University of Antwerp

Antwerp, Belgium

Prof. Dr. Hein Heidbuchel

AF Screening and Wearable Devices

CASSA SYMPOSIUM 2022 | Virtual Series
March 5th 2022

University of Antwerp

Disclosures

Scientific Advisory Board Member and Speaker for Abbott , Biotronik, Daiichi-Sankyo, Pfizer-BMS, Medscape, and Springer Healthcare Ltd.

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National Coordinator of RE-LY (Boehringer Ingelheim), ROCKET-AF (Bayer, Johnson&Johnson), ENGAGE-AF, ENSURE-AF and ELIMINATE-AF (Daiichi-Sankyo), EMANATE (Bristol-Myers Squibb/Pfizer), ICARIOS & PALLAS (Sanofi-Aventis), EAST and NOAH-AF (AFNet/EHRA), OCEAN (Ottawa Heart Institute)

Prof. Dr. H. Heidbüchel

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ESC AF Guidelines 2020
Screening recommendations

Recommendation	Class[a]	Level[b]
Opportunistic screening for AF by pulse taking or ECG rhythm strip is recommended in patients ≥65 years of age. [188,211,223,225]	I	B
It is recommended to interrogate pacemakers and implantable cardioverter defibrillators on a regular basis for AHRE.[c224,226]	I	B
Systematic ECG screening should be considered to detect AF in individuals aged ≥75 years, or those at high risk of stroke.[212,224,227]	IIa	B

When screening for AF it is recommended that:[217,218]
- The individuals undergoing screening are informed about the significance and treatment implications of detecting AF.
- A structured referral platform is organized for screen-positive cases for further physician-led clinical evaluation to confirm the diagnosis of AF and provide optimal management of patients with confirmed AF.
- Definite diagnosis of AF in screen-positive cases is established only after physician reviews the single-lead ECG recording of ≥30 s or 12-lead ECG and confirms that it shows AF.

I	B

ESC Guidelines for Atrial Fibrillation, Hindricks, Potpara et al., Eur Heart J 2020

Many unknows about AF screening...

- Minimum duration of silent AF episodes associated with significant risk of stroke

Device-detected subclinical AF in ASSERT

2580 pacemaker or ICD patients, >65y, with hypertension, without prior AF
Time-dependent risk of stroke related to longest single episode of AF recorded
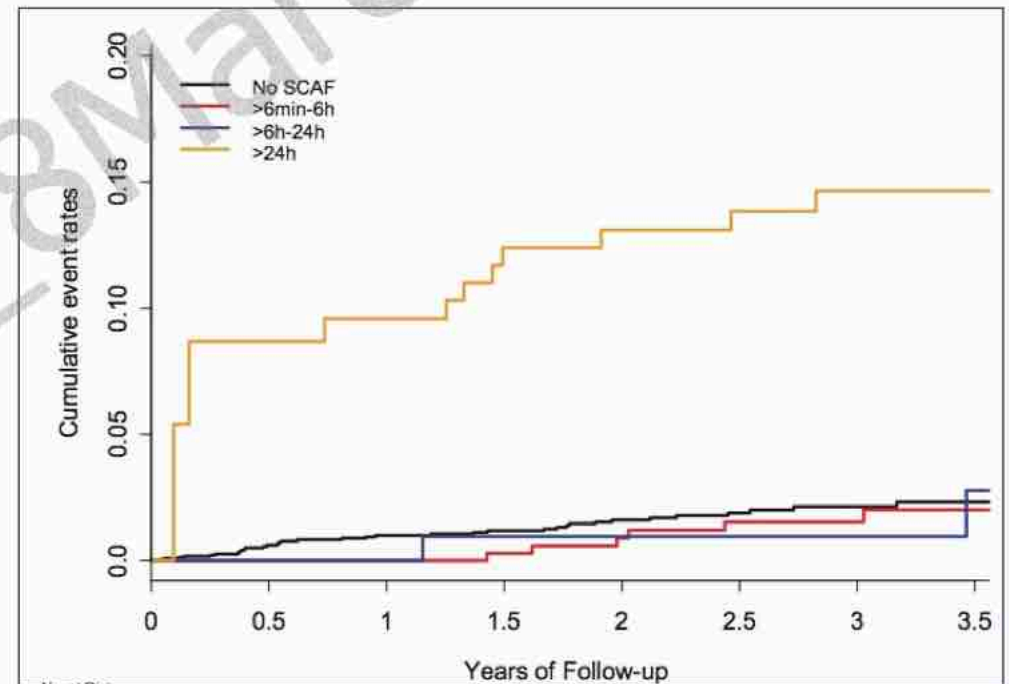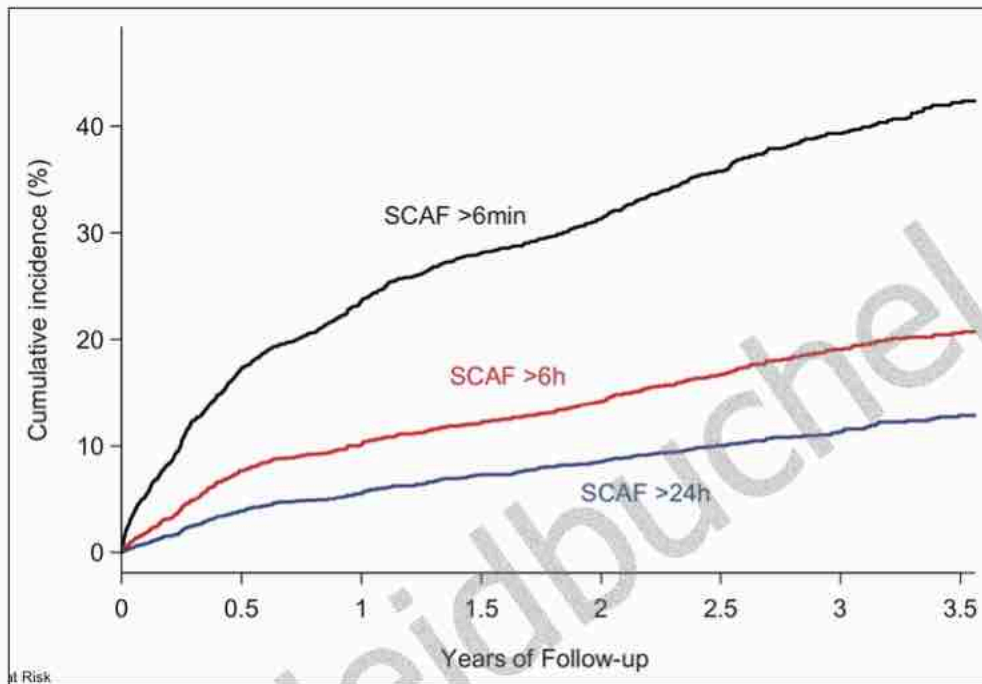
Van Gelder, Healey, et al., Eur Heart J 2017

Silent AF
Proposed clinical decision making

CHA$_2$DS$_2$-VASc score	Duration of AHRE	Recommendation
≥2	>5.5 h (lower duration if multiple stroke risk factors are present)*	♥ (green)
1 (male) or 2 (female)	>5.5 h*	♥ (yellow)

Gorenek et al (on behalf of EHRA), Europace 2017

		Risk of stroke (reassess regularly)		
		Low risk CHA$_2$DS$_2$-VASc = 0 (men) CHA$_2$DS$_2$-VASc = 1 (women)	**Intermediate risk** CHA$_2$DS$_2$-VASc = 1 (men) CHA$_2$DS$_2$-VASc = 2 (women)	**High risk** CHA$_2$DS$_2$-VASc ≥2 (men) CHA$_2$DS$_2$-VASc ≥3 (women)
Risk of clinical AF (reassess regularly)	Short, rare AHREs	An 'innocent bystander'	An 'innocent bystander'	Observe for high AHRE burden or AF development
	Short, frequent AHREs (high daily burden)	Observe for AF development	Observe for AF development	• Close follow-up for AF development • Enrolment in clinical trials‡ • ? Consider OAC in selected patients§
	Long AHREs (>24 h)	Observe for AF development	Observe for AF development	• Close follow-up for AF development • Enrolment in clinical trials‡ • ? Consider OAC in selected patients§
	Long, frequent AHREs (>24 h), high monthly burden	Observe for AF development	• Observe for AF development • Enrolment in observational studies or clinical trials • ?? Consider OAC use in highly selected patients* at low risk of bleeding	• Close follow-up for AF development • Enrolment in clinical trials‡ • ? Consider OAC in selected patients with prior stroke and/or age ≥75 years, or ≥3 CHA$_2$DS$_2$-VASc risk factors, with acceptable bleeding risk

Freedman et al, Nature Reviews 2015

Many unknowns about AF screening...
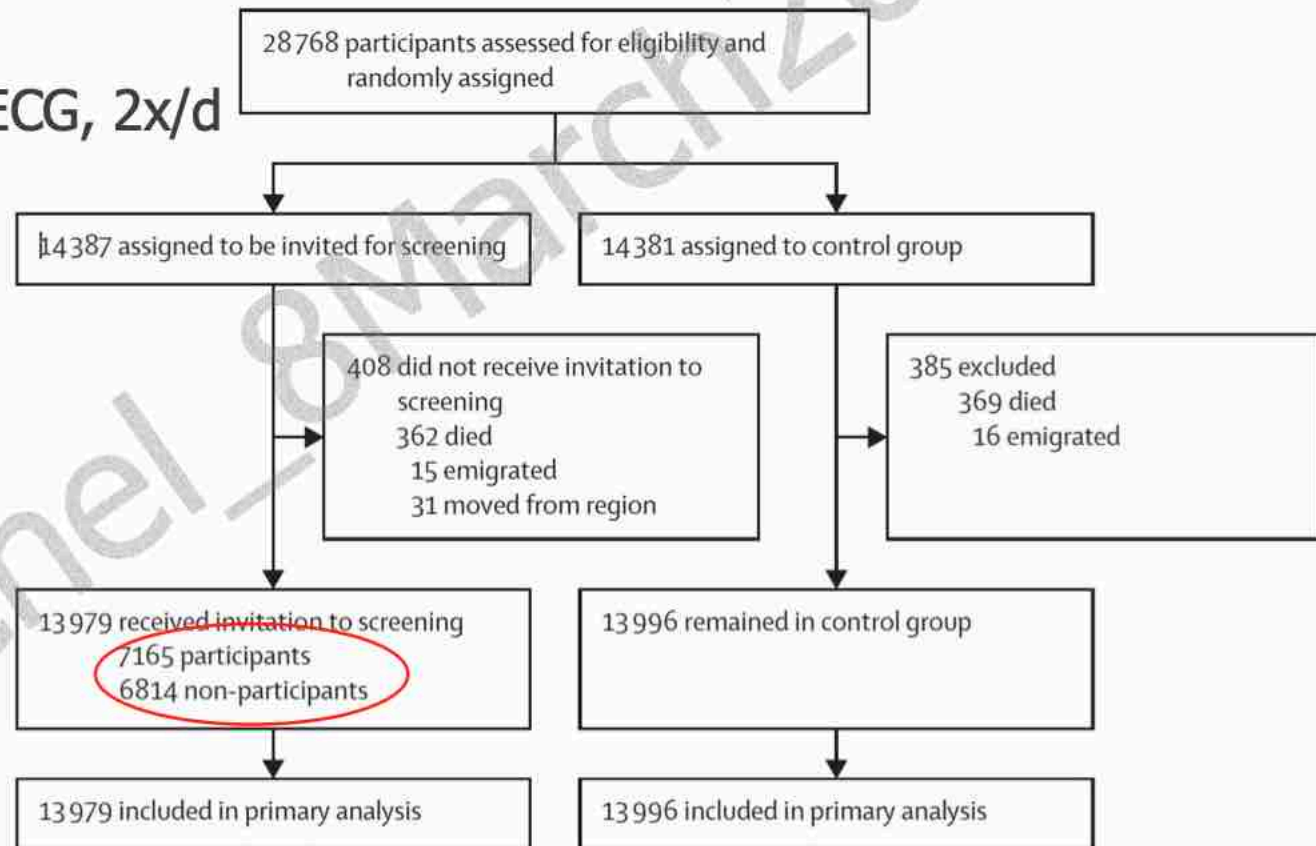
- Minimum duration of silent AF episodes associated with significant risk of stroke

- Will anticoagulation after screen-detected AF reduce stroke risk?

STROKESTOP
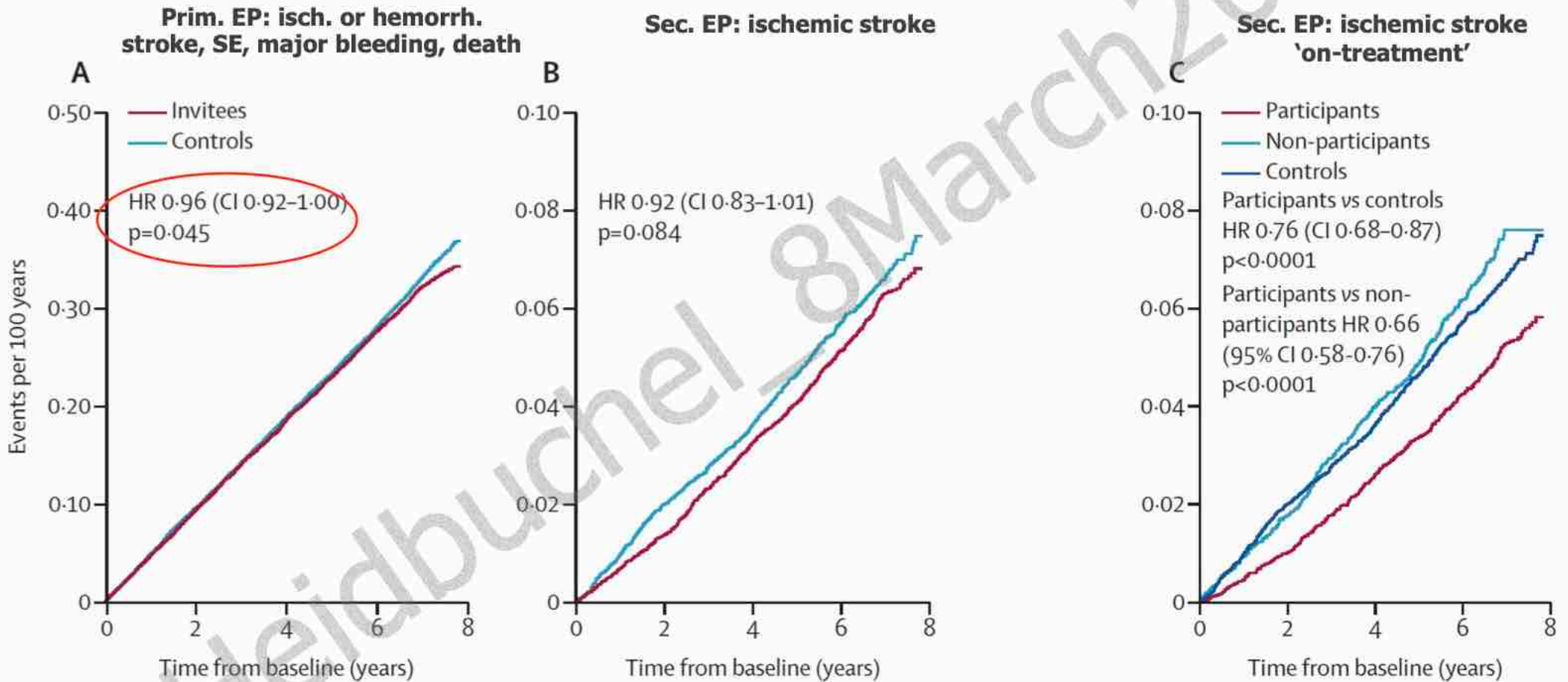## All 75-76 y/o individuals Stockholm region

- Screening vs. no-screening
- Screening = 14d, handheld ECG, 2x/d
  - 1L, Zenicor II, 2x/d
  - AF = 30 sec, or 2x 1—29 sec
- OAC if AF
- Follow-up 6.9 years

```
28768 participants assessed for eligibility and
randomly assigned
```

```
14387 assigned to be invited for screening
```

```
14381 assigned to control group
```

```
408 did not receive invitation to
screening
362 died
    15 emigrated
    31 moved from region
```

```
385 excluded
369 died
    16 emigrated
```

```
13979 received invitation to screening
7165 participants
6814 non-participants
```

```
13996 remained in control group
```

```
13979 included in primary analysis
```

```
13996 included in primary analysis
```

Presented at EHRA 2021 congress; Svennberg et al. Lancet 2021

STROKESTOP
All 75-76 y/o individuals Stockholm region

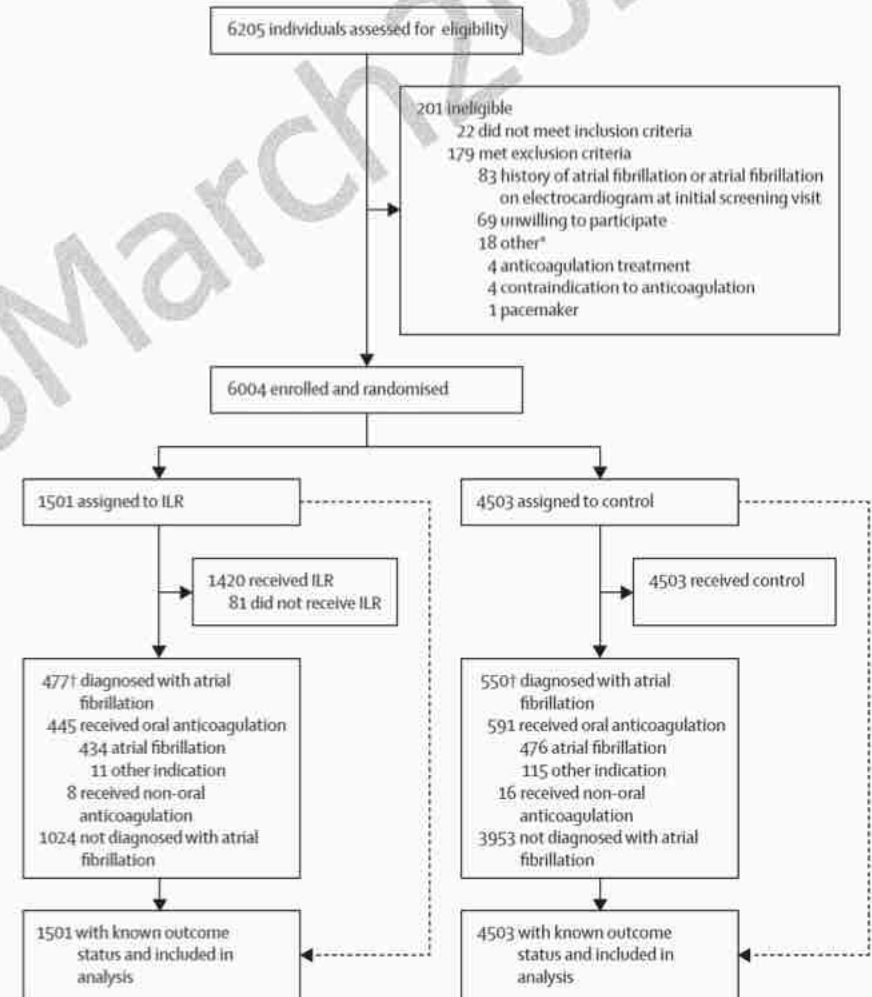**A** — Prim. EP: isch. or hemorrh. stroke, SE, major bleeding, death

- Invitees
- Controls

HR 0.96 (CI 0.92–1.00) p=0.045

Events per 100 years / Time from baseline (years)

B — Sec. EP: ischemic stroke

HR 0.92 (CI 0.83–1.01) p=0.084

Time from baseline (years)

C — Sec. EP: ischemic stroke 'on-treatment'

- Participants
- Non-participants
- Controls

Participants vs controls HR 0.76 (CI 0.68–0.87) p<0.0001

Participants vs non-participants HR 0.66 (95% CI 0.58-0.76) p<0.0001

Time from baseline (years)

Presented at EHRA 2021 congress; Svennberg et al. Lancet 2021

LOOP
6205 individuals, 70-90y, ≥1 extra stroke risk factor
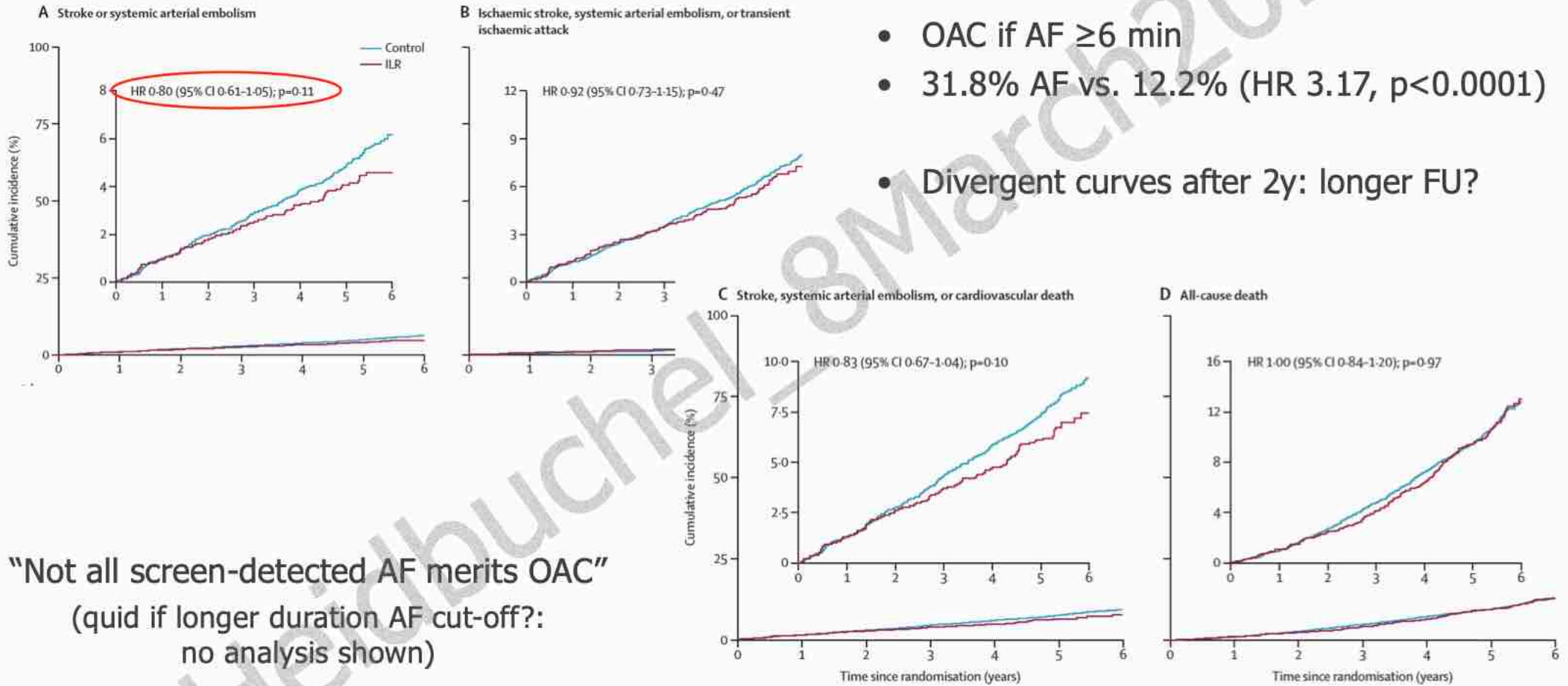
- 1501 (25%) ILR
- Avg. age 74.7 y
- Follow-up 64.5 months
- OAC if AF ≥6 min

Svendsen et al, Lancet 2021

6205 individuals assessed for eligibility

201 ineligible
  22 did not meet inclusion criteria
  179 met exclusion criteria
    83 history of atrial fibrillation or atrial fibrillation on electrocardiogram at initial screening visit
    69 unwilling to participate
    18 other*
    4 anticoagulation treatment
    4 contraindication to anticoagulation
    1 pacemaker

6004 enrolled and randomised

1501 assigned to ILR

1420 received ILR
81 did not receive ILR

477† diagnosed with atrial fibrillation
  445 received oral anticoagulation
    434 atrial fibrillation
    11 other indication
  8 received non-oral anticoagulation
1024 not diagnosed with atrial fibrillation

1501 with known outcome status and included in analysis

4503 assigned to control

4503 received control

550† diagnosed with atrial fibrillation
  591 received oral anticoagulation
    476 atrial fibrillation
    115 other indication
  16 received non-oral anticoagulation
3953 not diagnosed with atrial fibrillation

4503 with known outcome status and included in analysis

LOOP
6205 individuals, 70-90y, ≥1 extra stroke risk factor

A Stroke or systemic arterial embolism

HR 0·80 (95% CI 0·61–1·05); p=0·11

Control
ILR

B Ischaemic stroke, systemic arterial embolism, or transient ischaemic attack

HR 0·92 (95% CI 0·73–1·15); p=0·47

- OAC if AF ≥6 min

- 31.8% AF vs. 12.2% (HR 3.17, p<0.0001)

- Divergent curves after 2y: longer FU?

C Stroke, systemic arterial embolism, or cardiovascular death

HR 0·83 (95% CI 0·67–1·04); p=0·10

D All-cause death

HR 1·00 (95% CI 0·84–1·20); p=0·97

Time since randomisation (years)

Time since randomisation (years)

"Not all screen-detected AF merits OAC"

(quid if longer duration AF cut-off?:
no analysis shown)

Svendsen et al, Lancet 2021

Many unknows about AF screening...

- Minimum duration of silent AF episodes associated with significant risk of stroke

- Will anticoagulation after screen-detected AF reduce stroke risk?

- Most effective approach for screening for AF
  - Which technology?
  - Applied by whom?
  - Duration?
  - In specific patient groups?
  - How structured?
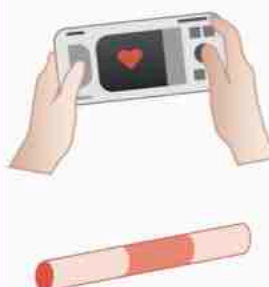
Tools to screen for AF...

Patient initiated (or medical professional) oscillometric blood pressure cuff

Pulse palpitation, auscultation

Patient initiated photoplethysmogram on smartphone

Semi-continuous photoplethysmogram on a smartwatch or wearable

Patient initiated (or medical professional) intermittent ECG rhythm strip using smartphone or dedicated connectable device
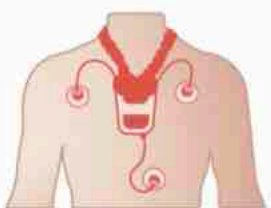
Intermittent smartwatch ECG initiated by semi-continuous photoplethysmogram with prompt notification of irregular rhythm or symptoms
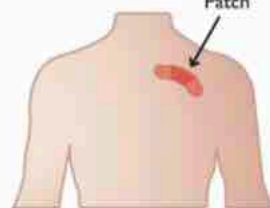
Wearable belts for continuous recordings
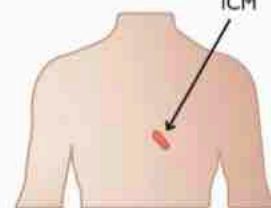
Stroke unit/in hospital telemetry monitoring

Long-term Holter

1-2 week continuous ECG patches

Implantable cardiac monitors

Patch

ICM

ESC Guidelines for Atrial Fibrillation, Hindricks, Potpara et al., Eur Heart J 2020

In-hospital handheld ECG study

- Non-randomised blinded observational study
- 503 hospitalised patients (344 cardiology and 159 geriatrics)
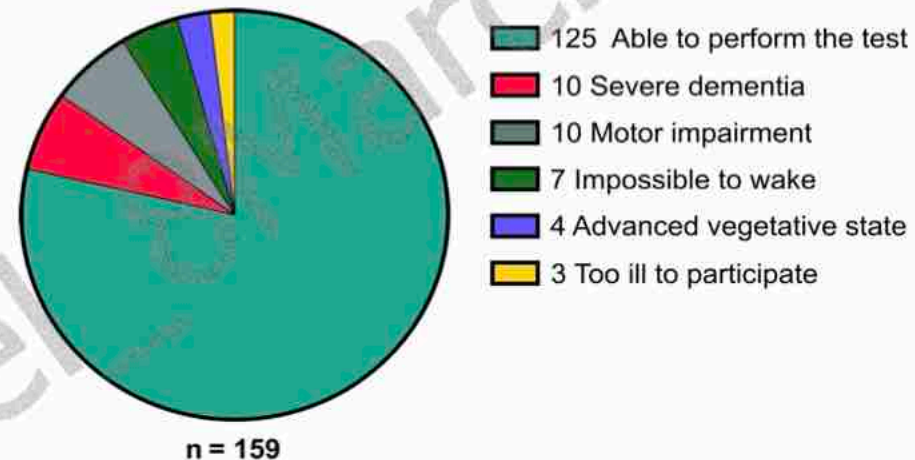 - Screening for AF with two handheld ECG devices

- Validation of both devices
  - Simultaneous 12-lead or 6-lead ECG recording

  - Automated algorithm
  - Handheld ECG tracings were reviewed blinded and independently by 2 electrophysiologists

Desteghe, ..., Heidbuchel, EP Europace 2016

In-hospital handheld study
Results in 503 patients

- Recording not possible:
  - cardiology: 7% (344 → 320)
  - geriatrics: 21.4% (159 → 125)

Legend:
- 125 Able to perform the test
- 10 Severe dementia
- 10 Motor impairment
- 7 Impossible to wake
- 4 Advanced vegetative state
- 3 Too ill to participate

n = 159

Desteghe, ..., Heidbuchel, EP Europace 2016

In-hospital handheld study
Results – excluding patients with an implanted device

- Sens. and spec. of automated algorithm

Department	MyDiagnostick		AliveCor	
	Sens	Spec	Sens	Spec
Cardiology (n=320 / 265)	60.5 / 81.8	93.3 / 94.2	36.8 / 54.5	96.1 / 97.5
Geriatrics (n=125 / 113)	81.8 / 89.5	96.1 / 95.7	72.7 / 78.9	98.1 / 97.9

- Sens. and spec. of interpretation by an electrophysiologist

Department		MyDiagnostick		AliveCor	
		Sens	Spec	Sens	Spec
Cardiology	Physician 1	68.4 / 77.3	91.1 / 93.0	68.4 / 90.9	92.6 / 94.7
	Physician 2	55.3 / 72.7	94.3 / 95.9	63.2 / 90.9	95.7 / 96.3
Geriatrics	Physician 1	90.9 / 100	81.6 / 84.0	94.7 / 94.7	86.4 / 87. 2
	Physician 2	90.9 / 94.7	90.3 / 90.4	94.7 / 94.7	89.3 / 88.3

Desteghe, ..., Heidbuchel, EP Europace 2016

In-hospital handheld study
Results

- Number of newly detected AF patients
  - Cardiology: 0.31% (1/320)
  - Geriatrics: 1.6% (2/125)
- Hospital screening costs **to prevent one stroke per year**
  - Population without an AF history or an implanted device

Desteghe, ..., Heidbuchel, EP Europace 2016
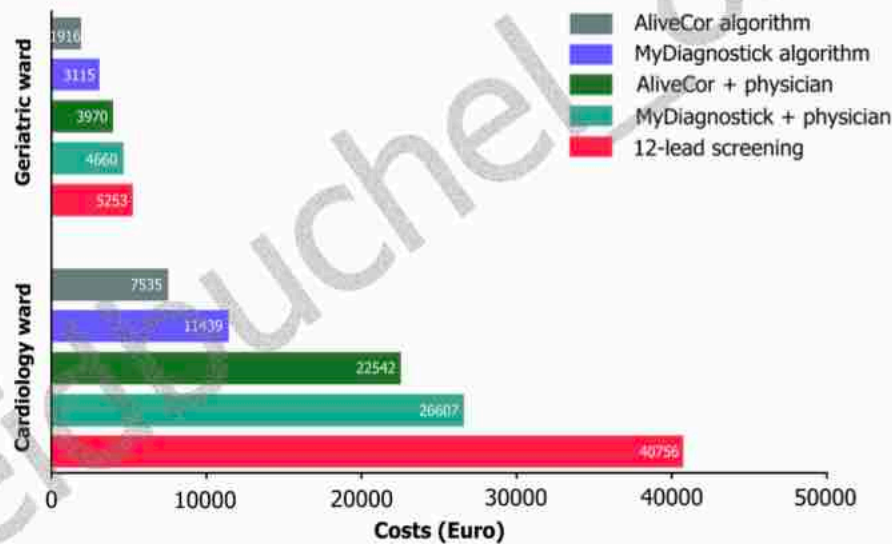
EHRA Consensus document (2017)
Screening for atrial fibrillation
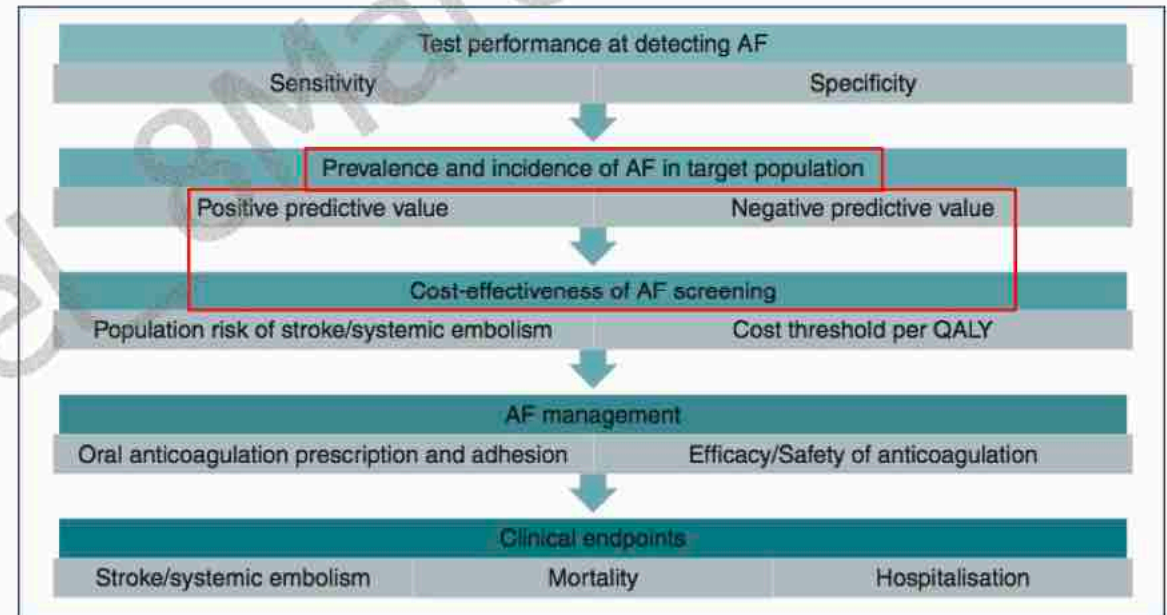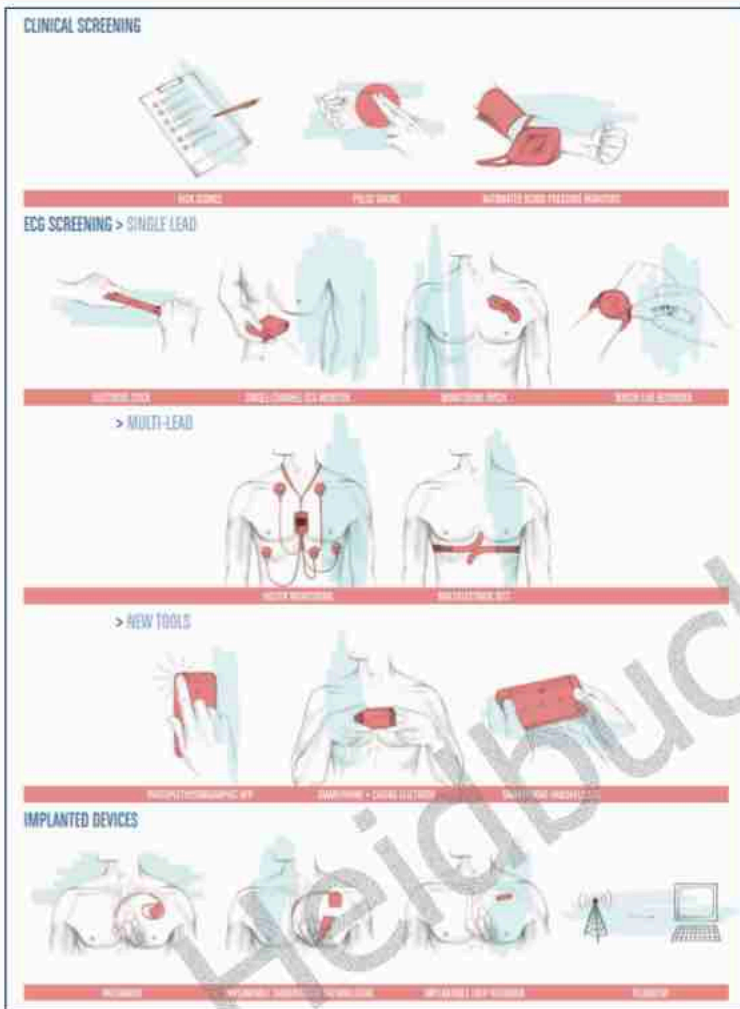
Mairesse et al (on behalf of EHRA), Europace 2017

ESC AF Guidelines 2020
Sensitivity and specificity of screening tools

	Sensitivity	Specificity
Pulse taking[203]	87 - 97%	70 - 81%
Automated BP monitors[204–207]	93 - 100%	86 - 92%
Single lead ECG[208–211]	94 - 98%	76 - 95%
Smartphone apps[188,189,191,195,212,213]	91.5 - 98.5%	91.4 - 100%
Watches[196,198,213,214]	97 - 99%	83 - 94%

AF = atrial fibrillation; BP = blood pressure; ECG = electrocardiogram.

ILR	96.1%	85.4%[1]
Pacemaker	89-100%	84-97%[2]

ESC Guidelines for Atrial Fibrillation, Hindricks, Potpara et al., Eur Heart J 2020
1. Hindricks et al, Circ AE 2010; 2. Solari et al, Int J Cardiol 2017; cf. also Carpenter and Frontera, EP Europace 2016
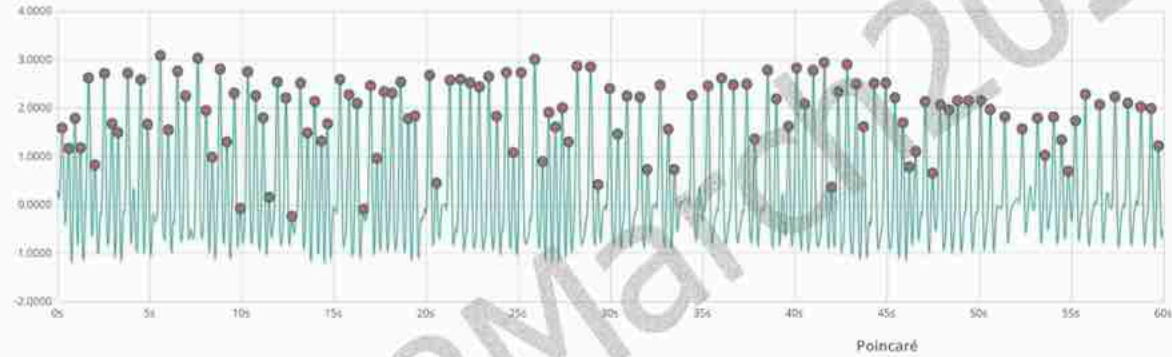
Man, 64 years, intermittent palpitations
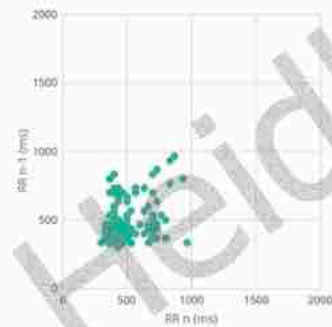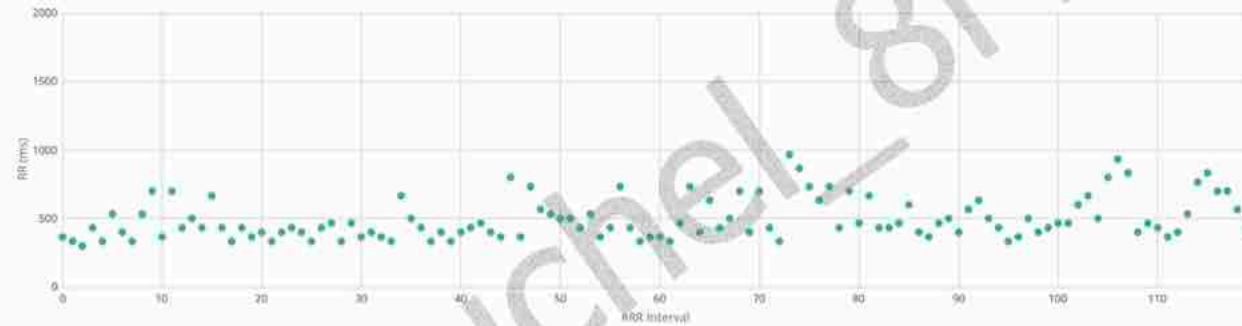## FibriCheck® measurements (smartphone PPG)
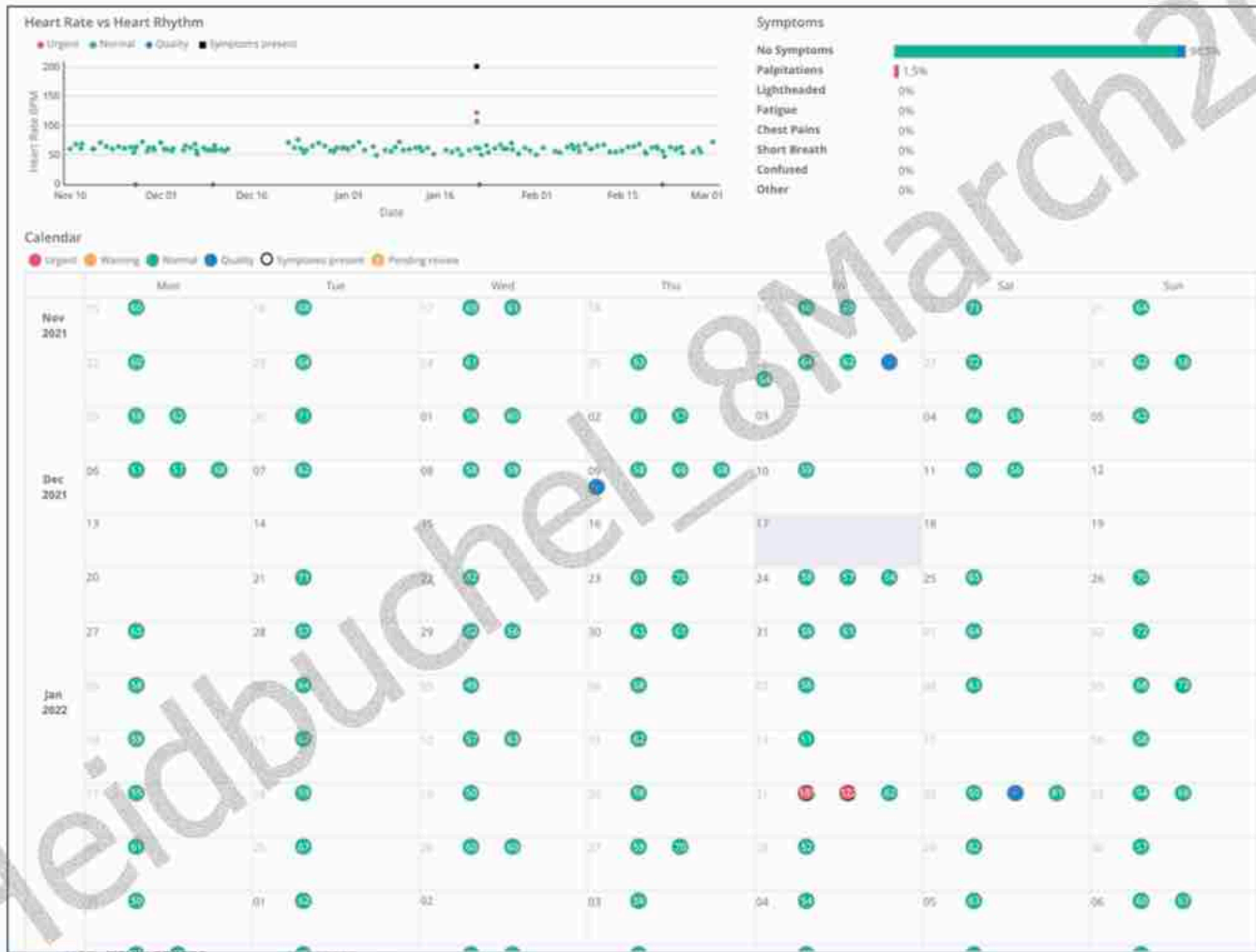
Man, 64 years, intermittent palpitations
## FibriCheck® measurements (smartphone PPG)

Groups:	UZA - Inbound patients
Heartbeat:	122
Heart rhythm:	Urgent
Time:	Fri 21/01/22 23:43
Status:	Reviewed
Review:	Atrial Fibrillation
Symptoms:	Palpitations
Activity:	Sleeping
FibriCheck:	1.12.7 (version)
Device:	Apple iPhone10,6

RR tachogram

Poincaré

Man, 64 years, intermittent palpitations
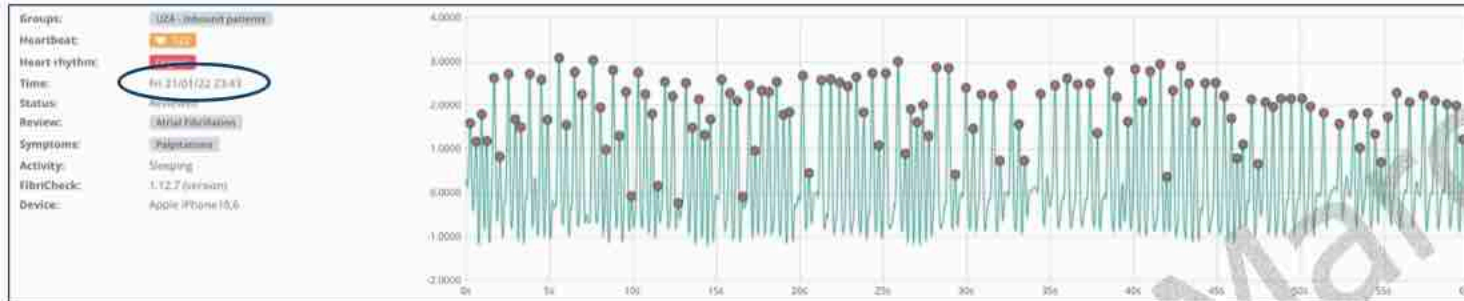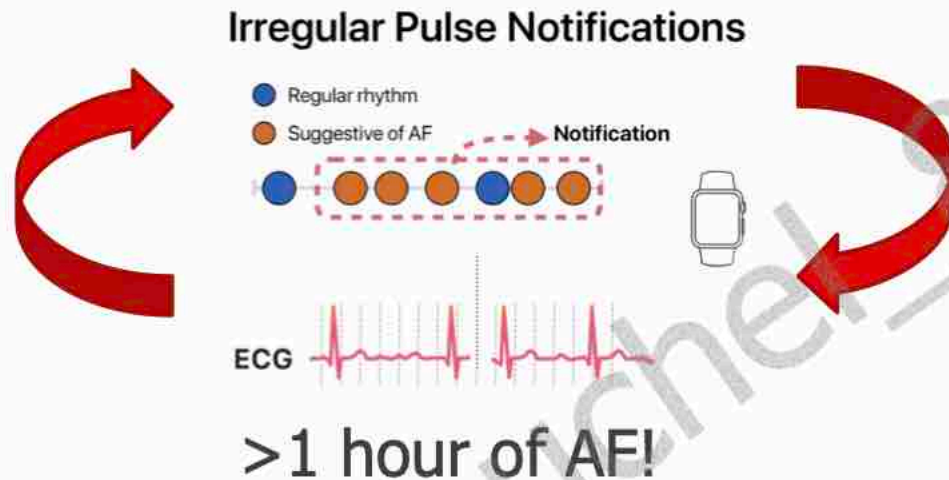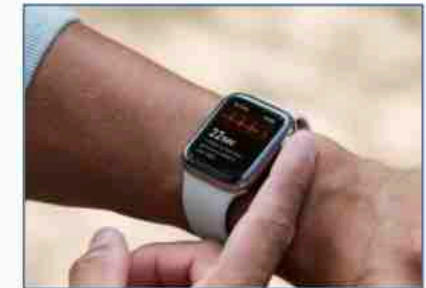## FibriCheck® measurements (smartphone PPG)
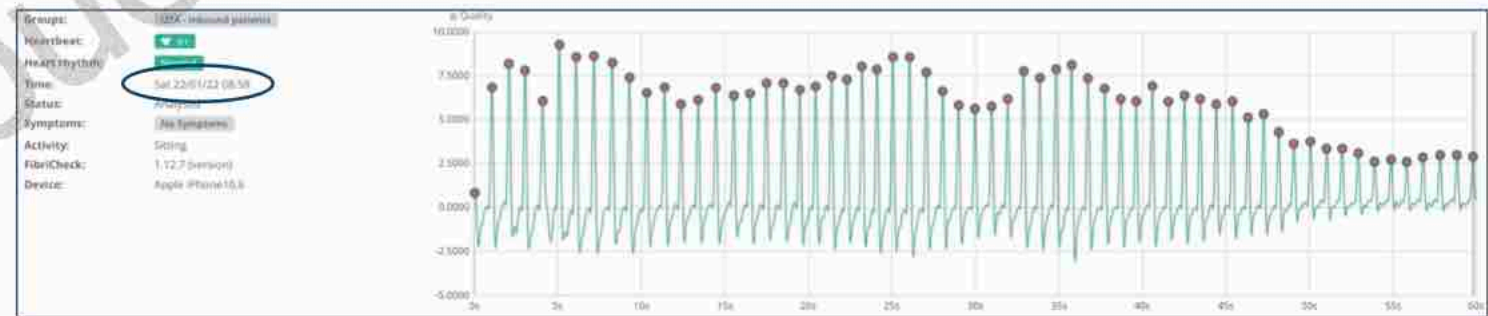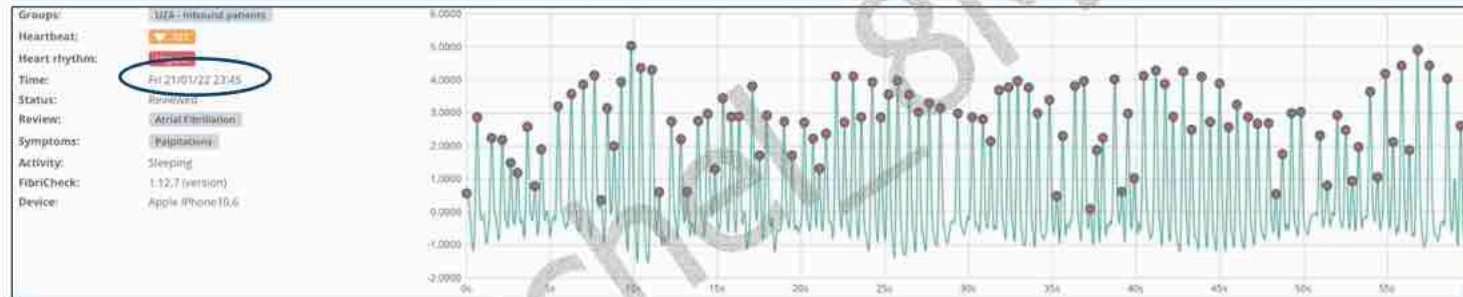
Apple Heart Study (n = 419 297)
Strengths

- Specificity of the algorithm

Potential for further improvement with immediate ECG verification

Irregular Pulse Notifications

- Regular rhythm
- Suggestive of AF ---> **Notification**

ECG

>1 hour of AF!

Apple Watch 4+

- Integration of structured management plan if notification

ACC & EHRA Congress 2019;   Perez MV, … Turakhia M, New Engl J Med 2019

The battle of the giants...

	Apple Heart Study	Huawei Heart Study	FitBit
N	419.297	187.912	455.699
Avg age	41	35	-
>65 years	5.9%	1.8%	12.1%
Approach	PPG watch	PPG watch / band	PPG watch/band
if notification	patch	ECG+Holter+clinical	patch
Minimum duration AF	±1 h	-	30 min
Notification	0.52%	0.23%	1%
in group >65y	3.1%	2.78%	3.6%
Confirmation AF	x%	87%	32.2%
if concomitantly: PPV	84%	?	?
if concomitantly: Sens	?	?	97.5%

1. Perez MV, ... Turakhia M, New Engl J Med 2019; 2. Guo et al, JACC 2019; 3. Lubitz et al., AHA presentation 2021

Ongoing HEARTLINE study

- n=180.000, >65y (sponsored by Apple & J&J)

- 2x2 randomisation design:
  - Apple Watch detection [& iPhone app to optimise NOAC adherence]

- Virtual study
  - no enrollment via physicians; CLAIMS outcome ascertainment (vs. adjudication)

- Primary endpoints
  - number (%) of clinically confirmed diagnoses of AF (and time to diagnosis)
  - [percent days covered with NOAC prescription]

- Secondary endpoints
  - combined cardiovascular outcome (stroke, MI, all-cause death)

* M. Gibson, ACC 2019

Many unknowns about AF screening…

- Minimum duration of silent AF episodes associated with significant risk of stroke

- Will anticoagulation after screen-detected AF reduce stroke risk?

- Most effective approach for screening for AF
  - Which technology?
  - Applied by whom?
  - Duration?
  - In specific patient groups?
  - How structured?

- Which approach is most feasible and cost-effective?

Too many approaches to test => modelling

- ## 45 AF screening strategies compared to no screening
  - Discrete modalities vs. continuous or nearly continuous modalities (with variable duration)

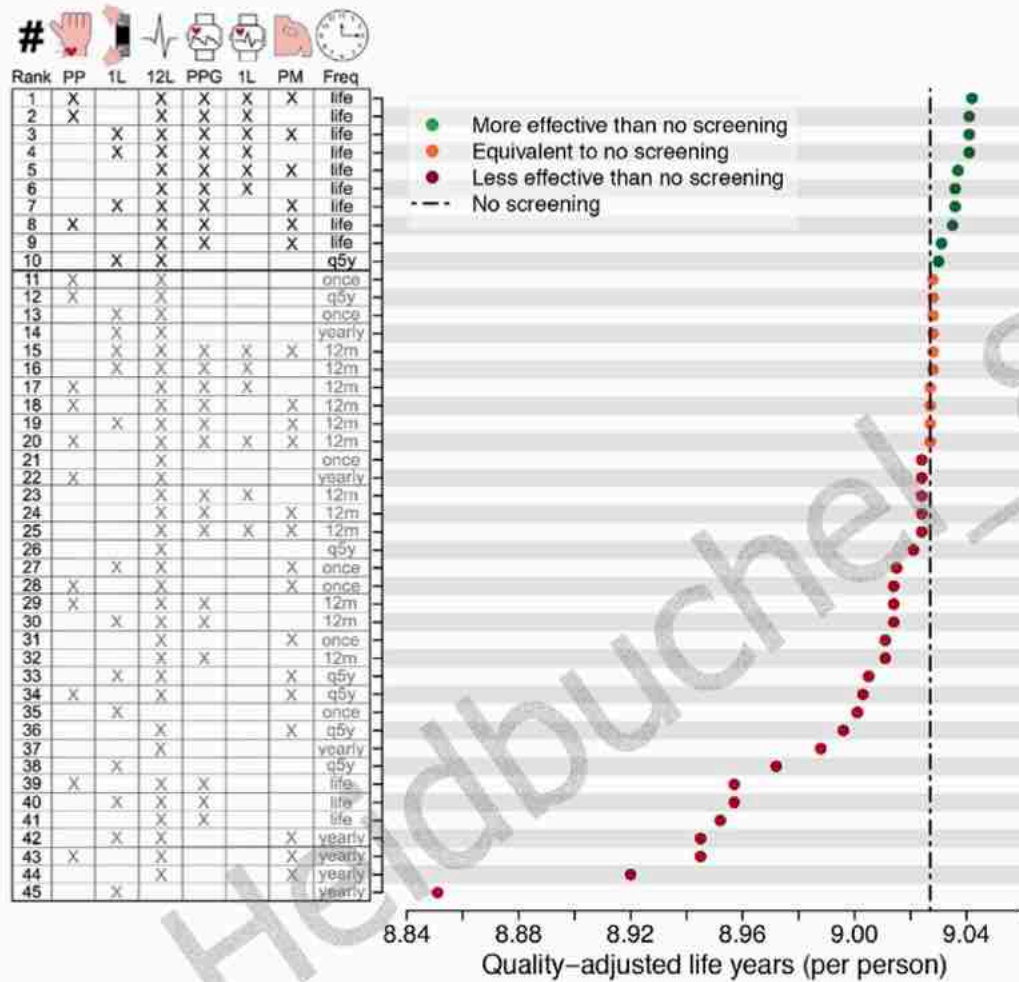

PP 1L 12L PPG 1L PM Freq

- ## Decision-analytic model, 50 million individuals >65y ("US popul. profile")

- ## "Effective" = QALY gained
  (based on incident strokes and bleedings)

Khurshid S et al, J Am Heart Assoc 2021
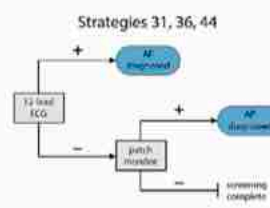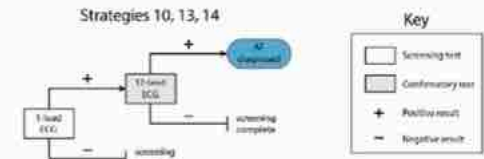
Modelling: 10 of 45 strategies "effective"
9 of those involved (nearly) continuous modalities

Test specificity was the most influential model parameter on screening effectiveness

=> less bleeding

Khurshid S et al, J Am Heart Assoc 2021

Do you feel confident to correctly interprete a single-lead ECG?

AliveCor

GP Survey (N = 470, 19 countries)

Which support would you like for interpretation of a single-lead ECG?

Not confident

Slightly confident

Somewhat confident

Fairly confident

59.3%

Completely confident
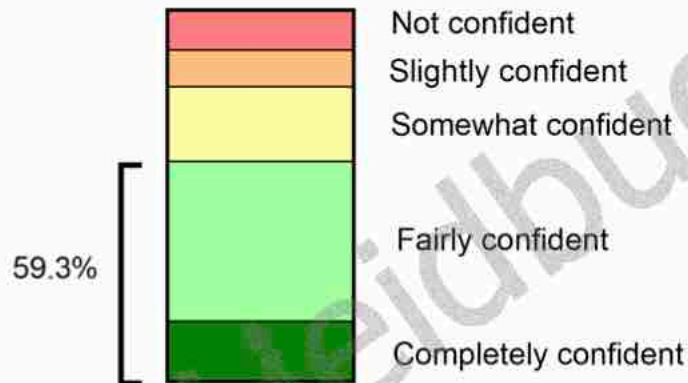
	% answers
More **education** on ECG in general and novel ECG devices in particular	30.1
Tele-healthcare service for upload of the ECG/tracing and rapid advice within the same day	23.4
Standardized follow-up pathway and possibility for rapid referral to a cardiologist	24.8
Nothing: I am already confident in ruling out AF based on a single-lead ECG; no external help needed	18.2

The problem of patient compliance
mSToPS RCT: self-applied patch at home 4w

1039862 Health plan members assessed for eligibility

680701 Excluded
- 470094 Did not meet inclusion criteria
- 210607 Had an exclusion criteria

359161 Met eligibility criteria

5318 Matched observational controls identified

50000 Invited by direct mail to participate[a]
52553 Invited by email to participate[a]

2820 Consented — 2.7%

161 Determined ineligible[b]

2659 Randomized

1366 Randomized to immediate monitoring

1293 Randomized to delayed monitoring

33.5% — 458 Never wore electrocardiogram patch

459 Never wore electrocardiogram patch

1842 Dropped from follow-up due to their actively monitored matches not being included in 12-mo analysis

908 Wore electrocardiogram patch

834 Wore electrocardiogram patch

2 Without 1-y claims data

2 Without 1-y claims data

1.7% — 906 Actively monitored with 12-mo follow-up data

832 Actively monitored with 12-mo follow-up data

3476 Matched observational controls with 12-mo follow-up data

Steinhubl et al, JAMA 2018

The logistics of mHealth...
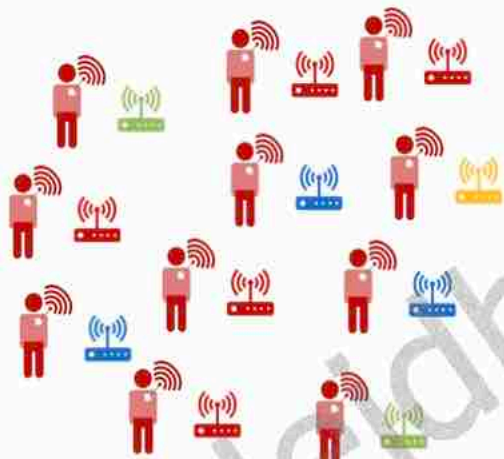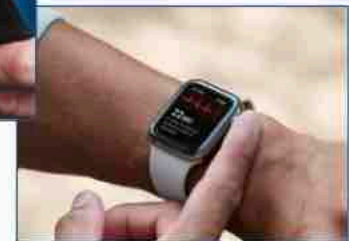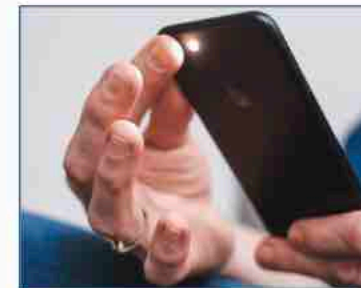## ... and related medico-legal framework

Hemodynamic monitoring

Long-term ECG recordings

Non-cardiac sensors

CIEDs

Smart phones & watches

Where does this lead us to?

- The combination of PPG and on-demand ECG is a potent future combo
  - PPG: near-continuous and ubiquitous
    - with market penetration of smartwatches expected to increase among public
  - ECG: further improving diagnostic accuracy

- Sets the stage for randomised clinical studies
  - Cf. HEARTLINE
  - ...

- *We* have to take up the challenge to deal with massive patient-initiated information...

University of Antwerp

Thank you!