

AF Detection During Drug Development: What Constitutes a “Signal”

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Disclosure

- Dr. Kowey has consulted for dozens of companies who found AF in their clinical development program and didn't know what to do with it (he wasn't sure either).
- Dr. Kowey has also consulted for several companies that make equipment that is used for AF detection, for better or for worse.

Jane Wagner

“Reality is the leading cause of stress among those in touch with it.”

Case Example

- New chemical entity
- Antibody to treat relatively rare but lethal cancer
- Scant pre-clinical information but no obvious cardiac safety signal
- Minor changes in ECG parameters in phase 1
- Small but consistently and statistically unbalanced incidence of “AF” in phase 2/3

What is the Concern?

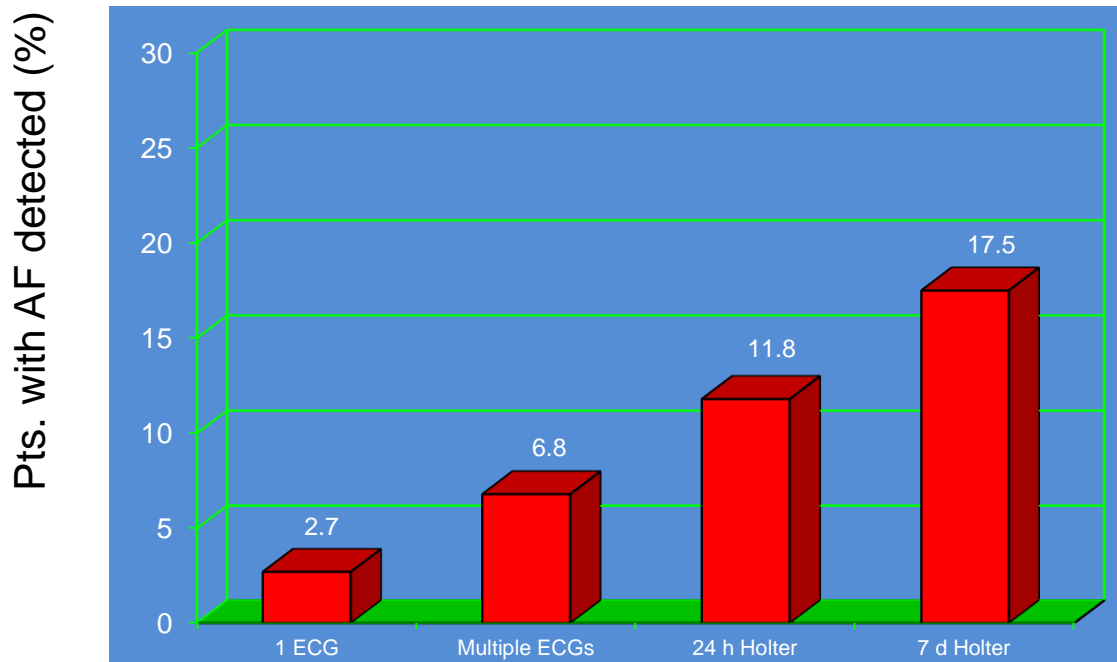
- Undiagnosed AF with a rapid ventricular response could lead to heart failure (already a concern with many chemo Rx agents)
- Drugs used to treat AF might have a PK or PD interaction with multiple drugs used to treat cancer (e.g. dofetilide)
- Unrecognized AF could cause a stroke to which patients may be particularly disposed
- Anticoagulants confer a particularly high bleeding risk in many cancer patients

Pragmatic Issues to Consider

- Biological plausibility based on MOA, pre-clinical data, cardiac electrophysiology
- Validity of the data in hand
- Further exploration
 - More ECGs
 - Short/long term external monitoring
 - Monitored “sample” versus total cohort
 - Implanted technology

AF Detection: 7 days Holter

- More intensive monitoring results in more AF detection



Population-Specific Hazards

Does the study population have a higher than expected incidence of clinical factors that enhances the risk of a CVA with AF (CHADS-VASc)

- Hypertension
- Heart failure
- Diabetes
- Age
- Prior cerebrovascular event
- Vascular disease
- Female gender

Disease-Specific Hazards

Does the intended treatment population have clinical characteristics that would predict a particularly high risk of developing AF?

e.g. HATCH (hypertension, age, TIA/stroke, COPD, heart failure)

Does the treatment population have a higher risk of developing complications from AF (stroke or CHF) e.g. CHADS-VASc

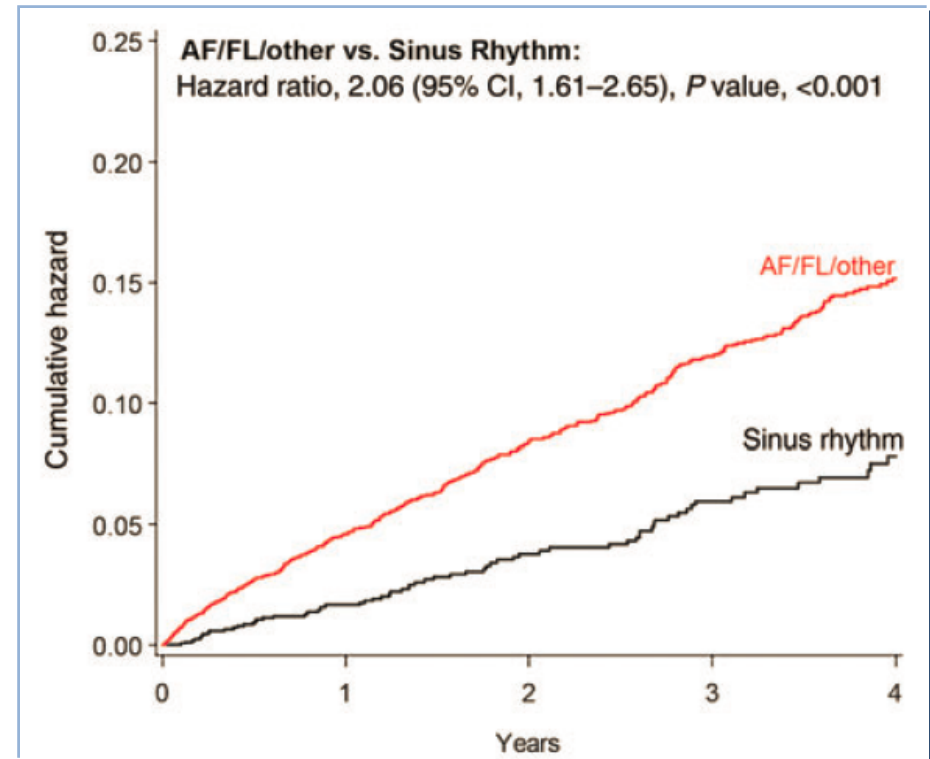
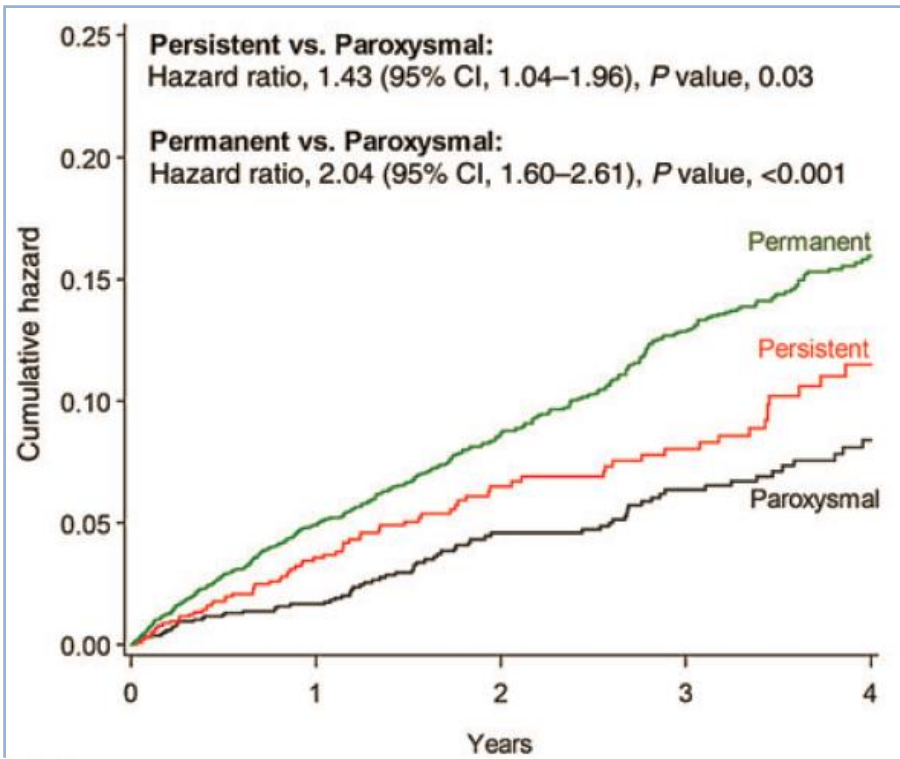
Definitions

Is there a characteristic, pattern or density of AF that is of particular concern?

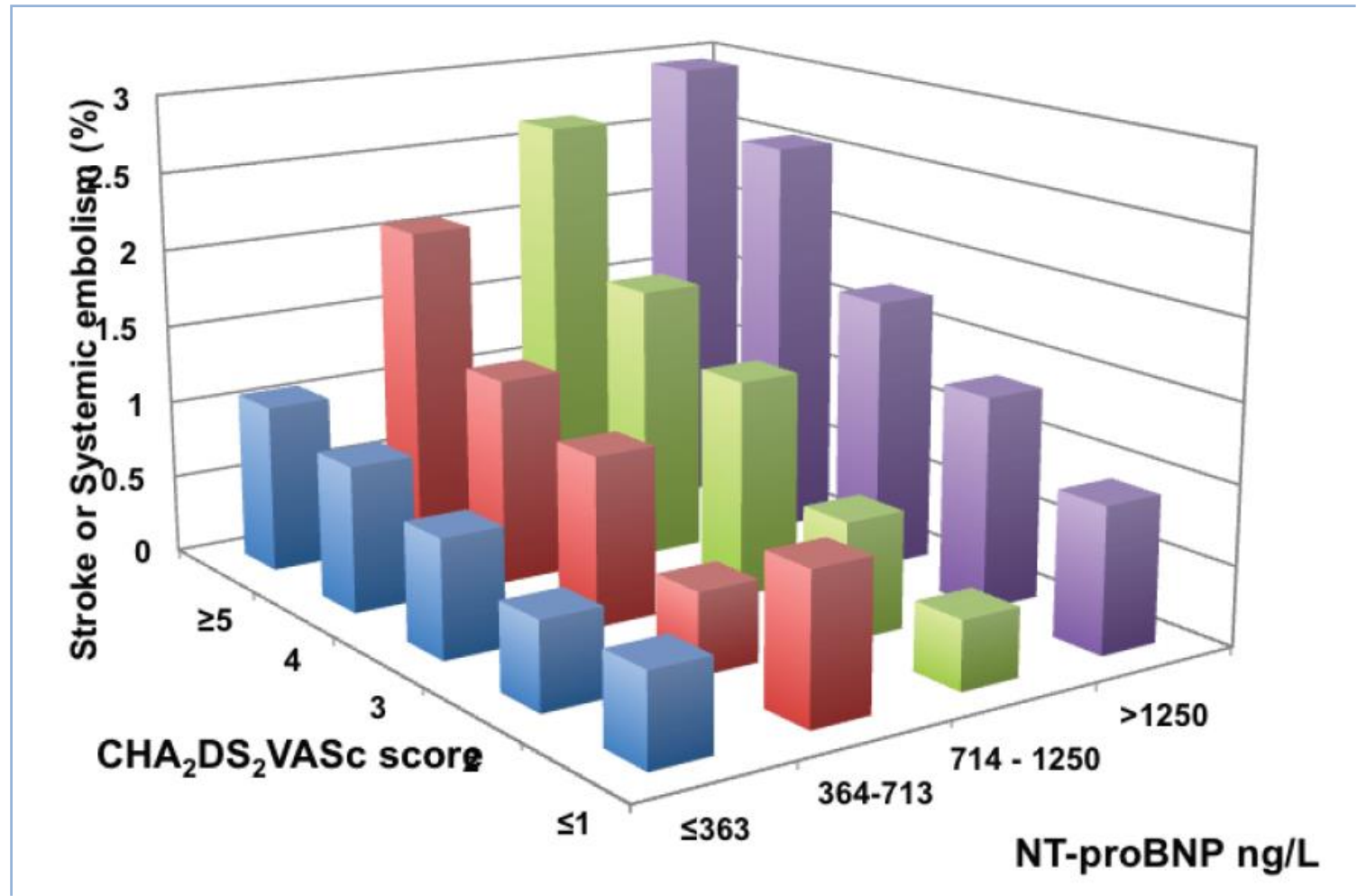
Are there accessory data (e.g. biomarkers) that might be helpful in predicting the risk of AF or of stroke?

Pattern of AF and Embolic Stroke:

6563 ASA-treated patients from ACTIVE-A and AVERROES



Risk of Stroke By Quartiles of NT-proBNP



ASSERT RESULTS: Using Un-Adjudicated AHRE

	RR of clinical AT	P	RR of Primary Outcome* (Ischemic Stroke and Non-CNS Embolism)	P
AHRE > 6min	5.25	<0.001	2.04	0.04
AHRE > 30 min	5.37	<0.001	2.10	0.04
AHRE > 6 hrs	7.83	<0.001	4.32	<0.001

ASSERT: Stroke/ SEE Risk According to CHADS₂

CHADS ₂ Score	No. of Patients	Subclinical Atrial Tachyarrhythmias between Enrollment and 3 Months						Hazard Ratio for Ischemic Stroke or Systemic Embolism with Subclinical Atrial Tachyarrhythmias (95% CI)*
		Present			Absent			
		<i>no. of patients</i>	<i>no. of events</i>	<i>%/yr</i>	<i>no. of patients</i>	<i>no. of events</i>	<i>%/yr</i>	
1	600	68	1	0.56	532	4	0.28	2.11 (0.23-18.9)
2	1129	119	4	1.29	1010	18	0.70	1.83 (0.62-5.40)
>2	848	72	6	3.78	776	18	0.97	3.93 (1.55-9.95)

*The P value for trend is 0.35.

CAVEATS

- Only 15% of patients with SCAF had SCAF > 6 min within 1 month of stroke.
- Most SCAF occurring before stroke was far shorter than 48 hours.
- Most patients with 6 min episodes of SCAF did not require long-lasting episodes for stroke to occur.

Evidence gaps:

How much SCAF warrants oral anticoagulation, and is that dependent on the underlying stroke risk of individual patients?

What is the cause – effect relationship of AF and stroke in patients with device-detected subclinical AF?

Is SCAF simply a marker of hypercoagulability, endothelial damage, inflammation?

Or should we simply anticoagulate all subjects presenting with SCAF?

Harry S. Truman

“If you can’t convince them,
confuse them.”

Conclusions

- AF is ubiquitous and of high incidence in aging populations
- It is likely to be detected by chance in any clinical trial
- Imbalances in incidence or prevalence are likely by the play of chance but must be explored/explained given the consequences
- If/how to apply extended monitoring is unclear especially since we have not been able to define “signal.”