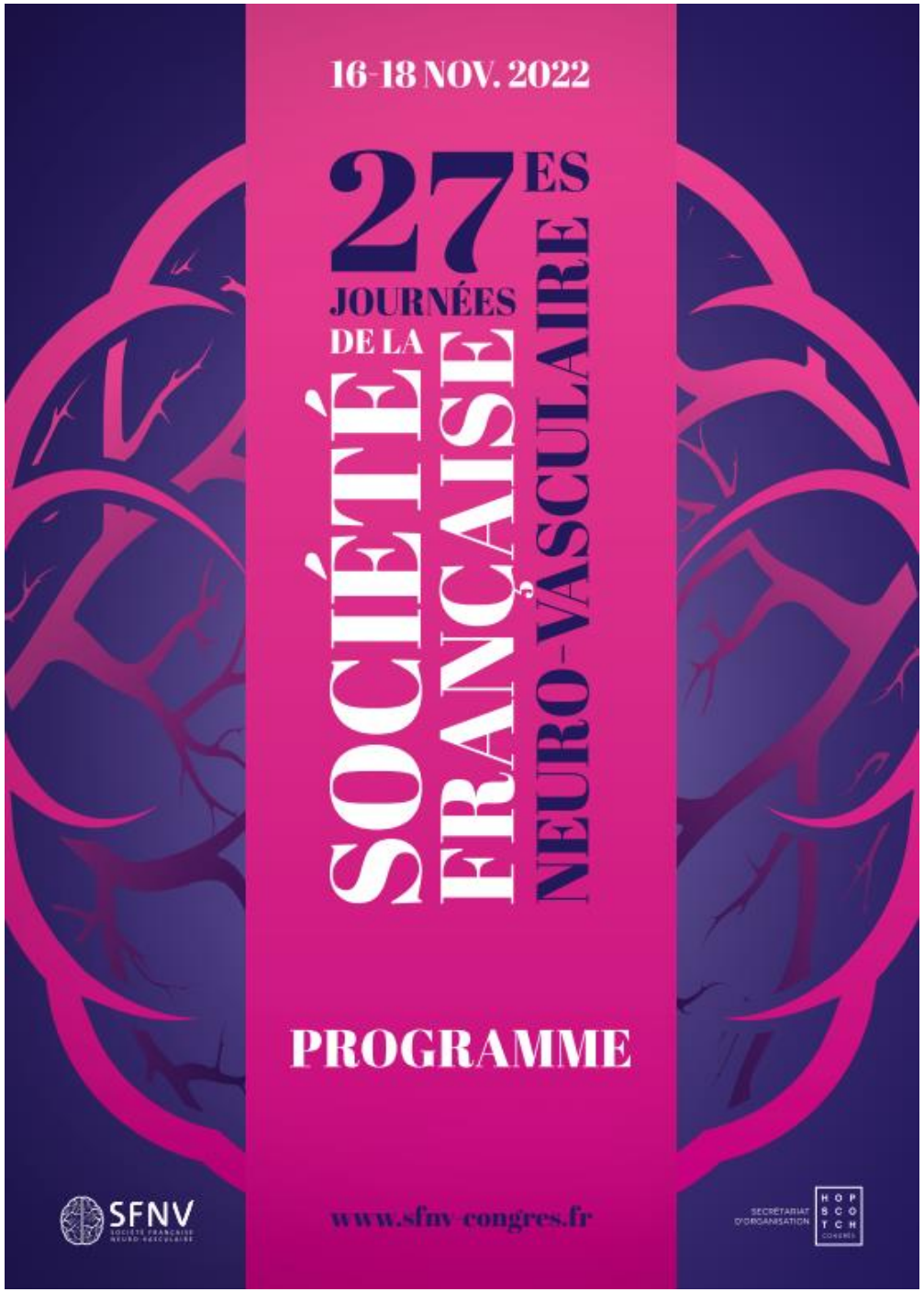


Anticoagulation en post –ESUS
La fin d'un concept?

Jean-Claude Deharo, Marseille

Assistance Publique Hôpitaux de Marseille

Aix*Marseille université

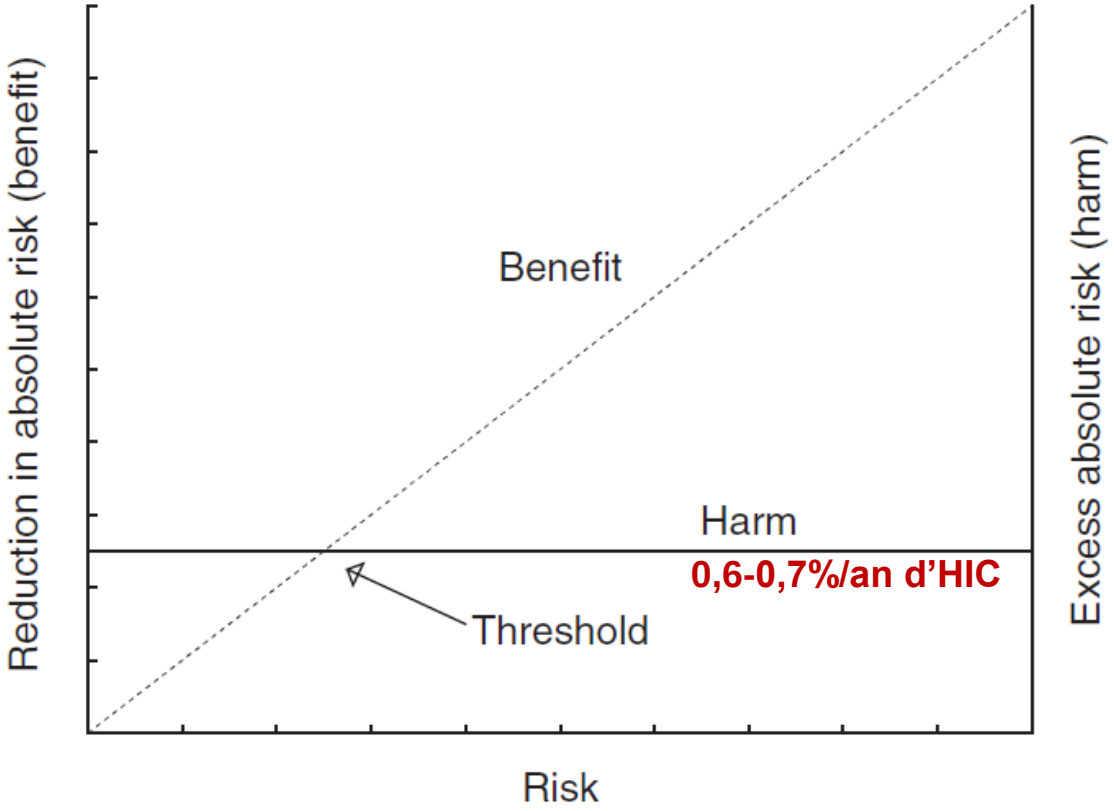
Liens d’intérêt

Honoraires pour présentations à des congrès; bourses de recherche

- Abbott
- Medtronic
- Boston Scientific
- Biotronik
- Microport
- Bewys
- Viatris
- Bayer
- BMS Pfizer

Trials	Patients enrolled	Intervention/treatments	Primary outcome(s)	Results
NAVIGATE-ESUS	7213	Drug: rivaroxaban	Incidence rate of the composite efficacy Outcome (includes ischemic, hemorrhagic, undefined, TIA, and systemic embolism)	Study halted early due to no efficacy improvement over aspirin at an interim analysis concluding very little chance of showing overall benefit if study were completed
		Drug: acetylsalicylic acid (aspirin)		
		Other: rivaroxaban-placebo		
		Other: aspirin-placebo	Incidence rate of a major bleeding event according to ISTH criteria	
RESPECT-ESUS	5390	Drug: optional aspirin as comedication	Adjudicated recurrent stroke (ischemic, hemorrhagic, or unspecified)	No benefit of anticoagulation for secondary stroke prevention in the overall ESUS population
		Drug: placebo to aspirin		
		Drug: placebo to optional aspirin as comedication		
		Drug: placebo to dabigatran etexilate	First major bleed defined according to ISTH criteria	
		Drug: aspirin		
		Drug: dabigatran etexilate		

From GW Albers et al., Stroke 2021



Sutton AJ et al., J Clin Epidemiol 2005

NAVIGATE ESUS: **3% de FA** (pas de recherche systématique) – Suivi médian 11 mois

RESPECT ESUS : **0,7 à 0,9% de FA** (6% d'ILR) – Suivi médian 19 mois

FA clinique

Risks of thromboembolism and bleeding with thromboprophylaxis in patients with AF: A net clinical benefit analysis in a 'real world' nationwide cohort study

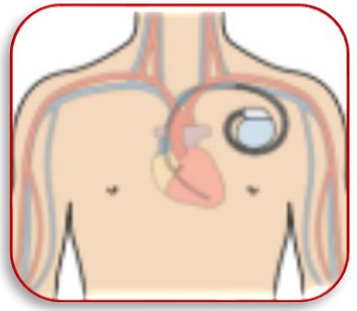
Olesen, Lip et al. *Thromb Hemostat 2011*

Net clinical benefit = (ischaemic stroke rate with no treatment - ischaemic stroke rate on treatment) - 1.5(ICH rate on treatment - ICH rate with no treatment)

Net clinical benefit* (%, 95%CI) **VKA vs. no Rx**

		HAS-BLED ≤2	HAS-BLED ≥3
$CHADS_2$	Score 0	-0.02 (-0.09 to 0.06)	0.19 (-1.39 to 1.77)
	Score 1	0.84 (0.70 to 0.99)	0.56 (0.16 to 0.95)
	Score 2-6	1.95 (1.70 to 2.20)	2.68 (2.33 to 3.04)
CHA_2DS_2-VASc	Score 0	-0.11 (-0.20 to -0.03)	…
	Score 1	-0.02 (-0.15 to 0.11)	0.25 (-0.86 to 1.36)
	Score 2-9	1.19 (1.07 to 1.32)	2.21 (1.93 to 2.50)

La FA infra-clinique (silencieuse)



- Episodes d'arythmie atriale rapide *après*

confirmation qu'il s'agit bien de FA, Flutter ou TA

ou

- FA détectée par:
  - Moniteur ECG implantable

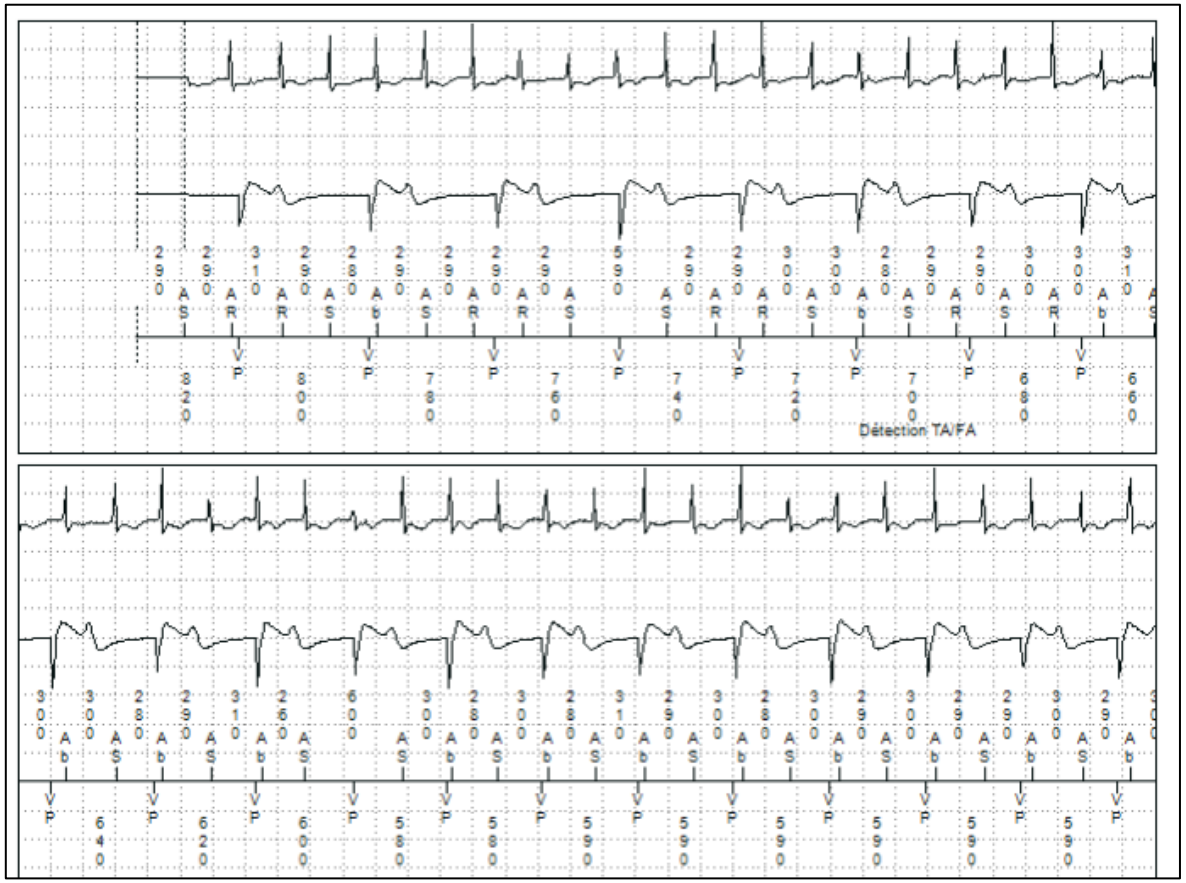
  ou
  - Objet connecté

et confirmée par l'analyse des électrogrammes ou de l'ECG

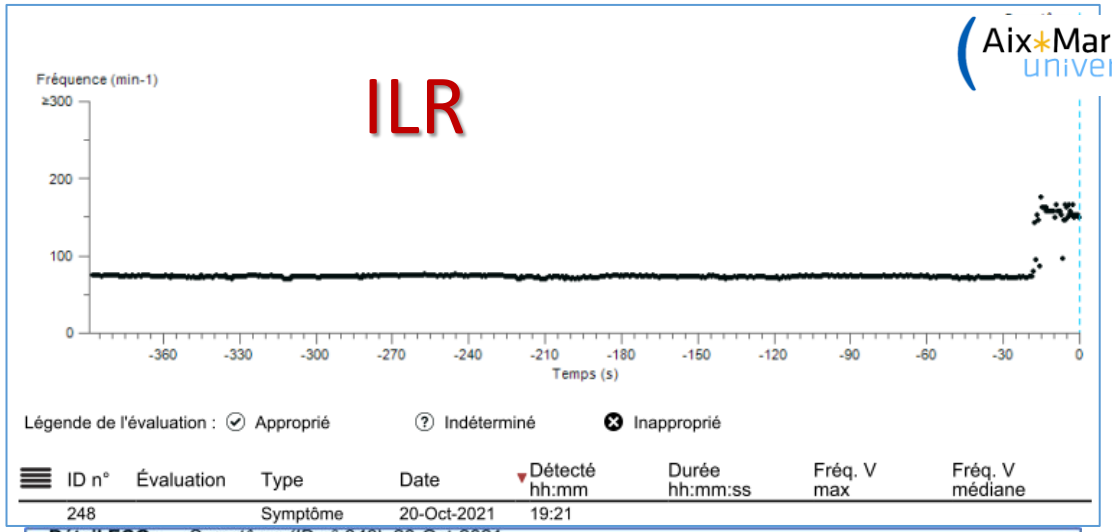
une piste

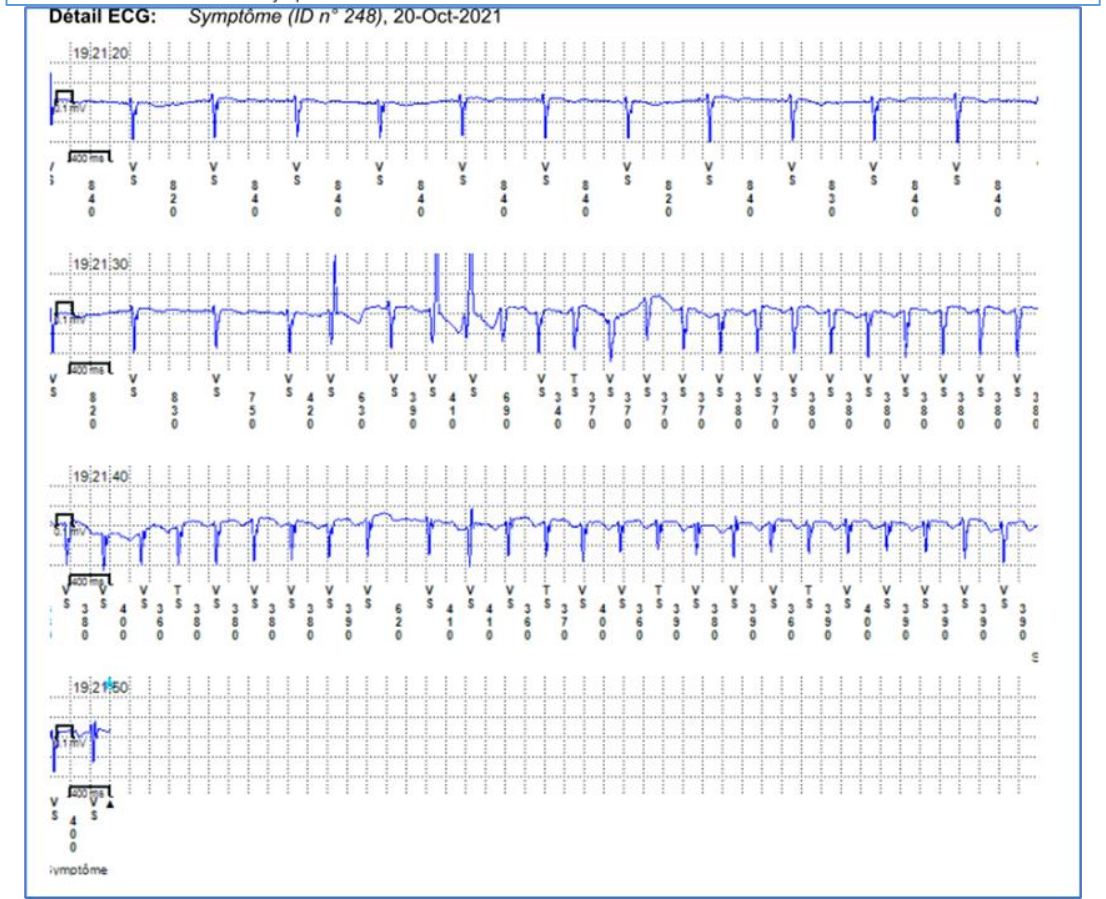
From AF ESC guidelines 2020

Défibrillateur

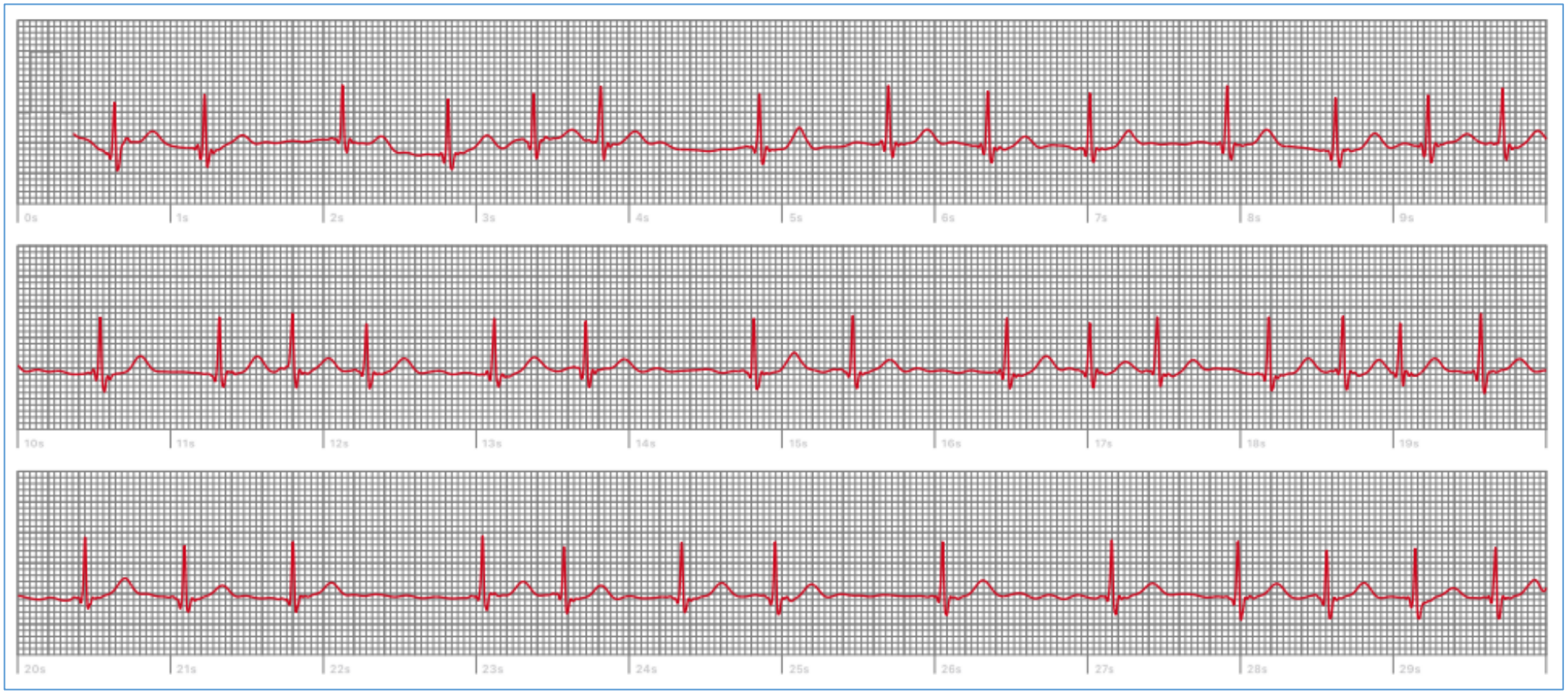


ILR

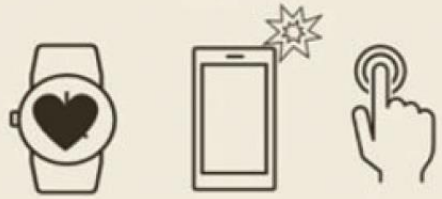




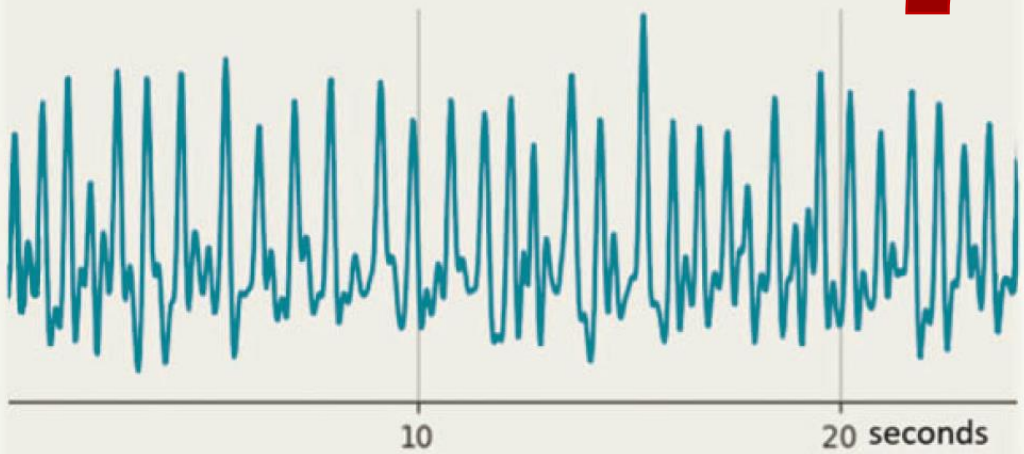
Smartwatch ECG



PPG



- Sensor-based light source & photodetector
- Measures changes in tissue blood volume based on reflected light
- Generates *pulse waveform*
- Heart *rate* is derived
- Abnormal heart *rhythm* can be detected by embedded algorithms



Alerte

ECG

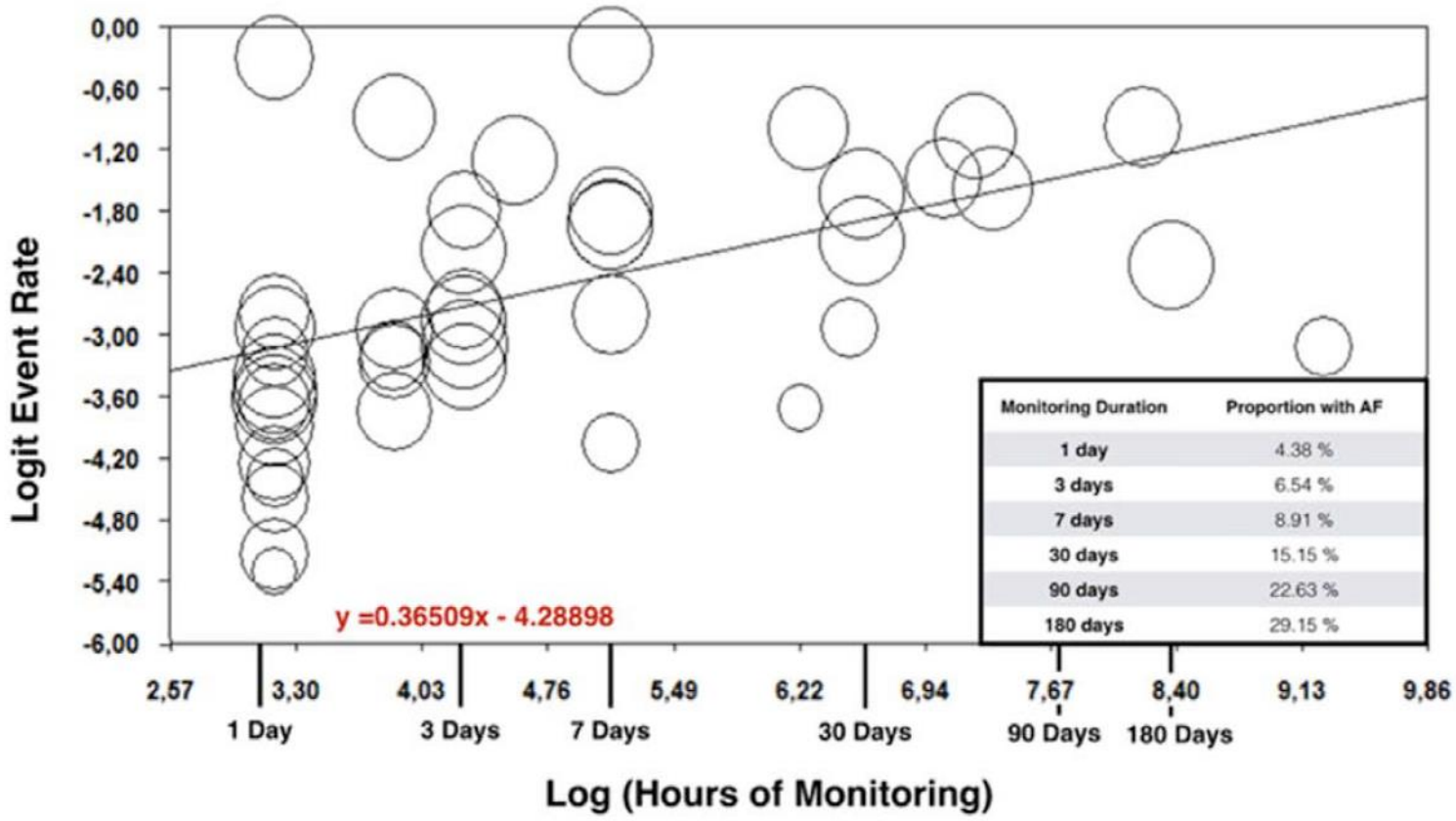
- Electrode-based
- Generates an electrocardiographic (ECG) tracing
- Allows direct analysis/diagnosis of heart *rhythm*

Can be diagnostic

- Clinician oversight is required for *rhythm confirmation*

Svennberg E et al. Europace 2022

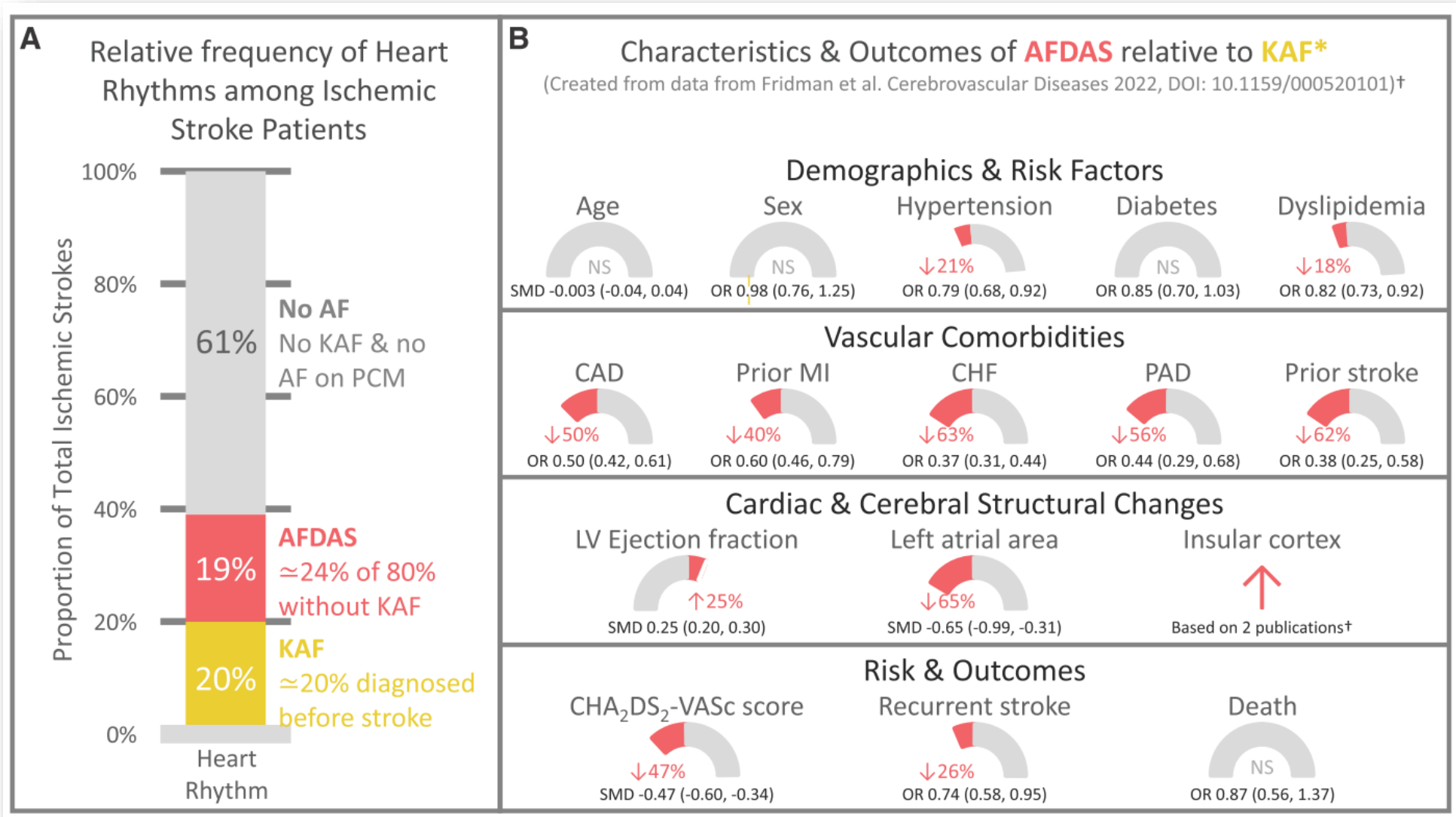
Relationship between duration of monitoring and AF detection rate



Dussault et al., Circ AEP 2015

FA infra-clinique et risque d'AVC

Author	# pts (Setting)	*Risk*
Glotzer Circulation , 2003	312 (SSS)	***Death or stroke x 2.5***
Capucci Clinical Research in Cardiology, 2020	725 (PAF)	***AT/AF > 24 h → risk of embolism x 3.1***
Glotzer Circ Arrythm Electrophysiol, 2009	2486 (≥1 RFS)	***Daily AF burden > 5.5 h in the 30 previous days → risk of stroke x 2***
Ziegler Stroke, 2010	163 (Stroke)	***New AF in 28% of pts with stroke***
Healey New Engl J Med, 2016	2580 (>65, HTN)	***Risk of stroke or embolism x 2.5***
Shanmugan Europace, Feb 2012	560 (CRT)	***AF burden > 3.8 h → increased risk of TE***



Sposato et al. Stroke 2022

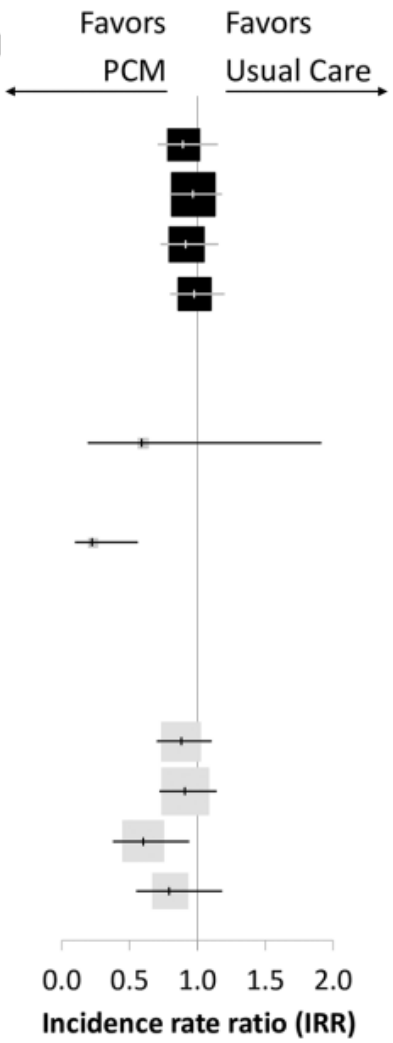
Temporal relationship: *No!*

Year	Trial	No. of patients with TE event	Definition of AF episode	Any AF detected before TE event	AF detected only after TE event	No AF in 30 days before TE event	Any AF in 30 days before TE event
2011	TRENDS[53]	40	5 minutes	20/40 (50%)	6/40 (15%)	29/40 (73%)	11/40 (27%)
2014	ASSERT[54]	51	6 minutes	18/51 (35%)	8/51 (16%)	47/51 (92%)	4/51 (8%)
2014	IMPACT[55]	69	36/48 atrial beats $\geq$200 bpm	20/69 (29%)	9/69 (13%)	65/69 (94%)	4/69 (6%)

Glotzer & Ziegler, Heart Rhythm 2015

Prolonged cardiac monitoring and risk of recurrent cerebrovascular events

OUTCOME	STUDIES (n)	FOLLOW-UP PERS-MONTH	IRR (95% CI)
Randomized controlled trials			
Recurrent ischemic stroke*	**4**	**52,332**	**0.90 (0.71, 1.15)**
Recurrent ischemic stroke or TIA	6	68,556	0.97 (0.80, 1.18)
Recurrent stroke (ischemic or hemorrhagic)	4	55,932	0.94 (0.74, 1.18)
Recurrent stroke (ischemic or hemorrhagic) or TIA	4	52,332	0.98 (0.80, 1.20)
Observational studies			
Recurrent ischemic stroke	2	9,913	0.60 (0.19, 1.91)
Recurrent ischemic stroke or TIA	1	5,730	—
Recurrent stroke (ischemic or hemorrhagic)	3	9,620	0.23 (0.10, 0.56)
Recurrent stroke (ischemic or hemorrhagic) or TIA	1	5,730	—
All studies			
Recurrent ischemic stroke	6	62,245	0.88 (0.70, 1.10)
Recurrent ischemic stroke or TIA	7	74,286	0.91 (0.72, 1.14)
Recurrent stroke (ischemic or hemorrhagic)	7	65,552	0.56 (0.33, 0.95)
Recurrent stroke (ischemic or hemorrhagic) or TIA	5	58,062	0.80 (0.55, 1.18)



Sposato et al. Stroke 2022

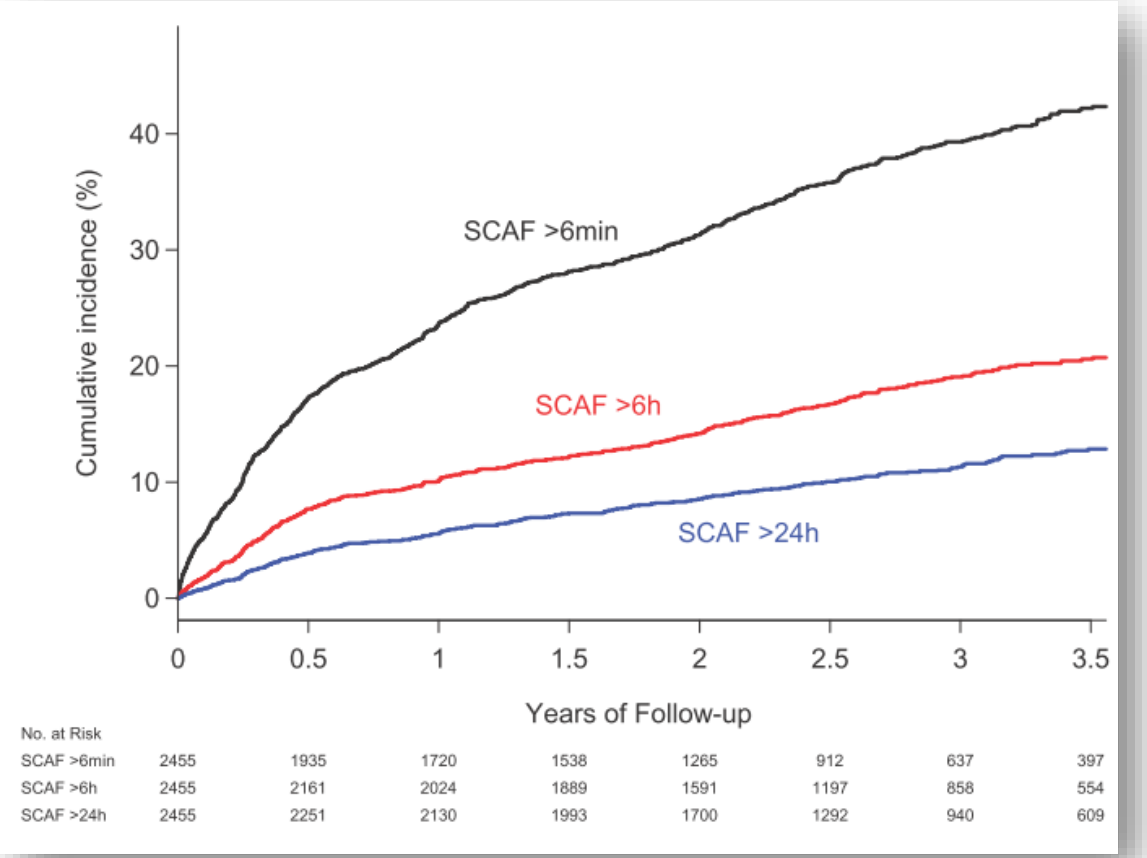
Duration and number of episodes of AT and risk of stroke or systemic embolism

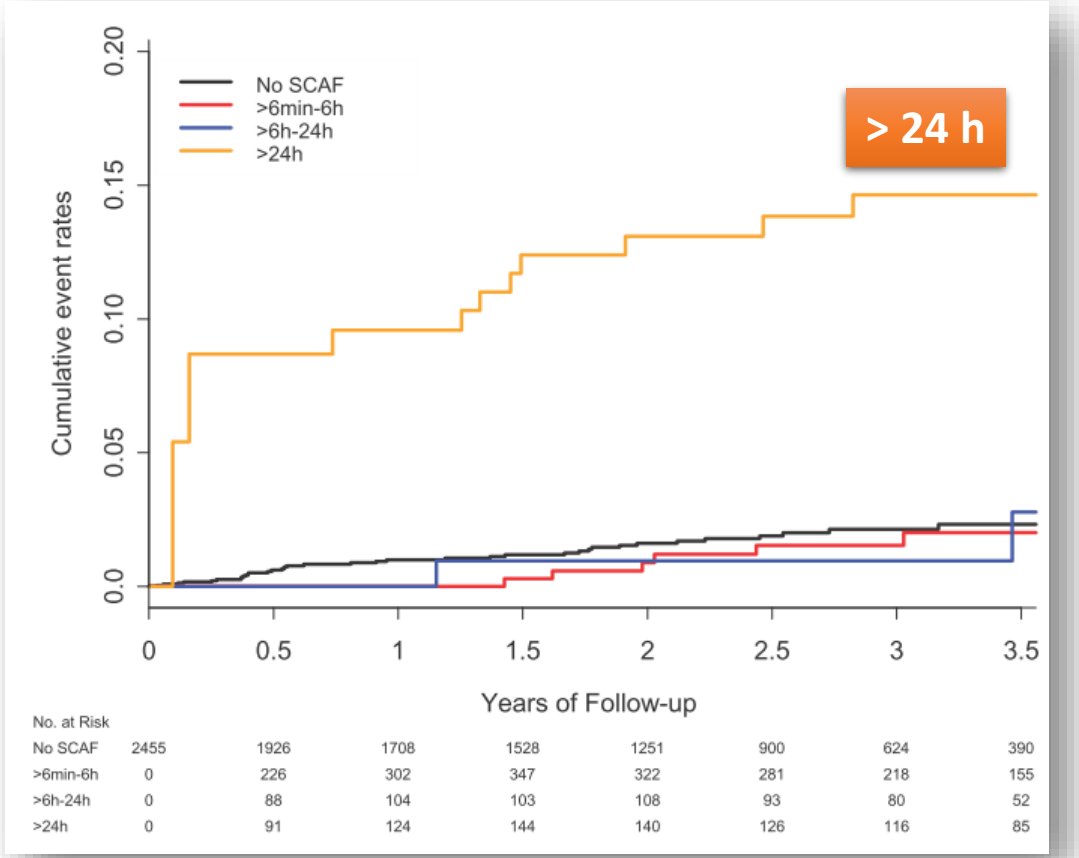
Duration (longest)	< 0.86 h	0.87 - 3.63 h	3.64 - 17.72 h	> 17.72 h
Annual rate	1.23	0	1.18	4.89

# of episodes	1	2	3 or 4	> 4
Annual rate	1.20	2.15	1.89	1.93

Healey JS et al, NEJM 2012

Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT





Van Gelder et al, Eur heart J 2017

FA infra-clinique et risque TE: influence de la charge en arythmie

- **TRENDS:** 2486 patients avec ≥1 facteur de risque (insuffisance cardiaque, HTA, diabète, âge≥65, ATCD TE)

- **Analyse en fonction de la charge quotidienne maximale en AF/AT sur 30 jours**

Table 2. TE Rates for the Overall Study Group (Unadjusted)

AT/AF Burden Subset	Annualized TE Rate (95% CI), %	Annualized TE Rate Excluding TIAs (95% CI), %
Zero AT/AF burden	1.1 (0.8–1.6)	0.5 (0.3–0.9)
Low AT/AF burden (<5.5 h)	1.1 (0.4–2.8)	1.1 (0.4–2.8)
High AT/AF burden (5.5 h)	2.4 (1.2–4.5)	1.8 (0.9–3.8)

Table 3. Hazard Ratios for Thromboembolic Events Associated With AT/AF Burden Adjusted for Stroke Risk Factors and Antithrombotic Therapy

Category	Variable	Hazard Ratio (95% CI)*	*P* Value
AT/AF burden	Low burden vs zero burden	0.98 (0.34, 2.82)	0.97
	High burden vs zero burden	2.20 (0.96, 5.05)	0.06

Glotzer TV, Circ AE 2009;2:474-480

The AF-ESUS score

Covariate	OR (95%CI)	*p* value	log OR (95%CI)	Points assigned for score calculation
Age				
60 to 70 years	5.55 (2.62–11.78)[a]	<0.001	1.71 (0.96–2.47)	3
>70 to 80 years	4.95 (2.35–10.46)[a]	<0.001	1.60 (0.85–2.35)	3
>80 years	5.26 (2.28–12.16)[a]	<0.001	1.66 (0.82–2.50)	3
Arterial hypertension	2.47 (1.40–4.37)	<0.01	0.90 (0.33–1.47)	2
Left ventricular hypertrophy[b]	0.52 (0.31–0.87)	0.01	−0.65 (−1.16 to −0.14)	−1
Left atrial diameter > 40 mm	2.59 (1.59–4.20)	<0.001	0.95 (0.46–1.43)	2
Left ventricular ejection fraction <35%	0.26 (0.10–0.71)	0.001	−1.34 (−2.33 to −0.34)	−3
Any supraventricular extrasystole[c]	1.89 (1.18–3.05)	<0.01	0.64 (0.16–1.11)	1
Subcortical infarct	0.44 (0.27–0.72)	0.001	−0.81 (−1.30 to −0.33)	−2
Non-stenotic carotid plaque[d]	0.24 (0.15–0.40)	<0.001	−1.42 (−1.93 to −0.91)	−3

Ntaios et al., Int J Stroke 2020

Cardiopathie atriale et ESUS: prévalence

Markers of Atrial Cardiomyopathy in ESUS.

Markers of AC		Study	ESUS (n)	Rate/Mean value
Electrocardiographic marker	PTFV1> 5.000 µV*ms	Jalini [20]	158	23.4%
		Lattanzi [18]	109	28.4%
Imaging Markers	LAVI (mL/m^2)	Kamel [25]	531	33.3 ± 13.6
		Jordan [24]	485	28.9 ± 12.6$^+$
		Lee [19]	194	29.9 (23.7–35.3)
		Gąsiorek [22]	65	27.0 ± 11$^+$
	Severe LAE (LAd ≥4.7 cm)	Jalini [20]	158	5%
		Chen [27]	245	5.3%
Imaging Markers	Atrial Fibrosis in MRI%	Tandon [26]	10	16.8%
		Fonseca [21]	52	18.0%
	LAA Non-Chicken wing morphology in CT/MRI%	Fonseca [21]	52	80.2%
		Chang [17]	109	82.6%
		Yaghi [23]	51	59.0%
Serum Biomarkers	NT-proBNP (pg/mL)	Gąsiorek [22]	65	391 (107.9–1249.2)
		Lee [19]	194	136 (55.1–295)$^{++}$
		Chen [27]	245	32.7%

European Journal of Internal Medicine 2022

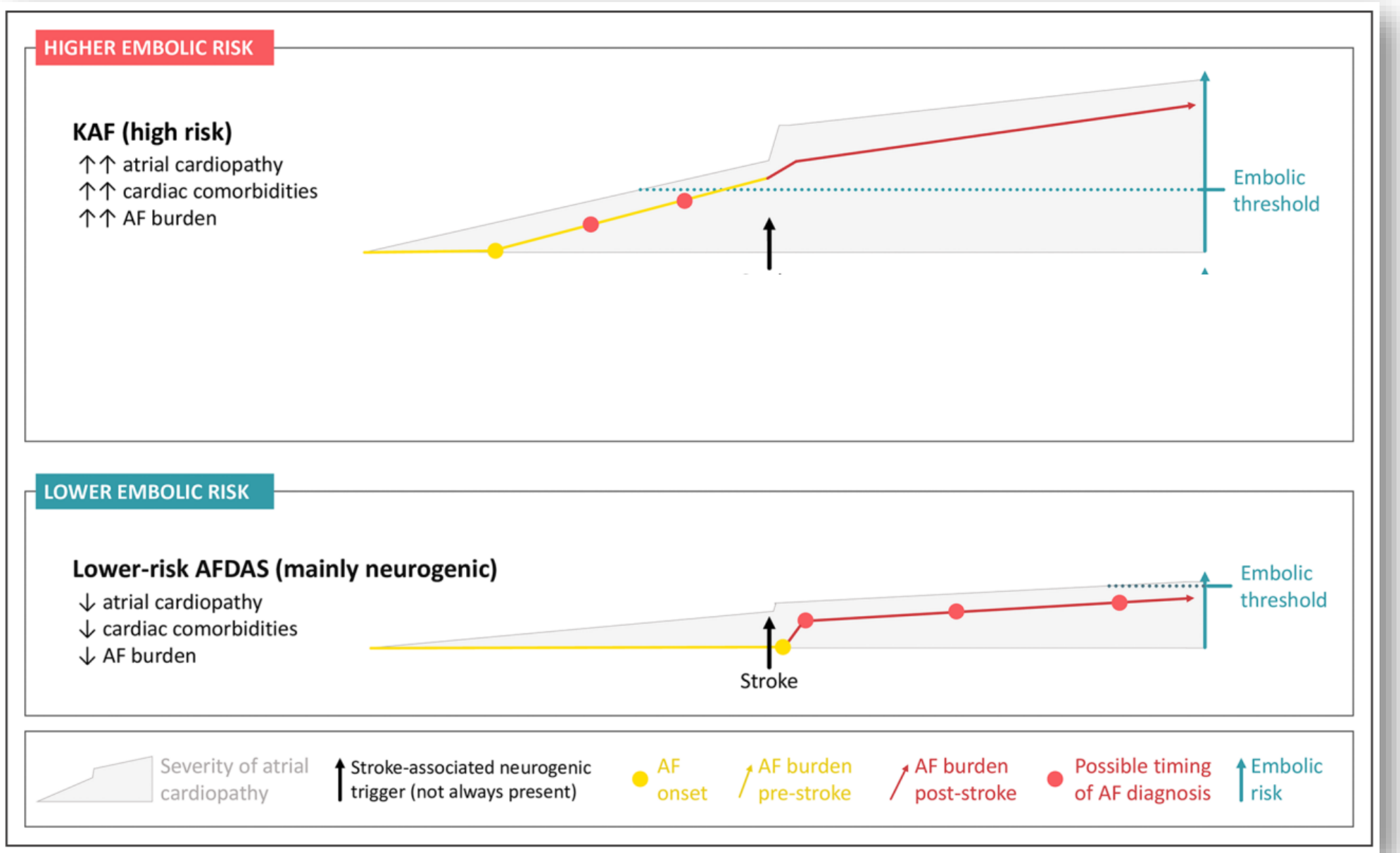
Cardiopathie atriale: ESUS vs Cardioembolic Stroke

Study	Marker	ESUS vs CE *t*-test
Jalini [20]	PTFV1 > 5.000μV*ms	
	Severe LAE (LAd≥4.7 cm)	5.0% vs 25% $p<0.001$*
Chen [27]	Severe LAE (LAd≥4.7 cm)	–
	NT-proBNP (pg/ml)	
Jordan [24]	LAVI (mL/m^2)	28.9 vs 41 $p<0.001$*
Kamel [25]	LAVI (mL/m^2)	33.3 vs 48.8 $p<0.001$*
Yaghi [23]	NCW-LAA	58.8% vs 58.7% $p = 0.1$
Chung [17]	NCW-LAA	83% vs 72% $p = 0.64$
Fonseca [21]	NCW-LAA	80% vs 94% $p = 0.31$

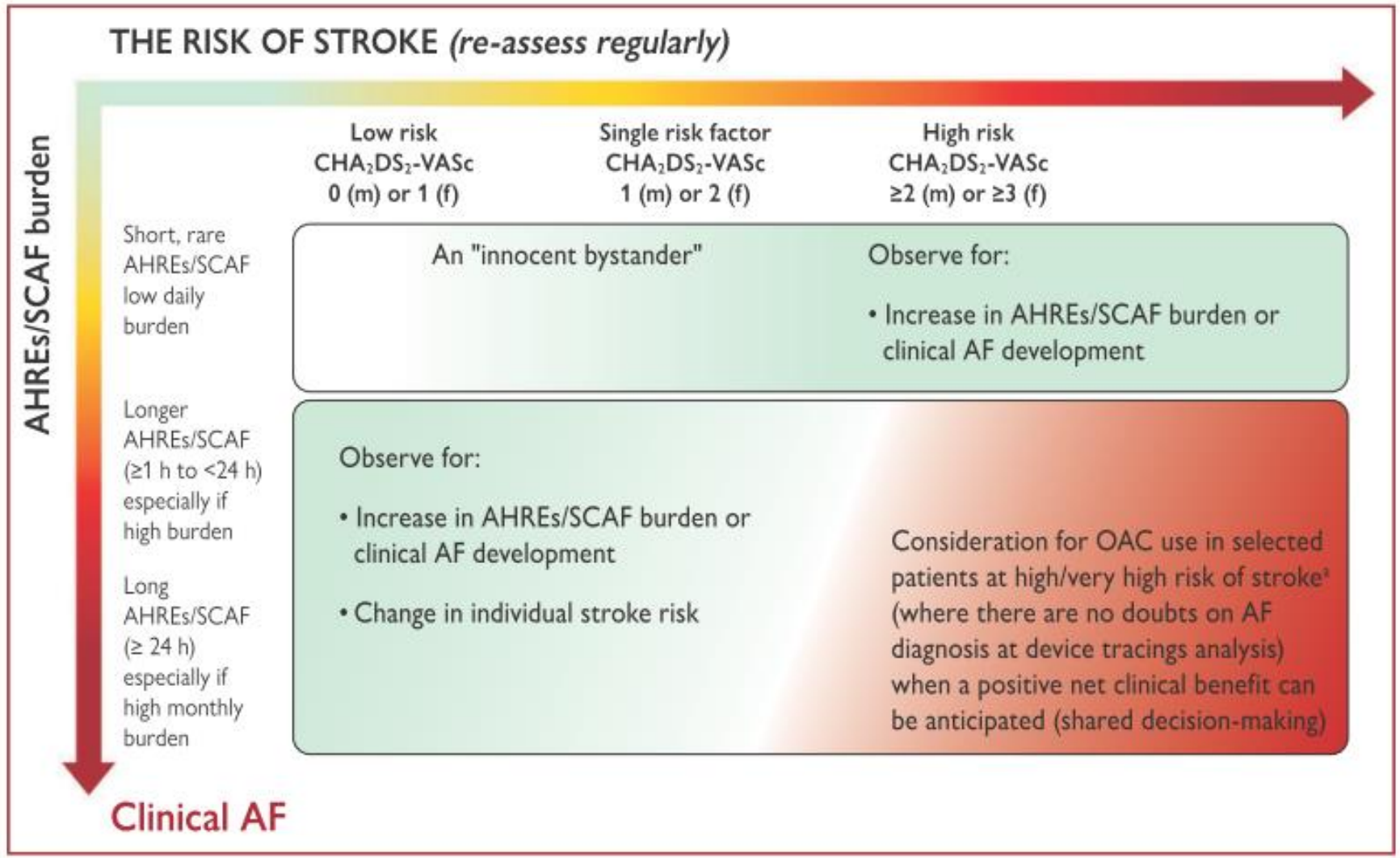
European Journal of Internal Medicine 2022

ARCADIA	1100 (estimated)	Drug: apixaban Drug: aspirin	Incidence of recurrent stroke (ischemic, hemorrhagic, or of unclear type)	Estimated primary outcome January 2022/trial completion April 2022
ATTICUS	352	Drug: apixaban Drug: aspirin	Occurrence of at least one new ischemic lesion identified by MRI	Primary outcome completed August 2020/ estimated trial completion December 2022

From GW Albers et al., Stroke 2021



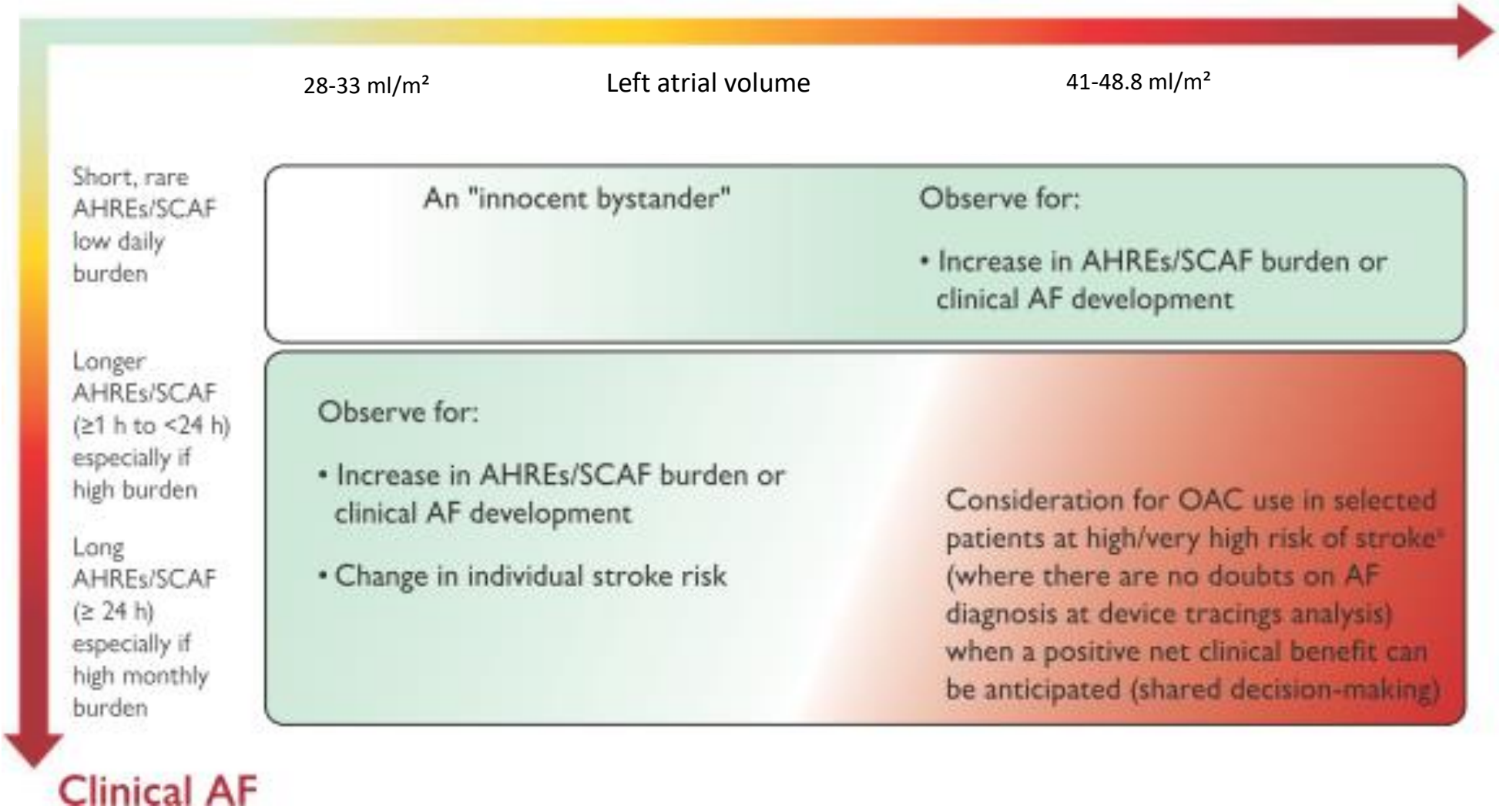
Sposato et al. Stroke 2022



ESC Guideline AF 2020

ESUS

Markers of atrial cardiomyopathy



Adapted From ESC Guideline AF 2020