Controversial Areas Concerning Stroke Reduction in Patients with Atrial Fibrillation

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My Top 10 Unknowns When It Comes to Stroke Reduction in Patients with Atrial Fibrillation
- A View From the Trenches -

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Conflicts of Interest

- Consultant Medtronic, Atricure, Abbot Medical, St Jude
- Research Support: Boston Scientific, St Jude Medical

Unknown #1:

What is the relationship between AF and stroke?
How does AF burden impact stroke risk?
What is the temporal link between AF and stroke?

Up until recently it was believed that stroke risk in AF patients did not differ regardless of AF type and AF burden.

Reflecting this belief are the AF anticoagulation guidelines which do not differentiate between AF type.

A highly cited analysis of data from the Trends Study makes it clear that AF patients have strokes even when they are having little to no AF.

Temporal relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored device data: A subgroup analysis of TRENDS

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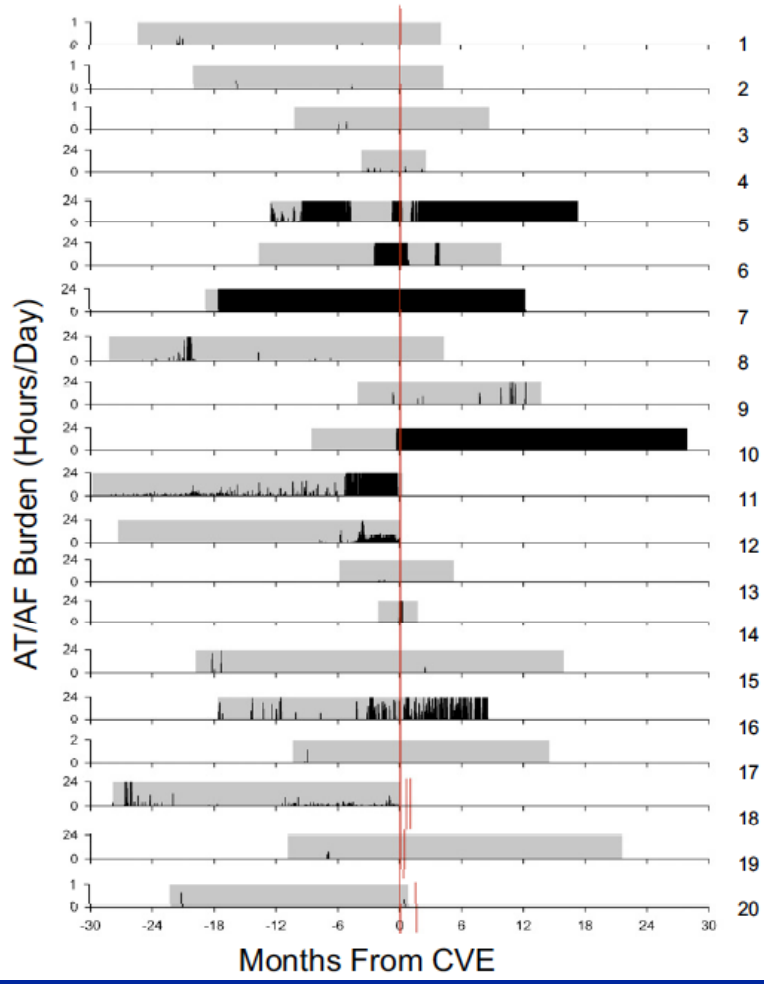


Patient #	$CHADS_2$ Score	Baseline Antithrombotic Therapy
1	2	None
2	3	ASA
3	6	None
4	5	ASA
5	1	OAC
6	4	ASA
7	2	ASA
8	1	OAC/ASA
9	1	OAC
10	3	ASA
11	4	OAC/ASA
12	5	ASA
13	2	None
14	2	None
15	3	ASA
16	3	None
17	3	OAC/ASA
18	4	OAC/ASA
19	2	ASA
20	2	None

The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke Risk

The TRENDS Study

Table 3. Hazard Ratios for Thromboembolic Events Associated With AT/AF Burden Adjusted for Stroke Risk Factors and Antithrombotic Therapy

Category	Variable	Hazard Ratio (95% CI)*	*P* Value
AT/AF burden	Low burden vs zero burden	0.98 (0.34, 2.82)	0.97
	High burden vs zero burden	2.20 (0.96, 5.05)	0.06

that TE risk is a quantitative function of AT/AF burden. AT/AF burden ≥5.5 hours on any of 30 prior days appeared to double TE risk. Additional studies are needed to more precisely investigate the relationship between stroke risk and AT/AF burden. (*Circ Arrhythmia Electrophysiol.* 2009;2:474-480.)

European Heart Journal (2016) **37**, 1591–1602
doi:10.1093/eurheartj/ehw007

META-ANALYSIS
Arrhythmia/electrophysiology

The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis

Anand N. Ganesan[1,2,3,4], Derek P. Chew[1,2,3], Trent Hartshorne[1], Joseph B. Selvanayagam[1,2,3], Philip E. Aylward[1,2,3], Prashanthan Sanders[3,4], and Andrew D. McGavigan[1,2]*

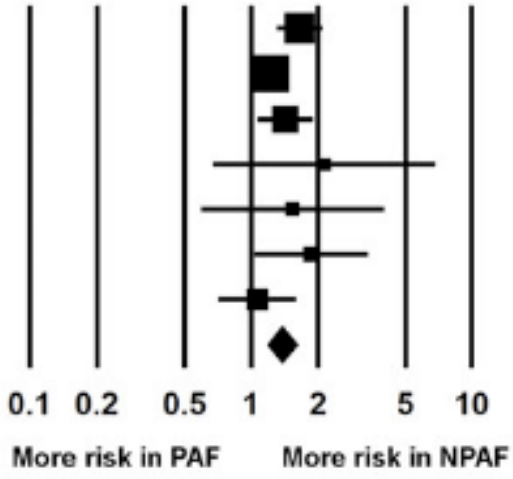
B

Stroke or Systemic Embolism (adjusted)

Study name	Hazard ratio	Lower limit	Upper limit	p-Value
ACTIVE A/AVERROES	1.658	1.316	2.089	0.000
ROCKET-AF	1.220	1.060	1.403	0.006
ARISTOTLE	1.429	1.072	1.904	0.015
GISSI-AF	2.141	0.677	6.774	0.195
Euro Heart Survey	1.538	0.595	3.980	0.374
SPORTIF	1.870	1.041	3.359	0.036
Active W	1.064	0.714	1.586	0.761
OVERALL	1.384	1.191	1.608	0.000

Statistics for each study

Hazard ratio and 95% CI



European Heart Journal (2016) **37**, 1591–1602

#2:
Which NOAC for which patient ? How to choose?

Currently there are 4 NOACs on the market
(pradaxa, xarelto, apixaban, and edoxaban)

Clinicians are often asked which is “the best”.

Some experts in the field argue that physicians need to be familiar with all 4 and tailor the use to a particular patient.

Others argue that they are more similar than different and it makes sense to use one predominantly.

How Does One Pick a NOAC ?

The Tailored Approach **?** *The Practical Approach*

The Tailored Approach

1. *Comprehensive knowledge of each NOAC*
2. *Selection based on multiple variables:*
    - *Compliance (women > men, meds > no meds)*
    - *Renal function*
    - *GI history (dyspepsia)*
    - *h/o GI bleeding*
    - *Concomitant meds (P-gp / CYP3A4 inhib/induc)*
    - *Out of pocket cost*
    - *Reversal agent*
    - *Once versus twice a day preference*
    - *Patient preference*
    - *TV advertisements from Plaintiff's lawyers*

Pharmacologic Properties of the NOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Time to C_{max} (h)	2	2–4	3–4	1–2
Half-life (h)	12–17	5–9	~12	10–14
Bioavailability (%)	3–7	≥80	50	62
Renal elimination (%)	80a	33b	27b	50b
Protein binding (%)	35	92–95	87	55
Transporters	P-gp	P-gp/BCRP	P-gp	P-gp
Potential drug interactions	P-gp inhibitors and inducers	Potent dual inhibitors of CYP3A4 and P-gp	Potent dual inhibitors of CYP3A4 and P-gp	Potent P-gp inhibitors and inducers

[a]Intravenously administered dose. [b]Orally administered dose. BCRP, breast cancer resistance protein; C_{max}, maximum concentration; CYP3A4, cytochrome P450 isozyme 3A4; PK, pharmacokinetics; P-gp, P-glycoprotein.

Absorption and Metabolism of the New Anticoagulant Drugs

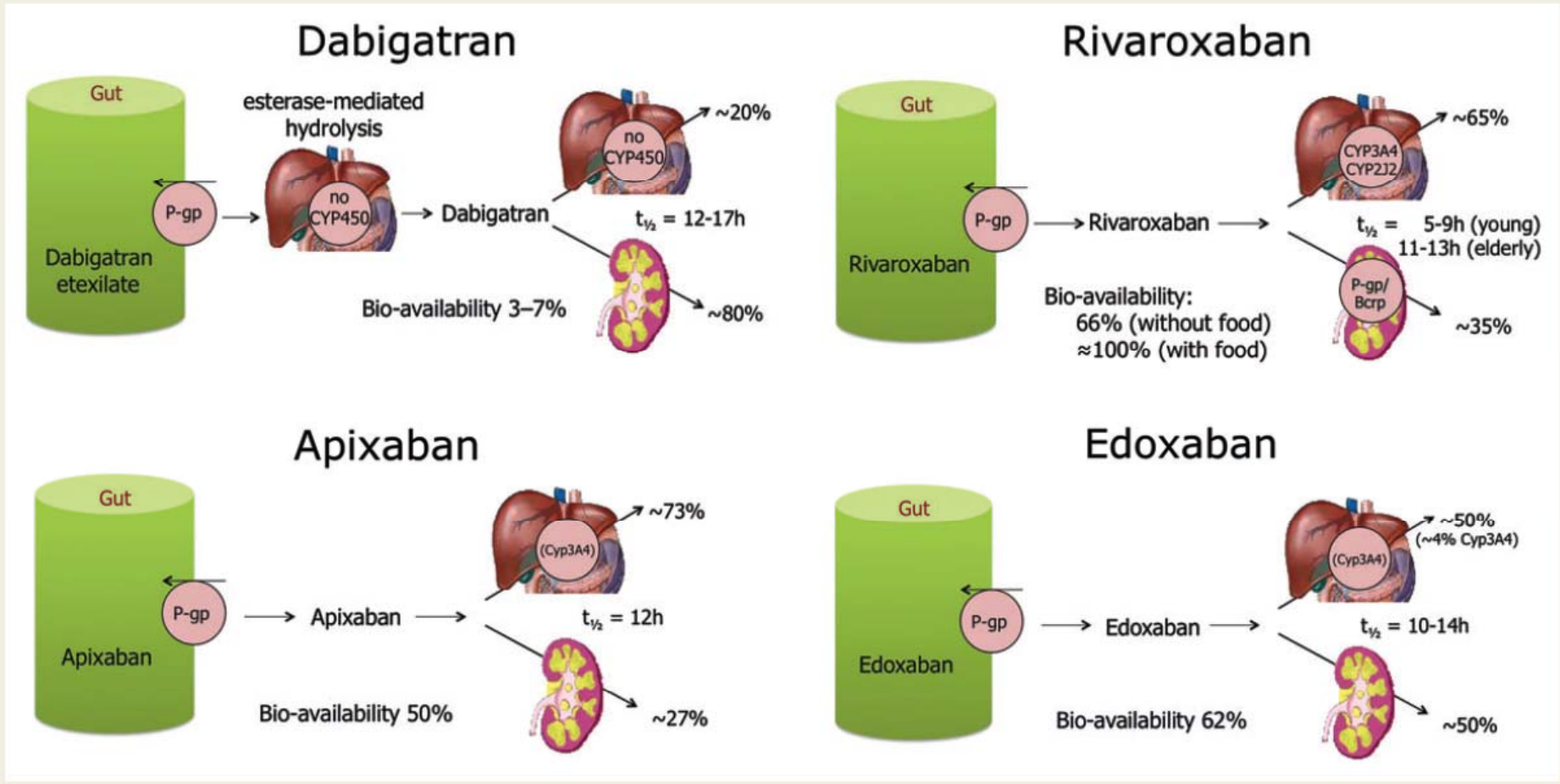


Figure 3 Absorption and metabolism of the different new anticoagulant drugs. There are interaction possibilities at the level of absorption or first transformation, and at the level of metabilization and excretion. See also *Table 5* for the size of the interactions based on these schemes.

EHRA Practical Guide 2015 Europace 17. 1467-1507

NOAC Dosing in Chronic Kidney Disease

Table 8 Approved European labels for NOACs and their dosing in CKD

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fraction renally excreted of absorbed dose	80%	27%[52–55]	50%[36]	35%
Bioavailability	3–7%	50%	62%[51]	66% without food Almost 100% with food
Fraction renally excreted of administered dose	4%	12–29%[52–55]	37%[36]	33%
Approved for CrCl ≥ …	≥30 mL/min	≥15 mL/min	≥15 mL/min	≥15 mL/min
Dosing recommendation	CrCl ≥ 50 mL/min: no adjustment (i.e. 150 mg BID)	Serum creatinine ≥1.5 mg/dL: no adjustment (i.e. 5 mg BID)[a]	CrCl ≥ 50 mL/min: no adjustment (i.e. 60 mg OD)[b]	CrCl ≥ 50 mL/min: no adjustment (i.e. 20 mg OD)
Dosing if CKD	When CrCl 30–49 mL/min, 150 mg BID is possible (SmPC) but 110 mg BID should be considered (as per ESC guidelines)[5] Note: 75 mg BID approved in US only[c]: if CrCl 15–30 mL/min if CrCl 30–49 mL/min and other orange factor *Table 6* (e.g. verapamil)	CrCl 15–29 mL/min: 2.5 mg BID If two-out-of-three: serum creatinine ≥ 1.5 mg/dL, age ≥80 years, weight ≤60 kg: 2.5 mg BID	30 mg OD when CrCl 15–49 mL/min	15 mg OD when CrCl 15–49 mL/min
Not recommended if	CrCl < 30 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min

Red: contra-indicated/not recommended. **Orange**: reduce dose as per label. **Yellow**: consider dose reduction if two or more 'yellow' factors are present (see also *Table 6*).
CKD, chronic kidney disease; CrCl, creatinine clearance; BID, twice a day; OD, once daily; SmPC, summary of product characteristics.
[a]The SmPC specifies dose reduction from 5 to 2.5 mg BID if two of three criteria are fulfilled: age ≥80 years, weight ≤60 kg, serum creatinine >1.5 mg/dL.
[b]FDA provided a boxed warning that 'edoxaban should not be used in patients with CrCL > 95 mL/min'. EMA advised that 'edoxaban should only be used in patients with high CrCl after a careful evaluation of the individual thrombo-embolic and bleeding risk' because of a trend towards reduced benefit compared to VKA.
[c]No EMA indication. FDA recommendation based on PKs. Carefully weigh risks and benefits of this approach. Note that 75 mg capsules are not available on the European market for AF indication.

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attorneys at law

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Pradaxa Lawsuit

Pradaxa, also known as Dabigatran, is a new blood thinner from the class of direct thrombin inhibitors.

It was released to the American public in October 2010. Pradaxa is approved to prevent blood clots in patients with Atrial fibrillation not caused by heart valve disease and at least one other risk factor for stroke. Also recent hip or knee replacement operations. However, users of Pradaxa have experienced serious health problems including uncontrollable bleeding.

Call **1-866-222-9990** to find out your legal options if you were harmed as a result of taking Pradaxa.

Risk factors for stroke include:

- Congestive heart failure
- High blood pressure (hypertension)

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Xarelto Lawsuits

Individual Injury Lawsuits, Wrongful Death Lawsuits and Xarelto Class Action Lawsuits Reviewed Nationwide.

REQUEST A FREE CONSULTATION

Lawyers for Xarelto Bleeding Injury or Death

The product liability lawyers at Saiontz & Kirk, P.A. are reviewing potential lawsuits for individuals who have experienced severe bleeding problems while using Xarelto.

As a result of the drug makers' failure to adequately warn about the risks associated with the anticoagulant, financial compensation may be available through an Xarelto lawsuit for individuals who have experienced:

- Internal Bleeding or Gastrointestinal Bleeding
- Brain Hemorrhage
- Hemorrhagic Stroke
- Wrongful Death From Bleeding Problems

To review whether you, a friend or family member may have a Xarelto case against the drug makers, request a free consultation and claim evaluation.

Xarelto Bleeding Problems

Free Consultation & Case Evaluation

To contact our office and review a potential case, provide your contact information below, or call our toll free hotline at (800) 522-0102. **No fees unless a recovery is obtained.**

First Name:
Last Name:
Phone:
Cell:
Email:
Best Time To Contact

Please Provide Details About The Case

Submit

The Tailored Approach in Action

Not currently anticoagulated = NOAC

On Coumadin with good INR TTR =? Coumadin

On coumadin poor INR TTR = NOAC

CrCl 30-50 = apixaban/ rivaroxaban/edoxaban

CrCl < 15 ml/min = Coumadin

Dyspepsia = apixaban/ rivaroxaban/edoxaban

Recent GI bleed = apixaban

P-gp & CYP3A4 use = dabigatran / edoxaban

Poor compliance = rivaroxaban/edoxaban

Ischemic stroke on warfarin, rivaroxaban, or edoxaban = dabigatran (150 mg bid)

The Practical Approach

1. Pick one NOAC agent
2. Learn in detail how to prescribe it and when to adjust the dose and/or not use it
3. Ignore the other NOACs unless a patient specifically requests it.
4. In this case look up the prescribing information.

Which Approach Would I Recommend ?

The Practical Approach

#3:
Risks and benefits of the pill in the pocket approach for anticoagulation of patients with atrial fibrillation.

Anticoagulation is associated with an increased risk of bleeding.

Many patients who should be prescribed anticoagulants for stroke prevention refuse to take anticoagulants.

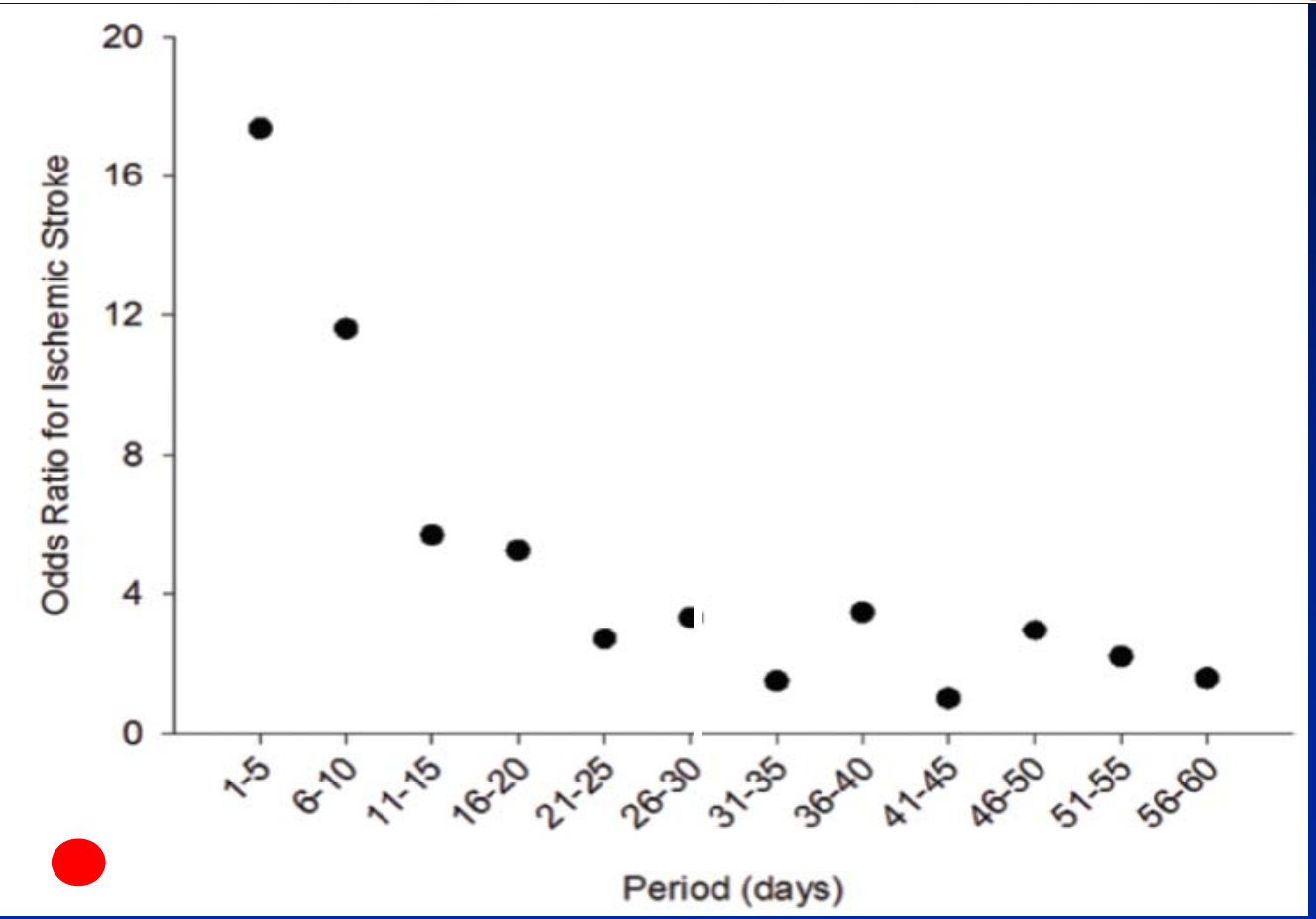
If stroke risk is linked to AF episodes, then it may be possible to only anticoagulate patients during and for 30 days post an AF episode.

This strategy is likely to reduce exposure to anticoagulants while reducing stroke risk.

Atrial Fibrillation Burden and Short-Term Risk of Stroke

Case-Crossover Analysis of Continuously Recorded Heart Rhythm From Cardiac Electronic Implanted Devices

Mintu P. Turakhia, MD, MAS; Paul D. Ziegler, MS; Susan K. Schmitt, PhD; Yuchiao Chang, PhD; Jun Fan, MS; Claire T. Than, MPH; Edmund K. Keung, MD; Daniel E. Singer, MD



N=9,850 (187 stroke events)

"Our findings suggest that transient use of rapidly acting anticoagulants linked to onset and offset of AF episodes could be a successful stroke-prevention strategy and merits a definitive randomized trial."

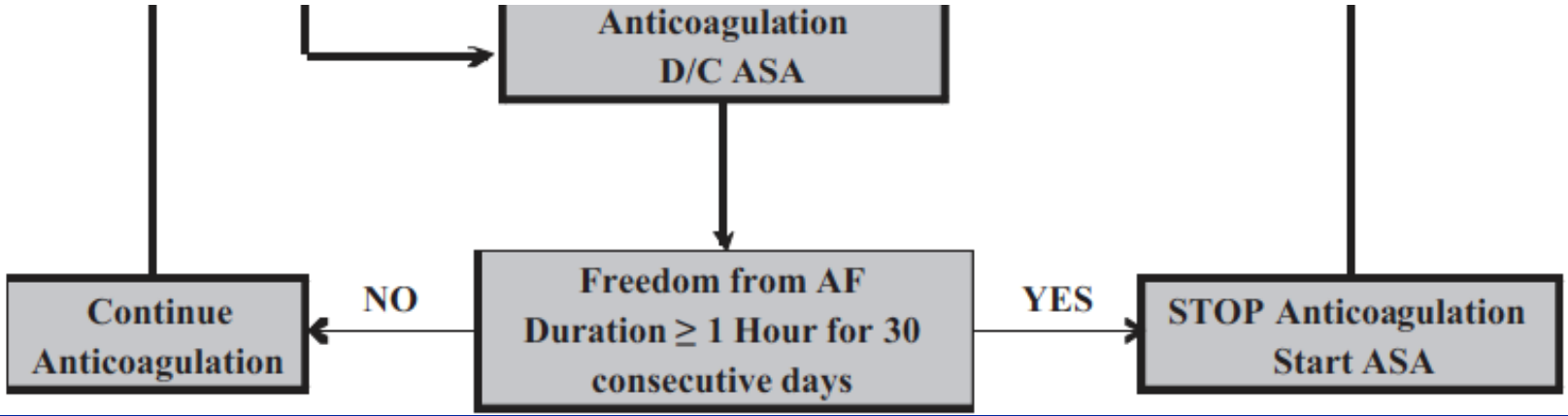
Targeted Anticoagulation for Atrial Fibrillation Guided by Continuous Rhythm Assessment With an Insertable Cardiac Monitor: The Rhythm Evaluation for Anticoagulation With Continuous Monitoring (REACT.COM) Pilot Study

ROD PASSMAN, M.D., M.S.C.E.,* PETER LEONG-SIT, M.D.,† ADIN-CRISTIAN ANDREI, PH.D.,‡ ANNA HUSKIN, R.N., B.S.N.,‡ TODD T. TOMSON, M.D.,‡ RICHARD BERNSTEIN, M.D. PH.D.,* ETHAN ELLIS, M.D.,§ JONATHAN W. WAKS, M.D.,§ and PETER ZIMETBAUM, M.D.§

AF Monitoring

Results: **Among 59 enrollees, 75% were male, age 67 ± 8 years, 76% paroxysmal AF, 69% had prior AF ablation, and mean $CHADS_2$ score 1.3 ± 0.5. Over 466 ± 131 mean days of follow-up there were 24,004 ICM transmissions with a compliance rate of 98.7%. A total of 35 AF episodes ≥ 1 hour occurred in 18 (31%) patients, resulting in a total time on NOAC of 1,472 days. This represents a 94% reduction in the time on NOAC compared to chronic anticoagulation. There were three traumatic bleeds (all on aspirin), three potential transient ischemic attacks (all on aspirin with $CHADS_2$ score of 1), and no strokes or deaths.**

Conclusions: **A targeted strategy of ICM-guided intermittent NOAC administration is feasible. A large-scale trial is necessary to evaluate the safety of this approach.** *(J Cardiovasc Electrophysiol, Vol. 27, pp. 264-270, March 2016)*



#4:

Should patients with asymptomatic AF detected on a PPM be anticoagulated – and if so how much AF is needed?

#5:

What about AF in which there is a trigger? Can anticoagulation be stopped.

#6:

What is the true safety, efficacy, and clinical role of LA appendage occlusion devices ?

Stroke Treatment Options: LAA Ligation, LAA Clips and LAA Closure

LAA Closure (LAAC) Devices

- *First LAAC device (2001)*
- *Device no longer available*

PLAATO

- *Only LAAC device with 2 Randomized Controlled Trials*
- *FDA approved with specific indication to reduce the risk of thromboembolism*

WATCHMAN™ Device

ClinicalTrials.gov identifiers:
NCT00129545 (PROTECT AF)
NCT01182441 (PREVAIL)

- *US Trial halted in 2013*
- *AMPLATZER™ Cardiac Plug Clinical Trial*

ACP

ClinicalTrials.gov identifier: NCT01118299

LAA Clip

***EXCLUDE** Trial (completed)*

- *AtriClip Device was FDA approved in 2010 for LAA closure*
  - *No specific indication for Stroke Reduction*

ClinicalTrials.gov identifier: NCT00779857

LARIET

"Safety and Efficacy of Left Atrial Appendage Occlusion Devices"
Observational Study (retrospective)

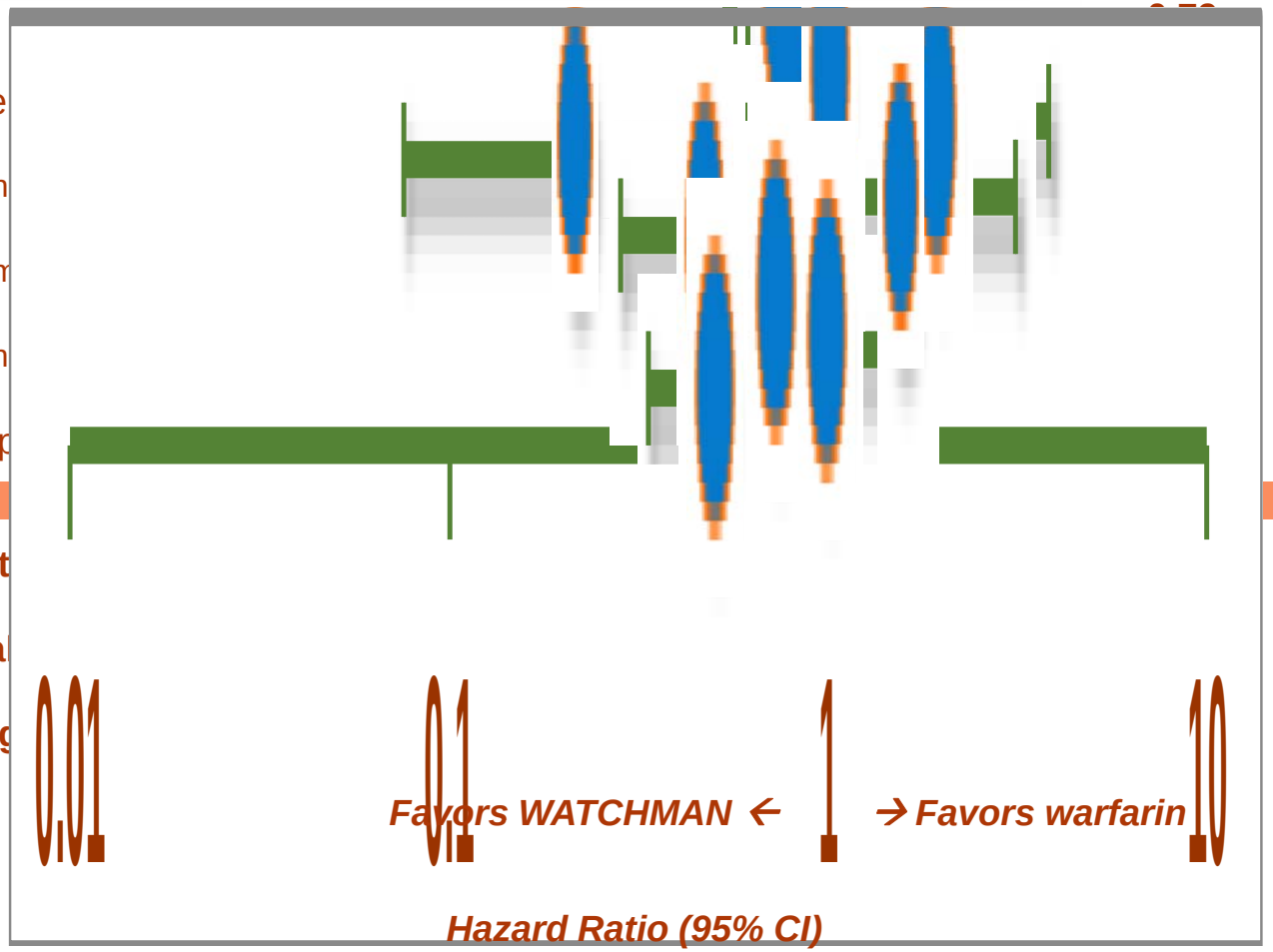
- *To compare LARIAT® vs. WATCHMAN™*
- *LARIAT currently does not have a specific indication for LAA Closure or Stroke Reduction*

ClinicalTrials.gov identifier: NCT01695564

Meta-Analysis Shows Comparable Primary Ef

WATCHMAN
LEFT ATRIAL APPENDAGE
CLOSURE DEVICE

	HR	p-value
Efficacy		0.22
All stroke		0.94
Isch		0.05
Hem		0.004
Isch		0.21
CV/unexp		0.006
All-cause deat		0.07
Major bleed, a		0.98
Major bleeding		0.002



Source: Holmes DR, et al. Holmes, DR et al. JACC 2015; In Press. Combined data set of all PROTECT AF and PREVAIL WATCHMAN patients versus chronic warfarin patients
SH-230506-AD June15

#7:

Can anticoagulation be stopped in a patient who has had a successful AF ablation ?

#8:

If anticoagulation is stopped, how much monitoring for AF recurrence is needed?

#9:

Can AF ablation be performed safely on an uninterrupted NOAC?

#10:

If a patient has been on uninterrupted anticoagulation, is a TEE pre ablation needed?

Conclusion

- Stroke prevention is the most important component of AF management.
- While progress has been made in the field many questions remain.
- There is an urgent need to address the many unanswered questions that exist.
- Perhaps of greatest importance is an improved knowledge of the pathophysiologic basis linking stroke risk and atrial fibrillation.
- Is AF just a marker and burden and timing do not matter?
- Atrial appendage occlusion is a promising new approach.

My Predictions

- Clinical trials will demonstrate that AF burden does matter and that stroke are linked to AF episodes. The pill in the pocket approach will play a role.
- Control of AF with catheter ablation will be shown to lower stroke risk.
- Appendage occlusion is for real and many patients will choose appendage occlusion over life long anticoagulant therapy.


THANK YOU!