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Early Clinical Assessment: Can It Be Used to Replace

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Disclosures

- Dr. Kowey has provided consultation regarding cardiac safety to multiple companies, including advice about the proarrhythmic potential of non-cardiac drugs.
- Dr. Kowey's financial arrangements are purely fee for service. He holds no equity interest in any pharmaceutical company.
- Dr. Kowey tends to be surly and impatient when dealing with QT issues, especially when the benefit greatly trumps putative risk.
- I am not a Yankees fan.

Lawrence Peter (Yogi) Berra

"You can observe a lot just by watching."

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The Seductive QT interval

- Easily obtainable, highly recognizable biomarker
- The acquired disease mirrors the congenital form
- Linkage between an ECG parameter and a catastrophic outcome
- Risk roughly proportional to the magnitude of QT prolongation
- Cottage Industry

Yogi Berra at His Best

"If I didn't believe it, I wouldn't have seen it."

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TQT: Clinical Development Benefit

- Quantitative answer (in most cases)
- Predictable pathway to labeling
- Workable methodology (once you get the hang of it)
- Appears to work to keep unsafe drugs off the market or at least labeled properly

Yogi

"If the world was perfect,
it wouldn't be."

TQT: Pitfalls

- The measurement isn't perfect
- Timing is everything
- The methodology is not always applicable
- Limited consideration of pre-clinical information
- Enormous assumptions about pre-eminence of Cmax
- High cost that places a burden on development (esp for small companies)
- Defining the "supra-therapeutic" dose
- Premature demise of new chemical entities
- Not all QT prolonging drugs carry risk
- Labeling fatigue

Yogi Again

"If you don't know where you're going, you might end up some place else."

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Now What?

- We need better pre-clinical information that can be supplemented by a more reasonable clinical paradigm
- We also need better and more reliable post-marketing surveillance for real events
- We don’t need a monolithic approach that fails to account for the vast differences in chemical entities

The Future

- Movement away from assessment of single cardiac currents (e.g. hERG)
- Discovery and consideration of multiple mechanisms of proarrhythmia
- Better use of in vitro/in vivo models with scrupulous standardization and validation (established via clinical events, not surrogates)
- Strategic use of intensive ECG methods
- Quantification of clinical events from new age data sets/analyses

What Has the New Study Done for Us?

- Suggests that one can use careful methods to quantify a QT signal within the context of ordinary clinical development
- Possibly eliminated the need for a positive comparator
- Increased the burden for high quality pre-clinical assessment
- Emphasizes the need for reliable PK/PD sampling to avoid equivocal results
- Does not absolve sponsors of the need for continued clinical surveillance for drugs that have mixed results (and there may be a lot of them)
- But it may free up sponsors to explore other aspects of cardiac and non-cardiac safety that may have more relevance for the entity under consideration

You can’t make this stuff up

Kentucky coach to basketball player: “What is it with you son? Is it ignorance or is it apathy?”

Player to coach: “Coach, I don’t know and I don’t care.”

What About Clinicians?

- This study will have no impact on the vast majority of cardiologists who are ignorant of the issues we are addressing today
- Even most EPs don't care about the current paradigm
- This should not deter us because there are a lot of things they don't care about—like properly controlled studies
- Their concern is ***relative*** cardiac safety and instructions for use.
- Shift in methods will not impact them substantially—unless it fails and drugs are withdrawn
- Consider educational events at professional society meetings—may have traction given recent interest in safety of oncology drugs and anti-infectives, but I doubt it

Yogi, One More Time

"The future ain't what is used to be."