When does enhanced monitoring for atrial fibrillation add value?

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• Spectranetics

Full disclosures available at https://www.dcri.org
AF Adversely Affects QoL


*P < .05 AF vs controls
Why Monitor?
Natural History of Atrial Fibrillation

Death
Stroke
Heart Failure
TIA
CV Hospitalization
The importance of outcomes beyond stroke

![Graph showing cumulative incidence of various outcomes over years following diagnosis of incident atrial fibrillation.](image)

- Death
- Heart failure
- Myocardial infarction
- Stroke
- Gastrointestinal bleeding

Years following diagnosis of incident atrial fibrillation

Cumulative incidence, %

Persistent AF is associated with worse survival

Steinberg, BS. Eur Heart J. 2014; In press.

Adjusted HR_{\text{paroxysmal}} = 0.79 (0.67 – 0.94)

p=0.0061
AFB is associated increased risk of hospitalization in pacemaker patients: BRADY CARE
• Pts <67 years HR 1.81 (95% CI 1.11-2.94)
  – Independent of clinical stroke.

• Strongly associated with duration of exposure to AF
Effectiveness Endpoints in Trials of Surgical Interventions for AF

Primary Endpoints

• Electrocardiographically documented AT/AF $\geq 30$ seconds
• Antiarrhythmic therapy
• Cardioversion
• Repeat surgical/catheter ablation

Secondary Endpoints

• AF burden
• Symptom scores
• Quality of life
• Exercise tolerance
• LVEF
• Atrial transport function
• Left atrial size
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24-Hour Continuous ECG Monitoring before TAVR

No known AF
n=266

- Newly diagnosed paroxysmal AF/IA n=28 (10.5%)
  - Therapy change n=16 (57.1%)
  - No therapy change n=12 (42.9%)

- No AF/IA n=238 (89.5%)
  - Change in medical treatment n=11 (45.8%)
  - Temporary pacing wire n=1 (4.2%)
  - Permanent pacemaker implantation n=5 (20.8%)

No permanent pacemaker implantation
n=373

- Advanced AVB or severe bradycardia n=24 (6.4%)
  - Therapy change n=17 (70.8%)
  - No therapy change n=7 (29.2%)

- No advanced AVB or severe bradycardia n=349 (93.4%)
  - Antiarrhythmic therapy n=9 (32.1%)
  - Anticoagulation therapy n=12 (42.9%)

Marina Urena et al. *Circulation.* 2015;131:469-477
Cerebrovascular events within 30-days after TAVR

- Newly diagnosed AF/AT: 7.1% (n = 28)
- Known AF/AT: 4.2% (n = 169)
- No AF/AT: 0.4% (n = 238)

P = 0.005
Effect of ranolazine on AF in NSTEMI (MERLIN TIMI 36): continuous ECG during the first 7 days

Clinically insignificant AF (<0.01%)
Paroxysmal AF (0.01–98%)
Predominantly chronic AF (>98%)

Global $x^2$  
$p < 0.01$

No. patients

Placebo
Ranolazine

20 (7)
48

28
18

5
Clinical AF events in patients treated with ranolazine or placebo

AF Burden in patients with paroxysmal AF

- Placebo (n = 48)
  - Median = 16.1%
- Ranolazine (n = 18)
  - Median = 4.4%

P-value = 0.015

Patients with an atrial fibrillation adverse event (%)

- Placebo
- Ranolazine

HR 0.71 (95% CI 0.55–0.92)
P = 0.010

Days from randomization

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PASCAL: Importance of AF burden in clinical trials

**ITT Population, % Change in AFB from Baseline**

- Placebo: 200 mg bid
- 400 mg bid
- 600 mg bid

Median Percent Change from Baseline:
- 11.2 (p=0.07)
- -12.6 (p=0.013)
- -54.4 (p=0.0013)

Dose Response: p=<0.0001

Jonckheer-Terpstra test

**Wilcoxon rank sum test vs Placebo**

N=18
N=20
N=15

Ezekowitz M et al; Abstract
Enhanced Late $I_{na}$ and Arrhythmogenesis

**EP Phenotype**

- $\uparrow$ Late $I_{Na}$
- GS-6615 (eleclazine)
- GS967
- $\uparrow$ Diastolic Depolarization
- $\uparrow$ APD Prolongation
- $\uparrow$ QTc

**Ca$^{2+}$\textsubscript{i}**

**NCX**

Abnormal automaticity

VT

Triggers

Substrate

Dispersion

Spatial

Endo

Epi

Temporal

APD

Belardinelli et al, Heart Rhythm 12: 440-448, 2015
Changes in AF Burden Over 12 Weeks

≥70% Reduction in AFB

Overall Changes in AFB

Reiffel JA. Circ Arrhythm Electrophysiol. 2015;8:1048-56.
CAT HF: Arrhythmia Substudy Design

Overall CAT-HF Population

MV-triggered ASV

~50 dual-chamber devices

Control Arm

~50 dual-chamber devices

Arrhythmia Core Lab Adjudication

1° and 2° Events at 0, 3, 6 months
Genotype-Directed Therapy of AF in HF: Bucindolol

\[ \beta_{1389} \text{Arg/Arg} (n = 441; 36 \text{ events}) \]

- Risk reduction 74%
- Hazard Ratio = 0.26 (0.12 – 0.57)
- \( P \)-value = 0.0003

\[ \beta_{1389} \text{Gly carriers} (n = 484; 44 \text{ events}) \]

- No risk reduction
- Hazard Ratio = 1.01 (0.56 – 1.84)
- \( P \)-value = 0.969

Interaction \( p = 0.008 \)
Genetically Targeted Therapy for the Prevention of Symptomatic AF in Patients With Heart Failure (GENETIC-AF)

LVEF <0.50, Class II-III HF w/in 90 days
No contra-indications to β-blockers
β₁389 Arg/Arg genotype

Recent onset Sx
AF, 1 wk – 1 yr;
Class I-III HF

n = 100 (310)
Bucindolol

ECV @ 3 wks if still in AF

n = 100 (310)
Toprol-XL

Time 0 (chemical conversion to SR or ECV)
AF free/event: from 24 hrs after ECV

1° Endpoint = Recurrent AF or ACM at 24 weeks
Co-Primary for Phase 2b = AF Burden

ClinicalTrials.gov Identifier: NCT01970501
Overaccessorize much?
Patch-Based Holter Monitoring

Smart Phone-Based Event Monitoring

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Monitoring Dofetilide Antiarrhythmic Drug Therapy

AliveCor: QTC = 470 msec

QT = 440 msec
RR = 880 msec

ECG: QTC = 460 msec

QT = 440 msec
RR = 920 msec

Chung EH. J Electrocardiol. 2015;48:8-9
"Pill in Pocket" Anticoagulation: react.com

Slide courtesy of Rod Passman, Northwestern University.
Conclusions

• AF symptoms are the tip of the iceberg

• AF burden is an important biosignature
  – Associated with a variety of important outcomes
    including stroke, hospitalization, and all-cause mortality

• AF burden can assist in trials, particularly in early clinical development

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• Safety first.
• Be aggressive with your ACT targets.
• Bridging therapy is associated with a higher risk of bleeding complications.

Emerging theme >> Anticoagulation transitions carry more risk than continued anticoagulation.

Once a diagnosis of AF is made, stroke prophylaxis should be guided by risk stratification alone (and not rhythm).