



THE BATTLE OF ORAL ANTICOAGULANTS

Soheir Adam, MD

Asst. Professor

Duke University Medical Center

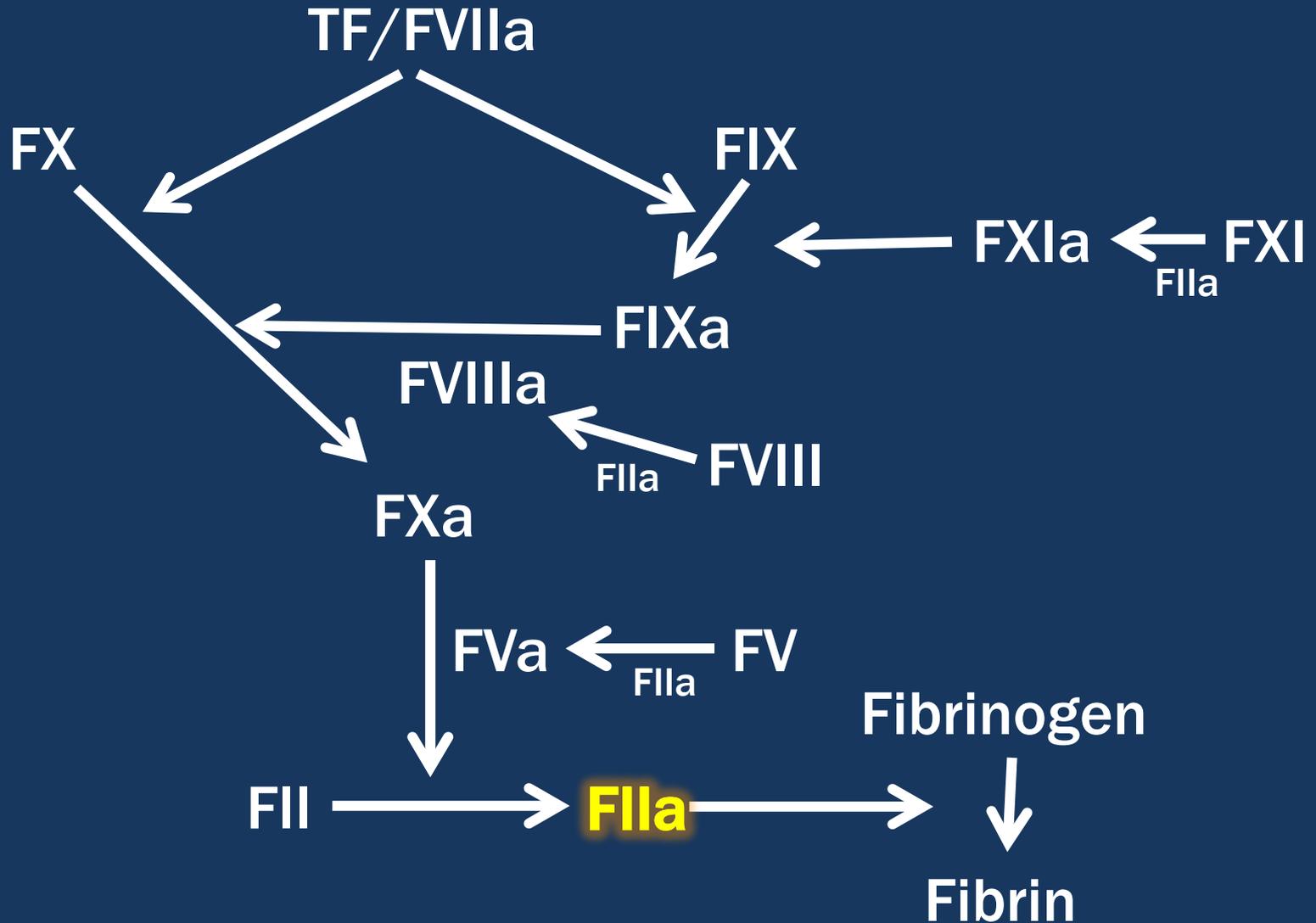
Durham, NC

AUDIENCE POLL

What number of patients in your practice are currently on new oral anticoagulants ?

- None
- 1 to 10
- 10 to 20
- >20

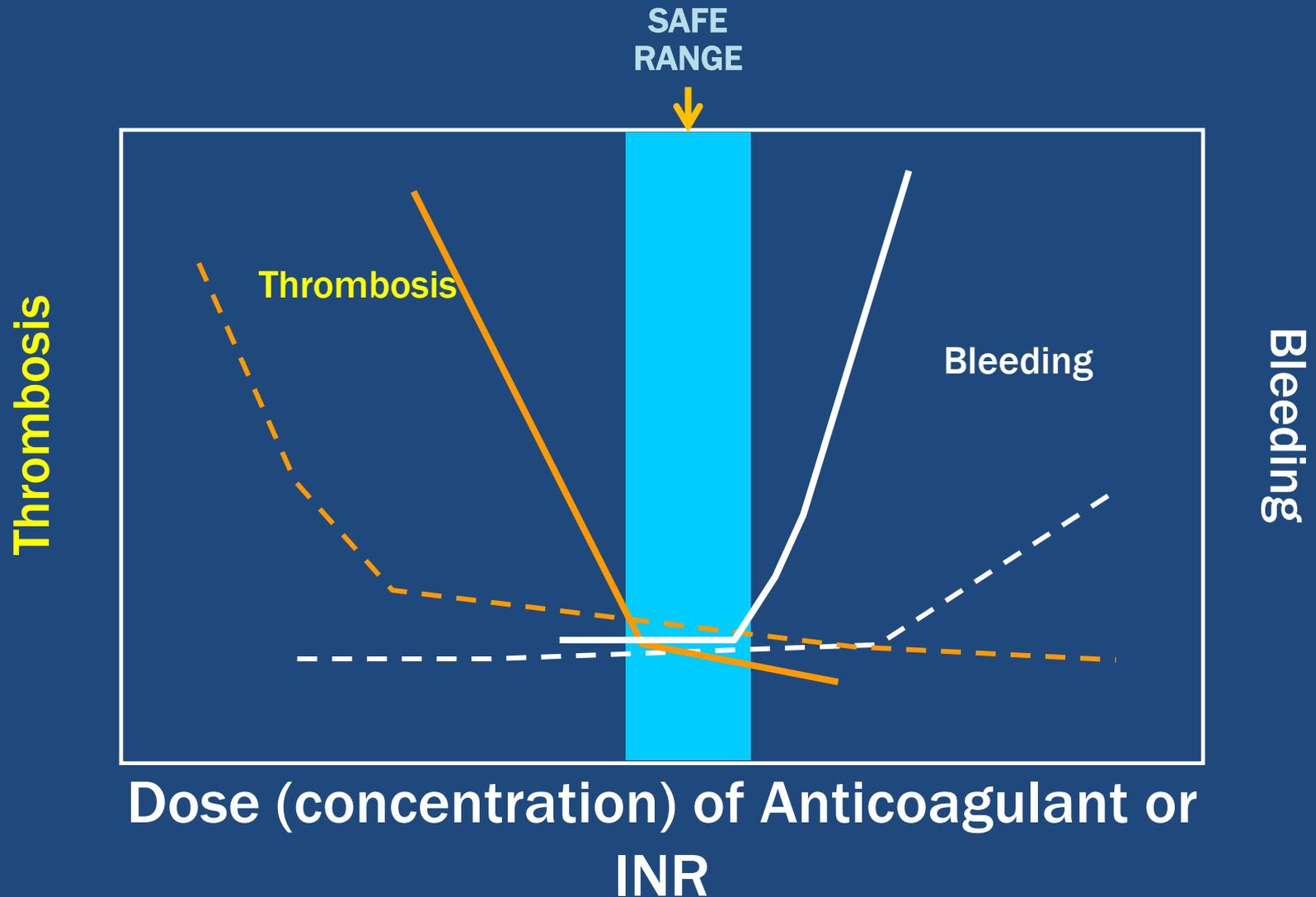
SECONDARY HEMOSTASIS



VITAMIN K ANTAGONISTS

- Vitamin K-dependent proteins include coagulation factors II, VII, IX, and X, proteins C and S, and several matrix and bone-related proteins.
- Highly effective in preventing recurrent VTE and stroke/ peripheral embolism in patients with atrial fibrillation and prosthetic heart valves
- No long-term side effects (bleeding and teratogenicity)
- Inexpensive, once daily dose
- INR monitoring :“forced” compliance
- Specific antidote (vitamin K), but reversal takes time

NARROW THERAPEUTIC WINDOW



ADDITIONAL LIMITATIONS OF WARFARIN

- Need to monitor regularly (INR)
- Interactions with multiple foods and drugs
- Slow onset and offset of action
- Genetic contributions to dose variability

AUDIENCE POLL

In your opinion, what is the biggest challenge you face while managing patients on long-term anticoagulation?

1-Lack of compliance

2-Drug interactions

3-Patient not getting tested as directed

4-Lack of communication or patient education

5-Patient not reporting relevant complications

WHY DO WE NEED ADDITIONAL OPTIONS?

100 North American patients with AF and at least one additional risk factor for stroke

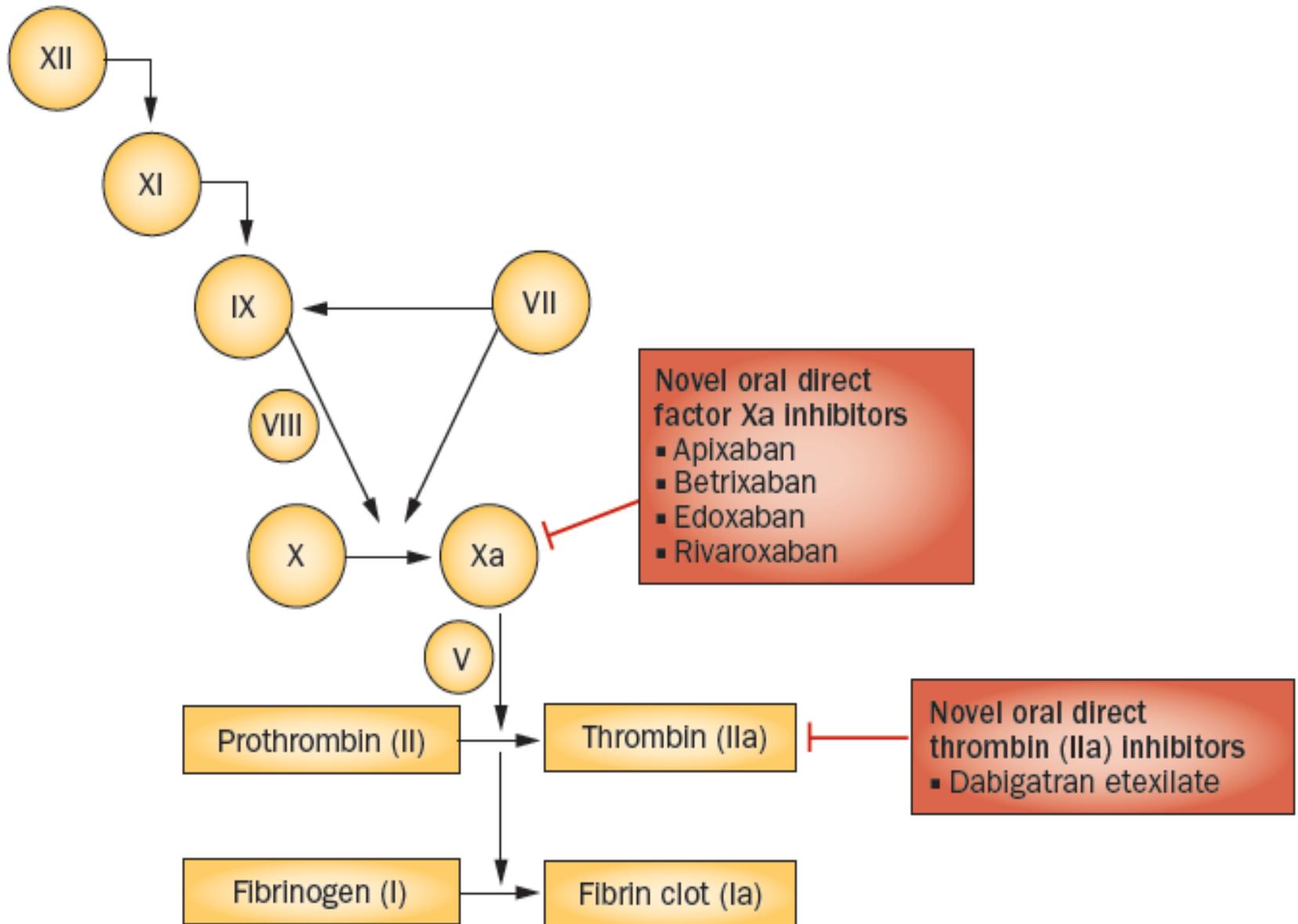
One half do not receive warfarin

One half receive warfarin

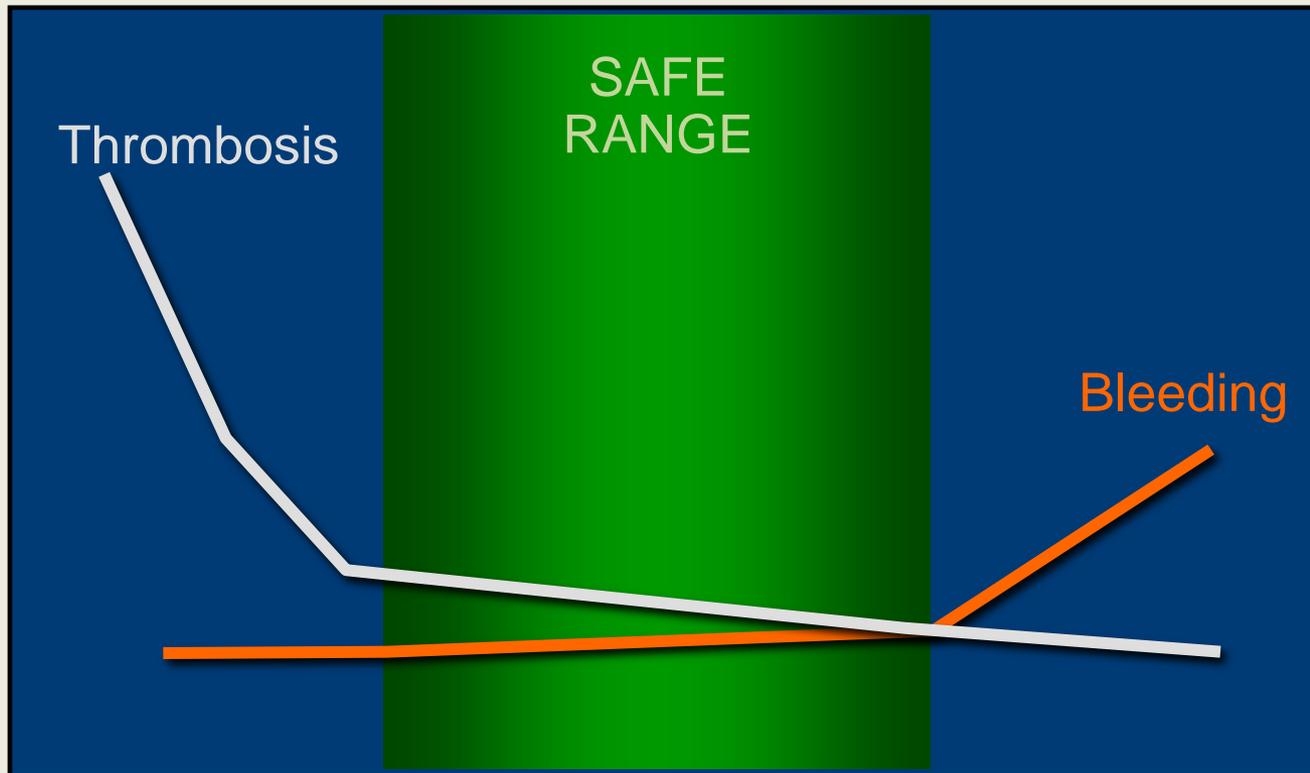
One half adequate Warfarin treatment

One half inadequate warfarin treatment

1-2 million inadequately treated or untreated AF patients who will experience 50,000-100,000 strokes



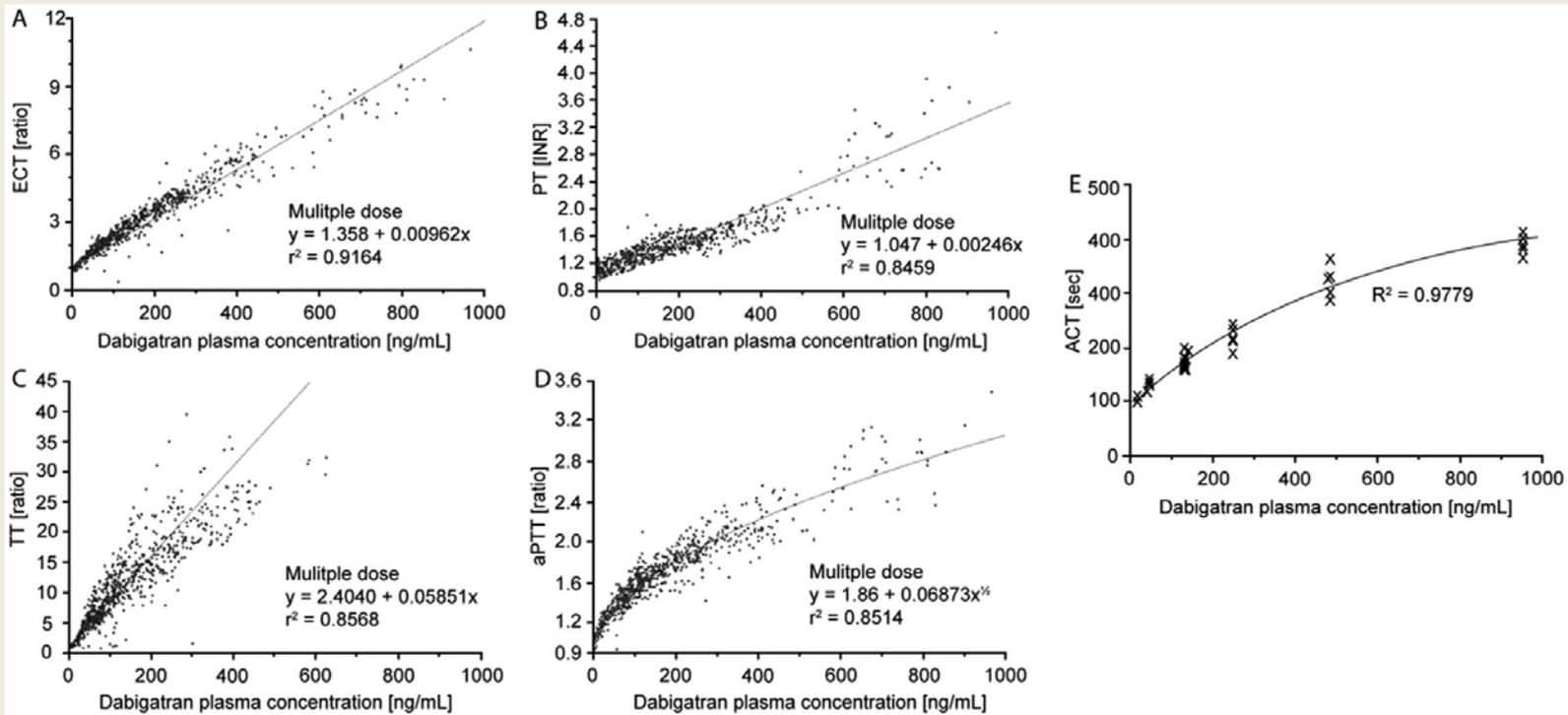
THERAPEUTIC RANGE OF THE NOAC'S



Dose (concentration) of
Anticoagulant

	Vitamin K Antagonists	FXa Inhibitors			DTI
	Warfarin	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Mode of action	Inhibition of hepatic synthesis of vitamin K-dependent coagulation factors	Direct inhibition of FXa	Direct inhibition of FXa	Direct inhibition of FXa	Direct inhibition of clot-bound and free thrombin (FIIa)
Time to peak effect (hours)	72–96	0.5–3	3	1.5	2–3
Half-life hours	20–60	5–9 (9–13 in elderly)	8–13	9–11	14–17
Bioavailability %	100	80	66	50	6.5
Recommended therapeutic dose and frequency	Adjusted-dose based on INR; once daily	20 mg; once daily	5 mg; twice daily	30 mg or 60 mg; once daily	150 mg; twice daily
Monitoring	Required using INR	Not required In case of hemorrhage or renal impairment, FXa-dependent assays may be used	Not required due to predictable pharmacokinetics In hemorrhage or renal impairment, FXa-dependent assays may be used	Not required due to predictable pharmacokinetics	Not required except in subgroups such as patients with renal impairment Ecarin clotting time can be used if needed
Renal excretion	1% excreted unchanged in the urine	66% renal elimination	50% renal elimination	45% renal elimination	80% renal elimination
Interactions	CYP2C9, CYP1A2, CYP3A4 inhibitors Dietary vitamin K	Potent CYP3A4 inhibitors and P-glycoprotein inhibitors	Potent CYP3A4 inhibitors	P-glycoprotein inhibitors	P-glycoprotein inhibitors Proton pump inhibitors

	Vitamin K Antagonists	FXa Inhibitors			DTI
	Warfarin	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Drug reversal	Vitamin K, fresh frozen plasma, prothrombin complex concentrate, recombinant FVIIa	Prothrombin complex FVIIa ?	No available antidote	No available antidote	It is partially dialyzable Prothrombin complex FVII ?
Precautions	Severe active bleeding, pregnancy, breast feeding, documented hypersensitivity Severe renal impairment (glomerular filtration rate < 30 mL/min/1.73m ²)	Severe active bleeding; severe renal impairment	Severe active bleeding; severe renal impairment	Severe active bleeding; severe renal impairment	Severe active bleeding, severe renal impairment
FDA indications	<ol style="list-style-type: none"> Prophylaxis and treatment of thromboembolic complications associated with AF and or cardiac valve replacement Prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism Reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction 	<ol style="list-style-type: none"> Prevention of VTE in patients undergoing orthopedic surgery Prevention of stroke in AF 	None	None	Prevention of stroke in AF



The relationship of Dabigatran concentration to various coagulation assays.

Mechanism	Dabigatran		Rivaroxaban	
P-gp inhibition	Interacting drug	Δ exposure	Interacting drug	Δ exposure
	Ketoconazole	+150%	Ketoconazole	+160%
	Quinidine	+53%		
	Amiodarone	+60%		
	Verapamil	+50%		
P-gp induction	Rifampicin	-67%	Rifampicin	-50%
	St John's Wort	Not determined	St John's Wort	Not determined
CYP3A4 inhibition			Ketoconazole	+160%
			Clarithromycin	+50%
			Ritonavir	+50%
CYP3A4 induction			Rifampicin	-50%
			St John's Wort	Not determined

	Apixaban	Dabigatran	Rivaroxaban
Oral activated charcoal	Yes	Yes	Yes
Hemodialysis	No	Yes	No
Hemoperfusion with activated charcoal	Possible	Yes	Possible
FFP	No	No	No
Activated FVII a	Unclear	Unclear	Unclear
3-factor PCC (II, IX, X, no VIIa)	Unclear	Unclear	Unclear
4-factor PCC (not in the US)	Possible	Possible	Possible

Reversal Of Rivaroxaban And Dabigatran

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart
Association® 
Learn and Live™

**Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate
: A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects**
Elise S. Eerenberg, Pieter W. Kamphuisen, Meertien K. Sijpkens, Joost C. Meijers,
Harry R. Buller and Marcel Levi

Factors II, VII, IX AND X

50 IU /kg

Prothrombotic properties

VA-ESP PROJECT

The Comparative Effectiveness of Warfarin and Newer Oral Anticoagulants for the Long-term Prevention and Treatment of Arterial and Venous Thromboembolism.

Soheir Adam, MD; Jennifer McDuffie, PhD; Thomas Ortel, MD, PhD; Avishek Nagi, John Williams Jr., MD

OUTLINE OF METHODS

- **Topic development**
 - Key questions
 - Protocol
- **Systematic searches of the literature**
- **Study selection via eligibility criteria**
 - Screening
 - Full text review
- **Data abstraction and quality assessment**
- **Data synthesis and report generation**
- **Peer review**

KEY QUESTION 1

- **For patients with chronic nonvalvular AF, what is the comparative effectiveness of long-term anticoagulation using newer oral anticoagulants versus warfarin on stroke incidence, mortality, health-related quality of life (HRQOL), and patient treatment experience ?**

KEY QUESTIONS 2

- For patients with venous thromboembolism, are there differential effects of newer oral anticoagulants versus warfarin or low molecular weight heparins on recurrent thromboembolism, mortality, HRQOL, and patient treatment experience?

KEY QUESTION 3

- For patients with mechanical heart valves, what is the comparative effectiveness of newer oral anticoagulants versus warfarin on the incidence of thromboembolic complications, mortality, HRQOL, and patient treatment experience?
- No studies identified

KEY QUESTION 4

- **When used for long-term anticoagulation treatment, what is the nature and frequency of adverse effects for newer oral anticoagulants versus warfarin?**

LITERATURE SEARCH STRATEGY

- **Databases : MEDLINE[®] (via PubMed[®]), Embase[®], and the Cochrane Database of Systematic Reviews for English-Language**
- **Search terms included new or novel anticoagulants; direct thrombin inhibitors, including dabigatran, and ximelagatran; factor Xa inhibitors, including edoxaban, rivaroxaban, apixaban, betrixaban, YM150; and the names of the conditions of interest: atrial fibrillation, venous thromboembolism, and mechanical heart valve.**
 - **Consult master librarian**
 - **Key words and MeSH Analyzer**

SUPPLEMENTAL SEARCHES

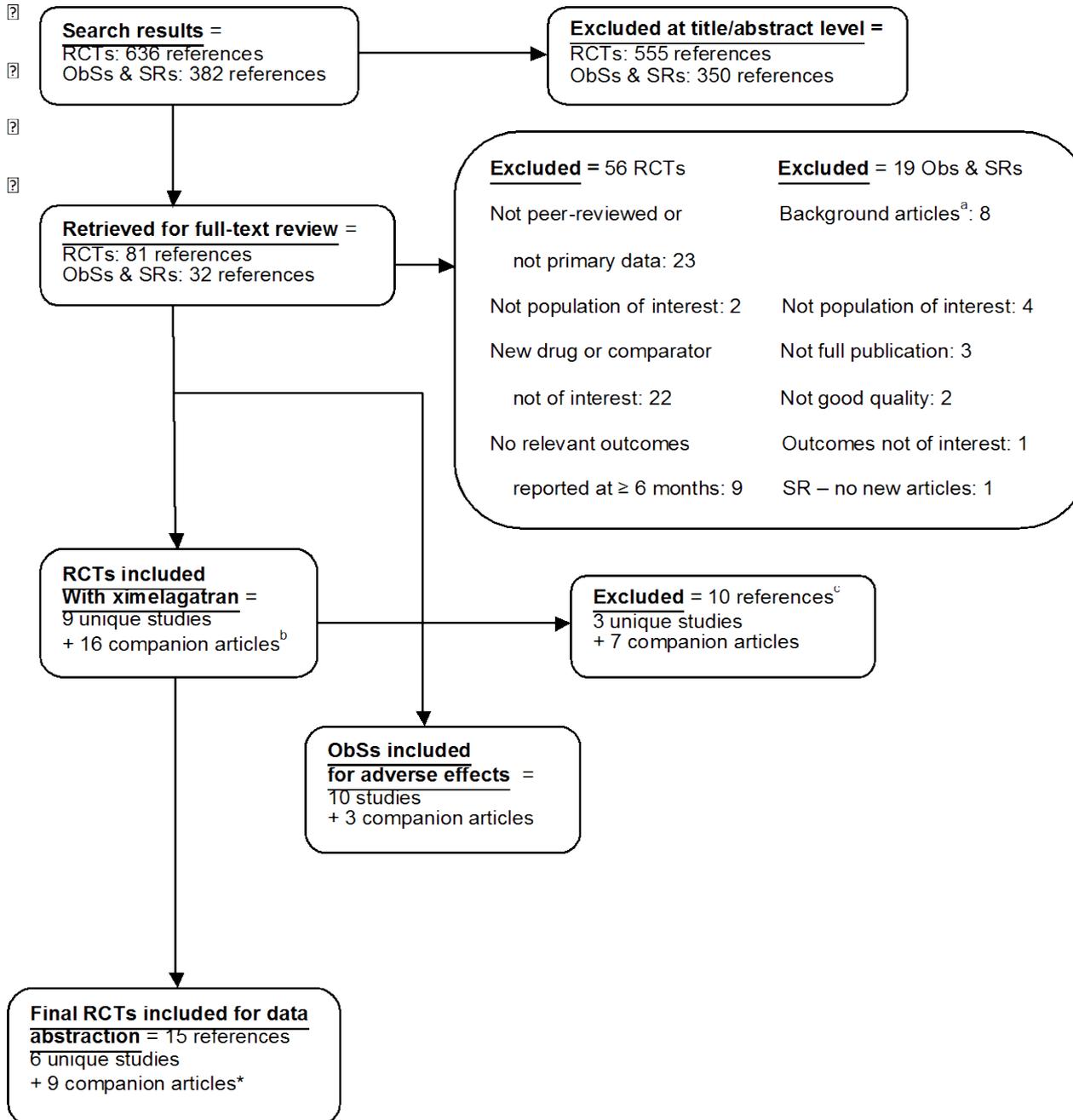
- Supplemental searches
 - Adverse events:
 - Observational studies
 - FDA databases
 - ClinicalTrials.gov for completed but unpublished studies

STUDY INCLUSION CRITERIA

- RCT or a secondary data analysis from an RCT comparing a new oral anticoagulant to an eligible comparator (warfarin and LMWH)
- Sample population with history of chronic nonvalvular AF, deep venous thromboembolism, or mechanical valve replacement. Atrial fibrillation may be assessed by any accepted threshold on any valid diagnostic tool (e.g., electrocardiogram and/or echocardiogram).
- Sample population ~~to~~ 18 years of age
- Outpatient setting (community clinic, medical clinic or office, or transitioning from inpatient for acute treatment to long-term outpatient management)
- Random allocation to the intervention groups
- Reports at least one of the included outcomes:
 - KQs 1–3: The main outcome is a thromboembolic event. Thromboembolic events must be documented radiologically and produce clinical symptoms. Asymptomatic thromboembolism (e.g., detected on surveillance imaging) will not be included.
 - KQs 1–3: Other outcomes are mortality, health-related quality of life, and patient treatment experience—the latter two measured by a validated instrument.
 - KQ 4: Adverse effects will be specific to the interventions examined and will include bleeding complications, myocardial infarction, and gastrointestinal adverse effects.
- Study duration of at least 6 months (acute treatment) or at least 12 months (chronic treatment)
- Peer-reviewed publication

STUDY EXCLUSION CRITERIA

- Non-English language publication
- Cross-sectional studies
- Pregnant population
- Studies with sample size <50
- Studies with <6 months postrandomization outcomes



DATA ABSTRACTION

- Extraction of pertinent information from each eligible article into a customized, uniform database in DistillerSR®
- Performed by 1st reviewer and independently over-read by a 2nd reviewer
- Disagreements are resolved by discussion and consensus or referral to a 3rd reviewer

QUALITY ASSESSMENT

- **Elements rated for RCTs**
 - Adequacy of randomization
 - Adequacy of allocation concealment
 - Comparability of groups at baseline
 - Blinding of subjects and/or investigators
 - Completeness of and differential loss to followup
 - Management of incomplete data
 - Validity of outcome measures
 - Potential conflicts of interest
- **Elements rated for observational studies**
 - Selection bias
 - Performance bias
 - Detection bias
 - Reporting bias
- **Reference: Agency for Healthcare Research and Quality's (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews***

DATA SYNTHESIS

- Summary table of key outcomes
- Quantitative meta-analysis, if feasible
 - DerSimonian and Laird random effects model
 - Dichotomous outcomes combined using RR (summary estimates and 95 percent confidence intervals).
 - When the number of studies was sufficient we conducted a subgroup analysis of mixed treatment effects to compare treatment effects by drug class.
 - Continuous outcomes combined using standardized mean difference and a random effects model
 - Tests for statistical heterogeneity using graphical displays and test statistics (I^2)
- Qualitative synthesis otherwise (e.g., too few studies or subgroup and sensitivity analyses)
- Assessment of publication bias

STRENGTH OF EVIDENCE

- **Assessment of four domains**
 - Risk of bias
 - Consistency
 - Directness
 - Precision
- **The strength of the evidence for the proposed answer to each key question is graded – high, moderate, low or insufficient**
- **Reference: AHRQ's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews***

Table 1. Study Characteristics

Study, Year (Reference)	Participants					Intervention Group		Control Group	
	Patients, <i>n</i>	Men, <i>n</i> (%)	Mean Age, <i>y</i>	Baseline CHADS ₂ Score ≥3, <i>n</i> (%)	Unprovoked, <i>n</i> (%)	Drug (Class)	Dosage	Drug	Time in Range, %
Chronic nonvalvular atrial fibrillation									
RE-LY, 2009 (32)	18 113	7649 (63.2)	≥70	3914 (32.3)	–	Dabigatran (DTI)	150 mg, twice daily	Warfarin	64.0
ARISTOTLE, 2011 (33)	18 201	11 785 (64.7)	≥70	5508 (30.2)	–	Apixaban (FXa inhibitor)	5 mg, twice daily	Warfarin	66.0
ROCKET AF, 2011 (34)	14 264	8601 (60.3)	≥70	12 411 (87.0)	–	Rivaroxaban (FXa inhibitor)	20 mg, once daily	Warfarin	55.0
VTE									
EINSTEIN-DVT, 2010 (36)	3449	1960 (56.8)	50–60	–	2138 (62.0)	Rivaroxaban (FXa inhibitor)	20 mg, once daily	Warfarin	57.7
RE-COVER, 2009 (35)	2564	1484 (58.4)	50–60	–	0	Dabigatran (DTI)	150 mg, twice daily	Warfarin	60.0
EINSTEIN-PE, 2012 (16)	4833	2556 (52.9)	50–60	–	3117 (64.5)	Rivaroxaban (FXa inhibitor)	20 mg, once daily	Warfarin	62.7

ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; DTI = direct thrombin inhibitor; FXa = factor Xa; RE-LY = Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF = Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation; VTE = venous thromboembolism.

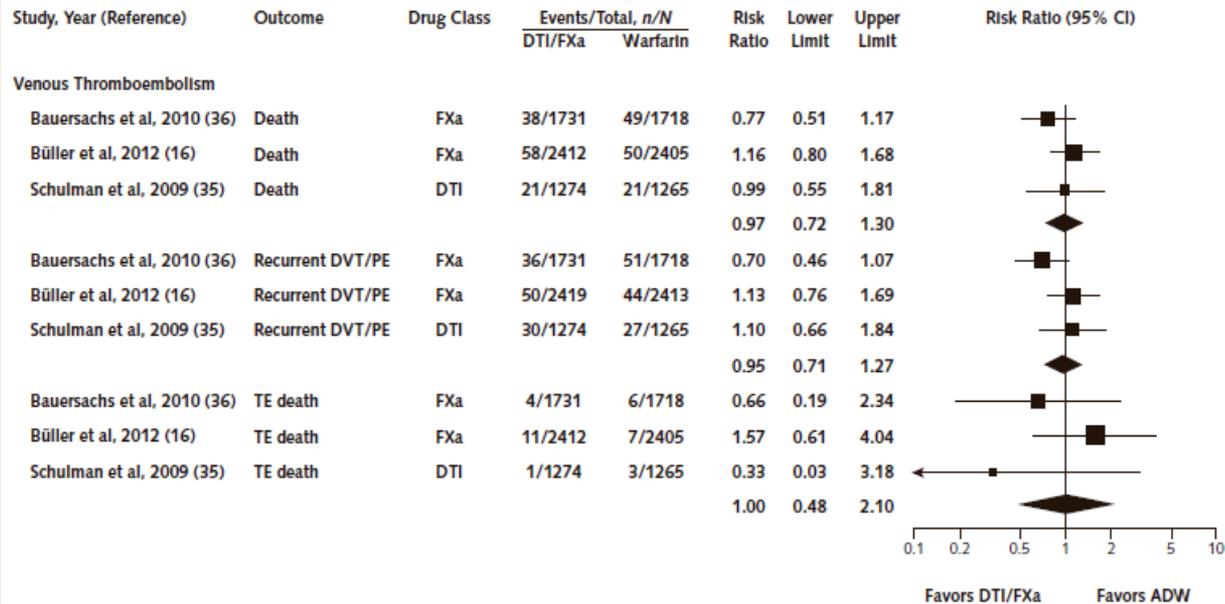
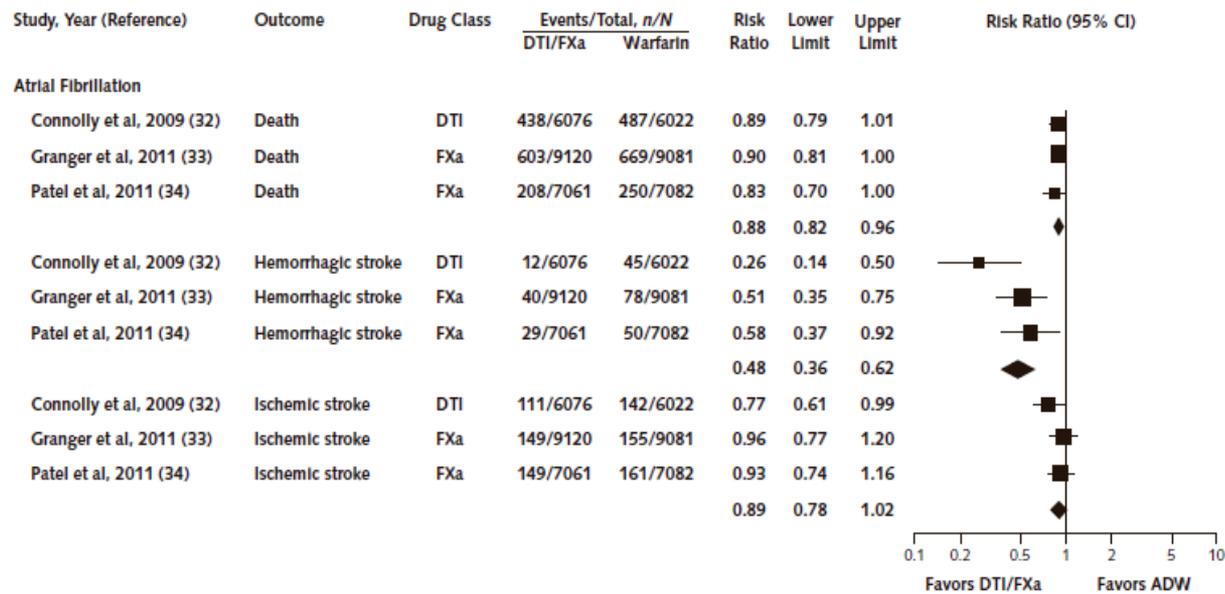
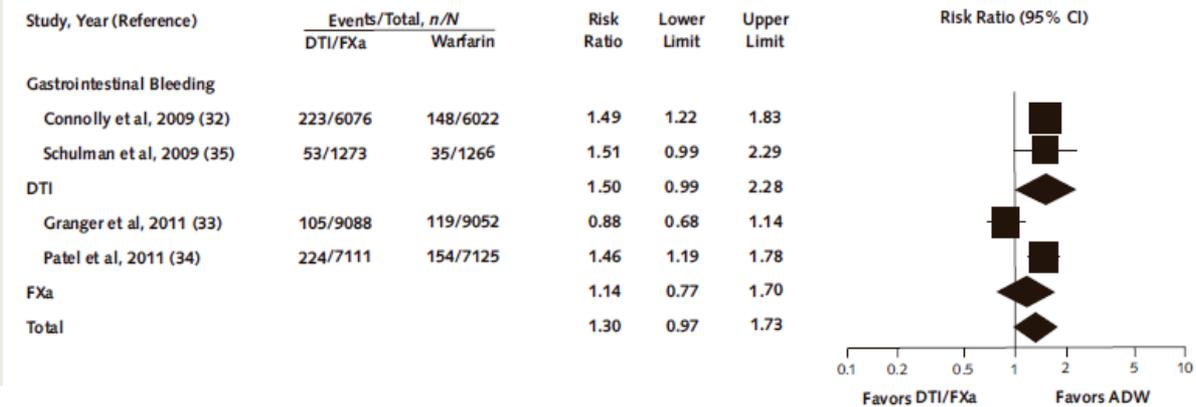
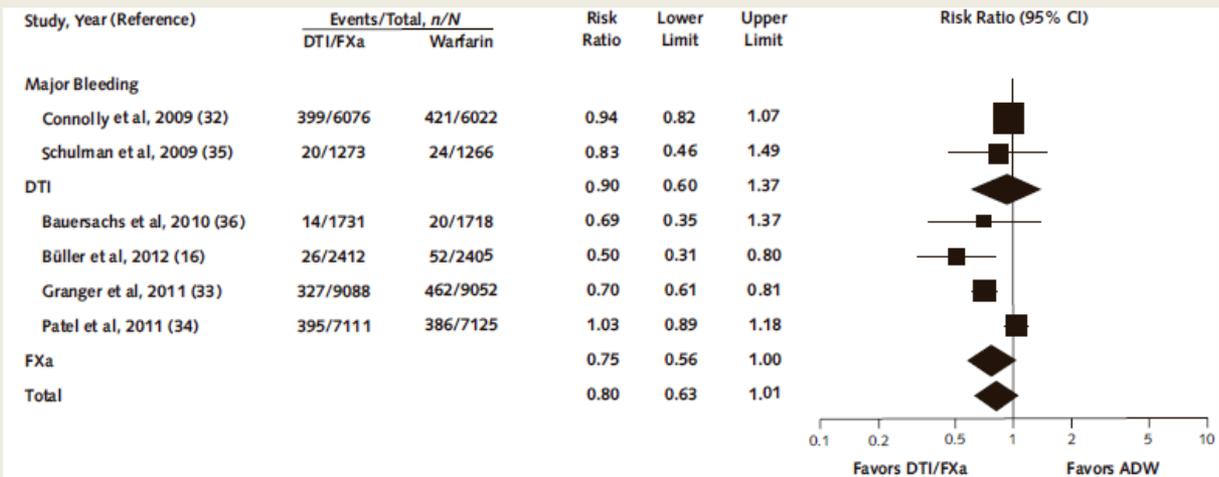
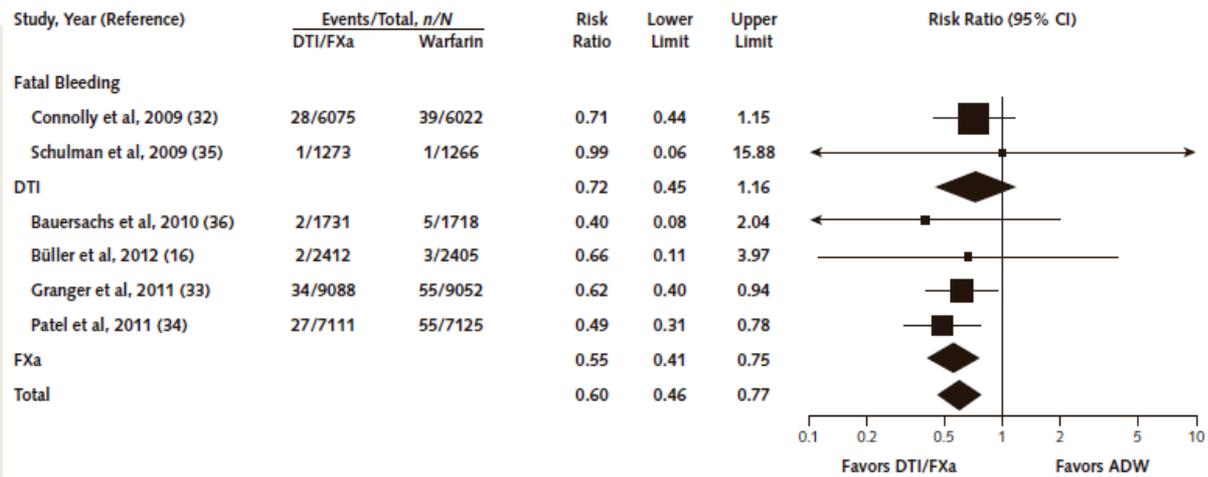


Table 2. Summary of Strength of Evidence for Major Outcomes, by Diagnosis

Outcome	Studies (Patients), <i>n</i>	Study Design	Quality	Consistency	Directness	Precision	Strength of Evidence	Effect Estimate (95% CI)
Atrial fibrillation								
All-cause mortality	3 (44 442)	RCT	Good	Consistent	Direct	Precise	High	RR, 0.88 (0.82 to 0.96) RD, 8 fewer deaths/1000 patients (3 to 11 fewer)
VTE-related mortality	2 (30 299)	RCT	Good	Some inconsistency	Direct	Some imprecision	Moderate	RR, 0.77 (0.57 to 1.02)
Ischemic stroke	3 (44 442)	RCT	Good	Consistent	Direct	Some imprecision	Moderate	RR, 0.89 (0.78 to 1.02)
Hemorrhagic stroke	3 (44 442)	RCT	Good	Some inconsistency	Direct	Some imprecision	Moderate	RR, 0.48 (0.36 to 0.62) RD, 4 fewer hemorrhagic strokes/1000 patients (2 to 5 fewer)
DVT/PE								
All-cause mortality	3 (10 805)	RCT	Good	Consistent	Direct	Some imprecision	Moderate	RR, 0.97 (0.72 to 1.30)
VTE-related mortality	3 (10 805)	RCT	Good	Consistent	Direct	Important imprecision	Low	RR, 1.00 (0.48 to 2.10)
Recurrent DVT/PE	3 (10 820)	RCT	Good	Some inconsistency	Direct	Some imprecision	Moderate	RR, 0.95 (0.71 to 1.27)

DVT = deep venous thrombosis; PE = pulmonary embolism; RCT = randomized, controlled trial; RD = risk difference; RR = risk ratio; VTE = venous thromboembolism.



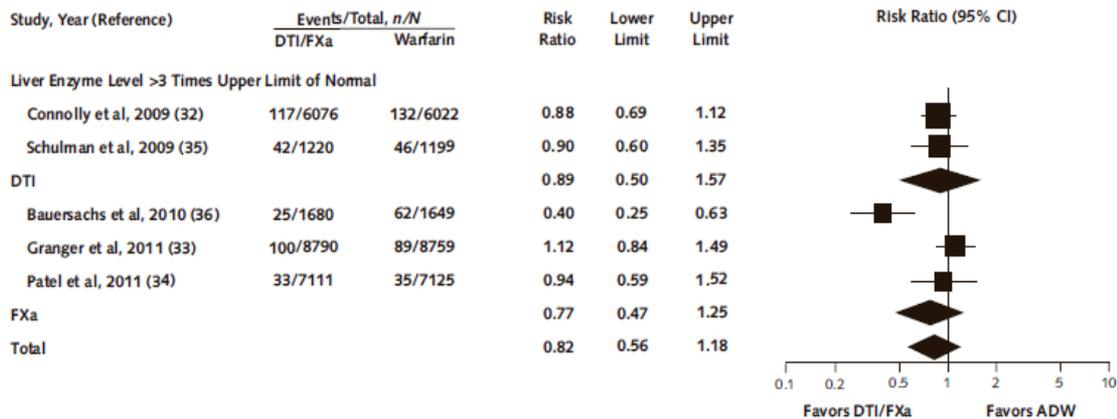
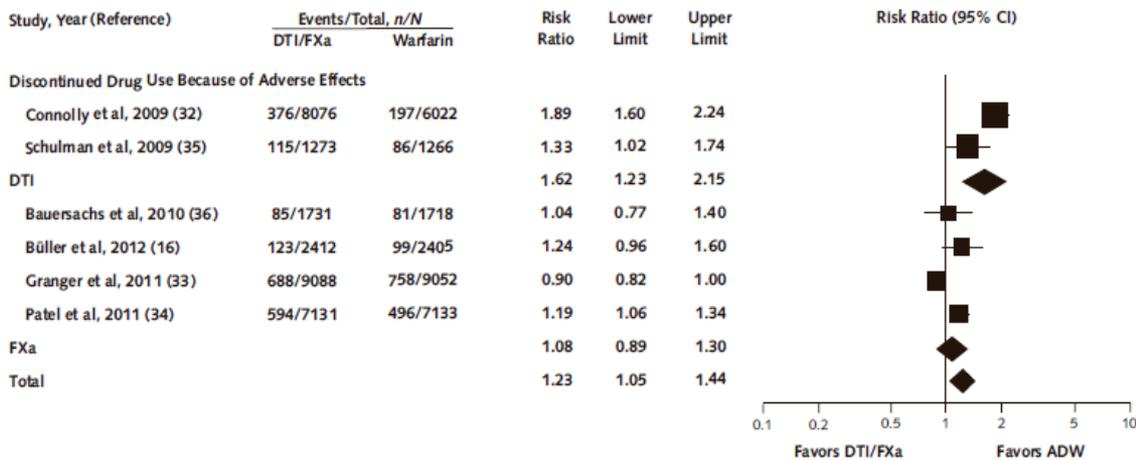
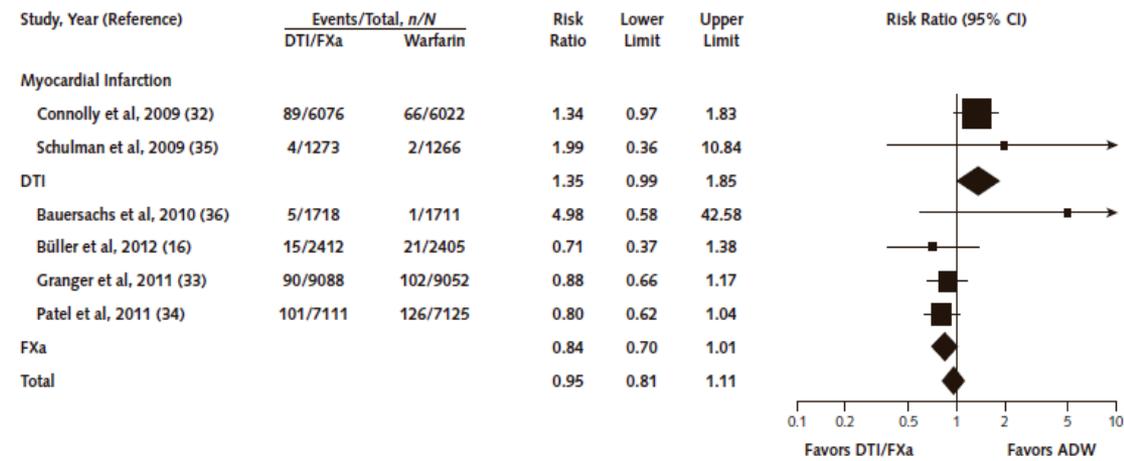


Table 3. Summary of the Strength of Evidence for Adverse Effects for Atrial Fibrillation and Venous Thromboembolism Combined

Outcome	Strength of Evidence	Summary
Fatal bleeding	Moderate	The risk for fatal bleeding was lower with NOACs (RR, 0.60 [95% CI, 0.46 to 0.77]). Risk difference was 1 fewer death per 1000 patients.
Major bleeding	Low	The risk for major bleeding was lower with NOACs (RR, 0.80 [CI, 0.63 to 1.01]), but the CI included no effect. In 2011, the FDA issued a notice that it was evaluating reports of serious bleeding with dabigatran.
Gastrointestinal bleeding	Low	The risk for gastrointestinal bleeding was increased with NOACs (RR, 1.30 [CI, 0.97 to 1.73]).
Myocardial infarction	Low	The risk for myocardial infarction was not different with NOACs (RR, 0.95 [CI, 0.81 to 1.11]). In a subgroup analysis, the risk was increased with dabigatran (RR, 1.35 [CI, 0.99 to 1.85]) compared with FXa inhibitors (RR, 0.84 [CI, 0.70 to 1.01]) ($P = 0.010$).
Discontinuation due to adverse effects	Low	Discontinuation due to adverse effects was higher with NOACs (RR, 1.23 [CI, 1.05 to 1.44]), but the CI was large and included no effect. In subgroup analysis, rates of discontinuation were higher for dabigatran than for FXa inhibitors.
Liver dysfunction	Low	The risk for liver dysfunction was not different with NOACs (RR, 0.82 [CI, 0.56 to 1.18]).

FDA = Food and Drug Administration; FXa = factor Xa; NOAC = new oral anticoagulant; RR = risk ratio.

Observational Studies

Bleeding :

- seven case reports; typically older patients >75 years and some with fatal outcome. Other risk factors include renal impairment and concomitant thrombolytic therapy.

Treatment failure:

- Two case reports; thrombolytic therapy successfully used in both.

RELY STUDY

- 40% were \geq 75 years
- Higher risk of extracranial but not intracranial bleeding with Dabigatran vs. Warfarin in patients >75 years
- Not in younger patients
- Greatest benefit of Dabigatran 150 mg bid was seen in those <65
- Dabigatran 110 mg not superior to 150 mg bid in >75 yo
- Dose modification in elderly is thus unnecessary

RELY STUDY

- Gastrointestinal bleeding increased
- Lower bioavailability which increases the concentration of active drug in the feces.
- Discontinuation of drug higher in dabigatran vs. warfarin (21% to 17%) mainly due to GI symptoms
- GI symptoms increased due to Tartaric acid(necessary for absorption) and a high concentration of active drug in the colon.

Blech, Drug Metab Dispos. 2008
Connolly, N Engl J Med. 2009
Shulman, Blood, 2012

ROCKET-AF STUDY

- Rivaroxaban associated with increased risk of GI bleeding
- Dabigatran and rivaroxaban may complicate the management of inflammatory bowel disease, angiodysplasia and diverticulosis.

Patel, N Eng J Med. 2011

Subanalysis

Myocardial infarction:

- SR including seven RCT's ; two on AF, three on thromboprophylaxis in orthopedic surgery and one on acute coronary syndrome.
- Three compared dabigatran to adjusted dose warfarin
- RE-LY study dominated other RCT's
- Dabigatran was associated with a higher risk for MI than control treatments (RR, 1.32 [CI, 1.02 to 1.69])

FDA Reports

Dabigatran

- In 2011 there were 3781 reports attributed to dabigatran; 2367 hemorrhages, 291 acute renal failure, 644 strokes, 542 deaths and 15 cases of suspected liver failure.
- More often in the elderly >80 years
- Recommendation to re-evaluate dose in elderly and those with renal impairment.

Rivaroxaban

- Post-treatment discontinuation events higher with rivaroxaban compared to ADW (HR, 1.51 [CI, 1.02 to 2.23])
- Could be attributed to subtherapeutic INR when transitioning from ADW to rivaroxaban

Key Points

- NOAC viable option for patients on long-term anticoagulation
- Benefits compared to warfarin are evident in centers with less warfarin therapy control
- Older adults and those with renal failure may need dose adjustments
- Long-term complications not evaluated thus far
- No head to head comparisons to evaluate drug classes or individual drugs
- FDA issued reports on bleeding complications
- Cost effective but not cost saving

Summary And Key Points

In AF populations:

- NOAC are superior to adjusted dose warfarin for some clinical outcomes, including mortality and hemorrhagic stroke

In VTE populations:

- Main clinical outcomes were similar in NOAC treatment groups compared to adjusted dose warfarin

Summary And Key Points

Bleeding by drug class

- Fatal bleeding was statistically significantly lower with FXa than with warfarin (<0.001) but not with dabigatran ($p=0.175$)
- Gastrointestinal bleeding showed a non-statistical increase with dabigatran compared to FXa.

Adverse events by drug class

- Discontinuation due to adverse events higher with dabigatran (RR, 1.62 [CI, 1.23 to 2.15]; low SOE) than FXa inhibitors (RR, 1.08 [CI, 0.89 to 1.30]) (P 0.024 for subgroup comparison)
- Myocardial infarction higher with dabigatran treatment (RR, 1.35 [CI, 0.99 to 1.85]), compared to treatment with FXa inhibitors (RR 0.84[CI, 0.70to 1.01]).

Is Warfarin Still The Preferred Option?

- Elderly patients >75
- Patients with a CrCl <30ml/min
- Patients with mechanical heart valves
- Patients with GI disease
- Non-compliant patients

AUDIENCE POLL

Will you change your practice based on the information presented today ?

- Highly likely
- Likely
- Unlikely
- Not sure