



Prospective evaluation of advanced ECG/Holter markers to differentially assess the QT interval with drugs that affect autonomic state vs. impaired repolarization

**Bringing Clarity to
Cardiac Safety**

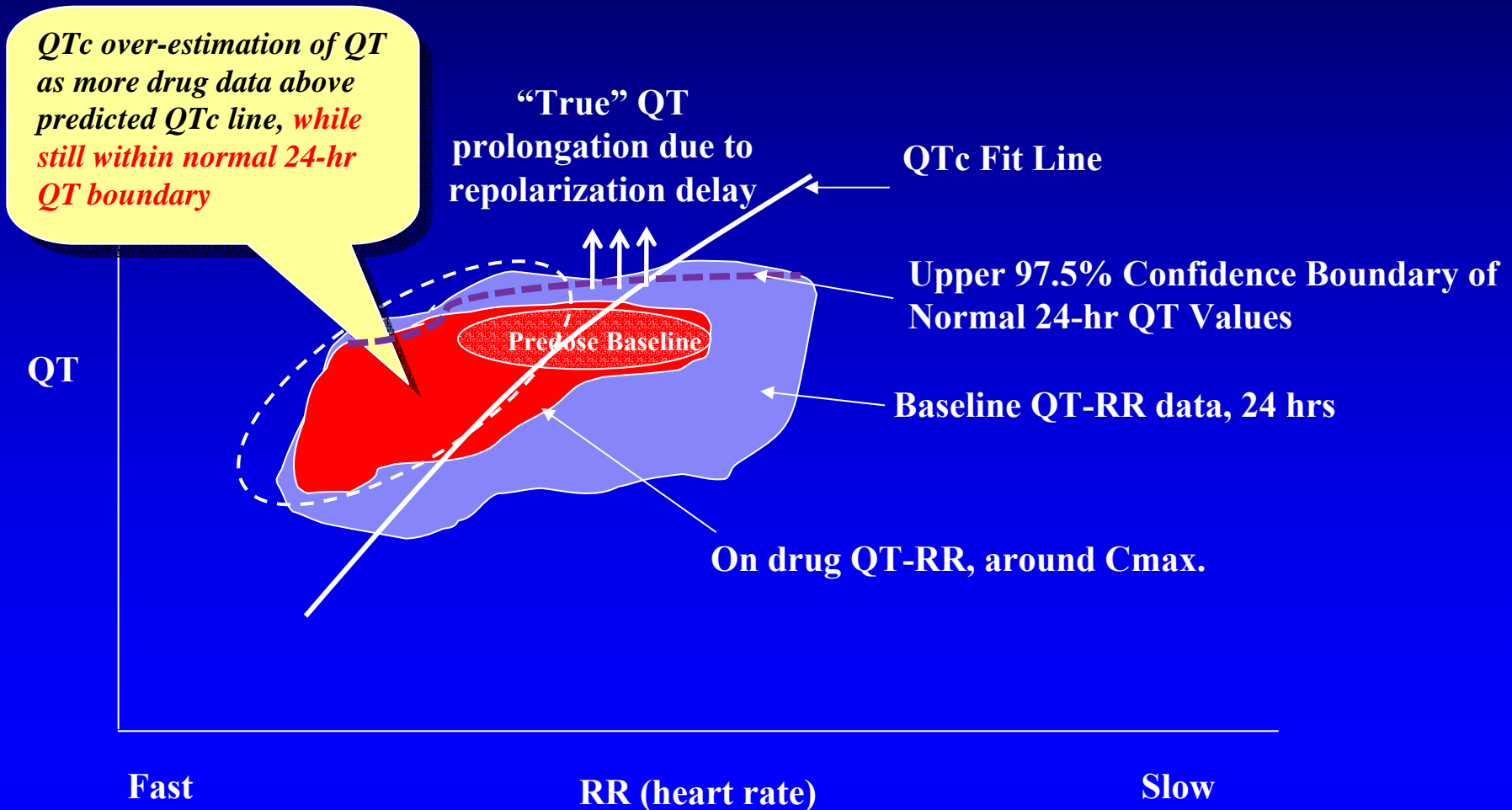
Anthony Fossa, PhD

anthony.fossa@icardiac.com

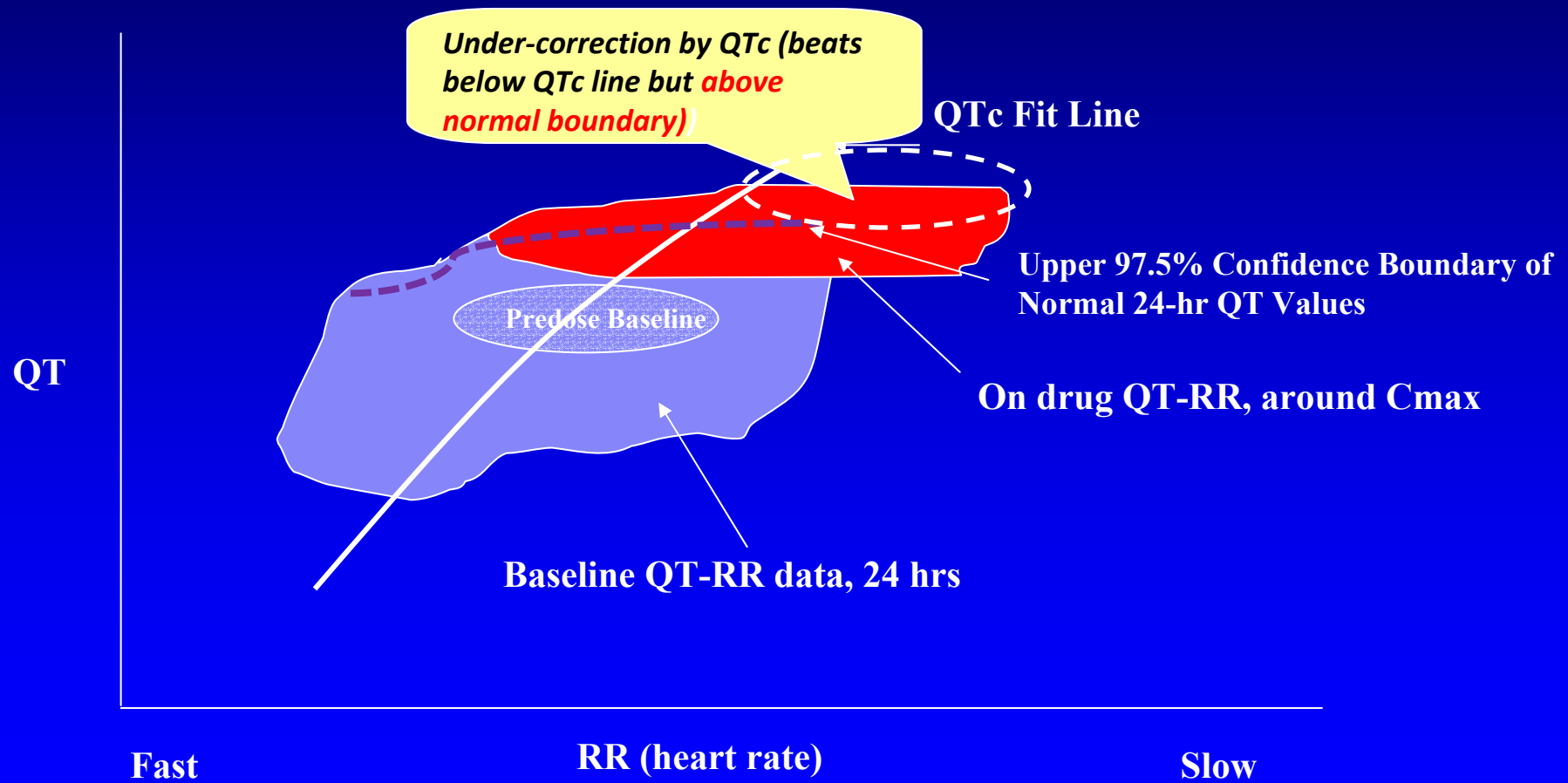
Why a prospective study?

- Compare new continuous ECG measures vs. QTc
- Demonstrate differentiation of autonomic state vs. impaired repolarization
- Assess ability to quantify arrhythmia vulnerability against known outcomes

QTc may be overestimated when heart rate is increased



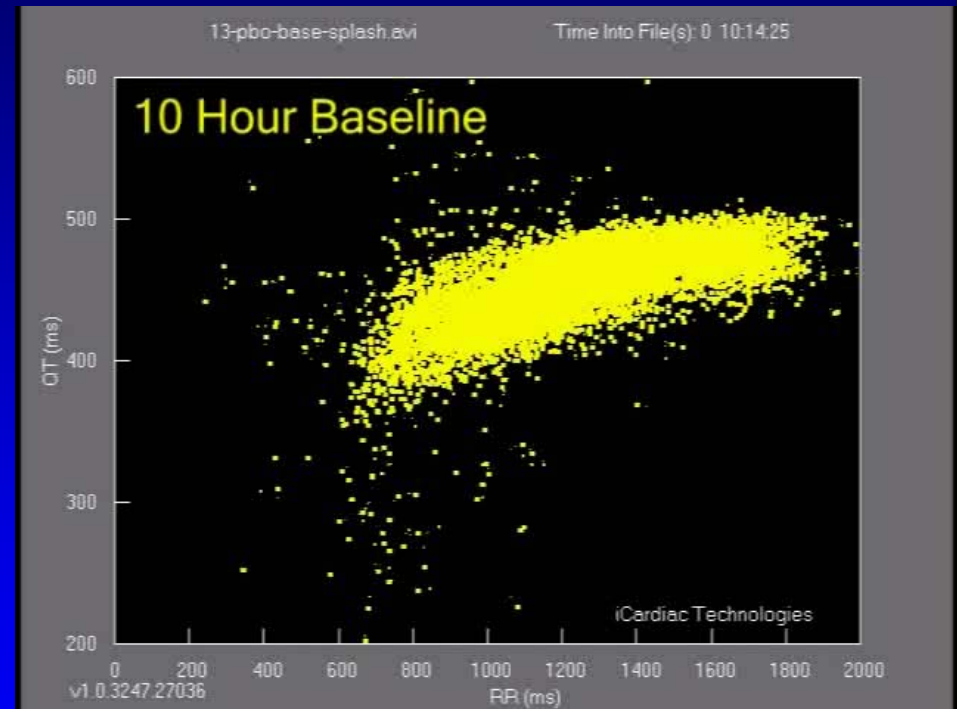
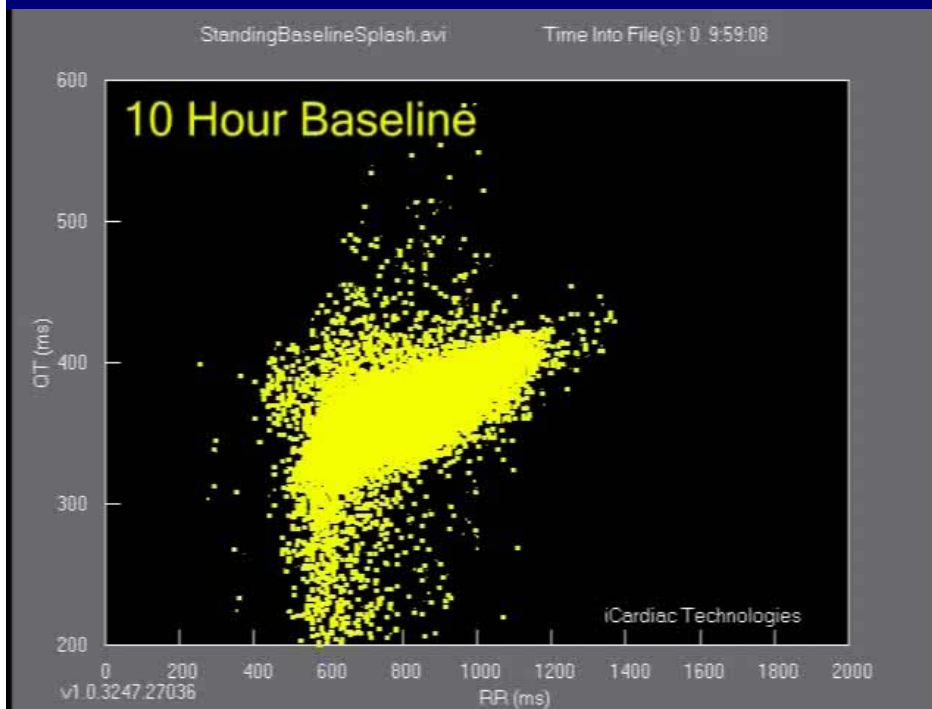
QTc may be underestimated when heart rate is decreased



QT-RR Dynamics: Delayed Repolarization vs. Normal Autonomic Change

Rapid standing from supine baseline

Moxifloxacin (400 mg) at 2.5h Cmax



$\Delta QTcF = 8$ msec
 $\Delta QTbtb = -3$ msec

$\Delta QTcF = 11$ msec
 $\Delta QTbtb = 23$ msec

QTcF cannot differentiate between normal reflex tachycardia and delayed repolarization

Impact of a False-Positive QT

- Estimated 10 -20% of drug candidates/year terminated prior to Phase III due to a false-positive QT (includes preclinical to Phase II)
 - Autonomic mediated (i.e. PDE5 inhibitors, vasodilators, anticholinergics)
 - Non-arrhythmogenic QT prolongation (ranolazine, ziprasidone, chloroquine, tamoxifen)
- Probability of reaching market after Phase II ~30%



- **Result: ~ 3 potential new drugs/year lost at current rate of new drug approvals!**
- **Essentially adds at least 100 million/NDA cost**

How we can move forward

- Prospective study of autonomic agents with QTc prolongation vs. known arrhythmogens
- Collaborate on design, support and execution
- Compare new methodologies against each other and QTc
- Data stored in THEW and available to regulators, academics, PhRMA for future testing

Drug to be considered for prospective study

Arrhythmia Outcome	YES	False Negative Alpha-agonists? Bradycardic agents	Known Arrhythmogens Dofetilide Sotalol (d vs. dl) Moxifloxacin Thioridazine									
	NO	Placebo controls	False Positives <table border="1"><thead><tr><th><u>hERG (-)</u></th><th><u>hERG (+)</u></th></tr></thead><tbody><tr><td>Nitrates</td><td>Ranolazine</td></tr><tr><td>Sildenafil</td><td>Ziprasidone</td></tr><tr><td>Hydralazine</td><td>Chloroquine</td></tr><tr><td></td><td>Risperidone</td></tr></tbody></table>	<u>hERG (-)</u>	<u>hERG (+)</u>	Nitrates	Ranolazine	Sildenafil	Ziprasidone	Hydralazine	Chloroquine	
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	Risperidone											
		NO	YES									
		QTc Clinical Signal										

Best candidates?

Arrhythmia Outcome
YES
NO

False Negative

Known Arrhythmogens

Dofetilide
Moxifloxacin

Placebo controls

False Positives
hERG (-) hERG (+)

Hydralazine Ranolazine

NO

YES

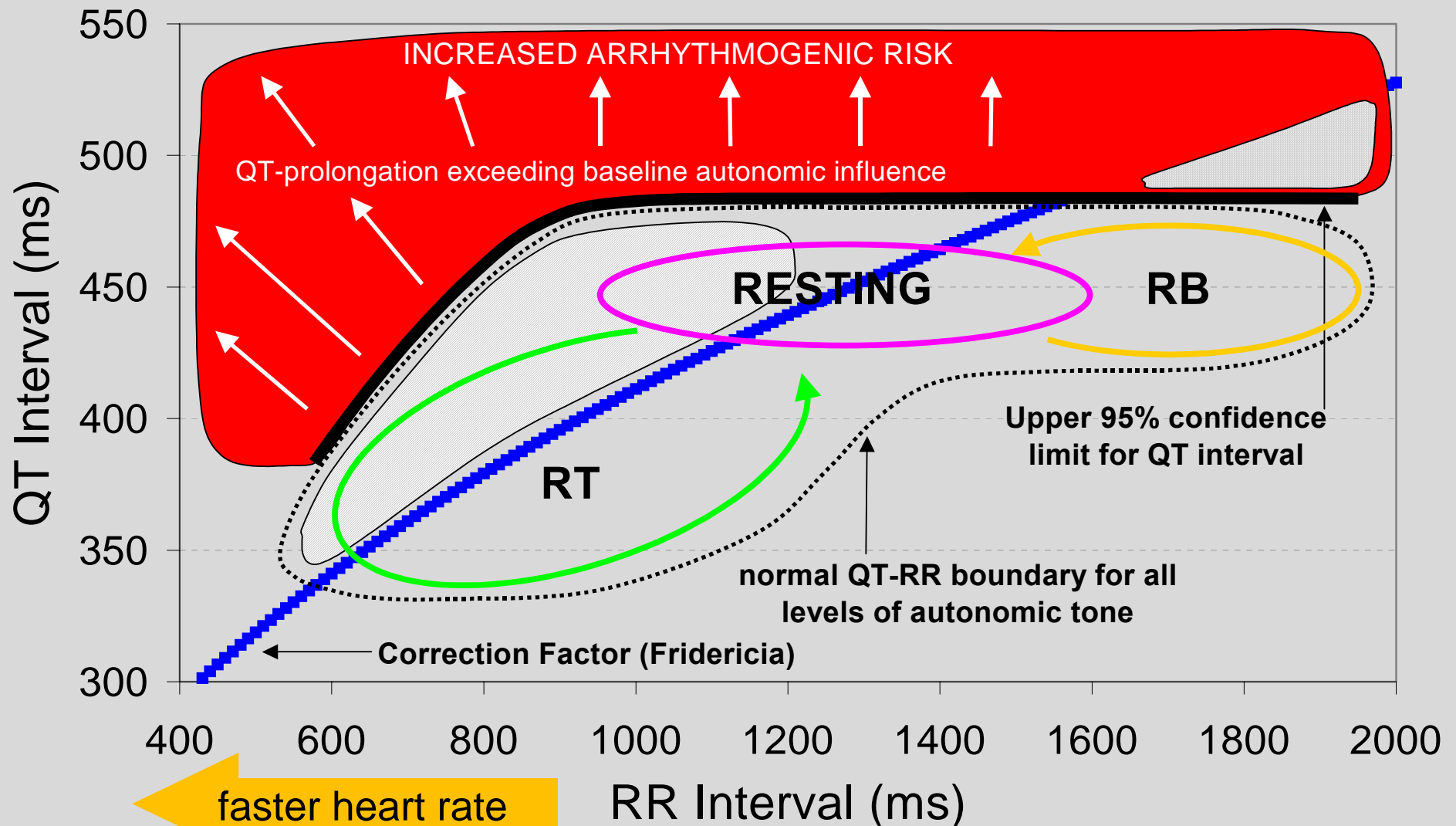
QTc Clinical Signal

Draft Prospective Study

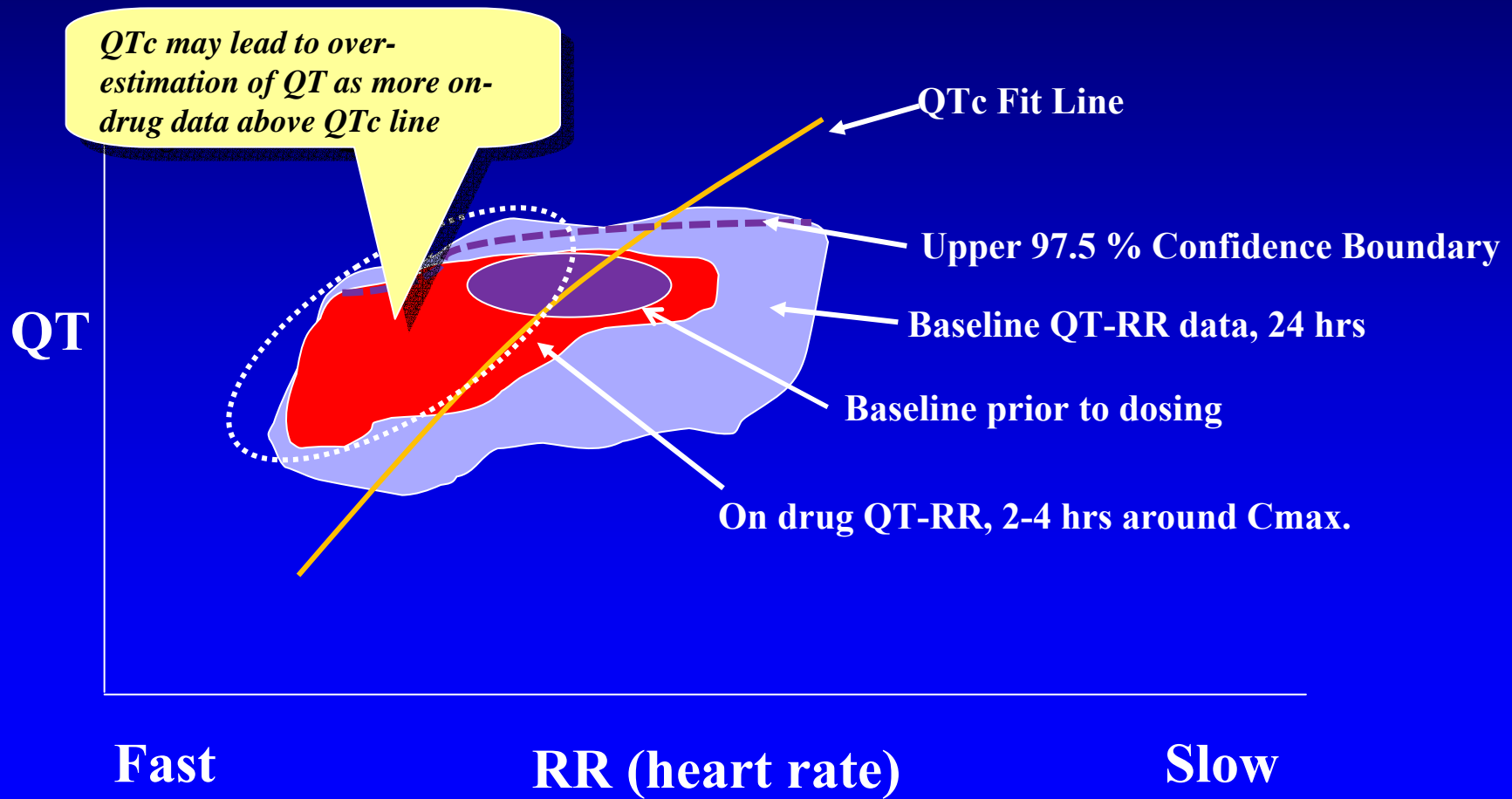
- Assess static and dynamic states
 - Incorporate autonomic maneuvers: like standing
 - Baroreflex test: Phenylephrine challenge
- Incorporate advanced measures
 - Academic (e.g. individual corrections, Holter bin)
 - COMPAS (e.g. ERD, LRD spatial measures)
 - QTbtb (iCardiac)
 - Arrhythmia measures (e.g. QT variability, RR-turbulence, QT-TQ restitution)
- Oversight (Academic/regulatory/sponsors)
- Financial support:
 - iCardiac plus others for a 5-arm study

Thank you – Discussion?

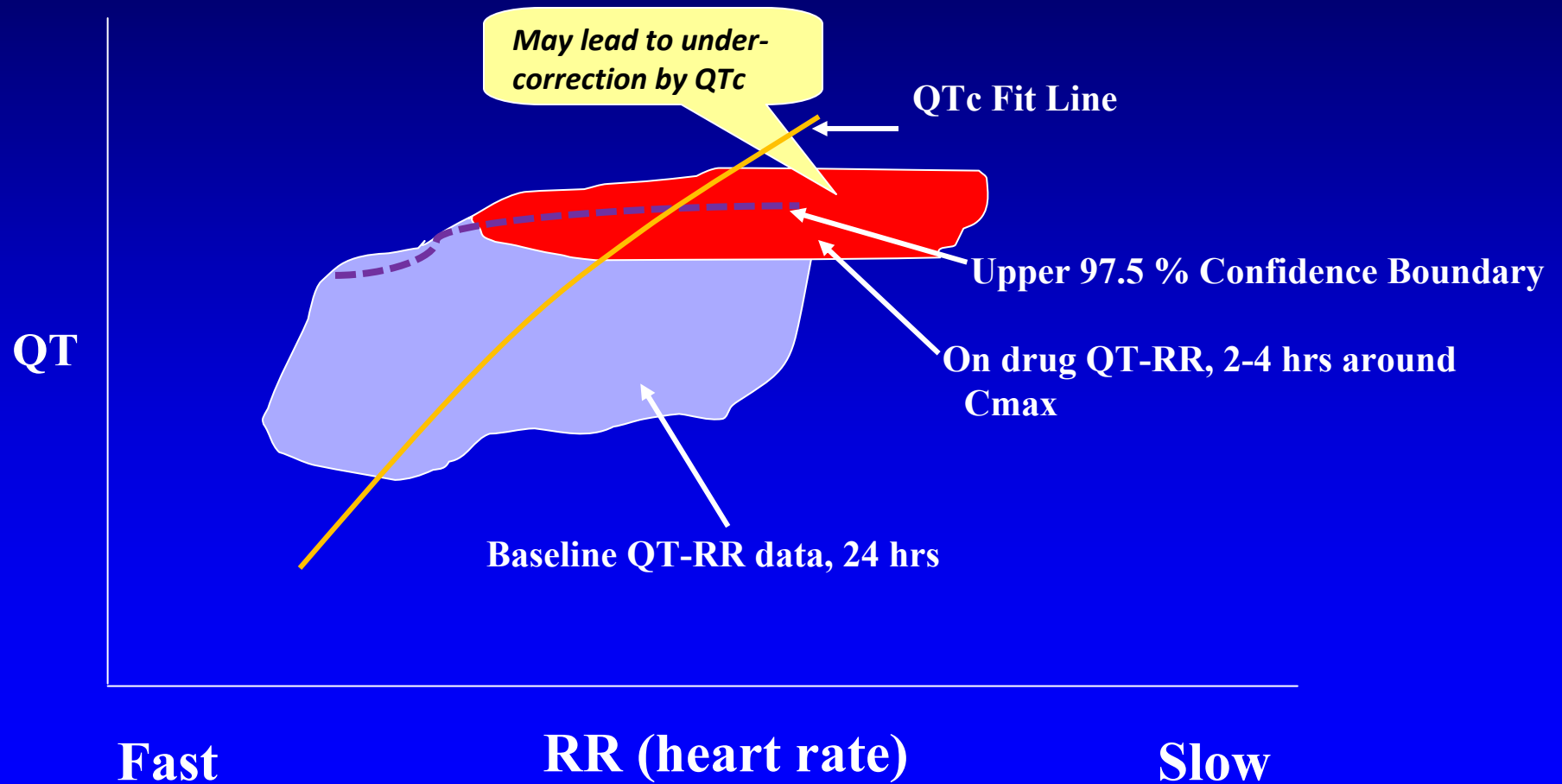
Using Holter acquired E-14 type data in a prospective study



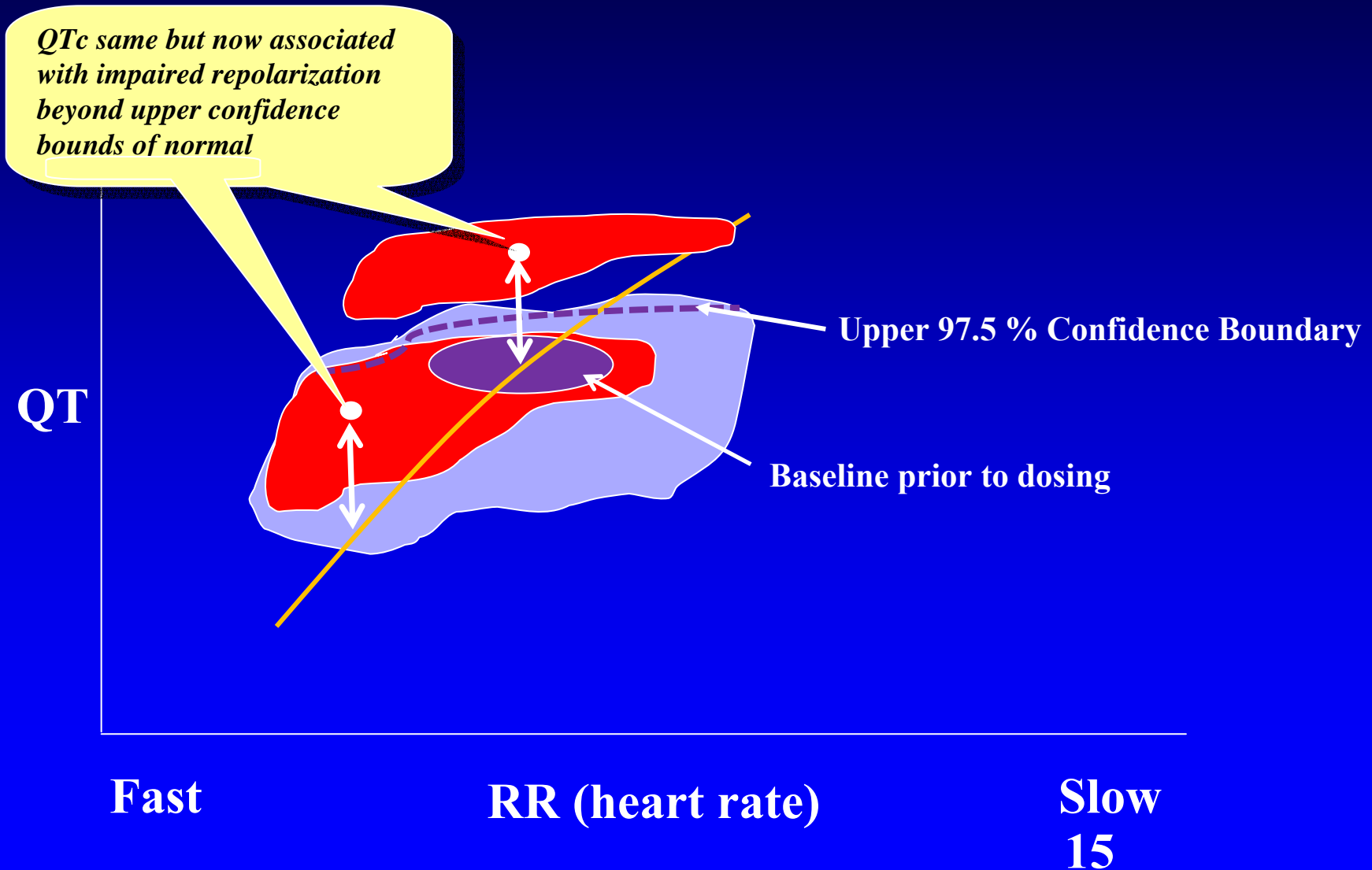
QTc Overestimated When Heart Rate is Increased



QTc Underestimated When Heart Rate is Decreased



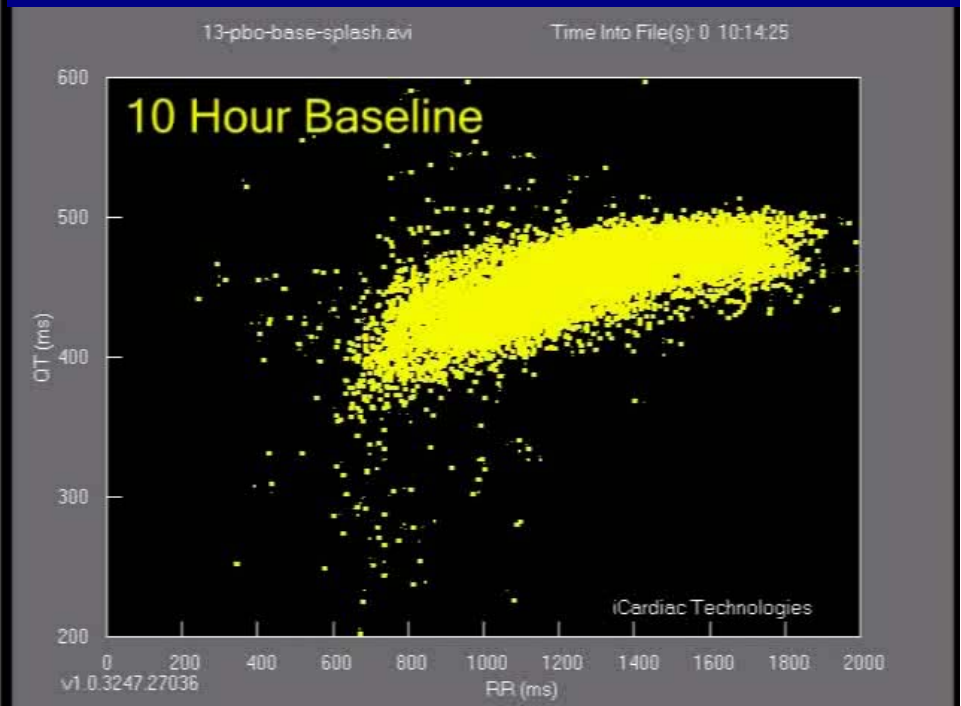
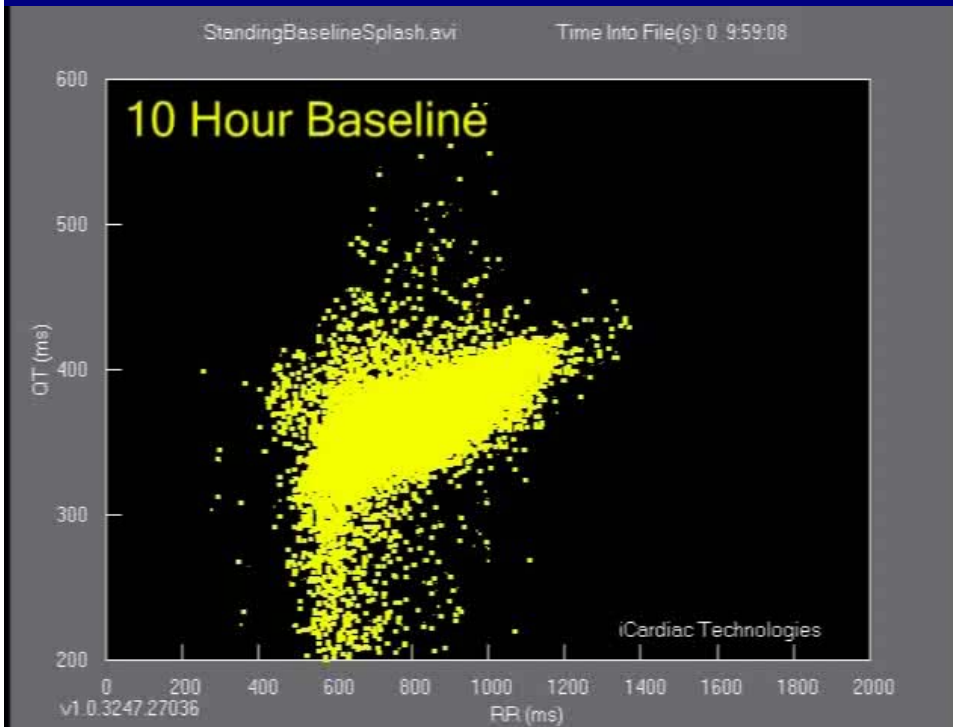
QTc cannot differentiate impaired repolarization from normal autonomic states



Autonomic state vs. impaired repolarization

Rapid Standing

Moxifloxacin 400 mg: 2.5 h Cmax



	<u>Baseline</u>	<u>Δ Standing</u>	<u>Baseline</u>	<u>Δ Moxi</u>
QTbtb	372	- 2	375	100
QTcF	406	26	412	52