Therapies of the Future in LQTS

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LQT1:
Genotype- and Drug-Specific First Cardiac Event Rates on Beta-Blockers

	LQT1 (n = 379) (Total CE = 87)		
Time-Dependent Variable	First CE‡	Hazard Ratio§ (95% CI)	p Value
Atenolol	21/105 (20.0%)	0.43 (0.22-0.86)	0.02
Metoprolol	3/20 (15.0%)	0.44 (0.13-1.54)	0.2
Propranolol	26/72 (36.1%)	0.38 (0.19-0.73)	0.004
Nadolol	22/125 (17.6%)	0.50 (0.25-0.98)	0.04
Test of equality of 4 drug-specific hazard ratios‖¶			0.83

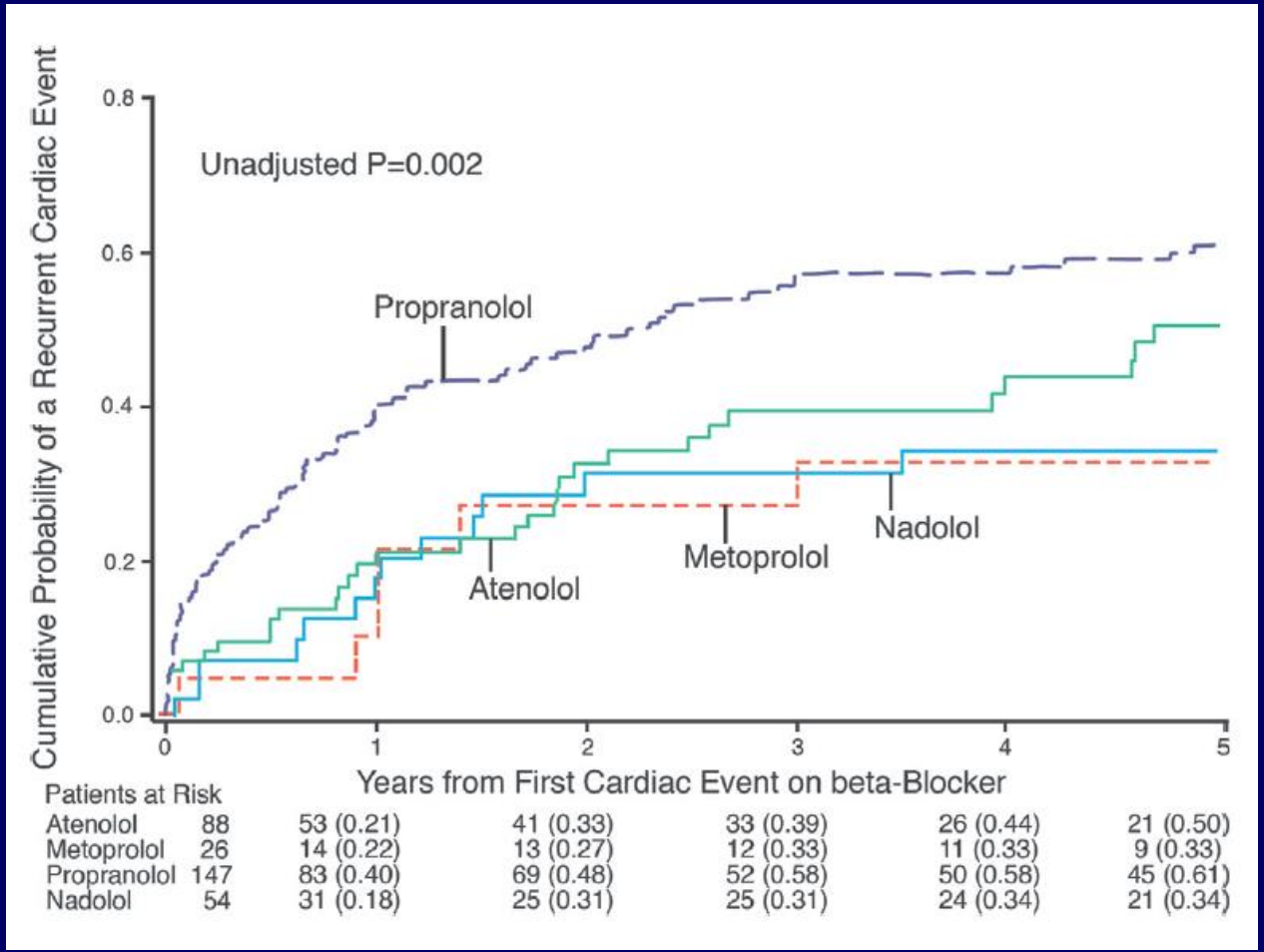
Abu-Zeitone et al. J Am Coll Cardiol 2014;64:1352–8

LQT2:
Genotype- and Drug-Specific First Cardiac Event Rates on Beta-Blockers

Time-Dependent Variable	LQT2 (n = 406) (Total CE = 85) First CE‡	Hazard Ratio§ (95% CI)	p Value
Atenolol	28/114 (24.6%)	1.04 (0.48–2.27)	0.92
Metoprolol	10/46 (21.7%)	0.82 (0.32–2.09)	0.67
Propranolol	28/100 (28.0%)	0.65 (0.29–1.42)	0.28
Nadolol	10/109 (9.2%)	0.40 (0.16–0.98)	0.04
Test of equality of 4 drug-specific hazard ratios‖¶			0.04

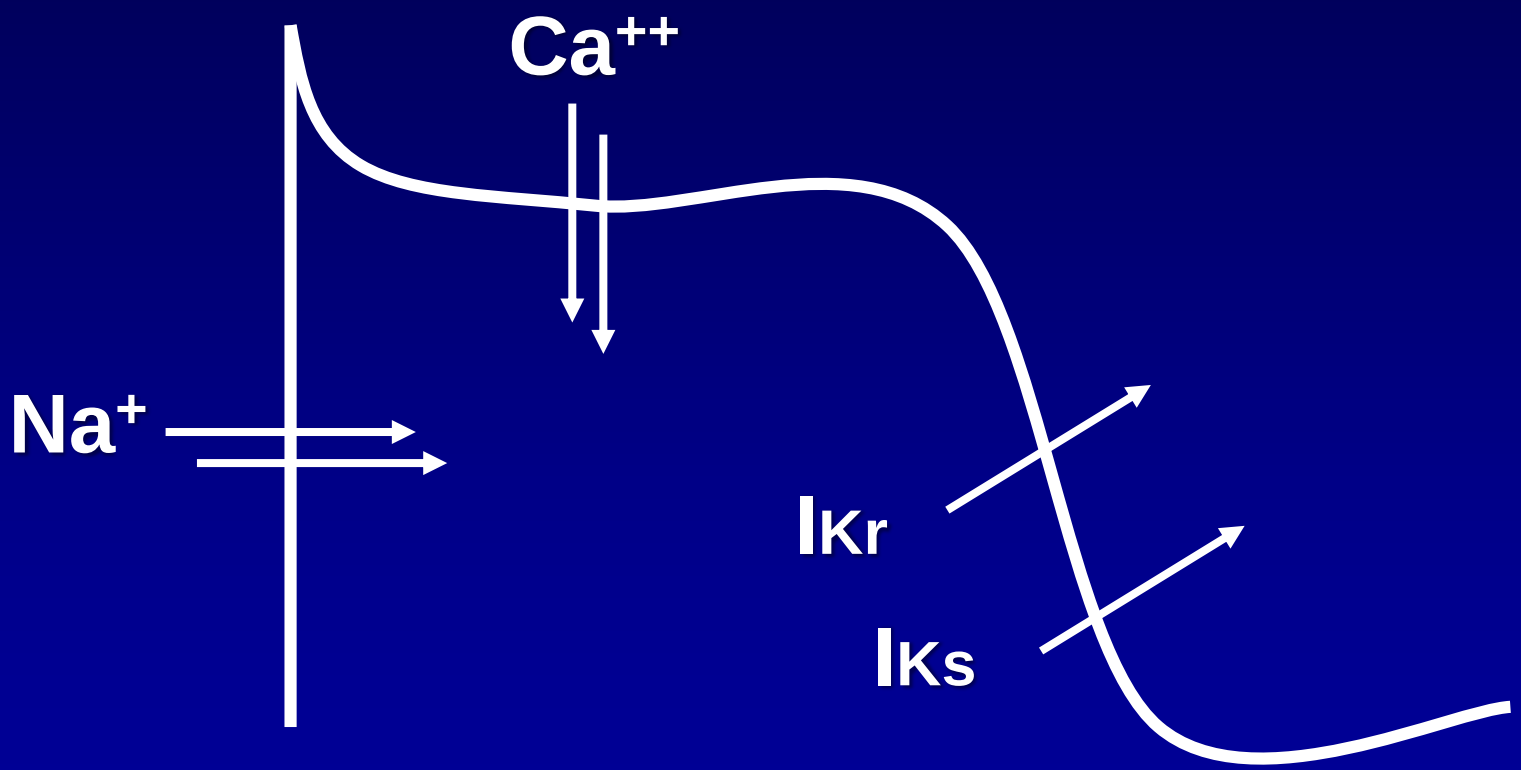
Abu-Zeitone et al. J Am Coll Cardiol 2014;64:1352–8

Cumulative Probability of a Subsequent Cardiac Event Among Patients With Cardiac Event While Taking B-Blockers

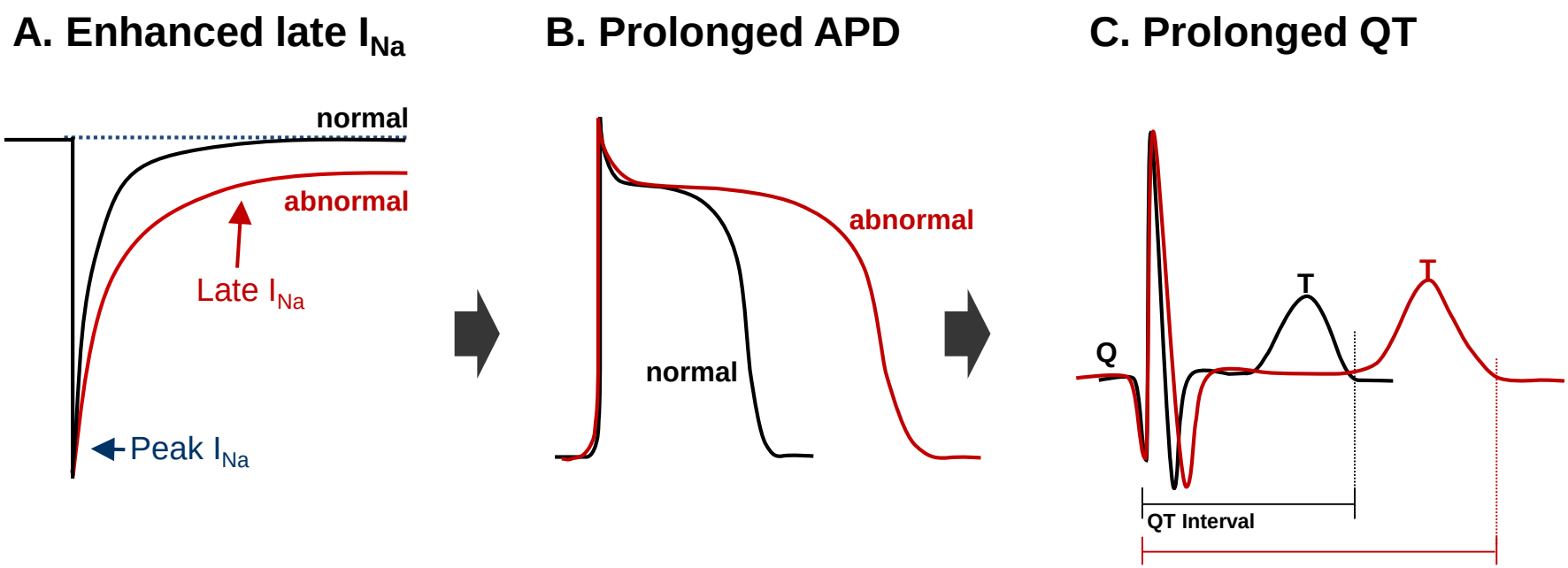


Abu-Zeitone et al. J Am Coll Cardiol 2014;64:1352–8

Ventricular Action Potential

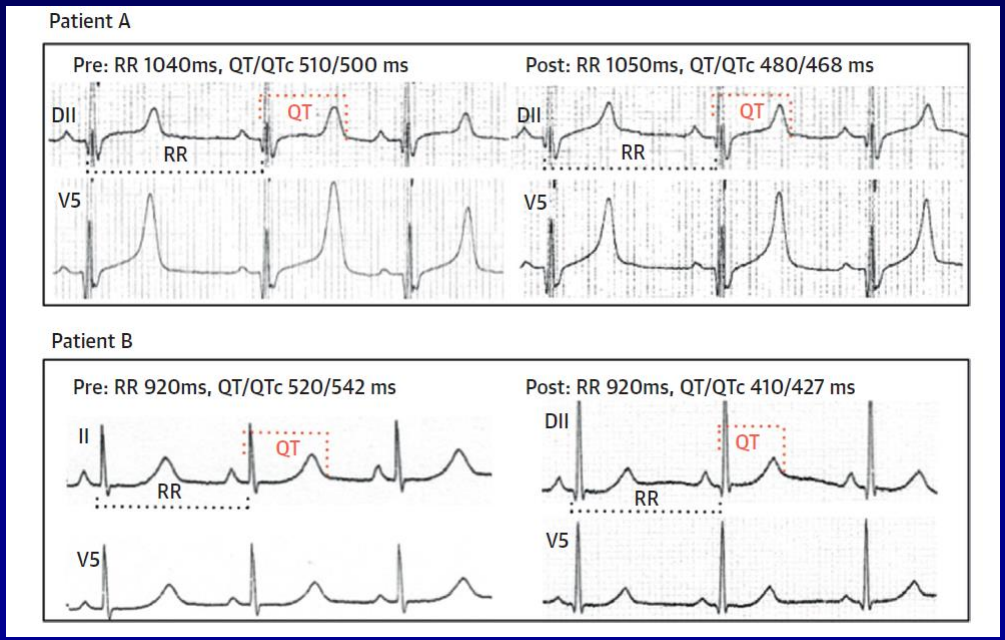


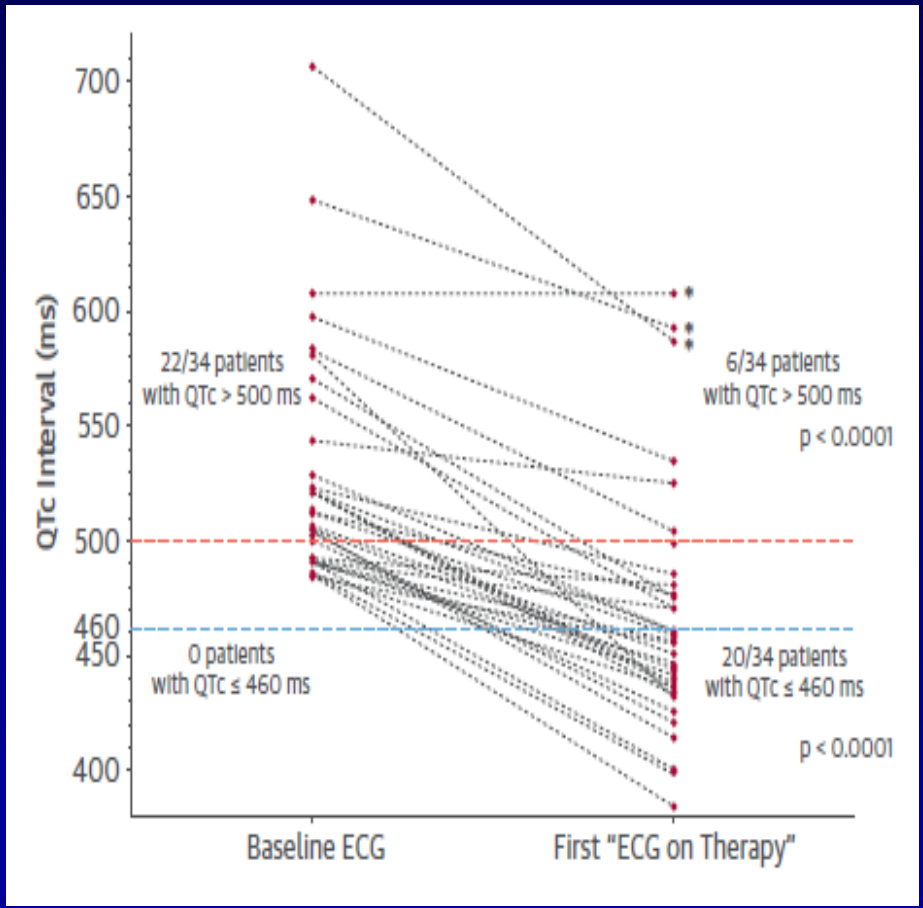
Proof of Pharmacological Activity of Late I_{Na} Inhibitor in Humans



LQT3: A monogenic disorder caused by mutations in the *SCN5A* resulting in enhanced **late I_{Na}**, prolonged APD and QT

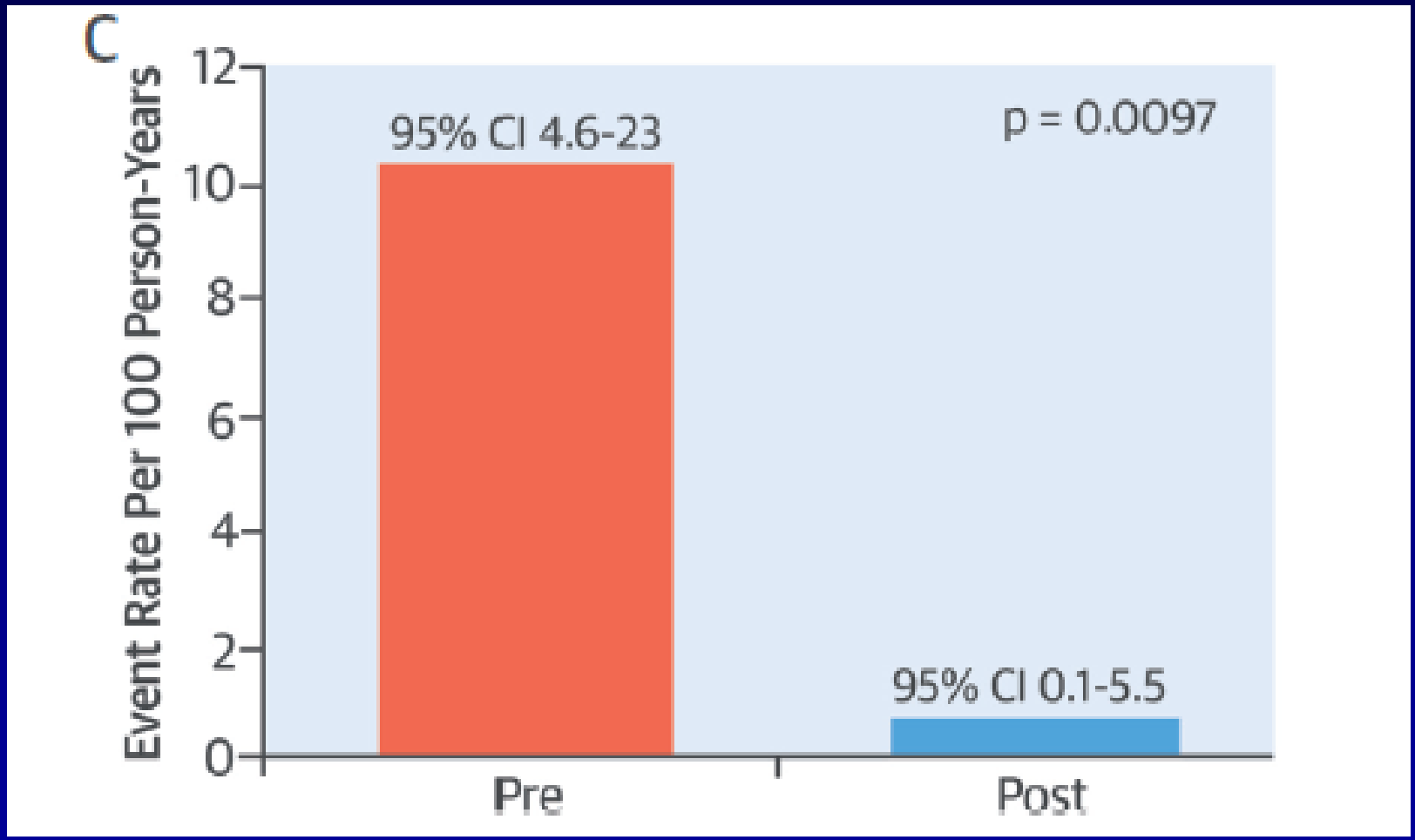
Effect of Mexiletine on QTc Interval Values





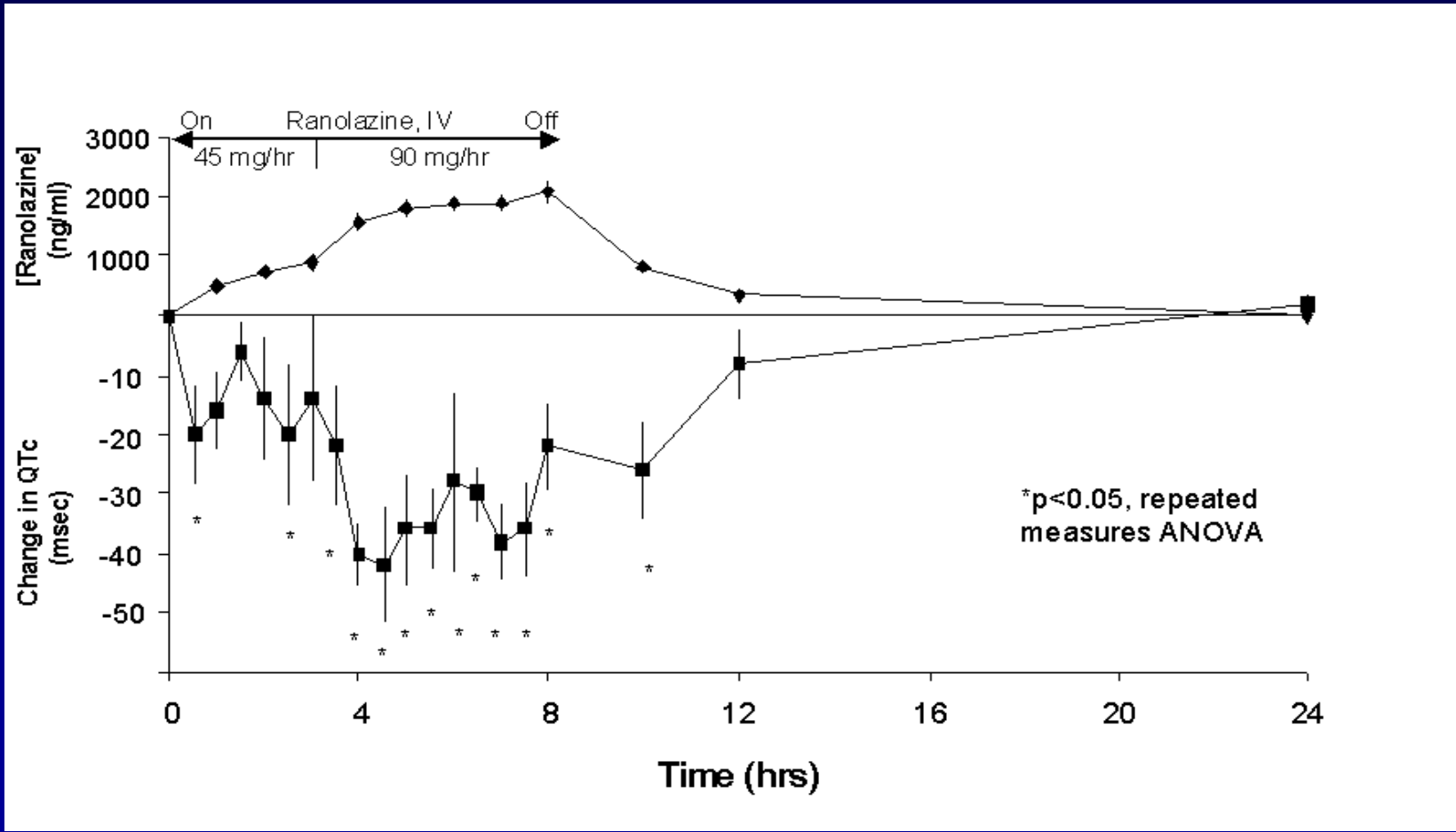
Mazzanti et al. J Am Coll Cardiol 2016;67:1053–8

Effect of Mexiletine on Cardiac Events in LQT3 Patients



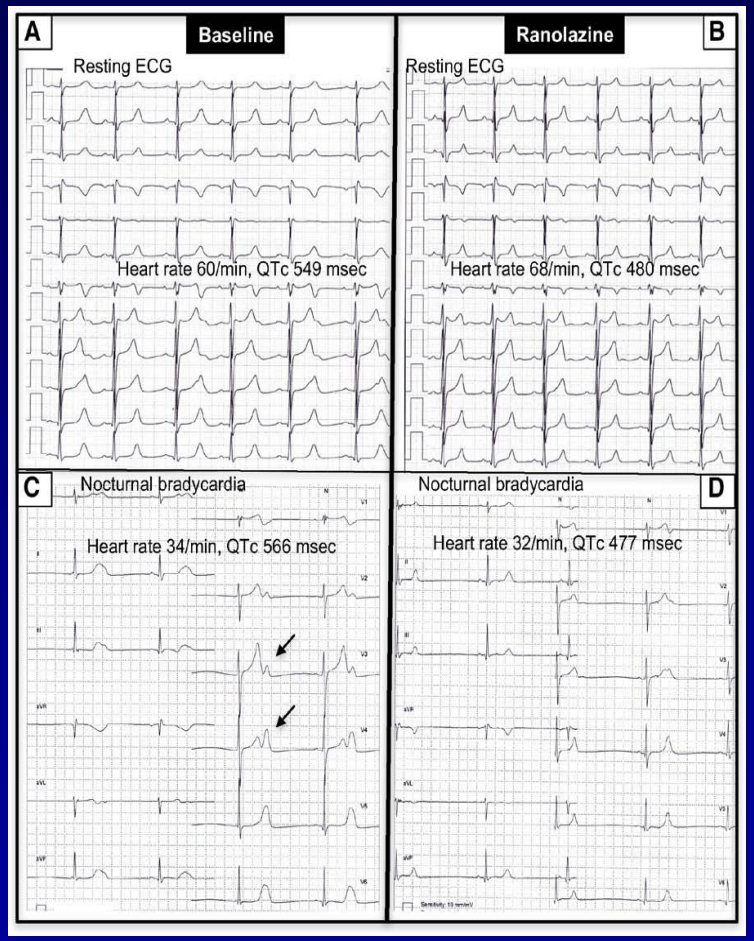
Mazzanti et al. J Am Coll Cardiol 2016;67:1053–8

Time and dose-dependent effect of i.v. Ranolazine on QTc interval in the ΔKPQ LQT3 patients (n=5)

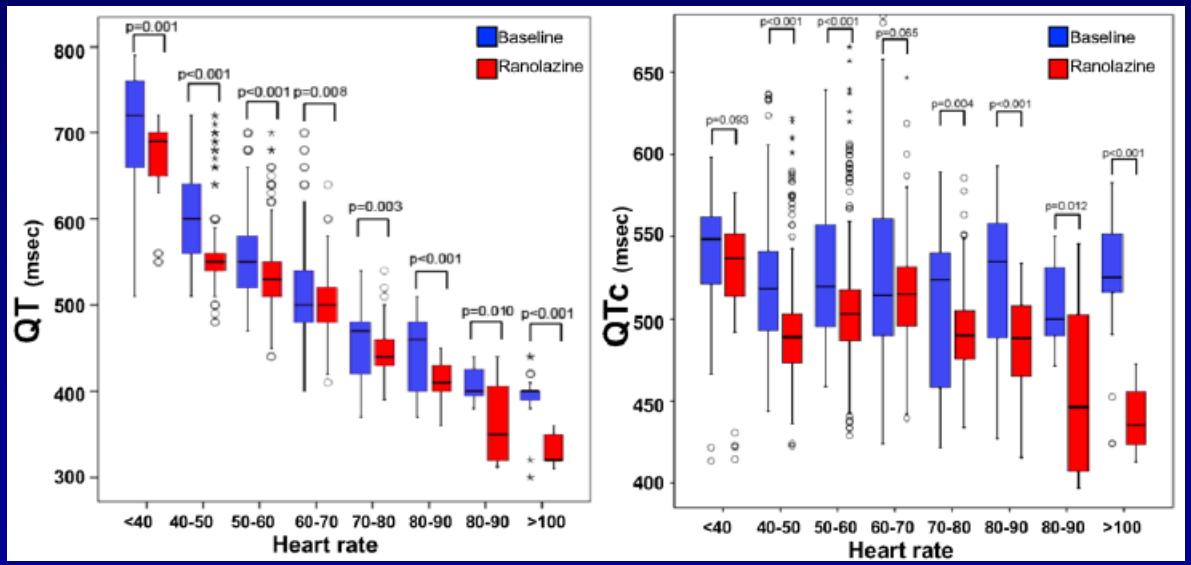


Moss AJ et al. J Cardiovasc Electrophysiol 2008

Ranolazine in the D1790G LQT3 Mutation (n=8)

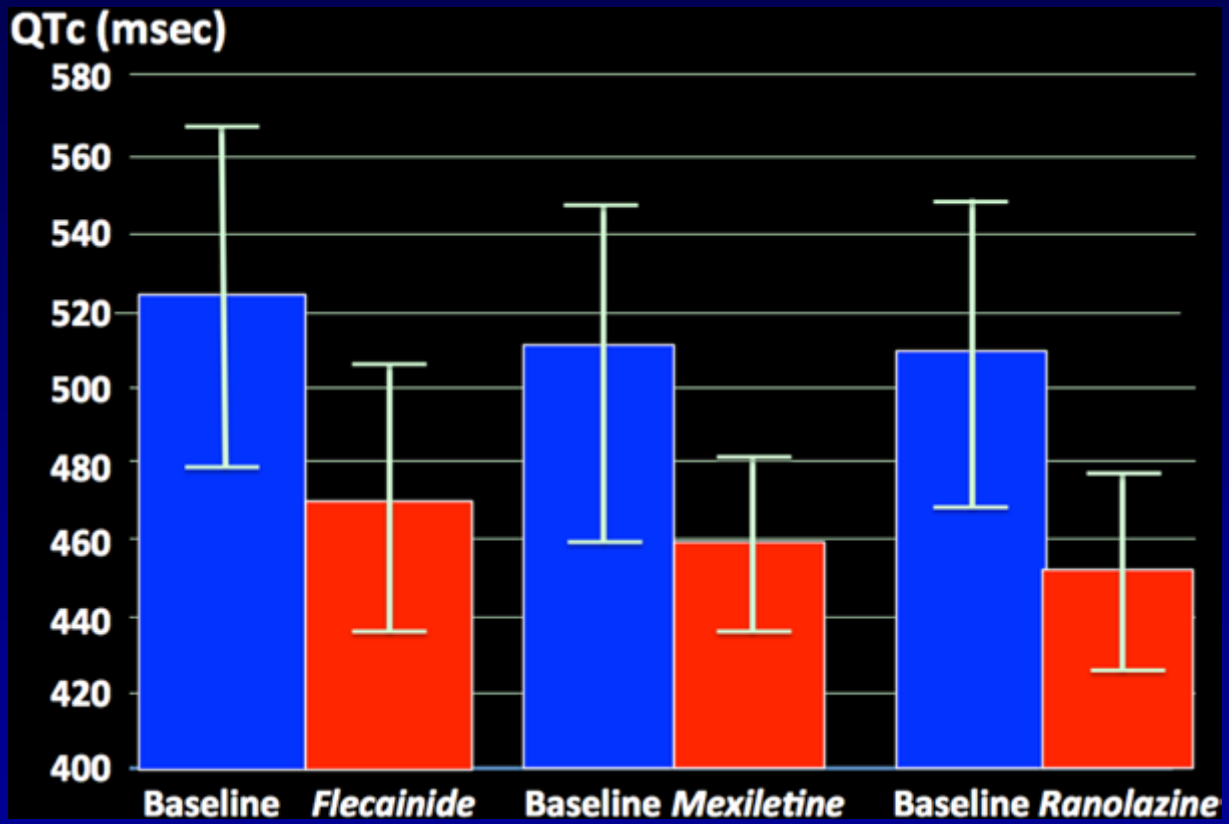


Ranolazine shortened the QTc from 509±41 to 451±26 ms, a mean decrease of 56±52 ms (10.6%; *P*=0.012).



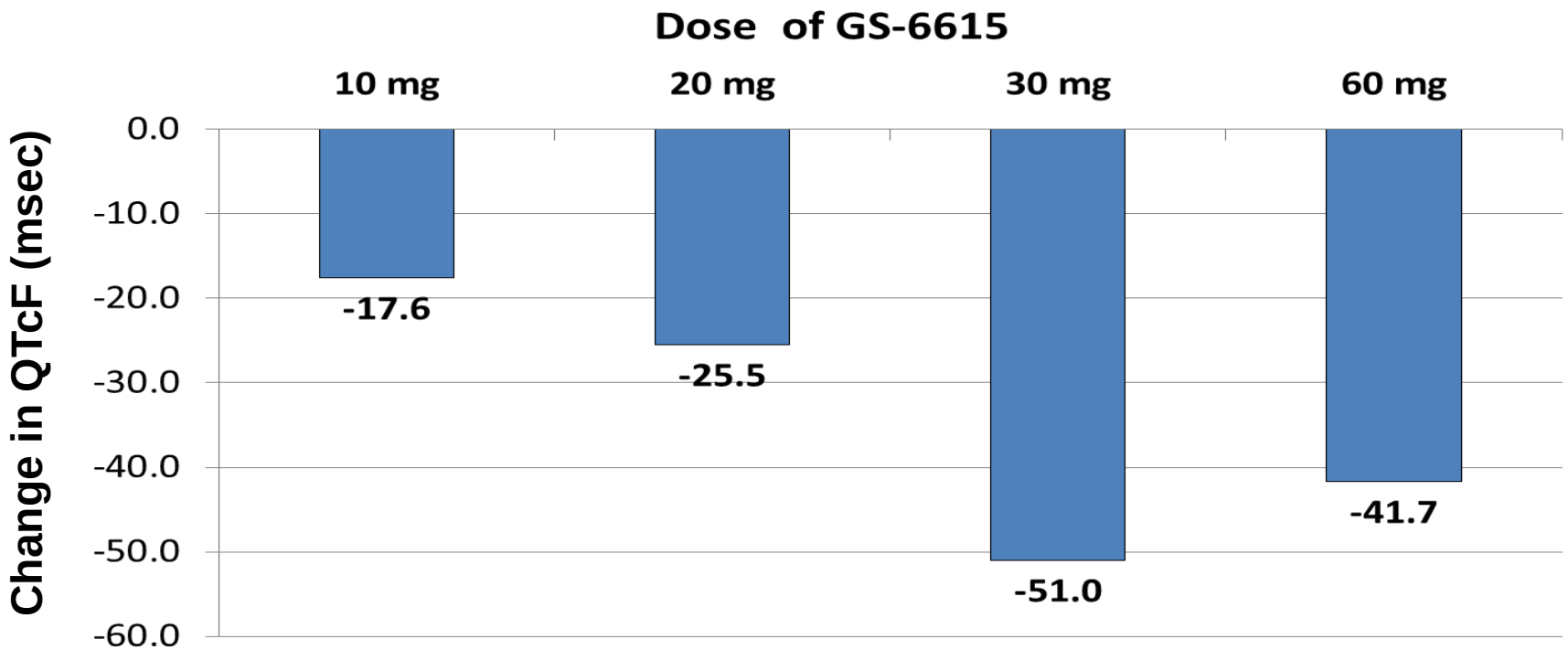
Chorin E et al. Circ Arrhythm Electrophysiol. 2016;9:e004370

QT-shortening Effects of Different Sodium Channel Blocker in LQT3



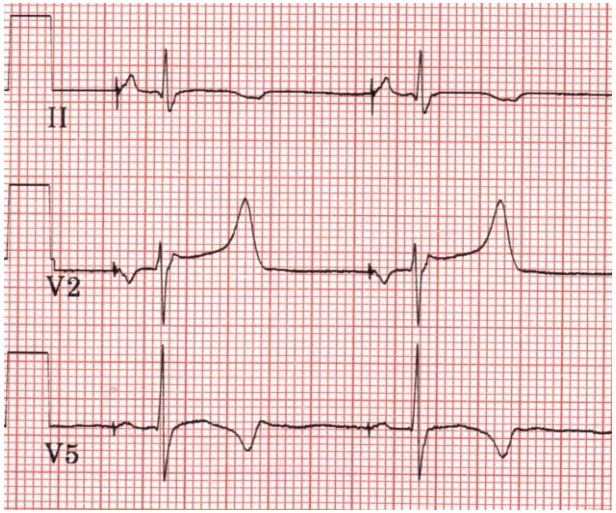
Chorin E et al. Circ Arrhythm Electrophysiol. 2016;9:e004370

Average QTcF change in Lead V5 between 4-12 hrs after GS-6615 (Day 1 vs. Day -1)

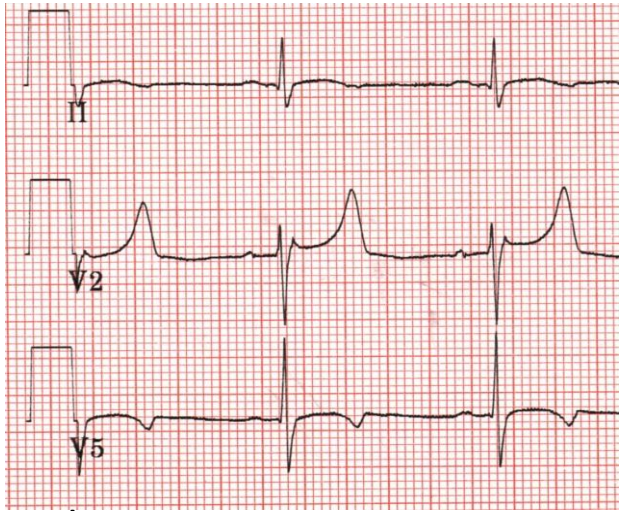


Doses	10 mg (n=3)	20 mg (n=3)	30 mg (n=3)	60 mg (n=4)
Mean Cmax (ng/mL)	119	237	300	638

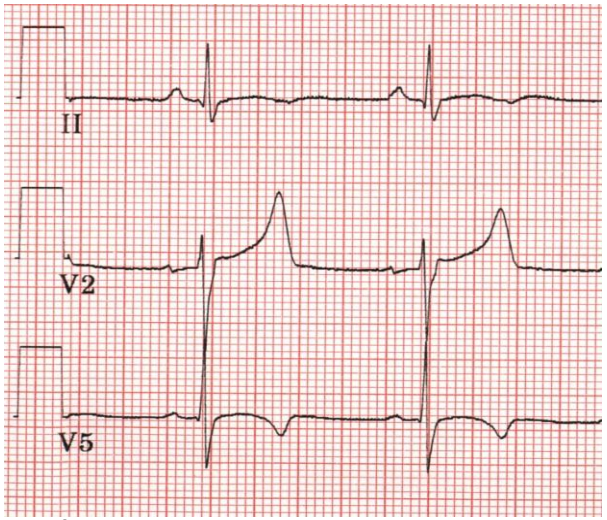
An Example: Time-Course (0-48 hrs Post-dose)



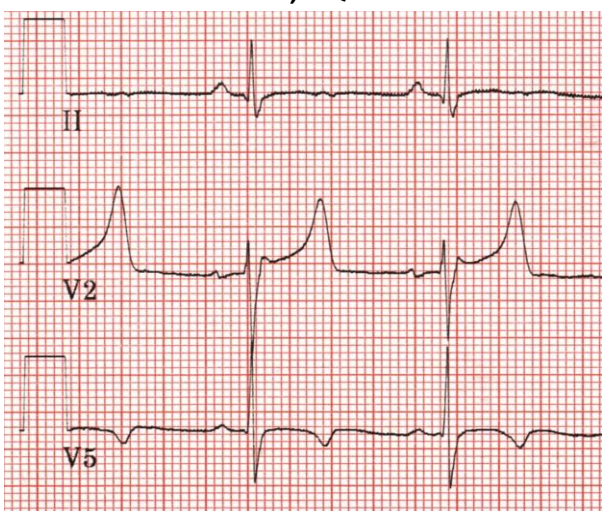
0 hours: QTcF=508 ms
RR=1200 ms; QT=540 ms



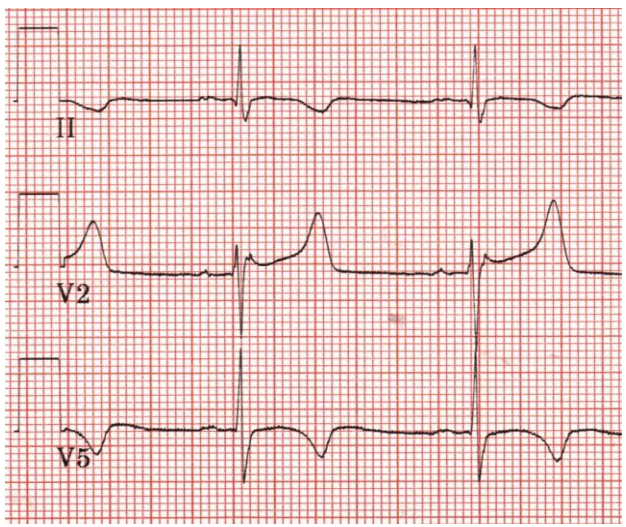
4 hours: QTcF=440 ms
RR=1060 ms; QT=440 ms



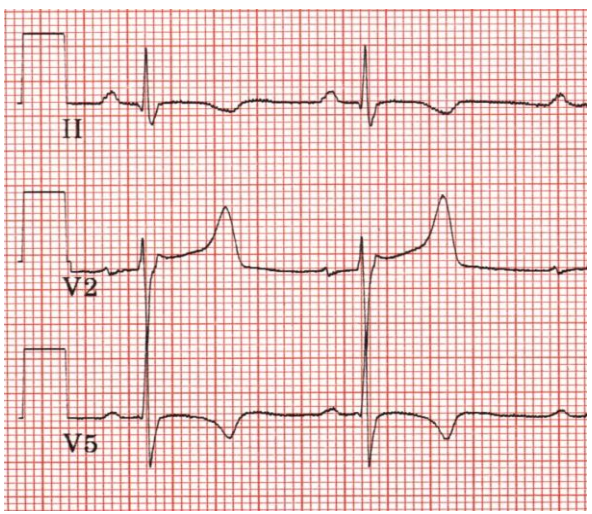
8 hours: QTcF=457 ms
RR=1020 ms; QT=460 ms



12 hours: QTcF=449 ms
RR=940 ms; QT=440 ms

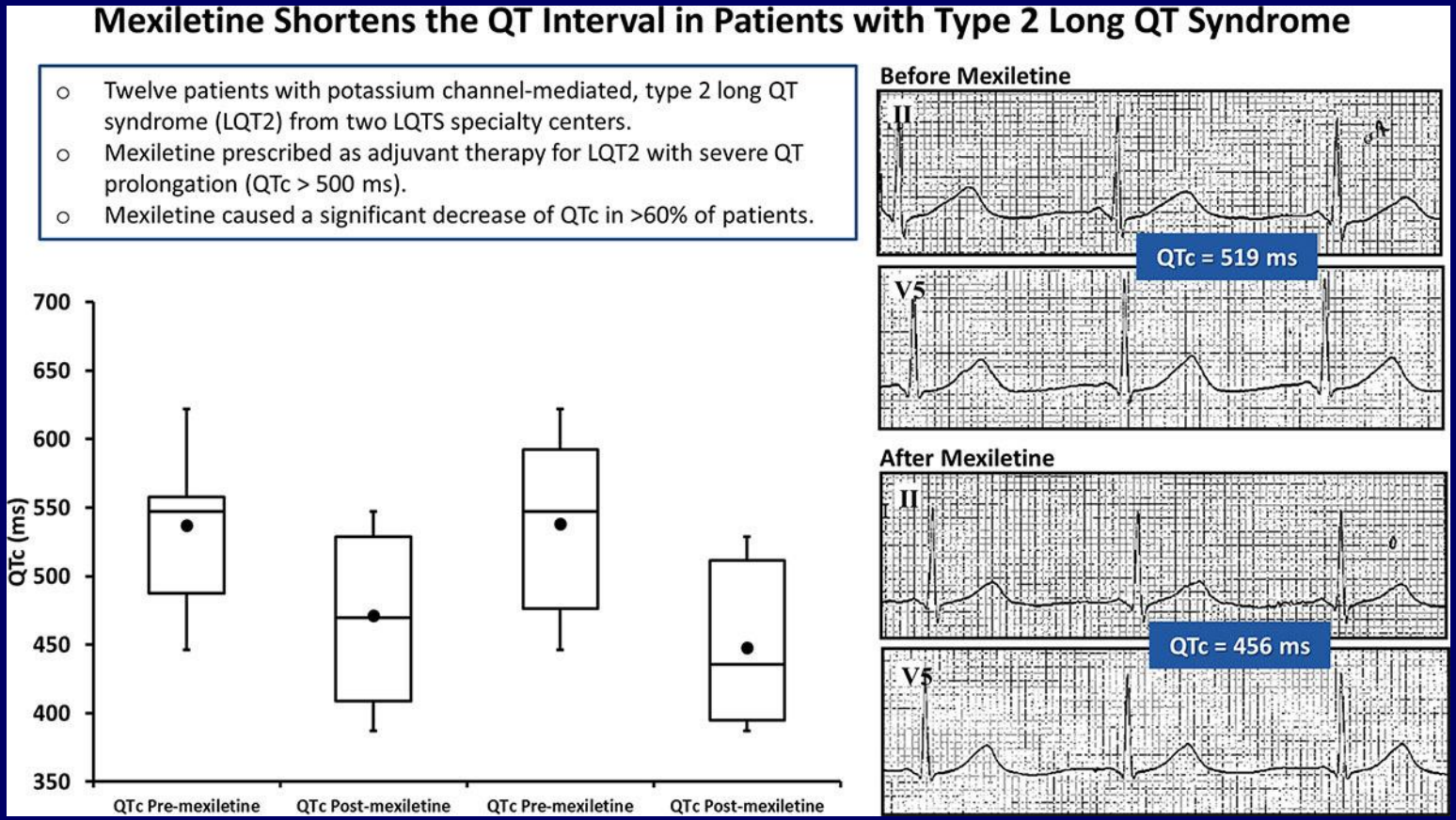


24 hours: QTcF=460 ms
RR=1140 ms; QT=480 ms



48 hours: QTcF=500 ms
RR=1000 ms; QT=500 ms

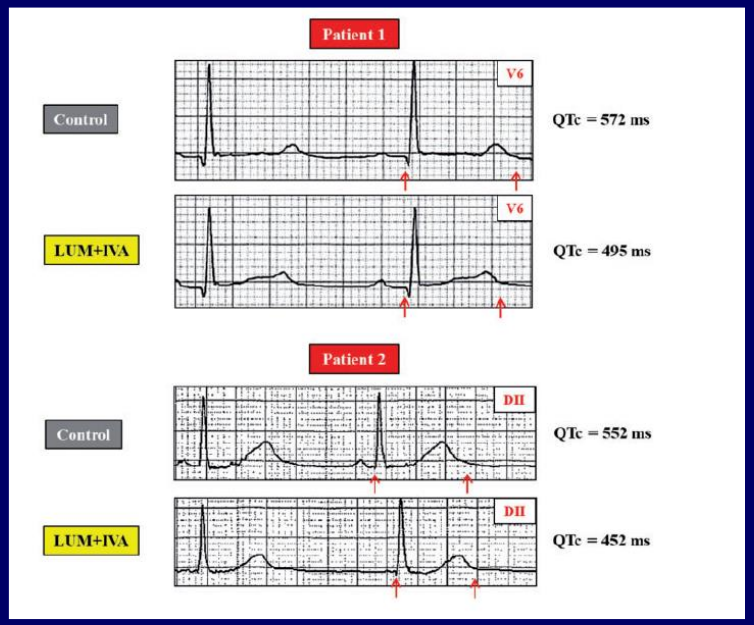
Mexiletine in LQT2 Patients:
Median QTc Shortening by 65+/-45 ms (* pts >40 ms)

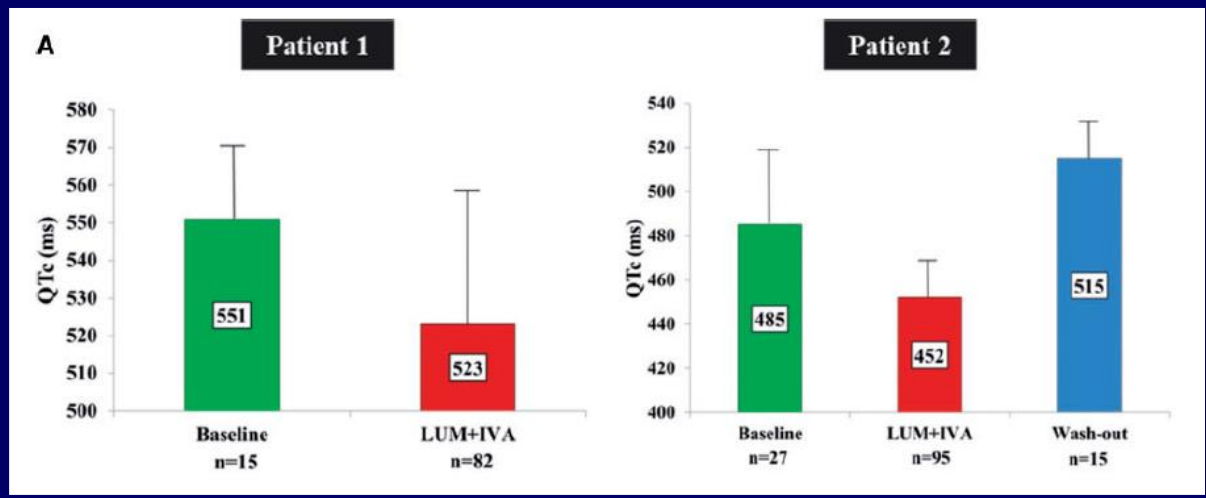


Bos et al. Circ AE 2019

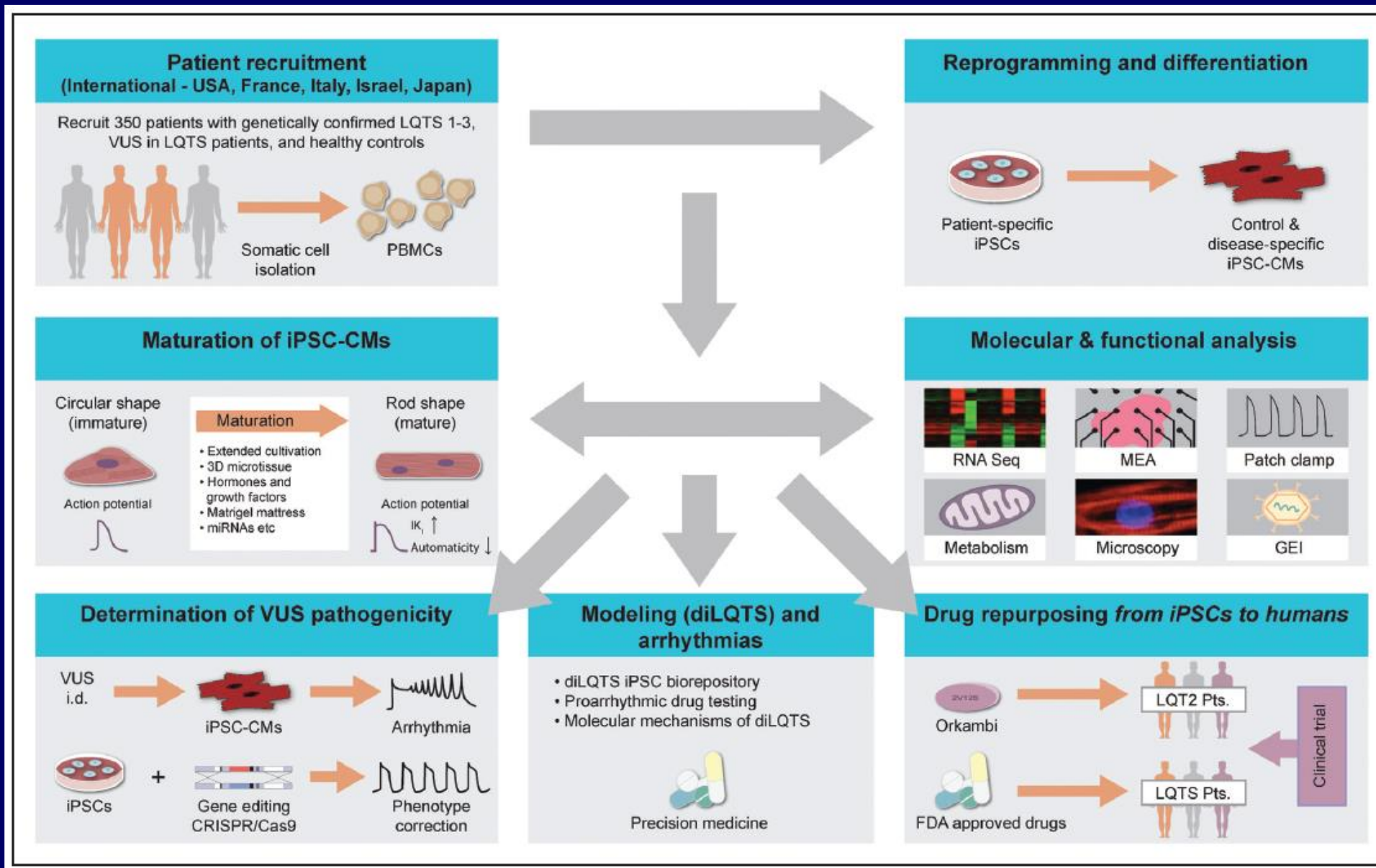
From patient-specific induced pluripotent stem cells to clinical translation in long QT syndrome Type 2

Schwartz et al. European Heart Journal (2019) 40, 1832–1836





Lumacaftor (VX-809) is an investigational treatment for patients with cystic fibrosis.


Patient recruitment
(International - USA, France, Italy, Israel, Japan)
Recruit 350 patients with genetically confirmed LQTS 1-3, VUS in LQTS patients, and healthy controls
Somatic cell isolation
PBMCs
Reprogramming and differentiation
Patient-specific iPSCs
Control & disease-specific iPSC-CMs
Maturation of iPSC-CMs
Circular shape (immature)
Action potential
Maturation
• Extended cultivation
• 3D microtissue
• Hormones and growth factors
• Matrigel mattress
• miRNAs etc
Rod shape (mature)
Action potential
IK1 ↑
Automaticity ↓
Molecular & functional analysis
RNA Seq
MEA
Patch clamp
Metabolism
Microscopy
GEI
Determination of VUS pathogenicity
VUS i.d.
iPSC-CMs
Arrhythmia
iPSCs
+
Gene editing CRISPR/Cas9
Phenotype correction
Modeling (diLQTS) and arrhythmias
• diLQTS iPSC biorepository
• Proarrhythmic drug testing
• Molecular mechanisms of diLQTS
Precision medicine
Drug repurposing from iPSCs to humans
Orkambi
LQT2 Pts.
FDA approved drugs
LQTS Pts.
Clinical trial

LQTS Therapy Summary

- LQTS patients with QTc>550, syncope on BB, multiple mutations or LQT2 mutation are at high risk of ICD shocks and benefit from ICD therapy

- Sodium current blockers might benefit LQT3 and LQT2 patients.
- BB and sodium current blocker therapies will be increasingly tailored to patient-specific mutations
- Pluripotent stem cell research provides opportunity to identify and develop new compunds acting on ion channels.