

Tailored Anticoagulation in Atrial Fibrillation

CURRENT TRENDS and FUTURE PERSPECTIVES

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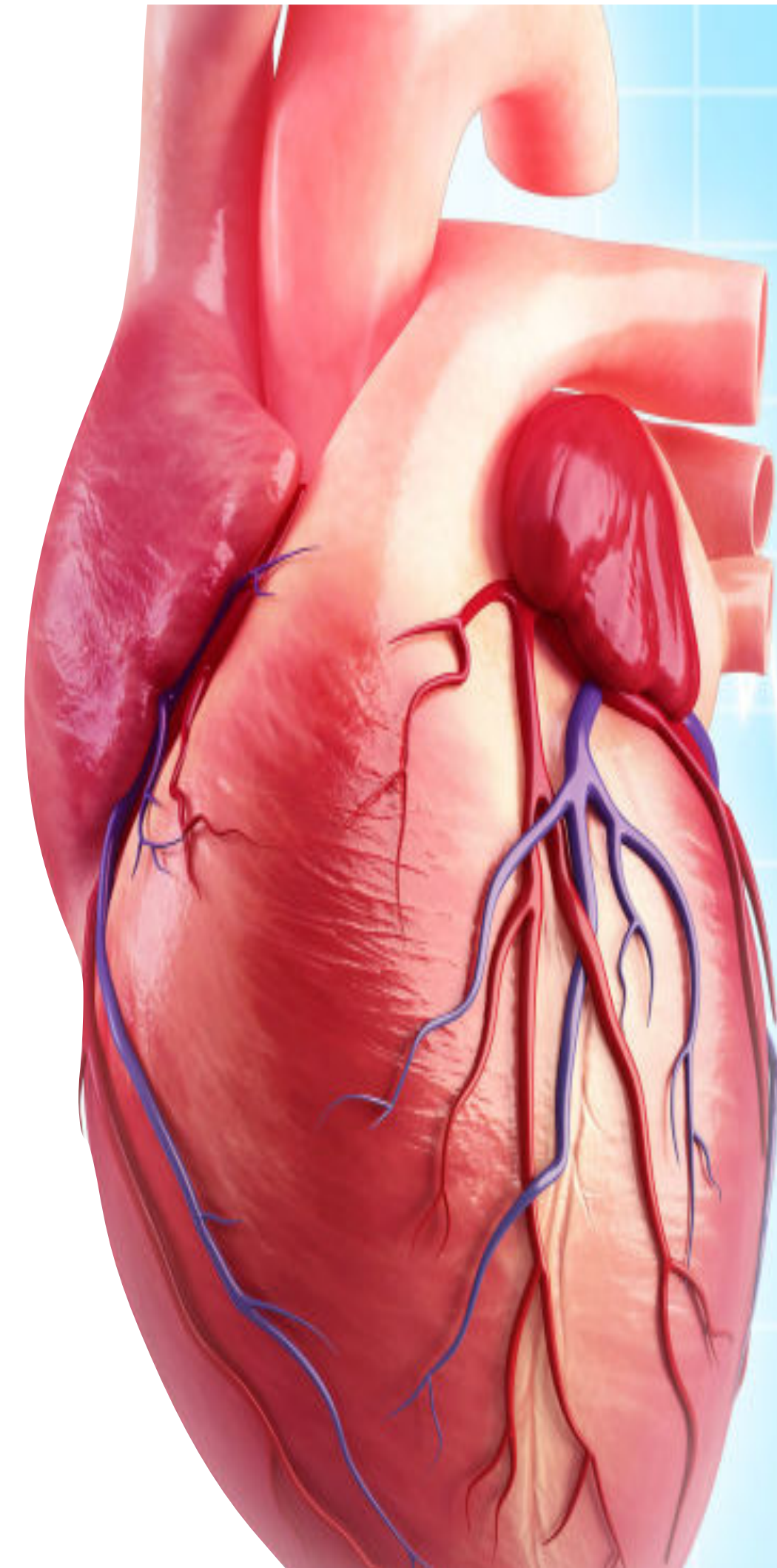
Disclosures

- Advisory Board: Boehringer Ingelheim, Menarini
- Speakers' honorarium: Boehringer Ingelheim, Menarini, Servier, LRI Therapharma, Otsuka, Amgen
- **I have no investment in pharmaceutical and medical device companies**



At the turn of the 21st Century

- Atrial fibrillation continue to pose significant health burden
- Guidelines recommend chronic anticoagulation for high stroke risk (CHADSVASC score) for paroxysmal, persistent, permanent; for symptomatic or asymptomatic
- Non-Vitamin K oral anticoagulants (NOACs) revolutionized stroke prevention



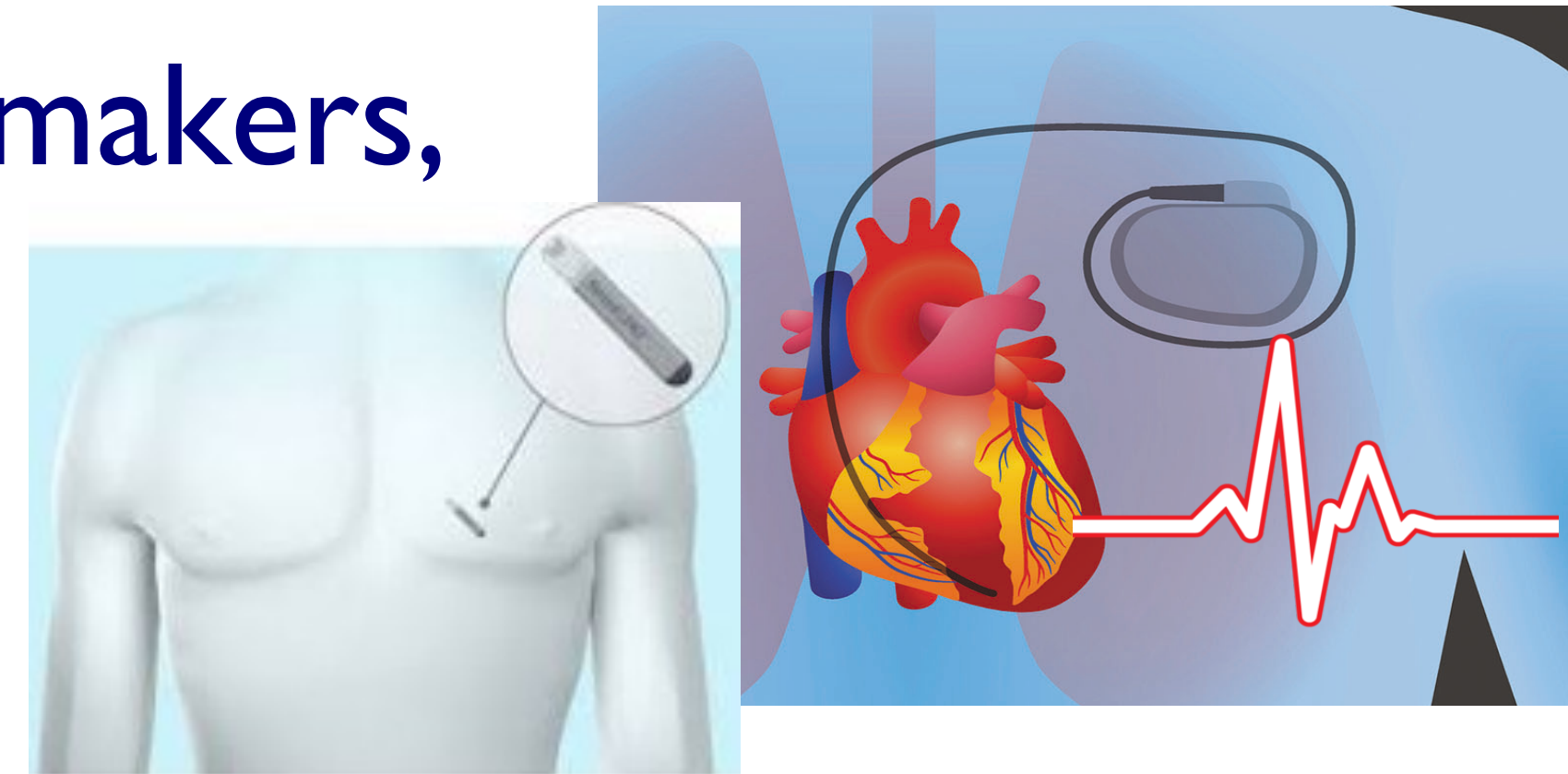
At the turn of the 21st Century

- Convergence of medicine and technology
- Tremendous boom in cardiovascular technology
- Advent of mobile electronic health applications
- Advent of mobile electronic health applications —> benefits of using mobile health in modifying behavior to improve cardiovascular health



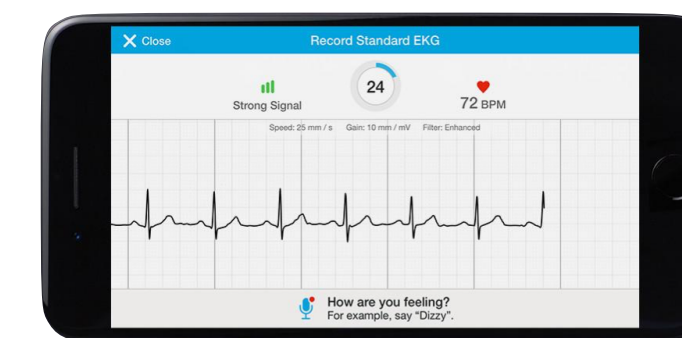
At the turn of the 21st Century

- Cardiac implantable electronic devices (pacemakers, defibrillators, loop recorders) have improved capabilities to detect arrhythmias



- Wearable technology has allowed for monitoring for and detecting arrhythmias such as AF

- Smartphones now capable of recording ECG tracings and detecting abnormal rhythms

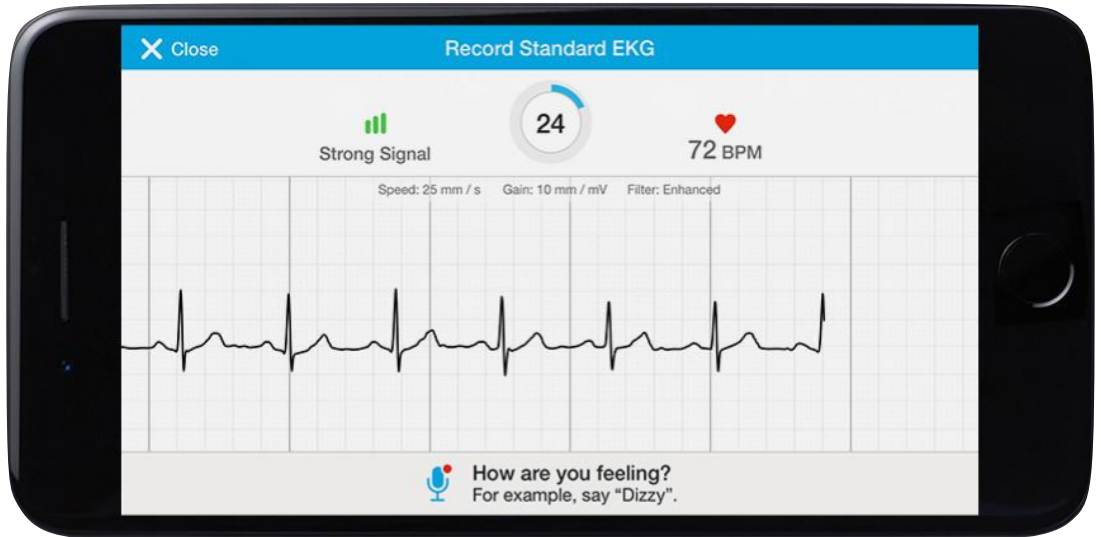


Atrial Fibrillation

- Palpitations, heart failure, stroke, mortality
- Majority of episodes are asymptomatic
- Anticoagulation is warranted for high stroke risk regardless of presence of symptoms, regardless of duration of AF
- Recent data allude to AF burden in relation to thromboembolic risk
- Devices have allowed for an improved and intensive continuous monitoring for episodes of AF, including asymptomatic episodes.



Devices have changed the landscape of AF detection

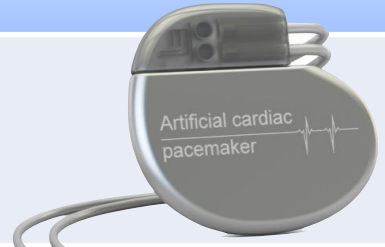






Terminology

Term	Definition/Criteria
Asymptomatic AF	AF diagnosed incidentally or by ECG in patients with no symptoms, or with EHRA score 1 Clearly established AF diagnosis, undergoing defined clinical management but who remain asymptomatic based on physician's evaluation
Silent AF	synonymous with asymptomatic AF; AF diagnosis established through screening; documented AF in the absence of any symptoms or prior diagnosis often presented with a complication (i.e. stroke)
Atrial high rate episodes (AHRE)	atrial tachycardia episodes (rate >190 bpm) recorded by intra-atrial electrode of cardiac implantable electronic devices
Subclinical AF	AF diagnosed through screening programs, incidental findings on ECG, or after implanted device electrograms analysis, with lack of correlated symptoms
Clinical AF	AF whether symptomatic or asymptomatic, that is diagnosed by surface ECG



Improving AF Detection: Implanted Cardiac Devices

STUDY	AF Detection Tool	Results	Remarks
MOST Trial 	AF detected as AHRE on cardiac pacemakers	Subclin AF predicted clinical AF (HR 5.9)	Subclin AF associated with stroke/mortality HR 2.8
ASSERT Trial 	AF detected (as atrial high rate episodes AHRE) on cardiac pacemakers	Subclin AF in >40% without previous AF, led to ECG documented AF in 15% cases	Subclin AF associated with 2.5 increase in stroke
EMBRACE Trial 	AF detection on prolonged ambulatory ECG (event recorder) vs Holter	AF detected 16.1% on prolonged monitoring vs 3.2% (absolute diff 12.9%, NNT 8)	improved AF detection in cryptogenic stroke
CRYSTAL AF Trial 	AF detected on implanted cardiac monitoring devices	Improved AF detection on longer monitoring: 8.9% at 6 mos., 12.4% at 12 mos., 30% at 36 mos.	improved AF detection in cryptogenic stroke 8.8x more than standard monitoring AF detection prompted anticoagulation in 97%
REVEAL AF Trial 	AF detected on implanted cardiac monitoring devices	AF detected 6.2% at 30 days; 29.3% at 18 mos; 40% at 30 mos.	AF detection prompted anticoagulation in 56.3%

Smartphone ECG Studies: Improving AF Detection

STUDY	Features	Results	Remarks
Desteghe et al. Europace 2016	AliveCor and MyDiagnostik ECG screening for AF in 445 hospitalized geriatric pts	Cardiology MyDiagnostik: Sens 81.8% Specif 94.2% AliveCor Sens 54.5% Specif 97.5% Geriatrics MyDiagnostik: Sens 89.5% Specif 95.7% AliveCor Sens 78.9% Specif 97.9%	
Chan P et al. Circulation 2016	AliveCor and Microlife WatchBP office AFIB for AF screening in 2,052 pts	AliveCor Sens 56.6% Specif 99.4% Microlife Sens 83.3% Specif 98.7%	
Chan and Choy. Heart 2017	Smartphone AliveCor ECG screening of 13,122 Hong Kong citizens	0.8% newly diagnosed AF (65% asymptomatic) Sens 67% Specif 99%	CHADSVASC score of new AF 3.5
Halcox J et al. REHEARSE-AF study. Circulation 2017	Smartphone AliveCor ECG screening of 65 yo and above with CHADSVASC ≥ 2 ; 1,004 pts	AliveCor yielded 3.9x better diagnosis of AF	
SPOT AF trial 2018	Kardia Mobile AliveCor use to detect AF vs Holter monitoring in 294 pts with acute stroke or TIA	AliveCor: detected AF in 8.5% of stroke pts Holter: 2.7%	Detected AF triggered treatment with anticoagulant in 44%

Chan N-Y, Choy C-C. Heart. 2017;103(1): 24–31.

Desteghe L, Raymaekers Z, Lutin M et al. Europace. 2016; doi:10.1093/europace/euw025

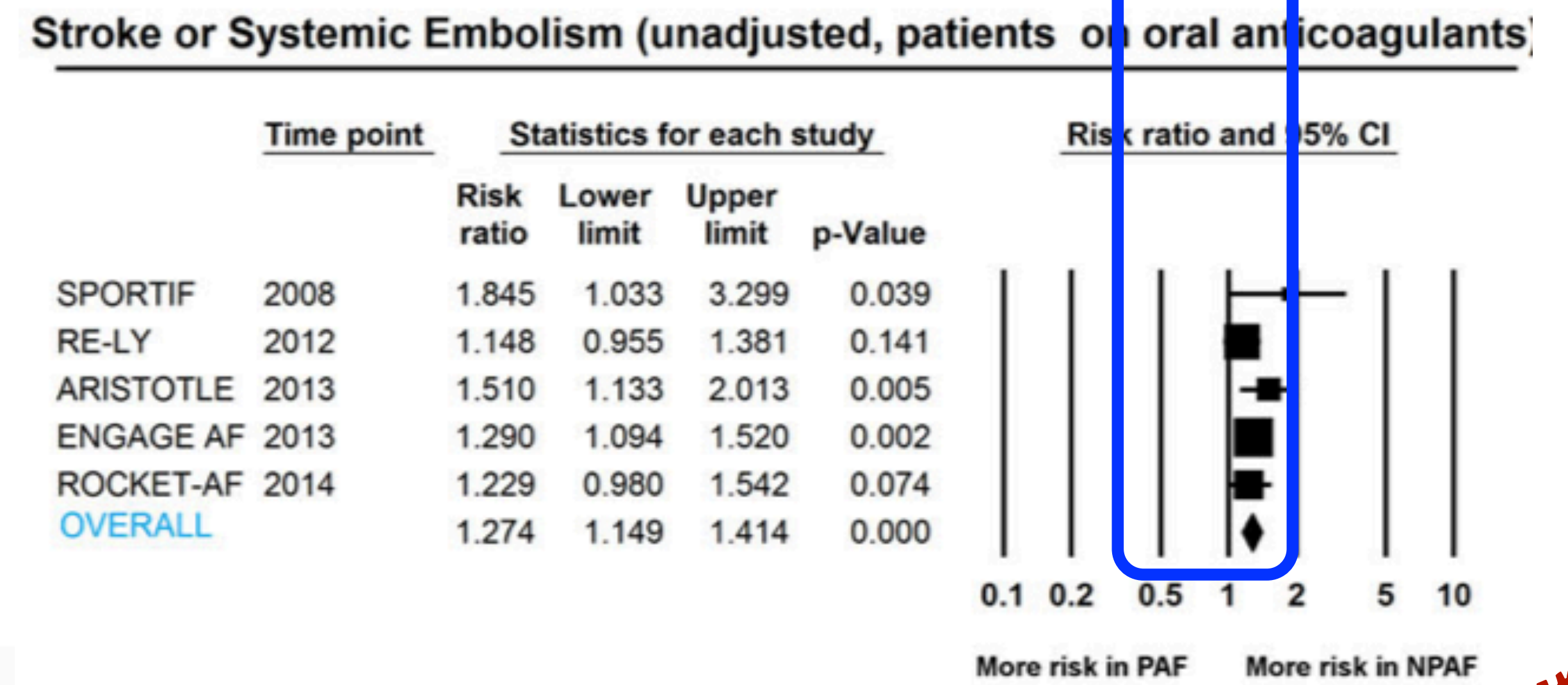
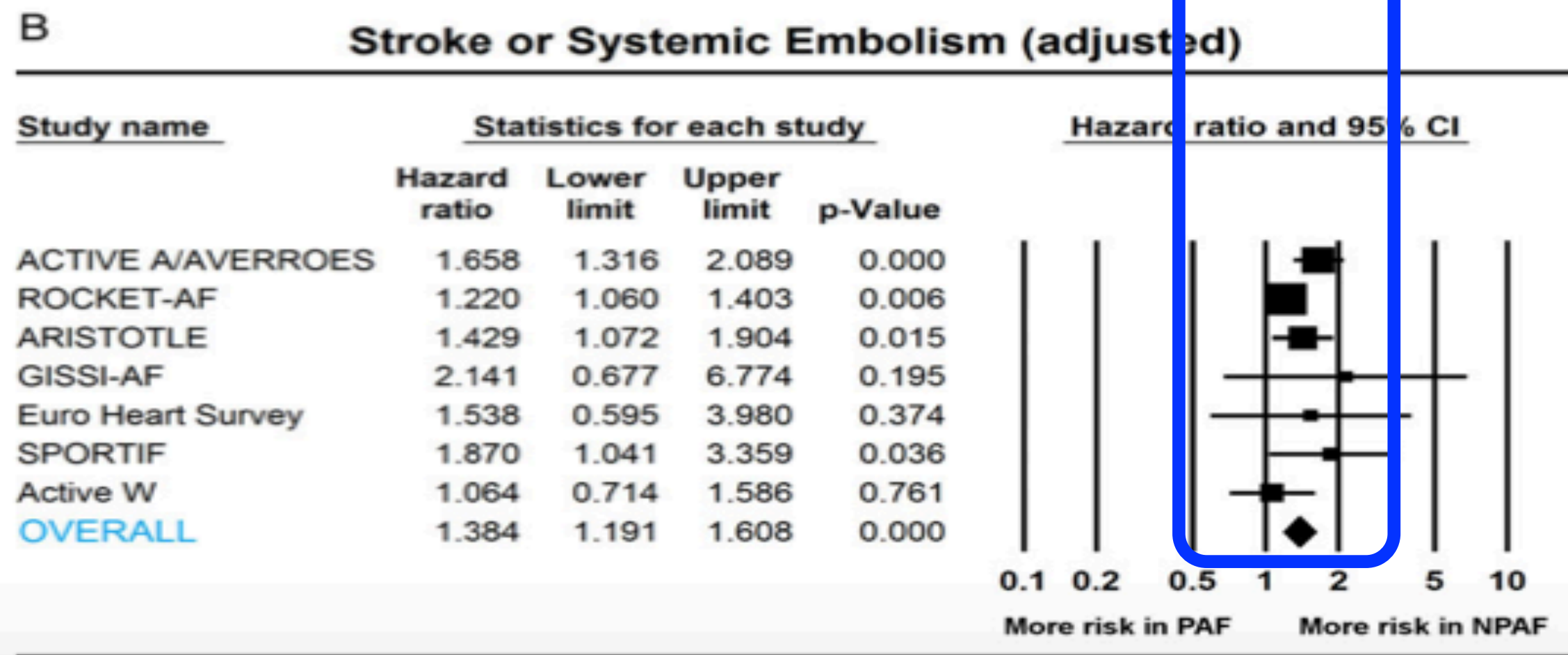
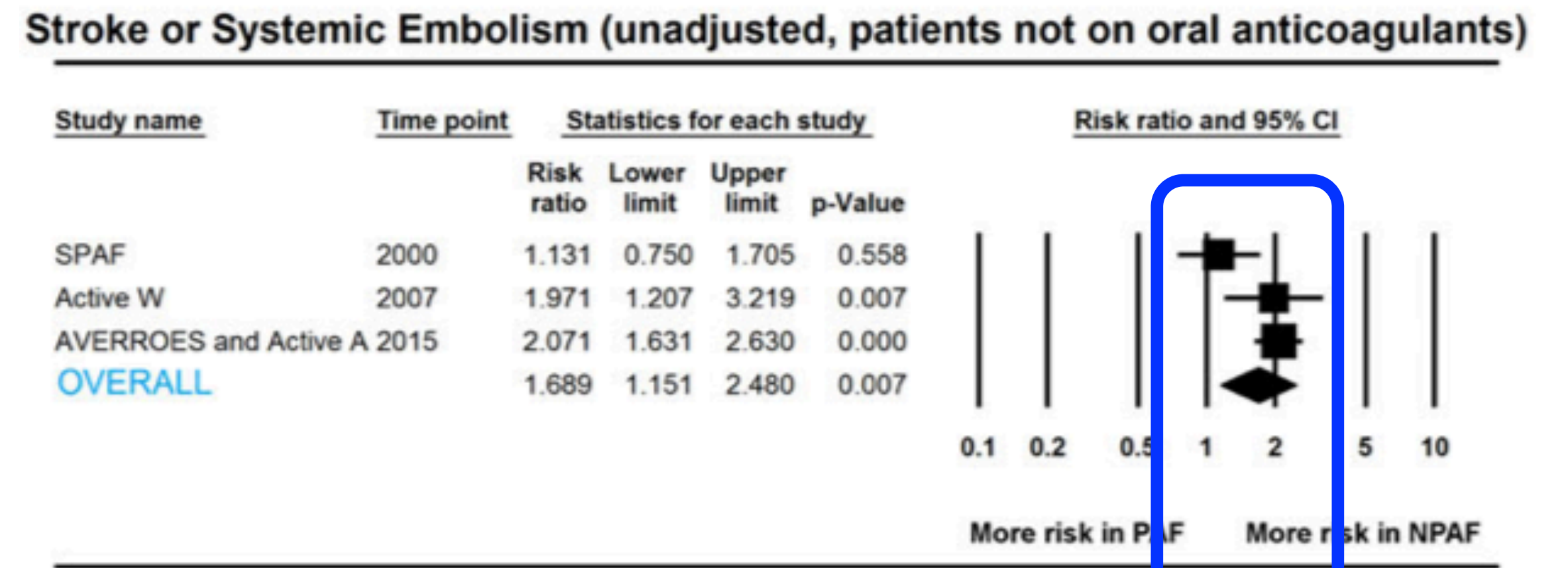
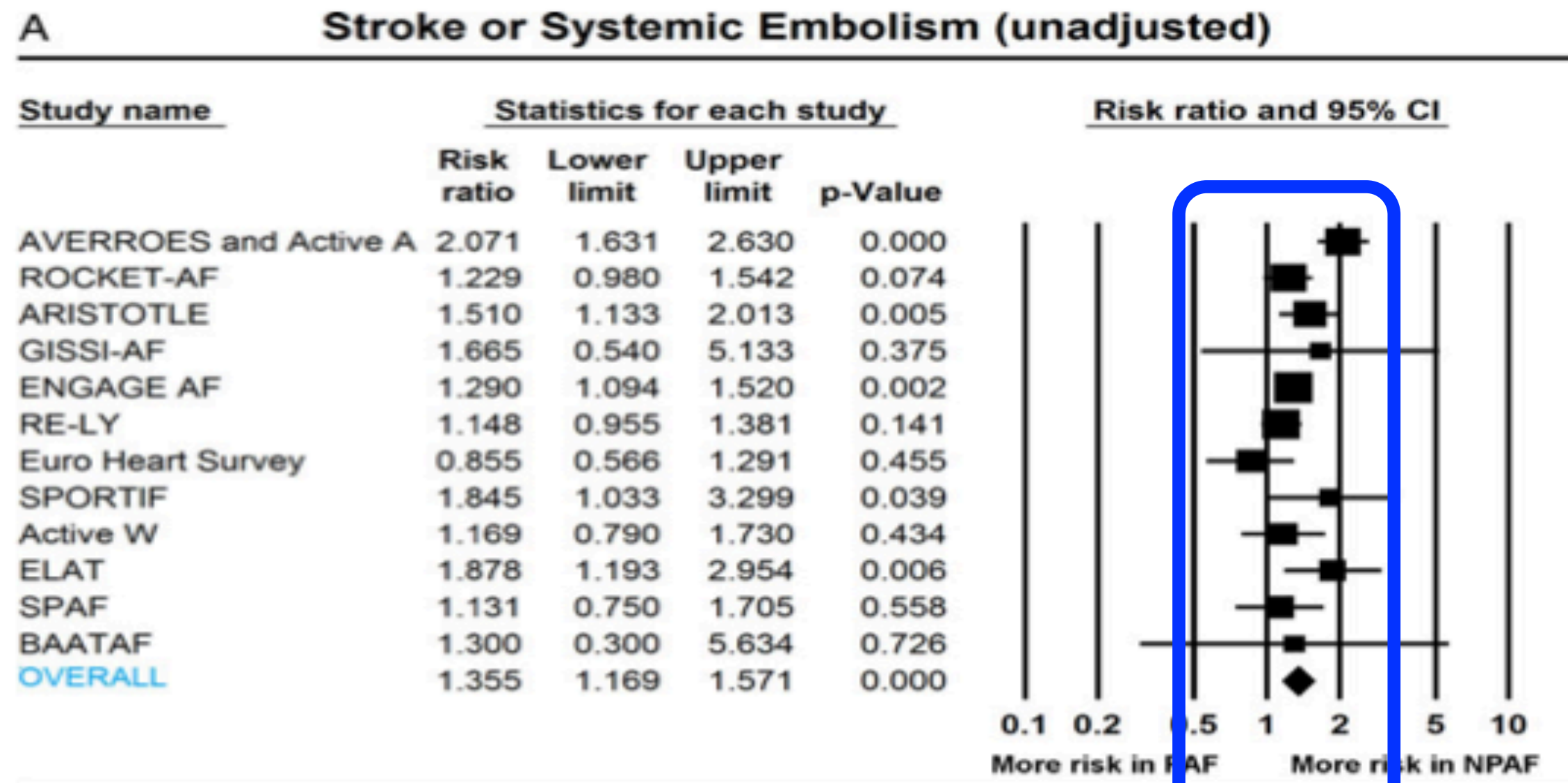
Chan P, Wong C, Pun L et al Circulation. 2016; 135:110–2

Studies of Atrial High Rate Episodes and Stroke Risk

Study (Author, Year)	Type of CIED	Study Type and Follow-up	Population Studied	History of AT (Yes, No, or Both)	AHRE Definition or Duration Analyzed	Stroke Incidence	Other Outcomes
MOST (Glotzer et al, ⁶⁹ 2003)	PPM	<ul style="list-style-type: none"> Ancillary study of RCT Median 27 mo 	<ul style="list-style-type: none"> n = 312 Sinus node dysfunction Sinus rhythm at implantation 	Both	<ul style="list-style-type: none"> Definition: atrial rate 220 BPM for 10 beats Only episodes ≥5 min analyzed 	<ul style="list-style-type: none"> 8 (2.2%/y) strokes in AHRE group 2 (0.58%/y) strokes in non-AHRE group 	AHREs independently associated with <ul style="list-style-type: none"> Total mortality (HR 2.48, 95% CI 1.25–4.91; <i>P</i> = .0092) Death or nonfatal stroke (HR 2.79, 95% CI 1.51–5.15; <i>P</i> = .0011) AF (HR 5.93, 95% CI 2.88–12.2; <i>P</i> = .0001)
Capucci et al, ⁷⁰ 2005	PPM	<ul style="list-style-type: none"> Prospective multicenter observational study Median 22 mo 	<ul style="list-style-type: none"> n = 725 Bradycardia Symptomatic atrial tachyarrhythmias 	Yes	<ul style="list-style-type: none"> AHRE >5 min AHRE >1 d 	<ul style="list-style-type: none"> 7 (0.6%/y) total patients with ischemic stroke (AHRE status not reported) 	<ul style="list-style-type: none"> AHRE >5 min = not associated with embolic events AHRE >1 d = adjusted HR of 3.1 (95% CI 1.1–10.5; <i>P</i> = .044) for ischemic stroke, TIA, or peripheral arterial embolism
TRENDS (Glotzer et al, ⁷¹ 2009)	PPM, ICD, or CRT	<ul style="list-style-type: none"> Prospective multicenter observational study Mean 1.4 y 	<ul style="list-style-type: none"> n = 2486 1 or more stroke risk factors 	Both	<ul style="list-style-type: none"> Zero burden Low burden (<5.5 h) High burden (≥5.5 h) 	<ul style="list-style-type: none"> 20 (0.59%/y) total patients with stroke (AHRE status not reported) 	Adjusted TE risk (vs zero burden): <ul style="list-style-type: none"> Low burden (<5.5 h) = HR 0.98 (95% CI 0.34–2.82; <i>P</i> = .97) High burden (≥5.5 h) = 2.20 (95% CI 0.96–5.05, <i>P</i> = .06)
ASSERT (Healey et al, ²⁶ 2012)	PPM or ICD	<ul style="list-style-type: none"> Prospective multicenter observational analysis (with an ancillary RCT) Mean 2.5 y 	<ul style="list-style-type: none"> n = 2580 Age ≥65 y History of hypertension on medical treatment 	No	<ul style="list-style-type: none"> Definition: atrial rate ≥190 BPM for >6 min. 	<ul style="list-style-type: none"> 10 (1.5%/y) patients with stroke in AHRE group 36 (0.62%/y) patients with stroke in AHRE-free group 	AHRE = adjusted HR 2.50 (95% CI 1.28–4.89; <i>P</i> = .008) for primary outcome of stroke and systemic embolism



Data suggests that Stroke Risk in Paroxysmal AF is less compared to Persistent AF



Ganesan AN, et al. Eur Heart J. 2016 May 21;37(20):1591-602

What if?

**Continuously monitor
AF episodes
with a device**



**initiate anticoagulant
as needed**



**prevent stroke
minimize bleeding**

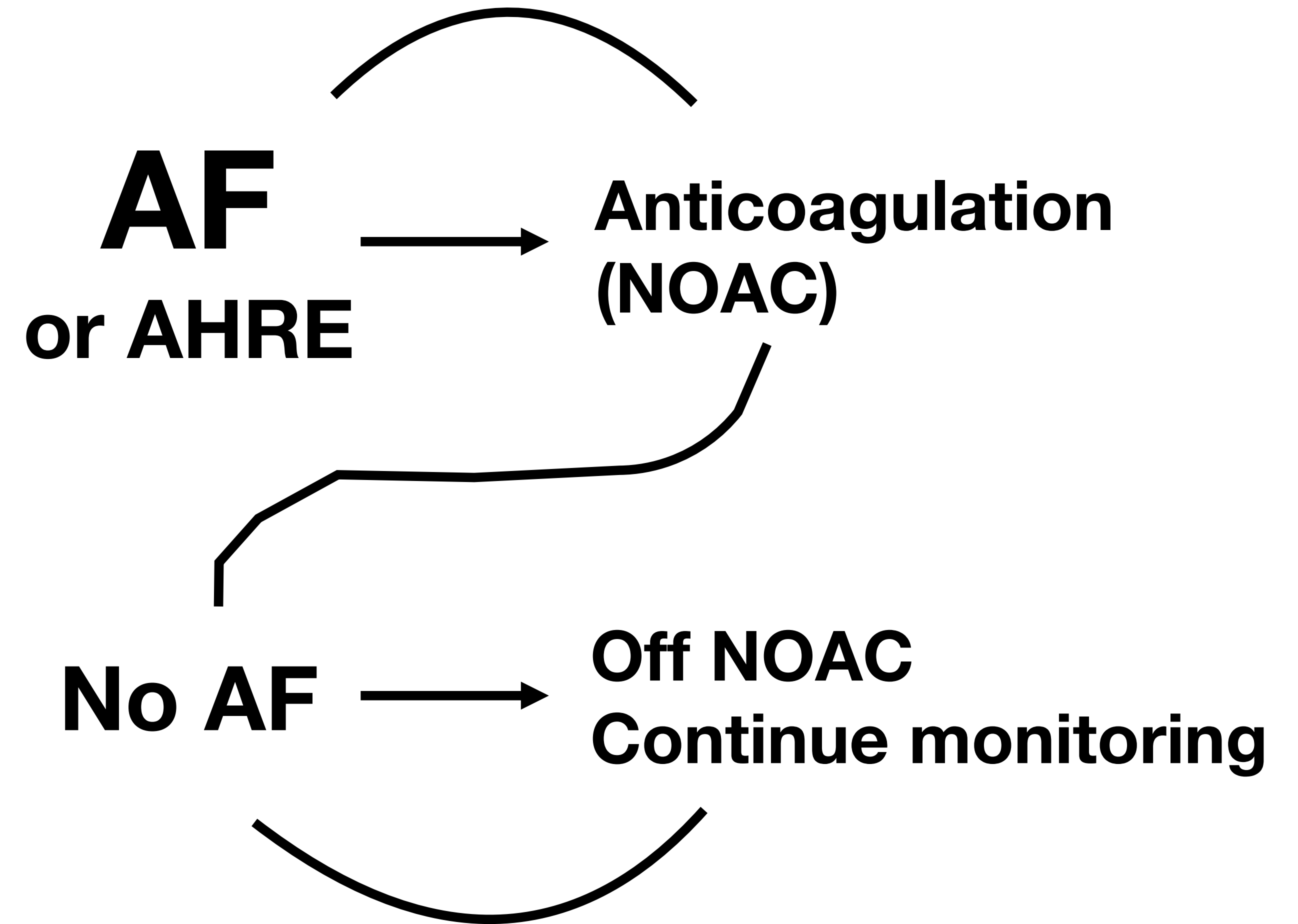
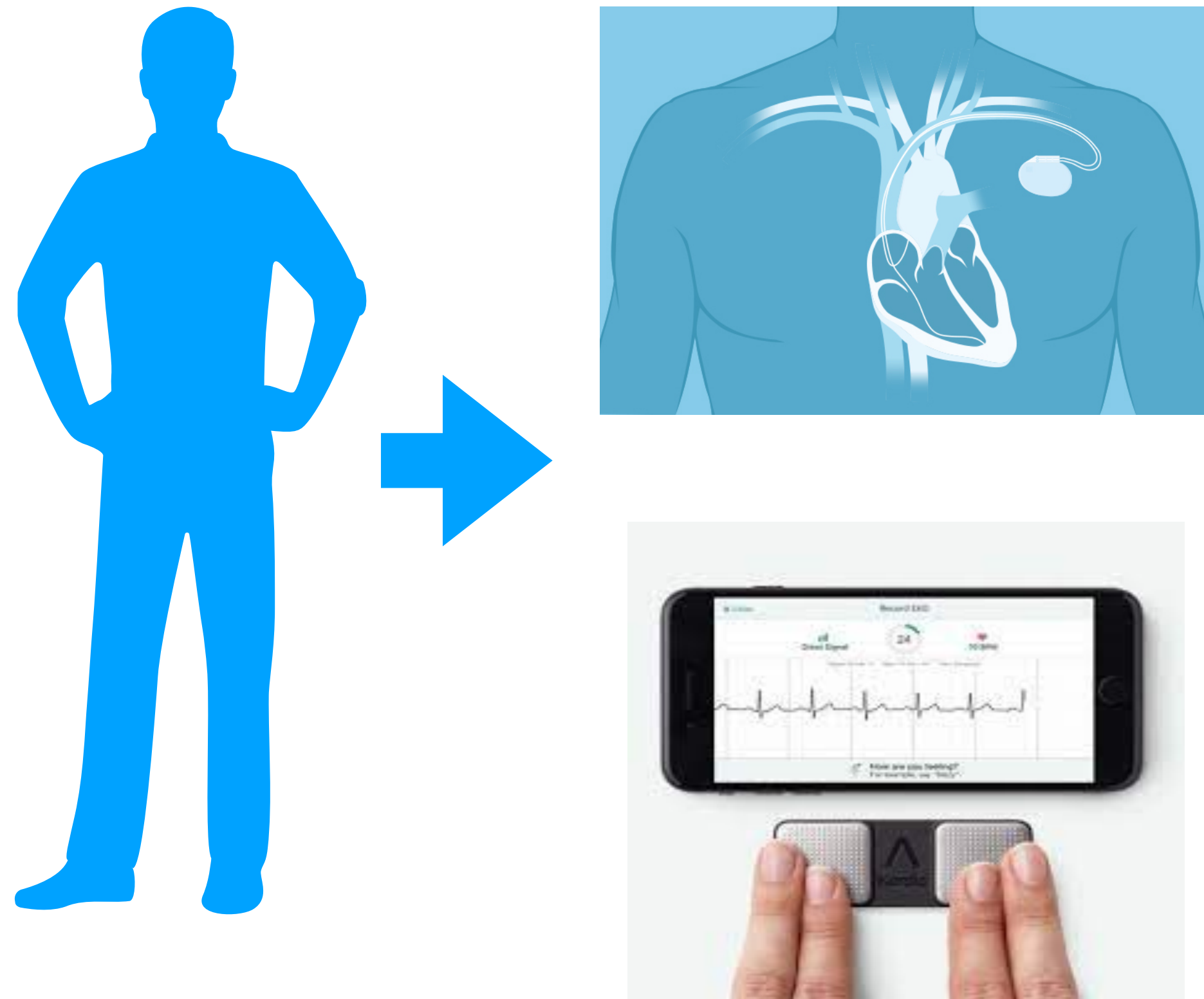


Intermittent, On-demand, “Pill in the Pocket” anticoagulation

- Strategy of continuously monitoring for AF with implanted or wearable technology (i.e. pacemaker, ICD, loop recorder, smartphone, watch, handheld ECG) and then initiating oral anticoagulation for a limited time afterward
- Rationale:
 - prevention of stroke related to the onset of AF
 - minimally exposing patient to risk of bleeding from anticoagulant
 - NOACs have more rapid onset/offset of action than warfarin, feasible for “on-demand” strategy



Mechanism of “Pill in the Pocket Anticoagulation”



Caveats / Controversies

- Controversy about temporal relationship between AF episodes and stroke
- Length of AF episode to trigger a stroke
- Whether AF duration, burden or density is a better measure of stroke risk is unknown.
- Duration of stroke risk after AF episode
- No consensus on anticoagulation strategy for subclinical AF/AHRE



Temporal relationship of AF to Stroke events

Year	Trial	Number of patients with TE event	Definition of AF episode	Any AF detected prior to TE event	AF detected only after TE event	No AF in 30 days prior to TE event	Any AF in 30 days prior to TE event
2011	TRENDS ²⁴	40	5 min	20/40 (50%)	6/40 (15%)	29/40 (73%)	11/40 (27%)
2014	ASSERT ²⁵	51	6 min	18/51 (35%)	8/51 (16%)	47/51 (92%)	4/51 (8%)
2014	IMPACT AF ²⁶	69	36/48 atrial beats ≥200 bpm	20/69 (29%)	9/69 (13%)	65/69 (94%)	4/69 (6%)

- Occurrence of AHRE/AF and stroke do not always correlate temporally.
- Most patients with AHRE/AF who get a stroke are not experiencing AHRE/AF at the time of diagnosis.
- The period following the AHRE and the overall presence of AHRE is associated with significant increase in stroke.



What do the Guidelines say?

NOTHING

But...

states that the need for and choice of anticoagulant therapy should be reevaluated at regular intervals.



What do the data show?

Small pilot studies



Studies on Tailored Anticoagulation for AF

Trial Patient population and profile	Monitoring device	Methodology	Follow-up	Outcomes
Zuern et al 2015				
65 pts post AF ablation free from AF 3 mos after AF ablation CHADS 1-3	Insertable cardiac monitor	Post-ablation, ICM inserted and OAC stopped Daily monitoring of ICM for AF >1 hour	32 mos	63% with AF burden <1 hr/day stayed off OAC No stroke, TIA and other embolic events
Mascarenhas et al 2016				
70 pts history of paroxysmal AF in sinus rhythm on antiarrhythmic drugs CHADSVASC >2 and HASBLED >3	Insertable cardiac monitor	OAC discontinued if NSR or low AF burden (<1%) for >3 mos	23 mos	53 (76%) pts on NSR or <1% AF burden for 3 months discontinued OACs No adverse events 24% on OACs developed severe bleeding

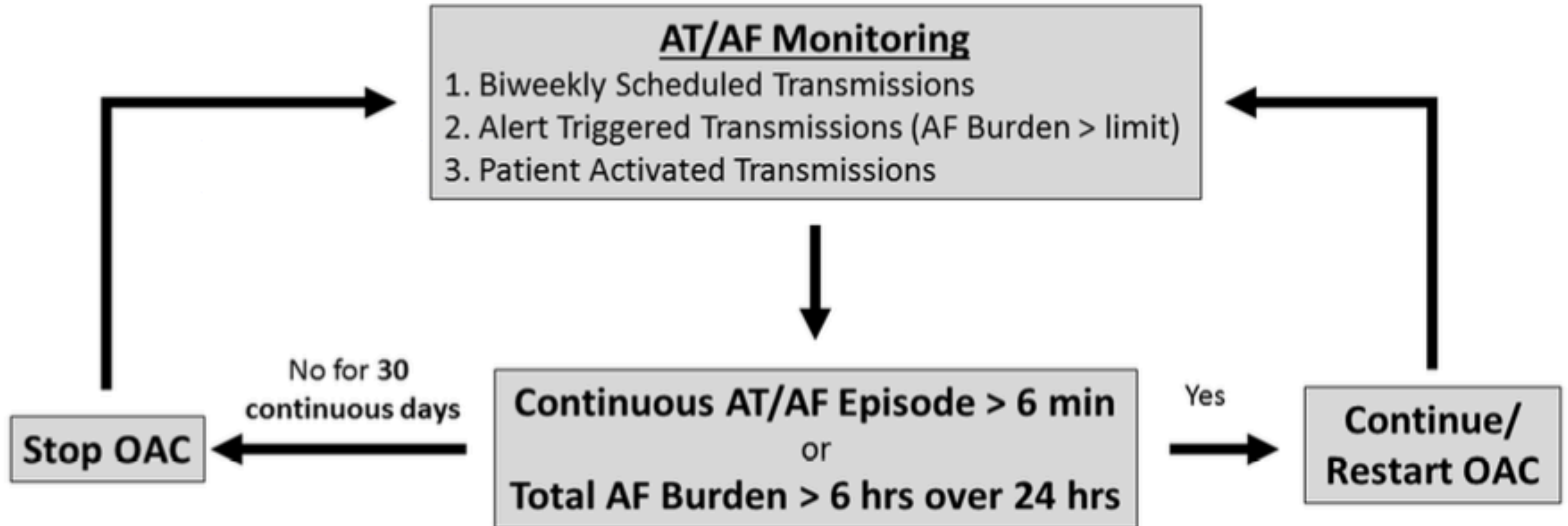
Studies on Tailored Anticoagulation for AF

Trial Patient population and profile	Monitoring device	Methodology	Follow-up	Outcomes
IMPACT Trial				
2718 pts Heart failure *80% on Warfarin	DDD and CRT-D ICDs	2 arms: Chronic oral anticoagulation vs Start and Stop oral anticoagulation based on remote monitoring	stopped after 2 years for futility	No difference in stroke/systemic embolism and bleeding

Studies on Tailored Anticoagulation for AF

Trial	Patient population and profile	Monitoring device	Methodology	Follow-up	Outcomes
REACT.COM Trial					
	59 pts Non-permanent AF on NOAC CHADS 1-2	Insertable cardiac monitor	stopped NOAC after 60 day period without AF >1 hour; restarted NOAC after any AF > 1hour, continued for 30 days	14 months	Decreased total time on NOAC by 94%; No stroke events 1 TIA not preceded by AF 2 major bleeds in patients not on NOAC
TACTIC AF trial					
	48 pts Non-permanent AF on NOACs CHADS1-3, no previous stroke	DDD pacemaker and ICD with atrial lead	standard chronic NOAC vs pill in the pocket NOAC stopped NOAC if no AF>6 mins and AF burden <6 hours/day for 30 days Reinitiate NOAC for 30 days if with AF	12 months	Decreased total time on NOAC by 74.3% No stroke events 1 major bleed in patient not on NOAC

TACTIC AF Study



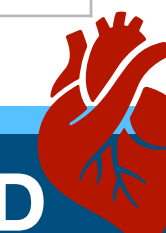
TACTIC AF Study

Reasons for Resuming Anticoagulation in the Tailored Anticoagulation Patients

Reason for Restarting/Continuing DOAC	Total Days on DOAC	% Study Time on DOAC	% Total Time on DOAC
Days on DOAC after 1 st 30 days	1,777	12.0%	47.2%
AT/AF episode ≥6 min	1,317	8.8%	35.0%
Total AT/AF ≥6 hrs/day & AT/AF episode ≥6 min	283	1.9%	7.5%
Total AT/AF ≥6 hrs/day	209	1.4%	5.6%
Peri-operative management	117	0.8%	3.1%
Unable to transmit/travel	59	0.4%	1.6%
Transmitter malfunction	1	0.0%	0.0%
Total Days on DOAC	3,763	25.4%	100%

Total possible days on anticoagulation=14,826

Decreased total time on NOAC by 74.3%
No stroke events
1 major bleed in patient not on NOAC



What we know and don't know (so far)

- Pill in the pocket anticoagulation strategy is feasible.
- But not definite if it's safe (providing stroke prevention compared to chronic anticoagulation).
- Further studies needed.



Future Study

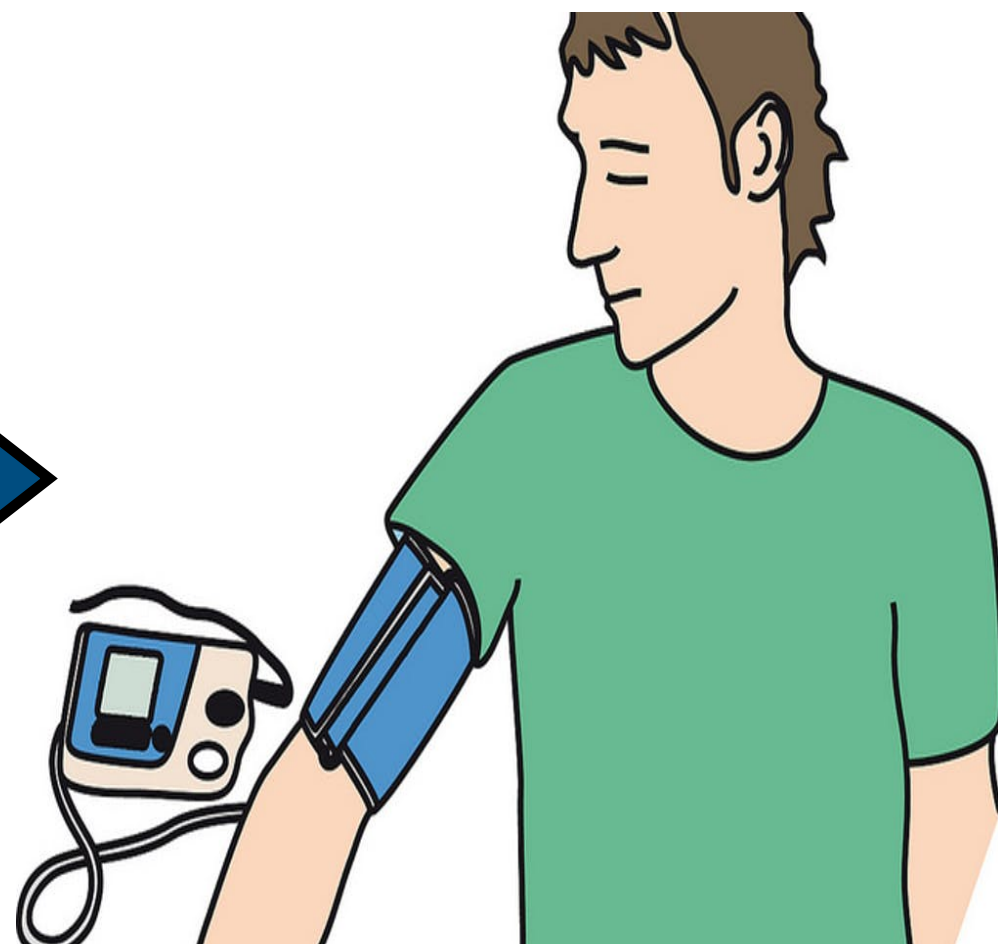
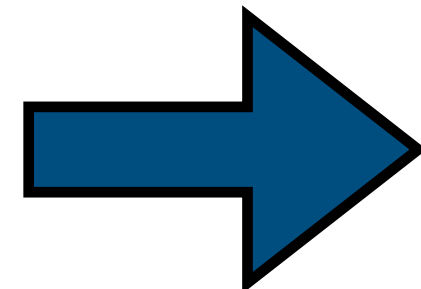
REACT AF Trial Monitoring device Methodology Endpoints

plan 5000 pts Paroxysmal AF CHADSVASC 1-4	Apple Watch s4	2 arms: Chronic NOAC vs pill in the pocket NOAC AF > 1 hour	stroke, systemic embolism, CV death in 3 years Secondary - bleeding
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Positive points of Tailored Strategy

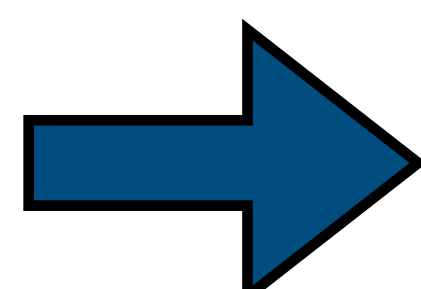
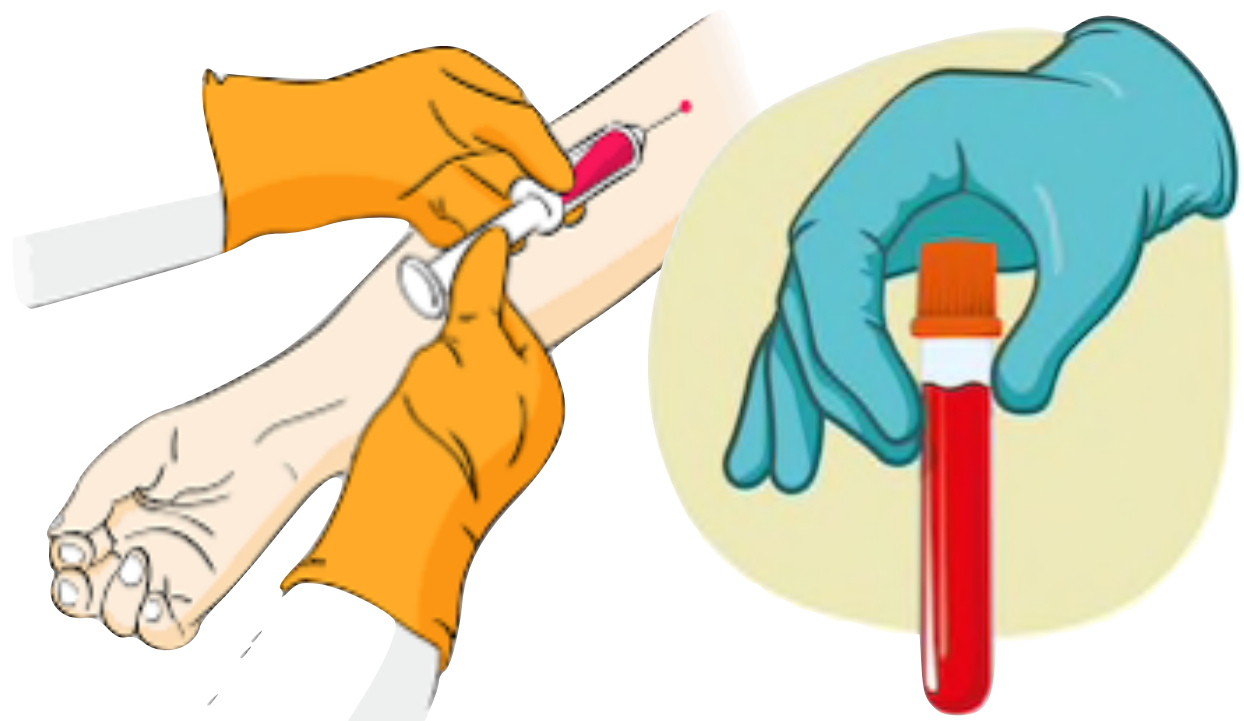
- Patient-directed approach to anticoagulation in response to AF/AHRE
- Strategy gets patients more engaged in their own care, be active participants in the management
- Can have positive effects on other preventive health behaviors





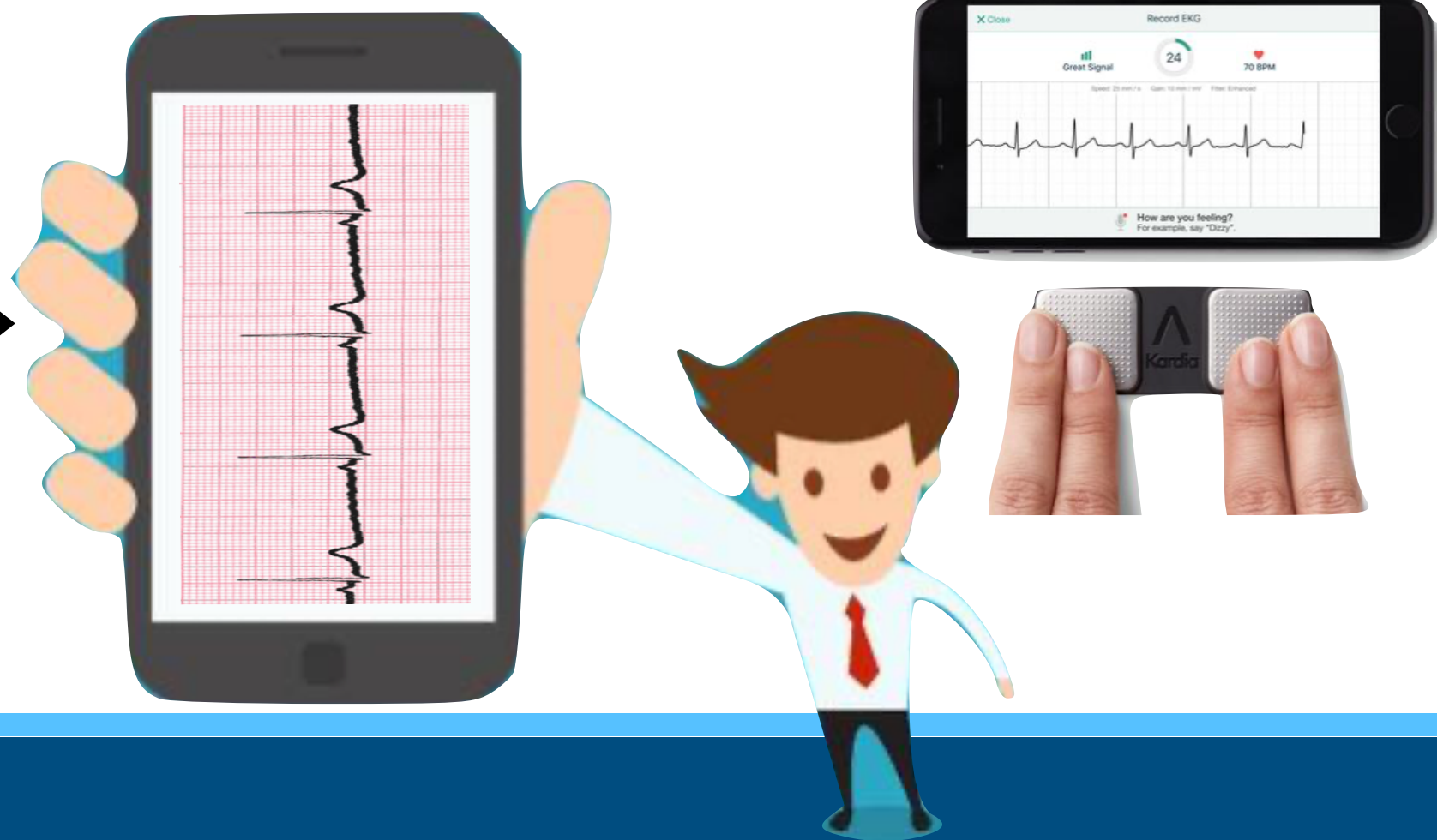
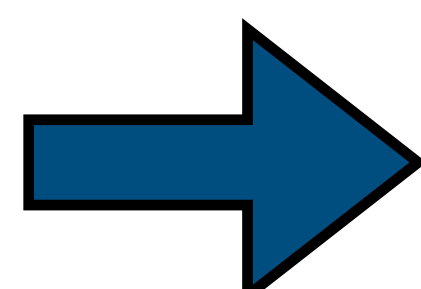
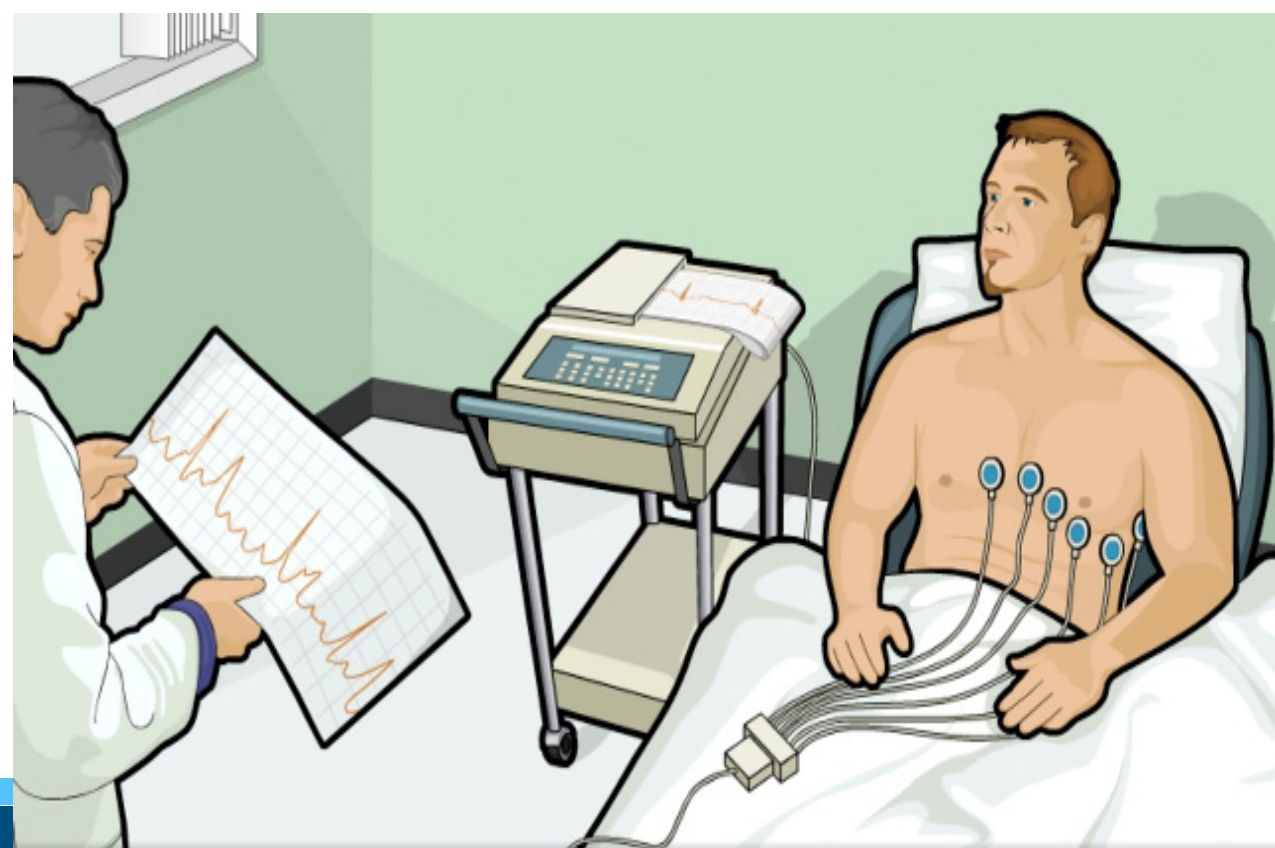
HYPERTENSION & DIABETES

- High prevalence
- Low immediate impact situations



ATRIAL FIBRILLATION

- Low prevalence
- Early treatment has high immediate impact



Best candidates for Pill in the Pocket Anticoagulation Strategy

- Paroxysmal AF
- Low CHADSVASC (1-2)
- Younger, more active patients
- Post-AF ablation
- Taking anti-arrhythmic drugs (rhythm control strategy)

==> 1/2 of the AF population

Future Perspectives

- Tailored, pill in the pocket anticoagulation strategy is feasible, has potential to decrease bleeding, reduce cost, and improve quality of life, and maintain stroke protection.
- This strategy is worth looking into for selected cases.
- More studies are needed.
- Emerging evidence shows that AF burden might be an important stroke risk factor.



Thank You

