Newer Oral Anticoagulants

What is the Hype?

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I have no disclosures


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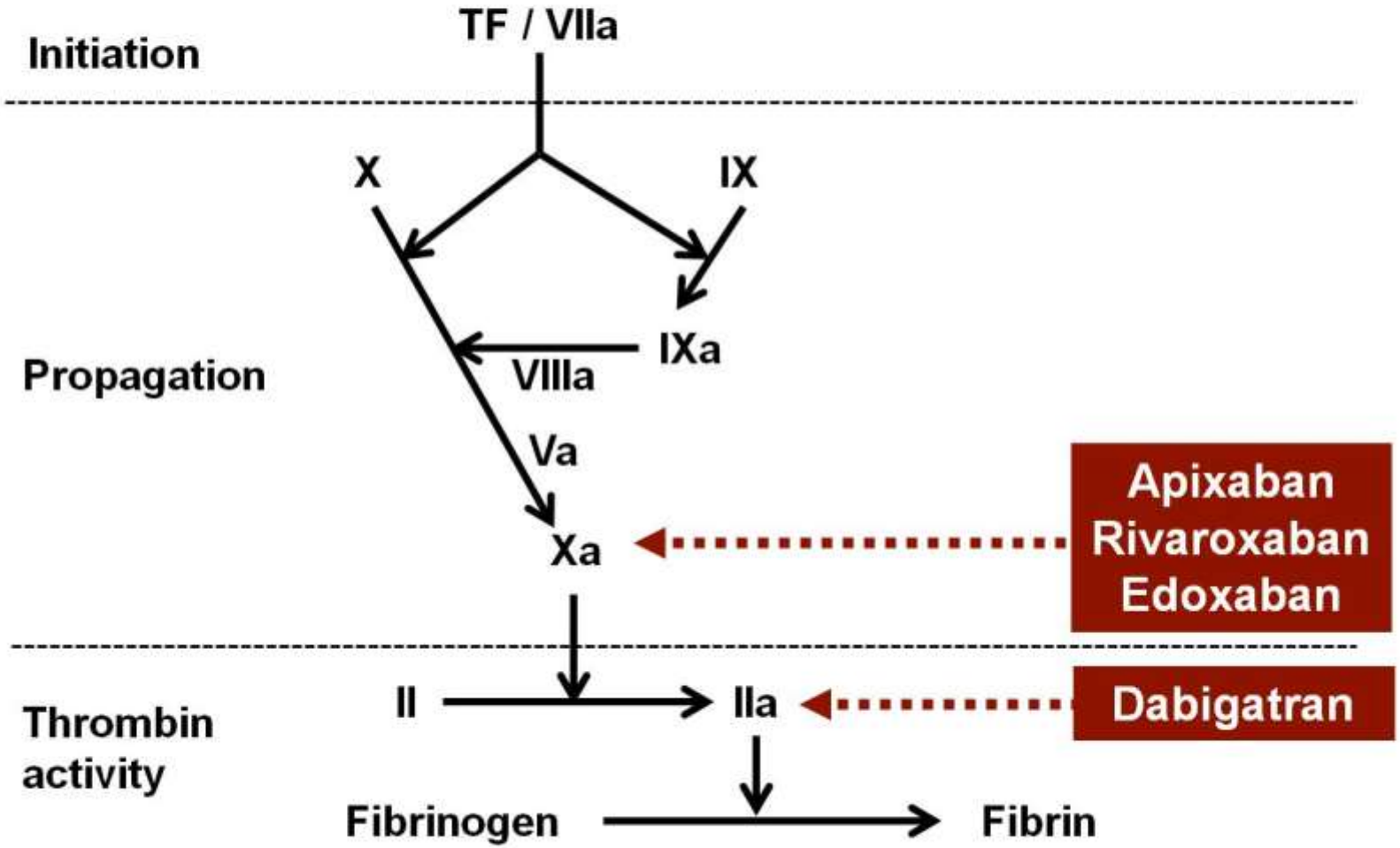
Why the hype?

Effects of Warfarin

- Acts by inhibiting vitamin K
- Interactions with food and drugs
- Narrow therapeutic window
- Individualised dosing
- INR monitoring

Mechanism of Action of NOACs

Sites of Action in Coagulation System Novel Factor Xa and DT Inhibitors



Weitz JI, Bates SM. *J Thromb Haemost.* 2005;3:1843-1853.[1]

Brief Overview of NOACs

	Dabigatran[a]	Rivaroxaban[a,b]	Apixaban[a,c]	Edoxaban[d-f]
Target	IIa (thrombin)	Xa	Xa	Xa
Hours to C_{max}	1.25-3	2-4	3-4	1-2
CYP metabolism	None	32%	Minimal	< 4%
Bioavailability	6%	80%	60%	62%
Transporters	P-gp	P-gp/BCRP	P-gp/ BCRP	P-gp
Protein binding	35%	93%	87%	50%
Half-life	14-17 h	7-11 h	8-15 h	8-10 h
Renal elimination	80%	35%	25%	50%

a. Eriksson BI, et al. *Clin Pharmacokinet*. 2009;48:1-22.[2]
b. Xarelto® PI 2011.[3]
c. Eliquis Summary of Product Characteristics. Bristol Myers Squibb/Pfizer EEIG, UK. 2012.[4]
d. Ruff CT, et al. *Hot Topics in Cardiology*. 2009;18:7-14.[5]
e. Matsushima N, et al. AAPS 2011. Poster T2632.[6]
f. Ogata K, et al. *J Clin Pharmacol*. 2010;50:743-753.[7]

NOACs

Important Comparative Features

Dabigatran

- Oral direct thrombin inhibitor
- Twice-daily dosing
- Renal clearance 80%

Rivaroxaban

- Direct factor Xa inhibitor
- Once daily
- Renal clearance 33%

Apixaban

- Direct factor Xa inhibitor
- Twice-daily dosing
- Renal clearance 25%

Edoxaban

- Direct factor Xa inhibitor
- Once-daily dosing
- Renal clearance 35%

Eikelboom JW, Weitz JI. *Circulation*. 2010;121:1523-1532.[8]

NOACs vs Warfarin

Advantages

- Rapid onset/offset of action
- No food interactions; less drug interactions
- Greater convenience, no need for monitoring
- Lower risk of bleeding complications
- Fixed dosing
- No bridging needed

Disadvantages

- Contraindicated or dose reduction in patients with renal impairment
- Limited availability of measuring drug levels
- Costs
- Short half life
- Twice a day
- Specific antidote not yet available
- Fixed dosing

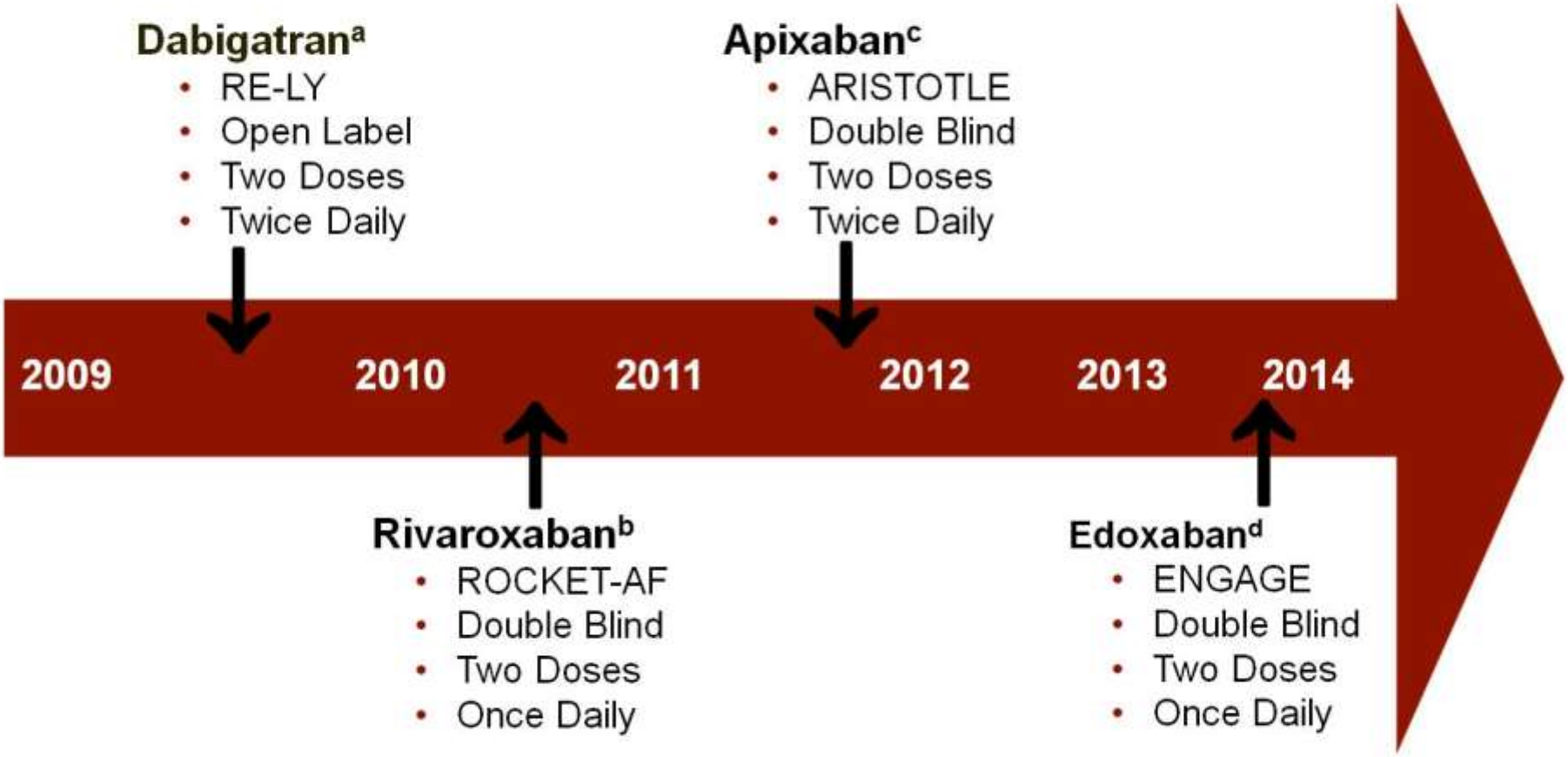
Licensed Uses

1. Stroke prevention in non-valvular AF
2. Prophylaxis of VTE following knee and hip surgery
3. Treatment and prevention of recurrent DVT and PE
4. Use in cancer patients with increased risk of VTE

Licensed Uses - 1

Stroke prevention in non-valvular AF

Novel Anticoagulants for Stroke Prevention in AF



a. Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151.[9]
b. Patel MR, et al. *N Engl J Med*. 2011;365:883-891.[10]
c. Granger CB, et al. *N Engl J Med*. 2011;365:981-992.[11]
d. Giuliano RP, et al. *N Engl J Med*. 2013;369:2093-2104.[12]

AF Studies
Superior Outcomes

Hemorrhagic Stroke

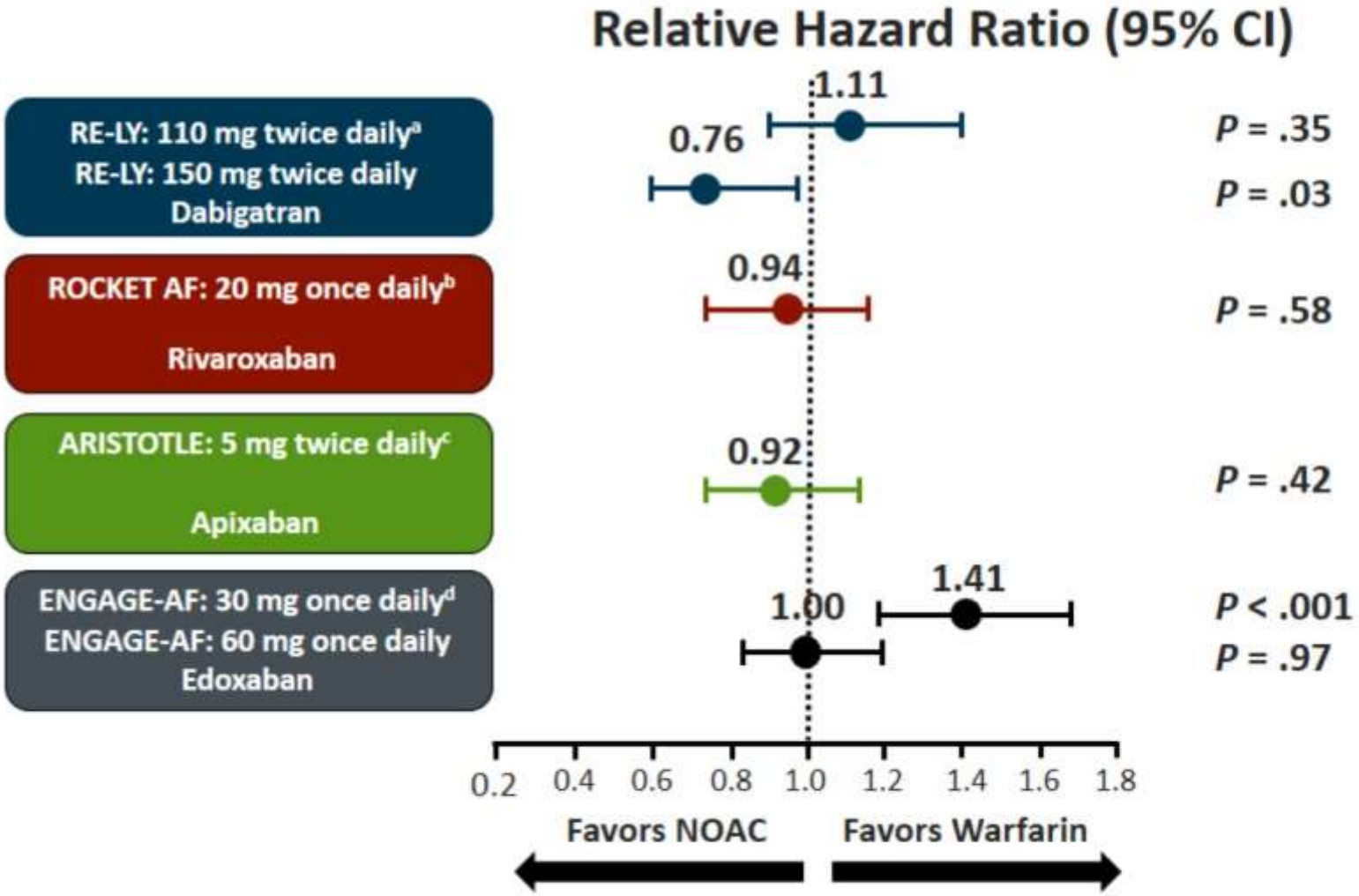
Study	Drug	Warfarin	HR	*P* Value
ARISTOTLE[a], %	0.24	0.47	0.47	.001
RE-LY[b] Dabigatran 150 mg, % Dabigatran 110 mg, %	 0.10 0.12	0.38	 0.26 0.31	 < .001 < .001
ENGAGE AF-TIMI 48[c] Edoxaban, %	0.26	0.47	0.54	< .001
ROCKET-AF[d] Rivaroxaban, %	0.5	0.7	0.67	.02

Ischemic Stroke

RE-LY[b] Dabigatran, %	0.92	1.20	0.76	.03

a. Granger CB, et al. *N Engl J Med*. 2011;365:981-992[12]; b. Connolly S, et al. *N Engl J Med*. 2009;361:1139-1151[11]; c. Giugliano R, et al. *N Engl J Med*. 2013;369:2093-2104[14]; d. Fox KAA, et al. *Eur Heart J*. 2011;32:2387-2394.[13]

Ischemic Stroke in NOAC Trials



a. Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151[4]; b. Patel MR, et al. *N Engl J Med*. 2011;365:883-891[5]; c. Granger CB, et al. *N Engl J Med*. 2011;365:981-992[6]; d. Giugliano RP, et al. *N Engl J Med*. 2013;369:2093-2104.[7]

Conclusions for AF

- NOACs non-inferior to Warfarin in efficacy
- FDA approved dose of Dabigatrin 150mg bd decreased the risk of ischaemic stroke over warfarin
- All decreased mortality by 10%/year compared to warfarin

Conclusions for AF

- Rates of bleeding similar or slightly higher than warfarin with Dabigatran and Rivobaxaran; Apixaban significantly lower rate of bleeding
- Rate of intracranial haemorrhage risk 50% lower than Warfarin
- Dabigatran and Rivaboxaran increased GI bleed over Warfarin

Licensed Uses - 2

Prophylaxis of VTE following knee and hip surgery

RECORD Trial

Rivaroxaban started 6-8 hrs post op

- 2 trials THR; 2 trials TKR
- All 4 showed Rivaroxaban superior to enoxaparin in preventing VTE
- Pooled analysis showed small increase in bleeding with Rivaroxaban

Licensed Use - 3

Treatment and prevention of recurrent DVT and PE

Acute VTE Treatment Trials

Initial Treatment Studies

	Dabigatran		Rivaroxaban		Apixaban	Edoxaban
	RE-COVER	RE-COVER II	EINSTEIN-DVT	EINSTEIN-PE	AMPLIFY	Hokusai-VTE
Treatments & dosage	Enoxaparin/ dabigatran (150 mg bid) vs enoxaparin/ warfarin	Enoxaparin/ dabigatran (150 mg bid) vs enoxaparin/ warfarin	Rivaroxaban (15 mg bid for 3 weeks, then 20 mg once daily) vs enoxaparin/ warfarin	Rivaroxaban (15 mg bid for 3 weeks, then 20 mg once daily) vs enoxaparin/ warfarin	Apixaban (10 mg bid for 7 days, then 5 mg bid) vs enoxaparin/warfarin	LMWH/edoxaban (60 mg once daily; 30 mg once daily if creatinine clearance 30-50 mL/min or body weight < 60 kg) vs UFH or LMWH/warfarin
Time, mo	6	6	3, 6, or 12	3, 6, or 12	6	Variable, 3-12
Efficacy results	Recurrent VTE or fatal PE: 2.4% under dabigatran vs 2.1% under warfarin	Recurrent VTE or fatal PE: 2.3% under dabigatran vs 2.2% under warfarin	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs 3.0% under warfarin	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs 1.8% under warfarin	Recurrent VTE or fatal PE: 2.3% under apixaban vs 2.7% under warfarin	Recurrent VTE or fatal PE: 3.2% under edoxaban vs 3.5% under warfarin
Safety results	Major bleeding: 1.6% under dabigatran vs 1.9% under warfarin	Major bleeding: 15 patients under dabigatran vs 22 patients under warfarin	Major or CRNM bleeding: 8.1% under rivaroxaban vs 8.1% under warfarin	Major or CRNM bleeding: 10.3% under rivaroxaban vs 11.4% under warfarin	Major bleeding: 0.6% under apixaban vs 1.8% under warfarin	Major or CRNM bleeding: 8.5% under edoxaban vs 10.3% under warfarin

Konstantinides S, et al. *Eur Heart J*. 2014 Aug 29.[1]

Extended Treatment of VTE With NOACs

Study	Active	Comparator	Treatment Duration, m	RR for Recurrent VTE, %	Major or CRNM Bleeding in Active Group
RE-SONATE	Dabigatran 150 mg bid	Placebo	6	92	5.3
RE-MEDY	Dabigatran 150 mg bid	Warfarin (INR 2-3)	18-36	Risk difference 0.38 vs VKA	5.6 (vs 10.2 in warfarin arm)
EINSTEIN-EXT	Rivaroxaban 20 mg daily	Placebo	6-12	82	6.0
AMPLIFY-EXT	Apixaban 5 mg bid	Placebo	12	80	4.2
	Apixaban 2.5 mg bid			81	3.0

Konstantinides S, et al. *Eur Heart J*. 2014 Aug 29.[1]

Conclusions with DVT/PE

- Rivaroxaban non-inferior in efficacy
- Non major bleeding safety outcome was not significant
- Rivaboxaran reduced recurrence rate by 82% compared to placebo
- Apixaban non-inferior
- Eliminate need for bridging

ESC 2014
PE Anticoagulation Recommendations

- Class I; Level B
  - In parallel to parenteral anticoagulation, treatment with a VKA is recommended, targeting an INR of 2.5 (range 2.0-3.0)
  - Replace combination of parenteral anticoagulation and VKA with anticoagulation and
    - Rivaroxaban (15 mg bid for 3 weeks, followed by 20 mg once daily)

    OR
    - Apixaban (10 mg bid for 7 days, followed by 5 mg bid)
  - Following acute-phase parenteral anticoagulation, replace VKA treatment with
    - Dabigatran (150 mg bid, or 110 mg bid for patients ≥ 80 years of age)

    OR
    - Edoxaban (when approved)

Konstantinides S, et al. *Eur Heart J*. 2014 Aug 29.[1]

ESC 2014 Guideline Recommendations for Extended Treatment Using NOACs

- Class IIa; Level B
  - Rivaroxaban (20 mg once daily), dabigatran (150 mg bid, or 110 mg bid for patients ≥ 80 years of age or those under concomitant verapamil treatment), or apixaban (2.5 mg bid) should be considered as an alternative to VKA (except for patients with severe renal impairment) if extended anticoagulation treatment is necessary

Konstantinides S, et al. *Eur Heart J*. 2014 Aug 29.[1]

Licensed Uses - 4

Use in cancer patients with increased risk of VTE

NOAC Trials: Outcomes in Cancer Patients

Prespecified Subgroup Analyses

NOAC Trial	Patients With Active Cancer	Recurrent VTE	Clinically Relevant Bleeding
EINSTEIN-DVT	Rivaroxaban = 6.8% VKA = 5.2%	Rivaroxaban = 3.4% VKA = 5.6%	Rivaroxaban = 14.4% VKA =15.9%
EINSTEIN-PE	Rivaroxaban = 4.7% VKA = 4.5%	Rivaroxaban = 1.8% VKA = 2.8%	Rivaroxaban = 12.3% VKA = 9.3%
EINSTEIN-EXT	Rivaroxaban = 4.5% Placebo = 4.4%	Not Reported	NR
AMPLIFY	Apixaban = 2.5% VKA = 2.8%	Not Reported	NR
AMPLIFY-EXT	Placebo = 2.2% 2.5 mg apixaban = 1.8% 5 mg apixaban = 1.1%	Not Reported	NR
RE-COVER	Dabigatran = 5% VKA = 4.5%	Dabigatran = 3.1% VKA = 5.3%	NR
RE-MEDY	Dabigatran = 4.2% VKA = 4.1%	Dabigatran = 3.3% VKA = 1.7%	NR
Hokusai-VTE	Edoxaban = 2.6% VKA = 2.4%	Edoxaban = 3.7% VKA = 7.1%	Edoxaban = 18.3% VKA = 25.3%

Bauersachs R , et al. *N Engl J Med*. 2010;363:2499-2510[6]; Büller HR , et al. *N Engl J Med*. 2012;366:1287-1297[7]; Agnelli G, et al. *N Engl J Med*. 2013;369:799-808[8]; Agnelli G, et al. *N Engl J Med*. 2013;368:699-708[9]; Schulman S, et al. *N Engl J Med*. 2009;361:2342-2352[10]; Schulman S, et al. *N Engl J Med*. 2013;368:709-771[11]; Hokusai-VTE Investigators. *N Engl J Med*. 2013;369:1406-1415[12]; Raskob GE, et al. *Blood*. 2013;122. Abstract 211.[13]

Meta-Analysis

- 9 RCTs were included
- LMWH showed significant reduction in recurrent VTE over VKA
- LMWH was associated with a nonsignificant increase in major bleeding
- NOACs showed a nonsignificant reduction (RR 0.78)

Carrier M, et al. *Thromb Res.* 2014;134:1214-1219.[14]

NOACs
Limitations in Cancer Patients

- Paucity of clinical trial data
  - Cancer patients constituted <10% of the population
- No comparison with LMWHs
  - Comparisons with warfarin in clinical trials
- Patients were not representative of cancer patients
- Drug interactions with chemotherapy agents may be clinically important
- Liver and renal dysfunction is common in cancer patients
  - NOACs are cleared renally to varying extent
  - NOACs are metabolized in the liver to varying extent

American Society of Clinical Oncology Clinical Practice Guideline Update

- LMWH is recommended for the initial 5 to 10 days of treatment for patients with established DVT and PE, as well as for long-term (6 months) secondary prophylaxis
- Use of NOACs is not currently recommended for patients with malignancy and VTE
- Oncology professionals should provide patient education about the signs and symptoms of VTE

Lyman GH, et al. *J Clin Oncol.* 2013;31:2189-2204.[2]

Chronic Treatment of VTE in Patients With Cancer

- Guidelines recommend continuing anticoagulation beyond 6 months
- May include
  - Continuation of LMWH
  - Transition to VKA
  - Potentially transition to NOACs (if patient is clinically stable)*
- Decision to continue should be individualized, taking into consideration
  - VTE recurrence vs bleeding risk
    - Metastatic disease, chemotherapy, rapidly progressing disease, and tumor type may influence VTE recurrence risk
    - Creatinine clearance, metastatic disease, and recent major bleeding may influence bleeding risk
  - Patient preference
  - Drug cost

*Not endorsed by the guidelines

Kearon C, et al. *Chest*. 2012;141:e419S-e94S[1]; Lyman GH, et al. *J Clin Oncol*. 2013;31:2189-204[2]; Konstantinides SV, et al. *Eur Heart J*. 2014;35:3033-3069[16]; nccn.org.[17]

Side effects

Bleeding Risk Factors

- Increasing age
- Prone to falling
- History of bleeding: GI bleeding, stroke, TIA
- Impaired renal function
- Thrombocytopenia
- Concurrent use of antiplatelet agents

GI Bleeding
NOACs vs Warfarin

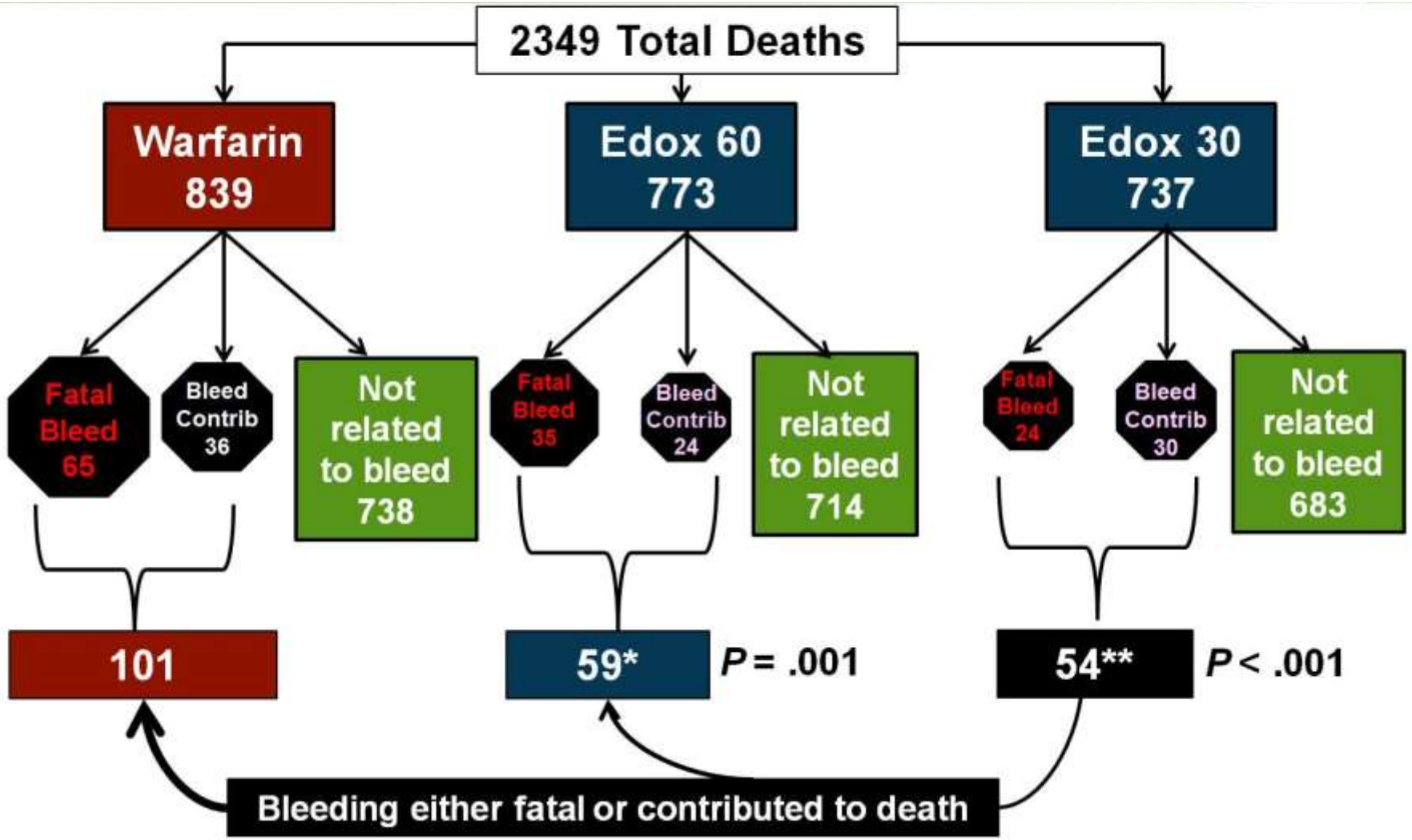
	NOAC, %	Warfarin, %	Hazard Ratio (95% CI)	*P*
RE-Ly[a] (Dabigatran, 150 mg)	3.00	1.99	1.50* (1.19-1.89)	< .001
RE-LY[a] (Dabigatran, 110 mg)	2.21	1.99	1.10* (0.86-1.41)	0.43
ROCKET Af[b] (Rivaroxaban)	3.15	2.16	NA	NA
ARISTOTLE[c] (Apixaban)	1.16	1.32	0.89 (0.70-1.15)	.37
ENGAGE AF-TIMI 48[d] (Edoxaban, 60 mg)	3.31	2.71	1.23 (1.02-1.50)	.03
ENGAGE AF-TIMI 48[d] (Edoxaban, 30 mg)	1.84	2.71	0.67 (0.53-0.83)	< .001

Relative Risk (95% CI; 1.25, 1.01-1.55); *P* = .043[e]

*Relative Risk

a. Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151[4]; b. Patel MR, et al. *N Engl J Med*. 2011;365:883-891[5]; c. Granger CB, et al. *N Engl J Med*. 2011;365:981-992[6]; d. Giugliano RP, et al. *N Engl J Med*. 2013;369:2093-2104[7] ; e. Ruff CT, et al. *Lancet*. 2014;383:955-962.[8]

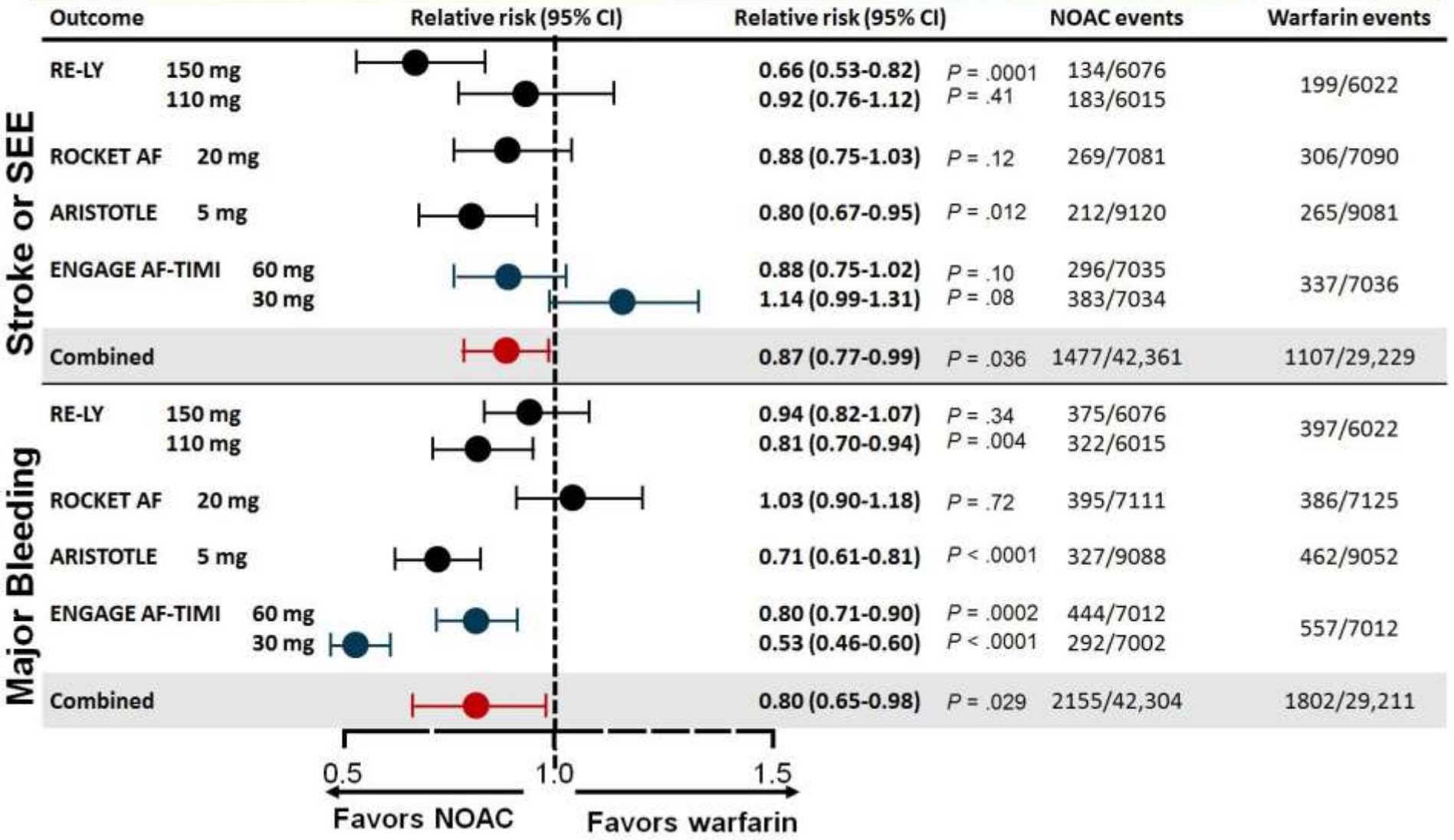
Relationship of Bleeding to Deaths



Giugliano RP, et al. ESC 2014; abstract 4874.[10]

SAFETY

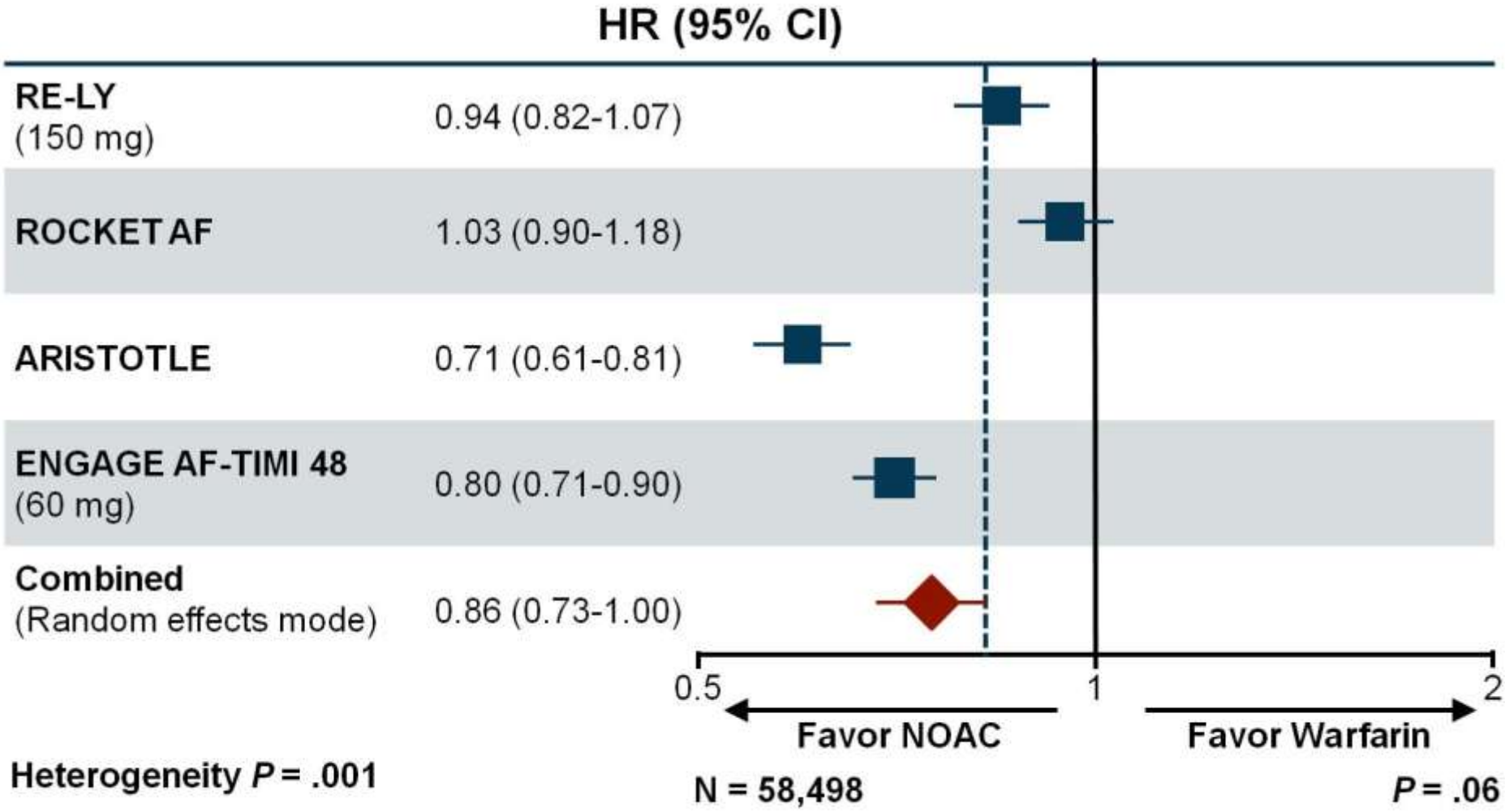
Comparative Efficacy and Safety of NOACs and Warfarin



Reprinted from Ruff CT, et al. *Lancet*. 2014; 383:955-62, Copyright 2014, with permission from Elsevier[7]

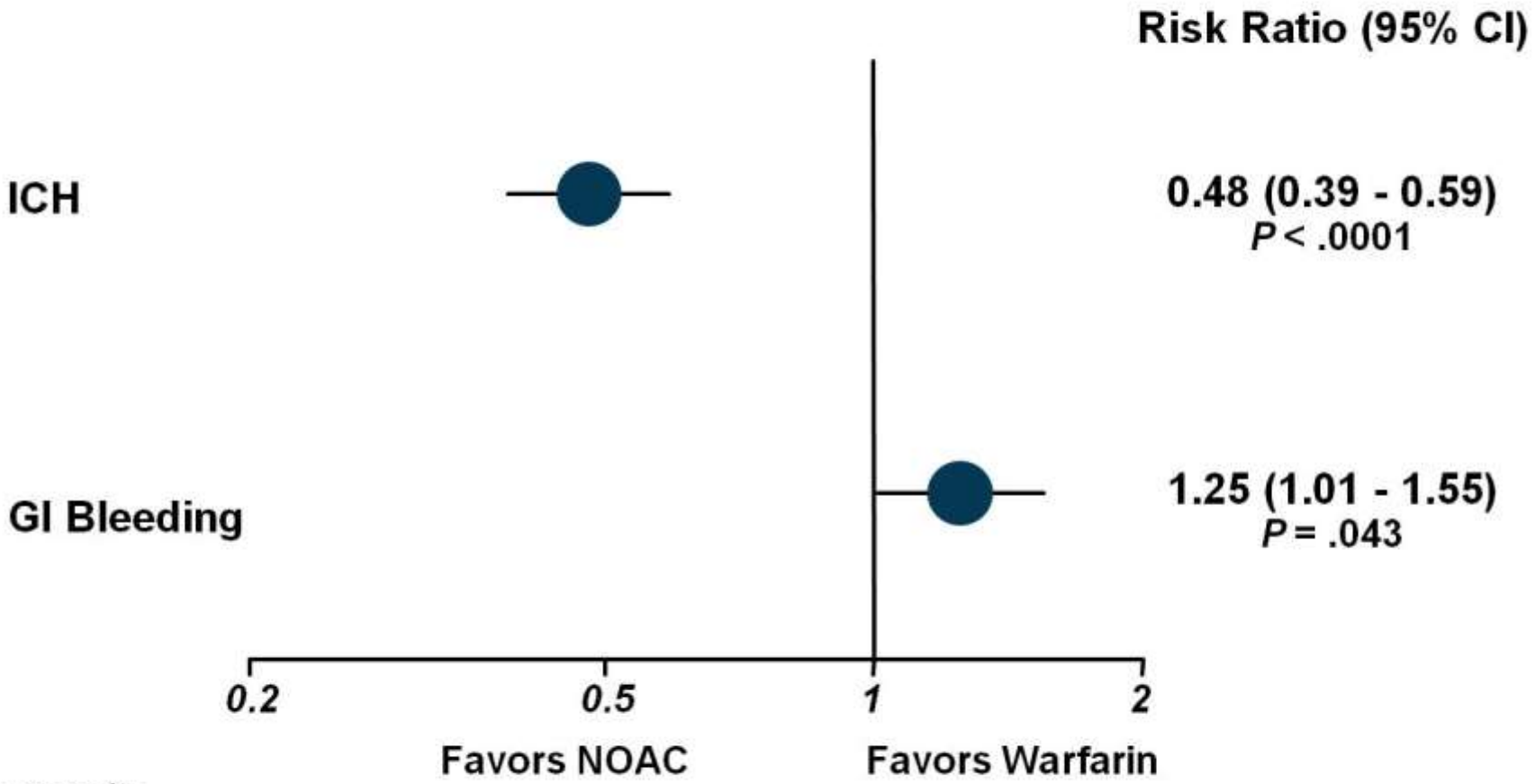

DOSING

"High-Dose" NOACs
Stroke or SEE



Ruff CT, et al. *Lancet*. 2014;383:955-962.[7]

"High-Dose" NOACs
Safety Outcomes

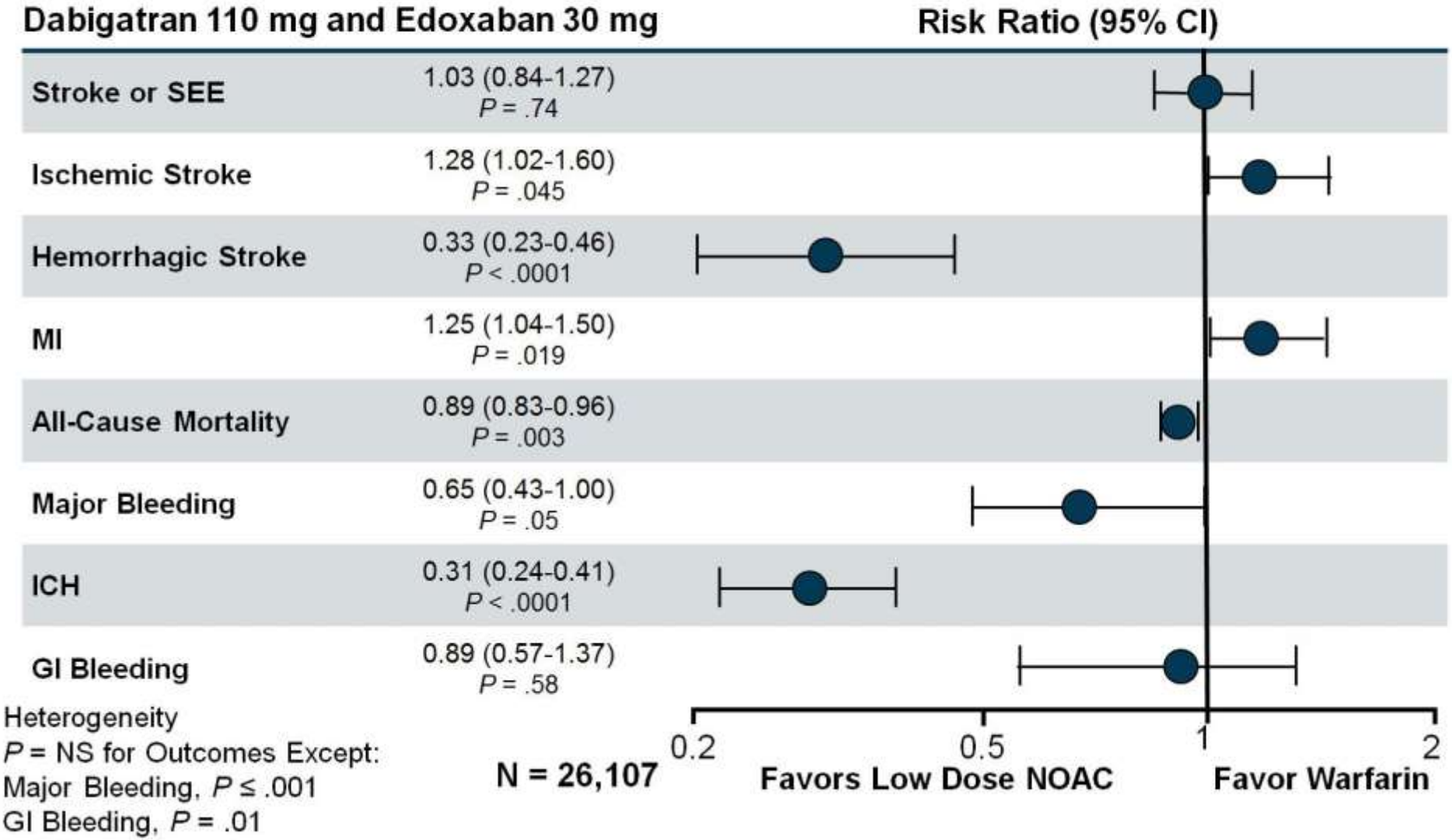


Heterogeneity
ICH, *P* = .22
GI Bleeding, *P* = .009

Heterogeneity *P* = .001

Ruff CT, et al. *Lancet*. 2014;383:955-962.[7]

“Low-Dose” NOAC Regimens Efficacy and Safety Outcomes



Ruff CT, et al. *Lancet*. 2014;383:955-62[7]

Lower NOAC Dose
Clinical Implications

- Dabigatran 110 mg twice-daily dose, used in the RE-LY trial, not available in the United States
- Lower doses used in fragile patient populations: frail or elderly patients, low body weight, patients with renal insufficiency
- Low-dose edoxaban was associated with a 41% increase in ischemic stroke, which is counterbalanced by a 67% reduction in hemorrhagic stroke
  - Important consideration in fragile patient populations that present with greater risk of hemorrhagic stroke

Drug Interactions

Examples of possible drug-drug interactions with the newer anticoagulants

Drugs directly affecting bleeding risk	Drugs affecting the kidney	Inducers of hepatic metabolism	Inhibitors of hepatic metabolism	Inducers of P-glycoprotein	Inhibitors of P-glycoprotein
other anticoagulants NSAIDs antiplatelets thrombolytic agents selective serotonin re-uptake inhibitors serotonin-noradrenaline re- uptake inhibitors	diuretics NSAIDs ACE inhibitors angiotensin -II- receptor antagonists	rifampicin St John's Wort carbamazepine phenytoin phenobarbital	azole antifungals verapamil amiodarone ciclosporin tacrolimus HIV protease inhibitors	rifampicin, St John's Wort, carbamazepine phenytoin, phenobarbital dronedarone quinidine azole antifungals amiodarone	diltiazem verapamil clarithromycin ticagrelor HIV protease inhibitors

Dosing Under Review

	via	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Antiarrhythmic drugs					
Amiodarone	P-gp competition	+12-60%	"no effect"	+40%	minor effect (caution if CrCl 15-50 mL/min)
Digoxin	P-gp competition	no effect	no effect	no effect	no effect
Diltiazem	P-gp competition and weak CYP3A4 inhibition	no effect	+40%	no data yet	minor effect (caution if CrCl 15-50 mL/min)
Dronedarone	P-gp and CYP3A4 inhibitor	+70-100% (US: 2 x 75 mg)	no data yet: caution	+85% (Reduce dose by 50%)*	Moderate effect but no PK data yet: caution
Quinidine	P-gp competition	+53%	no data yet	+80% (Reduce dose by 50%)§	+?%
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12-180% (reduce dose and take simultaneously)	no data yet	+53% (SR) (Reduce dose by 50%)*	minor effect (use with caution if CrCl 15-50 mL/min)
Other cardiovascular drugs					
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%	no data yet	no effect	no effect
...					

*No EMA approval yet. Needs update after EHRA Practical Guide for use of NOAC in AF (2013)
*No EMA approval yet. Needs update after finalisation of SmPC

Heidbuchel H, et al. *Europace*. 2013;15:625-651.[26]

ANTIDOTES

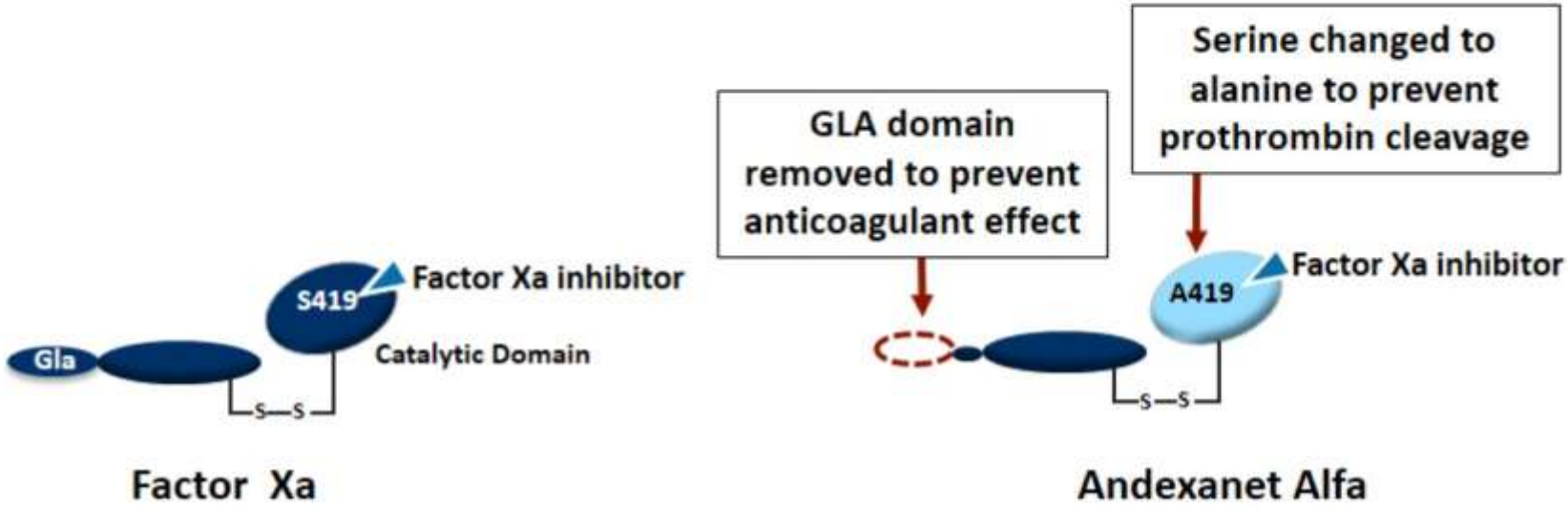
NOAC Antidotes in Clinical Trials

Andexanet[a] (PRT064445)	• Antidote for factor Xa inhibitors • Recombinant protein, targets and sequesters direct and indirect factor Xa inhibitors with high specificity
Aripazine[b] (PER977)	• Antidote for factor Xa inhibitors, DTIs, LMWH, and fondaparinux • Synthetic small molecule; reversal effect through direct binding to anticoagulant
Idarucizumab[c] (BI 655075)	• Antidote for DTIs • Fully humanized antibody fragment

DTI = direct thrombin inhibitor; LMWH = low-molecular-weight heparin

a. ClinicalTrials.gov website[11]; b. Dolgin E. *Nat Med*. 2013;19:251[12]; c. ClinicalTrials.gov website.[13]

Andexanet Alfa (PRT064445)



- ANNEXA (ongoing)
  - ANNEXA-A : Apixaban + andexanet alfa/placebo[a]
  - ANNEXA-R: Rivaroxaban[c] + andexanet alfa/placebo[b]

- March 2015: Submissions to EMA, FDA, and Health Canada for approval of idarucizumab, a specific reversal agent to dabigatran etexilate

a.Clinical Trials.gov. NCT02207725[13]; b. Clinical Trials.gov. NCT02220725.[14]
Images courtesy of Portola Pharmaceuticals, Inc

When to Monitor

Assessing drug levels helpful in

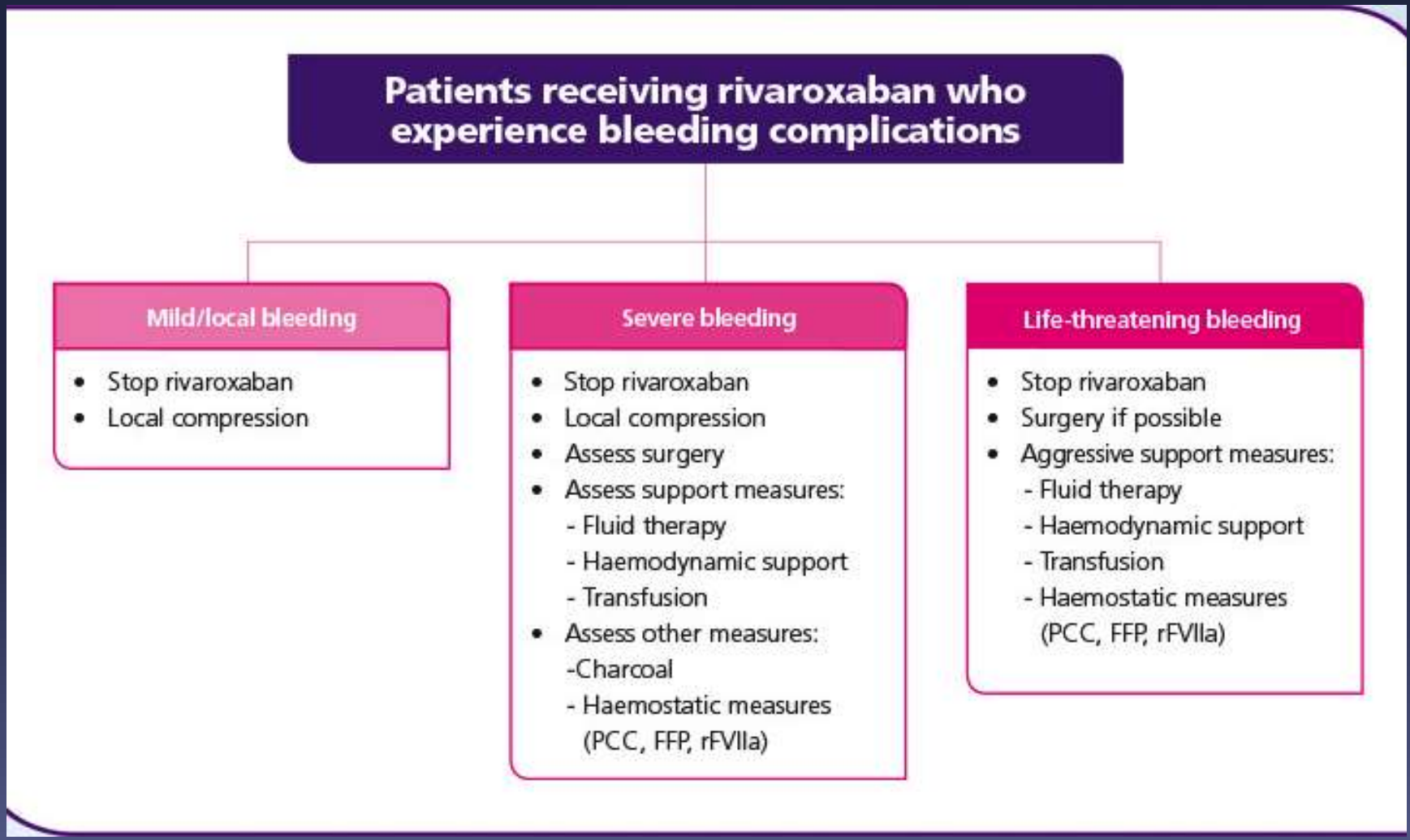
- **Bleeding – due to overdose vs in therapeutic range**
- **Change in clinical scenario – urgent surgery, new or worsening real failure, non-compliance, recurrent or extension of thromboembolism**

Recommended Testing

Drug	Tests in Bleeding	Tests in change in clinical scenarios
Dagbigatran	TT is most sensitive	Dilute TCT (HEMOCLOT thrombin inhibitor assay)
Rivaroxaban	PT (thromboplastin sensiltve to rivaroxaban)	Drug specific anti-FXa Assay
Apixaban	Drug specific anti-FXa Assay (not yet commercially available)	Drug specific anti-FXa Assay (not yet commercially available)

Management for Surgical Events

Treatment of Bleeding Complications



Surgery Bleeding Risk

Interventions not necessarily requiring discontinuation of anticoagulation

- Dental interventions
  - Extraction of 1 to 3 teeth, periodontal surgery, incision of abscess, implant positioning
- Ophthalmology
  - Cataract or glaucoma intervention
- Endoscopy without surgery
- Superficial surgery (eg, abscess incision; small dermatologic excisions)

Interventions with low bleeding risk

- Endoscopy with biopsy
- Prostate or bladder biopsy
- Electrophysiological study or radiofrequency catheter ablation for supraventricular tachycardia (including left-sided ablation via single transseptal puncture)
- Angiography
- Pacemaker or ICD implantation (unless complex anatomical setting, eg, congenital heart disease)

Interventions with high bleeding risk

- Complex left-sided ablation (pulmonary vein isolation; VT ablation)
- Spinal or epidural anaesthesia; lumbar diagnostic puncture
- Thoracic, abdominal or major orthopedic surgery
- Liver biopsy, transurethral prostate resection, kidney biopsy

For each patient, individual factors relating to bleeding and thromboembolic risk need to be taken into account, and be discussed with the intervening physician.

Heidbuchel H, et al. *Europace*. 2013;15:625-651.[26]

Preoperative Interruption and Postoperative Resumption of NOACs[a]

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Half-life, h[b]	12-14	5-9	8-15	8-10

	Low Bleeding Risk Surgery	High Bleeding Risk Surgery
Preoperative Interruption	2 or 3 drug half-lives between last dose and surgery	4 or 5 drug half-lives between last dose and surgery
Postoperative Resumption	Resume on day after surgery (24 h postoperative)	Resume 2-3 days after surgery (48-72 h postoperative),

a. Spyropoulos AC. *Blood*. 2012;120:2954-62.[10];
b. Heidbuchel H, et al. *Europace*. 2013;15:625-51[1]

Restarting NOACs

- High risk for bleeding and moderate-to-high risk for stroke
  - Wait a full 48-72 hours before restarting therapeutic doses of the NOACs
- + Risk for DVT
  - Prophylactic doses during interim period/or UFH, LMWH
  - When period of bleeding risk is over (~ < 72 hours), start full-dose NOAC

Urgent Surgery

- Defer surgery if possible to allow anticoagulation to wear off
- Be prepared for possibility of more bleeding if surgery cannot be delayed


1-800-555-1212

Medicolegal

- 2014 Pradaxa settled with 4000 individual $650,000,000US claims
- Plaintiffs claim lack of merit; lengthy litigation
- Xarelto - $600,000 bad lawyer ads

Personalising Care:

How to use and cause no harm

Assess stroke risk

$CHADS_2$

CCF	1
Hypertension	1
Age > 75 years	1
Diabetes	1
Previous stroke	1

$CHADS_2$-VASC

Vascular Disease	1
Female	1
Age > 65 years	1

Assess Bleeding Score: HAS

Hypertension	**1**
Age > 65 years	1
Stroke	1
Bleeding history	1
Labile INRs	1
Drug and ethanol abuse	1 each
Renal/liver dysfunction	1 each

Assessing Risk of Stroke and Haemorrhage

$CHADS_2$ Score		HAS-BLED Score	
Score	Risk of Stroke	Score	Risk of Hemorrhage
0	1.9	0	1.13
1	2.8	1	1.02
2	4.0	2	1.88
3	5.9	3	3.74
4	8.5	4	8.7
5	12.5	5	12.5
6	18.2	6	< 12.5

Characteristic	Drug choice	Rationale
Mechanical valves or valvular AF	Warfarin	No studies
Liver dysfunction with increase INR	Warfarin	Hepatic metabolism
Poor compliance	Warfarin	Shorter half life
Thrombophilia	Warfarin	No studies
Stable on Warfarin	Warfarin	patient request
CrCl< 30ml/min	Warfarin	Excluded from trials
CrCl 30-50ml/min	Rivaroxaban or Apixaban	Less amount renal excretion
Dyspepsia/UGI symptom	Rivaroxaban or Apixaban	Dyspepsia in up to 10% given dabigatran
Recent GI bleed	Apixaban	More gastrointestinal bleeding with dabigatran (150 mg twice daily) or rivaroxaban than with warfarin
Recent ischemic stroke on warfarin	Dagbigatrin 150mg bd	Lower risk of ischaemic stroke than warfarin
Recent acute coronary syndrome	Rivaroxaban or Apixaban	Small myocardial infarction signal with dabigatran
Poor comliance bd or request for od	Rivaroxaban	Only one od

Conclusion

- Important differences in metabolism, renal elimination and dosing strategies across the NOACs that will alter the risk/benefit profile in specific populations
- Routine monitoring unnecessary – tailoring dose due to clinical features may be enough to improve efficacy and decrease bleeding
- There may be a best NOAC and a best dose for each individual patient
- Organised education and follow-up required
- Management of bleeding, surgeries and interventional procedures may require different strategies

Possible Contraindications

- Prosthetic Valves
- Valvular AF
- Pregnancy
- Thrombophilia
- Severe renal impairment

Older anticoagulants prefered

- ICU setting
- Haemodynamically unstable PE or extensive DVT

Organisation of Patient Care for NOACs

Initiation of Therapy

- Indication for anticoagulation
- Choice of Anticoagulant
- Baseline bloods – FBC, renal and kidney function
- **Education**
- Arrange follow up

Follow up

- Check compliance
- Thrombo-embolic events
- Bleeding events
- Interaction with OTCs
- Need for blood sampling

Take home message - 1

- The benefits and risks of anticoagulation should be carefully assessed using validated tools.
- An informed discussion, of risks and benefits relative to warfarin, should take place with the patient if a newer anticoagulant is to be used.
- Patients who are already well controlled on warfarin should not have their therapy changed.

Take home message - 2

- Renal function should be measured prior to initiation of the newer anticoagulants and periodically thereafter; where required, the dose adjusted as recommended.
- It should be noted that significant drug-drug interactions may occur with the newer agents.
- Switching from warfarin to a newer agent and vice versa should be done with care and monitoring of renal function and international normalised ratio (INR) where appropriate.


THANK YOU

References

1. Welsh Medical resources Centre Bulletin.New Oral Anticoagulants; November 2013
2. Weitz J, Gross P;Newer anticogulants, which one should my patient use?. ASH Education Book 2012; 536-540
3. Tran et al; New oral Anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural management: Internal Medicine Journal 44 2014: 526-535