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DELLA TROMBOSI E LA
SORVEGLIANZA DELLE TERAPIE
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XXIX
Congresso Nazionale

Fibrillazione atriale: è sempre necessario ricercarla, e come?

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SOD Medicina Interna Interdisciplinare
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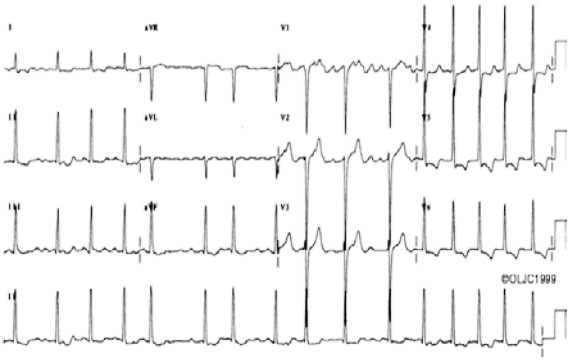
23-10-2018

Disclosure

Fees for lectures and Advisory board membership:
Bayer, Sobi



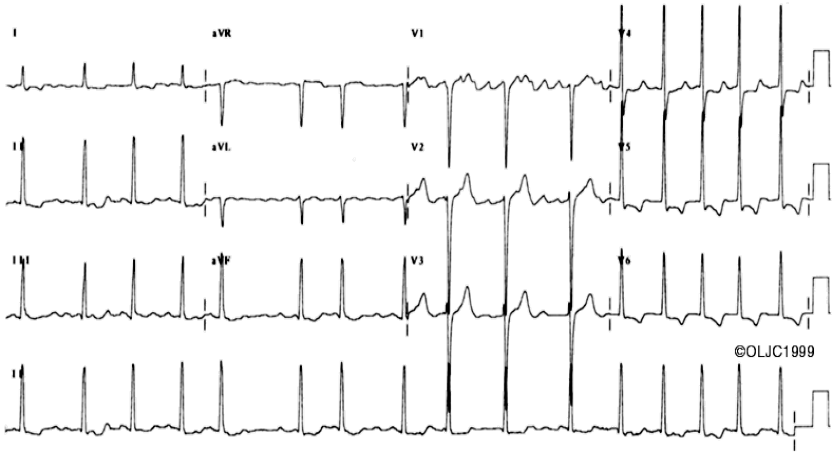
Atrial Fibrillation

Not so Harmless

Table 3 Clinical events (outcomes) affected by AF

Outcome parameter	Relative change in AF patients
1. Death	Death rate doubled.
2. Stroke (includes haemorrhagic stroke and cerebral bleeds)	Stroke risk increased; AF is associated with more severe stroke.
3. Hospitalizations	Hospitalizations are frequent in AF patients and may contribute to reduced quality of life.
4. Quality of life and exercise capacity	Wide variation, from no effect to major reduction. AF can cause marked distress through palpitations and other AF-related symptoms.
5. Left ventricular function	Wide variation, from no change to tachycardiomyopathy with acute heart failure.

AF ESC Guidelines. European Heart Journal (2010) 31, 2369–2429



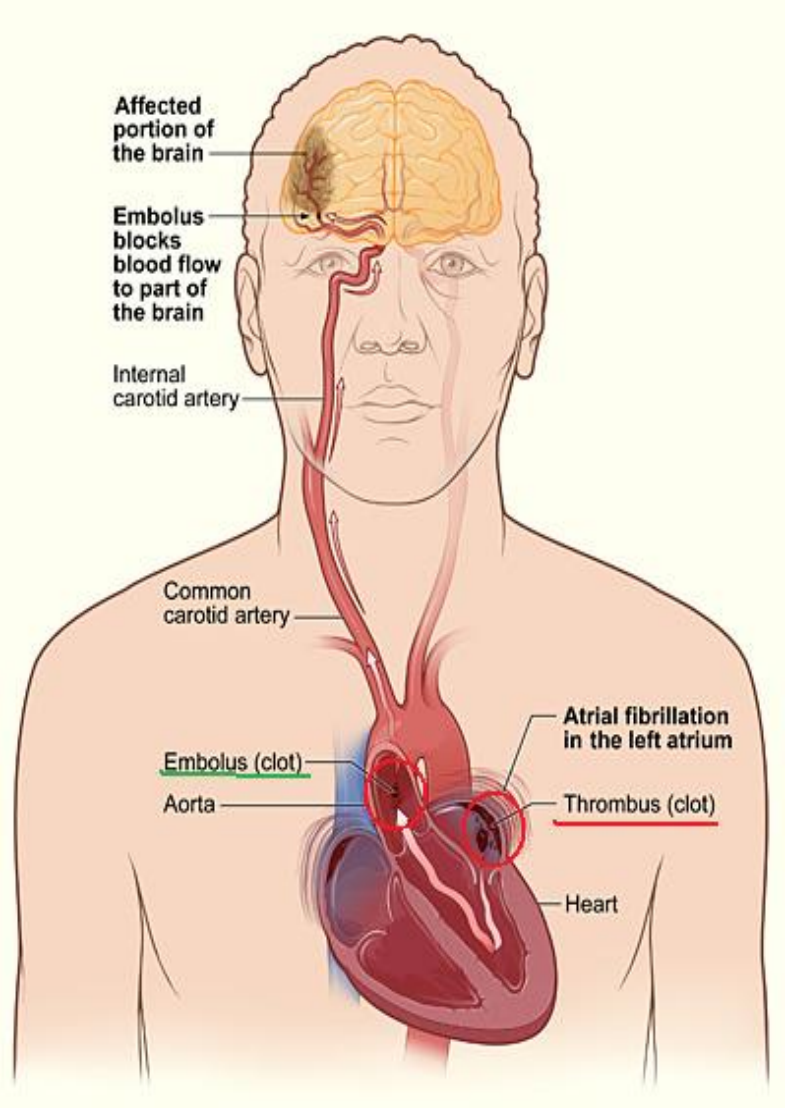
Atrial Fibrillation

Risk of stroke ⬆ x 5

Risk of Heart Failure ⬆ x 3

Risk of mortality ⬆ x 2

Ma certamente la complicanza principale della fibrillazione atriale è lo stroke !

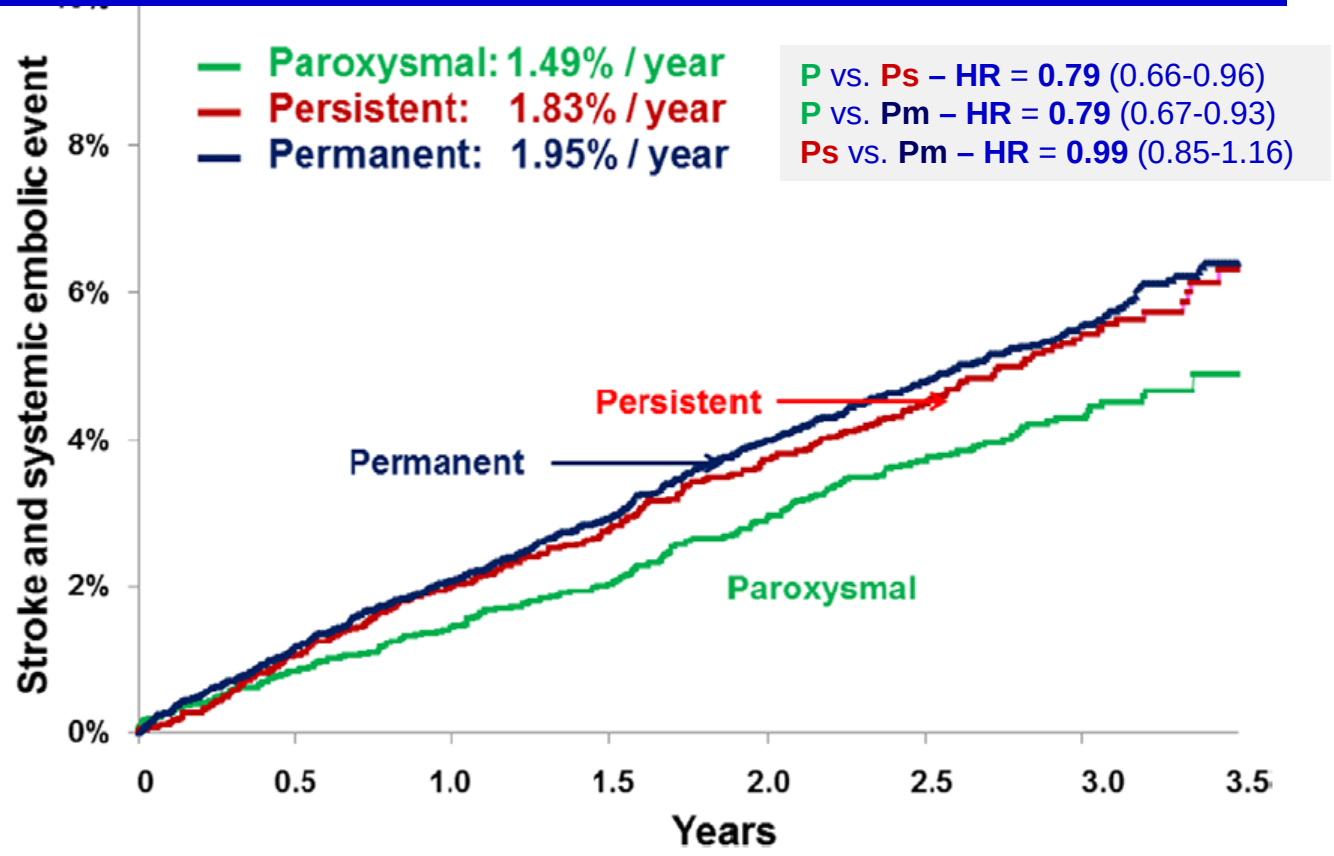


Stroke and Mortality Risk in Patients With Various Patterns of Atrial Fibrillation

Results From the ENGAGE AF-TIMI 48 Trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48)

Circulation
Arrhythmia and Electrophysiology

Stroke and systemic embolic event by AF pattern
(Paroxysmal, P – N=5366, 25%, 70 y; Persistent, Ps – N=4868, 23%, 70 y; Permanent, Pm – N=10865, 51%, 71 y; Follow-up: 2.8 y)



Link MS, 2017

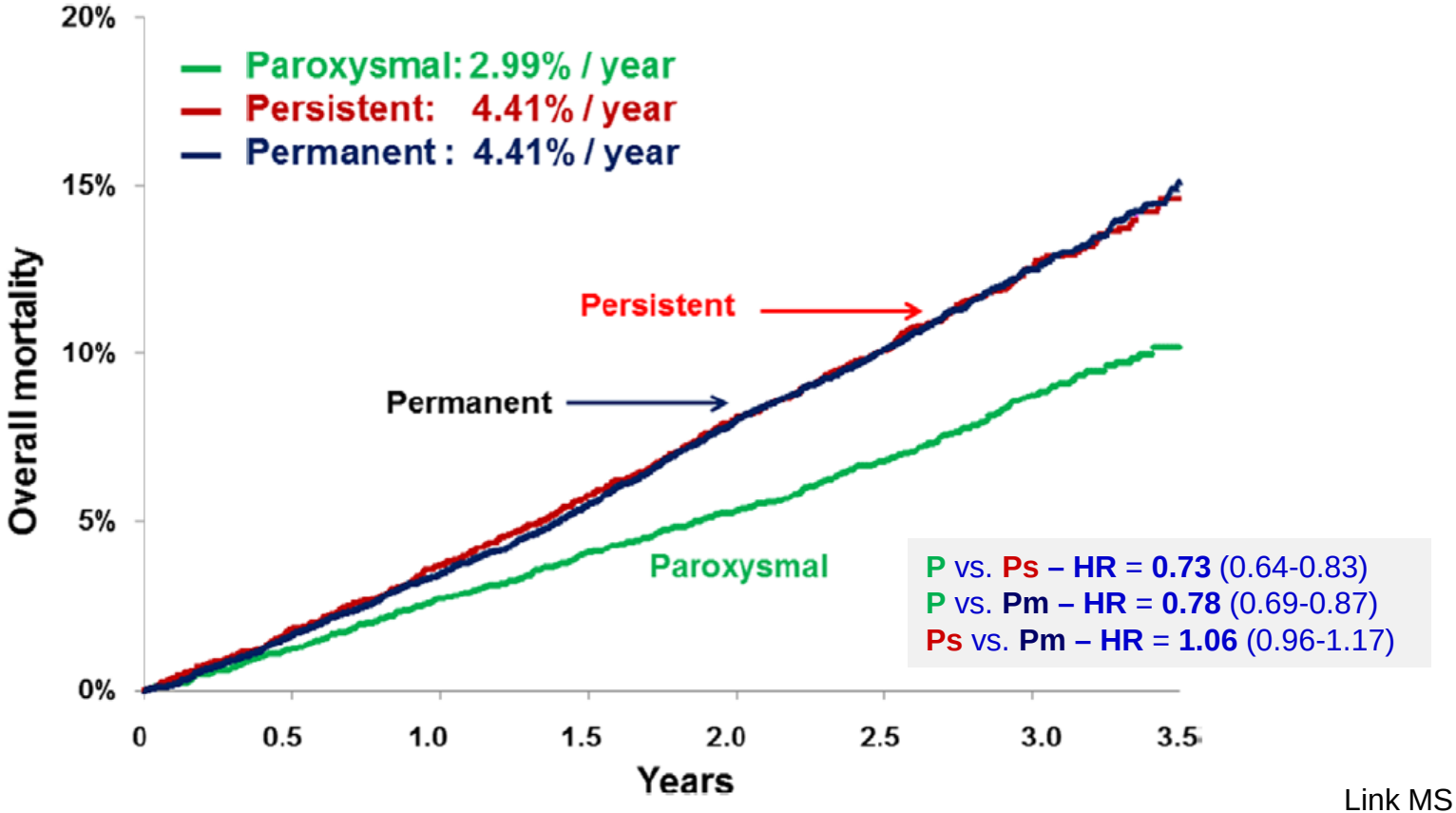
Stroke and Mortality Risk in Patients With Various Patterns of Atrial Fibrillation

Results From the ENGAGE AF-TIMI 48 Trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48)

Circulation
Arrhythmia and Electrophysiology

Overall mortality by AF pattern

(Paroxysmal, P – N=5366, 25%, 70 y; Persistent, Ps – N=4868, 23%, 70 y; Permanent, Pm – N=10865, 51%, 71 y; Follow-up: 2.8 y)



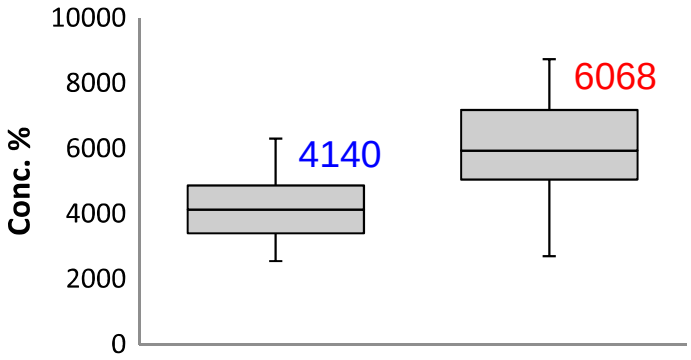
Link MS, 2017

Increased Level of Thrombotic Biomarkers in Patients with Atrial Fibrillation Despite Traditional and New Anticoagulant Therapy

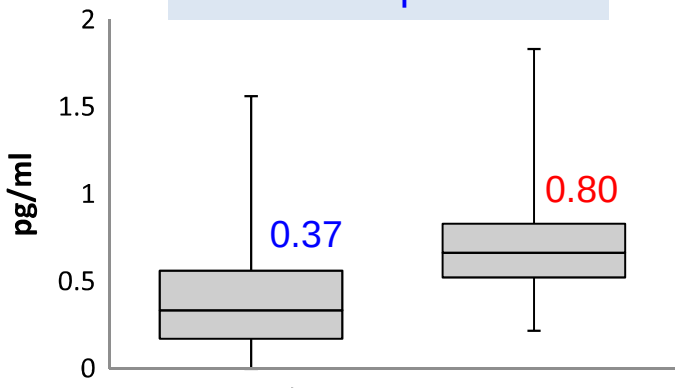
Clinical and Applied Thrombosis/Hemostasis

Levels of biomarkers in control and AF groups

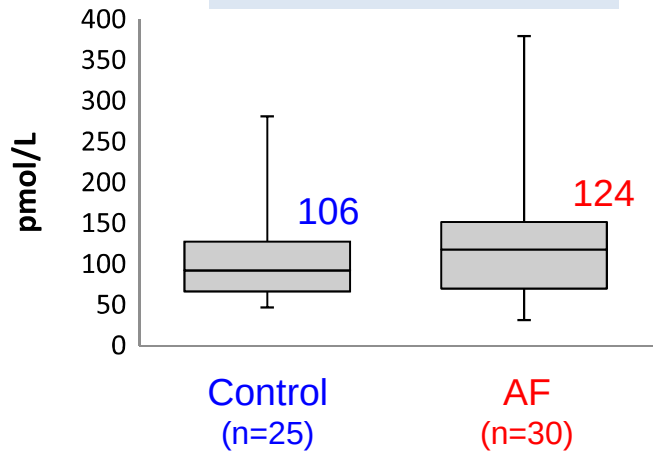
vWF – p<0.001



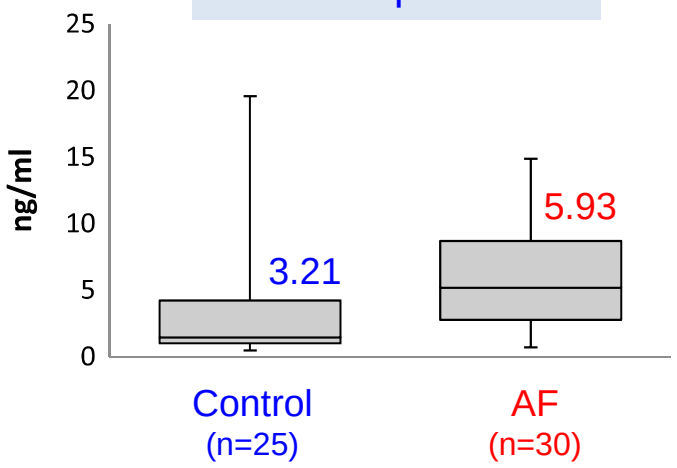
MP-TF – p<0.001



F1.2 – p=0.270



PAI-1 – p=0.001

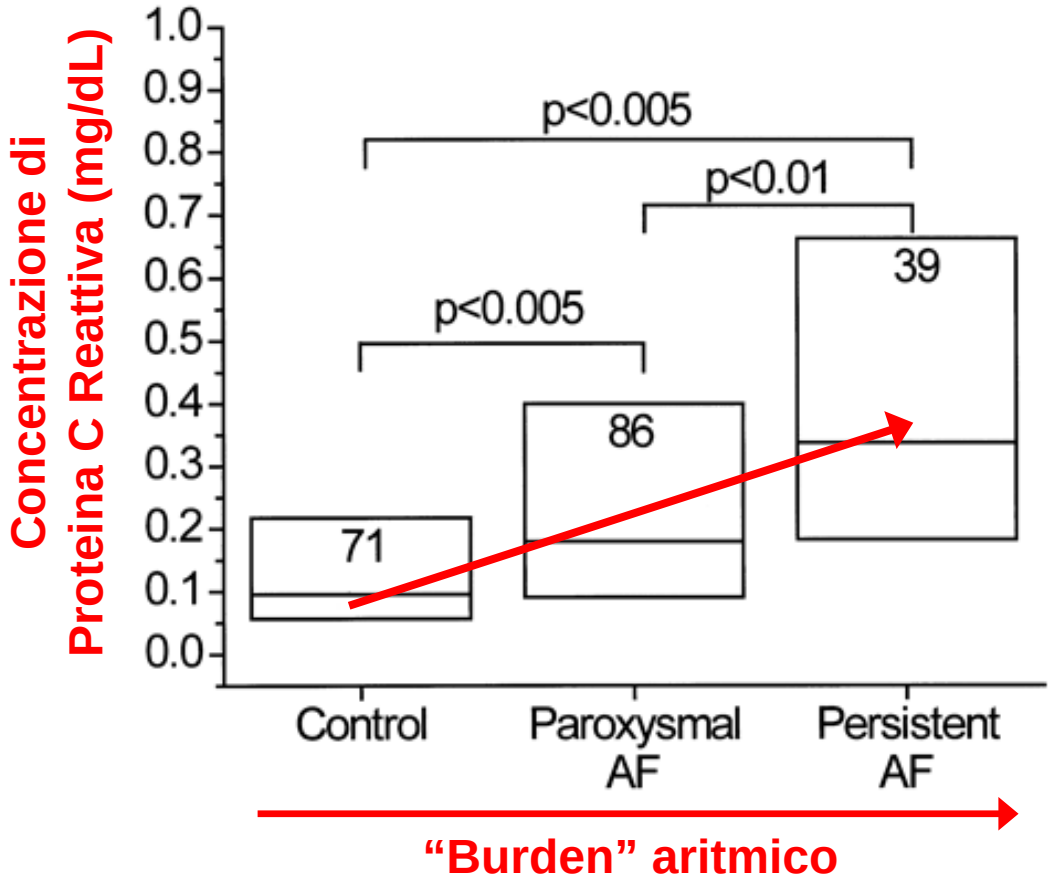


vWF: von Willebrand Factor
MP-TF: Microparticle tissue factor
F1.2: Prothrombin fragment 1+2
PAI-1: Plasminogen activator inhibitor

Liles J, 2016

C-Reactive Protein Elevation in Patients With Atrial Arrhythmias

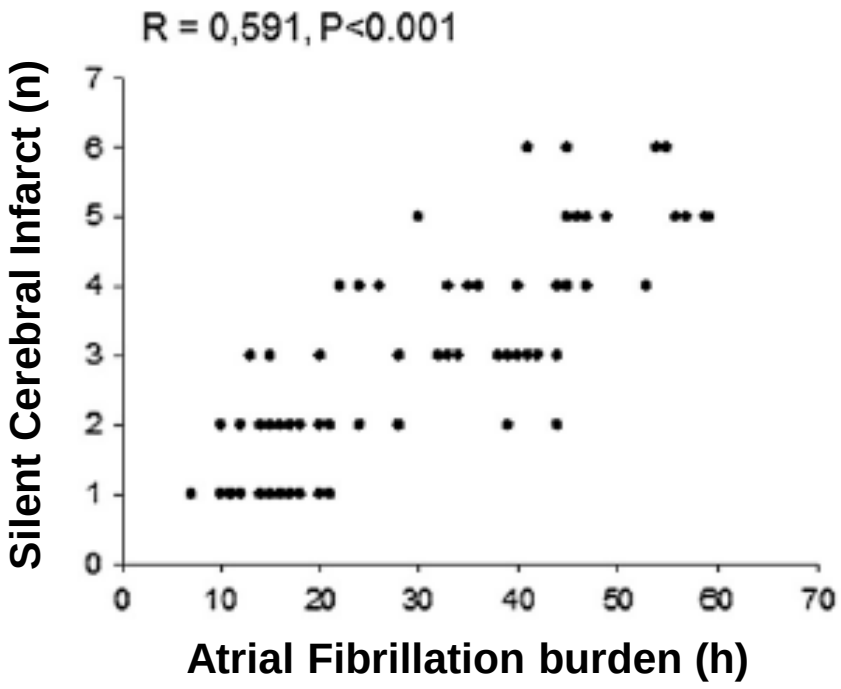
Inflammatory Mechanisms and Persistence of Atrial Fibrillation

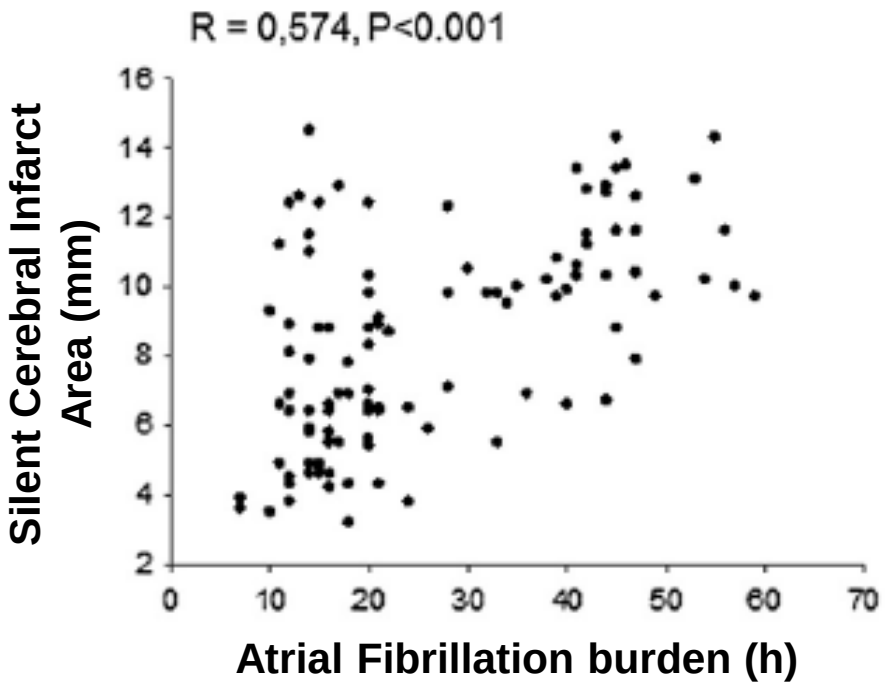


Chung, Circulation, 2001

Brief Episodes of Silent Atrial Fibrillation Predict Clinical Vascular Brain Disease in Type 2 Diabetic Patients

Relation Between silent cerebral infarct and episodes of atrial fibrillation

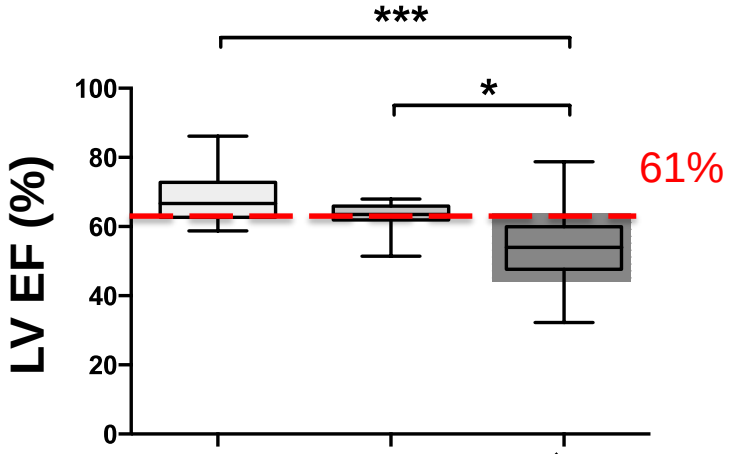


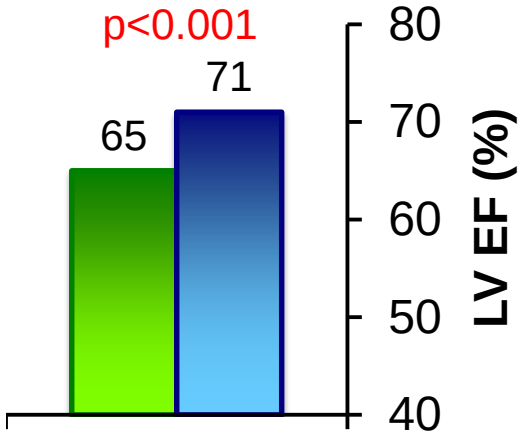


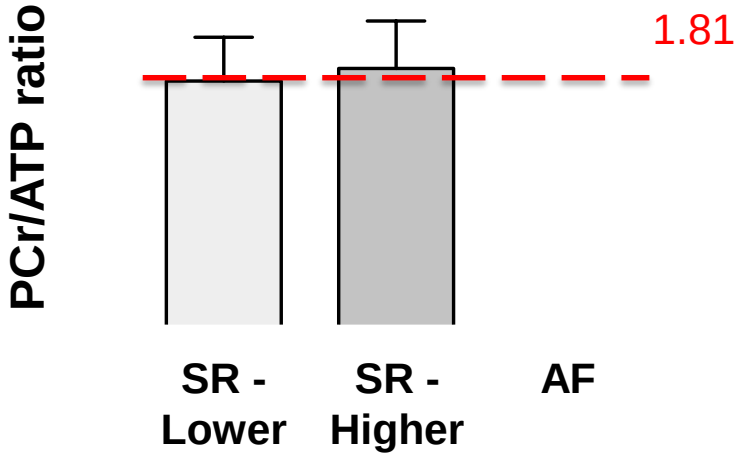
Marfella R et al. 2013

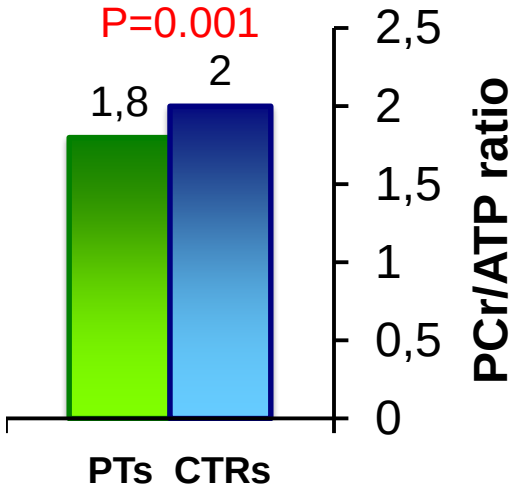
Lone Atrial Fibrillation Is Associated With Impaired Left Ventricular Energetics That Persists Despite Successful Catheter Ablation

LVEF & myocardial energetics in AF patients before ablation and in controls







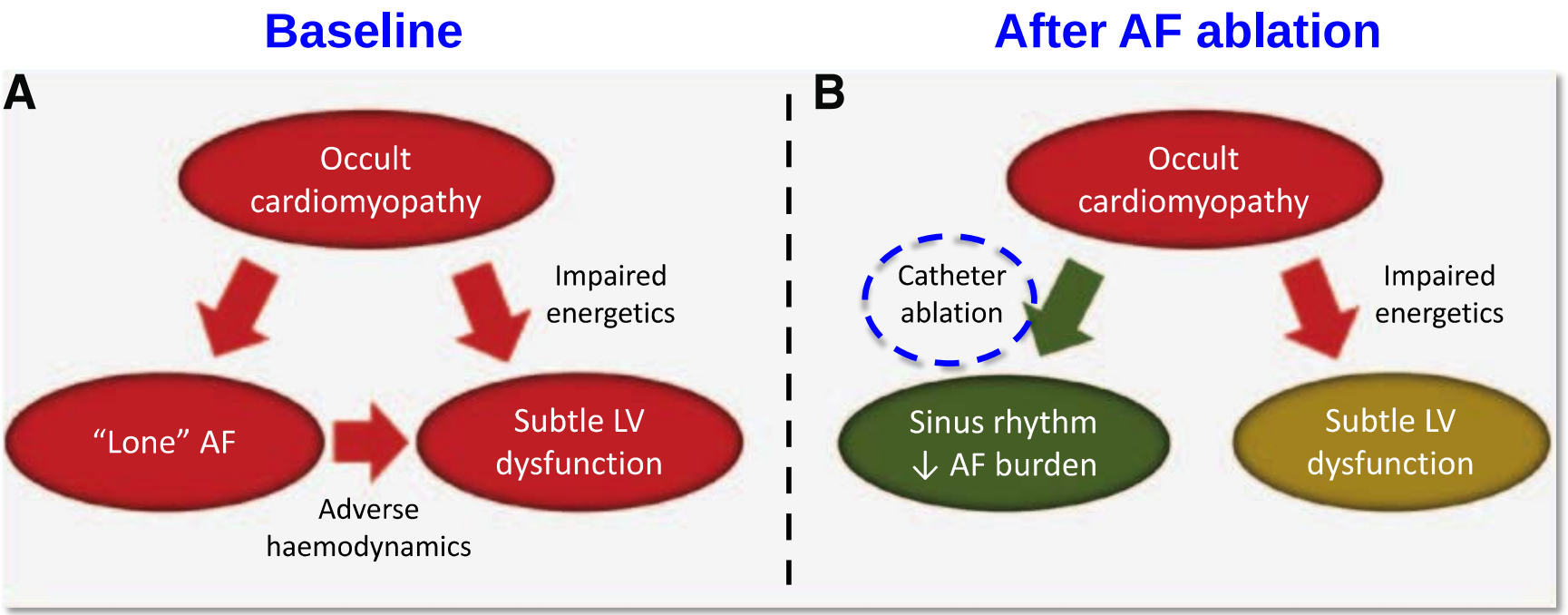


PTs: Patients at the 7-month evaluation (N=53)
CTRs: Controls (N=25)

Wijesurendra RS, 2016

Lone Atrial Fibrillation Is Associated With Impaired Left Ventricular Energetics That Persists Despite Successful Catheter Ablation

Schematic representation of the relationships between lone atrial fibrillation, subtle left ventricular dysfunction and upstream cardiomyopathy, and the effect of ablation

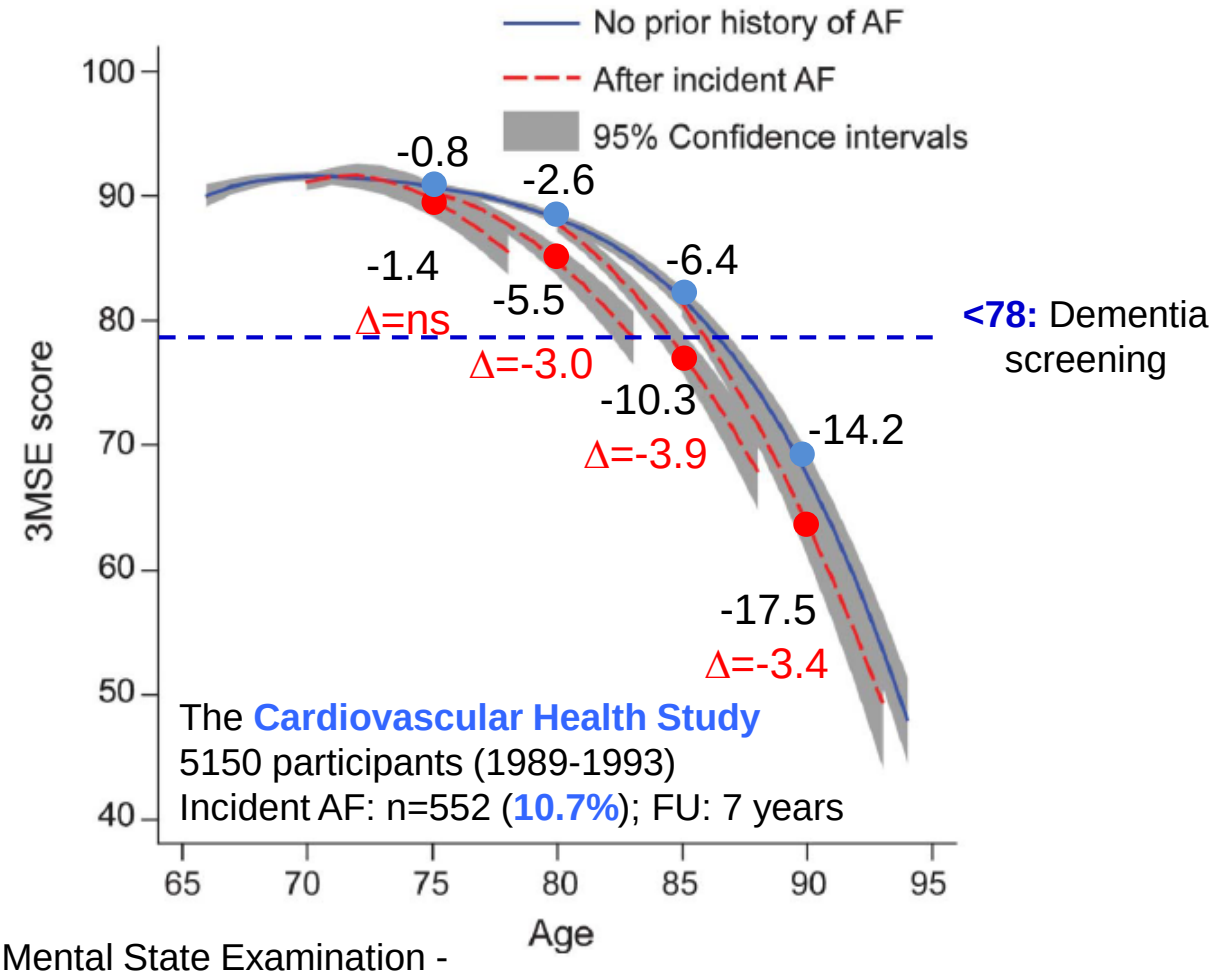


Wijesurendra RS, 2016

Atrial fibrillation and cognitive decline

A longitudinal cohort study

Model-predicted 3MSE score trajectories in CHS participants with and without incident AF (74.4 vs. 72.9 years)

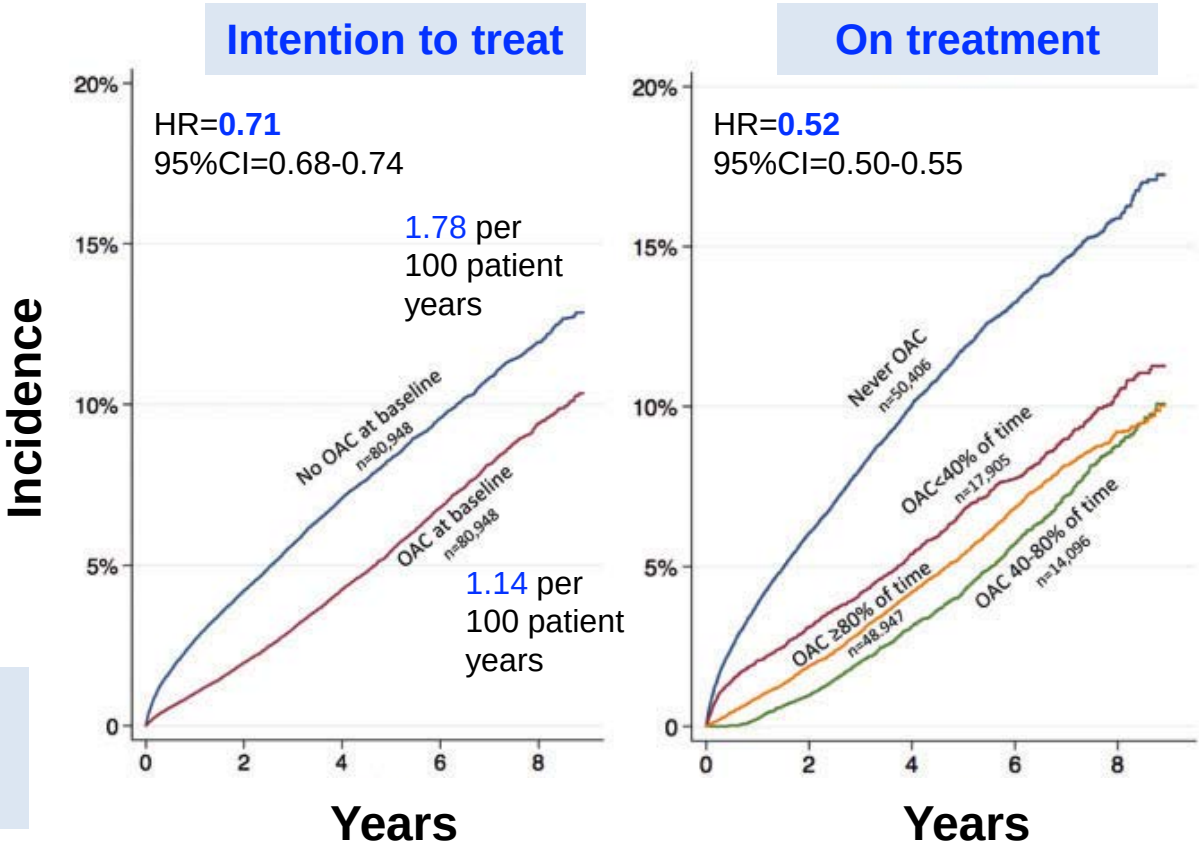


3MSE: Modified Mini-Mental State Examination - Scores range from 0 (worst) to 100 (best)

Thacker EL et al. Neurology 2013

Less dementia with oral anticoagulation in atrial fibrillation

Incidence of dementia in relation to oral anticoagulant treatment (OAT) among 161896 patients with AF (propensity score matched for the likelihood of OAT; Dementia - N=26210/ 444106 – 1.73 per 100 patient years; Age – Dementia: 81 vs. No dementia: 74 years; CHA_2DS_2-VASc – Dementia: 4.2 vs. No dementia: 3.4)



Swedish Patient Register and the Dispensed Drug Register (2006-14)

Friberg L, Eur Heart J 2018

Come possiamo combattere lo stroke nei pazienti con FA

- Scoprendo la fibrillazione atriale inconsapevole
- Trattando i pazienti con farmaci anticoagulanti
- Ove non sia possibile
  - ❖Chiusura della auricola
  - ❖Ablazione dei circuiti che determinano la fibrillazione atriale

AF-Related Stroke

- High mortality rate: 24% mortality at 30 days
- 75% of patients with AF are unaware they have it
- First manifestation of AF is stroke in about 20% of patients
- How much AF requires stroke prevention therapy?

Hylek EM, et al. *Stroke*. 2006;37:1075-1080; Israel CW, et al. *J Am Coll Cardiol*. 2004;43:47-52; Page RL, et al. *Circulation*. 1994;89:224-227.

Cosa è la Fibrillazione atriale inconsapevole?

- La presenza di una battito irregolare cardiaco senza che il paziente se ne accorga.

- Quando è sintomatica la fibrillazione atriale si manifesta con:
  - Palpitazioni
  - Vertigini
  - Testa vuota
  - Svenimento
  - Mancanza di respiro

Screening for atrial fibrillation

Recommendations	Class	Level
Opportunistic screening for AF is recommended by pulse taking or ECG rhythm strip in patients >65 years of age.	I	B
In patients with TIA or ischaemic stroke, screening for AF is recommended by short-term ECG recording followed by continuous ECG monitoring for at least 72 hours.	I	B
It is recommended to interrogate pacemakers and ICDs on a regular basis for atrial high rate episodes (AHRE). Patients with AHRE should undergo further ECG monitoring to document AF before initiating AF therapy.	I	B
In stroke patients, additional ECG monitoring by long-term non-invasive ECG monitors or implanted loop recorders should be considered to document silent atrial fibrillation.	IIa	B
Systematic ECG screening may be considered to detect AF in patients aged >75 years, or those at high stroke risk.	IIb	B

European Heart Journal - doi:10.1093/eurheartj/ehw210

Cryptogenic Stroke: Prevalence

- In the United States, there are ~800,000 ischemic strokes annually
  - 1/4 are cryptogenic = unknown cause
- Cryptogenic strokes require a thorough work-up looking for cardiac sources of embolism, hypercoagulability, and other nonatherosclerotic causes of stroke

Mozaffarian D, et al. *Circulation*. 2015:e29-e322.

Cryptogenic Stroke: Diagnostic Workup

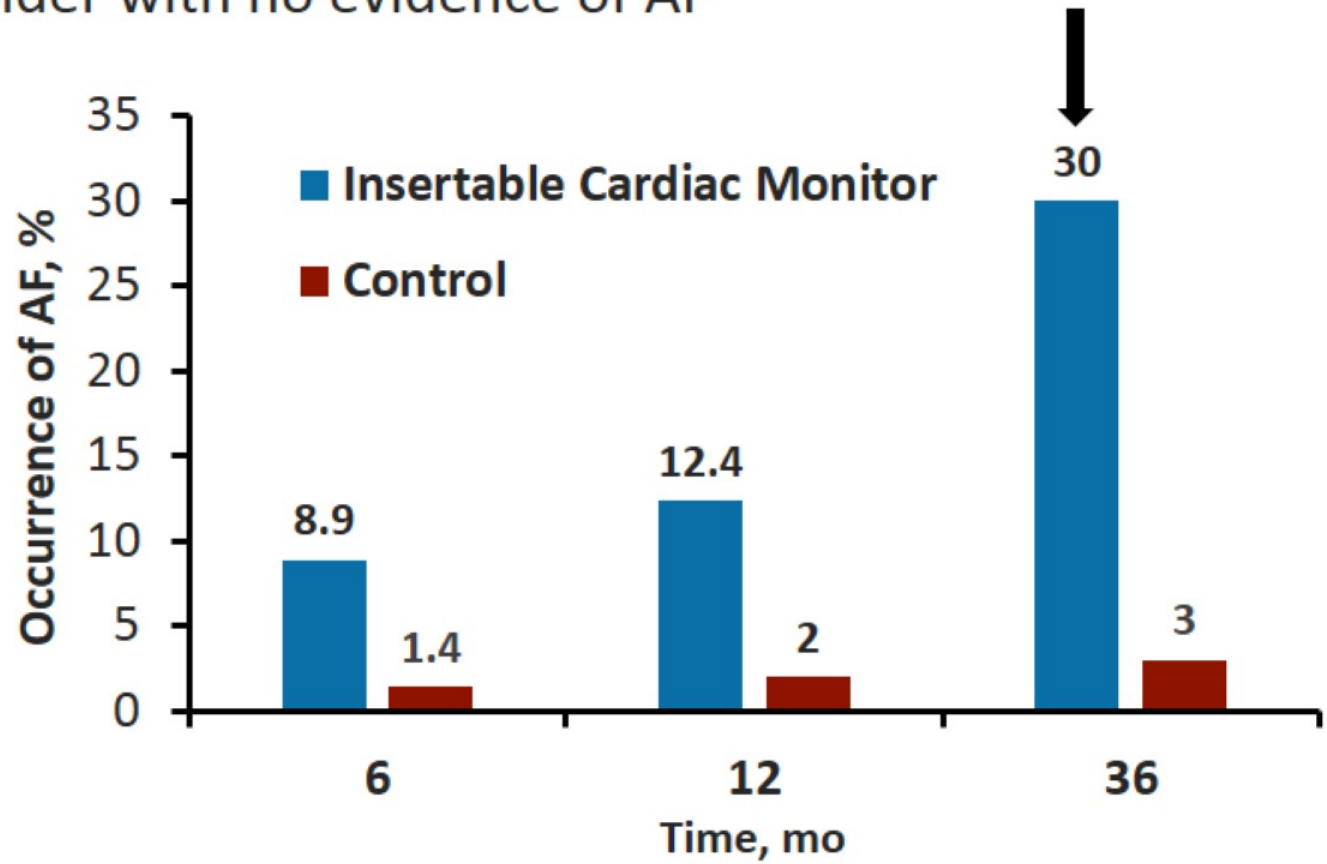
- Carotid ultrasound
- Computed tomography angiography
- Magnetic resonance angiography
- Echocardiogram
- Hypercoagulable diagnostic state work-up
- Monitoring; for how long?
  - Guidelines: 30-day monitoring

Kernan WN, et al. *Stroke*. 2014;45:2160-2236.

CRYSTAL AF

Results at 36 Months

- N = 441 patients with cryptogenic stroke aged 40 years or older with no evidence of AF

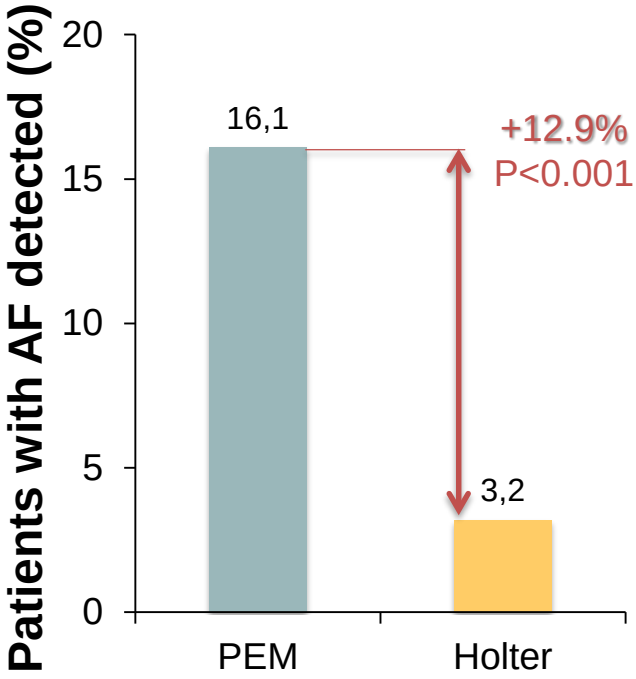


Brachmann J, et al. *Circ Arrhthm Electrophysiol*. 2016;9:e003333.

The NEW ENGLAND JOURNAL of MEDICINE

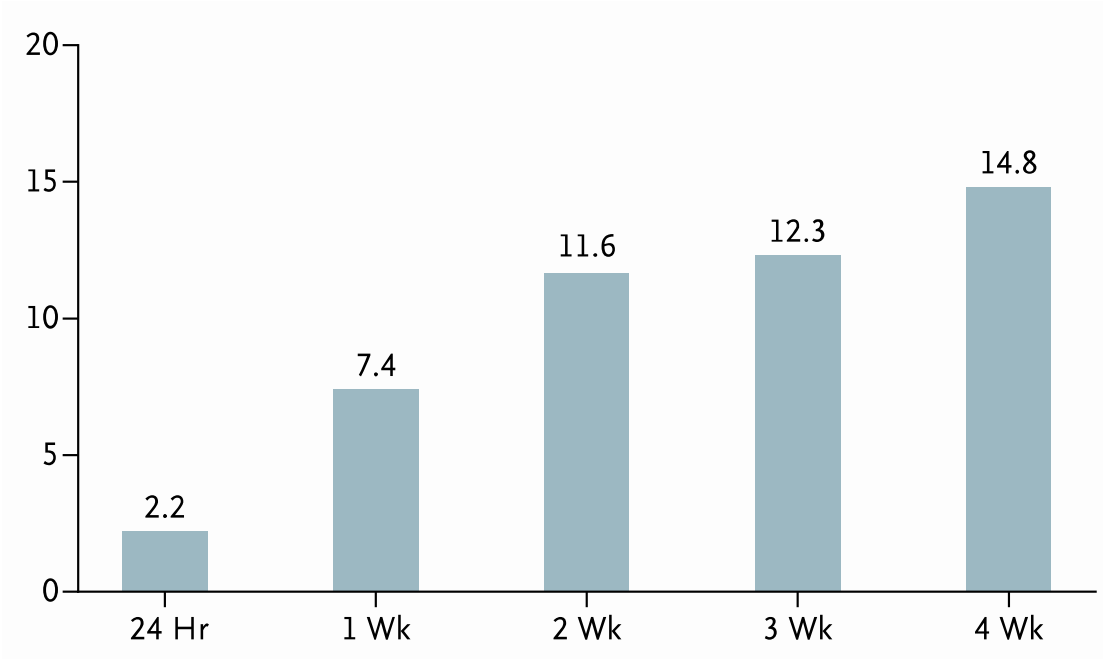
Atrial Fibrillation in Patients with Cryptogenic Stroke

Detection of AF in the Two Monitoring Groups at 90 days



PEM: Prolonged ECG Monitoring
PEM: N=280; Holter: N=277

Incremental Yield of Prolonged ECG Monitoring for the Detection of AF After Cryptogenic Stroke or TIA



Age: 72 y; CHA_2DS_2 score: 3
Stroke/TIA: 63/37%; Random: 75 days

Gladstone DJ, 2014

Monitoring for AF

Holter monitors

- If AF is detected, patients require anticoagulation
  - If not, further monitoring may be indicated
- Patients may not be adherent, may not want wires, etc.

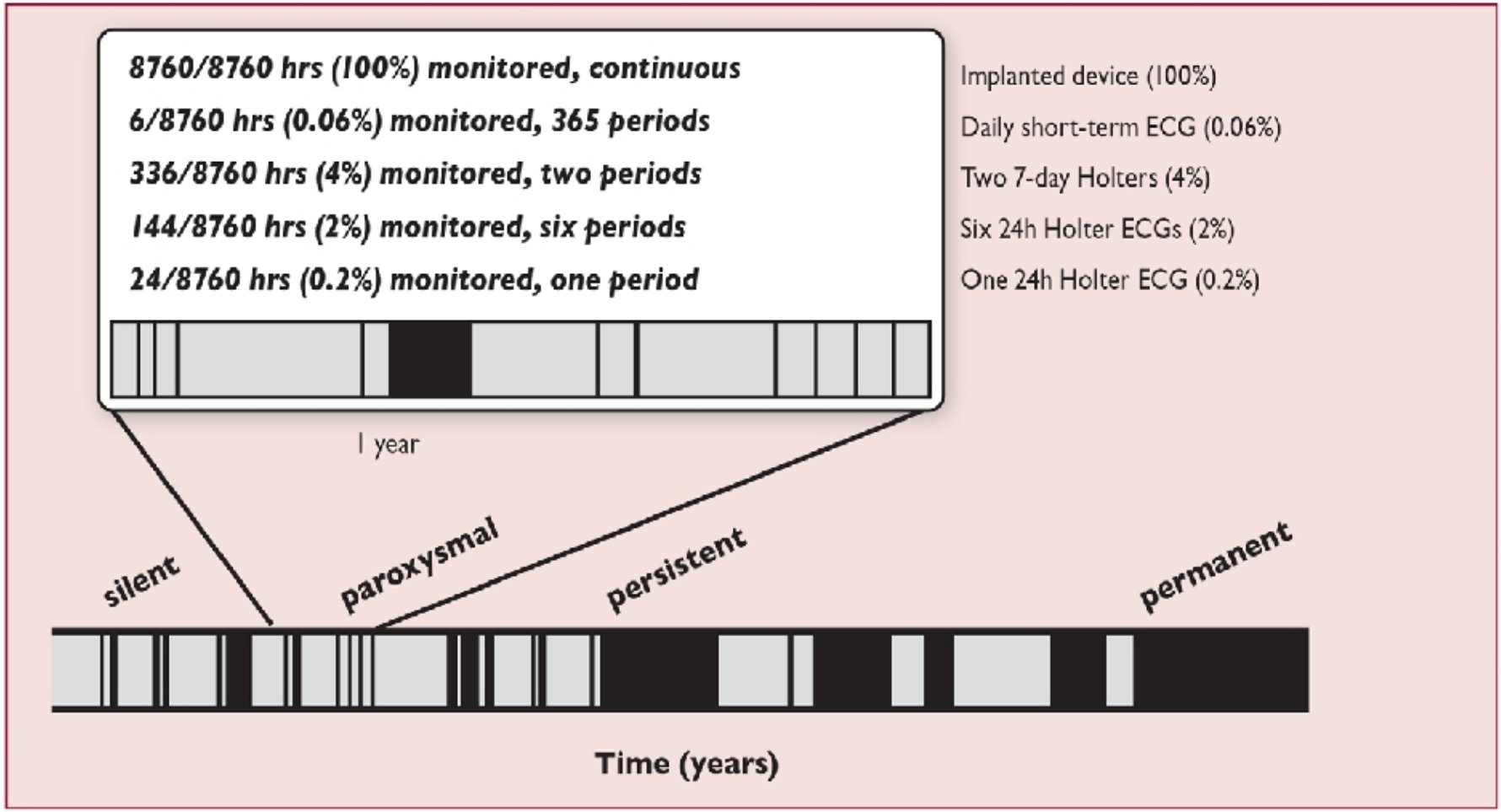
Patch monitors

- Allows bathing, less cumbersome to use
- Older patients may have fragile skin and may not tolerate patch adhesive

Implantable/insertable monitors

- Improves adherence
- Monitoring should be managed by electrophysiologist/cardiologist

Diagnostic yield of different ECG screening techniques for paroxysmal or silent atrial fibrillation



European Heart Journal - doi:10.1093/eurheartj/ehw210

Presence and Duration of Atrial Fibrillation Detected by Continuous Monitoring: Crucial Implications for the Risk of Thromboembolic Events

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STEFANO FAVALE, M.D.,†† GIULIO MOLON, M.D.,‡‡ RENATO RICCI, M.D.,‡
MAURO BIFFI, M.D.,§§ GIOVANNI RUSSO, M.D.,* MARCO VIMERCATI, PH.D.,¶¶
GIORGIO CORBUCCI, PH.D.,¶¶ and GIUSEPPE BORIANI, M.D., PH.D.§§

Data from 568 pts continuously monitored for 1 year. 14 pts (2.5%) had a cardioembolic stroke

TABLE 2

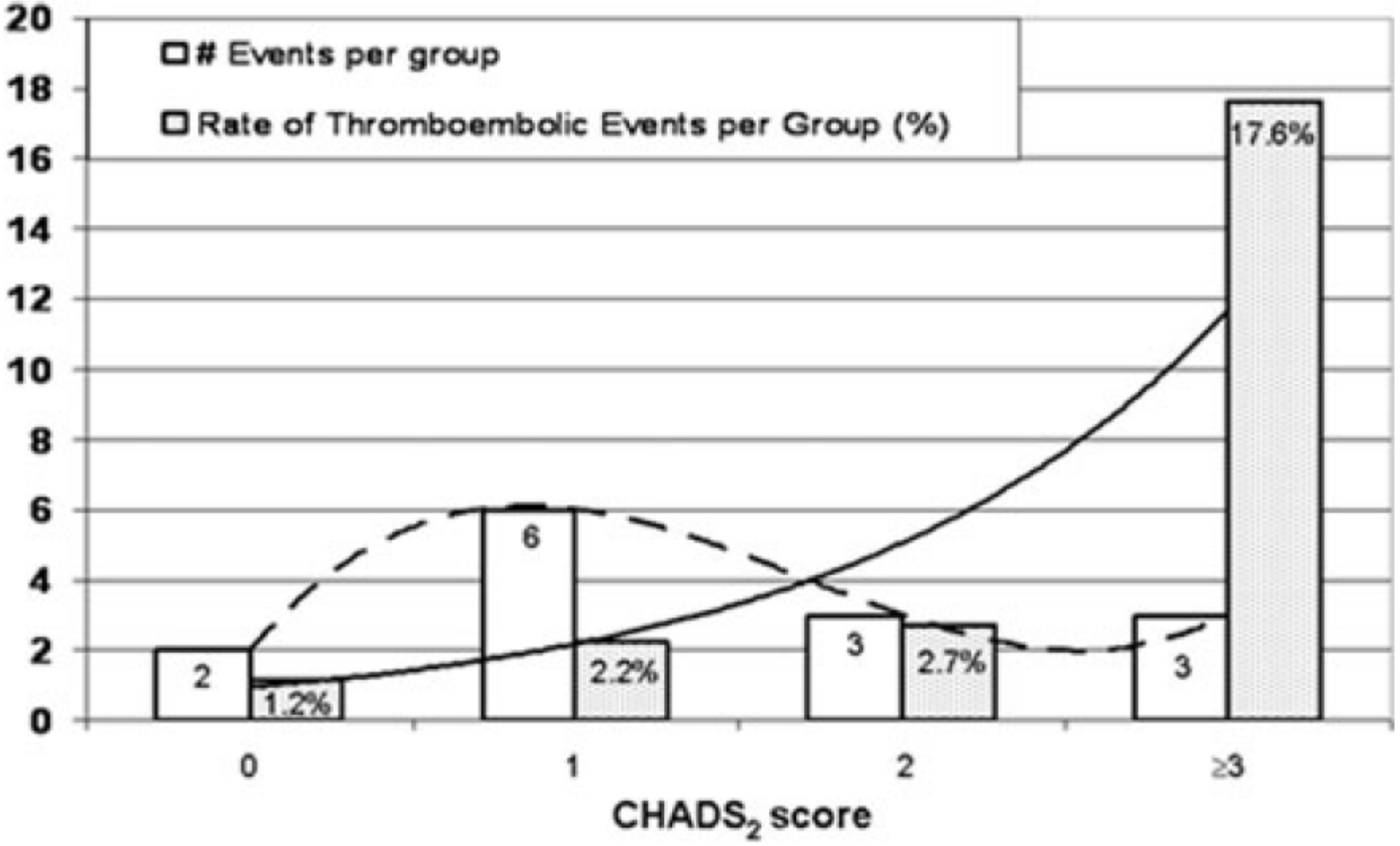
Patient Population and Thromboembolic Events Observed During the Follow-Up According to $CHADS_2$ Score (Panel A) and AF Episode Duration (Panel B), as Detected Through Device Diagnostics

Panel A	$CHADS_2$ Score	Pts (%)	Thromboembolic Events	Stroke	TIA	PAE
	0	171 (30)	2	0	2	0
	1	269 (47)	6	2	2	2
	2	111 (20)	3	3	0	0
	≥3	17 (3)	3	3	0	0

Panel B	AF classification	Pts (%)	Thromboembolic events	Stroke	TIA	PAE
	No AF	166 (29)	2	2	0	0
	AF >5 minutes	179 (31)	3	0	2	1
	AF >24 hours	223 (39)	9	6	2	1

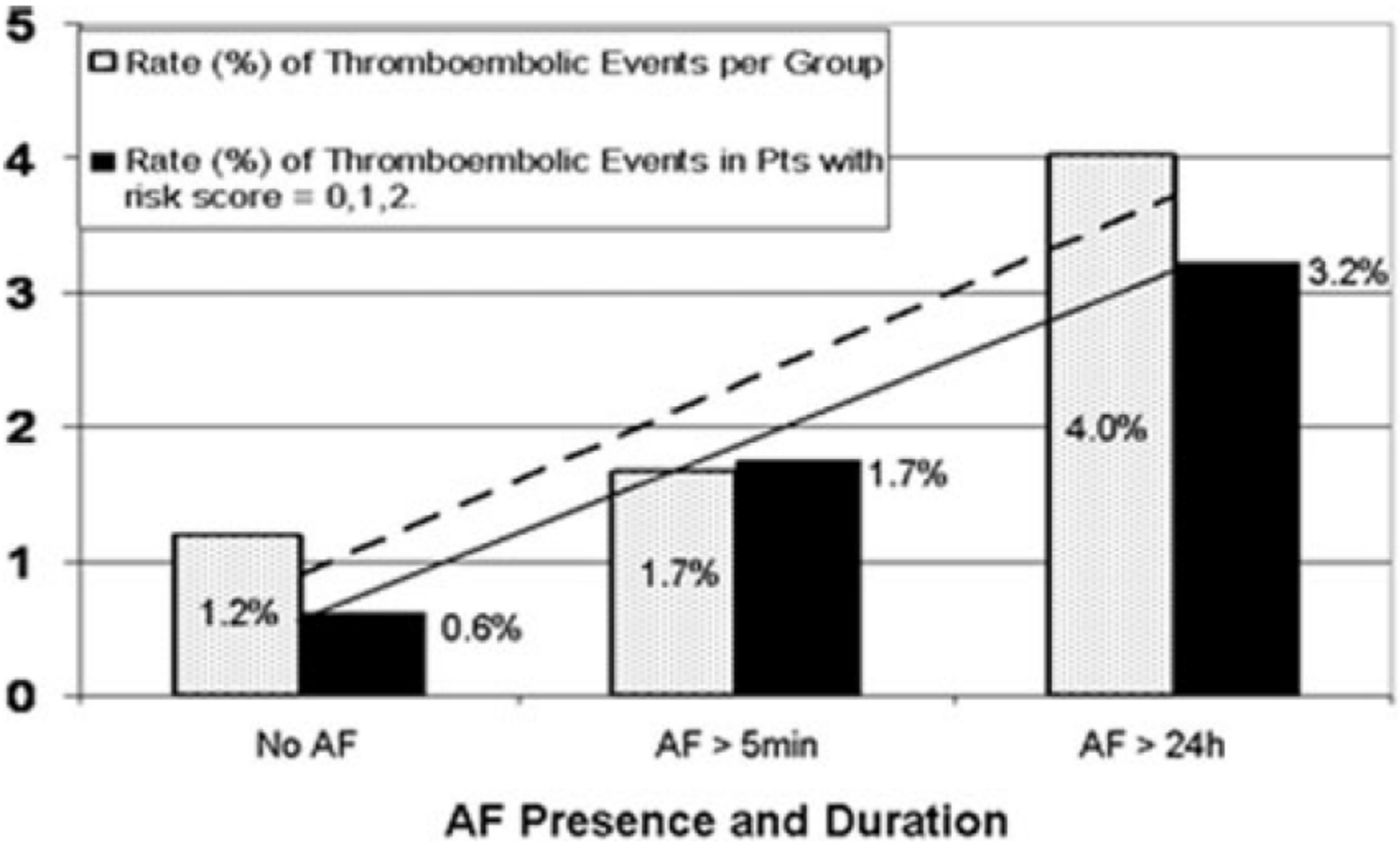
Botto GL, Journal Cardiovasc Electrophysio, 2008

Rate of thromboembolic events according to the CHADS2 score



Botto GL, Journal Cardiovasc Electrophysio, 2008

Rate of thromboembolic events related to presence and duration of AF



Botto GL, Journal Cardiovasc Electrophysio, 2008

Conclusion

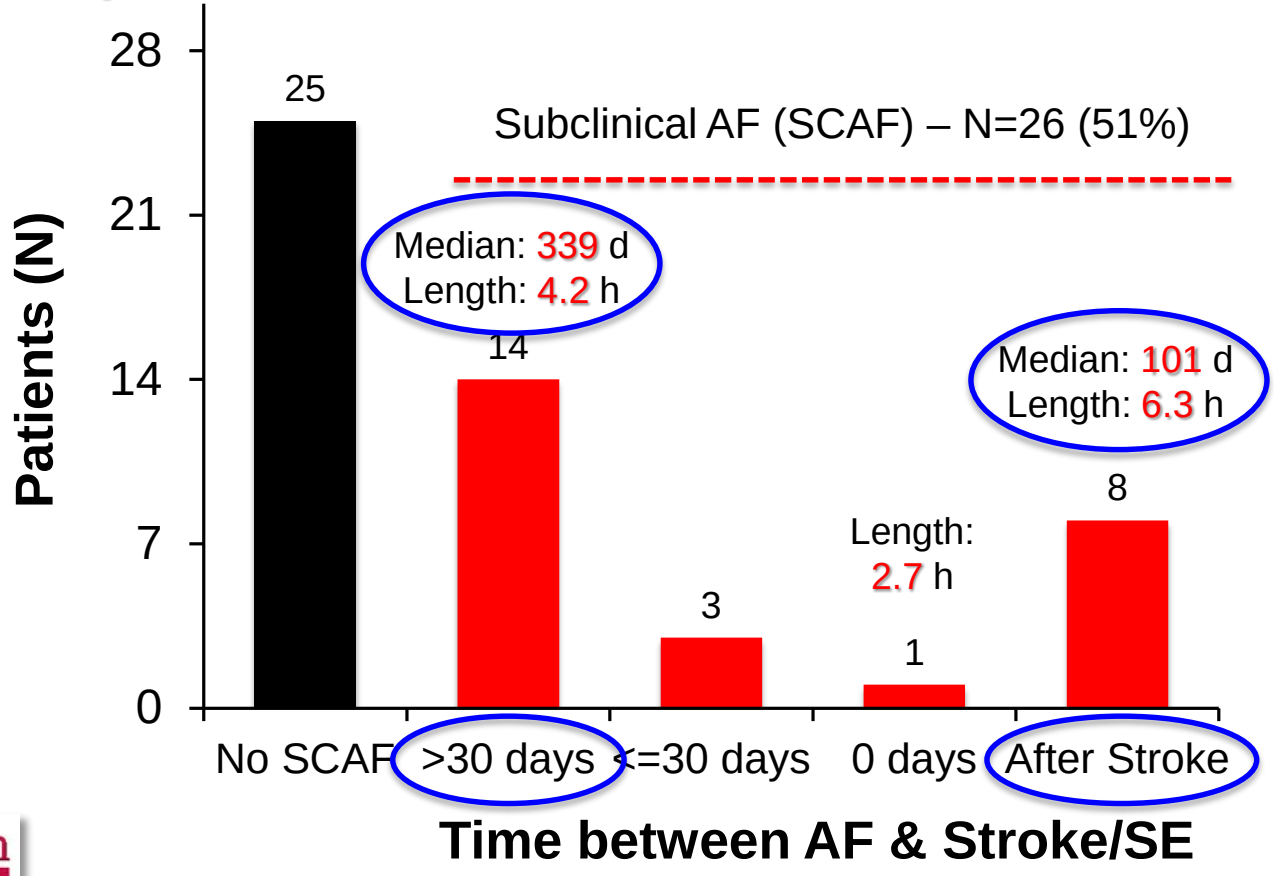
In patients affected by frequently recurrent, clinically documented AF episodes undergoing implantation of a dual chamber pacemaker, **risk stratification for thromboembolic events can be improved by combining CHADS2 score with data on AF presence/duration** derived from continuous monitoring of arrhythmic episodes by the implanted device

Botto GL, Journal Cardiovasc Electrophysio, 2008

Temporal Relationship Between Subclinical Atrial Fibrillation and Embolic Events

Subclinical AF and stroke or systemic embolism in the ASSERT trial (N=2580; Age: 78 years, CHA_2DS_2-VASc: 5)

Pts with pacemaker and defibrillator without history of AF for a mean f-up of 2.5 yrs



Circulation

Brambatti M, 2014

Sensitivity and Specificity of Different Methods of Screening for Atrial Fibrillation

Device	Method of Interpretation	Sensitivity (%)	Specificity (%)	Reference
Pulse palpation		94 (84–97)	72 (69–75)	Cooke et al[55]
Handheld single-lead ECGs				
AliveCor (Kardia) heart monitor	Algorithm only (based on presence of P wave and RR irregularity)	98 (89–100)	97 (93–99)	Lau et al[56]
Merlin ECG event recorder	Cardiologist interpretation	93.9	90.1	Kearley et al[57]
Mydiagnostick	Algorithm only (based on RR irregularity)	94 (87–98)	93 (85–97)	Tieleman et al[58]
				Vaes et al[59]
Omron HCG-801	Algorithm only (based on RR irregularity)	98.7 (93.2–100)	76.2(73.3–78.9)	Kearley et al[57]
Omron HCG-801	Cardiologist interpretation	94.4	94.6	Kearley et al[57]
Zenicor EKG	Cardiologist interpretation	96	92	Doliwa et al[60]
Modified blood pressure monitors				
Microlife BPA 200 Plus	Algorithm only (based on pulse irregularity)	92	97	Marazzi et al[61]
Microlife BPA 200	Algorithm only (based on pulse irregularity)	97 (81.4–100)	90 (83.8–94.2)	Wiesel et al[62]
Omron M6	Algorithm only (based on pulse irregularity)	100	94	Marazzi et al[61]
Omron M6 comfort	Algorithm only (based on pulse irregularity)	30 (15.4–49.1)	97 (92.5–99.2)	Wiesel et al[62]
Microlife WatchBP	Algorithm only (based on pulse irregularity)	94.9 (87.5–98.6)	89.7 (87.5–91.6)	Kearley et al[57]
Plethysmographs				
Finger probe	Algorithm only (based on pulse irregularity)	100	91.9	Lewis et al[63]
iPhone photo-plethysmograph	Algorithm only (based on pulse irregularity)	97.0	93.5	McManus et al[64]*

Friedman B, Circulation 2017

Risk of Stroke and Death in Untreated Screen-Detected AF

Screen-detected AF as found on single-timepoint screening or intermittent 30-second recordings over 2 weeks **is not a benign condition** and, with additional stroke risk factors, carries sufficient risk of stroke to justify consideration of screening and therapy to prevent stroke.

Friedman B, Circulation 2017

Which Patients or Individuals to Screen?

Single-timepoint screening of people ≥65 years of age in the clinic or community appears justified based on yield of screening and likely cost-effectiveness.

For those >75 years of age or in younger age groups at high risk of AF or stroke, **2 weeks of twice-daily intermittent AF screening** may be warranted.

Friedman B, Circulation 2017

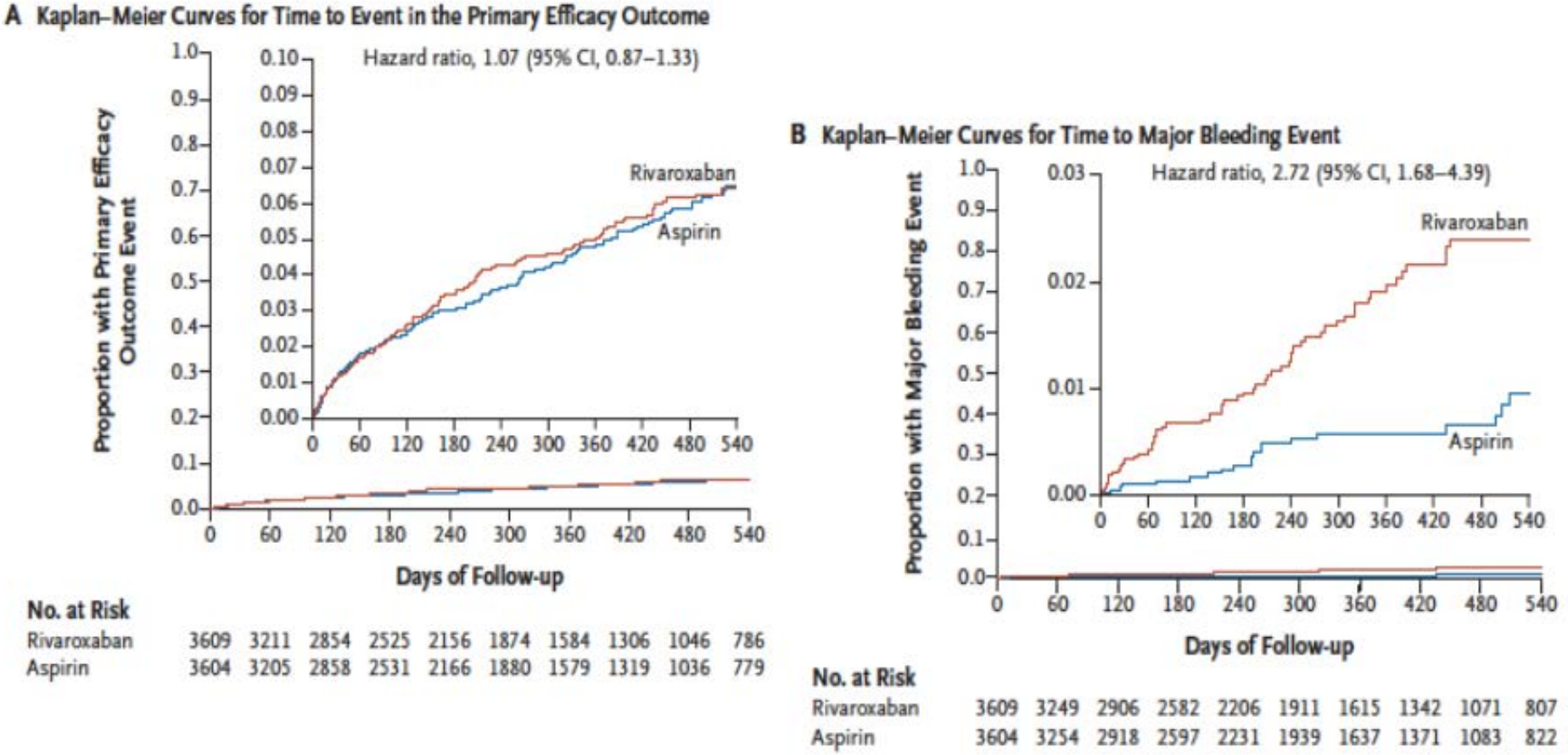
Ischemic Stroke and ESUS

Long-term continuous rhythm monitoring using either external or implanted devices or extended intermittent patient-activated recordings **may diagnose clinically important of in individuals with recent ESUS**

Friedman B, Circulation 2017

Navigate

Figure 1. Cumulative Incidence of the Primary Efficacy Outcome and the Primary Safety Outcome, According to Treatment Assignment.



DOI: 10.1056/NEJMoa1802686

Future needs

There is a **need to perform large randomized controlled studies using hard end points** (including stroke, systemic embolism, and death) of strategies for screening, to strengthen the evidence base to inform guidelines and national systematic screening strategies.

Friedman B, Circulation 2017

17. A short summary of the management of atrial fibrillation patients

Here, we provide 17 simple rules to guide the diagnosis and management of AF patients according to the 2016 ESC Guidelines for the management of atrial fibrillation developed in cooperation with EACTS.

(1) Use ECG screening in at-risk populations for AF, especially stroke survivors and the elderly.
(2) Document AF by ECG before starting treatment.
(3) Evaluate all AF patients by clinical evaluation, ECG, and echocardiogram for underlying cardiovascular conditions such as hypertension, heart failure, valvular heart disease, and others.
(4) Provide tailored information and education to AF patients to empower them to support AF management.
(5) Propose lifestyle changes to all suitable AF patients to make their management more effective.
(6) Treat underlying cardiovascular conditions adequately, e.g. valve repair or replacement in AF patients with significant valvular heart disease, treatment of heart failure, or management of hypertension, among others.
(7) Use oral anticoagulation in all AF patients unless they are at low risk for stroke based on the CHA_2DS_2VASc score or have true contraindications for anticoagulant therapy.
(8) Anticoagulate patients with atrial flutter similar to AF. Offer isthmus ablation to symptomatic flutter patients.
(9) Reduce all modifiable bleeding risk factors in all AF patients on oral anticoagulation, e.g. by treating hypertension, minimizing the duration and intensity of concomitant antiplatelet and non-steroidal anti-inflammatory drug therapy, treating anaemia and eliminating causes for blood loss, maintaining stable INR values in patients on VKAs, and moderating alcohol intake.
(10) Check ventricular rate in all AF patients and use rate control medications to achieve lenient rate control.
(11) Evaluate AF-related symptoms in all AF patients using the modified EHRA symptoms scale. Whenever patients have AF-related symptoms, aim to improve symptoms by adjustment of rate control therapy and by offering antiarrhythmic drugs, cardioversion, or catheter or surgical ablation.
(12) Select antiarrhythmic drugs based on their safety profile and consider catheter or surgical ablation when antiarrhythmic drugs fail.
(13) Do not offer routine genetic testing in AF patients unless there is suspicion of an inherited cardiac condition.
(14) Do not use antiplatelet therapy for stroke prevention in AF.
(15) Do not permanently discontinue oral anticoagulation in AF patients at increased risk of stroke unless such a decision is taken by a multidisciplinary team.
(16) Do not use rhythm control therapy in asymptomatic AF patients, nor in patients with permanent AF.
(17) Do not perform cardioversion or catheter ablation without anticoagulation, unless an atrial thrombus has been ruled out transoesophageal echocardiogram.

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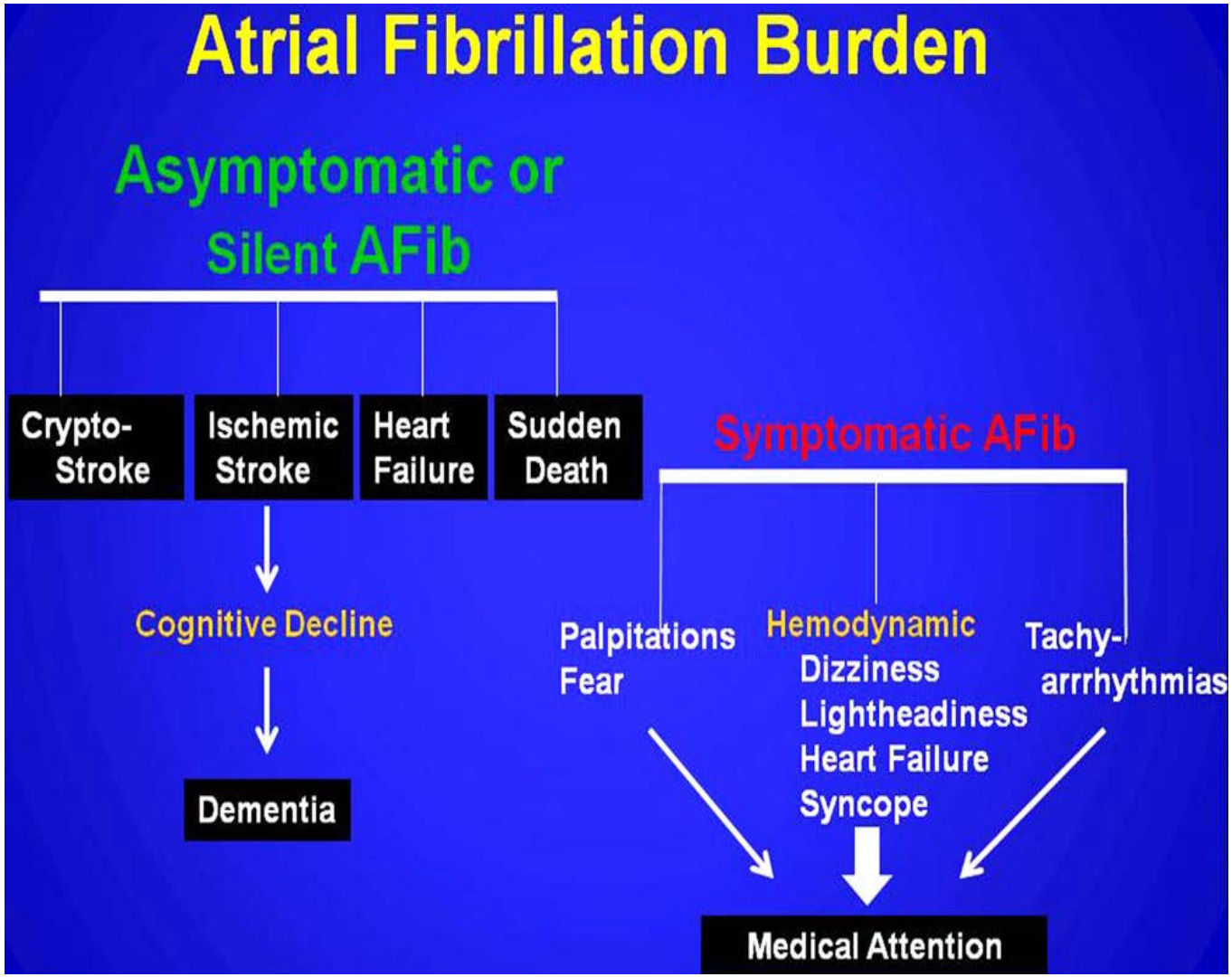
Kirchhof P. et al. European Heart Journal; August 27, 2016

Conclusions (1)



Courtesy of Vittorio Pengo

Conclusions (2)

- Patient differences will modulate the type and intensity of screening (eg, ESUS requires higher intensity).

-**The setting for screening is highly dependent on the health system in each country** and needs to be individualized but must crucially be linked to a pathway for appropriate diagnosis and management.

-Large and adequately powered randomized outcomes trials of a strategy of screening would strengthen the evidence for the adoption of larger scale systematic screening programs for AF to reduce ischemic stroke/systemic embolism and death

Friedman B, Circulation 2017