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ΠΑΝΕΛΛΗΝΙΟ ΣΥΝΕΔΡΙΟ

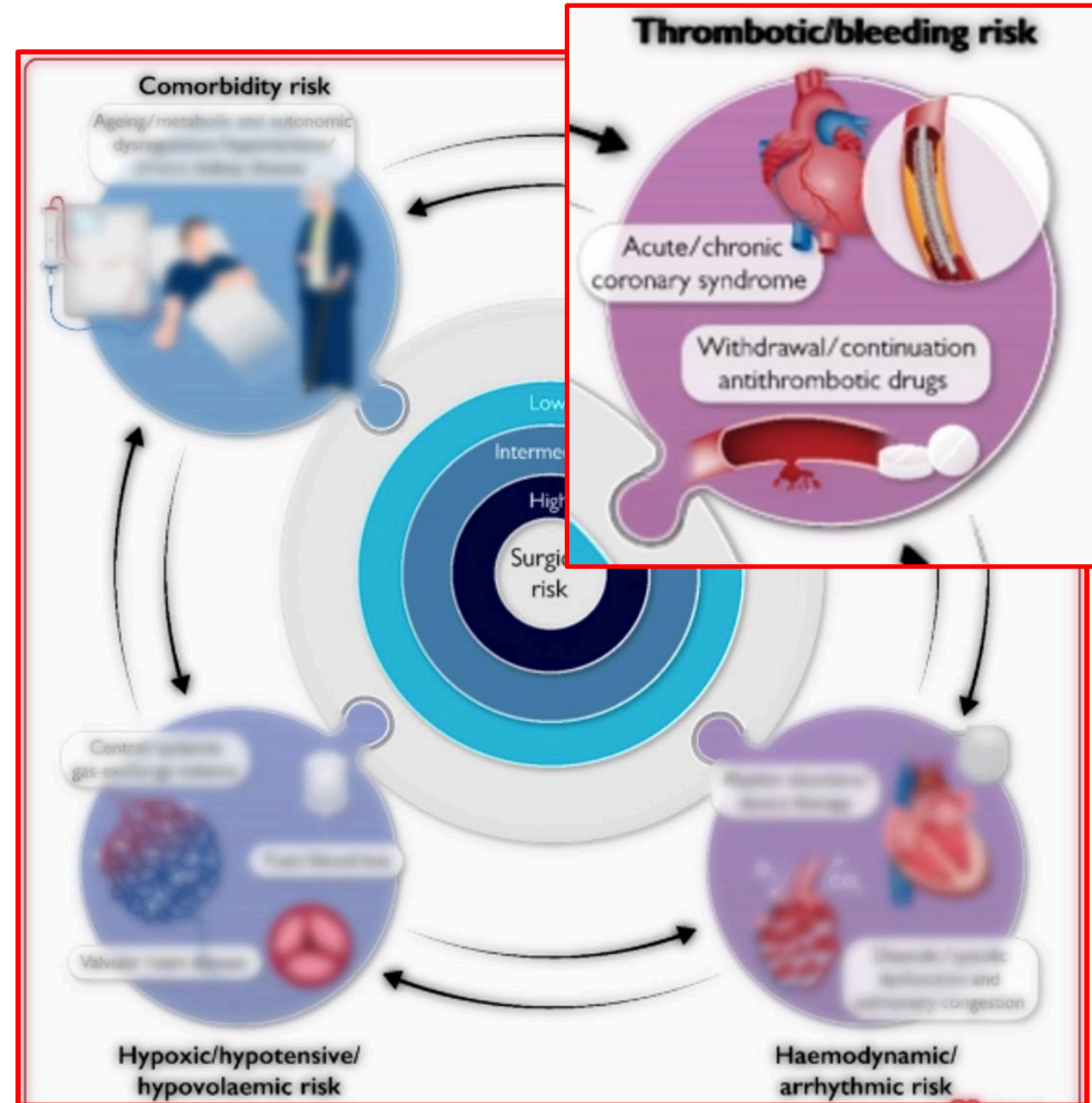
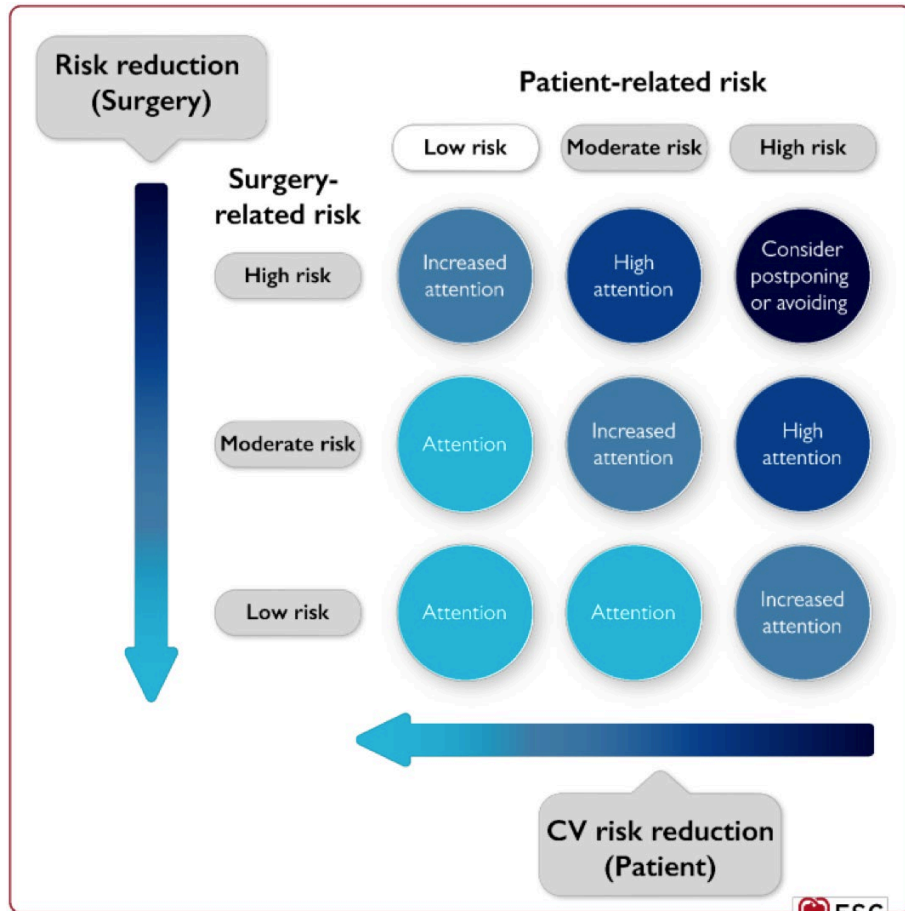
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"Διλήμματα στην Κλινική Παθολογία"



30 Μαρτίου έως
01 Απριλίου
2023

The complex interplay between the intrinsic risk of surgery and the patient risk of peri-operative cardiovascular complications





ESC

European Society
of Cardiology

European Heart Journal (2022) **43**, 3826–3924

<https://doi.org/10.1093/eurheartj/ehac270>

ESC GUIDELINES

2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery

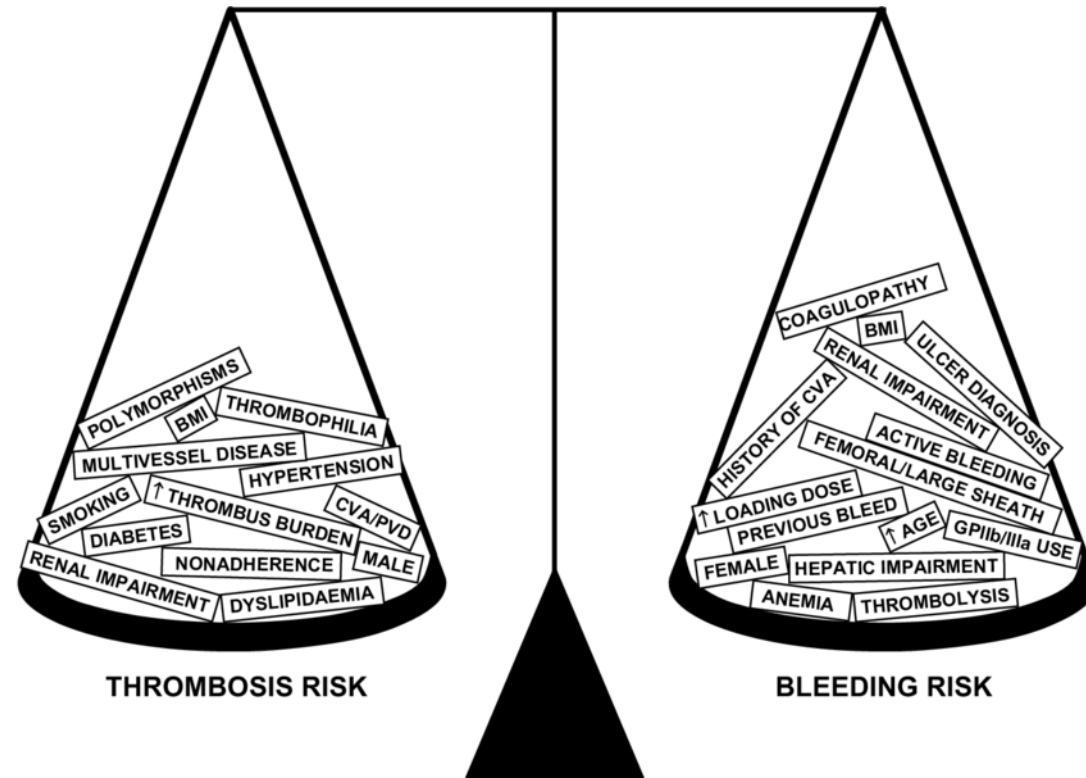
Developed by the task force for cardiovascular assessment and management of patients undergoing non-cardiac surgery of the European Society of Cardiology (ESC)

Endorsed by the European Society of Anaesthesiology and Intensive Care (ESAIC)

Surgical risk estimate according to type of surgery or intervention

Low surgical risk ($<1\%$)	Intermediate surgical risk ($1-5\%$)	High surgical risk ($>5\%$)
<ul style="list-style-type: none">• Breast• Dental• Endocrine: thyroid• Eye• Gynaecological: minor• Orthopaedic minor (meniscectomy)• Reconstructive• Superficial surgery• Urological minor: (transurethral resection of the prostate)• VATS minor lung resection	<ul style="list-style-type: none">• Carotid asymptomatic (CEA or CAS)• Carotid symptomatic (CEA)• Endovascular aortic aneurysm repair• Head or neck surgery• Intraperitoneal: splenectomy, hiatal hernia repair, cholecystectomy• Intrathoracic: non-major• Neurological or orthopaedic: major (hip and spine surgery)• Peripheral arterial angioplasty• Renal transplants• Urological or gynaecological: major	<ul style="list-style-type: none">• Adrenal resection• Aortic and major vascular surgery• Carotid symptomatic (CAS)• Duodenal-pancreatic surgery• Liver resection, bile duct surgery• Oesophagectomy• Open lower limb revascularization for acute limb ischaemia or amputation• Pneumonectomy (VATS or open surgery)• Pulmonary or liver transplant• Repair of perforated bowel• Total cystectomy

Management of patients taking antithrombotic agents and needing an invasive procedure should consider patient- and procedure-related risk of bleeding and thrombosis



Bleeding risk associated with different types of interventions

Surgery with minor bleeding risk	Surgery with low bleeding risk (infrequent or with low clinical impact)	Surgery with high bleeding risk (frequent or with significant clinical impact)
<ul style="list-style-type: none"> • Cataract or glaucoma procedure • Dental procedures: extractions (1–3 teeth), periodontal surgery, implant positioning, endodontic (root canal) procedures, subgingival scaling/cleaning • Endoscopy without biopsy or resection • Superficial surgery (e.g. abscess incision, small skin excisions/ biopsy) 	<ul style="list-style-type: none"> • Abdominal surgery: cholecystectomy, hernia repair, colon resection • Breast surgery • Complex dental procedures (multiple tooth extractions) • Endoscopy with simple biopsy • Gastroscopy or colonoscopy with simple biopsy • Large-bore needles procedures (e.g. bone marrow or lymph node biopsy) • Non-cataract ophthalmic surgery • Small orthopaedic surgery (foot, hand arthroscopy) 	<ul style="list-style-type: none"> • Abdominal surgery with liver biopsy, extracorporeal shockwave lithotripsy • Extensive cancer surgery (e.g. pancreas, liver) • Neuraxial (spinal or epidural) anaesthesia • Neurosurgery (intracranial, spinal) • Major orthopaedic surgery • Procedures with vascular organ biopsy (kidney or prostate) • Reconstructive plastic surgery • Specific interventions (colon polypectomy, lumbar puncture, endovascular aneurysm repair) • Thoracic surgery, lung resection surgery • Urological surgery (prostatectomy, bladder tumour resection) • Vascular surgery (e.g. AAA repair, vascular bypass)

Ischemic risk associated with clinical and procedural factors

TABLE 1 Clinical and Procedural Factors Conferring Increased Risk for Perioperative Ischemic Complications

Clinical Factors (9,10,19)	Procedural Characteristics (10,11,19)
<ul style="list-style-type: none">• Polyvascular disease• Diabetes mellitus• Heart failure• Renal failure• Inpatient admission• RCRI score ≥ 3<ul style="list-style-type: none">• Elevated surgical risk• Ischemic heart disease• Congestive heart failure• Prior TIA or stroke• Insulin use• Creatinine >2.0 mg/dL• ACS as indication for PCI	<ul style="list-style-type: none">• 3 vessels treated• ≥ 3 stents implanted• ≥ 3 lesions treated• Bifurcation with 2 stents implanted• Total stent length >60 mm• Chronic total occlusion• Ostial or distal PCI• Left main artery PCI• Calcified lesion• Length of atherosclerotic target lesion

The pharmacokinetic and pharmacodynamic characteristics of antiplatelet drugs

	ASA	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor	Eptifibatide	Tirofiban
Target (type of blockade)	COX-1 (irreversible)	P2Y ₁₂ (irreversible)	P2Y ₁₂ (irreversible)	P2Y ₁₂ (reversible)	P2Y ₁₂ (reversible)	GPIIB/IIIa (reversible)	GPIIB/IIIa (reversible)
Application	Oral	Oral	Oral	Oral	i.v.	i.v.	i.v.
Time to C_{max}	0.5–1.0 h	2 h (after 600 mg LD) ^a	0.5 h (after 60 mg LD) ^a	0.5 h (after 180 mg LD) ^a	2 min	5 min	5 min
Prodrug	No	Yes	Yes	No	No	No	No
Bioavailability (%)	~50	~50	80	36	100	100	100
Drug interactions	NSAIDs (in particular ibuprofen + naproxen)	CYP3A4, CYP3A5, or CYP2C19 inhibitors or inducers	CYP3A4/A5 and CYP2B6 inhibitor	CYP3A4 inducers or inhibitors	None	None	None
Plasma half-life	20 min	0.5–1 h (active metabolite)	0.5–1 h (active metabolite)	6–12 h	3–6 min	2.5–2.8 h	1.2–2 h
Duration of action after last dose	7–10 days	3–10 days ^b	7–10 days ^b	3–5 days	1–2 h	4 h	8 h
Renal clearance of the active metabolite (%)	NR	NR	NR	NR	58	~50	65
Dose regimen	<i>o.d.</i>	<i>o.d.</i>	<i>o.d.</i>	<i>b.i.d.</i>	Bolus, infusion	Bolus, infusion	Bolus, infusion

The pharmacokinetic and pharmacodynamic characteristics of anticoagulants

	Warfarin	Phenprocoumon	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Target (type of blockade)	VKORC1	VKORC1	FXa	FIIa	FXa	FXa
Application	Oral	Oral	Oral	Oral	Oral	Oral
Time to C_{max}	2–6 h	1.52 h ± 1.52	3–4 h	1.25–3 h	1–2 h	2–4 h
Prodrug	No	No	No	Yes	No	No
Bioavailability (%)	>95	100	50	6.5	62	80–100
Drug interactions	CYP2C9, CYP2C19, CYP2C8, CYP2C18, CYP1A2, CYP3A4, vitamin K	CYP2C9, CYP2C8, vitamin K	CYP3A4 inhibitors or inducers, P-glycoprotein inhibitors or inducers	P-glycoprotein inhibitors or inducers	P-glycoprotein inhibitors	CYP3A4 inhibitors or inducers, P-glycoprotein inhibitors or inducers
Plasma half-life	36–48 h	~100 h	12 h	12–14 h	6–11 h	7–11 h (11–13 h in the elderly)
Duration of action after last dose	~5 days	~7 days	24 h	24 h	24 h	24 h
Renal clearance of the active metabolite (%)	Non-renal	Non-renal	27	85	37–50	33
Dose regimen	Adjusted according to INR	Adjusted according to INR	<i>b.i.d.</i>	<i>b.i.d.</i>	<i>o.d.</i>	<i>o.d./b.i.d.</i>

Risk factors for MACE after non cardiac surgery (NCS)

- ✓ Time from PCI to surgery, with the highest risk in the first month
- ✓ Primary PCI for ST-segment elevation myocardial infarction (STEMI)
- ✓ Dual antiplatelet therapy (DAPT) interruptions/discontinuation
- ✓ Lesion characteristics, including ostial and distal lesions
- ✓ Urgency of surgery

Aspirin in Patients Undergoing Noncardiac Surgery

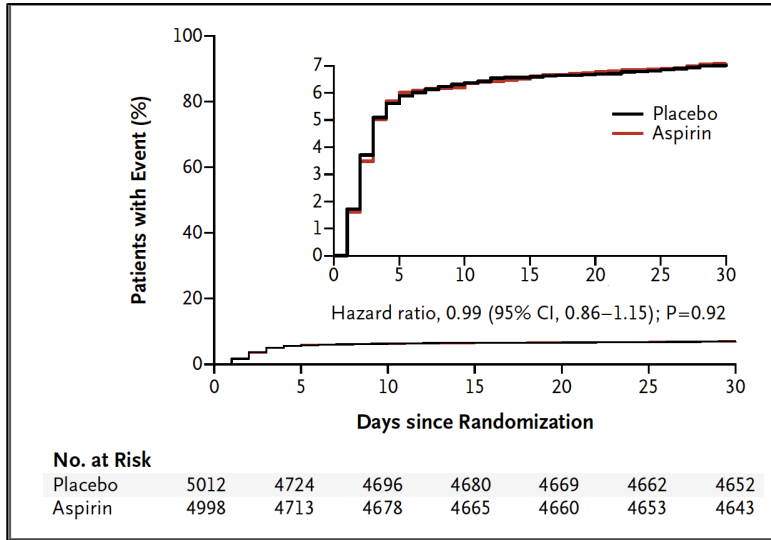
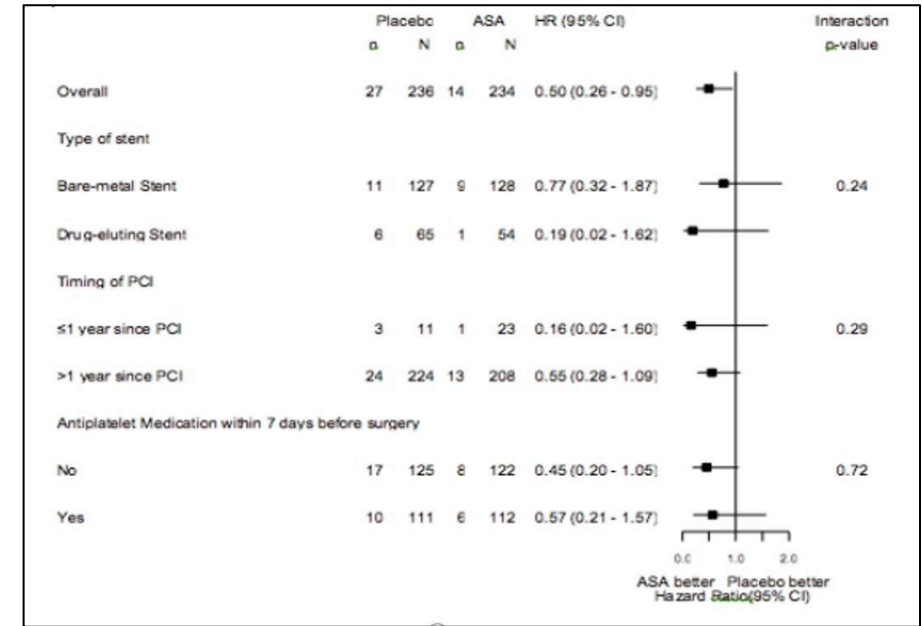


Table 3. Absolute Increase in the Risk of a Composite of Life-Threatening or Major Bleeding with Aspirin Therapy, Starting on Each of the First 10 Postoperative Days until 30 Days after Surgery.*

Day at Start of Risk Analysis	Aspirin†	Placebo†	Absolute Increase in Risk with Aspirin	P Value
	no./total no. (%)	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



Aspirin before surgery and throughout the early postsurgical period has no significant effect on the rate of a composite of death or nonfatal myocardial infarction but increased the risk of major bleeding (**POISE 2 trial**)

Among patients with previous PCI, in the absence of a very high bleeding risk, low-dose aspirin should be continued during the peri-operative period. (**POISE 2 Trial post hoc analysis**)

➤ If the bleeding risk outweighs the potential CV benefit, aspirin should be discontinued for at least 7 days (e.g. undergoing spinal surgery or certain neurosurgical or ophthalmological operations)

Elective Noncardiac Surgery on DAPT

- The frequency of NCS after PCI for 30 days, 6 months, and 1 year is 1%, 5%, and 9%, respectively.
- MACE (including cardiac death, MI, and stent thrombosis) range between 2–8% in PCI patients undergoing NCS, with a more than two-fold increased risk compared with non-stented patients

Management of perioperative DAPT

- Risk of stent thrombosis (ST) with premature DAPT interruption
- Intra-procedural bleeding (DAPT continuation)

Interdisciplinary approach

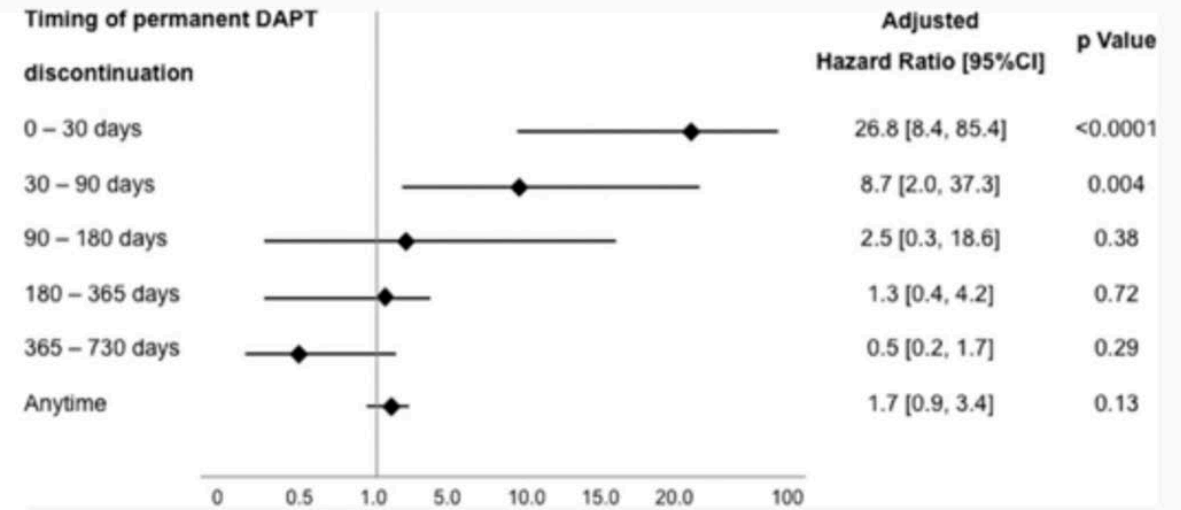
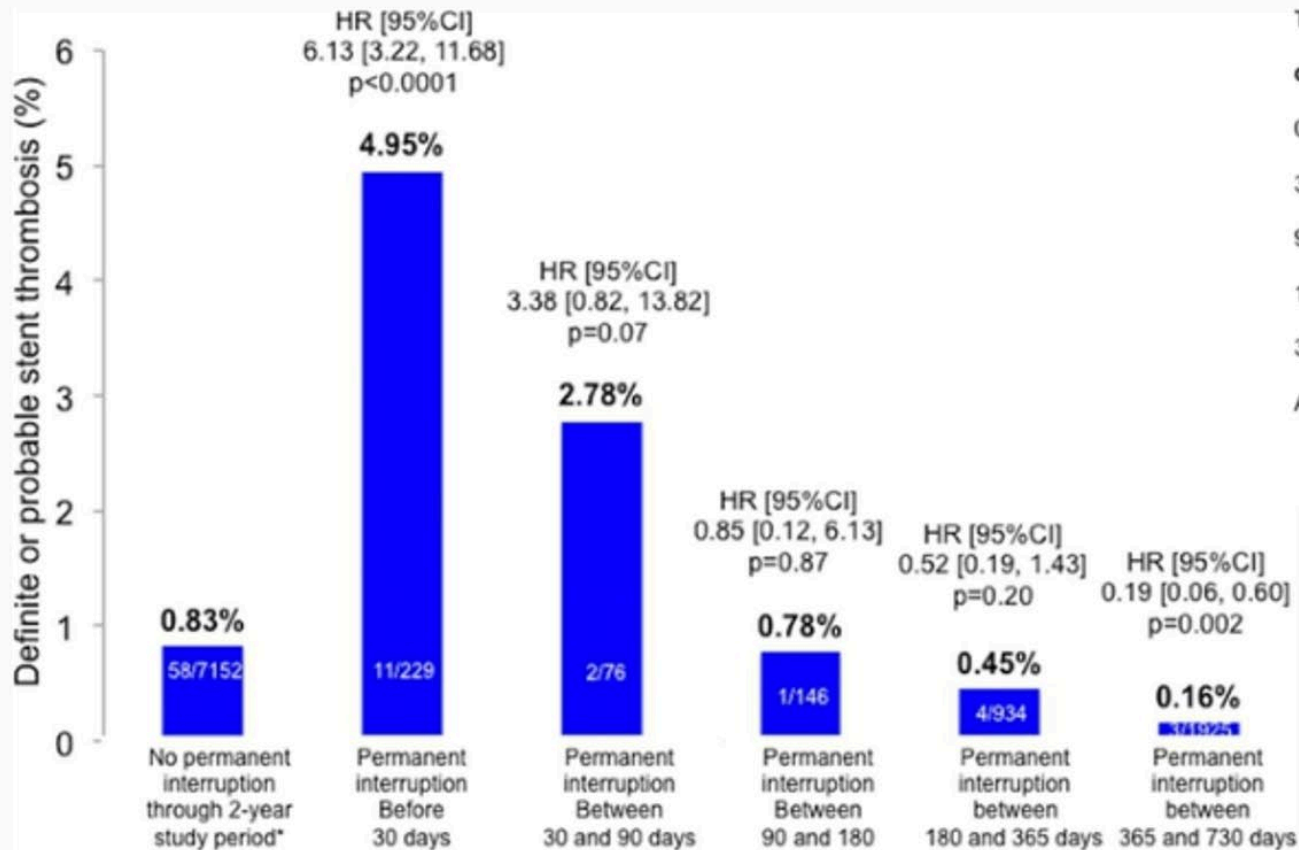
The management of antiplatelet therapy in patients who have undergone recent PCI and are scheduled for NCS should be discussed by the surgeon and cardiologist:

The risk of life-threatening surgical bleeding on antiplatelet therapy (best understood by the surgeon)

The risk of life-threatening stent thrombosis due to premature DAPT discontinuation (best understood by the cardiologist)

Stent Thrombosis and DAPT Interruption With Everolimus-Eluting Stents

pooled analysis of 11 219 patient from 3 randomized trials and 4 registries



Short vs longer DAPT duration

MASTER-DAPT

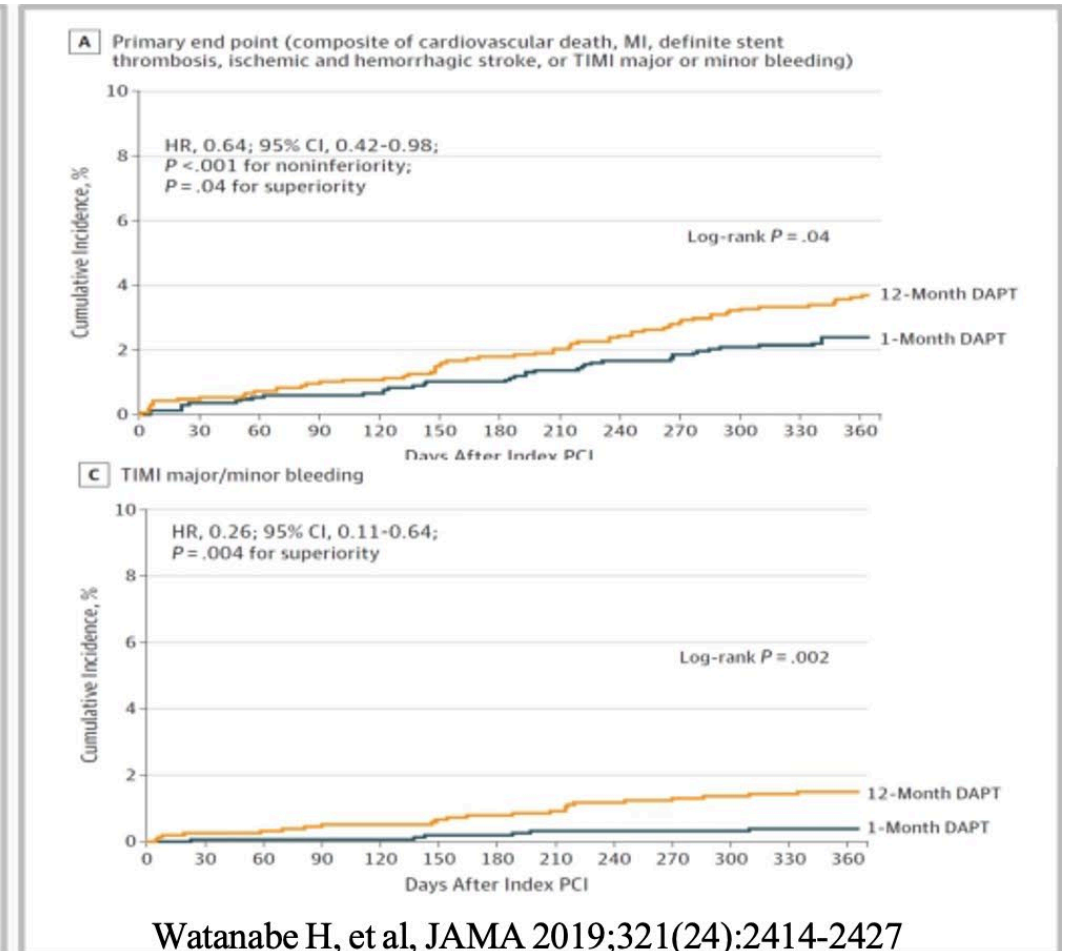
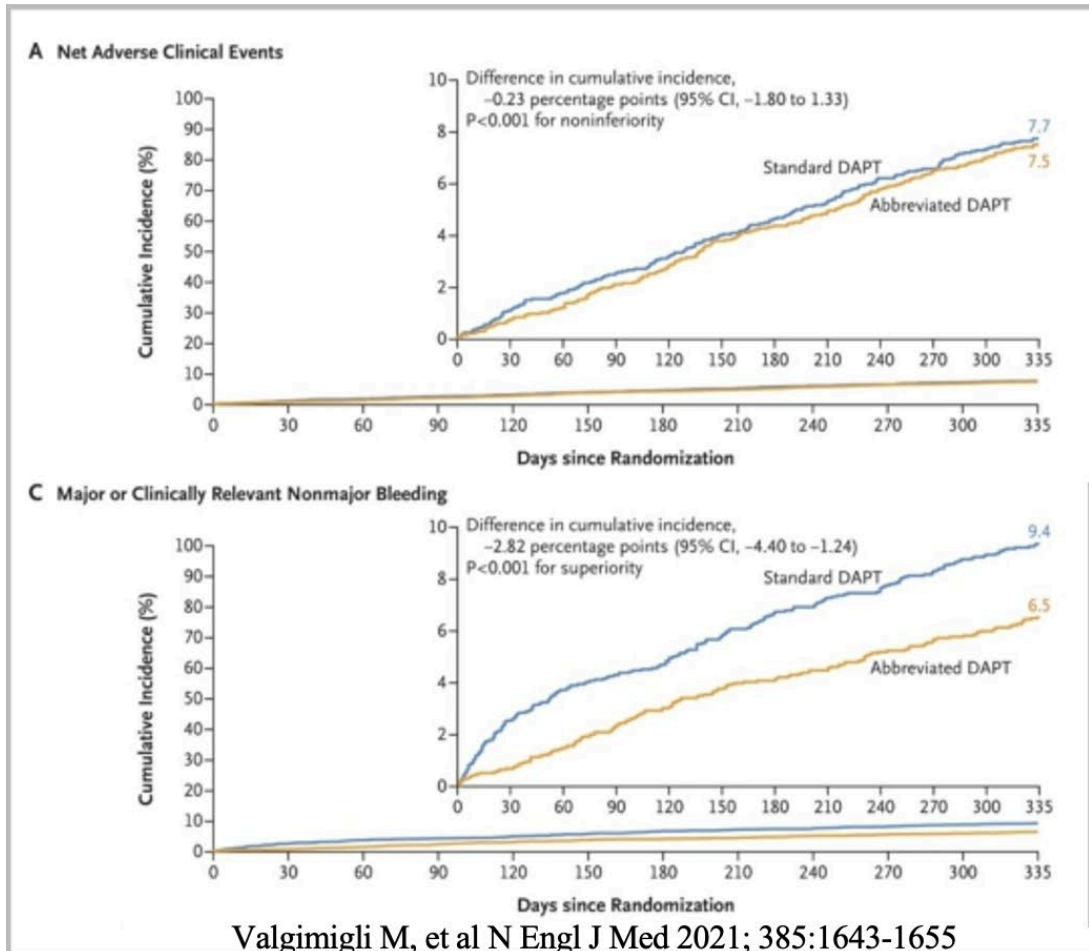
(One month DAPT vs. continuation for at least 2 additional months)

36.5 % NST-ACS, 12% STEMI

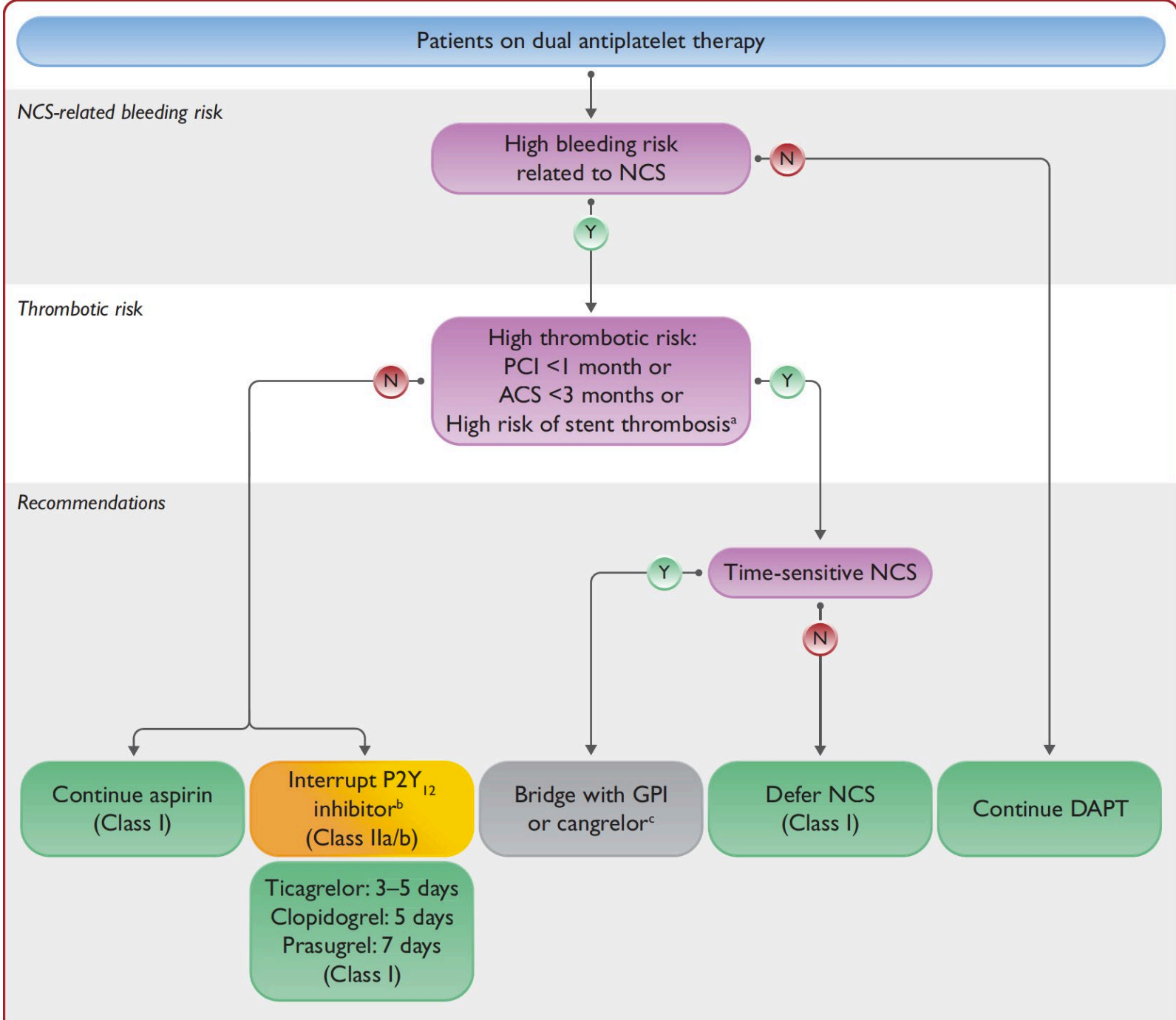
STOPDAPT-2

(One-month vs. 12-month DAPT)

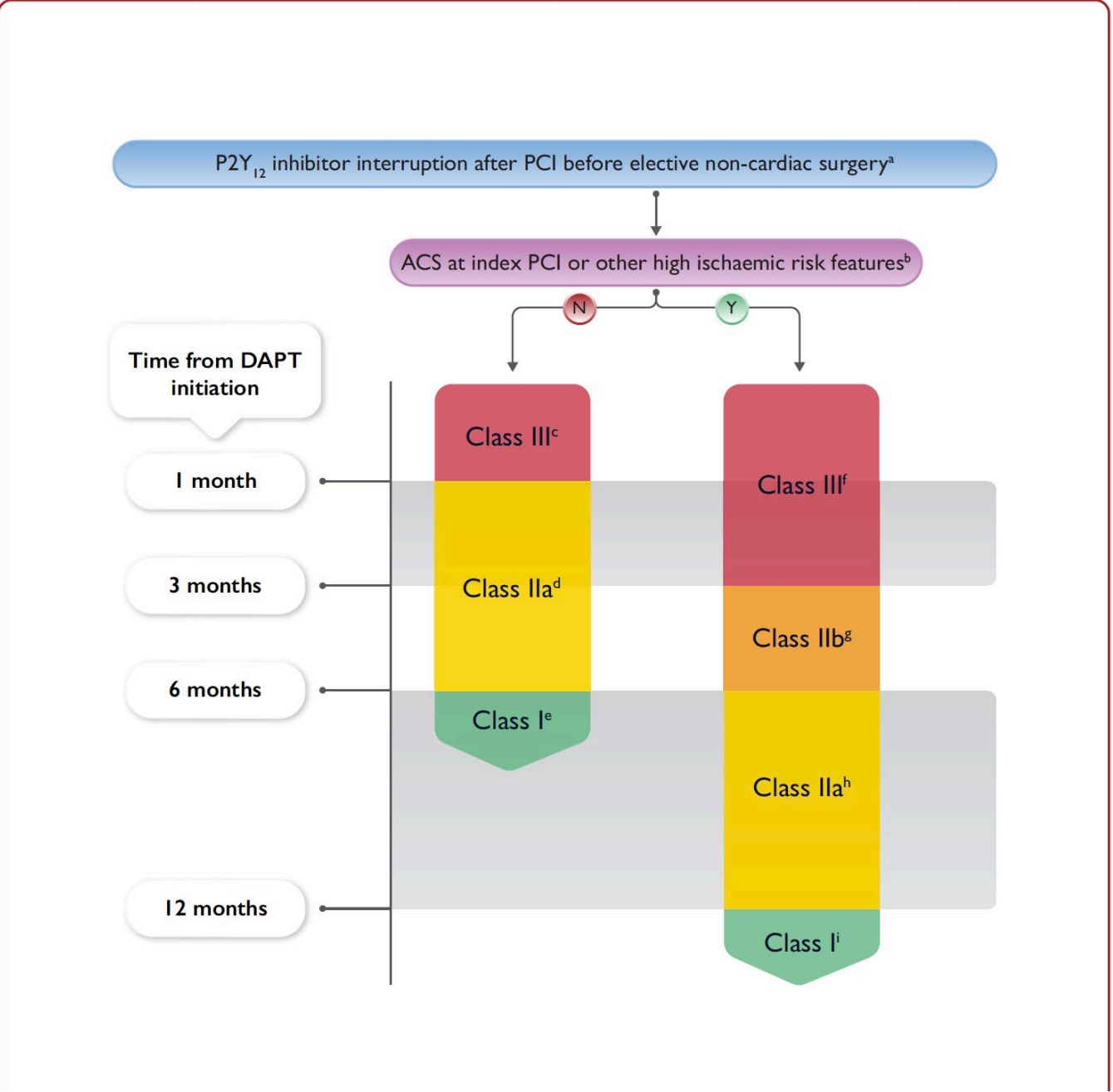
19.5 % NST-ACS, 18.6% STEMI



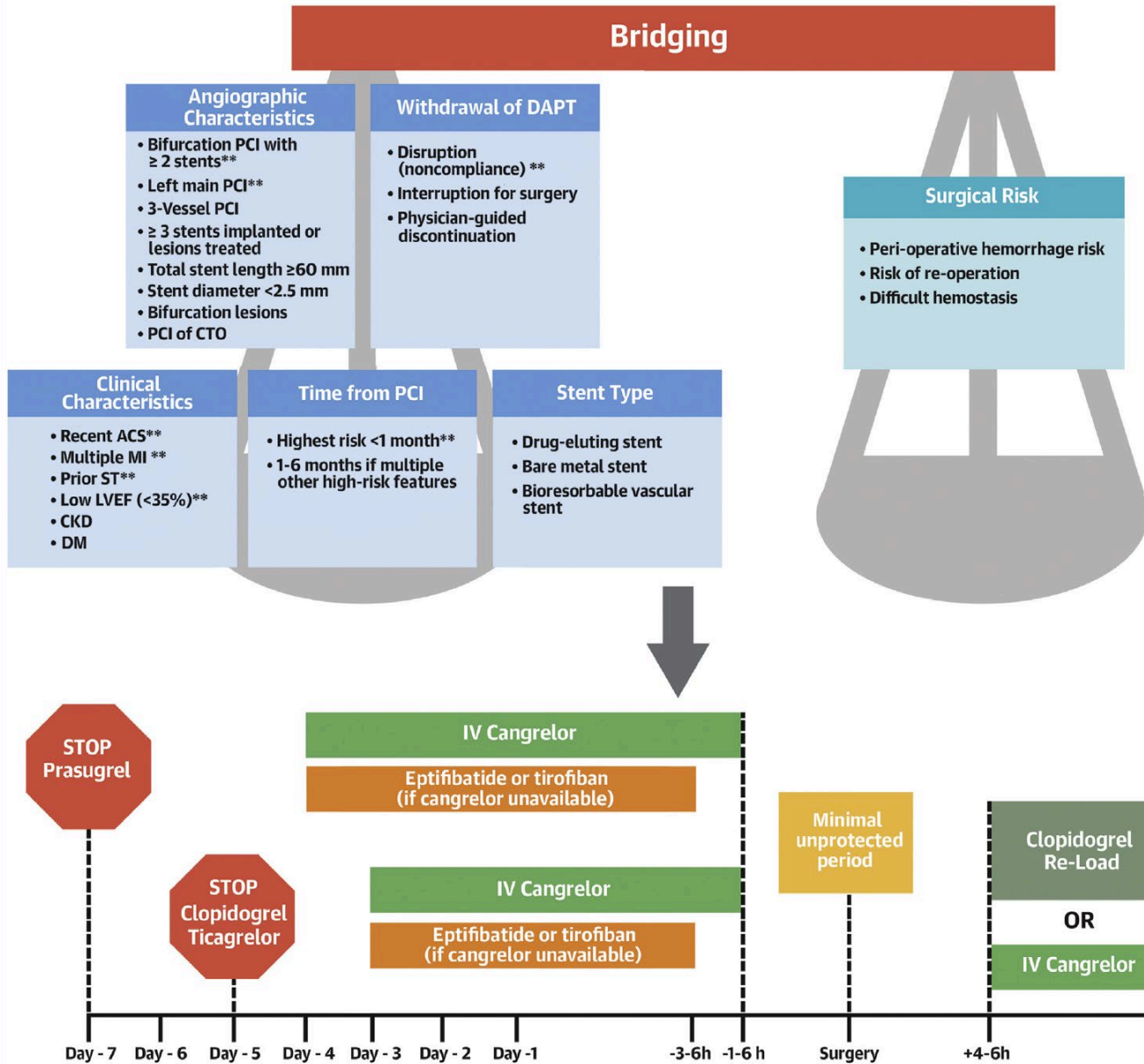
Patients on DAPT undergoing surgery



P2Y12 inhibitor interruption after percutaneous coronary intervention before elective non-cardiac surgery



Bridging



Sullivan, A.E. et al. J Am Coll Cardiol. 2021;78(15):1550-1563.

Bridging strategies

✓ Bridging with i.v. compounds (eptifibatide/tirofiban or cangrelor) might be applicable when DAPT cannot be interrupted (e.g. in patients with very high risk of stent thrombosis, history of recurrent MI, recent PCI)

✓ For patients undergoing surgery, the established cangrelor dosing regimen is associated with less severe bleeding than glycoprotein IIb/IIIa inhibitors.

Elective Non-Cardiac Surgery on Anticoagulation therapy

- ✓ One in four patients taking anticoagulant therapy will require a surgical or invasive procedure within 2 years.
- ✓ Peri-operative management of oral anticoagulant (OAC) therapy depends on surgery and patient related factors and the specific OAC agent (vitamin K antagonist or NOAC)

Surgery-related factors include urgency of the intervention and the procedure-related bleeding risk

Patient-related factors include age, individual thrombotic risk, history of bleeding complications, renal function, concomitant medication, comorbidity, etc.

Patients with mechanical heart valves to bridge or not to bridge...

✓ Major surgical procedures needing INR ≤1.5 require VKA interruption, and heparin bridging should be considered

PERIOP2 trial

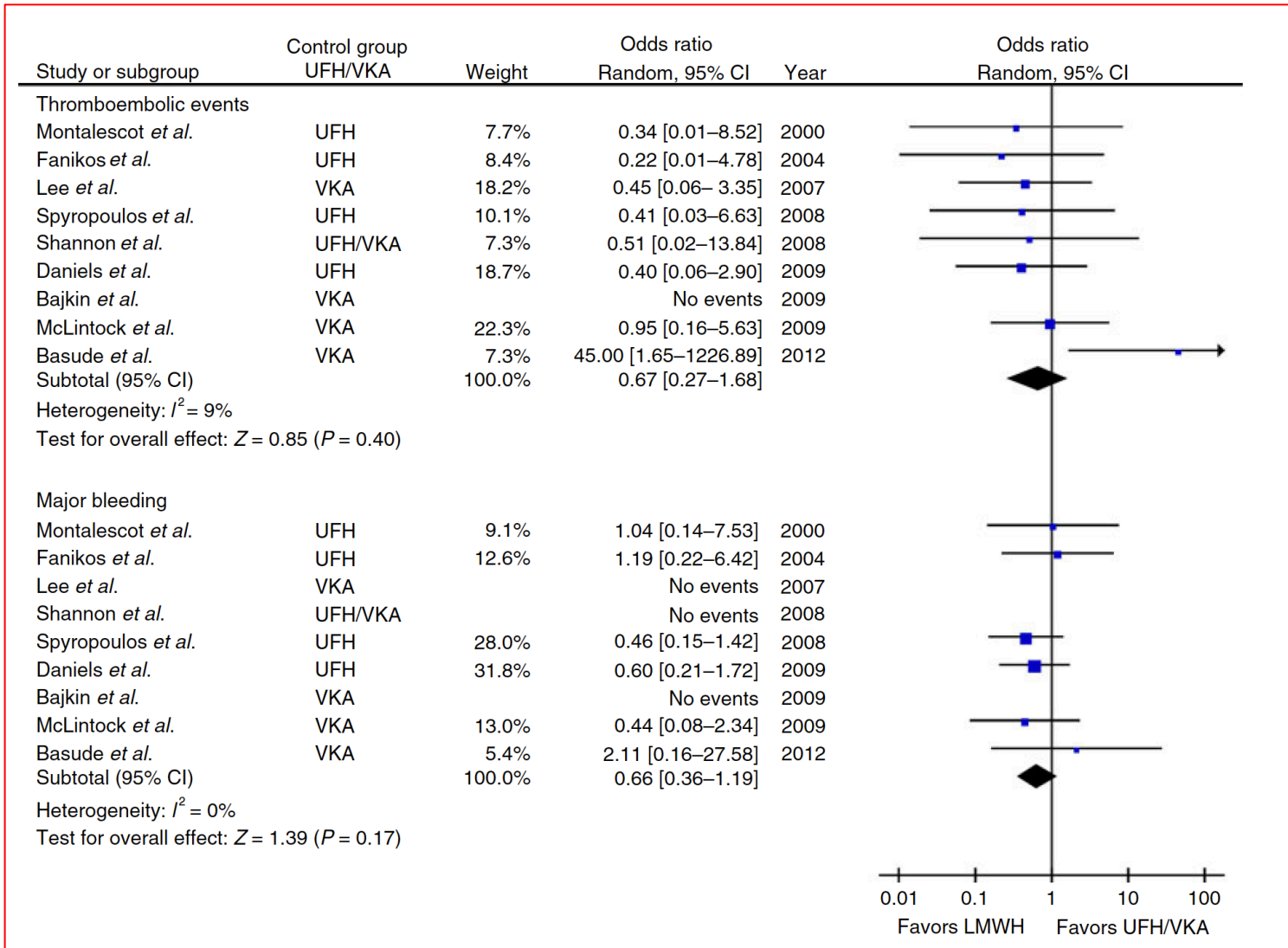
Outcomes	Whole study population				Atrial fibrillation				Mechanical valve†			
	No bridging (n=650)	Bridging (n=820)	P value	Risk difference (95% CI)	No bridging (n=496)	Bridging (n=670)	P value	Risk difference (95% CI)	No bridging (n=154)	Bridging (n=150)	P value	Risk difference (95% CI)
Primary												
Major thromboembolism*	8 (1.2)	8 (1.0)	0.64	-0.3 (-1.3 to 0.8)	8 (1.6)	7 (1.0)	0.39	-0.6 (-1.9 to 0.8)	0	1 (0.7)	0.49	0.7 (-0.6 to 2.0)
Secondary												
Ischaemic stroke	3 (0.5)	1 (0.1)	0.33	—	3 (0.6)	1 (0.2)	0.32	—	—	—	—	—
Transient ischaemic attack	0	1 (0.1)	1	—	—	—	—	—	0	1 (0.7)	0.49	—
Symptomatic myocardial infarction	3 (0.4)	3 (0.5)	1	—	3 (0.6)	3 (0.5)	0.70	—	—	—	—	—
Peripheral embolism	—	—	—	—	—	—	—	—	—	—	—	—
Valve thrombosis	—	—	—	—	—	—	—	—	—	—	—	—
Venous thromboembolism	2 (0.3)	3 (0.4)	1	—	3 (0.6)	3 (0.5)	1	—	—	—	—	—
Vascular death	3 (0.5)	0	0.09	—	3 (0.6)	0	0.08	—	—	—	—	—
All deaths	8 (1.2)	6 (0.7)	0.33	-0.5 (-1.5 to 0.5)	6 (1.2)	5 (0.8)	0.54	-0.5 (-1.6 to 0.7)	2 (1.3)	1 (0.7)	1	-0.6 (-2.8 to 1.6)
Major bleeding	13 (2.0)	11 (1.3)	0.32	-0.7 (-2.0 to 0.7)	10 (2.0)	10 (1.5)	0.49	-0.5 (-2.1 to 1.0)	3 (2.0)	1 (0.7)	0.62	-1.3 (-3.8 to 1.3)
Clinically relevant non-major bleeding	25 (3.9)	50 (6.1)	0.05	2.3 (0.1 to 4.5)	20 (4.0)	42 (6.3)	0.09	2.2 (-0.3 to 4.8)	5 (3.3)	8 (5.3)	0.37	2.1 (-2.5 to 6.6)
Trivial bleeding	16 (2.5)	22 (2.7)	0.79	—	14 (2.8)	18 (2.7)	0.89	—	2 (1.3)	4 (2.7)	0.44	—
Major thromboembolism or major bleeding	21 (3.2)	19 (2.3)	0.28	-0.9 (-2.6 to 0.8)	18 (3.6)	17 (2.5)	0.28	-1.1 (-3.1 to 0.9)	3 (2.0)	2 (1.3)	1	-0.6 (-3.5 to 2.2)
Major thromboembolism or major bleeding, or death	25 (3.9)	24 (2.9)	0.33	-0.9 (-2.8 to 1)	20 (4.0)	21 (3.1)	0.41	-0.9 (-3.1 to 1.3)	5 (3.3)	3 (2.0)	0.72	-1.3 (-4.8 to 2.3)

*Major thromboembolism—any one of first seven secondary outcomes: ischaemic stroke, transient ischaemic attack, symptomatic myocardial infarction, peripheral embolism, valve thrombosis, venous thromboembolism (pulmonary embolism or deep vein thrombosis), or vascular death.

†With or without atrial fibrillation.

Patients with mechanical heart valves

LMWH or UFH...



Anti-factor Xa activity monitoring with target levels from 0.5–1.0 U/mL may be useful when the dosage may be difficult to determine

Vitamin K antagonists for atrial fibrillation / venous thromboembolism

- If low bleeding, risk surgery can be performed without VKA interruption
- If interruption is necessary due to high bleeding risk, the BRIDGE trial in AF patients showed that 3–5 days of warfarin interruption without bridging was superior to heparin bridging.
- Bridging therapy may be considered for patients with a high thrombotic risk (i.e. AF with CHA2DS2-VASc score >6, recent cardioembolic stroke <3 months, or high risk of VTE recurrence) weighing the risk of bleeding against the risk of thromboembolism

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*

Table 3. Study Outcomes.

Outcome	No Bridging (N=918) <i>number of patients (percent)</i>	Bridging (N=895) <i>number of patients (percent)</i>	P Value
Primary			
Arterial thromboembolism	4 (0.4)	3 (0.3)	0.01*, 0.73†
Stroke	2 (0.2)	3 (0.3)	
Transient ischemic attack	2 (0.2)	0	
Systemic embolism	0	0	
Major bleeding	12 (1.3)	29 (3.2)	0.005†
Secondary			
Death	5 (0.5)	4 (0.4)	0.88†
Myocardial infarction	7 (0.8)	14 (1.6)	0.10†
Deep-vein thrombosis	0	1 (0.1)	0.25†
Pulmonary embolism	0	1 (0.1)	0.25†
Minor bleeding	110 (12.0)	187 (20.9)	<0.001†

* P value for noninferiority.

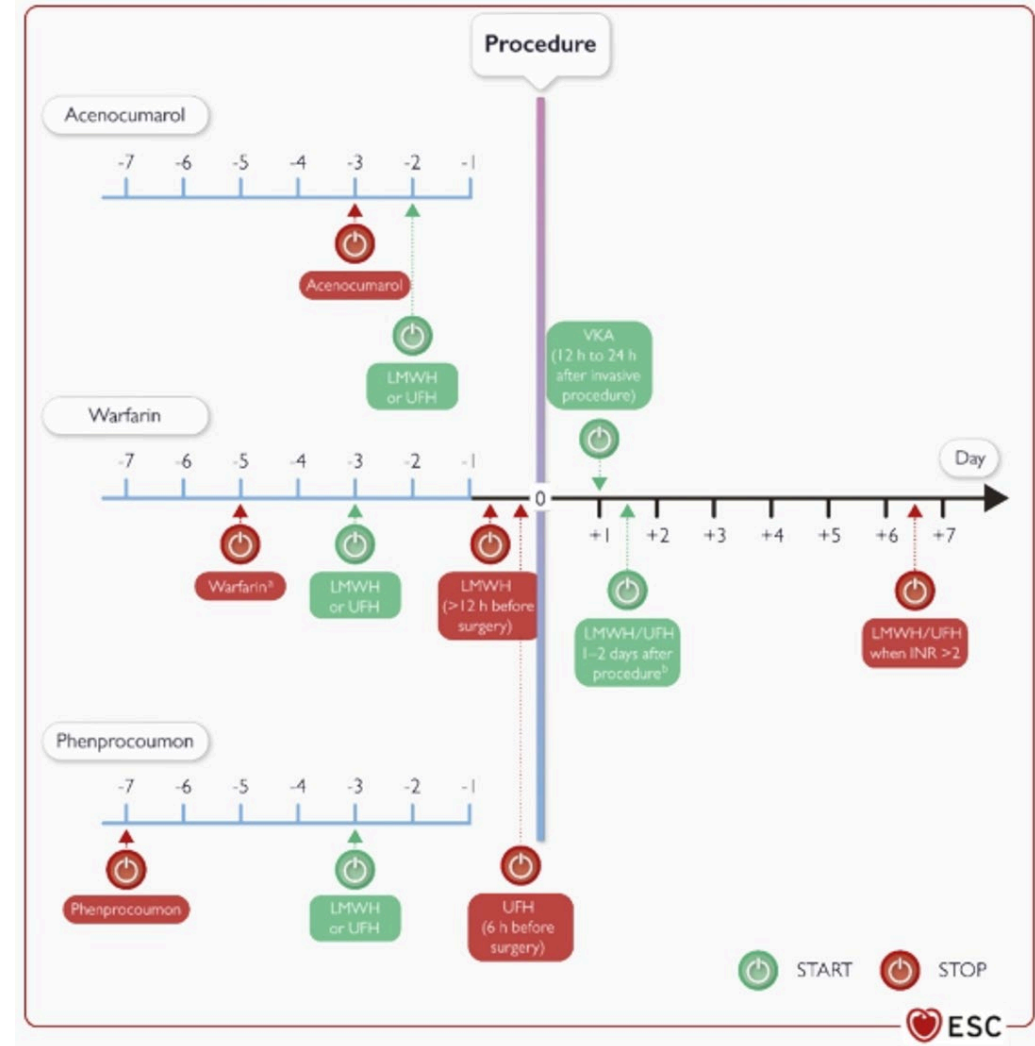
† P value for superiority.

Restarting vitamin K antagonists after surgery

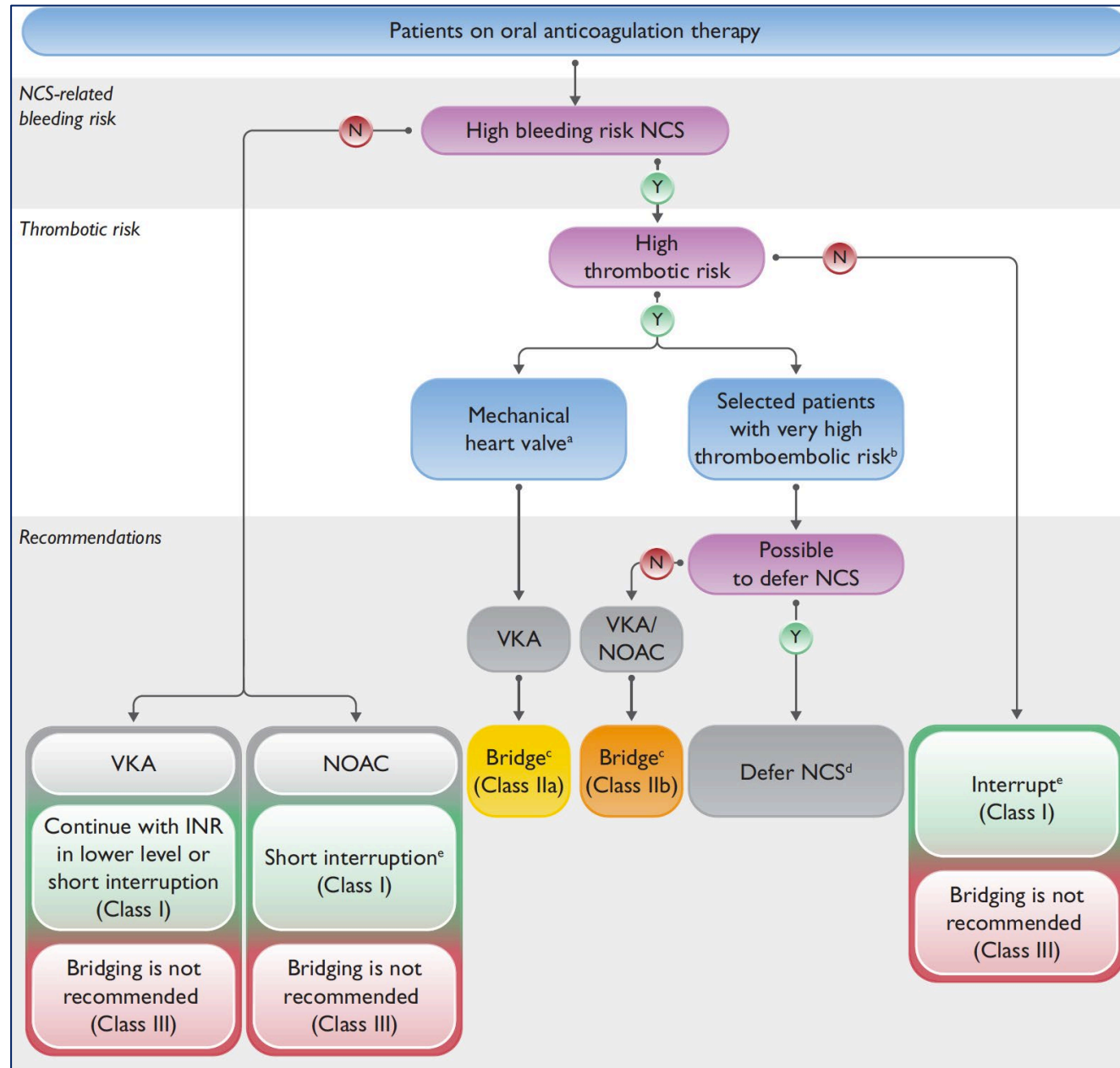
- Patients who have interrupted VKA treatment before surgery should restart the OAC 12–24 h after the invasive procedure.

restarting dose should be the maintenance dose plus a boosting dose of 50% for 2 days

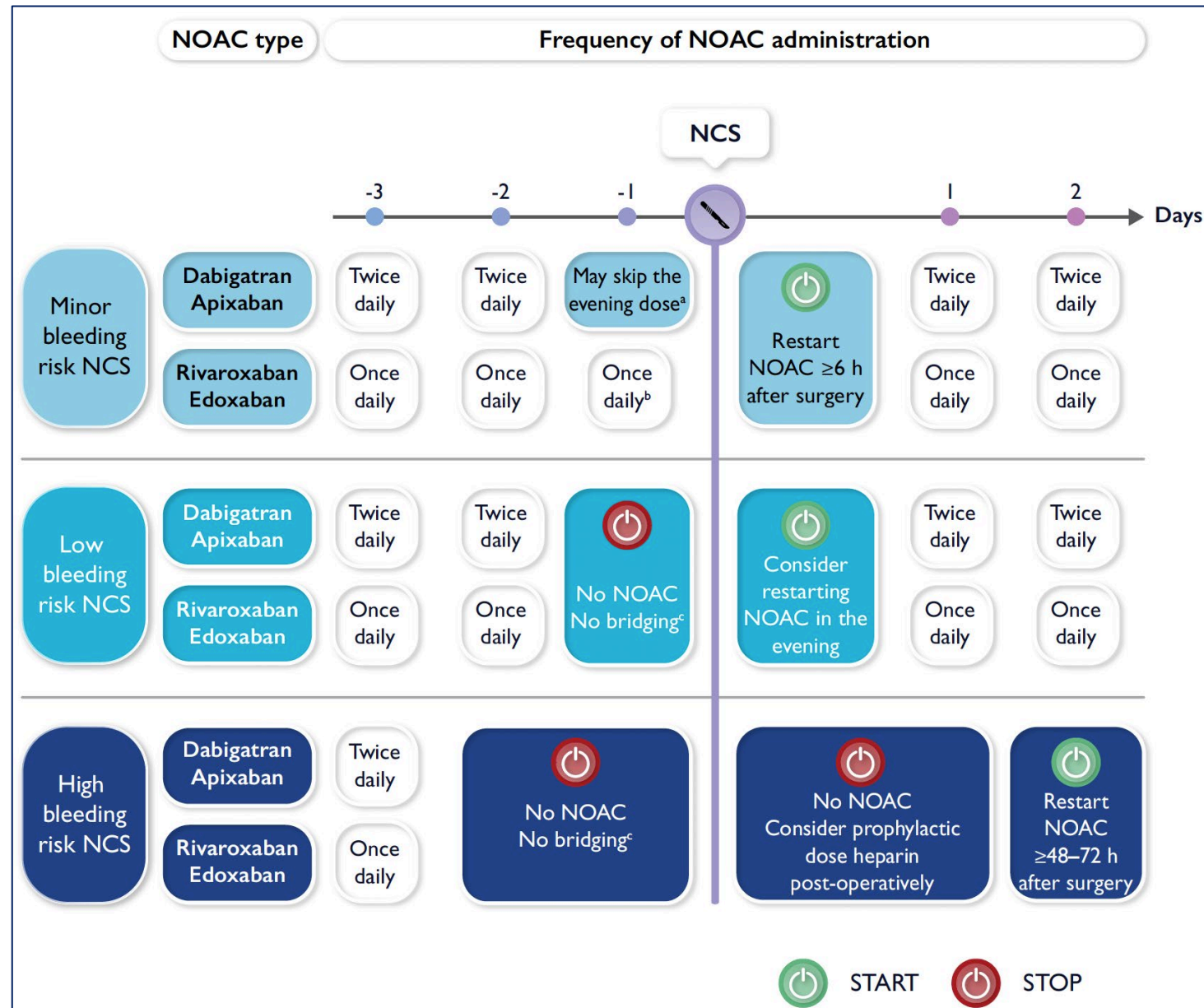
- Patients managed with bridging therapy should start LMWH or UFH together with VKA 24 h after surgery, if the bleeding is well controlled and maintained, until the INR has reached the therapeutic range



Management of oral anticoagulation therapy in patients undergoing surgery



Peri-operative management of NOAC according to the periprocedural risk of bleeding in patients with normal renal function




Timing of last NOAC dose before elective NCS according to renal function

Minor bleeding risk NCS

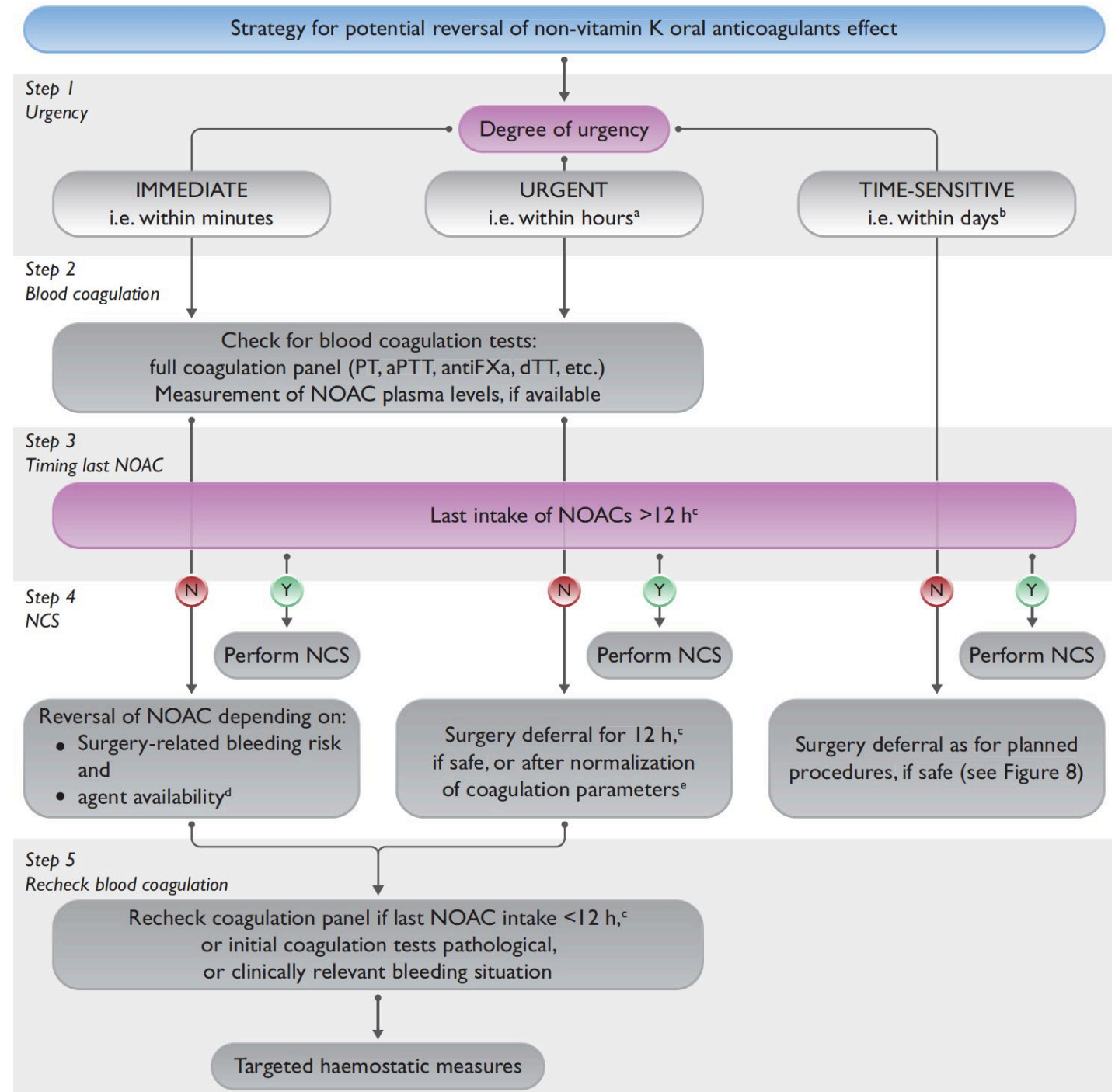
Perform intervention at NOAC trough level (i.e. 12 h or 24 h after last intake for twice or once daily regimens, respectively). Resume same day or latest next day.

Low and high bleeding risk NCS

 Renal function (estimated GFR, mL/min)	Low bleeding risk NCS	High bleeding risk NCS	Low bleeding risk NCS	High bleeding risk NCS
	Dabigatran		Apixaban, rivaroxaban, edoxaban	
≥80	≥24 h	≥48 h	≥24 h	≥48 h
50–79	≥36 h	≥72 h		
30–49	≥48 h	≥96 h		
15–29	Not indicated	Not indicated	≥36 h	
<15	No formal indication for use			

Suggested strategy for potential reversal of NOAC effect

- Idarucizumab (for dabigatran) has only been tested in patients undergoing urgent surgery.
- Andexanet (for FXa inhibitors) has not been tested in patients requiring urgent surgery.
- Andexanet binds all FXa inhibitors (including UFH) nonspecifically.
- When specific reversal agents are unavailable, prothrombin complex concentrate (PCC) should be considered, although there is a lack of evidence



Conclusions/Gaps in evidence

- Complex clinical decision, Interdisciplinary consensus
- Rapidly changing field involving newer drugs and drug-device interactions
- Need for more evidence regarding the need for bridging of anticoagulation in patients with MHVs
- Lack of evidence regarding the optimal strategies before emergent or time-sensitive NCS for patients on antithrombotic treatment at high risk of thromboembolic events
- Insufficient evidence regarding the need for and benefit of anticoagulation in NCS patients with post- operative AF is still lacking