Drug-Induced Torsades de Pointes: Mechanistic Insights and Scientific Rationale for CiPA

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Outline

- Congenital long-QT syndromes inform on drug-induced long QT syndrome and Torsades
- Setting the Stage for Torsades; the roles of delayed repolarization and triggers
- Multiple currents (beyond iKr/hERG) define ventricular repolarization and are unintended drug targets that modulate TdP risk
- Delayed, exaggerated repolarization heterogeneity and cellular triggers contribute to TdeP risk
- QTc prolongation is a poor surrogate marker of drug-induced Torsades-de-Pointes risk
Torsades de Pointes: a unique (& rare) arrhythmia

- Twisting of points; a rare (but potentially lethal) ventricular arrhythmia
- May spontaneously resolve or degenerate to ventricular fibrillation
- Ventricular tachyarrhythmia related to non-stationary patterns of excitation/conduction
- Both congenital- and drug-induced LQT syndromes linked to effects on repolarization

Yap and Camm, 2003
Lessons Learned from Congenital LQT Syndromes

Three predominant currents affected by channel mutations in congenital LQTS: IKs (KCNQ1), IKr (KCNH2, hERG), INa (SCN5A)

Mutations may contribute to modest QTc prolongation at baseline, exaggerated response to QT prolonging drugs
Lessons Applied to Acquired (Drug-Induced) LQT: Drug Targets and Triggers

- Originally linked to antiarrhythmic drugs only (quinidine -a fib)
- Link between idiosyncratic drug reaction aLQT and cLQT by Schwartz and Moss – drugs sharing pharm. activity with quinidine
- Delayed repolarization (QTc) as substrate: essential but not sufficient to elicit TdP; extent of prolongation, other factors enhance risk; trigger necessary
- Block of iKR/hERG cited as a common feature; oversimplified, as does not consider multiple currents that define repolarization
Integration of Cellular Responses Lead to QT Interval Prolongation, Increased Risk of Proarrhythmia

Repolarization:
- the integration of multiple inward and outward currents defines cellular repolarization (action potential)
- integration of cellular activity defines QT interval effects on ECG

*Net* outward (repolarizing) current:
- defines repolarization and terminates each cardiac cycle
- reduced net outward current leads to delayed repolarization, QT prolongation

- We understand the cellular mechanisms that cause delayed repolarization that enable TdP
hERG (iKr) Current: One of Multiple Currents that Defines Ventricular Repolarization

- Potency of hERG current block alone (IC50 values) not always predictive of delayed repolarization
  - IC50 relative to clinical exposures
  - Kinetics of hERG block a consideration in assessing net current balance during highly sensitive action potential plateau
- Multiple cardiac currents define net current balance; essential to comprehensively review drug effects on prominent currents if iKr reduced

Repolarization reserve: ability to sustain repolarization when challenged by reduced net outward (repolarizing) current – qNET
Drugs Block *Multiple Currents*: Inward Currents May Balance Outward Currents

Drugs with low torsade risk may have balanced block of outward current (hERG/iKr) current and inward current (late sodium or L-type calcium block)

More comprehensive mechanistic-based assessment of integrated effects of drug on repolarization is necessary.
Drug-Induced Delayed Repolarization “Set the Stage” for Torsades Arrhythmia

Mechanisms of Torsades-de-Pointes

- Drug Induced ↓ Net Repolarizing Current
  - Excessive Delayed Repolarization, Altered Time Course
  - Triggered Activity Early After-depolarizations (EAD)

- ↑ Heterogeneity (Dispersion) of Intracardiac Repolarization
  - Unidirectional Block, Intramural Reentry
  - Torsades de Pointes

- Non-sustained TdP: Syncope
  - Sustained TdP: VF

Drug Effects on Cellular Repolarization

Consequences on Conduction-Excitation

Arrhythmia Rotor

- Non-Fixed Position: Polymorphic VT/TdS
- Fixed Position: Monomorphic VT

Page et al., J Pharm Tox Methods, 2016

AbbVie
Evaluating Proarrhythmic Risk of Drugs Based on Cellular (In vitro) & Cardiac (In Vivo)-Based Electrophysiologic Effects of Drugs

TdP risk based on mechanistic assessment of repolarization effects using human in silico reconstructions and checked using human stem cell cardiomyocytes, human QT/morphology.

CiPA Non-clinical

In Silico Reconstruction
Cellular Human Ventricular Electrophysiology

Repolarization-Human Stem Cell Derived Ventricular Cardiomyocytes

Mechanisms of Torsades-de-Pointes

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Torsades de Pointes
Non-sustained TdP: Syncope Sustained TdP: VF

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CiPA Clinical

Unanticipated Effects Clinical Phase I Studies

QT Morphology Mechanistic Studies J-Tpk, Tpk-Tend

Vicente et al. 2017
QT Prolongation: A Poor Surrogate Marker of TdP Risk

Precise measures of delayed repolarization (QTc-concentration-response modeling) do not provide precise measures of Torsades risk.

CiPA: Risk assigned based on repolarization studies using human in silico reconstructions (numerical integration), nonclinical studies (cellular level integration) and clinical level (organ level integration- QT morphology)
Thank you

8:15am-9:45am Session I: Overview
Moderator: Gary Gintant, PhD (AbbVie)

- TdP mechanisms and insights- scientific rationale for CiPA Gary Gintant, PhD (AbbVie)(15 min)
- The need for a new approach to assessing the proarrhythmic potential of drugs and overview of CiPA Philip Sager, MD (Stanford University)(15 min)
- The potential role of CiPA on drug discovery, development, and regulatory pathways David Strauss, MD, PhD (US FDA)(20 min)

Q&A / Panel Discussion (40 min) Speakers and
  - Krishna Prasad, MD (EMA)
  - Corina Dota, MD, PhD (AstraZeneca)
  - Peter Kowey, MD (Jefferson Univ)

9:45am-10:00am Break