10:45 – 11:45 am

Practical Considerations for Anticoagulation for Prevention of Venous Thromboembolism and Stroke Due to Atrial Fibrillation

SPEAKER
Christian Ruff, MD, MPH

Presenter Disclosure Information

The following relationships exist related to this presentation:

- Christian Ruff, MD, MPH: Advisory Board for Boehringer Ingelheim Pharmaceuticals, Inc. and Daiichi Sankyo. Consultant for Boehringer Ingelheim Pharmaceuticals, Inc. and Daiichi Sankyo.

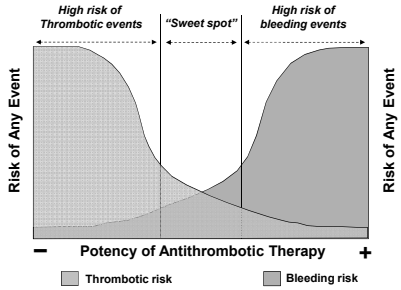
Off-Label/Investigational Discussion

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Learning Objectives

- **Implement appropriate risk stratification for patients with atrial fibrillation (AF).**
- **Assess the risks and benefits of oral anticoagulation options for stroke prevention in patients with AF.**
- **Select and initiate an appropriate anticoagulant strategy for patients at risk for recurrent venous thromboembolism (VTE).**

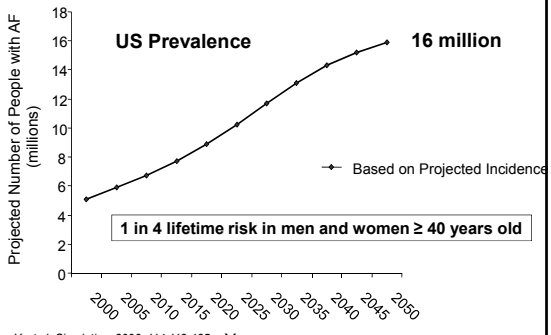
Anticoagulation: Balancing Risks



Adapted from Ferreiro JL et al. Thromb Haemost. 2010;103:1-8.

Stroke Prevention in Atrial Fibrillation

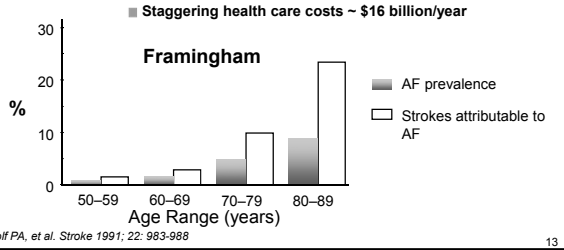
Atrial Fibrillation: An Epidemic



Miyakasa Y, et al. Circulation. 2006; 114:119-125.

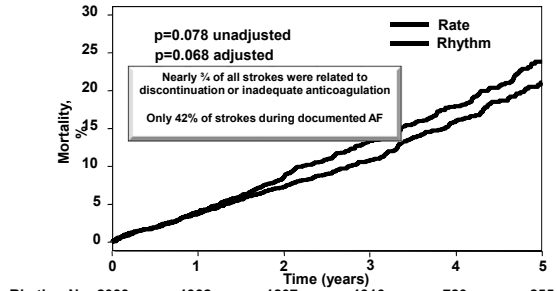
Stroke in AF

- Approximately 5X increased risk of stroke
- Risk varies significantly depending on clinical factors
- Embolic strokes from AF have worse outcomes
- Substantial morbidity and mortality
- Staggering health care costs ~ $16 billion/year



Wolf PA, et al. Stroke 1991; 22: 983-988

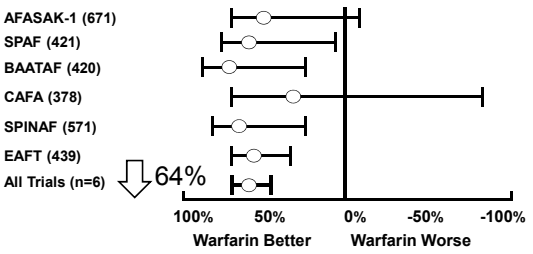
AFFIRM: Rate vs. Rhythm Control



Rhythm N:	2033	1932	1807	1316	780	255
Rate N:	2027	1925	1825	1328	774	236

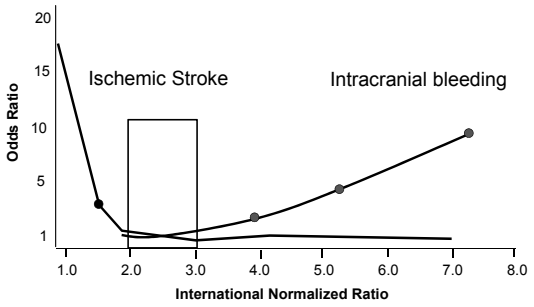
The AFFIRM Investigators. N Engl J Med. 2002;347:1825-1833.

Stroke Prevention in AF Warfarin vs. Placebo



Hart RG, et al. Ann Intern Med 2007;146:857-867.

Efficacy and Safety of Warfarin



Fang MC, et al. Ann Intern Med 2004; 141:745.
Hylek EM, et al. N Engl J Med 1996; 335:540.

$CHADS_2$ Risk Score

Risk Factor	Points
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75	1
Diabetes Mellitus	1
Stroke or TIA	2
Maximum Score	6

$CHADS_2$	Stroke (% / yr)	
0	1.9	40-50% of Patients
1	2.8	3% / year
2	4.0	
3	5.9	
4	8.5	
5	12.5	
6	18.2	

Gage BF, et al. JAMA. 2001;285:2864-2870.
VanWalraven C, et al. Arch Intern Med 2003; 163:936.
Nieuwlaat R, et al. (EuroHeart survey) Eur Heart J 2006 (E-published).
Go A, et al. JAMA 2003; 290: 2685.
Gage BF, et al. Circulation 2004; 110: 2287.

Redefining Risk: CHA_2DS_2-VASc

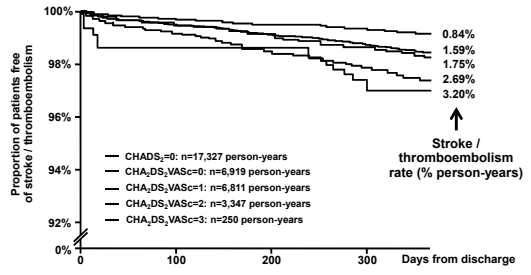
Risk Factor	Points
CHF / LV Dysfunction	1
Hypertension	1
Age ≥ 75	2
Diabetes Mellitus	1
Stroke / TIA / Embolism	2
Vascular Disease	1
Age 64-74	1
Sex Category (female)	1
Maximum Score	9

CHA_2DS_2-VASc Score	Stroke (% / yr)
1	0 %
2	1.3 %
3	2.2 %
4	4.0 %
5	6.7 %
6	9.8 %
7	9.6 %
8	6.7 %
9	15.2 %

ESC Guidelines: Eur Heart J . 2010;31:2369-2429.

CHA_2DS_2VASc refines Stroke Risk Stratification in $CHADS_2$=0

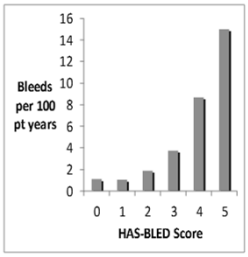
A nationwide Danish cohort study in 47,576 non-warfarin treated non-valvular AF patients with a $CHADS_2$ score = 0-1 at baseline (1997-2008)



Olesen et al. Thromb Haemost 2012; 107:1172-1179

Redefining Risk: 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



Pisters R, et al. Chest 2010; 138(5): 1093-1100

ESC Guidelines: Eur Heart J . 2010;31:2369-2429

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Anticoagulation in AF Benefit vs. Risk

For every 1000 patients with AF in clinical trials treated with warfarin for 1 year

Benefit	Risk
35 fewer thromboembolic events	1 more intracranial or major bleed

Adapted from Alberts et al. Ann Neurol 1991;30:511-518.

Reasons for Underuse of Anticoagulation

- Real contraindications
- Unwillingness from patient's side
- Doctor's perception of patient's unsuitability
  - The frail patient
  - The elderly patient
  - History of falls

De Caterina & Hylek. Am J Med 2011;124:793-799

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Anticoagulation in Patients at Risk For Falls

"…persons taking warfarin must fall about 295 (535/1.81) times in 1 year for warfarin **not** to be the optimal therapy…"

Man-Son-Hing M, et al. Arch Intern Med 1999;159:677-685

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Limitations of Warfarin

- Delayed onset/offset
- Multiple food and drug interactions
- Genetic variability in metabolism (VKORC1 and CYP2C9)
- Requires frequent monitoring of INR due to limited therapeutic index

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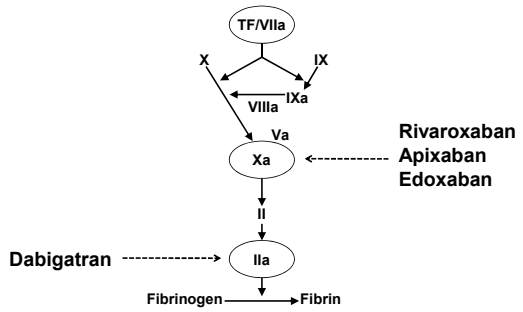
NOACS
Novel or Non-Vitamin K Oral Anticoagulants

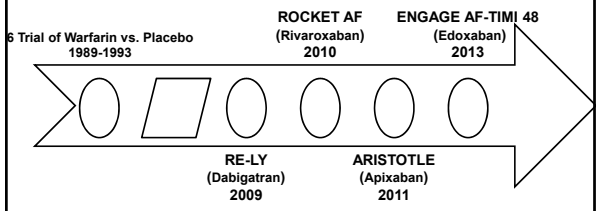


Adapted from: Weitz JI, Bates SM. J Thromb Haemost 2005;3:1843-1853.

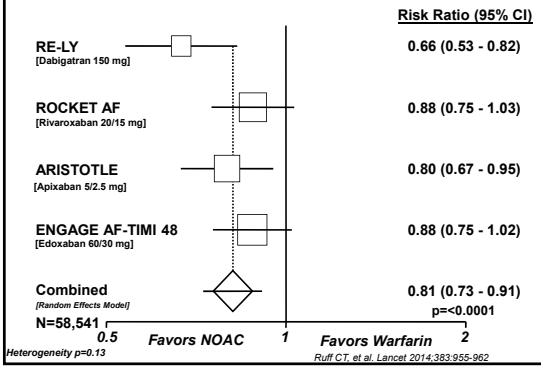
Pivotal Warfarin-Controlled Trials
Stroke Prevention in AF

Warfarin vs. Placebo
2,900 Patients

NOACs vs. Warfarin
71,683 Patients



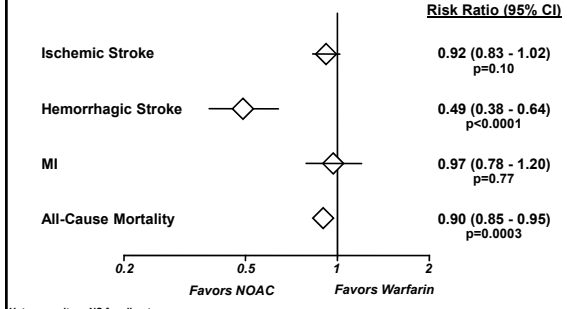
All NOACS: Stroke or Systemic Embolic Event (SEE)



Heterogeneity p=0.13

Ruff CT, et al. Lancet 2014;383:955-962

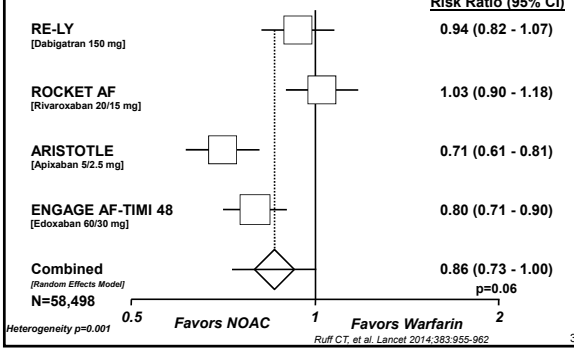
Secondary Efficacy Outcomes



Heterogeneity p=NS for all outcomes

Ruff CT, et al. Lancet 2014;383:955-962

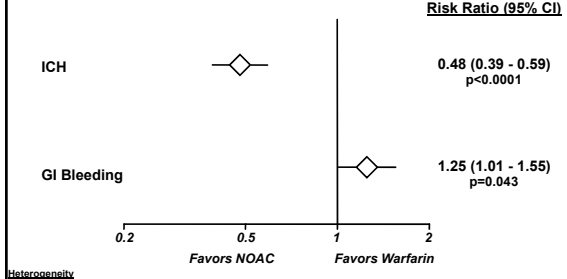
All NOACS: Major Bleeding



Heterogeneity p=0.001

Ruff CT, et al. Lancet 2014;383:955-962

Secondary Safety Outcomes



Heterogeneity
ICH, p=0.22
GI Bleeding, p=0.009

Ruff CT, et al. Lancet 2014;383:955-962

Limitations of NOACs

- Problem of missed doses due to short biologic effect
- No easy way to verify compliance
- Tends to cause more gastrointestinal bleeding compared with warfarin
- Requires adjusting dose if renal function worsens
- Cost

Comparison of New AF Guidelines

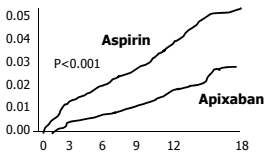
Risk Profile	Recommended Therapy	
	ESC 2012	AHA/ACC/HRS 2014
No risk factors CHA_2DS_2-VASc= 0	Nothing	Nothing
CHA_2DS_2-VASc= 1	NOAC > VKA	Nothing or ASA or OAC
CHA_2DS_2-VASc $\geq$ 2	NOAC > VKA	NOAC or VKA
Mechanical Valve	Warfarin: INR 2.0-3.0 for aortic Warfarin: INR 2.5-3.5 for mitral	

VKA = vitamin K antagonist

ESC Guidelines: Eur Heart J . 2012; 33:2719-2247.
AHA/ACC/HRS Guidelines. JACC 2014 [on-line March 28].

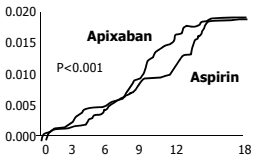
AVERROES: The End for Aspirin?

Stroke or SEE



HR 0.45 (0.32-0.62)

Major Bleeding



HR 1.13 (0.74-1.75)

Connolly SJ, et al. N Engl J Med 2011 (epub)

Conclusions

- A refinement of risk prediction strategies will result in a *greater proportion of patients* being eligible for anticoagulation.
- Physicians and patients tend to *overestimate bleeding risks* with anticoagulation.
- Warfarin remains a *very effective and affordable anticoagulant* for many patients.
- New therapies provide *more convenient anticoagulation with a lower risk of bleeding.*

Treatment of Venous Thromboembolism

Pulmonary Emoblism: Significant Mortality

- 100,000-180,000 PE-related deaths occur annually in the U.S. alone.
- PE is the most preventable cause of death among hospitalized patients.

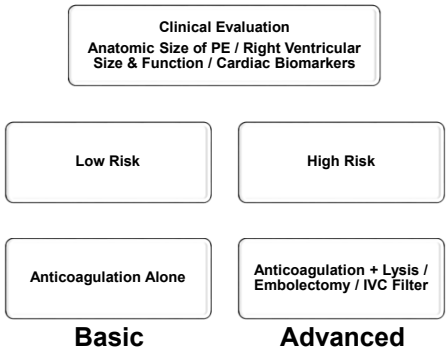
www.surgeongeneral.gov/topics/deepvein/calltoaction

Definitions of PE: AHA PE Guidelines 2011

- **Massive PE (5-10%): sustained hypotension, pulselessness, or persistent bradycardia**
- **Submassive PE (20-25%): RV dysfunction or myocardial necrosis, without hypotension**
- **Low Risk PE (70%): no markers of adverse prognosis**

Circulation 2011; 123: 1788-1830

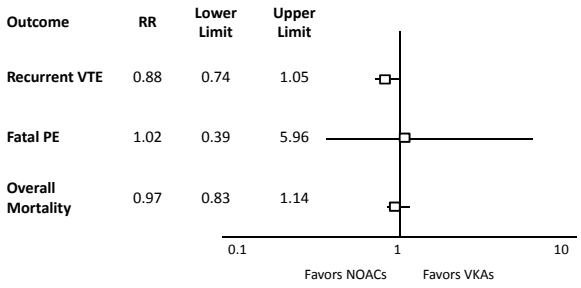
Risk Stratification & Treatment



Acute VTE Treatment Trials

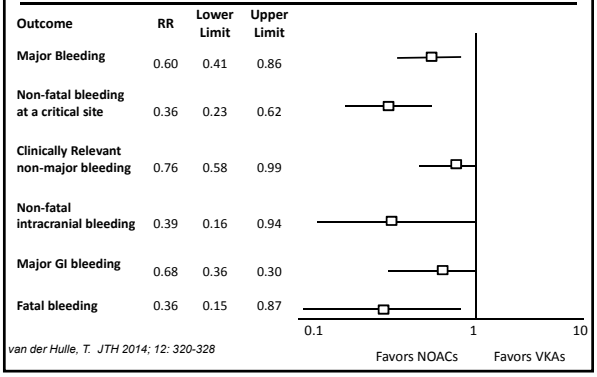
Trial	Initial Heparin/ Fondaparinux	Duration (months)	Regimen
Rivaroxaban			
EINSTEIN DVT	No	3, 6, or 12	Daily
EINSTEIN PE	No	3, 6, or 12	Daily
Dabigatran			
RE-COVER	Yes	6	Twice Daily
RE-COVER II	Yes	6	Twice Daily
Apixaban			
AMPLIFY	No	6	Twice Daily
Edoxaban			
Hokusai-VTE	Yes	3–12	Daily

NOAC vs. Warfarin: Acute VTE Efficacy



van der Hulle, T. JTH 2014; 12: 320-328

NOAC vs. Warfarin: Acute VTE Safety



van der Hulle, T. JTH 2014; 12: 320-328

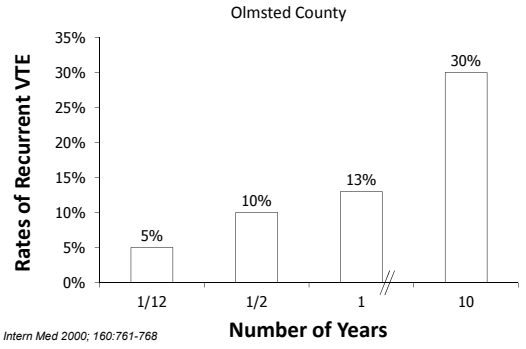
ACUTE VTE Treatment

- All 4 NOACs are similar to low molecular weight heparin / warfarin for efficacy.
- Meta-analysis (N=24,455)*: NOACS 40% lower major and 64% lower fatal bleeding than low molecular weight heparin / warfarin.
- Edoxaban: prespecified submassive PE subgroup showed superiority.

* Edoxaban is not currently approved by the FDA

**van der Hulle, T. JTH 2014; 12: 320-328*

Rates of Recurrent VTE



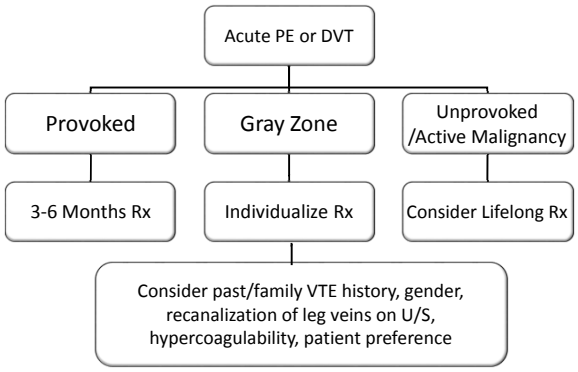
Arch Intern Med 2000; 160:761-768

Predictors of Recurrence

1) Immobilization
2) Cancer
3) Overweight, obesity
4) Male gender
5) Family history and thrombophilia
6) Symptomatic PE
7) Elevated D-dimer after d/c anticoagulant
8) Failure to recanalize leg veins

Goldhaber SZ, Piazza G. Circulation 2011;123:664-667

Optimal Duration Strategy



Goldhaber, Piazza. Circ 2011; 123: 664-667

CHEST ACCP Guidleines 2012 Duration of Treatment

- **If provoked by surgery or a nonsurgical transient risk factor, anticoagulation for 3 months (Grade 1B).**
- **If unprovoked with low to moderate bleeding risk, we suggest extended anticoagulant therapy rather than 3 months (Grade 2B).**

CHEST 2012; 141(2)(Suppl):e419S-e494S

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Long-term Rx After 6-12 Months Standard Anticoagulation

Drug/ Dose	Reduction vs Placebo	Citation
Warfarin (INR 2-3)	95%	NEJM 1999
Warfarin (INR 1.5-2)	64%	NEJM 2003: Ridker "PREVENT"
Aspirin 100 mg	32%	NEJM 2012; "WARFASA"/ "ASPIRE"
Rivaroxaban 20 mg	82%	NEJM 2010; "EINSTEIN-EXT"
Apixaban 2.5 mg	80%	NEJM 2013; "AMPLIFY-EXT"
Dabigatran 150 mg	92%	NEJM 2013; "RE-SONATE"

Take Home Messages

- **Warfarin and NOACs offer *effective and safe* acute and extended PE/ DVT therapy.**
- **NOACS tend to have a *lower bleeding risk* than warfarin.**
- **Consider *indefinite duration anticoagulation for idiopathic VTE* because recurrence rate is high.**

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Unresolved Questions in Clinical Practice

- Do clinical trials results apply to patients in the "real world"?
- What is non-valvular AF?
- How to manage bleeding with NOACs?
- Are NOACs safe to use NOACs without an antidote?

FDA Dabigatran Medicare Study 2014 (N=134,000)

	Incidence rate per 1,000 person-years		Adjusted hazard ratio (95% CI)
	Dabigatran	Warfarin	
Ischemic stroke	11.3	13.9	0.80 (0.67-0.96)
Intracranial hemorrhage	3.3	9.6	0.34 (0.26-0.46)
Major GI bleeding	34.2	26.5	1.28 (1.14-1.44)
Acute MI	15.7	16.9	0.92 (0.78-1.08)
Mortality	32.6	37.8	0.86 (0.77-0.96)

Table 1. Incidence rates and adjusted hazard ratios comparing matched new user cohorts treated with dabigatran 75 mg or 150 mg* or warfarin for non-valvular atrial fibrillation based on 2010-2012 Medicare data. Warfarin is the reference group.

* Primary findings for dabigatran are based on analysis of both 75 and 150 mg together without stratification by dose.

http://www.fda.gov/Drugs/DrugSafety/ucm396470.htm.

"Non-Valvular" AF: A Misnomer

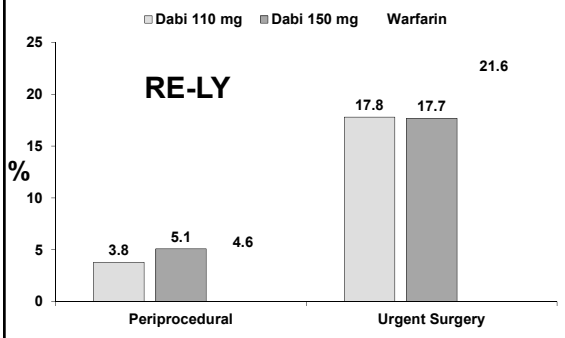
ARISTOTLE: 26% of patients had a history of moderate or severe valvular heart disease

Any Valvular Heart Disease*	4,808	100.0%
Any mitral valve disease	3,578	74.4%
Any aortic valve disease	1,150	23.9%
Tricuspid regurgitation	2,124	44.2%
Prior valve surgery	251	5.2%

*Patients may be included in more than one category.

Avezum A, et al. Eur Heart J 2013;34(Abst_Suppl):809.

Peri-procedural Major Bleeding



Healey JS, et al. Circulation 2012; 126:343-348

Coagulation Tests

Test	Apixaban/Rivaroxaban/Edoxaban	Dabigatran
Qualitative Present / Absent	PT rivaroxaban>edoxaban>apixaban [sensitivity depends on reagents]	TT>aPTT
Quantitative test	Chromogenic anti-FXa [requires specific calibration to drug]	Dilute TT, chromogenic anti-FIIa [requires specific calibration]

- Normal PT or aPTT *does not guarantee* absence of anticoagulant effect
- Quantitative tests are not standardized or FDA approved

Tripodi A, et al. Thromb Haemost 2011; 105:735-736
Barrett YC, et al. Thromb Haemost 2010; 104:1263-1271
van Ryn J, et al. Thromb Haemost 2010; 103:1116-1127
Stangier J, et al. Br J Clin Pharmacol 2007; 64:292-303
Cuker A, et al. JACC 2014; 64(11):1128-1139

Non-Specific Reversal Agents

Only After D/C drug and Supportive Care (fluids / transfusions)

Agent	Clotting Factors Replaced	Dose
4 Factor-PCC	Factors II, VII, IX, X	25-50 units/kg
3 Factor-PCC	Factors II, IX, X	25-50 units/kg
aPCC	Factors II, VIIa, IX, X	80 units/kg
rFVIIa	FVIIa	90 ug/kg

Antidotes in Development

Idarucizumab (BI 655075)
Target: Dabigatran
Structure: Humanized antibody fragment (FAb) to dabigatran

Andexanet alpha (PRT064445)
Target: FXa inhibitors
Structure: FXa lacking catalytic & binding activity

Aripazine (PER977; Ciraparantag)
Target: Universal - all NOACs, heparin, LMWH
Structure: Synthetic small molecule (D-arginine)