Can newer telemetry approaches help evaluate a safety signal when there isn't a placebo/comparator group

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The problem – background arrhythmias

- Important to detect any drug induced arrhythmias
  - Problem – background incidence of arrhythmias
  - How to distinguish between background and drug induced arrhythmias?
- Best option: large trials with placebo/standard of care arm
- Not always an option – especially in Oncology
- Second best option: screening/predose rhythm monitoring
- Third best option: if arrhythmia detected, repeat monitoring after trial

Even “normal” individuals have arrhythmias

Sample size	Age range (y)	Sampling duration time (h)	Prevalence of ventricular ectopy (%)	Prevalence of multiform ventricular ectopy (%)	Prevalence of NSVT (%)
65	25-39	2.5	0	0	0
27	NK	8-12	44	NK	NK
35	NK	10	14	NK	NK
53	20-70	24	8	2	0
86	16-65	48	73	15	2
23	35-65	48	[illegible]	9	0
74	20-80	24	76	38	1
50	23-27	24	50	12	2
30	Mean age 47	24	33	7	3
23	NK	48	35	0	0
189	20-70	24	41	7	NK
13	60-84	24	100	8	0
131	10-13	48	26	25	0
33	24-34	24	9	NK	0
100	20-70	24	21	3	0
50†	22-28	24	54	10	2
101	16-68	24	39	NK	0
300	40-59	24	76	33	2
98	60-85	24	80	35	4
20‡	19-28	24	70	20	0
70‡	Mean age 23	16	39	3	3
260	40-79	24	69	23	2
80‡	<40	24	30	NK	1
170	18-70	24	41	15	2
100	14-16	48	41	10	3
101[b]	20-59	24	34	9	1
111	20-79	24	61	NK	1
147	15-65	24	46	12	1
50	22-57	24	22	8	2
100	40-69	24	63	22	3
40	Mean age 56	48	83	10	5
60	Mean age 25	24	40	0	0
152	18-59	24	19	<1	2
624	NK	24	60	NK	1

Literature review from CSRC white paper about ventricular arrhythmias in early clinical trials

Prevalence of VPCs – up to 80% on 24 hour holter

Prevalence of nonsustained VT – as high as 4% on 24 hour holter

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Arrhythmias seen on holter in “normals”

- Simple ectopy (APCs, VPCs) – very common
- Nonsustained SVT – 3-5 beat episodes
- Nonsustained VT – 2-4%
- Profound bradycardia, AV Block – esp. at night, athletes
- Vagally mediated bradycardia, AV Block – phlebotomy, IV placement, vomiting

- Sustained SVT, VT very rare in healthy individuals (also, almost never seen in clinical trials)

Strategies when placebo/comparator unavailable

- "Screening" holter or outpatient telemetry/event recorder
  - Additional cost; may require an extra visit
  - For high risk compounds, avoid highest risk patients
- Pre-dose holter or outpatient telemetry/event recorder
  - Intended to document baseline arrhythmias, not exclude patients
  - Additional cost, may require an extra visit
- Pre-dose inpatient telemetry to establish baseline
  - Additional cost
  - Requires additional inpatient confinement

Case Study #1 – Value of a placebo group

- Respiratory combination product – LAMA and LABA
  - During large Phase III trial, holter substudy in 200+ patients
  - 24 hour holters at baseline, week 12, week 26
- AF: 10 at baseline; 4 with chronic AF included; only 1 new case of AF; no change in VR of 4 pts w. chronic AF
- AV Block: no imbalance of Mobitz I; 2:1 AV Block only in pts w. prior Mobitz I
- SVT: one pt. w. sustained SVT – baseline holter frequent SVT-NS
- VT: VT-NS on 24 baseline holters; 15 pts. w. VT-NS during trial; no imbalance

Case study 2: value of screening and f/u data

- MAD study of agent: no known CV effects; routine telemetry
- During MAD – two subjects with AV Block
  - 41 yo female: Wenckebach on D7
    - Unable to review pre-dose telemetry strips
    - Wenckebach present on holter 6 d, 6 weeks post last dose
  - 63 yo female: Wenckebach on D1, D7
    - Telem for 12 d post last dose: frequent Wenckebach
    - Frequent Wenckebach still present 8 wks post last dose
    - Pre-dose telem reviewed: Wenckebach present
- Added screening holters – 15/109 had AV Block; excluded

Potential value of newer technologies

- Sensitivity of 24 hour holter may be inadequate
- Longer duration outpatient telemetry for screening may be advantageous
  - High risk compound: might exclude subjects with arrhythmias or conduction disturbances
  - Low risk compound: might not necessarily exclude, but protects trial if events occur during study
  - Protect patients and program; avoid anxiety and cost if events detected in trial

Potential value of newer technologies

Alternatively, use longer duration outpatient telemetry after trial for patients with arrhythmias or symptoms

- **More likely to document infrequent events that might be missed by a holter**
- **May help overcome imbalance in duration of monitoring prior to and during trial**
  - **Screening holter: typically 24 hours**
  - **Telemetry during trial: may last for several days**
  - **Yield of continuous ECG monitoring directly related to duration**