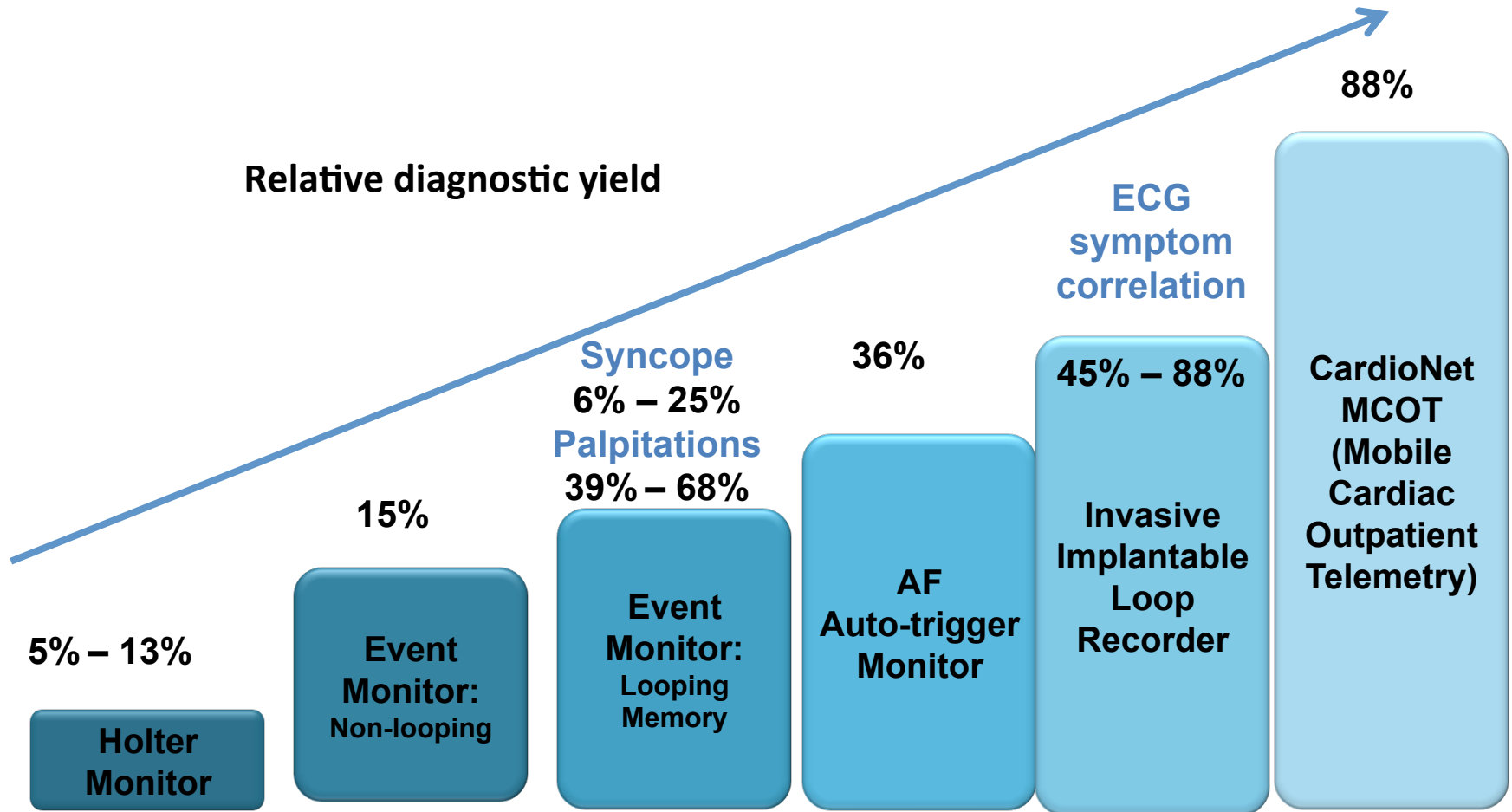


# **Fibrillazione atriale subclinica e rischio di ictus ischemico**

# Background

- 25% of all ischemic strokes are cryptogenic, and subclinical atrial fibrillation (AF) is suspected to be a possible cause in many of these.
- The prevalence and prognosis of subclinical AF has been difficult to assess.
- Cardiac Implantable Electronic Devices (CIEDs) have the capacity to record episodes of atrial tachyarrhythmia.
- The significance and management strategies of device-detected subclinical AF are not clearly defined.

# As Cardiac Monitoring Evolves, Diagnostic Yield Improves

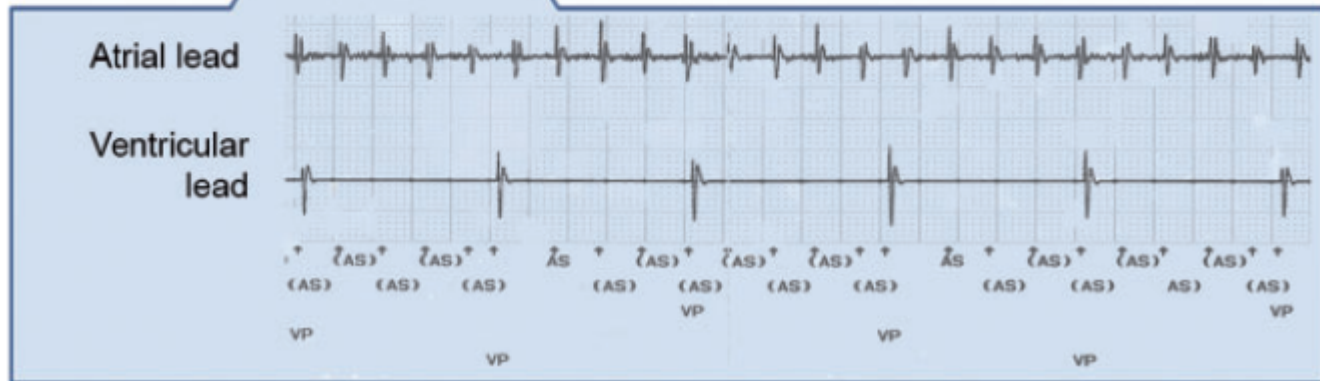
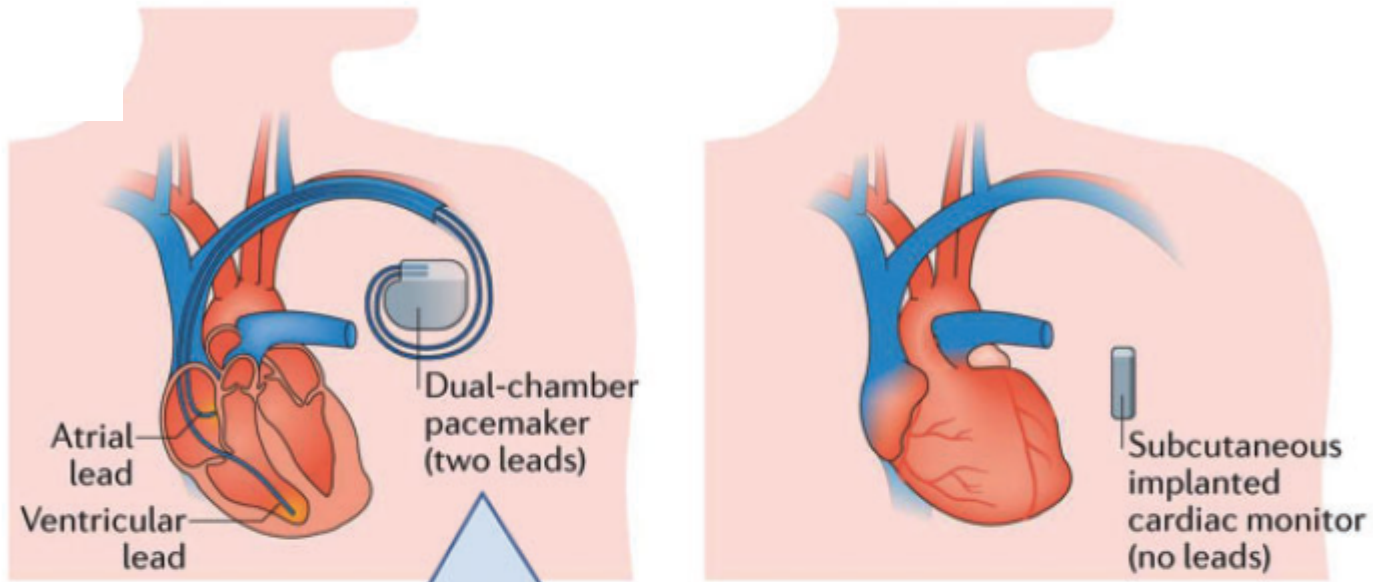


The technology available for arrhythmia monitoring has evolved since the Holter monitor was first developed in the late 1940s. The diagnostic yield of these methods has increased substantially over time: MCOT is the latest milestone on the road to better arrhythmia diagnosis and management.

## References:

Assar MD et al. *Am J Cardiol.* 2003;92:1231-3. Fechter P. *Schweiz Med Wochenschr.* 1991;121:1488-92. Fogel RI et al. *Am J Cardiol.* 1997;79:207-8. Gibson TC et al. *Am J Cardiol.* 1984;53:1013-7. Kinlay S et al. *Ann Intern Med.* 1996;124:16-20. Krahn AD et al. *Circulation.* 2001;104:46-51. Krahn AD et al. *PACE.* 2004;27:657-64. Linzer M et al. *Am J Cardiol.* 1990;66:214-9. Reiffel JA et al. *Am J Cardiol.* 2005;95:1055-9. Rothman SA et al. *J Cardiovasc Electrophysiol.* 2007;18:241-7. Zeldis SM et al. *Chest.* 1980;78:456-61. Zimetbaum P et al. *Am J Cardiol.* 1997;79:371-2.

# Atrial High Rate Episodes (AHRE)



## Incidence of CIEDs-detected AHREs in patients with risk factors for stroke

| Study                   | Patients characteristics   | AHRE burden threshold | Incidence of AHRE (%) |
|-------------------------|--|-----------------------|-----------------------|
| <i>ASSERT II, 2016</i>  | $\geq 65$ years,<br>CHA <sub>2</sub> DS <sub>2</sub> -VASc $\geq 2$ or OSA or<br>BMI > 30,<br>with enlarged left atrium or<br>NT-proBNP $\geq 290$ pg/ml | AF $\geq 5$ min       | 34.4 at 12 months     |
| <i>REVEAL-AF, 2017</i>  | CHADS <sub>2</sub> $\geq 3$ or =2 additional<br>risk factors (OSA, CAD, COPD<br>or GFR 30-60 ml/min)   | AF $\geq 6$ min       | 20.4 at 12 months     |
| <i>PREDATE-AF, 2017</i> | CHA <sub>2</sub> DS <sub>2</sub> -VASc $\geq 2$  | AF $\geq 6$ min       | 22.4 at 451 days      |

## Relationship between AF burden and stroke

| Author                  | No. of patients           | AF burden associated with stroke | HR (95%, CI)     |
|-------------------------|---------------------------|----------------------------------|------------------|
| <i>Glotzer , 2003</i>   | 312 with SSS              | $\geq 5$ min                     | 2,79 (1.51-5.15) |
| <i>Capucci, 2005</i>    | 725 with bradyarrhythmias | > 24 h                           | 3.1 (1.1-10.5)   |
| <i>Glotzer, 2009</i>    | 2486 with PM or AICD      | $\geq 5.5$ h                     | 2.2 (0.96-5.05)  |
| <i>Healey, 2012</i>     | 2580, no history of PAF   | > 6 min                          | 2.49 (1.28-4.85) |
| <i>Shanmugan, 2012</i>  | 560 with CRT              | $\geq 3.8$ h                     | 9.4 (1.8-47.0)   |
| <i>Boriani, 2013</i>    | 10016 with a CIED         | $\geq 1$ h                       | 2.11 (1.22-3.64) |
| <i>Van Gelder, 2017</i> | 2580, no history of PAF   | $\geq 24$ h                      | 3.24 (1.51-6.95) |

# Relationship between AF and tromboembolic events in patients with CIEDs

| Autors                 | No. of TE events | AF before TE (%) | AF in the 30 days before TE (%) | AF at the time of TE events (%) | AF only after TE events (%) |
|------------------------|------------------|------------------|---------------------------------|---------------------------------|-----------------------------|
| <i>Daoud, 2011</i>     | 40               | 50               | 28                              | 15                              | 15                          |
| <i>Boriani, 2012</i>   | 33               | 64               | 33                              | 15                              | NA                          |
| <i>Shanmugan, 2014</i> | 11               | 64               | NA                              | 27                              | NA                          |
| <i>Brambatti, 2014</i> | 51               | 35               | 8                               | 2                               | 16                          |
| <i>Martin, 2015</i>    | 69               | 13               | 6                               | NA                              | 7                           |

# Subclinical device-detected atrial fibrillation and stroke risk: a systematic review and meta-analysis

**Rajiv Mahajan<sup>1</sup>, Tharani Perera<sup>1</sup>, Adrian D. Elliott<sup>1</sup>, Darragh J. Twomey<sup>1</sup>, Sharath Kumar<sup>1</sup>, Dian A. Munwar<sup>1</sup>, Kashif B. Khokhar<sup>1</sup>, Anand Thiyagarajah<sup>1</sup>, Melissa E. Middeldorp<sup>1</sup>, Chrishan J. Nalliah<sup>1,2</sup>, Jeroen M. L. Hendriks<sup>1</sup>, Jonathan M. Kalman<sup>2</sup>, Dennis H. Lau<sup>1</sup>, and Prashanthan Sanders<sup>1\*</sup>**

<sup>1</sup>Centre for Heart Rhythm Disorders, South Australian Health and Medical Research Institute (SAHMRI), University of Adelaide and Royal Adelaide Hospital, Adelaide, SA 5000, Australia; and <sup>2</sup>Department of Cardiology, Royal Melbourne Hospital and the University of Melbourne, Melbourne, Australia



# Methods

## Search strategy

The English scientific literature was searched using Pubmed and Embase with keywords ('subclinical' OR 'device-detected') AND atrial fibrillation' AND ('pacemaker' OR Implantable Cardioverter Defibrillator OR Cardiac Resynchronization Therapy Device OR CIED) up to 1 April 2016.

## Inclusion and exclusion criteria

The **articles of interest** were those **describing the association of device-detected subclinical AF and stroke in patients with CIEDs with implanted atrial leads.**

The exclusion criteria were: (i) intermittent monitoring for AF detection; (ii) conference abstracts, editorials, reviews, letters, and case reports; (iii) reviews were excluded but their reference lists hand searched for potential relevant publications; (iv) case series with less than 50 patients.

Where multiple studies described the same population (substudies, follow-up studies), the study with the most comprehensive data was included.

## Study selection and data extraction

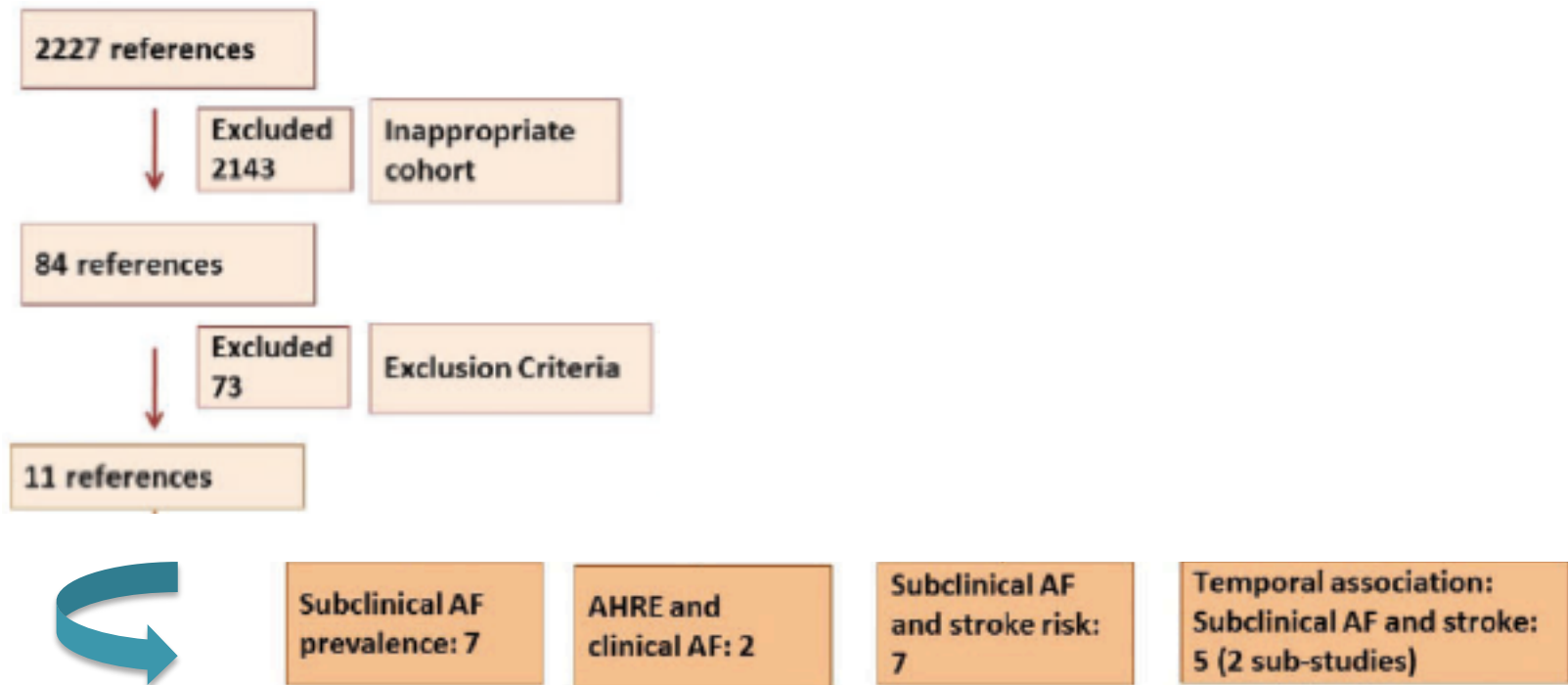
The study selection and data extraction were performed by the authors using a priori determined criteria.

The methodological qualities of the included studies were assessed using the modified Newcastle-Ottawa Scale.

The outcomes of the analysis were defined as: (i) definition of subclinical AF in different studies and cutoff for recognizing subclinical AF; (ii) prevalence of subclinical AF; (iii) association of subclinical and clinical AF; (iv) association of subclinical AF and stroke risk; and (v) temporal relationship of subclinical AF and stroke in patients with CIEDs.

# Results

## Search and synthesis of the literature



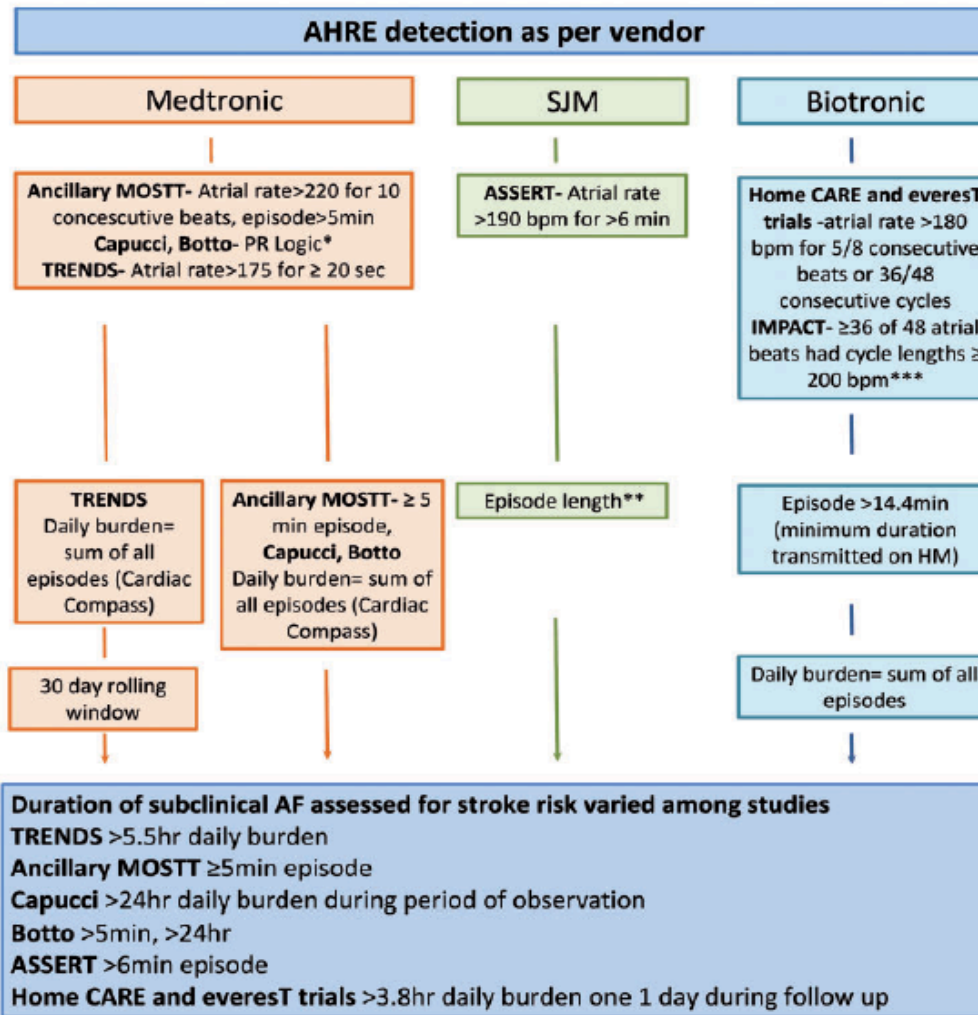
# Criteria and cut-off for detection of subclinical AF

## AHRE detection as per vendor

**Criteria for AHRE**

**Minimum cut-off to recognise subclinical AF**

**Duration of subclinical AF assessed for stroke risk**



Positive predictive value for AF detection

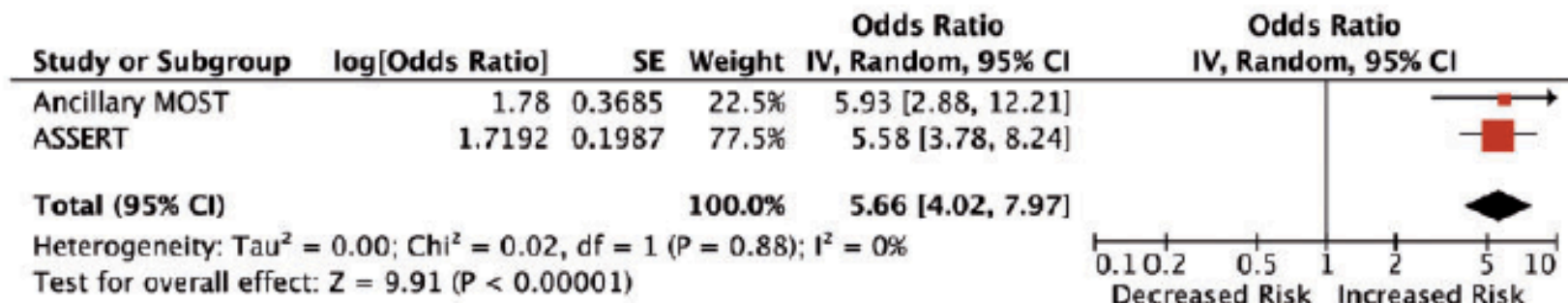
- \* 95.3%
- \*\* 96.7% for episodes >6 hr; 82.7% for episodes >6 min to 6-hr
- \*\*\*91%

From: Subclinical device-detected atrial fibrillation and stroke risk: a systematic review and meta-analysis  
Eur Heart J. 2018;39(16):1407-1415. doi:10.1093/eurheartj/ehx731

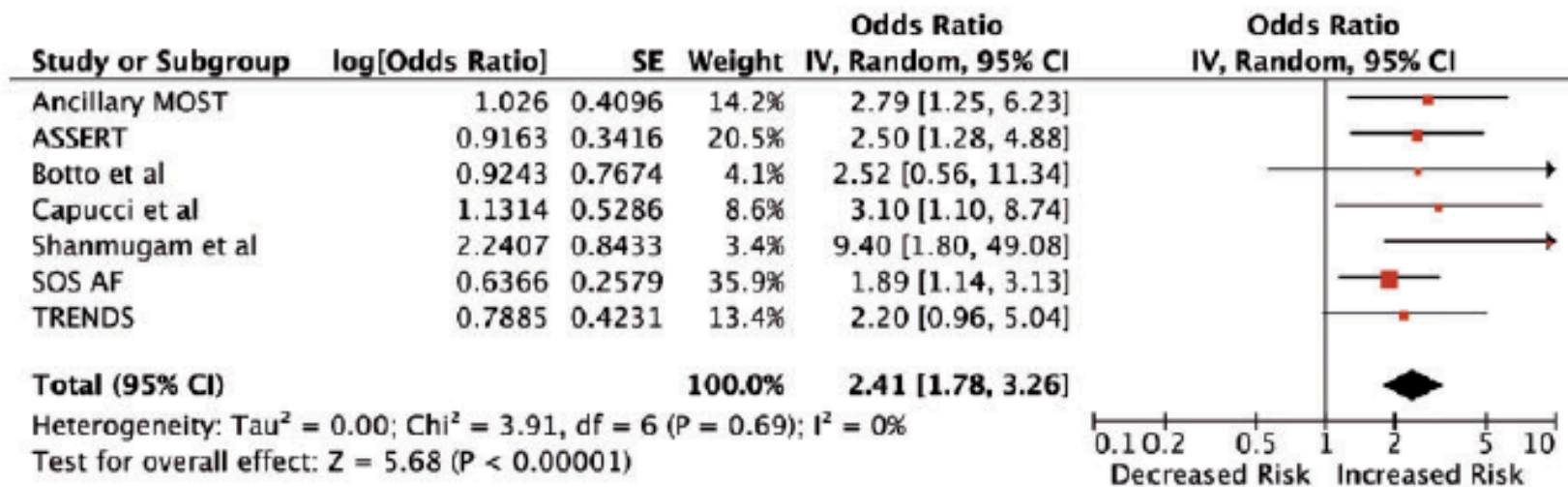
# Study design and definition of subclinical AF in the included studies

| Study                        | Study design                           | Sample size        | Follow up | AF at time of enrollment  | Cut-off for AF/AHRE detection and duration associated with stroke risk  |
|------------------------------|--|--------------------|-----------|---|---|
| Ancillary MOSTT              | Retrospective observational            | 312                | 2.3       | Sinus node dysfunction. Sinus rhythm at randomization                                   | Atrial rate >220 b.p.m. for 10 consecutive beats<br>AHRE $\geq 5$ min <b>episode</b> . Medtronic pacemakers<br>PR logic <sup>b</sup>  |
| Capucci                      | Prospective multi-centre observational | 725                | 1.8       | Bradycardia with dual chamber pacing indication. Previous AF. Permanent AF excluded     | <b>24 h AF</b> (cardiac compass) <b>episode during period of observation</b> . Medtronic pacemakers<br>PR logic <sup>b</sup>  |
| Botto                        | Retrospective observational            | 568                | 1         | Brady-tachy syndrome. Permanent AF excluded   | AHRE $>5$ min <b>on 1 day of year, 24 h</b> (cardiac compass). Medtronic pacemakers   |
| TRENDS                       | Prospective observational              | 2486               | 1.4       | Patients with or without prior PAF. CHADS <sub>2</sub> $\geq 1$ . Permanent AF excluded | Atrial rate >175 b.p.m. for $\geq 20$ s<br>AHRE $\geq 5$ min. <b>Rolling window, day burden &gt;5.5 h AF on 1 day</b> . Medtronic pacemakers  |
| ASSERT                       | Randomized                             | 2580               | 2.5       | Excluded prior AF. Hypertension.  | Atrial rate >190 b.p.m. for >6 min <b>&gt;6 min AF episodes</b> . St Jude Medical pacemakers  |
| Home CARE and everesT trials | Prospective observational              | 560                | 1         | 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.<br><b>3.8 h AF burden on 1 day during follow-up</b> . Biotronik ICD/CRT CIEDs |
| SOS AF                       | Three registries                       | 10016 <sup>c</sup> | 2         | Prior history of paroxysmal or persistent AF included. Permanent AF excluded            | Atrial rate >175 b.p.m. for $\geq 20$ s<br>$\geq 1$ h <b>AF burden on 1 day during follow-up</b>  |
| IMPACT <sup>d</sup>          | Randomized                             | 2718               | 2         | CHADS <sub>2</sub> $\geq 1$ . Only permanent AF excluded                                | $\geq 36$ of 48 atrial beats had cycle lengths $\leq 200$ b.p.m.<br><b>&gt;5.5 h AF burden</b> . Biotronik ICD/CRT CIEDs  |

# Association between subclinical and clinical AF



# Association between subclinical AF and stroke risk



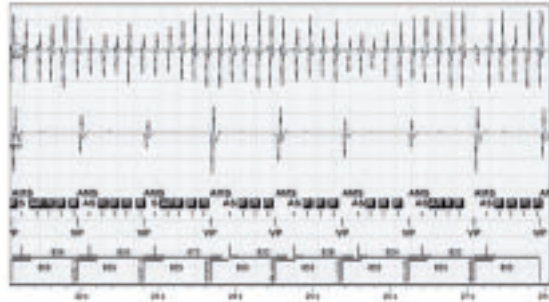
# Temporal association between subclinical AF and stroke

| Studies                      | Total strokes | AHRE absent<br>Strokes without AHRE | AHRE present            |                           |                            |                |   |
|------------------------------|---------------|-------------------------------------|-------------------------|---------------------------|----------------------------|----------------|---|
|                              |               |                                     | Total Strokes with AHRE | AHRE preceding stroke (%) | AHRE at time of stroke (%) |                | AHRE after stroke (%)   |
| Ancillary MOSTT              | 10            | 2                                   | 8                       | —                         | 7 <sup>a</sup> (87)        | 1 (13)         | —   |
| TRENDS                       | 40            | 14                                  | 26                      | 14 (54)                   | 6 (23)                     | 6 (23)         | Temporal analysis performed using 20 s threshold (rather than 5.5 h burden) for AF detection utilized AHRE preceded stroke by a range of 3–642 in the group of patients with AHRE preceding stroke 11 strokes occurred with AHRE in preceding 30 days. These patients had significantly greater daily AF burden (0.87 [0.37–4.28] h/day as compared to those with AHRE >30 days prior to stroke (0.00 [0.00–0.05] h/day) 5/20 received oral anticoagulants  |
| ASSERT                       | 51            | 25                                  | 26                      | 17 (65)                   | 1(4)                       | 8 (31)         | Four strokes occurred with AHRE in preceding 30 days 14 patients with AHRE preceding stroke>30 days had the most recent episode 339 [211–619] 10/18 patients with AHRE preceding strokes had an episode e> 24 h of AHRE preceding the stroke No anticoagulation at baseline. 18% of patients with subclinical AF commenced on oral anticoagulant during study 6/18 with AHRE patients with stroke commenced on oral anticoagulants during study (five prior to stroke) 12% received oral anticoagulation. 7.2% (AHRE group), 8.6% (No AHRE group), 19.6% (Prior Hx AF, AHRE group), 21% (Prior Hx AF, No AHRE group) received oral anticoagulants |
| Home CARE and everesT trials | 11            | 2                                   | 9                       | 4 (45)                    | 3 (33)                     | 2(22)          | Home monitoring guided anticoagulation study Control: 25.2% met protocol specific criteria. 60% anticoagulated Intervention: 25.6% met protocol specific criteria. 72.2% anticoagulated   |
| IMPACT                       | 69            | 40                                  | 29                      | 20 (69)                   | 0 (0)                      | 9 (31)         |   |
| <b>Total</b>                 | <b>181</b>    | <b>83</b>                           | <b>98</b>               | <b>55 (55)</b>            | <b>17 (17)</b>             | <b>26 (27)</b> |   |



# Key-messages

- Subclinical AF is highly prevalent in patients with CIEDs and predicts clinical AF.



**AHRE detected in 13.9% patients annually**

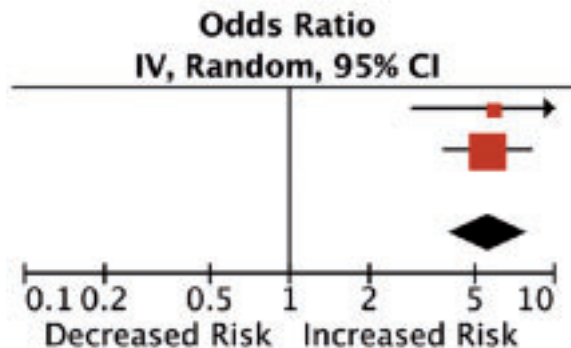
## PPV of AHRE

SJM- 83% >6min - 6 hour

97% >6 hour

Medtronic- 95%

Biotronik- 91%

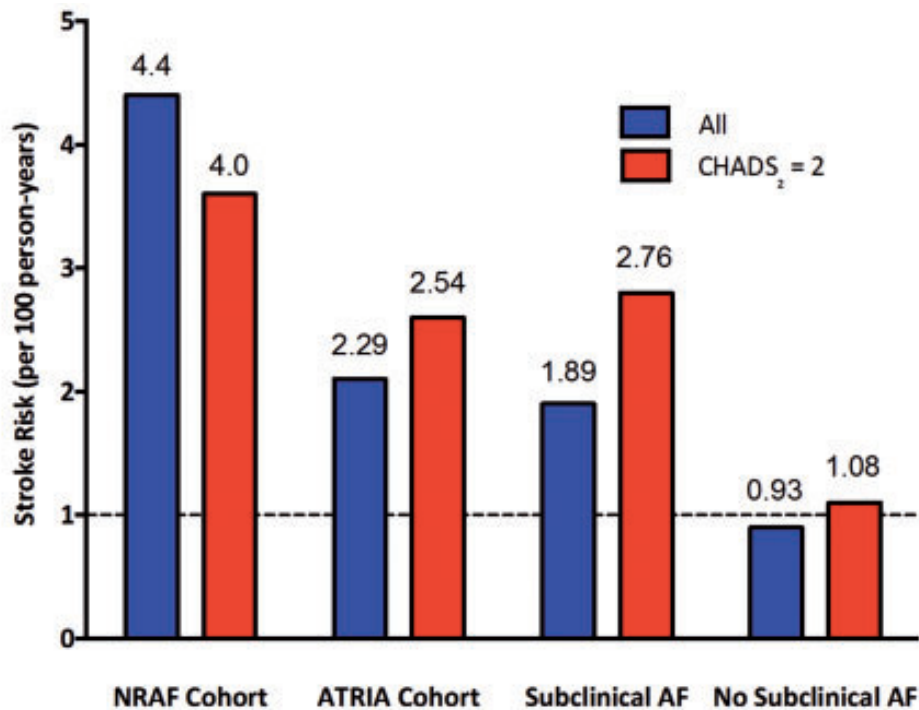


**Patients with AHRE 5.7 fold more like to have clinical AF**

From: Subclinical device-detected atrial fibrillation and stroke risk: a systematic review and meta-analysis  
Eur Heart J. 2018;39(16):1407-1415. doi:10.1093/eurheartj/ehx731

# Key-messages

- Subclinical AF was associated with a 2.4-fold increase in stroke risk. However, the overall absolute annual risk of stroke was 1.89 per 100 person-years.
- For studies that provided CHADS<sub>2</sub> score, the absolute annual stroke risk is higher at 2.76 per 100 person-years for a mean CHADS<sub>2</sub> score of 2.1.



## Subclinical AF and stroke risk



# Key-messages

- Short episodes of subclinical AF (<described cut-off) were uniformly associated with low risk of stroke (0.93 per 100 person-years).
- Although temporal dissociation of subclinical AF and stroke is reported, the studies have certain biases.

## **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)

# Conclusions

- Subclinical AF is frequent in patients with CIEDs and is strongly associated with clinical AF.
- The stroke risk with subclinical AF is low as compared to clinical AF and could potentially represent smaller burden.
- Further research is required to define the role of AF burden in stroke risk.