Cryptogenic Stroke:
The role of silent Atrial Fibrillation

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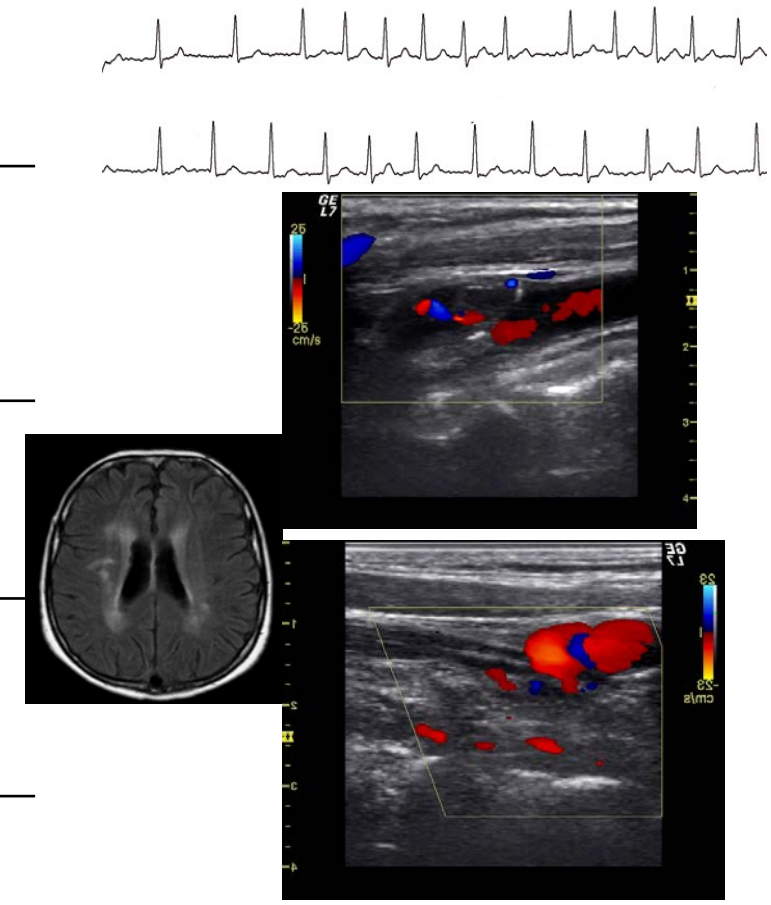
Agenda

1. What is a “cryptogenic?” stroke
   - Understanding the burden of cryptogenic stroke

     for individual patients and for society
2. Why bother with paroxysmal Atrial Fibrillation (AF)?
3. How to reliably detect (rare episodes of) paroxysmal AF?
   - Strategies
   - Can we predict paroxysmal AF?
4. What to do then?
   - discussion

What is a “cryptogenic” stroke ? – Stroke classification according to TOAST

Cardio-embolic stroke	**Atrial fibrillation**, Ventricular aneurysm / thrombus etc.	**~30%**
atherothrombosis	**Carotid stenosis / intracranial stenosis > 50%** Aortic plaques, **instable carotid plaque?**	**~15%**
Lacunar stroke	Cerebral **microangiopathy** (Hypertension, Diabetes)	**~15%**
Other defined etiologies	**Periprocedural**, dissections, vasculitis, **PFO,** etc.	**~10%**
Undetermined etiology	Concurring etiologies, incomplete work-up **cryptogenic strokes**	**~30%**



Adams HP Jr, et. Al. Stroke. 1993;24:35-41.

What is a cryptogenic stroke ? – And understanding the burden of it

A cryptogenic stroke is a stroke of unknown cause.

The diagnosis demands a thorough and complete work-up of embolic or thrombotic sources

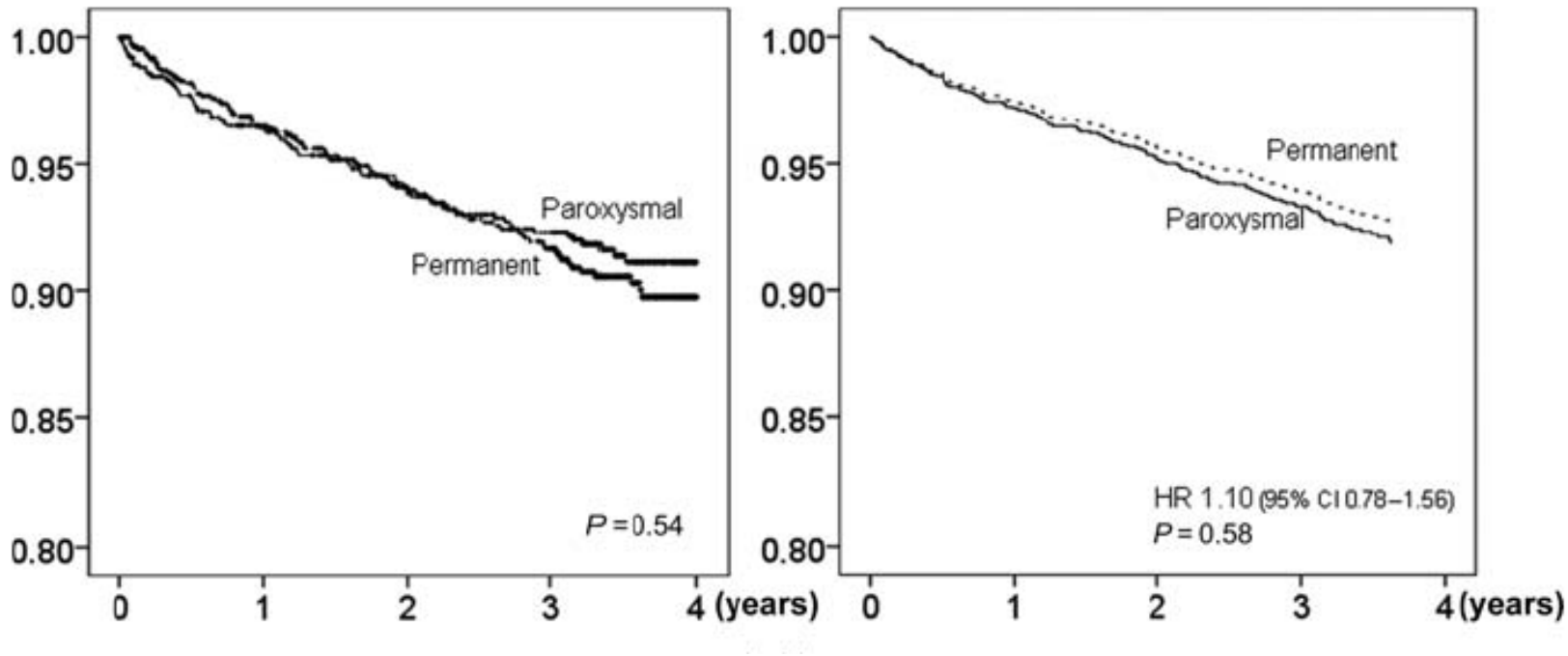
20-30% of all strokes have to be labeled as “cryptogenic”.

That is about 40.000 Germans or 30.000 Italians each year!

The diagnosis leaves doctors and patients unsure of the risk of future stroke and optimal secondary prevention – big psychological problem!

We suspect that a number of these patients does have AF we did not detect.

Why bother with paroxysmal atrial fibrillation ?



Because risk of stroke does not differ greatly between paroxysmal or permanent AF!

1981 patients, Follow-up: 3.6 years

Incidence rate of ischemic stroke: **Cumulative 2,6% (pAF) vs. 2,9% (cAF) per year**

Friberg L, et al. Eur Heart Journal 2009

How to track (rare episodes of) paroxysmal AF?

Simple answer: Increase the time of monitoring!

- **Do Holter ECG !**
- **Repeat Holter**
- **Do telemetry while in hospital !**
- **Do 3-7 day Holter**
- **Use external loop recorder (MCOT)**
- **Do continuous Monitoring (implantable cardiac monitors, ICM)**

Study overview:
Detection rates of iAF with extended monitoring methods

Table 1: Yield of long-term cardiac rhythm monitoring studies.

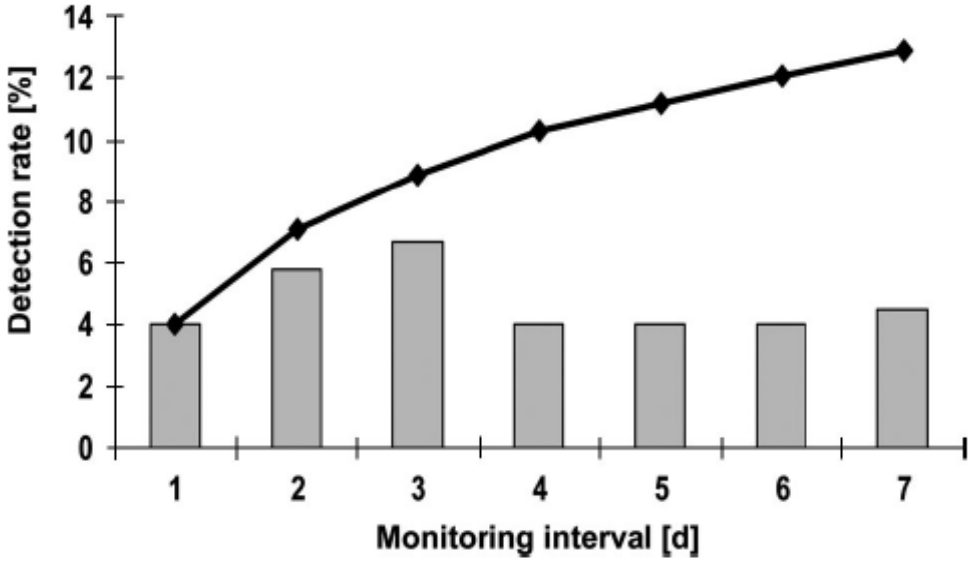
Study	Patient population	Duration (days)	Sample size	No. diagnosed	Percentage
Barthélémy et al. 2003 [6]	Stroke/TIA	4	28	4	14.3
Sposato et al. 2012 [7]	Stroke/TIA	5	155	21	13.5
Stahrenberg et al. 2010 [8]	Stroke/TIA	7	220	28	12.7
Jabaudon et al. 2004 [9]	Stroke/TIA	7	88	5	5.7
Tayal et al. 2008 [10]	Stroke/TIA	21	56	13	23
Miller et al. 2013 [11]	Stroke/TIA	21	156	27	17.3
Bhatt et al. 2011 [12]	Stroke/TIA	21	62	15	24
Elijovich et al. 2009 [13]	Stroke/TIA	30	20	4	20
Gaillard et al. 2010 [14]	Stroke/TIA	30	98	9	9.2
Flint et al. 2012 [15]	Stroke	30	239	29	12.1
Ziegler et al. 2010 [16]	Stroke/TIA	365	163	45	28
Total			1285	200	15.5

Definition of iAF varied widely

In many studies episodes <30s of AF were accepted, and accounted for >50% of all pt.!

Khan M, Miller DJ. Detection of paroxysmal atrial fibrillation in stroke/tia patients. Stroke Res Treat. 2013;2013:840265.

Increased monitoring times after stroke result in higher yields of silent AF!



Stahrenberg R. Stroke. 2010; 41: 2884-2888.

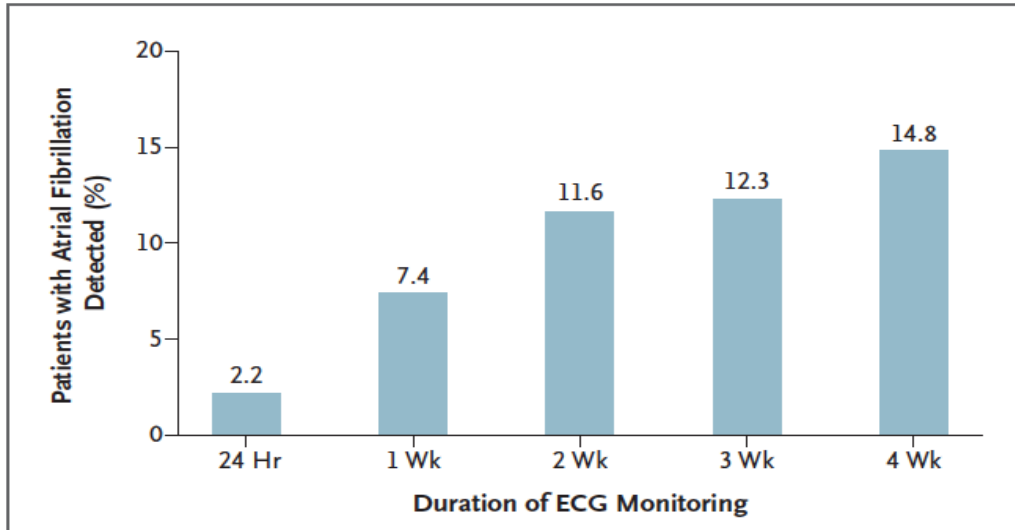


Figure 2. Incremental Yield of Prolonged ECG Monitoring for the Detection of Atrial Fibrillation in Patients with Cryptogenic Stroke or TIA.

Gladstone DJ. NEJM. 2014; 370;26: 2467

Only 69% of patients tolerated the device 5 days or more!

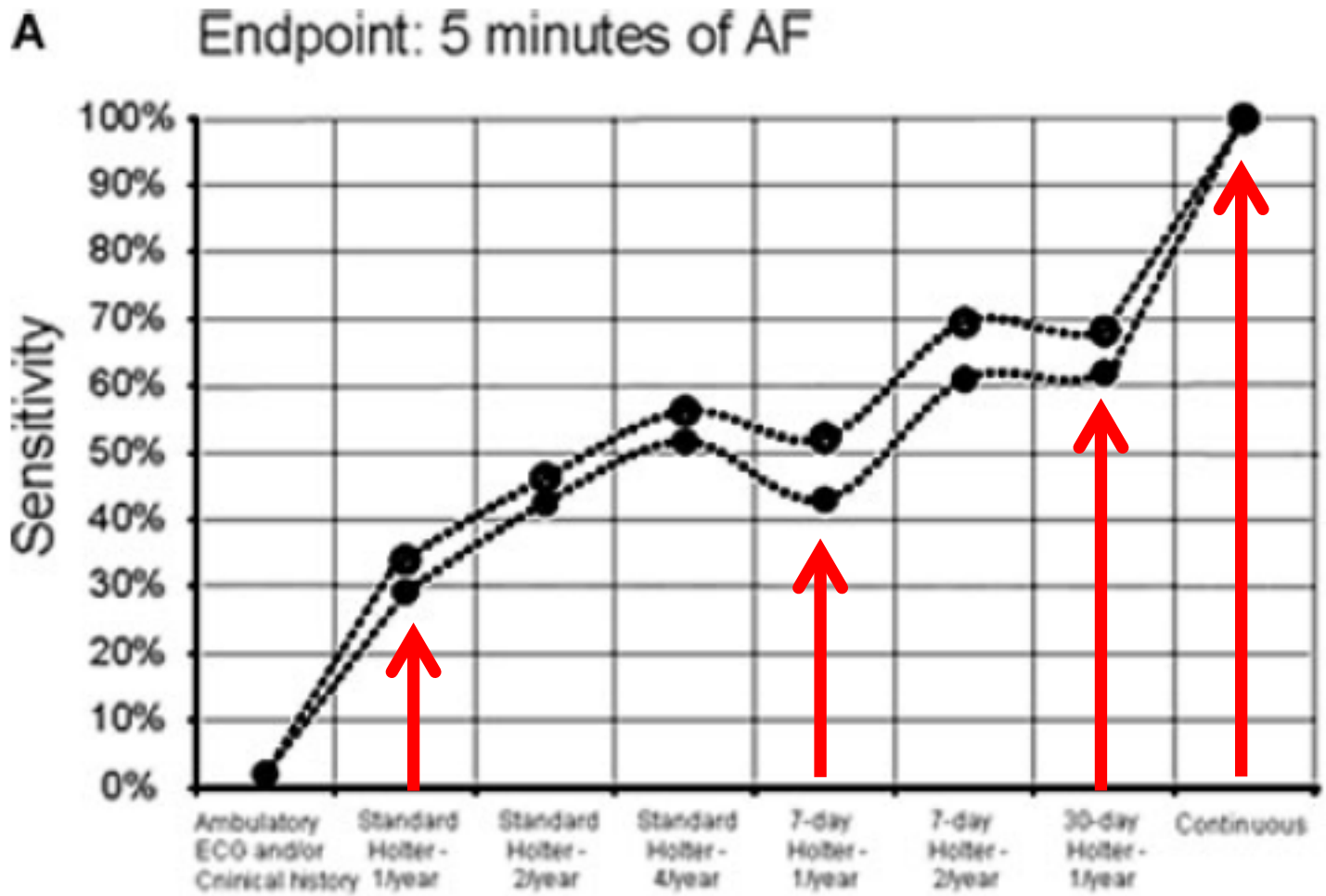
Only 4 out of 5 patients had data for 21 days or more!

Prolonged Monitoring = higher Yield

Comparison studies in stroke patients

Autor	n	Methodik / Dauer	Yield
Stahrenberg *Stroke 2010*	224	7d Holter vs. 24h Holter	12,5 % vs. 4,8%
Grond *Stroke 2013*	1135	72h Holter vs. 24h Holter	4,3% vs. 2,9%
Rizios *Stroke 2013*	496	72h stroke unit monitoring (dedicated analysis tool) vs. 24h Holter	7,6% vs. 2,8%
Gladstone *NEJM 2014*	572	30d externer loop recorder vs. 24h Holter	16,1% vs. 2,2%
Ritter ***Stroke 2013***	**60**	**ICM (Reveal XT®) vs. 7d Holter**	**17,1% vs. 1,6%**

Continuous monitoring has the highest diagnostic yield



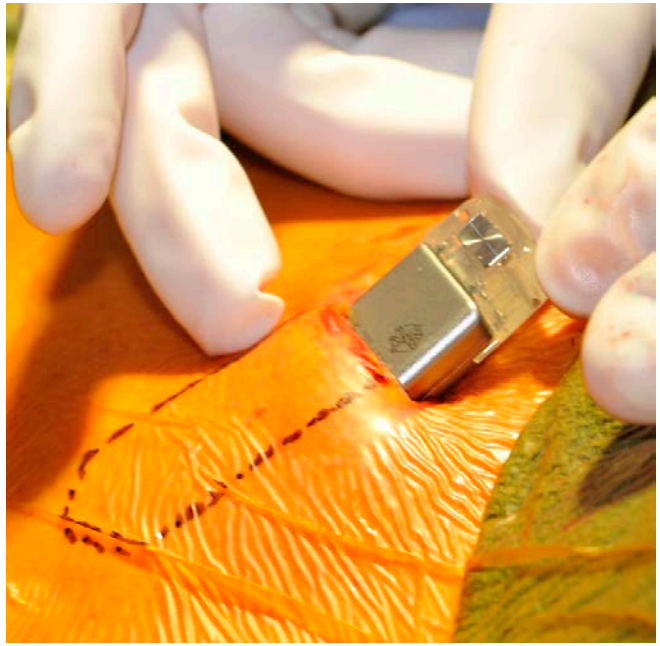
Implantable cardiac monitors (ICMs) should have the highest yield

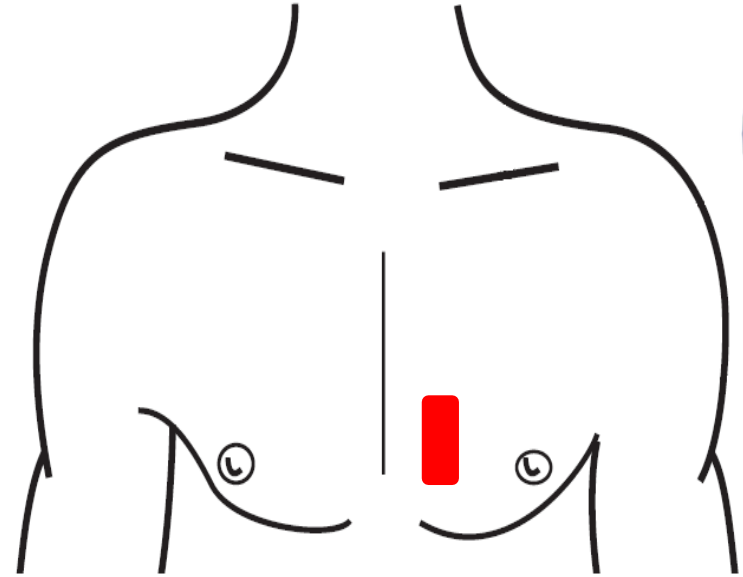
Botto G, et al. J Cardiovasc Electrophysiol 2009; 20: 241–248.

ICMs are implanted subcutaneously under local anesthesia

e.g.: Reveal XT™ algorithm detects episodes >2 min. (programmable)

XPECT study, : sensitivity (96,1%) and specificity (85,4%) vs. Cardiologist evaluated Holter monitoring in pt. c. known iAF





Hindricks G, et al.. Circ Arrhythm Electrophysiol. 2010

Pilotstudies using ICMs in cryptogenic stroke patients

Autor	n	Duration of monitoring	Median until first episode of iAF	Additional Yield
Ritter *Stroke 2013*	60	Median 397 d	64 d	17.1%
Cotter *Neurology 2013*	51	Median 229 d (withoutAF)	48 d	25.5%
Etgen *Stroke 2013*	22	1 year	153 d	27.3%
Christensen *Eur J Neurol 2014*	85	Mean 569 d	Mean 109 (±48) d	16.1%

CRYSTAL-AF, n=441

Key Inclusion/Exclusion Criteria

Inclusion:

- ≥40 years of age
- Cryptogenic stroke (or clinical TIA), with infarct seen on MRI or CT, within the previous 90 days; and no mechanism (including AF) determined after:
  - 12-lead ECG
  - 24-hour ECG monitoring (e.g. Holter)
  - Transesophageal echocardiography (TEE)
  - CTA or MRA of head and neck to rule out arterial source
  - Screening for hypercoagulable states in patients <55 years old

Exclusion:

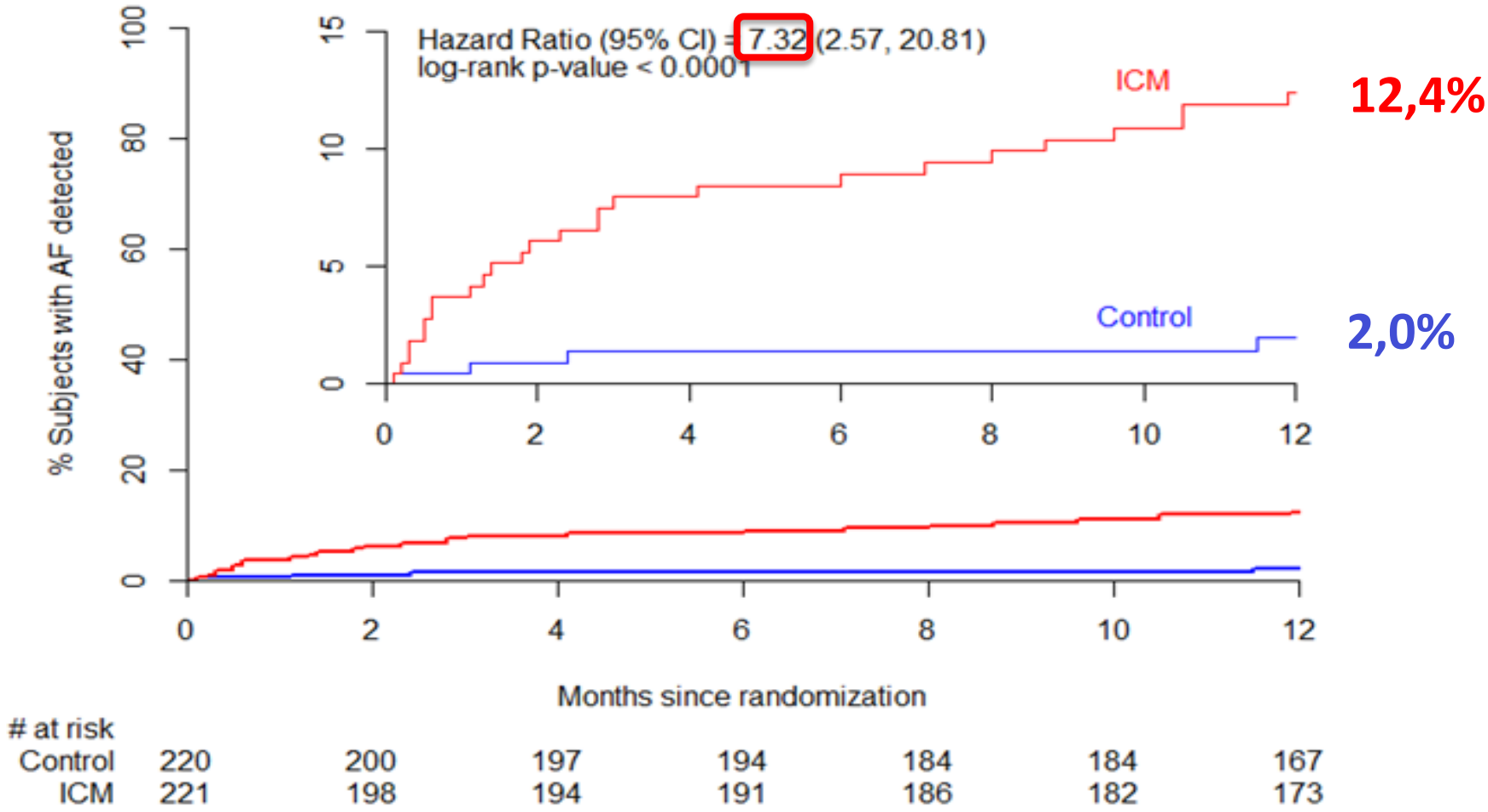
- History of AF or Atrial Flutter
- Permanent indication or contraindication for anticoagulation
- Indication for pacemaker or implantable cardioverter defibrillator

Sanna T., et al: N Engl J Med 2014;370:2478-86.

CRYSTAL AF: Baseline Characteristics:

	ICM	Control
Age	61.6 ± 11.4 years	61.4 ± 11.3 years
Gender - Male	142 (64.3%)	138 (62.7%)
Index Event – Stroke	200 (90.5%)	201 (91.4%)
Index Event – TIA	21 (9.5%)	19 (8.6%)
Pre-enrollment AF screening – Holter Monitoring	71.5% of patients Median of 23 hours (IQR 21-24)	70.9% of patients Median of 24 hours (IQR 22-24)
Pre-enrollment AF screening – Telemetry	29.9% of patients Median of 48 hours (IQR 36-96)	29.5% of patients Median of 72 hours (IQR 48-96)
Time between index event and randomization	36.6 ±28.2 days	39.6 ±26.9 days
Time to randomization and device insertion	8.7 ± 27.6 days	n/a

CRYSTAL AF, Secondary Endpoint: Detection of AF at 12 months



Sanna T., et al; N Engl J Med 2014;370:2478-86.

Can we predict iAF?
Can we select the ideal patient for prolonged monitoring?

- Clinical predictors:
  - age
  - $CHADS_2$ andCHA_2DS_2-Vasc Score
- Echoparameters:
  - E.g. atrial size
- ECG parameters
  - e.g. SPBs

Predict iAF by clinical scores?

– no significant clinical predictors in our study

	noAF (n=50)	**iAF (n=10)**	
age	61; 30-81	**66; 30-85**	n.s.
Female % (n)	40 (20)	**60 (6)**	n.s.
Hypertension % (n)	70 (35)	**70 (7)**	n.s.
Diabetes % (n)	14 (7)	**0**	p=0.1
CHF % (n)	0	**0**	n.s.
Vascular disease % (n)	8 (4)	**0**	n.s.
$CHADS_2$-Score	3; 2-3	**3; 2.25-3**	n.s.
CHA_2DS_2-VASC Score	4; 3-5	**4; 3-5**	n.s.
Insular cortex involvement	14 (7)	**10 (1)**	n.s.
Total monitoring time[d]	397; 337-504	**312; 242-397**	n.s.
Time to implantation after event [d]	13; 10-65	**30; 10-80**	n.s.

Ritter MA et al.; Stroke 2013

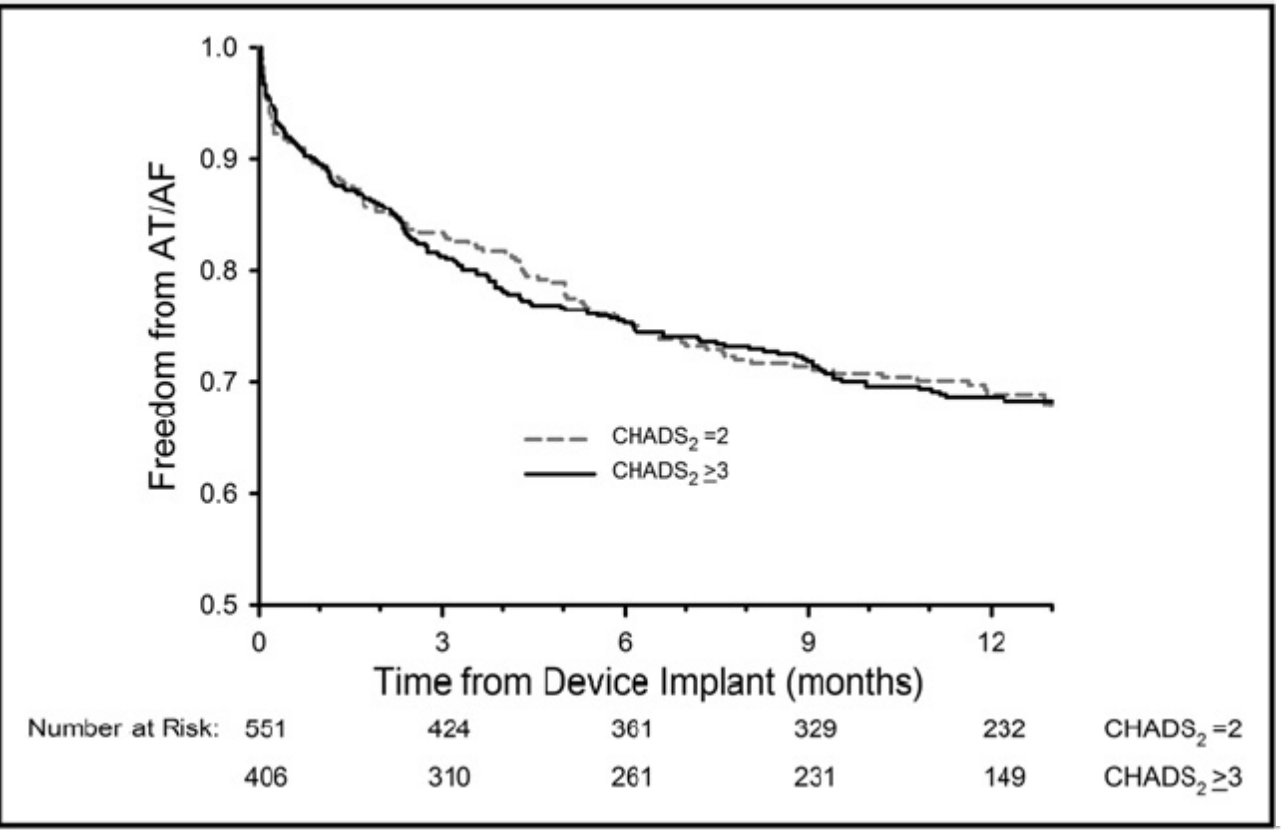
Cotter et al.: Classical risk factors predict iAF

	All	No AF	AF	p Value
Age, y	51.5 (13.9)	48.9 (13.9)	59.2 (11.0)	0.018
Male, n (%)	28 (54.9)	22 (57.9)	6 (46.2)	0.5
Interval to insertion, d	174 (134)	181 (148)	151 (74)	0.5
CHADS2	2 (2-3)	2 (2-3)	3 (2-3.5)	0.003
CHA2DS2-VASc	3 (2-4)	3 (2-3)	4 (3.5-4)	0.001
Pre-ILR monitoring, d	1 (1-2)	1 (1-2)	1 (1-1.5)	0.9
APC per day	5 (1-23)	5 (1-13)	44 (5-765)	0.004
LA volume indexed, mL/m^2	25.6 (9.57)	23.1 (9.6)	30.6 (10.0)	0.025
Max P-wave duration, ms	121 (14.6)	120.5 (15.3)	125.8 (8.6)	0.3
Interatrial block, n (%)	25 (49)	16 (48.5)	9 (90.0)	0.02
PFO[b]	22/30	18/25	4/5	0.71

Abbreviations: AF = atrial fibrillation; APC = atrial premature contraction; LA = left atrial; PFO = patent foramen ovale.
[a] Values are mean or median (SD or interquartile range) or proportions unless stated.
[b] In those with known PFO status (29 cases had shunt investigation).

Cotter PE, et al. Incidence of atrial fibrillation detected by implantable loop recorders in unexplained stroke. Neurology. 2013 Apr 23;80(17):1546-50.

Prediction of iAF according to purely clinical risk scores is ineffiecient!



1368 patients screened

416 had AF within 1,1 y.

No differences in $CHADS_2$-score

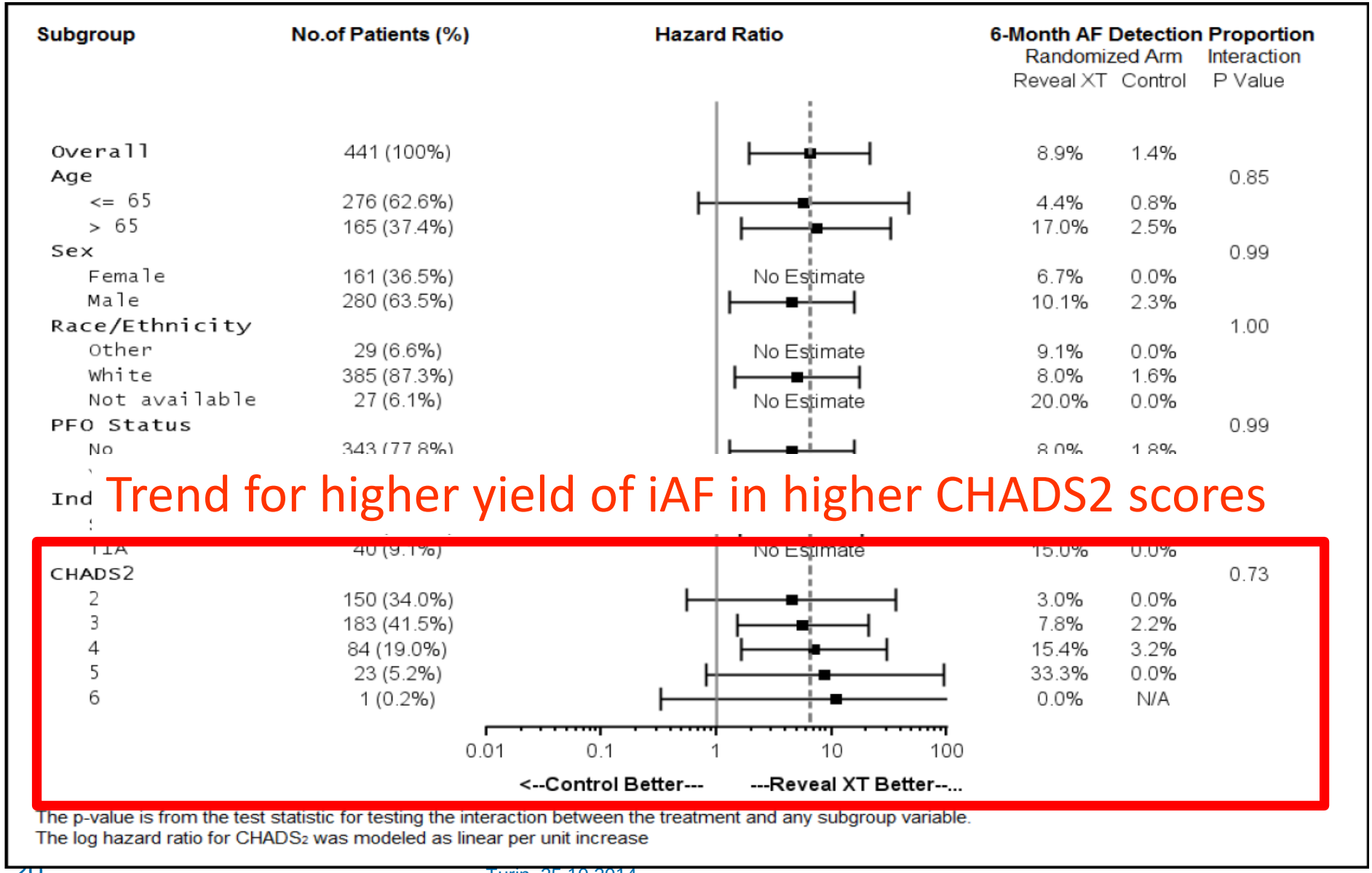
<u>However:</u>

Different population (TRENDS study, known cardiac disease)

Different devices (ICD, PM, CRT)

Ziegler PD et al. Am J Cardiol. 2012:110:1309-1314

Subgroup Analysis of CRYSTAL AF:



Trend for higher yield of iAF in higher CHADS2 scores

The p-value is from the test statistic for testing the interaction between the treatment and any subgroup variable.
The log hazard ratio for $CHADS_2$ was modeled as linear per unit increase

Cotter et al.: Classical risk factors predict iAF - and also echo and ECG parameters!

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Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association | American Stroke Association

Supraventricular Premature Beats and Short Atrial Runs Predict Atrial Fibrillation in Continuously Monitored Patients With Cryptogenic Stroke

Simon Kochhäuser, Dirk G. Dechering, Ralf Dittrich, Florian Reinke, Martin A. Ritter, Shahrai Ramtin, Thomas Duning, Gerrit Frommeyer and Lars Eckardt

Stroke. published online January 14, 2014;

Table. Baseline Characteristics of Participants

Characteristic	All	Atrial Fibrillation	No Atrial Fibrillation	*P* Value
No. of participants	70	12	58	…
Age, y	58.8±13.4	57.7±13.4	64.2±12.0	0.13
Women, n (%)	27 (39)	7 (58)	20 (35)	0.19
CHADS2 score	2.9±0.8	3.0±0.9	2.9±0.8	0.80
CHA2DS2-VASc score	3.8±1.3	4.4±1.2	3.7±1.2	0.08
Supraventricular extrasystoles/h, median (IQR)	1.5 (0.4–9.1)	22.8 (3.2–106.9)	1.2 (0.4–3.1)	<0.0001
Supraventricular runs/h, n, median (IQR)	0.0 (0.0–1.3)	0.7 (0.1–2.8)	0.0 (0.0–0.4)	<0.0001
Cardiovascular disease and risk factors				
Coronary heart disease, n (%)	4 (6)	0 (0)	4 (7)	…
Arterial hypertension, n (%)	23 (33)	3 (25)	20 (35)	0.74
Diabetes mellitus, n (%)	7 (10)	1 (8)	6 (10)	1.00
Left atrial parameters				
Left atrial diameter, mm	37.0±4.0	38.0±5.0	36.7±3.7	0.32
Left atrial volume index, mL/m^2	28.9±8.0	31.7±9.6	28.3±7.6	0.20

CHADS indicates congestive heart failure, hypertension, age, diabetes, stroke; IQR, interquartile range; and VASc, vascular disease, age, sex.

Thoughts on consequences for future patient selection for ICMs - 1

ILRs are much more sensitive than 7 day Holter!

Most patients detected within 3 mo. from implantation, but there is significant yield beyond this!

7 or 30 days of monitoring are not enough!

Emergent questions:

How long should a monitoring be performed (in order to attribute a positive result to the recent event)?

Is anticoagulation really the answer for all patients with iAF (“AF burden”)

How about PFO and iAF?

Thoughts on consequences for future patient selection for ICMs – 2

Who is a candidate for extensive monitoring = ICM ?

Complete work-up performed and stroke is „cryptogenic“

Patients with numerous SBPs and SVRs on 24h Holter

You think it‘s AF (stroke pattern plus risk factors but you can not prove it yet!)

Relatively fit patients

Compliance with telemetry

„a lot to lose“

Summary

1. 10-20% of patients with cryptogenic stroke do have iAF
2. Detection requires at least 3-12 months extensive monitoring
3. It is not possible to predict the occurrence of AF according to clinical risk factors the final word on paraclinical parameters (echo, 24h Holter) has not been spoken
4. Up to now any diagnosis of AF according to cardiological guidelines is currently relevant and should be followed by anticoagulaton


Thank you for your attention!