Περιεγχειρητικοί χειρισμοί ασθενών που λαμβάνουν αντιπηκτικά ή αντιαιμοπεταλιακά φάρμακα

ΤΣΑΓΑΛΟΥ ΕΛΕΥΘΕΡΙΑ

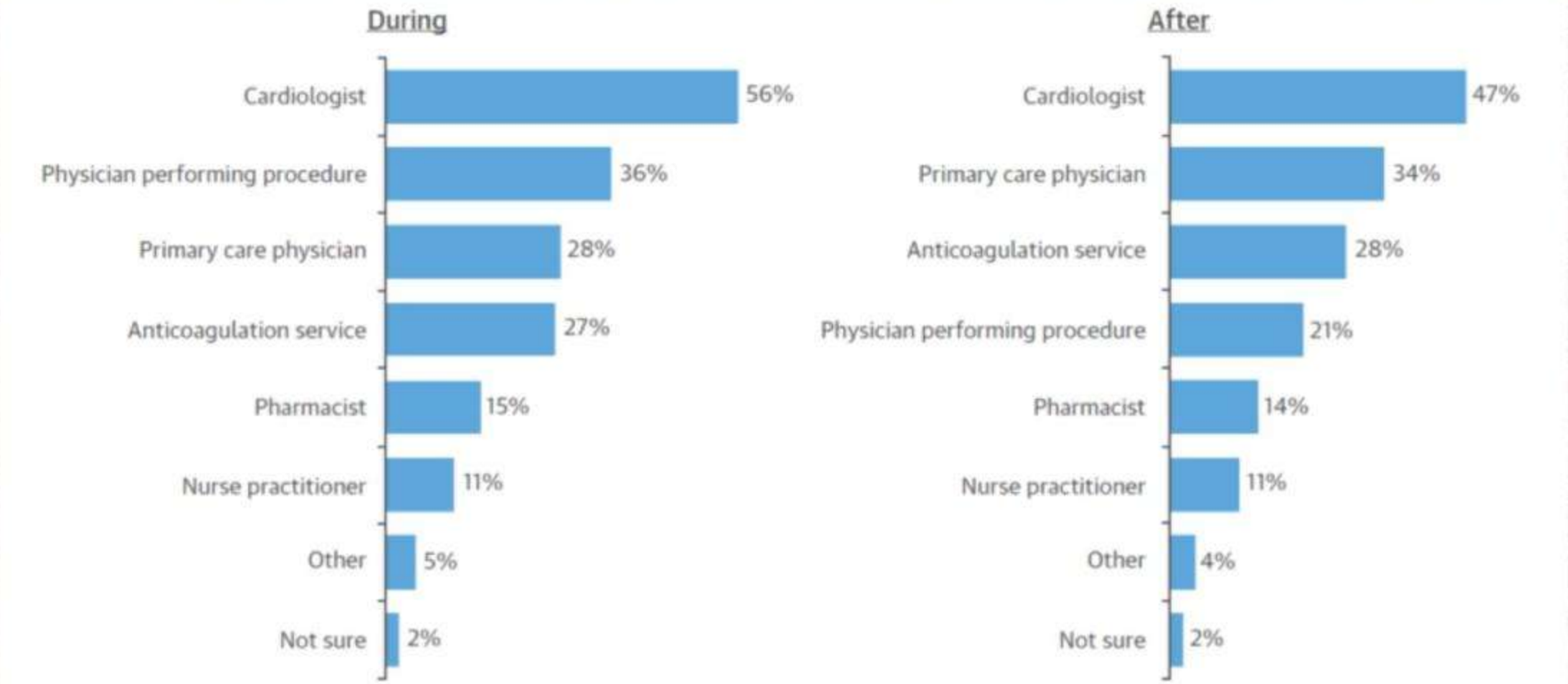
ΕΠΙΜΕΛΗΤΡΙΑ ΕΣΥ

ΑΘΗΝΑ 2018

The problem

- 10-15% of patients on any long-term oral anticoagulation require surgery
- 20% undergo surgery that has an extremely low risk of bleeding
- 10% undergo surgery that has an extremely high risk of bleeding
- periprocedural risk of bleeding is about double the risk of thrombotic complications
- periprocedural risk of stroke is tripled in patients with AF
- periprocedural risk of myocardial infarction is five times higher in stented patients

WHO MANAGES PERIPROCEDURAL ANTICOAGULATION



J Am Coll Cardiol 2016;68:217–26

Percentage of Respondents Who Would Interrupt AC and Administer Parenteral AC in a Patient Who Is Not Low Risk for Stroke

	General Cardiologists (n = 158)	Electrophysiologists (n = 163)	Interventional Cardiologists (n = 161)	Internists (n = 152)	Gastroenterologists (n = 160)	Orthopedic Surgeons (n = 153)
Dental cleaning	4%	9%	5%	29%	31%	29%
Cataract removal	9%	15%	9%	46%	40%	31%
Upper endoscopy	16%	21%	17%	37%	44%	39%
Dental extraction	16%	23%	14%	45%	39%	37%
Pacemaker or defibrillator replacement	15%	10%	15%	57%	56%	53%
Colonoscopy	23%	28%	19%	45%	46%	45%
Coronary angiography	18%	24%	16%	49%	53%	49%
Pacemaker or defibrillator implantation	17%	12%	17%	57%	59%	52%
Catheter ablation	27%	13%	24%	53%	53%	48%
Epidural injection for back pain relief	22%	36%	25%	53%	42%	41%

AC = anticoagulation; VKA = vitamin K antagonist.

Periprocedural management of anticoagulation

BLEEDING RISK

- Procedure dependent
- Patient dependent

BLEEDING CONSECUENSES

THROMBOTIC RISK or

THROMBOEMBOLIC RISK

Periprocedural antithrombotic pathway

- Whether to interrupt
  - When to interrupt
  - Whether to bridge
    - How to bridge
- When and how to restart

Patient bleed factors

- Recent bleeding event
- Bleed history in previous bridging
- Bleed history with similar procedure
- INR above the therapeutic range at the time of the procedure
- Qualitative or quantitative platelet abnormality
- Periprocedural aspirin

Online Appendix

Common Procedures and Associated Procedural Bleed Risk

Electrophysiology Section Leadership Council of the American College of Cardiology 2
Interventional Section Leadership Council of the American College of Cardiology 3
Surgeons' Section Leadership Council of the American College of Cardiology 4
American Academy of Ophthalmology 9
American Academy of Orthopaedic Surgeons 10
American Association of Neurological Surgeons 11
American Association of Oral and Maxillofacial Surgeons 12
American College of Chest Physicians 13
American College of Obstetricians and Gynecologists 14
American College of Physicians 16
American College of Rheumatology 17
American Society of Breast Surgeons 18
American Society of Gastrointestinal Endoscopy 19
American Society of Nephrology 20
American Society of Regional Anesthesia and Pain Medicine 22
American Urological Association 23
Heart Rhythm Society 24
Society for Cardiovascular Angiography and Interventions 25
Society for Vascular Surgery 26
Society of Thoracic Surgeons 27

American Association of Neurological Surgeons

Procedure Name	Bleed Risk Level			
	Low	Intermediate	High	Uncertain
Craniotomy	☐	☐	☒	☐
Laminectomy	☐	☐	☒	☐
Discectomy	☐	☐	☒	☐
Fusion, spinal	☐	☐	☒	☐
Endarterectomy, carotid	☐	☐	☒	☐
Angiogram, cerebral	☐	☒	☐	☐
Stent, carotid	☐	☒	☐	☐
Embolization, intracranial	☐	☐	☒	☐
Embolization, spinal	☐	☒	☐	☐
Embolectomy, stroke	☐	☐	☒	☐
Decompression, peripheral nerve	☐	☒	☐	☐
Stimulation, deep brain	☐	☐	☒	☐
Stimulation, spinal cord	☐	☐	☒	☐
Craniectomy	☐	☐	☒	☐
VP (ventriculoperitioneal) shunt	☐	☐	☒	☐
Lumbar puncture	☐	☐	☒	☐
Pituitary surgery	☐	☐	☒	☐

American Association of Oral and Maxillofacial Surgeons

Procedure Name	Bleed Risk Level				
	Not clinically relevant	Low	Intermediate	High	Uncertain
Local anesthesia by infiltration	☒	☐	☐	☐	☐
Local anesthesia by inferior alveolar nerve blocks	☐	☒	☐	☐	☐
Dental extractions, simple or erupted, 1-3 teeth	☐	☒	☐	☐	☐
Incision and drainage, intra-oral swellings	☐	☒	☐	☐	☐
Dental extractions (surgical), complex, >3 teeth	☐	☐	☒	☐	☐
Extractions, impacted teeth flap, bone removal	☐	☐	☒	☐	☐
Dental implant surgery	☐	☐	☒	☐	☐
Bone grafting, alveolar ridge	☐	☐	☒	☐	☐
Biopsy or excisions, oral soft tissue lesions	☐	☐	☒	☐	☐
Preprosthetic surgery	☐	☐	☒	☐	☐
Facial trauma repair by open techniques	☐	☐	☐	☒	☐
Corrective jaw or facial surgery	☐	☐	☐	☒	☐
Excision, bone or large soft tissue pathology	☐	☐	☐	☒	☐

American Academy of Ophthalmology Procedure Name

Procedure Name	Bleed Risk Level				
	Very Low	Low	Intermediate	High	Uncertain
Intravitreal injection with a pharmacologic agent	☒	☐	☐	☐	☐
Cataract Surgery with Intraocular Lens	☒	☐	☐	☐	☐
After-cataract laser surgery	☒	☐	☐	☐	☐
Complex cataract surgery	☒	☐	☐	☐	☐
Closure of tear duct opening	☒	☐	☐	☐	☐
Trabeculoplasty by laser surgery	☒	☐	☐	☐	☐
Revision of eyelashes	☒	☐	☐	☐	☐
Treatment of extensive or progressive retinopathy, photocoagulation	☒	☐	☐	☐	☐
Destruction of localized lesion of retina, photocoagulation	☒	☐	☐	☐	☐
Revision of iris	☒	☐	☐	☐	☐
pars plana vitrectomy (particularly in diabetics)	☐	☒	☐	☐	☐
Orbital surgery	☐	☒	☐	☐	☐
certain eyelid procedures such as blepharoplasty	☐	☒	☐	☐	☐

Interventional Section Leadership Council of the American College of Cardiology

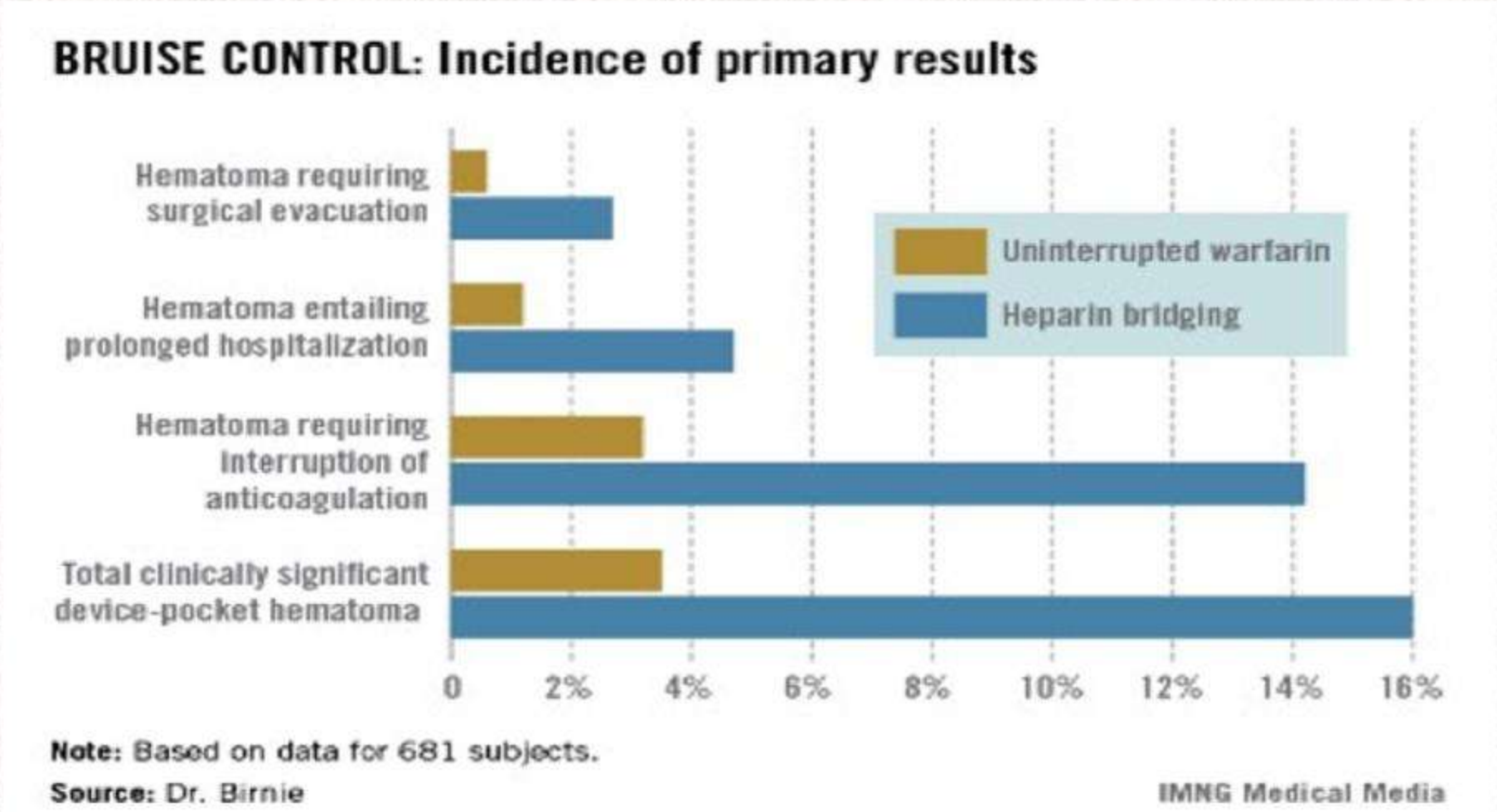
Procedure Name	Bleed Risk Level			
	Low	Intermediate	High	Uncertain
Coronary angiography, transradial	☒	☐	☐	☐
Coronary angiography, transfemoral*	☐	☐	☐	☒
PCI (percutaneous coronary intervention), transradial	☒	☐	☐	☐
PCI (percutaneous coronary intervention), transfemoral	☐	☒	☐	☐
TAVR (transaortic valve replacement)	☐	☐	☒	☐
Valvuloplasty, aortic	☐	☐	☒	☐
Pericardiocentesis	☐	☒	☐	☐
Mitral valve repair, percutaneous (MitraClip procedure)	☐	☒	☐	☐
Right heart catheterization	☒	☐	☐	☐

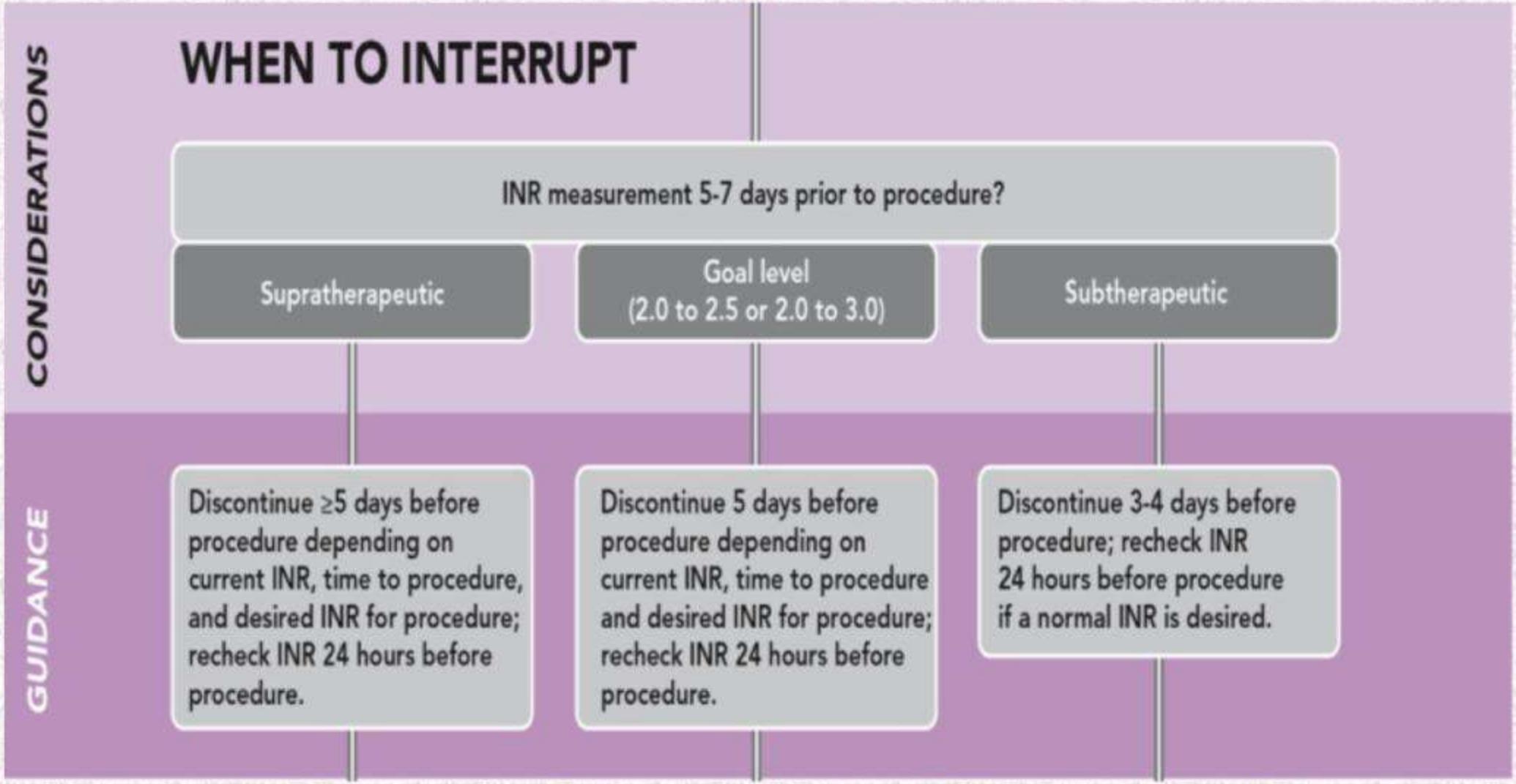
Ablation, structural VT (ventricular tachycardia)*	☒	☒	☐	☐
Ablation, PVC (premature ventricular complex)*	☒	☒	☐	☐
Ablation, atrial fibrillation*	☒	☒	☐	☐
Ablation, atrial flutter	☒	☐	☐	☐
Implant or generator replacement, CIED (cardiac implantable electronic device)	☒	☐	☐	☐
Implant, subcutaneous ICD (implantable cardioverter defibrillator)	☒	☐	☐	☐

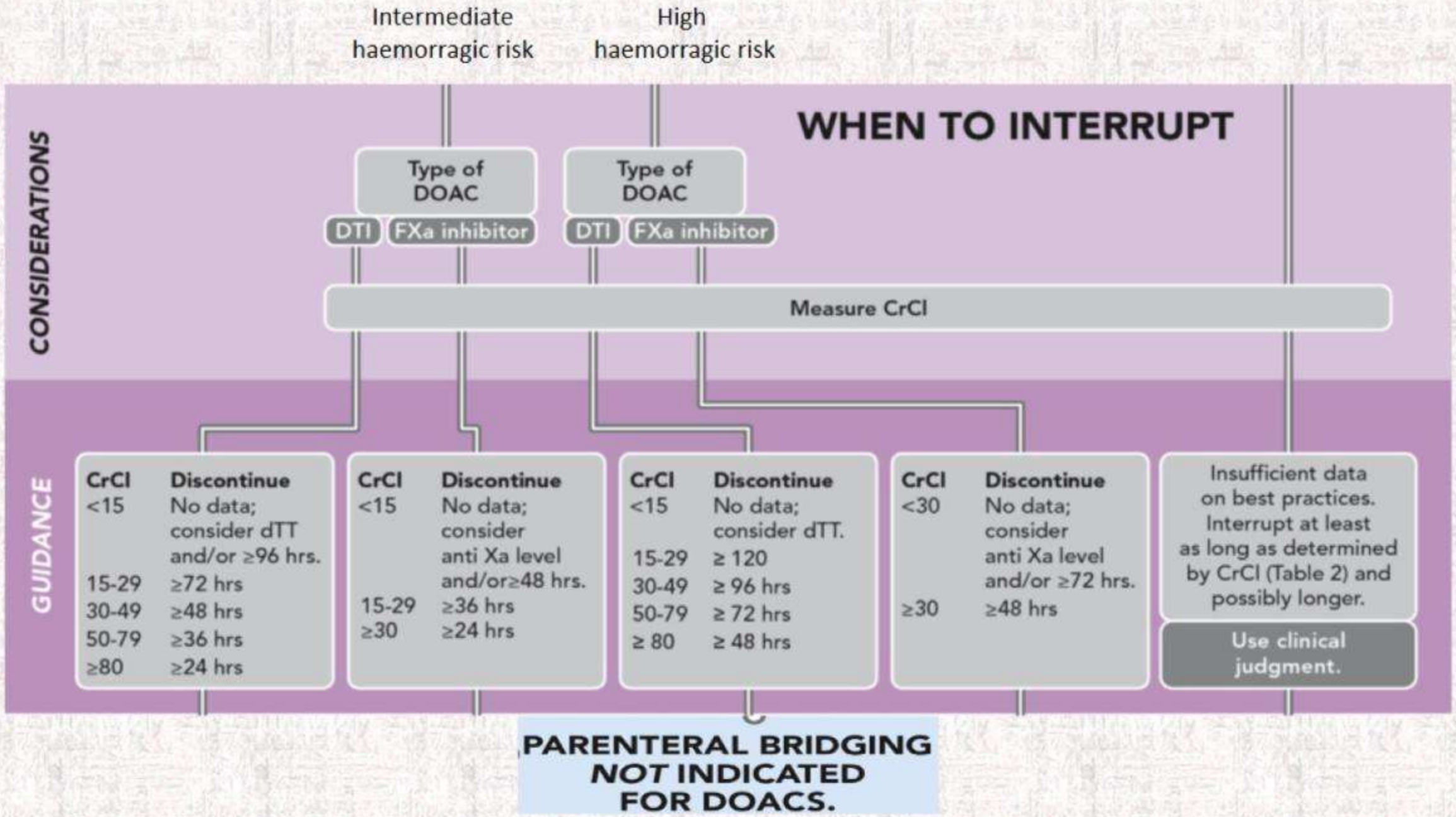
Patients thrombosis factor

- Metallic valve (especially mitral valve)
- Recent pulmonary embolism (<3mo)
- Prior ischemic stroke, TIA, or systematic embolism (especially <3mo)
- Cancer
- CHA2DS2-VASc score >4

Continuing anticoagulation does not mean excessive bleeding




CONSIDERATIONS
WHEN TO INTERRUPT
INR measurement 5-7 days prior to procedure?
Supratherapeutic
Goal level
(2.0 to 2.5 or 2.0 to 3.0)
Subtherapeutic
GUIDANCE
Discontinue ≥5 days before procedure depending on current INR, time to procedure, and desired INR for procedure; recheck INR 24 hours before procedure.
Discontinue 5 days before procedure depending on current INR, time to procedure and desired INR for procedure; recheck INR 24 hours before procedure.
Discontinue 3-4 days before procedure; recheck INR 24 hours before procedure if a normal INR is desired.


Intermediate haemorragic risk
High haemorragic risk
CONSIDERATIONS
WHEN TO INTERRUPT
Type of DOAC
DTI
FXa inhibitor
Type of DOAC
DTI
FXa inhibitor
Measure CrCl
GUIDANCE
CrCl Discontinue
<15 No data; consider dTT and/or ≥96 hrs.
15-29 ≥72 hrs
30-49 ≥48 hrs
50-79 ≥36 hrs
≥80 ≥24 hrs
CrCl Discontinue
<15 No data; consider anti Xa level and/or≥48 hrs.
15-29 ≥36 hrs
≥30 ≥24 hrs
CrCl Discontinue
<15 No data; consider dTT.
15-29 ≥ 120
30-49 ≥ 96 hrs
50-79 ≥ 72 hrs
≥ 80 ≥ 48 hrs
CrCl Discontinue
<30 No data; consider anti Xa level and/or ≥72 hrs.
≥30 ≥48 hrs
Insufficient data on best practices. Interrupt at least as long as determined by CrCl (Table 2) and possibly longer.
Use clinical judgment.
PARENTERAL BRIDGING NOT INDICATED FOR DOACS.

Discontinuation of DOAC for patients undergoing interventional spine and pain procedures

Drug	Half-life	Recommended Interval Between Stoppage of Drug and Pain Procedure (5 Half-lives)*	Recommended Interval Between Procedure and Resumption of Drug†
Dabigatran	12–17 h 28 h (renal disease)	4 d 5–6 d (patients with renal disease)	24 h
Rivaroxaban	9–13 h	65 h (3 d)	24 h
Apixaban	15.2 ± 8.5 h	75 h (3 d)	24 h
Edoxaban	9–14 h	70 h (3 d)	24 h

Reg Anesth Pain Med 2018;

To bridge or not to bridge (VKA)

- The BRIDGE Trial:
  - Arterial thromboembolism met the preset criterion for noninferiority
  - Major bleeding rates were nearly tripled among those who were bridge

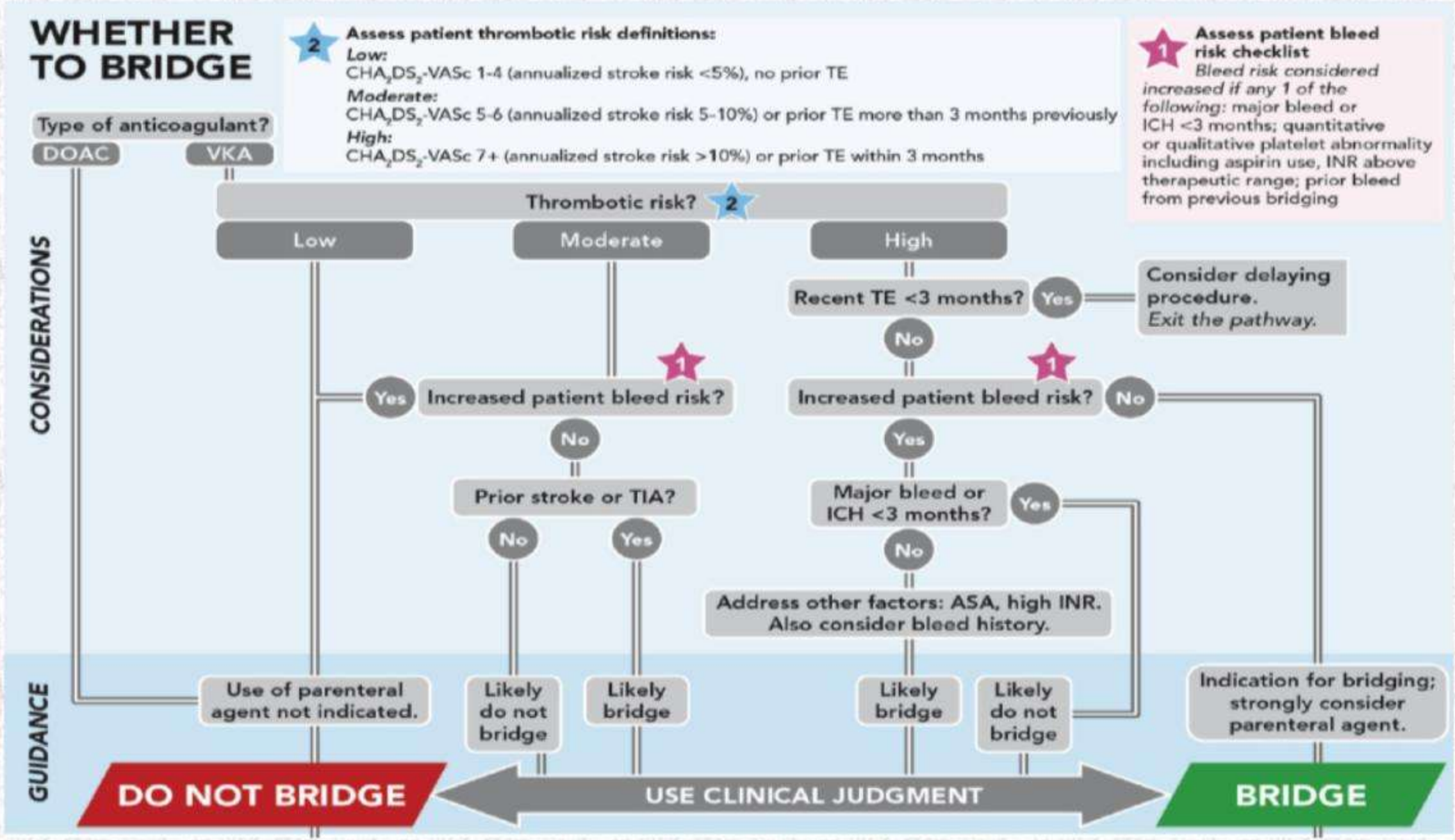
N Engl J Med. 2015;373:823–833

- ORBIT-AF Registry Study:
  - More bleeding with bridging (5% vs 1,3%)
  - The incidence of a composite end point (MI, stroke, SE, major bleeding, hospitalization, or death within 30 days) was higher in bridged than nonbridged patients (13% versus 6.3%)

Circulation. 2015;131:488–494

- RE-LY analysis:
  - Bridging was associated with more major bleeding (OR,4.62, P<0.001)

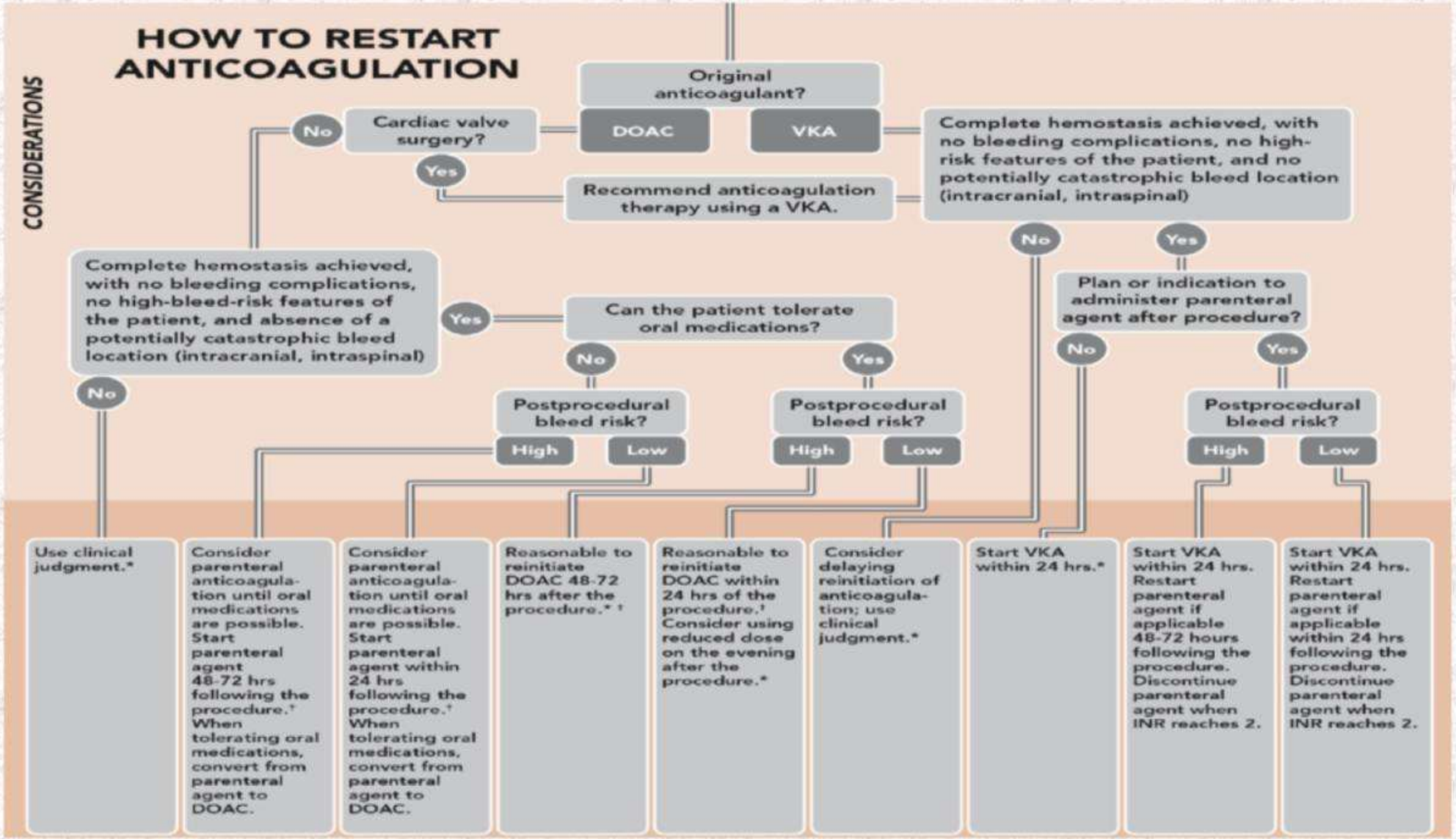
Thromb Haemost. 2015;113:625–632


WHETHER TO BRIDGE
2 Assess patient thrombotic risk definitions:
Low:
CHA2DS2-VASc 1-4 (annualized stroke risk <5%), no prior TE
Moderate:
CHA2DS2-VASc 5-6 (annualized stroke risk 5-10%) or prior TE more than 3 months previously
High:
CHA2DS2-VASc 7+ (annualized stroke risk >10%) or prior TE within 3 months
1 Assess patient bleed risk checklist
Bleed risk considered increased if any 1 of the following: major bleed or ICH <3 months; quantitative or qualitative platelet abnormality including aspirin use, INR above therapeutic range; prior bleed from previous bridging
CONSIDERATIONS
Type of anticoagulant?
DOAC
VKA
Thrombotic risk? 2
Low
Moderate
High
Recent TE <3 months?
Yes
Consider delaying procedure.
Exit the pathway.
No
1
Increased patient bleed risk?
Yes
No
1
Increased patient bleed risk?
No
Yes
Prior stroke or TIA?
No
Yes
Major bleed or ICH <3 months?
Yes
No
Address other factors: ASA, high INR. Also consider bleed history.
GUIDANCE
Use of parenteral agent not indicated.
Likely do not bridge
Likely bridge
Likely bridge
Likely do not bridge
Indication for bridging; strongly consider parenteral agent.
DO NOT BRIDGE
USE CLINICAL JUDGMENT
BRIDGE

How to bridge

Start UFH when the INR is <2 or after omitting 2-3 doses of the OAC if the INR is not measured. Discontinue >4 hours prior to the procedure and if the aPTT is the normal range.*

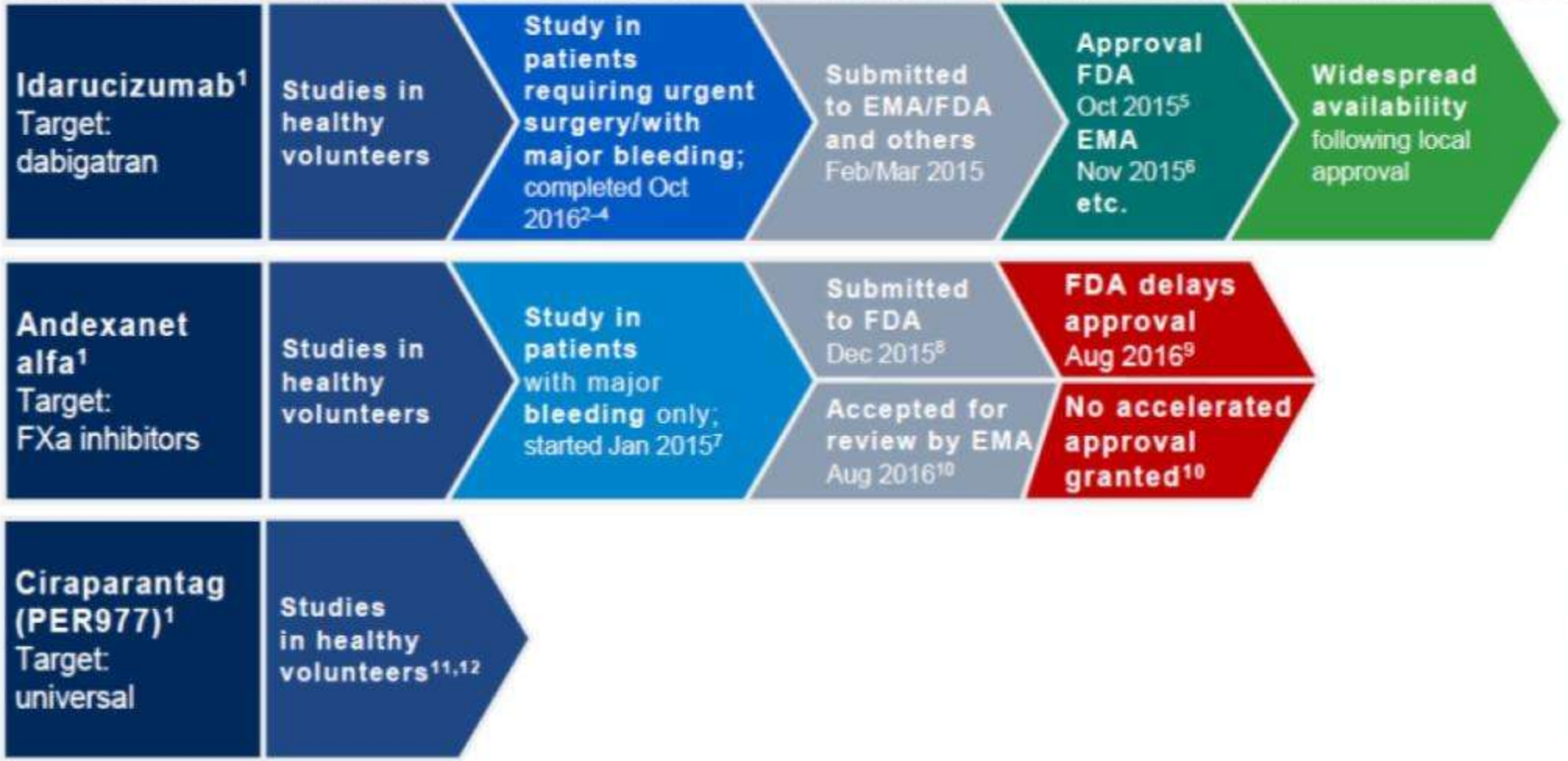
Start LMWH when the INR is <2 or after omitting 2-3 doses of the OAC if the INR is not measured. Discontinue >12-24 hours prior to the procedure based on renal function and whether you are administering it once daily or q12 hours.


HOW TO RESTART ANTICOAGULATION
CONSIDERATIONS
Original anticoagulant?
DOAC
VKA
Cardiac valve surgery?
No
Yes
Recommend anticoagulation therapy using a VKA.
Complete hemostasis achieved, with no bleeding complications, no high-risk features of the patient, and no potentially catastrophic bleed location (intracranial, intraspinal)
No
Yes
Plan or indication to administer parenteral agent after procedure?
No
Yes
Complete hemostasis achieved, with no bleeding complications, no high-bleed-risk features of the patient, and absence of a potentially catastrophic bleed location (intracranial, intraspinal)
Yes
Can the patient tolerate oral medications?
No
Yes
No
Postprocedural bleed risk?
High
Low
Postprocedural bleed risk?
High
Low
Postprocedural bleed risk?
High
Low
Use clinical judgment.*
Consider parenteral anticoagulation until oral medications are possible. Start parenteral agent 48-72 hrs following the procedure.† When tolerating oral medications, convert from parenteral agent to DOAC.
Consider parenteral anticoagulation until oral medications are possible. Start parenteral agent within 24 hrs following the procedure.† When tolerating oral medications, convert from parenteral agent to DOAC.
Reasonable to reinitiate DOAC 48-72 hrs after the procedure.* †
Reasonable to reinitiate DOAC within 24 hrs of the procedure.† Consider using reduced dose on the evening after the procedure.*
Consider delaying reinitiation of anticoagulation; use clinical judgment.*
Start VKA within 24 hrs.*
Start VKA within 24 hrs. Restart parenteral agent if applicable 48-72 hours following the procedure. Discontinue parenteral agent when INR reaches 2.
Start VKA within 24 hrs. Restart parenteral agent if applicable within 24 hrs following the procedure. Discontinue parenteral agent when INR reaches 2.

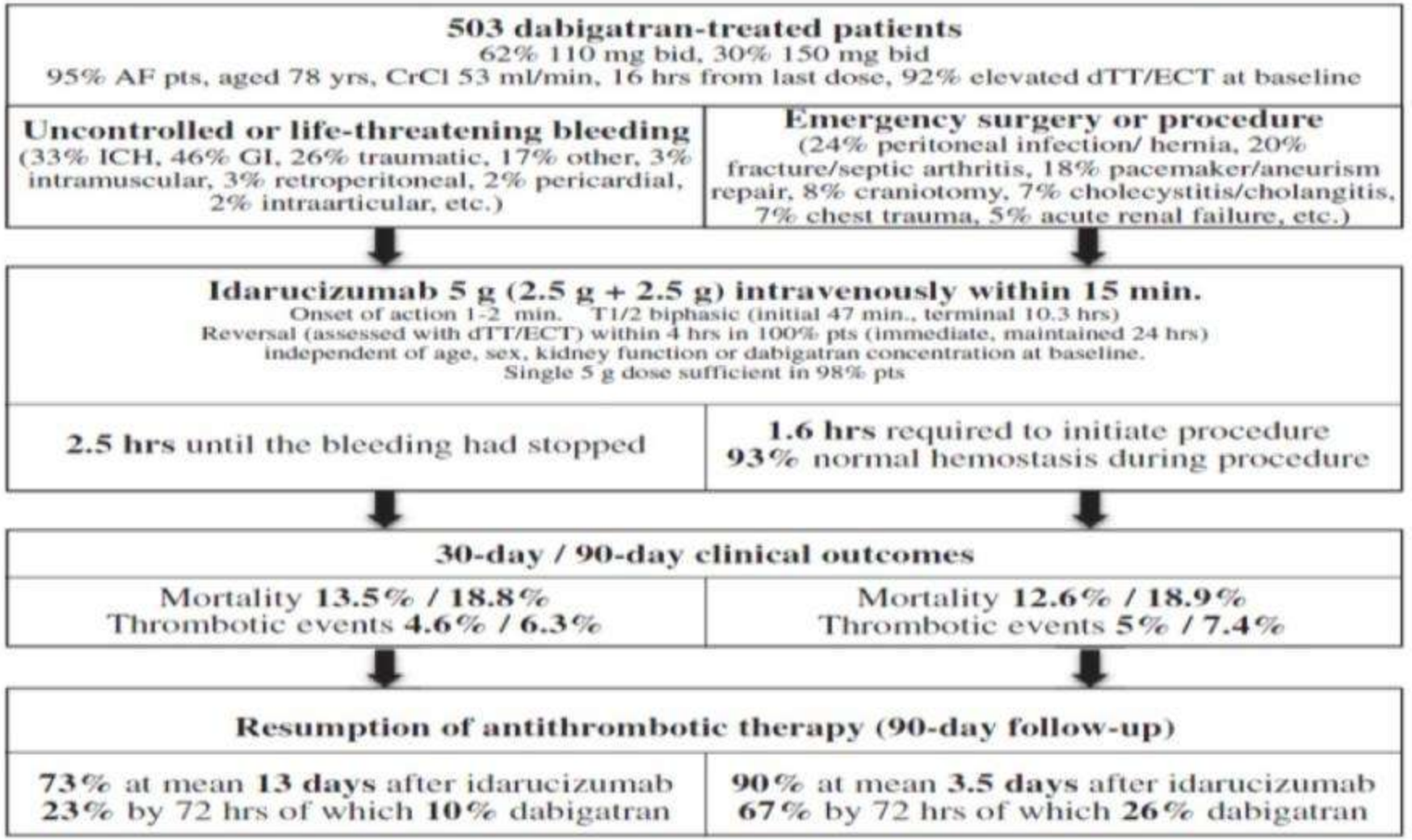
Post procedural timing of reinitiation

- ✓ In most situations, a VKA can be restarted **in the first 24 hours** after the procedure at the patient's usual therapeutic dose
- ✓ Following procedures with low postprocedural bleed risk where TI is indicated, it is reasonable to **resume DOAC therapy at full dose on the day following the procedure**
- ✓ Following high postprocedural bleed-risk procedures, it is reasonable to **wait at least 48 to 72 hours** before resuming DOAC therapy at full dose if complete hemostasis has been achieved.

DOAC reversal agents

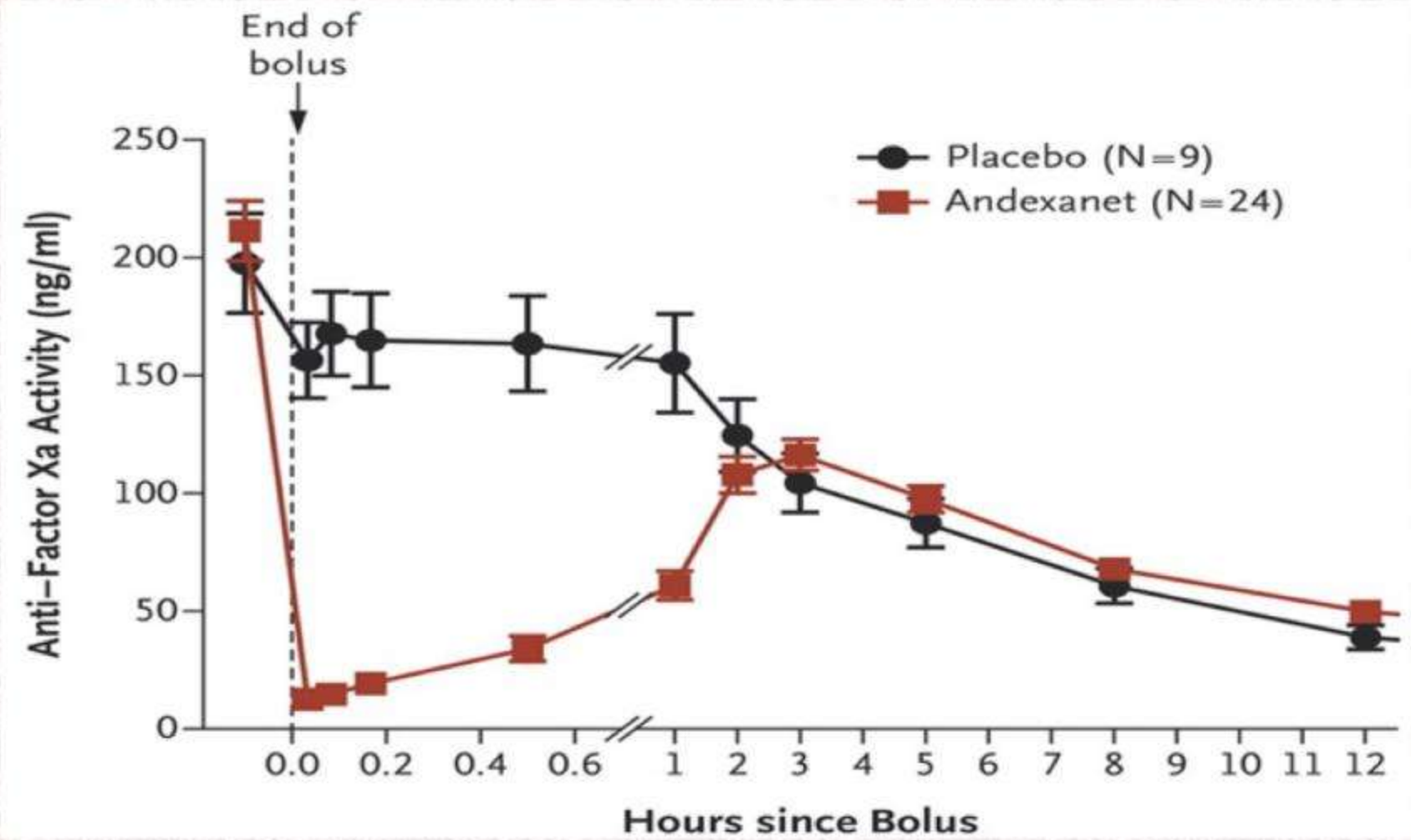


RE-VERSE AD study



N Engl J Med 2017; 377:431-441

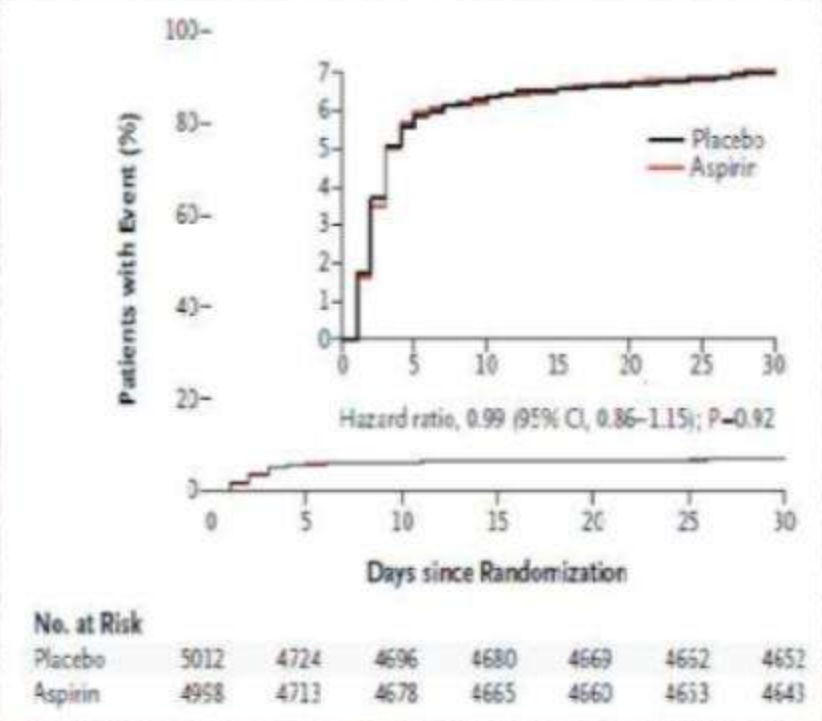
Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

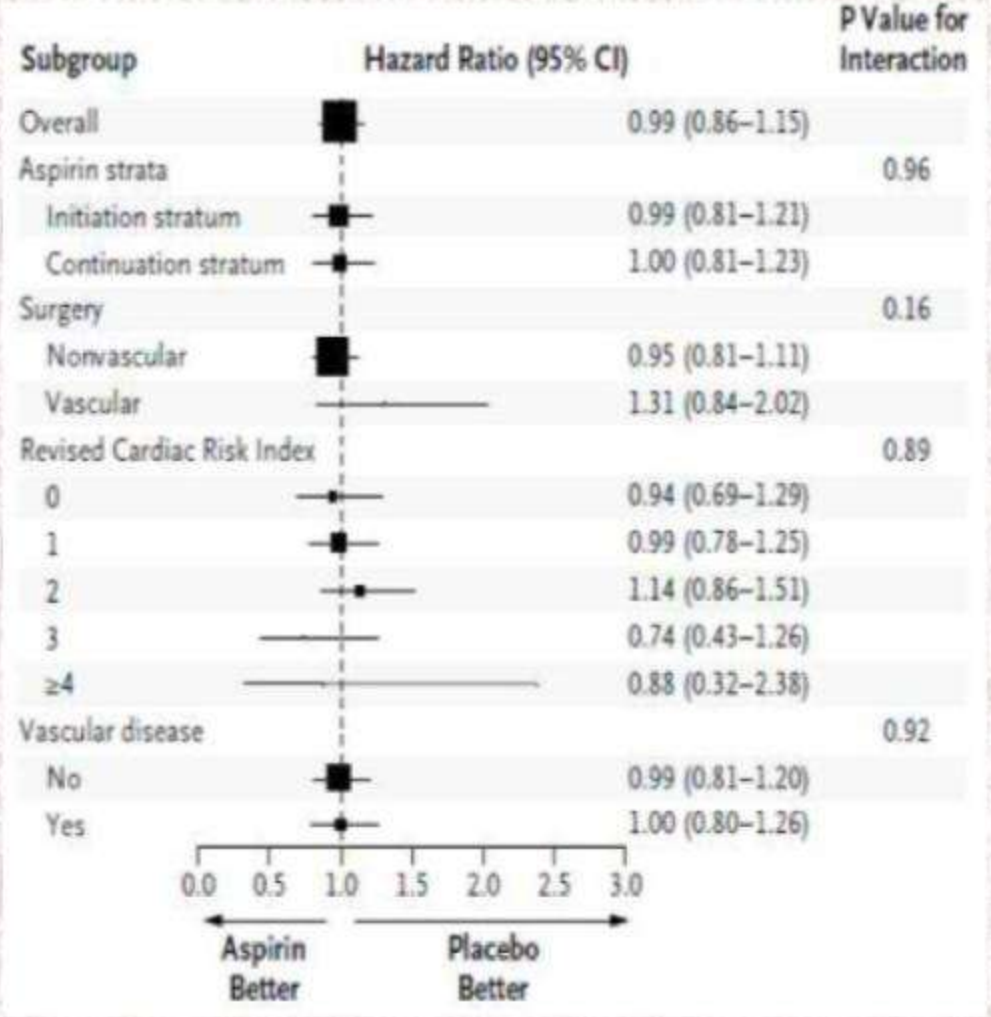


N Engl J Med 2016;375:1131-41.

Περιεγχειρητικοί χειρισμοί ασθενών που λαμβάνουν αντιαιμοπεταλιακά φάρμακα

Periprocedural aspirin
(POISE 2 study)





N Engl J Med 2014;370:1494–503

Table 3. Absolute Increase in the Risk of a Composite of Life-Threatening or Major Bleeding with Aspirin Therapy, Starting on Each of the First 10 Postoperative Days until 30 Days after Surgery.*

Day at Start of Risk Analysis	Aspirin†	Placebo†	Absolute Increase in Risk with Aspirin	P Value
	no./total no. (%)		*percentage points*	
Day of surgery	311/4953 (6.3)	254/4978 (5.1)	1.2	0.01
Day 1 after surgery	191/4832 (4.0)	129/4852 (2.7)	1.3	<0.001
Day 2 after surgery	138/4779 (2.9)	92/4813 (1.9)	1.0	0.002
Day 3 after surgery	102/4741 (2.2)	59/4777 (1.2)	1.0	<0.001
Day 4 after surgery	73/4710 (1.6)	33/4748 (0.7)	0.9	<0.001
Day 5 after surgery	59/4693 (1.3)	27/4739 (0.6)	0.7	<0.001
Day 6 after surgery	43/4674 (0.9)	25/4736 (0.5)	0.4	0.03
Day 7 after surgery	39/4667 (0.8)	22/4731 (0.5)	0.3	0.03
Day 8 after surgery	20/2623 (0.8)	14/2662 (0.5)	0.3	0.29
Day 9 after surgery	15/2617 (0.6)	14/2660 (0.5)	0.1	0.82
Day 10 after surgery	14/2614 (0.5)	12/2657 (0.5)	0.0	0.67

ESC recommendations on peri-operative aspirin use

Recommendations	Class	Level
Continuation of aspirin in patients previously treated with aspirin may be considered in the peri-operative period (based on risk of bleeding and thrombosis).	IIb	B
Discontinuation of aspirin in patients previously treated with that drug should be considered in patients in whom haemostasis is anticipated to be difficult to control during surgery.	IIa	B

www.escardio.org/guidelines

European Heart Journal (2014) 35, 2383–2431
doi:10.1093/eurheartj/ehu282

EUROPEAN SOCIETY OF CARDIOLOGY®

Patients with coronary stents

Recommendations	Class[a]	Level[b]
It is recommended to continue aspirin peri-operatively if the bleeding risk allows, and to resume the recommended antiplatelet therapy as soon as possible post-operatively.[232–236]	I	B

European Heart Journal (2018) 39, 213–254

Possible exceptions

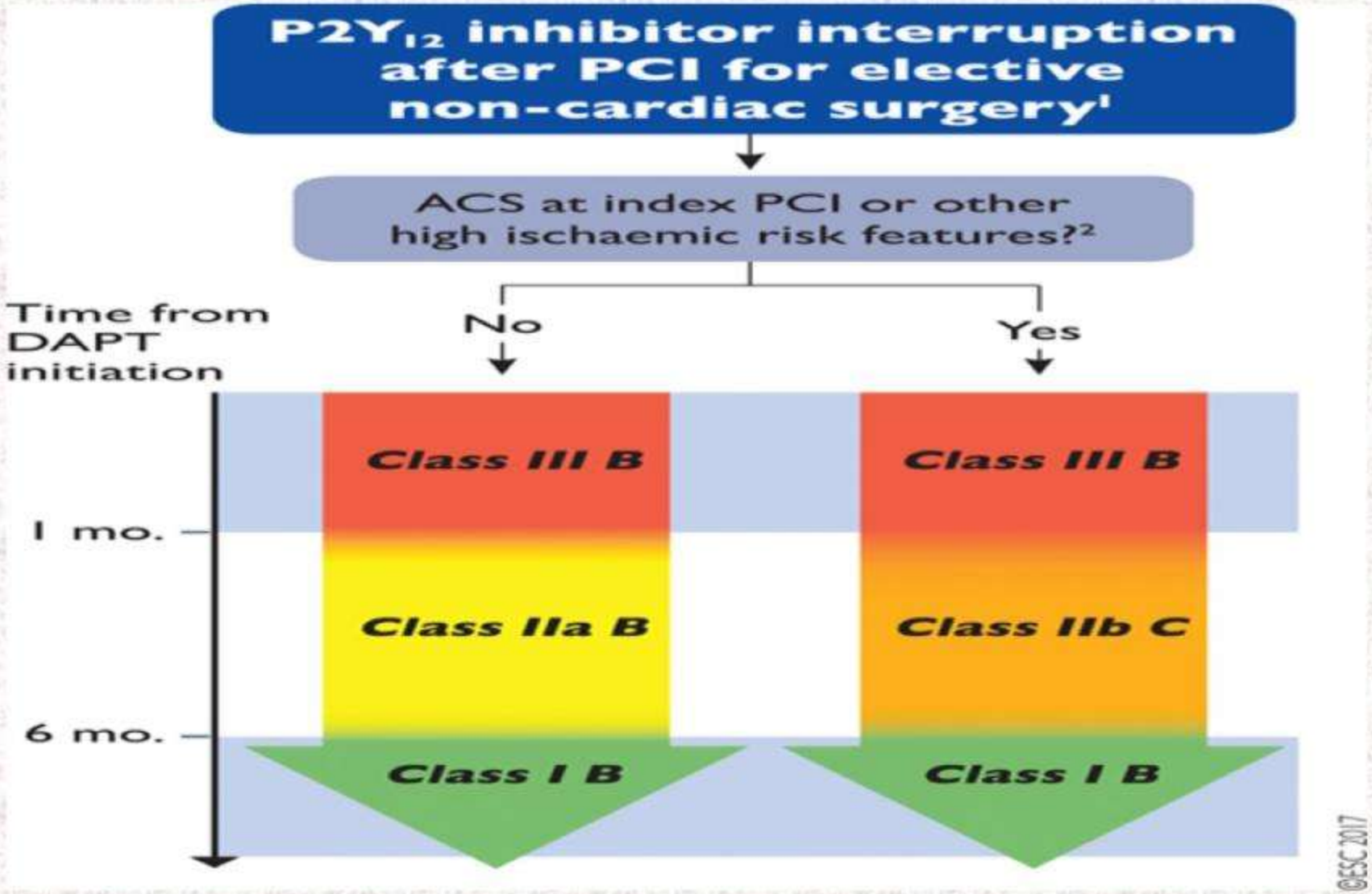
- intracranial procedures
- transurethral prostatectomy
- intraocular procedures
- operations with extremely high bleeding risk

European Heart Journal (2018) 39, 213–254

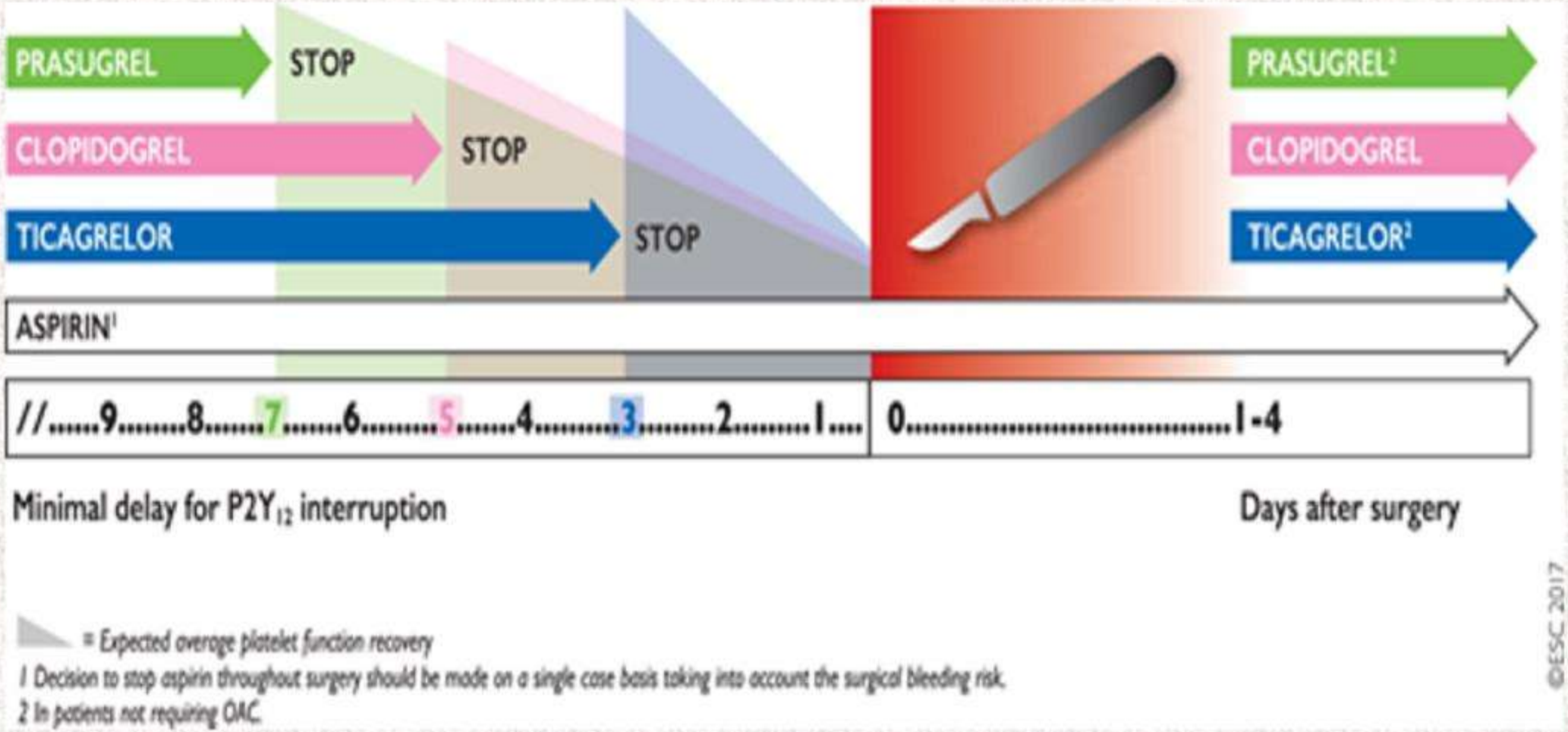
Risk Factors Associated With Adverse Cardiac Events

	n	Myocardial Infarction	Myocardial Infarction OR (95% CI)	Cardiac Death	Cardiac Death OR (95% CI)	All-Cause Mortality	All-Cause Mortality OR (95% CI)
Timing of surgery*							
≤1 month	635	46 (7.2)	15.84 (9.12-27.50)	31 (5.0)	13.71 (7.13-26.35)	57 (9.0)	4.42 (3.11-6.28)
>1-12 months	3,668	18 (0.5)		13 (0.4)		80 (2.1)	
ACS†							
ACS	2,291	50 (2.2)	3.64 (1.89-7.01)	32 (1.5)	5.14 (2.00-13.23)	76 (3.3)	1.41 (0.96-2.05)
SAP	2,012	11 (0.5)		5 (0.2)		43 (2.1)	
Emergency surgery							
Acute	1,123	42 (4.5)	5.58 (3.31-9.38)	28 (3.2)	4.92 (2.65-9.13)	93 (10.1)	6.44 (4.47-9.27)
Elective	3,180	22 (0.7)		16 (0.5)		44 (1.4)	
Stent generation							
First	2,594	36 (0.6)	0.84 (0.51-1.39)	25 (1.0)	0.75 (0.41-1.37)	69 (2.7)	0.66 (0.47-0.92)
Second	1,709	28 (1.6)		19 (1.1)		68 (4.0)	
Stent length							
>20 mm	2,269	37 (1.6)	0.81 (0.49-1.34)	28 (1.2)	0.64 (0.34-1.18)	79 (3.5)	0.81 (0.58-1.15)
≤20 mm	2,034	27 (1.3)		16 (0.8)		58 (2.8)	
No. of stents							
>1	1,729	24 (1.4)	1.12 (0.67-1.87)	23 (1.3)	0.62 (0.34-1.12)	61 (3.5)	0.83 (0.59-1.17)
1	2,574	40 (1.6)		21 (0.9)		76 (3.0)	
Age							
>70 yrs	1,789	26 (1.5)	0.96 (0.58-1.59)	25 (1.5)	1.88 (1.04-3.44)	88 (4.9)	2.60 (1.82-3.70)
≤70 yrs	2,514	38 (1.5)		19 (0.7)		49 (1.9)	
Sex							
Female	1,265	13 (1.0)	0.61 (0.33-1.12)	11 (0.9)	0.80 (0.41-1.60)	47 (3.7)	1.26 (0.88-1.81)
Male	2,987	51 (1.7)		33 (1.1)		90 (3.0)	

J Am Coll Cardiol 2016;68:2622–32



European Heart Journal (2018) 39, 213–254


PRASUGREL
STOP
CLOPIDOGREL
STOP
TICAGRELOR
STOP
PRASUGREL[2]
CLOPIDOGREL
TICAGRELOR[2]
ASPIRIN[1]
//.....9.....8.....7.....6.....5.....4.....3.....2.....1....
0.....1-4
Minimal delay for P2Y12 interruption
Days after surgery
= Expected average platelet function recovery
1 Decision to stop aspirin throughout surgery should be made on a single case basis taking into account the surgical bleeding risk.
2 In patients not requiring OAC.
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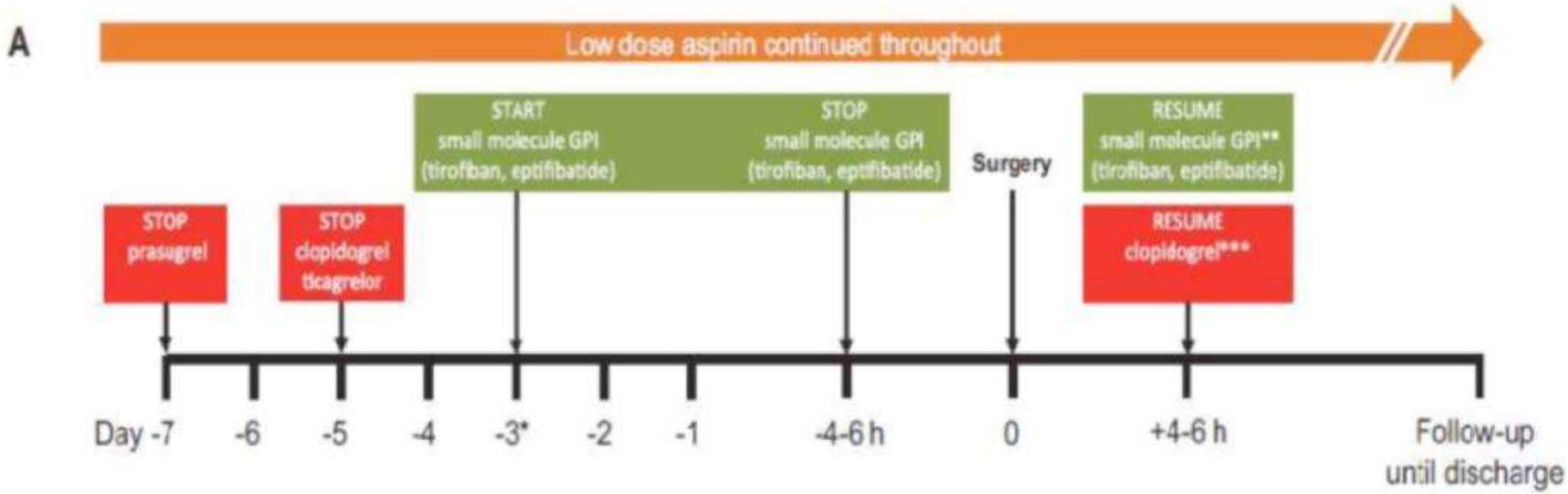
Bridging therapy 1



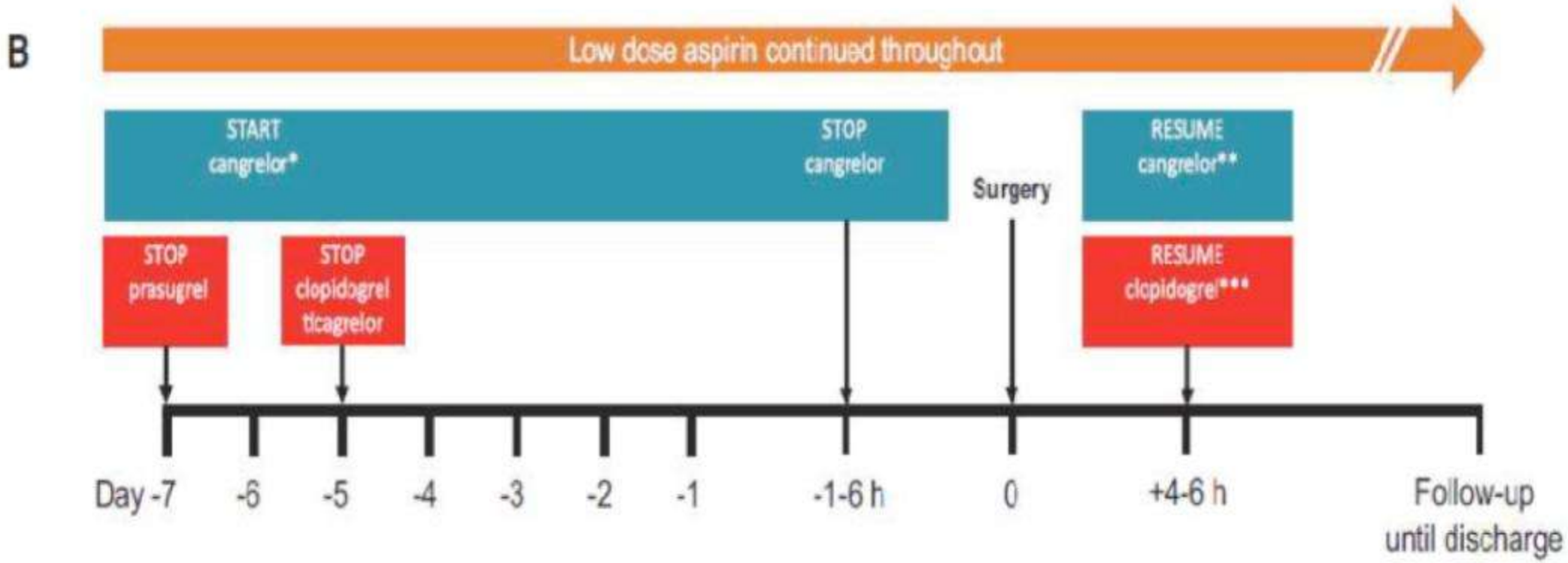
*Tirofiban: 0.1 mcg/Kg/min; If creatinine clearance <50 mL/min, adjust to 0.05 mcg/Kg/min. Eptifibatide: 2.0 mcg/Kg/min; If creatinine clearance is <50 mL/min, adjust to 1.0 mcg/Kg/min.

**If oral administration not possible

***With 300-600 mg loading dose, as soon as oral administration possible. Prasugrel or ticagrelor discouraged

Circulation. 2013;128:2785–2798

Bridging therapy 2



*Initiate within 72 hours from $P2Y_{12}$ inhibitor discontinuation at a dose of 0.75 µg/Kg/min for a minimum of 48 hours and a maximum of 7 days.

**If oral administration not possible

***With 300-600 mg loading dose, as soon as oral administration possible. Prasugrel or ticagrelor discouraged

Circulation. 2013;128:2785–2798

Conclusions

- peri-procedural management of patients treated with antithrombotic/antiplatelet therapy is challenging
- there are areas in the periprocedural management of AC where clinical evidence is clear-cut
- there are others where guidance needs to be tempered by clinical judgment
- it makes sense to develop consistently applied clinical pathways with standardized institutional protocols
- coordination among specialties, pharmacists, nursing, and other health professionals has great potential for enhancement of care