Contemporary Management of Anticoagulant Therapies- Therapeutic Selection, Periprocedural Management and Reversal Agents

John D. Fisher, MD

Montefiore Medical Center

Professor of Medicine,

Albert Einstein College of Medicine, NY

Thanks to the organizers for inviting me to Saudi Arabia

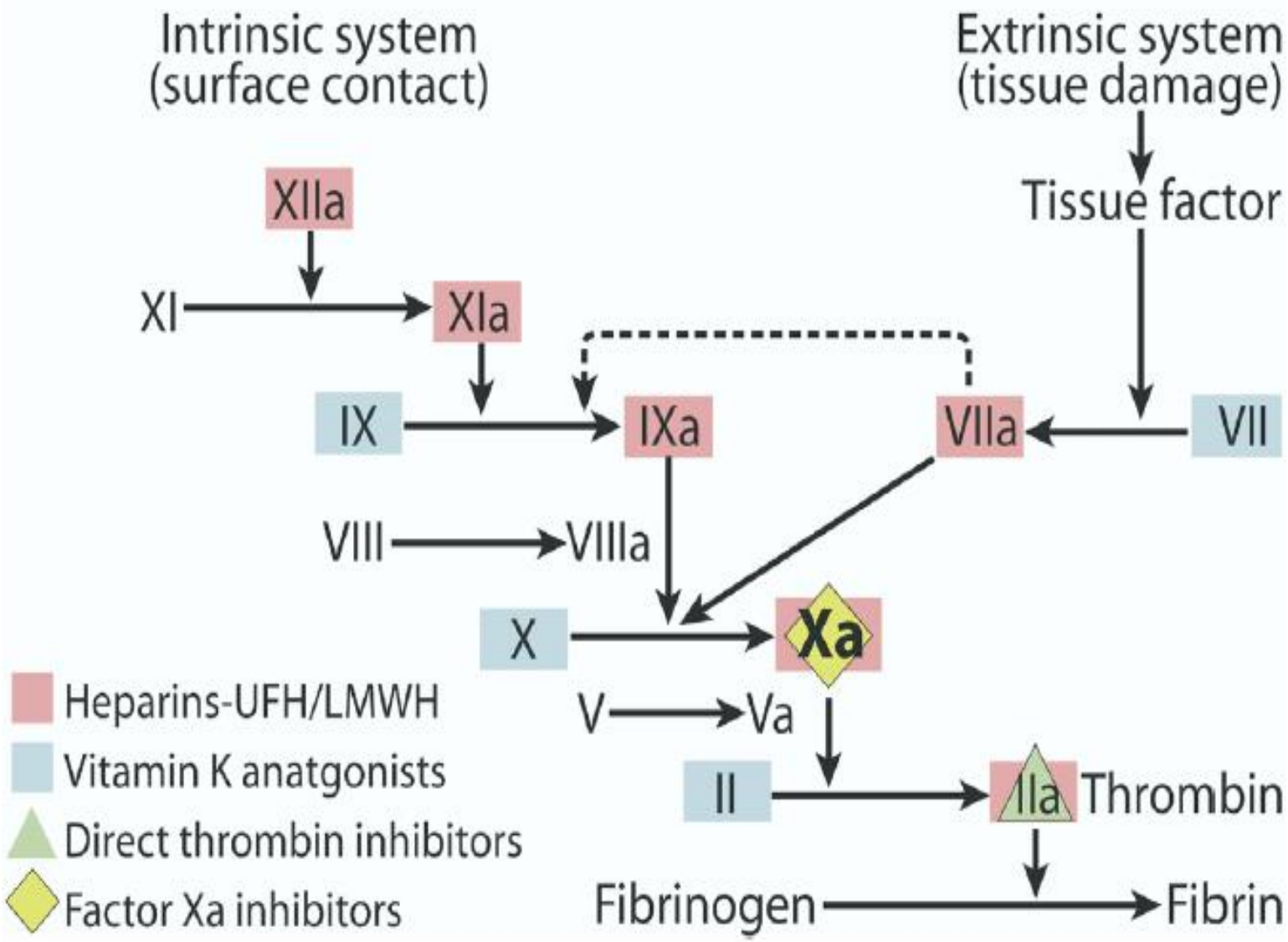
Disclosures

- None relevant to this presentation.

Anticoagulants

- Recall Dr. Gorenek's talk.

Anticoagulation Drugs-Targets



Jay, Lui 2006

Therapeutic Selection

- VKAs:
  - Cheap, time-tested.
  - Reversible in hours (Vitamin K).
  - Imposes burdens:
    - Diet, need to check INR.
- NOACs:
  - Clearly preferable for non-valvular AF.

What is “Non-Valvular AF”?

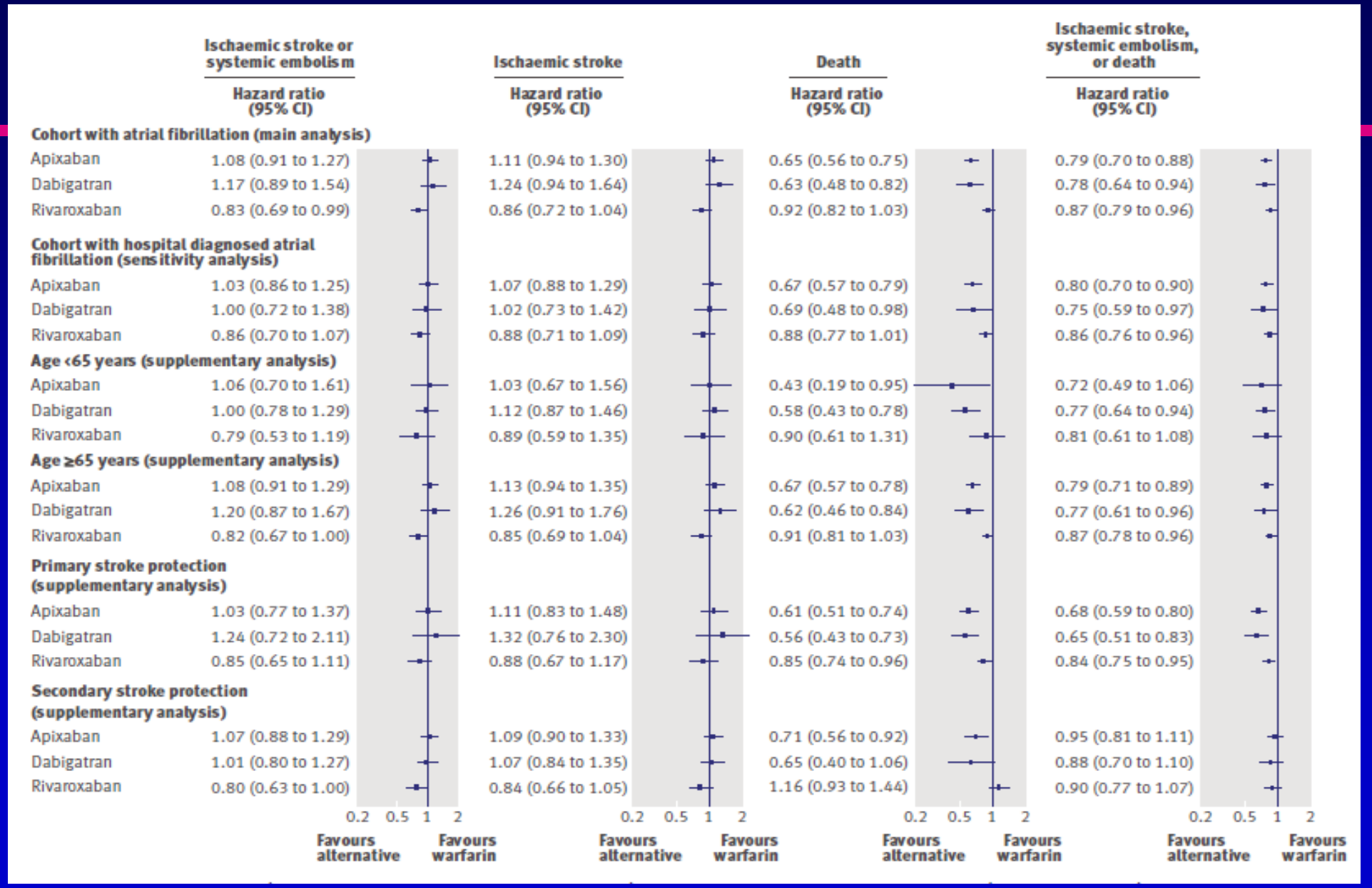
- **Definitions has evolved over the years, and are not yet settled.**

BMJ 2016;353:i3189

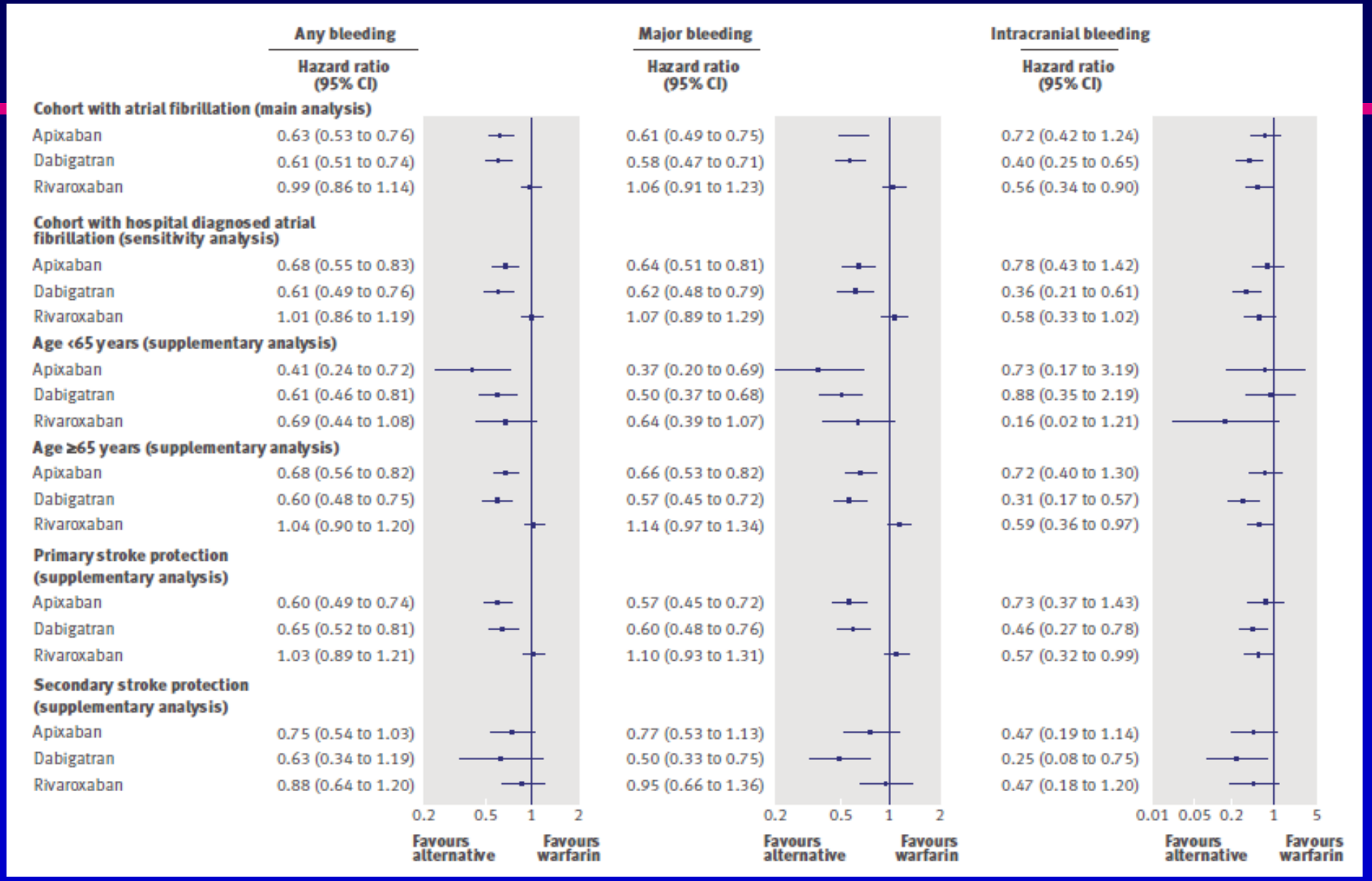
Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study

Torben Bjerregaard Larsen,[1,2] Flemming Skjøth,[2,3] Peter Brønnum Nielsen,[2] Jette Nordstrøm Kjældgaard,[2] Gregory Y H Lip[2,4]

NOACs vs. Warfarin: Stroke, embolism, death: (BMJ 2016)



NOACs vs. Warfarin: Bleeding: (BMJ 2016)



2014 AHA/ACC/HRS Guidelines
Use of Factor Specific Agents

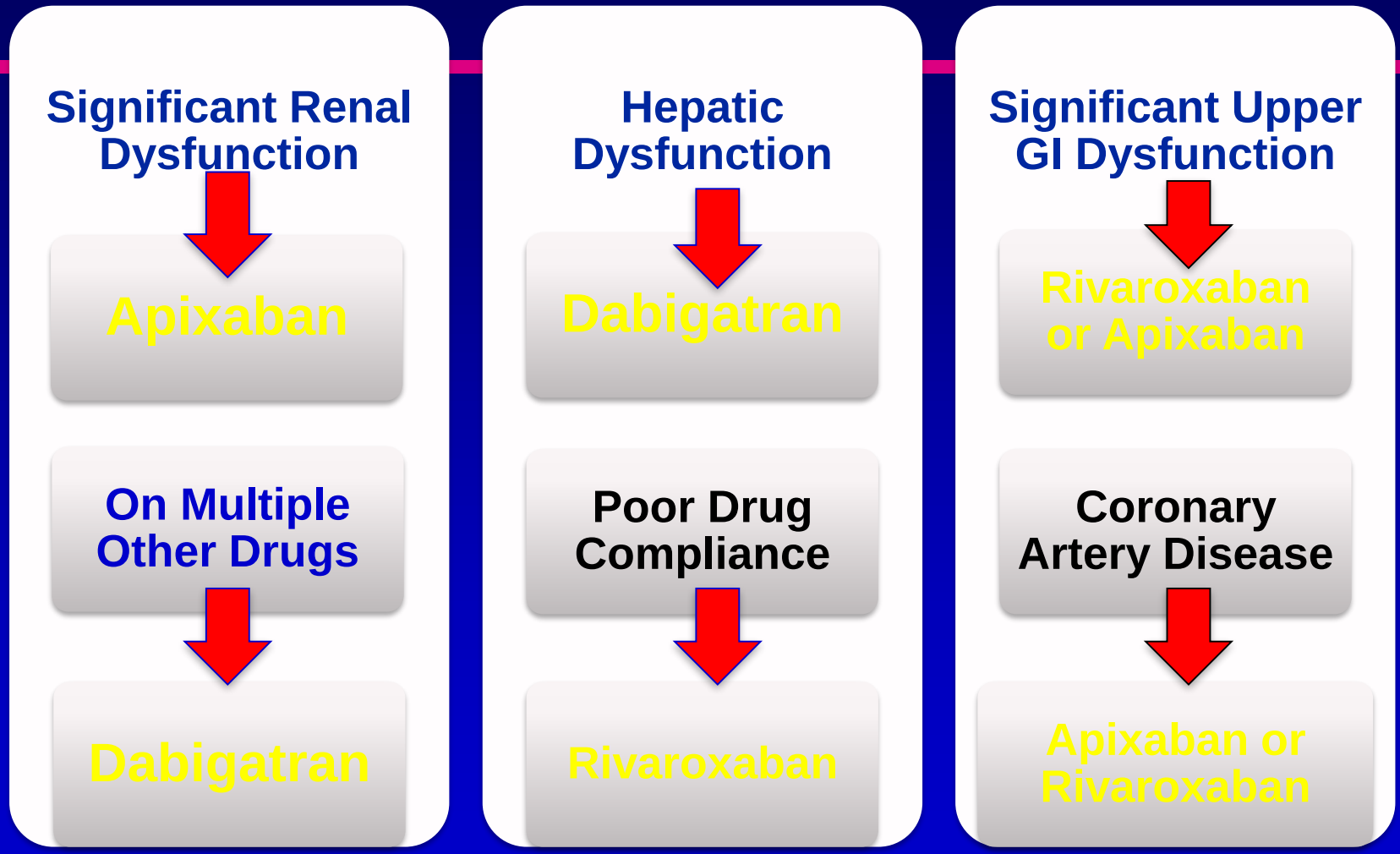
- **Class I recommendation:**
  - **For pts with nonvalvular AF with CHA2DS2-VASc score of ≥ 2, oral anticoagulation recommended with warfarin, dabigatran, rivaroxaban, or apixaban.**
  - **For pts with nonvalvular AF unable to maintain a therapeutic INR level with warfarin, use of direct thrombin inhibitor or Xa inhibitor is recommended**
  - **Renal function should be evaluated prior to initiation of direct thrombin inhibitor or Xa inhibitor, and repeated at least annually**

2014 AHA/ACC/HRS Guidelines
Use of Factor Specific Agents

- **Class IIB recommendation:**
  - **Dabigatran and rivaroxaban are NOT recommended in pts with AF and end-stage CKD or on hemodialysis (lack of evidence)**

- **Class III:**
  - **Dabigatran should not be used in pts with AF and mechanical heart valve**

Potential Algorithm for Anticoagulation Selection



Adapted from Iyer, Harsimran & Reiffel (2012) *J Cardiovasc PharmaTher.*

Periprocedural Management

- **Major Evolution.**
  - **Torpedoes? Full speed ahead!**

Anticoagulation and Arrhythmia Procedures: Traditional (Example)

- Stop warfarin 48 hours to allow INR to return to baseline (or <1.8 – 2.0).
  - If there is a mechanical valve, use heparin until a few hours before the procedure.
  - Start heparin without a bolus 6 hours after procedure.
- Start warfarin the night of the procedure.

Bridging

The NEW ENGLAND JOURNAL of MEDICINE

2013;368:2084

ORIGINAL ARTICLE

Pacemaker or Defibrillator Surgery without Interruption of Anticoagulation

David H. Birnie, M.D., Jeff S. Healey, M.D., George A. Wells, Ph.D., Atul Verma, M.D., Anthony S. Tang, M.D., Andrew D. Krahn, M.D., Christopher S. Simpson, M.D., Felix Ayala-Paredes, M.D., Benoit Coutu, M.D., Tiago L.L. Leiria, M.D., and Vidal Essebag, M.D., Ph.D., for the BRUISE CONTROL Investigators*

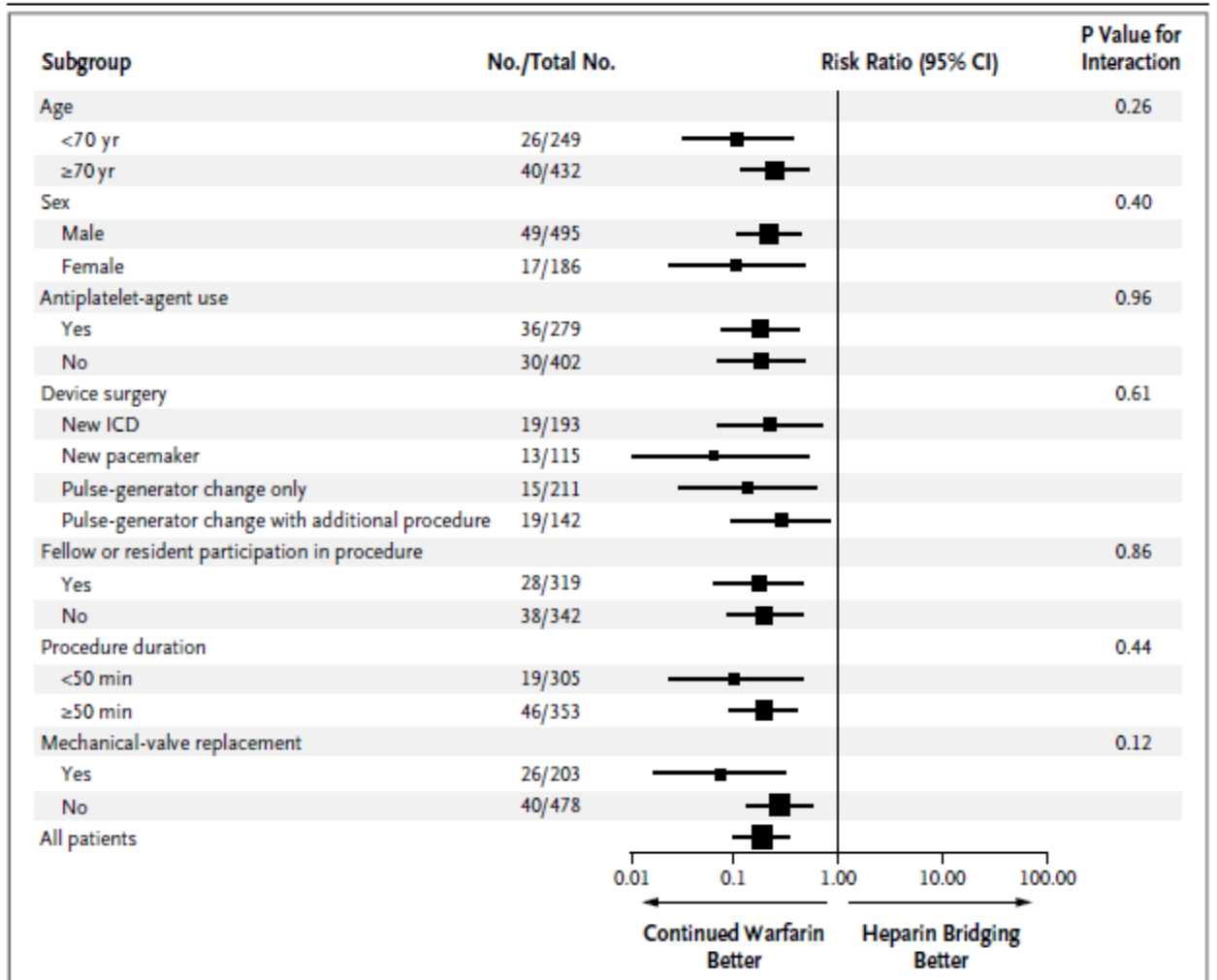


Figure 2. Subgroup Analyses of Clinically Significant Device-Pocket Hematoma.

Risk ratios and 95% confidence intervals are shown for the primary outcome of clinically significant device-pocket hematoma in each subgroup. ICD denotes implantable cardioverter–defibrillator.

Atrial Fibrillation Ablation in Patients With Therapeutic International Normalized Ratio

Comparison of Strategies of Anticoagulation Management in the Periprocedural Period

Oussama M. Wazni, MD; Salwa Beheiry, RN; Tamer Fahmy, MD; Conor Barrett, MD; Steven Hao, MD; Dimpi Patel, DO; Luigi Di Biase, MD; David O. Martin, MD, MPH; Mohamed Kanj, MD; Mauricio Arruda, MD; Jennifer Cummings, MD; Robert Schweikert, MD; Walid Saliba, MD; Andrea Natale, MD

Background—The best approach to management of anticoagulation before and after atrial fibrillation ablation is not known.

Methods and Results—We compared outcomes in consecutive patients undergoing pulmonary vein antrum isolation for persistent atrial fibrillation. Early in our practice, warfarin was stopped 3 days before ablation, and a transesophageal echocardiogram was performed to rule out clot. Enoxaparin, initially 1 mg/kg twice daily (group 1) and then 0.5 mg/kg twice daily (group 2), was used to "bridge" patients after ablation. Subsequently, warfarin was continued to maintain the international normalized ratio between 2 and 3.5 (group 3). Minor bleeding was defined as hematoma that did not require intervention. Major bleeding was defined as either cardiac tamponade, hematoma that required intervention, or bleeding that required blood transfusion. Pulmonary vein ablation was performed in 355 patients (group 1=105, group 2=100, and group 3=150). More patients had spontaneous echocardiographic contrast in groups 1 and 2. One patient in group 1 had an ischemic stroke compared with 2 patients in group 2 and no patients in group 3. In group 1, 23 patients had minor bleeding, 9 had major bleeding, and 1 had pericardial effusion but no tamponade. In group 2, 19 patients had minor bleeding, and 2 patients developed symptomatic pericardial effusion with need for pericardiocentesis 1 week after discharge. In group 3, 8 patients developed minor bleeding, and 1 patient developed pericardial effusion with no tamponade.

Conclusions—Continuation of warfarin throughout pulmonary vein ablation without administration of enoxaparin is safe and efficacious. This strategy can be an alternative to bridging with enoxaparin or heparin in the periprocedural period.
(***Circulation***. **2007;116:2531-2534.**)

What do the Guidelines say?

- AHA-ACC-HRS 2014
- ESC 2016

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http://dx.doi.org/10.1016/j.jacc.2014.03.021

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

Bridging. Class I
AHA-ACC-HRS 2014

Bridging therapy with unfractionated heparin or low-molecular-weight heparin (LMWH) is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions on bridging therapy should balance the risks of stroke and bleeding. *(Level of Evidence: C)*

For patients with AF without mechanical heart valves who require interruption of warfarin or new anticoagulants for procedures, decisions about bridging therapy (LMWH or unfractionated heparin) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated. *(Level of Evidence: C)*

European Heart Journal (2016) **37**, 2893–2962
doi:10.1093/eurheartj/ehw210

ESC GUIDELINES

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC

Endorsed by the European Stroke Organisation (ESO)

Bridging:
ESC 2016

- Most cardiovascular interventions (e.g. percutaneous coronary intervention or pacemaker implantation) can be performed safelyon continued OAC. When interruption of OAC is required, bridging does not seem to be beneficial, except in patients with mechanical heart valves.

Guidelines Generally Agree:

- Bridging is recommended in patients with mechanical heart valves.
  - This may be obsolescent.
- Advanced renal impairment:
  - AHA-ACC: Warfarin/VKAs preferred.
    - Creat Cl < 15-30.
  - ESC: No evidence about NOACs.
    - Creat Cl <30

Cardioversion and TEE (TOE)

Recommendations	Class	Level
Stroke prevention in patients designated for cardioversion of AF		
Anticoagulation with heparin or a NOAC should be initiated as soon as possible before every cardioversion of AF or atrial flutter.	IIa	B
For cardioversion of AF/atrial flutter, effective anticoagulation is recommended for a minimum of 3 weeks before cardioversion.	I	B
Transoesophageal echocardiography (TOE) is recommended to exclude cardiac thrombus as an alternative to preprocedural anticoagulation when early cardioversion is planned.	I	B
Early cardioversion can be performed without TOE in patients with a definite duration of AF <48 hours.	IIa	B
In patients at risk for stroke, anticoagulant therapy should be continued long-term after cardioversion according to the long-term anticoagulation recommendations, irrespective of the method of cardioversion or the apparent maintenance of sinus rhythm. In patients without stroke risk factors, anticoagulation is recommended for 4 weeks after cardioversion.	I	B
In patients where thrombus is identified on TOE, effective anticoagulation is recommended for at least 3 weeks.	I	C
A repeat TOE to ensure thrombus resolution should be considered before cardioversion.	IIa	C

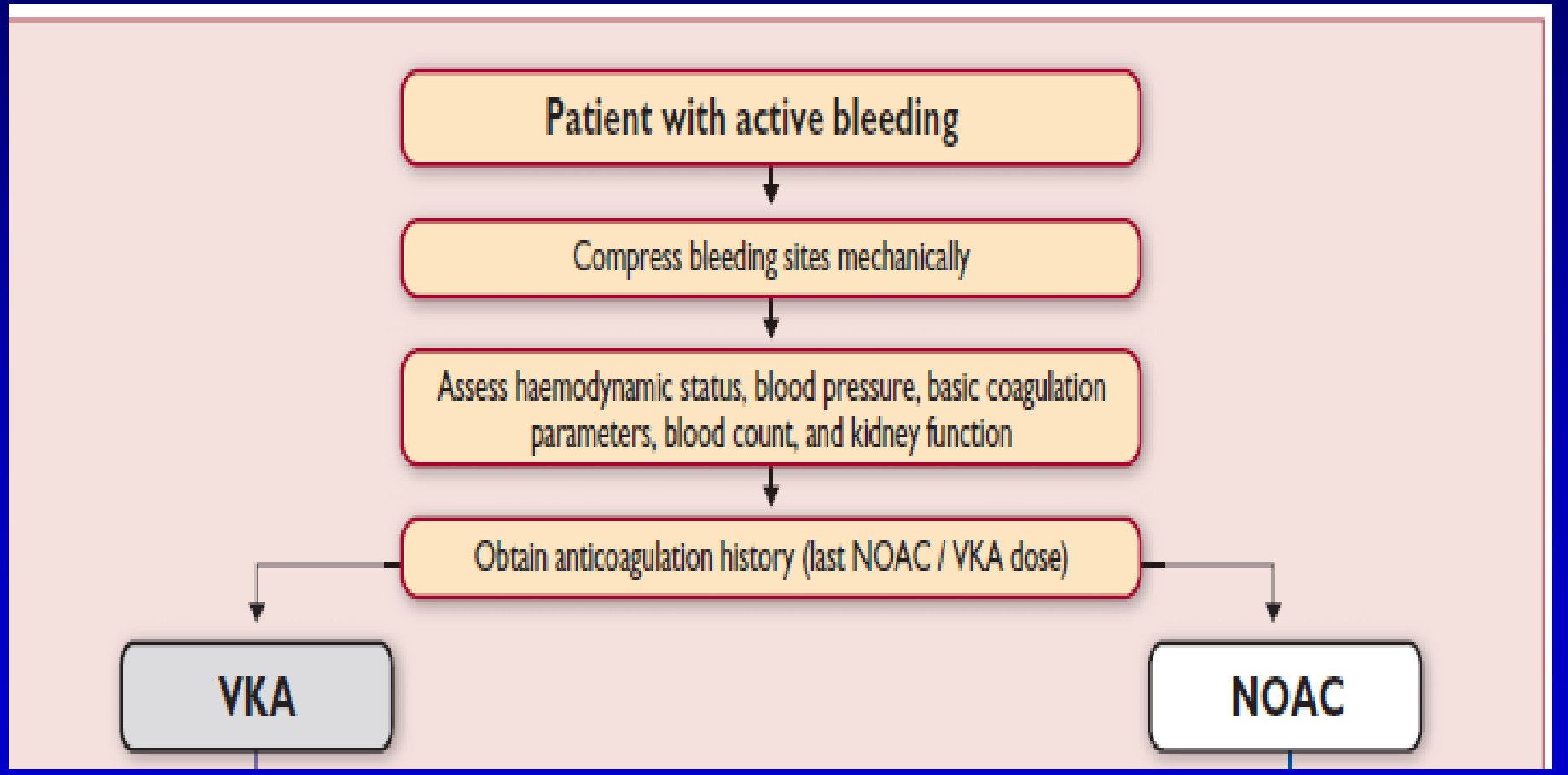
European Heart Journal - doi:10.1093/eurheartj/ehw210

Preventing postoperative atrial fibrillation

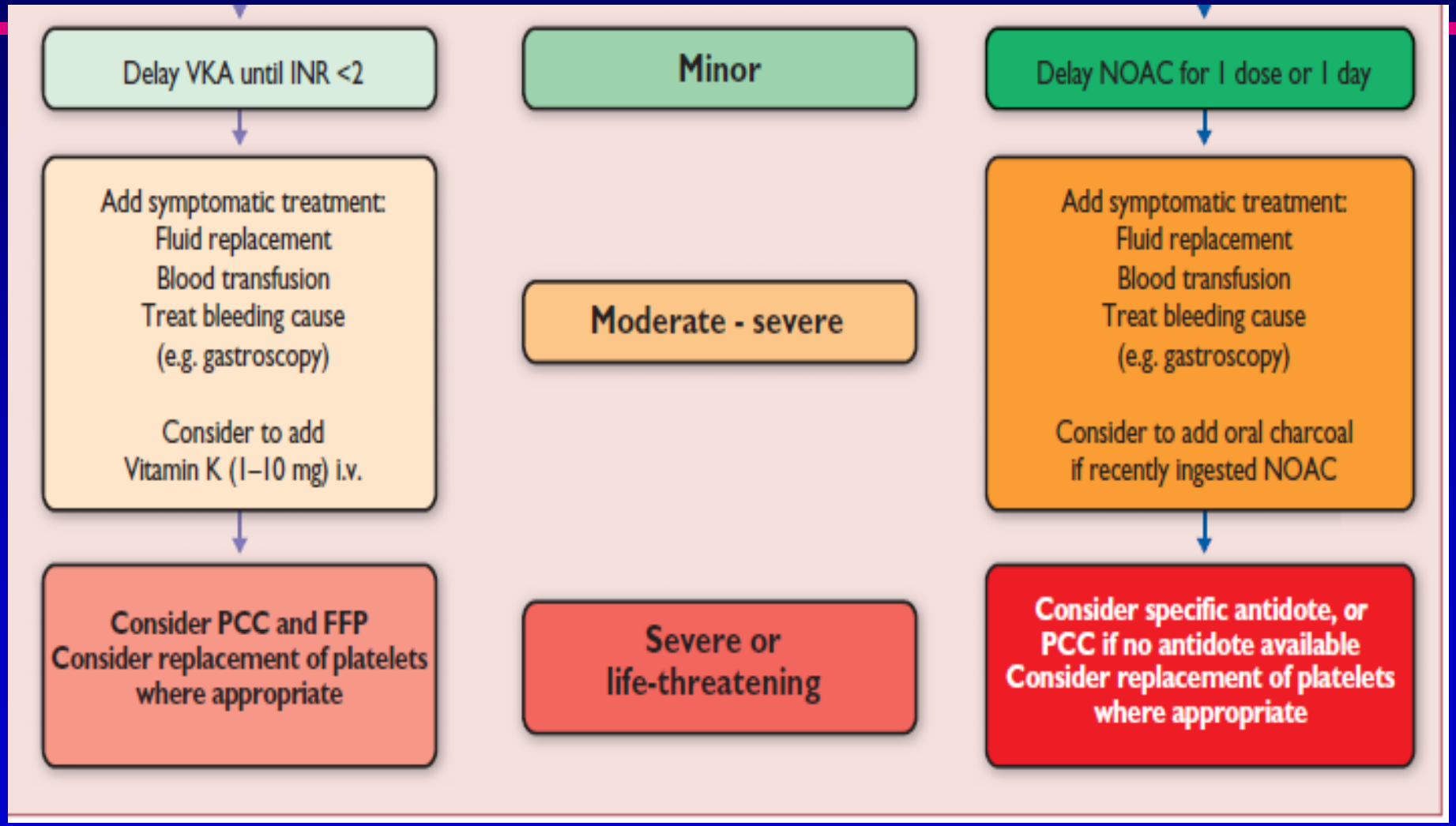
Recommendations	Class	Level
Peri-operative oral beta-blocker therapy is recommended for the prevention of postoperative AF after cardiac surgery.	I	B
Restoration of sinus rhythm by electrical cardioversion or antiarrhythmic drugs is recommended in postoperative AF with haemodynamic instability.	I	C
Long-term anticoagulation should be considered in patients with AF after cardiac surgery at risk for stroke, considering individual stroke and bleeding risk.	IIa	B
Antiarrhythmic drugs should be considered for symptomatic postoperative AF after cardiac surgery in an attempt to restore sinus rhythm.	IIa	C
Peri-operative amiodarone should be considered as prophylactic therapy to prevent AF after cardiac surgery.	IIa	A
Asymptomatic postoperative AF should initially be managed with rate control and anticoagulation.	IIa	B
Intravenous vernakalant may be considered for cardioversion of postoperative AF in patients without severe heart failure, hypotension, or severe structural heart disease (especially aortic stenosis).	IIb	B

European Heart Journal - doi:10.1093/eurheartj/ehw210

ESC Bleeding Algorithm (1)



ESC Bleeding Algorithm (2)



PCC = Prothrombin Complex Concentrate, factors II, VII, I(, X

Reversal:
Products originally designed for specific factor deficiencies, e.g. hemophilia.
Hu et al 2016

- Utility in anticoagulation reversal and achieving hemostasis has been described with warfarin.
- Efficacy in NOAC bleeding has not been validated by RCTs.
  - Inactivated PCC; Activated PCCs; factor VII, small amounts of FII, FVII, FIX, and FX • Recombinant FVIIa ○ Activated FVII

RE-VERSE AD Study
Reversal occurred within minutes (Praxbind)

The NEW ENGLAND JOURNAL of MEDICINE

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.

Other NOAC Reversal Agents

- Ciraparantag/PER977: NOACs and heparin antidote.
  - “Universal reversal agent”.
  - Xa and dabigatran.
    - In trials
- Andexanet alfa: factor Xa inhibitor antidote.

Conclusions

- Therapeutic Selection;
  - NOACs gaining favor in non-valvular AF.
  - Similarities are > differences.
- Perioprocedural management:
  - Continue AC (!)
- Reversal agents:
  - Heparin: Protamine sulphate.
  - Warfarin: Blood products and Vitamin K.
  - NOACs: Specific reversal agents.

All Done!

Thank You for your attention.

Dosing Considerations

- Dabigatran
  - Reduce Dose 75 mgs BID for CrCl 15-30 ml/min
- Rivaroxaban
  - Reduce Dose 15 mgs daily for CrCl 15-50 ml/min
- Apixaban
  - Reduce Dose 2.5 mgs BID Age>80/ Wgt<60kg/ Cr>1.5 (Two/Three)
  - ESRD / Dialysis 5 mgs BID
- Edoxaban
  - DO Not Use CrCl > 95 ml/min
  - Reduce Dose 30 mgs daily CrCl 15-50 ml/min

ROCKET-AF

Study Design

Atrial Fibrillation

Risk Factors
- CHF
- Hypertension
- Age ≥ 75
- Diabetes

At least 2 or 3 required*

OR
- Stroke, TIA or Systemic embolus

Rivaroxaban

20 mg daily
15 mg for Cr Cl 30-49 ml/min

Randomize
Double Blind / Double Dummy
(n ~ 14,000)

Warfarin

INR target - 2.5
(2.0-3.0 inclusive)

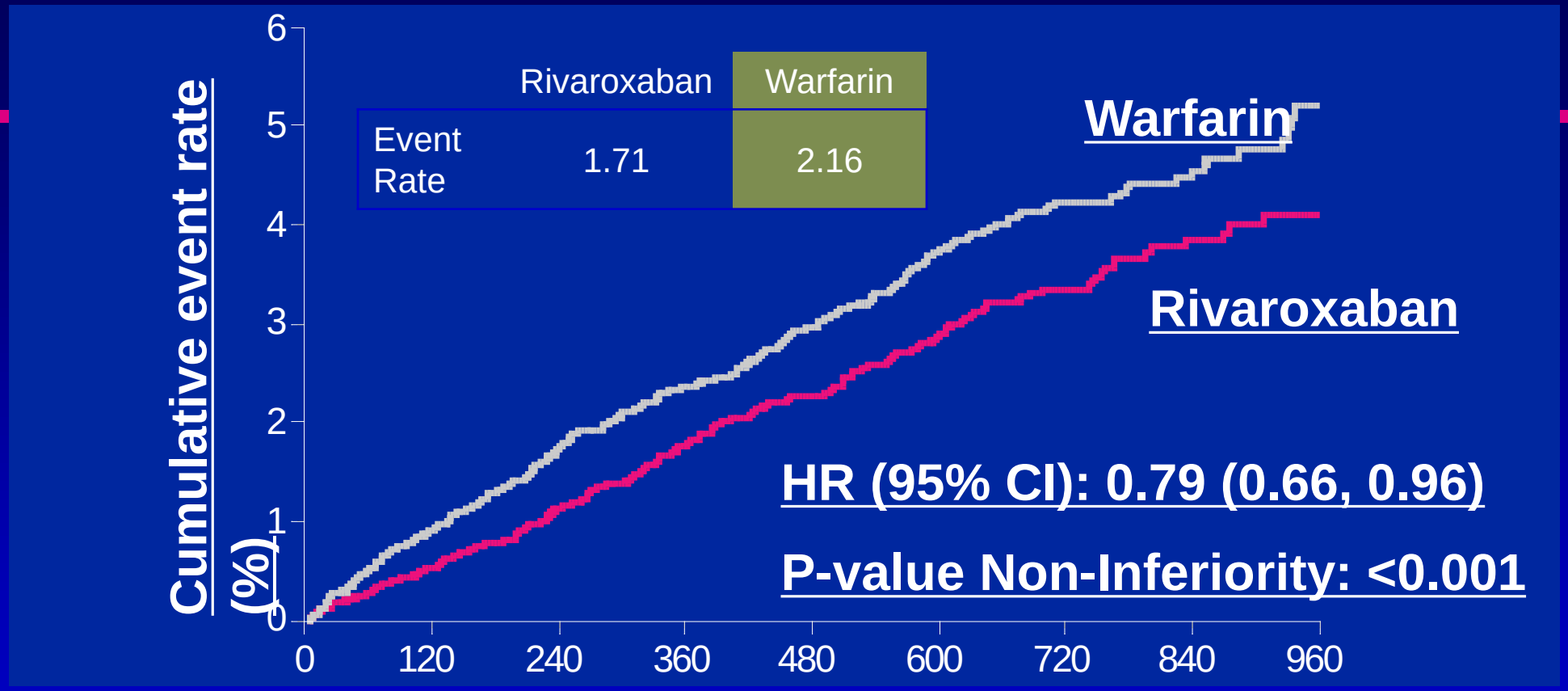
Monthly Monitoring
Adherence to standard of care guidelines

Primary Endpoint: Stroke or non-CNS Systemic Embolism

* Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%

Rocket AF: Primary Efficacy Outcome

Stroke and non-CNS Embolism

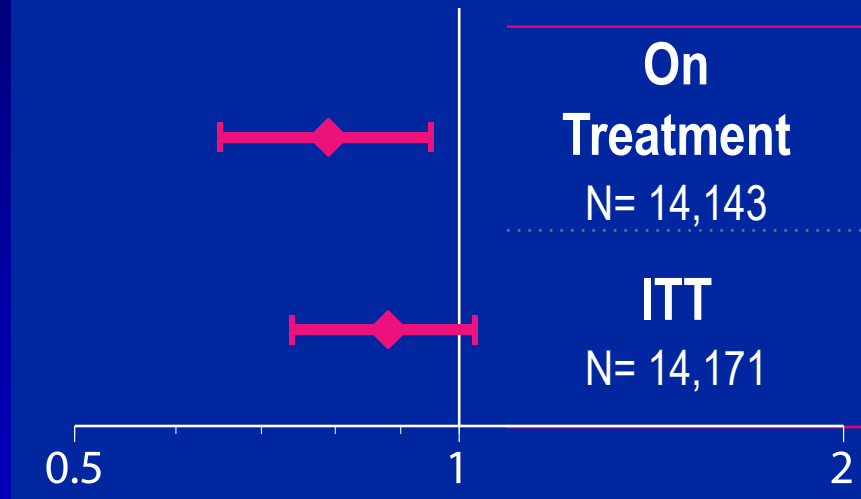


No. at risk:									
Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

Event Rates are per 100 patient-years

Based on Protocol Compliant on Treatment Population

Primary Efficacy Outcome
Stroke and non-CNS Embolism



	Rivaroxaban Event Rate	Warfarin Event Rate	HR (95% CI)	P-value
On Treatment N= 14,143	1.70	2.15	0.79 (0.65,0.95)	0.015
ITT N= 14,171	2.12	2.42	0.88 (0.74,1.03)	0.117

Event Rates are per 100 patient-years
Based on Safety on Treatment or Intention-to-Treat thru Site Notification populations

Key Secondary Efficacy Outcomes

	Rivaroxaban	Warfarin		
	Event Rate	Event Rate	HR (95% CI)	P-value
Vascular Death, Stroke, Embolism	4.51	4.81	0.94 (0.84, 1.05)	0.265
Stroke Type				
Hemorrhagic	0.26	0.44	0.58 (0.38, 0.89)	0.012
Ischemic	1.62	1.64	0.99 (0.82, 1.20	0.916
Unknown Type	0.15	0.14	1.05 (0.55, 2.01)	0.871
Non-CNS Embolism	0.16	0.21	0.74 (0.42, 1.32	0.308
Myocardial Infarction	1.02	1.11	0.91 (0.72, 1.16)	0.464
All Cause Mortality	4.52	4.91	0.92 (0.82, 1.03)	0.152
Vascular	2.91	3.11	0.94 (0.81, 1.08)	0.350
Non-vascular	1.15	1.22	0.94 (0.75, 1.18)	0.611
Unknown Cause	0.46	0.57	0.80 (0.57, 1.12)	0.195

Event Rates are per 100 patient-years
Based on Intention-to-Treat Population

Primary Safety Outcomes

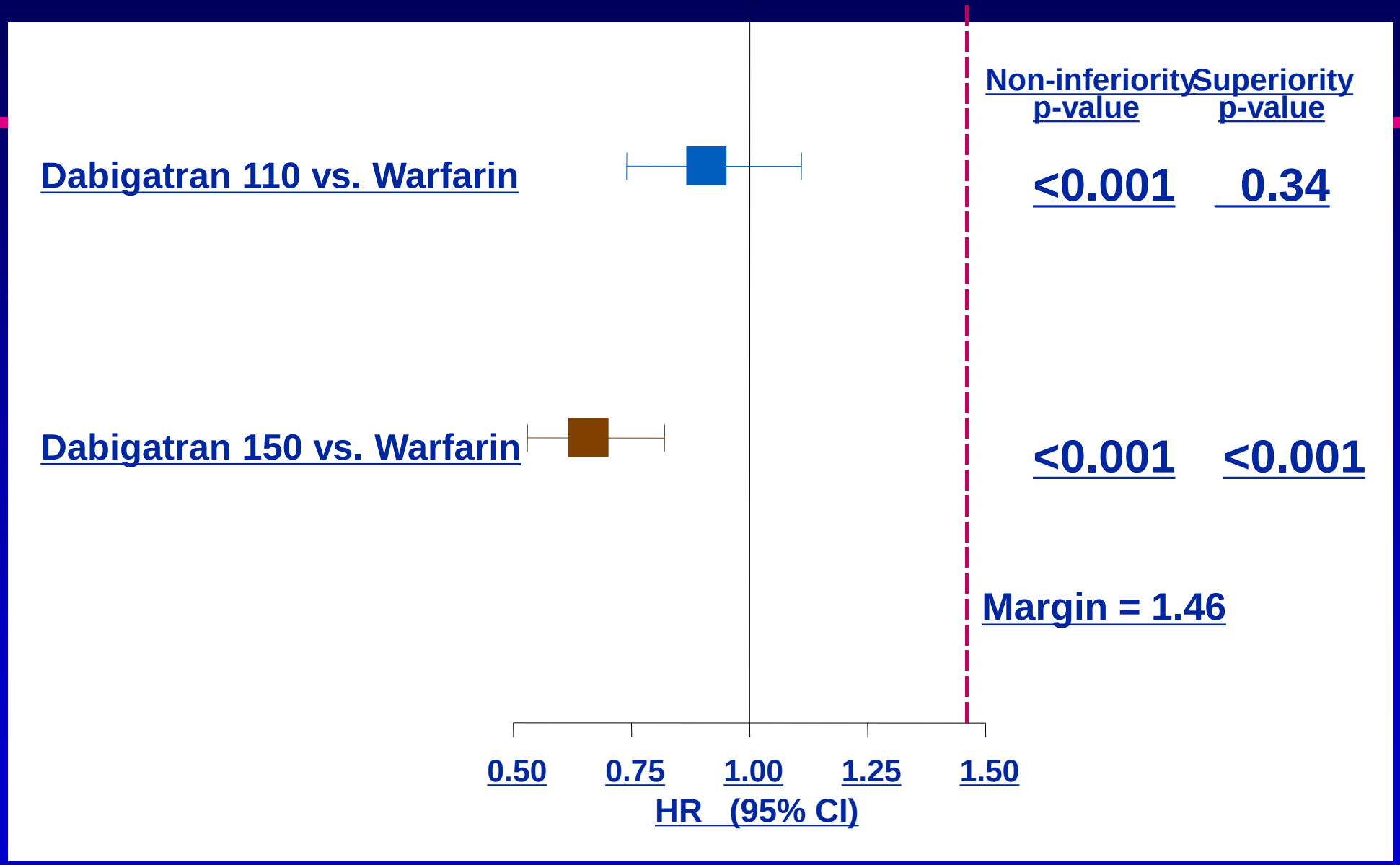
	Rivaroxaban	Warfarin		
	Event Rate or N (Rate)	Event Rate or N (Rate)	HR (95% CI)	P-value
Major	3.60	3.45	1.04 (0.90, 1.20)	0.576
≥2 g/dL Hgb drop	2.77	2.26	1.22 (1.03, 1.44)	0.019
Transfusion (> 2 units)	1.65	1.32	1.25 (1.01, 1.55)	0.044
Critical organ bleeding	0.82	1.18	0.69 (0.53, 0.91)	0.007
Bleeding 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

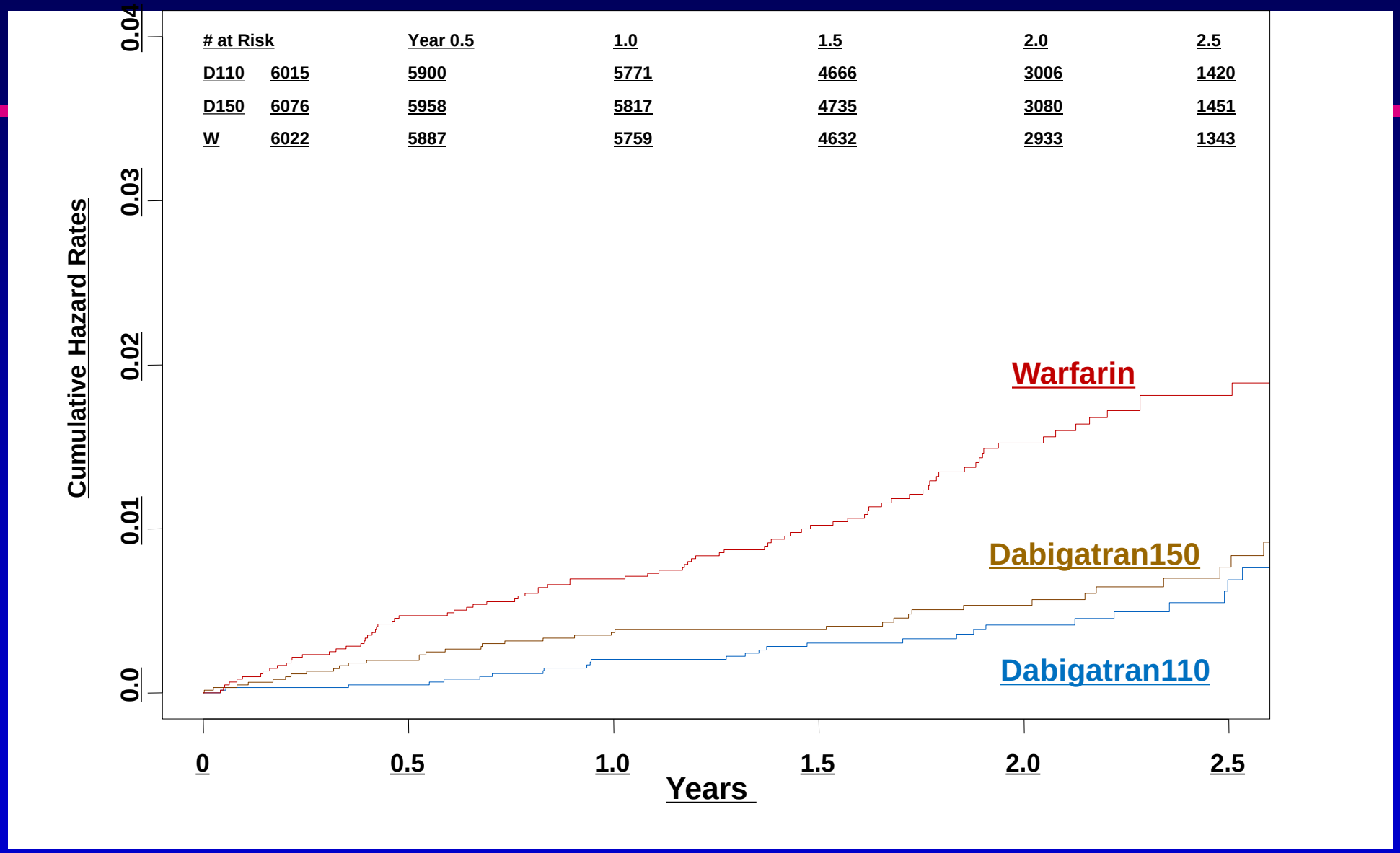
Rocket AF: Conclusions

- **Efficacy:**
  - Rivaroxaban was non-inferior to warfarin for prevention of stroke and non-CNS embolism.
  - Rivaroxaban was superior to warfarin while patients were taking study drug.
  - By intention-to-treat, rivaroxaban was non-inferior to warfarin but did not achieve superiority.
- **Safety:**
  - Similar rates of bleeding and adverse events.
  - Less ICH and fatal bleeding with rivaroxaban.
- **Conclusion:**
  - Rivaroxaban is a proven alternative to warfarin for moderate or high risk patients with AF.

RE-LY: Stroke or Systemic Embolism



RE-LY: All Intracranial Bleeding



# at Risk		Year 0.5	1.0	1.5	2.0	2.5
D110	6015	5900	5771	4666	3006	1420
D150	6076	5958	5817	4735	3080	1451
W	6022	5887	5759	4632	2933	1343

TRENDS: Annualized TE Event Rates

	Annualized Rate	Annualized Rate (Excluding TIAs)
Zero Burden	1.1%/Year	0.5%/Year
Low Burden < 5.5 hours	1.1%/Year	1.1%/Year
High Burden ≥ 5.5 hours	2.4%/Year	1.8%/Year

TRENDS: Results

Cox proportional hazard model adjusting for baseline stroke risk factors & time dependent AT/AF burden & antithrombotic therapy

Variable	Hazard Ratio*	95% Confidence Interval	p-value
Low Burden < 5.5 hours	0.98	0.34 to 2.82	0.97
High Burden ≥ 5.5 hours	2.20	0.96 to 5.05	0.06

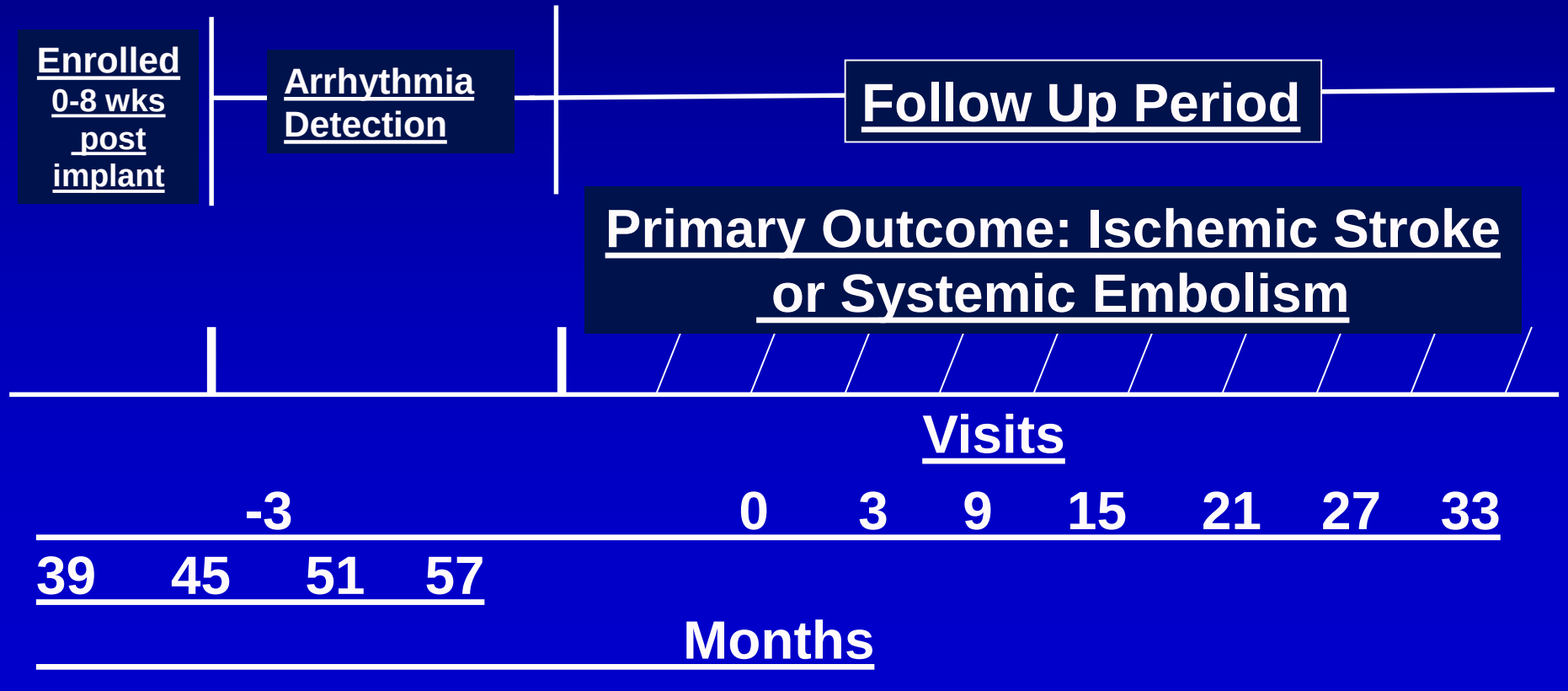
compared to no AT/AF burden

Study Design

Prospective Cohort Design

To determine if device-detected atrial tachyarrhythmias are associated with an increased risk of stroke or embolism?

Minimum Follow up	1.75 yrs
Maximum Follow Up	5 yrs
Median Follow Up	2.8 yrs



ASSERT: Study Design

- **Patient Eligibility**
  - Enrolled after new dual-chamber pacemaker or ICD
  - Age ≥ 65 years
  - History of hypertension
  - Excluded if any history of AF
  - Excluded if on Vitamin K antagonist
- **Pre-specified primary analysis:**
  - Monitor from enrolment to 3 month visit for atrial tachyarrhythmia defined as >6 minutes and an atrial rate of >190 bpm
  - Prospective follow up for ischemic stroke or systemic embolism from 3 month visit onwards
- **Statistical power to detect ≥ 1% per year increase in primary outcome**
- **Adjudication of all available AHRE**

ASSERT: Study Results

- 2580 patients enrolled following implant of first pacemaker or ICD (St. Jude Medical)
  - 2451 pacemaker, 129 ICD patients
- 136 participating centres, 23 countries
- Mean follow up 2.8 yrs
- 36% of patients had at least one device-detected atrial tachyarrhythmia
  - >6 min, >190 bpm; at mean FU of 2.8 years
- Cumulative rate of VKA use <2% per year

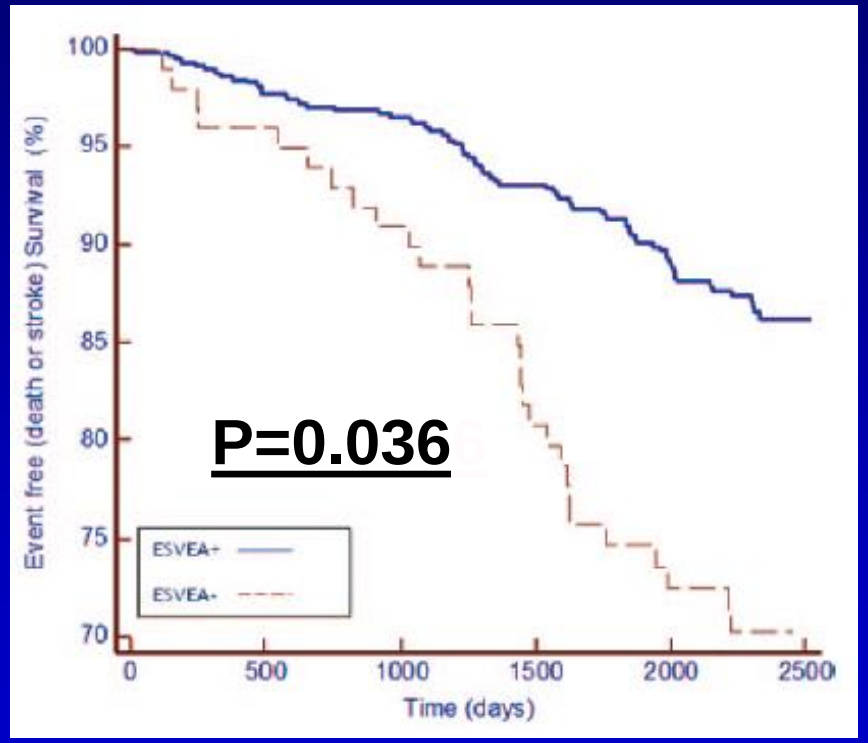
ASSERT: Relationship between AHRE and Stroke

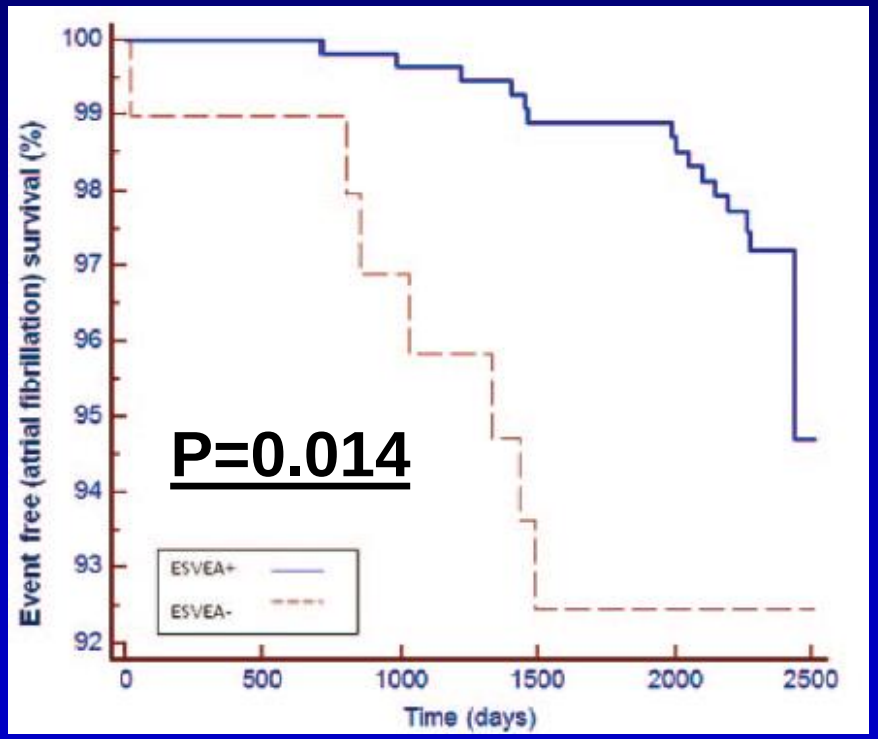
- In ASSERT, 59 patients had stroke or SE
- 30 had no AHRE
  - 9 had AHRE but only AFTER their stroke
- 20 patients had at least one AHRE > 6 minutes prior to their stroke or SE
  - 3 developed persistent AF at least one month before, but only recognized clinically in 1 pt.
  - 2 patients had 9-day long episodes 1-2 weeks prior
  - 1 patient had 2.7 hour episode beginning 48 hours prior
  - None of remaining 14 pts. had ANY AHRE > 6 minutes in 30 days before stroke or SE

Beyond the Pacemaker Population

- Copenhagen Holter Study (COHORT)
  - Circulation 2010; 121
  - 678 healthy men and women
  - 55-75 years old
- One 48 hour holter
- Positive defined as > 30 PACs per hour or any run ≥ 20 beats
- Mean follow-up of 6.3 years

Outcomes of Cohort Study

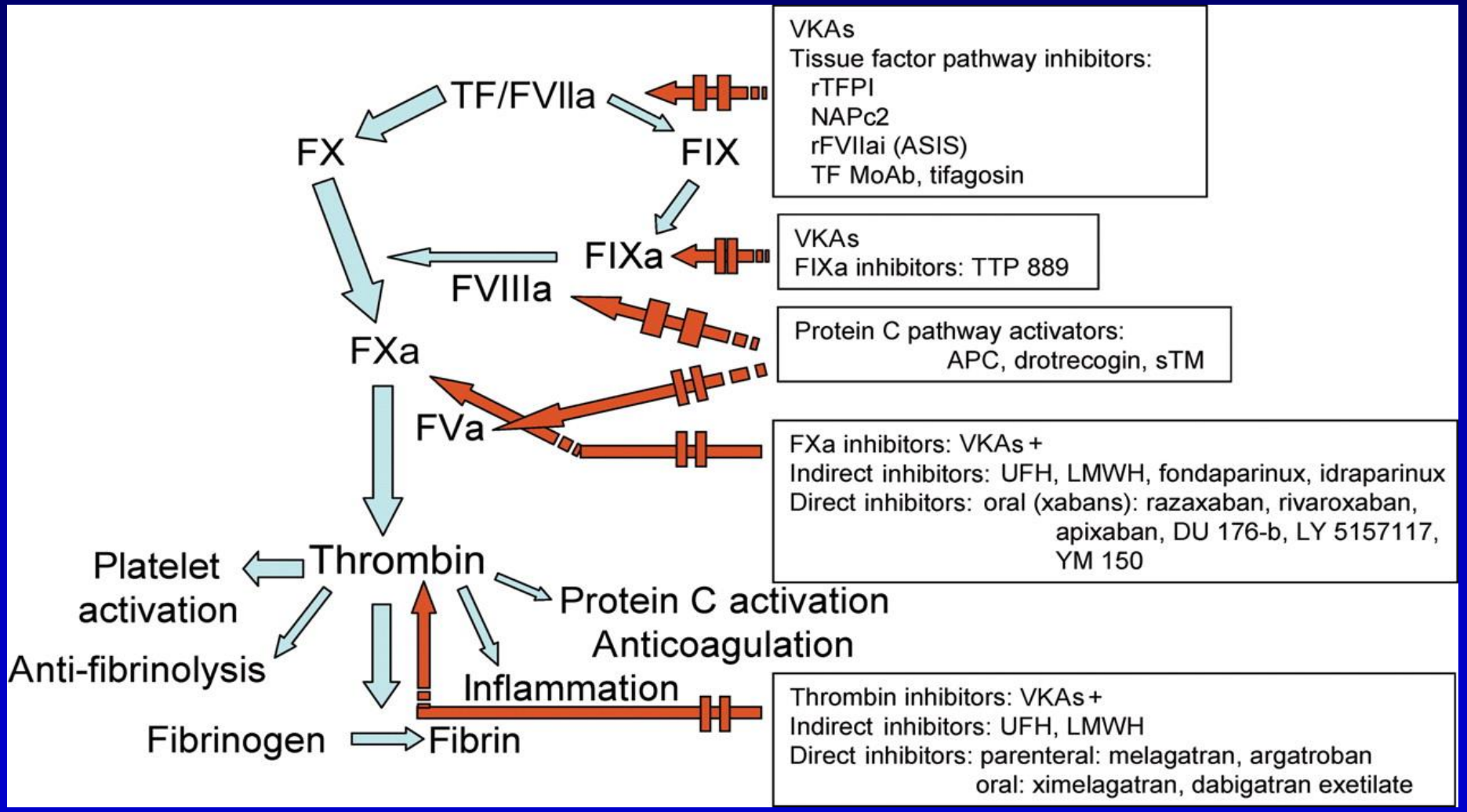




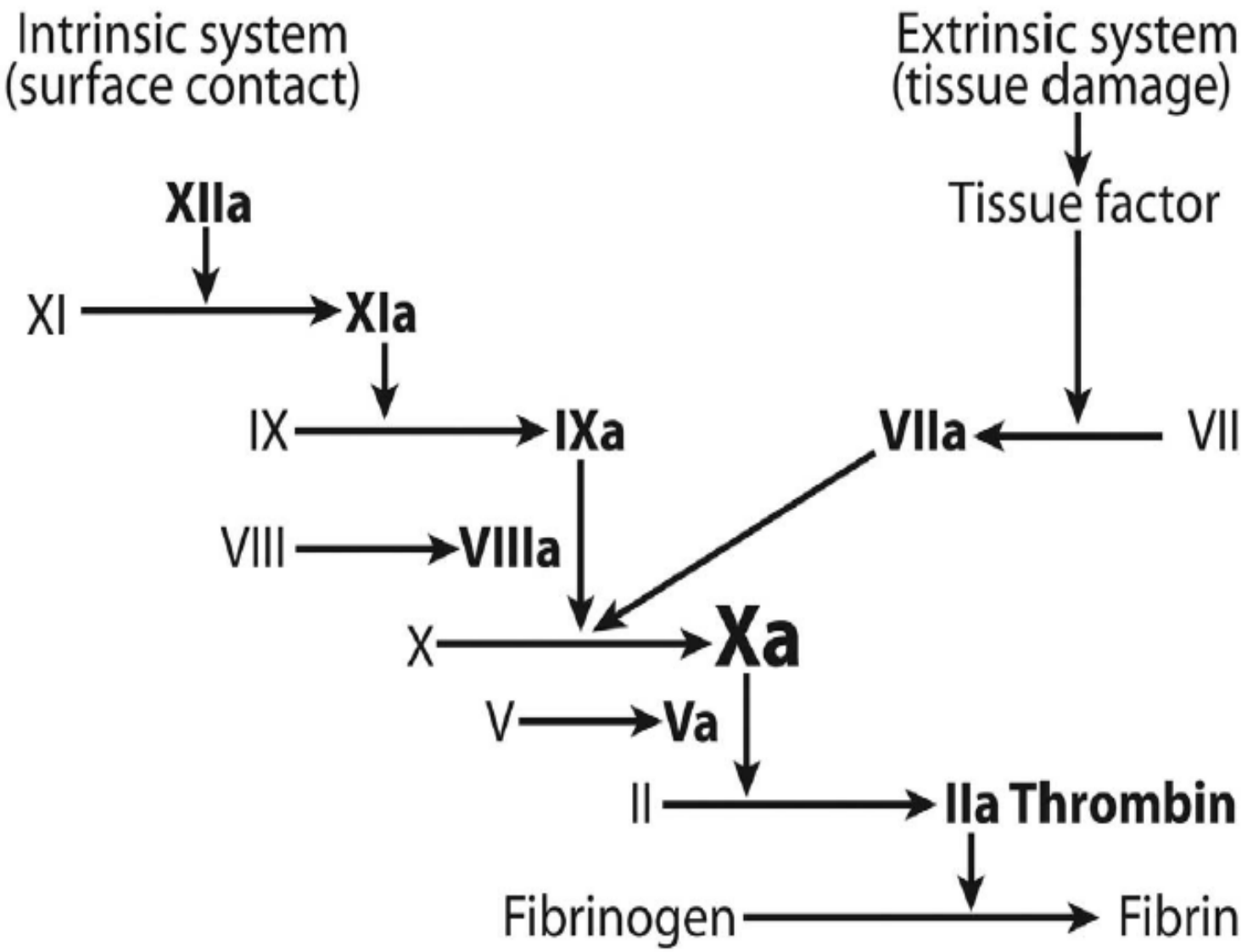
Death or Stroke

Hospitalization for AF

Clotting Cascade and ACs

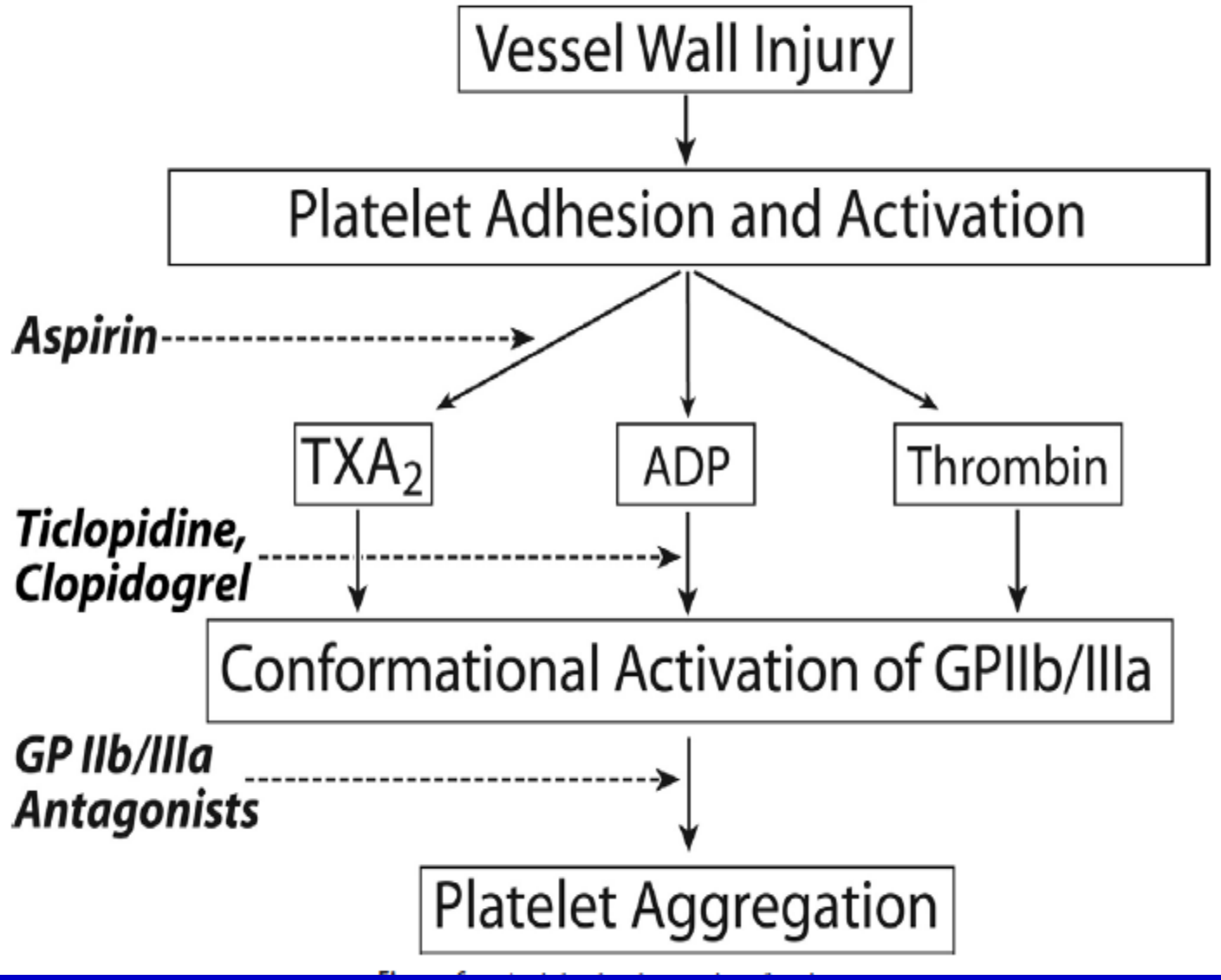


Classical Coagulation Cascade



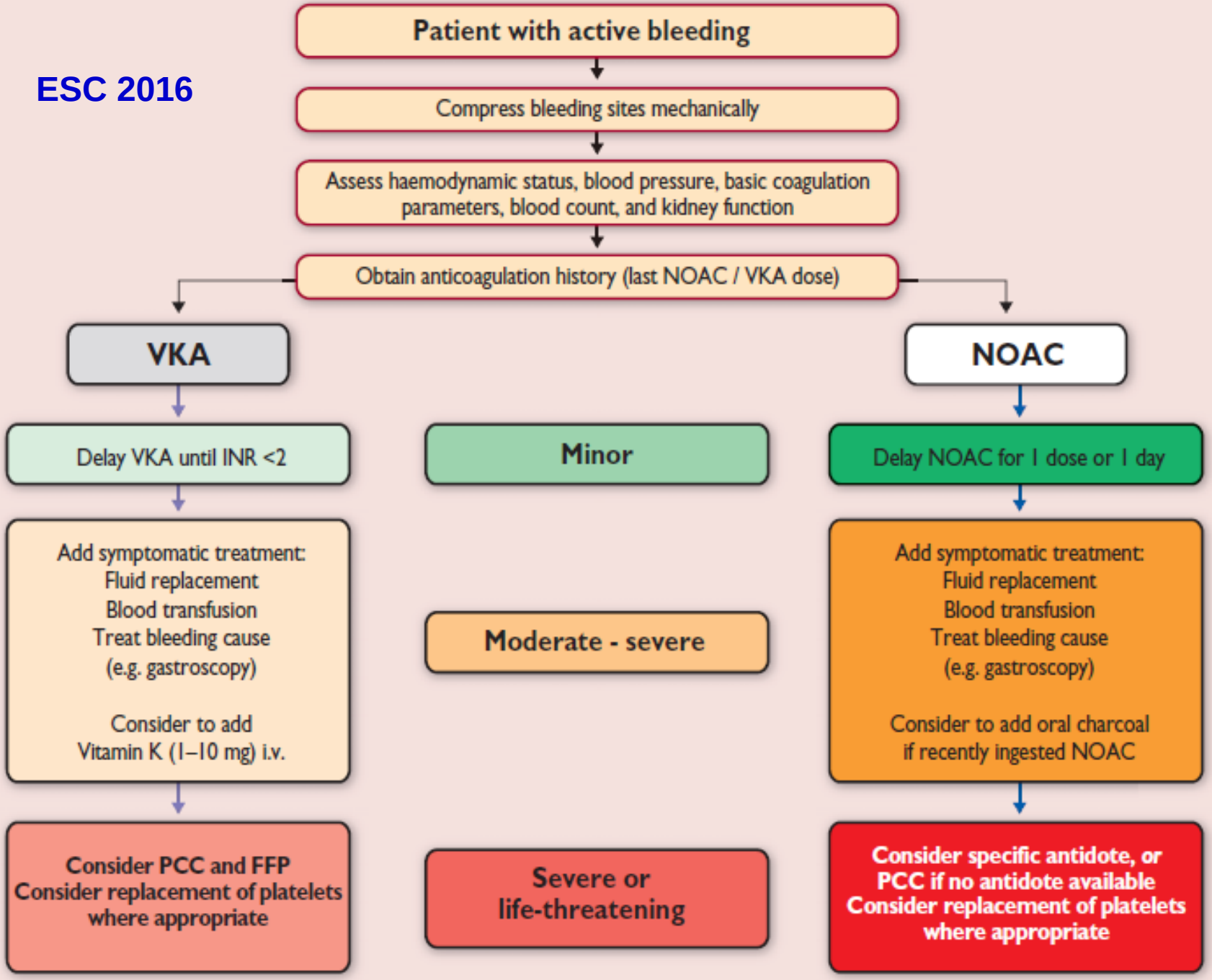
Jay, Lui 2006

Antiplatelet Drugs



Jay, Lui 2006

ESC 2016


Patient with active bleeding
Compress bleeding sites mechanically
Assess haemodynamic status, blood pressure, basic coagulation parameters, blood count, and kidney function
Obtain anticoagulation history (last NOAC / VKA dose)
VKA
NOAC
Delay VKA until INR <2
Minor
Delay NOAC for 1 dose or 1 day
Add symptomatic treatment:
Fluid replacement
Blood transfusion
Treat bleeding cause
(e.g. gastroscopy)
Consider to add
Vitamin K (1–10 mg) i.v.
Moderate - severe
Add symptomatic treatment:
Fluid replacement
Blood transfusion
Treat bleeding cause
(e.g. gastroscopy)
Consider to add oral charcoal
if recently ingested NOAC
Consider PCC and FFP
Consider replacement of platelets
where appropriate
Severe or
life-threatening
Consider specific antidote, or
PCC if no antidote available
Consider replacement of platelets
where appropriate