Conoscere e Curare il Cuore 2019

GIOVEDI' 28 FEBBRAIO

FIBRILLAZIONE ATRIALE SUBCLINICA. QUANDO PRESCRIVERE I NAO?

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Conflicts of interest

- Astra Zeneca
- PIAM
- MSD
- Sigma Tau
- Malesci
- Sanofi
- Amgen
- BI
- Bayer
- BMS
- Pfizer
- Daiichi Sankyo

Agenda

- Prevalence of silent/subclinical AF
- Detection of silent/subclinical AF
- Outcome in pts with silent/subclinical AF
- What is the threshold of AF burden able to impair prognosi, where OAC initiation may have a net clinical benefit?
- Temporal association between AF and stroke
- Current recommendations and ongoing studies

Definitions

- Silent AF:

Documented AF in the absence of any symptoms or prior diagnosis, often presenting with AF-related complications (e.g. stroke, HF)

- Atrial high rate episode (AHRE):

Atrial tachy-arrhythmic episodes with rate >190 bpm, detected by cardiac implantable electronic devices (CIEDs)

- Subclinical AF:

AHRE (>6 minutes), with lack of correlated symptoms in pts with CIEDs, detected with continuous EKG monitoring (intracardiac) and without prior diagnosis of AF at EKG

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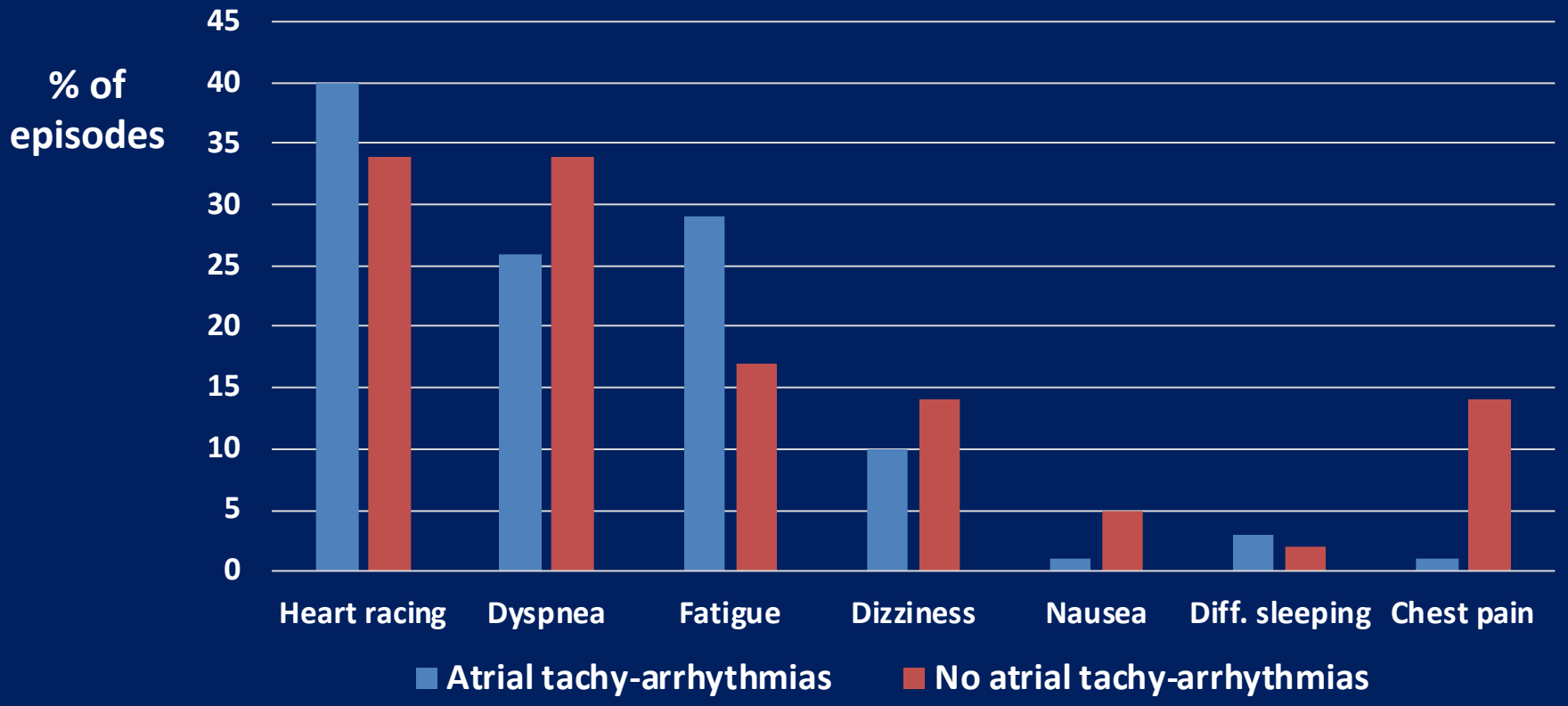
Relationship between device-detected atrial tachy-arrhythmias and symptoms

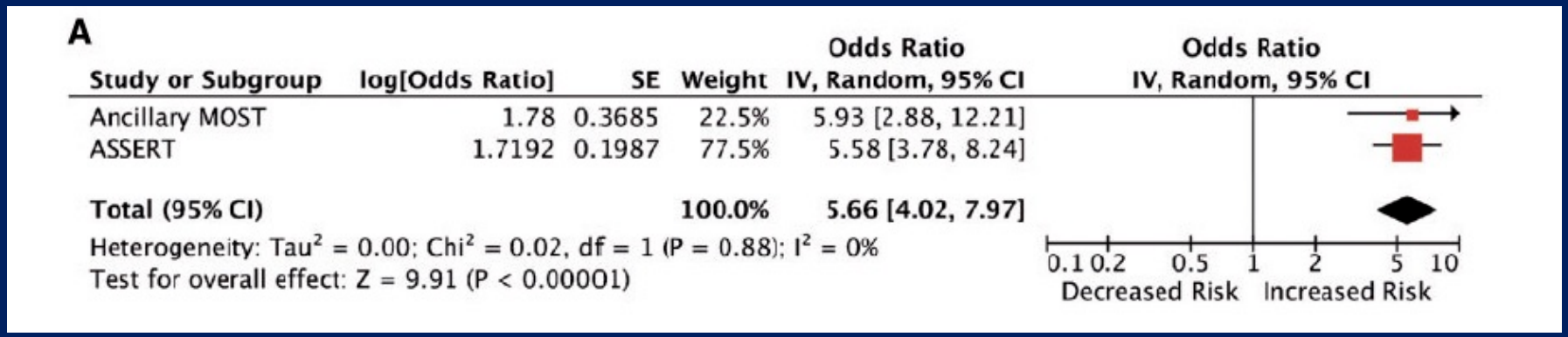


- Symptoms were reported in 6% of devide-detected AHRE
- PPV of the relationship between symptoms and tachy-arrhythmias: 17%

Strickberger SA, et al. Heart Rhythm 2005;2:125

Subclinical AF: Prevalence and risk of future clinical AF

Subclinical AF was observed after CIED implant in 35% of pts (IR 34-42) of unselected patients with pacing indication over 1-2.5 yrs (approximately 14%/year)



Predictors of future clinical AF

- **Higher burden at baseline**
- **Higher $CHADS_2$ score**

Mahajan R. Eur Heart J 2018;39:1407


Overt AF
Silent AF

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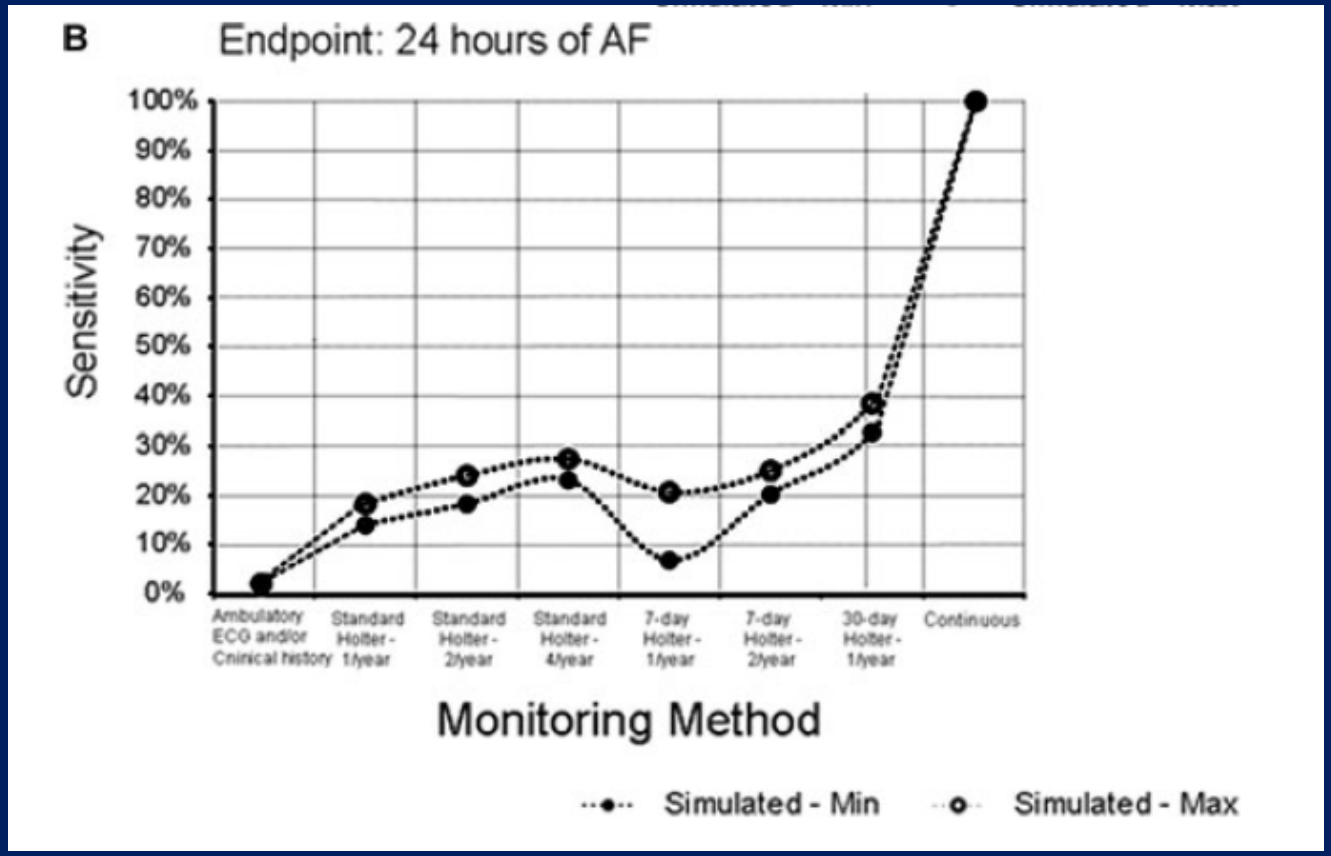
Sensitivity of repeated/prolonged Holter EKG to detect subclinical AF



Botto GL. J Cardiovasc Electrophysiol 2009

Prevalence of clinical/echocardiographic features in patients with subclinical AF

Table 1. Baseline characteristics of patients with and without pacemaker-detected atrial fibrillation

	No pacemaker-detected AF (n=199)	Pacemaker-detected AF (n=246)	*P* value
Age	71.7 ± 14.4	74.3 ± 13.7	0.046*
Male (%)	58.8	58.1	0.92
HTN (%)	65.8	72.4	0.15
Diabetes (%)	34.7	28.5	0.18
Heart failure/ LVD (%)	21.6	22.8	0.82
Stroke/TIA (%)	13.6	18.7	0.16
Coronary artery disease (%)	43.7	39.0	0.33
Vascular disease (%)	6.0	9.8	0.17
Smoking (%)	32.2	29.3	0.54
History of AF (%)	19.1	29.7	0.01*
$CHADS_2$ score	2.02 ± 1.30	2.23 ± 1.47	0.10
CHA_2DS_2-VASc score	3.60 ± 1.73	3.87 ± 1.90	0.13
Systolic BP (mm Hg)	134.5 ± 26.8	132.7 ± 26.1	0.76
Diastolic BP (mm Hg)	76.5 ± 24.2	73.5 ± 19.6	0.54
Height (cm)	168.4 ± 17.5	166.0 ± 19.1	0.50
Weight (kg)	80.2 ± 24.0	71.5 ± 26.3	0.07
ASA (%)	60.8	58.1	0.63
Clopidogrel (%)	19.1	15.0	0.31
Warfarin (%)	21.6	32.9	0.01*
Dabigatran (%)	0	2.4	0.035*

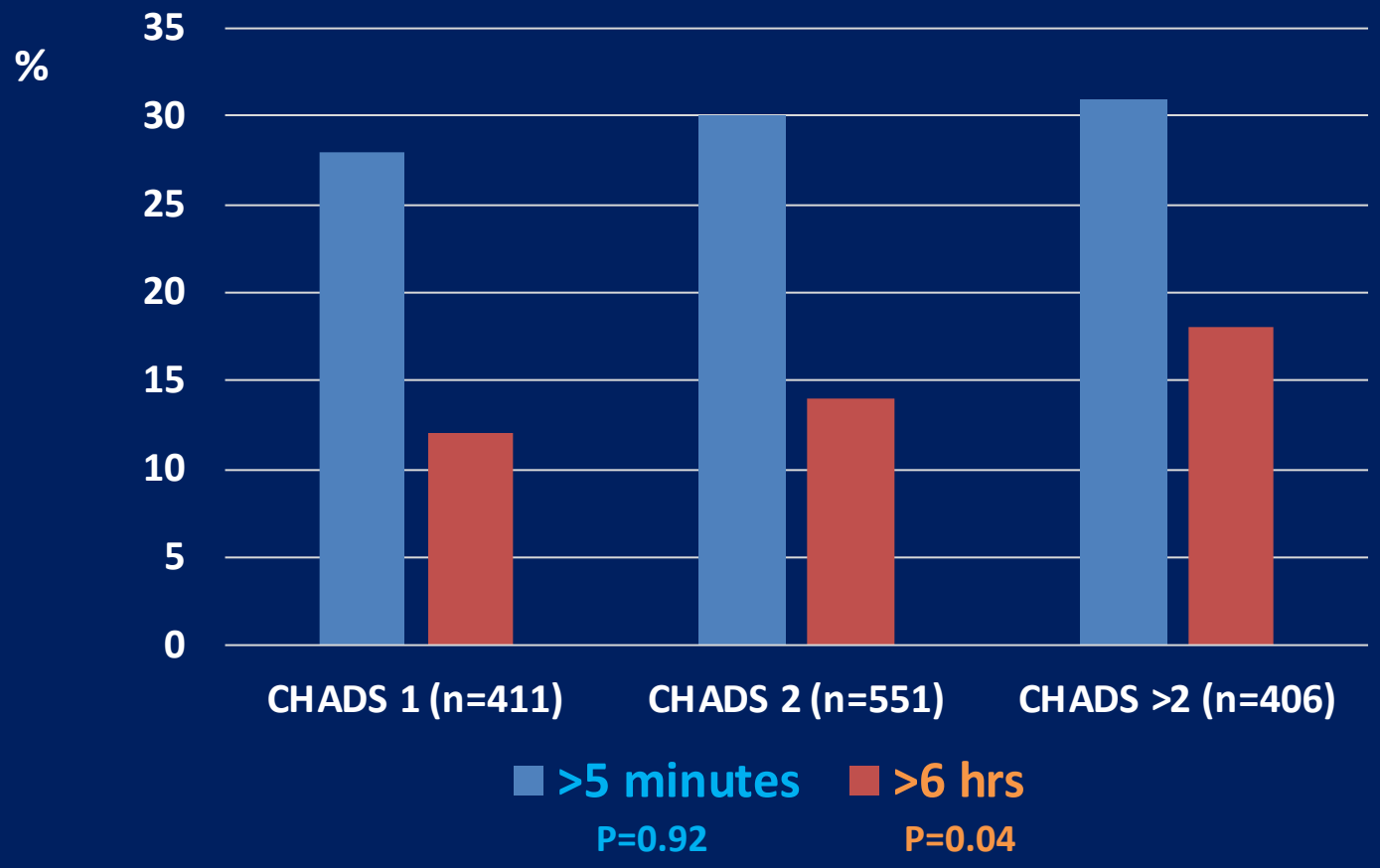
Table 2. Echocardiographic results (147/445, within 6 months of pacemaker implant)

	Pacemaker-detected AF = no (n = 62)	Pacemaker-detected AF = yes (n = 85)	*P* value
LV mass (g)	187.7 ± 65.3	188.2 ± 76.2	0.96
LV mass index (g/m2)	99.3 ± 30.3	101.6 ± 76.2	0.68
LA diameter (cm)	3.67 ± 0.64	3.82 ± 0.64	0.17
LA volume (mL)	57.0 ± 20.3	65.2 ± 23.1	0.027*
LA volume index (mL/m^2)	30.0 ± 9.9	34.6 ± 11.8	0.019*
E/A ratio	1.17 ± 0.96	1.21 ± 0.61	0.87
DT (sec)	250.2 ± 85.9	212.8 ± 75.4	0.12
E/e′ septal	13.4 ± 8.0	19.9 ± 13.8	0.14
RVSP (mm Hg)	38.1 ± 9.6	38.5 ± 12. 8	0.84
LVEF (%)	54.0 ± 14.1	53.4 ± 16.1	0.78

Healey JS. Can J Cardio 2013

Capability of continuous monitoring to detect silent AF according to $CHADS_2$ score. Data from the MOST substudy

Incidence of AF >5 min and >6 hours of AF as a function of $CHADS_2$ score



Glotzer T. Circulation 2003;107:1614

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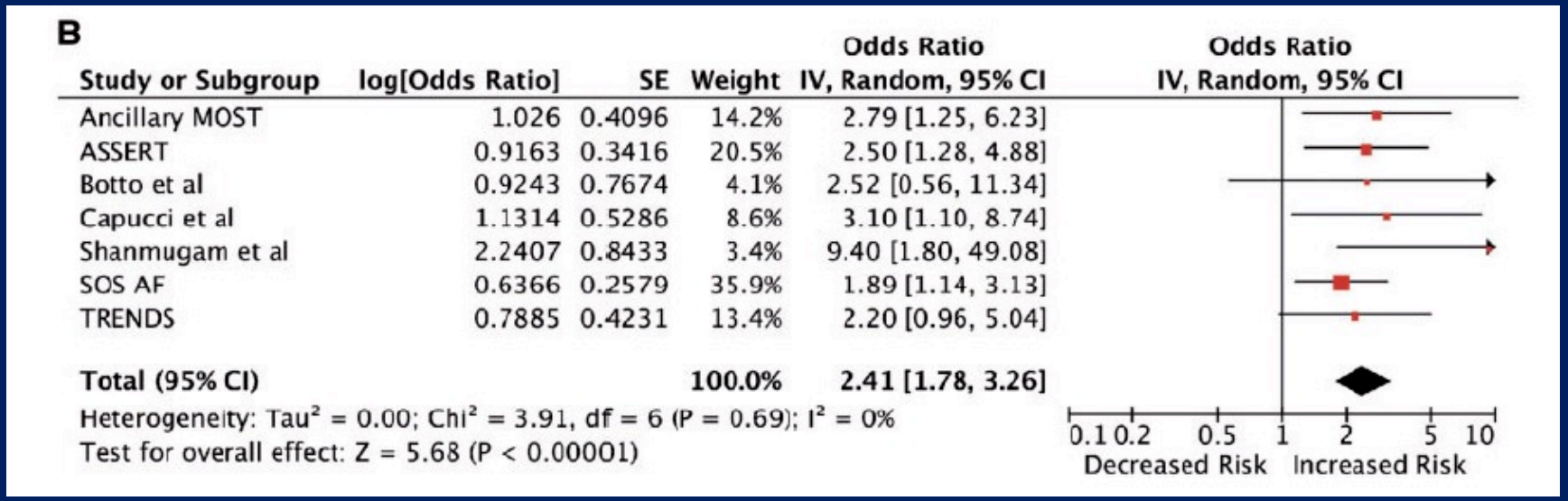
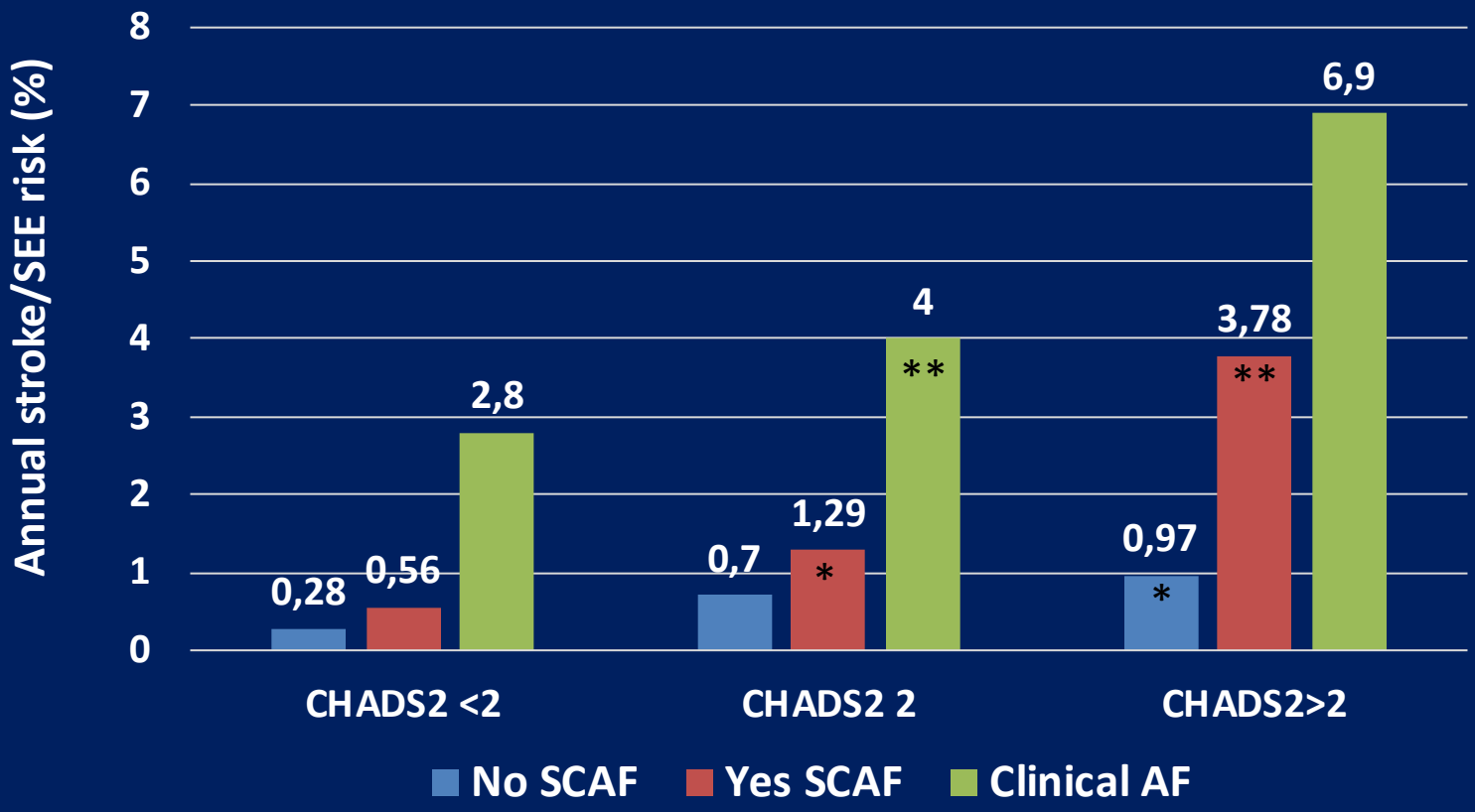
Subclinical AF and risk of future stroke



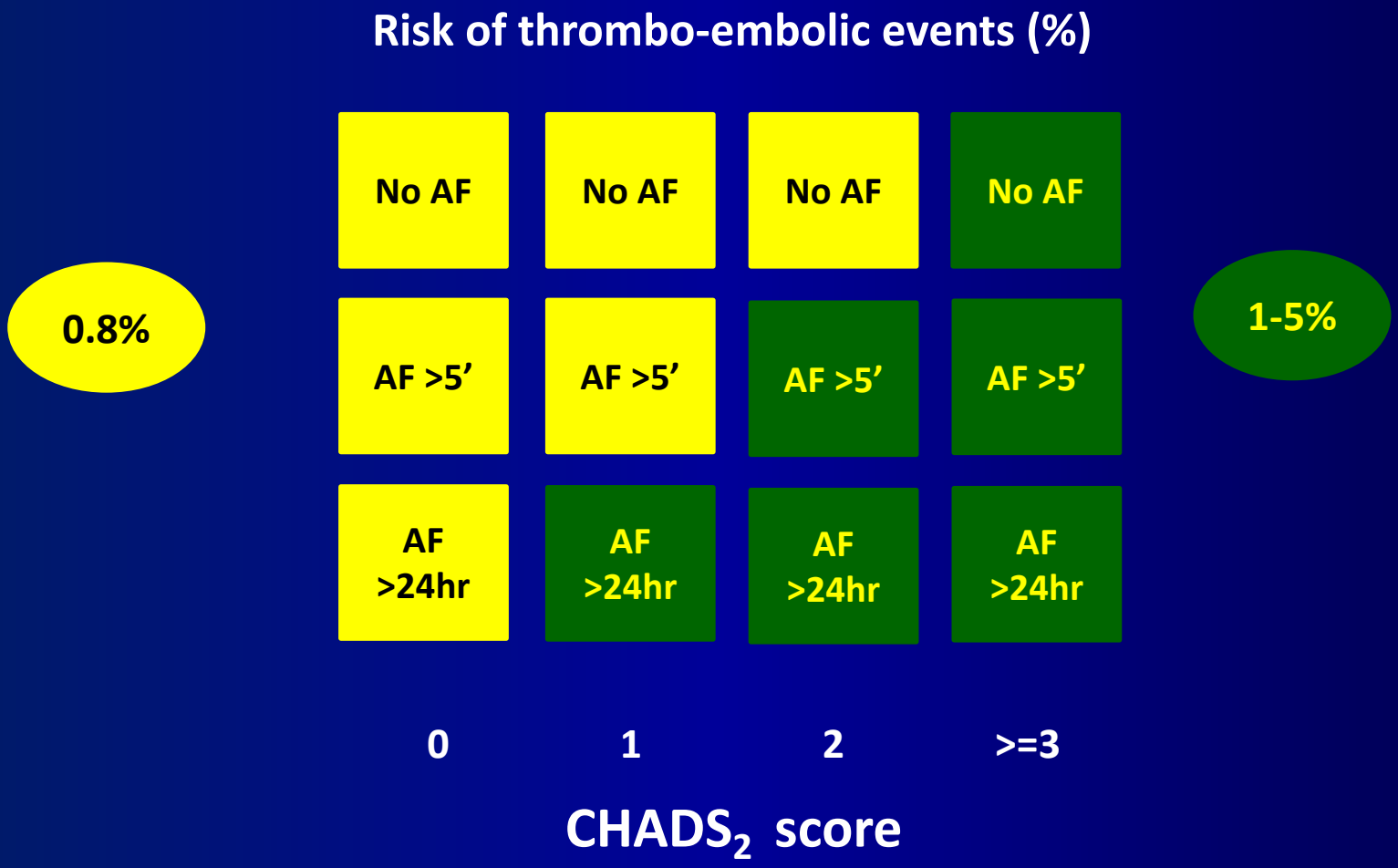
Mahajan R. Eur Heart J 2018;39:1407

Risk of stroke/systemic embolic events according to type of device-detected AHRE and to TE risk



Lau CP. Europace 2015

AF Presence/Duration and thrombo-embolic risk (N=568 pt)



Botto GL. J Cardiovasc Electrophysiol 2009

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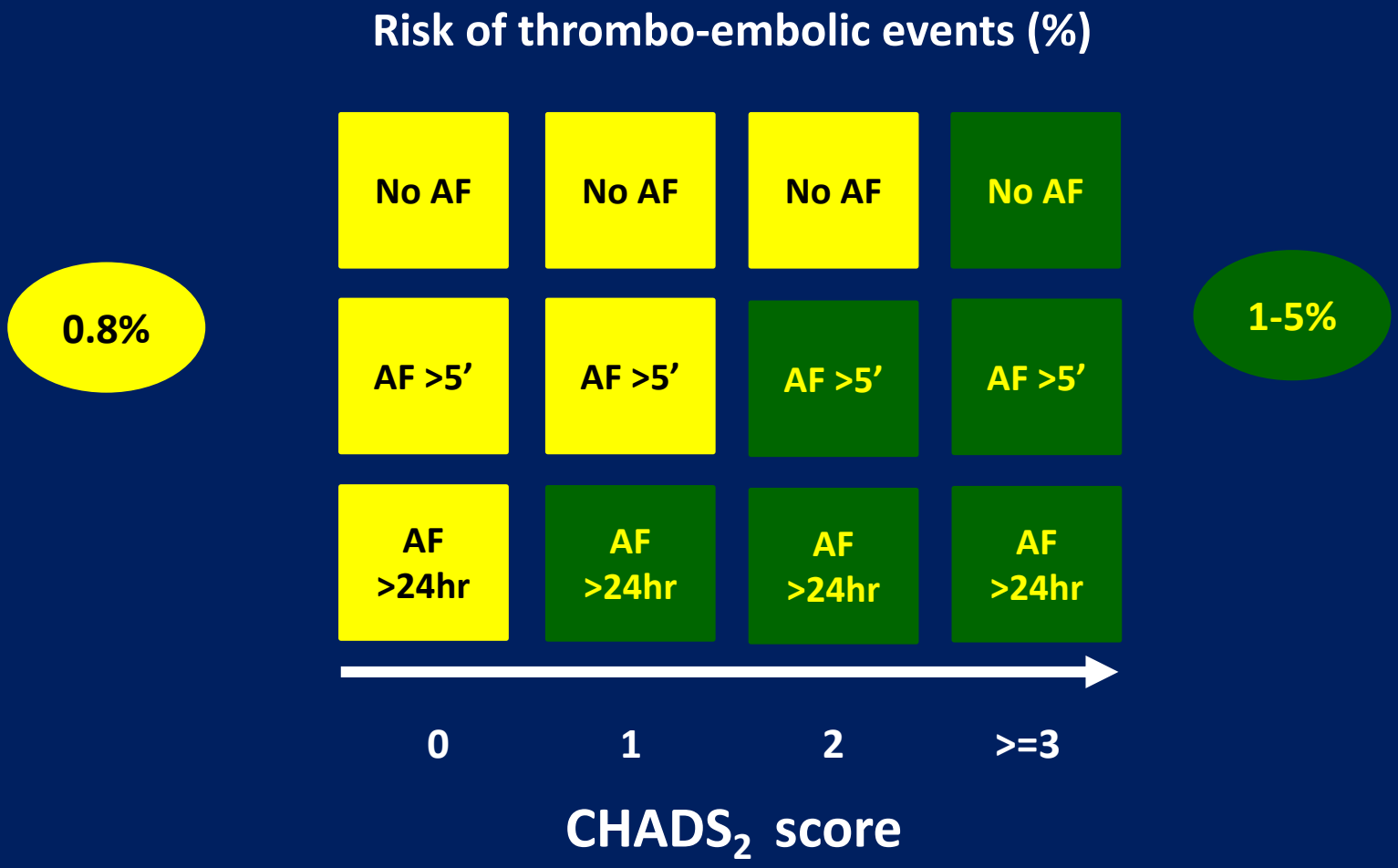

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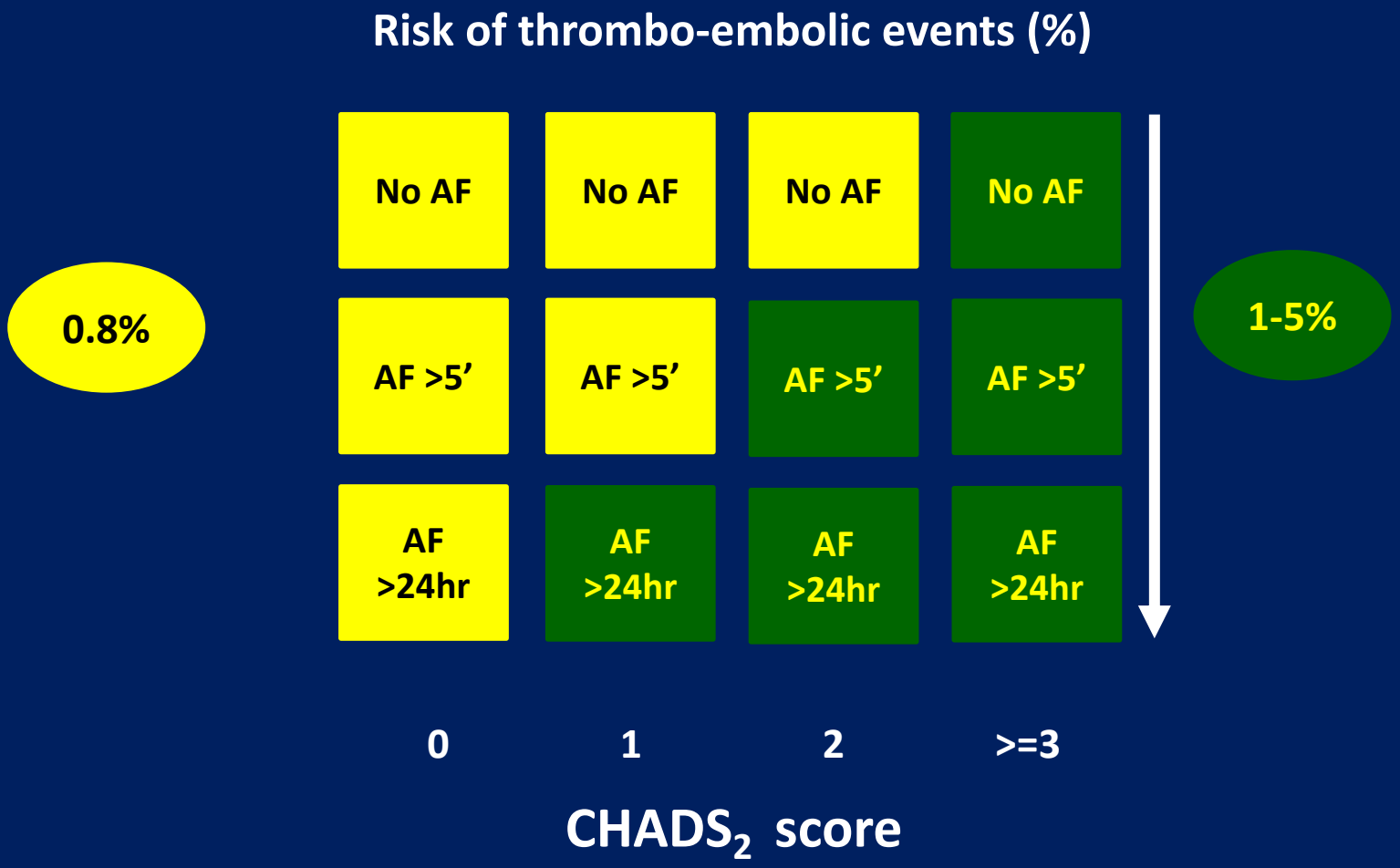

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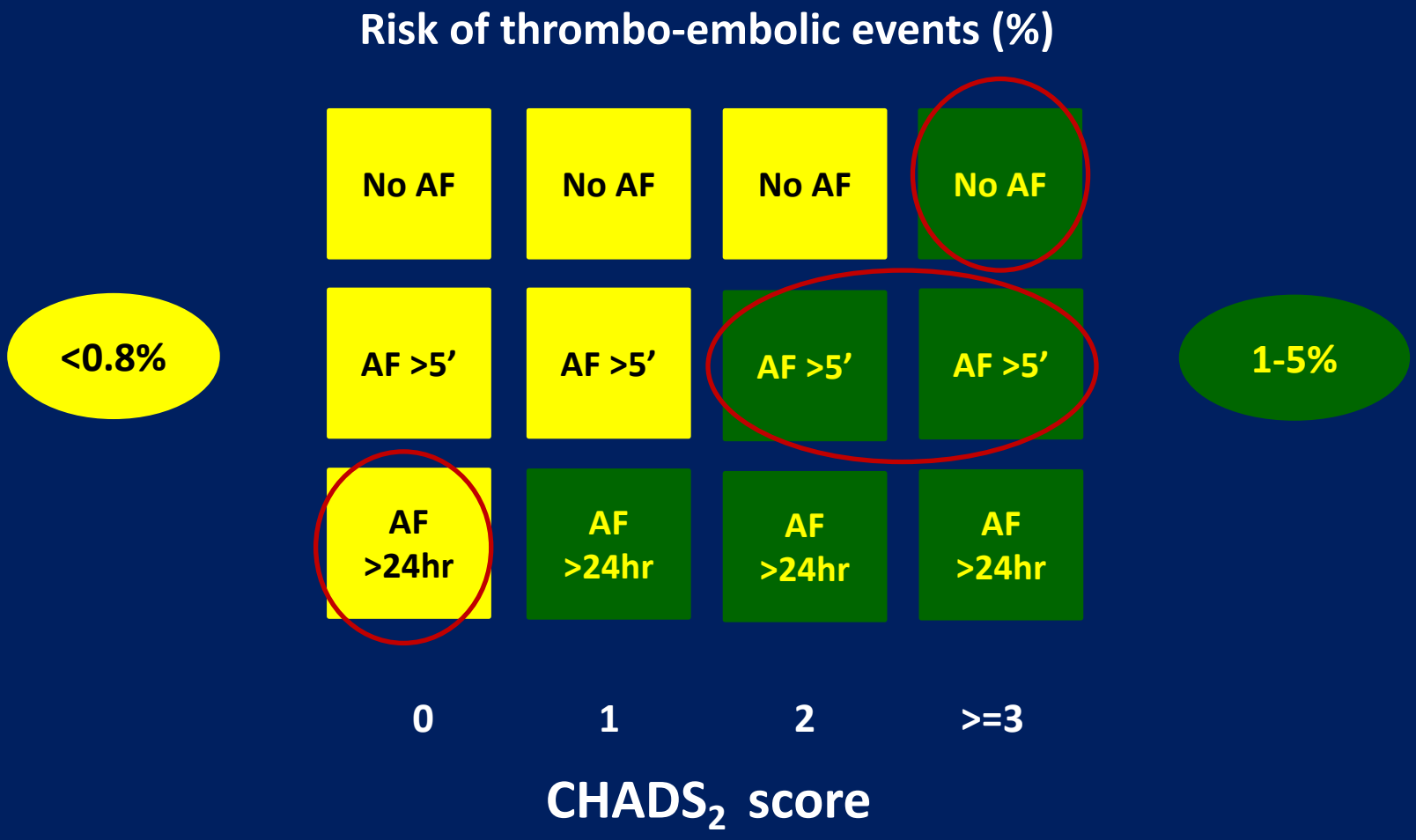

Botto GL. J Cardiovasc Electrophysiol 2009

Silent ischemic brain lesions related to AHRE >5 min in 109 pts with CIEDs

Table 3 Risk of IBLs on CT scan in the overall study population and in the subgroup of patients without prior history of AF or stroke/TIA

	OR	CI 95%	*P* value
Overall study population			
Age	1.09	1.02–1.17	**<0.05**
Sex (male)	1.06	0.44–2.53	0.88
$CHADS_2$ score	2.67	1.71 ± 4.16	**<0.001**
$CHAD_2S_2VASc$ score	2.28	1.56 ± 3.33	**<0.001**
High blood pressure	2.38	0.64 ± 8.79	0.19
Diabetes	1.63	0.66 ± 4.01	0.28
Structural heart disease	1.53	0.62 ± 3.76	0.34
History of heart failure	0.61	0.12 ± 3.03	0.55
History of stroke/TIA	10.57	3.61 ± 30.88	**<0.001**
History of AF	3.19	1.19 ± 8.56	**<0.05**
Chronic kidney disease	2.08	0.78 ± 5.50	0.13
Small-vessel disease	1.96	0.82 ± 4.67	0.12
AHRE > 5 min	3.04	1.20 ± 7.70	**<0.05**

Impact on cognitive decline?

Benezet-Macuezos J. Europace 2015;17:364

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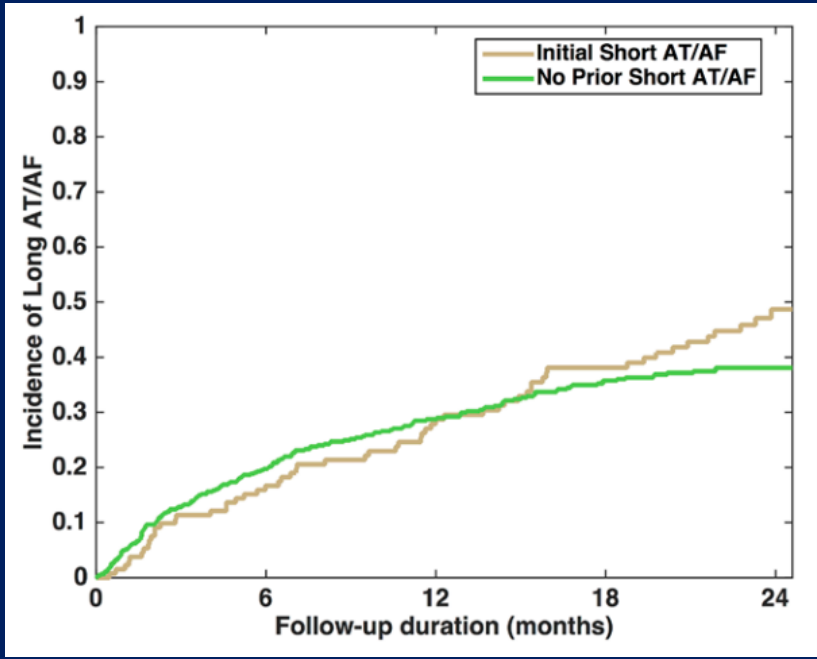
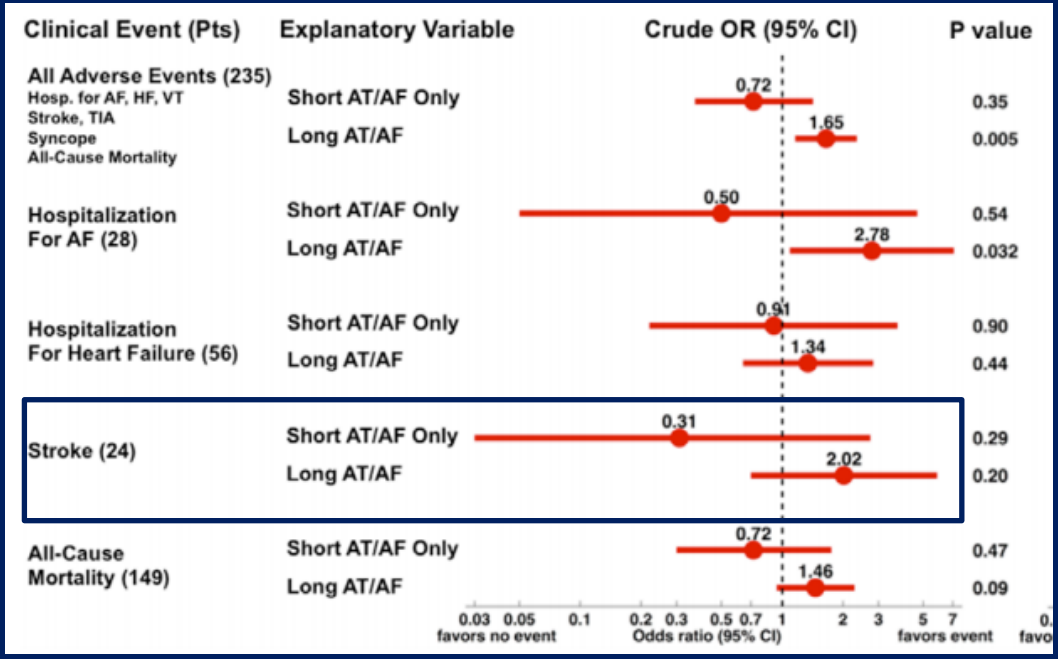
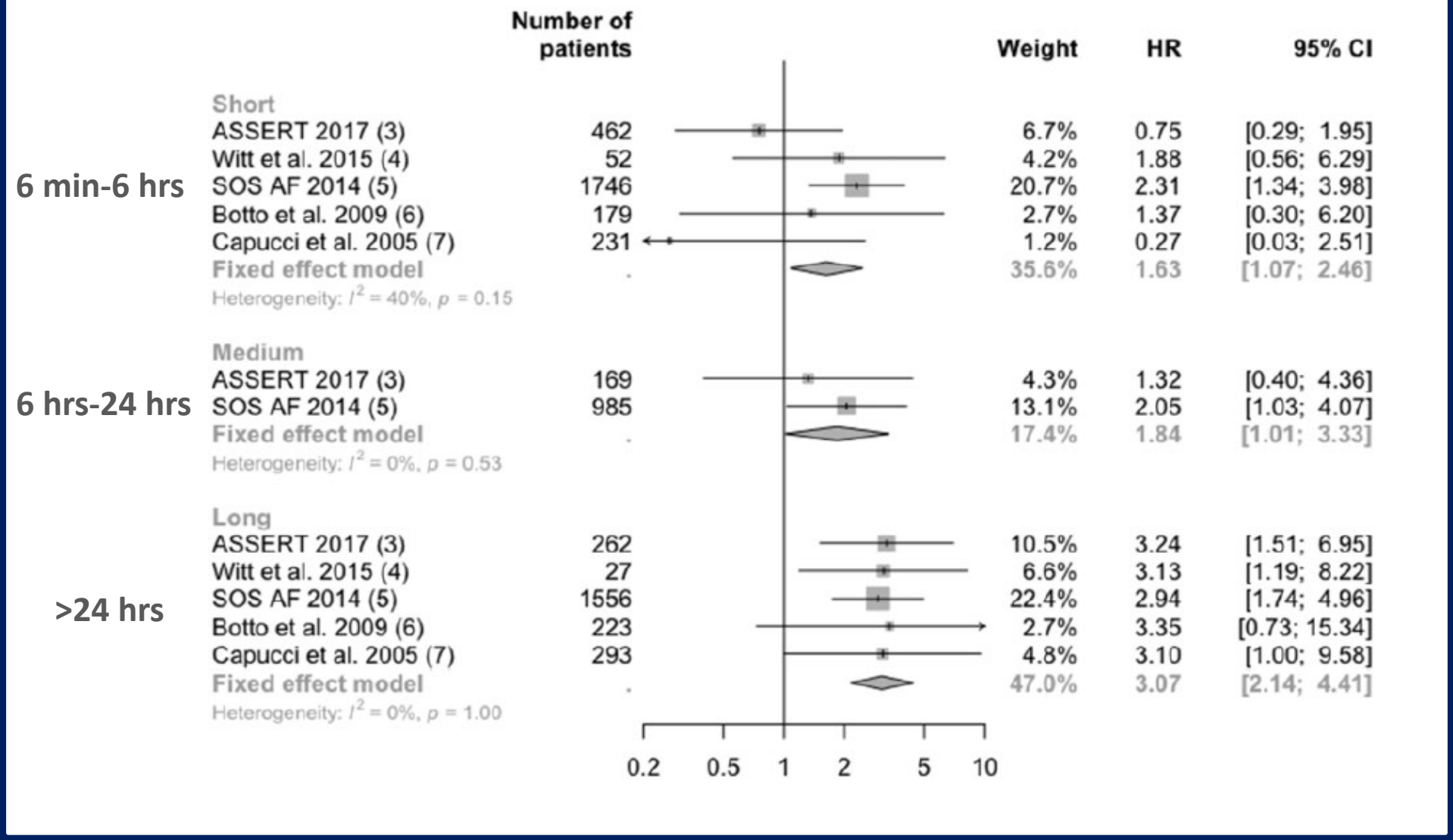
Clinical implications of very brief episodes of AHRE detected by CIED (duration from 3 ACPs to 20 seconds)





Swiryn S, et al. Circulation 2016;134:1130

Risk of stroke or systemic embolism by categories of subclinical AF duration



Rahimi K. Eur Heart J 2017;38:1345

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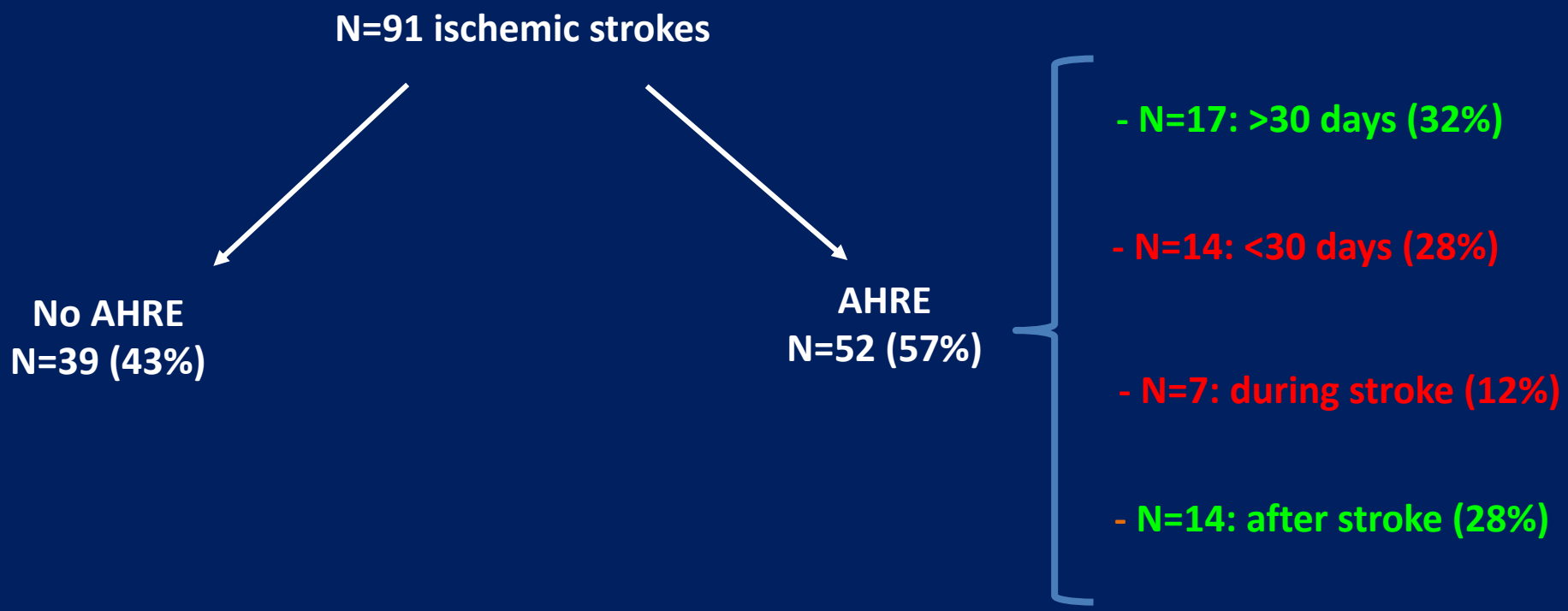
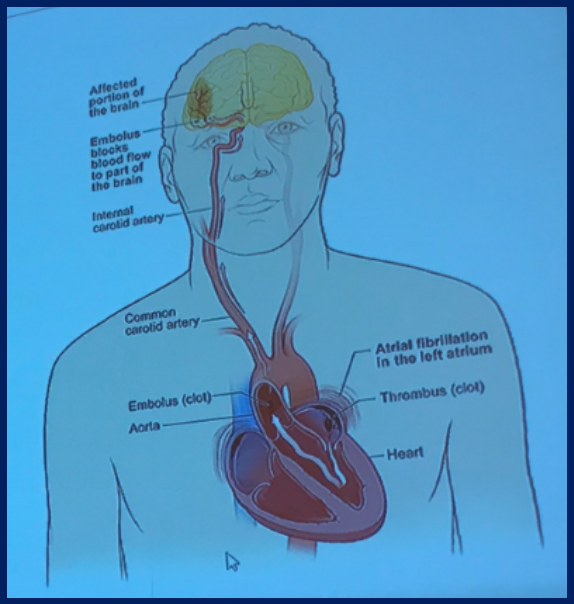
Temporal association of subclinical AF and stroke

Pooled analysis from TRENDS and ASSERT



- In stroke pts with AHRE <30 days, the daily burden of AHRE was greater than that in pts with AHRE >30 days

Mahajan R. Eur Heart J 2018;39:1407



AF ⟹ atrial thrombus ⟹ cardioembolic stroke

Is this the only mechanism of AF-related strokes?

Athero-emboli from aorta

Cardioemboli from LAA

STROKE

Cerebral vascular disease

Atrial cardio-myopathy

AF as a marker of risk

AF as a direct cause

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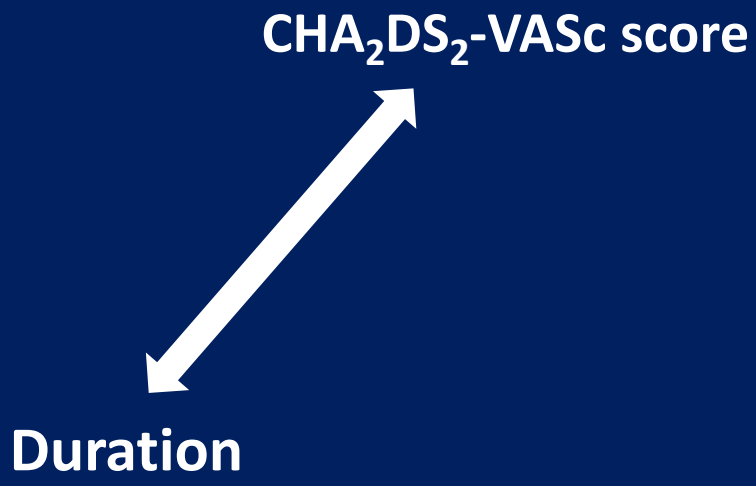
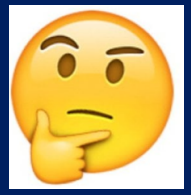
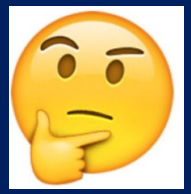
NOAC initiation in pts with subclinical AF



NOAC initiation in pts with subclinical AF
EHRA/HRS/APHRS/SOLEACE 2017

	CHA_2DS_2-VASc score			
	0	1	2-3	>=4
Duration <6’				
Duration 6’ to 6 hrs				
Duration 6 h to 24 hrs				
Duration >24 hrs				

Ongoing studies

Table 2 On-going studies on potentially subclinical and asymptomatic atrial fibrillalation

Study	Study identifier	Inclusion criteria	Randomization/ Design	Size	Endpoint	Est. completion date
ARTESiA[13]	Clinicaltrials.gov NCT01938248	Permanent pacemaker, ICD or CRT CHA_2DS_2-VASc score of ≥ 4. Age ≥65 At least one episode of symptomatic AF ≥ 6 min (Atrial rate >175/min if an atrial lead is present), but no single episode >24 h in duration. Only patients without clinical AF	Randomized to: Apixaban 5 mg ×2 (or 2.5 mg ×2) vs. Aspirin 81 mg ×1 daily Randomized, double-blind, double-dummy.	4000 patients planned	1. Composite of ischemic stroke and systemic embolism 2. Major Bleeding	2019
NOAH AFNET 6[14]	Clinicaltrials.gov NCT02618577	Permanent pacemaker or defibrillator. Age ≥65+additional CHA_2DS_2-VASc score point of ≥ 2, i.e. CHA_2DS_2-VASc ≥3 At least one episode of AHRE ≥6 min (Atrial rate >180/min if an atrial lead is present), but no single episode >24 h in duration. Only patients without overt AF	Randomized to: Edoxaban 60 mg ×1 (or 30 mg if renal impairment) vs. Aspirin 100 mg ×1 daily or placebo[a] Randomized, double-blinded double dummy.	3400 patients planned	Composite of time to the first stroke, systemic embolism, or cardio-vascular death	2019
The (Danish) LOOP study[15]	Clinicaltrials.gov NCT02036450 www.loop-study.dk	Age >70 years and at least one of the following diseases: • Diabetes • Hypertension • Heart failure • Previous stroke	Randomization to receive an ILR or be treated as standard of care (ratio 1:3; i.e. 1500 randomized to ILR and 4500 randomized to standard care)	6000 patients planned	Composite of ischemic stroke and systemic embolism	2019

NOAC initiation in pts with subclinical AF