Anticoagulation in the Perioperative Period

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Disclosure Statement

- Consultant
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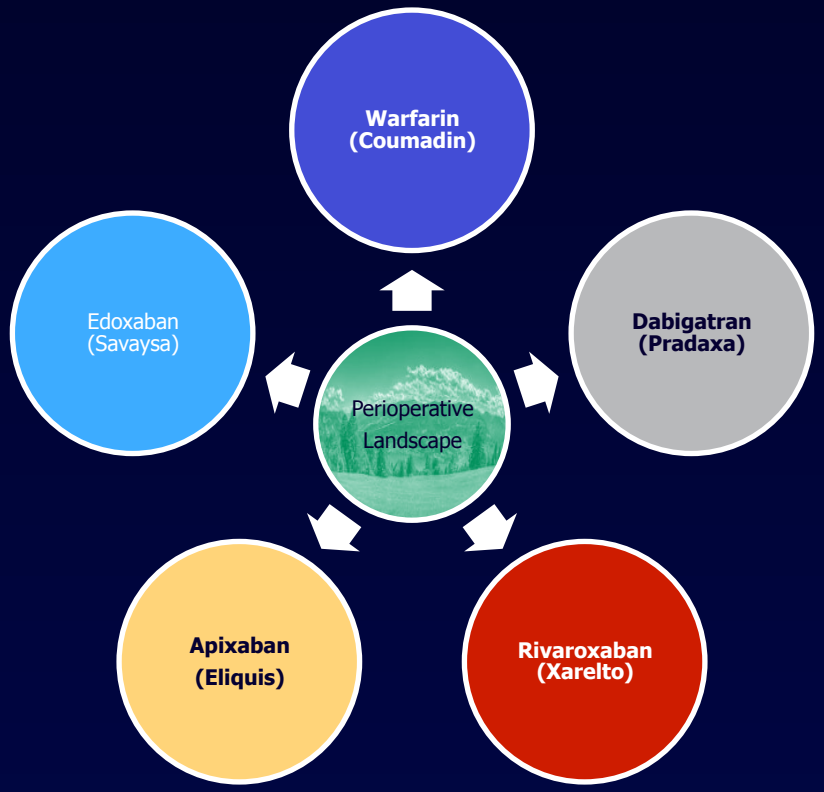
- Research and Grant Support
  - NHLBI, Astra-Zeneca
- Board Member
  - Society of Perioperative Assessment and Quality Improvement (SPAQI)

Anticoagulation in the Perioperative Period has Become More Challenging



- Pharmacokinetics of the Direct Oral Anticoagulants (DOACs) are different
- Lack of Level 1 evidence
- Varying Knowledge about DOACs amongst clinicians
- Litigation

Mr. S

A 60 year-old man with a mechanical bileaflet Mitral valve replacement 5 years ago is scheduled for ventral Hernia repair. He is on warfarin and his last INR was 2.5. He has no other significant PMH.

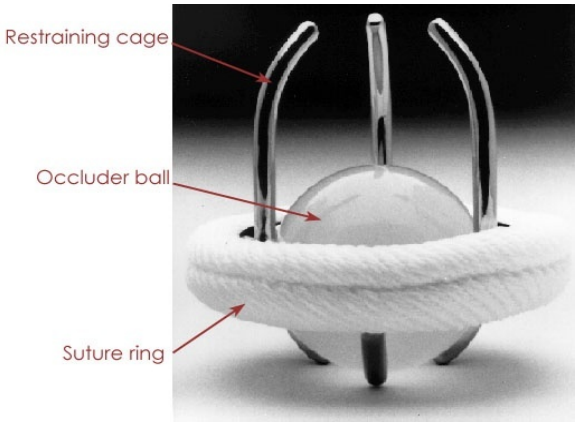
What would you recommend for Perioperative Anticoagulation Management?

1. Stop warfarin 5 days preop and proceed to surgery; restart warfarin night of the procedure
2. Stop warfarin 5 days preop, bridge with LMWH preop, restart warfarin and full dose LMWH 1 day postop
3. Stop warfarin 5 days preop, bridge with LMWH preop, restart warfarin 1 day postop and prophylactic dose LMWH 1-3 days postop followed by full dose of LMWH
4. Stop warfarin 5 days preop, admit for IV UFH, restart warfarin and full dose UFH 1 day postop
5. Stop warfarin 1 day preop and restart it 1 day postop

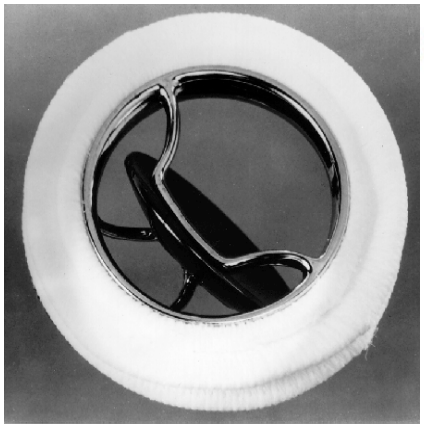
Thrombotic Risk with Mechanical Heart Valves

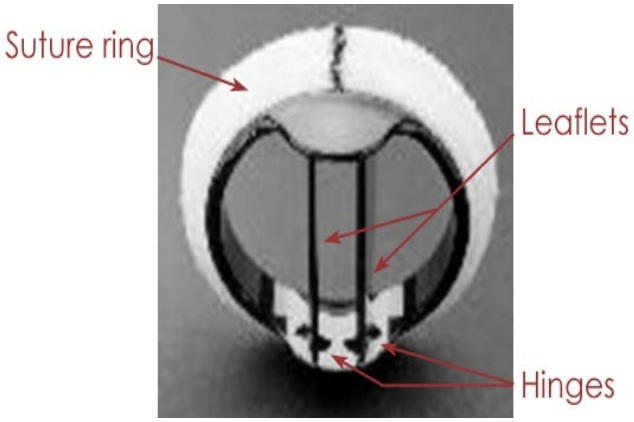
mitral >> aortic

caged ball > tilting disc > bileaflet



Starr-Edwards





→ decreasing thrombotic risk →

Ninth American College of Chest Physicians (ACCP) Recommendations
Risk Stratification

Risk	MHV	AF	VTE
High (>10%/yr risk of TE)	Any MV, older Valve, recent stroke or TIA	CHADS2=5 or 6, recent stroke or TIA or RHD	VTE<3 mths, severe thrombophilia
Moderate (5-10% risk of TE)	Bileaflet AV and one of the following: CHADS	CHADS2=3 or 4	VTE 3-12 mths, recurrent VTE, active cancer
Low (< 5% TE)	Bileaflet AV without AF and no other RF	CHADS2=0-2 (No stroke or TIA)	Single VTE> 12 mths

Douketis et al. *Chest* 2012;141: e326S-350S

Ninth ACCP Recommendations
Perioperative Management of Patients Receiving Vitamin K Antagonists

- High Risk for Thromboembolism
  - bridging anticoagulation (Grade 2C)
- Moderate Risk for Thromboembolism
  - Bridging or no bridging depending on the individual patient or surgery related factors
- Low risk for Thromboembolism,
  - No bridging (Grade 2C)

Values and preferences:

Patients who place a higher value on avoiding perioperative bleeding than on avoiding perioperative thromboembolism are likely to decline heparin bridging

Douketis et al. *Chest* 2012;141: e326S-350S

Managing the patient on Antithrombotic Therapy undergoing an Elective Surgery?

Patient Risk Factors

1. Identify the Type of Antithrombotic, dose and indication
2. Patient's risk factors for thromboembolism (TE) and bleeding
3. Renal Function (CrCl-Cockroft & Gault Formula)
4. Hepatic function

Surgical Risk Factors

1. Type of Surgery or Procedure
2. Quantify risk of bleeding
3. Quantify risk of thromboembolism
4. Time off antithrombotic therapy
5. Type of Anesthesia

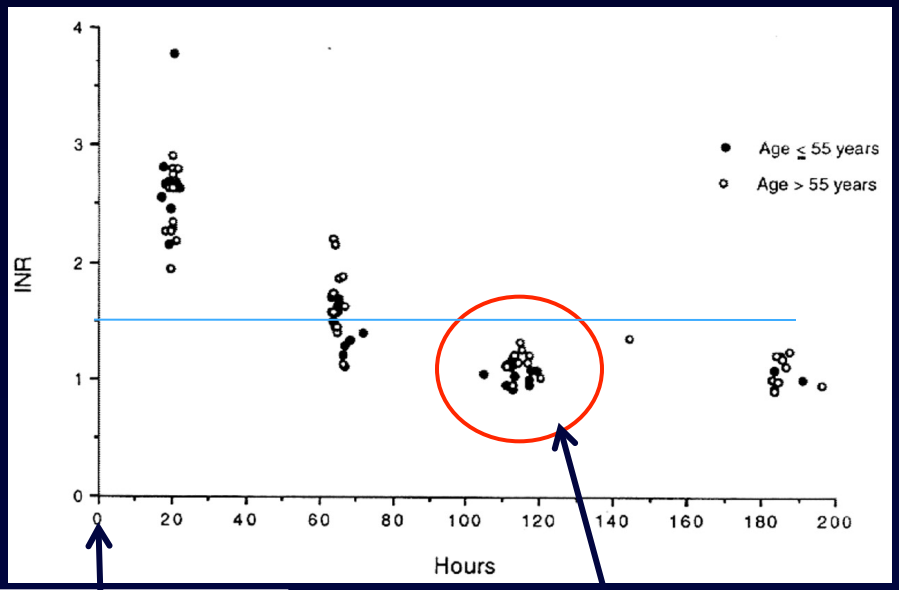
Weigh Consequences of Thrombosis, Thromboembolism & Bleeding (Patient and Provider Preferences)

↓

Establish an Individualized Perioperative Management Plan

How long before elective surgery should Warfarin be discontinued ?

- INR decreases exponentially
- Wide interpatient variation
- Increased age --> slower decrease
- INR 2-3, and goal INR<1.2, hold warfarin for 4 doses
- INR 3-4, and goal INR<1.2, hold warfarin for 5 doses
- Always check INR before surgery



White RH et al. *Annals of Internal Med. 1995* ; 122(1):40-2

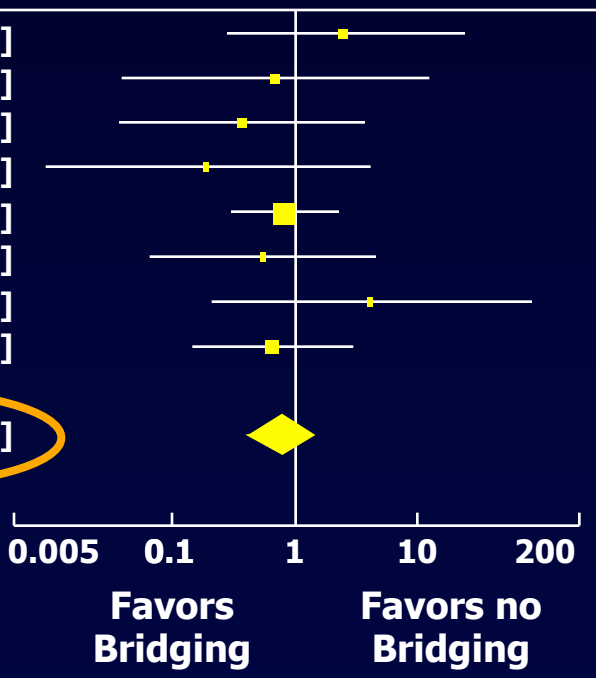
Thromboembolism: Bridging Vs No Bridging

Study or Subgroup	Bridging Events	Bridging Total	No Bridging Events	No Bridging Total	Weight	Odds Ratio M-H, Random, 95% CI
Daniels et al., 2009	4	342	1	213	8.8%	2.51 [0.28, 22.60]
Garcia et al., 2008	0	108	7	1185	5.2%	0.72 [0.04, 12.76]
Jaffer et al., 2010	1	229	3	263	8.2%	0.38 [0.04, 3.68]
Marquie et al., 2006	0	114	2	114	4.6%	0.20 [0.01, 4.14]
McBane et al., 2010	10	514	6	261	40.5%	0.84 [0.30, 2.35]
Tompkins et al., 2010	1	155	6	513	9.4%	0.55 [0.07, 4.59]
Varkarakis et al., 2005	0	25	3	762	4.7%	4.25 [0.21, 84.56]
Wysokinski et al., 2008	3	204	4	182	18.6%	0.66 [0.15, 3.01]
Total (95% CI)		1691		3493	100.0%	0.80 [0.42, 1.54]
Total events	19		32			

Heterogeneity: $Tau^2=0.00$; $Chi^2=3.68$, df=7 (P=0.82); $I^2=0\%$

Test for overall effect: Z=0.67 (P=0.50)

0.9% vs 0.6%



Siegel et al. Circulation 2012; 112.105221

Is a Simple Calculation really Accurate to Predict the Perioperative Risk of Thromboembolism?

- Rate of thromboembolism assumption
  - 0.011 % per day for 10 days =0.11 %
  - This rate is at least 10 times lower than what we see in practice
  - How do we explain this discrepancy?

Is the phenomenon of Perioperative Hypercoagulability the Answer?

- The surgical milieu can induce a hypercoagulable state
- The risk of VTE is 100-fold greater during the perioperative period relative to the non-operative period
  - Increased levels of plasminogen activator inhibitor-1.
- Studies demonstrate increases in factors that suggest "Rebound Hypercoagulability" may occur after discontinuation of oral anticoagulation
  - Prothrombin fragments F1+2
  - Thrombin-antithrombin (TAT) complexes
  - Fibrinopeptide A
  - D-dimer
  - Factor VIII

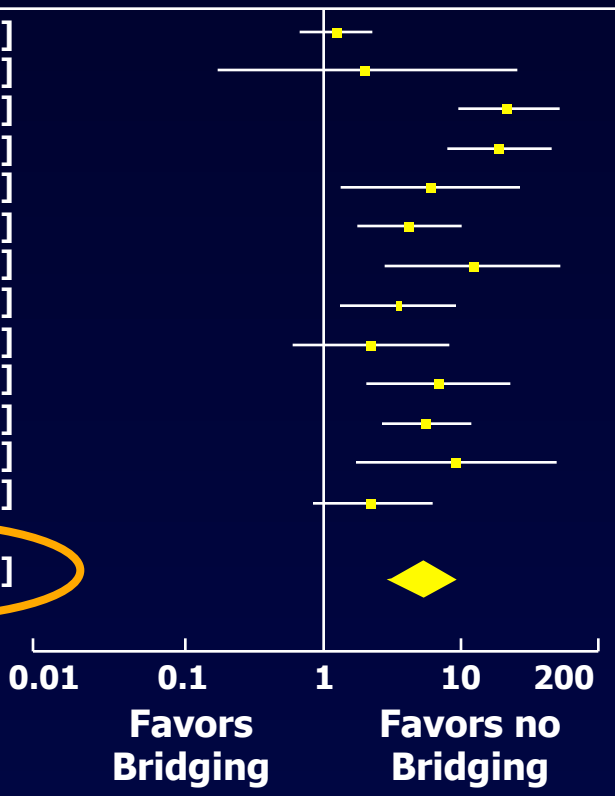
Genewein et al. Haemostasis and thrombosis 1996;92:479-485
Grip et al. European Heart Journal 1991;1225-1233
Palareti et al. Thrombosis and Haemostasis 1994; 72:222-226
Kearon et al. NEJM 1997;336:1506-11

Overall Bleeding: Bridging Vs No Bridging

Study or Subgroup	Bridging Events	Bridging Total	No Bridging Events	No Bridging Total	Weight	Odds Ratio M-H, Random, 95% CI
Daniels et al., 2009	36	342	18	213	9.8%	1.27 [0.70, 2.31]
Dotan et al., 2002	2	20	1	20	3.7%	2.11 [0.18, 25.35]
Ercab et al., 2010	11	44	21	1421	9.0%	22.22 [9.92, 49.81]
Garcia et al., 2008	14	108	9	1185	8.8%	19.46 [8.21, 46.14]
Ghanbari et al., 2010	6	29	3	74	6.5%	6.17 [1.43, 26.68]
Jaffer et al., 2010	24	229	7	263	8.8%	4.28 [1.81, 10.14]
Marquie et al., 2006	21	114	2	114	6.4%	12.65 [2.89, 55.34]
McBane et al., 2010	34	514	5	261	8.4%	3.63 [1.40, 9.39]
Robinson et al., 2009	20	113	3	35	7.2%	2.29 [0.64, 8.24]
Tischenko et al., 2009	9	38	5	117	7.6%	6.95 [2.16, 22.33]
Tompkins et al., 2010	23	155	15	513	9.5%	5.78 [2.94, 11.40]
Varkarakis et al., 2005	2	25	7	762	5.9%	9.38 [1.85, 47.64]
Wysokinski et al., 2008	15	204	6	182	8.4%	2.33 [0.88, 6.13]
Total (95% CI)		1935		5150	100.0%	5.40 [3.00, 9.74]
Total events	217		102			

Heterogeneity: $Tau^2=0.83$; $Chi^2=52.47$, df=12 ($P<0.00001$); $I^2=77\%$

Test for overall effect: $Z=5.61$ ($P<0.00001$)



13.6% vs 3.4%

Siegel et al. Circulation 2012; 112.105221

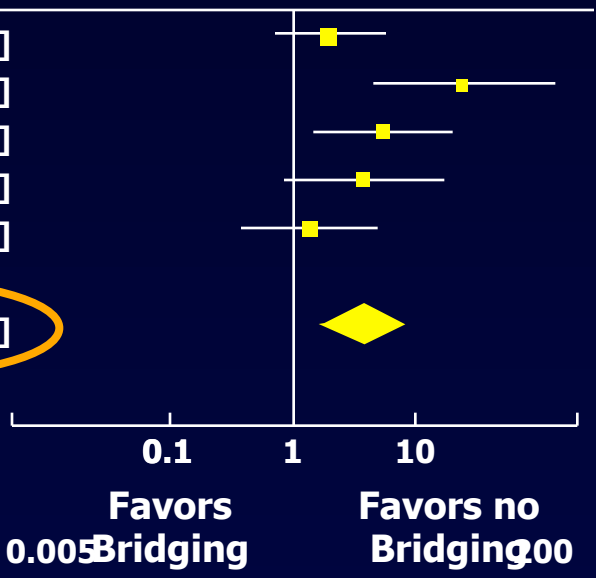
Major Bleeding: Bridging Vs No Bridging

Study or Subgroup	Bridging Events	Bridging Total	No Bridging Events	No Bridging Total	Weight	Odds Ratio M-H, Random, 95% CI
Daniels et al., 2009	15	342	5	213	24.9%	1.91 [0.68, 5.33]
Garcia et al., 2008	4	108	2	1185	15.3%	22.75 [4.12, 125.68]
Jaffer et al., 2010	13	229	3	263	21.0%	5.22 [1.47, 18.54]
McBane et al., 2010	14	514	2	261	17.9%	3.63 [0.82, 16.08]
Wysokinski et al., 2008	6	204	4	182	20.8%	1.35 [0.37, 4.86]
Total (95% CI)		1397		2104	100.0%	3.60 [1.52, 8.50]
Total events	52		16			

Heterogeneity: $Tau^2=0.50$; $Chi^2=8.41$, df=4 (P=0.08); $I^2=52\%$

Test for overall effect: Z=2.92 (P=0.004)

3.2% vs 0.9%



Siegel et al. Circulation 2012; 112.105221

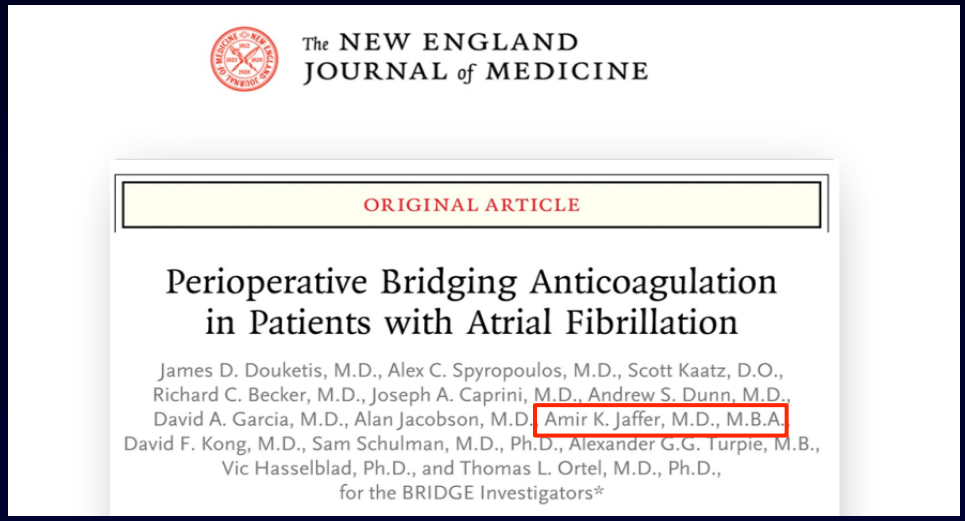
Mrs. X

A 78 year-old woman with atrial fibrillation and history of HTN and T2DM on warfarin is scheduled for a total abdominal hysterectomy. Her last INR was 2.2. Her CHADS2 score=3

What would you recommend for Perioperative Anticoagulation Management?

1. Stop warfarin 3 days preop and restart 1 day postop
2. Stop warfarin 5 days preop and restart 1 day postop
3. Stop warfarin 5 days preop, bridge with full dose LMWH preop, restart warfarin and full dose LMWH 1 -day postop
4. Stop warfarin 5 days preop, admit for IV UFH, restart warfarin and UFH 1 day postop

BRIDGE


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

James D. Douketis, M.D., Alex C. Spyropoulos, M.D., Scott Kaatz, D.O., Richard C. Becker, M.D., Joseph A. Caprini, M.D., Andrew S. Dunn, M.D., David A. Garcia, M.D., Alan Jacobson, M.D., Amir K. Jaffer, M.D., M.B.A., David F. Kong, M.D., Sam Schulman, M.D., Ph.D., Alexander G.G. Turpie, M.B., Vic Hasselblad, Ph.D., and Thomas L. Ortel, M.D., Ph.D., for the BRIDGE Investigators*

Bridging Anticoagulation in Patients Who **R**equire Temporary **I**nterruption of Warfarin Therapy for an Elective Proce**d**ure or Sur**ge**ry

Thomas L. Ortel, MD, PhD,
on behalf of the BRIDGE Investigators and Committees

The BRIDGE trial was funded by the U.S. National Heart, Lung, and Blood Institute of the U.S. National Institutes of Health

Duke Clinical Research Institute

NIH National Heart, Lung, and Blood Institute

Hypotheses

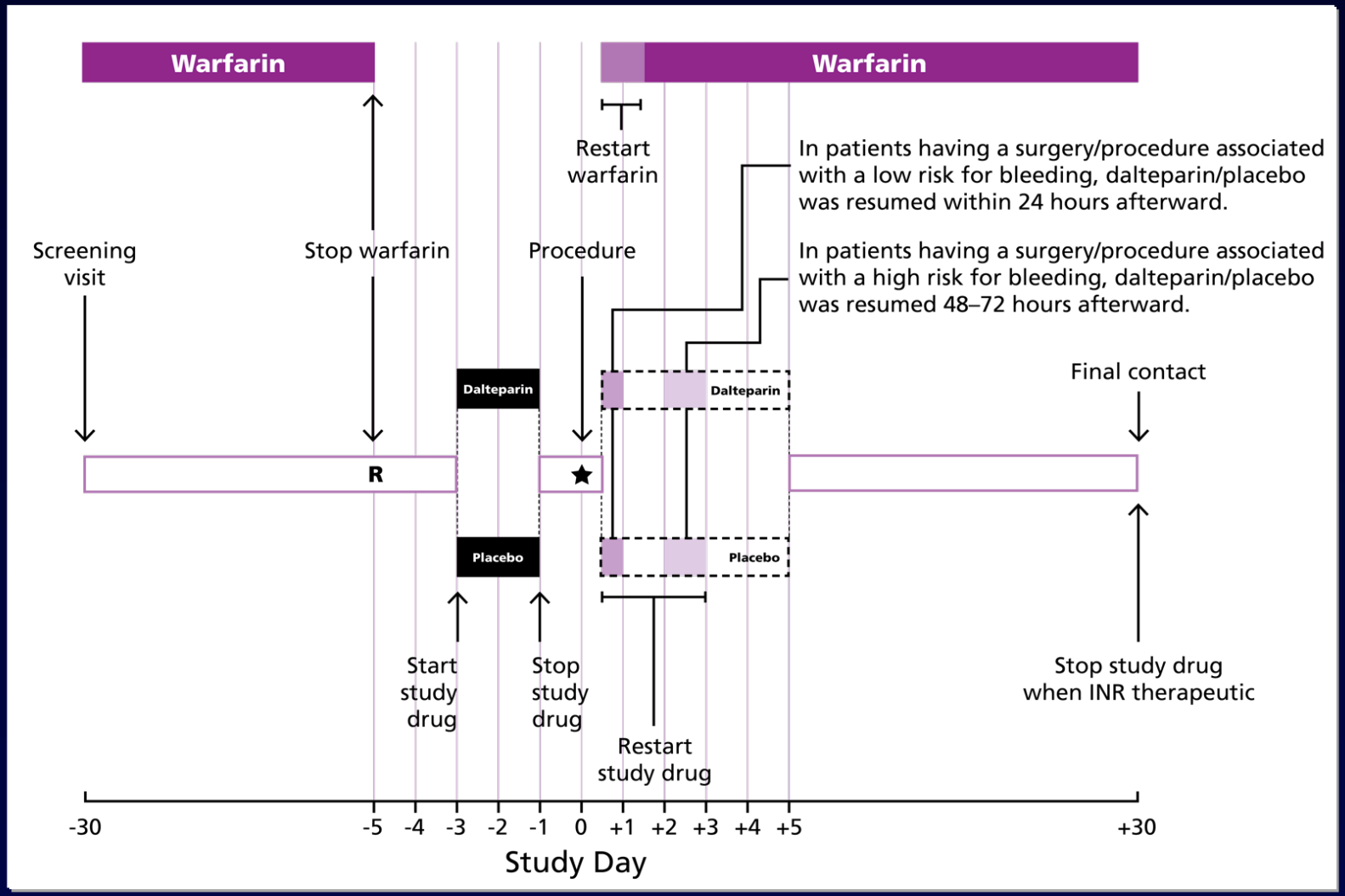
We hypothesized that:

1. Forgoing bridging anticoagulation in patients with atrial fibrillation (AF) who needed warfarin held for an operation or invasive procedure would be non-inferior to bridging with LMWH for the prevention of perioperative arterial thromboembolism (ATE)

   - and –

2. Forgoing bridging anticoagulation would be superior to bridging with respect to major bleeding

Trial Design



Inclusion Criteria

- 18 years or older
- Chronic (permanent or paroxysmal) AF or atrial flutter, confirmed by electrocardiography or pacemaker interrogation
- AF associated with valvular disease, including mitral valve disease
- Received warfarin therapy for 3 months or longer, with a target INR therapeutic range of 2.0–3.0
- Undergoing an elective operation or invasive procedure requiring warfarin interruption
- At least one of the following $CHADS_2$ stroke risk factors:
  - Congestive heart failure or left ventricular dysfunction
  - Hypertension
  - 75 years or older
  - Diabetes mellitus
  - Previous ischemic stroke, systemic embolism, or transient ischemic attack (TIA)

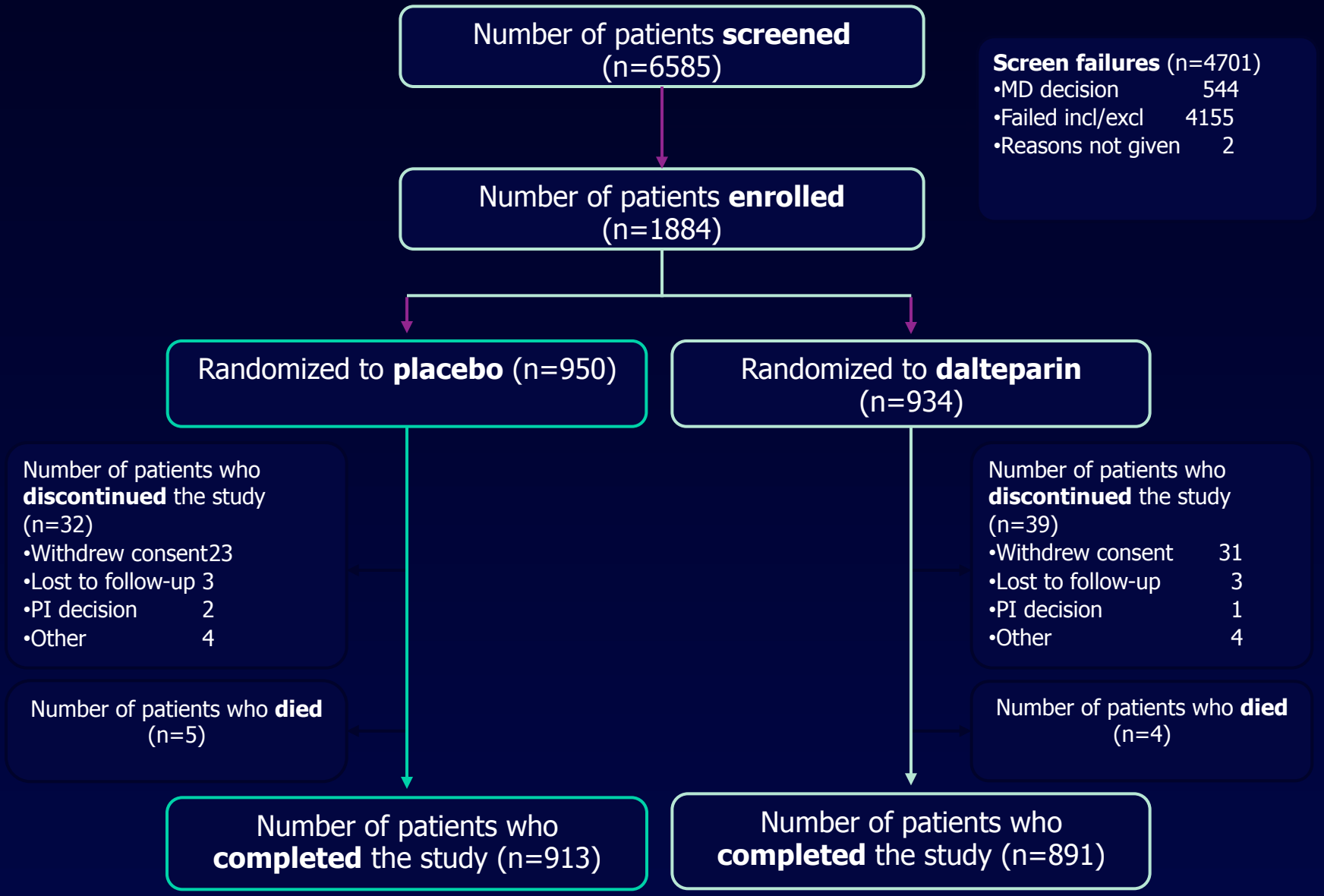
Exclusion Criteria

- Mechanical heart valve
- Stroke, systemic embolism, or TIA within previous 12 weeks
- Major bleeding within previous 6 weeks
- Venous thromboembolism within the previous 12 weeks
- Creatinine clearance <30 mL/min
- Platelet count $<100\times10^3$ per cubic millimeter
- Planned cardiac, intracranial, or intraspinal surgery
- Unable or unwilling to provide informed consent

Outcomes

- Primary Outcomes
  - Arterial thromboembolism
    - Stroke, systemic embolism, or TIA
  - Major bleeding
- Secondary Outcomes
  - Acute myocardial infarction, venous thromboembolism, or death
  - Minor bleeding

Patient Population



Patient Characteristics

Characteristic	No Bridging (N=950)	Bridging (N=934)
Age, yr	71.8±8.74	71.6±8.88
Male sex, no. (%)	696 (73.3)	686 (73.4)
Race, no. (%)		
White	860 (90.5)	849 (90.9)
Nonwhite	88 (9.3)	82 (8.8)
Unknown	2 (0.2)	3 (0.3)
Weight, kg	96.2±24.87	95.4±23.50
$CHADS_2$ score		
Mean	2.3±1.03	2.4±1.07
Distribution, no. (%)		
0	1 (0.1)	1 (0.1)
1	216 (22.7)	212 (22.7)
2	382 (40.2)	351 (37.6)
3	229 (24.1)	232 (24.8)
4	96 (10.1)	106 (11.3)
5	23 (2.4)	27 (2.9)
6	3 (0.3)	5 (0.5)

Patient Characteristics

Characteristic	No Bridging (N=950)	Bridging (N=934)
CHF or left ventricular dysfunction, no. (%)	289 (30.4)	310 (33.2)
Hypertension, no. (%)	833 (87.7)	806 (86.3)
Diabetes mellitus, no. (%)	390 (41.1)	382 (40.9)
Stroke, no. (%)	79 (8.3)	99 (10.6)
TIA, no. (%)	79 (8.3)	77 (8.2)
Mitral valve disease, no. (%)	165 (17.4)	142 (15.2)
Stenosis	19 (2.0)	10 (1.1)
Regurgitation	142 (14.9)	133 (14.2)
Prolapse	13 (1.4)	5 (0.5)
Laboratory values		
INR	2.4±0.57	2.4±0.57
Creatinine clearance, mL/min	88.1±39.50	87.6±40.14

Surgeries and Procedures*

Surgery/Procedure Type	No Bridging	Bridging
Minor, no. (%)	(n=781)	(n=758)
Gastrointestinal	391 (50.1)	357 (47.1)
Cardiothoracic	139 (17.8)	151 (19.9)
Orthopedic	54 (6.9)	47 (6.2)
Urologic	41 (5.3)	45 (5.9)
Other	156 (19.9)	158 (20.9)
Major, no. (%)	(n=94)	(n=89)
Orthopedic	29 (30.9)	29 (32.6)
Urologic	26 (27.7)	20 (22.5)
General surgery	16 (17.0)	14 (15.7)
Other	23 (24.5)	26 (29.2)

** Initial classification of surgery/procedure was not always aligned to post-procedure bleeding risk designation*

Perioperative Anticoagulant Management

Variable		No Bridging (N=950)	Bridging (N=934)	P Value
Warfarin treatment				
Preprocedure time not taking warfarin	Patients with data, no.	872	839	0.28
	Mean, days	5.2±1.4	5.3±1.8	
Time to first post procedure warfarin dose	Patients with data, no.	735	696	0.40
	Mean, days	1.5 (1.3)	1.4 (1.0)	
Aspirin treatment, no./total no. (%)				
Interruption ≥7 days before procedure		92/324 (28.4)	92/329 (28.0)	
Interruption <7 days before procedure		41/324 (12.7)	33/329 (10.0)	0.53
No interruption		191/324 (59.0)	204/329 (62.0)	

Perioperative Anticoagulant Management

Variable		No Bridging (N=950)	Bridging (N=934)	P Value
LMWH or placebo				
Preprocedure dose	Patients with data, no.	796	768	0.61
	Mean no. of doses	5.0±0.7	5.0±1.4	
Patients in whom last dose was taken on the morning of the day before the procedure, no./total no.		778/796 (97.7)	734/768 (95.6)	0.01
Time to first postprocedure dose				
Major surgery/ procedure (high bleeding risk)	Patients with data, no.	235	223	0.74
	Mean, hr	53.3±31.6	51.3±27.9	
Minor surgery/ procedure (low bleeding risk)	Patients with data, no.	526	497	0.74
	Mean, hr	21.1±2.3	21.0±2.4	
Post procedure doses	Patients with data, no.	764	721	0.47
	Mean no. of doses	15.7±7.4	16.1±8.4	

Primary Outcomes

Outcome No. (%)	No Bridging (N=918)	Bridging (N=895)	P Value
ATE (non-inf) (sup)	4 (0.4)	3 (0.3)	0.01 0.73
Stroke	2 (0.2)	3 (0.3)	
TIA	2 (0.2)	0 (0)	
Systemic embolism	0 (0)	0 (0)	
Major bleeding (sup)	12 (1.3)	29 (3.2)	0.005

The mean CHADS2 score in patients who sustained a thromboembolic event was 2.6 (range, 1-4)
The median time to an arterial thromboembolic event was 19.0 days (IQR, 6.0-23.0 days)
The median time to a major bleeding event after a procedure was 7.0 days (IQR, 4.0-18.0 days)

Secondary Outcomes

Outcome No. (%)	No Bridging (N=918)	Bridging (N=895)	P Value
Death (sup)	5 (0.5)	4 (0.4)	0.88
Myocardial infarction (sup)	7 (0.8)	14 (1.6)	0.10
Deep vein thrombosis (sup)	0 (0)	1 (0.1)	0.25
Pulmonary embolism (sup)	0 (0)	1 (0.1)	0.25
Minor bleeding (sup)	110 (12.0)	187 (20.9)	<0.001

Limitations

- Few patients had a high CHADS2 score (e.g., 5–6)
- Most patients underwent low-risk procedures, such as colonoscopy or ambulatory surgery
- Overall rate of ATE was lower than initial projections
- Findings should not be applied to patients with mechanical heart valves or venous thromboembolism
- Findings are not applicable to patients with AF treated with a direct oral anticoagulant

BRIDGE: Conclusion

- For patients with AF who require temporary interruption of warfarin treatment for an elective operation or invasive procedure, a strategy of forgoing bridging anticoagulation was non-inferior to perioperative bridging with LMWH for prevention of arterial thromboembolism
- Forgoing bridging treatment also decreased the risk of major bleeding compared to perioperative bridging with LMWH

Mrs. Z

- 76 yo female with HTN, DM, HF and Atrial Fibrillation is undergoing Laminectomy for severe back pain. The patient's Creatinine is 1.8. She weighs about 75 kg. She takes Dabigatran 150 mg po BID.

The last dose of Dabigatran should be taken when?

1. 5-days before surgery (8-doses)
2. 4-days before surgery (6-doses)
3. 3-days before surgery (4-doses)
4. 2-days before surgery (2-doses)
5. 1-day before surgery (hold only day of surgery doses)

Overview of Pharmacology of DOACs: Impact of PK/PD

	Dabigatran[1]	Rivaroxaban[2]	Apixaban[3]	Edoxaban[4-7]
Drug class	Direct factor IIa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Time to C_{max}	1 h	2-4 h	3-4 h	1-2 h
CYP metabolism	None	CYP3A4/5, CYP2J2, and hydrolysis are the major means of biotransformation	Mainly by CYP3A4	62% fecal elimination
Renal excretion (unchanged drug)	80% of absorbed dose	66% of total dose; 36% of absorbed dose	27%	35% of total dose; 49% of absorbed dose
Half-life	12-17 h	5-9 h	≈12 h	9-11 h
Dosing frequency for NVAF	BID	QD	BID	QD

C_{max}, time to maximum concentration; PK/PD, pharmacokinetics/pharmacodynamics

1. Pradaxa (dabigatran etexilate mesylate) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc.; 9/2014. 2. Xarelto (rivaroxaban) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 9/2014. 3. Eliquis (apixaban) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 8/2014. 4. Camm AJ et al. *Drugs*. 2011;71:1503-1526. 5. Ogata K et al. *J Clin Pharmacol*. 2010;50:743-753. 6. Eikelboom JW et al. *Circulation*. 2010;121:1523-1532. 7. Bathala M et al. *Drug Metab Dispos*. 2012;40:2250-22

Preoperative Interruption of DOACs: An Empiric Formulation

Drug (Half-Life)	Renal Function	Aim for No or Minimal Residual Anticoagulant Effect at Surgery (4-5 Drug Half-Lives Separate Last Dose & Surgery)	Aim for Mild-moderate Residual Anticoagulant Effect at Surgery (2-3 Drug Half Lives Separate Last dose & Surgery)
Dabigatran $t_{1/2}$ = 14 hrs	Normal or Mild Impairment (CrCl >50 mL/min)	Last dose: Day -3 before surgery (skip 4 doses)	Last dose: Day -2 before surgery (skip 2 doses)
$t_{1/2}$ = 15-18 hrs	Moderate Impairment (CrCl 30-50 mL/min)	Last dose: Day -4 to Day -5 before surgery (skip 6-8 doses)	Last dose: Day -3 before surgery (skip 4 doses)
Rivaroxaban $t_{1/2}$ = 9 hrs	Normal or Mild Impairment (CrCl >50 mL/min)	Last dose: Day -3 before surgery (skip 4 doses)	Last dose: Day -3 before surgery (skip 2 doses)
Apixaban $t_{1/2}$ = 9 hrs	as with rivaroxaban	as with rivaroxaban	as with rivaroxaban

Douketis. Current Pharmaceutical Design, 2010, Vol 16, No 31

Postoperative Resumption of DOACs: An Empiric Formulation

	Minor surgery or Procedure (low bleeding risk)	Major surgery (high bleeding risk)
Dabigatran	resume on day after surgery (24 hrs postoperatively), 150 mg twice-daily	resume 2 days after surgery (48 hrs postoperatively), 150 mg twice-daily*
Rivaroxaban	resume on day after surgery (24 hrs postoperatively), 10 mg daily	resume 2 days after surgery (48 hrs postoperatively), 10 mg daily
Apixaban	as with rivaroxaban	as with rivaroxaban

*for patients at high risk for thromboembolism, consider administering a reduced dose of dabigatran eg., 110-150 mg once-daily) on evening after surgery and on the first postoperative day.

Douketis. Current Pharmaceutical Design, 2010, Vol 16, No 31

Periprocedural Management of DOACs: Postprocedure Timing of DOAC Resumption

- Depends solely on the postoperative risk for bleeding[1,2]
  - Risk for major bleeding complications postsurgery clearly outweighs risk for thromboembolism[1]
    - For major abdominal or urologic surgery: Delay DOACs until no drainage or signs of active bleeding
    - For procedures with good hemostasis shortly afterwards: Resume NOACs a minimum of 4-6 h postsurgery
    - In the case of bowel paralysis, bridging with a parenteral anticoagulant may be required
- Dabigatran, rivaroxaban, and apixaban should be resumed 24-48 h after minor procedure, or 48-72 h after major surgery, assuming that hemostasis achieved[2]
- Dabigatran, Rivaroxaban, Abixaban resume with half-dose for 1-3d depending on surgery, then resume usual maintenance dose[1]

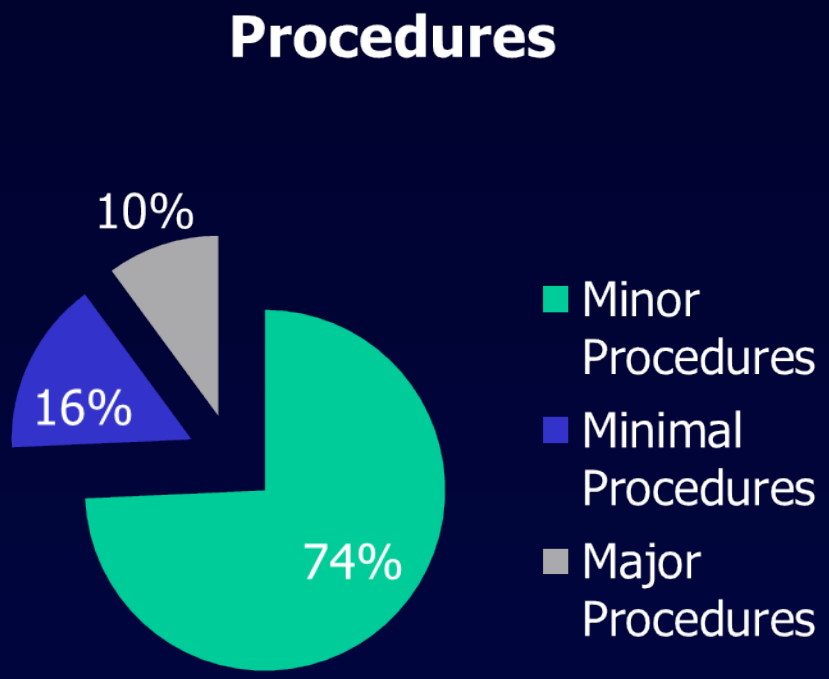
1. Schulman S et al. *Blood*. 2012;119:3016-3023. 2. Nutescu EA. *Am J Health-Syst Pharm*. 2013;70(Suppl 1)S2-S11

Do you recommend Bridging with LMWH given a CHADS2 score of 4?

1. Yes
2. No

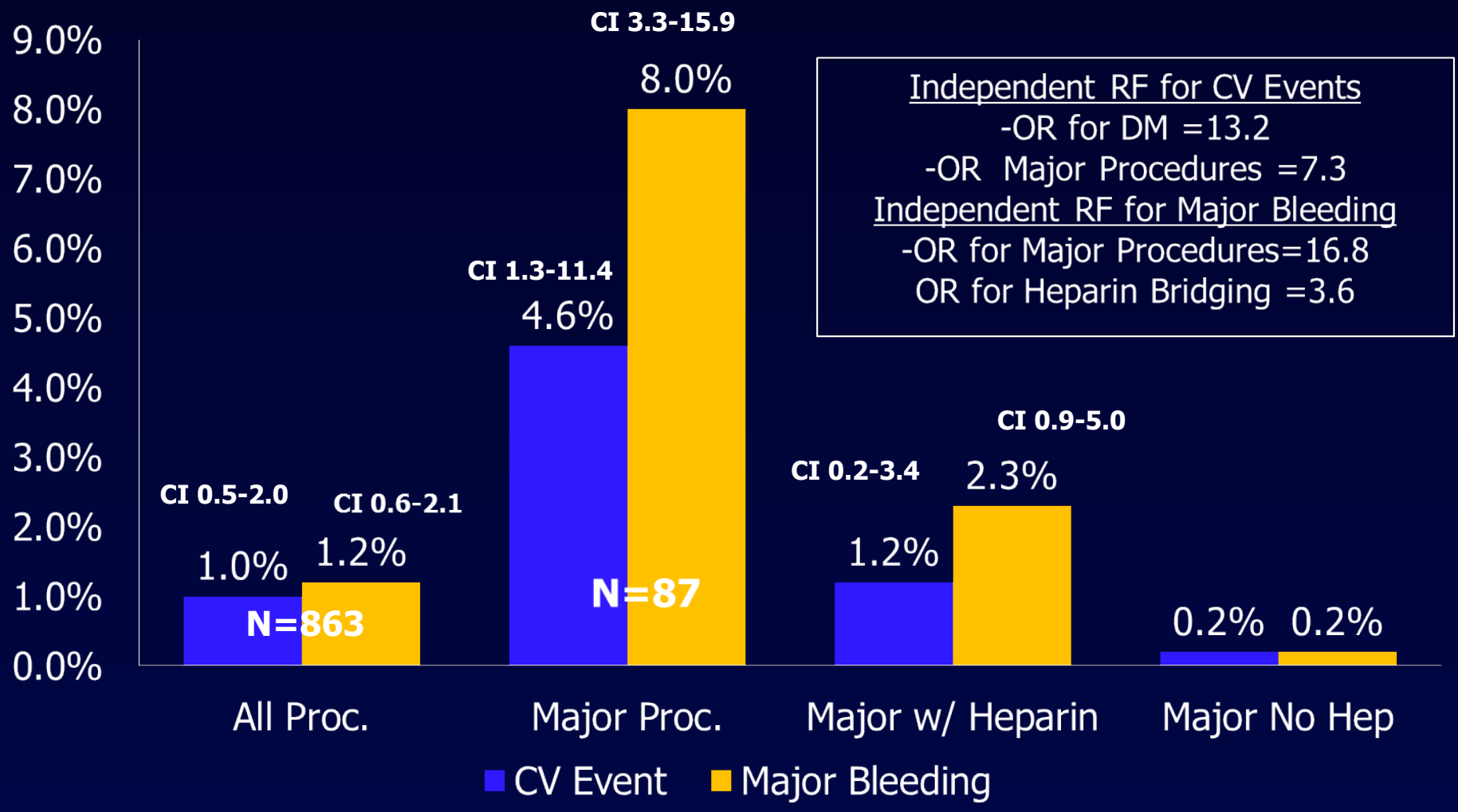
Peri-interventional Management of NOACs: Results from the Dresden Registry

- Evaluation of NOAC management in unselected patients from daily care
- 2179 Patients on NOACs
- 595 underwent 863 procedures, median age 74
- Outcomes adjudicated using standard event definitions

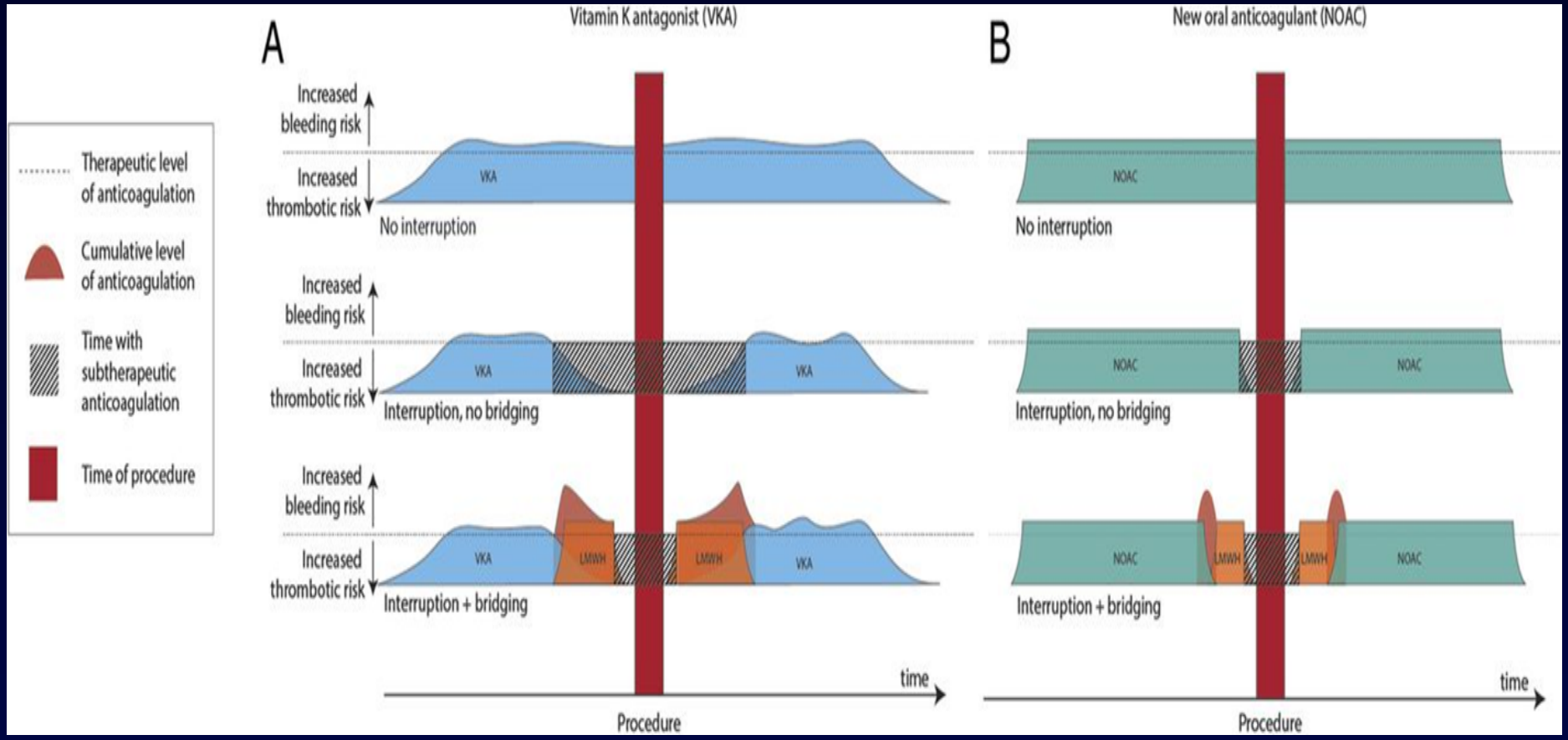


Minimal Procedures were procedures with little tissue trauma
Minor procedures were procedures with little tissue trauma but relevant bleeding risk
Major procedures were procedures with relevant tissue trauma and high bleeding risk

Results


9.0%
8.0%
7.0%
6.0%
5.0%
4.0%
3.0%
2.0%
1.0%
0.0%
CI 0.5-2.0
1.0%
CI 0.6-2.1
1.2%
N=863
CI 1.3-11.4
4.6%
CI 3.3-15.9
8.0%
N=87
CI 0.2-3.4
1.2%
CI 0.9-5.0
2.3%
0.2%
0.2%
All Proc.
Major Proc.
Major w/ Heparin
Major No Hep
CV Event
Major Bleeding
Independent RF for CV Events
-OR for DM =13.2
-OR Major Procedures =7.3
Independent RF for Major Bleeding
-OR for Major Procedures=16.8
OR for Heparin Bridging =3.6

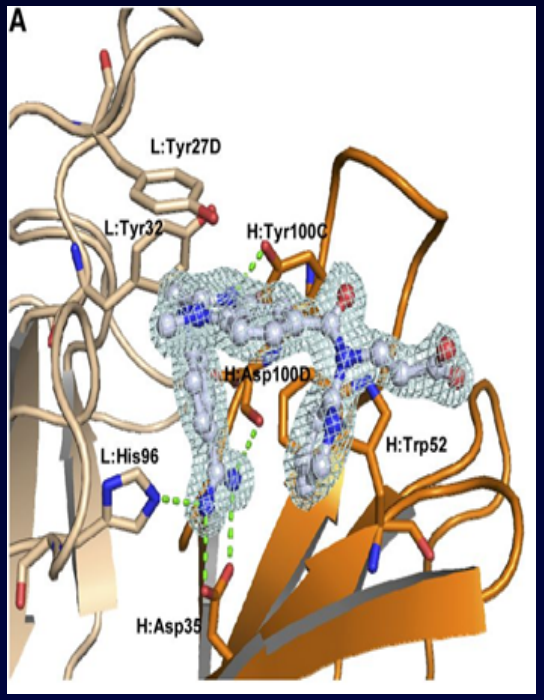
Periprocedural Management strategies for Anticoagulant Therapy.



Vanassche T et al. Eur Heart J 2014;eurheartj.ehu034

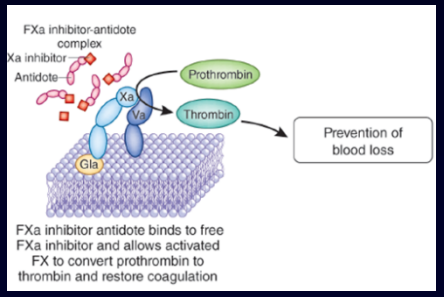
REVERSE-AD Interim Analysis

- 2.5 g IV of Idarucizumab (Praxabind) given in 2 doses
- 90 patients on Dabigatran {90% for Afib} (median age 76.5 years; 56% men; median creatinine clearance 58 mL/min)
- 51 patients in group A had serious bleeding (16 of them hemodynamically unstable) and 39 in group B (urgent procedure).
- Median patient-reported time from last dabigatran dose was 15.4 hours. Quick Reversal Confirmed
- Median maximum percentage reversal of anticoagulation (primary endpoint) was 100% (95% CI 100-100) in groups A and B, as assessed by both dilute thrombin time and ecarin clotting time. Reversal occurred soon after 1st dose
- Serious Adverse Events: 21 patients (13 in group A and 8 in group B). Plus Deaths: 18 deaths and 5 thrombotic events, these included GI hemorrhage in 2 patients and post-op wound infection, delirium, right ventricular failure, and pulmonary edema in 1 patient each.

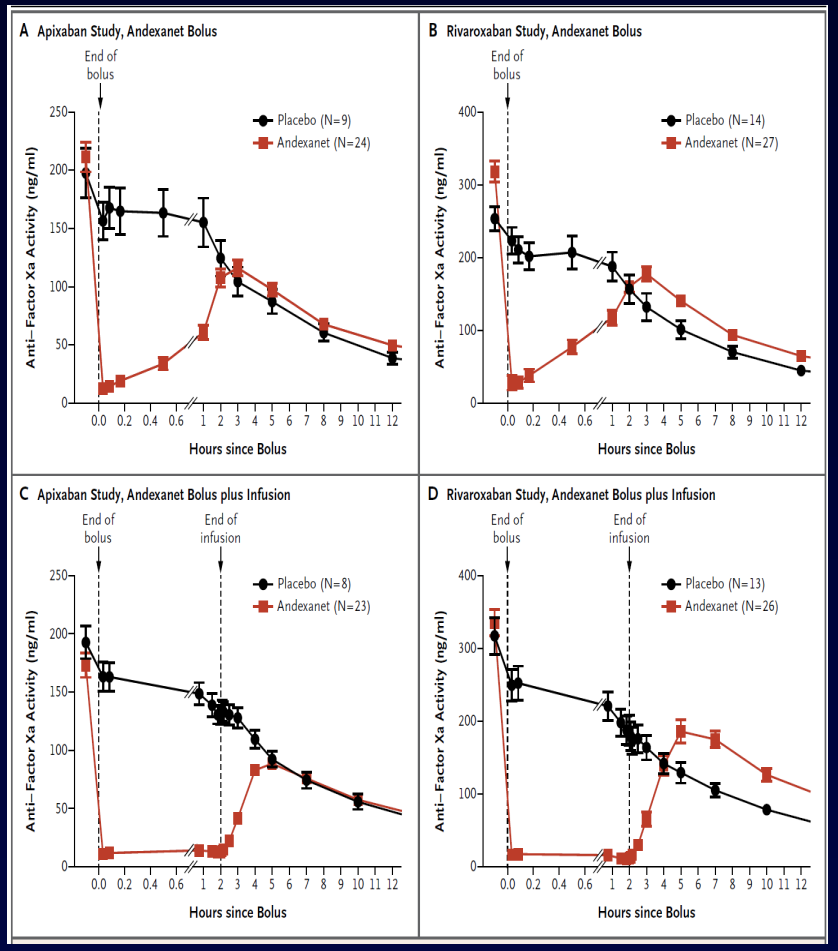


Pollack et al. NEJM 2015; 373:511-20

Andexanet Alpha

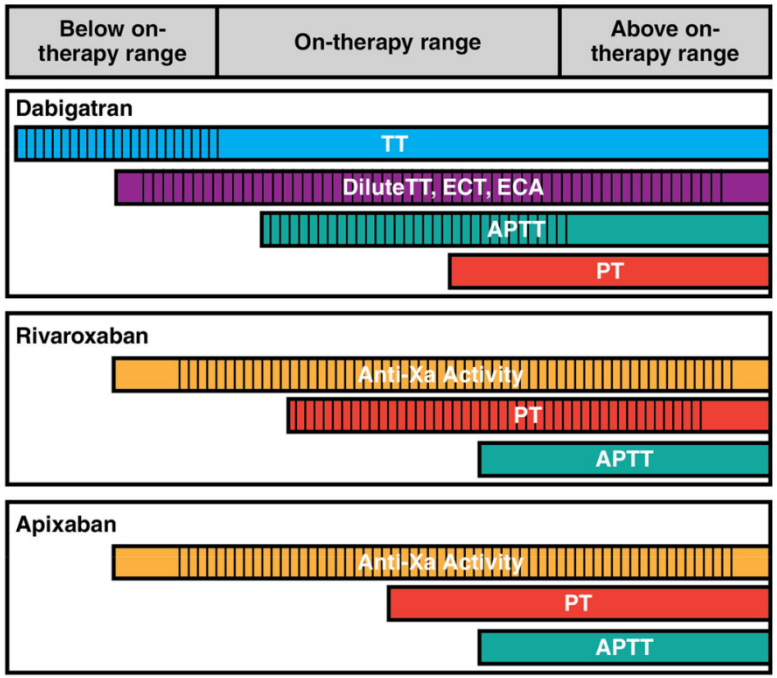


- Half life 1-hr
- Dose dependent reversible anticoagulant effect
- Annexa A and Annexa R were RCTs
- Anti-Xa levels were reduced 94% vs 21% & 92% vs. 18% respectively
- Dose different for apixaban and rivaroxaban
- Andexanet reveresd the activity within minutes after adminsitration and without clinical toxic effects



Siegal DM. N Engl J Med. 2015 Dec 17;373(25):2413-24.

Testing with DOACs



Horizontal bars and vertical hatching correspond to the approximate range of detectability (i.e., sensitivity) and linearity, respectively, of each assay to below, within, and above typical on-therapy concentrations of dabigatran, rivaroxaban, and apixaban. Ranges are approximations and may vary on the basis of choice of reagent.
APTT = activated partial thromboplastin time; ECA = ecarin chromogenic assay; ECT = ecarin clotting time; PT = prothrombin time; TT = thrombin time.

Burnett et al.
J of Thromb and Thrombolysis
2015: 41 (1) Issue 1 , 206-232

Conclusion

- Patients on antithrombotic therapy require an individualized custom tailored approach during the perioperative period
- Increased bleeding when using full dose LMWH for bridging
- Discussion of perioperative anticoagulation strategy with patient, anesthesiologist and surgeon is key
- Recommendations for timing of preoperative cessation for NOACs based on elimination half-life

Perioperative Medicine Summit

Evidence Based Perioperative Medical Care

Petra

Questions