

Cardiac Disease and Stroke

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NEUROLOGY



OUTLINE

- ▀ Ischemic Stroke Background
- ▀ Occult afib and other arrhythmias
- ▀ ESUS and atrial cardiopathy
- ▀ PFO
- ▀ Troponin and AIS

Neurology

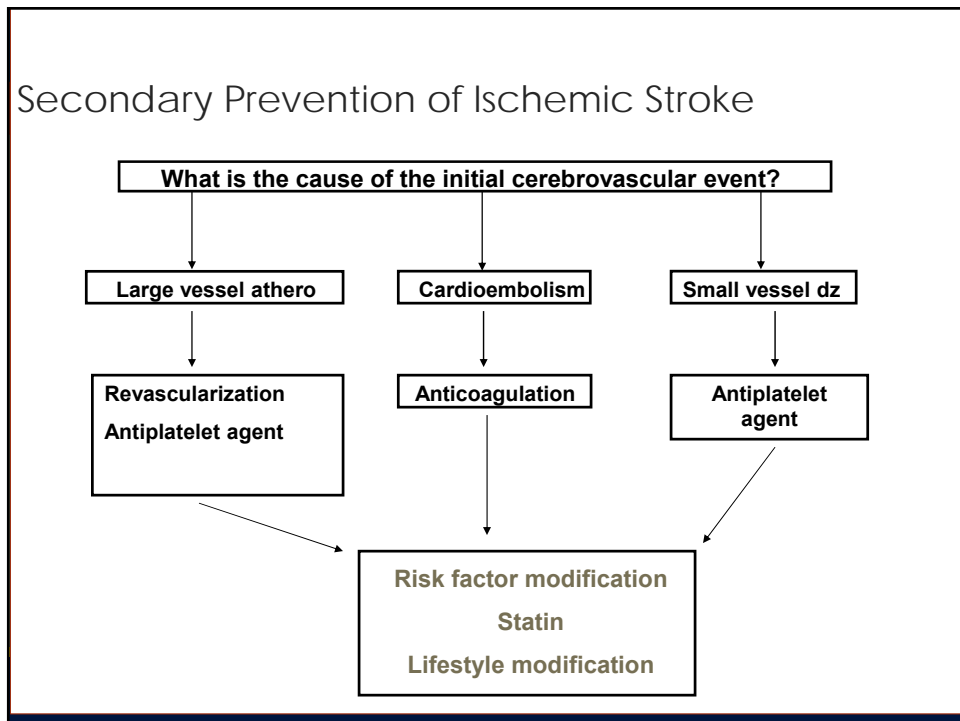
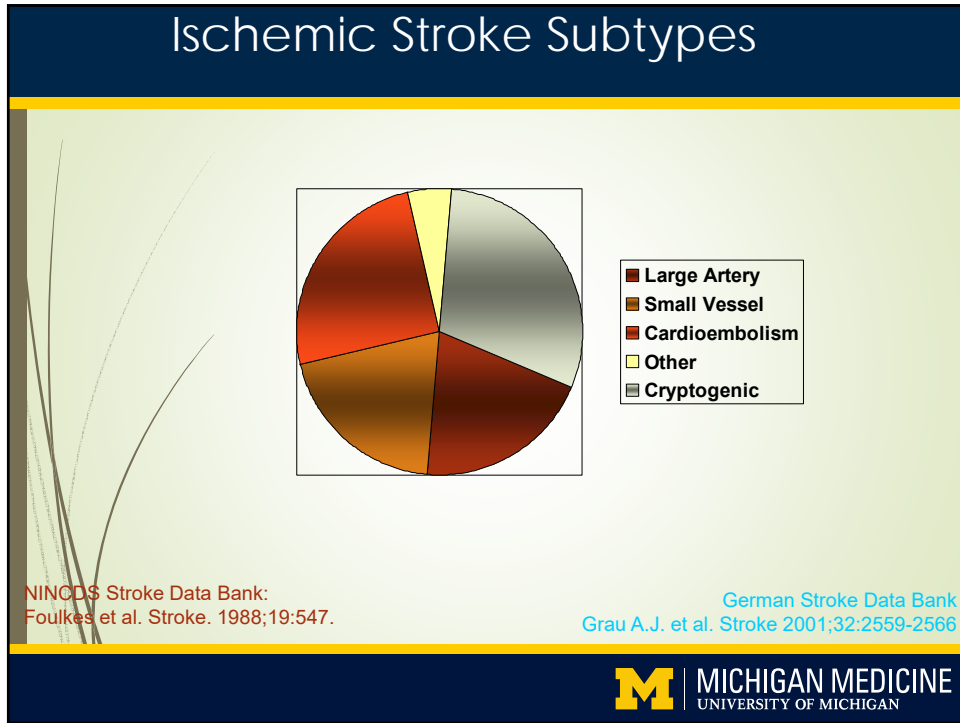
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Secondary Prevention of Ischemic Stroke

What is the cause of the initial cerebrovascular event?

Other

**Specific therapy for
specific etiology**



Cardioembolic Stroke Importance

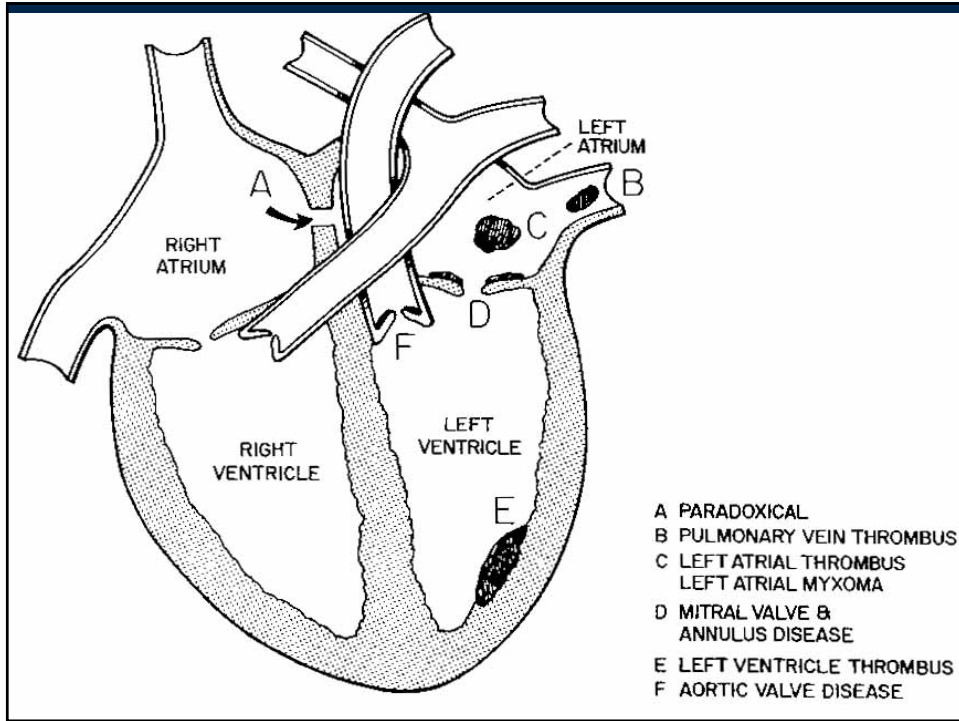
- ▶ 15-20% of ischemic stroke
- ▶ Worse prognosis than other stroke subtypes
- ▶ Larger infarct size
 - ▶ Larger sized thromboemboli
 - ▶ Abrupt onset of vascular occlusion, no collateral flow developed
- ▶ Hemorrhagic transformation more common
 - ▶ 51-71% cardioembolic vs 2-21% non

Higher Case Fatality After Cardioembolic Stroke

TABLE 4. Kaplan-Meier Estimates of Probabilities of Death After First Ischemic Stroke for Common Ischemic Stroke Subtypes, 1985–1989

Time after First Stroke	% Dead (95% CI) Among Each Ischemic Stroke Subtype			
	Atherosclerosis With Stenosis	Cardioembolic	Lacunar	Ischemic Stroke of Uncertain Cause
7 d	4.1 (0.0–8.5)	15.2 (9.0–21.3)	0.0 (0.0–1.0)	7.3 (3.3–11.3)
30 d	8.1 (1.9–14.3)	30.3 (22.5–38.1)	1.4 (0.0–4.1)	14.0 (8.7–19.3)
90 d	8.1 (1.9–14.3)	37.9 (29.6–46.2)	2.8 (0.0–6.6)	17.7 (11.8–23.5)
6 mo	8.1 (1.9–14.3)	40.9 (32.5–49.3)	2.8 (0.0–6.6)	22.6 (16.2–29.0)
1 y	10.8 (3.7–17.9)	53.0 (44.5–61.5)	6.9 (1.1–12.8)	25.6 (18.9–32.3)
2 y	18.9 (10.0–27.8)	61.4 (53.1–69.7)	12.5 (4.9–20.1)	32.3 (25.2–39.5)
5 y	32.2 (21.1–43.8)	80.4 (73.1–88.1)	35.1 (23.6–47.6)	48.6 (40.5–56.8)

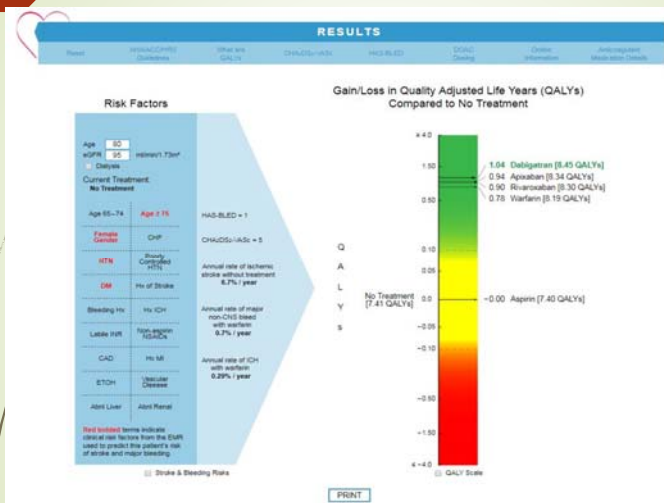
Both 30-day and long-term death rates were significantly different among subtypes (log rank, $P < 0.0001$).



AFIB!!!

- The most important and prevalent cause of cardioembolic stroke
- Afib increases risk of stroke five-fold
- Up to 25% of all strokes in the elderly are related to afib
- Inherently treatable!

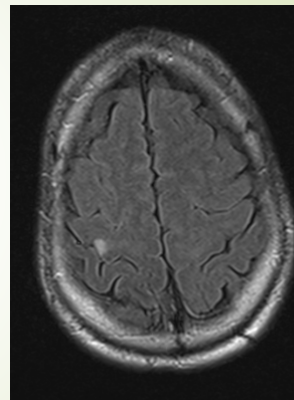
Decision Support Tool for Afib Patients



Courtesy of Mark Eckman, MD

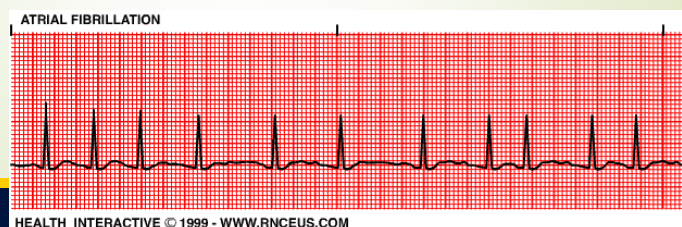
Etiology?

- ▶ 68-year-old man with mild left face and arm weakness and mild neglect
- ▶ Risk factors: hypertension, prior smoker
- ▶ Neuroimaging: small right cortical infarction
- ▶ Carotid ultrasound: no significant stenosis
- ▶ EKG: sinus rhythm, normal
- ▶ Echo (transthoracic): EF 50%, no major wall motion abnormalities, normal valves, no source
- ▶ Labs: LDL 95




ESUS: Are We Missing Paroxysmal Atrial Fibrillation?

- ▶ Biological and genetic plausibility
- ▶ Detection of asymptomatic / occult AF
- ▶ Diagnostic dilemma




AF detection after stroke


	N	Technique	Prevalence	Predictors
Tayal, 2008	56	MCOT	23% any PAF	n/a
Ziegler, 2010	163	ICD/PPM	28% PAF/AT >5m	n/a
Gaillard, 2010	98	Daily patient-triggered EKG	9%	<ul style="list-style-type: none"> ■ >100 PACs 24h Holter ■ Non-lacunar anterior circulation DWI + lesions
Bhatt, 2011	62	MCOT	24% PAF >30s	<ul style="list-style-type: none"> ■ PVC >2m ■ Stroke >TIA ■ Multiple vs. single DWI
Cotter, 2013	51	ILR	25.5%	<ul style="list-style-type: none"> ■ Age ■ Left atrial volume ■ Interatrial block, PACs
Gladstone, 2014	287	Event Monitor Belt	16%	<ul style="list-style-type: none"> ■ Age >75
CRYSTAL-AF, 2014	225	REVEAL-XT	12% (1 yr)	



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Implantable Monitors

- Implanted under skin
- Records up to 3 years






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Bottom Line: Look Harder for Occult AFib

- ▶ At least 20% of cryptogenic stroke pts have occult AF
- ▶ Most AF episodes are asymptomatic
- ▶ AF yield increased with longer monitoring duration
 - ▶ Unknown optimal duration (forever?)
- ▶ AF >6 hours: Doubles 1 yr stroke risk
- ▶ Short AF episodes likely predict longer episodes and increased stroke risk
- ▶ Treatment options for AFib expanding every day

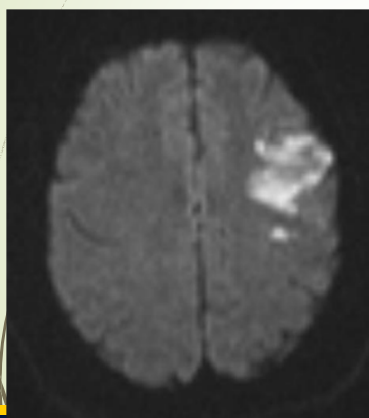
Is Prolonged Cardiac Monitoring Cost Effective?

- ▶ Net gain: 34 quality-adjusted life-years (QALY)
- ▶ Cost-utility ratio \$13,000 per QALY
- ▶ Remained cost-effective over a wide range of model inputs in sensitivity analyses, including changes in the cost and yield of monitoring (even as low as 1%).

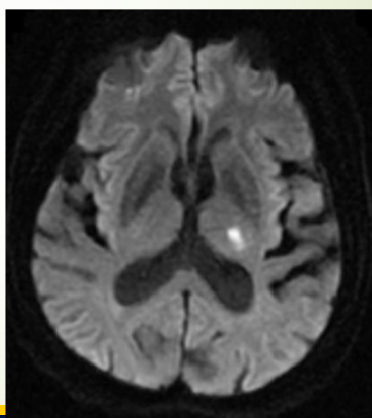
Can we identify patients who are highly likely to harbor occult AF?

- ▀ Clinical features
 - Age
 - CHADS2Vasc
 - Classic syndromes
- ▀ Echocardiographic characteristics
 - Left atrial size
- ▀ Radiographic patterns
 - Acute cortical or wedge-shaped infarcts
 - Multiple acute infarcts in >1 territory
 - Prior cortical or cerebellar infarcts

Yes



Yes?



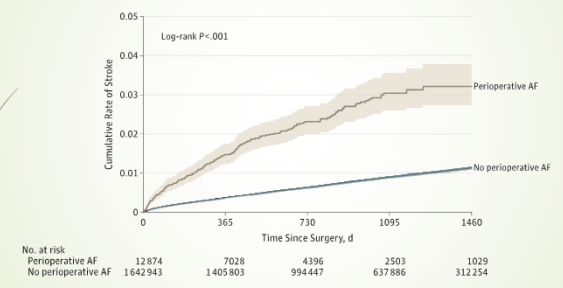
What about self-limited AF?

- Perioperative AF assumed to be self-limited
- Not seen as long-term risk factor for ischemic stroke
- No recommendations for long-term follow-up or management
- But link with long-term stroke is unknown

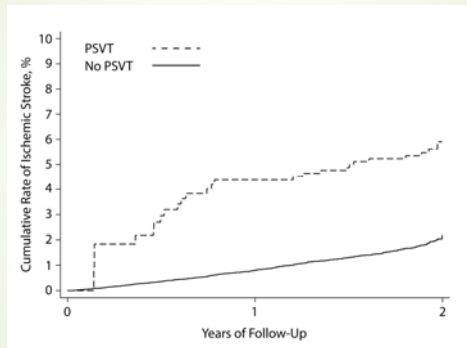
Epstein et al, *Chest*, 2005

What about self-limited AF?

Figure 1. Cumulative Rates of Ischemic Stroke After Hospitalization for Noncardiac Surgery



Other atrial arrhythmias <> stroke



NAVIGATE ESUS

NAVIGATE ESUS:

New Approach r*iv*aroxaban Inhibition of Factor Xa in a Global trial vs Aspirin to prevent Embolism in Embolic Stroke of Undetermined Source

www.clinicaltrials.gov NCT02313909
EudraCT number: 2013-000768-27

Equivalent risks of recurrent stroke, higher risk of bleeding with Rivaroxaban

STOPPED FOR FUTILITY

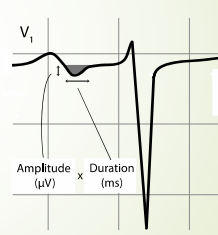
Other atrial derangements in AF

- **AF is associated with many other atrial derangements besides dysrhythmia**
 - Endothelial dysfunction
 - Fibrosis
 - Impaired myocyte function
 - Chamber dilatation
- **Dysrhythmia = marker for these derangements?**

Cai et al, *Circulation*, 2002; Frustaci et al, *Circulation*, 1997; Mihm et al, *Circulation*, 2001; Vaziri et al, *Circulation*, 1994

Atrial Cardiopathy

- A commonly used ECG measure of left atrial abnormality ($PTFV_1$) is associated with stroke risk independently of AF
 - Especially in blacks



Updated hypothesis

- ▀ **Atrial cardiopathy can cause thromboembolism even in the absence of AF**
 - ▀ Dysrhythmia that defines AF is a common manifestation of atrial cardiopathy
 - ▀ Dysrhythmia in itself increases stroke risk via stasis and remodeling, but is not necessary to cause left atrial thromboembolism

Kamel et al, *Stroke*, 2016

Proposed StrokeNet ARCADIA Trial

- **Primary hypothesis:**
 - Apixaban is superior to aspirin for prevention of recurrent stroke or death in patients with cryptogenic stroke **and** atrial cardiopathy
- **Atrial cardiopathy defined as ≥ 1 of following:**
 - PTFV₁ >4000 $\mu\text{V}\cdot\text{ms}$ on 12-lead ECG
 - Left atrial size >42 mm in women or >46 mm in men on echocardiogram (mod-to-severe LAE)
 - Serum NT-proBNP >185 pg/mL

Patent Foramen Ovale (PFO)

02014217 17 Jan 02 TIs 1.2 MI 1.3
P4-2 A.Card/LR 9:59:57 am 60 Hz 17.9cm

Map 3
150dB/C 3
Persist Low
2D Opt:HPen
Fr Rate:High

CONTRAST

ATL

115 BPM

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02112324 18 Jan 02 TIs 0.8 MI 1.3
P4-2 A.Card/AM 10:22:53 am 72 Hz 14.4cm

Map 3
150dB/C 3
Persist Low
2D Opt:HPen
Fr Rate:High

CONTRAST

ATL

77 BPM

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PFO closure?

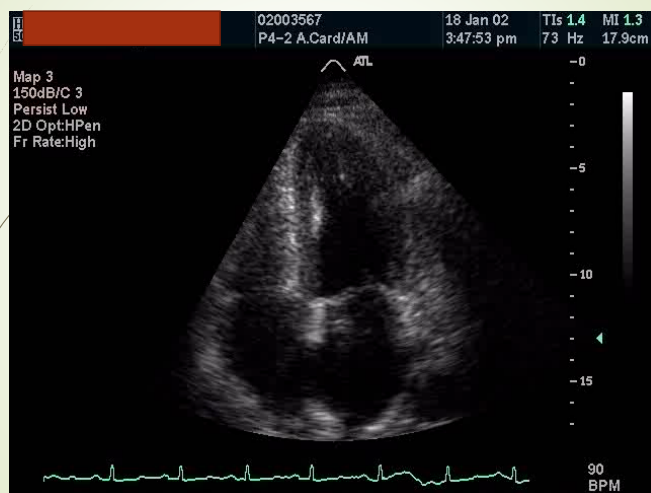


Summary of PFO Closure RCTs

	CLOSURE	PC	RESPECT	Gore Reduce	CLOSE
Inclusion	PFO+CIS	PFO+CIS or TIA or peripheral embolism	PFO+CIS	PFO + CIX	PFO + CIS + large shunt and/or ASA
Follow Up	2 years	4 years	2 years	3yrs	5.4yrs
Primary EP	Stroke/TIA/death	Stroke/TIA/death/peripheral embolism	Stroke/death	Clinical recurrent stroke, all stroke (including silent)	stroke
Technical Success Rate	89%	96%	96%	94%	93%
Medical Arm	Local PI discretion	Local PI discretion	Local PI discretion	Standardized options, must tx post closure	AP vs. AC
Hazard Ratio	0.78 (p=0.37)	0.63 (p=0.34)	0.49 (0.08)	0.29 (0.04)	0.03 (p<0.0001) vs. AP Ns vs. AC
Device	StarFlex	Amplatzer	Amplatzer	Helex Septal Occluder	*approved devices*

PFO caveats

- Thorough evaluation for other causes needed
- Data is very limited for those over 65
- Best data is for those “high-risk” PFOs, with atrial septal aneurysms and/or larger shunts
- Complications are still not infrequent during procedure
 - 4.9% in <65yo, 10.9% in >65yo



Troponin Elevations in Acute Ischemic Stroke

- Elevated troponin independently increases risk of mortality within a population

Table 3. Multivariate Odds of Death After AIS in Those With Complete Cardiac Evaluation, Excluding Those With Concurrent AMI (N=1328/1377)

Variable	Dead by 30 d; OR (95% CI)	Dead by 1 y; OR (95% CI)	Dead by 3 y; OR (95% CI)
Hypertroponinemia	3.45 (2.11–5.64)*	3.06 (2.14–4.37)*	2.91 (2.06–4.11)*
Age (per 10-y increase)	1.59 (1.25–2.03)*	1.80 (1.53–2.13)*	1.96 (1.70–2.27)*
Atrial fibrillation	0.98 (0.56–1.72)	1.34 (0.90–1.98)	1.36 (0.95–1.94)
Hx of cardiac disease	1.46 (0.80–2.68)	1.02 (0.69–1.50)	1.36 (0.97–1.89)
Hx of diabetes mellitus	0.61 (0.36–1.03)	1.04 (0.74–1.47)	1.08 (0.80–1.47)
Hx of CKD	0.99 (0.54–1.82)	1.70 (1.13–2.56)*	1.36 (0.92–1.99)
Hx of dementia	1.29 (0.72–2.32)	1.25 (0.80–1.94)	1.73 (1.11–2.69)*
Current smoking	1.41 (0.73–2.71)	1.60 (1.04–2.47)*	2.01 (1.38–2.91)*
mRS 0–1	0.58 (0.32–1.05)	0.51 (0.35–0.75)*	0.47 (0.34–0.64)*
rNIHSS (5-point increase)	1.91 (1.70–2.17)*	1.55 (1.41–1.72)*	1.41 (1.28–1.54)*

AIS indicates acute ischemic stroke; AMI, acute myocardial infarction; CI, confidence interval; CKD, chronic renal disease; Hx, history; mRS, modified Rankin scale; OR, odds ratio; and rNIHSS, retrospective National Institutes of Health stroke score.

*Statistically significant.

- 85% of AIS had troponin measured
- 20% of those were abnormal
- Mortality risk even after adjusting for CAD/CHF and concurrent MI



Troponin and Cause of Death

	Centered Troponin Levels				p-value
	Quartile 1 (<0.3)	Quartile 2 (0.3 to <0.7)	Quartile 3 (0.7 to 2.6)	Quartile 4 (>2.7)	
All cause death by 1 year	N=100 39 (39%)	N=128 53 (41%)	N=101 38 (38%)	N=112 63 (56%)	0.02
Cardiac death by 1 year	5 (5%)	9 (7%)	13 (13%)	21 (19%)	<0.01
Non-cardiac death by 1 year	34 (34%)	44 (34%)	25 (25%)	42 (38%)	0.23

- Troponin only associated with cardiac causes of death
 - Even after excluding AMI
- “Dose Effect” the higher the troponin, the higher the mortality
 - Even after adjusting for cardiac hx or MI



Troponin and Recurrence

- ▶ 2,334 IS patients
- ▶ 20% with abnormal troponin
- ▶ 13% with recurrent IS
- ▶ After adjustment for sociodemographics, stroke severity and vascular risk factors:
 - ▶ Elevated troponin associated with increased risk of recurrence HR 1.5 (1.1, 2.0)

Summary

- ▶ Cardiac disease and stroke are tightly linked and of great public health importance
- ▶ Looking for occult afib is very important
 - ▶ Changes treatment decisions
 - ▶ Atrial cardiopathy may be important?
- ▶ PFO closure may be reasonable for young patients with cryptogenic stroke
- ▶ Troponin elevations in the acute setting are likely prognostic indicators of badness