What You Need to Know about Undiagnosed Atrial Fibrillation
An Under-Recognized Stroke Risk Factor

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Major Lecture Themes
• Need to know that AFib, even if it is undiagnosed or asymptomatic, is still a risk factor for stroke
• Need to identify patients who do not have AFib but are at higher risk of stroke if they do develop it
• Need to know about new and emerging approaches for prolonged or intermittent ECG screening in patients likely to have undiagnosed AFib
• Need to prescribe oral anticoagulation for those high-risk patients with newly identified AFib

What We Know
• AFib with risk factor(s) and diagnosed in routine care has 5X risk of stroke
• Even short episodes (>6 min) of “silent” AFib are a risk factor for stroke
• Silent AFib is common: 30% of pts with pacers, 1.4% of population ≥ 65 y/o (500,000 in US alone)
• CHA2DS2VASc features are risk factors for stroke with or without AFib

What We Do Not Know
• Is the risk of silent AFib detected by pacers and screening reduced by oral anticoagulants?
• If so, what is the threshold for when treatment should be used?
• What is the role of monitoring devices and detection strategies?

AFib, even if it is undiagnosed or asymptomatic, is still a risk factor for stroke.

Relationship Between Atrial Fibrillation and Age

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Permanent AFib is a greater risk factor than paroxysmal AFib

Pattern of AFib and Embolic Stroke

6563 Aspirin-treated Patients from ACTIVE-A and AVERROES Trials

Permanent, persistent, paroxysmal AFib
AFib vs normal sinus rhythm at enrollment

Studies Evaluating Risk of Stroke Versus AFib Burden

Even Small AFib Burden Increases Stroke Risk

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>n</th>
<th>AFib Burden Measure</th>
<th>HR for stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>MOST</td>
<td>312</td>
<td>5 min</td>
<td>6.7</td>
</tr>
<tr>
<td>2005</td>
<td>Capucci</td>
<td>725</td>
<td>( &gt;24 ) hrs</td>
<td>3.1</td>
</tr>
<tr>
<td>2009</td>
<td>Botto</td>
<td>968</td>
<td>CHADS + AF burden</td>
<td>6.2</td>
</tr>
<tr>
<td>2012</td>
<td>Home monitor CRT</td>
<td>590</td>
<td>3.8 hrs</td>
<td>9.4</td>
</tr>
<tr>
<td>2012</td>
<td>TRENDS</td>
<td>2466</td>
<td>3.5 hrs</td>
<td>2.4</td>
</tr>
<tr>
<td>2012</td>
<td>ASSERT</td>
<td>2080</td>
<td>6 min</td>
<td>2.5</td>
</tr>
</tbody>
</table>


Is even modest AFib enough to increase risk of stroke?

New Models of AFib Diagnosis and Management

- New Approaches for AFib
- New technologies – e.g. AliveCor, Reveal LINQ, WatchBP Home, Health Stations
  - Long-term and intermittent monitoring
  - Self-monitoring
- Management of newly diagnosed AFib; guides to anticoagulant treatment
  - Assessment of stroke risk
  - Assessment of disease burden

Chen LY et al. Circulation. 2018;137:00-00. DOI: 10.1161/CIR.0000000000000568

Atrial Fibrillation Burden

- Current guidelines recommend using vascular risk factors (as measured by the CHA2DS2-VASc score) and not considering AFib burden when making decisions regarding anticoagulation for stroke prevention in AFib
- The strongest evidence, however, suggests that patients with persistent AFib are at higher risk of stroke than those with paroxysmal AFib
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AFib Burden: What We Don’t Know

- Optimal monitoring frequency and duration to measure AFib burden
- Threshold of AFib burden that results in an increased risk of stroke, heart failure, dementia, and other AFib-related outcomes
- Prevalence of subclinical AFib and effects of AFib burden in community-based cohorts
- Risk factors and determinants of AFib burden in broad community-based cohorts
- Lack of temporal relationship between AFib burden and stroke in AFib patients
- How AFib burden will need to be redefined in the era of widespread, long-term continuous cardiac monitoring
- Threshold of AFib burden that indicates need for anticoagulation in patients with higher risk of stroke (e.g. CHA2DS2-VASc score ≥2)

Chen LY et al. Circulation. 2018;137:00–00. DOI: 10.1161/CIR.0000000000000568

Screening for Undiagnosed AFib Is Effective

- Screening can increase detection rate of new cases of AFib: 1.63% a year compared with 1.04% without systematic or opportunistic screening
- Systematic screening: invitation for electrocardiography
- Opportunistic screening: pulse taking and electrocardiography if the pulse is irregular
- Use of new technologies for large-scale population screening
  - Hand-held ECG devices; personal-monitoring devices
- Incidence of previously unknown AFib was found to be 1.4% in ≥65 year olds


Whom to Screen

- People over 65 years of age
- People at high cardiovascular disease risk
- People with predisposing conditions:
  - Hypertension
  - Heart failure
  - Coronary artery disease
  - Obesity
  - Diabetes mellitus
  - Chronic kidney disease
  - Obstructive sleep apnea
  - Diabetes mellitus
  - Chronic kidney disease
  - Obstructive sleep apnea


- Diabetes mellitus
- Chronic kidney disease
- Obstructive sleep apnea

CHA2DS2-VASc Risk Score

This Can Be Useful to Identify Patients At-risk for Stroke

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A2 Age ≥75 year</td>
<td>2</td>
</tr>
<tr>
<td>D Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S2 Prior stroke or TIA</td>
<td>2</td>
</tr>
<tr>
<td>V Vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>A Age 65-74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sc Sex category – female</td>
<td>1</td>
</tr>
</tbody>
</table>

CHA2DS2-VASc Risk Score Annual Stroke Risk Rate

0 | 0.8%
1 | 2.5%
2 | 3.7%
3 | 5.9%
4 | 9.3%
5 | 15.3%
6 | 19.7%
7 | 21.5%
8 | 23.6%
9 | 26.6%


It is important to consider new and emerging approaches for prolonged or intermittent ECG screening in patients likely to have undiagnosed AFib.

ASSERT: Study Design

Do Device-detected Atrial Tachyarrhythmias Predict Increased Stroke Risk?

Prospective Cohort Design

- 2580 pts enrolled after pacemaker or ICD
- Age ≥65 years
- History of hypertension
- Excluded if any history of AF or on VKA
- Minimum follow up 1.75 yrs
- Maximum follow up 5 yrs

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**ASSERT Trial: Subclinical AFib and Risk of Stroke**

*Atrial Tachyarrhythmias > 6 min ≤ 3 Months After Pacemaker or Defibrillator Implantation*

- **HR 2.49 (1.28 – 4.85)**
- **Subclinical atrial tachyarrhythmias present**

**ASSERT Trial**

Un-adjudicated Atrial High Rate Episodes (AHRE)

<table>
<thead>
<tr>
<th>RR of clinical AFib</th>
<th>P</th>
<th>RR of Primary Outcome (Ischemic Stroke and Non-CNS Embolism)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHRE &gt; 6min</td>
<td>5.25</td>
<td>&lt;0.001</td>
<td>2.04</td>
</tr>
<tr>
<td>AHRE &gt; 30 min</td>
<td>5.37</td>
<td>&lt;0.001</td>
<td>2.10</td>
</tr>
<tr>
<td>AHRE &gt; 6 hrs</td>
<td>7.83</td>
<td>&lt;0.001</td>
<td>4.32</td>
</tr>
</tbody>
</table>

**CHADS2 Score**

- **Total Pts.**
- **Sub-clinical Atrial Tachyarrhythmia between enrollment and 3 months Present vs. absent**
- **Pts. Events %/yr**

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>Total Pts.</th>
<th>Sub-clinical Atrial Tachyarrhythmia between enrollment and 3 months</th>
<th>Pts. Events %/yr</th>
<th>HR</th>
<th>95% CI</th>
<th>P (trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>600</td>
<td>68</td>
<td>0.56</td>
<td>2.11</td>
<td>0.23 – 15.9</td>
<td>0.352</td>
</tr>
<tr>
<td>2</td>
<td>1028</td>
<td>199</td>
<td>1.29</td>
<td>1.83</td>
<td>0.60 – 5.40</td>
<td>0.035</td>
</tr>
<tr>
<td>≥2</td>
<td>848</td>
<td>72</td>
<td>0.87</td>
<td>3.05</td>
<td>1.35 – 7.05</td>
<td>0.005</td>
</tr>
</tbody>
</table>

**How close is the temporal relationship between AFib episodes and stroke?**

- Of 51 patients with stroke/SE, 26 (51%) had Subclinical AFib (SCAF).
- In 18 patients (35%), SCAF was before stroke.
- Only 4 patients (8%) had SCAF within 30 days before stroke, and only 1 of 4 patients had SCAF at time of stroke (B).
- In 14 patients with SCAF detected >30 days before stroke, most recent episode was median of 335 days (26th to 76th percentile, 211–619) earlier.
- Eight patients (16%) had SCAF detected only after stroke, despite continuous monitoring for median of 228 days before event.

**Duration of Device-Detected Subclinical AFib and Occurrence of Stroke in ASSERT**


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ARIESIA Study Protocol Overview

**Objective:** To test if apixaban is superior to aspirin for prevention of stroke and systemic embolism in patients with device-detected subclinical AF.

**Design:** Double-blind, double-dummy randomized clinical trial

**Sample Size:** 4000 patients

**Population:** Patients with at least one episode of SCAF ≥ 6 min but none > 24 hrs; CHA2DS2-Vasc ≥ 4; without clinical AFib and without any contraindication to NOAC or aspirin.

**Intervention:** 5 mg bid apixaban vs 81 mg daily aspirin

**Follow-up:** Event driven, estimated 3 years average

**Outcomes:** 1º efficacy: composite of stroke/TIA with imaging and systemic embolism 1º safety: ISTH major bleeding


What proportion of patients with cryptogenic stroke have underlying undetected AFib?

GERPLA Protocol Overview


AFib in Patients with Cryptogenic Stroke


CRYSTAL AF Study of Continuous Cardiac Monitoring to Assess AFib After Cryptogenic Stroke


CRYSTAL AF Risk of Stroke By Quartiles of N-terminal Pro B-type Natriuretic Peptide (NT-proBNP)


% patients with AFib detected

Risk factors:

Cryptogenic Stroke and Underlying AFib


Hazard ratios: 6.4 (95% CI: 1.3 - 27.3)
P=0.001 by log-rank test

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There is a need to know about new and emerging approaches for prolonged or intermittent ECG screening in patients likely to have undiagnosed AFib.

Screening to Identify Unknown Atrial Fibrillation
A Systematic Review

- 1.4% of population ≥65 years have AF on screening
- 34,991,753 people in US ≥age 65
- This translates into 490,000 Americans

Prognosis of Asymptomatic AFib Detected Incidentally
A Case for Screening

European Guidelines
2016 Update

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class of Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opportunistic screening for AFib is recommended by pulse taking or ECG rhythm strip in patients ≥65 years of age</td>
<td>1</td>
<td>B</td>
</tr>
<tr>
<td>Systematic ECG screening may be considered to detect AFib in patients aged &gt;75 years, or those at high stroke risk</td>
<td>1B</td>
<td>B</td>
</tr>
</tbody>
</table>

Canadian Cardiovascular Society Guidelines
2014 Update

- New recommendations for investigation and management of silent AFib (conditional recommendation)
- Oral anticoagulation (OAC) for patients ≥65 years or CHADS2 ≥ 1 with silent AFib > 24 hours or for shorter episodes in high risk patients (e.g., recent cryptogenic stroke)
- All patients with AFib, whether paroxysmal or persistent, should be stratified for stroke risk and OAC therapy prescribed for most patients aged ≥65 years or CHADS2 score > 1
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U.S. Preventive Services Task Force (UPSTF)

Conclusion: Insufficient evidence to determine whether benefits of screening for AFib outweigh harms

- Benefit
  - Screening with ECG detected more new AFibs than no screening
- Potential risks linked to misdiagnosis of abnormal ECG results
  - Avoidable patient anxiety
  - Unnecessary testing
  - Inappropriate treatments or invasive procedures
- Patient management considerations involve more than clinical evidence alone
- Future Work
  - Need for more controlled trial data on asymptomatic patients

Curry SJ et al. JAMA 2018;320:478-484

Representative Screening Devices

AliveCor ECG Analyzer in Mobile Health

"Consumerized" ECG Analysis

- Check heart health anywhere, anytime on a mobile device
- Share information with patients that typically only doctors could see
- Backed up by professional healthcare services
- Large database (~2.5 million) of ECGs
- More accurate and consistent than human interpretations

Provider Dashboard

- For health professionals with patients who use the heart monitor
- Helps provider to review patients’ ECG data
- Free secure web-based portal
- Simply “invite” a patient by entering their email address

http://www.alivecor.com/posts/the-provider-dashboard

A Complete Monitoring Solution

Mobile Alerts
Streamlined Reports
Improved CareLink® User Interface

Reveal LINQ: MyCareLink™ Patient Monitor
Simplified Insertion Procedure

Reveal LINQ™ ICM
MyCareLink™ Patient Monitor
Cellular

Reveal LINQ: A Complete Monitoring Solution

Improved CareLink® User Interface

Reveal LINQ

Easy-to-Use, Clinically Actionable Reports

The Information You Need When You Need It

Comprehensive
Get the full picture with diagnostic trends on simplified reports

Customizable
Optional CareAlert® Notifications with auto-generated reports
95% of physicians found the Reveal LINQ reports easy to use and clinically actionable1

1 Revealed LINQ usability study. October 22, Medtronic, Inc. 2013.
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Device-Detected AFib

How much AF is necessary to warrant treatment?
- Depending on their clinical characteristics, 10% to 20% of people with implantable devices have AF detected over time.
- Continuous monitoring devices are finding more AF than ever before.
- The greater the severity of associated diseases, the less AF it took to be associated with stroke (REACH registry).

REVEAL AF: Detection Rates

<table>
<thead>
<tr>
<th>Time from Device Implant (months)</th>
<th>Freedom from AT/AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>3 mo.</td>
<td>0.6</td>
</tr>
<tr>
<td>6 mo.</td>
<td>0.7</td>
</tr>
<tr>
<td>9 mo.</td>
<td>0.8</td>
</tr>
<tr>
<td>12 mo.</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Number at Risk: 163 127 111 106 67

89% of NDAF patients identified beyond 1 day
78% of NDAF patients identified beyond 7 days
60% of NDAF patients identified beyond 30 days

Ziegler P. et al. Stroke. 2010;41:256-260

Value of Long Term Continuous Monitoring: Detect Intermittent AFib

TRENDS Study Subgroup Analysis

<table>
<thead>
<tr>
<th>Time from Device Implant (months)</th>
<th>Newly Detected AFib (NDAF) in Patients with Thromboembolic Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>93 patients with previous ischemic stroke/TIA who had AF, were continuously monitored via pacemaker or Implantable Cardioverter Defibrillator</td>
</tr>
<tr>
<td>3 mo.</td>
<td>NDAF &gt; 5 minute duration were found in 23% patients</td>
</tr>
<tr>
<td>6 mo.</td>
<td>77% of patients had newly detected AFib or &gt; 50% of follow-up days</td>
</tr>
</tbody>
</table>

85% of NDAF patients identified beyond 1 day
75% of NDAF patients identified beyond 7 day
60% of NDAF patients identified beyond 30 day

Community AFib Screening: AFinder Program

Opportunistic screening in Hong Kong

- 11,574 citizens; aged 50 years or older
- 10,735 had interpretable smartphone ECG records
- 244 (2.3%) had AFib
- 74 (0.69%) had newly diagnosed AFib
- Number needed to screen for 1 newly diagnosed Aib: 145


There is a need to prescribe oral anticoagulation (and anticoagulant options) for those high-risk patients with newly identified AFib.

Drugs Approved for Stroke Prevention in Patients with AFib

- Warfarin (vitamin K antagonist)
- Apixaban (factor Xa inhibitor)
- Dabigatran (thrombin inhibitor)
- Edoxaban (factor Xa inhibitor)
- Rivaroxaban (factor Xa inhibitor)
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Efficacy of Warfarin to Prevent Stroke in AF
Warfarin vs Placebo (Pooled Analysis of 2900 Participants)

Hart RG et al.
Ann Intern Med.
2007;146:857-867.

AFASAK-1 (671)
SPAF (421)
BATAF (420)
CAFA (379)
SPINAF (571)
EAF (439)
All Trials (n=58,541) 64%

Non-vitamin K Antagonist Oral Anticoagulants

Adapted from: Weitz JI, Bates SM.
J Thromb Haemost.

Which anticoagulant?

Efficacy and Safety of DOACs
Meta-analysis of Randomized Trials

Ruff CT et al.
Lancet.
2014;383:955-962.

ENGAGE AF-TIMI 48
ARISTOTLE
ROCKET AF
RE-LY
Combined

All DOACS: Stroke or Systemic Embolic Event (SEE)


Secondary Efficacy Outcomes

Risk Ratio (95% CI)
P

Ischemic Stroke
0.80 (0.83 - 0.87) 0.10

Hemorrhagic Stroke
0.90 (0.85 - 0.95) 0.003

MI
0.80 (0.79 - 1.30) 0.77

All-Cause Mortality
0.90 (0.85 - 0.95) 0.003
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2016 ESC Guidelines for the Management of AFib
Developed in Collaboration with EACTS*

Important changes:
• Avoid the misleading term “non-valvular AF”
• No recommendation to use bleeding scores to withhold oral anticoagulation (only to identify modifiable factors)
• NOACs preferred over warfarin (IA)
• Aspirin is a class III LOE A recommendation (harm) for stroke prevention in AFib

DOAC Dosing

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Standard Dose</th>
<th>Reduced Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>150 mg BID (CrCl &gt;30 mL/min)</td>
<td>75 mg BID (CrCl 15–30 mL/min; dronedarone or ketoconazole)</td>
</tr>
<tr>
<td></td>
<td>110 mg BID (CrCl 15–30 mL/min; metoprolol)</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>20 mg QD with evening meal (CrCl &gt;50 mL/min)</td>
<td>15 mg QD with evening meal (CrCl 15–50 mL/min; statin, DPP-4 inhibitor, sulfonylurea, metformin)</td>
</tr>
<tr>
<td></td>
<td>(CrCl &gt;50 mL/min)</td>
<td>Avoid use with P-gp + CYP 3A4 inducer/inhibitor</td>
</tr>
<tr>
<td>Apixaban</td>
<td>5 mg BID (Most patients)</td>
<td>2.5 mg BID (≥2 of the following: age ≥80 y; weight ≤60 kg; SCr ≥1.5 mg/dL; OR strong dual inhibitors P-gp and CYP 3A4)</td>
</tr>
<tr>
<td></td>
<td>(≥2 of the following: age ≥80 y; weight ≤60 kg; SCr ≥1.5 mg/dL; OR strong dual inhibitors P-gp and CYP 3A4)</td>
<td>Avoid use with strong dual inducers of P-gp and CYP 3A4</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>60 mg QD (CrCl 15–50 mL/min)</td>
<td>30 mg QD (CrCl 15–50 mL/min)</td>
</tr>
</tbody>
</table>

2016 ESC/EACTS Guidelines for Management of AFib

Doses of DOACs According to Renal Function

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Important changes:
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*EACTS: European Association for Cardio-Thoracic Surgery


2016 ESC Guidelines for the Management of AFib
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Summary

- Undetected or silent AFib is relatively common
- It is associated with risk of stroke, related to burden and risk factors
- Whether treating with oral anticoagulant has overall benefit is being investigated in trials
- For the time being:
  - Treat if > 6 to 24 hours, depending on risk factors
  - After cryptogenic stroke, generally treat if > 30 seconds to 2 minutes of AFib
- Whether, when, whom and how to screen is being studied
- In the meantime, patient preferences should be considered for screening

Conclusions

- Reducing stroke risk is essential, regardless of whether a patient is symptomatic or not
- Screening for AF has been made easier by the development of new affordable technology and should be encouraged
- Oral anticoagulants have demonstrated a reduction in stroke risk in patients with AFib, and are superior to no treatment or aspirin
- The prescription of anticoagulation should be based on stroke risk assessed using the CHA2DS2-VASc scoring system

Freedman et al: Circ, 2017
Screening for Atrial Fibrillation
A Report of the AF-S4AF2 International Collaboration

Conclusions

- Screen-detected AFib is not a benign condition and with additional stroke risk factors warrants consideration of OAC
- The setting for AFib screening should be both country and health-system specific

Based on current knowledge
“This white paper provides a strong case for AFib screening now while recognizing that large randomized outcomes studies would be helpful to strengthen the evidence-base.”


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