NSVT without QT Prolongation Is it Relevant in Clinical Development? Role of More Intensive Monitoring?

Preston M. Dunnmon, MD, MBA, FACP, FACC
Division of Cardiovascular and Renal Products
US Food and Drug Administration

December 2, 2015

Disclaimer

The findings and conclusions in this presentation have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination or policy. The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services.

NSVT w/o QT Prolongation

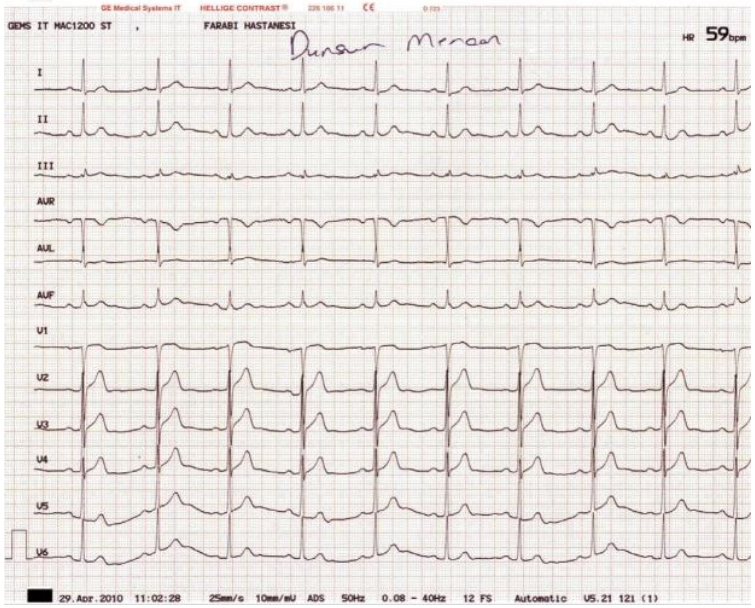
- Monomorphic or polymorphic
- Potential mechanisms relevant to drug development
  - Ischemia
  - Thrombosis
  - Fibrosis
  - Myocarditis
  - Pericarditis
  - Catacholaminergic effects

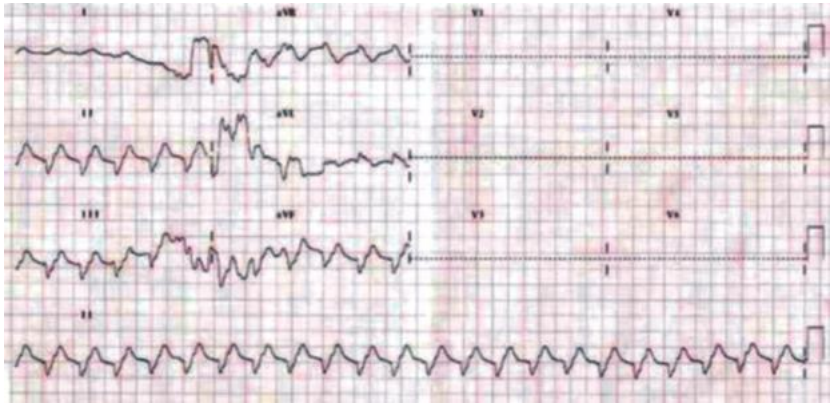
Drug A (metabolic blocker)

- Approved drug for fatal disease
- Animal studies – cardiac failure, fibrosis, hemorrhage, TnT elevations
- V-tach reported in clinical trials (? Long QT)
- Labeled warnings
  - Cardiac failure (decreased LVEF)
  - Myocardial infarction-DVT-PE (thrombotic process)
  - Restrictive cardiomyopathy (fibrotic process)
  - Death due to cardiac arrest within one day of administration

Drug B (metabolic blocker)

- Approved for fatal disease
- Acute STT-wave change c/w ischemia
- Presumed vasospasm
- First exposure predominance
- Pulseless VT and primary VF





Hippokratia. 2011 Jan-Mar; 15(1): 93–95

Sympathomimetics

- Drug C
  - Labeled warning for ventricular arrhythmias
  - Used for ventricular arrhythmia induction at electrophysiology study
- Ephedra-induced ventricular tachycardia

Drug D (metabolic blocker)

- First in class for potentially fatal disease
- No QT prolongation in animals/human, but elevated cardiac troponin I seen in several animals of two species
- One animal had 4 beat fun of NSVT
- FIH and SAD study in humans no issues
- First human MAD study, two DR/TE AEs
  - Transient low-grade cTnI elevation
  - NSVT per the following EGC

Drug D: Should Development Path Change?