Non-sustained VT in Drug Development

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A Recurring Dilemma

In my practice as a consultant to pharmaceutical sponsors, this is a common scenario:

• NSVT recorded during Holter or telemetry monitoring in an early-in-man study

• Incidence greater in drug compared to placebo recipients (or, no placebo in the study design)

• Concern arises by sponsor, potential partners and FDA:
  • Should the drug be killed?
  • Can the drug be developed further without first quantifying or disproving the relationship between drug and NSVT?
  • How can the relationship between drug and NSVT be evaluated in a scientifically sound manner?
  • What type of monitoring will be required during and after the drug’s development?
First: Exclude False NSVT

- SVT with aberrancy
- Artifact superimposed on NSR
- Ventricular bigeminy with aberrancy
- Neural stimulators
- High field MRI
- Tremor
Bottom Line

For the time being, I do not recommend Holter or other forms of monitoring to detect NSVT (and other arrhythmias) in clinical drug development, unless a prior observation forces it.
Why?

• At present we do not know:
  • The daily incidence of NSVT in normal subjects
  • The day-to-to variability of the incidence of NSVT in normal subjects
  • The age and sex-related variation in the incidence of NSVT in normal subjects
  • The distribution of the duration of NSVT in normal subjects
  • The distribution of the time-of-day of NSVT in normal subjects
  • The frequency, duration and timing of monitoring required to reliably detect NSVT in normal subjects
  • The frequency, duration and timing of monitoring required to reliably detect a drug-related change in the incidence or duration of NSVT in normal subjects
  • The risk posed by presence of NSVT in normal subjects and various patient subsets
  • The influence of frequency, duration and timing on risk

• New research, underway, may provide this missing information (except for the last two bullets)
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Risk – Much Ado About Nothing?

We really don’t know if or to what extent NSVT is a risk for more threatening arrhythmias in normal subjects.

- 73 normal subjects with complex VEA on HM followed for mean 6.5 years; 26 had NSVT
- Two deaths (1 cancer, 1 sudden)
- Expected number of deaths 7.4

**Long-Term Follow-up of Asymptomatic Healthy Subjects with Frequent and Complex Ventricular Ectopy**

Harold L. Kennedy, M.D., M.P.H., James A. Whitlock, B.S., Michael K. Sprague, Lisa J. Kennedy, Thomas A. Duckingham, M.D., and Robert J. Goldberg, Ph.D.


- 193 healthy military aviators followed for mean 10.6 years
- No sustained VT events documents
- Three sudden deaths: CAD, DCM, MVP

**Nonsustained ventricular tachycardia in 193 U.S. military aviators: long-term follow-up.**

Gardner RA², Kruyer WB, Pickard JS, Celio PV

- 193 healthy military aviators followed for mean 10.6 years
- No sustained VT events documents
- Three sudden deaths: CAD, DCM, MVP
Exceptions - scenarios in which monitoring should be done if NSVT detected, despite knowledge gaps

• Ventricular ectopy documented in animal studies
• The drug prolongs QT or QRS interval
• The drug has known, strong cardiac ion channel blocking properties ($I_{Kr}$, $I_{Ks}$, $I_{K1}$, $I_{Na}$, $I_{CaL}$)
• Caveat: Not clear what the monitoring regimen should be
A Temporary Solution to the NSVT problem (which I recommend)

• Do not do arrhythmia analyses on Holter data collected in early clinical drug development.

• If you employ telemetry monitoring in early clinical drug development, establish written, liberal rules allowing for episodes of NSVT without further assessment.

• The same rule setting could be used for other “normal” abnormal rhythms (such as second degree AV block and sinus pauses).
Why the Temporary Solution?

I know of two studies designed to define NSVT (and other arrhythmia) incidence in normal subjects. Without the epidemiological information these studies will provide:

• How can you design a science-based monitoring regimen to evaluate baseline NSVT occurrence?
• How can you endeavor to prove presence or absence of drug-induced NSVT?
• Is such an endeavor too expensive and time consuming to undertake during drug development?
• Are phase 4 monitoring programs more practical?
Pending Research

• These studies will retrospectively determine the incidence of NSVT on 24-hour recordings from normal subjects who participated in clinical trials

• Will determine the variability of the incidence of NSVT on serial recordings

• May identify factors that affect reproducibility

• Will include factors that may affect risk (to be proven later)
Factors That May Influence Occurrence, Reproducibility and Risk of NSVT in Normal Subjects

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<tr>
<th>Subject</th>
<th>Rhythm</th>
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<td>• Confined vs outpatient</td>
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<td>• Activity level</td>
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Overwhelming Difficulty of Proving Proarrhythmia


Spontaneous variability of ventricular arrhythmias in patients with chronic heart failure.
Anastasiou-Nana M†, Meniove RL, Nanao JN, Mason JW.

- Patients with HF undergoing 3 consecutive Holter recordings on placebo
- To confidently identify an increase in VT events (i.e., exceeding the 95% CI of spontaneous variability) would have required a 6000% increase in events from the first to subsequent Holter recordings

Am J Cardiol. 1987 Jan 1,59(1) 97-9

Application of a frequency definition of ventricular proarrhythmia.
Morganroth J, Borland M, Ciao G.

- Patients with VEA undergoing 2 or more consecutive Holter recordings on placebo
- Using a 10-fold increase (1000%) criterion yielded a 3% false positive rate for VT exacerbation
My guess at what epidemiological studies will show

- NSVT is modestly frequent in normal subjects undergoing a single 24-hour monitoring period (2%?).
- NSVT is more frequent in normal subjects undergoing two 24-hour monitoring periods (3%).
- NSVT is not very reproducible from one day to the next (30%).
- Reproducibility of detected NSVT is directly related to its frequency on the first day.
- The frequency and duration of NSVT is influenced by sex and age and other subject characteristics.
- Reproducibility of detected NSVT is influenced by the duration of the detected NSVT.
- In most cases, proving or disproving drug-induced NSVT is too burdensome as a pre-NDA requirement.
Possible Phase 4 Approaches

• It is likely that in most cases true drug-induced NSVT can only reasonably be proven in the large numbers of patients that will be exposed in Phase 4.

• Post-marketing prospective registries could be used to follow an appropriate number of drug recipients
  • with pre-drug and on-drug holter recordings
  • periodic status assessments
    • documented arrhythmia event
    • sudden death
  • these event rates could be compared with comparable patient populations not receiving the drug, either prospectively or via AERS

• The post-marketing approach has the huge potential advantage of defining the risk posed by drug-induced NSVT