Updated AHA/ACC/HRS Guidelines For the Management of Atrial Fibrillation

2017

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Disclosures

Speakers Bureau – Actelion Pharmaceuticals, Bristol-Myers Squibb, Pfizer

Clinical Research Support– Sanofi Aventis

Case Study

65 year old female with a history of dyslipidemia presents to your office with complaints of palpitations that started last evening. No other past medical history. She admits to similar episodes on and off for the last few months

- Patient was found to be in atrial fibrillation with a rate of 114 bpm. You start her on oral Cardizem for rate control until you determine course of action (rate control vs rhythm control).

- What anticoagulation regimen (if any) should this patient be discharged home on?

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- What anticoagulation regimen (if any) should this patient be discharged home on? Oral Anticoagulation (Warfarin/DOAC)

Summary

- Background of Atrial Fibrillation
- Rate Control vs. Rhythm Control
- Anticoagulation
- Risks of Bleeding
- Interruption or Discontinuation of Oral Anticoagulation for Surgery/Procedures
- Device Based Solutions
- Management of Bleeding

Background

- Atrial fibrillation is the most common sustained arrhythmia
- Affects 2 million Americans-- AF is 0.4% to 1% in the general population
- Expensive- 16 billion
- 6% over the age of 65 experience it
- Responsible for 15% strokes
- Unfortunately, warfarin is received by only 30-60% of appropriate patients
- In the FHS, the lifetime risk of atrial fibrillation (AFib) for adults is 26% for men and 23% for women.
- The 2014 ACC/AHA/HRS Atrial Fibrillation guideline defines Non Valvular Atrial Fibrillation as **AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic valve or mitral valve repair** (January CT et al. Journal of the American College of Cardiology 2014 doi 10/1016 JACC 2014 0.3.022)

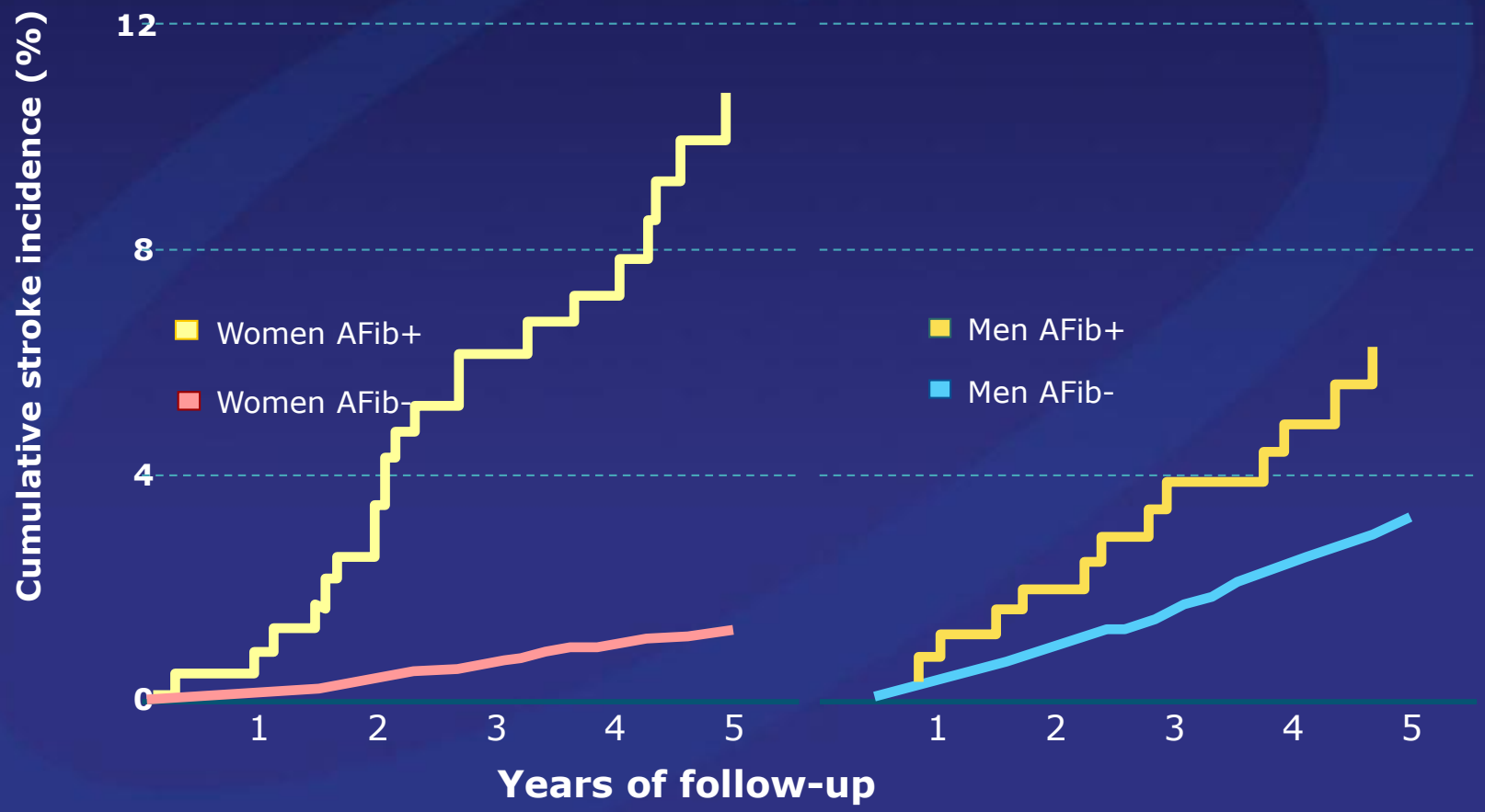
Classification of AFib Subtypes

Paroxysmal	Spontaneous termination usually < 7 days and most often < 48 hours
Persistent	Does not interrupt spontaneously and needs therapeutic intervention for termination (either pharmacological or electrical cardioversion)
Permanent	AFib in which cardioversion is attempted but unsuccessful, or successful but immediately relapses, or a form of AFib for which a decision was taken not to attempt cardioversion

Levy S, et al. *Europace* (2003) 5: 119

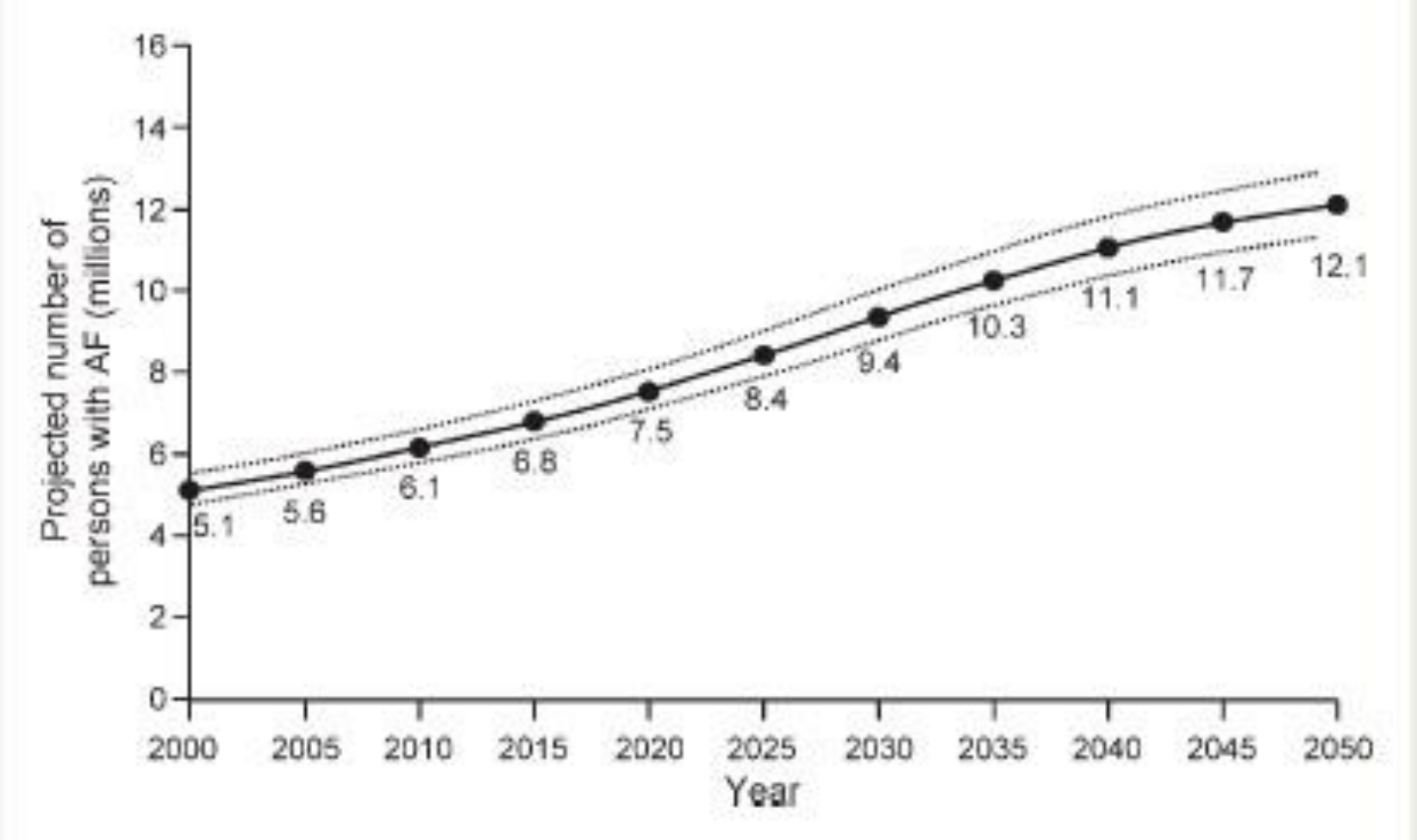
AFib is Responsible for 15-20% of all Strokes

- AFib is responsible for a 5-fold increase in the risk of ischaemic stroke



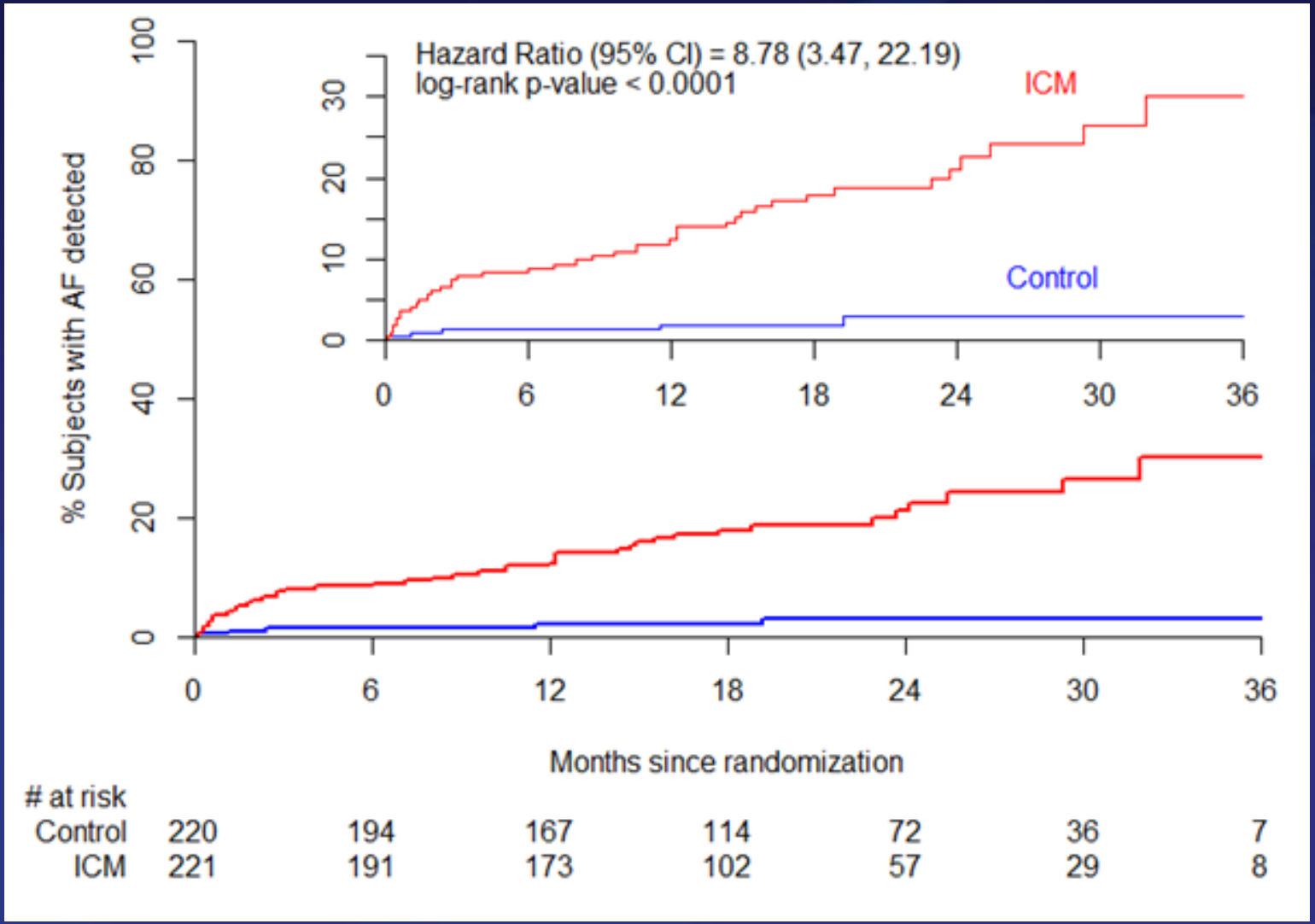
Wolf PA, et al. Stroke (1991) 22: 983
Go AS, et al. JAMA (2001) 285: 2370
Friberg J, et al. *Am J Cardiol* (2004) 94: 889

Atrial Fibrillation: Prevalence Estimates



Turpie A. New oral anticoagulants in atrial fibrillation. EHJ 2007; 29:155-65

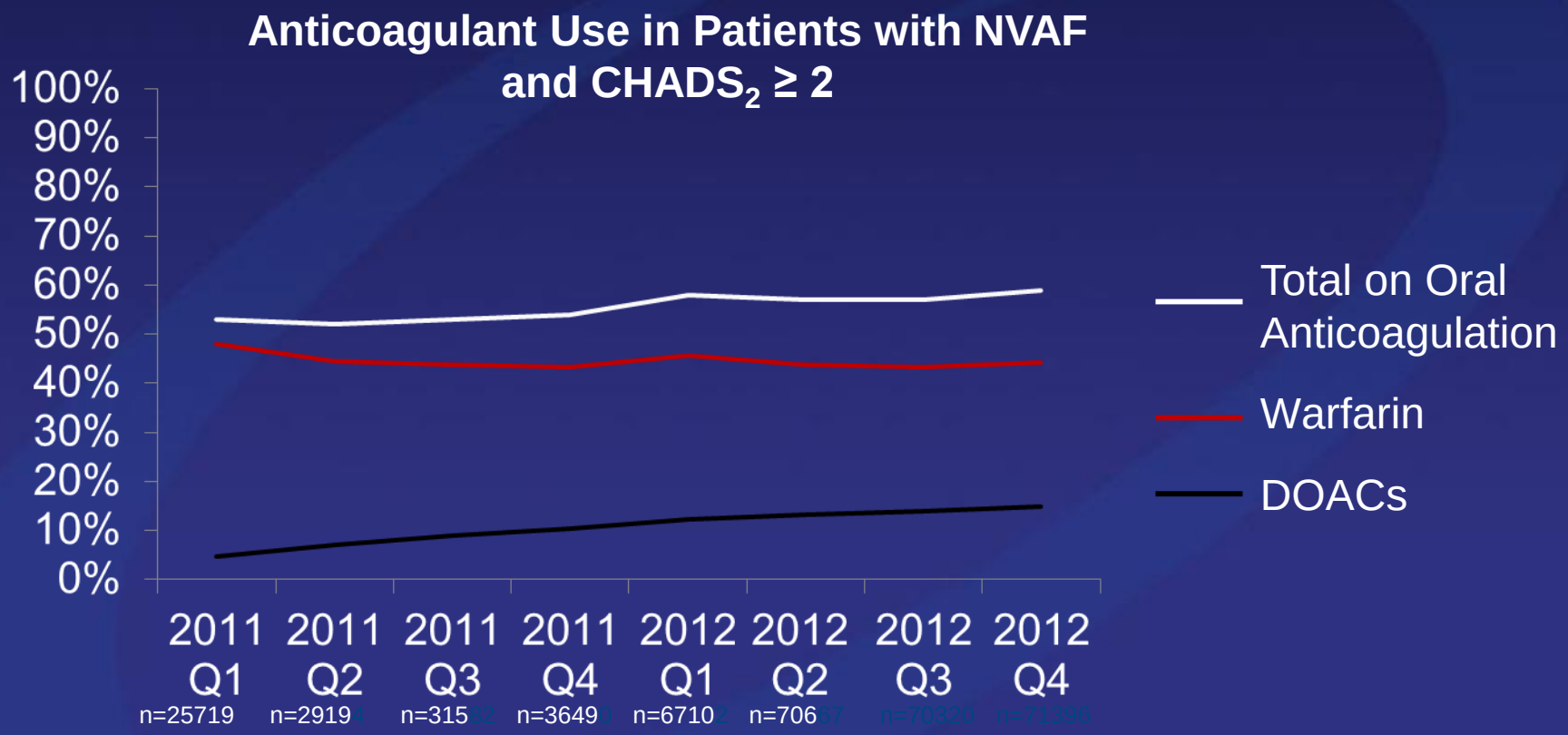
Detection of AF at 3 years



Rate of detection in ICM arm was 30.0% vs 3.0% in control arm

CRYptogenic STroke and underlying AtriaL Fibrillation (CRYSTAL AF), *Richard Bernstein, MD, Ph.D., et al.* NEJM June 26, 2014

Despite Increasing DOAC Adoption, Overall Rate of Anticoagulation in High Risk NVAF Patients has Not Improved



Results from the NCDR PINNACLE Registry[1]

1. Jani, et al. Uptake of Novel Oral Anticoagulants in Patients with Non-Valvular and Valvular Atrial Fibrillation: Results from the NCDR-Pinnacle Registry. ACC 2014
2. Boston Scientific **WATCHMAN™ Left Atrial Appendage Closure Device. Advancing Science for Life ppt presentation SH230-609-AD June 2015**

Atrial Fibrillation

- Rate Control vs. Rhythm Control
- Anticoagulation
- Bleeding Risk

Atrial Fibrillation

- Rate Control vs. Rhythm Control

Theoretical Benefit of Rhythm Control

- Improved hemodynamics
- Relief of symptoms
- Improved exercise tolerance
- Reduced risk of stroke
- Avoidance of anticoagulants

The New England
Journal of Medicine

VOLUME 347 DECEMBER 5, 2002 NUMBER 23

A COMPARISON OF RATE CONTROL AND RHYTHM CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

THE ATRIAL FIBRILLATION FOLLOW-UP INVESTIGATION OF RHYTHM MANAGEMENT (AFFIRM) INVESTIGATORS*

ABSTRACT

Background There are two approaches to the treatment of atrial fibrillation: one is cardioversion and treatment with antiarrhythmic drugs to maintain sinus rhythm, and the other is the use of rate-controlling drugs, allowing atrial fibrillation to persist. In both approaches, the use of anticoagulant drugs is recommended

ATRIAL fibrillation is the most common sustained cardiac arrhythmia, yet the optimal strategy for its management remains uncertain.[1-4] During atrial fibrillation, most symptoms (but perhaps not all) are caused by a poorly controlled or irregular ventricular rate, and the associated risk of death is doubled in patients who have

AFFIRM : 5 Year Outcomes

Survival	Rhythm Control	Rate Control
1 year	96%	96%
3 year	87%	89%
5 year	76%	79%

p = 0.058

NO Difference : death, disabling stroke, major bleed, or cardiac arrest

Sinus rhythm maintained in only 63% of rhythm control group

NEJM 2002;347:1825

AFFIRM Trial

- No survival advantage to rhythm control.
- Rhythm control patients were more likely to be hospitalized with adverse drug effects.
- Both groups had similar stroke risk (1% per yr)
  - Majority of strokes when warfarin stopped or INR subtherapeutic
  - Warfarin required long term even if sinus rhythm restored
- Torsades, bradycardic arrest more common with rhythm control.

Why haven't trials comparing restoration of sinus rhythm (rhythm control) with rate control shown a mortality benefit with rhythm control ?

- Attempts at restoration of sinus rhythm not always successful
  - AFFIRM Trial: only 63% of "rhythm control" group were in sinus rhythm
  - Antiarrhythmics used to maintain sinus rhythm associated with a 25-50% annual failure rate.
- Long term anticoagulation not mandated in the "rhythm control" group
  - Those in afib at risk for stroke
- Medications used to maintain sinus rhythm risk of proarrhythmia and other toxicity

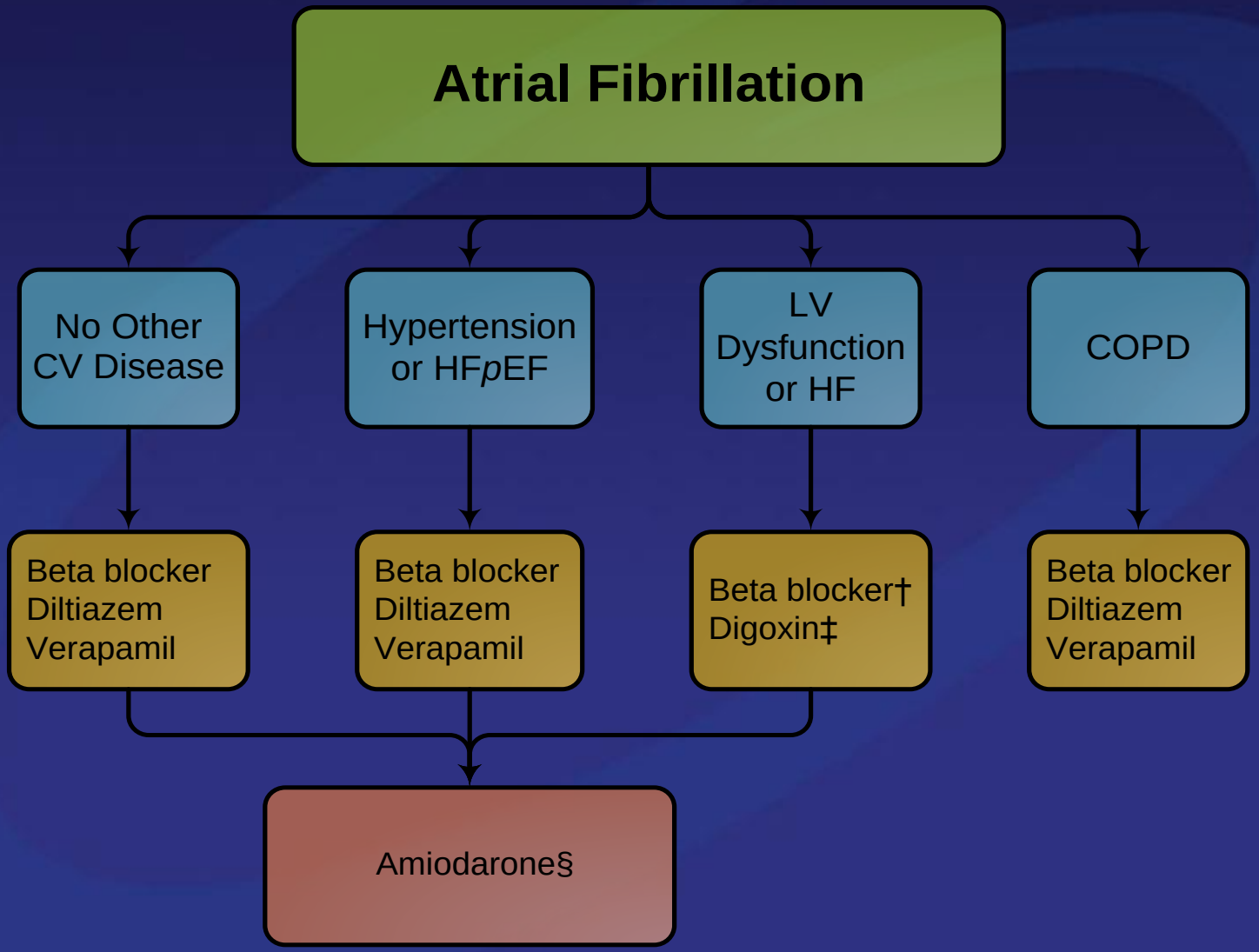
Our Approach (Evidence + Practice)

- Rhythm control as preferred therapy
  - First episode afib
  - Reversible cause (alcohol)
  - Symptomatic patient despite rate control
  - Patient unable to take anticoagulant (falls, bleeding, noncompliance)
  - CHF precipitated or worsened by afib
  - Young afib patient (to avoid chronic electrical and anatomic remodeling that occurs with afib)

Our Approach (Evidence + Practice)

- Rate control as preferred therapy
  - Age ≥ 65, less symptomatic, hypertension
  - Recurrent afib
  - Previous antiarrhythmic drug failure
  - Unlikely to maintain sinus rhythm (enlarged LA)

Approach to Selecting Drug Therapy for Ventricular Rate Control



Rate Control Options

- Beta blocker
  - Avoid carvedilol (Coreg) -less effective in AV node blockade
- Calcium channel blocker
  - Diltiazem, Verapamil
- Digoxin
  - Not as the sole agent- May be harmful
- **Digoxin-associated mortality: a systematic review and meta-analysis of the literature. Vamos M, Erath JW, Hohnloser SH.** *Eur Heart J. May 4 2015. DOI: http://dx.doi.org/10.1093/eurheartj/ehv143*

Conclusion

- This meta-analysis on the effects of digoxin on all-cause mortality indicates that digoxin is associated with increased mortality risk in patients with AF or congestive HF. The effect was strongest in AF patients. These observations call for randomised trials evaluating dose-adjusted digoxin therapy. Until those have been completed, digoxin should be used with great caution, especially when used for rate control in AF.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lenient versus Strict Rate Control in Patients with Atrial Fibrillation

Isabelle C. Van Gelder, M.D., Hessel F. Groenveld, M.D., Harry J.G.M. Crijns, M.D., Ype S. Tuininga, M.D., Jan G.P. Tijssen, Ph.D., A. Marco Alings, M.D., Hans L. Hillege, M.D., Johanna A. Bergsma-Kadijk, M.Sc., Jan H. Cornel, M.D., Otto Kamp, M.D., Raymond Tukkie, M.D., Hans A. Bosker, M.D., Dirk J. Van Veldhuisen, M.D., and Maarten P. Van den Berg, M.D., for the RACE II Investigators*

Lenient
Hr < 110 bpm

Strict
Rest hr < 80
Mod exerc hr < 110

ABSTRACT

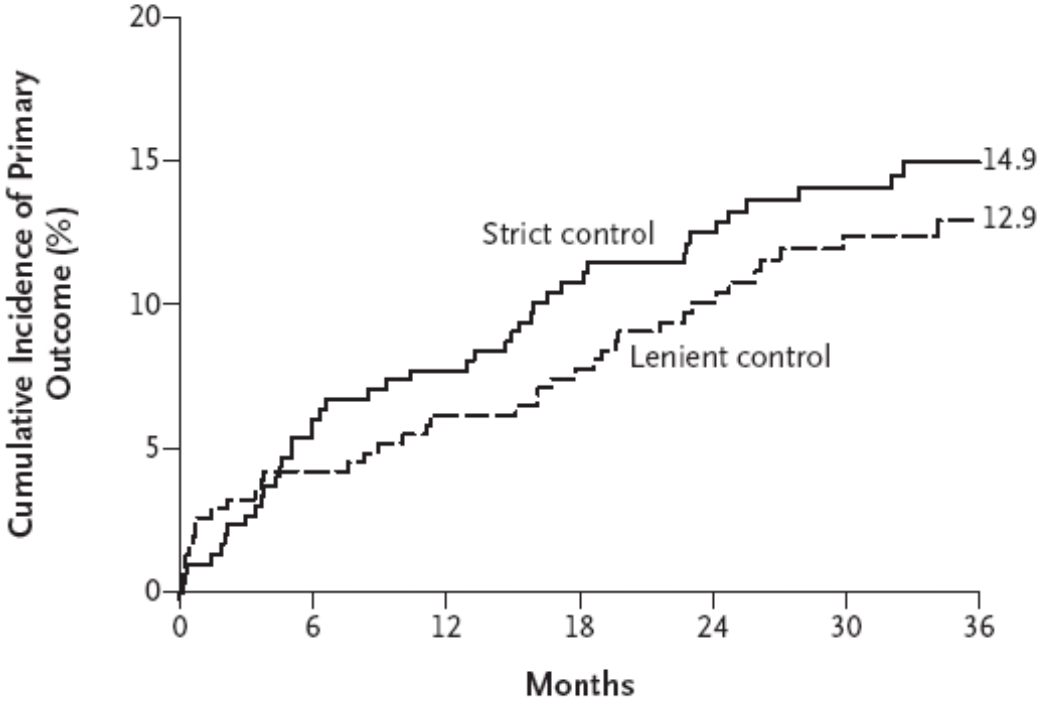
BACKGROUND

Rate control is often the therapy of choice for atrial fibrillation. Guidelines recommend strict rate control, but this is not based on clinical evidence. We hypothesized that lenient rate control is not inferior to strict rate control for preventing cardiovascular morbidity and mortality in patients with permanent atrial fibrillation.

METHODS

We randomly assigned 614 patients with permanent atrial fibrillation to undergo a lenient rate-control strategy (resting heart rate <110 beats per minute) or a strict rate-control strategy (resting heart rate <80 beats per minute and heart rate during moderate exercise <110 beats per minute). The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events. The duration of follow-up was at least 2 years, with a maximum of 3 years.

From the Department of Cardiology (I.C.V.G., H.F.G., H.L.H., D.J.V.V., M.P.V.B.) and the Trial Coordination Center, Department of Epidemiology (H.L.H., J.A.B.-K.), University Medical Center Groningen, University of Groningen, Groningen; the Interuniversity Cardiology Institute of the Netherlands, Utrecht (I.C.V.G.); Maastricht University Medical Center, Maastricht (H.J.G.M.C.); Deventer Hospital, Deventer (Y.S.T.); Academic Medical Center, University of Amsterdam (J.G.P.T.), and VU University Medical Center (O.K.) — both in Amsterdam; Amphia Hospital, Breda (A.M.A.); Medical Center, Alkmaar (J.H.C.); Kennemer Hospital, Haarlem (R.T.); and Rijnstate Hospital, Arnhem (H.A.B.) — all in the Netherlands. Address reprint requests to Dr Van Gelder



No. at Risk

Strict control	303	282	273	262	246	212	131
Lenient control	311	298	290	285	255	218	138

Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of the Primary Outcome, According to Treatment Group.

The numbers at the end of the Kaplan–Meier curves are the estimated cumulative incidence of the primary outcome at 3 years.

Primary Outcomes

Cardiac death
CHF
Stroke
Systemic embolism
Major bleed
Syncope
Sust VT
Cardiac arrest
Life threat compl of antiarrhythm
Pacemaker

Secondary Outcomes

Symptoms

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Strict
Rest hr < 80
Mod exerc hr < 110

Most patients in Lenient
HR < 100

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Anticoagulation Strategies

How do we determine stroke risk ?

- CHADS2
  - **Congestive heart failure - 1pt**
  - **Hypertension - 1pt**
  - **Age > 75 - 1 pt**
  - **Diabetes - 1pt**
  - **Stroke or TIA - 2 pts**

  - **0 points – low risk** (1.2-3.0 strokes per 100 patient years)
  - **1-2 points – moderate risk** (2.8-4.0 strokes per 100 patient years)
  - **≥ 3 points – high risk** (5.9-18.2 strokes per 100 patient years)

How do we determine stroke risk ?

CHEST

Original Research

THROMBOEMBOLISM

Refining Clinical Risk Stratification for Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach

The Euro Heart Survey on Atrial Fibrillation

Gregory Y. H. Lip, MD; Robby Nieuwlaat, PhD; Ron Pisters, MD; Deirdre A. Lane, PhD; and Harry J. G. M. Crijns, MD

Lip Y, et al. Chest 2010, 137(2):263

Stroke Risk Stratification in AF

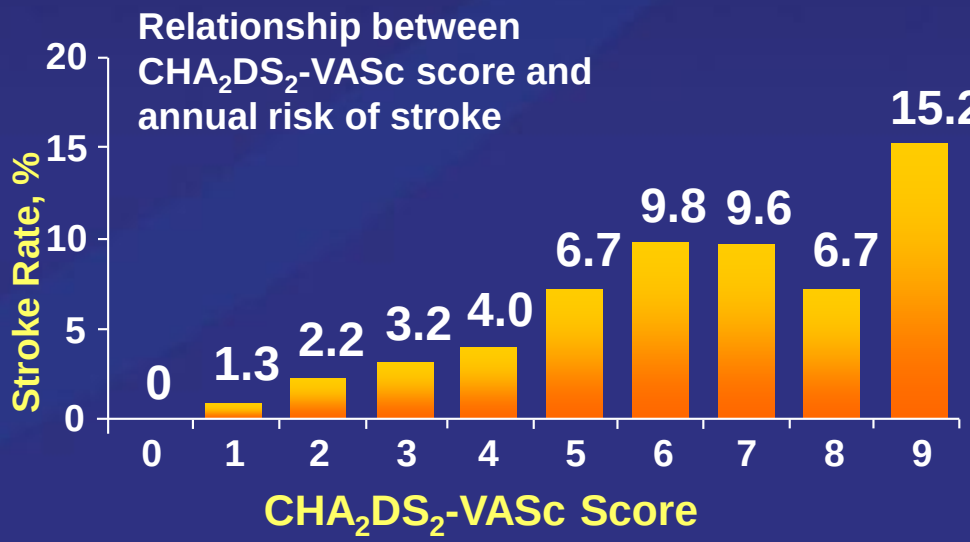
$CHADS_2$

Risk Factor	Score
Cardiac failure	1
HTN	1
Age ≥75 y	1
Diabetes	1
Stroke	2

Total Score	Annual Risk of Stroke (%)
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2

CHA_2DS_2-VASc

Risk Factor	Score
Cardiac failure	1
HTN	1
Age ≥75 y	2
Diabetes	1
Stroke	2
Vasc dz (MI, PAD, aortic ath)	**1**
Age 65-74 y	**1**
Sex **c**ategory (female)	**1**



Lip GY, Halperin JL. *Am J Med*. 2010;123(6):484-488.

Stroke Risk Stratification in AF

Validation of a Modified CHA_2DS_2-VASc Score for Stroke Risk Stratification in Asian Patients With Atrial Fibrillation

A Nationwide Cohort Study

Tze-Fan Chao, MD*; Gregory Y.H. Lip, MD*; Chia-Jen Liu, MD; Ta-Chuan Tuan, MD; Su-Jung Chen, MD; Kang-Ling Wang, MD; Yenn-Jiang Lin, MD; Shih-Lin Chang, MD; Li-Wei Lo, MD; Yu-Feng Hu, MD; Tzeng-Ji Chen, MD; Chern-En Chiang, MD, PhD; Shih-Ann Chen, MD

***Background and Purpose*—**The age threshold for an increased stroke risk for patients with atrial fibrillation may be different for Asians and non-Asians. We hypothesized that a modified CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74 years, female) scheme, $mCHA_2DS_2$-VASc, which assigned one point for patients aged 50 to 74 years, may perform better than CHA_2DS_2-VASc score for stroke risk stratification in Asians.

***Methods*—**This study used the Taiwan National Health Insurance Research Database, which included 224 866 newly diagnosed atrial fibrillation patients. The predictive accuracies of ischemic stroke of CHA_2DS_2-VASc and $mCHA_2DS_2$-VASc scores were compared among 124 271 patients without antithrombotic therapies. From the whole cohort, 15 948 patients had a CHA_2DS_2-VASc score 0 (males) or 1 (females), and 8654 patients had an $mCHA_2DS_2$-VASc score 1 (males) or 2 (females). The latter were categorized into 3 groups, that is, no treatment, antiplatelet therapy, and warfarin, and the risks of ischemic stroke and intracranial hemorrhage (ICH) were compared.

***Results*—**During a follow-up of 538 653 person-years, 21 008 patients experienced ischemic stroke. The $mCHA_2DS_2$-VASc performed better than CHA_2DS_2-VASc score in predicting ischemic stroke assessed by C indexes and net reclassification index. For 8654 patients having an $mCHA_2DS_2$-VASc score of 1 (males) or 2 (females) because of the resetting of the age threshold, use of warfarin was associated with a 30% lower risk of ischemic stroke and a similar risk of ICH compared with nontreatment. Net clinical benefit analyses also favored the use of warfarin in different weighted models.

***Conclusions*—**In this Asian atrial fibrillation cohort, the $mCHA_2DS_2$-VASc score performed better than the CHA_2DS_2-VASc and would further identify atrial fibrillation patients who may derive a positive net clinical benefit from oral anticoagulation. **(*Stroke*. 2016;47:00-00. DOI: 10.1161/STROKEAHA.116.013880.)**

Risk-Based Antithrombotic Therapy

Recommendations	COR	LOE
In patients with AF, antithrombotic therapy should be individualized based on shared decision making after discussion of the absolute risks and RRs of stroke and bleeding and the patient's values and preferences.	I	C
Selection of antithrombotic therapy should be based on the risk of thromboembolism irrespective of whether the AF pattern is paroxysmal, persistent, or permanent.	I	B
In patients with nonvalvular AF, the CHA_2DS_2-VASc* score is recommended for assessment of stroke risk.	I	B
For patients with AF who have mechanical heart valves, warfarin is recommended, and the target INR intensity (2.0 to 3.0 or 2.5 to 3.5) should be based on the type and location of the prosthesis.	I	B

***CHA_2DS_2-VASc indicates Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category.**

Summary- Non Valvular AF

Risk Category	CHADs-2-VASC Score	Recommended Therapy American College of Cardiology (ACC) / European Society of Cardiology (ESC)
Two or more Risk Factors	2	ACC- Oral Anticoagulation ESC- Oral Anticoagulation
One Risk Factor	1	ACC- Aspirin 81 mg or Oral Anticoagulation (Exception Female Gender only) ESC- Oral Anticoagulation
No Risk Factors	0	ACC- Aspirin 81 mg daily ESC- No Therapy

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. © American College of Cardiology Foundation and American Heart Association

Stroke Risk Stratification in AF

Journal of the American College of Cardiology

Volume 65, Issue 3, January 2015
DOI: 10.1016/j.jacc.2014.10.052

PDF Article

Benefit of Anticoagulation Unlikely in Patients With Atrial Fibrillation and a CHA_2DS_2-VASc Score of 1

Leif Friberg, Mika Skeppholm, Andreas Terént

⊞ Author + information

Abstract

Background Patients with atrial fibrillation (AF) and ≥1 point on the stroke risk scheme CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years, sex category) are considered at increased risk for future stroke, but the risk associated with a score of 1 differs markedly between studies.

Objectives The goal of this study was to assess AF-related stroke risk among patients with a score of 1 on the CHA_2DS_2-VASc.

Methods We conducted this retrospective study of 140,420 patients with AF in Swedish nationwide health registries on the basis of varying definitions of "stroke events."

Results Using a wide "stroke" diagnosis (including hospital discharge diagnoses of ischemic stroke as well as unspecified stroke, transient ischemic attack, and pulmonary embolism) yielded a 44% higher annual risk than if only ischemic strokes were counted. Including stroke events in conjunction with the index hospitalization for AF doubled the long-term risk beyond the first 4 weeks. For women, annual stroke rates varied between 0.1% and 0.2% depending on which event definition was used; for men, the corresponding rates were 0.5% and 0.7%.

Conclusions The risk of ischemic stroke in patients with AF and a CHA_2DS_2-VASc score of 1 seems to be lower than previously reported.

Atrial Fibrillation

- Anticoagulation Strategies
  - Aspirin
  - Warfarin
  - Dabigatran (Direct Thrombin Inhibitor)
  - Rivaroxaban (Factor Xa Inhibitor)
  - Apixaban (Factor Xa Inhibitor)
  - Endoxiban (Factor Xa Inhibitor)

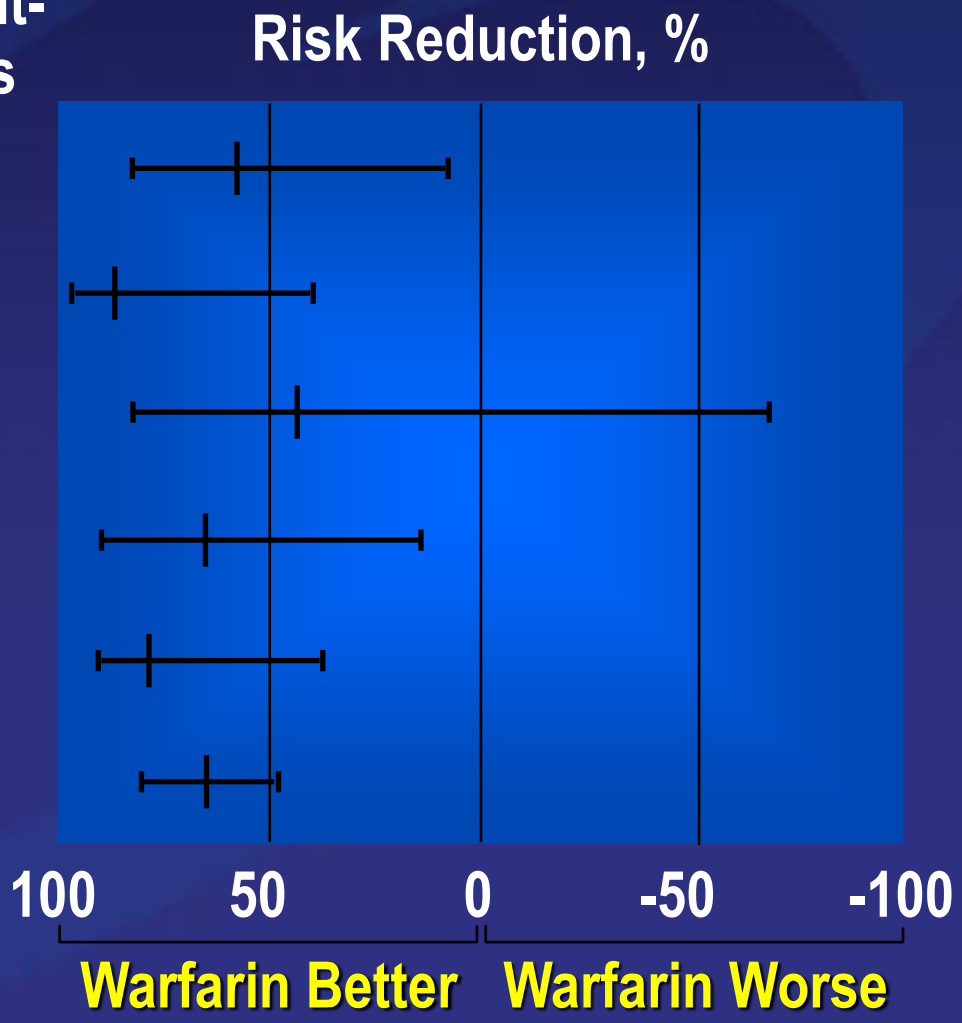
Atrial Fibrillation

- Anticoagulation Strategies

Efficacy of Warfarin

Compared with Control in Five Studies

	No. of Events	Patient-years
AFASAK	27	811
BAATAF	15	922
CAFA	14	478
SPAF	23	508
SPINAF	29	972
Combined*	108	3691



*Total risk reduction for all 5 studies combined is 68%

Warfarin

THE GOOD

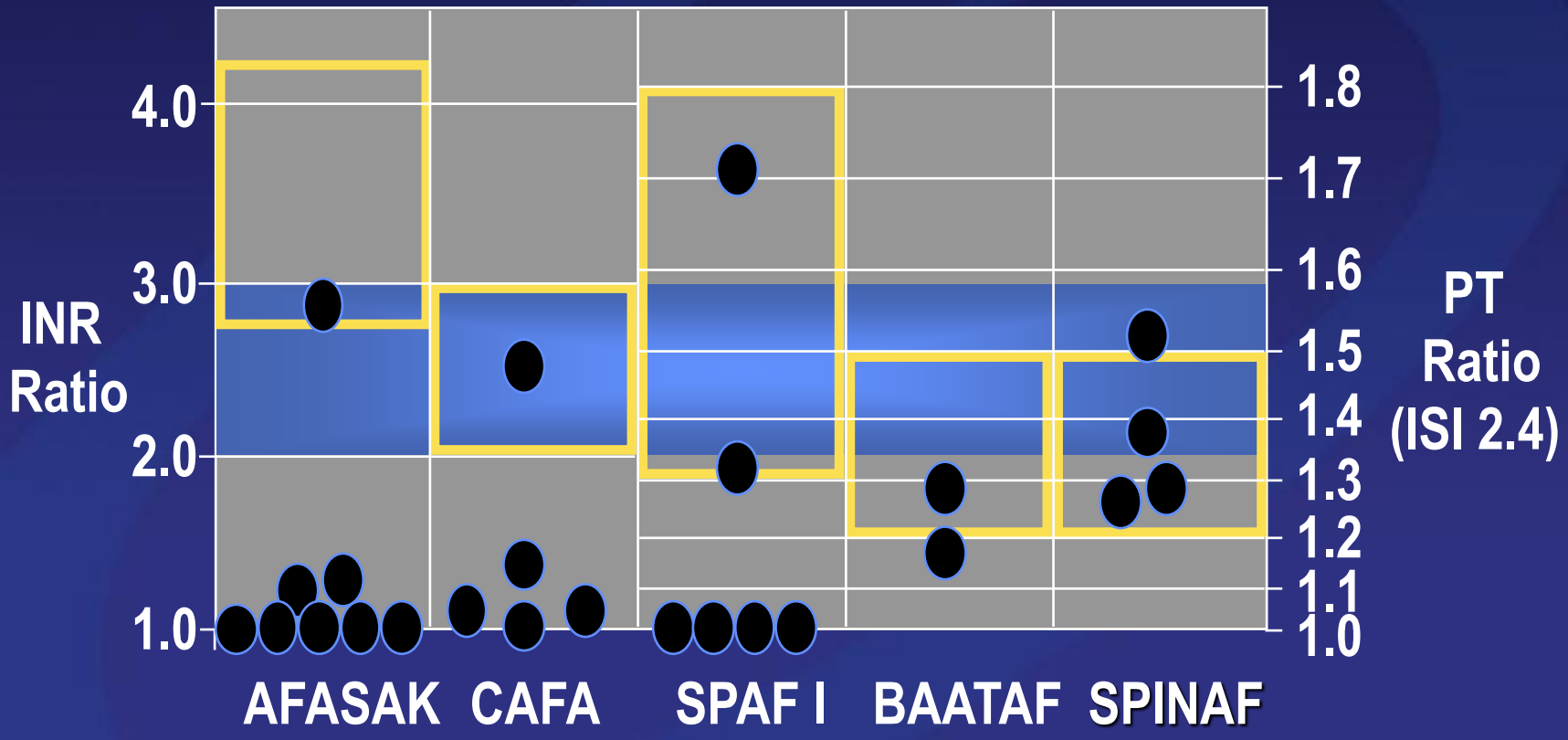
- Effective
- Reversible
- Inexpensive

THE BAD

- Slow onset of action
- Regular monitoring
- Food interaction
- Medication interaction
- Difficult titration-regular dose adjustments
- Variable response
- Bleeding risks
- “bridging”

Patients Assigned to Warfarin in AF Trials

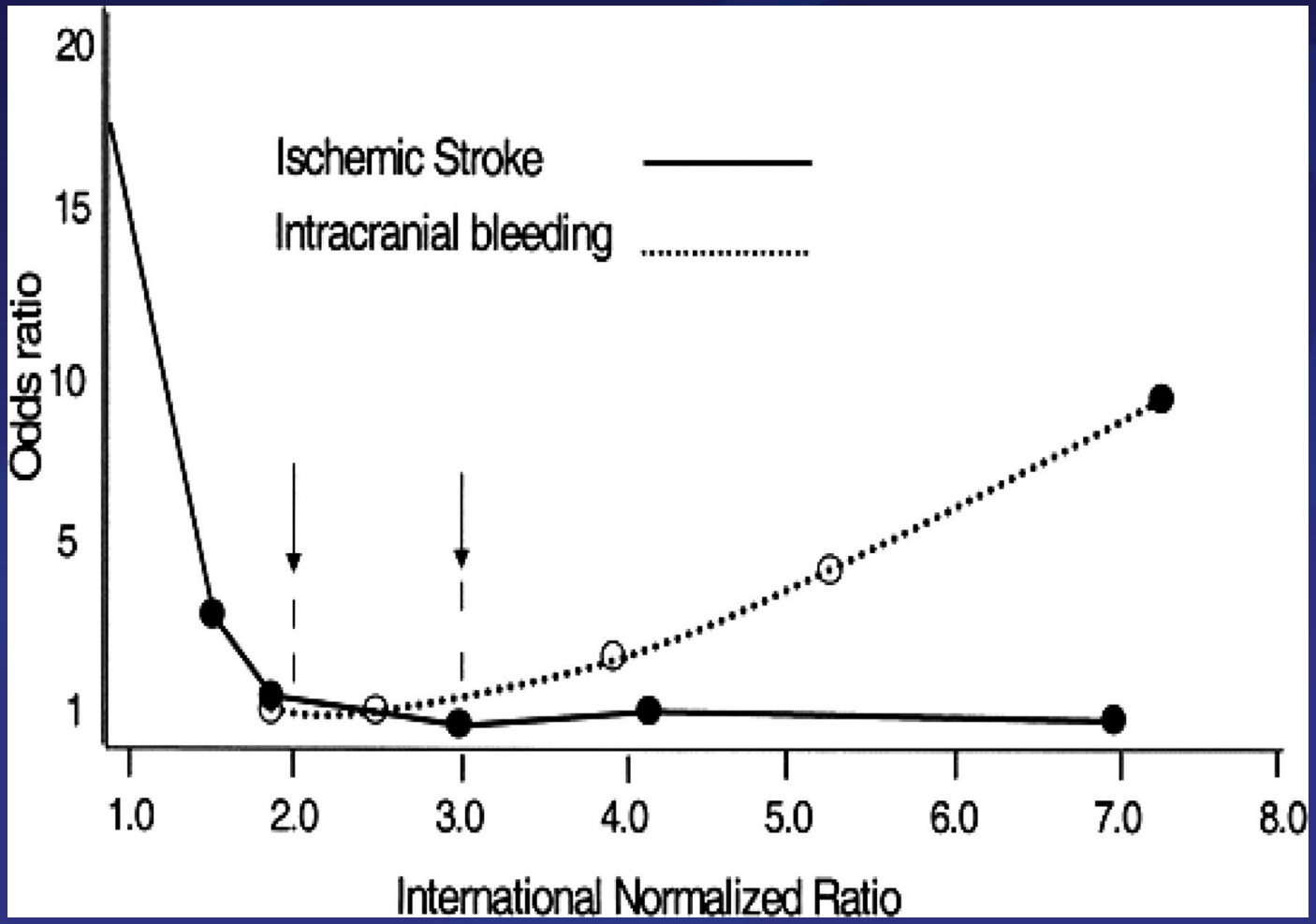
Intensity of Anticoagulation When Stroke Occurred



ACCP recommendation: INR: 2.0–3.0

Target range for individual study

Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation



Authors/Task Force Members, et al. Eur Heart J 2006 27:1979-2030; doi:10.1093/eurheartj/ehl176

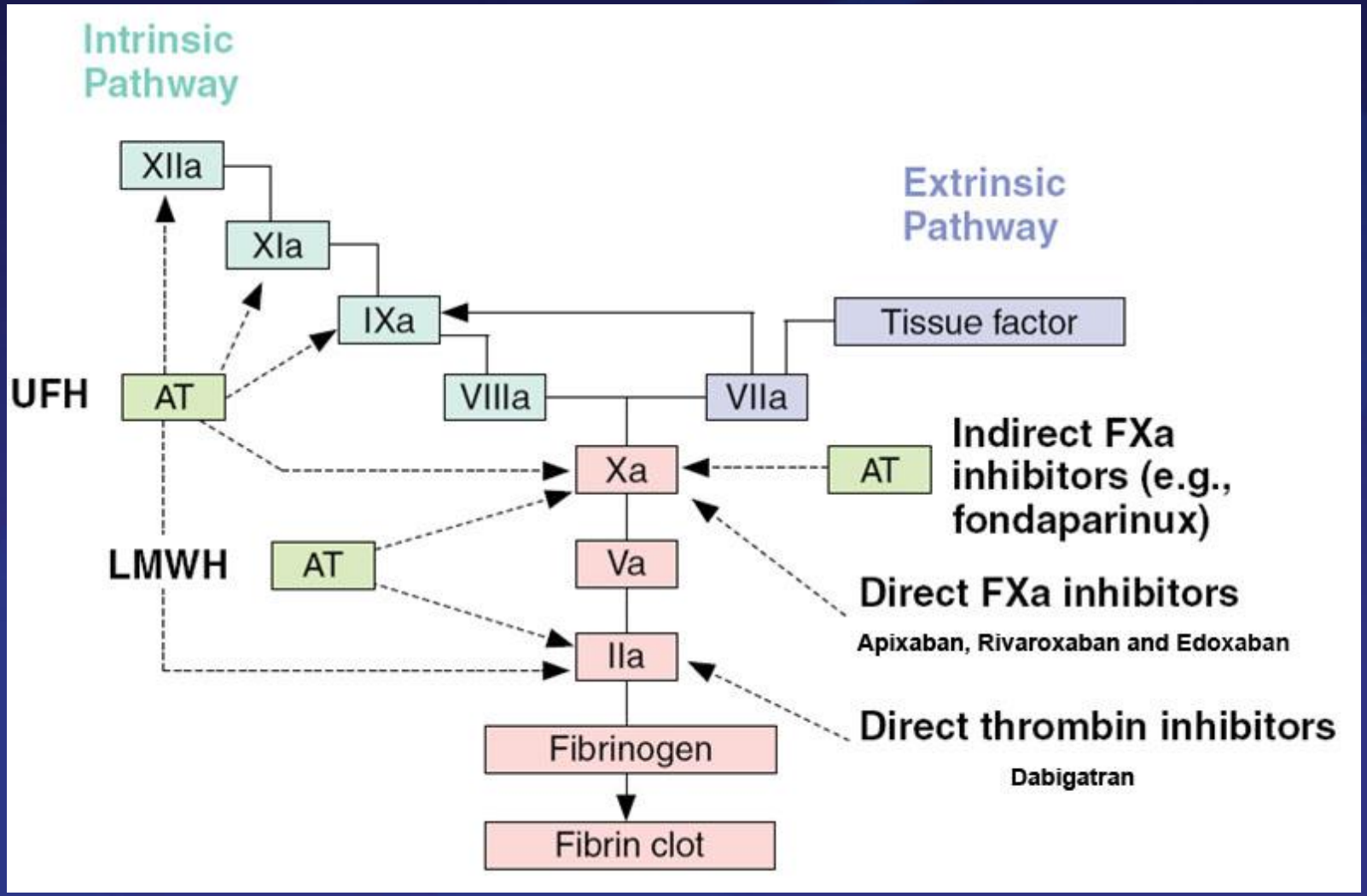
Time in Therapeutic Range (TTR)
INR Data

	Warfarin
INR range	Median (25th, 75th)
<1.5	2.7 (0.0 – 9.0)
1.5 to <1.8	7.9 (3.5 – 14.0)
1.8 to <2.0	9.1 (5.3 – 13.6)
2.0 to 3.0	57.8 (43.0 – 70.5)
>3.0 to 3.2	4.0 (1.9 – 6.5)
>3.2 to 5.0	7.9 (3.3 – 13.8)
>5.0	0.0 (0.0 – 0.5)

Based on Rosendaal method with all INR values included
Based on Safety Population

M. Califf, M.D., and the **ROCKET AF** Steering Committee, for the **ROCKET AF** Investigators. **N Engl J Med** 2011; 365:883-891 September 8, 2011

Emerging Therapies



Modified from the Am J Health-Syst Pharm;65:1520

The Ideal Anticoagulant

- Oral
- Once daily dosing
- Quick onset
- Limited monitoring
- Limited or no drug interactions
- Available and effective antidote
- Wide therapeutic index
- Low cost

DOAC Summary

Table 1: Study characteristics.

Studies		RE-LY (1)	ROCKET AF (2)	ARISTOTLE (3)	ENGAGE AF-TIMI 48 (4)
Trial size (n)		18,113	14,264	18,201	21,105
Patient characteristics	Mean age (years)	71.5	73	70	72
	Male (%)	63.5%	59.3%	64.5%	61.9%
	Mean $CHADS_2$	2.1	3.5	2.1	2.8
Intervention vs Comparator	Intervention	Two intervention arms: 1. Dabigatran 150 mg bid 2. Dabigatran 150 mg bid	Rivaroxaban 20 mg daily	Apixaban 5 mg bid	Two intervention arms: 1. Edoxaban 30 mg daily 2. Edoxaban 60 mg daily
	Dose modification	No	Yes, at randomisation	Yes, at randomisation	Yes, at randomisation and during study
	Criteria for modified dose	N/A	15 mg daily in patients with CrCl 30–49 ml/min	2.5 mg bid in patients who met 2 of the 3 following criteria: • age >80 years, • weight <60 kg, • creatinine >133 µmol/l	Half dose in patients with any of the following criteria: • CrCl 30–50 ml/min, • weight <60 kg, • concomitant use of potent p-glycoprotein inhibitors such as verapamil, quinidine, dronaderone. Standard dose resumed once these medications ceased.
	Comparators	Open label warfarin	Blinded warfarin	Blinded warfarin	Blinded warfarin
Outcomes	Primary efficacy	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism
	Primary safety	Major bleeding	Major bleeding + clinically relevant non major bleeding	Major bleeding	Major bleeding

Bid = twice-daily dose; CrCl = creatinine clearance as per Cockcroft Gault formulas; kg = kilogram; mg = milligram.

Chan et al. New oral anticoagulatns for stroke prevention in atrial fibrillation. Thromb Haemost 2014; 111: 798-807

Clinical Trials

- Reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
  - **RE-LY Trial**[1]
    - Dabigatran 110mg PO BID or 150mg PO BID (blinded) to open-label warfarin 1, 3, or 5mg (goal INR 2-3) in patients with non-valvular Afib and one or more of the following risk factors:
      - Previous stroke, TIA, or systemic embolism
      - LVEF<40%
      - Symptomatic heart failure, NYHA class ≥2
      - Age ≥75 years
      - Age ≥65 years with DM, CAD, or HTN
    - 18,113 patients randomized and followed for a median of 2 years
    - TTR for warfarin: 64% (mean)

RELY

- Dabigatran 150 mg twice daily
  - More effective than warfarin in stroke prevention
    - Dabigatran (150mg) 1.11%/yr
  - **Equivalent bleeding to warfarin but <u>Less</u> hemorrhagic stroke than warfarin**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

ABSTRACT

BACKGROUND

Warfarin reduces the risk of stroke in patients with atrial fibrillation but increases the risk of hemorrhage and is difficult to use. Dabigatran is a new oral direct thrombin inhibitor.

METHODS

In this noninferiority trial, we randomly assigned 18,113 patients who had atrial fibrillation and a risk of stroke to receive, in a blinded fashion, fixed doses of dabigatran — 110 mg or 150 mg twice daily — or, in an unblinded fashion, adjusted-dose warfarin. The median duration of the follow-up period was 2.0 years. The primary outcome was stroke or systemic embolism.

RESULTS

From the Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada (S.J.C., S.Y., J.E., J.P., E.T.); Lankenau Institute for Medical Research and the Heart Center, Wynnewood, PA (M.D.E., A.P.); Uppsala Clinical Research Center, Uppsala, Sweden (J.O., L.W.); Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (P.A.R., J.V., S.W.); Working Group on Cardiovascular Research the Netherlands, Utrecht, the Netherlands (M.A.); St. John's National Academy of Health Sciences, Bangalore, India (D.X.); FuWai Hospital, Beijing (J.Z.); Estudios Clínicos Latinoamérica, Rosario, Argentina (R.D.); Lady

Table 2 Recommendation for emerging antithrombotic agents

2011 Focused update recommendation	Comments
Class I	
1. Dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance <15 mL/min) or advanced liver disease (impaired baseline clotting function).[3] *(Level of Evidence: B)*	New recommendation

Wann et al. 2011 ACCF/AHA/HRS Focus Update on the Management of Patients with Atrial Fibrillation. March 2011

REVIEW ARTICLE

ONLINE FIRST

Dabigatran Association With Higher Risk of Acute Coronary Events

Meta-analysis of Noninferiority Randomized Controlled Trials

Ken Uchino, MD; Adrian V. Hernandez, MD, PhD

Background: The original RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) trial suggested a small increased risk of myocardial infarction (MI) with the use of dabigatran etexilate vs warfarin in patients with atrial fibrillation. We systematically evaluated the risk of MI or acute coronary syndrome (ACS) with the use of dabigatran.

Methods: We searched PubMed, Scopus, and the Web of Science for randomized controlled trials of dabigatran that reported on MI or ACS as secondary outcomes. The fixed-effects Mantel-Haenszel (M-H) test was used to evaluate the effect of dabigatran on MI or ACS. We expressed the associations as odds ratios (ORs) and their 95% CIs.

Results: Seven trials were selected (N = 30 514), including 2 studies of stroke prophylaxis in atrial fibrillation, 1 in acute venous thromboembolism, 1 in ACS, and 3 of short-term prophylaxis of deep venous thrombosis. Control arms included warfarin, enoxaparin, or placebo administration. Dabigatran was significantly associated with a higher risk of MI or ACS than that seen with agents used in the control group (dabigatran, 237 of 20 000 [1.19%] vs control, 83 of 10 514 [0.79%]; $OR_{M\text{-}H}$, 1.33; 95% CI, 1.03-1.71; $P = .03$). The risk of MI or ACS was similar when using revised RE-LY trial results ($OR_{M\text{-}H}$, 1.27; 95% CI, 1.00-1.61; $P = .05$) or after exclusion of short-term trials ($OR_{M\text{-}H}$, 1.33; 95% CI, 1.03-1.72; $P = .03$). Risks were not heterogeneous for all analyses ($I^2 = 0\%$; $P \geq .30$) and were consistent using different methods and measures of association.

Conclusions: Dabigatran is associated with an increased risk of MI or ACS in a broad spectrum of patients when tested against different controls. Clinicians should consider the potential of these serious harmful cardiovascular effects with use of dabigatran.

Arch Intern Med.
Published online January 9, 2012.
doi:10.1001/archinternmed.2011.1666

Rivaroxaban (Xarelto®)

- Once daily
- As effective or better than warfarin
- Less hemorrhagic stroke than warfarin
- Similar reduction in ischemic stroke
- Less bleeding than warfarin
- No routine lab testing
- No reversal
  - Half life 5-9 hours
- Coagulation testing: aPTT
- Discontinuation : increased stroke

Key Secondary Efficacy Outcomes

	Rivaroxaban	Warfarin		
	Event Rate	Event Rate	HR (95% CI)	P-value
Vascular Death, Stroke, Embolism	3.11	3.63	0.86 (0.74, 0.99)	0.034
Stroke Type				
Hemorrhagic	0.26	0.44	0.59 (0.37, 0.93)	0.024
Ischemic	1.34	1.42	0.94 (0.75, 1.17)	0.581
Unknown Type	0.06	0.10	0.65 (0.25, 1.67)	0.366
Non-CNS Embolism	0.04	0.19	0.23 (0.09, 0.61)	0.003
Myocardial Infarction	0.91	1.12	0.81 (0.63, 1.06)	0.121
All Cause Mortality	1.87	2.21	0.85 (0.70, 1.02)	0.073
Vascular	1.53	1.71	0.89 (0.73, 1.10)	0.289
Non-vascular	0.19	0.30	0.63 (0.36, 1.08)	0.094
Unknown Cause	0.15	0.20	0.75 (0.40, 1.41)	0.370

Event Rates are per 100 patient-years
Based on Safety on Treatment Population

M. Califf, M.D., and the **ROCKET AF** Steering Committee, for the **ROCKET AF** Investigators. **N Engl J Med** 2011; 365:883-891 September 8, 201

Primary Safety Outcomes

	Rivaroxaban	Warfarin		
	Event Rate or N (Rate)	Event Rate or N (Rate)	HR (95% CI)	P-value
Major	3.60	3.45	1.04 (0.90, 1.20)	0.576
≥2 g/dL Hgb drop	2.77	2.26	1.22 (1.03, 1.44)	0.019
Transfusion (> 2 units)	1.65	1.32	1.25 (1.01, 1.55)	0.044
Critical organ bleeding	0.82	1.18	0.69 (0.53, 0.91)	0.007
Bleeding causing death	0.24	0.48	0.50 (0.31, 0.79)	0.003
Intracranial Hemorrhage	55 (0.49)	84 (0.74)	0.67 (0.47, 0.94)	0.019
Intraparenchymal	37 (0.33)	56 (0.49)	0.67 (0.44, 1.02)	0.060
Intraventricular	2 (0.02)	4 (0.04)		
Subdural	14 (0.13)	27 (0.27)	0.53 (0.28, 1.00)	0.051
Subarachnoid	4 (0.04)	1 (0.01)		

Event Rates are per 100 patient-years
Based on Safety on Treatment Population

M. Califf, M.D., and the **ROCKET AF** Steering Committee, for the **ROCKET AF** Investigators. **N Engl J Med** 2011; 365:883-891 September 8, 2011

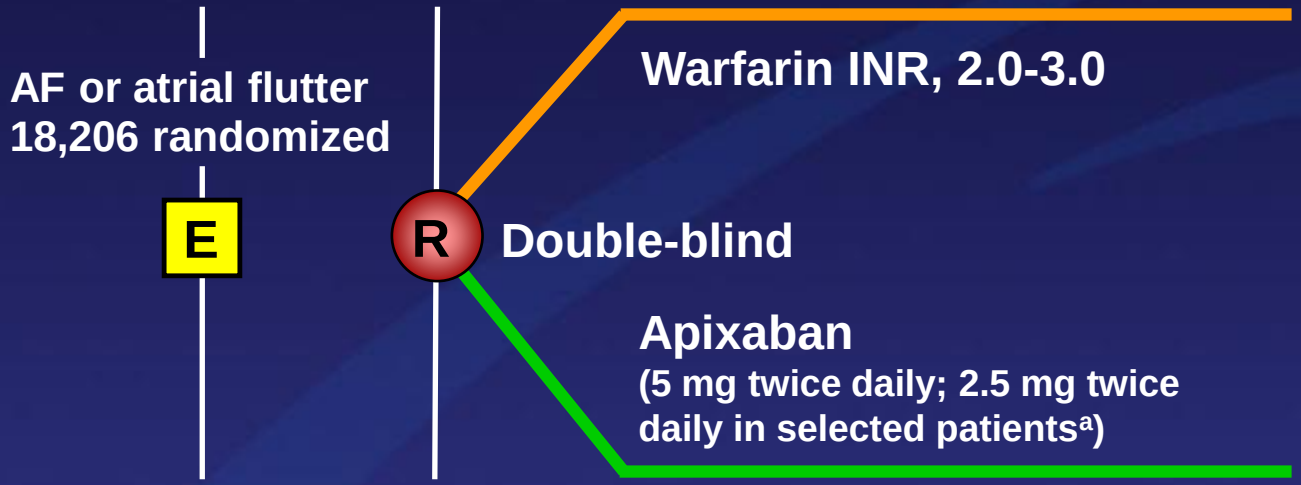
Apixaban (Eliquis®)

- Twice daily
- As effective or better than warfarin
- Less hemorrhagic stroke than warfarin
- Similar reduction in ischemic stroke
- Less bleeding than warfarin
- Lower overall mortality
- No routine lab testing
- No reversal
  - Half life 8-15 hours
- Coagulation testing: PT, aPTT

Apixaban (Eliquis®)

- **Class:** Factor Xa inhibitor
- **MOA:** Direct-acting, reversible factor Xa inhibitor. Inhibits the conversion of prothrombin to thrombin.
- **FDA approved indication:** Still in the late-stage of clinical development for the prevention and treatment of thromboembolic events.
- **Dose:**
  - 5 and 2.5 mg twice daily
    - Note: Doses being studied in clinical trials.
- 2.5mg PO BID for Scr $\geq$ 1.5mg/dL, age $\geq$ 80, body weight $\leq$ 60 kg

ARISTOTLE Trial: Apixaban[1,2]



- Is apixaban noninferior to standard therapy (warfarin) in preventing stroke and systemic embolism in moderate- to high-risk (stroke; at least 1 risk factor) AF patients?
- 1^0 efficacy end point: confirmed ischemic or hemorrhagic stroke, or systemic embolism
- 2^0 efficacy end points: composite of confirmed ischemic or hemorrhagic stroke, systemic embolism, and all-cause death
- 1^0 safety end point: time to first occurrence of confirmed major bleeding
- Treatment period: up to 4 years (until 448 primary outcome events have been observed — >90% power to demonstrate noninferiority);
  - Stratified by warfarin-naïve status

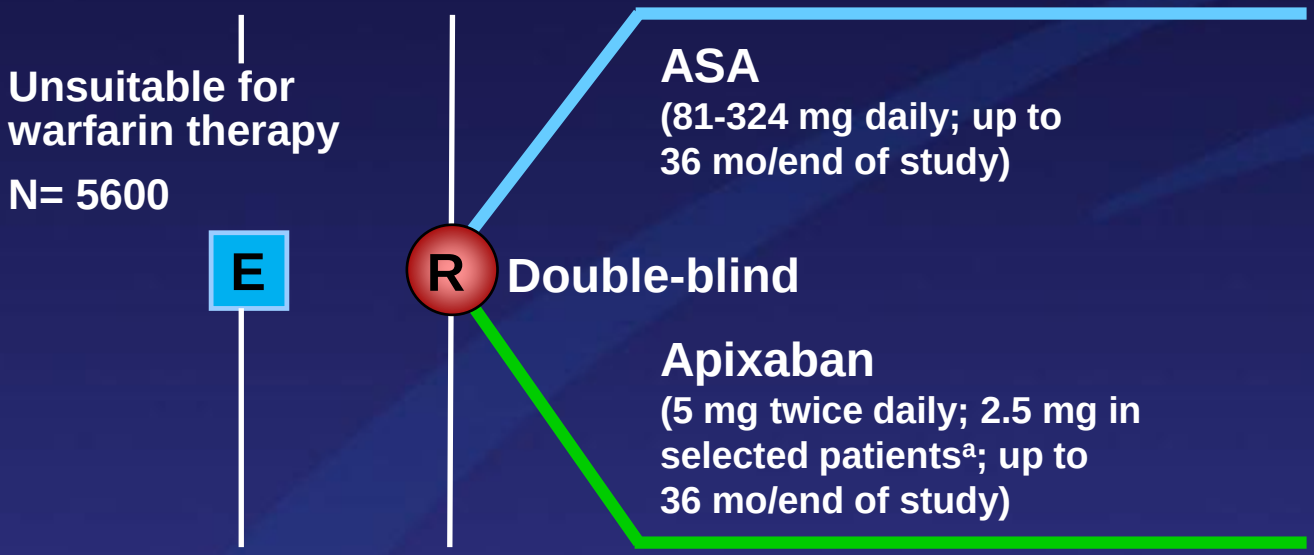
1. Lopes RD, et al. *Am Heart J.* 2010;159(3):331-339.
2. ClinicalTrials.gov identifier: NCT00412984
3. *AF 2011: Therapeutic Update Presentation.* Gerald V. Naccarelli M.D

Efficacy Outcomes

Outcome	Apixaban (N=9120) Event Rate (%/yr)	Warfarin (N=9081) Event Rate (%/yr)	HR (95% CI)	P Value
Stroke or systemic embolism*	1.27	1.60	0.79 (0.66, 0.95)	0.011
Stroke	1.19	1.51	0.79 (0.65, 0.95)	0.012
Ischemic or uncertain	0.97	1.05	0.92 (0.74, 1.13)	0.42
Hemorrhagic	0.24	0.47	0.51 (0.35, 0.75)	<0.001
Systemic embolism (SE)	0.09	0.10	0.87 (0.44, 1.75)	0.70
All-cause death*	3.52	3.94	0.89 (0.80, 0.998)	0.047
Stroke, SE, or all-cause death	4.49	5.04	0.89 (0.81, 0.98)	0.019
Myocardial infarction	0.53	0.61	0.88 (0.66, 1.17)	0.37

* Part of sequential testing sequence preserving the overall type I error

AVERROES Trial[1,2]



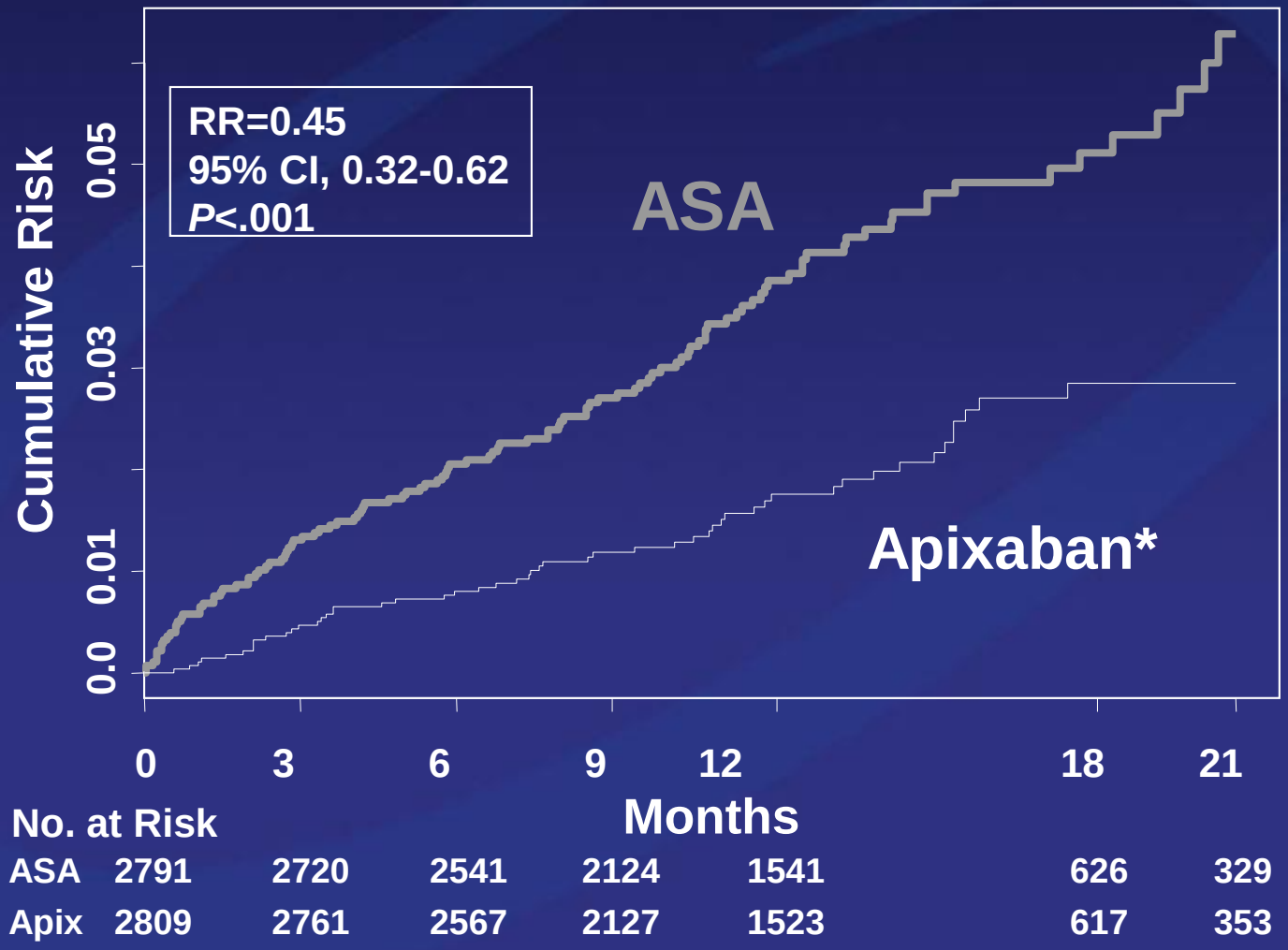
[a] At least 2 of: age ≥80 y, weight ≤60 kg, or serum Cr ≥1.5 mg/dL

- Is apixaban more effective than ASA in preventing stroke and systemic embolism in moderate to high-risk (stroke; at least 1 risk factor) AF patients?
- 1^0 efficacy end point: confirmed ischemic or hemorrhagic stroke or systemic embolism
- 2^0 study end points: as above, including MI or vascular death
- 1^0 safety end point: major bleeding
- Study period: until 226 primary outcome events have been observed
- In June 2010, BMS-Pfizer announced that the study had been stopped early because a predefined interim analysis revealed clear evidence of a clinically important reduction in stroke and systemic embolism. Results presented at ESC 2010, Stockholm, Sweden.

AVERROES, Apixaban Versus ASA to Reduce the Risk Of Stroke.

1. Eikelboom JW, et al. *Am Heart J.* 2010;159(3):348-353.e1.
2. ClinicalTrials.gov identifier: NCT00496769. http://www.theheart.org/article/1087291.do
3. *AF 2011: Therapeutic Update Presentation.* Gerald V. Naccarelli M.D

AVERROES:
Stroke or Systemic Embolic Event



1.AF 2011: Therapeutic Update Presentation. Gerald V. Naccarelli M.D

Connolly S., et al N Engl J Med 2011

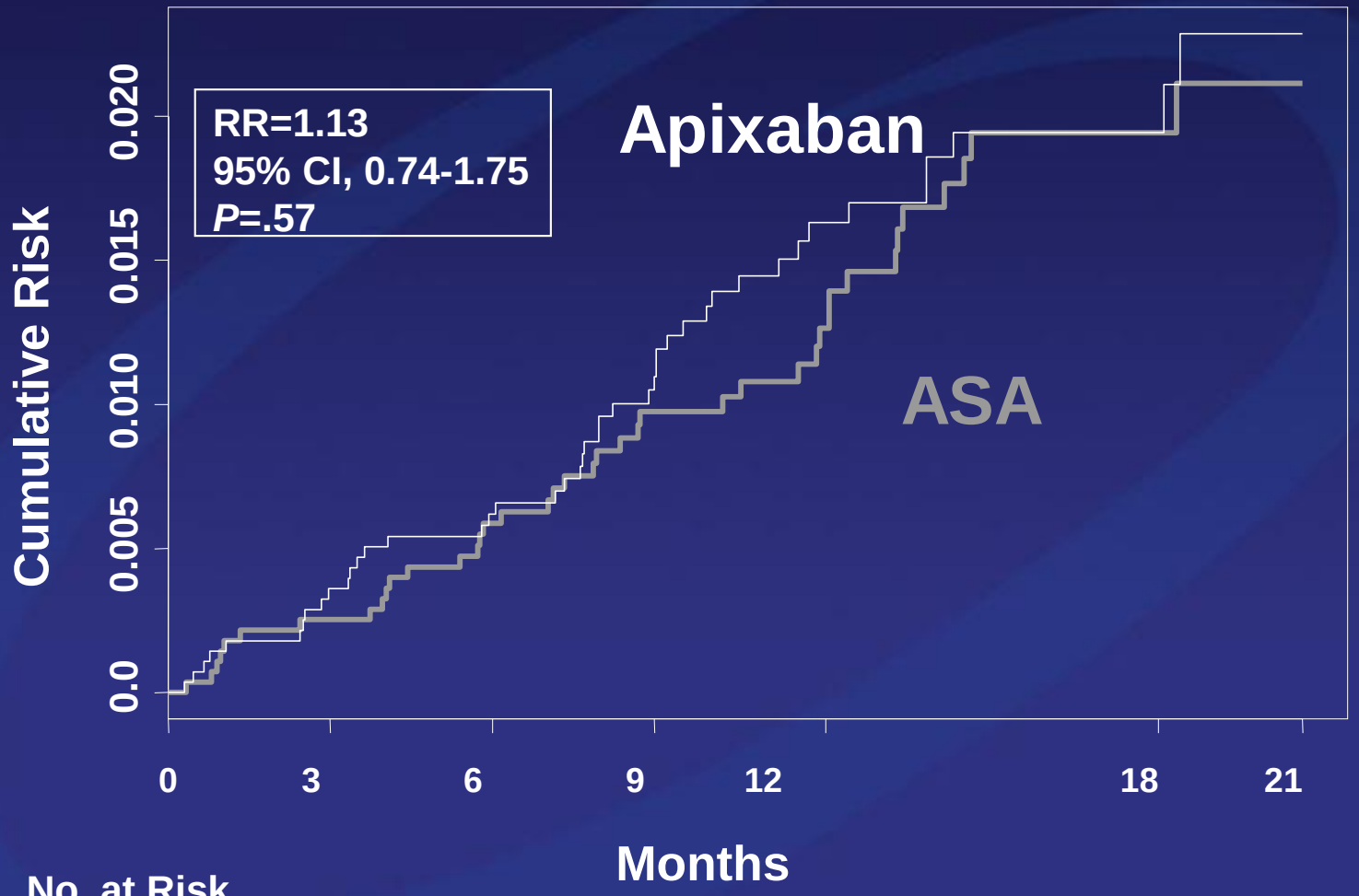
AVERROES: Results (efficacy)

- Apixaban significantly reduced risk of stroke or systemic embolic events by 54%
- The trial was stopped early when the data and safety monitoring board performed a prespecified interim analysis showing significant benefit with apixaban

Primary and secondary end points

Outcomes	Apixaban (n=2809), %	Aspirin (n=2791), %	Relative risk (95% CI)
Primary end point	1.6	3.6	0.46 (0.33–0.64)
Stroke, embolic event, MI, or vascular death	4.1	6.2	0.66 (0.53–0.83)
- MI	0.7	0.8	0.85 (0.48–1.50)
- Vascular death	2.5	2.9	0.86 (0.64–1.16)
CV hospitalization	11.8	14.9	0.79 (0.68–0.91)
Total death	3.4	4.4	0.79 (0.62–1.02)

AVERROES: Major Bleeding



No. at Risk								
ASA	2791	2744	2572	2152	1570		642	340
Apix	2809	2763	2567	2123	1521		622	357

Connolly S, et al. N Engl J Med 2011

AVERROES: Results (safety)

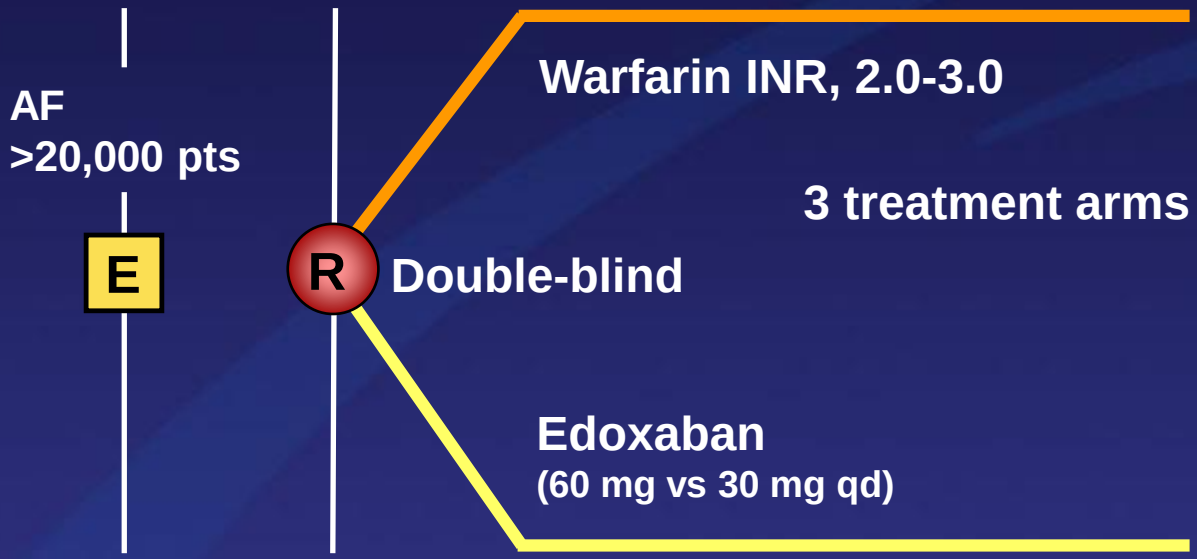
- The risk of major bleeding increased by a statistically nonsignificant 14%
- There was no increased risk of fatal or intracranial hemorrhage, two particular concerns with AF patients who receive anticoagulation therapy

Bleeding events

Outcomes	Apixaban (n=2809), %	Aspirin (n=2791), %	Relative risk (95% CI)
Major bleeding	1.4	1.2	1.14 (0.74–1.75)
Clinical relevant nonmajor bleeding	3.0	2.6	1.18 (0.88–1.58)
Minor bleeding	5.2	4.1	1.27 (1.01–1.61)
Fatal bleeding	0.1	0.1	0.84 (0.26–2.75)
Intracranial	0.4	0.3	1.09 (0.50–2.39)

1.AF 2011: Therapeutic Update Presentation. **Gerald V. Naccarelli M.D**

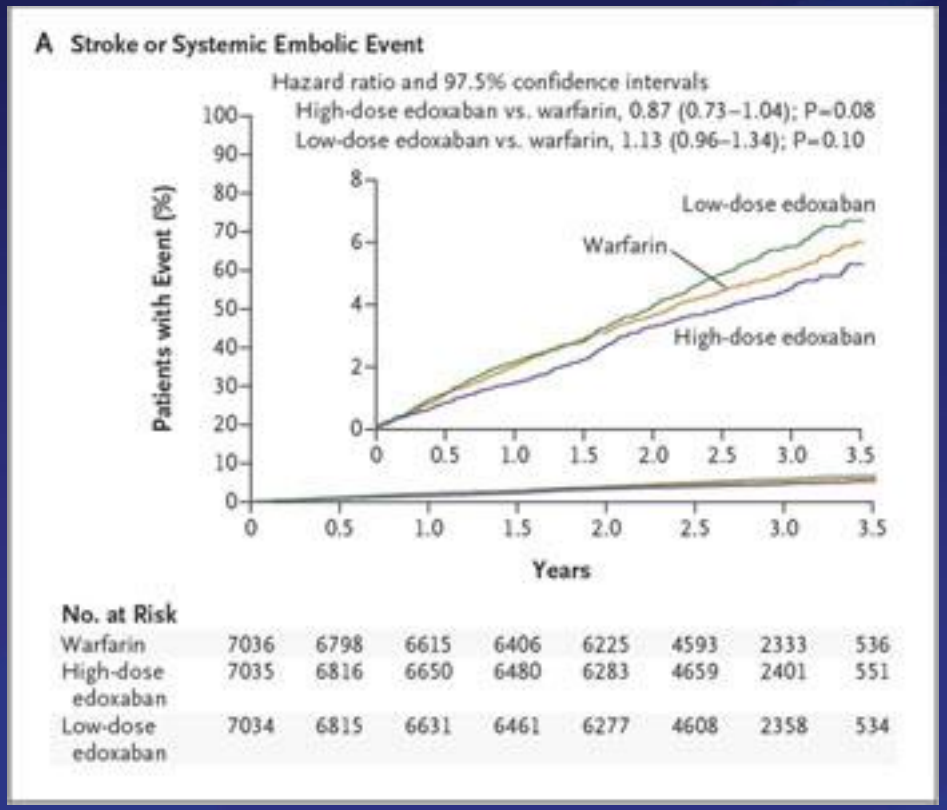
ENGAGE AF–TIMI 48: Edoxaban

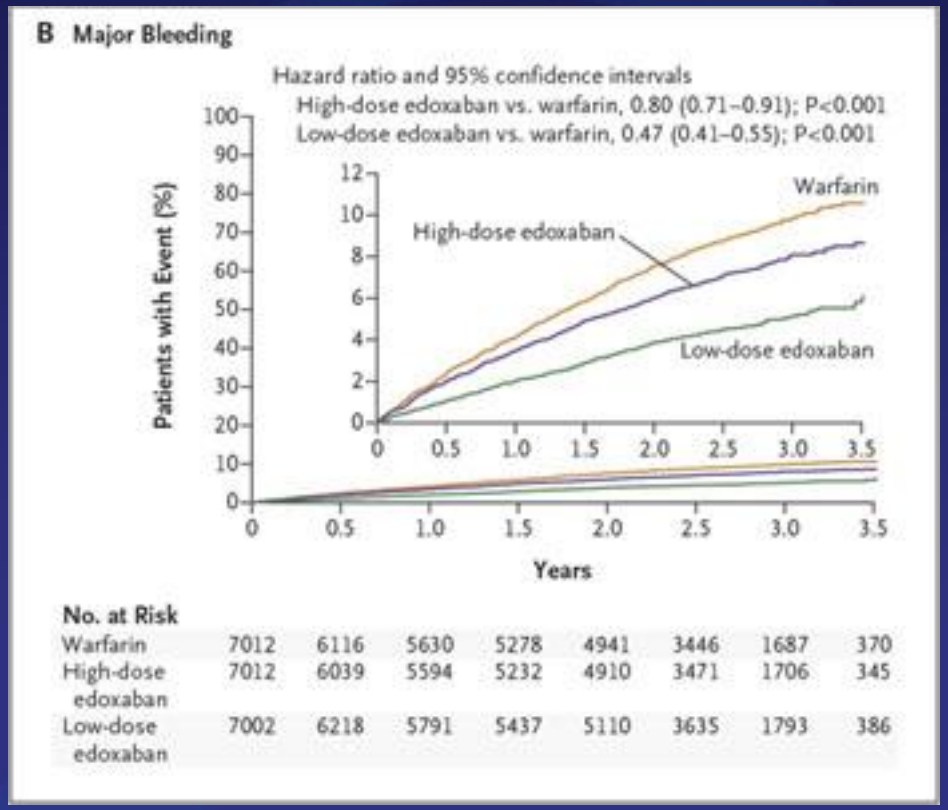


- Is edoxaban noninferior to standard therapy (warfarin) in preventing stroke and systemic embolism in moderate- to high-risk ($CHADS_2$ score ≥2) AF patients?
- 1^0 efficacy end point: composite primary end point of stroke and systemic embolic events
- 2^0 efficacy end points: composite clinical outcome of stroke, systemic embolic events,
  and all-cause mortality; also major bleeding events
- Treatment period: up to 2 years

ClinicalTrials.gov identifier NCT00781391. *AF 2011: Therapeutic Update Presentation.* Gerald V. Naccarelli M.D

ENGAGE AF–TIMI 48: Edoxaban



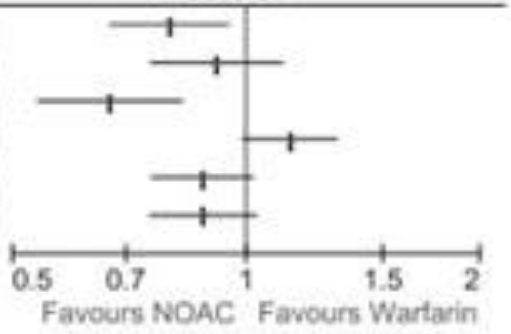


NEJM. Engage AF-TIMI 48

DOAC Events Summary

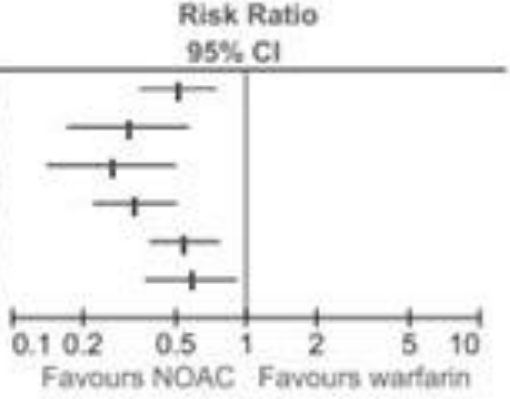
A. Primary Efficacy Outcome

Study or Subgroup	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Risk Ratio 95% CI
Apixaban 5mg bid	212	9120	265	9081	0.80 [0.67, 0.95]
Dabigatran 110mg bid	182	6015	199	6022	0.92 [0.75, 1.12]
Dabigatran 150mg bid	134	6076	199	6022	0.67 [0.54, 0.83]
Edoxaban 30mg daily	383	7034	337	7036	1.14 [0.99, 1.31]
Edoxaban 60mg daily	296	7035	337	7036	0.88 [0.75, 1.02]
Rivaroxaban 20mg daily	269	7081	306	7090	0.88 [0.75, 1.03]



B. Haemorrhagic stroke

Study or Subgroup	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Risk Ratio 95% CI
Apixaban 5mg bid	40	9120	78	9081	0.51 [0.35, 0.75]
Dabigatran 110mg bid	14	6015	45	6022	0.31 [0.17, 0.57]
Dabigatran 150mg bid	12	6076	45	6022	0.26 [0.14, 0.50]
Edoxaban 30mg daily	30	7034	90	7036	0.33 [0.22, 0.50]
Edoxaban 60mg daily	49	7035	90	7036	0.54 [0.39, 0.77]
Rivaroxaban 20mg daily	29	7061	50	7082	0.58 [0.37, 0.92]

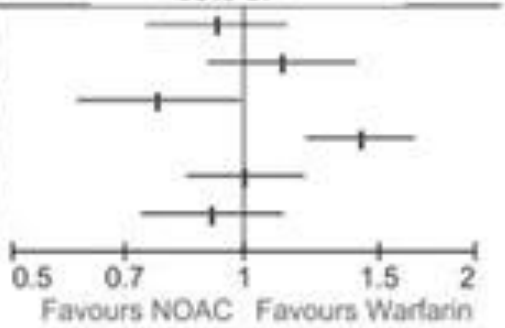


Chan et al. New oral anticoagulatns for stroke prevention in atrial fibrillation. Thromb Haemost 2014; 111: 798-807

DOAC Events Summary

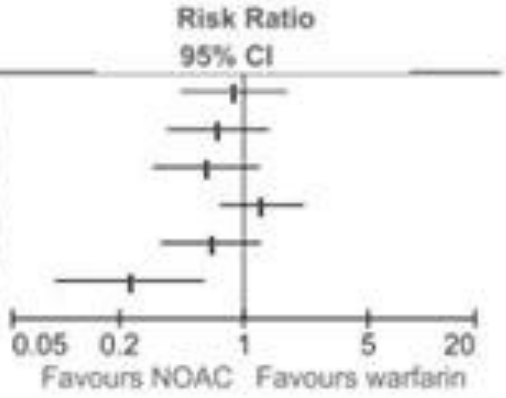
C. Non-haemorrhagic stroke

Study or Subgroup	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Risk Ratio 95% CI
Apixaban 5mg bid	162	9120	175	9081	0.92 [0.75, 1.14]
Dabigatran 110mg bid	159	6015	142	6022	1.12 [0.90, 1.40]
Dabigatran 150mg bid	111	6076	142	6022	0.77 [0.61, 0.99]
Edoxaban 30mg daily	333	7034	235	7036	1.42 [1.20, 1.67]
Edoxaban 60mg daily	236	7035	235	7036	1.00 [0.84, 1.20]
Rivaroxaban 20mg daily	156	7061	172	7082	0.91 [0.73, 1.13]



D. Systemic Embolism

Study or Subgroup	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Risk Ratio 95% CI
Apixaban 5mg bid	15	9120	17	9081	0.88 [0.44, 1.76]
Dabigatran 110mg bid	15	6015	21	6022	0.72 [0.37, 1.39]
Dabigatran 150mg bid	13	6076	21	6022	0.61 [0.31, 1.22]
Edoxaban 30mg daily	29	7034	23	7036	1.26 [0.73, 2.18]
Edoxaban 60mg daily	15	7035	23	7036	0.65 [0.34, 1.25]
Rivaroxaban 20mg daily	5	7061	22	7082	0.23 [0.09, 0.60]

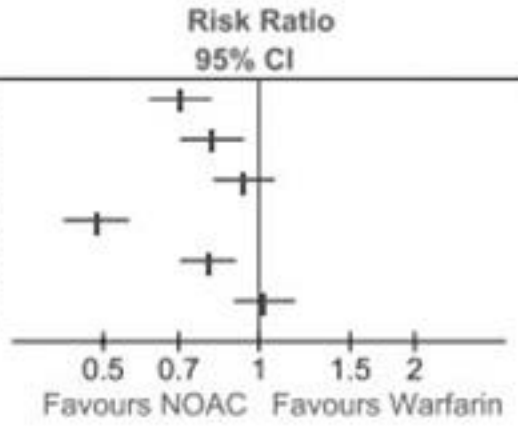


Chan et al. New oral anticoagulatns for stroke prevention in atrial fibrillation. Thromb Haemost 2014; 111: 798-807

DOAC Bleeding Summary

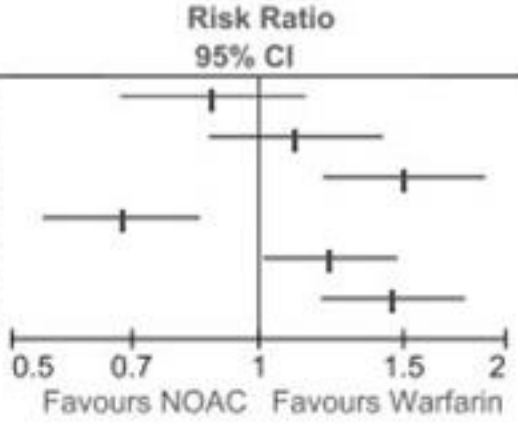
A. Major bleeding

Study or Subgroup	NOAC Events	NOAC Total	Control Events	Control Total	Risk Ratio 95% CI
Apixaban 5mg bid	327	9088	462	9052	0.70 [0.61, 0.81]
Dabigatran 110mg bid	322	6015	397	6022	0.81 [0.70, 0.94]
Dabigatran 150mg bid	375	6076	397	6022	0.94 [0.82, 1.07]
Edoxaban 30mg daily	254	7002	524	7012	0.49 [0.42, 0.56]
Edoxaban 60mg daily	418	7012	524	7012	0.80 [0.70, 0.90]
Rivaroxaban 20mg daily	395	7111	386	7125	1.03 [0.89, 1.18]



B. Major gastrointestinal bleeding

Study or Subgroup	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Risk Ratio 95% CI
Apixaban 5mg bid	105	9088	119	9052	0.88 [0.68, 1.14]
Dabigatran 110mg bid	133	6015	120	6022	1.11 [0.87, 1.42]
Dabigatran 150mg bid	182	6076	120	6022	1.50 [1.20, 1.89]
Edoxaban 30mg daily	129	7002	190	7012	0.68 [0.55, 0.85]
Edoxaban 60mg daily	232	7012	190	7012	1.22 [1.01, 1.47]
Rivaroxaban 20mg daily	224	7111	154	7125	1.46 [1.19, 1.78]

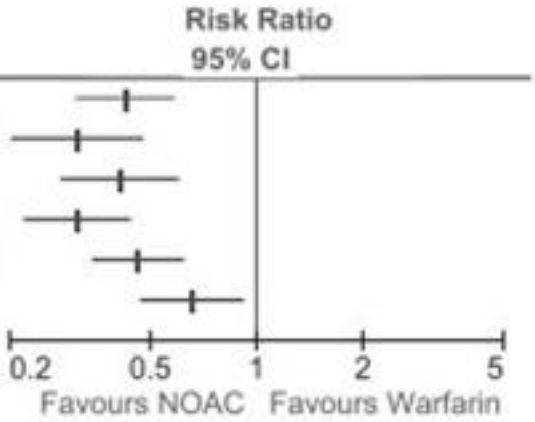


Chan et al. New oral anticoagulatns for stroke prevention in atrial fibrillation. Thromb Haemost 2014; 111: 798-807

DOAC Bleeding Summary

C. Intracranial bleeding

Study or Subgroup	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Risk Ratio 95% CI
Apixaban 5mg bid	52	9088	122	9052	0.42 [0.31, 0.59]
Dabigatran 110mg bid	27	6015	87	6022	0.31 [0.20, 0.48]
Dabigatran 150mg bid	36	6076	87	6022	0.41 [0.28, 0.60]
Edoxaban 30mg daily	41	7002	132	7012	0.31 [0.22, 0.44]
Edoxaban 60mg daily	61	7012	132	7012	0.46 [0.34, 0.62]
Rivaroxaban 20mg daily	55	7111	84	7125	0.66 [0.47, 0.92]



Chan et al. New oral anticoagulatns for stroke prevention in atrial fibrillation. Thromb Haemost 2014; 111: 798-807

Dose Selection of Oral Anticoagulant Options for Patients With Nonvalvular AF and CKD (Based on Prescribing Information for the United States)*

Renal Function	Warfarin	Dabigatran†	Rivaroxaban†	Apixaban†	Edoxiban†
Normal/mild impairment	Dose adjusted for INR 2.0–3.0	150 mg BID (CrCl >30 mL/min)	20 mg QD with the evening meal (CrCl >50 mL/min)	5.0 or 2.5 mg BID‡	CrCl >95 DO NOT USE CrCl 51-94 60 mg QD
Moderate impairment	Dose adjusted for INR 2.0–3.0	150 mg BID (CrCl >30 mL/min)	15 mg QD with the evening meal (CrCl 30–50 mL/min)	5.0 or 2.5 mg BID‡	30 mg QD CrCl 15–50 mL/min
Severe impairment	Dose adjusted for INR 2.0–3.0 §	75 mg BID‖ (CrCl 15–30 mL/min)	15 mg QD with the evening meal (CrCl 15–30 mL/min)	No recommendation ¶	Not recommended (CrCl <15 mL/min)
End-stage CKD not on dialysis	Dose adjusted for INR 2.0–3.0 §	Not recommended¶ (CrCl <15 mL/min)	Not recommended¶ (CrCl <15 mL/min)	No recommendation ¶	Not recommended (CrCl <15 mL/min)
End-stage CKD on dialysis	Dose adjusted for INR 2.0–3.0 §	Not recommended¶ (CrCl <15 mL/min)	Not recommended¶ (CrCl <15 mL/min)	Not recommended (CrCl <15 mL/min)	Not recommended (CrCl <15 mL/min)

Guidelines for Management of AF

Gastroenterology 2017;152:1014–1022

Gastrointestinal Safety of Direct Oral Anticoagulants: A Large Population-Based Study

Neena S. Abraham,[1,2,3] Peter A. Noseworthy,[2,4] Xiaoxi Yao,[2] Lindsey R. Sangaralingham,[2] and Nilay D. Shah[2,3,5]

[1]Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Scottsdale, Arizona; [2]Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, Minnesota; [3]Division of Health Care Policy and Research, Mayo Clinic, Rochester, Minnesota; [4]Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota; and [5]Optum Labs, Cambridge, Massachusetts

CONCLUSIONS: In a population-based study of patients receiving DOAC agents, we found apixaban had the most favorable GI safety profile and rivaroxaban the least favorable profile. GI bleeding events among patient aged 75 years or older taking DOACs increased with age; the risk was greatest among persons 75 years. Apixaban had the most favorable GI safety profile among all age groups.

Guidelines for Management of AF

Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation

Xiaoxi Yao, PhD; Neena S. Abraham, MD, MSCE; Lindsey R. Sangaralingham, MPH; M. Fernanda Bellolio, MD, MS; Robert D. McBane, MD; Nilay D. Shah, PhD; Peter A. Noseworthy, MD

Background—The introduction of non–vitamin K antagonist oral anticoagulants has been a major advance for stroke prevention in atrial fibrillation; however, outcomes achieved in clinical trials may not translate to routine practice. We aimed to evaluate the effectiveness and safety of dabigatran, rivaroxaban, and apixaban by comparing each agent with warfarin.

Methods and Results—Using a large US insurance database, we identified privately insured and Medicare Advantage patients with nonvalvular atrial fibrillation who were users of apixaban, dabigatran, rivaroxaban, or warfarin between October 1, 2010, and June 30, 2015. We created 3 matched cohorts using 1:1 propensity score matching: apixaban versus warfarin (n=15 390), dabigatran versus warfarin (n=28 614), and rivaroxaban versus warfarin (n=32 350). Using Cox proportional hazards regression, we found that for stroke or systemic embolism, apixaban was associated with lower risk (hazard ratio [HR] 0.67, 95% CI 0.46–0.98, P=0.04), but dabigatran and rivaroxaban were associated with a similar risk (dabigatran: HR 0.98, 95% CI 0.76–1.26, P=0.98; rivaroxaban: HR 0.93, 95% CI 0.72–1.19, P=0.56). For major bleeding, apixaban and dabigatran were associated with lower risk (apixaban: HR 0.45, 95% CI 0.34–0.59, P<0.001; dabigatran: HR 0.79, 95% CI 0.67–0.94, P<0.01), and rivaroxaban was associated with a similar risk (HR 1.04, 95% CI 0.90–1.20], P=0.60). All non–vitamin K antagonist oral anticoagulants were associated with a lower risk of intracranial bleeding.

Conclusions—In patients with nonvalvular atrial fibrillation, apixaban was associated with lower risks of both stroke and major bleeding, dabigatran was associated with similar risk of stroke but lower risk of major bleeding, and rivaroxaban was associated with similar risks of both stroke and major bleeding in comparison to warfarin. **(*J Am Heart Assoc.* 2016;5:e003725 doi: 10.1161/JAHA.116.003725)**

Guidelines for Management of AF

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Article FT-0400.R2/1237937

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BRIEF REPORT

Real-world evidence of stroke prevention in patients with nonvalvular atrial fibrillation in the United States: the REVISIT-US study

Craig I. Coleman[a], Matthias Antz[b], Kevin Bowrin[c], Thomas Evers[d], Edgar P. Simard[e], Hendrik Bonnemeier[f] and Riccardo Cappato[g]

[a]University of Connecticut School of Pharmacy, Storrs, CT, USA; [b]Hospital Oldenburg, Department of Cardiology, Oldenburg, Germany; [c]Bayer Pharma AG, Berlin, Germany; [d]Bayer Pharma AG, Wuppertal, Germany; [e]Aetion Inc., New York, NY, USA; [f]University Medical Center of Schleswig-Holstein, Department of Electrophysiology and Rhythmology, Kiel, Germany; [g]Arrhythmia and Electrophysiology Research Center, Humanitas Clinical and Research Center, Rozzano, MI, Italy

ABSTRACT

Background: Little data exists regarding the effectiveness and safety of rivaroxaban or apixaban versus warfarin in nonvalvular atrial fibrillation (NVAF) patients treated outside of clinical trials.

Methods: This was a retrospective study using MarketScan claims from January 2012 to October 2014. We included adults, newly initiated on rivaroxaban, apixaban or warfarin, with a baseline CHA_2DS_2-VASc score ≥2, ≥2 diagnosis codes for NVAF and ≥180 days of continuous medical and prescription benefits. Patients with a prior stroke, systemic embolism or intracranial hemorrhage (ICH) were excluded. Eligible rivaroxaban or apixaban users were 1:1 propensity-score matched individually to warfarin users. Cox regression was performed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for rivaroxaban and apixaban versus warfarin for the combined endpoint of ischemic stroke or ICH and each endpoint individually.

Results: Upon matching 11,411 rivaroxaban to 11,411 warfarin users, rivaroxaban was associated with a significant reduction of the combined endpoint of ischemic stroke or ICH versus warfarin (HR = 0.61, 95% CI = 0.45–0.82). ICH was significantly (HR = 0.53, 95% CI = 0.35–0.79) and ischemic stroke nonsignificantly reduced (HR = 0.71, 95% CI = 0.47–1.07) by rivaroxaban versus warfarin. After matching 4083 apixaban and 4083 warfarin users, apixaban was found to nonsignificantly reduce the combined endpoint of ischemic stroke or ICH versus warfarin (HR = 0.63, 95% CI = 0.35–1.12) and to reduce ICH risk (HR = 0.38, 95% CI = 0.17–0.88). Ischemic stroke risk was nonsignificantly increased with apixaban (HR = 1.13, 95% CI = 0.49–2.63) versus warfarin.

Limitations: Sample size and number of combined events observed were relatively small. Residual confounding could not be ruled out.

Conclusions: Rivaroxaban and apixaban were associated with less ICH than warfarin and both are likely associated with reductions in the combined endpoint. Further investigation to validate the numerically higher rate of ischemic stroke with apixaban versus warfarin is required.

ARTICLE HISTORY
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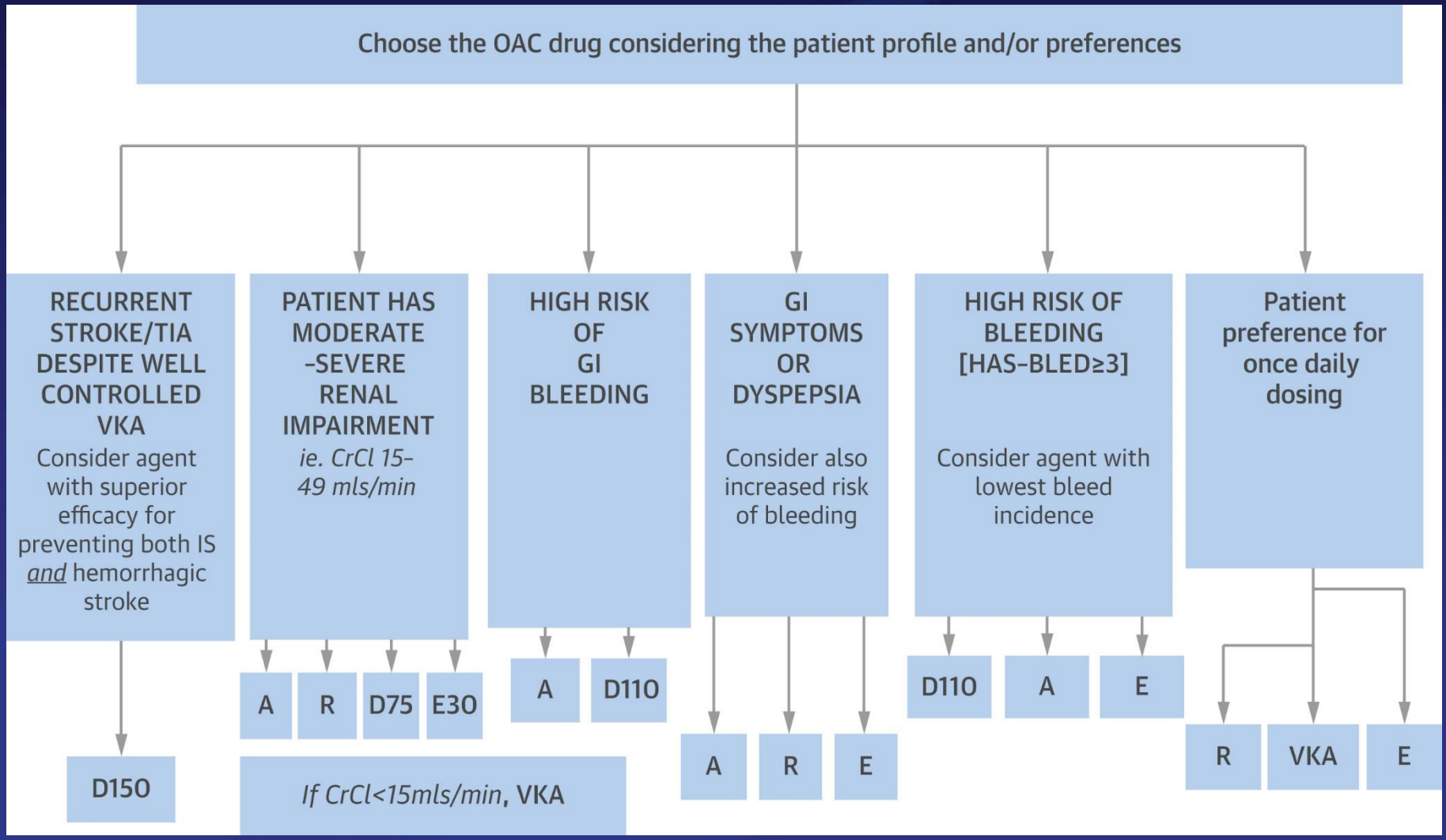
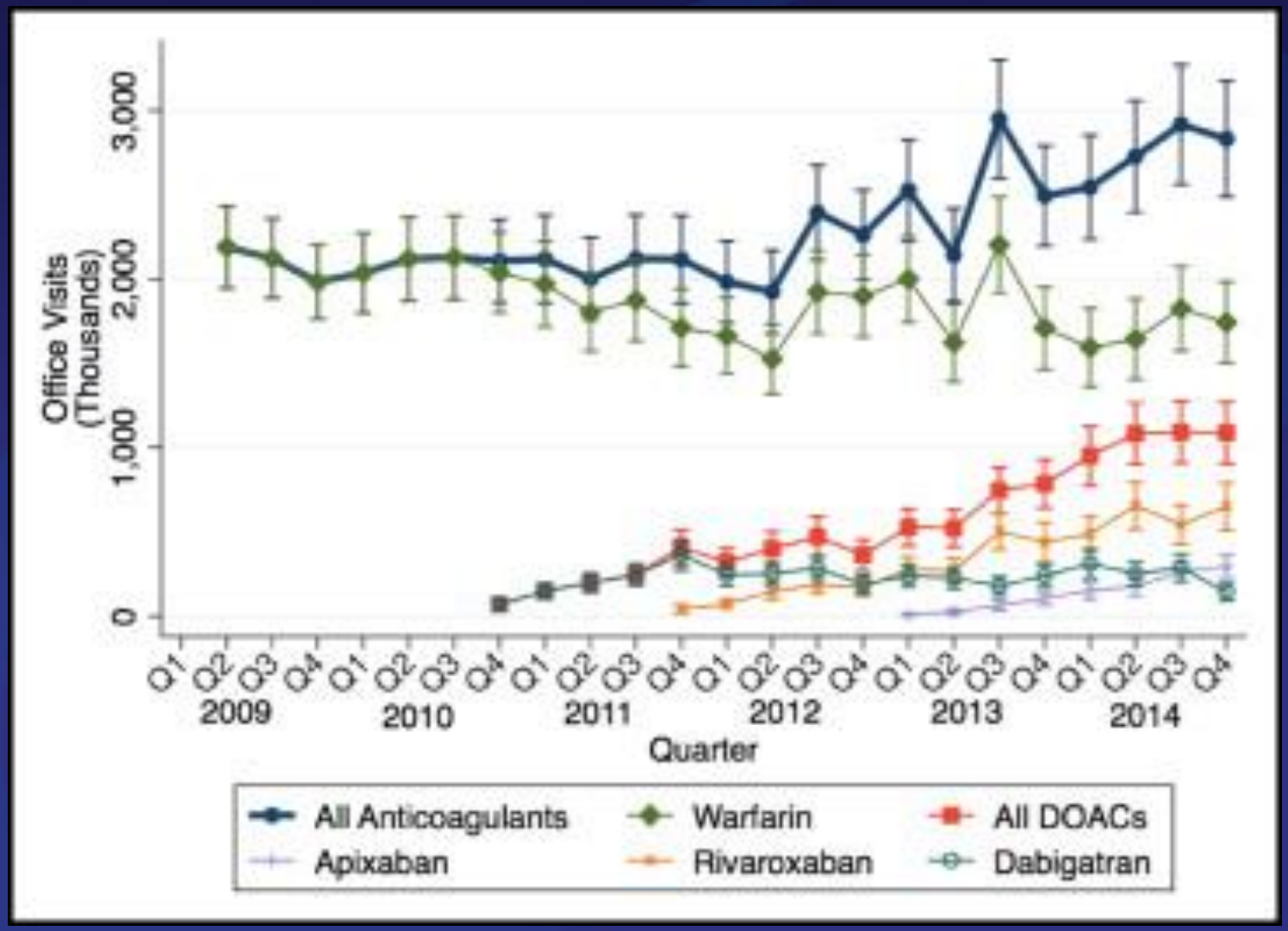
KEYWORDS
Anticoagulants; Apixaban; Nonvalvular atrial fibrillation; Rivaroxaban; Stroke prevention; Warfarin

Anticoagulation Strategies



J Am Coll Cardiol. 2015;66(21):2282-2284. doi:10.1016/j.jacc.2015.07.086

Trends in DOAC Prescription



Barnes et al. Am J Med 2015 . Antithrombotics and Endoscopy: Advice for Endoscopy Nurses from Cardiogastroenterology Clinic Antithrombotics and Endoscopy: *Mayo Clinic*

Who should remain on warfarin?

- Patient already receiving warfarin and stable whose INR is easy to control
- If dabigatran, rivaroxaban, apixaban or edoxaban not available
- Cost
- If patient not likely to comply with twice daily dosing (Dabigatran, Apixaban or edoxaban)
- Chronic kidney disease/ESRD (GFR < 15 ml/min)

How about Clopidogrel + Aspirin ?

ORIGINAL ARTICLE

Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation

The ACTIVE Investigators*

ABSTRACT

BACKGROUND

Vitamin K antagonists reduce the risk of stroke in patients with atrial fibrillation but are considered unsuitable in many patients, who usually receive aspirin instead. We investigated the hypothesis that the addition of clopidogrel to aspirin would reduce the risk of vascular events in patients with atrial fibrillation.

METHODS

A total of 7554 patients with atrial fibrillation who had an increased risk of stroke and for whom vitamin K–antagonist therapy was unsuitable were randomly assigned to receive clopidogrel (75 mg) or placebo, once daily, in addition to aspirin. The primary outcome was the composite of stroke, myocardial infarction, non–central nervous system systemic embolism, or death from vascular causes.

The members of the writing group (Stuart J. Connolly and Janice Pogue, Population Health Research Institute, Hamilton, ON, Canada; Robert G. Hart, University of Texas Health Center, San Antonio; Stefan H. Hohnloser, Goethe University Hospital, Frankfurt, Germany; Marc Pfeffer, Brigham and Women's Hospital, Boston; and Susan Chrolavicius and Salim Yusuf, Population Health Research Institute, Hamilton, ON, Canada) of Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) assume responsibility for the overall content and integrity of the article. Address

N Engl J Med online publication March 31, 2009

Vascular events and major bleeding: ACTIVE-W final results

End point	Clopidogrel+ ASA	Warfarin	Relative risk	p
Vascular events (%/year)	5.64	3.63	1.45	0.0002
Major bleeding (%/year)	2.4	2.2	1.06	0.67

Connolly S. American Heart Association Scientific Sessions 2005; Nov 13-16, 2005; Dallas, TX.

Guidelines for Management of AF

Barriers to Treatment-

- Patients are often reluctant

- Physicians' overestimation of the risks of anticoagulation is the most consistently cited explanation for warfarin under-use

- Physicians' risk perceptions may be influenced by their experiences with warfarin use
  - For example, in one small survey, physicians who reported having patients experience adverse events from anticoagulation were less likely to prescribe warfarin

- Different types of adverse events may have more influence on practice than others
  1. Bleeding in a patient to whom a physician prescribed warfarin
  2. Thromboembolic stroke in patient to whom a physician did not prescribe warfarin

Guidelines for Management of AF

- Is there a greater risk of stroke or bleeding?

Guidelines for Management of AF

HAS-BLED SCORE

Major Bleed:

Intracranial, intraocular, or retroperitoneal hemorrhage, death, clinically overt blood loss resulting in a decrease in hemoglobin of more than 2 g/dL

Transfusion of 2 or more units of packed RBCs or whole blood.

- 67% of the major bleeding events were gastrointestinal and 15% were intracranial.

HAS-BLED Score

	Clinical Characteristic	Score
H	Hypertension	1
A	Abnormal renal or liver function (1 each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly age	1
D	Drugs or alcohol (1 each)	1 or 2
	Maximum Score	9

Hypertension: SBP > 160 mmHg; Abnormal renal function: Chronic dialysis, renal transplant, serum creatinine ≥ 200µmol/L; Abnormal liver function: Chronic hepatitis, bilirubin > 2x upper limit of normal (ULN) in association with AST/ALT/ALP > 3 x ULN; Bleeding: Previous history, predisposition; Labile INRs: unstable/high INRs, in therapeutic range < 60%; Age > 65 years; Drugs/alcohol: Concomitant use of antiplatelet agents, non-steroidal anti-inflammatory drugs, etc.

Pisters R, et al. *Chest*, 2010;138:1093-100

CHA2DS2-VASc score	Patients (*n* = 7329)	Adjusted stroke rate (%/year)
0	1	0
1	422	1.3
2	1230	2.2
3	1730	3.2
4	1718	4.0
5	1159	6.7
6	679	9.8
7	294	9.6
8	82	6.7
9	14	15.2

HAS-BLED score	n	Bleeds, n	Bleeds/100 patients*
0	798	9	1.13
1	1286	13	1.02
2	744	14	1.88
3	187	7	3.74
4	46	4	8.70
5	8	1	12.50
Any score	3071	48	1.56

Accessing Risk in Patients with AF

ORIGINAL INVESTIGATION

Choosing Antithrombotic Therapy for Elderly Patients With Atrial Fibrillation Who Are at Risk for Falls

Malcolm Man-Son-Hing, MD, MSc, FRCPC; Graham Nichol, MD, MPH, FRCPC; Anita Lau; Andreas Laupacis, MD, MSc, FRCPC

Objective: To determine whether the risk of falling (with a possible increased chance of subdural hematoma) should influence the choice of antithrombotic therapy in elderly patients with atrial fibrillation.

Design: A Markov decision analytic model was used to determine the preferred treatment strategy (no antithrombotic therapy, long-term aspirin use, or long-term warfarin use) for patients with atrial fibrillation who are 65 years of age and older, are at risk for falling, and have no other contraindications to antithrombotic therapy. Input data were obtained by systematic review of MEDLINE. Outcomes were expressed as quality-adjusted life-years.

Results: For patients with average risks of stroke and falling, warfarin therapy was associated with 12.90 quality-adjusted life-years per patient; aspirin therapy, 11.17 quality-adjusted life-years; and no antithrombotic therapy, 10.15 quality-adjusted life-years. Sensitivity analysis demonstrated that, regardless of the patients' age or baseline risk of stroke, the risk of falling was not an important factor in determining their optimal antithrombotic therapy.

Conclusions: For elderly patients with atrial fibrillation, the choice of optimal therapy to prevent stroke depends on many clinical factors, especially their baseline risk of stroke. However, patients' propensity to fall is not an important factor in this decision.

Arch Intern Med. 1999;159:677-685

Accessing Risk in Patients with AF

Choosing Antithrombotic Therapy for Elderly Patients with AF Who are at Risk for Falls

- Persons taking Warfarin must fall about **295 times in 1 year** for warfarin to not be the optimal therapy

- Since approximately 1 in 10 falls cause major injury, including fractures, persons who fall are much more likely to suffer other serious morbidity before developing brain hemorrhage

(***Arch Intern Med. 1999; 159, 677-685***)

Interruption of anticoagulation for surgery/procedures and bridging

CLINICAL NEWS

JACC in a FLASH

Featured topics in the current and recent issues of the *JACC* family of journals

A Bridge Too Far?

While bridge anticoagulation is common, it is also a common dilemma for health care providers treating patients on anticoagulation therapy. A review article published Sept. 14 in *JACC* raises the question of just when this course of action is necessary.

More than 35 million prescriptions for oral anticoagulants are written each year and 15-20% of patients will undergo an invasive procedure or surgery that interrupts their chronic oral anticoagulation, which puts them at risk for thromboembolism, hemorrhage, or death. Periprocedural anticoagulation is a common clinical dilemma and may lead to significant adverse events in patients. There is large agreement on three important principles surrounding bridging: (1) oral anticoagulants should not be interrupted for procedures with low bleeding risk; (2) patients at high risk for thromboembolism without excessive bleeding risk should consider bridging, while those at low thromboembolism risk should not be bridged; and (3) cases with intermediate risk should be management by considering patient- and procedure-specific risk for bleeding and thromboembolism. Despite these recommendations, surveys show that 30% of physicians choose to bridge patients at low risk of thrombo-

Bridging will be a key topic at the ACC's Anticoagulation Roundtable on Oct. 24. The Roundtable will bring together key stakeholders from across the health care

and bridging, including the recent BRIDGE trial. They note that recent data suggest that 40-60% of oral anticoagulant interruptions may be unnecessary, and furthermore, that the interruption and re-initiation of warfarin can be associated with an increased incidence of stroke. Additionally, certain operations like orthopedic surgeries may tolerate the continuation of anticoagulants.

Overall, their review found that the rate of periprocedural thromboembolism for unbridged oral anticoagulation interruption is rare, at an estimated 0.53% from over 23,000 interruptions in 17 studies between 1966 and 2015. The rate of thromboembolism for patients who are bridged is only slightly higher at 0.92%. Rates of bleeding and thromboembolism vary by oral anticoagulation indication. The risk of thromboembolism with mechanical heart valves is around 1%. In left ventricular assist devices, where the management of anticoagulants is complex and lacking consensus, data show a 1.5% risk of thromboembolism. Most recent studies show a periprocedural bleeding to thrombosis ratio of 13:1 with bridging and 5:1 without bridging, "suggesting that the net effect of bridging is unbalanced toward bleeding." In one study, 14 atrial fibrillation (AF) patients on oral anticoagulants died after heparin bridging compared to no deaths in the control group without heparin. bridged group should have had higher scores. The study also found that bridging was associated with a 4-fold increased risk of bleeding.

The BRIDGE trial, recently published in the *New England Journal of* Medicine, "provides the most compelling evidence that routine bridging in moderate risk patients is harmful," according to Rechenmacher and Fang. In the study, AF patients undergoing a procedure with planned warfarin interruption were randomized to anticoagulation bridging with low-molecular weight heparin, dalteparin or placebo. A large majority (89.4%) of the patients were designated as low bleeding risk. The rate of thromboembolism in the placebo group was noninferior to the bridging group, while major and minor bleeding in the placebo group was significantly less in the non-bridging group.

Moving forward, Rechenmacher and Fang note that the upcoming PERIOP2 study may help to answer the question about whether to bridge patients with AF and a high $CHADS_2$. They also point out that "novel anticoagulants may also offer a safer and simpler periprocedural management strategy than warfarin" in the future. However, more studies are needed to determine the safety of interrupting and restarting these new therapies.

"While awaiting the results of additional randomized trial, physicians should carefully reconsider the practice of routine bridging and whether periprocedural anticoagulation interruption is even necessary," they write. They recommend avoiding interru-

Periprocedural anticoagulation is a common clinical dilemma and may lead to significant adverse events.

strategies should be considered.

"This excellent comprehensive review by Rechenmacher et al, provides further evidence that physicians need to be more careful regarding the use of bridging anticoagulation around the time of procedures," says **Robert P. Giugliano, MD**, associate professor of medicine and Brigham and Women's Hospital and the editorial lead of the ACC's Anticoagulant Community. "This paper further supports the notion that we should use bridging anticoagulation less frequently, reserving it only for patients at the highest risk for thromboembolism."

He adds that it is important to avoid the easy comparison of exchanging one bleed for one stroke. "If you use brida-

ACCP 2012 Bridging Guidelines

Risk Stratum	Indication for VKA Therapy		
	Mechanical Heart Valve	Atrial Fibrillation	VTE
High[a]	Any mitral valve prosthesis Any caged-ball or tilting disc aortic valve prosthesis Recent (within 6 mo) stroke or transient ischemic attack	$CHADS_2$ score of 5 or 6 Recent (within 3 mo) stroke or transient ischemic attack Rheumatic valvular heart disease	Recent (within 3 mo) VTE Severe thrombophilia (eg, deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
Moderate	Bileaflet aortic valve prosthesis and one or more of the of following risk factors: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age > 75 y	$CHADS_2$ score of 3 or 4	VTE within the past 3-12 mo Nonsevere thrombophilia (eg, heterozygous factor V Leiden or prothrombin gene mutation) Recurrent VTE Active cancer (treated within 6 mo or palliative)
Low	Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	$CHADS_2$ score of 0 to 2 (assuming no prior stroke or transient ischemic attack)	VTE > 12 mo previous and no other risk factors

ACCP 2012 Bridging Guidelines

- In patients with a mechanical heart valve, Afib, or VTE at **high risk** for thromboembolism, we suggest **bridging** anticoagulation during interruption of VKA therapy (Grade 2C)
  - *$CHADS_2$ 5-6, < 3 months CVA/TIA, or rheumatic valve disease*
- In patients at moderate risk for thromboembolism, the bridging or no bridging approach is based on individual patient- and surgery-related risk factors
  - *$CHADS_2$ 3-4*
- In patients at **low risk**, we suggest **no bridging** during interruption of VKA therapy (Grade 2C)
  - *$CHADS_2$ 0-2, no TIA/CVA*

Mayo 2013 Bridging Guidelines

Condition	Bridging Therapy Required	No Bridging Therapy	Comments
Mechanical heart valve	Mitral-valve replacement, two or more mechanical valves, non-bileaflet aortic-valve replacement, or aortic-valve replacement with other risk factors	Aortic-valve replacement, bileaflet prosthesis, and no additional risk factors	Other risk factors include prior stroke, TIA, intracardiac thrombus, or cardioembolic event
Nonvalvular atrial fibrillation	Prior stroke or embolic event, cardiac thrombus, or $CHADS_2$ score of ≥4	No prior stroke or embolic event, absence of cardiac thrombus, or $CHADS_2$ score of <4	Prior stroke, TIA, intracardiac thrombus, or cardioembolic event increases risk
Venous thromboembolism	Venous thromboembolism within previous 3 mo or severe thrombophilia	Venous thromboembolism >3 mo previously or no additional risk factors (e.g., active cancer and nonsevere thrombophilia)	Consider inferior vena cava filter if venous thromboembolism occurred <1 mo previously, if urgent or emergency surgery is required, or if there is a contraindication to anticoagulation therapy

Differences with ACCP:

- **No uncertainty with moderate risk group**
- **Anyone with stroke/TIA was high risk regardless of timing of index event**
- **Includes cardiac thrombus**
- **Excludes valvular afib**

Baron, T., Kamath, P., & Mcbane, R. (2013). Management of Antithrombotic Therapy in Patients Undergoing Invasive Procedures. *New England Journal of Medicine N Engl J Med,* 2113-2124.

New Data Regarding Bridge Therapy

- **BRIDGE investigators RCT (2015)**

- **1884 non-valvular atrial fibrillation patients**
  - ***May not apply to valvular afib, mechanical valves, LVADs, recently diagnosed thromboembolism (<3 months), Afib patients with CHF, post ACS setting etc.***

- **Elective endoscopic and surgical procedures**
- **Randomized to bridging vs. no bridging**
- **Bridging Group (when compared to no bridging)**
  - **More major bleeding (3.2% vs. 1.3%)**
  - **No difference in thromboembolism risk (0.3% vs, 0.4%)**

Douketis et al. NEJM 2015;373:823-833

Current Practice

- In high-risk patients (particularly those with mechanical valves, prior stroke, TIA, or systemic embolism), or when a series of procedures requires interruption of oral anticoagulant therapy for longer than a 10 day period, low-molecular-weight heparin may be administered subcutaneously.

Discontinuation of Oral Anticoagulation

Classification of elective surgical interventions according to bleeding risk

New Data Regarding Discontinuation of OAC

Interventions NOT necessarily requiring discontinuation of anticoagulation

- Dental interventions
  - Extraction of one to three teeth
  - Paradontal surgery
  - Incision of abscess
  - Implant positioning
- Ophthalmology
  - Cataract or glaucoma intervention
- Endoscopy without surgery
- Superficial surgery (e.g. abscess incision, small dermatologic excisions, etc.)

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2015 Oct;17(10):1467-507. doi: 10.1093/europace/euv309. Epub 2015 Aug 31

Temporary interruption of NOAC prior to endoscopic procedure

Drug (Creatinine Clearance)	Last dose prior to low–risk endoscopic procedure *	Last dose prior to high–risk endoscopic procedure **
Dabigatran (>50 mL/min)	1 day	2 days
Dabigatran (31- 50 mL/min)	2 days	4 days
Dabigatran (<30 mL/min)	4 days	6 days
Rivaroxaban/Apixaban/ Edoxaban (>50 mL/min)	1 days	2 days
Rivaroxaban/Apixaban/ Edoxaban (31 to 50 mL/min)	1-2 days	3-4 days
Rivaroxaban/Apixaban/ Edoxaban (< 30 mL/min)	2 days	4 days

** A low-risk procedure has a 48 hour risk of major bleeding of 0% to 2%; a high-risk procedure ** has a 48 hour risk of major bleeding of 2% to 4%*

Use of Direct Oral Anticoagulants in Patients with Bioprosethic Valves

Guidelines for Management of AF

Non–Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation and Valvular Heart Disease

Giulia Renda, MD, PhD,[a] Fabrizio Ricci, MD,[a] Robert P. Giugliano, MD, SM,[b] Raffaele De Caterina, MD, PhD[a]

ABSTRACT

BACKGROUND Valvular heart disease (VHD) and atrial fibrillation (AF) often coexist. Phase III trials comparing non–vitamin K antagonist oral anticoagulants (NOACs) with warfarin excluded patients with moderate/severe mitral stenosis or mechanical heart valves, but variably included patients with other VHD and valve surgeries.

OBJECTIVES This study aimed to determine relative safety and efficacy of NOACs in patients with VHD.

METHODS We performed a meta-analysis of the 4 phase III AF trials of the currently available NOACs versus warfarin in patients with coexisting VHD to assess pooled estimates of relative risk (RR) and 95% confidence intervals (CIs) for stroke/systemic embolic events (SSEE), major bleeding, intracranial hemorrhage (ICH), and all-cause death.

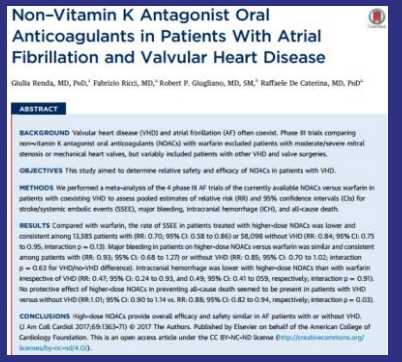
RESULTS Compared with warfarin, the rate of SSEE in patients treated with higher-dose NOACs was lower and consistent among 13,585 patients with (RR: 0.70; 95% CI: 0.58 to 0.86) or 58,098 without VHD (RR: 0.84; 95% CI: 0.75 to 0.95; interaction p = 0.13). Major bleeding in patients on higher-dose NOACs versus warfarin was similar and consistent among patients with (RR: 0.93; 95% CI: 0.68 to 1.27) or without VHD (RR: 0.85; 95% CI: 0.70 to 1.02; interaction p = 0.63 for VHD/no-VHD difference). Intracranial hemorrhage was lower with higher-dose NOACs than with warfarin irrespective of VHD (RR: 0.47; 95% CI: 0.24 to 0.93, and 0.49; 95% CI: 0.41 to 059, respectively; interaction p = 0.91). No protective effect of higher-dose NOACs in preventing all-cause death seemed to be present in patients with VHD versus without VHD (RR:1.01; 95% CI: 0.90 to 1.14 vs. RR: 0.88; 95% CI: 0.82 to 0.94, respectively; interaction p = 0.03).

CONCLUSIONS High-dose NOACs provide overall efficacy and safety similar in AF patients with or without VHD.

Guidelines for Management of AF

- In patients with AF and VHD (other than moderate/ severe mitral stenosis or mechanical heart valves) NOACs are attractive alternatives to VKAs because the coexistence of VHD does not affect the overall relative efficacy or safety of NOACs in terms of prevention of SSEE and major bleeding. Current definitions of “valvular” and “nonvalvular” AF are misleading, and the use of NOACs should be permitted in most patients with VHD.

- The recently proposed term “MARM-AF,” standing for “Mechanical And Rheumatic Mitral valvular AF” could be useful to identify the true high risk AF patients for whom VKAs are the anticoagulants of choice



Non–Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation and Valvular Heart Disease

Giulia Renda, MD, PhD,[a] Fabrizio Ricci, MD,[b] Robert P. Giugliano, MD, SM,[b] Raffaele De Caterina, MD, PhD[a]

ABSTRACT

BACKGROUND Valvular heart disease (VHD) and atrial fibrillation (AF) often coexist. Phase III trials comparing non–vitamin K antagonist oral anticoagulants (NOACs) with warfarin excluded patients with moderate/severe mitral stenosis or mechanical heart valves, but variably included patients with other VHD and valve surgeries.

OBJECTIVES This study aimed to determine relative safety and efficacy of NOACs in patients with VHD.

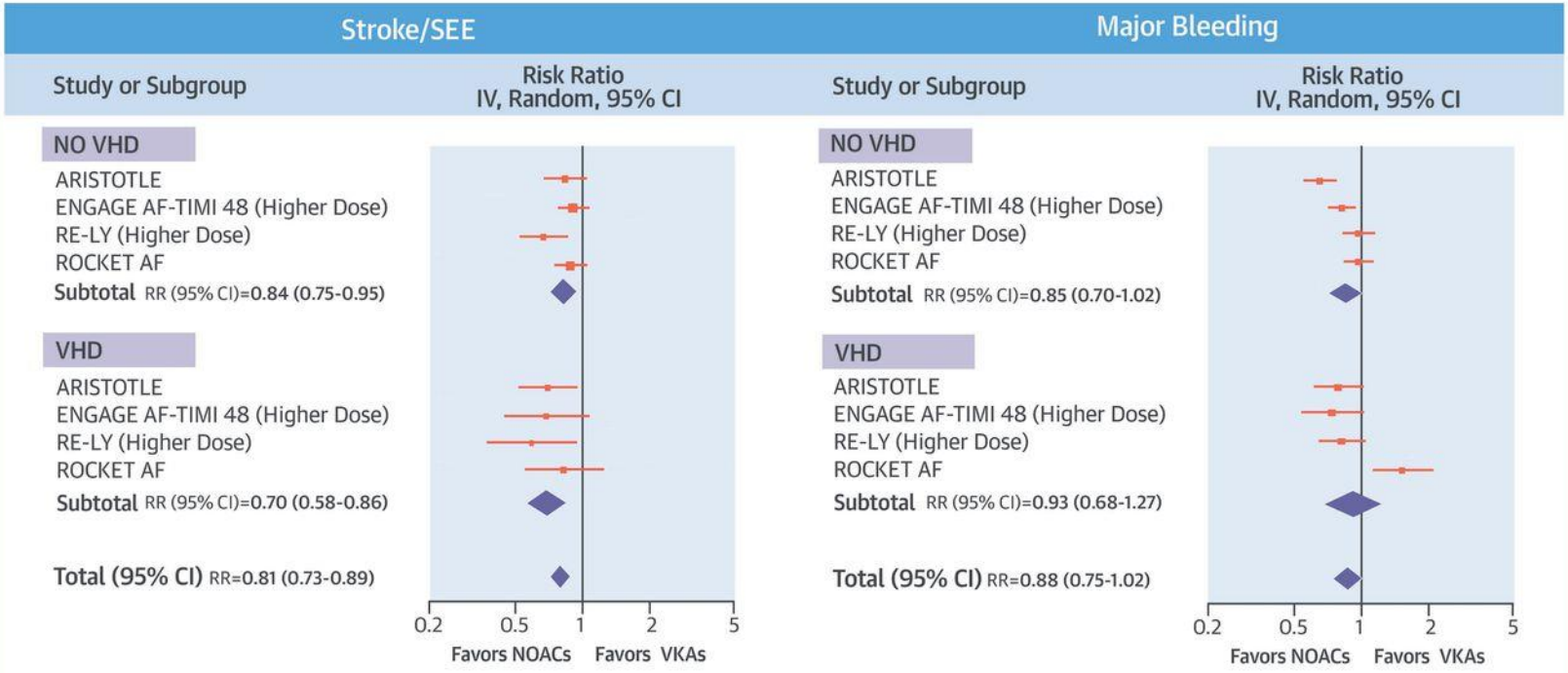
METHODS We performed a meta-analysis of the 4 phase III AF trials of the currently available NOACs versus warfarin in patients with coexisting VHD to assess pooled estimates of relative risk (RR) and 95% confidence intervals (CIs) for stroke/systemic embolic events (SSEE), major bleeding, intracranial hemorrhage (ICH), and all-cause death.

RESULTS Compared with warfarin, the rate of SSEE in patients treated with higher-dose NOACs was lower and consistent among 13,585 patients with (RR: 0.70; 95% CI: 0.58 to 0.86) or 58,098 without VHD (RR: 0.84; 95% CI: 0.75 to 0.95; interaction $p = 0.13$). Major bleeding in patients on higher-dose NOACs versus warfarin was similar and consistent among patients with (RR: 0.93; 95% CI: 0.68 to 1.27) or without VHD (RR: 0.85; 95% CI: 0.70 to 1.02; interaction $p = 0.63$ for VHD/no-VHD difference). Intracranial hemorrhage was lower with higher-dose NOACs than with warfarin irrespective of VHD (RR: 0.47; 95% CI: 0.24 to 0.93, and 0.49; 95% CI: 0.41 to 059, respectively; interaction $p = 0.91$). No protective effect of higher-dose NOACs in preventing all-cause death seemed to be present in patients with VHD versus without VHD (RR:1.01; 95% CI: 0.90 to 1.14 vs. RR: 0.88, 95% CI: 0.82 to 0.94, respectively; interaction $p = 0.03$).

CONCLUSIONS High-dose NOACs provide overall efficacy and safety similar in AF patients with or without VHD.

(J Am Coll Cardiol 2017;69:1363–71) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation.

CENTRAL ILLUSTRATION: SSEE and Major Bleeding in Patients Without and With VHD, Treated With Higher-Dose NOACs or Warfarin

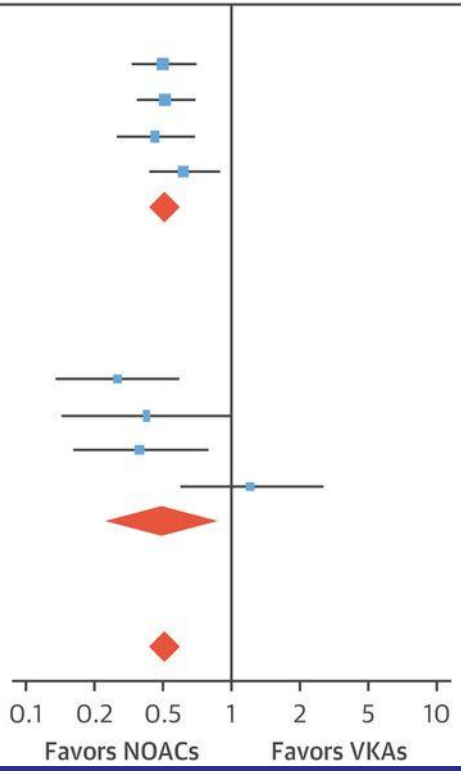


Renda, G. et al. J Am Coll Cardiol. 2017;69(11):1363-71.

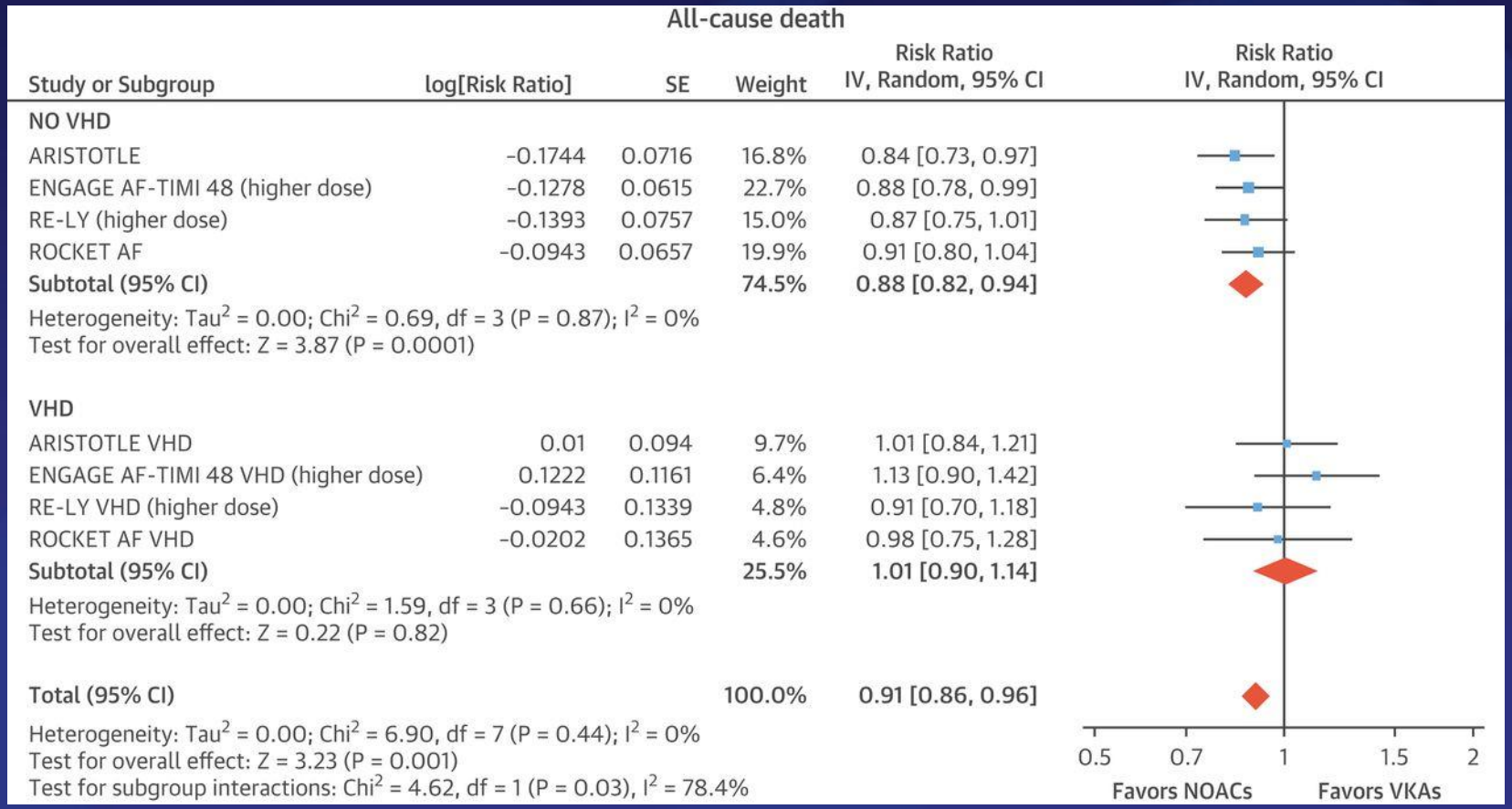
Giulia Renda et al. JACC 2017;69:1363-1371

Intracranial hemorrhage

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
NO VHD				
ARISTOTLE	-0.755	0.1804	19.5%	0.47 [0.33, 0.67]
ENGAGE AF-TIMI 48 (higher dose)	-0.734	0.1612	21.8%	0.48 [0.35, 0.66]
RE-LY (higher dose)	-0.844	0.2189	15.6%	0.43 [0.28, 0.66]
ROCKET AF	-0.5276	0.1983	17.6%	0.59 [0.40, 0.87]
Subtotal (95% CI)			**74.5%**	**0.49 [0.41, 0.59]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.30$, df = 3 (P = 0.73); $I^2 = 0\%$				
Test for overall effect: Z = 7.67 (P < 0.00001)				
VHD				
ARISTOTLE VHD	-1.273	0.3537	7.8%	0.28 [0.14, 0.56]
ENGAGE AF-TIMI 48 VHD (higher dose)	-0.9416	0.4875	4.5%	0.39 [0.15, 1.01]
RE-LY VHD (higher dose)	-1.0217	0.3828	6.8%	0.36 [0.17, 0.76]
ROCKET AF VHD	0.239	0.3999	6.4%	1.27 [0.58, 2.78]
Subtotal (95% CI)			**25.5%**	**0.47 [0.24, 0.93]**
Heterogeneity: $Tau^2 = 0.32$; $Chi^2 = 8.94$, df = 3 (P = 0.03); $I^2 = 66\%$				
Test for overall effect: Z = 2.17 (P = 0.03)				
Total (95% CI)			**100.0%**	**0.48 [0.39, 0.60]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 10.33$, df = 7 (P = 0.17); $I^2 = 32\%$				
Test for overall effect: Z = 6.65 (P < 0.00001)				
Test for subgroup interactions: $Chi^2 = 0.01$, df = 1 (P = 0.91), $I^2 = 0\%$				



Giulia Renda et al. JACC 2017;69:1363-1371



Giulia Renda et al. JACC 2017;69:1363-1371

Device Based Solutions

Unable To Take Warfarin or DOAC?

- Frail, numerous falls
- GI bleeds
- Cerebral bleeds
- Stroke despite therapeutic warfarin
- Non-compliant / labile INR
- (Do not want warfarin or DOAC)

Introducing the WATCHMAN™ LAAC Device

A **first-of-its-kind, proven alternative** to long-term warfarin therapy for stroke risk reduction in patients with non-valvular AF

Most studied LAAC therapy, only one proven with long-term data from randomized trials or multi-center registries

Comparable stroke risk reduction, **and statistically superior reductions in hemorrhagic stroke, disabling stroke and cardiovascular death** compared to warfarin over long-term follow-up[1,2]

1. **Reddy, V et al. JAMA 2014; Vol. 312, No. 19.**
2. **Reddy, V et al. Watchman I: First Report of the 5-Year PROTECT-AF and Extended PREVAIL Results. TCT 2014.**
3. Boston Scientific **WATCHMAN™ Left Atrial Appendage Closure Device. Advancing Science for Life ppt presentation SH230-609-AD June 2015**

WATCHMAN Therapy

Indications for Use

The WATCHMAN™ Device is indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who:

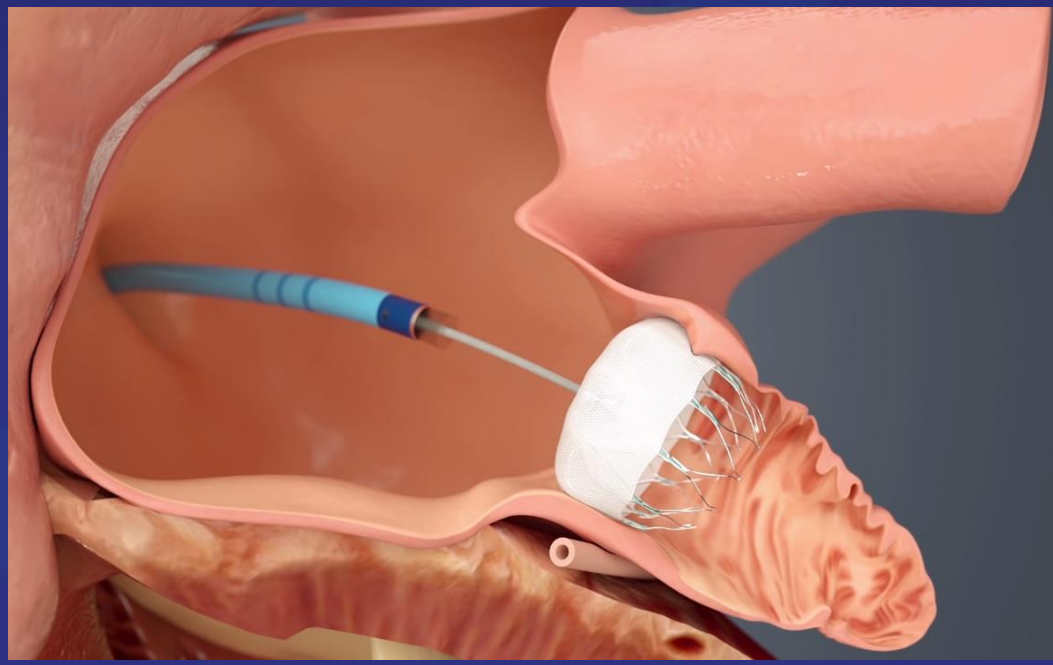
- Are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for warfarin; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

1. Boston Scientific **WATCHMAN™ Left Atrial Appendage Closure Device. Advancing Science for Life ppt presentation SH230-609-AD June 2015**

WATCHMAN™ Left Atrial Appendage Closure (LAAC) Device Procedure

- One-time implant that does not need to be replaced
- Performed in a cardiac cath lab/EP suite, does not need hybrid OR
- Performed by a Heart Team
  - IC/EP or IC&EP, TEE, General Anesthesia, Surgical Back- up, WATCHMAN Clinical Specialist
- Transfemoral Access: Catheter advanced to the LAA via the femoral vein (Does not require open heart surgery)

- **General anesthesia***
- **1 hour procedure***
- **1-2 day hospital stay***



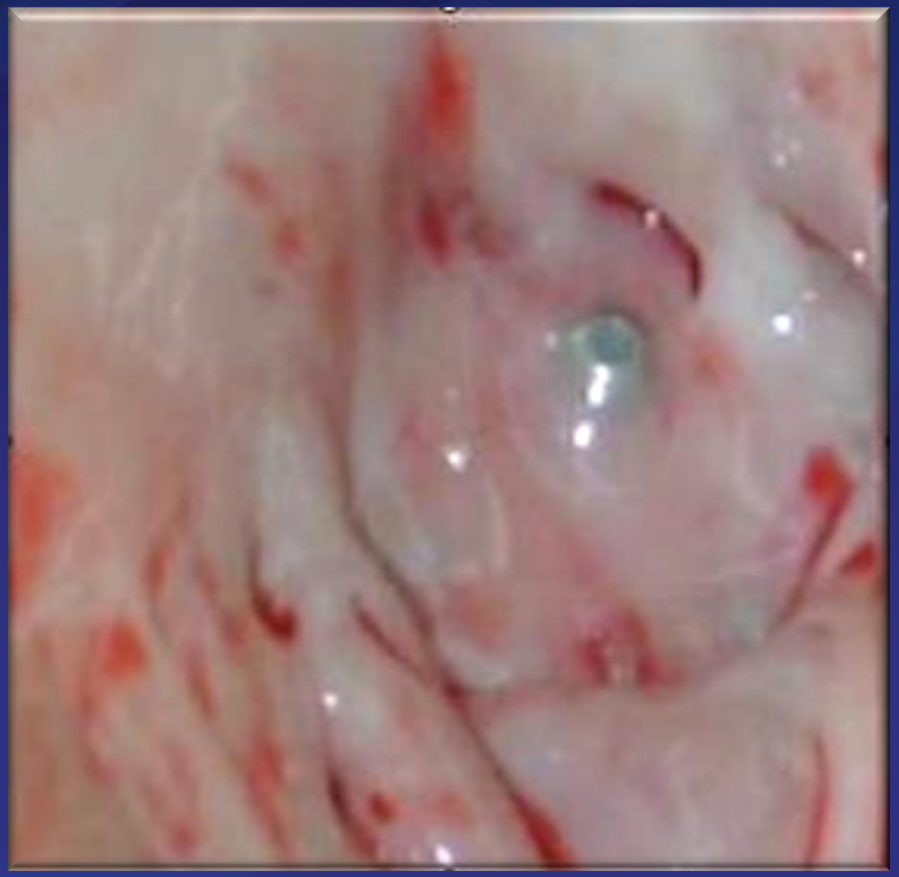
*** Typical to patient treatment in U.S. clinical trials**

1. Boston Scientific **WATCHMAN™ Left Atrial Appendage Closure Device. Advancing Science for Life ppt presentation SH230-609-AD June 2015**

WATCHMAN™ Device Endothelialization

Canine Model – 30 Day

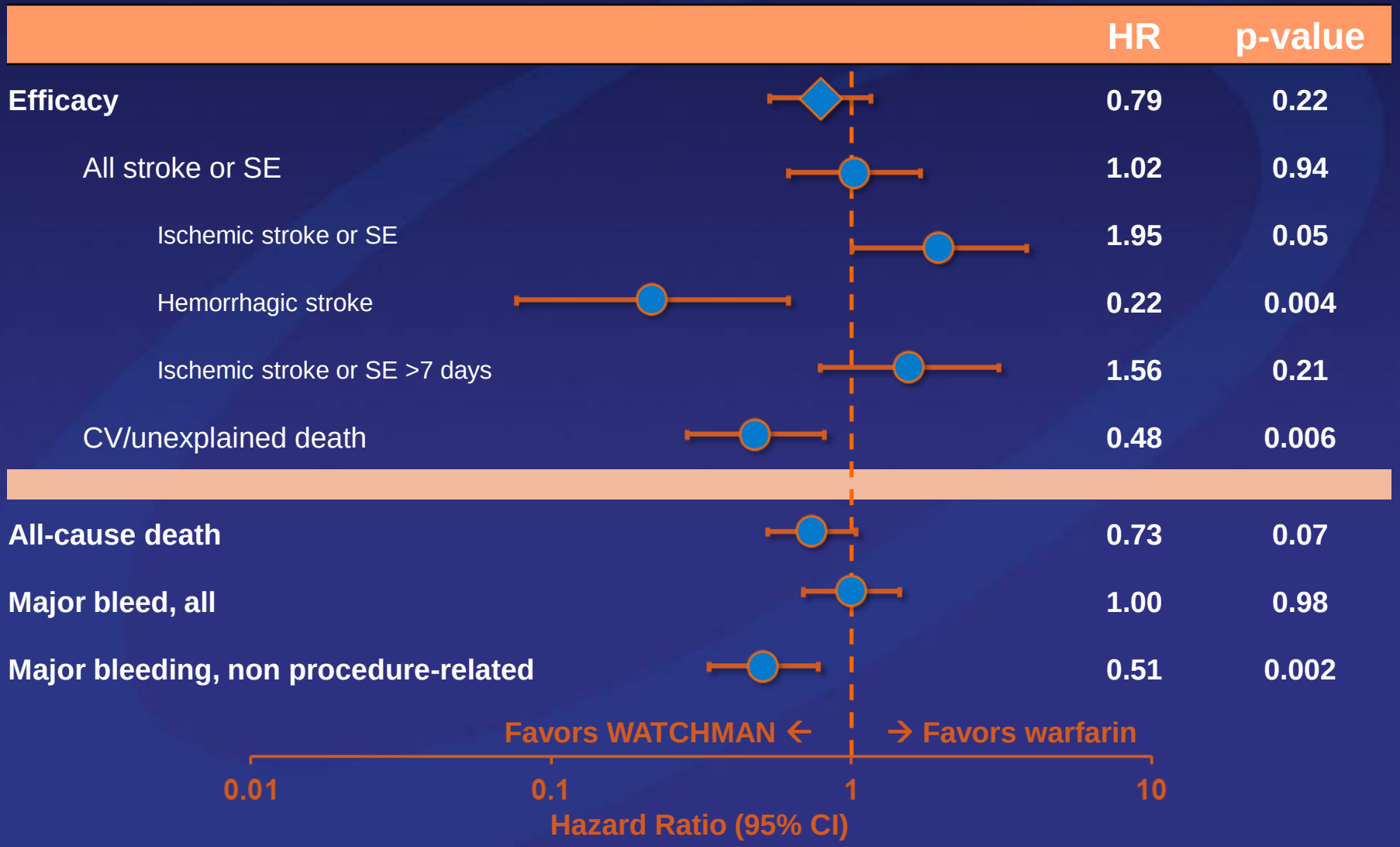
Canine Model – 45 Day



Human Pathology – 9 Months Post-implant
(Non-device related death)

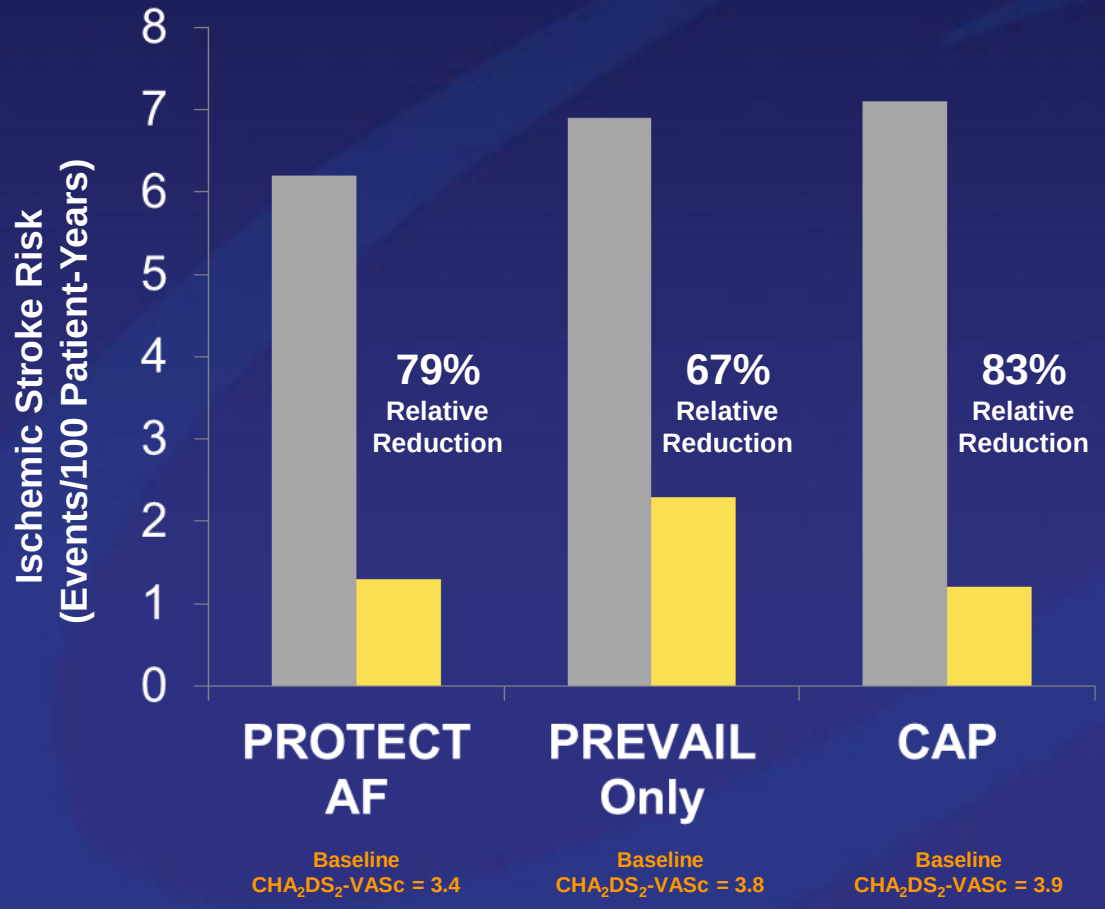
Images on file at Boston Scientific Corporation.
Results in animal models may not necessarily be indicative of clinical outcomes.

Meta-Analysis Shows Comparable Primary Efficacy Results to Warfarin



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

WATCHMAN™ Device Reduces Ischemic Stroke Over No Therapy



- Imputed Ischemic Stroke Rate*
- Observed WATCHMAN Ischemic Stroke Rate

* Imputation based on published rate with adjustment for CHA_2DS_2-VASc score (3.0); Olesen JB. Thromb Haemost (2011)

FDA Oct 2014 Panel Sponsor Presentation. Hanzel G, et al. TCT 2014 (abstract)

Device Based Solutions

- Biggest difference is recommended anti-platelet regimen.
- After treatment of a LAA occlusion device, patients are treated with oral anticoagulation (OAC) plus aspirin for 45 days followed by clopidogrel plus aspirin out to six months. Aspirin is continued for life.
- If OAC contraindicated- clopidogrel plus aspirin for six months.

Uptodate.com

Cryptogenic CVA

Background

- 30% of ischemic strokes are of unknown mechanism (Cryptogenic stroke)
- Detection of AF usually prompts long term anticoagulation instead of antiplatelet therapy
- Optimal monitoring duration to detect AF is currently undetermined
- AF may be paroxysmal, occur rarely, and be asymptomatic, making detection with routine methods difficult.

CRYptogenic STroke and underlying AtriaL Fibrillation (CRYSTAL AF), *Richard Bernstein, MD, Ph.D., et al.* NEJM June 26, 2014

EMBRACE Study – also published in NEJM

- Canadian Study
- N = 572
- Subjects were ≥55 years old
- Two arms
  - 30 day event-triggered recorder
  - Standard care (24 hour Holter)
- Primary Outcome
  - AF episodes of 30 seconds or longer within 90 days
- Secondary Outcomes
  - AF episodes of 2.5 minutes or longer within 90 days
  - Anticoagulation status at 90 days

CRYptogenic STroke and underlying AtriaL Fibrillation (CRYSTAL AF), *Richard Bernstein, MD, Ph.D., et al.* NEJM June 26, 2014

EMBRACE Results

- Primary Outcome
  - Event recorder detected AF episodes ≥30 seconds in 16.1% of patients vs. 3.2% in control arm
- Secondary Outcome
  - Event recorder detected AF episodes ≥2.5 minutes in 9.9% of patients vs. 2.5% in control arm

OAC prescribed in 18.6% of patients in event recorder arm vs. 11.1% in control arm

CRYptogenic STroke and underlying AtriaL Fibrillation (CRYSTAL AF), *Richard Bernstein, MD, Ph.D., et al.* NEJM June 26, 2014

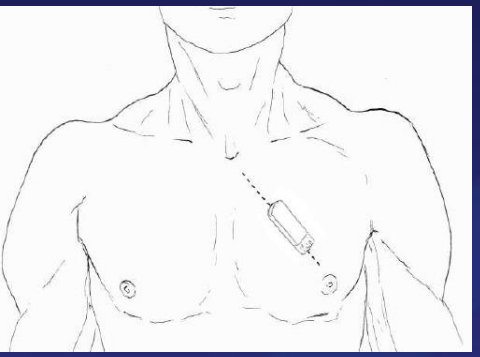
Objectives of CRYSTAL-AF

- To assess whether a long-term cardiac monitoring strategy with an implantable cardiac monitor (ICM) is superior to standard monitoring for the detection AF in patients with Cryptogenic stroke.
- Determine the proportion of patients with cryptogenic stroke that have underlying AF.
- Determine actions taken after patient is diagnosed with AF
- **Primary endpoint: Detection of AF at 6 months**

CRYptogenic STroke and underlying AtriaL Fibrillation (CRYSTAL AF), *Richard Bernstein, MD, Ph.D., et al.* NEJM June 26, 2014

Comparison of Monitoring Strategies

Continuous Monitoring Arm: Implantation of REVEAL® XT



Minimally invasive outpatient procedure

Local anesthetic and no leads or fluoroscopy

15-30 minute procedure

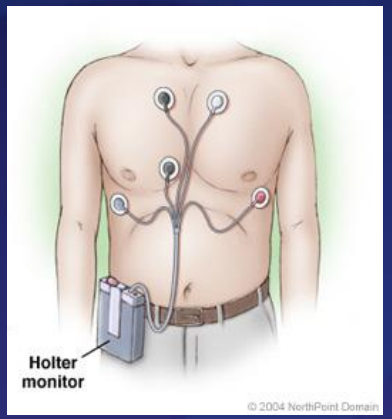
Device can be followed remotely

MRI conditional

3 year device longevity

Automatic AF detection algorithm

Standard Monitoring Arm



Cardiac monitoring performed according to local standards, after mandated testing completed

Symptoms consistent with AF were evaluated by study physicians

CRYptogenic STroke and underlying AtriaL Fibrillation (CRYSTAL AF), *Richard Bernstein, MD, Ph.D., et al.* NEJM June 26, 2014

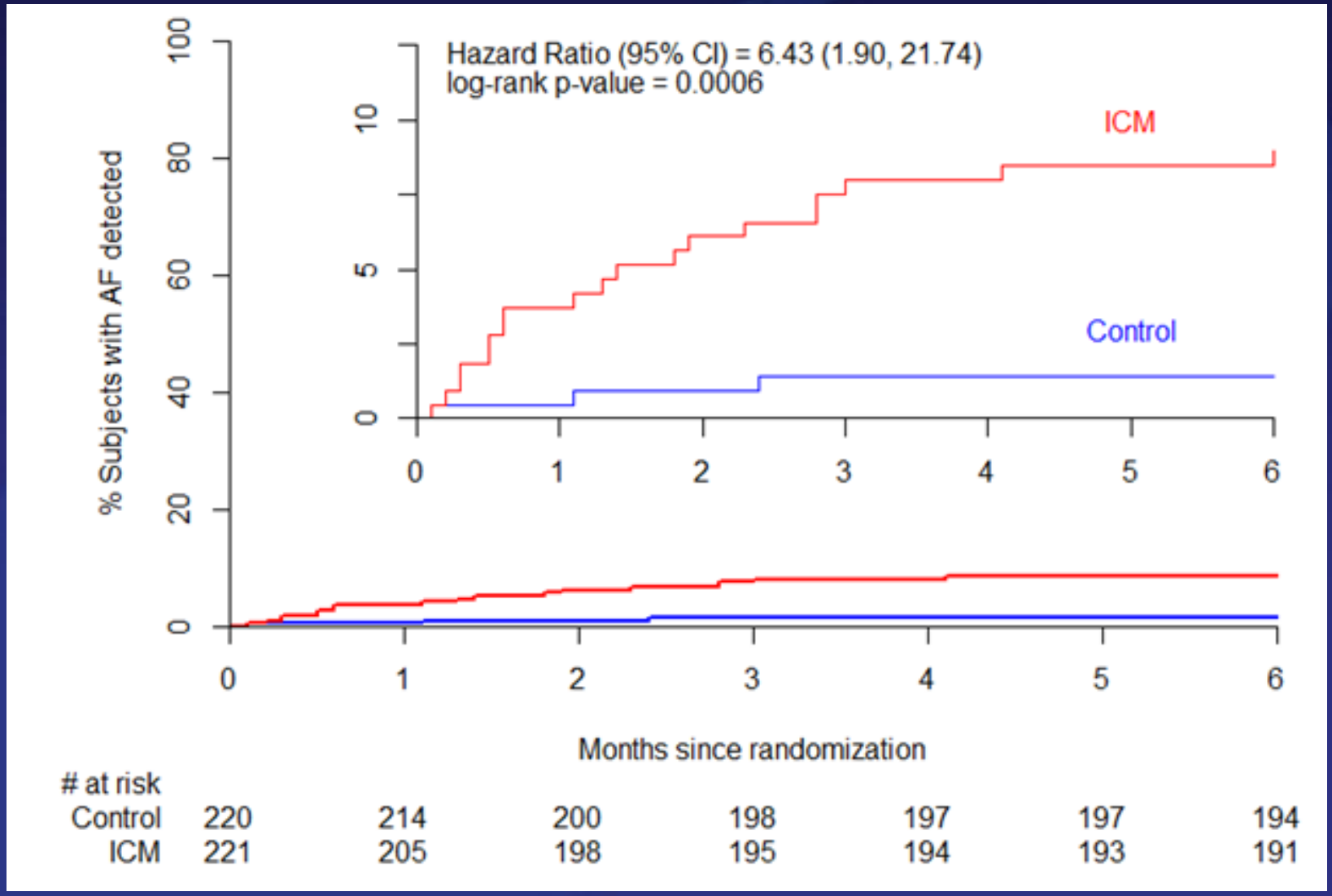
Patient Follow-up

- Patients in both arms received scheduled follow-up visits at:
  - 1 month
  - 6 months
  - 12 months
  - Every 6 months thereafter until study closure

- Follow-up visits recorded:
  - Cardiac symptoms
  - Treatment modifications
  - Recurrence of stroke or TIA
  - Modified Rankin Scale
  - Health status (EQ-5D)

CRYptogenic STroke and underlying AtriaL Fibrillation (CRYSTAL AF), *Richard Bernstein, MD, Ph.D., et al.* NEJM June 26, 2014

Primary Endpoint: DETECTION OF AF AT 6 MONTHS



Rate of detection in ICM arm was 8.9% vs 1.4% in control arm

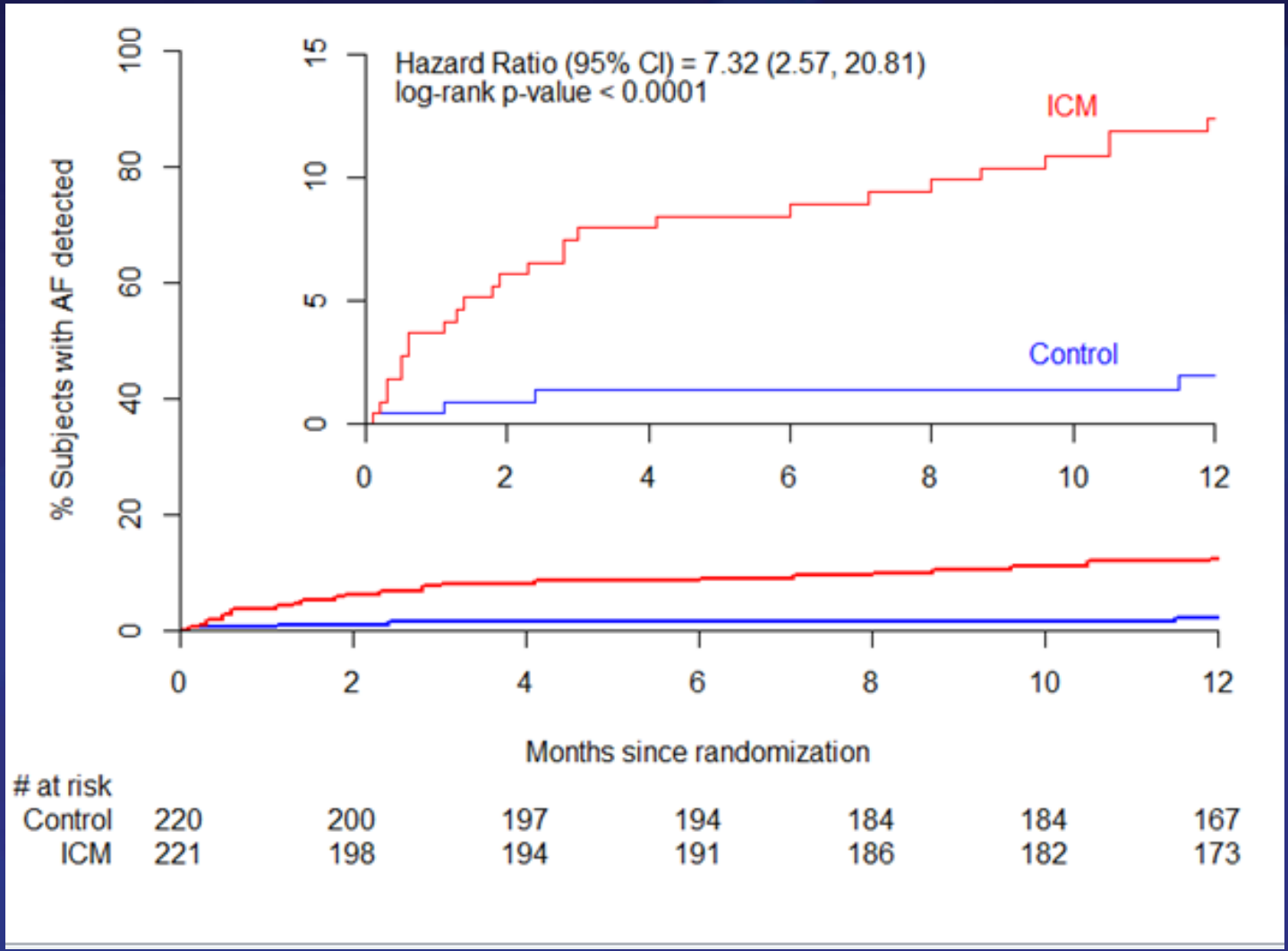
CRYptogenic STroke and underlying AtriaL Fibrillation (CRYSTAL AF), *Richard Bernstein, MD, Ph.D., et al.* NEJM June 26, 2014

6 Month Endpoints

	ICM	Control
Median Time from Randomization to AF Detection	41 days	32 days
Patients found to have AF	19	3
% Asymptomatic Episodes	74%	33%
Oral Anticoagulation Usage, overall	10.1%	4.6%
OAC use in patients with detected AF	94.7%	66.7%
Testing required to detect AF	Automatic AF detection	88 ECGs 20 24-hour Holters 1 event recorder

CRYptogenic STroke and underlying AtriaL Fibrillation (CRYSTAL AF), *Richard Bernstein, MD, Ph.D., et al.* NEJM June 26, 2014

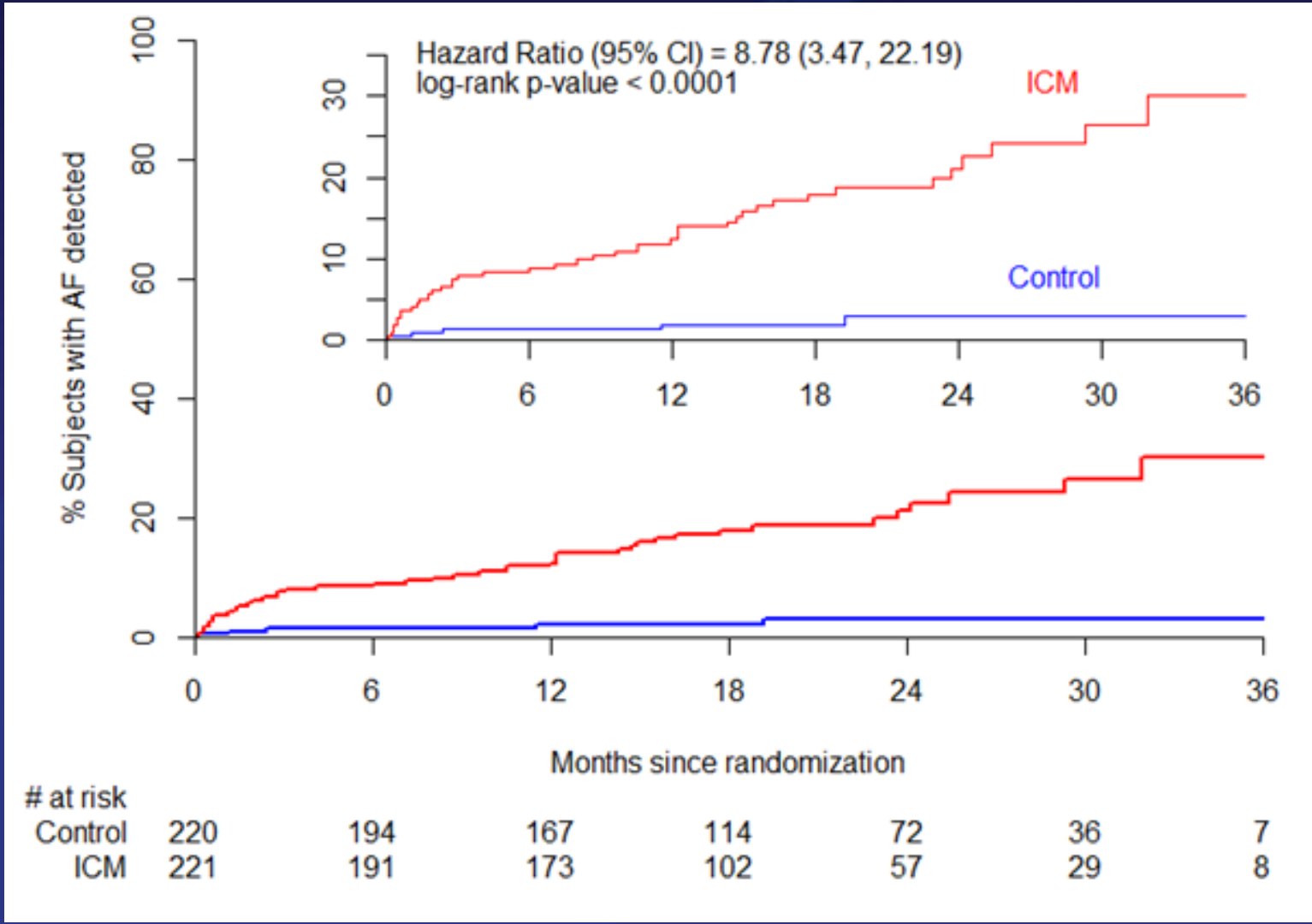
Secondary Endpoint: Detection of AF at 12 months



Rate of detection in ICM arm was 12.4% vs 2.0% in control arm

CRYptogenic STroke and underlying AtriaL Fibrillation (CRYSTAL AF), *Richard Bernstein, MD, Ph.D., et al.* NEJM June 26, 2014

Detection of AF at 3 years



Rate of detection in ICM arm was 30.0% vs 3.0% in control arm

CRYptogenic STroke and underlying AtriaL Fibrillation (CRYSTAL AF), *Richard Bernstein, MD, Ph.D., et al.* NEJM June 26, 2014

Conclusions

- ICM is superior to standard monitoring in detection of AF at 6 months (HR = 6.43), 12 months (HR=7.32), and 36 months (HR=8.78) in patients with cryptogenic stroke
- AF was detected in 8.9%, 12.4%, and 30% of patients at 6 months, 12 months, and 36 months in the ICM arm
- 92.3% of patients with AF in the ICM arm had a day with greater than 6 minutes of AF
- Detection of AF changed management to anticoagulation in 97% of patients
- Long-term continuous monitoring should be performed in patients with cryptogenic stroke

“Triple Therapy” Recommendations and the Risk of Bleeding

"Triple therapy" in patients with CAD/AF/ACS

To date, only two trials, WOEST and ISAR-TRIPLE, randomized patients requiring chronic anticoagulation and undergoing PCI to triple therapy (i.e. aspirin, clopidogrel, and VKA) or dual therapy (clopidogrel plus VKA).

In WOEST, almost 70% received OAC because of AF, but only a minority of patients had an ACS. WOEST demonstrated that triple therapy (continued for a full year) doubles the risk of bleeding complications compared with a single antiplatelet (SAPT) agent (clopidogrel) plus VKA. Although this small open-label study was underpowered for evaluation of efficacy outcomes, clopidogrel plus VKA was associated with an intriguing significantly lower mortality rate, the mechanism of which remains elusive.

Of note, no data are available on how SAPT therapy with aspirin + VKA would have performed. In ISAR-TRIPLE, 6 weeks of triple therapy (i.e. aspirin + VKA + clopidogrel) was compared with a 6-month strategy with the same therapy in patients exclusively treated with a DES. There was no significant difference in both bleeding or thrombotic events, or their combination, between the two strategies.

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2015 Oct;17(10):1467-507. doi: 10.1093/europace/euv309. Epub 2015 Aug 31

“Triple therapy” in patients with CAD/AF/ACS

There are currently three ongoing large-scale outcome studies evaluating combinations of NOAC or VKA and antiplatelets in patients with AF that undergo a PCI with stenting (elective or due to an ACS), providing hope that within the next few years there will be more evidence in this field.

1. The PIONEER AF PCI study (NCT01830543) evaluates the safety of two different rivaroxaban treatment strategies vs. VKA: (i) 15 mg rivaroxaban OD plus clopidogrel; (ii) 2.5 mg BID plus low-dose aspirin 75–100 mg plus clopidogrel, prasugrel or ticagrelor, followed by rivaroxaban 15 mg OD (or 10 mg for subjects with moderate renal impairment) plus aspirin for 12 months; or (iii) VKA treatment strategy utilizing similar combinations of antiplatelet therapy.
2. The RE-DUAL PCI study (NCT02164864) evaluates dual antithrombotic therapy regimens of (i) 110 mg dabigatran BID plus clopidogrel or ticagrelor, or (ii) 150 mg dabigatran BID plus clopidogrel or ticagrelor, with (iii) a triple antithrombotic therapy combination of warfarin plus clopidogrel or ticagrelor plus low-dose aspirin for 1–3 months.
3. Finally, apixaban will be evaluated vs. VKA in AF patients with a recent ACS in the AUGUSTUS trial (NCT02415400). All patients will be receiving a P2Y12 inhibitor and will be randomized in a 2 × 2 factorial design to 6 months of apixaban 5 mg BID vs. VKA, and aspirin vs. placebo.
4. A similar trial with edoxaban, EVOLVE-AF-PCI, is likely to start.

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2015 Oct;17(10):1467-507. doi: 10.1093/europace/euv309. Epub 2015 Aug 31

Management of Bleeding

Management of DOAC Bleeding

Initial Assessment and Risk Stratification: The ABC's
A= Airway; B= Breathing; C= Circulation

Mild Bleeding

- Delay next dose
- Anticoagulant effect dissipates 24 h (with no renal failure)
- T1/2= 12-17 h

Moderate-Severe Bleeding

- Correct hemodynamics to perfuse kidneys
- Blood-product transfusion
- Endoscopic evaluation
- +/- hemodialysis with renal failure
- Oral charcoal (if ingestion <2h)*; PPI probably helpful if recent ingestion (decreases absorption)

Life-Threatening Bleeding

- Consider rFVIIa or **PCC
- Charcoal filtration

van Ryan et al. *Thromb Heamost* 2010.
Neena S. Abraham MD, MSc . Presentation- Antithrombotics and Endoscopy: Advice for Endoscopy Nurses from Cardiogastroenterology Clinic *Mayo Clinic*

*Recommendations based on limited nonclinical data
** PCC= prothrombin concentrate complex

Management of Factor Xa Inhibitor Bleeding

- Hold drug(s)
- *No Vit K*
- Resuscitation (i.v. access, fluid administration, blood product transfusion)
- Maintain diuresis to clear drug
- Mechanical compression and surgical methods to stop bleeding

DOAC reversal agents

- **Idarucizumab (Praxbind®)**
  - Humanized monoclonal antibody with high affinity for dabigatran; binds free and thrombin-bound dabigatran
  - Clinical outcomes (Pollock CV et al. NEJM 2015):
    - N=90 bleeding patients on Dabigatran or with need for surgery.
    - 2.5 gram bolus IV X 2 normalized dilute thrombin time in 93-98% of patients.
    - Cessation of bleeding in 11.4 hours; normal surgical hemostasis in 92%
  - Approved 10/16/15 by FDA for “life threatening hemorrhage/need for emergency surgery or procedures”; REVERSE-AD trial ongoing (N=450)

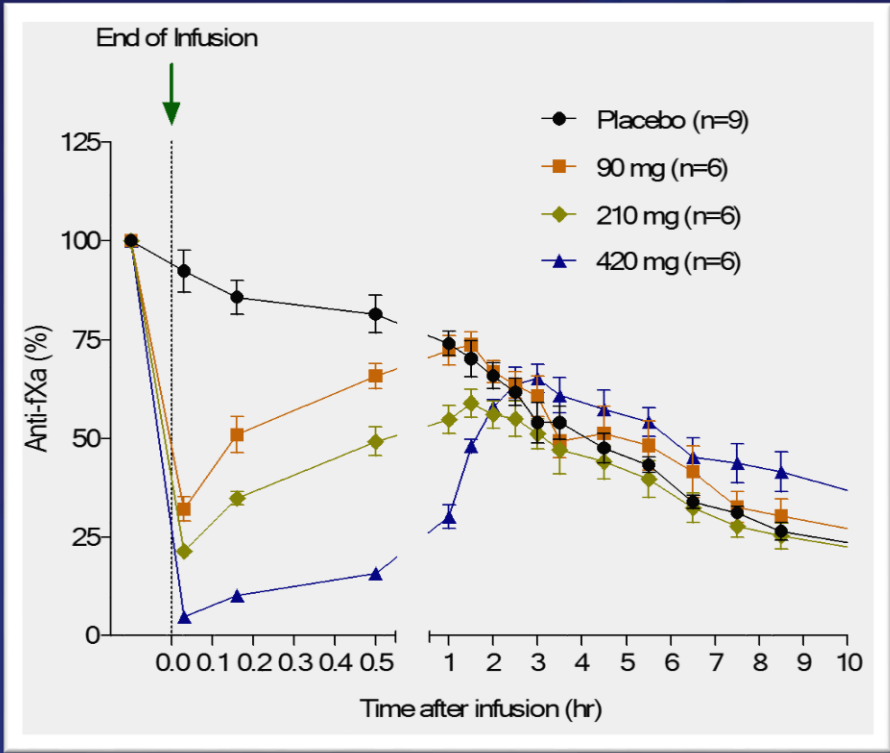
DOAC reversal agents: In Development

- **Andexanet alpha**
  - Phase II study in healthy volunteers
  - Decreased anti-Xa activity and plasma concentration of free apixaban
  - Future studies required in the setting of major hemorrhage

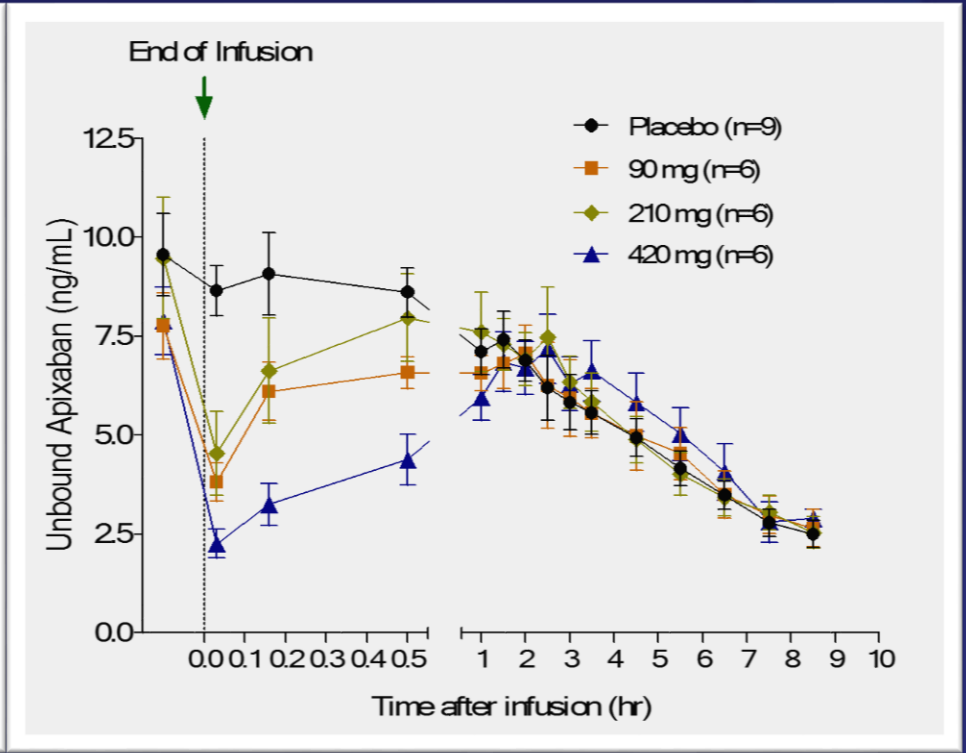
- **Aripazine (PER977)**
  - Synthetic molecule binds to heparin, LMWH and DOACs in animals
  - Whole blood clotting time (*in vitro*) show reduction of edoxaban effect within 10 minutes of IV infusion (restoration to 10% over baseline)
  - Needs human studies and clinical trials

Dose-dependent reversal of Apixaban-induced Anti-FactorXa activity correlates with reduction in Apixaban plasma free fraction

Anti-fXa activity



Apixaban free fraction

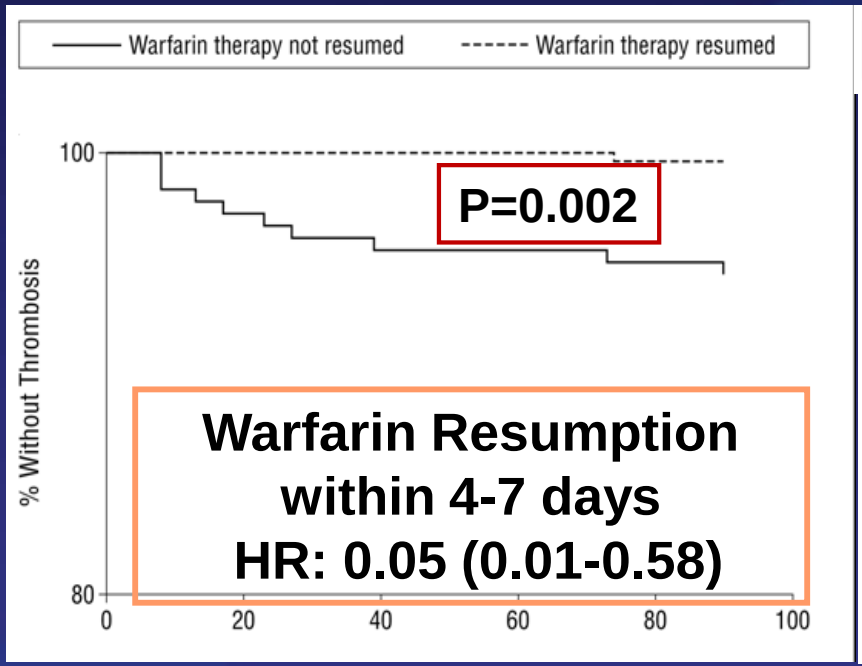


Mean ± SEM

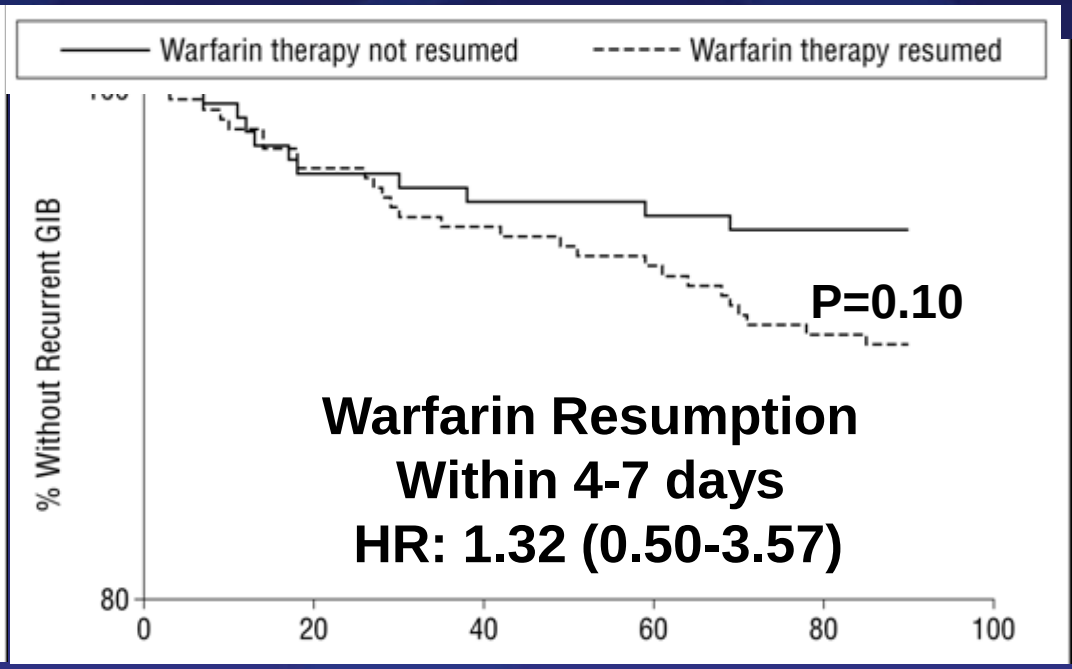
Resuming Warfarin After GI Bleeding (GIB)

Witt DM et al. *Arch Intern Med* 2012

90-Day Thrombosis



90-Day Recurrent GI Bleeding



Patients with warfarin-associated GIB and indications for continued long-term antithrombotic therapy should resume anticoagulation within the first week following hemorrhage.

Warfarin therapy resumption within 4-7 days of GI bleeding associated with lower risk of all-cause death: HR 0.31 (0.15-0.62)

Use of the Direct Oral Anticoagulants in Obese Patients

Guidelines for Management of AF

VIA MEDICA

REVIEW ARTICLE

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The use of anticoagulants in morbidly obese patients

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Abstract

Due to its constantly growing incidence, obesity is an increasingly serious social and medical problem. Available data on the use of novel oral anticoagulants in morbidly obese and obese patients are very limited. However, we tried to summarize the available knowledge on the use of anticoagulants in this subpopulation of patients in everyday clinical practice. Studies on the clinical use of anticoagulants provide a poor basis for any adjustment of doses in obese patients as compared to patients with normal body weight. In our opinion, further studies are required in this particular population. (Cardiol J 2016; 23, 1: 12–16)

Conclusions

- Atrial Fibrillation is significantly underestimated
- CHADS-2 VASC scoring system allows for a more accurate method of assessing risk and appropriate treatment
- DOACs provide opportunity to minimize growing burden of potentially preventable thromboembolism (especially AF)
- Reductions in both stroke and bleeding translate into important benefits for patients
- Most bleeding can be managed without specific antidotes
- Specific antidotes in development will provide reassurance to physicians
- Device based approaches to detecting the incidence of AF and reducing the risk of thromboembolism are readily available.

Thank You for your attention!

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