wave Morphology Assessment in a Randomized Double-Blind Crossover Study of Four hERG Potassium Channel Blocking Drugs

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Introduction

Congenital long QT syndrome type 2 patients have:

_ LQST2

- Reduced hERG potassium channel current
- ★ T waves

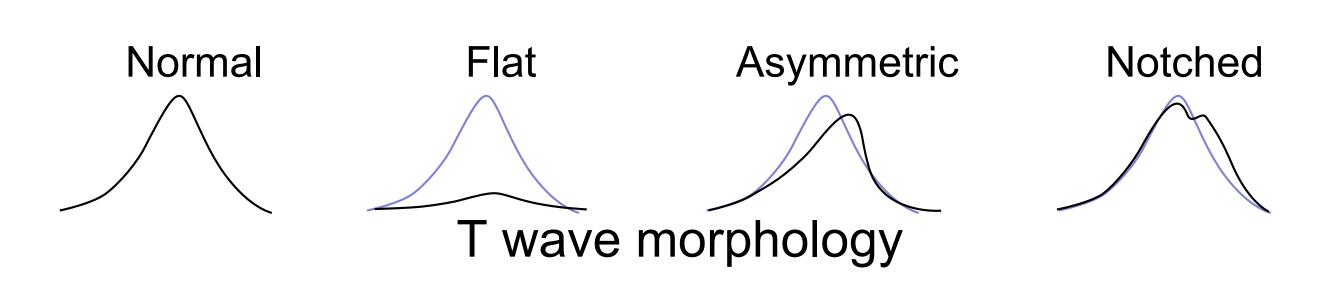
 - Asymmetric - Notched
- > Similar observations in hERG blocking drugs.
- How additional calcium and sodium block affect T wave morphology is not known.

Objective

>To assess T wave morphology changes induced by a pure hERG blocker (dofetilide) and three drugs that also block calcium or sodium (quinidine, ranolazine and verapamil)

Methods

- > 22 subjects received a single dose of each drug along with placebo in a 5-period crossover study.
- > At 15 timepoints postdose:
- ★ Subjects supine and 10-second 12-lead ECGs extracted
- → Blood samples for plasma drug concentration withdrawn
- T wave flatness, asymmetry and presence of notch automatically assessed with QT-Guard+ (GE Healthcare).
- > Regression models to assess the relationship between plasma drug concentration and T wave

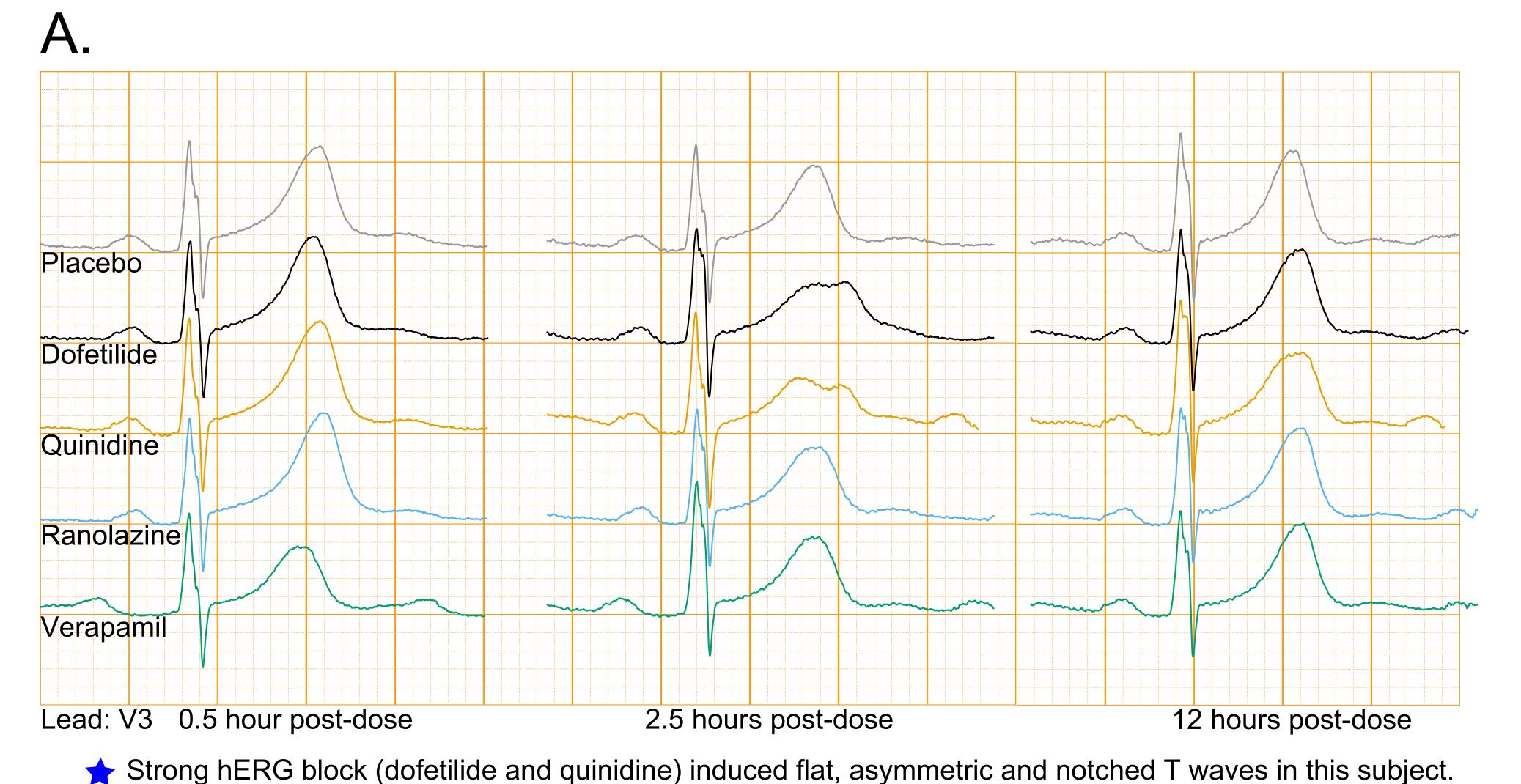


References

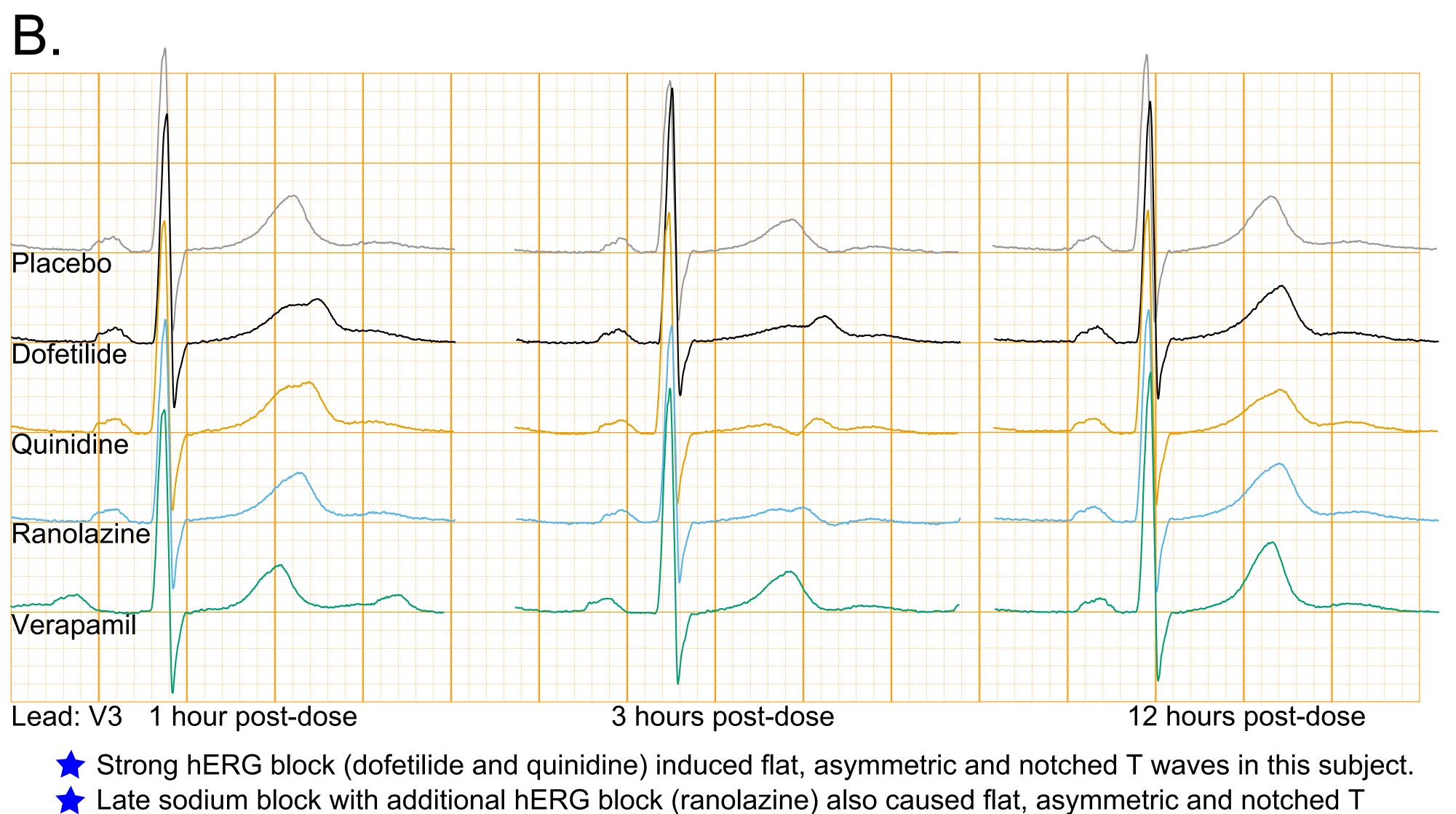
[3] Andersen et al. J Electrocardiol. 2008 Nov-Dec;41(6):557-61

[1] Johannesen et al. Clin Pharmacol Ther. 2014 Nov;96(5):549-58. [2] Andersen et al. Comput Cardiol (2007). 2007;34:341-344.

ECG traces of 2 different subjects.



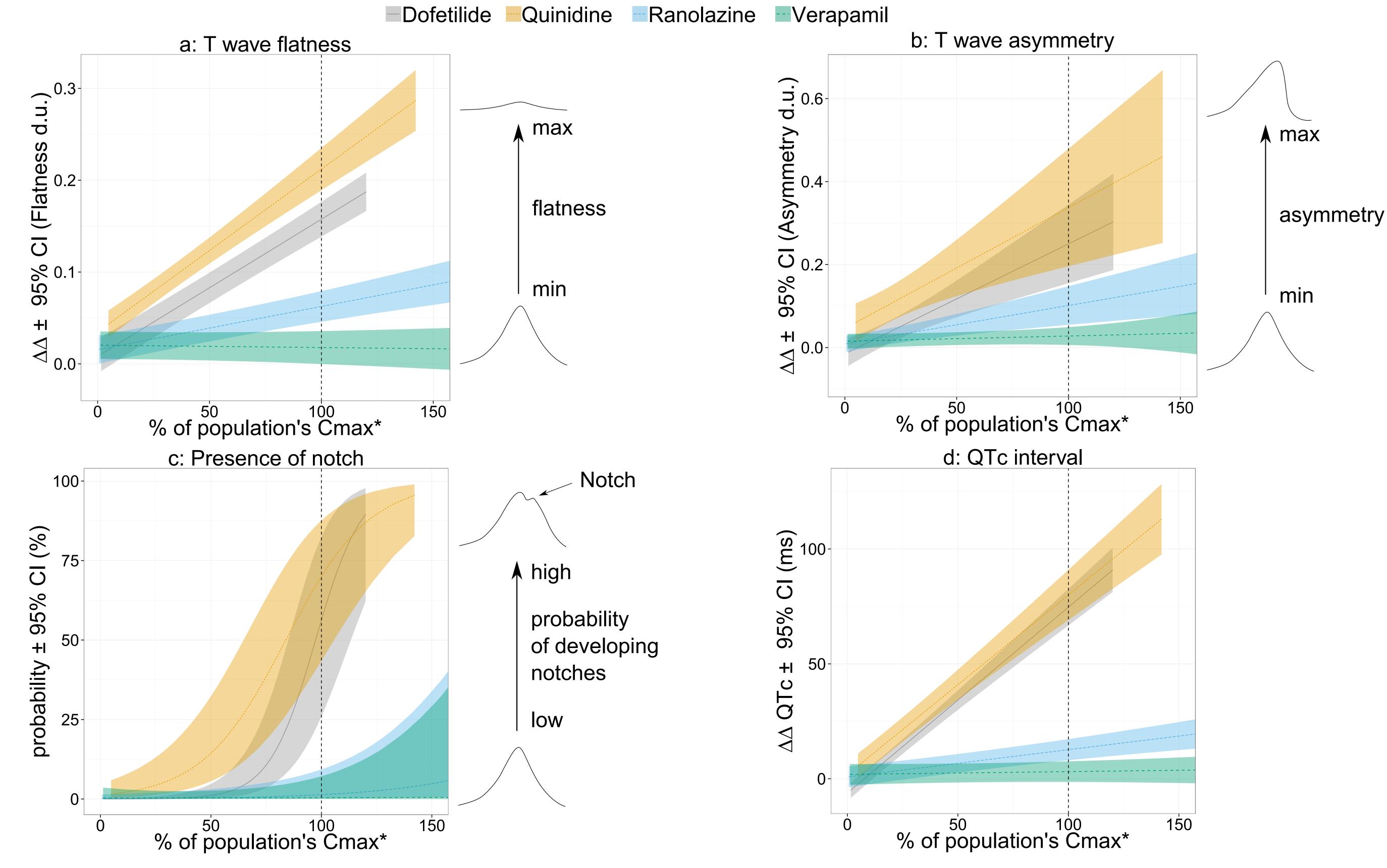
- 🛨 Late sodium block with additional hERG block (ranolazine) caused some flatness and asymmetry, but not
- The strong calcium block with additional hERG block (verapamil) caused PR prolongation, but no changes in T wave morpholgy.



- Strong calcium block with additional hERG block (verapamil) caused PR prolongation, but no changes in T wave morphology.

Results

Concentration-dependent analsysis



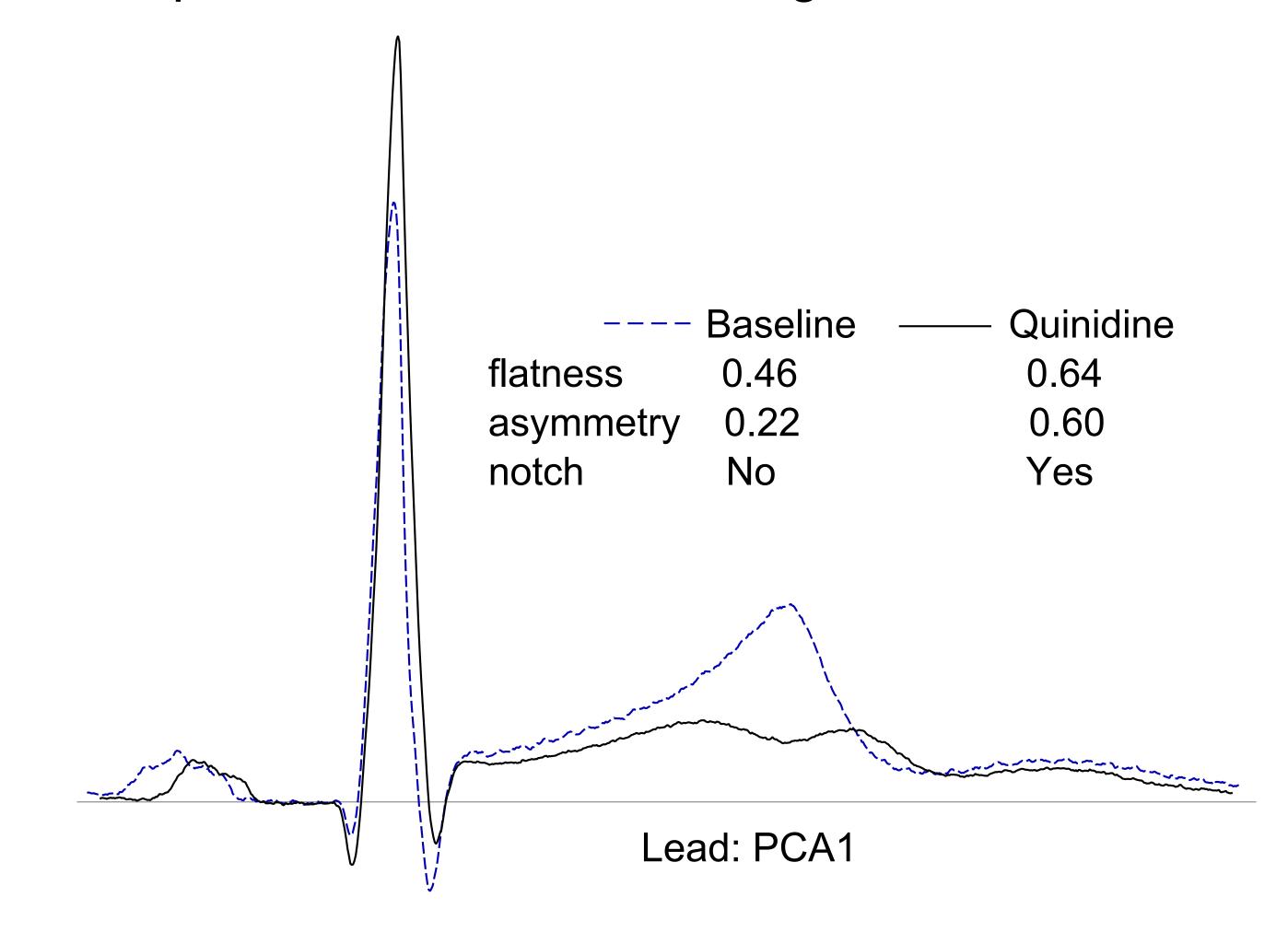
*Cmax: average maximum concentration

Table: Relationship between plasma drug concentrations and ECG measurements

	Dofetilide (ng/ml)	Quinidine (µg/ml)	Ranolazine (µg/ml)	Verapamil (ng/ml)
QTc	29.7 ***	43.6 ***	5.1 ***	0.01
(ms)	(26.5 to 33.0)	(37.3 to 49.8)	(3.2 to 6.9)	(-0.02 to 0.04, p=0.42)
T wave morphology				
Flatness	0.05 ***	0.10 ***	0.02 ***	0.0
(dimensionless units)	(0.05 to 0.06)	(0.08 to 0.11)	(0.01 to 0.03)	(0.0 to 0.0, p=0.68)
Asymmetry	0.10 ***	0.16 ***	0.04 ***	0.0
(dimensionless units)	(0.06 to 0.13)	(0.08 to 0.24)	(0.02 to 0.06)	(0.0 to 0.0, p=0.15)
Probability of Notch	3.48***	2.93 ***	1.13 **	2.23
(logit units·10 ⁻³ [†])	(2.38 to 4.58)	(2.09 to 3.77)	(0.28 to 1.97)	(-2.58 to 30.24, p=0.88)

Mean slopes \pm 95% confidence intervals; *p<0.05, **p<0.01, ***p<0.001; [†] from logistic regression model.

Example of measures in first Eigen lead after PCA



Conclusion

- >Strong hERG block (dofetilide and quinidine) caused substantial concentration-dependent T wave morphology changes.
- >Ranolazine (late sodium > hERG block) still caused T wave flatness and asymmetry, and some notching.
- >Verapamil did not cause T wave morphology changes likely because of a combination of strong calcium and weaker hERG block.
- >Additional outcomes research is needed to determine the potential value of T wave morphology for torsade de pointes risk assessment.

Acknowledgements

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