Managing Systemic Anticoagulation for the Peri-procedural Patient: A Cardiologist's Perspective

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Chief Scientific Officer

CorVita Science Foundation

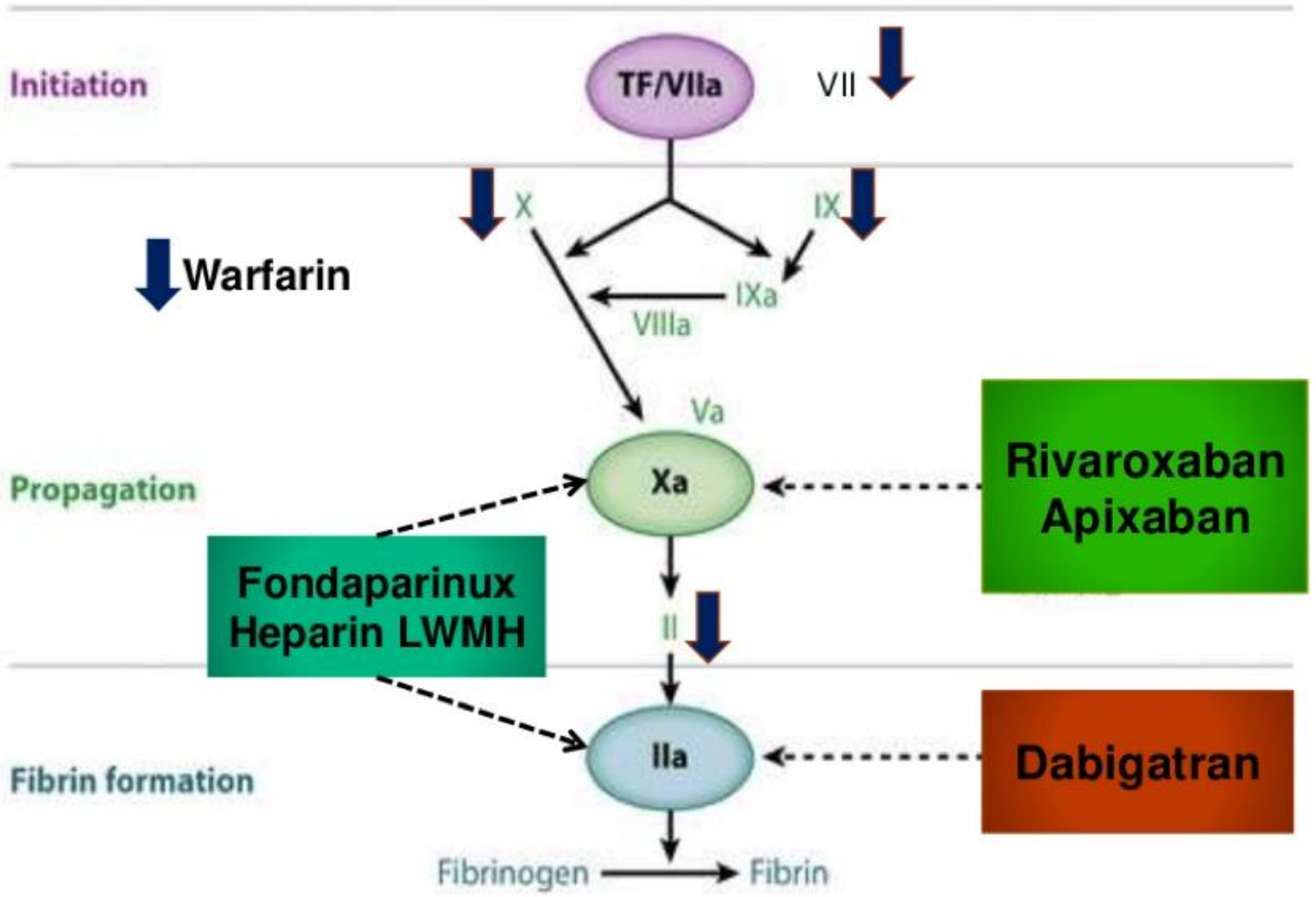
Disclosures

- Educational and clinical research grants
  - Astra Zeneca
  - Biosense Webster
  - Medtronic
  - Boston Scientific
  - Abbott
  - Pfizer

Clinical Considerations

- Type and combinations of Anticoagulant/antiplatelet therapy
- Coronary Stent Patient
- Atrial Fibrillation
- Biomechanical vs. Biologic Prosthetic Valves
- Genetic Hypercoaguable Patients
- Procedural Plan
- Bleeding management/Prevention in emergent cases
- Bridging therapy

Anticoagulant Mechanisms of Action



Adapted from Eriksson, *Ann Rev Med 62:41, 2011*

ROCKET-AF Trial

Baseline Patient Demographics: Comparison of ROCKET AF With Previous VKA-controlled Trials

	ROCKET AF[a]	RE-LY[b]	ACTIVE W[c]	AMADEUS[d]	SPORTIF V[e]
$CHADS_2$ score (%)					
0-1	<1	32	N/A	41	25
2	13	36	N/A	32	31
≥3	86	32	N/A	27	44
Median $CHADS_2$ score	≥3	2	2	2	2

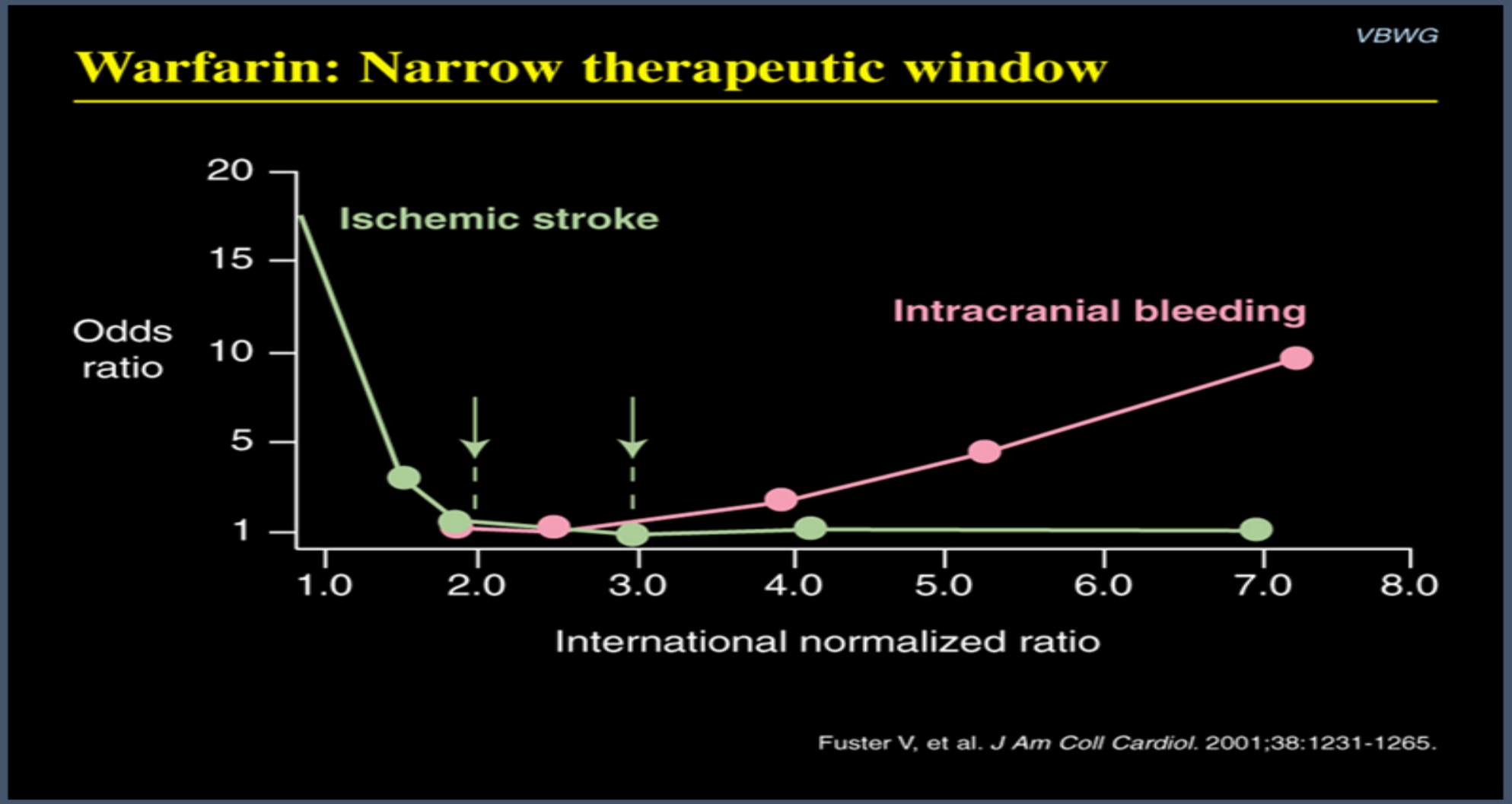
Baseline Patient Demographics (cont)

	ROCKET AF[a]	RE-LY[b]	ACTIVE W[c]	AMADEUS[d]	SPORTIF V[e]
Risk factors (%)					
CHF or LVEF ≤ 35%	63	32	30	23	39
Hypertension	90	79	82	77	81
Age ≥ 75 years	44	–	–	31	42
Diabetes	40	23	21	10*	19†
Prior stroke, TIA, or non-CNS SE	55	20	15	24	18

* Diabetes and age 65-75 years
† Diabetes and age ≥ 65 years

Patel et al. N Engl J Med 2011; 365:883-11

Warfarin Narrow Therapy Safety



NOAC Trial summaries

TABLE 2 Summary of Selected DOACs Clinical Trials

	RE-LY (33) (N = 18,113) (3 arms)*	ROCKET-AF (34) (N = 14,264)	ARISTOTLE (35) (N = 18,201)	ENGAGE AF-TIMI 48 (36) (N = 21,105) (3 arms)†
Drug, dose	Dabigatran, 150 mg bid	Rivaroxaban, 20 mg daily	Apixaban, 5 mg bid	Edoxaban, 60/30 mg daily
Adjusted dose?	No	Yes, at randomization only: 15 mg daily if CrCl 30–49 ml/min	Yes, at randomization only: 2.5 mg bid if 2 of: age ≥80 yrs, weight <60 kg, SCr ≥1.5 mg/dl	Yes, at randomization and during study: both doses halved if any 1 of the following: CrCl 30–50 ml/min, weight ≤60 kg, use of verapamil, quinidine, or dronedarone
Design	Randomized open-label	Randomized double-blind, double-dummy	Randomized double-blind, double-dummy	Randomized double-blind, double-dummy
Mean age, yrs	71.5	73	70	72
Prior stroke/ transient ischemic attack/systemic embolism	20%	55%	19%	28%
Mean $CHADS_2$	2.2	3.5	2.1	2.8
Warfarin-naïve	50.4%	37.6%	43%	41%
Comparator warfarin INR 2–3	67% TTR (median)	58% TTR (median)	66% TTR (median)	68% (median)
Comparator Warfarin INR 2–3	64% TTR (mean)	55% TTR (mean)	62% TTR (mean)	65% (mean)
Outcome, RR (95% CI)				
Stroke/systemic embolism	0.66 (0.53–0.82)	0.88 (0.75–1.03)	0.79 (0.66–0.95)	0.88 (0.75–1.03)
Ischemic stroke	0.76 (0.60–0.98)	0.94 (0.75–1.17)	0.92 (0.74–1.13)	1.00 (0.83–1.19)
Hemorrhagic stroke	0.26 (0.14–0.49)	0.59 (0.37–0.93)	0.51 (0.35–0.75)	0.54 (0.38–0.77)
Major bleeding	0.93 (0.81–1.07)	1.04 (0.90–1.20)	0.69 (0.60–0.80)	0.80 (0.71–0.91)
Intracranial hemorrhage	0.40 (0.27–0.60)	0.67 (0.47–0.93)	0.42 (0.30–0.58)	0.47 (0.34–0.63)
Gastrointestinal bleeding	1.50 (1.19–1.89)	1.39 (1.19–1.61)	0.89 (0.70–1.15)	1.23 (1.02–1.50)
Cardiovascular mortality	0.85 (0.72–0.99)	0.89 (0.73–1.10)	0.89 (0.76–1.04)	0.86 (0.77–0.97)
All-cause mortality	0.88 (0.77–1.00)	0.85 (0.70–1.02)	0.89 (0.80–0.998)	0.92 (0.83–1.01)

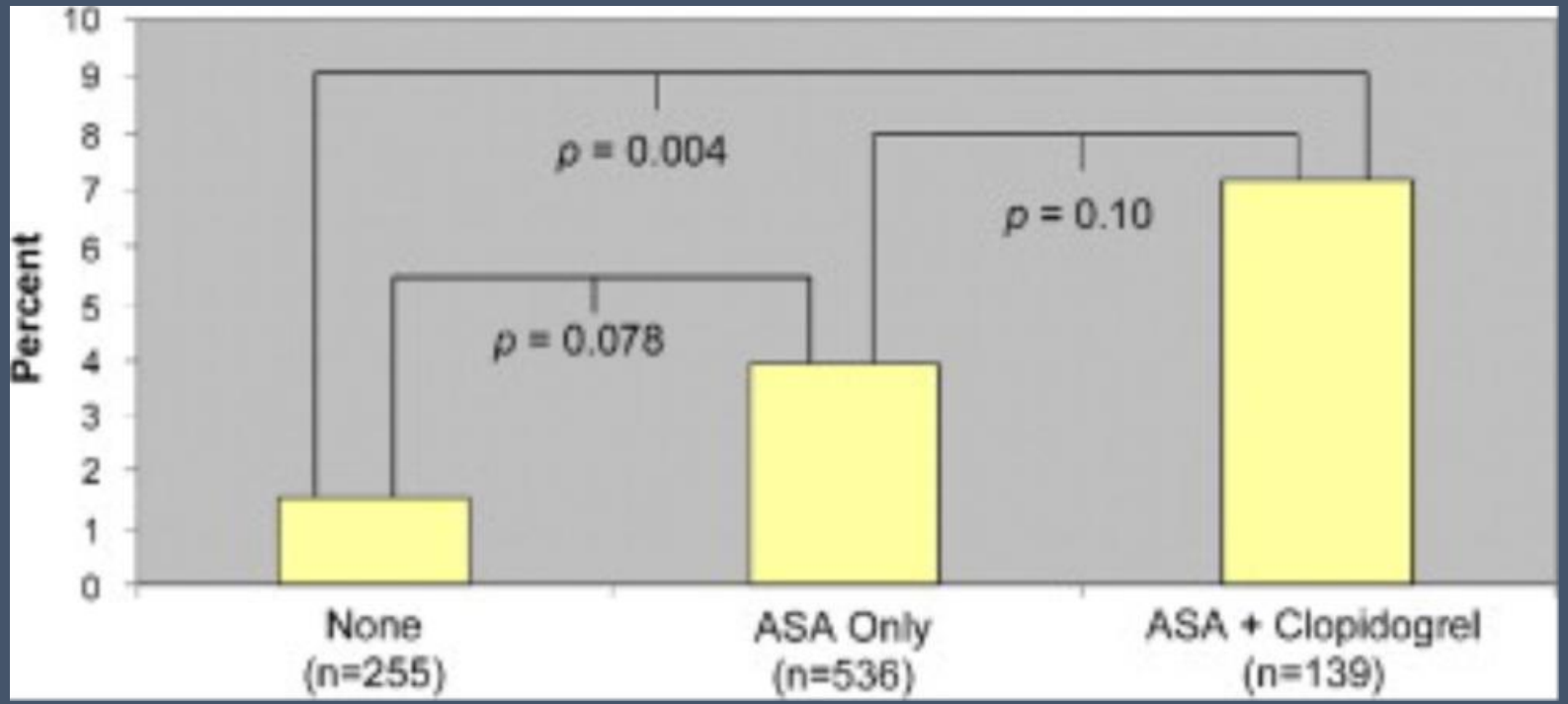
Estimate creatinine clearance (CrCl) using Cockcroft-Gault formula: ([140 − age] × weight [in kg] × 0.85 if female)/(72 × creatinine [in mg/dl]). *Results are shown for dabigatran 150 mg bid. †Results are shown for edoxaban 60 mg daily.

$CHADS_2$ = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke or transient ischemic attack; CI = confidence interval; CrCl = creatinine clearance; DOAC = direct-acting oral anticoagulant; INR = international normalized ratio; RR = risk ratio; SCr = serum creatinine; TTR = time in therapeutic range.

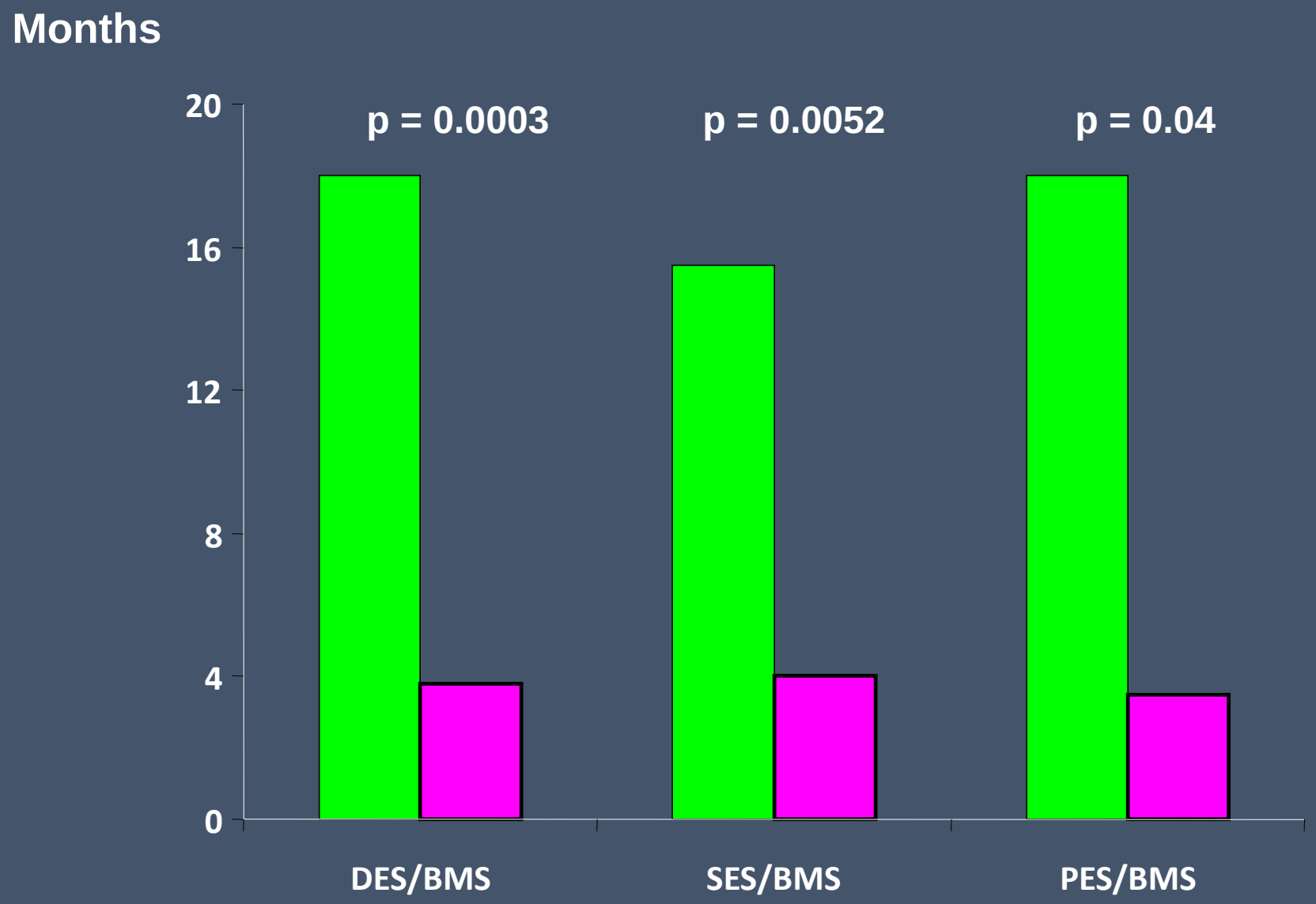
J AM Coll Cardiol. 2015; 65 (13): 1340-1360

Dual Antiplatelet Therapy and Heparin "Bridging" Significantly Increase the Risk of Bleeding Complications After Pacemaker or Implantable Cardioverter-Defibrillator Device Implantation

Tompkins et al. J Am Coll Cardiol. 2010;55(21):2376-2382. doi:10.1016/j.jacc.2009.12.056



Median Time of Late Stent Thrombosis

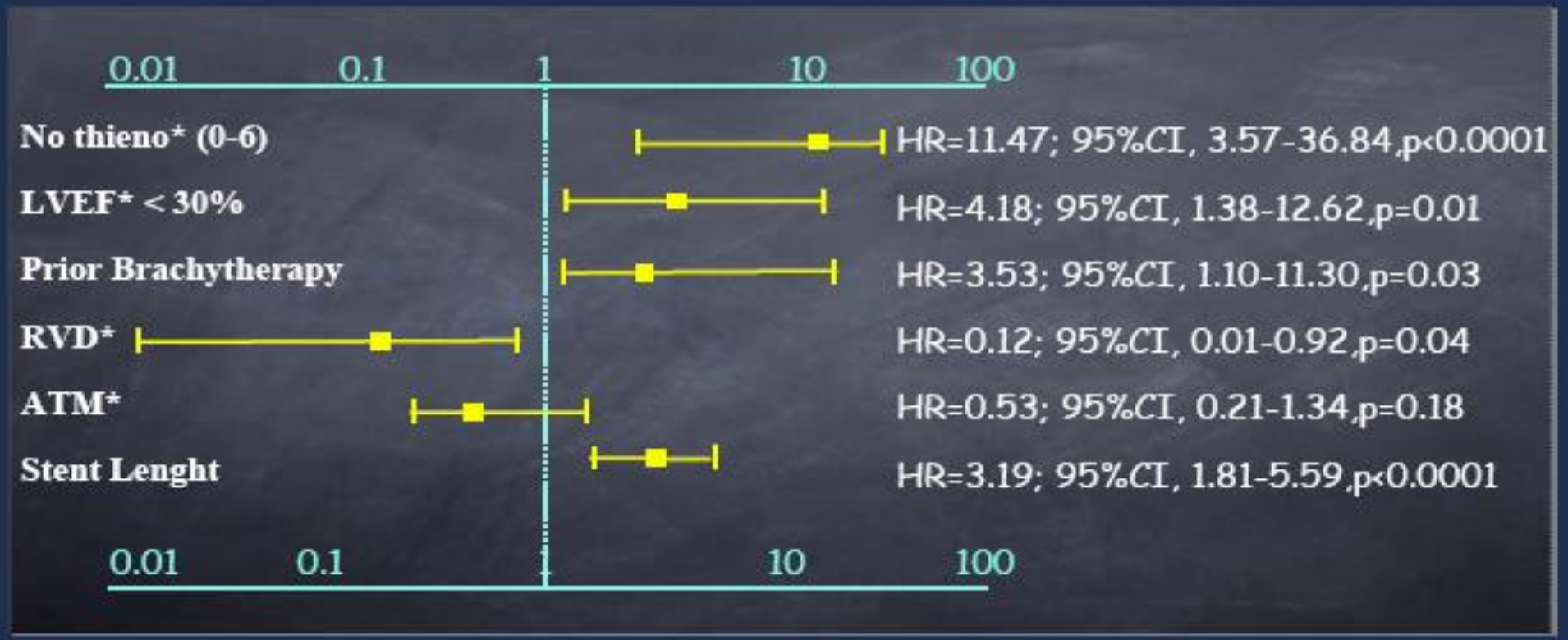


Bavry, Kumbhani, Helton, Borek, Mood, Bhatt. AJM 2006

CENTRO CUORE COLUMBUS

Predictors of stent thrombosis

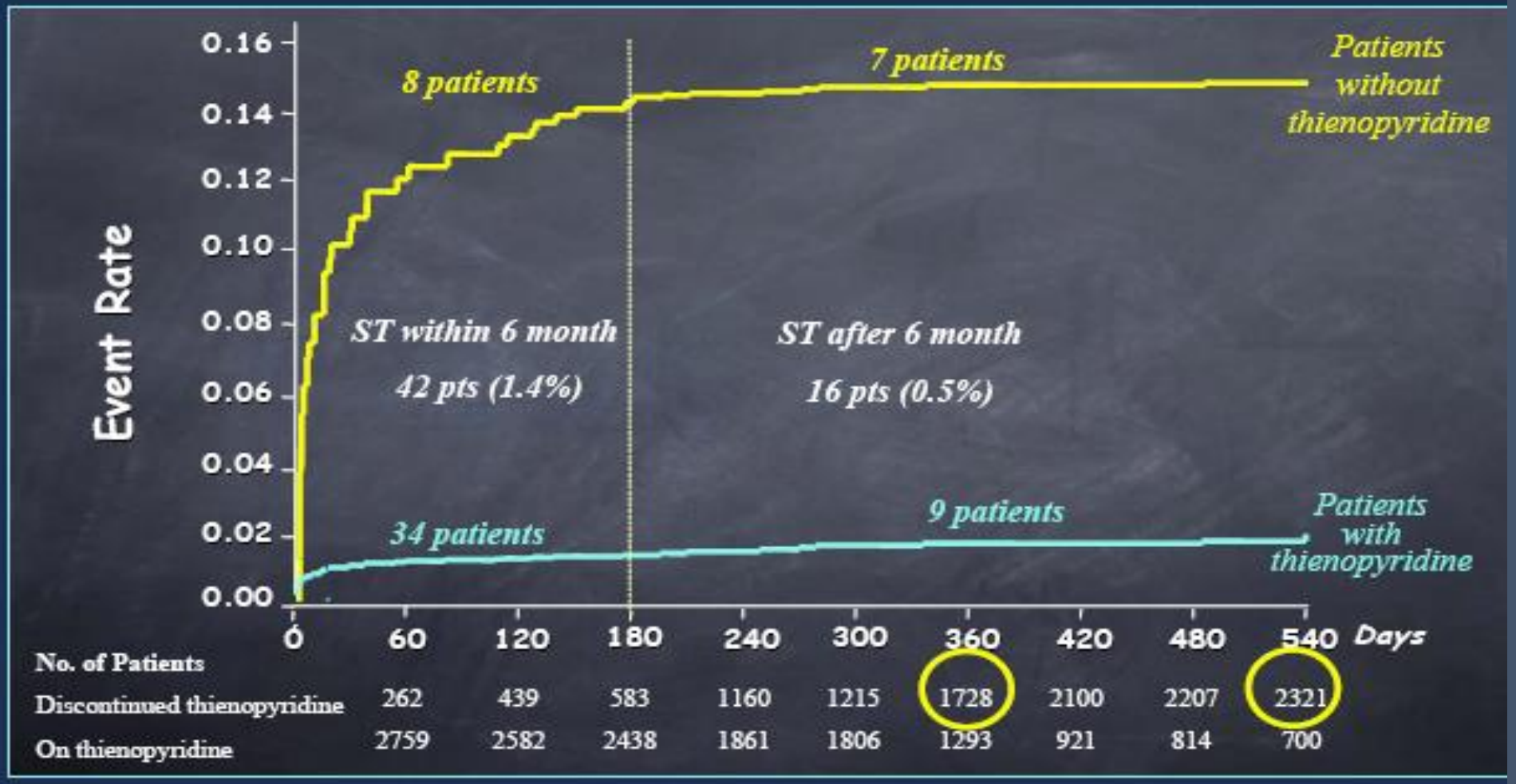
period 0-6 months



* Abbreviations: thieno=thienopyridine; LVEF=left ventricle ejection fraction; RVD=reference vessel ejection fraction; ATM= final stent atm inflation.

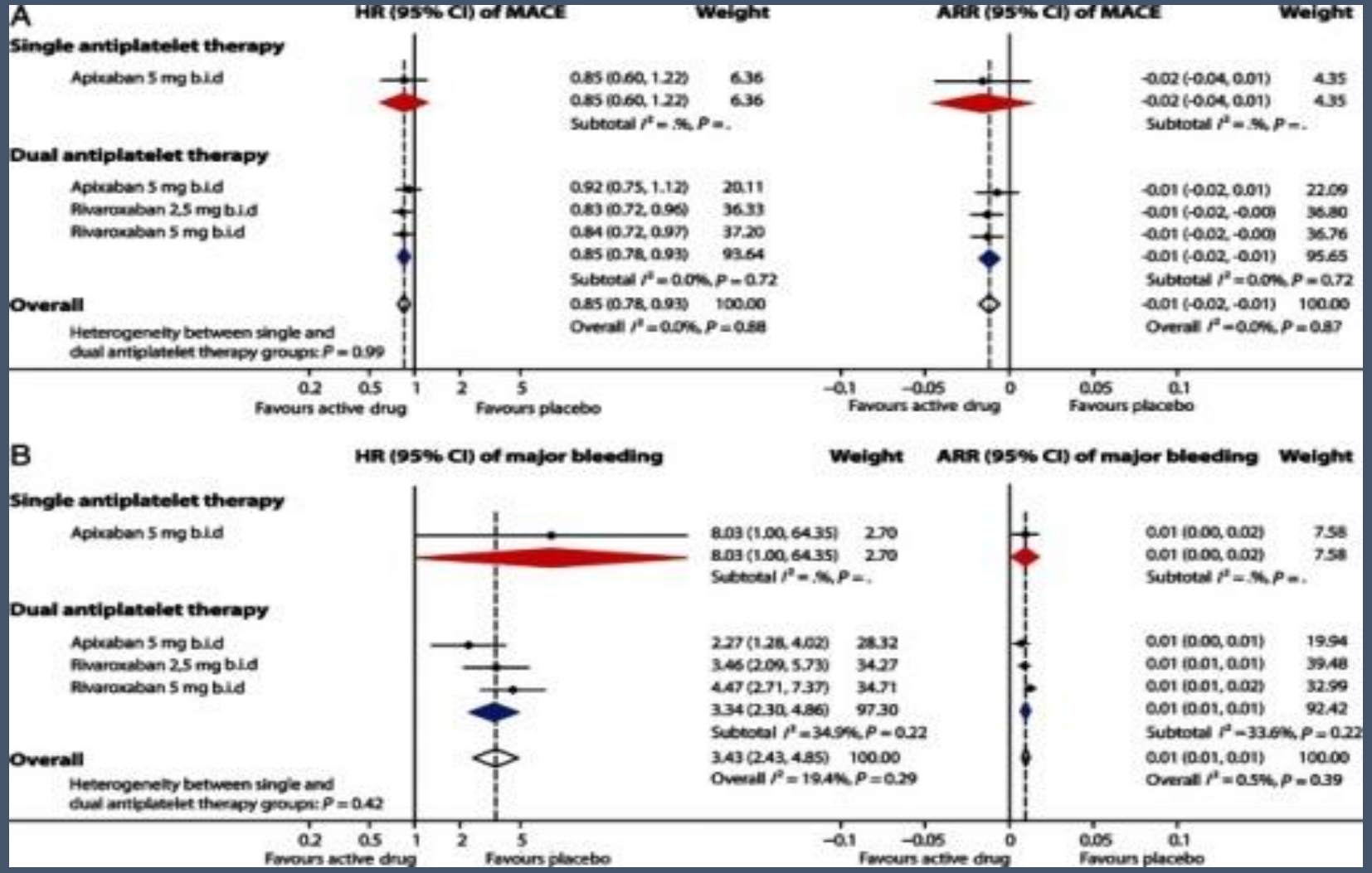
CENTRO CUORE COLUMBUS

Aalen-Nelson estimate of the cumulative hazard function



No. of Patients									
Discontinued thienopyridine	262	439	583	1160	1215	1728	2100	2207	2321
On thienopyridine	2759	2582	2438	1861	1806	1293	921	814	700

NOACS post ACS



European Heart J 2013

Perioperative Stent Patient Dose Management

- Emergent

- Elective
  - Aspirin hold 7-10 days but not a great idea
  - Thienpyridines hold 5-7 days pre operatively
  - Dual Therapy
  - Dipyridamole? At least 2 days
  - Aggrenox hold 7-10 days

Risk/Benefit

Table 2—*Suggested Patient Risk Stratification for Perioperative Arterial or Venous Thromboembolism*

Risk Stratum	Indication for VKA Therapy		
	Mechanical Heart Valve	Atrial Fibrillation	VTE
High	Any mitral valve prosthesis Older (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, or multiple abnormalities)
Moderate	Bileaflet aortic valve prosthesis and one of the following: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age > 75 yr	$CHADS_2$ score of 3 or 4	VTE within the past 3 to 12 mo Nonsevere thrombophilic conditions (*eg*, heterozygous factor V Leiden mutation, heterozygous factor II 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 (and no prior stroke or transient ischemic attack)	Single VTE occurred > 12 mo ago and no other risk factors

*$CHADS_2$ = Congestive heart failure-Hypertension-Age-Diabetes-Stroke.

Douketis JD et al. Chest 2012; 141(2) suppl. e3265-505

Atrial Fibrillation
Background

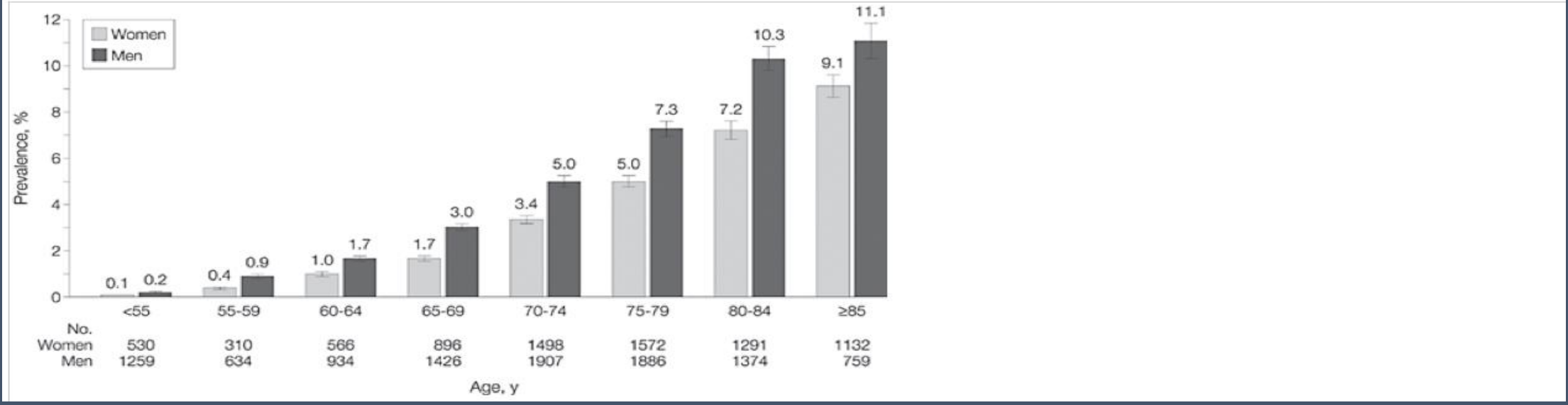
- Most common cardiac arrhythmia
  - *overall prevalence of ~1%*
- Increased risk of mortality, heart failure and thromboembolic events.
- Hospitalization rates increased by 23% from 2000 to 2010;
- In-hospital mortality 1% and as high as 1.9% for patients >80y/o; Concomitant heart failure up to 8.2%

Circulation. 2014 Jun; 129 (23): 2371-9.

Prevalence of Diagnosed Atrial Fibrillation in Adults: National Implications for Rhythm Management and Stroke Prevention: the AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) Study FREE

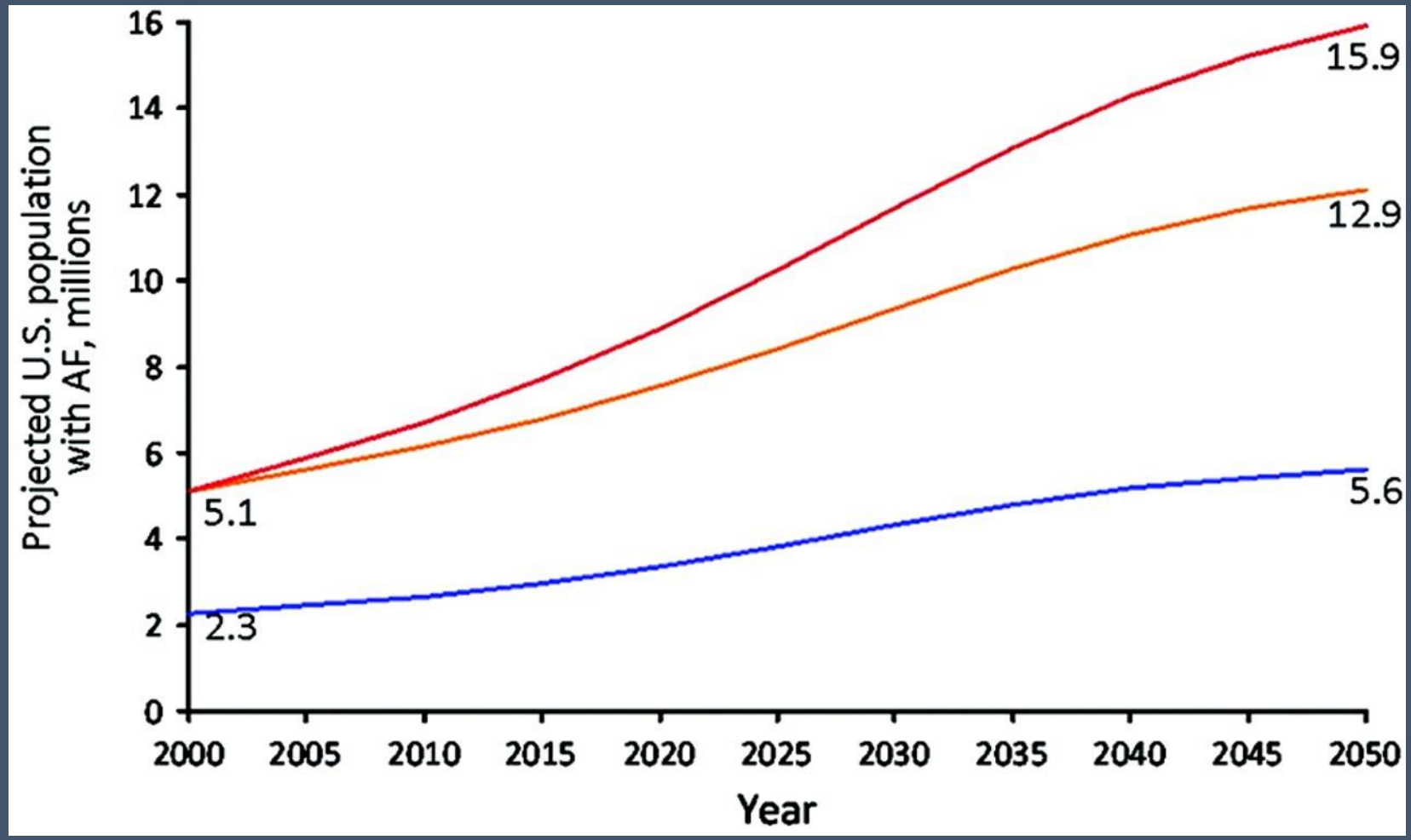
Alan S. Go, MD; Elaine M. Hylek, MD, MPH; Kathleen A. Phillips, BA; YuChiao Chang, PhD; Lori E. Henault, MPH; Joe V. Selby, MD, MPH; Daniel E. Singer, MD

JAMA. 2001;285(18):2370-2375. doi:10.1001/jama.285.18.2370.



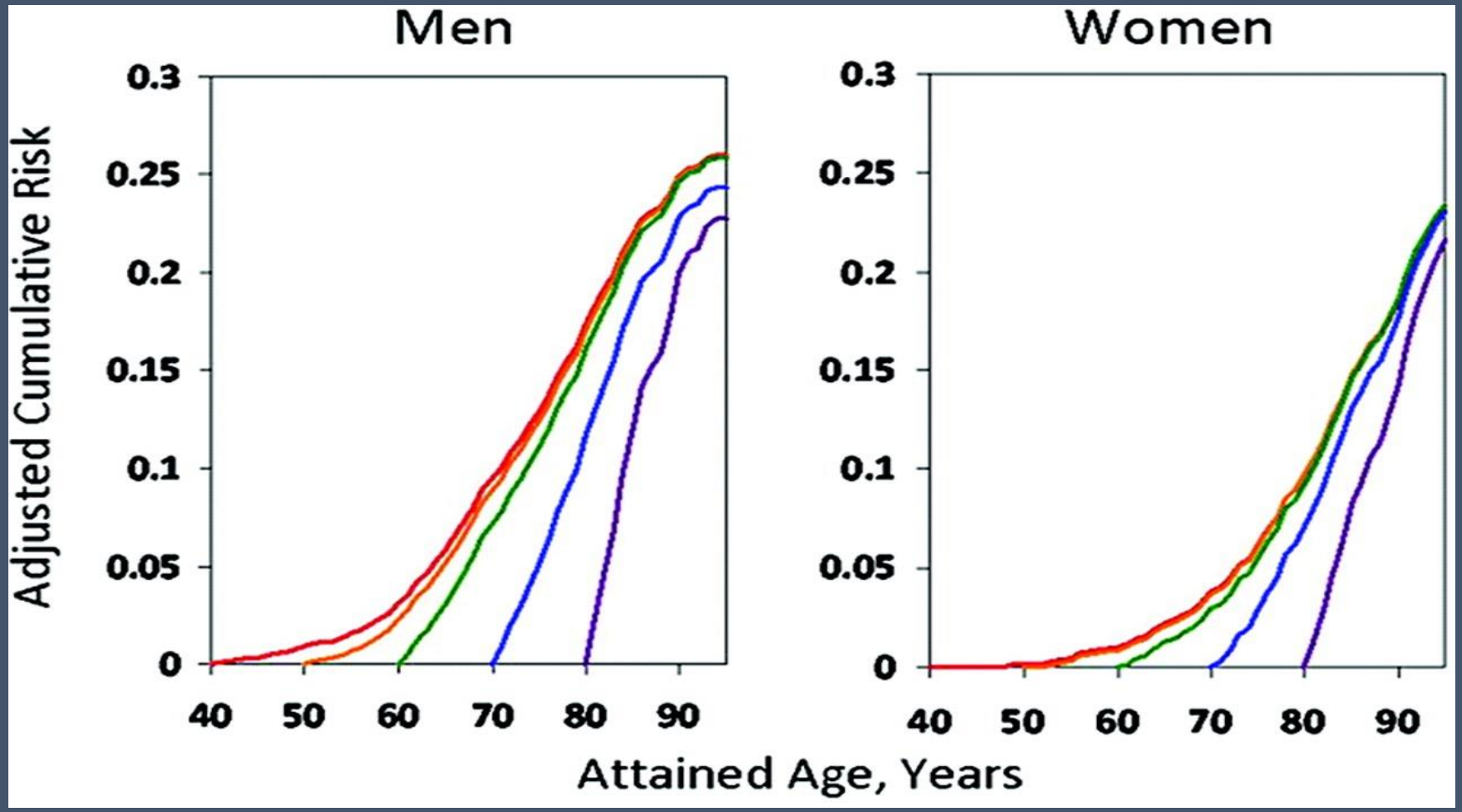
- Prevalence of atrial fibrillation increases with age
- Prevalence is higher in men than women in all age groups

The estimated US prevalence of atrial fibrillation (AF) in the year 2050 ranges from 5.6 million to as high as 15.9 million individuals.



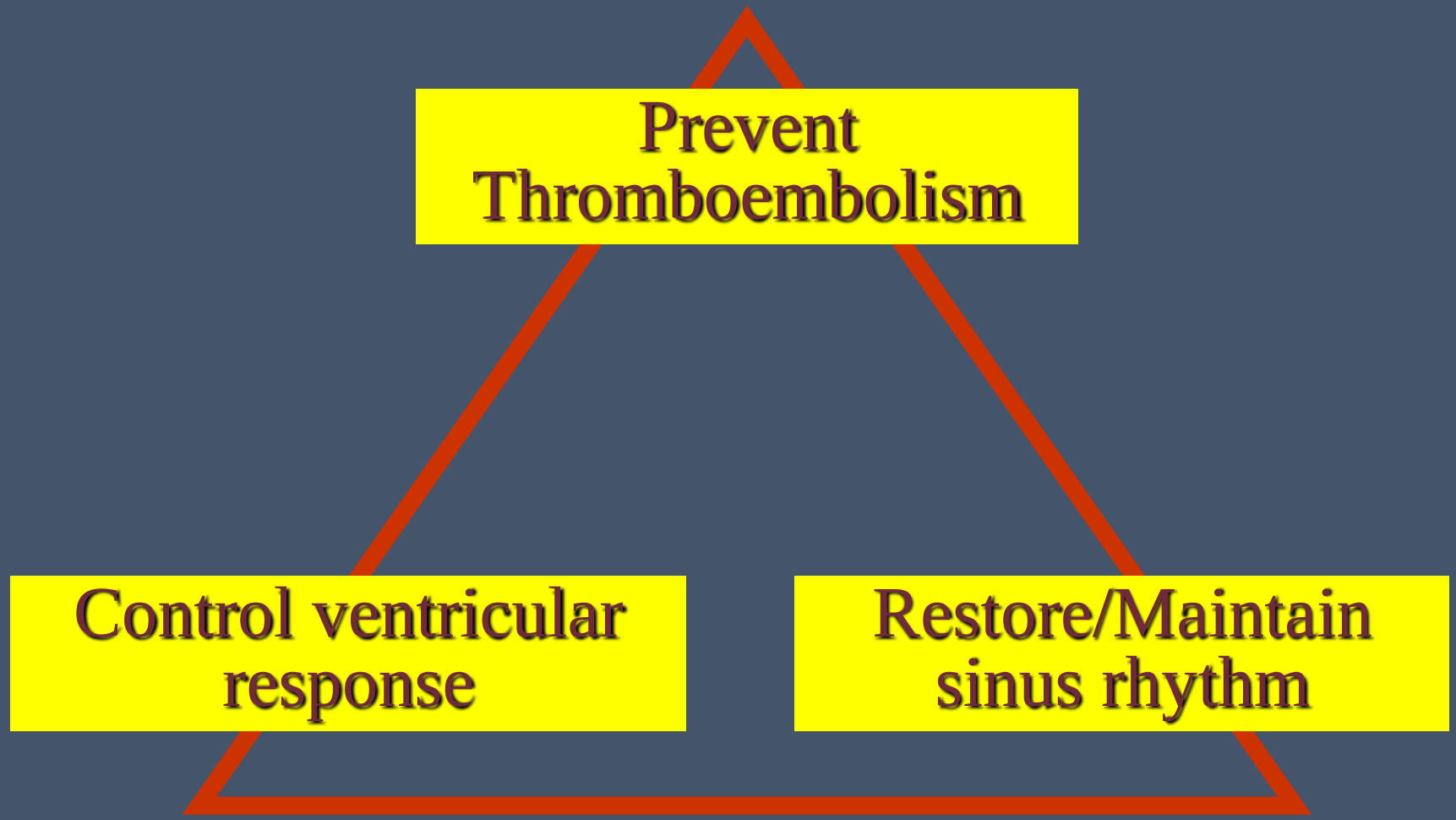
Jared W. Magnani et al. Circulation. 2011;124:1982-1993

Lifetime risk for developing atrial fibrillation (AF) from the Framingham Heart Study.



Jared W. Magnani et al. Circulation. 2011;124:1982-1993

Therapy for AF



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CLINICAL PRACTICE GUIDELINE

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

Developed in Collaboration With the Society of Thoracic Surgeons

J Am Coll Cardiol. 2014; 64 (21): 2246-2280

Types of Atrial Fibrillation

TABLE 3 **Definitions of AF: A Simplified Scheme**

Term	Definition
Paroxysmal AF	• AF that terminates spontaneously or with intervention within 7 d of onset. • Episodes may recur with variable frequency.
Persistent AF	• Continuous AF that is sustained >7 d.
Long-standing persistent AF	• Continuous AF >12 mo in duration.
Permanent AF	• The term "permanent AF" is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm. • Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of AF. • Acceptance of AF may change as symptoms, efficacy of therapeutic interventions, and patient and clinician preferences evolve.
Nonvalvular AF	• AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.

AF indicates atrial fibrillation.

J Am Coll Cardiol. 2014; 64 (21): 2246-2280

Prevention of Thromboembolism

Decision to anti-coagulate comes down to risk of embolism versus bleeding.

Guideline recommendation:

3. **In patients with nonvalvular AF, the CHA_2DS_2-VASc* score is recommended for assessment of stroke risk (68-70).**
   (Level of Evidence: B)

J Am Coll Cardiol. 2014; 64 (21): 2246-2280

CHADS2-Vasc Score

- CHADS2VASC increases the number of patients who meet criteria for anticoagulation therapy and more accurately identifies truly low risk patients

- More people who were considered low risk before (ie females, age 65-74, vascular dx) are moved to the higher risk categories to better reflect risk of embolization.

TABLE 6 Comparison of the $CHADS_2$ and CHA_2DS_2-VASc Risk Stratification Scores for Subjects With Nonvalvular AF

Definition and Scores for $CHADS_2$ and CHA_2DS_2-VASc		Stroke Risk Stratification With the $CHADS_2$ and CHA_2DS_2-VASc Scores	
	Score		Adjusted Stroke Rate (% per y)
$CHADS_2$		$CHADS_2$*	
Congestive HF	1	0	1.9
Hypertension	1	1	2.8
Age ≥75 y	1	2	4.0
Diabetes mellitus	1	3	5.9
Stroke/TIA/TE	2	4	8.5
Maximum score	6	5	12.5
		6	18.2
CHA_2DS_2-VASc		CHA_2DS_2-VASc†	
Congestive HF	1	0	0
Hypertension	1	1	1.3
Age ≥75 y	2	2	2.2
Diabetes mellitus	1	3	3.2
Stroke/TIA/TE	2	4	4.0
Vascular disease (prior MI, PAD, or aortic plaque)	1	5	6.7
Age 65–74 y	1	6	9.8
Sex category (i.e., female sex)	1	7	9.6
Maximum score	9	8	6.7
		9	15.20

J Am Coll Cardiol. 2014; 64 (21): 2246-2280

Guideline recommendation for anticoagulation in AF

- Anticoagulation recommended

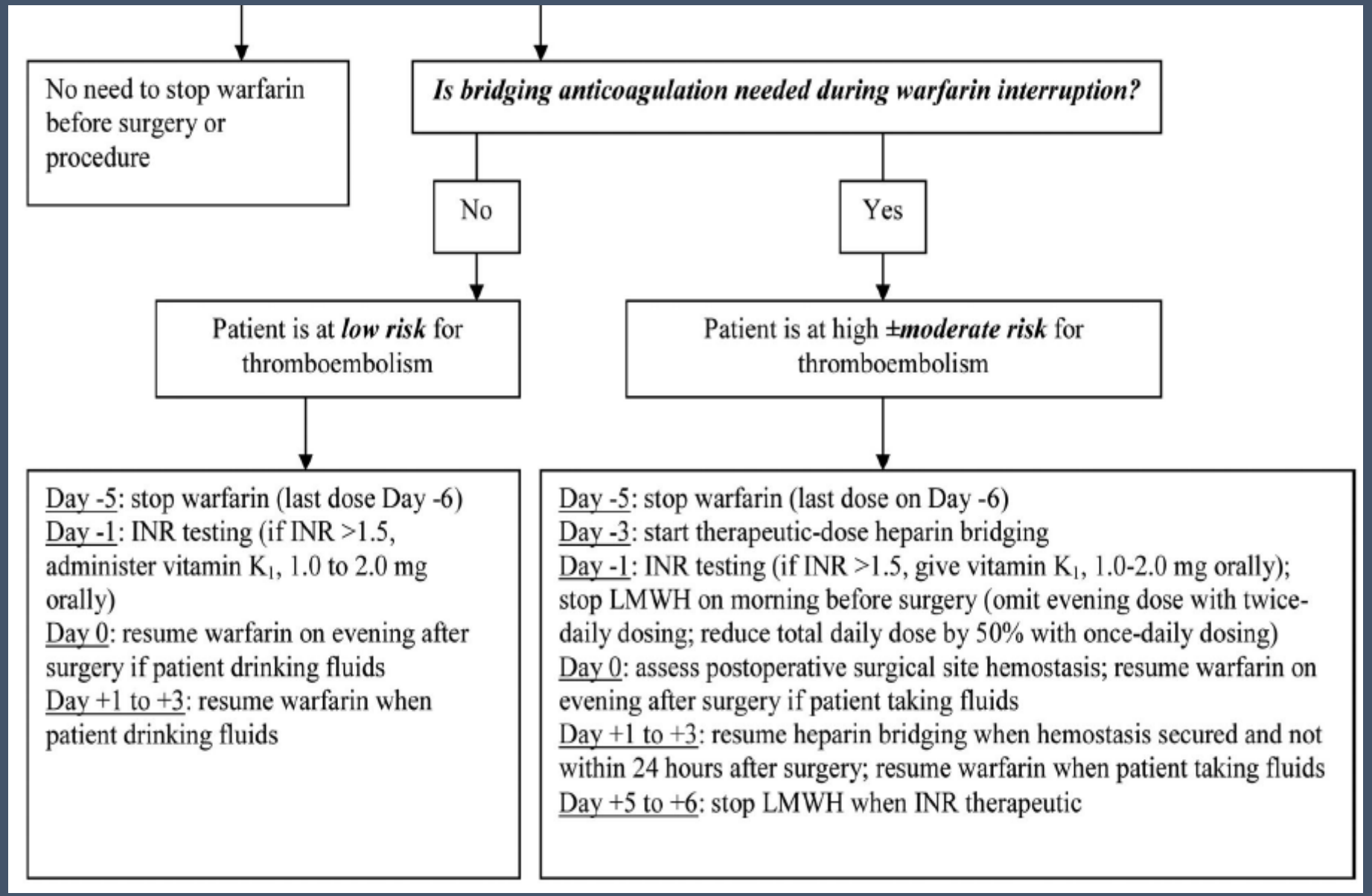
5. For patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a CHA_2DS_2-VASc score of 2 or greater, oral anticoagulants are recommended. Options include warfarin (INR 2.0 to 3.0) (68–70) *(Level of Evidence: A)*, dabigatran (74) *(Level of Evidence: B)*, rivaroxaban (75) *(Level of Evidence: B)*, or apixaban (76). *(Level of Evidence: B)*

J Am Coll Cardiol. 2014; 64 (21): 2246-2280

Managing Perioperative Anticoagulation

- Biomechanical Valves
  - Risk of thrombo-embolic event peri-operatively
  - Aortic ~2%
  - Mitral ~4%
  - Aortic/Mitral ~6%

Douketis JD et al. Chest 2012; 141(2) suppl. e3265-505



Douketis JD et al. Chest 2012; 141(2) suppl. e3265-505

Procedural back up

- In house catheterization lab capable of direct intervention
- Cardiac Surgical capabilities
- Advanced support options

Bleeding Risk

- Annual rate of major bleeding range between 2.1% to 3.6%
- Fatal bleeding occurs in up to 0.5%
- Major bleeding is associated with higher mortality
  - 30-day mortality after major bleeding episode 13% with warfarin and 9% with dabigatran

J AM Coll Cardiol. 2015; 65 (13): 1340-1360

HAS-BLED

Letter	Clinical Characteristic	Points
H	Hypertension	1
A	Abnormal Liver or Renal Function	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly (age > 65)	1
D	Drugs or Alcohol	1 or 2
Maximum Score		9

J Am Coll Cardiol. 2014; 64 (21): 2246-2280

Bleeding management

Agents to reverse anticoagulation

- More complicated as DOAC reversal is limited (*until recently*)
- Develop institutional plan
- Consult hematology

Bleeding management: Warfarin

- Vitamin K
  - Vit K 5-10mg slow IV infusion
    - IV Vitamin K does not begin to reduce INR for 6hrs (usually longer than 24hrs)
    - IV vitamin K allergic reaction if given as bolus
  - Subcutaneous and IM Vitamin K not recommended
  - PO Vitamin K used in minor bleeding
  - Does not work for DOAC

- Fresh frozen plasma
  - Along with blood transfusion provide volume
  - >1500 ml of FFP
  - Does not work for DOAC

Bleeding management: DOAC

- Prothrombin complex concentrate (PCC)
  - 10-30min infusion improves INR within minutes and last 24-48hrs
    - ♠Use Vitamin K along with this
  - Limited reversal of dabagatran and rivaroxiban in 2hrs in healthy volunteers
  - Small concern about myocardial infarction and arterial thromboembolism
  - Some have heparin therefore cautious use in patients with heparin-induced thrombocytopenia

♠ Throm Haemost. 2012; 108: 217-224

Bleeding management, reversal: *Dabigatran*

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

N Engl J Med 2015; 373:511-520 | August 6, 2015 | DOI: 10.1056/NEJMoa1502000

- antibody fragment developed to reverse the anticoagulation effects of dabigatran

Bleeding management, reversal: *Factor Xa inhibitors*

- Andexanet
  - Recombinant factor Xa with minor amino acid deletions; Therefore lacks pro or anticoagulation affects on its own
  - Active binding site of Andexanet functions as a decoy and binds to factor Xa inhibitors with high affinity
  - Overall factor Xa inhibitors concentration is reduced
  - Phase 3 ANNEXA trial

Bleeding management, reversal: *Factor Xa inhibitors*

- Aripazine
  - synthetic small molecule with broad activity against heparin, LMWH, and DOAC
  - IV dosing
  - reversal seen in 10 minutes in the phase I study

Thromboembolism Prevention Conclusions

- Decision to anti-coagulate should be guideline driven but individualized to the patient
- Use objective assessment tools for bleeding and embolic risk calculation.
- Direct oral anticoagulants (DOAC) provide good anticoagulation options to warfarin
- Bridging therapy in high risk patients remains controversial but new evidence suggests bridging might not necessary. However, additional trials are needed to validate this.