Epidemiology of Atrial Fibrillation
CA Heart Rhythm Symposium
September 25, 2009

Emelia J. Benjamin, MD, ScM

The NHLBI’s Framingham Heart Study
Boston University School of Medicine

No industry relationships to disclose
1R01HL092577

Atrial Fibrillation
An Epidemiologist’s Perspective

Epidemiology
Risk factors
Prognosis
Future Directions

Atrial Fibrillation
International Epidemiology

4.8% Framingham, USA 70-79 yo
5.4% Sheffield, UK ≥ 65 yo
0.2-0.3% Germany 25-64 yo
1.3% Japan ≥ 40 yo
2.1% Korea ≥ 65 yo
5.1% Netherlands ≥ 60 yo
2.3% Busselton, W. Australia ≥ 60 yo

6.2% men, 4.8% women
CHS: USA 4 sites ≥ 65 yo

Ryder, Benjamin Am J Cardiol 1999;84:131R

Atrial Fibrillation

US Population
Population with AF

Feinberg Arch Intern Med 1995;155:469 Age, y

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Incidence of AF in Men and Women

- Doubling incidence each decade of age
- Men ~1.5x women (adjusted)

AF Prevalence by Ethnicity
ATRIA Study – California HMO

Overall prevalence
- 2.2% White
- 1.5% Black
- *P<0.001

Ethnic variation is consistent, but not understood

Veterans Association Males
Racial Variation in AF

OR
Whites 1 1.84 1.77 1.15 1.42 NS

Projected Prevalence of AF

If rate of increase in incidence continues as evident in 1980-2000

Secular increase in AF Prevalence
- Aging population
- Survival heart disease
**AF: What it Means for Your Patient**

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**Remaining Lifetime Risk for AF**

![Remaining Lifetime Risk for AF](image1)

**Unrecognized AF**

*Prevalence - Cardiovascular Health Study*

- In 3 years of f/u 12% AF dx by annual ECG only
- Prevalence unrecognized AF in U.S. unknown

![Unrecognized AF](image2)

**Prevalence of asymptomatic AF in drug trials**

*Patients studied for 30 seconds every 2 weeks*

![Prevalence of asymptomatic AF in drug trials](image3)

**Annual Costs Per Patient**

*Medicare*

- Adjusted mean incremental annual Rx cost of AF was $14,199 (95% CI $13,201–15,001; \( p < 0.01 \))
- Some cost was attributable to incidence stroke & HF

![Annual Costs Per Patient](image4)
AF: What it Means for Your Patient

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Atrial Fibrillation
U.S. Cost 2001

- 350,000 hospitalizations
- 5 million office visits
- ~$6.65 billion 2005 dollars

Risk Factors for AF

Clinical
- Non-modifiable
  - Age, sex, ethnicity, genetic/familial
- Acquired
  - Traditional
    - HTN, DM, CAD (MI), CHF, VHD, COPD, hyperthyroidism, post-op

Population-Attributable Risk, %

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
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<tr>
<td>ECG-LVH</td>
<td>1.3</td>
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<td>MI</td>
<td>1.2</td>
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<tr>
<td>DM</td>
<td>1.6</td>
<td>1.4</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>HTN</td>
<td>1.4</td>
<td>1.5</td>
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</table>

Odds Ratio

Men

Women

AF & Obesity
Framingham Heart Study

- Vs. normal weight, obesity adjusted AF HR 1.5
- Mediated by left atrial enlargement

Wang et al JAMA 2004;292:2471
Risk of AF by Weekly Alcohol Consumption
Copenhagen City Heart Study Men

- Heavy alcohol consumption in men associated with higher adjusted AF risk unexplained by CHD or BP
- Risk not observed in women, but few drank heavily

Exercise & New-Onset AF
Cardiovascular Health Study
Older adults w/o CVD

- Mozaffarian Circulation 2008;118:800

Physicians Health Study

- Aizer AJC 2009;103;1572

Pulmonary and Sleep Pathology & New-Onset AF
Copenhagen City Study

- Buch Eur Respir J 2003;21:1012

Mayo Clinic

- Gami JACC 2007;49:565

AF Risk by BNP
Framingham Heart Study

- Wang et al NEJM 2004;350:655

CRP and Incidental AF
CHS

- CRP <median 1.92 mg/L
- CRP >median: 1.92 mg/L

BNP Adjusted AF Risk
>80th percentile
20 pg/ml men; 23 pg/ml women
HR = 1.91 (1.13 – 3.25)
P = 0.02

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P = 0.02
AF: What it Means for Your Patient

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Atrial Fibrillation

Echo Risk Factors No Prior History AF

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
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<tbody>
<tr>
<td>LA size</td>
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<tr>
<td>LV fractional shortening</td>
<td>1.3</td>
</tr>
<tr>
<td>LV wall thickness</td>
<td>1.3</td>
</tr>
</tbody>
</table>

RR Increment:  5 mm

• Vaziri Circulation 1994;89:724

Atrial Fibrillation

Post-CABG

• Incidence
  - Post CAGB 20-50%
  - Usually first 5 days
  - 90% resolution by wk 6-8

Post-CABG AF

Association with In-Hospital Outcome

<table>
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<th>Outcome</th>
<th>No vs. 1 Episode</th>
<th>1 vs &gt;1 Episode</th>
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<tr>
<td>MI</td>
<td>&lt;0.001</td>
<td>NS</td>
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<tr>
<td>HF</td>
<td>&lt;0.001</td>
<td>0.004</td>
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<tr>
<td>Stroke</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Encephalopathy</td>
<td>0.049</td>
<td>&lt;0.001</td>
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<tr>
<td>Renal failure</td>
<td>NS</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ARDS</td>
<td>NS</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sepsis</td>
<td>&lt;0.001</td>
<td>0.01</td>
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</tbody>
</table>

AF was associated with ↑ hospital LOS days
Median days (IQ range): AF 9 (7-12); no AF 7 (6-10)
$10,000 to hospital charges

AF Genetic Basis

Offspring AF risk by Parental h/o AF

- AF ≥ 1 parent  OR 1.9; (P=0.02)
- ≤75yo, w/o h/o heart disease OR 3.2; (P< 0.001)

AF Genetic Basis

Offspring AF risk by Parental h/o AF

- HTN - + + + + + + + +
- Diabetes - - - + + + + +
- Heart Disease - - - - - - -
- Parent h/o AF - - - - - - -

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AF: What it Means for Your Patient

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Atrial Fibrillation

Epidemiology
Risk factors
Stroke
CHF
Dementia
Mortality
Future Directions

Patterns of Atrial Fibrillation

First Detected

Paroxysmal 1–4
Self-terminating

Persistent 2–4
Not self-terminating

Permanent 3

1. Episodes generally last ≤ 7 days (most < 24h)
2. Usually > 7 days
3. Cardioversion failed or not attempted
4. Either paroxysmal or persistent AF may be recurrent

Progression to Permanent AF
Rates & Predictors

PREDICTORS
All studies
- Age
Multiple studies
- Heart failure
- Valvular heart disease
- Left atrial enlargement
One large study
- BMI or obesity

RATES
PAF to permanent
- ~5% per year
Persistent to permanent
- ~30% per year

Atrial Fibrillation
Relation to stroke

- % of strokes occurring in setting of AF
  - 15% of all strokes
  - Almost half of all cardioembolic strokes
- Stroke risk
  - Nonvalvular
  - Rheumatic

Bogousslavsky Neurology 1991;41:855
Wolf Neurology 1978;38:973

Vacca et al. JACC 2001;38:1248

Budeus et al. PACE 2007; 30:243-252; Kari et al., AHJ 2005; 149:489-96;
Ruigomez et al. BMC Cardiovascular Disorders 2005; 5:20;
Nieuwlaat et al. EHJ 2005; 26:2422-2434; Tsang et al. EHJ 2008 (in press)
Atrial Fibrillation
Relation to Stroke

- Vs. without AF, strokes in AF setting
  - Almost twice as likely to be fatal
  - More likely to have severe functional deficits & recurrent stroke
- SPINAF baseline CT, subjects w/o Sx
  - 15% had ≥ 1 silent cerebral infarct

AF & Stroke - Framingham Study
Relative & Population Attributable Risk

- Incidence of both increases with advancing age
- Both are associated with considerable morbidity and economic cost
- Both predispose to each other’s development

Atrial Fibrillation & Heart Failure
Timing of Occurrence

- About 40% individuals with AF or CHF will develop the other condition

Eligible Subjects
n=1470

- AF Only n=539 37%
- AF + HF n=382 26%
- HF Only n=549 37%

- AF First n=144 38%
- Same Day n=79 21%
- HF First n=59 41%

Wang…Benjamin Circulation 2003;107:2920
AF: What it Means for Your Patient

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Joint Influence AF & CHF on Mortality
Reference group: 1st condition without development of 2nd

- Male
  - Adjusted Mortality HR
  - 1st condition: AF
    - CHF: 2.7
    - AF: 3.1
  - Impact 2nd:
    - CHF: 1.6
    - AF: 2.7

- Female
  - Adjusted Mortality HR
  - 1st condition: AF
    - CHF: 3.1
    - AF: 2.7
  - Impact 2nd:
    - CHF: 1.6

Impact 2nd:

- CHF
  - AF: 0.0001
  - CHF: 0.01
- AF
  - CHF: 0.0001
  - AF: 0.0001

P value:

- 0.0001
- 0.01
- 0.0001
- 0.0001

AF & Total Mortality
Framingham Study

Incidence of Dementia in Rochester, MN
Population and in AF Cohort

AF (men) AF (women) General MN (men) General MN (women)

AF (men)
- Incidence/1,000 person–years
  - 20

AF (women)
- Incidence/1,000 person–years
  - 60

General MN (men)
- Incidence/1,000 person–years
  - AF (men)
  - AF (women)
  - General MN (men)
  - General MN (women)

5-year Stroke/Death Risk in AF

- RR men 1.5; RR women 1.9
- AF diminished survival advantage

- 60 yr old
- 70 yr old

SBP
- 130
- 150
- 170

DM
- N
- N
- N
- Y

Smoker
- N
- N
- N
- Y

Prior MI
- N
- N
- N
- Y

ECG LVH
- N
- N
- N
- Y

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AF: What it Means for Your Patient

Atrial Fibrillation

Epidemiology
Risk factors
Prognosis
Future Directions

Risk Factors
Nonmodifiable
- Age
- Sex
- Race
- Genetic
- Modifiable
- Hypertension
- Diabetes
- Obesity
- Smoking

Subclinical
- ECG
- Artery stiffness
- Biomarkers
- Genomics

Clinical
- Heart failure
- Myocardial infarct
- Valve disease
- Thyroid disease
- Sleep disordered breathing

Complications
- Heart failure
- Stroke
- Dementia
- Emboli
- Death

Electrical substrate
- Membrane ionic currents
- Regional heterogeneity
- Calcium dynamics

Triggers
- Ischemia
- Heart failure exacerbation
- Autonomic nervous system
- Inflammation
- Myocardial stretch

Benjamin, Chen et al, NHLBI Workshop Prevention AF
Circulation 2009;119:606

AF Prevention Meta-Analysis
ACE-I & ARB in LVH & ↓LVEF

<table>
<thead>
<tr>
<th>Component (AF Event or outcome based on class of drug)</th>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>RR [95%CI]</th>
<th>Weight %</th>
<th>No. [95%CI]</th>
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<tr>
<td>Val-De-Brez</td>
<td>0.75</td>
<td>0.715</td>
<td>0.73</td>
<td>0.73</td>
<td>0.73</td>
<td>0.73</td>
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<tr>
<td>Dobutamine</td>
<td>0.75</td>
<td>0.715</td>
<td>0.73</td>
<td>0.73</td>
<td>0.73</td>
<td>0.73</td>
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<tr>
<td>L-Arg</td>
<td>0.75</td>
<td>0.715</td>
<td>0.73</td>
<td>0.73</td>
<td>0.73</td>
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<tr>
<td>ACE-I</td>
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<td>Maxdose</td>
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<td>0.73</td>
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<td>Val-De-Brez</td>
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<tr>
<td>Total</td>
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<td>0.715</td>
<td>0.73</td>
<td>0.73</td>
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Statins – 6 Study Meta-Analysis
Antiarrhythmic Efficacy for AF?

<table>
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<th>Risk Factor</th>
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<th>CABG</th>
<th>ACS</th>
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<td>female</td>
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<td>0.18 - 0.85</td>
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<td>years</td>
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<tr>
<td>Body Mass Index</td>
<td>kg/m²</td>
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<td>120</td>
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<tr>
<td>Systolic Blood Pressure</td>
<td>mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment for Hypertension</td>
<td>yes (y) or no (n)</td>
<td>n</td>
<td>160</td>
<td></td>
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<tr>
<td>PR Interval</td>
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<tr>
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<td>n</td>
<td>160</td>
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Risk Function – Low Risk

AF Risk Prediction

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<th>Risk Factor</th>
<th>Units</th>
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<tbody>
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</tr>
<tr>
<td>Age</td>
<td>years</td>
<td>60</td>
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<tr>
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<tr>
<td>PR Interval</td>
<td>milliseconds</td>
<td>160</td>
</tr>
<tr>
<td>Significant Murmur</td>
<td>yes (y) or no (n)</td>
<td>n</td>
</tr>
<tr>
<td>Prevalent Heart Failure</td>
<td>yes (y) or no (n)</td>
<td>n</td>
</tr>
</tbody>
</table>

Your 10-Year Risk: 1.7%

Risk Function – High Risk

AF Risk Prediction

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<tbody>
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<td>Sex</td>
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<td>years</td>
<td>60</td>
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<tr>
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<td>120</td>
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<td>Treatment for Hypertension</td>
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<td>Significant Murmur</td>
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<tr>
<td>Prevalent Heart Failure</td>
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Your 10-Year Risk: 14.3%

Does Echo Improve Reclassification?

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<th>With echo variables</th>
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<td>&lt;5%</td>
<td>&lt;5%</td>
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<tr>
<td>5-15%</td>
<td>5-15%</td>
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<td>&gt;15%</td>
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<tr>
<td>Total</td>
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<td>Participants not developing AF</td>
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<td>3216</td>
<td>232</td>
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<td>1191</td>
<td>271</td>
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<td>Participants developing AF</td>
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<td>312</td>
<td>39</td>
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<tr>
<td>106</td>
<td>81</td>
</tr>
</tbody>
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NRI: 0.04 (95% CI -0.02-0.10, p=0.18)
Future Directions

- Transportability of score to other cohorts, races
- High risk individuals for prospective studies, RCTs
- Identification of individuals for primary prevention
- Benchmark to evaluate novel biomarkers, subclinical markers & genetic variability

Cohorts for Heart & Aging Research in Genomics Epidemiology
Atrial Fibrillation

<table>
<thead>
<tr>
<th>ARIC: A Alonso, D Arking, D Couper</th>
<th>AGES: V Gudnason, T Aspelund, T B. Harris, LJ Launer</th>
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<tbody>
<tr>
<td>CHS: SR Heckbert, K Rice</td>
<td>RS: JCM Witteman, C van Noord</td>
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<tr>
<td>FHS: KL Lunetta, MJ Pencina, MG</td>
<td>MONICA/KORA/AFNet</td>
</tr>
<tr>
<td>Larson, JW Magnani, LM Sullivan,</td>
<td>S Kääb, A Pfeiffer</td>
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<td>EJ Benjamin</td>
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<td>MGH: PT Ellinor, SA Lubitz</td>
<td>GHS: RB Schnabel</td>
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<td>SHIP: M Dörr</td>
<td>WGHS: CM Albert, B Keating</td>
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The ultimate goal is personalized medicine...
AF Summary

- **Epidemiology**
  - AF most common arrhythmia, ↑ prevalence
  - High lifetime risk and cost

- **Risk Factors**
  - CVD risk factors, CHF, CHD, valve disease
  - Family history and novel risk factors

- **Prognosis**
  - Increased risk of stroke, HF, dementia,
  - Increased all cause mortality

- **Future**
  - Prevention – 1º, AF & 2º, complications
  - Genetics