AF and implantable devices

Which AF definition to characterize the risk ?

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Disclosures

- Grant support to the institution from Medtronic
- Grant support from the Netherlands Cardiovascular Research Initiative: an initiative with support of the Dutch Heart Foundation, CVON 2014-9: RACE V and HBC-X
- Travel support BMS

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ESC European Society of Cardiology

EHRA European Heart Rhythm Association

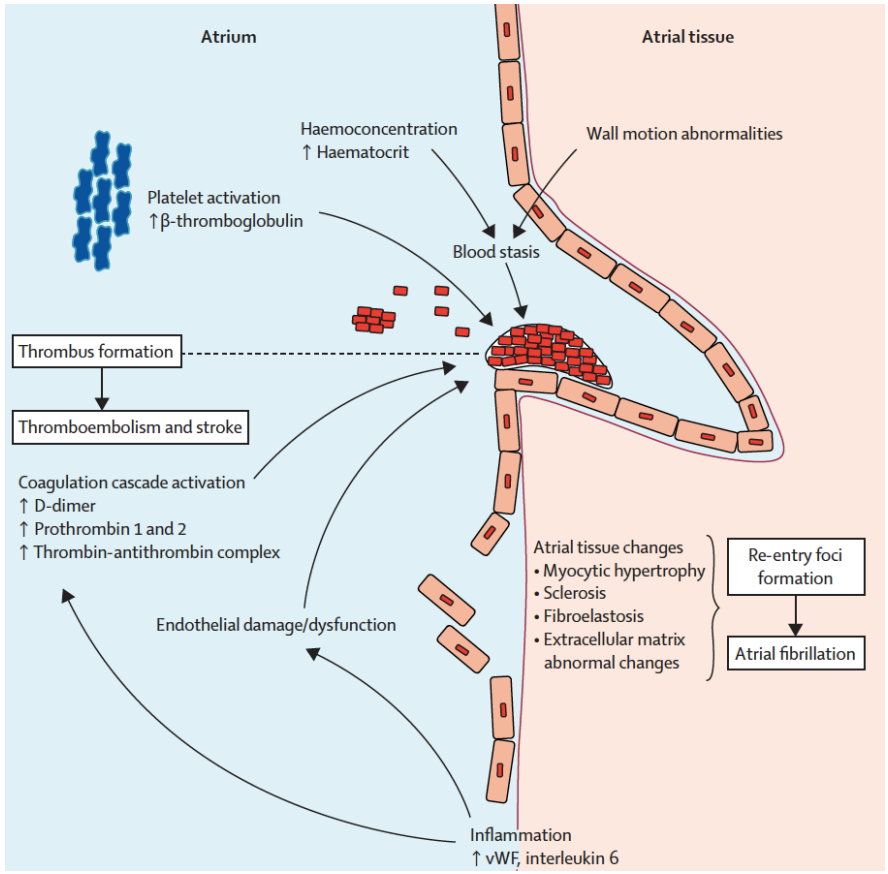
European Society of Cardiology

ESC Council Stroke

Content

- Stroke risk in clinical AF
- Prevalence of AF in patients with an ILR and CIED
- Stroke risk in AHRE/ subclinical AF depending on duration episodes

Virchow's triad for stroke in AF

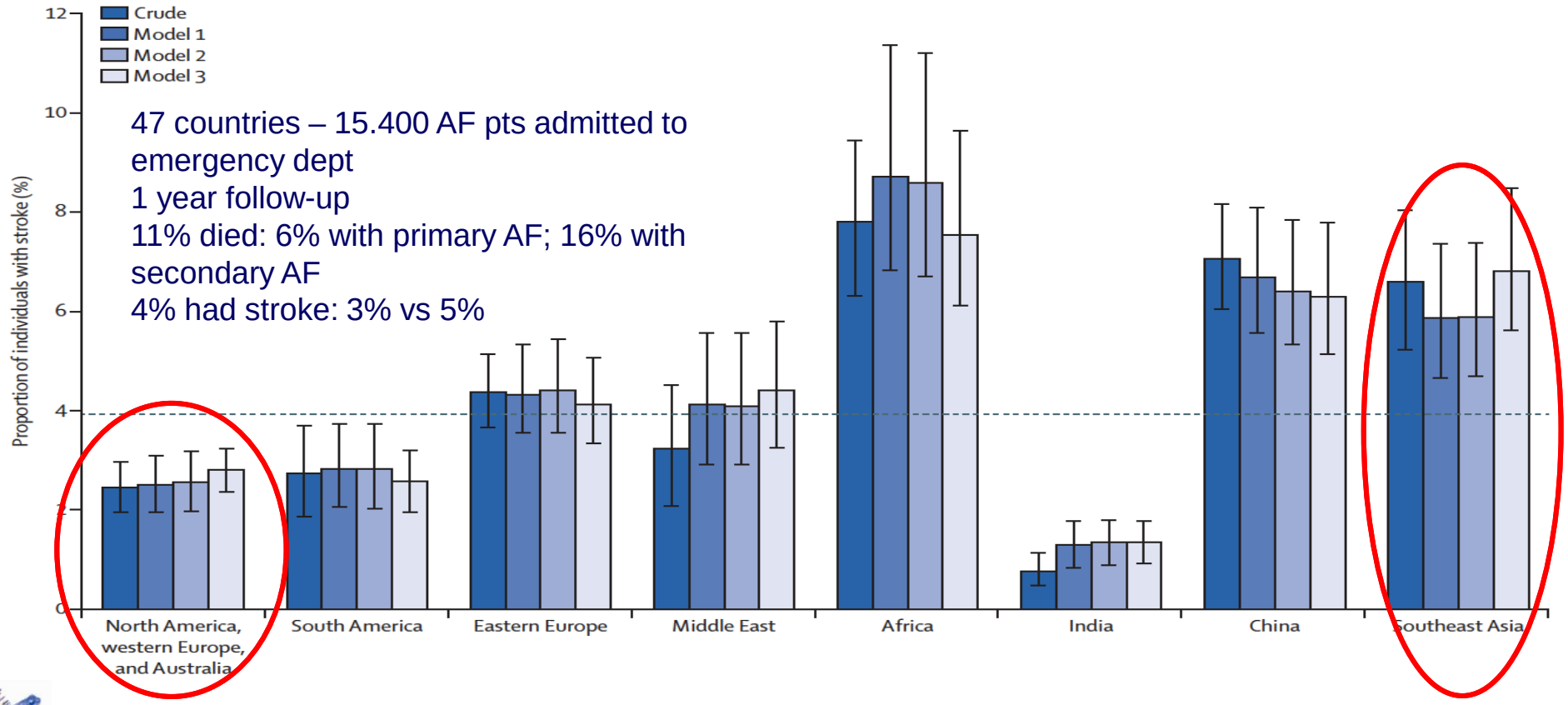


Atrial myopathy

- Changes in vessel wall
  - Atrial tissue changes
  - Endothelial dysfunction
- Changes in atrial flow
  - Stasis
- Changes in blood biomarkers
  - Hypercoagulability
  - Platelets
  - Inflammation

Lip Lancet 2009

Individuals with stroke



Healey RE-LY registry Lancet 2016

Stroke risk in clinical AF

CHA_2DS_2-VASc: Development and Validation

- Birmingham scheme proposed for NICE recommendations in 2006, refined in 2009
- Validated in the Euro Heart Survey cohort of 1084 NVAF patients not on OAC and known TE outcome (n = 25)
- OR for stroke if:
  - Female: 2.53 (1.08 – 5.92), p=0.029;
  - Vascular disease: 2.27 (0.94 – 5.46), p=0.063
- Further validated based on the Danish patient registry in 73,538 NVAF patients not on OAC
- TE included stroke, peripheral TE, PE

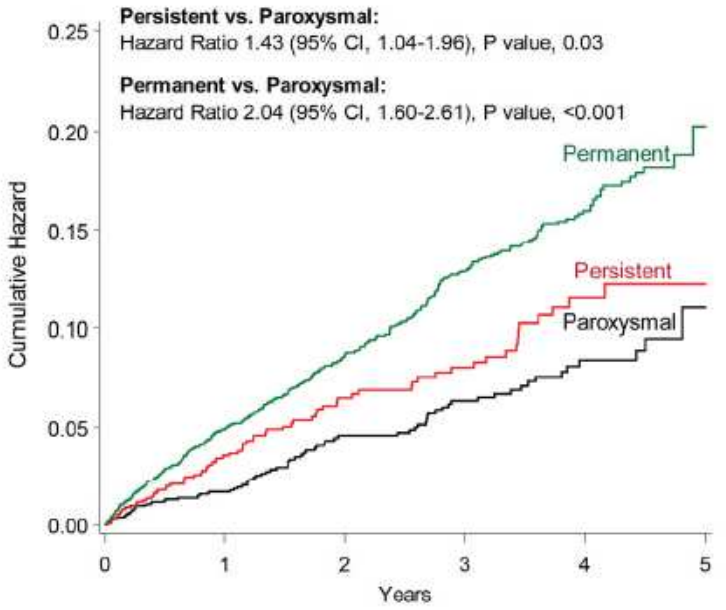
**TE rates at 1 year 0.6% , adjusted for ASA 0.7%*
Post-hoc stroke risk assessment based on SPORTIF trials

Lip GYH, et al. Chest 2010;1372:263-72
Olesen JB, et al. BMJ 2011;342:124

Score	Stroke at 1 year, %	
Cohort	Euro Heart	Danish
n	1084	73,538
0	0	0.78
1	1.3*	2.01
2	2.2	3.71
3	3.2	5.92
4	4.0	9.27
5	6.7	15.26
6	9.8	19.78
7	9.6	21.50
8	6.7	22.38
9	15.2	23.64

Clinical AF: Stroke risk depending on burden ?

N=6563, ASA-treated



No. at Risk						
Paroxysmal	1576	1226	766	604	310	17
Persistent	1136	846	502	386	174	7
Permanent	3854	2909	1975	1505	685	31

Figure 1. Kaplan-Meier cumulative hazard rates of embolic events according to pattern of AF occurence.

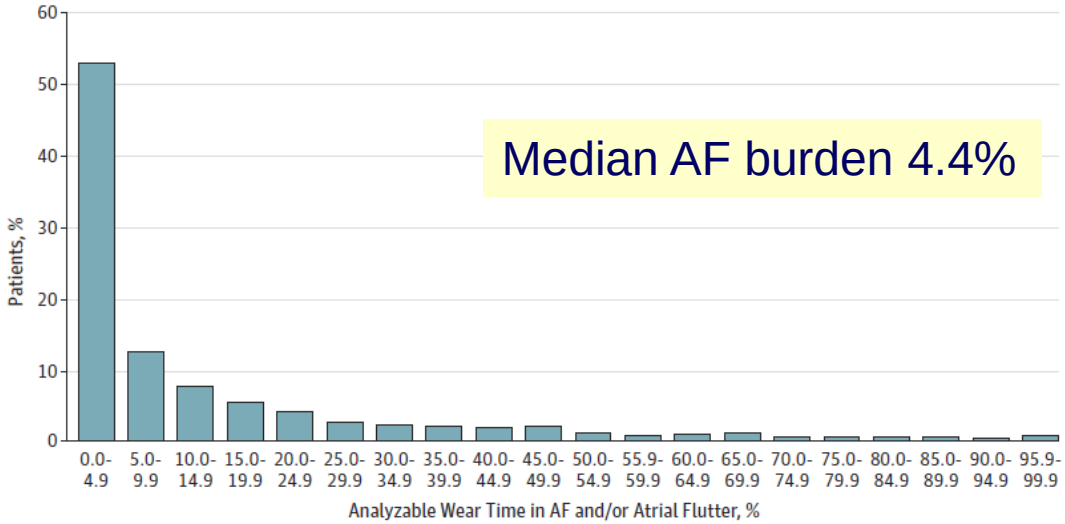
Stroke risk exceeds treatment threshold even for paroxysmal AF

Thus, there is an association between type of AF and stroke but type of AF does NOT influence decision to anticoagulate

Vannassche et al. ACTIVE and AVERROES study Eur Heart J 2015

Clinical PAF: Stroke risk depending on burden ?

- 1965 patients
- Mean age 69; 45% women
- Median CHA_2DS_2-VASc = 3
- AF burden during 14 days continuous monitoring
- Primary outcome: ischemic stroke while not on OAC



Go et al. KP Study JAMA Cardiol 2018

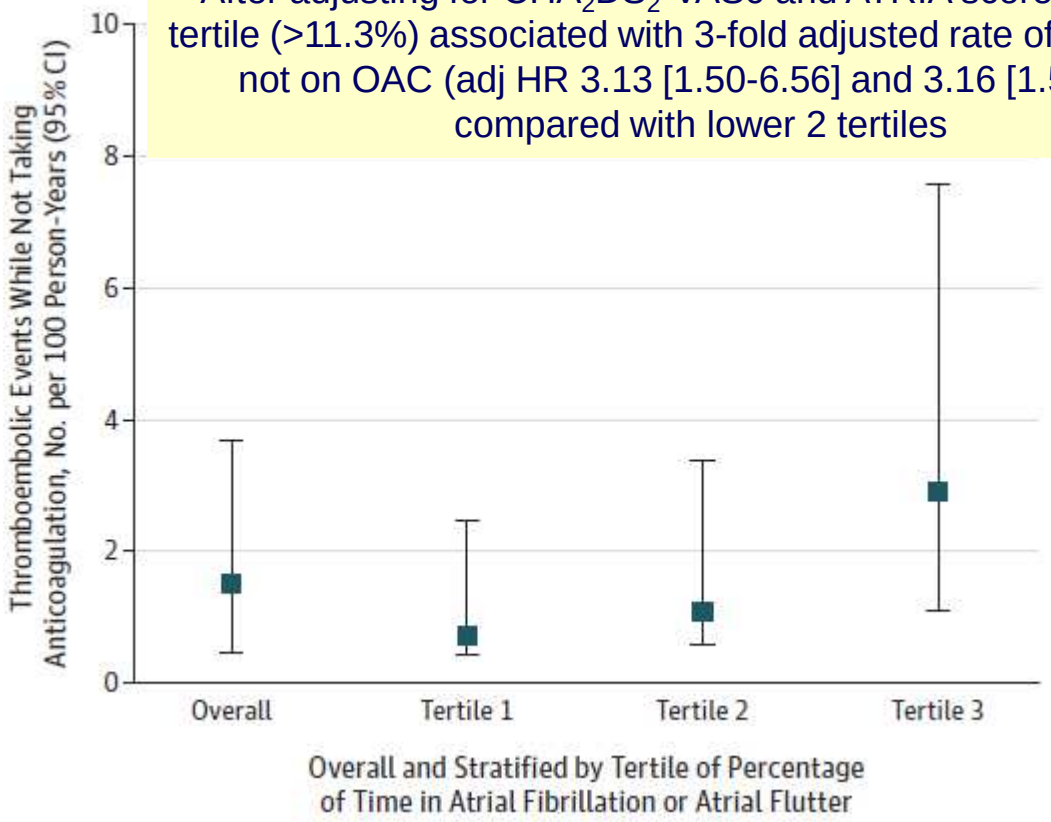
Clinical PAF: Stroke risk depending on burden ?

Characteristic	No. (%) Overall (N = 1965)	Burden of Atrial Fibrillation Tertile 1 (n = 679 [0.01%-2.03%])	Tertile 2 (n = 652 [2.05%-11.28%])	Tertile 3 (n = 634 [11.36%-99.99%])	*P* Value
Age, mean (SD), y	68.8 (11.8)	68.5 (12.4)	69.4 (11.2)	68.5 (11.6)	.27
Women	880 (44.8)	341 (50.2)	290 (44.5)	249 (39.3)	<.001
Race/ethnicity					
White/European	1469 (74.8)	500 (73.6)	485 (74.4)	484 (76.3)	.10
Black/African American	100 (5.1)	46 (6.8)	35 (5.4)	19 (3.0)	
Asian/Pacific Islander	266 (13.5)	91 (13.4)	85 (13.0)	90 (14.2)	
Other	130 (6.6)	42 (6.2)	47 (7.2)	41 (6.5)	
Hispanic ethnicity	198 (10.1)	72 (10.6)	64 (9.8)	62 (9.8)	<.001
ATRIA stroke risk score					
Mean (SD)	4.3 (2.8)	4.3 (2.8)	4.4 (2.8)	4.3 (2.9)	.61
Median (IQR)	4.0 (2.0-7.0)	4.0 (1.0-7.0)	4.0 (2.0-7.0)	4.0 (2.0-7.0)	.70
CHA_2DS_2-VASc					
Mean (SD)	2.6 (1.6)	2.6 (1.6)	2.6 (1.6)	2.6 (1.7)	.97
Median (IQR)	3.0 (1.0-4.0)	3.0 (1.0-4.0)	3.0 (1.0-4.0)	2.0 (1.0-4.0)	.95

Go et al. KP Study JAMA Cardiol 2018

Clinical PAF: Stroke risk depending on AF burden ?

After adjusting for CHA_2DS_2-VASc and ATRIA scores highest tertile (>11.3%) associated with 3-fold adjusted rate of TEC while not on OAC (adj HR 3.13 [1.50-6.56] and 3.16 [1.5-6.62] compared with lower 2 tertiles

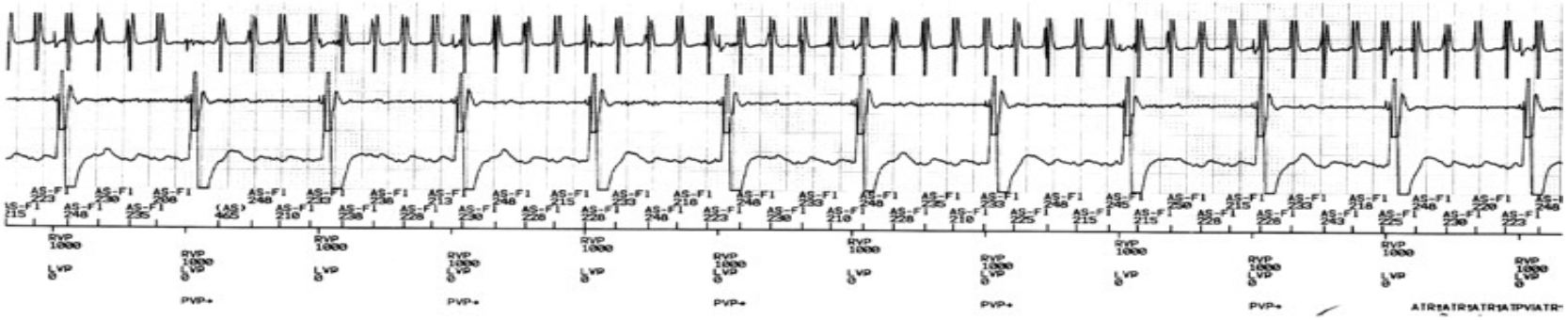


Go et al. KP Study JAMA Cardiol 2018

Clinical AF: OAC depending on burden ?

- Clinical AF
  - “Burden” of AF does NOT influence decision to anticoagulate
  - Stroke risk exceeds 2% per year for paroxysmal AF

Subclinical device detected AF



SCAF or AHRE is a variant of clinical AF but differs in that SCAF:

- would not be detected by means other than an implanted device with continuous (24/7) long-term recording
- is often asymptomatic; episodes short in duration (minutes to hours)

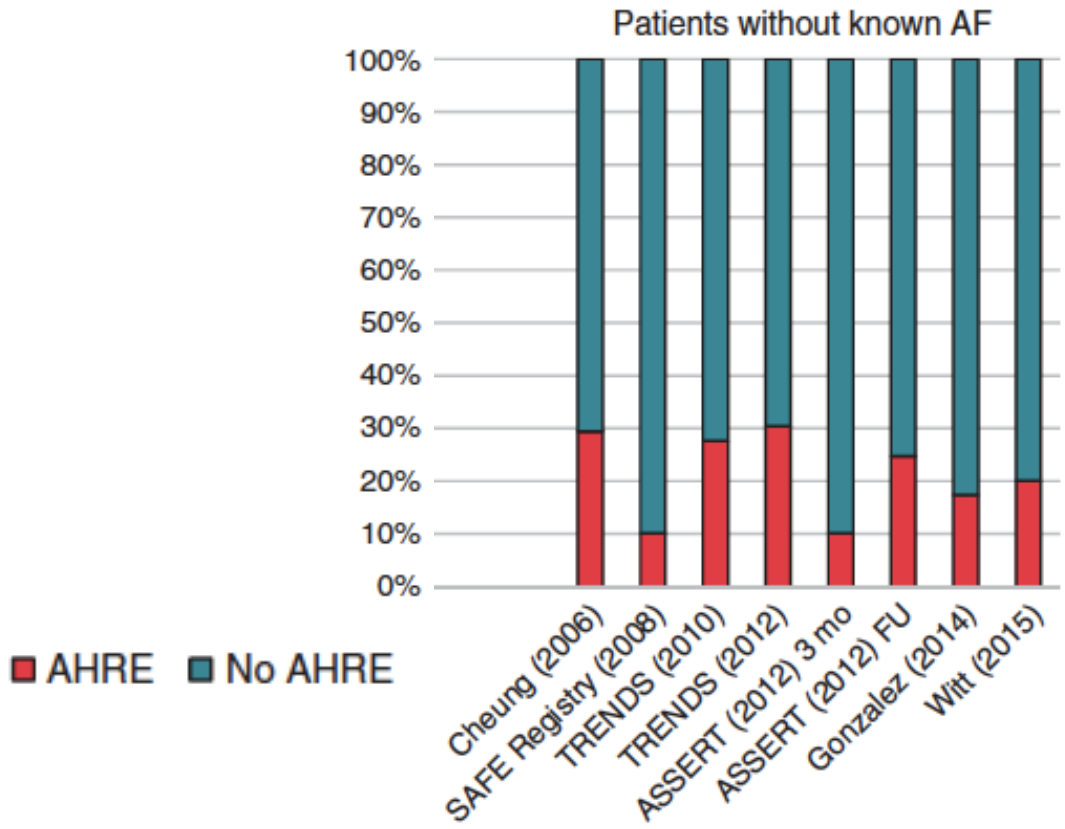
Incidence ILR detected AHRE in **high risk patients**

Study	Sample size	Device	Inclusion	Rate of AF detection
ASSERT-II[8]	250	SJM confirm	Age > 65 and CHADS-VASc ≥2 or OSA or BMI > 30; and LA > 58 mL or NT-ProBNP > 290 pg/mL	≥5 min 34.4% at 1 year
GRAF (NCT01461434)	200	MDT REVEAL-XT	Age ≥ 18 and CHADS-VASc≥4	Pending
REVEAL-AF[40]	450	MDT REVEAL-XT	Age ≥ 18, CHADS≥3, or CKD/COPD/OSA/CAD	29.3% at 18 months
PREDATE-AF[41]	245	REVEAL-LINQ	Age > 18 and CHADS-VASc≥2	≥6 min 22.4% at 451 days
DANISH LOOP[42]	6000	REVEAL-LINQ (1500)	Age > 70 One of hypertension, diabetes mellitus, HF, or stroke	Pending

Note that incidence rate is higher than in post-stroke trials
- EMBRACE-AF: 16.1% in 30 days triggered monitoring vs 3.2% in control group at 3 mths (patients included > 55 yrs)
- CRYSTAL AF: 12.4% in ICM group vs 2.0% in control group at 1 year (pts > 40 years)

Healey Eur Heart J 2019

Incidence CIED detected AHRE in high risk patients



AHRE in 10-30% of high risk patients without known AF

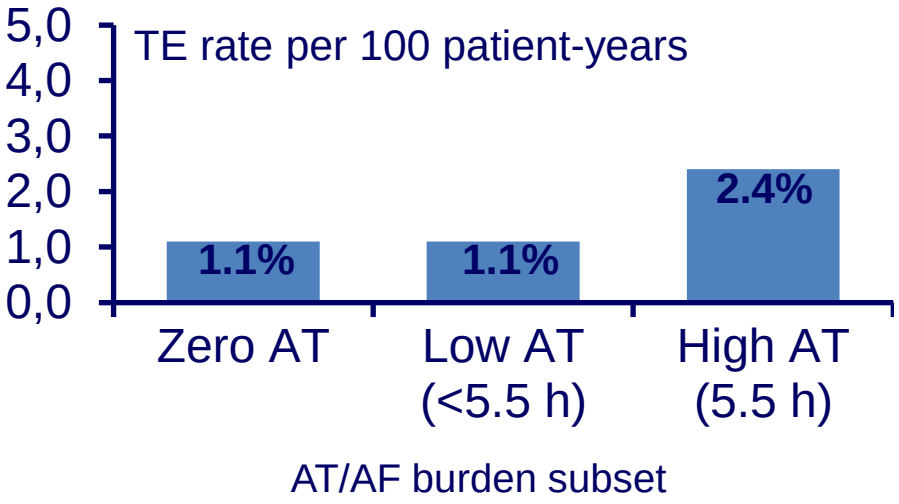
Bertaglia Europace 2019

Temporal relationship of device detected AF and TE

Year	Trial	Number of patients with TE Event	Definition of AF episode	Any AF Detected Prior to TE Event	AF Detected only after TE Event	No AF in 30 Days Prior to TE Event	Any AF in 30 Days Prior to TE Event
2011	TRENDS	40	5 minutes	20/40 (50%)	6/40 (15%)	29/40 (73%)	11/40 (27%)
2012	ANGELS	33	5 minutes	21/33 (64%)	NA	22/33 (77%)	11/33 (33%)
2014	ASSERT	51	6 minutes	18/51 (35%)	8/51 (16%)	47/51 (92%)	4/51 (8%)
2014	IMPACT	69	36/48 atrial beats ≥200bpm	20/69 (29%)	9/69 (13%)	65/69 (94%)	4/69 (6%)

Freedman Nature Reviews 2017 Brambatti Circ 2014 Martin EHJ 2015 Boriani Vascular Medcine 2015

TRENDS: Subclinical AF burden and stroke



AT/AF burden	HR for TE high vs zero burden
Low <5.5 h	**0.98** [0.34, 2.82]
High ≥5.5 h	**2.20** [0.96, 5.05]

Glötzer TV et al. Circulation AE 2009

Risk of ischemic stroke or embolism in SCAF

- 2580 patients with hypertension, > 65 yrs
- no AF, pacemaker or ICD
- Follow-up: 2.5 years
- Subclinical AF: > 6 min > 190 bpm

Healey New Engl J Med 2012 ASSERT Study

ASSERT: relation between AF and stroke

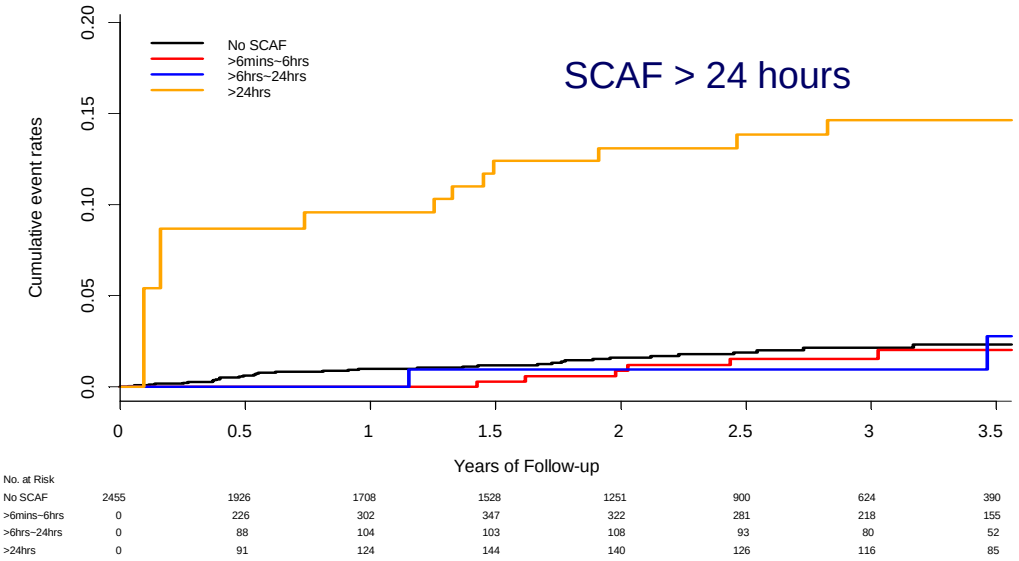
Both absolute and relative risks of stroke with SCAF are lower than with clinical AF

Event	Device-Detected Atrial Tachyarrhythmia				Device-Detected Atrial Tachyarrhythmia Present vs. absent		
	Absent N=2319		Present N= 261				
	events	%/year	events	%/ year	RR	95% CI	p
Ischemic Stroke or Systemic Embolism	40	0.69	11	1.69	2.49	1.28 – 4.85	0.007
Vascular Death	153	2.62	19	2.92	1.11	0.69 – 1.79	0.67
Stroke / MI / Vascular Death	206	3.53	29	4.45	1.25	0.85 – 1.84	0.27
Clinical Atrial Fibrillation or Flutter	71	1.22	41	6.29	5.56	3.78 – 8.17	<0.001

Healey New Engl J Med 2012 ASSERT Study

Longer subclinical AF: higher risk of stroke

- 2580 patients with hypertension, > 65 yrs
- no AF, pacemaker or ICD
- Follow-up: 2.5 years
- Subclinical AF: > 6 min > 190 bpm

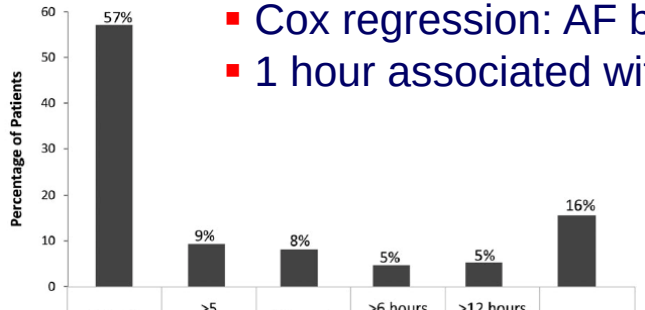


No. at Risk								
No SCAF	2455	1926	1708	1528	1251	900	624	390
>6mins~6hrs	0	226	302	347	322	281	218	155
>6hrs~24hrs	0	88	104	103	108	93	80	52
>24hrs	0	91	124	144	140	126	116	85

Van Gelder, Healey for the ASSERT Investigators Eur Heart J 2017

Longer subclinical AF: higher risk of stroke

- Pooled analysis from 5 prospective studies (no permAF, with CIED)
- 10.016 patients mean age 70 yrs
- Aim: stroke rate with pre-specified cut-off points of AF burden
- 24 months FU: 43% at least 1 day with 5 min of AF burden
- Cox regression: AF burden independent predictor of ischaemic stroke
- 1 hour associated with highest HR: 2.11 (95% CI: 1.22-3.64, p=0.008)



	0 to <5 minutes of AF burden	≥5 minutes to <1 hour AF burden	≥1 hour to <6 hours AF burden	≥6 hours to <12 hours AF burden	≥12 hours to <23 hours AF burden	≥23 hours AF burden
Median Follow Up, months	21	27	26	26	27	28
Person years	12966	2491	2077	1171	1375	4314
Stroke events, n(%)	31 (0.54%)	2 (0.21%)	7 (0.86%)	3 (0.65%)	4 (0.77%)	10 (0.64%)
Stroke rate, % per year	0.24%	0.08%	0.34%	0.26%	0.30%	0.23%
Stroke or TIA events, n(%)	41 (0.72%)	8 (0.86%)	14 (1.72%)	5 (1.08%)	6 (1.15%)	25 (1.61%)
Stroke or TIA rate, % per year	0.32%	0.32%	0.67%	0.43%	0.44%	0.49%

Table 3 Cox regression analysis performed on 8122 patients without oral anticoagulation at baseline, adjusted for the $CHADS_2$ score

	Total	Events	HR for AF burden ≥1 h vs. <1 h (95% CI)	*P*-value
Stroke	8122	44	2.09 (1.10, 3.96)	0.0239
Stroke + TIA	8122	69	2.05 (1.24, 3.39)	0.0051
Adjusting for $CHADS_2$ score				
Stroke	8122	44	1.90 (1.00, 3.61)	0.0487
Stroke + TIA	8122	69	1.89 (1.14, 3.12)	0.0135

Boriani for the AF SOS Investigators Eur Heart J 2014

Stroke Risk and AF Duration

- Analysis of 21,768 CIED non-coagulated patients from the Optum EMR
- Increased stroke risk with higher AF duration and higher CHA_2DS_2-VASc

Maximum Daily AF Duration	CHA_2DS_2-VASc Score				
	0 n=2922 (13.4%)	1 n=2151 (9.9%)	2 n=4554 (20.9%)	3-4 n=7164 (32.9%)	≥5 n=4977 (22.9%)
No AF n=16815 (77.2%)	0.33% 40 events	0.62% 46 events	0.70% 95 events	0.83% 139 events	1.79% 157 events
AF 6 min–23.5 h n=3381 (15.5%)	0.52% 11 events	0.32% 4 events	0.62% 17 events	1.28% 42 events	2.21% 36 events
AF >23.5h n=1572 (7.2%)	0.86% 4 events	0.50% 3 events	1.52% 19 events	1.77% 28 events	1.68% 13 events

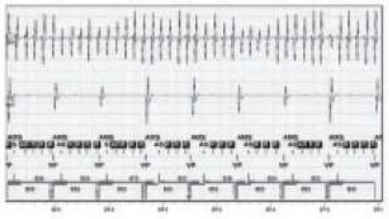
Kaplan Circulation 2019

Longer subclinical AF: higher risk of stroke

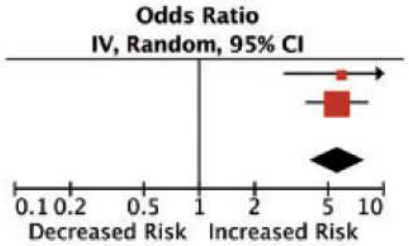
Study[a]	Study design	Sample size	Follow-up (years)	Adjudication 1 = Y, 0 = N	AF at time of enrolment	Cut-off for AF/AHRE detection and duration associated with stroke risk
Ancillary MOSTT	Retrospective observational	312	2.3	0	Sinus node dysfunction. Sinus rhythm at randomization	Atrial rate >220 b.p.m. for 10 consecutive beats AHRE ≥***5 min episode.*** Medtronic pacemakers
Capucci	Prospective multi-centre observational	725	1.8	1	Bradycardia with dual chamber pacing indication. Previous AF. Permanent AF excluded	PR logic[b] ***24 h AF*** (cardiac compass) ***episode during period of observation.*** Medtronic pacemakers
Botto	Retrospective observational	568	1	0	Brady-tachy syndrome. Permanent AF excluded	PR logic[b] AHRE ***>5 min on 1 day of year, 24 h*** (cardiac compass). Medtronic pacemakers
TRENDS	Prospective observational	2486	1.4	0	Patients with or without prior PAF. $CHADS_2 \geq 1$. Permanent AF excluded	Atrial rate >175 b.p.m. for ≥20 s AHRE ≥ 5 min. ***Rolling window, day burden >5.5 h AF on 1 day.*** Medtronic pacemakers
ASSERT	Randomized	2580	2.5	1	Excluded prior AF. Hypertension.	Atrial rate >190 b.p.m. for >6 min ***>6 min AF episodes.*** St Jude Medical pacemakers
Home CARE and everesT trials	Prospective observational	560	1	0	Prior history of AF in 178 of 382 patients. Heart failure cohort. Permanent AF excluded	Atrial rate >180 b.p.m. for 5/8 consecutive beats or 36/48 consecutive cycles, 14.4 min/day (1% home monitor burden) for detection. ***3.8 h AF burden on 1 day during follow-up.*** BiotroniK ICD/CRT CIEDs
SOS AF	Three registries	10016[c]	2	0	Prior history of paroxysmal or persistent AF included. Permanent AF excluded	Atrial rate >175 b.p.m. for ≥20 s ***≥1 h AF burden on 1 day during follow-up***
IMPACT[d]	Randomized	2718	2	1	$CHADS_2 \geq 1$. Only permanent AF excluded	≥36 of 48 atrial beats had cycle lengths ≤200 b.p.m. ***>5.5 h AF burden.*** BiotroniK ICD/CRT CIEDs

Mahajan, Sanders systematic review and meta analysis Eur Heart J 2018

Risk of stroke and requirement for therapy



AHRE detected in 13.9% patients annually



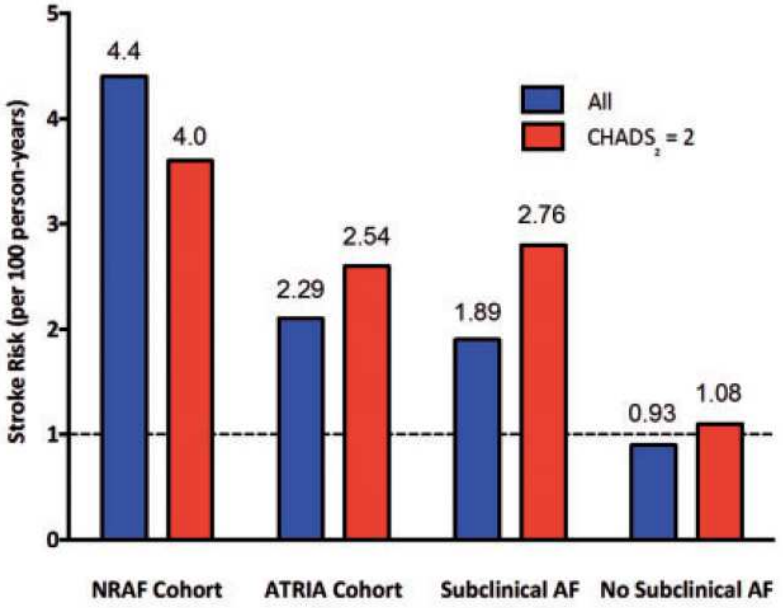
Patients with AHRE 5.7 fold more like to have clinical AF

PPV of AHRE

SJM- 83% >6min - 6 hour
97% >6 hour
Medtronic- 95%
Biotronik- 91%

AHRE duration associated with stroke risk

ASSERT- >6min episode (SJM)
TRENDS->5.5hr daily burden (Medtronic)
Home CARE and everesT trials-3.8hr daily burden (Biotronik)

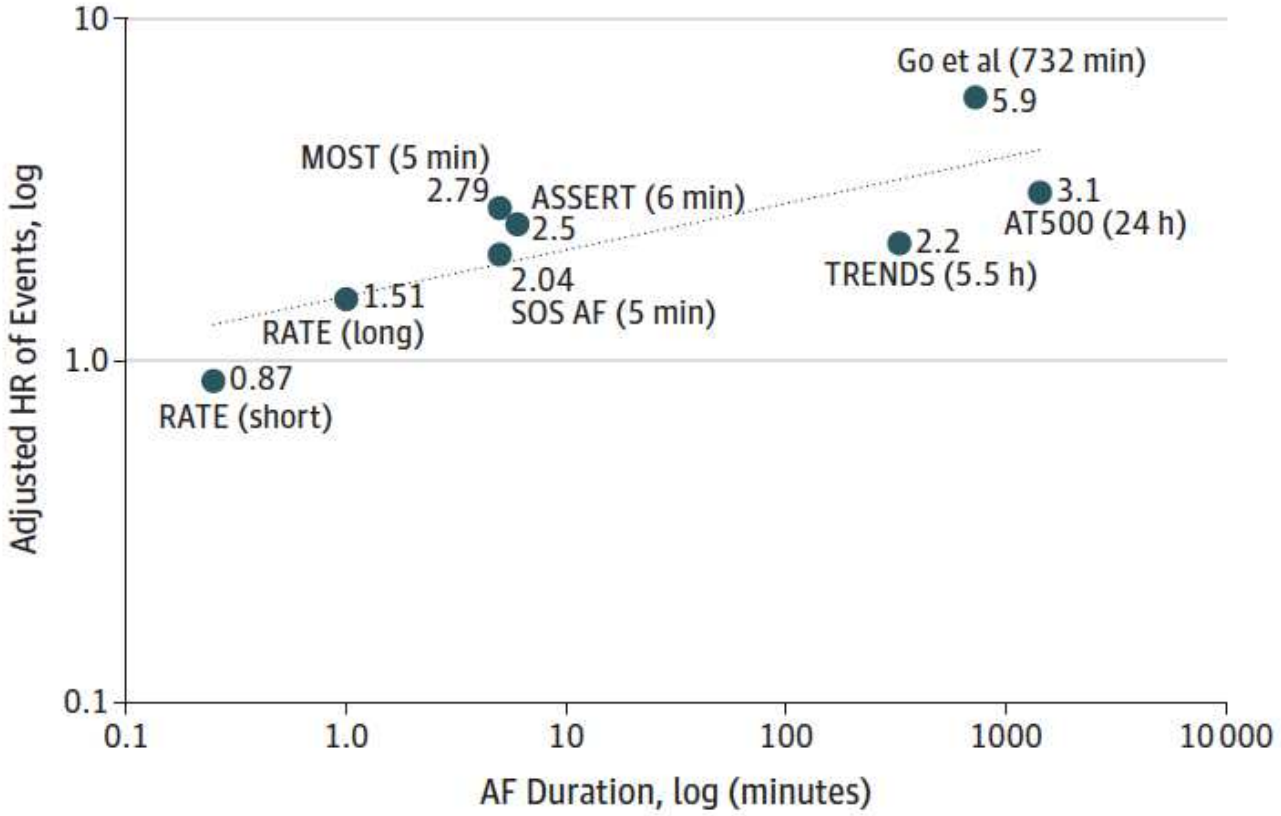


Subclinical AF and stroke risk

Subclinical AF strongly predicts clinical AF and is associated with elevated absolute stroke risk albeit lower than risk described for clinical AF.

Mahajan Eur Heart J 2018

Increased stroke risk according to AF burden



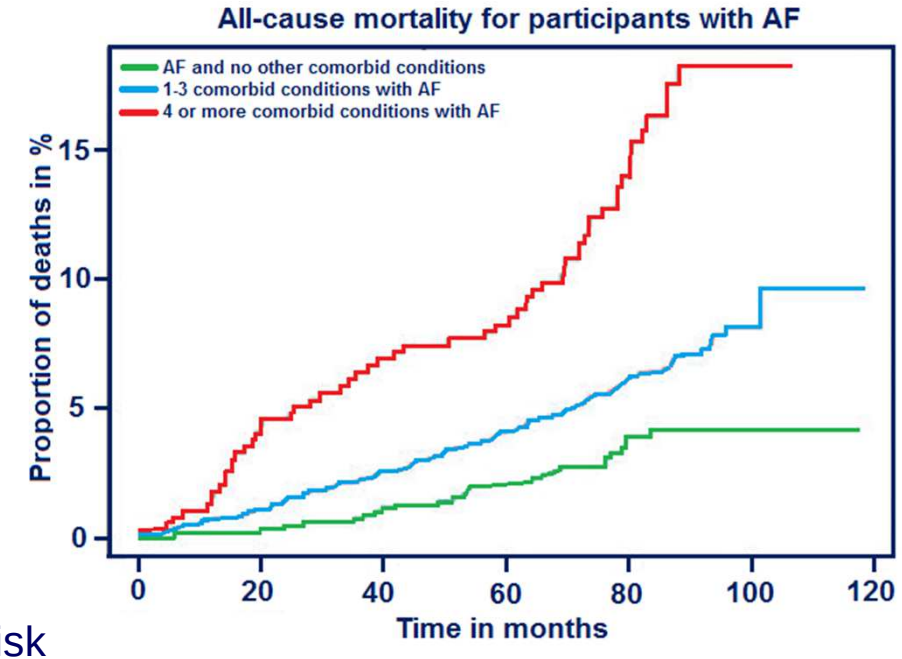
Piccini Editorial to Go et al. JAMA Cardiol 2018

But is not only AF !
It is the number of risk factors next to AF that matters

- Community cohort UK Biobank
- 502.637 participants (2006-2010)
- Age 37-73 years, 32% female
- FU 7 years
- 3651 (0.7%) developed AF
- All cause mortality 6.7%

- Presence of AF and > 4 risk factors:

  6-fold increased all cause mortality risk

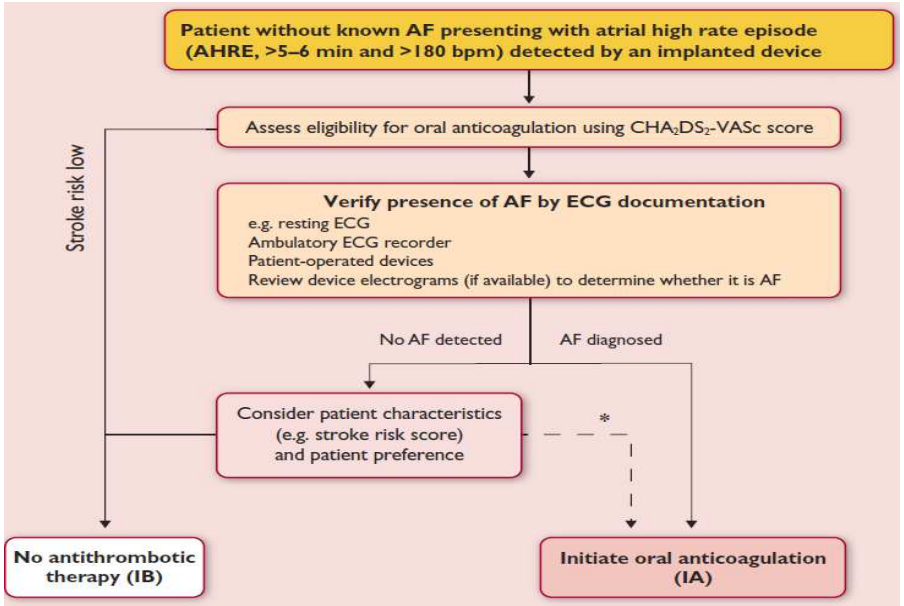


SCAF: OAC depending on burden ?

- Subclinical AF (AHRE)
  - Treatment of SCAF with anticoagulation has no proven benefit and has the possibility for harm. Stroke risk is lower !
  - Two large RCTs ongoing: NOAH-AFNET 6 and ARTESIA
  - With no indication for anticoagulation for the treatment of SCAF, AF burden cannot influence the treatment decision

SCAF: start OAC depends on burden ?

- **Search for AF on ECG or Holter**
- Anticoagulate when AF is documented by ECG
- Do not anticoagulate merely because of AHRE
- If you consider OAC, **discuss as off licence therapy**



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

Kirchhof AF ESC guidelines 2016 EHJ

Conclusions and take home messages

- In clinical AF stroke risk is influenced by number of comorbidities (higher CHA_2DS_2-VASc score)
- But also by type of AF
- SCAF/ AHRE differs from clinical AF !
- SCAF/ AHRE has a lower stroke risk
- For now SCAF duration matters
- Once SCAF/ AHRE has been seen: try to document clinical AF

Thank you for your attention

University Medical Center Groningen

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ESC Council Stroke