# Publication

## QT interval prolongation and cardiac risk assessment for novel drugs.

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*Abstract*

Fatal cardiac arrhythmias, known as torsades de pointes, can occur with a wide variety of medicinal drugs and are associated with prolongation of the QT interval. This review critically evaluates the major strategies for assessing QT prolongation risk: ion channel studies, in vitro cardiac electrophysiology, and in vivo cardiac electrophysiology and hemodynamics. Disease- or drug-induced QT prolongation is mainly associated with reduced amplitude of the repolarizing outward K+ current in myocardial cells, particularly those carried by the human ether-a-go-go-related gene (HERG) channel. Thus, measuring HERG currents using patch-clamp technology and cloned HERG channels represents a first approach for evaluating adverse effects of drugs on ion channel function, under physiological conditions. Evaluation of changes in transmembrane action potential in isolated rabbit or dog Purkinje fibers reflects mixed ion channel blocking properties of the test substance and therefore permits a greater understanding of the mechanisms underlying the genesis of arrhythmias. Both HERG channel and Purkinje fiber procedures are clinically predictive, however, no in vitro technique can fully reproduce the in vivo situation. Therefore, both in vitro and in vivo approaches should be employed to maximize the chances of an accurate assessment of risk in an area where prolonged QT can result in death.