ELENA BARBAGELATA

La terapia antiaggregante/anticoagulante in prossimità di diagnostica invasiva/chirurgia

La sottoscritta Elena Barbagelata
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

BACKGROUND

Ogni anno nel mondo eseguiti oltre 300 milioni di interventi di chirurgia maggiore

Quasi 85% chirurgia non cardiaca

Almeno il 50% dei pazienti candidati a procedure chirurgiche o invasive assume farmaci la cui assunzione va rivalutata nel peri-operatorio

La gestione della terapia antitrombotica è sempre più frequente nella pratica clinica e controversa

In un ampio registro di 37915 pazienti sottoposti a PTCA con stent medicato, 11% paz subiva chirurgia non cardiaca entro 1 anno, 24% entro i 3 anni

ESC European Society of Cardiology

European Heart Journal (2022) **43**, 3826–3924
https://doi.org/10.1093/eurheartj/ehac270

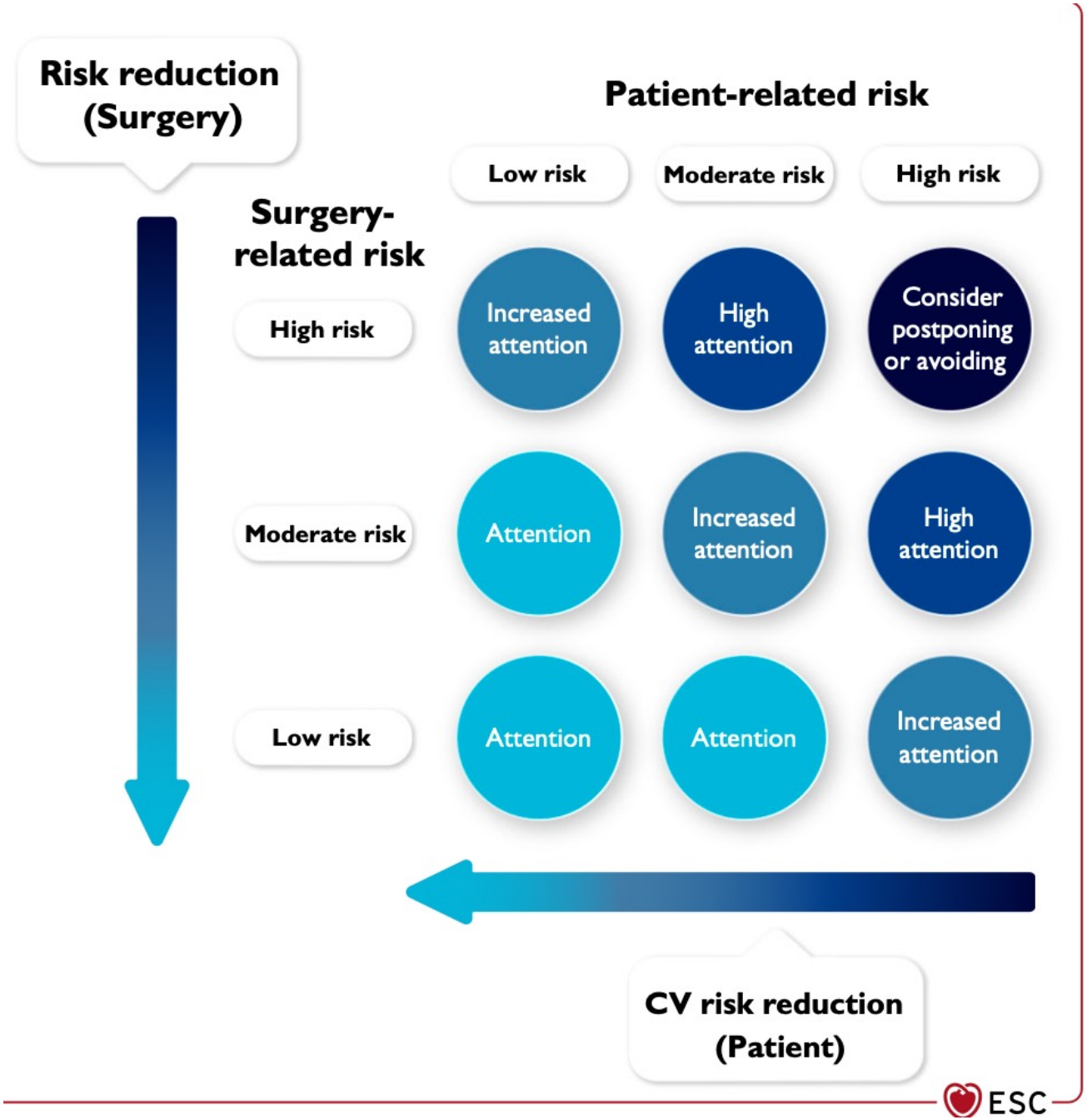
ESC GUIDELINES

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)

VALUTAZIONE PREOPERATORIA: STIMA DEL RISCHIO



RISCHIO CORRELATO ALL'INTERVENTO CHIRURGICO

Table 5 **Surgical risk estimate according to type of surgery or intervention**

Low surgical risk (<1%)	Intermediate surgical risk (1–5%)	High surgical risk (>5%)
• Breast • Dental • Endocrine: thyroid • Eye • Gynaecological: minor • Orthopaedic minor (meniscectomy) • Reconstructive • Superficial surgery • Urological minor: (transurethral resection of the prostate) • VATS minor lung resection	• 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	• 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

Adapted from data in Glance et al., Muller et al., Bendixen et al., and Falcoz et al.

RISCHIO CORRELATO AL PAZIENTE

Table 6 **Risk score calculators**

	Revised Cardiac Risk Index (RCRI) (1999)[a]	Surgical Risk Calculator (2011)	The American College of Surgery National Surgical Quality Improvement Program (ACS NSQIP) (2013)	Surgical Outcome Risk Tool (SORT) (2014)	The American University of Beirut (AUB)-HAS2 Cardiovascular Risk Index (2019)[b]
Variables	Ischaemic heart disease Cerebrovascular disease History of congestive heart failure Insulin therapy for diabetes Serum creatinine level ≥2 mg/dL High-risk surgery (each assigned 1 point)	Age ASA–PS grade Pre-operative dependent functional status Creatinine >1.5 mg/dL Type of surgery	Age Sex Functional status Emergency case ASA class Current steroid use Ascites within 30 days Systemic sepsis within 48 h Ventilator dependence Disseminated cancer Diabetes Hypertension on treatment Congestive HF Dyspnoea Current smoker History of severe COPD Dialysis Acute renal failure Body mass index Surgery code	ASA–PS grade Urgency of surgery High-risk surgical specialty Surgical severity (from minor to complex major) Cancer Age ≥65 years or over	History of **H**eart disease Symptoms of **H**eart disease (angina or dyspnoea) **A**ge ≥75 years **A**naemia (haemoglobin <12 g/dL) Vascular **S**urgery Emergency **S**urgery (2 H, 2 A and 2 S) (each assigned 1 point)
Score range	Score 1; risk 6.0% (4.9–7.4) Score 2; risk 10.1% (8.1–10.6) Score ≥3; risk 15% (11.1–20.0)	Absolute risk: 0–100%	Absolute risk: 0–100%	Absolute risk: 0–100%	Low risk (score 0–1); (0.3 and 1.6%)[c] Intermediate risk (score 2–3); (7.1 and 17%)[c] High risk (score >3); (>17%)[c]
Outcome	30 day MI, cardiac arrest, death	Intra-operative and 30 day MI or cardiac arrest	Serious complications and any complications at 30 days	30 day mortality	30 day death, MI, or stroke
Derivation population	1422	211 410	1 414 006	11 219	3284
Validation population	Externally validated in various surgical populations	257 385	Externally validated in various surgical populations	22 631	1 167 414
Model performance (AUC)	0.68–0.76	0.81–0.85	0.73	0.81–0.92	0.82
Interactive calculator	https://www.mdcalc.com/revised-cardiac-risk-index-pre-operative-risk	http://www.surgicalriskcalculator.com/miorcardiacarrest	https://riskcalculator.facs.org	http://www.sortsurgery.com	

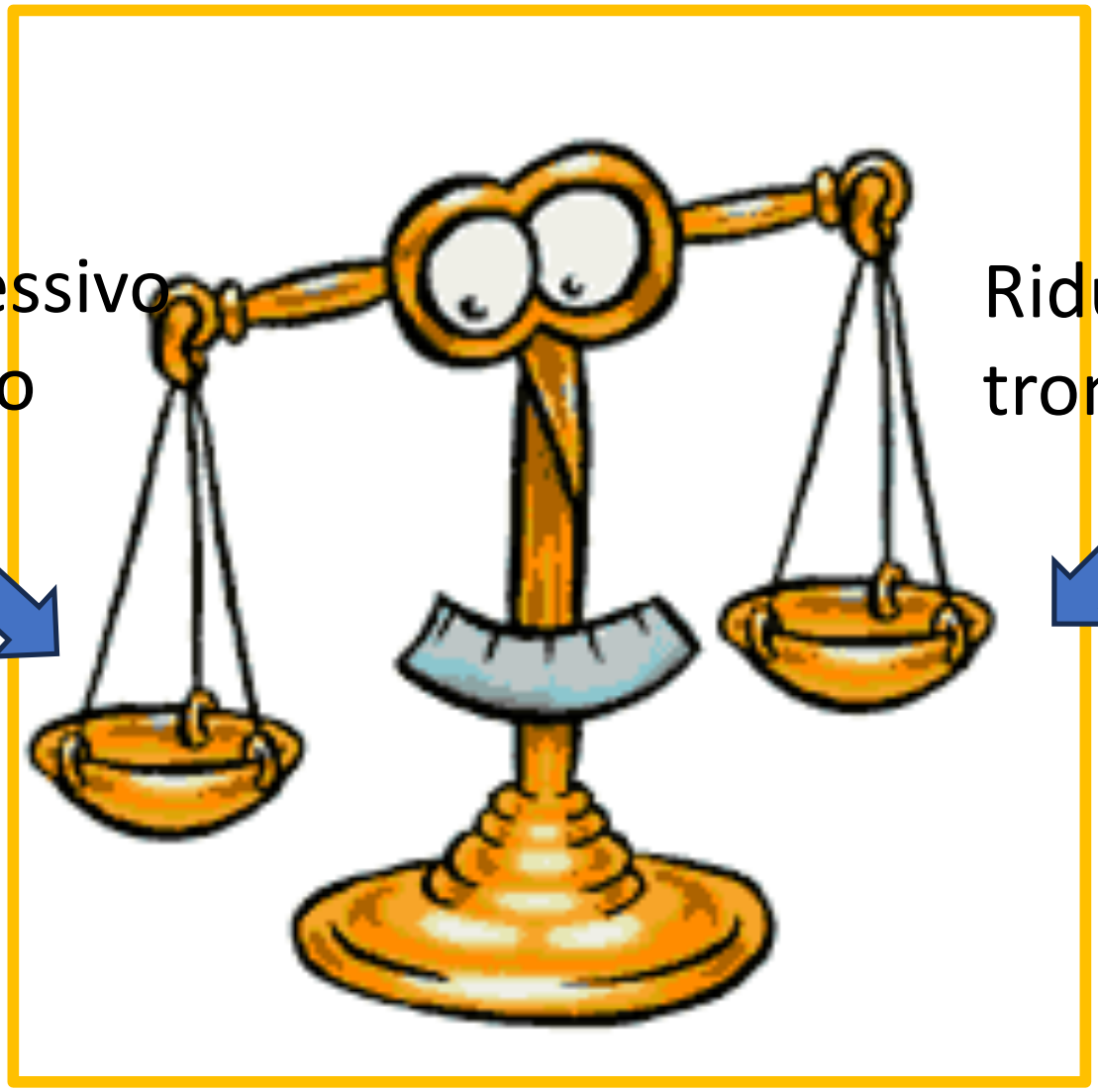
GESTIONE PERI-OPERATORIA DEL PAZIENTE IN TERAPIA ANTITROMBOTICA

Management di pazienti in terapia antitrombotica candidati a procedura chirurgica o invasiva è sfidante e deve considerare:

- il rischio correlato al paziente e i rischi emorragico e trombotico correlato alla procedura
- Caratteristiche di farmacocinetica e farmacodinamica dei farmaci antitrombotici
- Il rischio emorragico specifico per intervento
- Il rischio tromboembolico correlato alla sospensione dell'antitrombotico (5% di ospedalizzazioni per SCA)

GESTIONE PERI-OPERATORIA DEL PAZIENTE IN TERAPIA ANTITROMBOTICA

Prevenire eccessivo sanguinamento



Ridurre il rischio tromboembolico

Terapia antiaggregante

- ASA
- Clopidogrel
- Prasugrel o Ticagrelor

Table 7 Pharmacokinetic and pharmacodynamic characteristics of antiplatelets

	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	*o.d.*	*o.d.*	*o.d.*	*b.i.d.*	Bolus, infusion	Bolus, infusion	Bolus, infusion

Terapia anticoagulante

- Warfarin
- DOACs

Table 8 Pharmacokinetic and pharmacodynamic characteristics of oral 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 inductors, P-glycoprotein inhibitors or inductors	P-glycoprotein inhibitors or inductors	P-glycoprotein inhibitors	CYP3A4 inhibitors or inductors, P-glycoprotein inhibitors or inductors
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	*b.i.d.*	*b.i.d.*	*o.d.*	*o.d./b.i.d.*

VALUTAZIONE DEL RISCHIO EMORRAGICO

Table 9 **Bleeding risk according to type of non-cardiac surgery**

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)
• 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)	• 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)	• 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)

COME GESTIRE PAZIENTI IN TERAPIA ANTI-PIASTRINICA

- La chirurgia è la prima causa di sospensione prematura della terapia antiaggregante, con aumento significativo di mortalità e di eventi cardiaci maggiori, specie la trombosi di stent.
- l' intervento chirurgico, per lo stato pro-infiammatorio e pro-trombotico, può contribuire di per sé ad un aumento del rischio ischemico perioperatorio

1) Valutare rischio trombotico (legato al paziente)
2) Valutare rischio emorragico (dell'intervento)
3) Caratteristiche cliniche del paziente
4) Tipo di farmaco

COME GESTIRE PAZIENTI IN TERAPIA ANTI-PIASTRINICA

Periprocedural thrombotic risk for patients on antiplatelet therapy

Risk stratum	Indication for antiplatelet therapy		
	Coronary artery disease*	**Cerebrovascular disease**	**Peripheral arterial disease**
High thrombotic risk	Acute coronary syndrome ≤6 months Cardiac stent ≤6 months	Stroke or TIA ≤3 months	
Low thrombotic risk	Ischemic heart disease without stent Cardiac stent >6 months Acute coronary syndrome >6 months	Stroke or TIA >3 months	PAD without revascularization PAD with revascularization¶

AHA Scientific Statement

Secondary Prevention After Coronary Artery Bypass Graft Surgery

A Scientific Statement From the American Heart Association

Alexander Kulik, MD, MPH, FAHA, Chair; Marc Ruel, MD, MPH, FAHA, Co-Chair;

Antiplatelet Therapy Recommendations

1. **Aspirin should be administered preoperatively and within 6 hours after CABG in doses of 81 to 325 mg daily. It should then be continued indefinitely to reduce graft occlusion and adverse cardiac events (*Class I; Level of Evidence A*).**
2. **After off-pump CABG, dual antiplatelet should be administered for 1 year with combined aspirin (81–162 mg daily) and clopidogrel 75 mg daily to reduce graft occlusion (*Class I; Level of Evidence A*).**
3. **Clopidogrel 75 mg daily is a reasonable alternative after CABG for patients who are intolerant of or allergic to aspirin. It is reasonable to continue it indefinitely (*Class IIa; Level of Evidence C*).**
4. **In patients who present with acute coronary syndrome, it is reasonable to administer combination antiplatelet therapy after CABG with aspirin and either prasugrel or ticagrelor (preferred over clopidogrel), although prospective clinical trial data from CABG populations are not yet available (*Class IIa; Level of Evidence B*).**
5. **As sole antiplatelet therapy after CABG, it is reasonable to consider a higher aspirin dose (325 mg daily) rather than a lower aspirin dose (81 mg daily), presumably to prevent aspirin resistance, but the benefits are not well established (*Class IIa; Level of Evidence A*).**
6. **Combination therapy with both aspirin and clopidogrel for 1 year after on-pump CABG may be considered in patients without recent acute coronary syndrome, but the benefits are not well established (*Class IIb; Level of Evidence Level A*).**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Aspirin in Patients Undergoing Noncardiac Surgery

POISE-2 trial

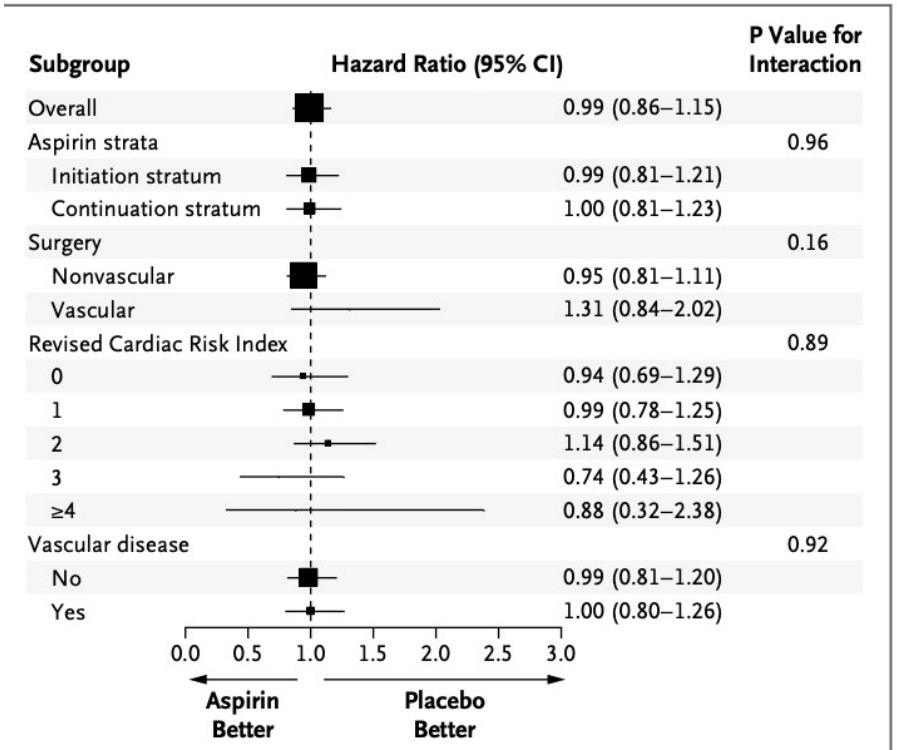


Figure 2. Subgroup Analyses of the Primary Outcome.

The primary composite outcome was death or nonfatal myocardial infarction at 30 days. The area of each square is proportional to the size of the corresponding subgroup. The Revised Cardiac Risk Index ranges from 0 to 6, with higher scores indicating greater risk.

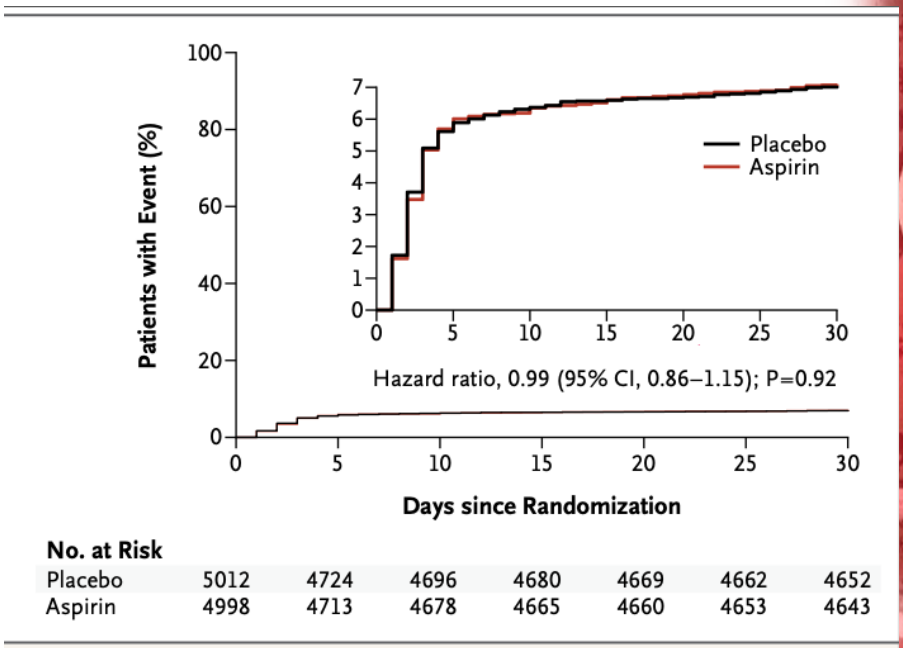


Figure 1. Kaplan–Meier Estimates of the Primary Composite Outcome of Death or Nonfatal Myocardial Infarction at 30 Days.

The inset shows the same data on an enlarged y axis.

N Engl J Med 370;16, 2014

Aspirin in Patients With Previous Percutaneous Coronary Intervention Undergoing Noncardiac Surgery

Michelle M. Graham, MD, Daniel I. Sessler, MD, Joel L. Parlow, MD, MSc, ... See More +

Annals of Internal Medicine®

Results:

In patients with prior PCI, aspirin reduced the risk for the primary outcome (absolute risk reduction, 5.5% [95% CI, 0.4% to 10.5%]; hazard ratio [HR], 0.50 [CI, 0.26 to 0.95]; *P* for interaction = 0.036) and for myocardial infarction (absolute risk reduction, 5.9% [CI, 1.0% to 10.8%]; HR, 0.44 [CI, 0.22 to 0.87]; *P* for interaction = 0.021). The effect on the composite of major and life-threatening bleeding in patients with prior PCI was uncertain (absolute risk increase, 1.3% [CI, −2.6% to 5.2%]). In the overall population, aspirin increased the risk for major bleeding (absolute risk increase, 0.8% [CI, 0.1% to 1.6%]; HR, 1.22 [CI, 1.01 to 1.48]; *P* for interaction = 0.50).

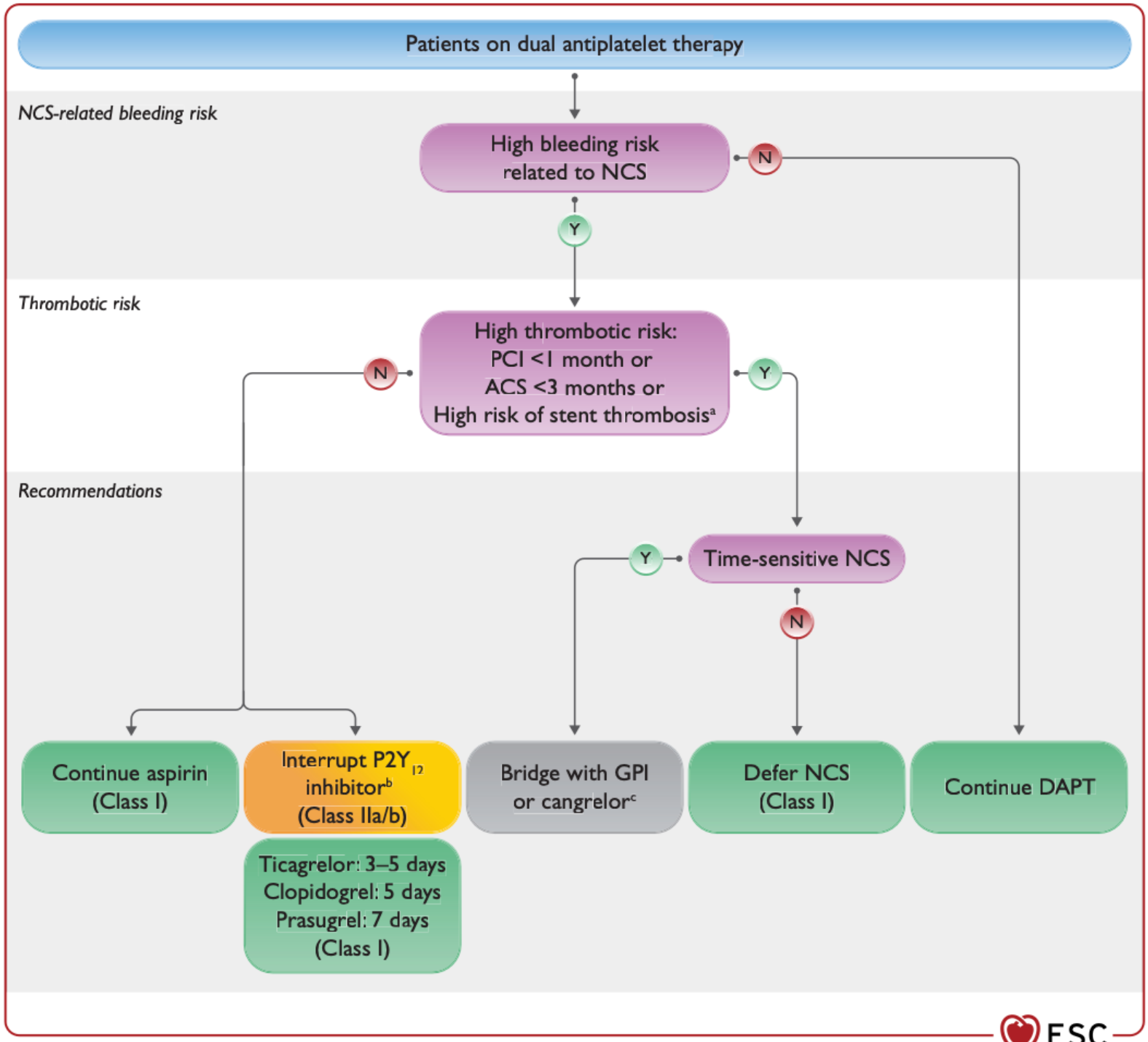
Conclusion:

Perioperative aspirin may be more likely to benefit rather than harm patients with prior PCI.

ESC GUIDELINES 2022

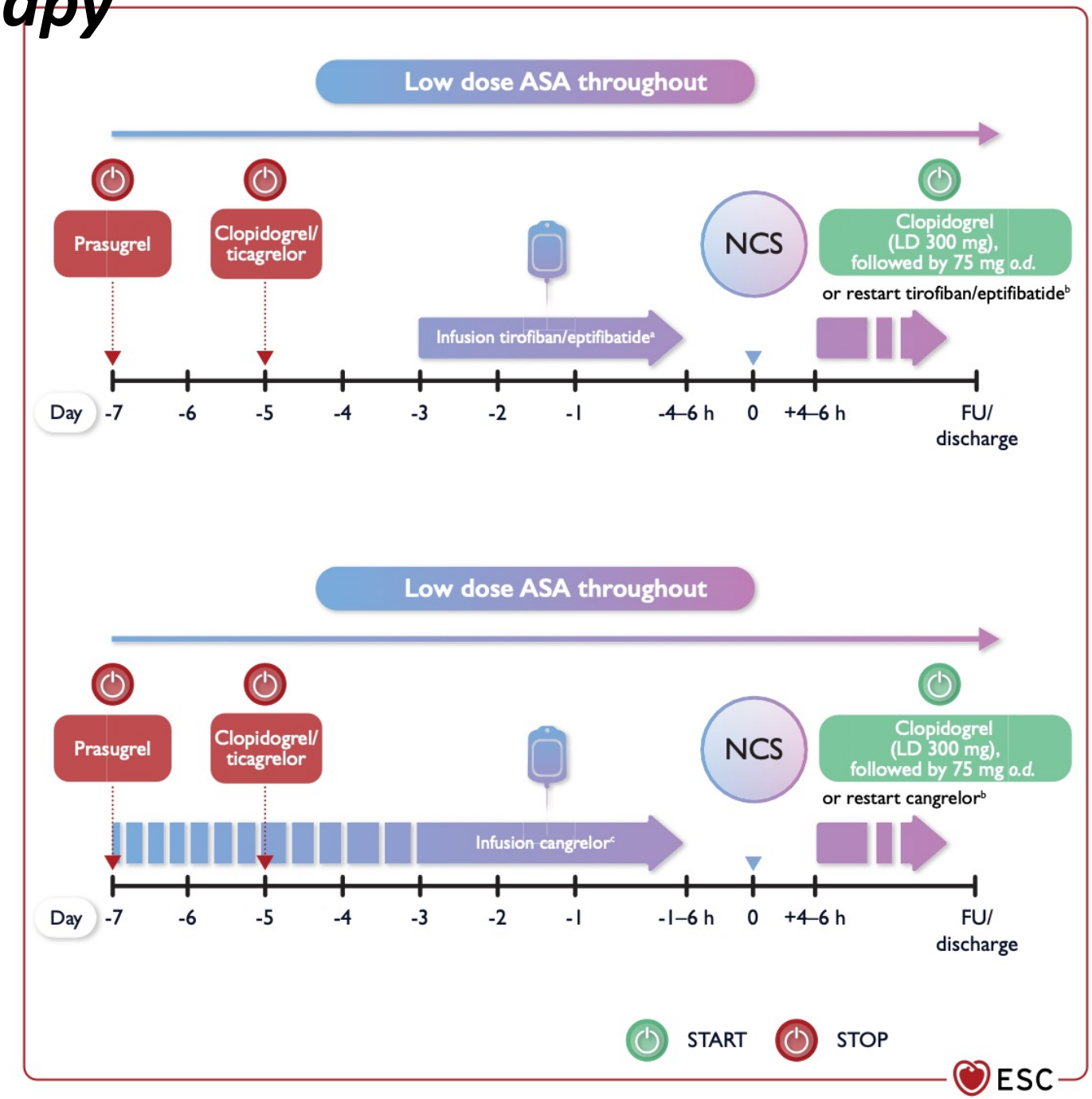
- The preferred management of patients on DAPT due to PCI **is to delay elective NCS** until completion of the full course of DAPT (6 months after elective PCI and 12 months after ACS).
- However, several recent trials have indicated that **shortening DAPT** duration to 1–3 months after implantation of modern DES is associated with acceptable rates of MACE and stent thrombosis in low- and moderate-risk patients.
- Based on these newer data, **it is recommended to delay time-sensitive NCS until a minimum of 1 month of DAPT** treatment. **In high-risk CV patients** a DAPT duration of at least **3 months** should be considered

European Heart Journal (2022) 43, 3826–3924

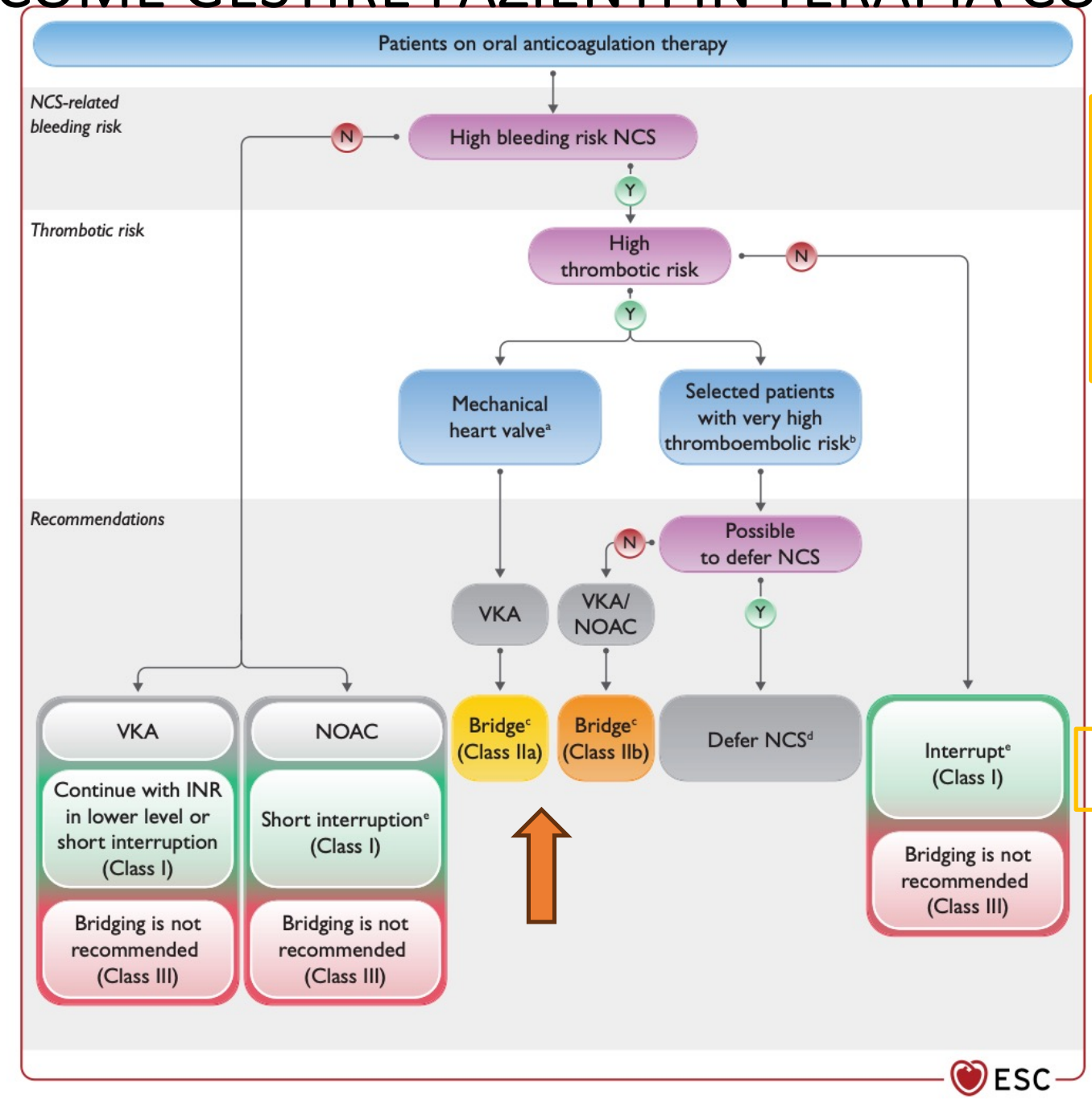

Patients on dual antiplatelet therapy
NCS-related bleeding risk
High bleeding risk related to NCS
N
Y
Thrombotic risk
High thrombotic risk: PCI <1 month or ACS <3 months or High risk of stent thrombosis[a]
N
Y
Recommendations
Y
Time-sensitive NCS
N
Continue aspirin (Class I)
Interrupt P2Y12 inhibitor[b] (Class IIa/b)
Ticagrelor: 3–5 days
Clopidogrel: 5 days
Prasugrel: 7 days
(Class I)
Bridge with GPI or cangrelor[c]
Defer NCS (Class I)
Continue DAPT
ESC

Bridging therapy

In paz ad alto R di trombosi stent, recente IMA, recente PCI



COME GESTIRE PAZIENTI IN TERAPIA CON ANTICOAGULANTE



1) Stratificare rischio emorragico (delle procedure)
2) Valutare rischio trombotico (del paz)

sicuro INR ≤1.5

VALUTAZIONE DEL RISCHIO TROMBO-EMBOLICO

Perioperative thrombotic risk

Thrombotic risk	Indication for anticoagulant therapy		
	Mechanical heart valve	Atrial fibrillation	VTE
High thrombotic risk*	Any mitral valve prosthesis Any caged-ball or tilting disc aortic valve prosthesis Recent (within 6 months) stroke or transient ischemic attack	$CHADS_2$ score 5-6 CHA_2DS_2-VASc score 7-9 Recent (within 3 months) stroke or transient ischemic attack Rheumatic valvular heart disease	Recent (within 3 months) VTE Severe thrombophilia (eg, deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
Moderate thrombotic risk	Bileaflet aortic valve prosthesis and 1 or more of the of following risk factors: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age >75 years	$CHADS_2$ score 3-4 CHA_2DS_2-VASc score 4-6	VTE within the past 3 to 12 months Nonsevere thrombophilia (eg, heterozygous factor V Leiden or prothrombin gene mutation) Recurrent VTE Active cancer (treated within 6 months or palliative)
Low thrombotic risk	Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	$CHADS_2$ score 0-2 CHA_2DS_2-VASc score 0-3 (assuming no prior stroke or transient ischemic attack)	VTE >12 months previous and no other risk factors

International Society on Thrombosis and Haemostasis Guidance Statement 2019
British Society of Gastroenterology and European Society of Gastrointestinal Endoscopy guidelines 2016

Paziente in terapia con:

Warfarin

Rischio trombotico

	ALTO	BASSO/MODERATO
Giorno -5	**Sospensione AVK**	**Sospensione AVK**
Giorno-4	Inizio eparina: paziente in acenocumarolo ed in range terapeutico al momento della sospensione	Inizio eparina: paziente in acenocumarolo ed in range terapeutico al momento della sospensione
Giorno-3	Inizio eparina: paziente in Warfarin ed in range terapeutico al momento della sospensione	Inizio eparina: paziente in Warfarin ed in range terapeutico al momento della sospensione
EBPM	Ogni 12 ore (per le dosi vedi schema)	Ogni 24 ore (dosi profilattiche vedi schema)
Ultima somministrazione eparina	Almeno 12/24 ore prima dell'intervento	Almeno 12 ore prima dell'intervento
Controllo INR	Prima dell'intervento. Si procede con INR <1.5	Prima dell'intervento. Si procede con INR <1.5

Bridging therapy

12 ore dopo	Riprendere eparina a dosi profilattiche se l'emostasi è sicura
Giorno + 1	Inizio AVK ad una dose 50% superiore a quella abituale (se l'emostasi è sicura e se il paziente è in grado di assumere farmaci per os)
Giorno + 2	Prosegue AVK ad una dose 50% superiore a quella abituale (se l'emostasi è sicura)
Giorno + 3 e successivi	Sospende eparina se INR > 2. Prosegue con dose abituale

Postoperative low molecular weight heparin bridging treatment for patients at high risk of arterial thromboembolism (PERIOP2): double blind randomised controlled trial

Michael J Kovacs,[1] Philip S Wells,[2] David R Anderson,[3] Alejandro Lazo-Langner,[1] Clive Kearon,[4]

Objective

To determine the efficacy and safety of dalteparin postoperative bridging treatment vs placebo for patients with atrial fibrillation or mechanical heart valves when warfarin is temporarily interrupted for a planned procedure

Intervention

Random assignment to dalteparin (n=821)or placebo (n=650) after the procedure

Main OutcoMe Measures

Major thromboembolism and major bleeding

Conclusions

In patients with atrial fibrillation or mechanical heart valves who had warfarin interrupted for a procedure, no significant benefit was found for postoperative dalteparin bridging to prevent major thromboembolism.

BMJ 2021;373

COME GESTIRE PAZIENTI IN TERAPIA CON ANTICOAGULANTI ORALI DIRETTI

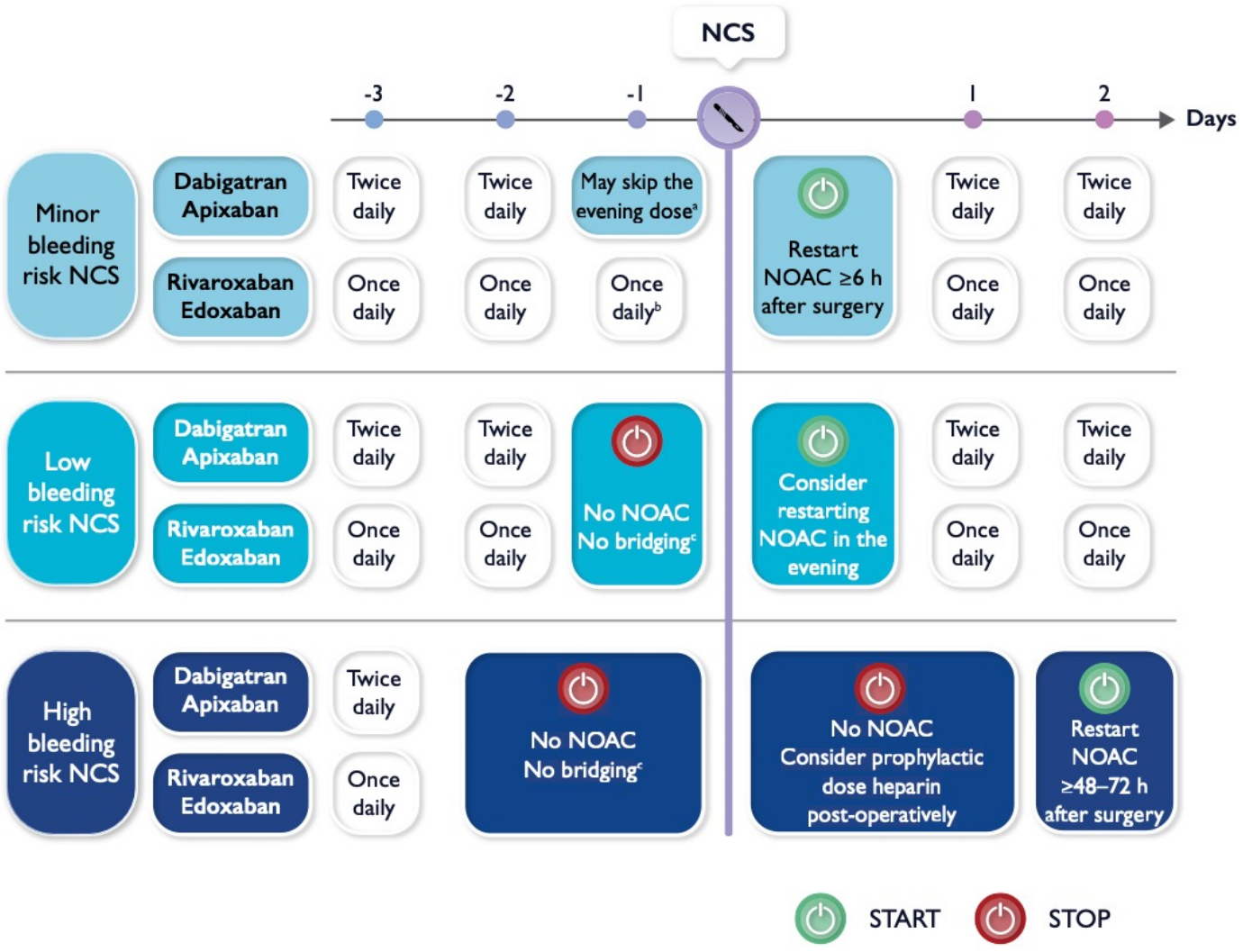
Timing for interruption of a direct oral anticoagulant (DOAC) before and after elective surgery

HIGH BLEEDING RISK procedure			Day of surgery	No major bleeding		
Regular DOAC dose	X	X	X	X	Regular DOAC dose	Regular DOAC dose

LOW BLEEDING RISK procedure			Day of surgery	No major bleeding		
Regular DOAC dose	Regular DOAC dose	X	X	Regular DOAC dose	Regular DOAC dose	Regular DOAC dose

Procedure ad alto R sanguinamento raccomandata sospensione 48 h o più prima
Se funzione renale alterata, necessaria sospensione più lunga (++ dabigatran)

Stopping and re-initiation of NOAC therapy in elective NCS according to the periprocedural risk of bleeding in patients with normal renal function



ESC

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

Minor bleeding risk NCS

Perform intervention at NOAC through 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)	Dabigatran: Low bleeding risk NCS	Dabigatran: High bleeding risk NCS	Apixaban, rivaroxaban, edoxaban: Low bleeding risk NCS	Apixaban, rivaroxaban, edoxaban: High bleeding risk NCS
≥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			

No peri-operative bridging with UFH/LMWH

ESC

Perioperative management of oral direct thrombin inhibitors and factor Xa inhibitors

Anticoagulant	Kidney function and dose	Interval between last dose and procedure NOTE: No anticoagulant is administered the day of the procedure		Resumption after procedure	
		High bleeding risk	Low bleeding risk	High bleeding risk	Low bleeding risk
Dabigatran	CrCl >50 mL/minute Dose 150 mg twice daily	Give last dose 3 days before procedure (ie, skip 4 doses on the 2 days before the procedure)	Give last dose 2 days before procedure (ie, skip 2 doses on the day before the procedure)	Resume 48 to 72 hours after surgery (ie, postoperative day 2 to 3)	Resume 24 hours after surgery (ie, postoperative day 1)
	CrCl 30 to 50 mL/minute Dose 150 mg twice daily	Give last dose 5 days before procedure (ie, skip 8 doses on the 4 days before the procedure)	Give last dose 3 days before procedure (ie, skip 4 doses on the 2 days before the procedure)		
Rivaroxaban	CrCl >50 mL/minute Dose 20 mg once daily	Give last dose 3 days before procedure (ie, skip 2 doses on the 2 days before the procedure)	Give last dose 2 days before procedure (ie, skip 1 dose on the day before the procedure)		
	CrCl 30 to 50 mL/minute Dose 15 mg once daily				
Apixaban	CrCl >50 mL/minute Dose 5 mg twice daily	Give last dose 3 days before procedure (ie, skip 4 doses on the 2 days before the procedure)	Give last dose 2 days before procedure (ie, skip 2 doses on the day before the procedure)		
	CrCl ≤50 mL/minute Dose 2.5 mg twice daily				
Edoxaban	CrCl 51 to 95 mL/minute Dose 60 mg once daily	Give the last dose 3 days before the procedure (ie, skip 2 doses on the 2 days before the procedure)	Give the last dose 2 days before the procedure (ie, skip 2 dose on the day before the procedure)		
	CrCl ≤50 mL/minute* Dose 30 mg once daily				

Bridging therapy quando terapia orale non può essere somministrata subito dopo intervento

Endoscopy in patients on antiplatelet or anticoagulant therapy: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guideline update

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2021

JAMA Internal Medicine

American Medical Associatio

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

James D. Douketis, MD, Alex C. Spyropoulos, MD, [...], and Sam Schulman, MD, PhD

DOAC	Surgical Procedure-Associated Bleeding Risk	Preoperative DOAC Interruption Schedule					Day of Surgical Procedure (No DOAC)	Postoperative DOAC Resumption Schedule			
		Day -5	Day -4	Day -3	Day -2	Day -1		Day +1	Day +2	Day +3	Day +4
Apixaban	High										
	Low										
Dabigatran etexilate (CrCl ≥50 mL/min)	High										
	Low										
Dabigatran etexilate (CrCl <50 mL/min)[a]	High										
	Low										
Rivaroxaban	High										
	Low										

▶ **Fig. 3** Perioperative direct oral anticoagulant (DOAC) management protocol. Reproduced with permission from JAMA Intern Med 2019:179 (11);1469–78. Copyright (2019) American Medical Association. All rights reserved. [rerif]
No DOAC was taken on certain days (shaded) and on the day of the elective surgery or procedure (including endoscopy). 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 procedure. Dark blue arrows refer to patients having a low-bleed-risk procedure. The thickened orange arrows refer to flexibility in timing of DOAC resumption after a procedure.

ORIGINAL RESEARCH ARTICLE

Circulation

Periprocedural Outcomes of Direct Oral Anticoagulants Versus Warfarin in Nonvalvular Atrial Fibrillation

Meta-Analysis of Phase III Trials

Table 1. Baseline Characteristics of the RCTs Included in the Meta-Analysis

	RE-LY[9,16,17]	ROCKET AF[10,18]	ARISTOTLE[11,19]	ENGAG
DOAC (vs warfarin)	Dabigatran	Rivaroxaban	Apixaban	Edo
Patients who underwent a procedure, n	4591	2130	5439	7
Analyzed procedures, n	4591	2980	9260	7
Mean age (SD), y	72.5 (7.8)	73 (8.2)	71 (8.0)	71.(
Female patients, %	31.6	36.5	31.0	3
Median weight: BMI, kg/m^2, or actual, kg	29.4†	28.4†	84.5‡	2
Mean creatinine clearance (SD), mL/min	70.5 (35.7)	68.0 (23.9)	>50.0 in 83.8%	76.4
$CHADS_2$ (SD)	2.1 (1.1)	3.4 (1.0)	2.1 (1.1)	2.8
HAS-BLED score (range or mean)	NR			2.6
0–1, %		8	32	
2, %		30	38	
≥3, %		62	30	
Coronary artery disease§ or prior myocardial infarction‖, %	35.2§	18.6‖	15.8‖	NR
Peripheral vascular disease, %	5.4	6.5	6.1	NR
Congestive heart failure, %	26.4	62.4	29.6	49.7
Diabetes mellitus, %	24.7	41.7	27.3	40.3
Hypertension, %	80.9	91.1	87.4	94.3
Long-term aspirin use, %	40.8	36.8	32.5	29.1

Table 2. Types of Procedures or Surgeries in Participants of Trials*

	RE-LY[16,17]† (n=4591), %	ROCKET AF[18] (n=2980), %	ARISTOTLE[19] (n=9260), %	ENGAGE AF‡ (n=7193), %	Weighted Average, %
Gastrointestinal endoscopy	8.6	17.0	17.5	12.0	14.1
Dental or oral	10.0	17.0	14.6	13.6	13.7
Abdominal/thoracic/ orthopedic	14.1	13.0	NR	13.8	13.7
Electrophysiological	10.3	9.0	6.1	12.7	9.2
Ophthalmologic	10.0	8.0	8.0	10.8	9.2
Coronary angiography with/ without intervention	6.2	6.0	8.3	9.6	8.0
Urologic	5.7	4.0	3.2	3.9	4.0
CABG or valve procedures	2.0	1.0	NR	0.5	1.1

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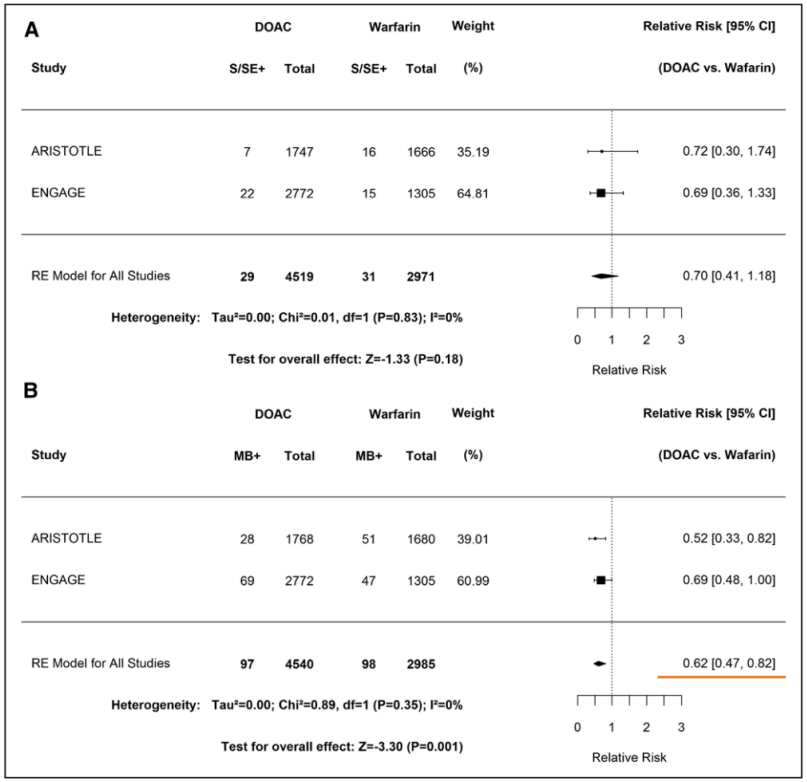
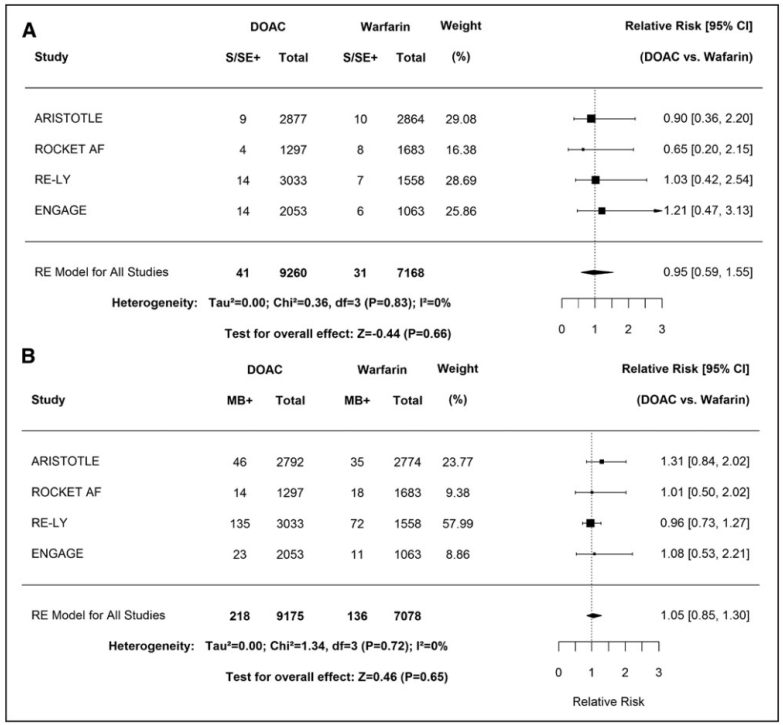


Figure 1. Forest plot of primary outcomes (direct oral anticoagulants [DOACs] vs warfarin) under an uninterrupted periprocedural anticoagulatio strategy.

A, Stroke/systemic embolism (S/SE+) outcomes and (**B**) major bleed outcomes (MB+). Relative risk <1 favors DOACs and >1 favors warfarin. ARISTOTLE indicates



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Under an uninterrupted anticoagulation strategy, 38% lower risk of major bleeding for DOACs a compared with warfarin.

CHIRURGIA D'URGENZA A MODERATO-ALTO RISCHIO DI SANGUINAMENTO IN PAZ IN TERAPIA CON ANTICOAGULANTI INDIRETTI

a. Infondere vitamina K 5- 10mg/100ml di sol. fisiologica ev in 30'

b. Dosaggio INR.

c. Infondere CONCENTRATO di complesso protrombinico a 3 fattori (unico al momento disponibile presso la nostra Azienda) 20 UI/Kg in attesa INR in circa 15-20 minuti
   - Se INR 1-2 STOP
   - Se INR 2-3 aggiungi complesso protrombinico 10 UI/kg
   - Se INR 3-4 aggiungi complesso protrombinico 20 UI/kg
   - Se INR > 4 aggiungi complesso protrombinico 30 UI/kg

d. Ripetere INR dopo circa 20 min. dalla fine dell'infusione

e. In caso target INR non raggiunto, eventuale ripetizione della somministrazione di CCP

CHIRURGIA D'URGENZA A MODERATO-ALTO RISCHIO DI SANGUINAMENTO IN PAZ IN TERAPIA CON ANTICOAGULANTI DIRETTI

- Tentare di posticipare intervento di almeno 12 ore (meglio 24 h)
- Eseguire test di laboratorio per valutare presenza attività dell'anticoagulante
- Se si rileva attività anticoagulante residua, si può infondere complesso protrombinico a 3 fattori o l'antidoto per dabigatran (Idarucizumab)

TAKE-HOME MESSAGE

A fronte della crescente complessità clinica dei pazienti e al fine di ridurre il rischio di complicanze emorragiche e trombo-emboliche
è necessario e indispensabile implementare all'interno di ogni Azienda Ospedaliera protocolli operativi sulla gestione peri-operatoria della terapia anti-trombotica frutto della condivisone e interazione multidisciplinare tra cardiologi, chirurghi, anestesisti e internisti.

Grazie per l'attenzione

EFFETTI DEGLI ANTICOAGULANTI SUI TEST COAGULATIVI

Drug class	Drug	Brand name(s)	PT	aPTT	Anti-factor Xa activity
Vitamin K antagonists	Warfarin	Jantoven	↑	↑/– *	–
	Acenocoumarol	Sintrom	↑	↑/– *	–
Heparins	Unfractionated heparin		– ¶	↑	↑
	LMW heparins		–	↑/–	↑
	Enoxaparin	Lovenox			
	Dalteparin	Fragmin			
	Nadroparin	Fraxiparine			
	Fondaparinux	Arixtra	–	↑/–	↑
Direct thrombin inhibitors	Argatroban	Acova	↑	↑	–
	Dabigatran	Pradaxa	↑/–	↑	–
Direct factor Xa inhibitors	Rivaroxaban	Xarelto	↑/–	↑/–	↑ Δ
	Apixaban	Eliquis	↑/–	↑/–	↑ Δ
	Edoxaban	Lixiana, Savaysa			↑ Δ