LA PRESCRIZIONE DI TERAPIA ANTICOAGULANTE DOPO IL RISCONTRO DI FIBRILLAZIONE ATRIALE TRAMITE MONITORAGGIO CON DEVICES IMPIANTABILI

Practice Variation in Anticoagulation Prescription and Outcomes After Device-Detected Atrial Fibrillation

Insights From the Veterans Health Administration

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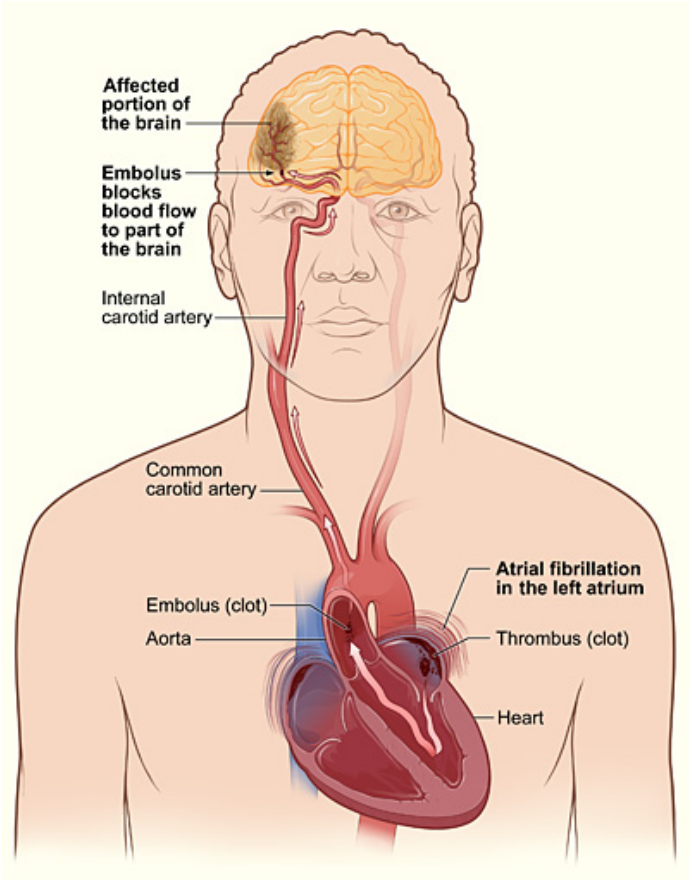
Circulation. 2019;139:2502–2512.

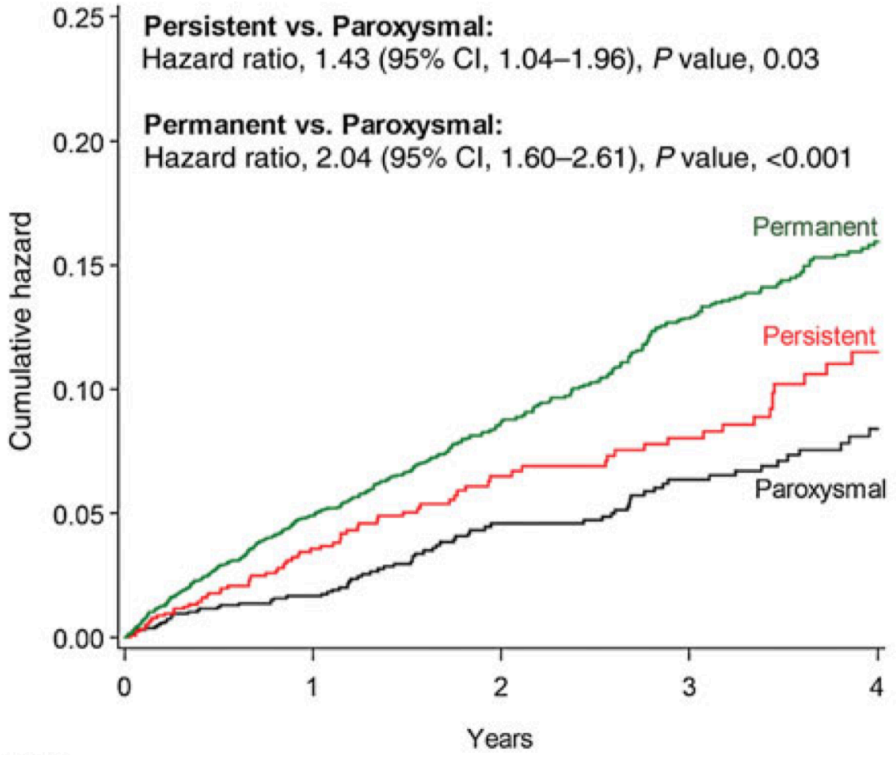
BACKGROUND

- In patients with clinical atrial fibrillation (AF), oral anticoagulation (OAC) has been shown to prevent stroke, with current consensus statements recommending OAC prescription based on clinical risk factors independent of AF pattern or burden

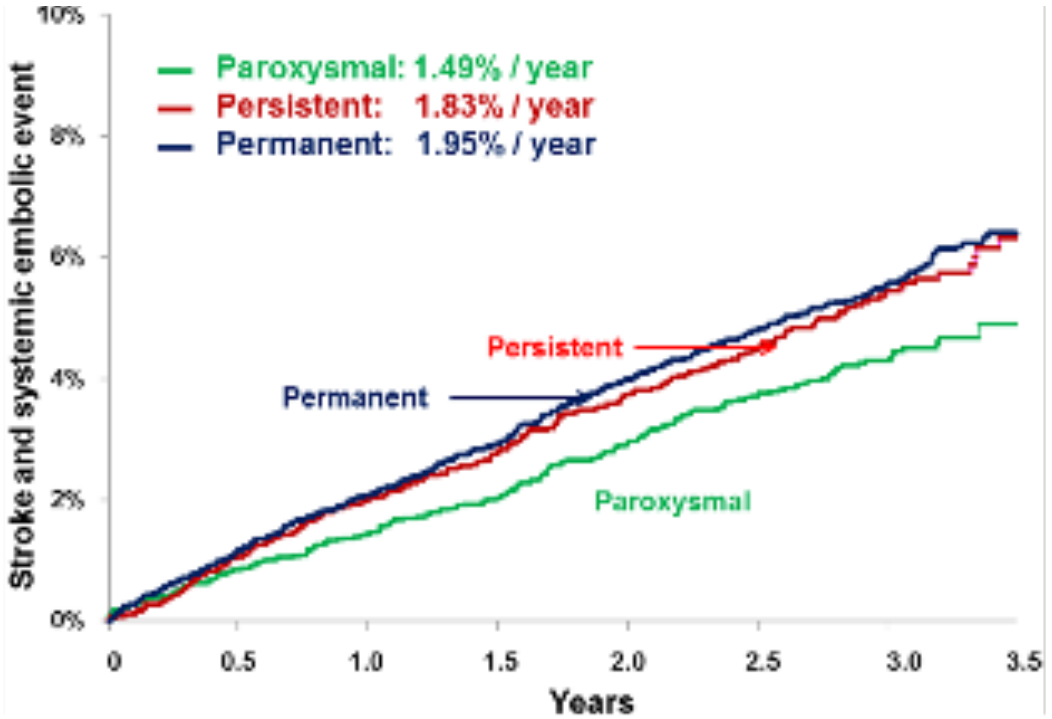


BACKGROUND

- AF pattern or burden may impact risk



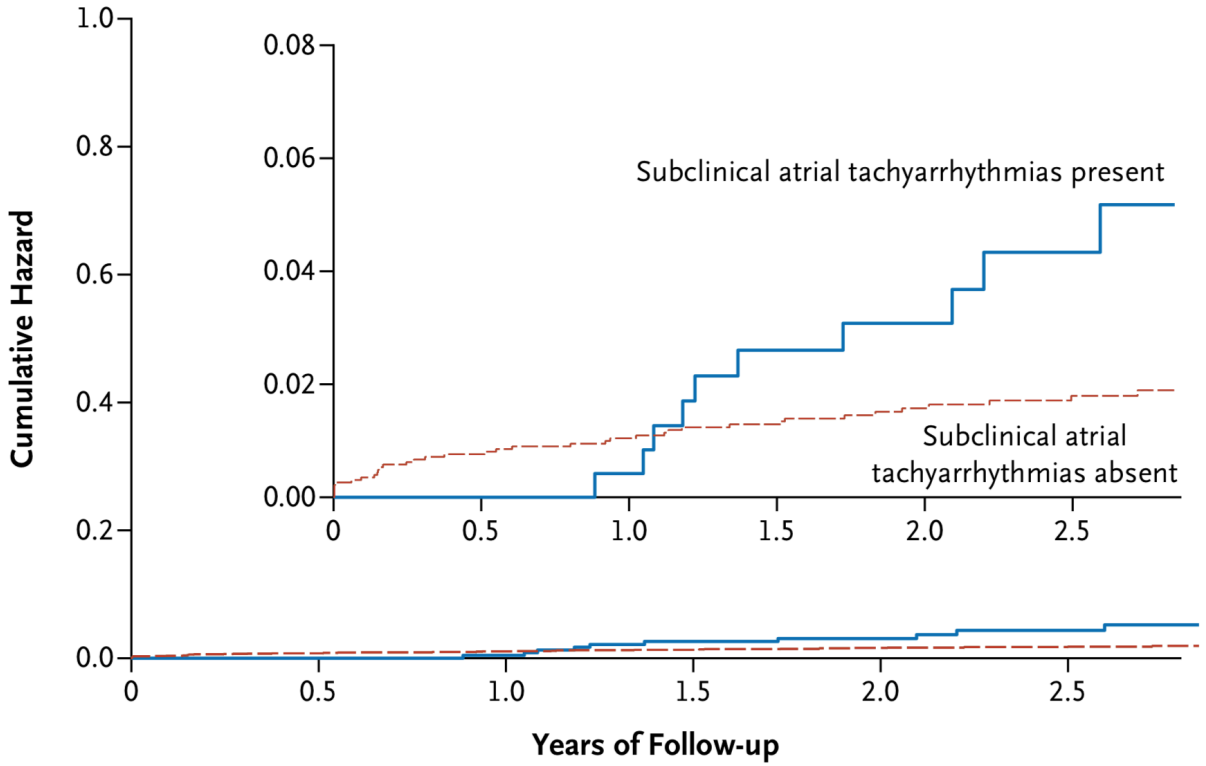
European Heart Journal (2015) 36, 281–287



Circ Arrhythm Electrophysiol. 2017;10:e004267.

BACKGROUND

- Atrial high rate episodes (AHRE) detected by cardiac implantable electronic devices (CIED) lasting 6 minutes or more have been associated with stroke



HR, 2.49; 95% CI, 1.28 to 4.85; P=0.007

N Engl J Med 2012;366:120-9.

Background- 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation

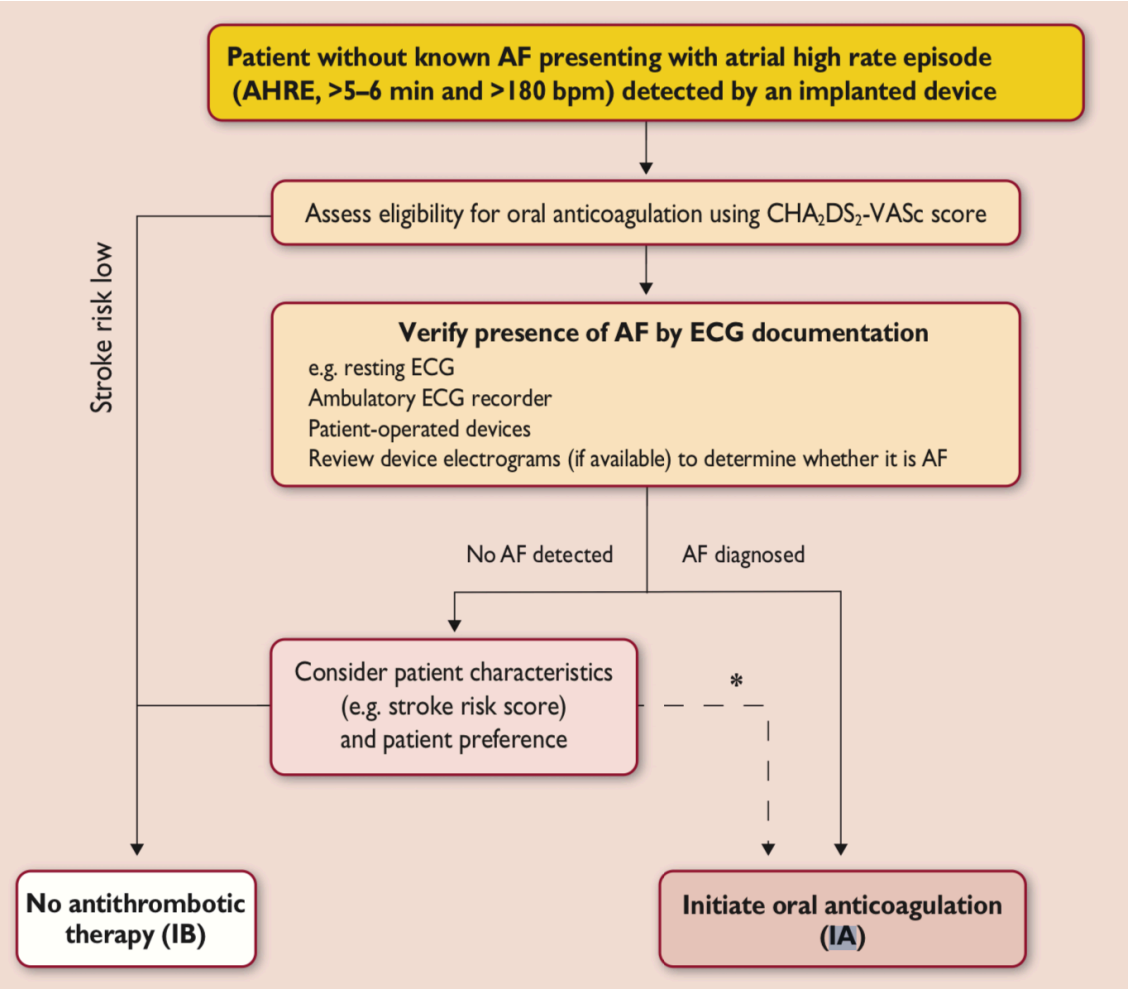
COR	LOE	Recommendations
I	B-NR	1. In patients with cardiac implantable electronic devices (pacemakers or implanted cardioverter-defibrillators), the presence of recorded atrial high-rate episodes (AHREs) should prompt further evaluation to document clinically relevant AF to guide treatment decisions (S7.12-1–S7.12-5).

1. Patients with AHREs detected by implanted devices are at increased risk of stroke and abundant data now link device-detected atrial tachycardia or AF (or AHREs) with the development of thromboembolic events (S7.12-1–S7.12-5). Remote monitoring with AHRE alerts increases the likelihood of detecting silent AF. However, it is unclear whether patients with AHREs benefit from oral anticoagulation. Careful review of stored electrograms may confirm the presence of AF and rule out false positive events. Occasionally, the addition of extended external electrocardiographic monitoring may be needed if data from the implanted device are uncertain. Prospective clinical trials of prophylactic anticoagulation based on device-detected AF are under way but have not been completed. Although increased duration of AHREs is associated with increased stroke risk, the threshold duration of AHREs that warrants anticoagulation is unclear. Current approaches factor in the duration of device-detected AF and the patient's stroke risk profile, bleeding risk, and preferences to determine whether to initiate long-term anticoagulation.

J Am Coll Cardiol. 2019 Jan 21. pii: S0735-1097(19)30209-8.

Background-2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS

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	141, 156



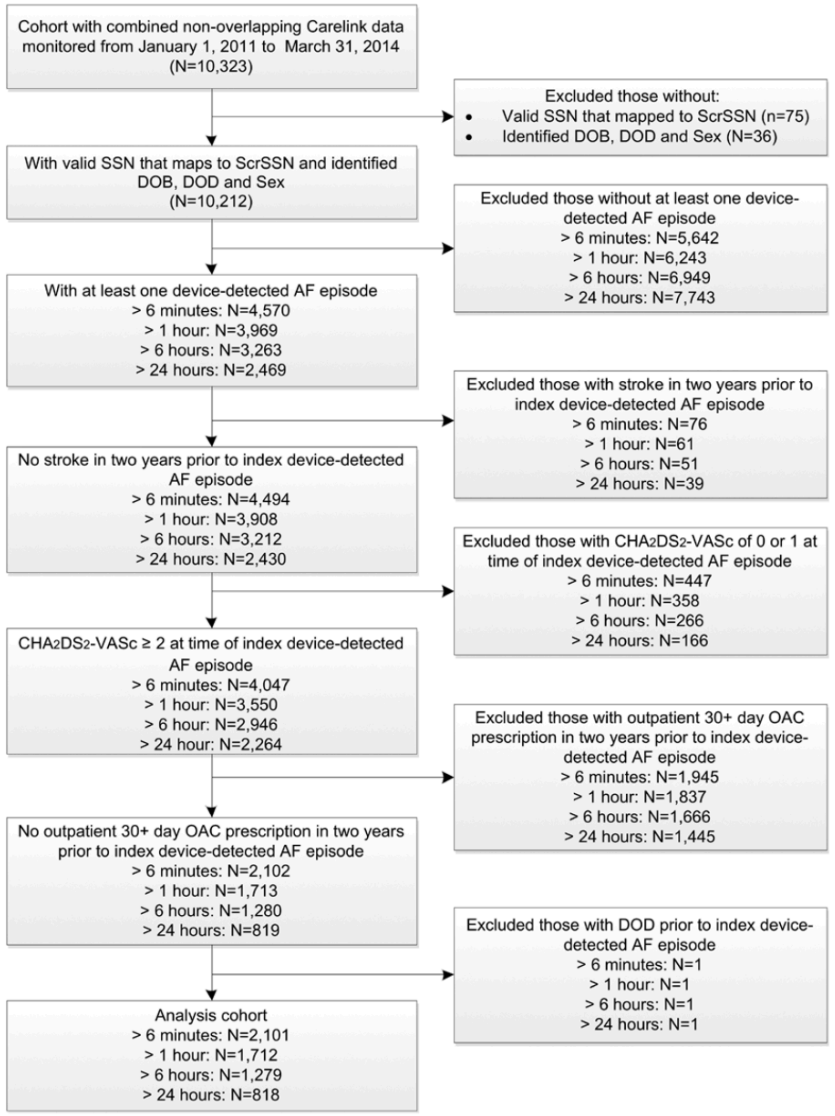
European Heart Journal (2016) 37, 2893–2962

AIM OF THE STUDY

- Examine practice variation in OAC prescription after device-detected AF, by linking datasets of CIED remote monitoring and data from the Veterans Health Administration, the largest integrated health care system in the United States

- Examine the association of OAC prescription to stroke by device- detected AF burden

COHORT SELECTION DIAGRAM



- **Inclusion criteria**
  - Enrollment in the VA NCDSP from January 1, 2011 through March 31, 2014
  - Medtronic CIED with an atrial lead capable of detecting and transmitting data on atrial tachyarrhythmias (pacemaker or defibrillator, with or without cardiac resynchronization) or insertable cardiac monitor
  - At least one day with device-detected AF burden ≥ 6 minutes (atrial rate > 170 beats per minute in most devices).
- **Exclusion criteria** (2y before index device-detected AF episode)
  - Primary diagnosis of stroke
  - Baseline CHA2DS2-VASc score of 0 or 1
  - OAC (warfarin or non-vitamin K antagonist oral anticoagulants [NOAC]) prescription of at least 30 days.

OUTCOME ANALYZED

- Primary outcome: OAC prescription (warfarin or NOAC) within 90- days of index episode of device-detected AF with day-level burden > 1 hour.
- Site variation of OAC prescription within 90-days of device-detected AF > 24 hours for sites included in the > 1 hour site variation analysis.
- Incidence rates of stroke as primary diagnosis and death by OAC prescription status and device-detected AF burden.

BASELINE CHARACTERISTICS

OAC in pts with more comorbidities

Demographics		ICD (N=1398)			PPM/ICM (N=314)		
	Total (N=1712)	No OAC (n=1171)	OAC (n=227)	*P* Value*	No OAC (n=268)	OAC (n=46)	*P* Value*
Age, y	71.5±9.6	71.1±9.5	68.9±8.4	0.001	75.1±9.8	73.0±8.0	0.18
Male	1686 (98.5)	1159 (99.0)	223 (98.2)	0.34	259 (96.6)	45 (97.8)	0.67
Race				0.21			0.57
White	1467 (85.7)	985 (84.1)	199 (87.7)		243 (90.7)	40 (87.0)	
Black	155 (9.1)	117 (10.0)	21 (9.3)		13 (4.9)	4 (8.7)	
Clinical AF†	598 (34.9)	388 (33.1)	85 (37.4)	0.21	99 (36.9)	26 (56.5)	0.01
Hypertension	1411 (82.4)	948 (81.0)	199 (87.7)	0.02	225 (84.0)	39 (84.8)	0.89
Heart failure	1239 (72.4)	952 (81.3)	203 (89.4)	0.0031	71 (26.5)	13 (28.3)	0.80
Prior stroke/TIA	161 (9.4)	108 (9.2)	17 (7.5)	0.40	32 (11.9)	4 (8.7)	0.52
Prior MI	196 (11.5)	141 (12.0)	38 (16.7)	0.05	13 (4.9)	4 (8.7)	0.29
Diabetes mellitus	814 (47.6)	556 (47.5)	129 (56.8)	0.001	104 (38.8)	25 (54.4)	0.05
Coronary artery disease	1267 (74.0)	933 (69.8)	185 (76.8)	0.03	147 (43.4)	25 (50.0)	0.38
Peripheral vascular disease	182 (10.6)	126 (9.4)	22 (9.1)	0.88	27 (8.0)	7 (14.0)	0.16
Charlson Comorbidity Index	3.0±1.7	3.1±1.7	3.4±1.6	0.04	2.4±1.7	2.4±1.9	0.99
$CHADS_2$ score	2.5±1.2	2.5±1.1	2.6±1.0	0.10	2.2±1.2	2.3±1.2	0.12

BASELINE CHARACTERISTICS

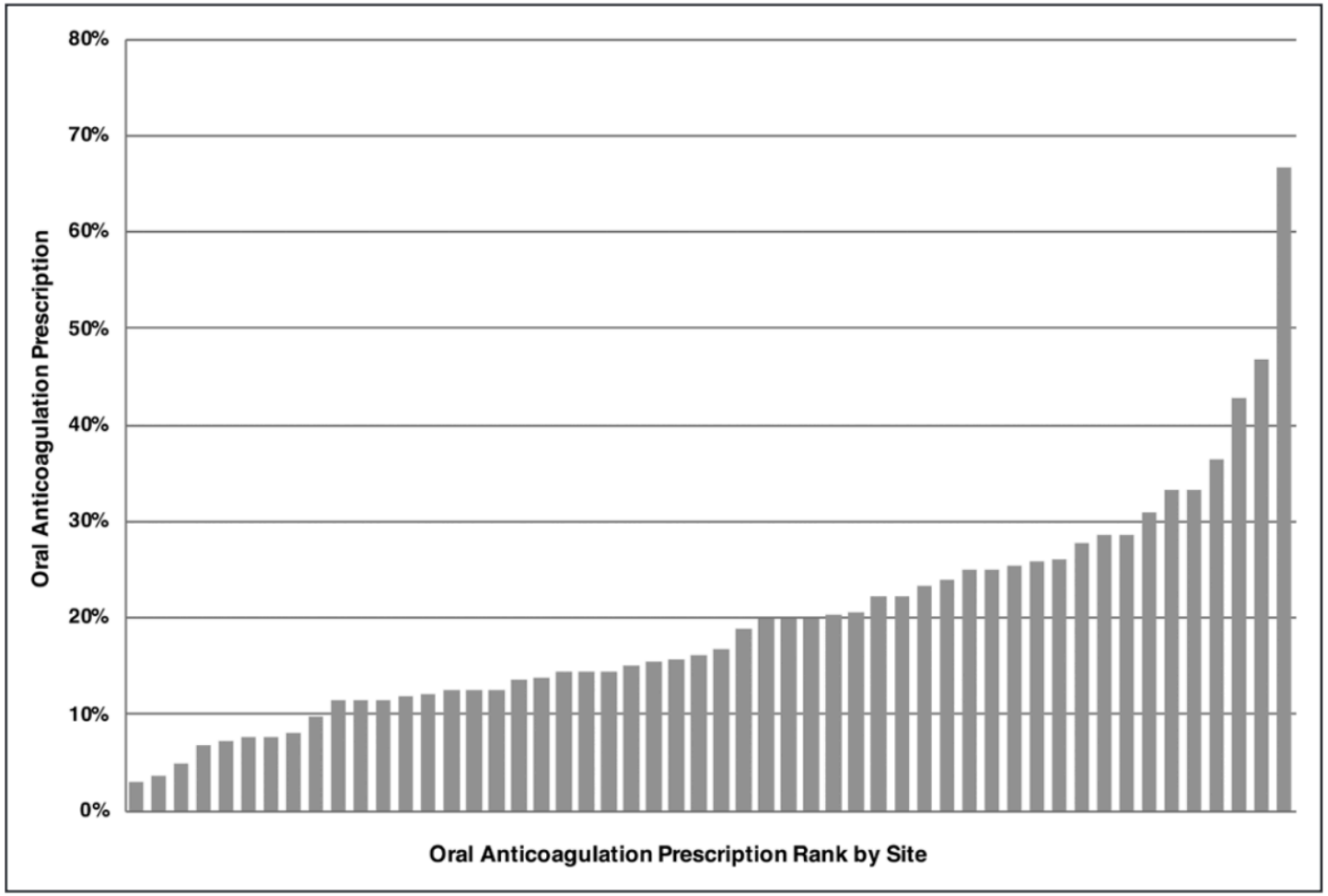
NO differences in ischemic or haemorragic risk

Demographics	Total (N=1712)	ICD (N=1398)			PPM/ICM (N=314)		
		No OAC (n=1171)	OAC (n=227)	*P* Value*	No OAC (n=268)	OAC (n=46)	*P* Value*
$CHADS_2$ score group				0.02			0.91
0–1	358 (20.9)	226 (19.3)	42 (17.4)		90 (33.6)	14 (30.4)	
2–3	1091 (63.7)	758 (64.7)	167 (73.6)		141 (52.6)	25 (54.4)	
4–6	263 (15.4)	187 (16.0)	32 (14.1)		37 (13.8)	7 (15.2)	
CHA_2DS_2-VASc score	4.0±1.4	4.0±1.4	4.1±1.3	0.42	3.7±1.5	3.7±1.5	0.91
HAS-BLED score‡	2.6±1.1	2.6±1.0	2.6±1.1	0.52	2.7±1.0	2.8±1.2	0.64
Baseline medications§							
Aspirin	385 (22.5)	257 (22.0)	54 (23.8)	0.54	64 (23.9)	10 (21.7)	0.75
Clopidogrel	218 (12.7)	149 (12.7)	28 (12.3)	0.87	36 (13.4)	5 (10.9)	0.63
ACE inhibitor/ARB	929 (54.3)	632 (54.0)	126 (55.5)	0.67	146 (54.5)	25 (54.4)	0.99
Diuretic	821 (48.0)	561(47.9)	112 (49.3)	0.69	128 (47.8)	20 (43.5)	0.59
Niacin/fibrates	157 (9.2)	107 (9.1)	13 (5.7)	0.09	34 (12.7)	3 (6.5)	0.23
Statin	1000 (58.4)	919 (58.2)	218 (56.0)	0.43	152 (56.7)	24 (52.2)	0.57
Class 1 AAD	22 (1.3)	16(1.4)	0	0.08	5 (1.87)	1 (2.2)	0.89
Class 3 AADǁ	80 (4.7)	54 (4.6)	8 (3.5)	0.47	16 (6.0)	2 (4.4)	0.66
Amiodarone	97 (5.7)	66 (5.6)	9 (4.0)	0.31	17 (6.3)	5 (10.9)	0.27
β-Blockers	1041 (60.8)	710 (60.6)	141 (62.1)	0.68	165 (61.6)	25 (54.4)	0.35
Calcium channel blockers¶	42 (2.5)	26 (2.2)	7 (3.1)	0.43	8 (3.0)	1 (2.0)	0.76

PROPORTION RECEIVING ORAL ANTICOAGULATION BY INDEX DEVICE-DETECTED AF EPISODE BURDEN

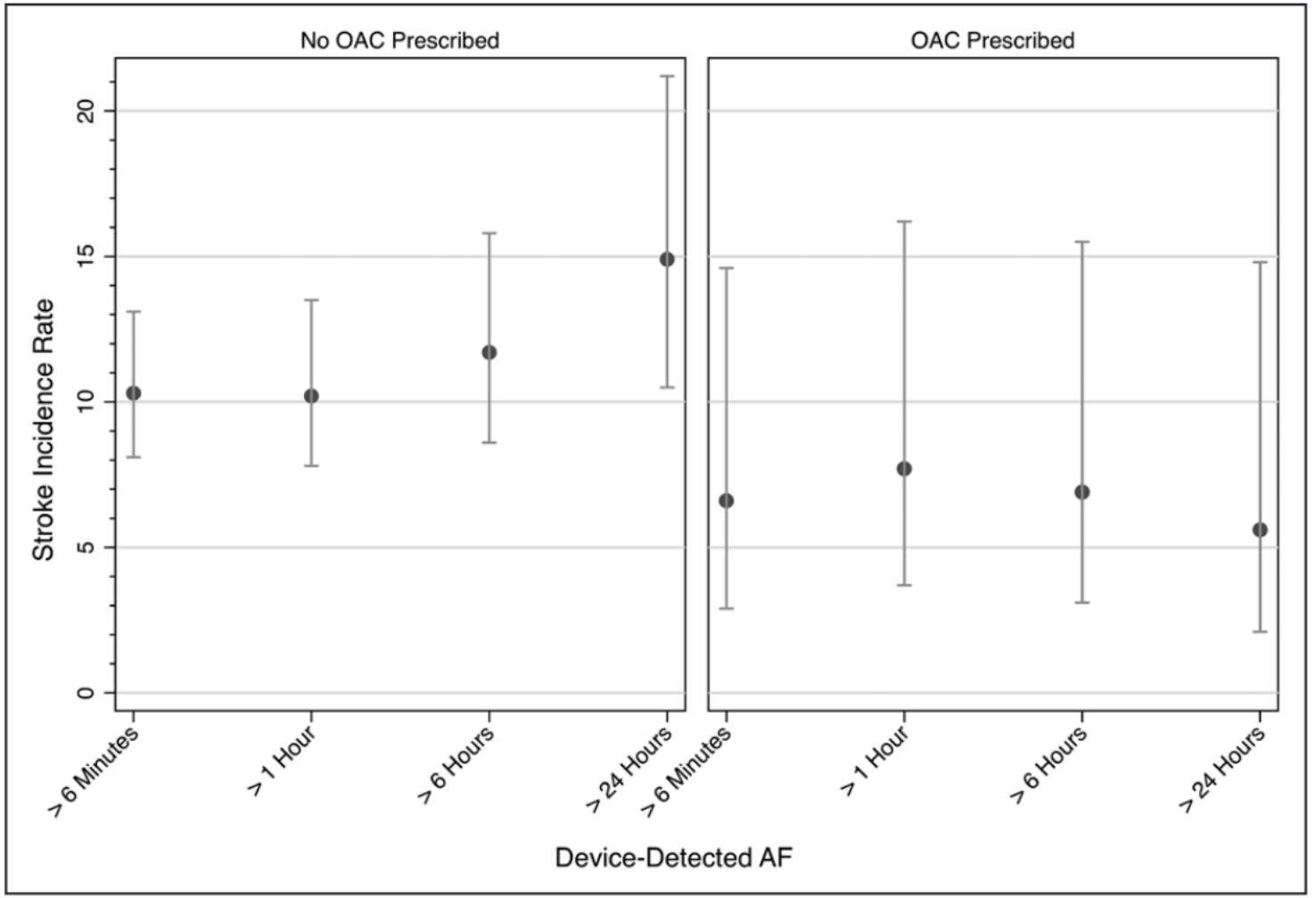
Cohorts' Baseline and Outcome Variables	Index Device-Detected AF Episode Burden			
	>6 min	>1 h	>6 h	>24 h
Included patients	2101	1712	1279	818
CHA_2DS_2-VASc score	3.9±1.4	4.0±1.4	4.0±1.4	4.2±1.4
HAS-BLED score*	2.7±1.1	2.6±1.1	2.7±1.1	2.8±1.1
OAC prescribed†‡	272 (13.0)	273 (16.0)	263 (20.6)	224 (27.4)
Warfarin	258 (94.9)	257 (94.1)	246 (93.5)	208 (92.9)
NOAC	14 (5.1)	17 (6.2)	18 (6.8)	18 (8.0)
Days from device-detected AF to OAC	31.2±24.6	31.9±24.4	30.7±24.0	33.3±24.1

OAC PRESCRIPTION FOR DEVICE-DETECTED AF>1 HOUR BY SITE



- Median site OAC prescription proportion: 16% (IQR: 12%-25%)
- 10% of sites with OAC prescription proportion less than 8%

STROKE INCIDENCE



STROKE INCIDENCE

Device-Detected AF Burden	Total		No OAC*		OAC*		
	n/N (%)	IR (95% CI)	n/N (%)	IR (95% CI)	n/N (%)	IR (95% CI)	*P* Value†
AF >6 min‡							
Stroke	72/2101 (3.4)	9.9 (7.8–12.4)	66/1829 (3.6)	10.3 (8.1–13.1)	6/272 (2.2)	6.6 (2.9–14.6)	0.28
Death	587/2101 (27.9)	92.5 (85.3–100.3)	518/1829 (28.3)	93.3 (85.6–101.7)	69/272 (25.4)	87.1 (68.6–110.3)	0.60
AF >1 h‡							
Stroke	58/1712 (3.4)	9.8 (7.6–12.7)	51/1439 (3.5)	10.2 (7.8–13.5)	7/273 (2.6)	7.7 (3.7–16.2)	0.50
Death	503/1712 (29.4)	99.4 (91.1–108.5)	429/1439 (29.3)	100.4 (91.3–110.3)	74/273 (27.1)	94.4 (75.1–118.5)	0.63
AF >6 h‡							
Stroke	47/1279 (3.7)	10.7 (8.1–14.3)	41/1016 (4.0)	11.7 (8.6–15.8)	6/263 (2.3)	6.9 (3.1–15.5)	0.23
Death	395/1279 (20.9)	106.1 (96.1–117.1)	324/1016 (31.9)	108.7 (97.5–121.2)	71/263 (27.0)	95.8 (75.9–120.9)	0.34
AF >24 h‡							
Stroke	35/818 (4.3)	12.5 (9.0–17.4)	31/594 (5.2)	14.9 (10.5–21.2)	4/224 (1.8)	5.6 (2.1–14.8)	0.04
Death	297/818 (36.3)	129.0 (115.1–144.5)	234/594 (39.4)	139.3 (122.5–158.3)	63/224 (28.1)	101.1 (79.0–129.4)	0.02

ASSOCIATION OF OAC PRESCRIPTION TO STROKE BY BURDEN OF DEVICE- DETECTED AF

IPTW: Inverse probability of treatment weights

Device-Detected AF Burden	Unadjusted*		Multivariable Regression*†		Propensity-Adjusted With IPTW*‡	
	HR§ (95% CI)	*P* Value	HR§ (95% CI)	*P* Value	HR§ (95% CI)	*P* Value
AF >6 min	0.63 (0.27–1.45)	0.27	0.62 (0.26–1.43)	0.29	0.67 (0.45–0.99)	0.04
AF >1 h	0.77 (0.35–1.71)	0.52	0.79 (0.35–1.77)	0.57	0.88 (0.57–1.36)	0.56
AF >6 h	0.57 (0.24–1.33)	0.19	0.52 (0.22–1.25)	0.14	0.59 (0.37–0.95)	0.03
AF >24 h	0.34 (0.12–0.95)	0.04	0.28 (0.10–0.81)	0.02	0.27 (0.14–0.54)	0.0002

Variables with univariate associations with $P < 0.10$

- CIED type
- age
- clinical AF
- hypertension
- heart failure
- myocardial infarction
- diabetes
- CHADS2 score
- niacin/fibrates prescription
- statin prescription

WHAT IS NEW?

- Among Veterans with CIED, device-detected AF is common.
- Large practice variation in 90-day OAC initiation after new device-detected AF with substantially lower treatment rates as compared to clinical AF.
- In pts not prescribed OAC, stroke incidence increased as burden of device-detected AF increased.
- The strongest association of OAC with reduction in stroke observed after device-detected AF > 24h.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Large variation in prescription of OAC after device-detected AF highlights the uncertainty in optimal treatment strategies, failure to effectively utilize available clinical data sources, or both.

- Higher stroke incidence with increasing burden of device-detected AF in patients not anticoagulated, supports treating AF as a non-binary entity.

- Although confirmation of treatment benefit awaits results from ongoing RCT, observational data supports initiation of oral anticoagulation after device-detected atrial fibrillation > 24 hours.

ONGOING RCTS

- **Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA)**
  - NCT01938248
  - 4000 pts
  - Aims to determine if treatment with apixaban, compared with aspirin, will reduce the risk of ischemic stroke and systemic embolism in patients with device-detected sub-clinical AF and additional risk factors for stroke.
- **Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes (NOAH)**
  - NCT02618577
  - 2686
  - The objective of the trial is to demonstrate that OAC using the NOAC edoxaban is superior to current therapy to prevent stroke, systemic embolism, or cardiovascular death in patients with AHRE and at least two stroke risk factors but without AF.