Diagnosing atrial fibrillation using implantable devices

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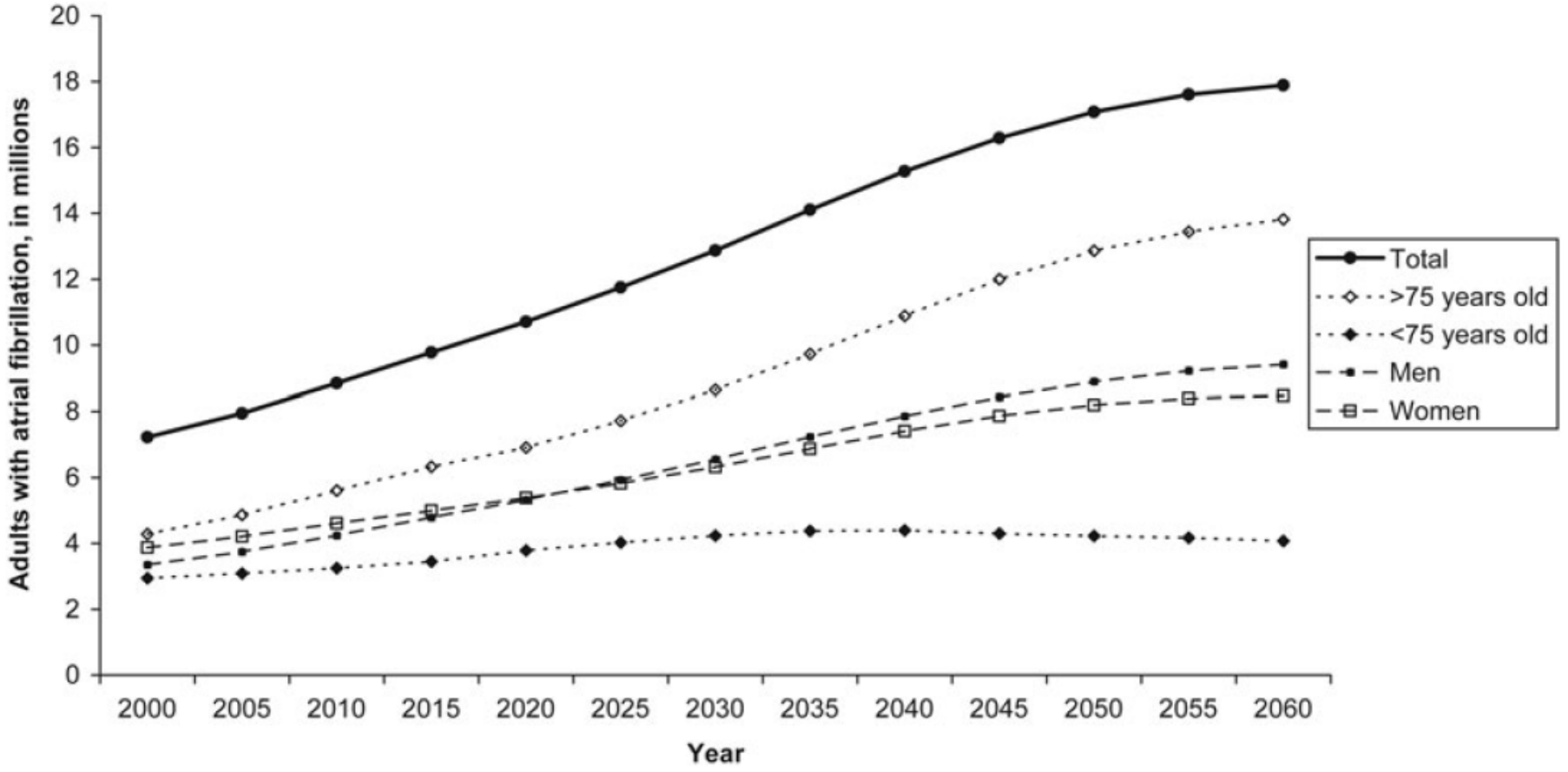
Epidemiology of atrial fibrillation (1)

- AF is the most common arrhythmia (1-2% of general population)
- More than 6 million people in Europe have AF (nearly 3 million in the USA)
- Assuming a world population of 7 billion people there are 100 million people with AF !!
- The number of new patients with AF is expected to double in 2020 (compared with 2000)

Projected number of adults with atrial fibrillation in the EU between 2000 and 2060



Krijthe BP et al. *Eur Heart J* 2013;34:2746-51

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Epidemiology of atrial fibrillation (2)

- A person (aged 40-55 years) has a 25% life-time risk of AF[1]
- AF increases risk of stroke 5-fold independent of other factors[2]
- Patients with AF-related strokes have a 30 day mortality of 25% and a one-year mortality of almost 50%[3,4]
- 30% of AF-related stoke patients remain permanently disabled (higher than non-AF strokes)
- Once a stroke has occurred the risk of subsequent cardio-embolic stroke is increased by a factor 2 – 3

1.Lloyd-Jones DM, et al. *Circulation* 2004;110:1042-6. 2.Wolf PA, et al. *Stroke* 1991;22:983-8. 3.Lin HJ, et al. *Stroke* 1996;27:1760-4. 4.Marini C, et al. *Stroke* 2005;36:1115-9

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Prevalence of asymptomatic atrial fibrillation

- In pacemaker patients (with AF history) asymptomatic AF-episodes are very common:
  - 38% of all AF episodes (Medtronic® AT500 PM)[1]
  - 81% of all AF-episodes (Vitatron® PM)[2]
- Asymptomatic AF is 12-fold more frequent than symptomatic events in patients with paroxysmal AF (5-day Holter)[3]
- Prior to PV isolation, 5% of patients had only asymptomatic AF (7-day Holter) whereas after ablation, 37% of patients had only asymptomatic AF (7-day Holter)[4]
- In symptomatic AF patients only 17-21% of symptoms assumed to be caused by AF are actually related to AF episodes (monitored by PM)[2,5]

1.Israel CW, et al. *J Am Coll Cardiol* 2004;43(1):47-52. 2.Quirino G, et al. *PACE* 2009;32:91-8. 3.Page RL, et al. *Circulation* 1994;89:224-7. 4.Hindricks G, et al. *Circulation* 2005;112:307-13. 5.Strickberger SA, et al. *Heart Rhythm* 2005;2:125-31

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Does silent AF matter?

- 4,618 residents from Olmsted County with a diagnosis of first AF between 1980 and 2000 (mean age 74 ± 14 years, 49% men)
- 1152 (25%) asymptomatic at AF diagnosis
- Three times more likely to have sustained ischemic stroke preceding their AF diagnosis

Tsang TS et al. *Can J Cardiol* 2011;27 (5, Suppl):S122

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Is it appropriate to screen for asymptomatic, i.e. subclinical, atrial fibrillation?

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with the recognised disease.
3. Facilities for diagnosis and treatments should be available.
4. There should be a recognisable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed upon policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a 'once and for all' project.

- Screening for subclinical AF meets many of the WHO criteria
  - Important health problem
  - Detectable asymptomatic period
  - Effective screening techniques exist
  - Socially acceptable treatments to mitigate its risk

Wilson JMG & Jungner G. WHO Public Health Papers No. 34 (1968)

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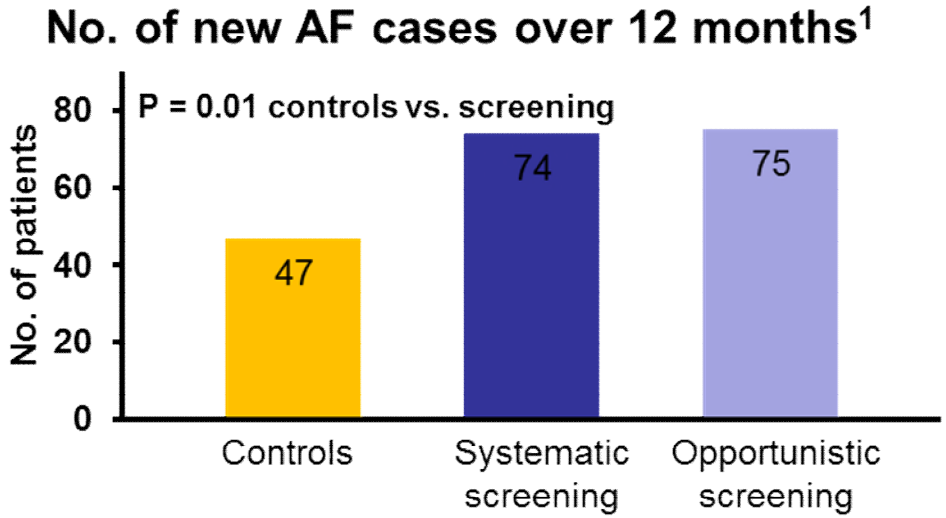
Opportunistic screening for the detection of AF in patients > 65 years of age with standard ECG



ESC guidelines on AF 2012 focused update[2]

Recommendations	Class[a]	Level [b]
Opportunistic screening for AF in patients ≥65 years of age using pulse-taking followed by an ECG is recommended to allow timely detection of AF.	I	B

1.Fitzmaurice DA et al. *BMJ* 2007;335:383
2.Camm AJ et al. *Eur Heart J* 2012;33:2719-47

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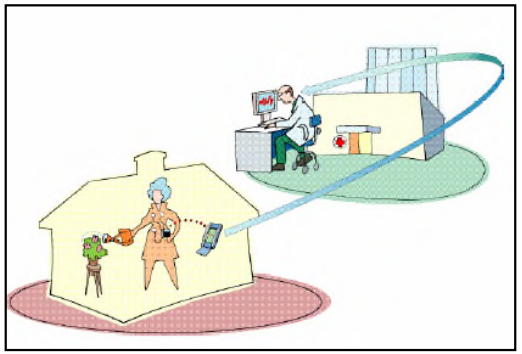
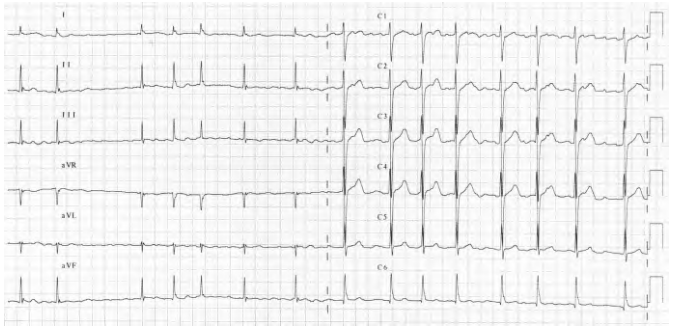
Screening tools for the detection of subclinical atrial fibrillation (SCAF)

MCOT/Telemetry



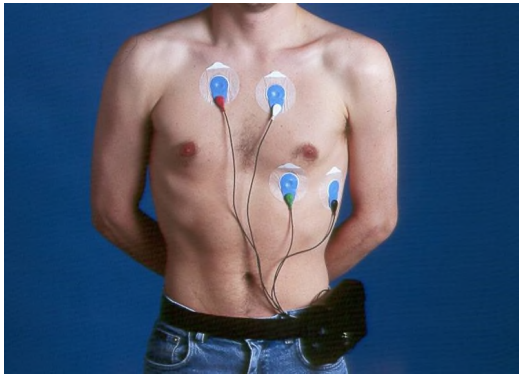
1 – 7 days

12-lead ECG



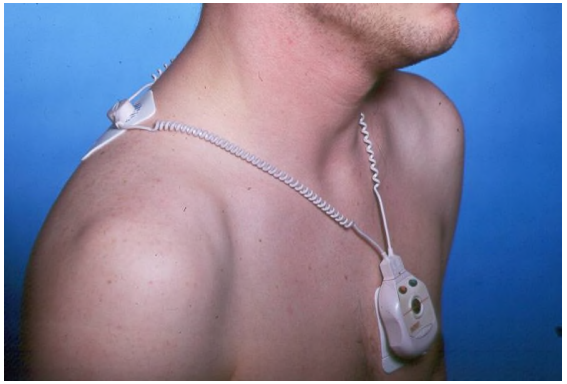
10 seconds

Holter monitoring



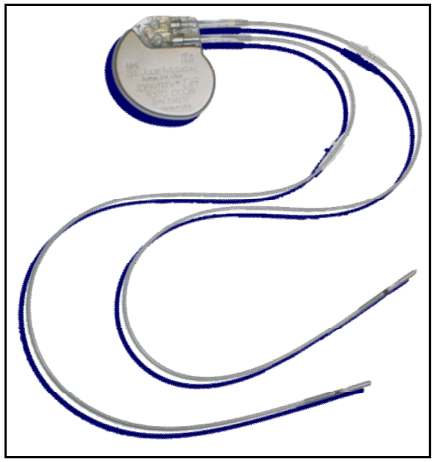
1 – 7 days

External loop recorder



7 – 30 days

Pacemaker/ICD



8 - 10 years

Implantable loop recorder

36 months

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Non-invasive devices for the detection of SCAF

- Holter monitoring = gold standard
- Event monitors (continuous or intermittent)
- Handheld, single lead devices
- Blood pressure monitors
- Smartphone devices

- Intermittent monitoring insufficient to detect infrequent arrhythmias[1-3]

1.Ziegler PD, et al. *Heart Rhythm* 2006;3:1445-52. 2.Botto GL, et al. *J Cardiovasc Electrophysiol* 2009;20:241-8. 3.Hanke T, et al. *Circulation* 2009;120(suppl 1):S177-84

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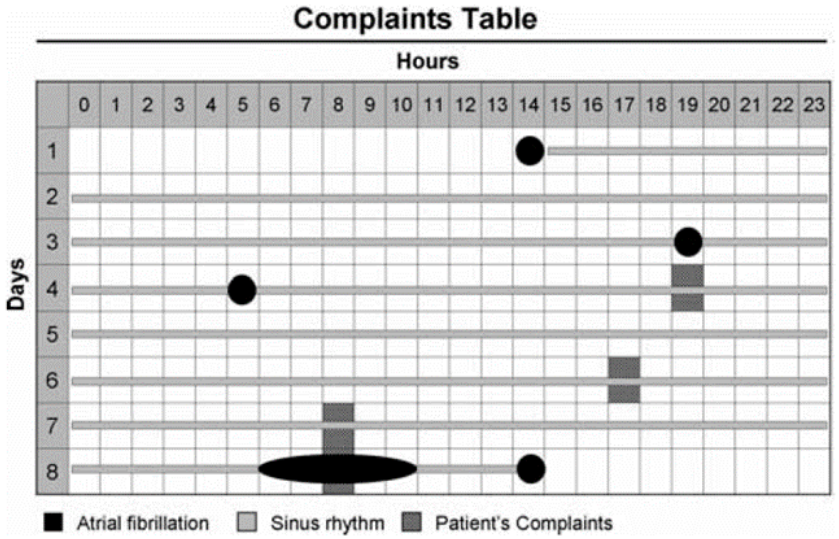
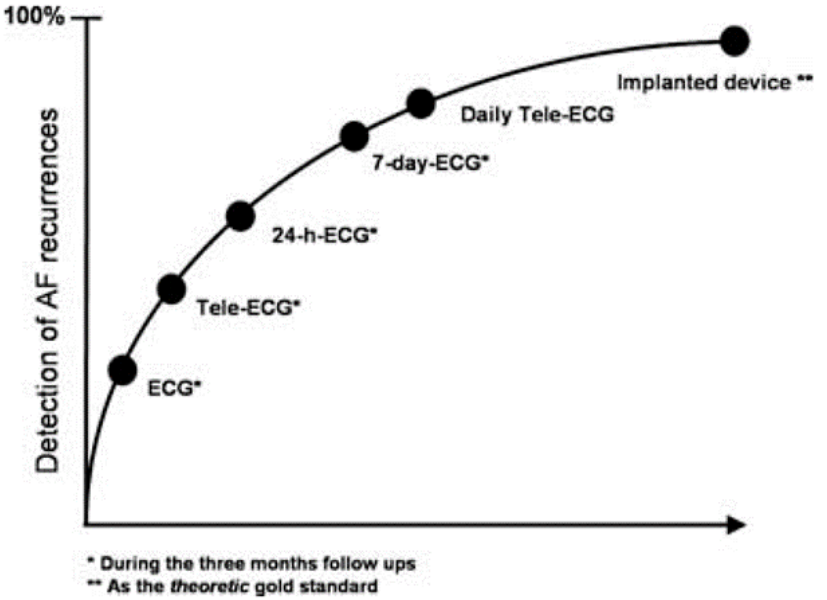
Detection af atrial fibrillation:
”The more we look, the more we see.”

- Weak correlation between AF episodes and symptoms
- Several studies have shown, that more intensive monitoring detects more AF after ablation





Arya A et al. *PACE* 2007;30:458-62

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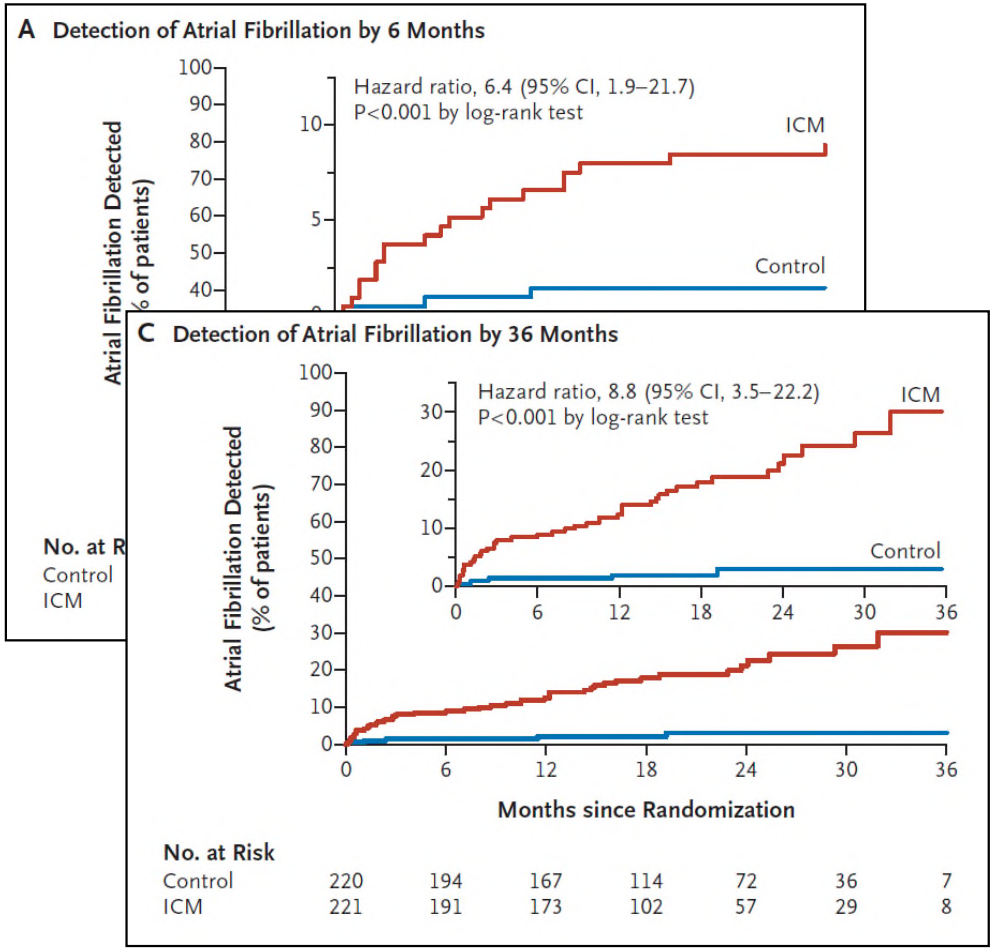
Implantable cardiac monitor (ICM) for detection of SCAF in stroke patients – CRYSTAL-AF Trial



- 441 pts. randomised to ICM or usual care, mean age 61.5 yrs, 36.5% women
- 91% stroke, 9% TIA as index event
- ICM implantation (Reveal® XT) up to 90 days from index stroke
- 1.° EP: time to 1st AF-episode at 6 months (2 min with ICM, 30 sec with usual care)
- 8.9% AF with ICM vs. 1.4% with usual care at 6 months

Sanna T, et al. *N Engl J Med* 2014;370:2478-86

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Atrial high rate episodes (AHREs) in patients with PM/ICD

- Detected in approx. half of patients with PM/ICD[1,2]
- Episode of AT/AF with atrial rate > 175 – 190 bpm
- Definition of AHRE varies between trials
- Patient populations are selected, as they have an indication for pacemaker/ICD, which might confound the prevalence of AF
- Clear association between device-detected AHREs and poor clinical outcome

1.Glotzer TV, et al. *Circulation* 2003;107:1614-9
2.Glotzer TV, et al. *Circ Arrhythm Electrophysiol* 2009;2:474-80

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Device-detected AHREs and clinical outcomes

- MOST Trial: at least 1 AHRE ≥ 5 min and > 220 bpm associated with 2.8-fold increased risk of stroke or death and 5.9-fold increased risk of developing permanent AF[1]
- TRENDS Study: daily burden of AHRE > 5.5 h associated with 2.4-fold increased risk of TE[2]
- Patients with HF and CRT device: AHRE > 180 bpm for > 3.8 h/day associated with 9-fold increase in TE events[3]
- ASSERT Trial: in patients w/o prior AF an AHRE of ≥ 6 min and > 190 bpm associated with 2.5-fold increased risk of stroke and SE[4]
- SOS AF (pooled analysis): AHRE > 1 h associated with 2.1-fold increased risk of ischemic stroke[5]

1.Glotzer TV, et al. *Circulation* 2003;107:1614-9. 2.Glotzer TV, et al. *Circ Arrhythm Electrophysiol* 2009;2:474-80. 3.Shanmugam N, et al. *Europace* 2012;14:230-7. 4.Healey JS, et al. *N Engl J Med* 2012;366:120-9. 5.Boriani G, et al. *Eur Heart J* 2014;35:508-16

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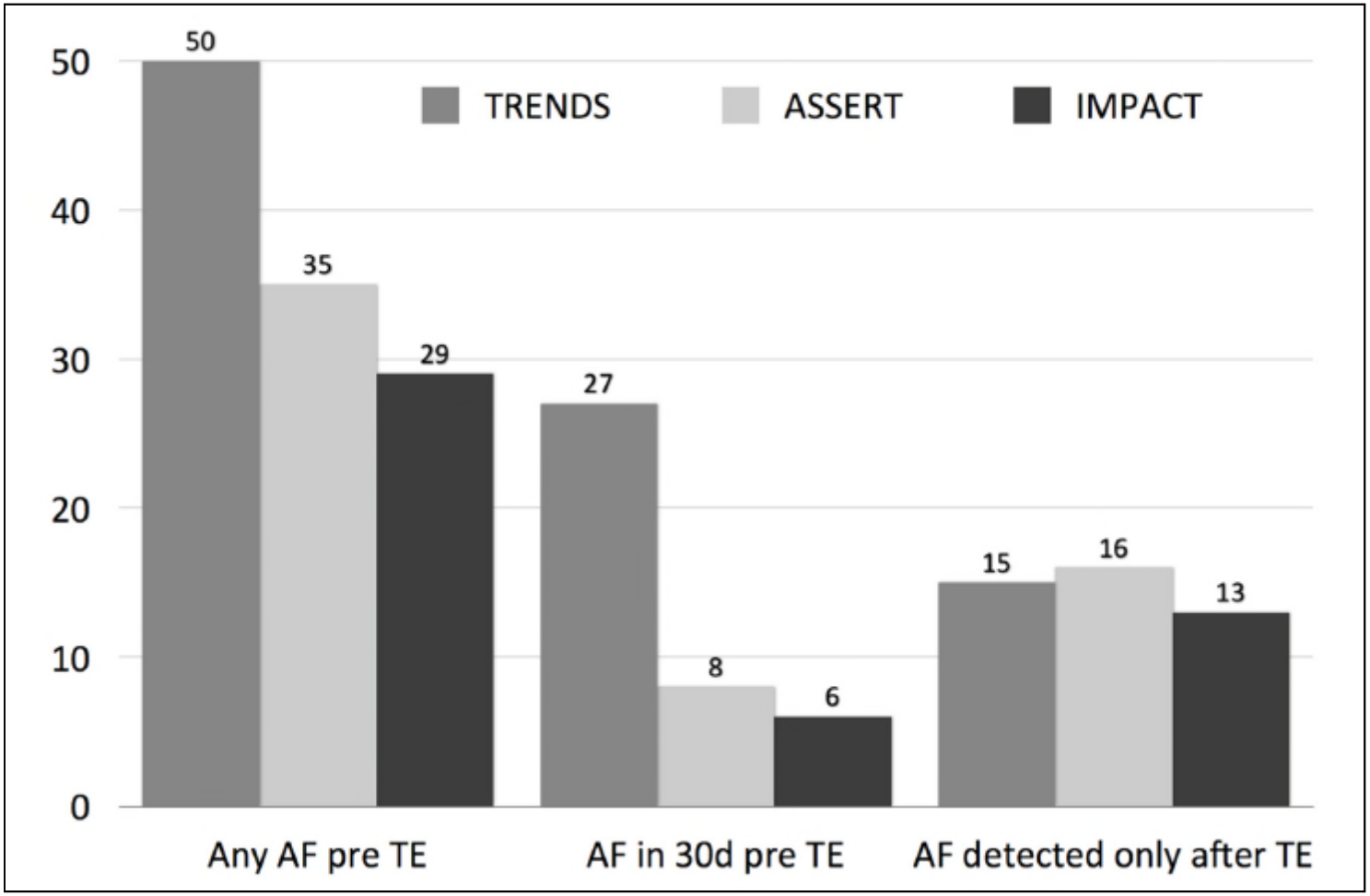
Weak temporal association between AHREs and subsequent stroke



Andrade JG, et al. *Front Physiol* 2015;6:100.doi:10.3389/fphys.2015.00100

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Who should receive an ICM for detection of SCAF? – What do guidelines tell us?

- No clear recommendations from guidelines:
  - **ESC**: 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 (IB)[1]. It is recommended to interrogate PMs and ICDs on a regular basis for AHRE. Patients with AHRE should undergo further ECG monitoring to document AF before initiating AF therapy (IB)[1]. 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 (IIaB)[1].
  - **CCS**: For patients being investigated for an acute embolic ischemic stroke or TIA, we recommend at least 24 hours of ECG monitoring to identify paroxysmal AF in potential candidates for OAC therapy (Strong Recommendation, Moderate-Quality Evidence).[2]
  - **CCS**: For selected older patients with an acute, nonlacunar, embolic stroke of undetermined source for which AF is suspected but unproven, we suggest additional ambulatory monitoring (beyond 24 hours) for AF detection, where available, if it is likely that OAC therapy would be prescribed if prolonged AF is detected (Conditional Recommendation, Moderate-Quality Evidence)[2]
  - **AHA/ACC/HRS**: Prolonged or frequent monitoring may be necessary to reveal episodes of asymptomatic AF.[3]
- **EHRA Position Paper on ILR**: The pre-test selection of the patients influences the subsequent findings. Include patients with a high likelihood of arrhythmic events.[4]

1.Kirchhof P, et al. *Eur Heart J* 2016;doi:10.1093/eurheartj/ehw210. 2.Verma A, et al. *Can J Cardiol* 2014;30:1114-30. 3.January CT, et al. *Circulation* 2014;130;e199-e267. 4.Brignole M, et al. *Europace* 2009;11:671-87

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Who should receive an ICM for detection of SCAF?

- Patients with cryptogenic stroke (?)
- Patients at high risk for developing AF?
- Patients at high risk for stroke/SE?
- Patients with advanced age?
- Risk-model based screening to identify high-risk subgroups

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Ongoing trials investigating the diagnosis of SCAF

	Population	Intervention	Primary outcomes
REVEAL-AF[1]	CHADS ≥3, or ≥2 + CAD, CKD, OSA or COPD *No history of AF*	Insertion of ILR (Medtronic Reveal® XT or LinQ)	AF episode >6 min, thromboembolism
ASSERT-II[2]	Age ≥65 + CHA2DS2-VASc ≥2 + LA enlargement or elevated p-BNP *No history of AF*	Insertion of ILR (St. Jude Medical Confirm® 2102)	AF episode >5 min, thromboembolism

Studies will further understanding of risk factors for subclinical AF, ICM for detection of AF, temporal relationship between AF episode and stroke

1.Reiffel J, et al. *Am Heart J* 2014;167:22-7
2.Healey J. Prevalence of Sub-Clinical Atrial Fibrillation Using an Implantable Cardiac Monitor (ASSERT-II). ClinicalTrials.gov identifier: NCT01694394. (Accessed 24 Apr 2016)

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Should we treat SCAF with OAC?

- Subclinical, *permanent* AF detected on routine device interrogation or after stroke → treat with OAC based on clinical risk factors
- Current evidence does not offer specific treatment recommendations for subclinical, *paroxysmal* AF (PAF)
- Duration and frequency of subclinical PAF poorly defined
- Burden of subclinical PAF necessary to warrant OAC treatment unclear and not fully understood
- Several ongoing studies to establish further evidence of treatment of PAF

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Ongoing trials investigating the efficacy/safety of OAC treatment of SCAF

	Population	Intervention	Primary outcomes
ARTESiA[1]	CHA2DS2-VASc ≥4 with at least a single AHRE ≥175 bpm lasting ≥6 min detected by ILR or intracardiac device *No history or ECG evidence of clinical AF*	Randomised to either ASA 81 mg OD (control) or apixaban 5 mg b.i.d. (intervention)	Incidence of stroke and major bleeding events
STROKESTOP[2]	All persons aged 75 and 76 years in two Swedish provinces *No history of AF*	Twice-daily ECG screening + OAC treatment if AF detected (single episode duration >30 s, or 2 or more episodes >10 s)	Incidence of stroke and major bleeding events
NOAH-AFNET 6[3]	CHA2DS2-VASc ≥2 with at least a single AHRE ≥180 lasting ≥6 min detected by intracardiac device *No history of AF*	Randomised to either ASA 100 mg/placebo OD (control) or edoxaban 60 mg (intervention)	Incidence of stroke, SE, CV death and major bleeding events

1.Healey J. Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA). ClinicalTrials.gov Identifier NCT01938248 (accessed 24 April 2016). 2.Friberg L, et al. *Europace* 2013;15:135-40. 3.Kirchhof P. Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes (NOAH). ClinicalTrials.gov Identifier NCT02618577 (accessed 24 Apr 2016)

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The LOOP Study

- **Population**:
  - Age >70 years + diabetes mellitus, hypertension, heart failure or previous stroke. *No history or ECG evidence of clinical AF*.
- **Intervention**:
  - Randomised to ICM (Medtronic Reveal® LinQ) or control in a 1 : 3 ratio
  - OAC treatment, if AF detected (single episode >6 min), in the intervention group and on the discretion of the patients' GP, if AF detected in the control group
- **Primary outcomes**:
  - Incidence of stroke/SE and major bleeding events
- **Impact on current knowledge**:
  - Will be the first trial investigating population-based screening of high-risk pts. for subclinical AF using an ICM and the effect on stroke prevention.

Svendsen JH. Atrial Fibrillation Detected by Continuous ECG Monitoring (LOOP). ClinicalTrials.gov Identifier: NCT02036450 (accessed 24 Apr 2016)

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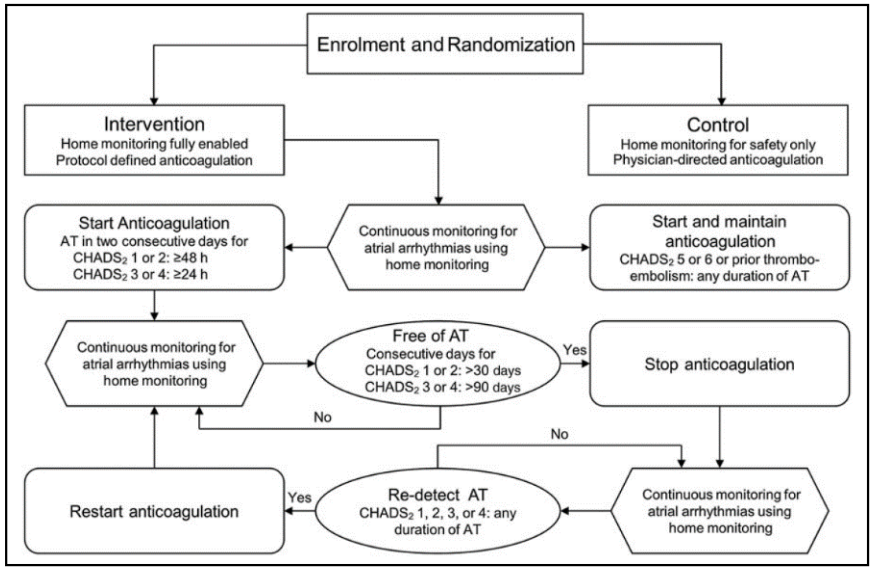
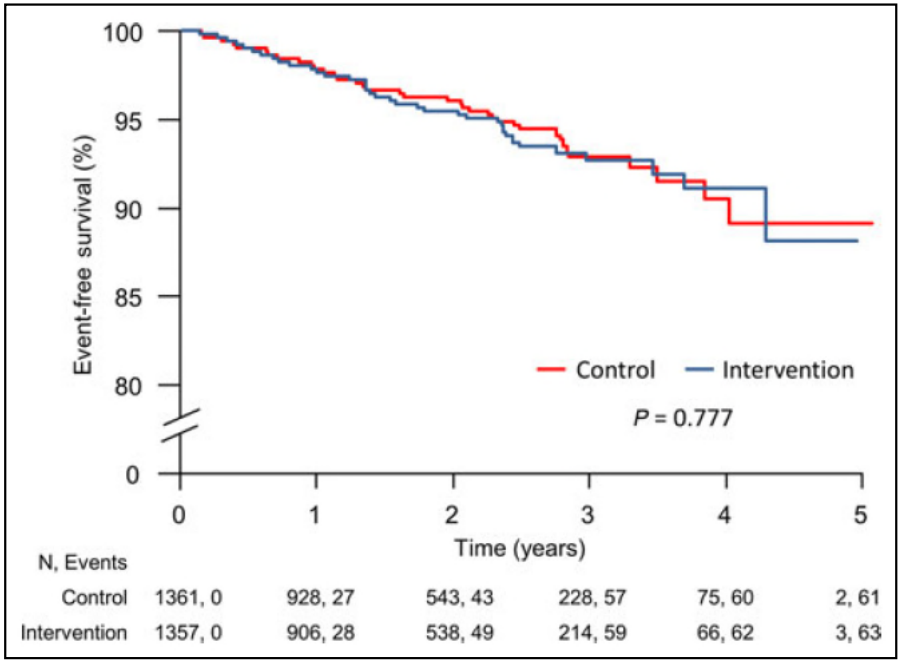
OAC treatment guided by AF burden on remote monitoring: IMPACT Trial

Study algorithm



Primary events (first stroke, SE or major bleeding event)



- 2718 pts. with dual chamber ICD or CRT-D, aged 64 yrs., 26% women
- Median time to initiate OAC 3 days (intervention) vs. 54 days (control), P < 0.001)
- No difference between groups regarding major bleeding and TE
- No temporal relationship between AT and stroke, although AT burden associated with TE

Martin DT, et al. *Eur Heart J* 2015;36:1660-8

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Ongoing trials investigating cessation and/or reinitiation of OAC based on AF burden

	Population	Intervention	Primary outcomes	Impact on current knowledge
REACT COM[1]	CHADS2 of 1 or 2, recently implanted Medtronic Reveal®XT No permAF or recent AF episode >1 h	Rapid initiation of 30 days of NOAC therapy following a remotely detected AF episode	OAC utilisation, incidence of stroke, death and major bleeding events	Will demonstrate safety/efficacy of treating PAF or permAF with NOAC only during times temporally related to AF episodes
TACTIC-AF[2]	History of PAF or persAF currently taking NOAC + intracardiac device (SJM) No permanent AF	Withdrawal/re-initiation of NOAC based on remote monitoring of atrial activity (AT/AF)	Incidence of stroke, death, cardiovascular complictions	Will demonstrate safety of OAC cessation in pts with low AF burden, temporal relationship between stroke and AF, effect of weekly remote device interrogation

1.Chicos AB. Rhythm Evaluation for AntiCoagulaTion With COntinuous Monitoring (REACT COM). ClinicalTrials.gov Identifier: NCT01706146 accessed 24 Apr 2016). 2.Zimetbaum P. Safety Study on Stopping Anticoagulation Medication in Patients With a History of Atrial Fibrillation (TACTIC AF). ClinicalTrials.gov Identifier: NCT01650298 (accessed 24 Apr 2016).

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Conclusions

- Who should we implant an ICM?
  - Patients with cryptogenic stroke and pts. at high risk for AF/thromboembolic events are likely appropriate. Risk-model based screening might identify a high-risk subgroup in a much larger population.
  - REVEAL-AF, ASSERT-II and LOOP may answer this question.
- Should SCAF be treated with OAC?
  - The burden of SCAF needed to increase stroke risk is not well understood. Thus, the risk-benefit ratio of OAC treatment is difficult to calculate.
  - ARTESiA and NOAH may answer this question.
- Will screening for SCAF reduce stroke?
  - LOOP and STROKESTOP may answer this question.

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