QT/QTc prolongation is frequently associated with severe life threatening forms of proarrhythmia: ventricular tachycardia (VT) and torsade de pointes (TdP). Although QT/QTc has become a biomarker for proarrhythmia, VT and TdP are not always a consequence of prolonged QT, as they may appear even with normal or shortened QT intervals. For example, Amiodarone increased QT prolongation (>50 msec), yet it is associated with a low risk of proarrhythmia. Despite these contradicting observations QT/QTc prolongation is still considered by the FDA as a weakly predictive biomarker, “since it is the only biomarker for proarrhythmia we have” (Dr. Throckmorton, FDA). There is presently no other agreed strategy to predict pro-arrhythmia. The need for a better strategy in assessment of drug-related risk of arrhythmia is evident.

A recent paper by Shah and Hondeghem (2005) proposes an improvement in the risk assessment strategy: “TRIaD” rather than mere QT prolongation should be used as a predictor of arrhythmogenic effects of new drugs, i.e. that QT prolongation in the absence of TRIaD augmentation is not clinically relevant.

TRIaD is a combination of Triangulation (=prolongation of APD30-90 in the canine Purkinje fiber) + Reverse use dependency + Electrical T wave Instablity + intramyocardial Dispersion of refractoriness (=transmural dispersion of repolarization).

"Block of hERG channel and QT interval prolongation should be considered warning signals for proarrhythmia but per se should not consitute a reason for considering a drug to be proarrhythmhmic. Conversely, the presence of TRIaD augmentation, even in the absence of QT interval prolongation, should be considered proarhythmic until proven otherwise.... Assessment of proarhythmic risk can be improved by considering changes in other ECG metrics, such as change in T-wave morphology and/or occurrence of U waves, time from T peak to Tend, or T-wave residuals... There is no evidence to indicate that agents lacking TRIaD augmentation can be torsadogenic, extensive preapproval cardiac safety evaluation may not be called for (if absence of effects on TRIaD has been demonstrated preclinically)."

The TRIaD strategy merits detailed consideration and exploration, a challenge to our future work for making drugs safer without deleting the promising and medically beneficial drug candidates.

**Literature:**