Perioperative Management of Anticoagulant and Antiplatelet Therapy:

What you need to know in 2019

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Last 3 years

4 Learning Objectives

1) VKA patients: *is heparin bridging needed*?

2) VKA/DOAC patients: *is interruption needed*?

3) DOAC patients: *how to manage*?

4) Dual antiplatelet therapy (coronary stent) patients: *how to manage*?

Case No. 1

- **70-yr old female with AF on warfarin with hypertension, diabetes, TIA 10 yrs ago ($CHADS_2$ = 5)**

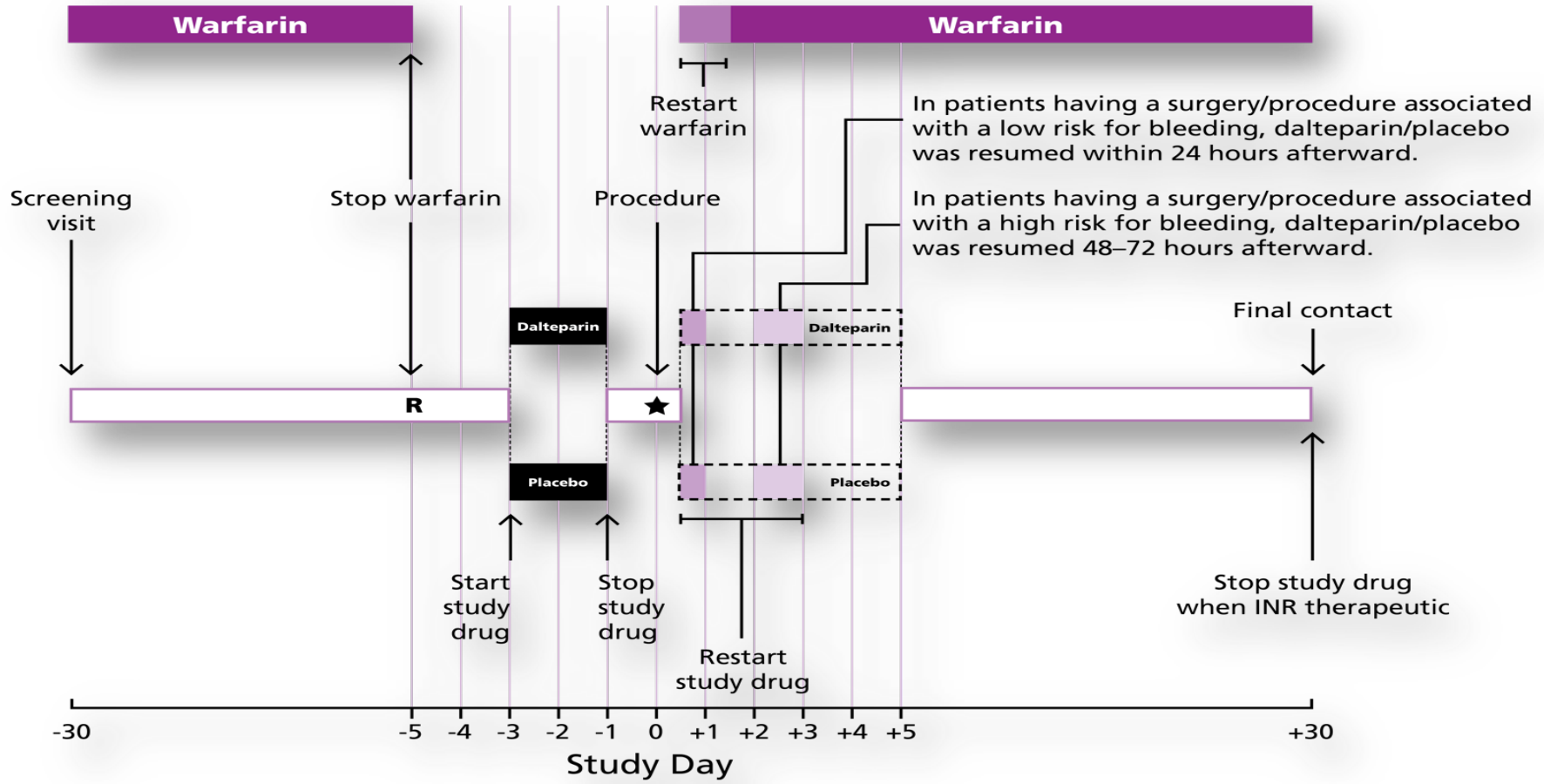
- **Scheduled for elective colon resection for incidentally found colon cancer…**

One doctor told her she needs to be assessed for heparin bridging.

Another doctor told her she does not need bridging.

Is heparin bridging needed?

BRIDGE: Trial Design



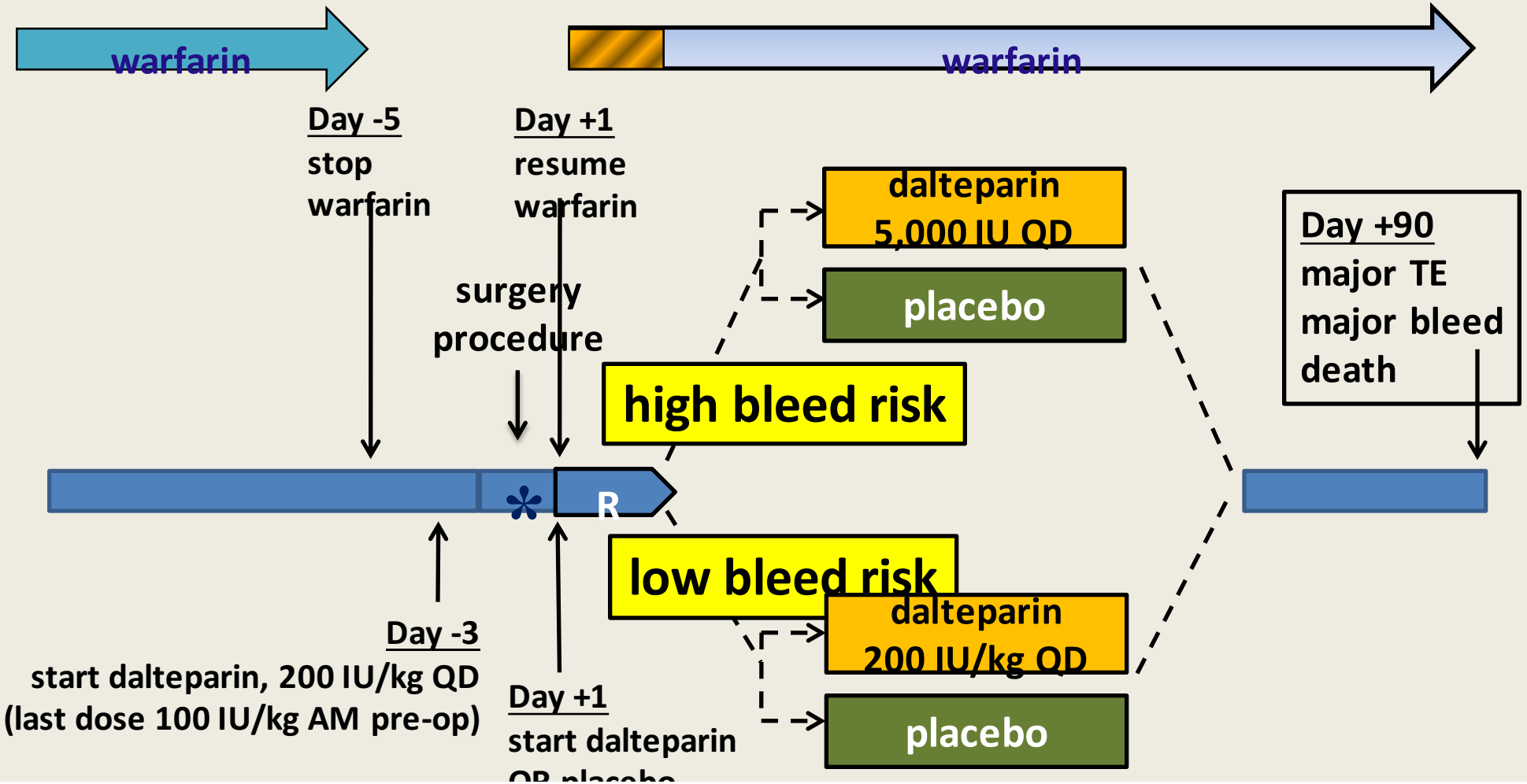
Douketis J, et al. *N Engl J Med* 2015

BRIDGE Trial: Primary Study Outcomes

Outcome No. (%)	No Bridging (N = 918)	Bridging (N = 895)	P- value
ATE	4 (0.4)	3 (0.3)	0.01 (non-infer.) 0.73 (super.)
- stroke	2 (0.2)	3 (0.3)	
- TIA	2 (0.2)	0 (0)	
- systemic embolism	0 (0)	0 (0)	
Major bleeding	12 (1.3)	29 (3.2)	0.005 (super.)

Douketis J, et al. *N Engl J Med* 2015

PERIOP-2: Trial Design



PERIOP-2: Patients

1,167 with atrial fibrillation

304 with mechanical heart valve (172 aortic, 132 mitral)

Baseline Characteristics			
Characteristics	**Total (N=1471)**	**No Bridging (N=650)**	**Bridging (N=821)**
Age – yr Mean (SD)	69.7 (12.3)	69.2 (12.9)	70.1 (11.9)
Male sex – No. (%)	946 (64.3)	428 (65.9)	518 (63.1)
Sub-Group: Atrial Fibrillation - No. (%)	1167 (79.3) N=1471	497 (76.5) N=650	670 (81.6) N=821
Sub-Group: Mechanical Valves – No. (%)	304 (20.7)	153 (23.5)	151 (18.4) *
With Atrial Fibrillation – No. (%)	99 (32.6) N=304	46 (30.1) N=153	53 (35.1) N=151
Mitral – No. (%)	132 (43.4) N=304	67 (43.8) N=153	65 (43.1) N=151
Aortic – No. (%)	172 (56.6) N=304	86 (56.2) N=153	86 (57.0) N=151

* One patient withdrew consent after randomization.

Kovacs MJ, et al. 2018 *Blood (abstract)*

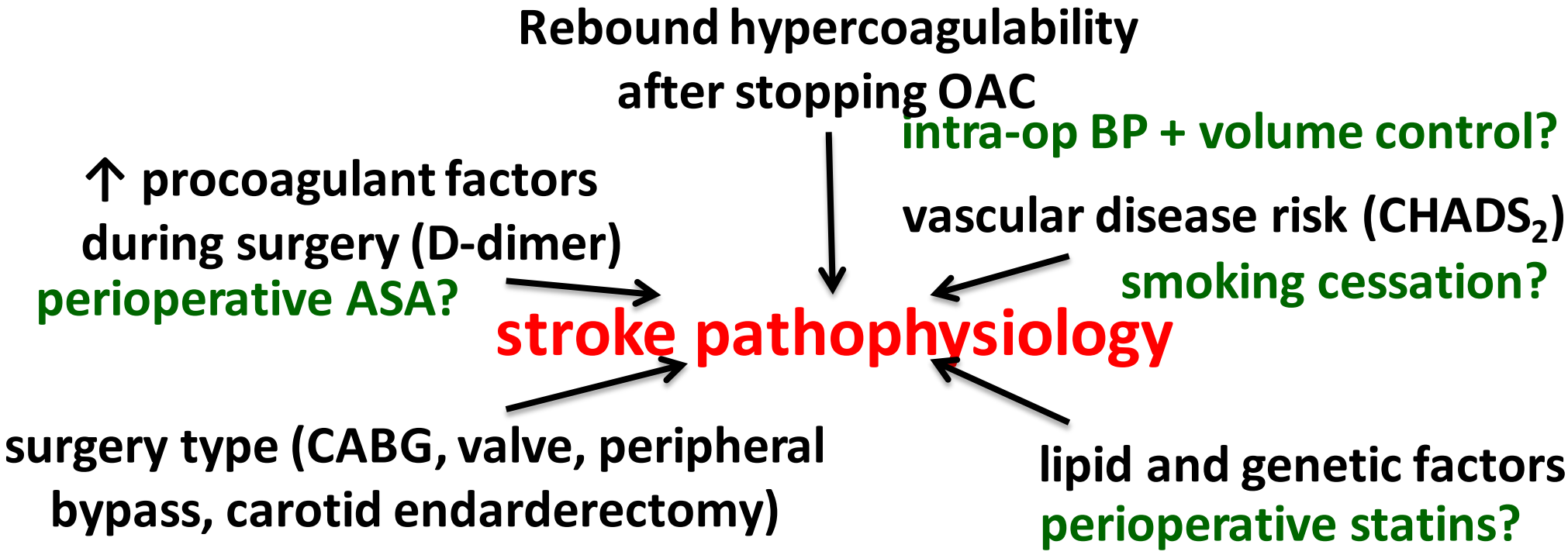
Table 2

Study Outcomes						
All Participants	**No Bridging (N=650) No. (%)**	**Bridging (N=820) No. (%)**	**P Value**	**Risk Diff Bridging-placebo**	**Lower 95% CI**	**Upper 95% CI**
Major Thromboembolism	7 (1.08)	6 (0.73)	0.48	-0.35	-1.33	0.64
All Deaths	6 (0.92)	6 (0.73)	0.69	-0.19	-1.13	0.75
Major Bleeding	16 (2.46)	12 (1.46)	0.16	-1	-2.45	0.45
Major Bleeding and Major Thromboembolism	23 (3.54)	18 (2.20)	0.12	-1.34	-3.1	0.4
Sub-group: Atrial Fibrillation	**No Bridging (N=497) No. (%)**	**Bridging (N=670) No. (%)**	**P Value**			
Major Thromboembolism	7 (1.41)	5 (0.75)	0.27			
Major Bleeding	13 (2.62)	11 (1.64)	0.25			
Sub- group: Mechanical Valves	**No Bridging (N=153) No. (%)**	**Bridging (N=150) No. (%)**	**P Value**			
Major Thromboembolism	0	1 (0.67)	0.50			
Major Bleeding	3 (1.96)	1 (0.67)	0.62			

PERIOP-2: Results

Kovacs MJ, et al. 2018 *Blood (abstract)*

What causes perioperative stroke in anticoagulated patients and how can we prevent it?



What effect of heparin bridging?

Case No. 2

- **75-kg old female with AF on rivaroxaban, 20 mg QD**
  - **hypertension, diabetes, TIA 10 yrs ago ($CHADS_2$ = 5)**
  - **CrCl = 50 mL/min**

- **Scheduled for cardiac pacemaker implantation this Monday 9AM, for tach-brady syndrome…**

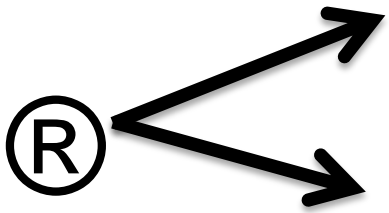
She needs to be off rivaroxaban for at least 2 days…

….she does NOT need to stop rivaroxaban.

BRUISECONTROL-1 Trial

- **Patients with AF on VKA having pacemaker/ICD**

681 patients



continue VKA (INR <3.0)

interrupt VKA + LWMH bridging

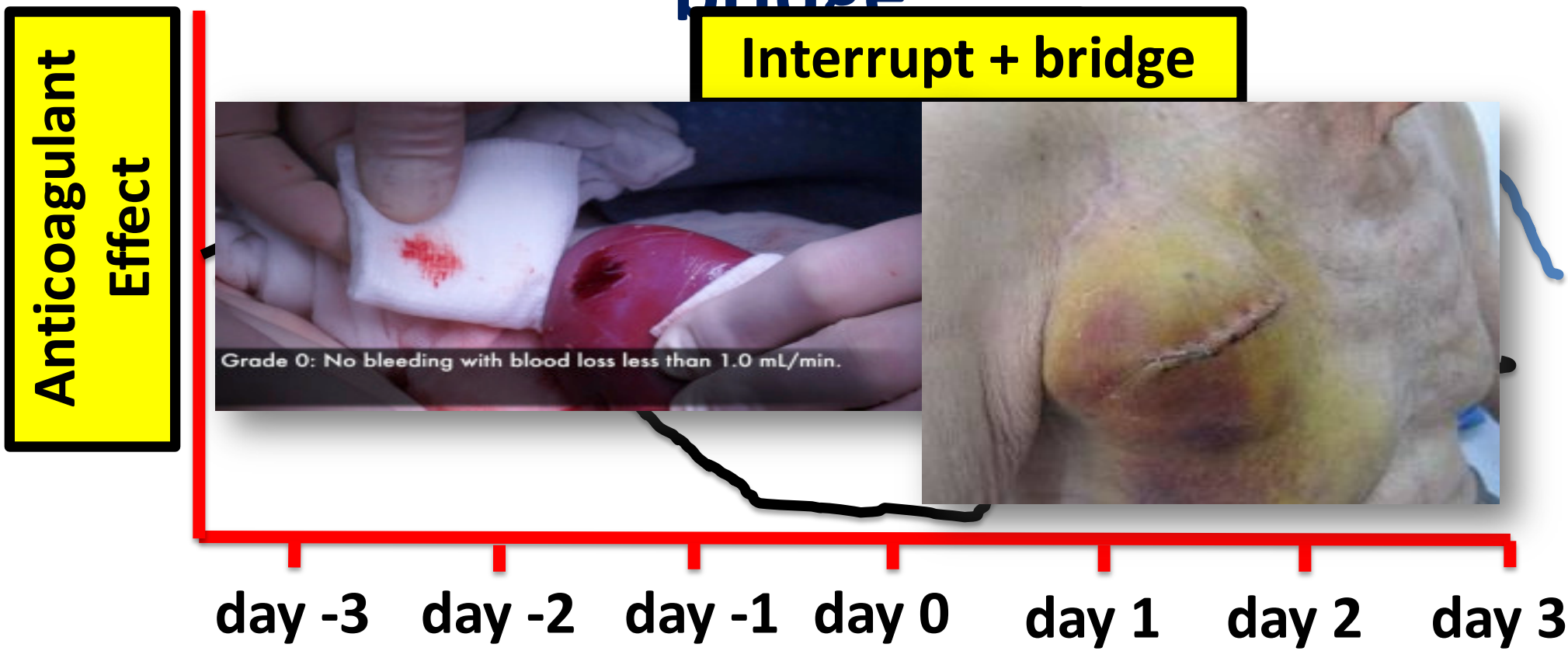
Outcomes	Continue	Interrupt	*P-value*
stroke/TIA (%)	0.3	0	*1.0*
hematoma* (%)	3.5	16.0	*<0.001*

*requiring treatment interruption

Birnie DH, et al. *N Engl J Med* 2013;368:2084

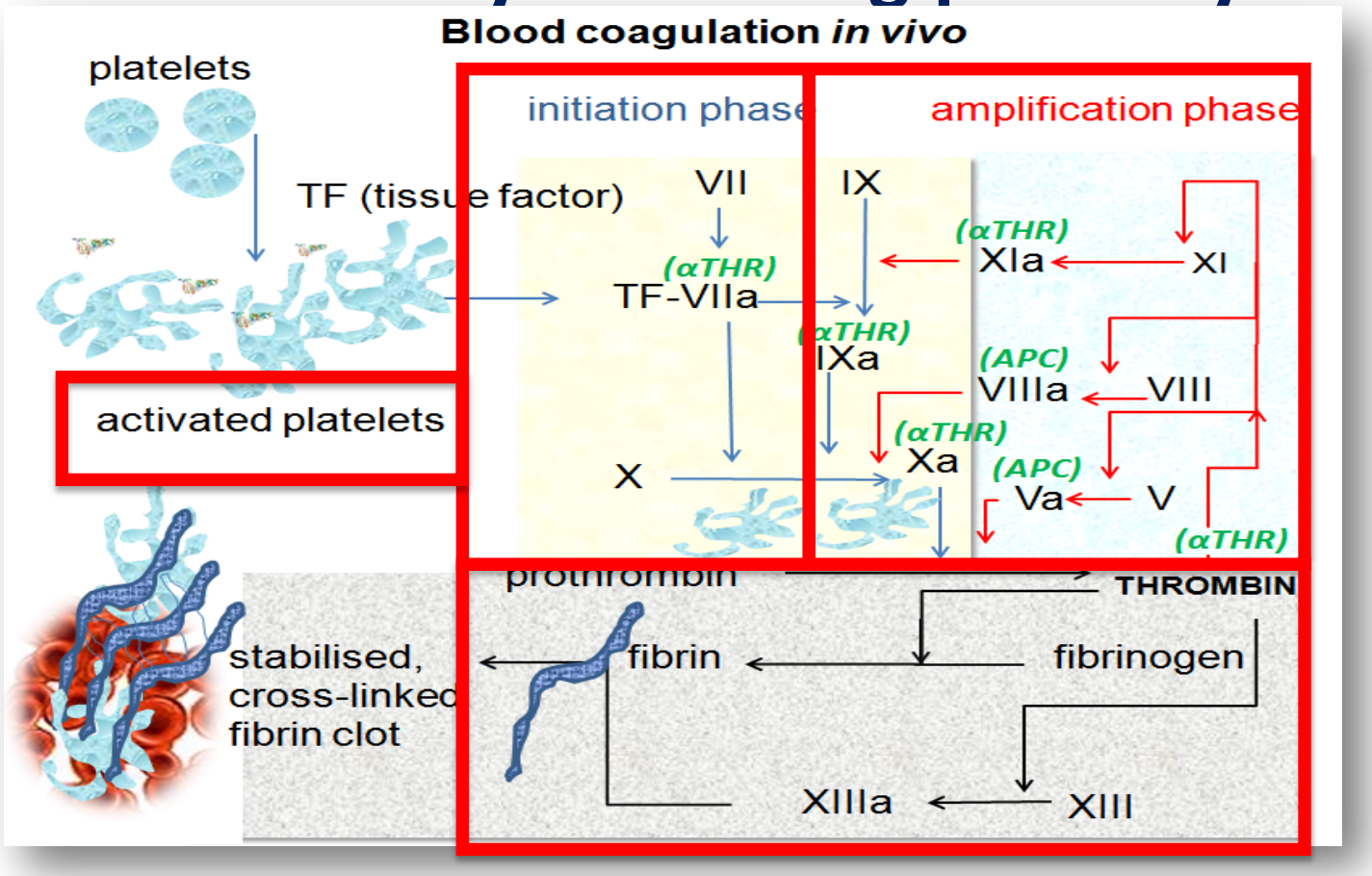
Perioperative Hemostasis:

(1) continue OAC vs. (2) interrupt + bridge



Safety of on-anticoagulation procedures?

…redundancy in clotting pathway



BRUISE CONTROL-2 Trial

- **Patients on DOAC having pacemaker/ICD**

continue DOAC (including day of procedure)

interrupt DOAC for 1 day pre-procedure

(2 days if on dabigatran and CrCl <50 mL/min)

Outcomes	Continue	Interrupt	*P-value*
stroke/TIA (%)	0.3	0.3	*1.0*
hematoma (%)	2.1	2.1	*0.97*

*requiring treatment interruption

Birnie DH, et al. *Eur Heart J* 2017

Case No. 3

- **75-yr old female with AF on apixaban, 5 mg BID**
  - **hypertension, diabetes, TIA 10 years ago ($CHADS_2$=5)**
  - **CrCl = 50 mL/min, for hip replacement Mon 9AM**

- ***She needs to be off apixaban for 2 days***

- ***…she needs to be off apixaban for 3 days and receive pre-op heparin bridging for 1-2 days and have coagulation testing prior to neuraxial anesthesia***

2015 ASRA/ESRA Guidelines on

Narouze S, et al. *Reg Anesth Pain Med* 2015

	Pre-op Interruption	Post-op Resumption
dabigatran	CrCl 30-50…120 hr CrCl 50-80… 96 hr	24 hrs
apixaban	CrCl >80……72 hr	24 hrs
rivaroxaban	……72 hr	24
/edoxaban	……72 hr	

ASRA 2018 update

Horlocker TT, et al. *Reg Anesth Pain Med* 2018

Research

JAMA Internal Medicine | Original Investigation

Perioperative Management of Patients With Atrial Fibrillation Receiving a Direct Oral Anticoagulant

James D. Douketis, MD; Alex C. Spyropoulos, MD; Joanne Duncan, BSc; Marc Carrier, MD, MSc; Gregoire Le Gal, MD; Alfonso J. Tafur, MD; Thomas Vanassche, MD; Peter Verhamme, MD; Sudeep Shivakumar, MD; Peter L. Gross, MD, MSc; Agnes Y. Y. Lee, MD, MSc; Erik Yeo, MD; Susan Solymoss, MD; Jeannine Kassis, MD; Geneviève Le Templier, MD; Stephen Kowalski, MD; Mark Blostein, MD; Vinay Shah, MD; Elizabeth MacKay, MD; Cynthia Wu, MD; Nathan P. Clark, PharmD; Shannon M. Bates, MDCM, MSc; Frederick A. Spencer, MD; Eleni Arnaoutoglou, MD, PhD; Michiel Coppens, MD, PhD; Donald M. Arnold, MD, MSc; Joseph A. Caprini, MD; Na Li, PhD; Karen A. Moffat, MLT; Summer Syed, MD, MSc; Sam Schulman, MD, PhD

Douketis J, et al. *JAMA Int Med* 2019 ePub Aug 5

Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) Study (NCT2228798)

- **Design:** Multi-centre prospective cohort study
- **Patients:** 2,961 patients with atrial fibrillation (987 per DOAC – dabigatran, rivaroxaban, apixaban)
- **Intervention:**
  - DOAC-specific pre-procedure interruption interval
  - flexible post-procedure resumption
  - no heparin bridging
  - pre-procedure blood sample

Douketis J, et al. *Thromb Haemost* 2017

Methods: Patient Eligibility and Intervention

Consecutive adults (≥18 years) with atrial fibrillation:

- receiving DOAC (apixaban, dabigatran, rivaroxaban)
- require DOAC interruption for *elective* surgery/procedure
- can adhere to planned DOAC interruption

Surg./proced. classified as HIGH or LOW bleeding risk

Excluded if:

- CrCl<30 mL/min (dabigatran, rivaroxaban)
- CrCl<25 mL/min (apixaban)
- cognitive impairment/psychiatric Illness
- non-consenting
- previous participation in study

Blood sample: day of (just before) surgery/procedure

Follow-up: weekly for 4 weeks post-procedure

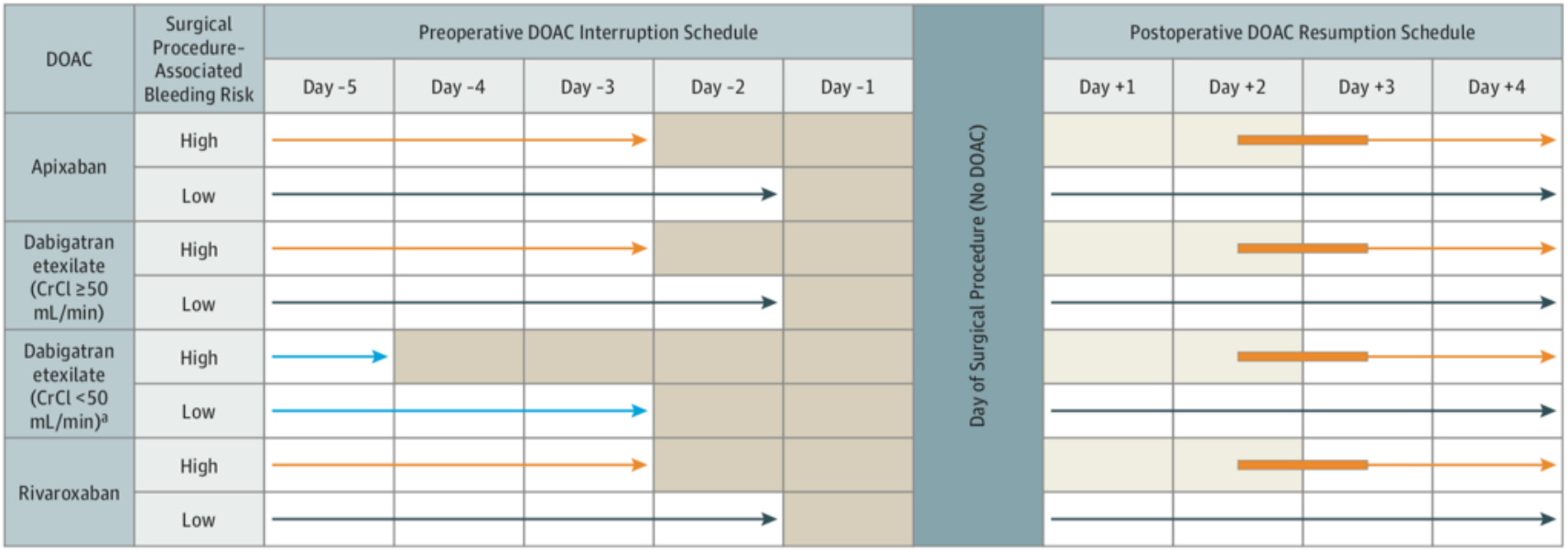
No heparin bridging (low-dose heparin as VTE prophylaxis OK)

Methods: Hypothesis Testing and Sample Size

- **Sample size = 2,961 (987 per DOAC) to show that perioperative management for *each DOAC* associated with:**
  - **risk for MB = 1% *(95% confidence to exclude 2%)***
  - **risk for ATE = 0.5% *(95% confidence to exclude 1.5%)***

Methods: Perioperative Management

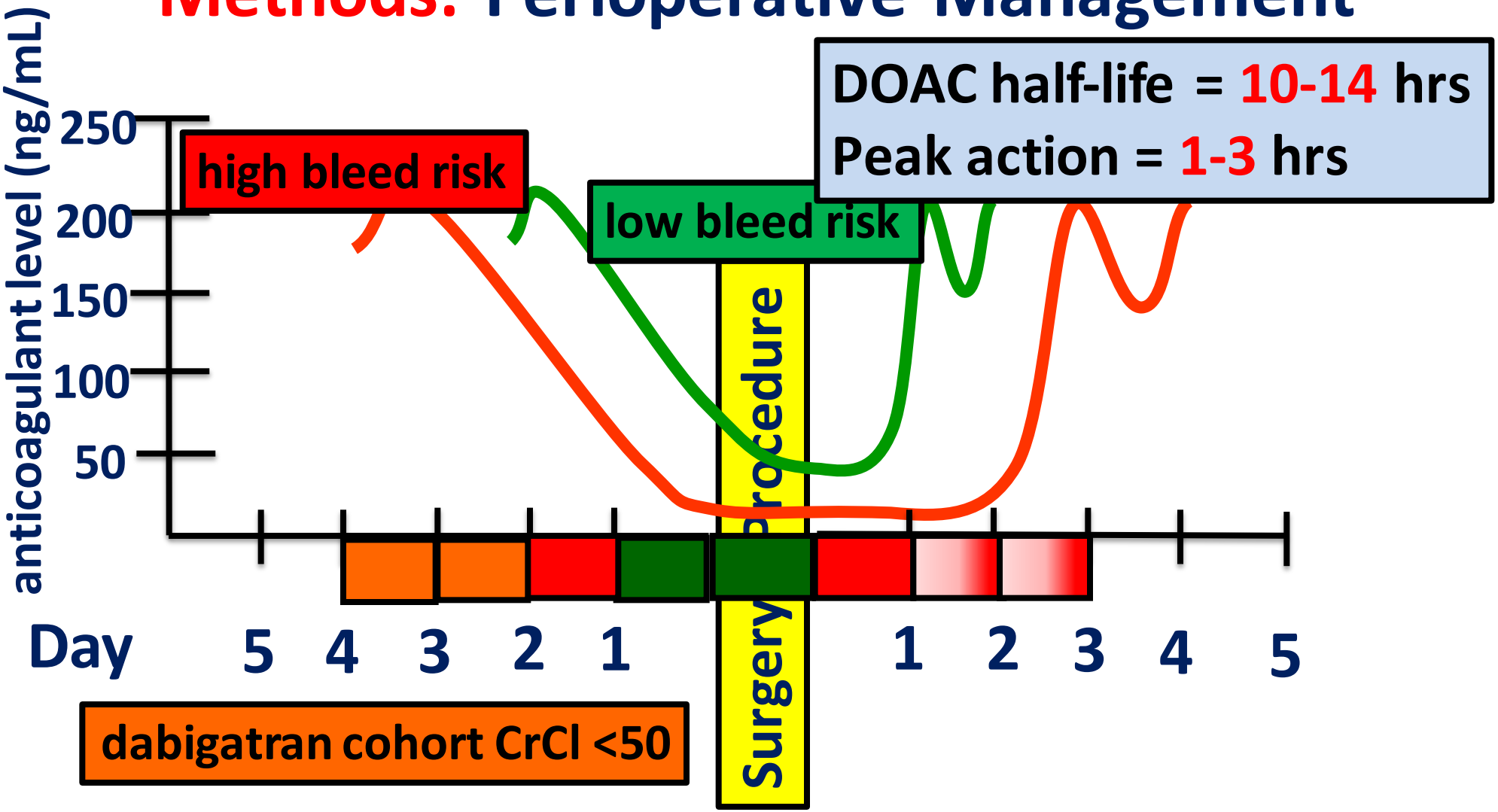
Figure. Perioperative Direct Oral Anticoagulant (DOAC) Management Protocol



No DOAC was taken on certain days (shaded) and on the day of the elective surgery or procedure. The light blue arrows refer to an exception to the basic management, a subgroup of patients taking dabigatran with a creatinine clearance (CrCl) less than 50 ng/mL. The orange arrows refer to patients having a high–bleed-risk surgical procedure. Dark blue arrows refer to patients having a low–bleed-risk surgical procedure. The thickened orange part of arrows refer to flexibility in the timing of DOAC resumption after a procedure.

[a] Cancer diagnosed within 3 months or has been treated within 6 months or metastatic.

Methods: Perioperative Management



Practical Points on Perioperative Management

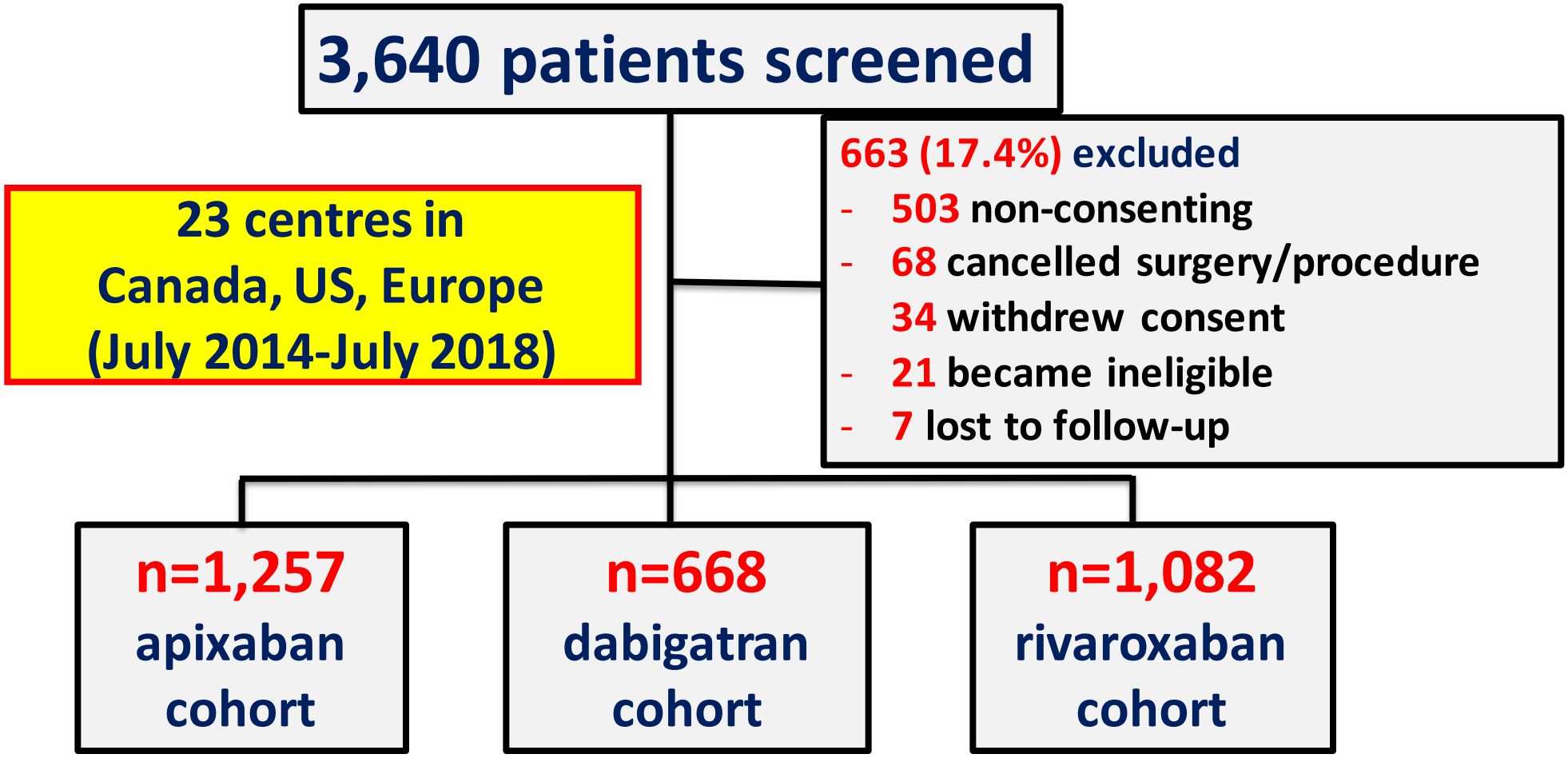
1) $CHADS_2$ score did NOT factor into management

2) Heparin or LMWH bridging was not indicated.

3) VTE prophylaxis post-operatively was acceptable for high-risk patients.

4) Pre-operative blood samples taken…but NOT used for clinical decision-making.

Results: Patient Recruitment



Results: Patient Characteristics

Characteristic	Cohort		
	Apixaban *n=1,257*	Dabigatran *n=668*	Rivaroxaban *n=1,082*
Age – mean	73.1	72.4	72.0
Male sex, %	64.0	68.6	67.0
$CHADS_2$ score – mean	2.1	2.2	2.0
Modified HASBLED score – mean	2.0	1.9	1.8
CrCl – mean, in mL/min	77.9	85.9	82.2
Lower-dose DOAC, %	20.0	37.1	16.7
ASA use, %	12.4	14.7	9.1
High bleed risk surgery/procedure, %	32.3	34.1	34.5

Results: Adherence to Pre- and Post-operative Management Protocols

- 3,007 patients in primary ITT analysis
  - 159 (5.3%) deviated pre-procedure protocol
  - 202 (6.7%) deviated from post-procedure protocol
  - 22 (0.7%) lost to follow-up
- 2,624 (87.3%) patients in per protocol analysis
  - adhered to pre- and post-procedure protocol and not lost to follow-up

Results: Primary Outcomes

per protocol analysis (87.3%)

Outcome (%, 95% CI) (expected)	Cohort		
	Apixaban *n=1257*	Dabigatran *n=668*	Rivaroxaban *n=1082*
*Arterial thromboembo- lism (0.5%)	0.16 (0-0.48) *n=2*	**0.5 (0-1.25) *n=3***	0.37 (0-0.82) *n=4*
**Major bleeding (1.0%)	**1.2 (0-1.89) *n=13***	0.90 (0-1.73) *n=6*	**1.7 (0-2.53) *n=16***

*Ischemic stroke, TIA, systemic embolism

**ISTH definition

Results: Bleeding According to Surgery/Procedure-related Bleed Risk

Table 4. Incidence of Major Bleeding by Elective Surgery or Procedure–Associated Bleeding Risk

Procedure-Associated Bleeding Risk	Apixaban Cohort (n = 1257)	Dabigatran Etexilate Cohort (n = 668)	Rivaroxaban Cohort (n = 1082)
Low bleeding risk			
No. (%)	851 (67.7)	440 (65.9)	709 (65.5)
30-d Postoperative rate of major bleeding, % (95% CI)	0.59 (0-1.20)	0.91 (0-2.01)	1.27 (0-2.17)
High bleeding risk			
No. (%)	406 (32.3)	228 (34.1)	373 (34.5)
30-d Postoperative rate of major bleeding, % (95% CI)	2.96 (0-4.68	0.88 (0-2.62)	2.95 (0-4.76)

Clinical Predictors of Major Bleeding: Multivariate analysis*

Predictor Variable	OR (95% CI)	P-value
DOAC group		
dabigatran vs. apixaban	0.67 (0.26-1.71)	0.401
rivaroxaban vs. apixaban	1.24 (0.64-2.40)	0.514
Hypertension	**3.93 (1.40-11.07)**	**0.010**
Female gender	0.62 (0.31-1.24)	0.174
Active cancer	**2.30 (1.10-4.81)**	**0.026**
Surgery bleed risk: low vs. high	0.59 (0.30-1.16)	0.126

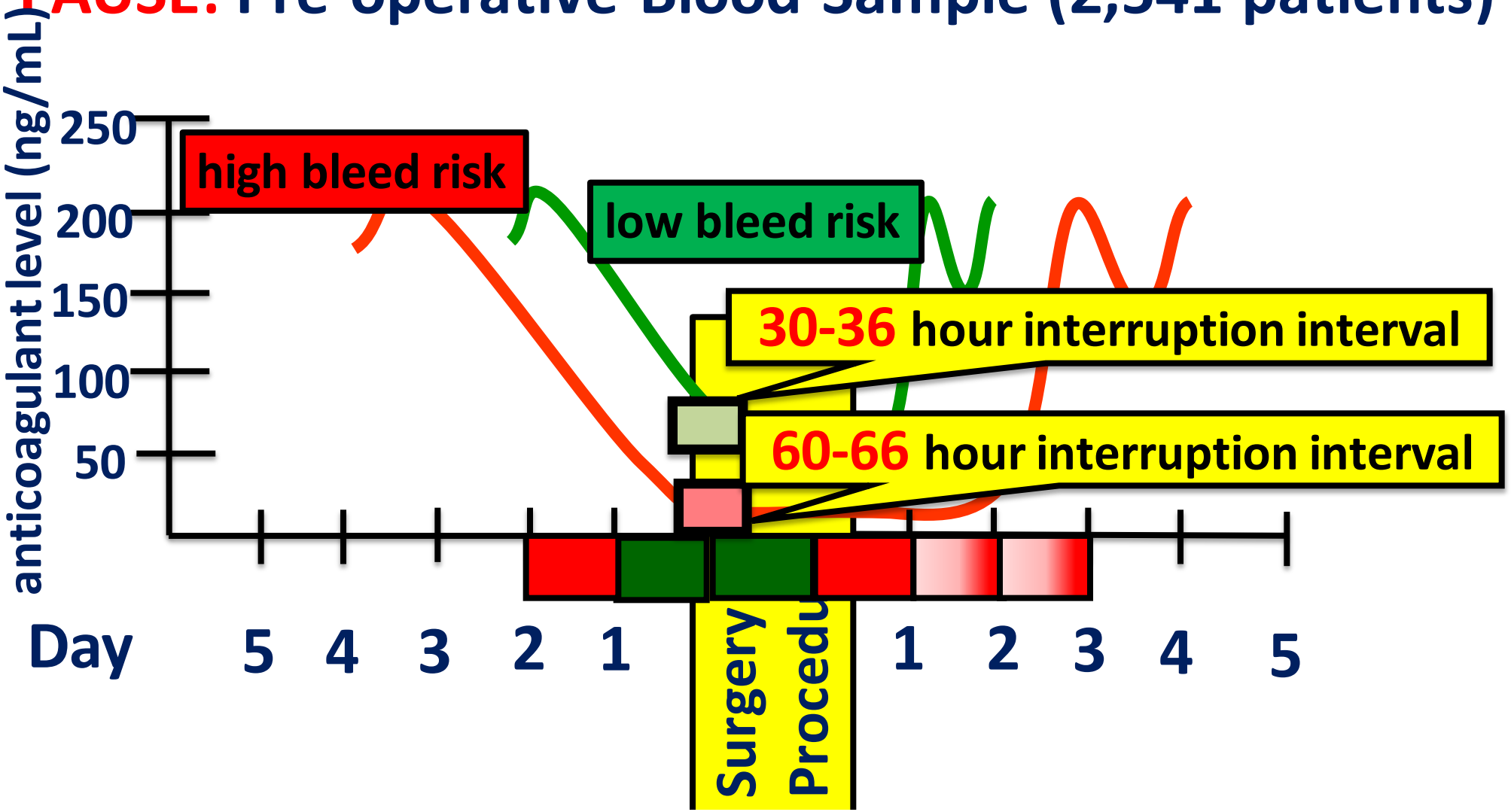
model AUC = 0.69

***unpublished data**

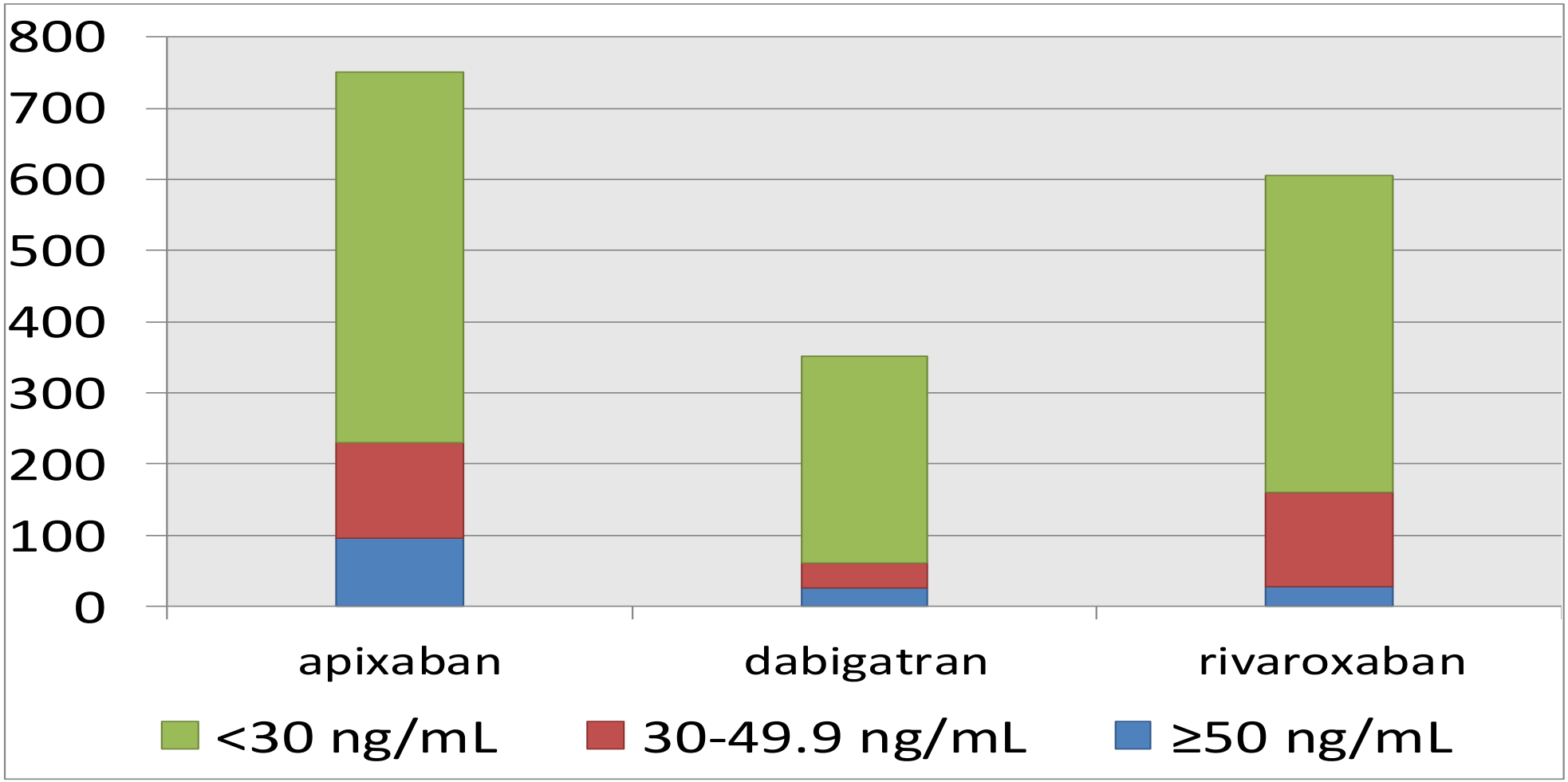
Is pre-operative coagulation function testing needed?

…don't tell me I need another blood test!

PAUSE: Pre-operative Blood Sample (2,541 patients)

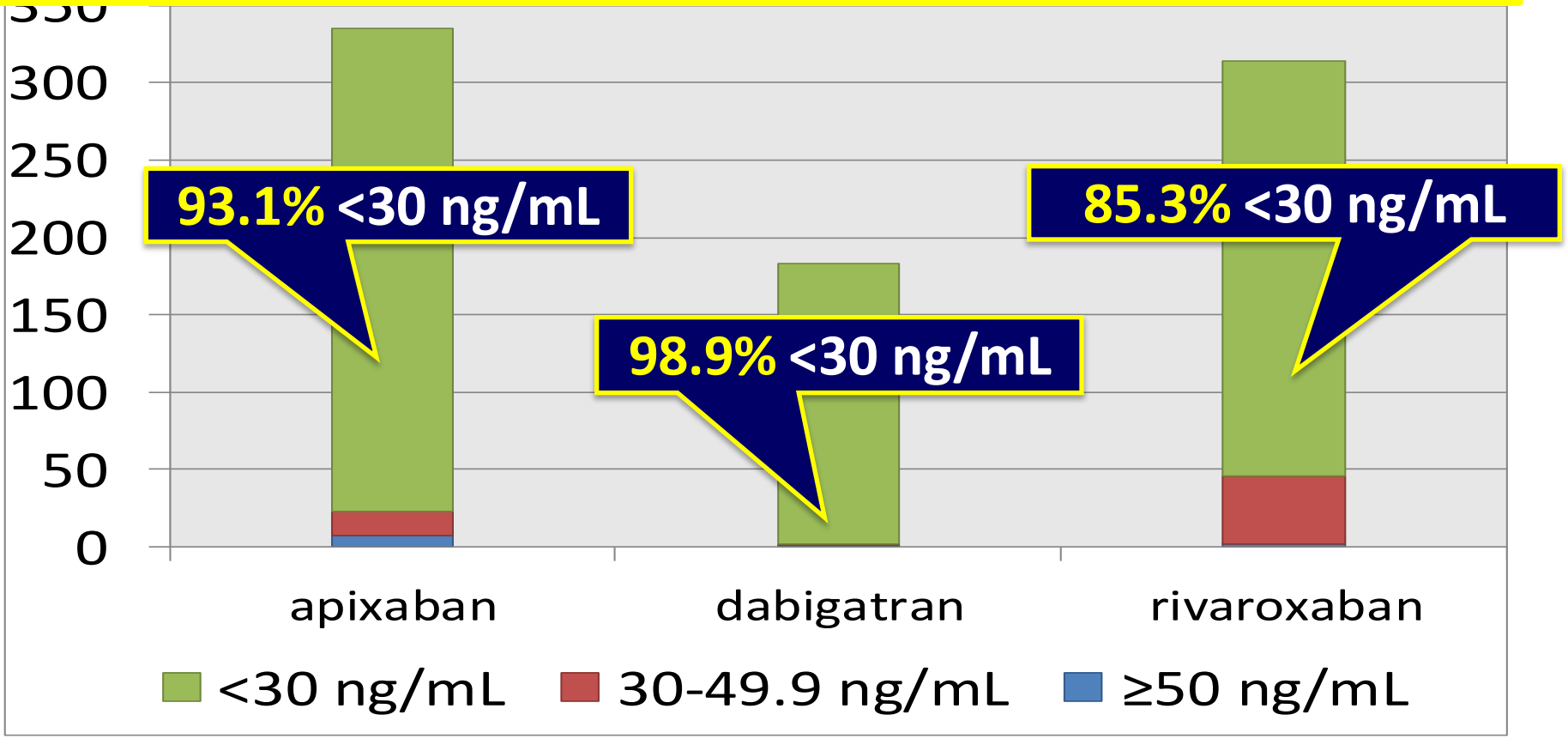


Low/Mod-Bleed-Risk: 1 d (30-36 hr) off pre-op



High-Bleed-Risk: 2 d (60-68 hr) off pre-op

98.9% (823/832) with DOAC level <50 ng/mL



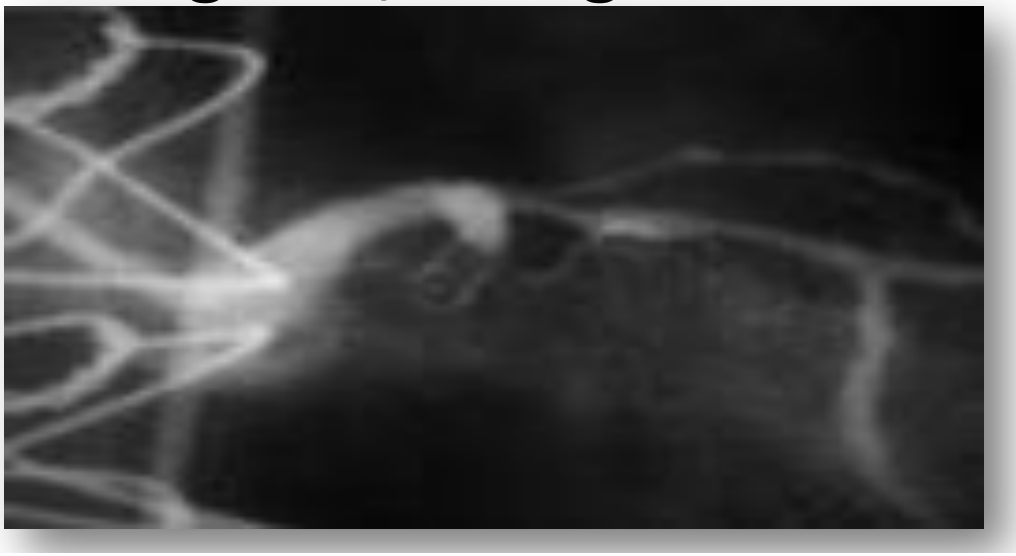
Lab Predictors of Bleeding: Effect of Residual DOAC Level on Major or Any Bleeding*

		Major Bleeding		Major + CRNM Bleeding	
		n, % (95% CI)	OR (95% CI)	*n, % (95% CI)*	OR (95% CI)
DOAC Level (ng/mL):					
<30	***n =2020***	***n=27 1.3 (0-1.8)***	**reference**	***n=69 3.4 (0-4.2)***	**reference**
30-49.9	***n=363***	***n=6 1.7 (0-3.2)***	**1.24 (0.5-2.8)**	***n=14 3.9 (0-5.9)***	**1.1 (0.6-2.0)**
≥50	***n=158***	***n=3 1.9 (0-4.7)***	**1.43 (0.3-4.1)**	***n=4 2.5 (0-5.5)***	**0.7 (0.3-2.0)**

***unpublished data**

Case No. 4

- 75-year old woman with CAD/CABG and drug-eluting stent (DES) 5 months ago after NSTEMI.
- Other medical problems: hypertension, obesity, type 2 diabetes
- Taking ASA, 81 mg daily, and ticagrelor, 90 mg BID
- Needs surgery for breast cancer resection



Risk factors for MACCE in 1,134 patients with stents during noncardiac surgery (observational study)

Antiplatelet interruption

	MACCE	
	OR (95% CI)	p
Complete OAT interruption		
No interruption	Reference	
≤5 days	0.67 (0.32 to 1.37)	0.272
>5 days	2.11 (1.23 to 3.63)	0.007
Preoperative haemoglobin		
>12 g/dl (or missing)	Reference	
10–12 g/dl	1.13 (0.62 to 2.08)	0.691
<10 g/dl	3.00 (1.23 to 7.29)	0.016
Creatinine clearance		
>60 ml/min (or missing)	Reference	
30–60 ml/min	1.32 (0.79 to 2.21)	0.287
<30 ml/min	3.51 (1.54 to 8.04)	0.003
Time between PCI and surgery		
0–3 months	0.97 (0.45 to 2.07)	0.938
4–6 months	1.11 (0.48 to 2.58)	0.803
7–12 months	0.70 (0.28 to 1.73)	0.437
More than 12 months	Reference	
Urgent surgery	3.08 (1.74 to 5.47)	<0.001
High-risk surgery	3.59 (2.34 to 5.51)	<0.001

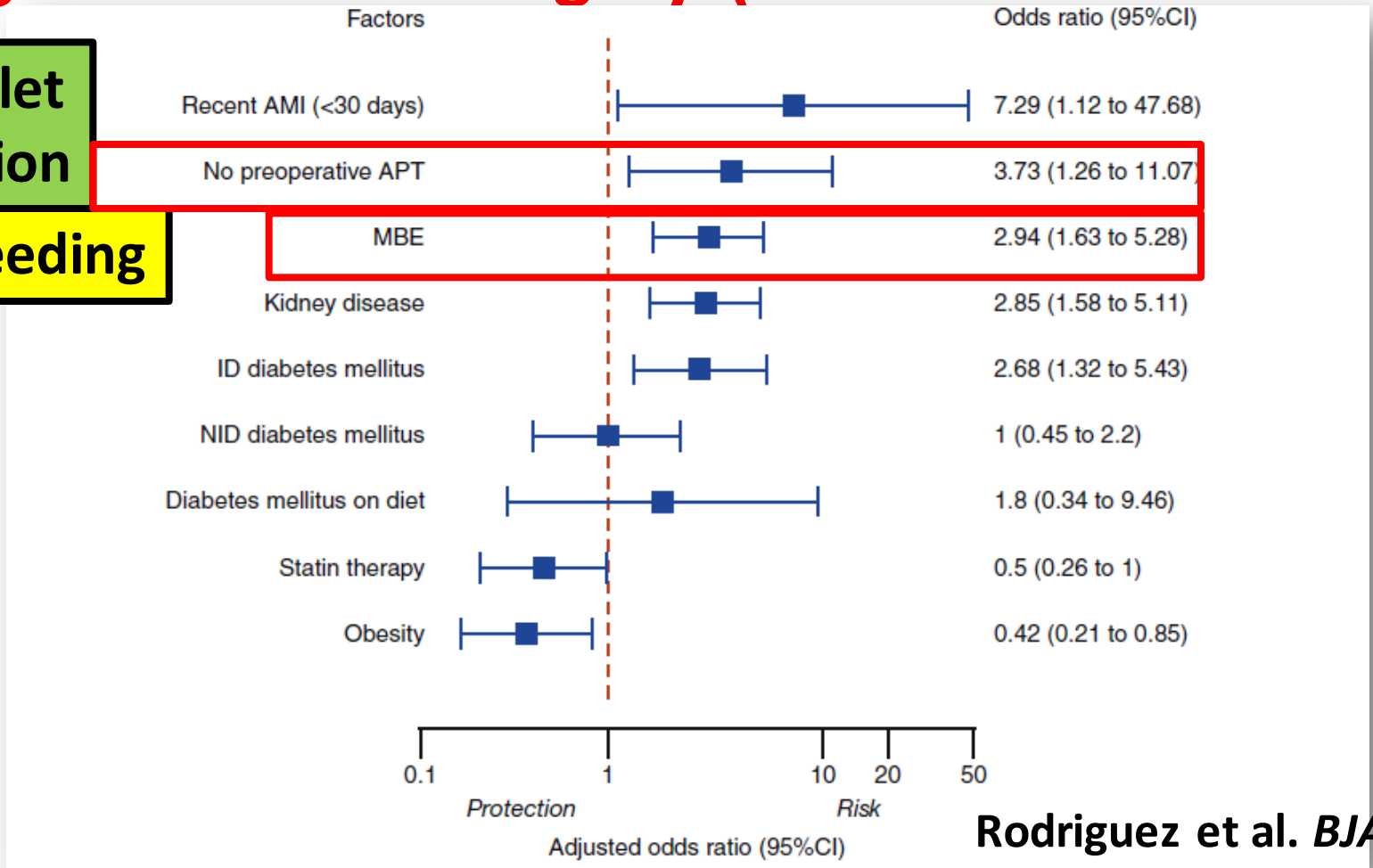
Surgery urgency

Albaladejo P, et al. *Heart* 2011

Risk factors for MACCE in 432 patients with stents during non-cardiac-surgery (observational study)

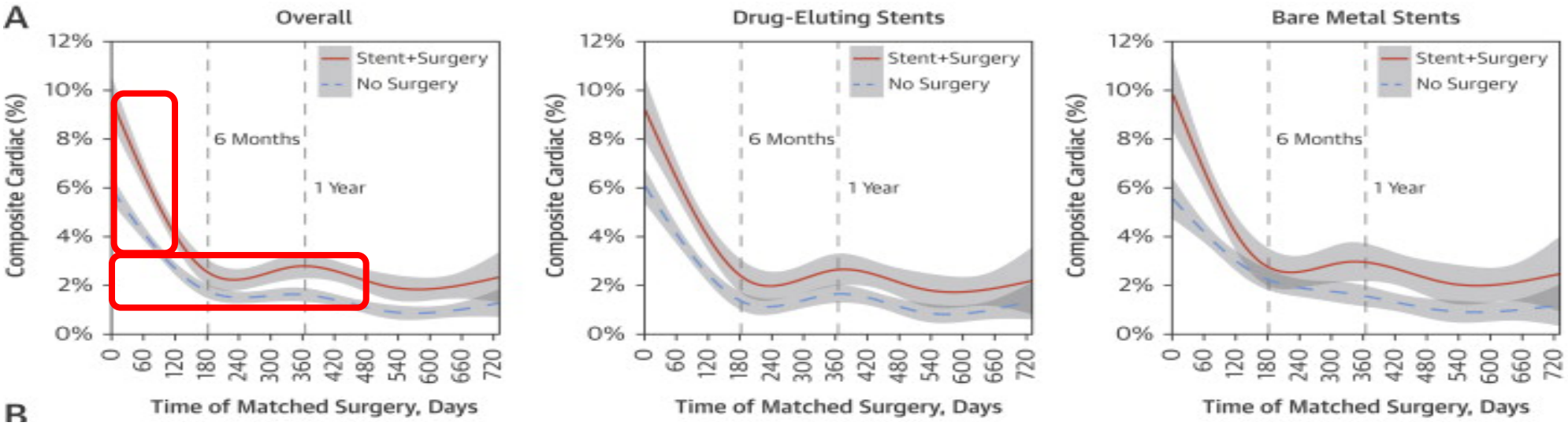
Antiplatelet interruption

Major bleeding



Rodriguez et al. *BJA* 2018

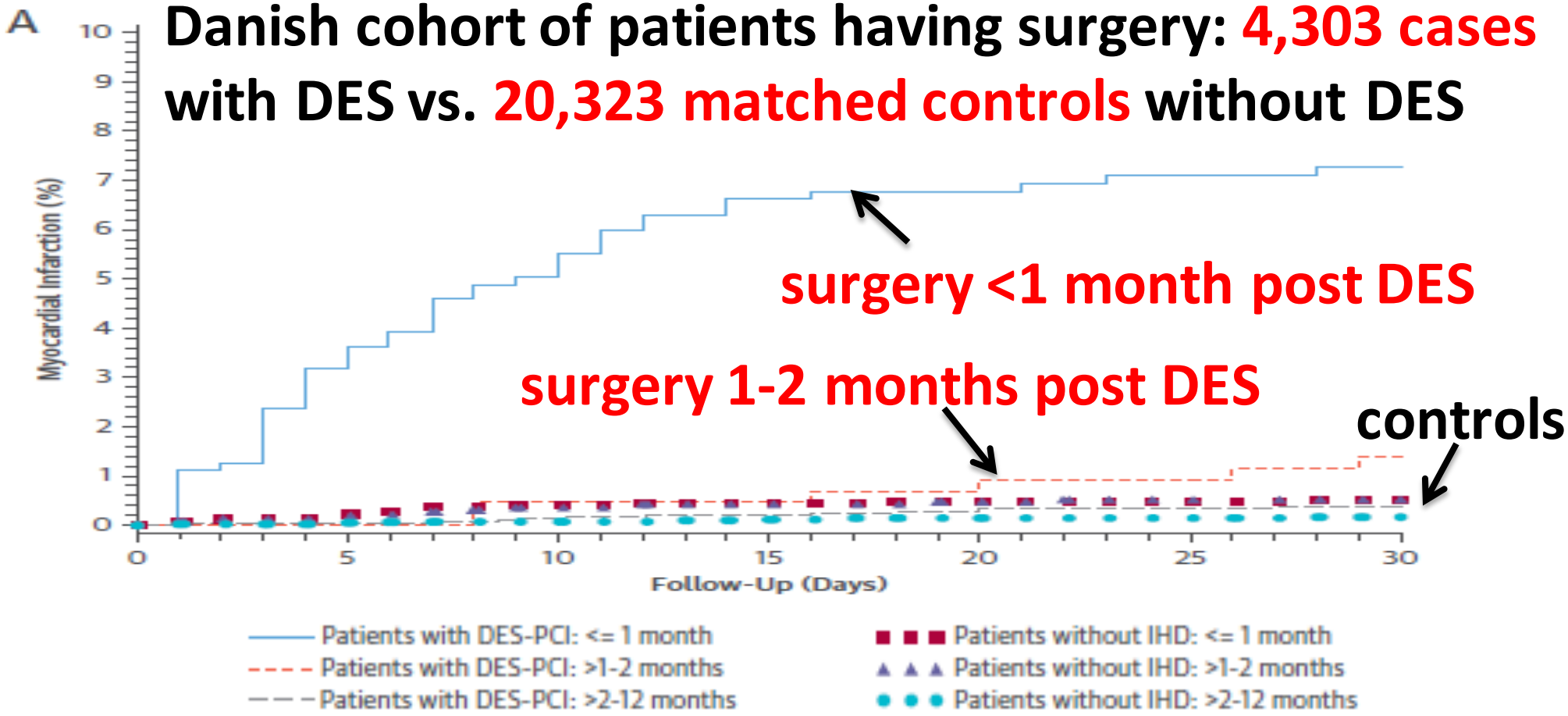
Perioperative risk for MI post-cardiac stent



- U.S. VA retrospective cohort study of patients with coronary stents
- 20,590 cases having surgery vs. 41,180 matched controls

Perioperative Risk for MI post-DES

Danish cohort of patients having surgery: 4,303 cases with DES vs. 20,323 matched controls without DES



Egholm G, et al. *JACC* 2016

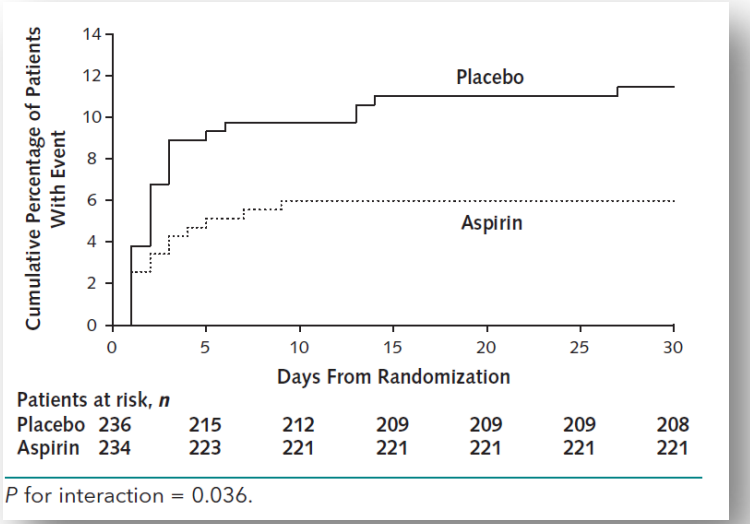
ASA before non-cardiac surgery: stop or continue?

- POISE-2 – double-blind 2 × 2 factorial RCT
  - ASA (continue/start) vs. placebo
- Inclusion criteria:
  - patients (≥45 yrs) with or at risk for CV disease having non-cardiac surgery ±taking ASA
- *Exclusion criteria*:
  - took ASA <72 hrs before surgery
  - BMS within 6 weeks, DES within 12 months

Devereaux PJ, et al. *N Engl J Med* 2014;370:1494

POISE-2 Subgroup with Coronary Stents (n=470)

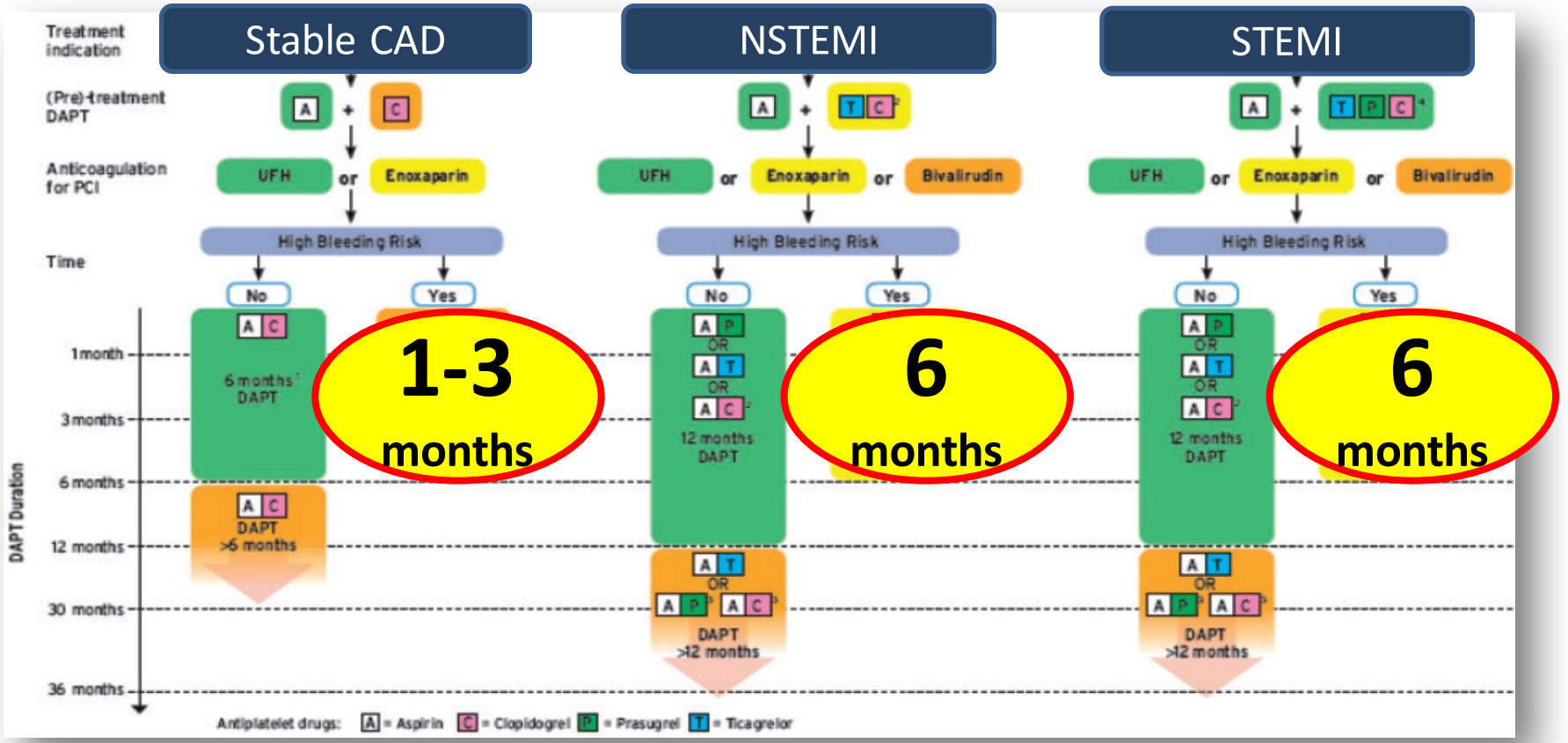
- **ASA decreased risk for CV events:**
  death + non-fatal MI…ARR=5.5%
  (CI: 0.4-10.5; p=0.04)
  myocardial infarction…ARR=5.9%
  (CI:1.0-10.8; p=0.02)



- **ASA conferred *non-significant* increased risk for bleeding:**
  major bleeding……ARI=1.3% (CI: –2.6-5.2)

Graham MM, et al. *Ann Intern Med* 2018

When to interrupt $P2Y_{12}$ inhibitor?



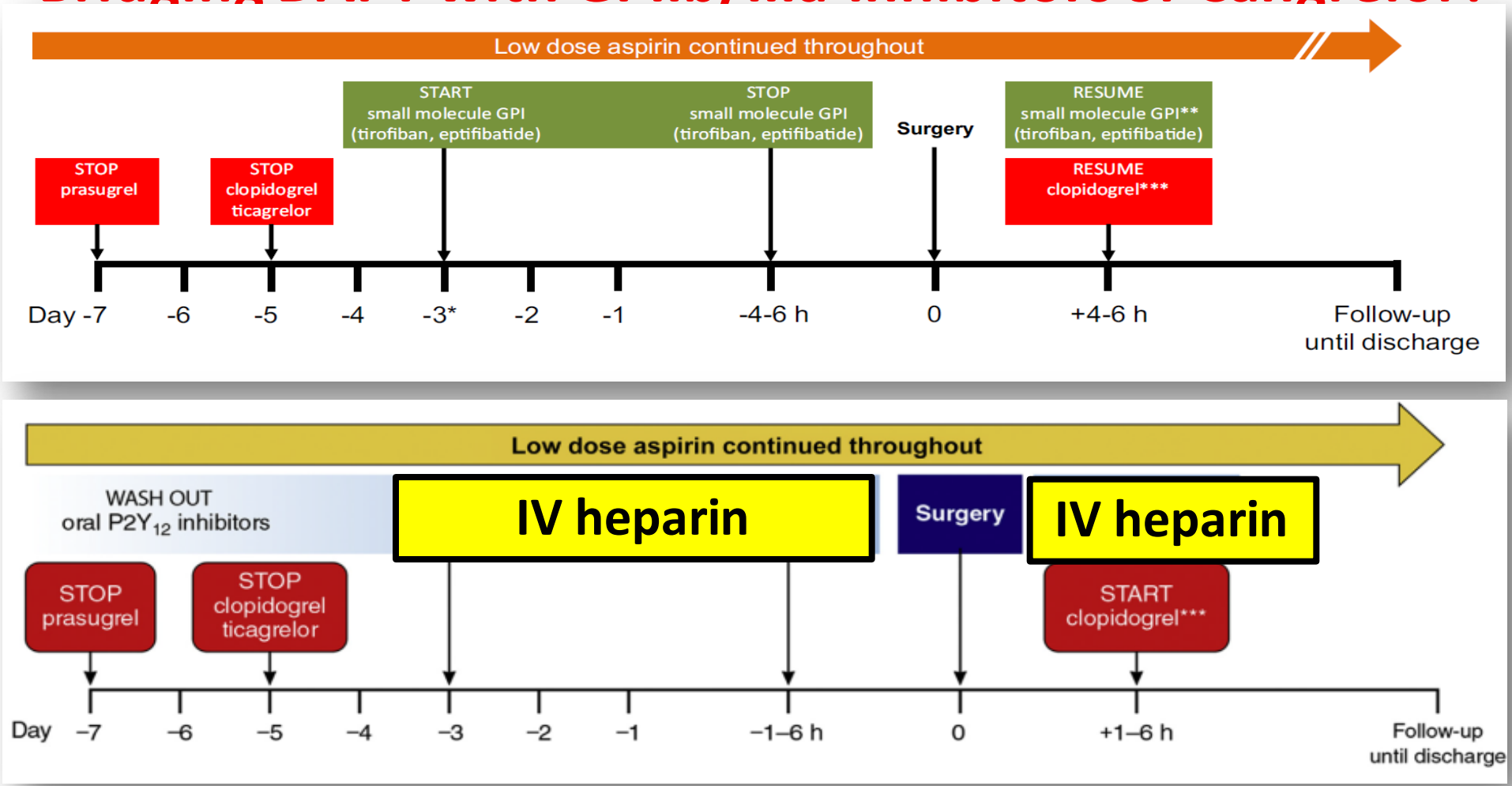
Neumann et al. *Eur Heart J* 2019

When (maybe) to NOT interrupt $P2Y_{12}$ inhibitor?

Clinical risk features	ACS at time of index PCI procedure Multiple previous MI Previous stent thrombosis on adequate APT LVEF <35% Chronic kidney disease Diabetes mellitus
Angiographic risk features	Long or multiple stents (at least 3 stents implanted or 3 lesions treated or total stent length >60 mm) Overlapping stents Small stent diameter (<2.5 mm) Bifurcation lesions (with 2 stents implanted) Extensive coronary artery disease Incomplete revascularization Treatment of chronic total occlusion

Rossini et al. *JACC:CI* 2018

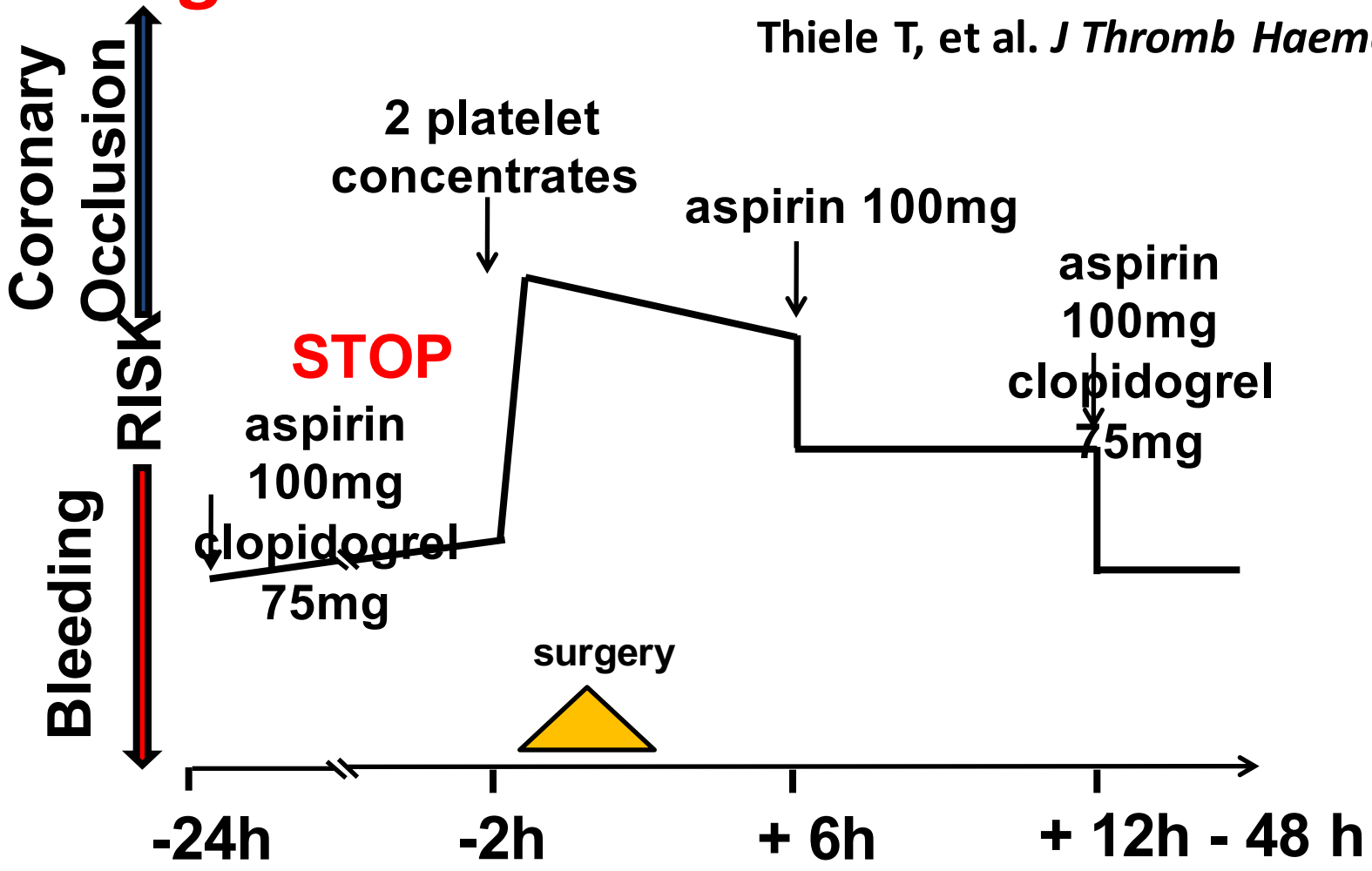
Bridging DAPT with GPIIb/IIIa Inhibitors or Cangrelor?



Rossini et al. *JACC:CI* 2018

Continuing DAPT and Transfusion of Platelets

Thiele T, et al. *J Thromb Haemost* 2012



…back to the Learning Objectives

1) VKA patients: *is heparin bridging needed*?

- few patients with atrial fibrillation
- most patients with mechanical heart valve (pre-op)

2) VKA/DOAC patients: *is interruption needed*?

- not for cardiac device procedures
- other minor procedures (eye, skin, dental)

…back to the Learning Objectives

3) DOAC patients: *how to manage*?

- omit 1 day before/after low-bleed-risk and 2 days before/after high-bleed-risk surgery or procedure
- no bridging or coagulation function testing

4) Dual antiplatelet therapy (coronary stent) patients: *how to manage*?

- in most patients, continue ASA and stop $P2Y_{12}$ inhibitor 5-7 days pre-surgery
- in a few patients, continue ASA + $P2Y_{12}$ ± platelet transfusion *OR* bridge with anticoagulant

Merci pour votre attention!