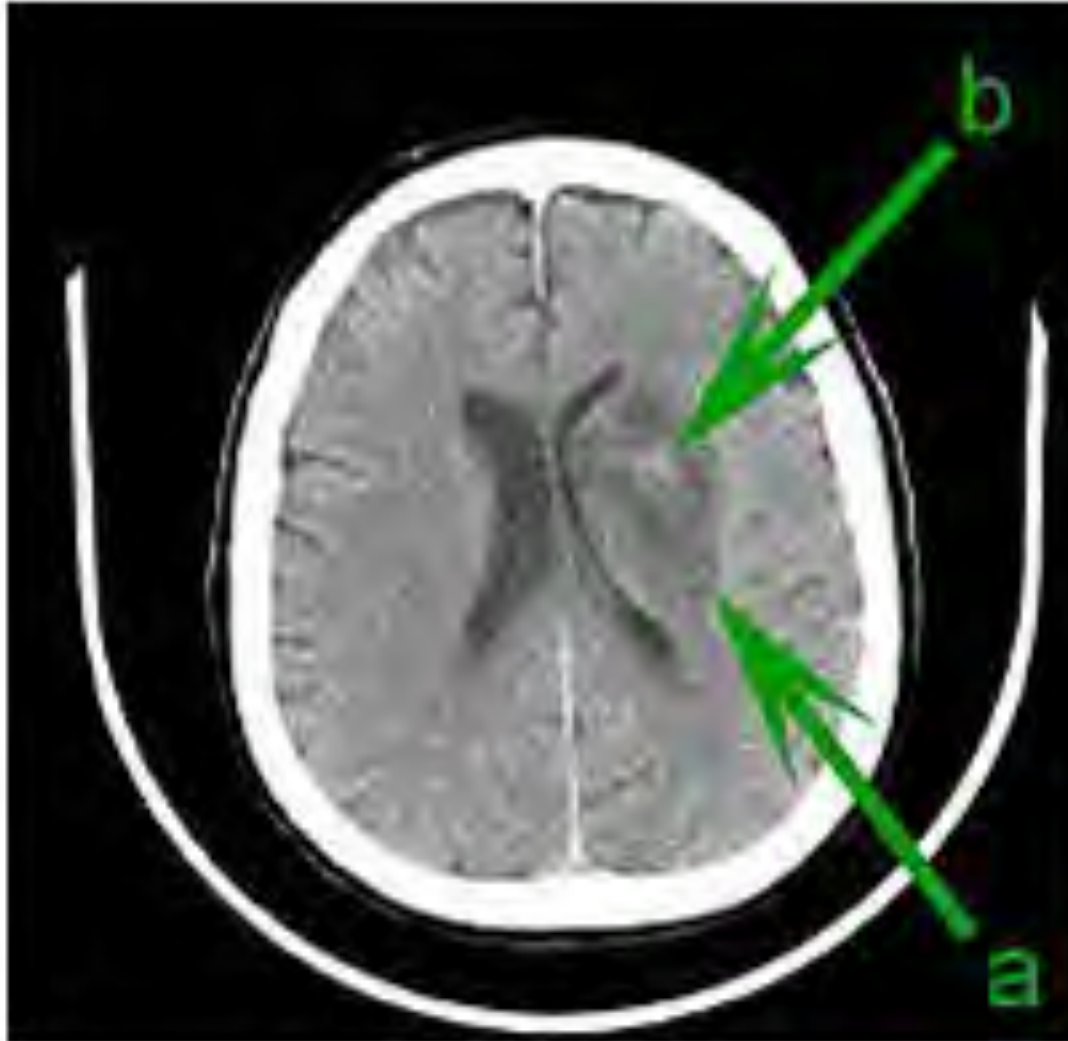# Fishing for Atrial Fibrillation
Where are we now?

Mårten Rosenqvist

Karolinska Institutet

Amsterdam, March 27 , 2017

Disclosures Mårten Rosenqvist 20150417

- Consulting: Bayer, Boehringer-Ingelheim , Medtronic, Pfizer, St. Jude Medical, Zenicor.

- Research grants: Bayer, Boehringer- Ingelheim, Pfizer, Roche, St Jude Medical.

- Lectures: Cardiome, Bayer, Boehringer- Ingelheim, St Jude Medical, Pfizer.

Can AF screening prevent this?

Atrial Fibrillation and ischemic stroke

- At least 30-35 % av all ischemic strokes are associated with AF.

- Risk factors can be identified.

- Oral anticoagulation reduces stroke with 70%

Silent Atrial Fibrillation

1/3 av all Atrial Fibrillation
No or atypical symptoms
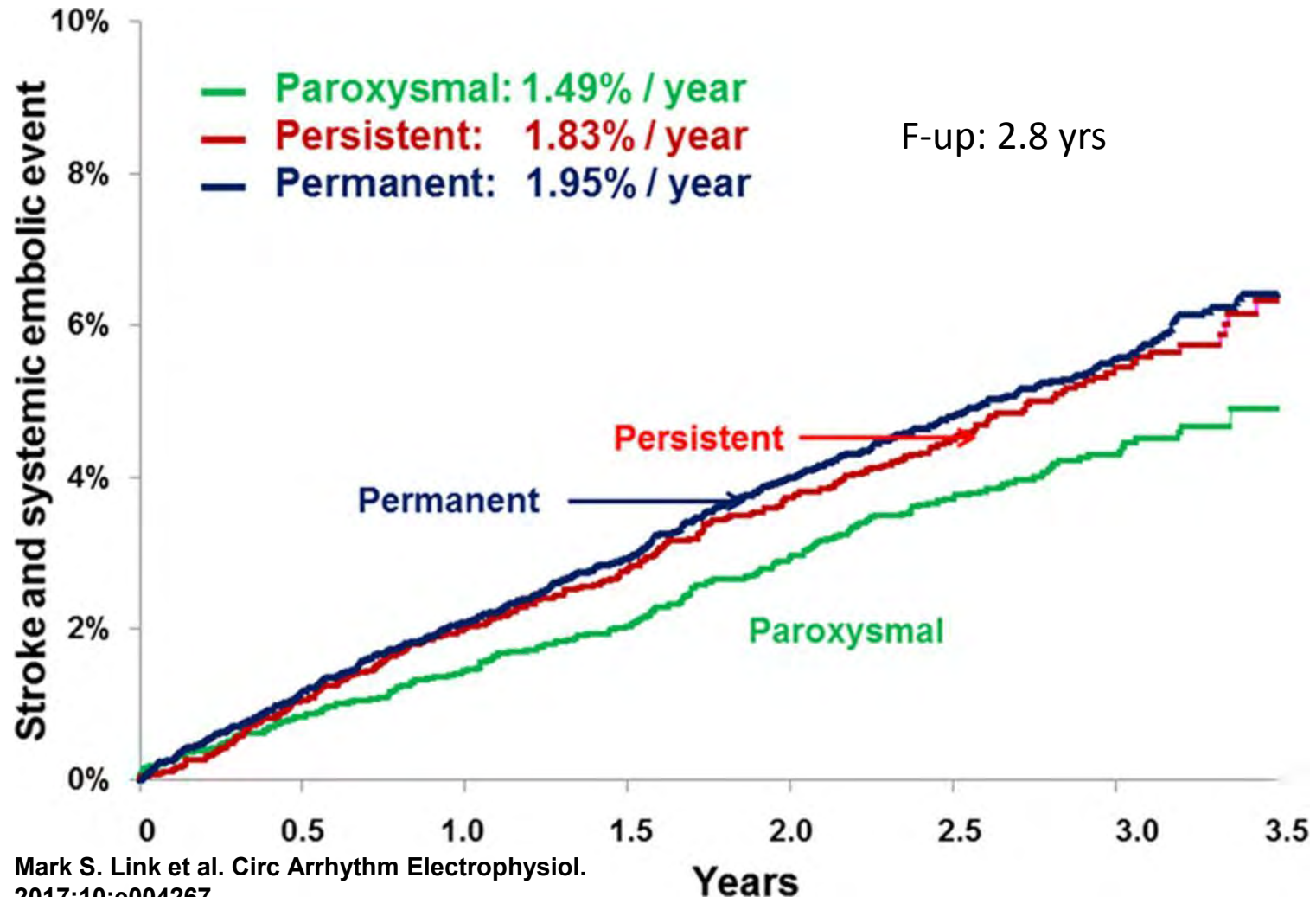Paroxysmal or permanent

Issues:
Is the duration of the AF
("AF burden")
is related to the risk for stroke?

Is permanent AF more "embolic" than
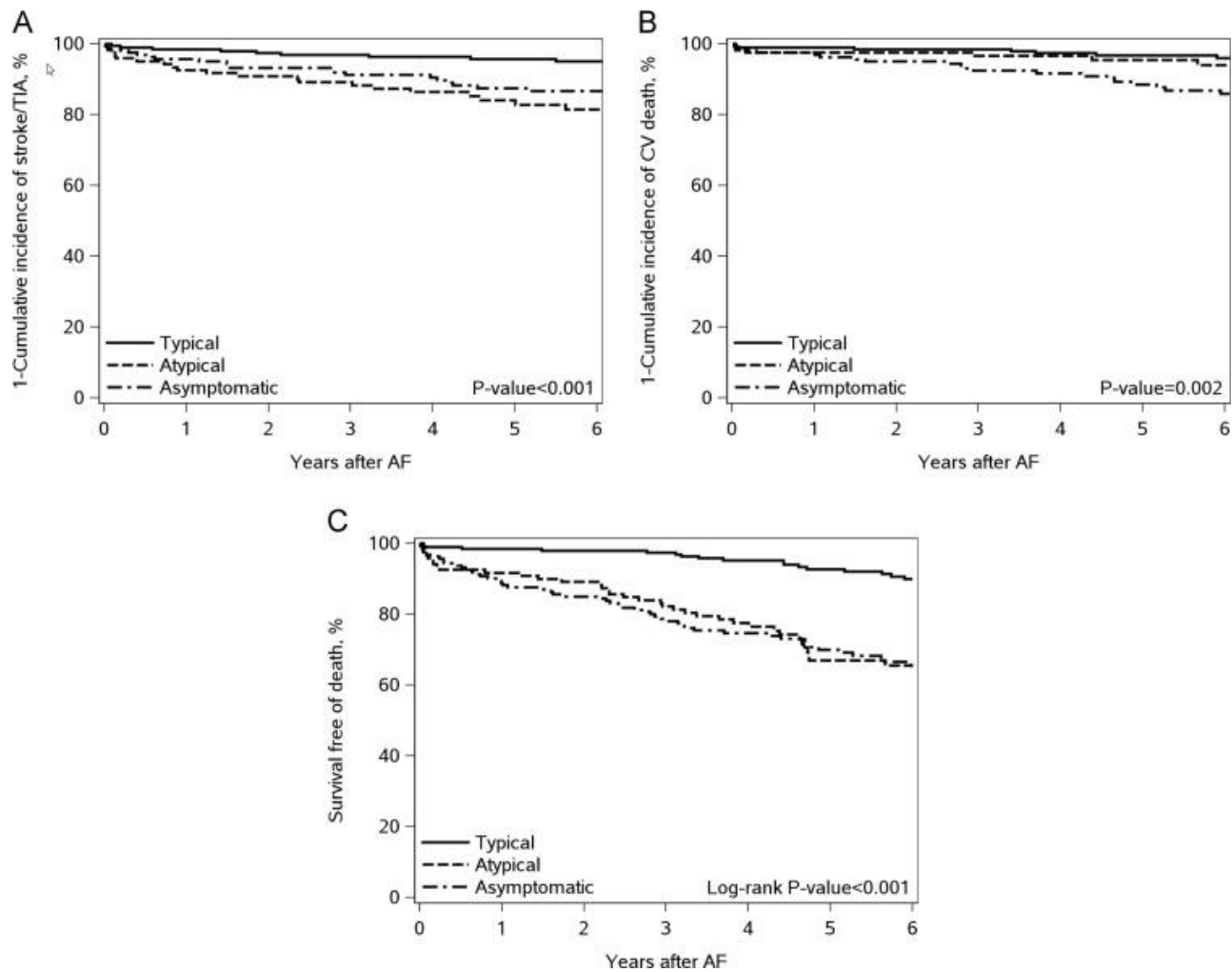**paroxysmal/ silent AF?**

Engage study
Stroke and systemic embolic event (SEE) occurred less frequently in the patients with paroxysmal atrial fibrillation (AF) (1.49%/y), as compared with persistent (1.83%/y; HR, 0.79; 95% CI, 0.66–0.96; P=0.015) and permanent AF (1.95%/y; HR, 0.79; 95% CI, 0.67–0.93; P=0.004)

Paroxysmal: 1.49% / year
Persistent: 1.83% / year
Permanent: 1.95% / year

F-up: 2.8 yrs

Persistent

Permanent

Paroxysmal

Stroke and systemic embolic event

Years

American Heart Association®

Siontus et al Heart Rhythm 2016

AF screening

- Do we have the optimal fishing equipment?
  - One method or several?
- Do we know the best fishing waters?
  - Which patients to screen?
- Do we improve catching?
  - Stroke reduction?

Screening for Atrial Fibrillation, is it motivated?

Ethical?

The Wilson-Jungner criteria
for appraising the validity of a screening programme
endorsed by World Health Organization (WHO) 1968

1. The condition sought should be an important health problem

2. There should be an accepted treatment for patients with recognized disease

3. Facilities for diagnosis and treatment should be available

4. There should be a recognizable latent or early symptomatic stage

5. There should 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 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.

2012 focused update of the ESC Guidelines for the management of atrial fibrillation

Recommendation for screening of AF

| 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

Regular pulse check

- Good sensitive to find permanent AF
- 1-1.5 % using resting ECG
- Overdiagnosis (false positive)
- Difficult to find paroxysmal AF

(Fitzmaurice BMJ 2005)

Devices for long-term AF screening

Event recorder
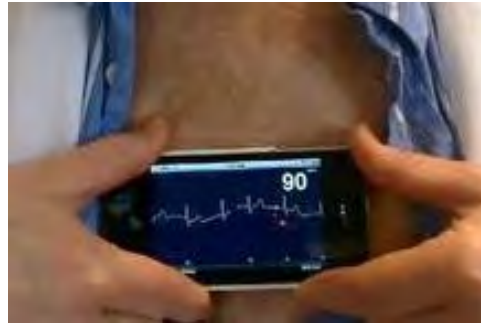
Smart phone ecg
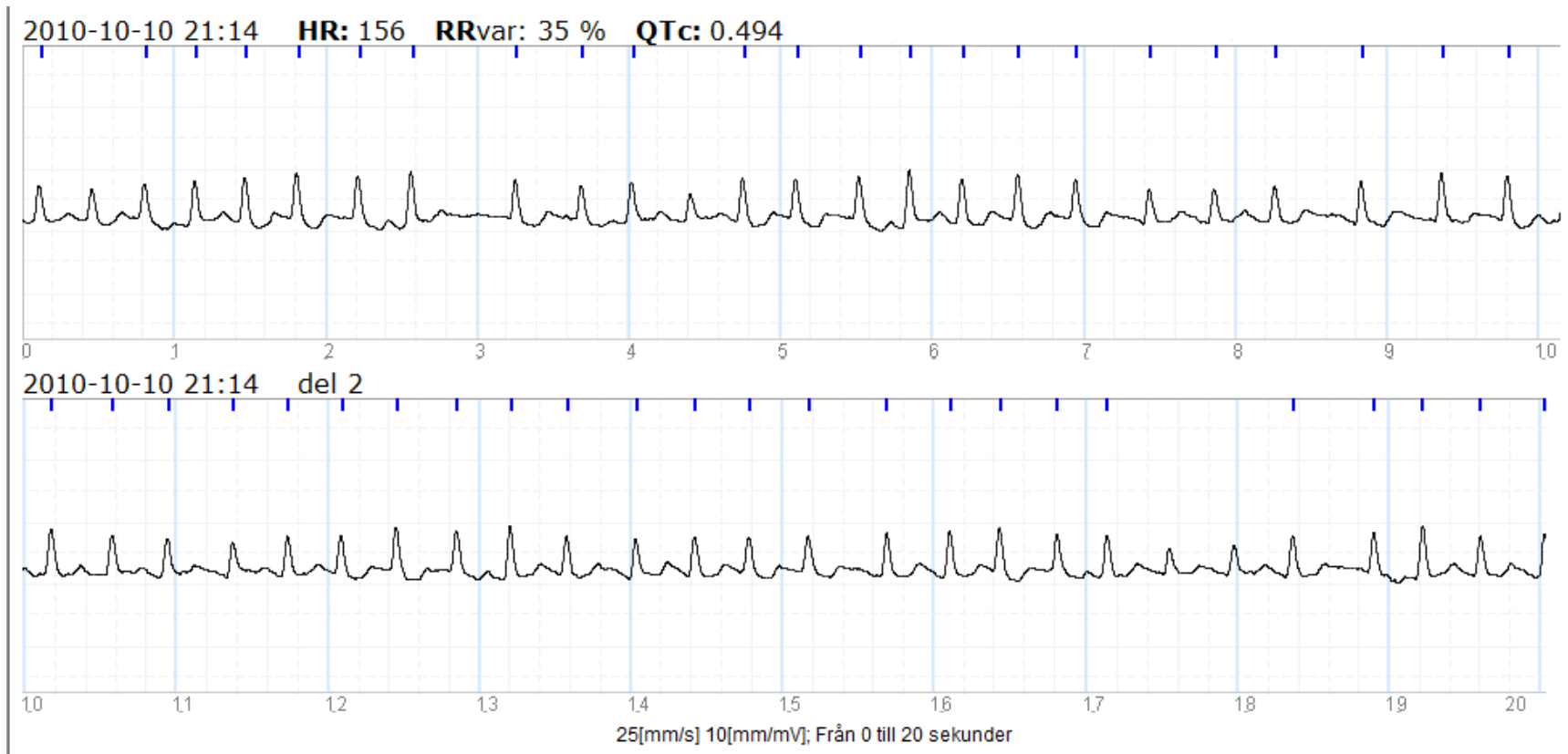

Holter ecg

Ecg patches

Loop recorder ecg

Thumb ecg

Thumb - ECG

- Inbuilt mobile phone
- Automatic transmission to a Web site
- 10-30 sec registrations
- Symptom marker
- Possibilities for semi-automatic ECG analysis

AF detected with Hand-held ECG

2-3 times more efficient to detect AF compared to 24 h Holter.

Sobocinski et al 2012 and 2014

Opportunistic AF screening

- 989 Primary Care patients
- $CHADS_2$ = 1 or more
- Mean age 65 yrs
- Intermittent ECG (10 s) twice a day, 30 days

- New AF : 3.8% (CI 2.7-5.2)

(Hendrikx et al, BMC Cardiovasc 2013)

Cohort screening of different age populations

Halmstadproject

- All 75-76 yrs invited for screening
- 948 invited
- 65% participated
- If one additional risk factor (CHADS2)
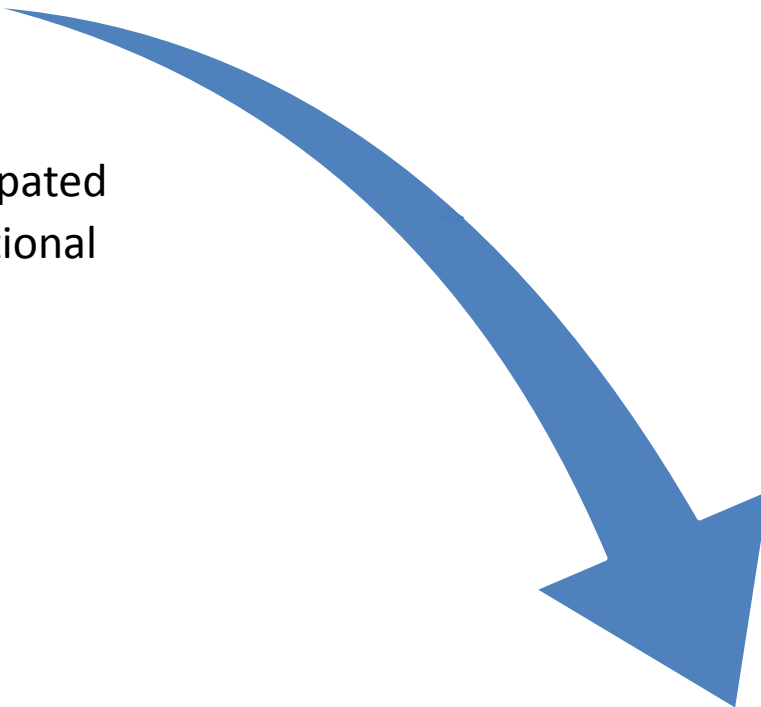
intermittent ECG
14 days 30 sec x 2

(Engdahl et al Circulation 2013)

Halmstad project

Results

Known AF – No OAC treatment	3 %
Resting ECG – New AF	1%
Intermittent ECG – New AF	4 %

Totally, 8% candidates for
oral anticoagulation treatment

(Engdahl et al Circulation 2013)

"STROKESTOP" study

- 28 757 individuals 75-76 yrs randomised for AF screening or no intervention

- Resting ECG and history

- If SR, Hand-held ECG 14 days, 2 x 30 sec.

- When AF is detected: Treatment with OAC

(Svennberg et al Circulation 2015)

Results

Attends screening clinic n= 6 887 (52%) → Declaration of health → Known AF n=636 (9,2 %) → OAC treatment n=492 / No OAC-treatment n= 144 (2.1%) → Referral to Cardiologist for OAC

Intermittent ECG-recordings 2 weeks AF 3.2%

Svennberg et al, Circulation 2015
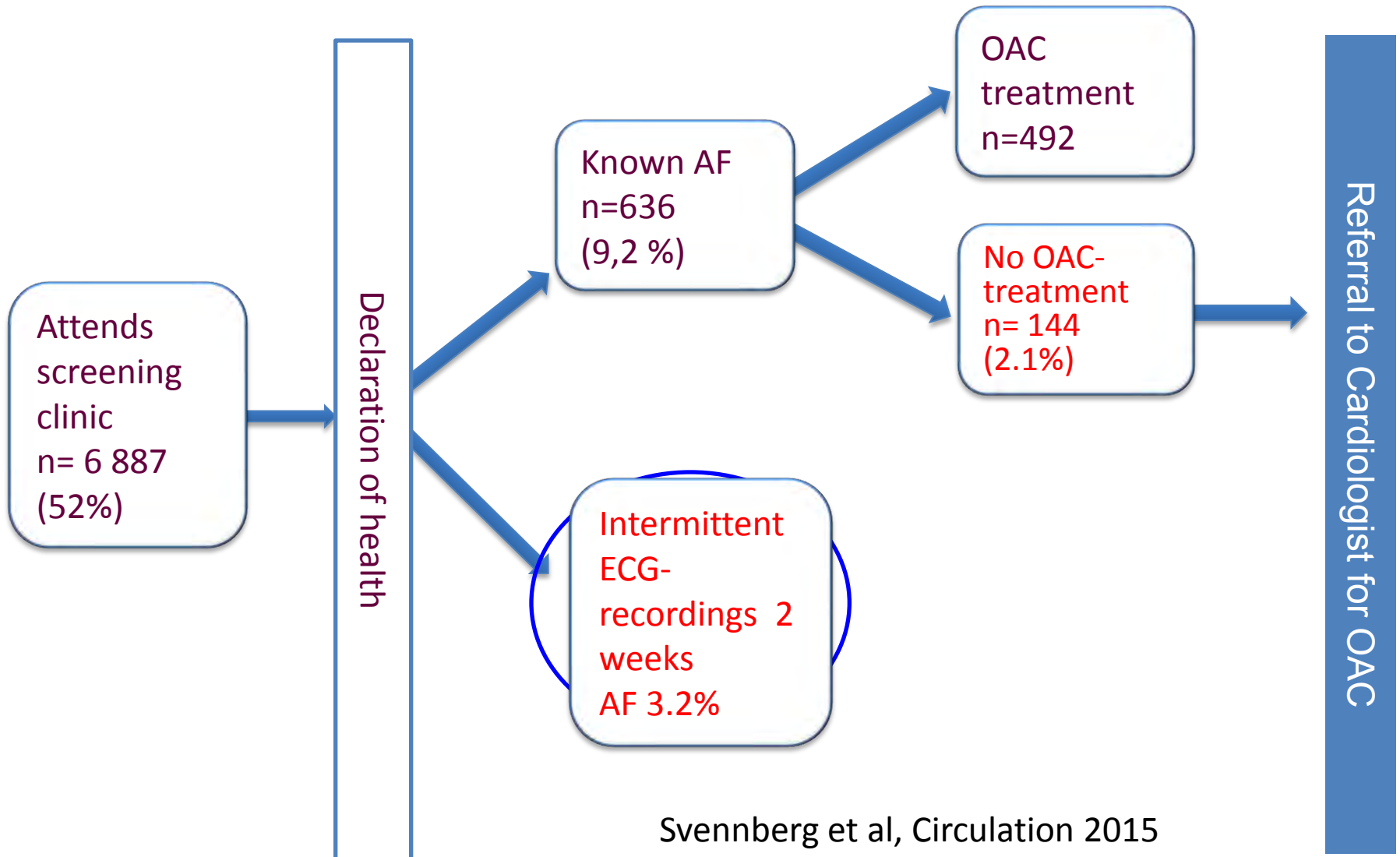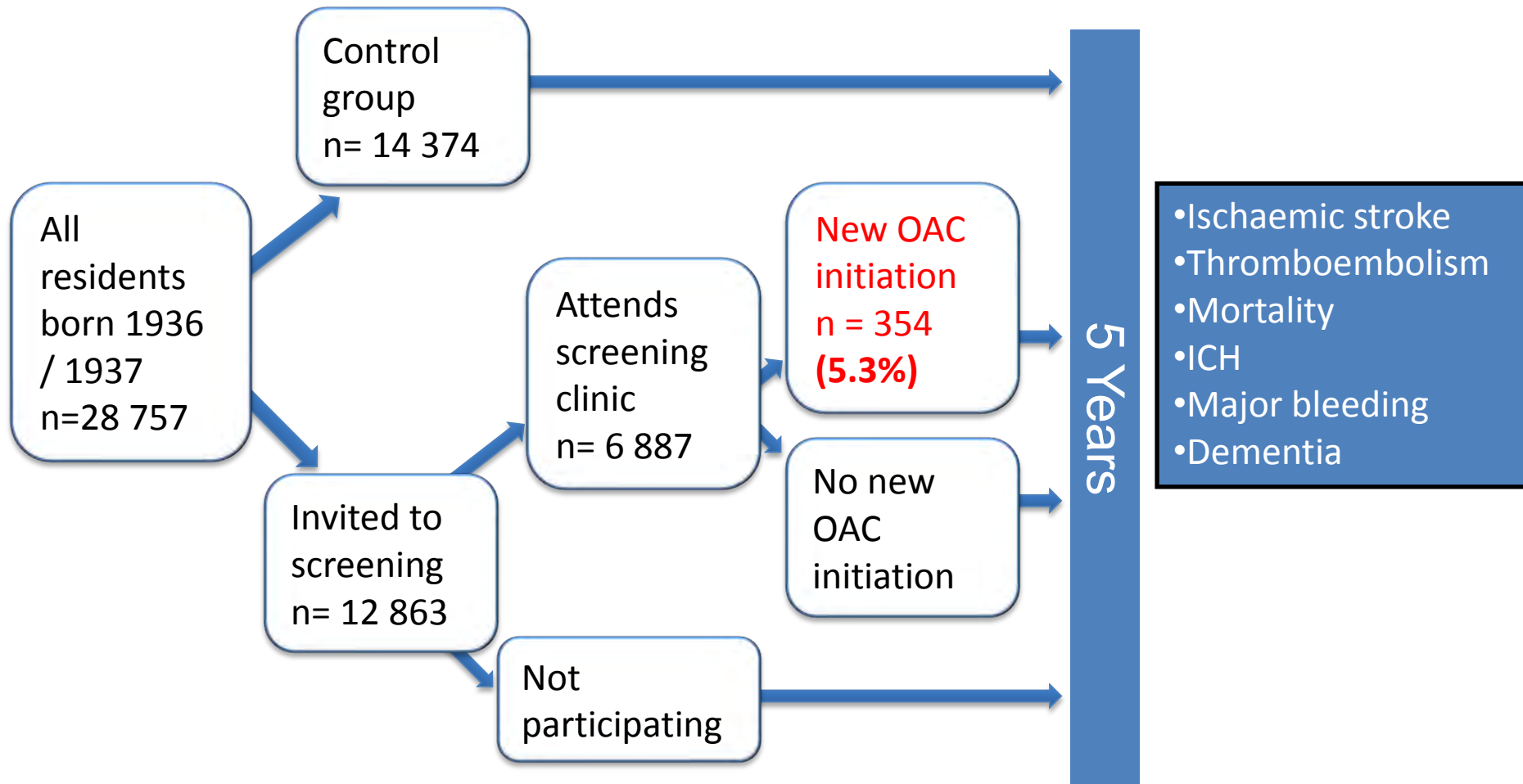
Svennberg et al, Circulation 2015

Patients with No OAC treatment Initiation of OAC:

New AF   94%

Old AF   60%

(**Svennberg et al Circulation 2015**)

Compliance of OAC treatment in the STROKESTOP pilot trial

Legend: OAC treated (green), Non-OAC treated (red), Deceased (light purple), Excluded/Lost (dark purple)
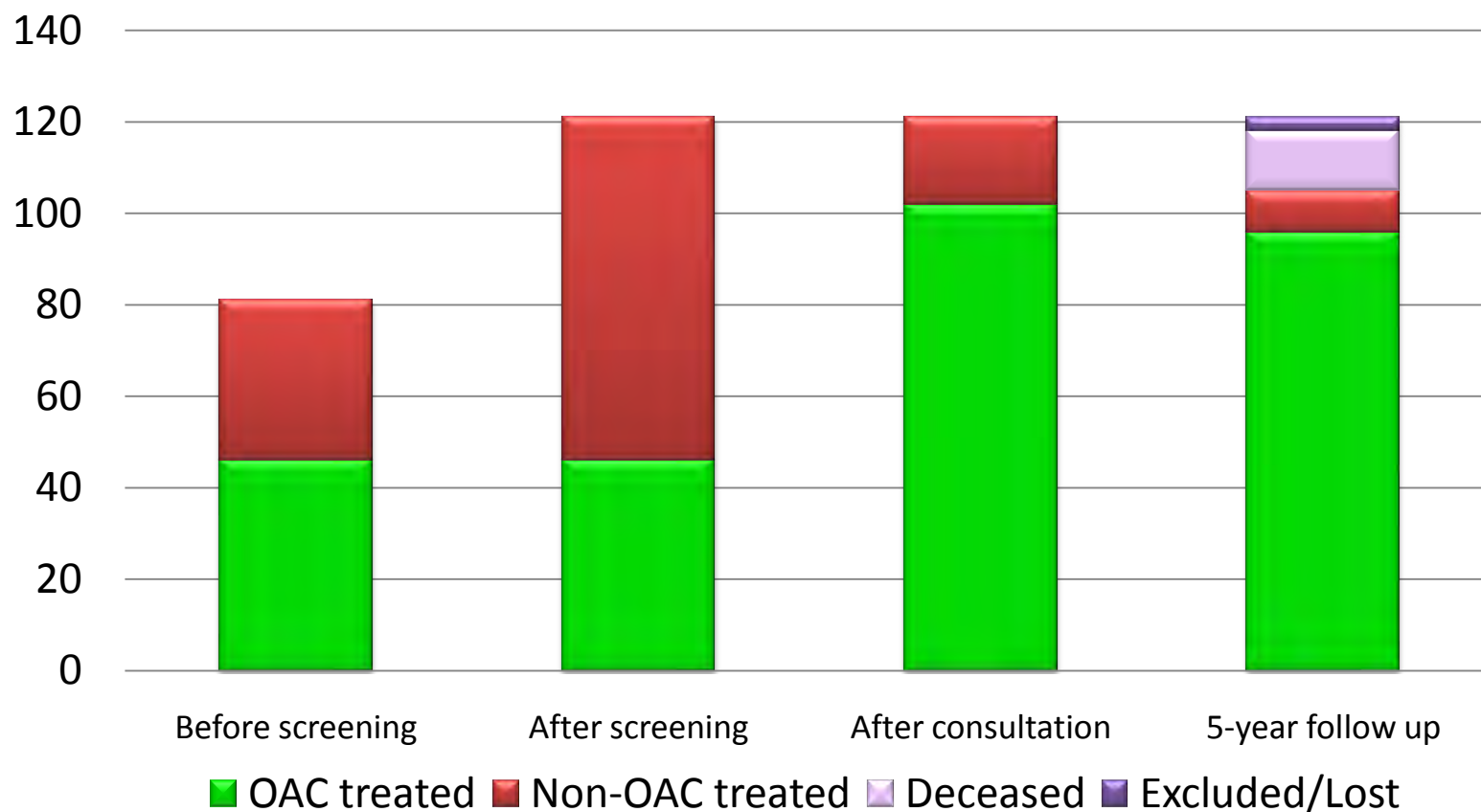
(Engdahl 2017 unpublished)

Participation in screening studies

- Strokestop 53.5 %
- Colon cancer screening 55-60%
- Health cohort studie 55%

- Which patients do not participate?

Geo-mapping of participation ratios (PRs) in Stockholm county (99 parishes)
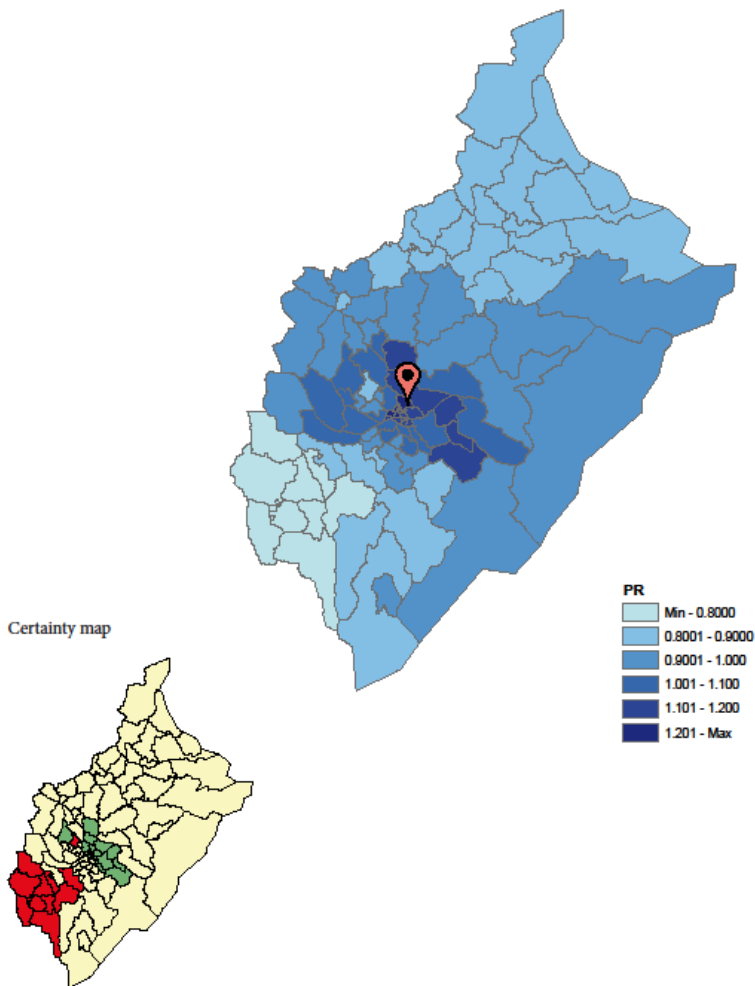
Geo-mapping of *educational-level-adjusted* PRs in Stockholm

Strömberg et al 2015
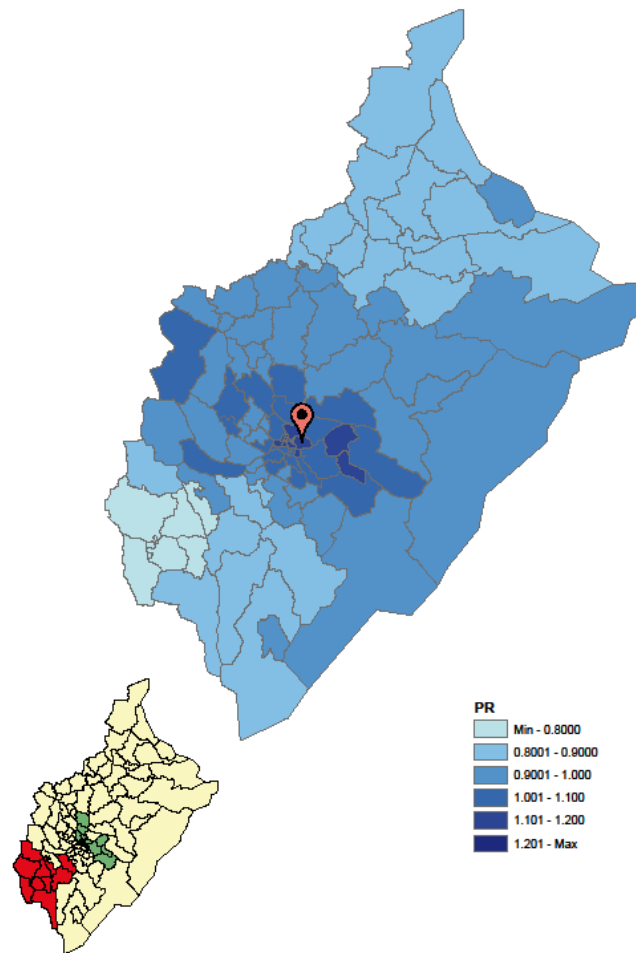
Screening programmes

	Further investigation	Candidates for treatment
AAA[1]	1,4-1,5 %	0,1-0,2 %
Colon Cancer [2] (2008)	2 %	0,8 %
Mammography screening [3]	3 %	0,5 %
Cervical cancer[4]	4,2 %	0,064 %
AF	**5 %**	**5 %**

[1] Hultgren et al Swedish medical journal 2013
[2] Törnberg et al. Swedish medical journal, 2010
[3] Törnberg et al. Vårdguiden, 2013
[4] Cancerfonden

CLINICAL RESEARCH

Cost-effectiveness of mass screening for untreated atrial fibrillation using intermittent ECG recording

Mattias Aronsson[1]*, Emma Svennberg[2], Mårten Rosenqvist[2], Johan Engdahl[3], Faris Al-Khalili[2,4], Leif Friberg[2], Viveka Frykman-Kull[2], and Lars-Åke Levin[1]

[1]Department of Medical and Health Sciences, Centre for Medical Technology Assessment, Linkoping University, SE-581 83 Linkoping, Sweden; [2]Karolinska Institutet, Department of Clinical Science, Cardiology Unit, Danderyd University Hospital, Stockholm, Sweden; [3]Department of Medicine, Halland Hospital, Halmstad, Sweden; and [4]Stockholm Heart Centre, Stockholm, Sweden

- 8 fewer strokes/1000 screened

- 12 QALYs / 1000 screened

- € 4313/QALY

At which age to screen?
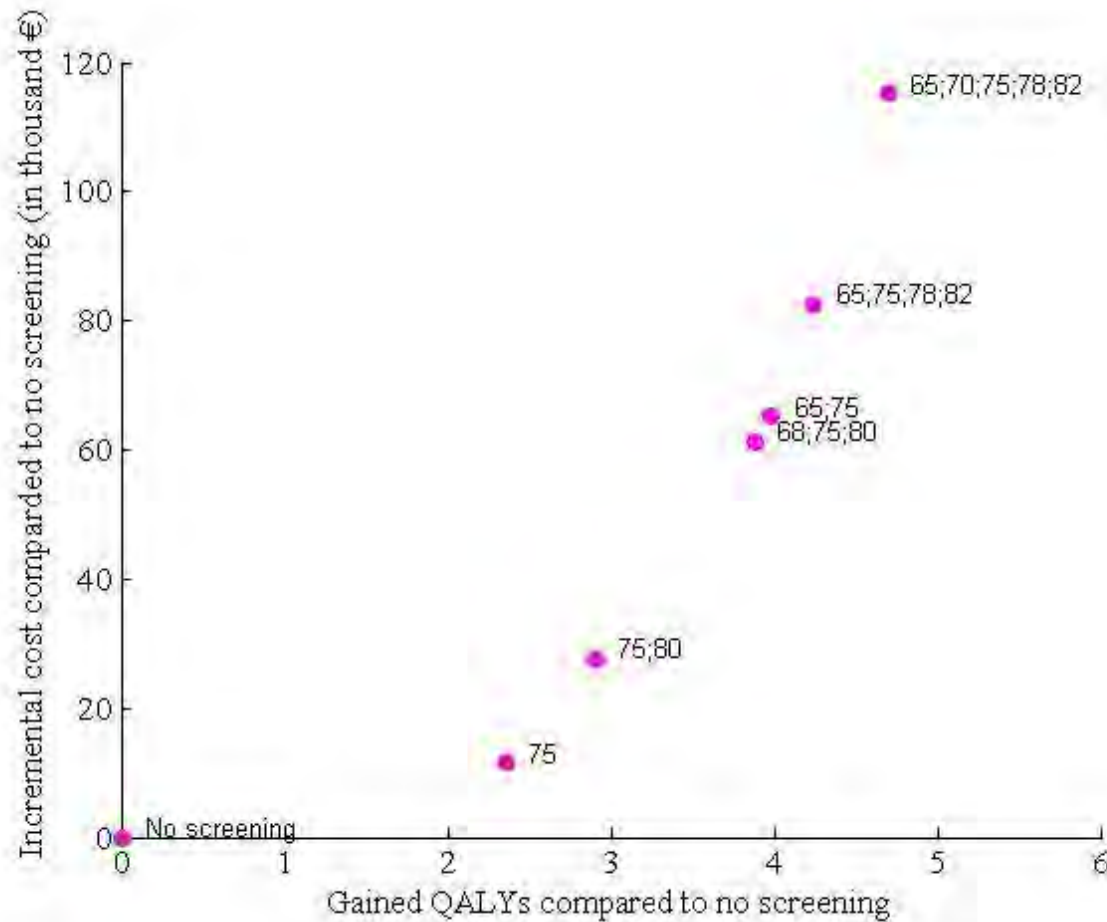
Aronsson Europace 2017

Biological markers
for AF - NT-proBNP?

- ***Background:*** *NT pro BNP is related to AF and risk for stroke.The lower the BNP the lower the risk for stroke*

- ***Hypothesis***: NT-proBNP will be significantly higher in subjects with clinically silent AF compared to individuals where AF is not diagnosed

Pilot study: In a substudy to the STROKESTOP study NT-proBNP was analysed in 886 individuals

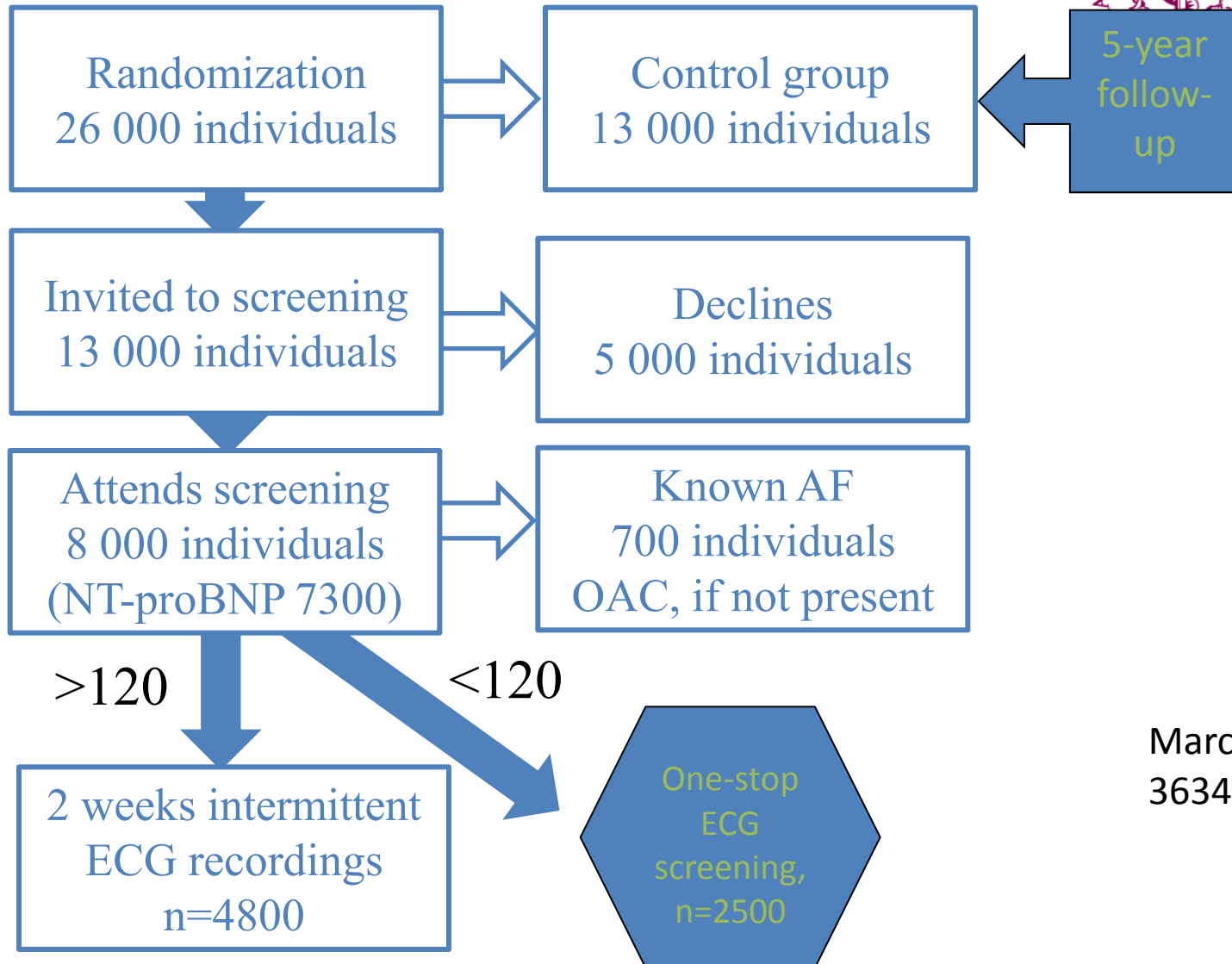|	New AF (n=96)	No AF (n=735)	p
Median NT-proBNP, ng/L	**330**	**172**	**<0.001**
IQR	513	190	
Congestive Heart Failure, n (%)	1 (1.1 %)	19 (2.6%)	0.355
Hypertension, n (%)	54 (56.3 %)	350 (48 %)	0.13
Diabetes Mellitus, n (%)	14 (14.6%)	85 (11.6%)	0.399
Prior Stroke/TIA, n (%)	9 (9.4%)	73 (10.1%)	0.83
Vascular disease, n (%)	14 (14.6)	72 (9.9%)	0.16
Female gender, n (%)	39 (41.1%)	325 (44.3%)	0.544
CHA_2DS_2-VASc median	3 (IQR 1)	3 (IQR 1)	
Length, cm (n=468)	173.3 (CI 171.5-175.1)	171.6 (CI 170.7-172.5)	0.99
Weight, kg	**83.3 (78.8-87.9)**	**75.4 (74.4-77.0)**	**0.002**
BMI	**27.8 (26.2-29.5)**	**25.7 (25.3-26.0)**	**0.014**

The One Stop STROKESTOP II study

Aim

To determine if the biomarker NT-proBNP together with single-lead ECG can be used as a primary population screening tool, to identify individuals with low risk for stroke

Method

```
┌─────────────────────┐         ┌─────────────────────┐        ┌──────────┐
│ Randomization       │ ──────▶ │ Control group       │ ◀───── │ 5-year   │
│ 26 000 individuals  │         │ 13 000 individuals  │        │ follow-  │
└─────────────────────┘         └─────────────────────┘        │ up       │
         │                                                     └──────────┘
         ▼
┌─────────────────────┐         ┌─────────────────────┐
│ Invited to screening│ ──────▶ │ Declines            │
│ 13 000 individuals  │         │ 5 000 individuals   │
└─────────────────────┘         └─────────────────────┘
         │
         ▼
┌─────────────────────┐         ┌─────────────────────┐
│ Attends screening   │ ──────▶ │ Known AF            │
│ 8 000 individuals   │         │ 700 individuals     │
│ (NT-proBNP 7300)    │         │ OAC, if not present │
└─────────────────────┘         └─────────────────────┘
```

>120   <120

```
┌─────────────────────┐         ⬡ One-stop
│ 2 weeks intermittent │           ECG
│ ECG recordings       │           screening,
│ n=4800               │           n=2500
└─────────────────────┘
```

March 20, 2017
3634 patients included

Karolinska Institutet

Screening for atrial fibrillation

Recommendations	Class	Level
Opportunistic screening for AF is recommended by pulse taking or ECG rhythm strip in patients >65 years of age.	I	B
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.	I	B
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
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.	IIa	B
Systematic ECG screening may be considered to detect AF in patients aged >75 years, or those at high stroke risk.	IIb	B

EUROPEAN
SOCIETY OF
CARDIOLOGY®

What do the authorities say?

As it is not known whether AF detected by screening has the same risk for Stroke, as clinically detected AF, a National screening program can for the moment being, not be recommended.

Swedish FDA 2017

Conclusion

- Primary screening for atrial fibrillation is effective if you choose the right patient groups
- Detection rate is high compared to other screening programmes.
- Acceptance for starting OAC is high
- Compliance is high
- Screening for AF looks cost effective
- Strokes can be prevented ?

AF episodes < 30 seconds (Micro AF) What happens over time?

Substudy strokestop 1

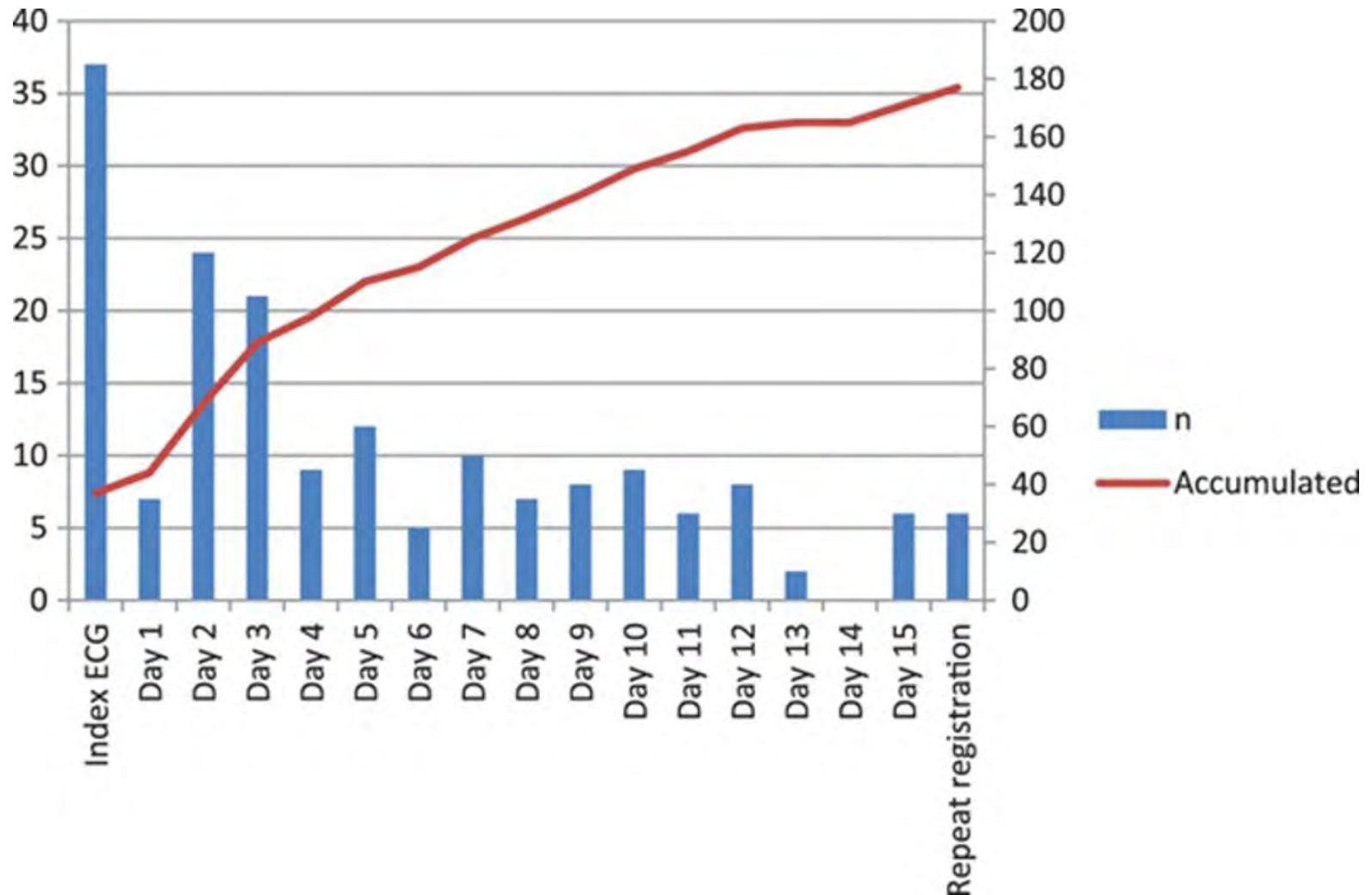N = 70 individuals with AF episodes < 30 seconds.

At least 5 SVEB:s

After 2 years 52 % had progressesed to AF > 30 seconds
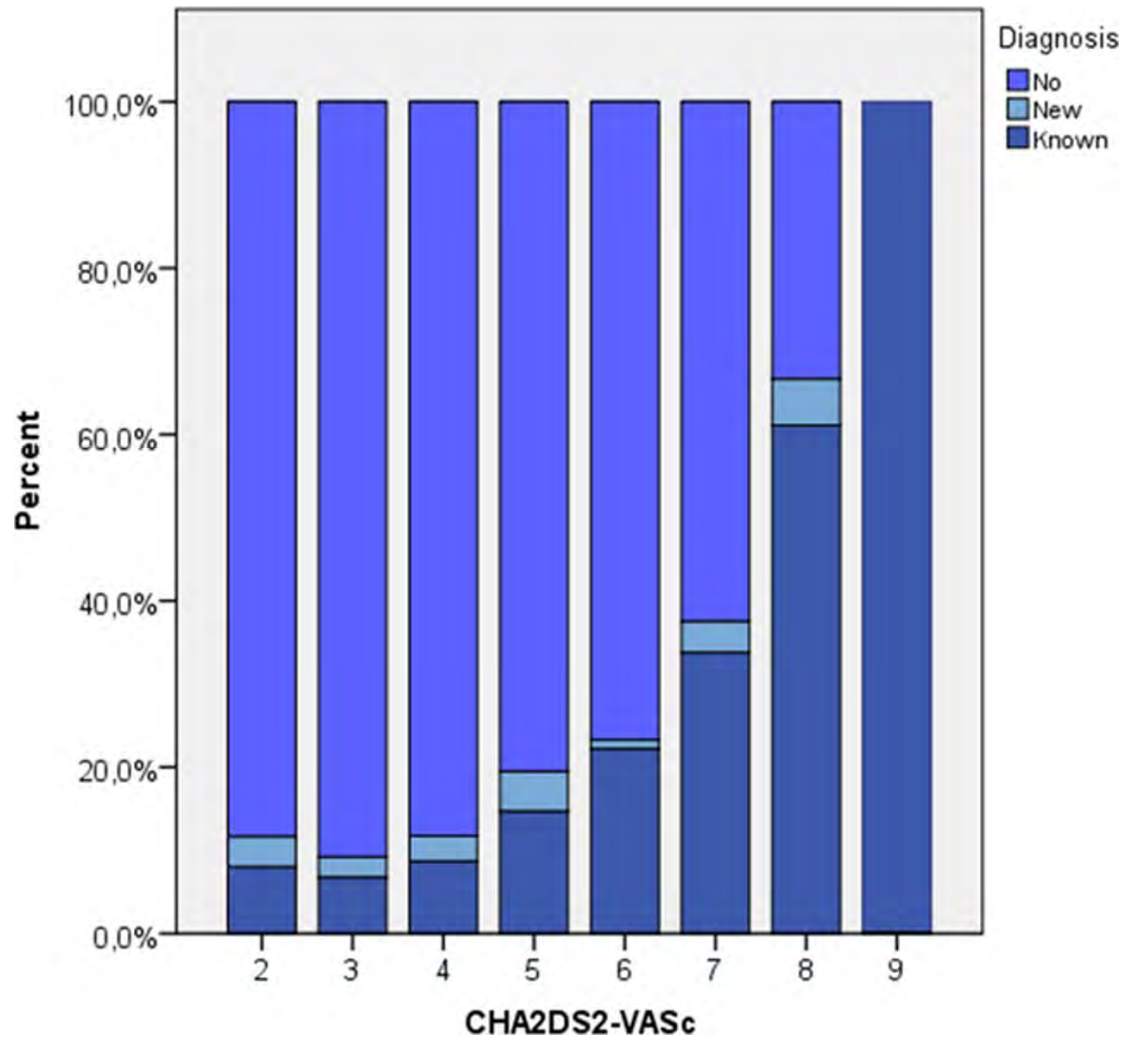
(Fredriksson et al ESC 206)

Time to first detection of atrial fibrillation among participants undergoing intermittent ECG registrations.

Association between CHA2DS2-VASc score and prevalence of atrial fibrillation (P<0.001, Kruskal-Wallis test).

Emma Svennberg et al. Circulation. 2015;131:2176-2184

Number of atrial fibrillation (AF) episodes recorded by intermittent ECG in individuals diagnosed with new AF.
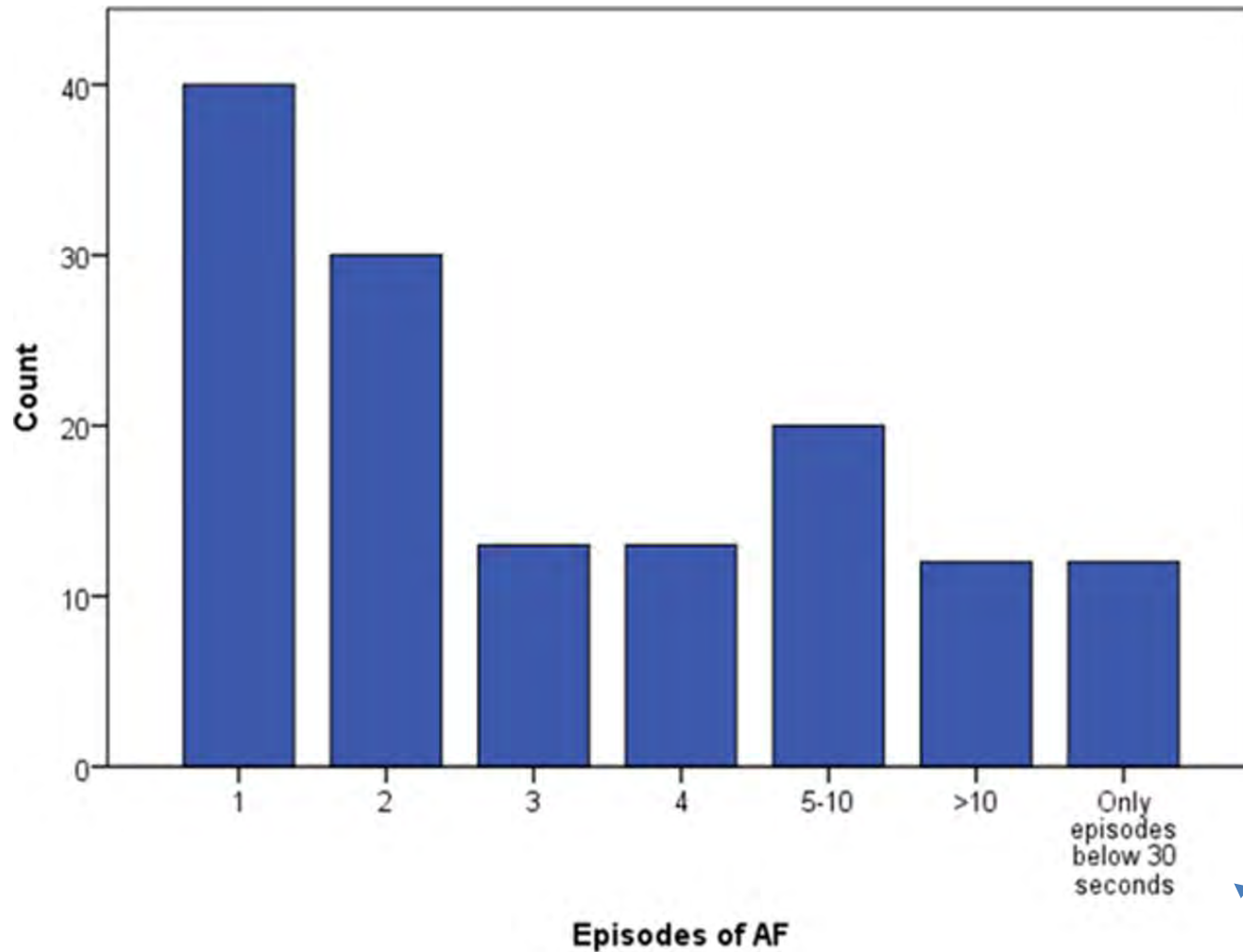
Emma Svennberg et al. Circulation. 2015;131:2176-2184

Long-term ECG, post cryptogenic stroke

Metaanalysis 6 studies n = 588 pts

The longer monitoring time, the more AF

24 - 48h	3.9-5.5%
72 h -159h	5.7-7.7 %

(Liao Stroke 2007)

Multivariate analysis for development of AF

Variable	Estimated ß (SE)	OR (95% CI)	*P* Value
Congestive heart failure (yes)	1.973 (0.168)	7.19 (5.18–9.98)	0.000
Hypertension (yes)	0.136 (0.091)	1.15 (0.96–1.37)	0.140
Diabetes mellitus (yes)	0.375 (0.126)	1.46 (1.14–1.86)	0.000
Previous stroke/TIA (yes)	0.821 (0.125)	2.27 (1.78–2.9)	0.000
Vascular disease (yes)	0.199 (0.137)	1.22 (0.93–1.6)	0.150
Sex (female)	−0.037 (0.132)	0.96 (0.74–1.25)	0.780
Height, cm	0.031 (0.008)	1.03 (1.02–1.05)	0.000
Weight, kg	0.014 (0.003)	1.01 (1.01–1.02)	0.000

(Svennberg et al Circulation 2015)

Screening for AF

- Aim:

    To find AF,

    treat with oral anticoagulation,

    before AF causes a stroke

CRYSTAL AF, NEJM 2014
Continuous monitoring after iscemic stroke (ILR)
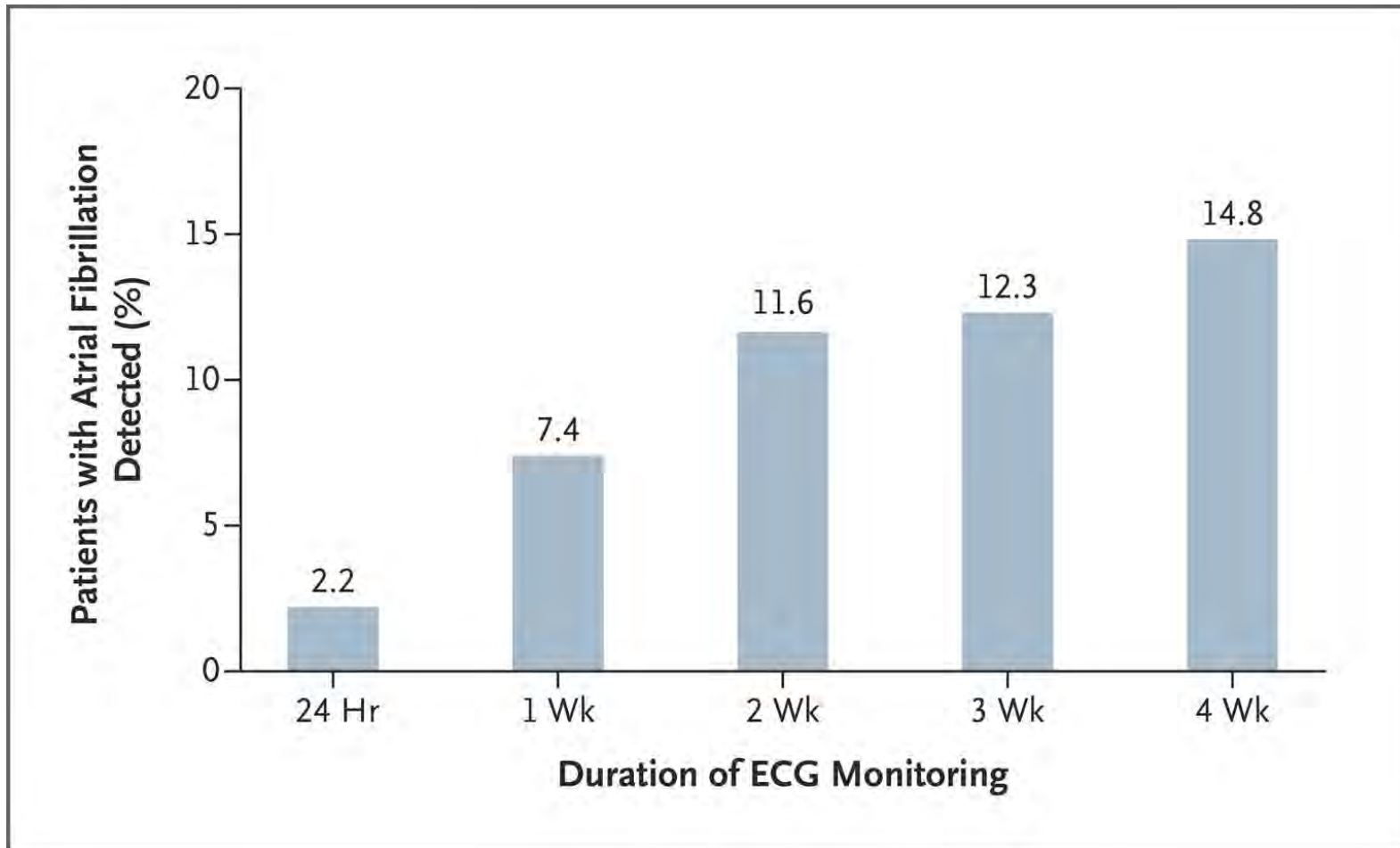
Patient case

- 76 year old woman
- Hypertension
- Diabetes type II
- No cardiac symptoms
- No previous diagnosis of AF

Patient case

She returns 5 weeks later with left hemiparesis.

Feb 2014 transient weakness left side, total recovery within 6 hours (TIA).

- 24 hour ECG monitoring: Sinus rhythm and one run of SVT, 5 beats
- CT: No infarct, no bleeding
- Carotid Doppler: normal
- Prescribed Clopidogrel and discharged

Can we find atrial fibrillation before a stroke and and prevent with oral anticoagulaton?

Realistic?
Cost effective?

Stroke Risk Stratification of AF Patients: The CHADS$_2$ VASC Score

Risk factor	Points
Congestive heart failure	1
Hypertension	1
Age >75	2
Diabetes mellitus	1
Stroke/TIA	2
Vascular disease	1
Age 65–74	1
Female sex	(1)
Maximum score	**9**

Annual stroke risk %

O	0.78
1	2.0
2	3.7
3	5.9
4	9.2
5	15.2
6	19.7
7	21.5
8	22.3

Paroxysmal versus permanenet AF Any difference in risk for stroke?

- In this 'real-world' contemporary observational registry, patients with non-paroxysmal AF had a worse outcome, in terms of all-cause mortality, which was related to a more severe clinical profile-

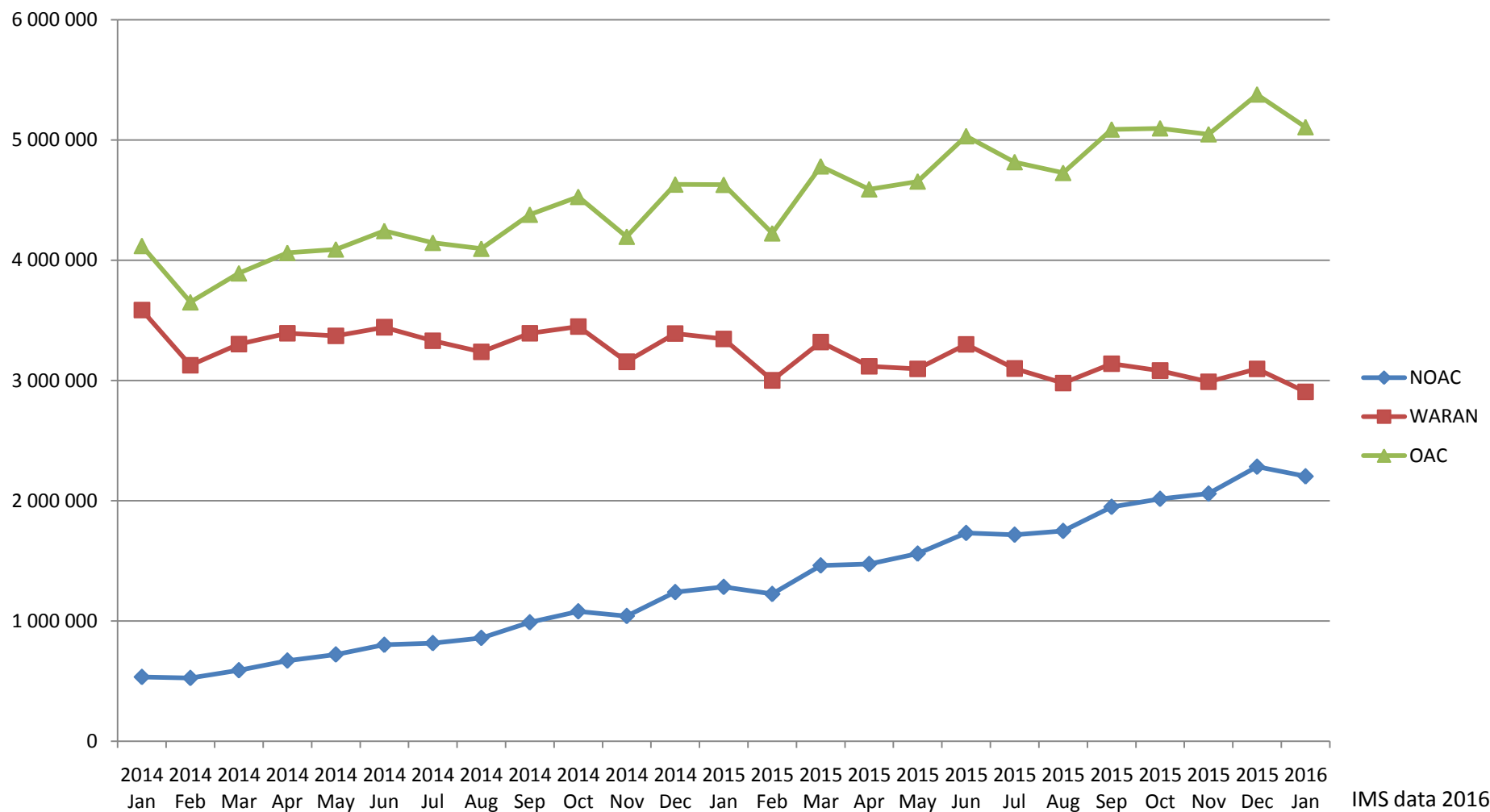- Boriani et al Europace 2016

Intermittent ECG

- Short episodes during a longer period

- Several times a day

- Certain times and when symptoms

Optimizing AF screening

- Do we have the optimal fishing equipment?
  - One method or several?
- Do we know the best fishing waters?
  - Which patients to screen?
- Do we improve catching?
  - Stroke reduction?

DDD by month in Sweden

IMS data 2016

Biological markers
for AF - NT-proBNP?

- ***Background:*** *NT pro BNP is related to AF and risk for stroke.The lower the BNP the lower the risk for stroke*

- ***Hypothesis***: NT-proBNP will be significantly higher in subjects with clinically silent AF compared to individuals where AF is not diagnosed

Pilot study: In a substudy to the STROKESTOP study NT-proBNP was analysed in 886 individuals

Screening for atrial fibrillation

Recommendations	Class	Leve
Opportunistic screening for AF is recommended by pulse taking or ECG rhythm strip in patients >65 years of age.	I	B
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.	I	B
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
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.	IIa	B
Systematic ECG screening may be considered to detect AF in patients aged >75 years, or those at high stroke risk.	IIb	B

EURO
SOCIE

Biological markers
for AF - NT-proBNP?

- ***Background:*** *NT pro BNP is related to AF and risk for stroke.The lower the BNP the lower the risk for stroke*

- ***Hypothesis***: NT-proBNP will be significantly higher in subjects with clinically silent AF compared to individuals where AF is not diagnosed

Pilot study: In a substudy to the STROKESTOP study NT-proBNP was analysed in 886 individuals

New groups to be screened
Risk factors for stroke CHADSVASC

65-75 yrs

> 50% have CHADSVASC 2p

Congestive Heart Failure

>40% have CHADSVASC 2p

Diabetics T2

>40% have CHADSVASC 2p

Renal insufficiency

DDD by month in Sweden

IMS data 2016
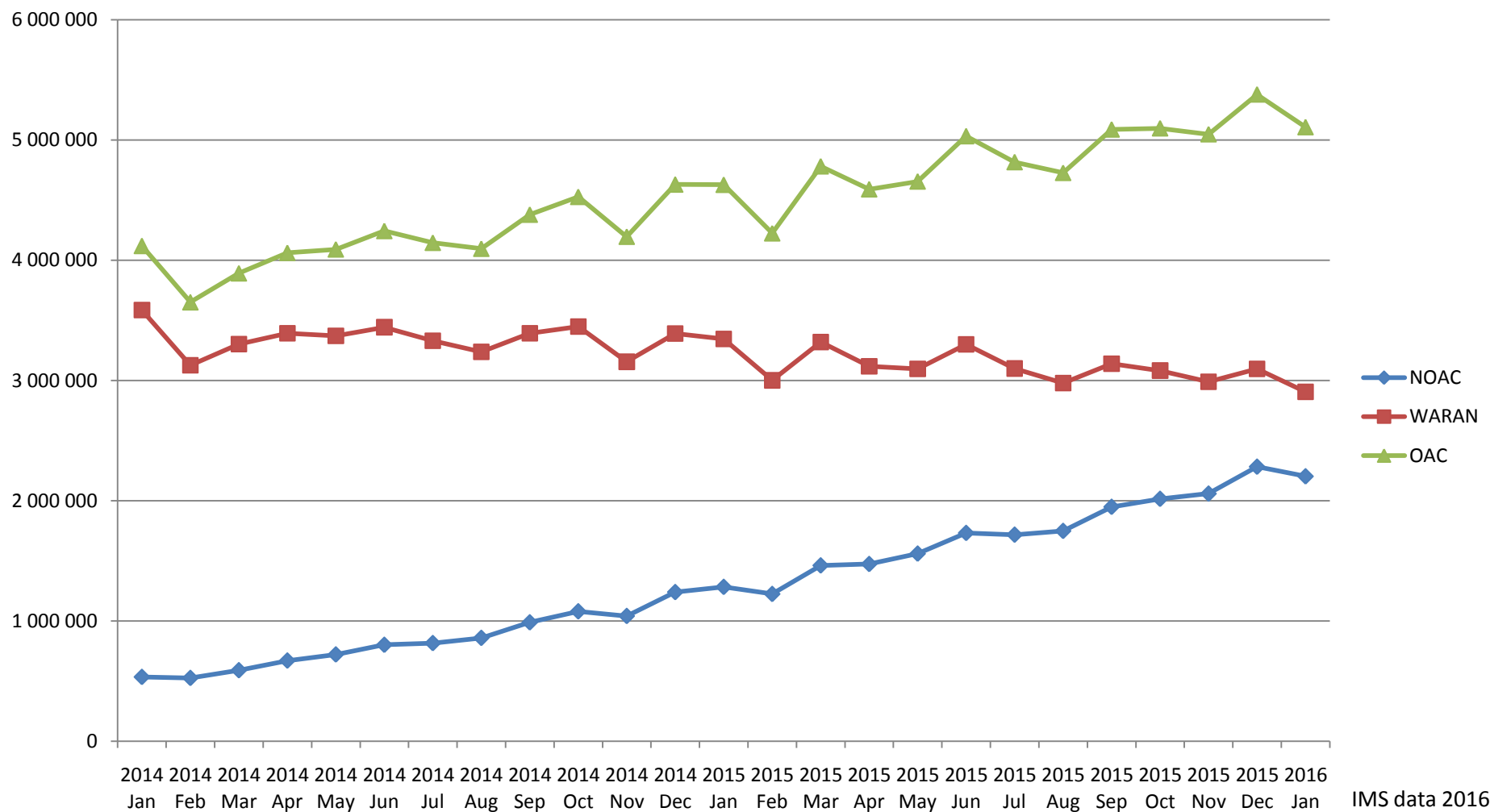
Most important

- Fishing for under treatment among patients with a diagnosis of AF!
- Inexpensive
- Catch guarantee

Atrial Fibrillation

3.4 % of the adult population

Five-fold increased risk for stroke

Risk patients can be identified

Many AF patients no symptoms

Screening according to
The Swedish Council on Health
Technology Assessment 2014

Screening should be reserved for risk groups only!

CHADSVASC 2 or more?

Improved participation

Decentralized screening

Home visits by district nurses to 75 yrs old

Different languages in invitation letter

Future tasks

- Further risk groups to be defined
- Screening program more efficient, biomarkers
- Improved participation rates
- Implementation of a National Screening Program

Uppcoming studies

A. Can the screening progam be more effective by using biomarkers?
pro-NT BNP, biomarker screening

B. Increase participation in the screening
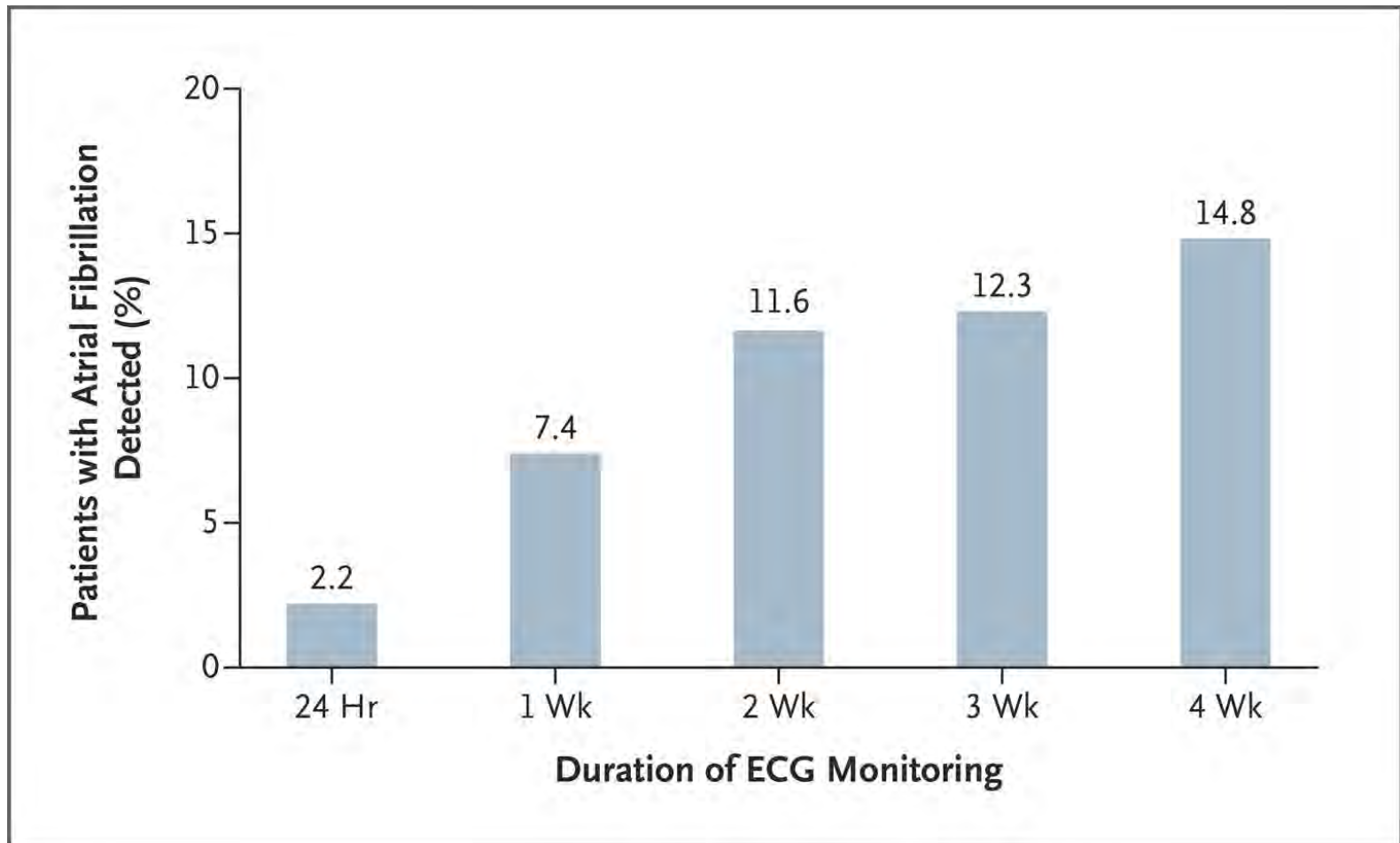

C. Other risk groups to be screened

Looking for atrial fibrillation, how?

- Regular pulse check
- Resting ECG
- Long term ECG 24, 48,72 hours
- Intermittent ECG
- Implantable loop tecorder

CRYSTAL AF, NEJM 2014
Continuous monitoring after iscemic stroke (ILR)

AF Detection on iPhone ECG
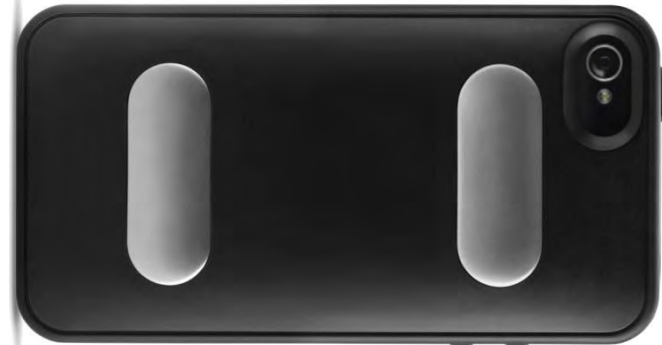
	Sensitivity	,Specificity	Accuracy	Kappa
Learning set (n = 109)				
Cardiologist A	100%	90%	94%	0.87
Cardiologist B	95%	94%	95%	0.88
Original algorithm	87%	97%	94%	0.86
Optimized algorithm	100%	96%	97%	0.94
Validation set (n = 204)	Algorithm was optimized by increasing weighting of absence of P waves			
Optimized algorithm	98%	97%	97%	0.92

Lau JK, et al. International Journal of Cardiology 2013;165:193-4

Stroke Risk Stratification of AF Patients: The CHADS$_2$ VASC Score

Risk factor	Points
Congestive heart failure	1
Hypertension	1
Age >75	2
Diabetes mellitus	1
Stroke/TIA	2
Vascular disease	1
Age 65–74	1
Female sex	1
Maximum score	**9**

Annual stroke risk %

O	0.78
1	2.0
2	3.7
3	5.9
4	9.2
5	15.2
6	19.7
7	21.5
8	22.3

147 684

Stroke Risk Stratification of AF Patients: The CHADS$_2$ VASC Score

Risk factor	Points
Congestive heart failure	1
Hypertension	1
Age >75	2
Diabetes mellitus	1
Stroke/TIA	2
Vascular disease	1
Age 65–74	1
Female sex	1
Maximum score	**9**

Annual stroke risk %

O	0.78
1	2.0
2	3.7
3	5.9
4	9.2
5	15.2
6	19.7
7	21.5
8	22.3

Stroke Risk Stratification of AF Patients: The CHADS$_2$ VASC Score

Risk factor	Points
Congestive heart failure	1
Hypertension	1
Age >75	2
Diabetes mellitus	1
Stroke/TIA	2
Vascular disease	1
Age 65–74	1
Female sex	1
Maximum score	**9**

Annual stroke risk %

O	0.78
1	2.0
2	3.7
3	5.9
4	9.2
5	15.2
6	19.7
7	21.5
8	22.3

Patient case

- 75 year old woman   3p
- Hypertension   1p
- Diabetes type II   1p
- Stroke/TIA   2p

                                                 Total 7p

Annual stroke risk 20%   (ESC guidelines)

Stroke Risk Stratification of AF Patients: The CHADS$_2$ VASC Score

Risk factor	Points
Congestive heart failure	1
Hypertension	1
Age >75	2
Diabetes mellitus	1
Stroke/TIA	2
Vascular disease	1
Age 65–74	1
Female sex	1
Maximum score	**9**

Annual stroke risk
%

O	0.78
1	2.0
2	3.7
3	5.9
4	9.2
5	15.2
6	19.7
7	21.5
8	22.3

Adherence to OAC

Beyer-Westdorf Europace 2016

gonist

150   200   250   300   350   400