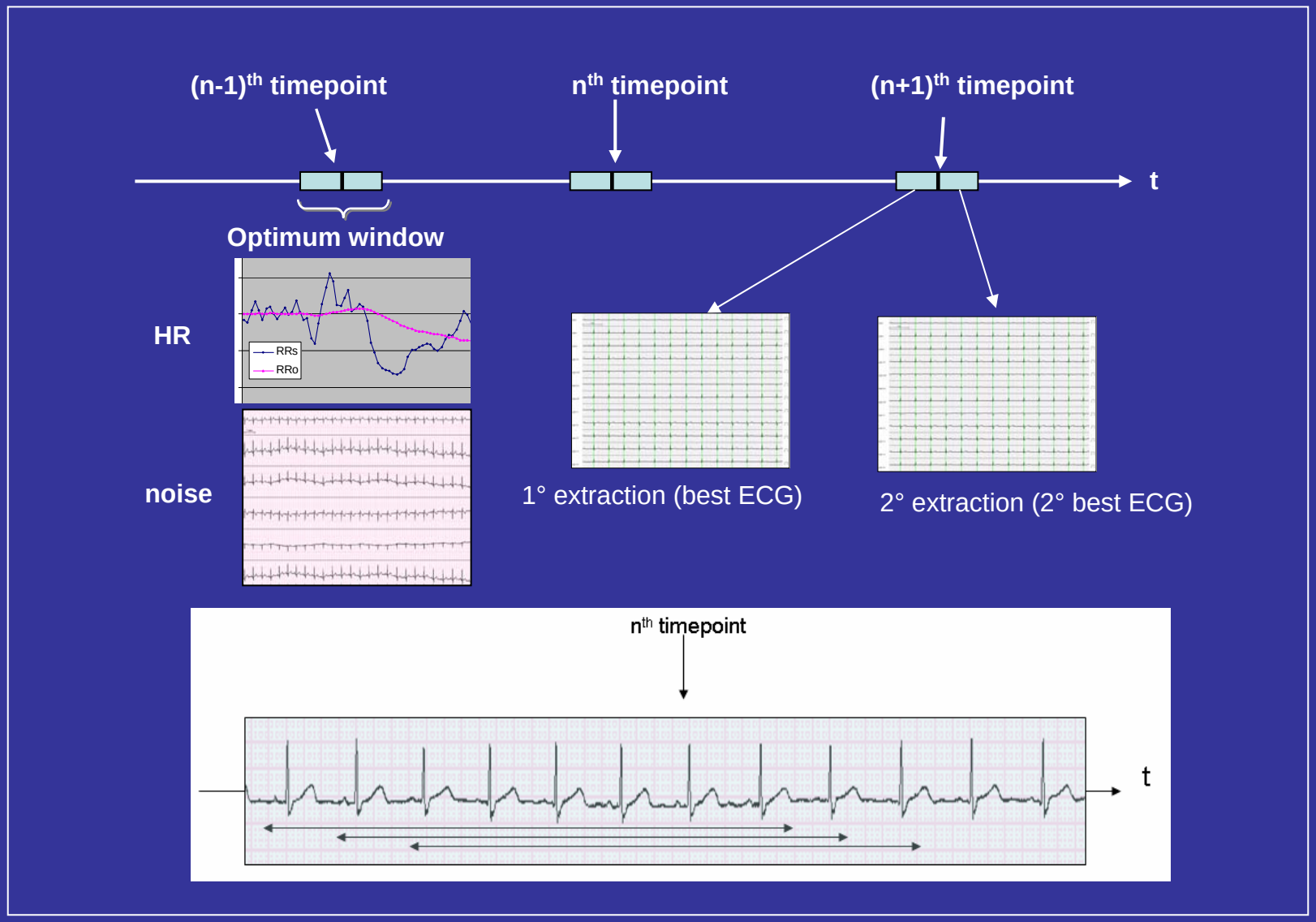
Holter Technology

Will focus on two aspects:

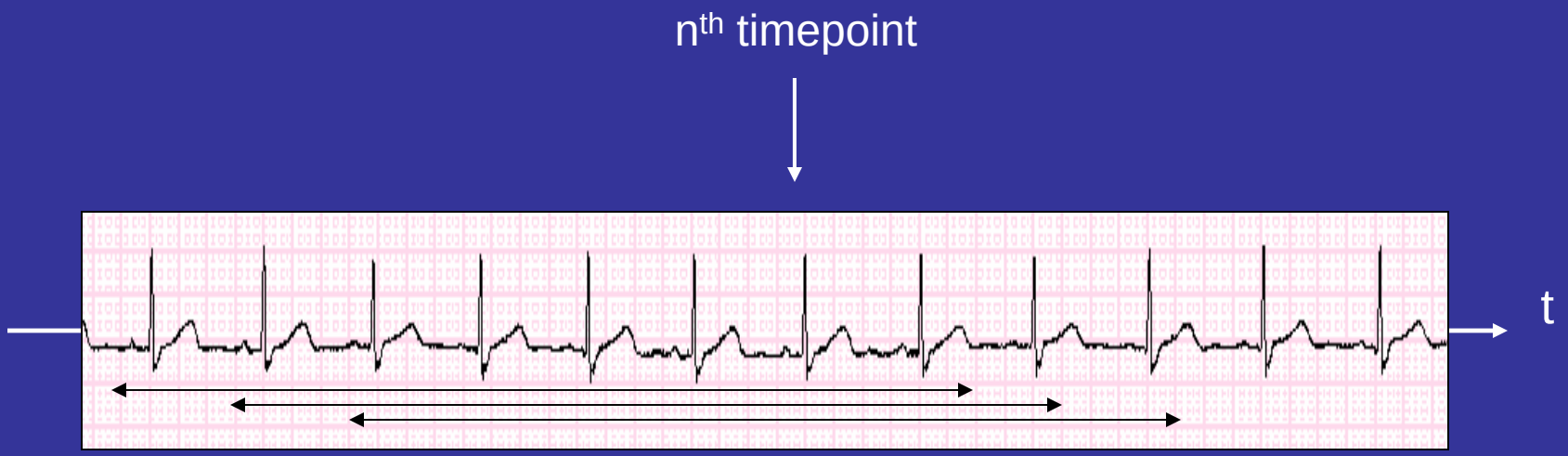
- **Controlling ECG extraction Quality**
- **Controlling Hysteresis (stable Heart Rate)**

Controlling Quality

Controlling Quality



Controlling Quality



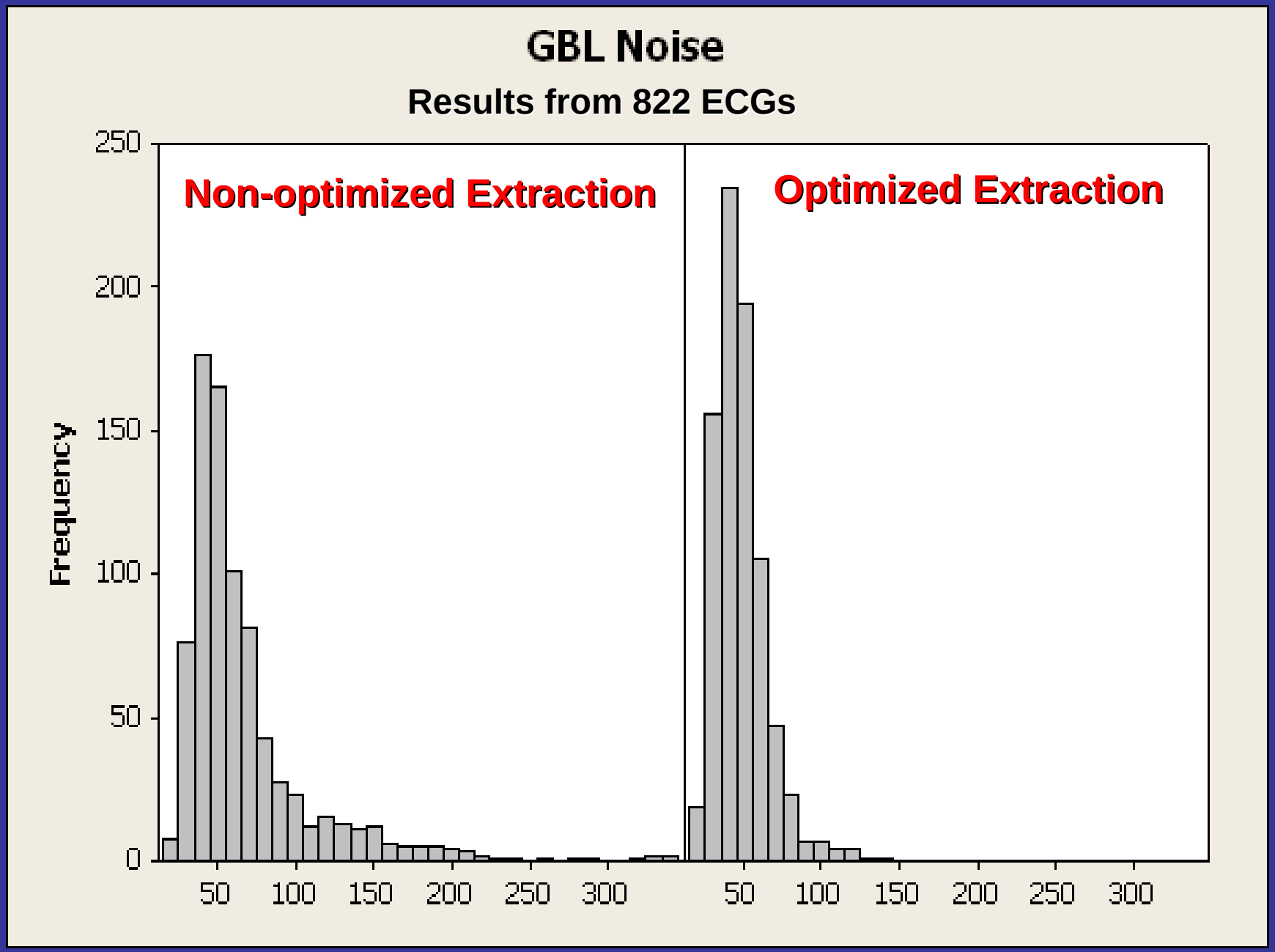
- **Number of potential (“candidate”) extractions depends on heart rate (# of beats available in the optimum window).**
- **If multiple extractions are requested, the selected extractions will NOT overlap (no single beat will be used more than once).**
- **A single abnormal beat can determine the exclusion all the potential extractions including that beat.**

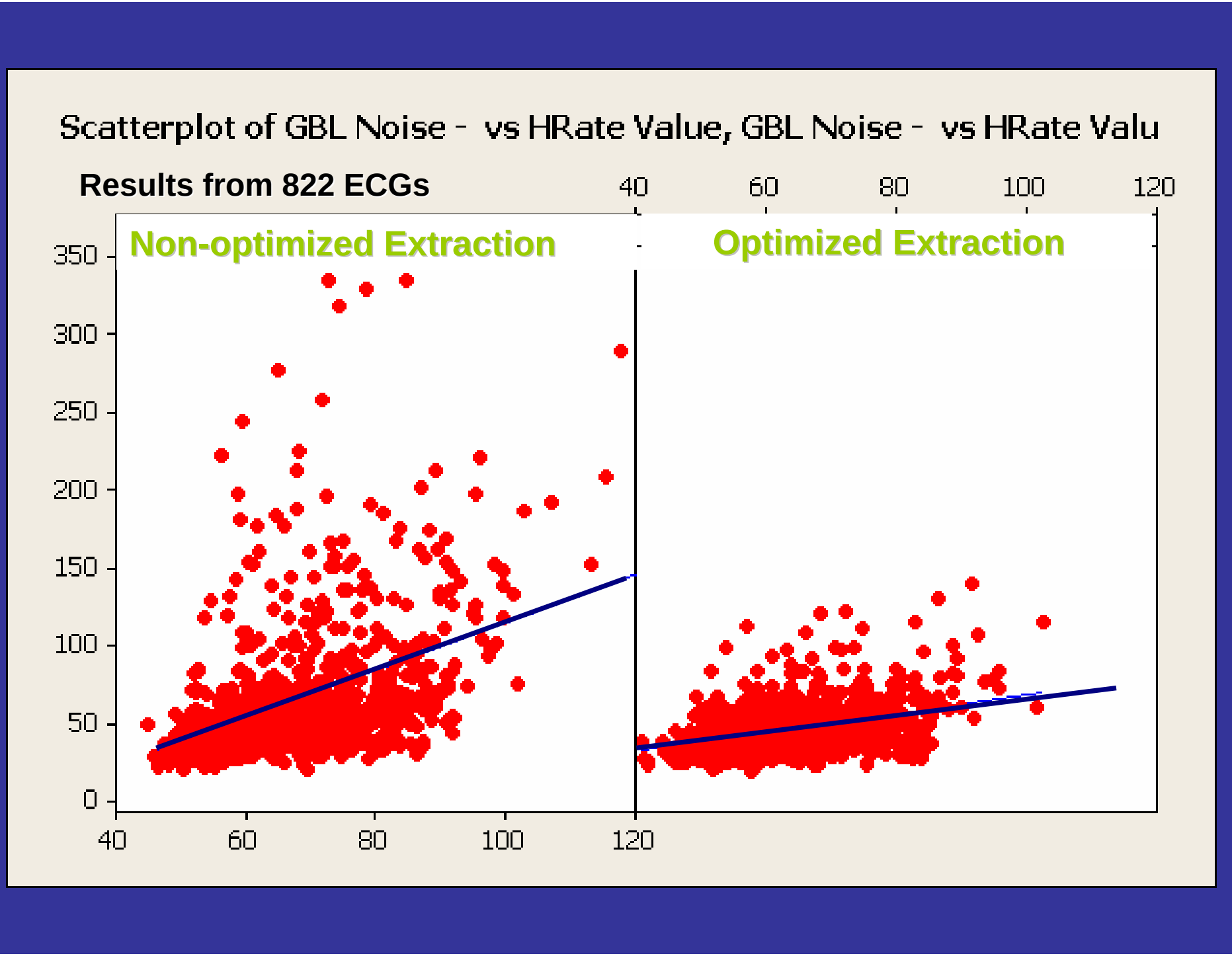
Results of an internal study

from 822 ECGs

Parameter	Fixed extraction	Optimized extraction	Δ (F – O)
Global Noise (µV)	76 ± 75	52 ± 38	24 ± 77*
HF Noise (µV)	0.86 ± 0.31	0.82 ± 0.22	0.03 ± 0.32*
LF Noise (µV)	93 ± 77	67 ± 41	26 ± 80*
HR (bpm)	69 ± 13	64 ± 11	5.1 ± 8.8*
QT (msec)	392 ± 39	394 ± 39	-2 ± 10*
QTcB (msec)	414 ± 32	402 ± 30	12 ± 17*

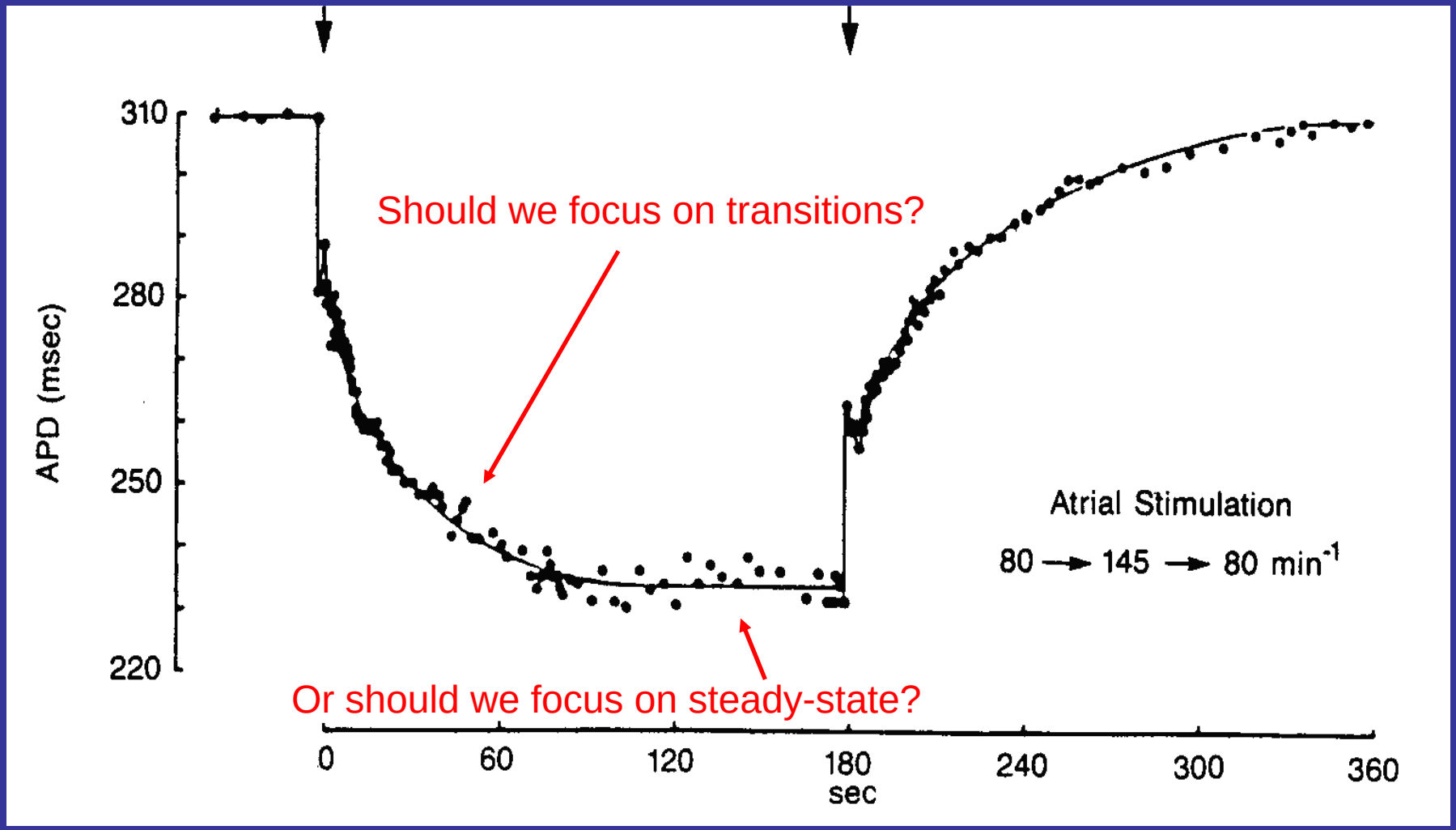
**: $p < 0.05$ with Student's paired t-test*


GBL Noise
Results from 822 ECGs
Non-optimized Extraction
Optimized Extraction
Frequency
250
200
150
100
50
0
50
100
150
200
250
300
50
100
150
200
250
300


Scatterplot of GBL Noise - vs HRate Value, GBL Noise - vs HRate Valu
Results from 822 ECGs
Non-optimized Extraction
Optimized Extraction
350
300
250
200
150
100
50
0
40
60
80
100
120

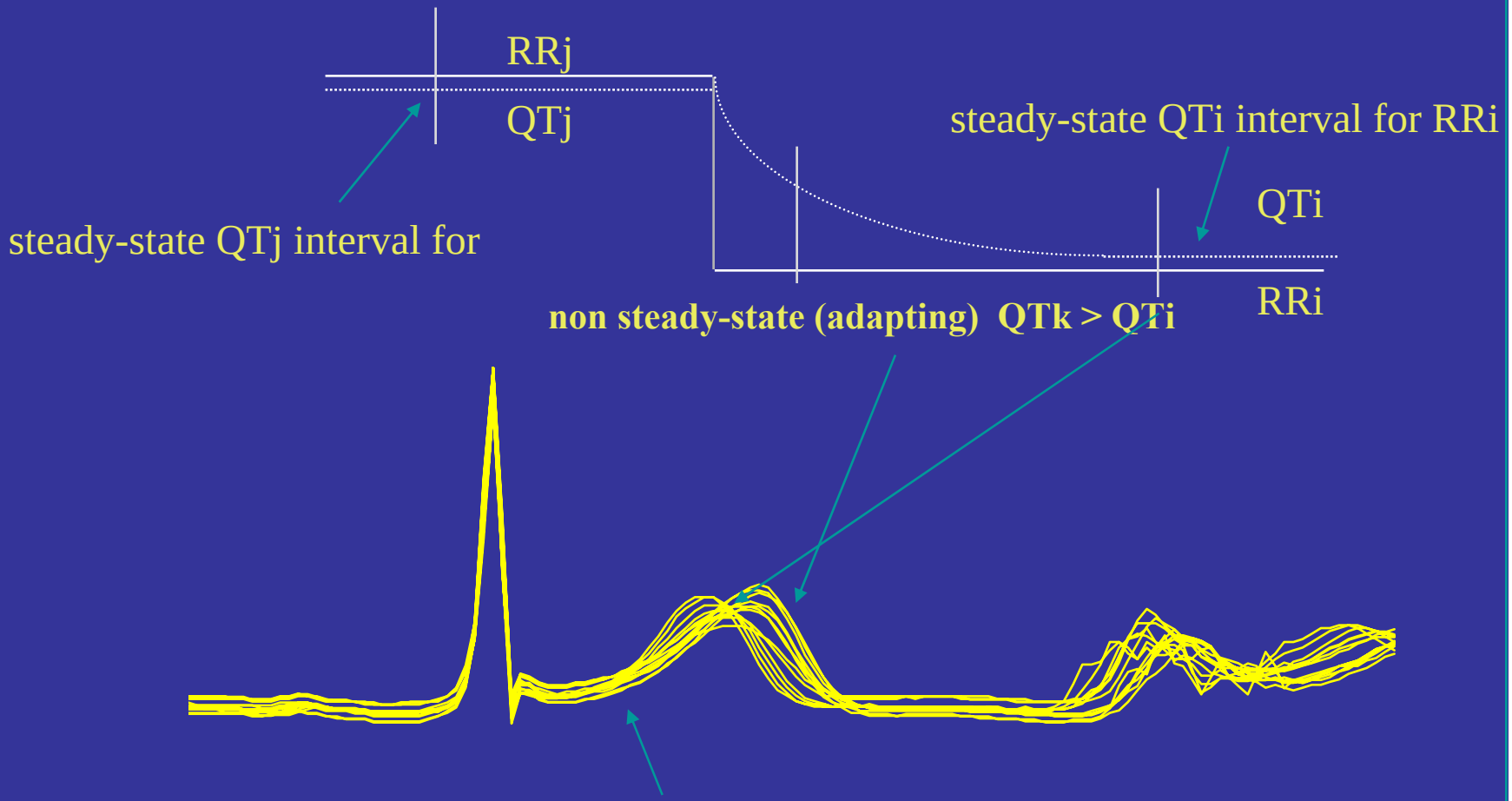
Controlling Hysteresis

Hysteresis


Should we focus on transitions?
Or should we focus on steady-state?
APD (msec)
310
280
250
220
0
60
120
180
240
300
360
sec
Atrial Stimulation
80 → 145 → 80 min-1

Hysteresis during Holter

Does it really exist?



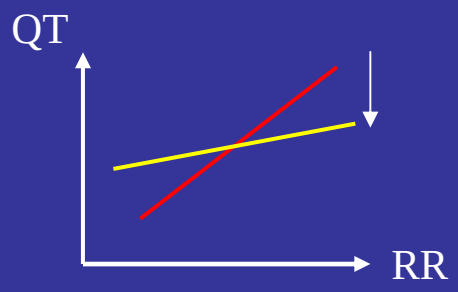
real QRS complexes with same RR intervals taken from the same subject in a 3 hour time frame

Ignoring Hysteresis:
what to expect...

Effect on QT interval:

$RR < \overline{RR}$	$RR > \overline{RR}$
QT ↑	QT ↓

Effect on QT/RR slope:



Effect of (ignoring) hysteresis on QT interval

Model	$QT_{RRm}(n)$	$QT_{RRm+50}(n)$	$QT_{RRm-50}(n)$
RR-1 only	345 (1406)	358 (318)	345 (213)
10 seconds	345 (1048)	360 (152)	345 (124)
20 seconds	345 (988)	360 (122)	343 (87)
30 seconds	345 (982)	362 (105)	343 (84)
60 seconds	345 (967)	362 (79)	340 (49)

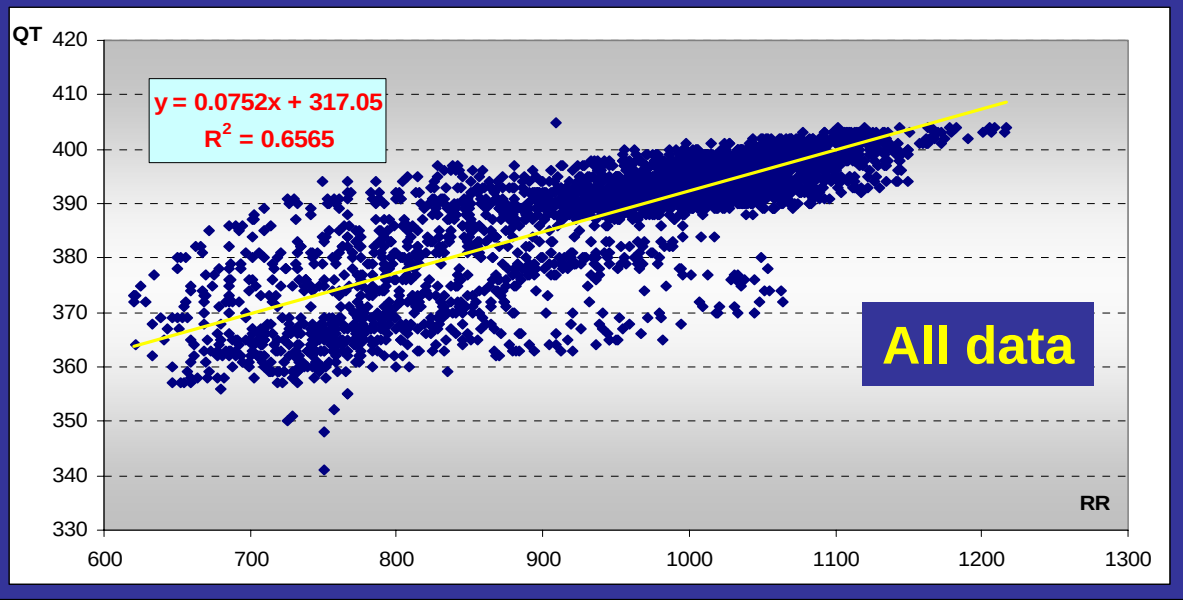
Data from a normal subject 16:00-18:00, RRm = 1000

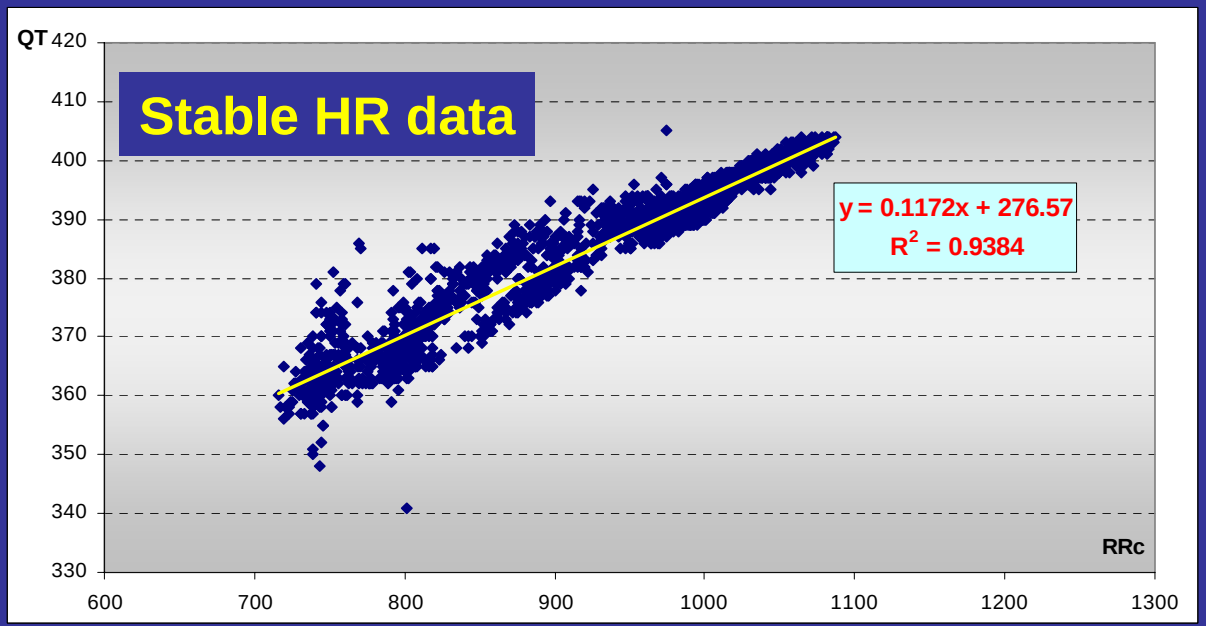
Example on sotalol

Tmax	All data		Stable HR data only	
	160	320	160	320
Mean ΔQT	40 ± 13	59 ± 12	30 ± 12	49 ± 14
Max ΔQT	54 ± 13	75 ± 11	44 ± 13	62 ± 11
ΔQT1000	44 ± 11	65 ± 12	32 ± 12	54 ± 11
Mean ΔQTci	45 ± 14	64 ± 13	37 ± 16	57 ± 14
Max ΔQTci	56 ± 14	76 ± 12	49 ± 16	69 ± 14

All tests p<0.005 with respect to baseline

Effect of hysteresis on QT/RR trends





Conclusions

- Holter is a powerful platform already extensively used in drug development, although its use is limited to a logistic support for 12 lead ECG extractions.
- The development of an Holter warehouse could be the best mean to favor a more extended usage of Holter technology, particularly with respect to the assessment and acceptance of new methods and biomarkers.